

highly colored oils from which it was not found possible to isolate a crystalline compound.

1,4-Dimethyl-2-carboxyl-3-ethyl-5-carbethoxypyrrole.—The procedure is essentially that of Fischer, Sturm and Friedrich.⁷ The yield is improved if the ethereal solution of the pyrrole is thoroughly dried over anhydrous sodium sulfate before proceeding with the chlorination. To obtain a satisfactory product for analysis it is also necessary to substitute 10% sodium carbonate for the sodium hydroxide used earlier; the yield was 30% on one-gram lots. For purification, the acid is dissolved in the minimum volume of acetone at room temperature. To about five times this volume of water a small seed of the acid is added and the water is then added slowly and with vigorous stirring to the acetone. The acid crystallizes out rapidly. It can then be recrystallized from diethyl ether. The solubility in diethyl ether decreases markedly on repeated recrystallization; m. p. 149–150° with slight decomposition.

Anal. Calcd. for $C_{15}H_{17}O_4N$: C, 60.19; H, 7.11. Found: C, 60.23; H, 7.13.

N-Methyl-methylethylmaleic Imide.—Further studies indicate that this compound may be prepared readily by two further techniques. (a) Forty-six hundredths of a gram of sodium is dissolved in 100 cc. of dry *t*-amyl alcohol contained in a 500-cc. flask equipped with a reflux condenser; 1.4 g. of methylethylmaleic imide is added and the solution allowed to stand for ten minutes. Then 2.52 g. of redistilled dimethyl sulfate is added, the mixture allowed to stand for half an hour and then heated on the steam-bath for ten minutes. The solution is filtered and the *t*-amyl alcohol evaporated off under reduced pressure. The oil which remains is dissolved in ether and the ethereal solution washed several times with 1-1 ammonia solution and finally with water. On evaporating off the ether, an oil boiling at 215–221° bath temperature, Siwoloboff method, is obtained.

(7) Fischer, Sturm and Friedrich, *Ann.*, **461**, 269 (1928).

(b) Methylethylmaleic imide (1.39 g.) is dissolved in the least possible amount of absolute alcohol and a saturated solution of 0.56 g. of potassium hydroxide in absolute alcohol is added with stirring. The potassium salt crystallizes out and is filtered and washed with a small amount of absolute ethyl alcohol. This product is soluble in water and leaves a residue when heated on a silver spatula. The potassium salt is then heated for ten minutes at 160–170° with an excess of dimethyl sulfate. After cooling, the solution is extracted with ether and the excess dimethyl sulfate washed out with 1-1 ammonia solution. The ethereal solution is washed with water and then dried over anhydrous sodium sulfate. After evaporating off the ether, a colorless oil boiling at 214–221° (Siwoloboff method) is obtained; yield, 0.7 g. or 46%.

On fractionally distilling this material, using an 8 in. $\times$ 8 mm. tube for a column, two fractions were obtained. The first fraction failed to solidify when placed in an ice-salt mixture; some solid material separated from the second fraction under the same conditions. The second fraction lost this property on standing in the vacuum desiccator for several days, an indication that it was due to the presence of water. That the impurity was not methylethylmaleic imide was shown by the fact that both fractions on saponification gave methylamine free from ammonia.

Summary

1. A group of unsymmetrical mono-N-methyldipyrrolymethanes has been prepared.

2. It has been demonstrated that the course of the unsymmetrical dipyrrolymethane condensation is strongly dependent upon the nature of the substituents upon each pyrrole ring entering the reaction.

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[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

An Anhydro Derivative of D-Mannosan $\langle 1,5 \rangle \beta \langle 1,6 \rangle$ (presumably 3,4-Anhydro-D-talosane $\langle 1,5 \rangle \beta \langle 1,6 \rangle$)

BY RAYMOND M. HANN AND C. S. HUDSON

In a recent publication¹ from this Laboratory it was pointed out that 2,3-isopropylidene-D-mannosan $\langle 1,5 \rangle \beta \langle 1,6 \rangle$ (I), a compound isolated as an intermediate in the preparation of D-mannosan $\langle 1,5 \rangle \beta \langle 1,6 \rangle$ by the pyrolysis of vegetable ivory, should prove to be a useful substance for various syntheses. We have recently employed it in a synthesis of the disaccharide 4-[β -D-glucopyranosido]-D-mannose² and of crystalline 4-methyl-D-mannose³; the present com-

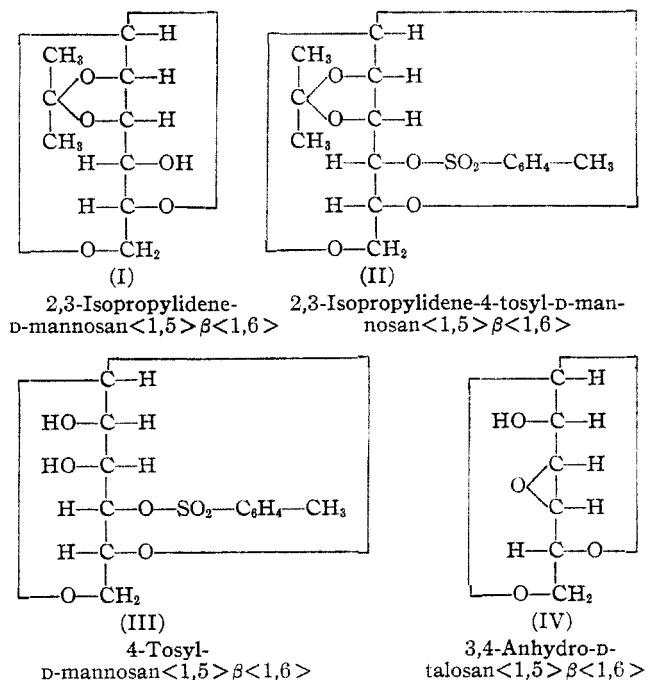
munication describes its further use for the synthesis of a new type of sugar derivative, a 3,4-anhydro-D-talosane $\langle 1,5 \rangle \beta \langle 1,6 \rangle$ (IV), which is an anhydro sugar anhydride, possessing three rings. The 2,3-isopropylidene-D-mannosan $\langle 1,5 \rangle \beta \langle 1,6 \rangle$ (I) was converted to 2,3-isopropylidene-4-tosyl-D-mannosan $\langle 1,5 \rangle \beta \langle 1,6 \rangle$ (II) by treatment with pyridine and *p*-toluenesulfonyl chloride. The isopropylidene group of the tosylated acetal (II) was removed by refluxing the compound in dilute acetic acid, and the solution on cooling deposited crystalline 4-tosyl-D-mannosan-

(1) Knauf, Hann and Hudson, *THIS JOURNAL*, **63**, 1447 (1941).

(2) Haskins, Hann and Hudson, *ibid.*, **63**, 1724 (1941).

(3) Haskins, Hann and Hudson, unpublished results.

$<1,5>\beta<1,6>$ (III). The latter substance, upon treatment with a molecular equivalent of aqueous sodium hydroxide solution, was detosylated with the simultaneous formation in quantitative yield of an anhydro-hexosan for which the structure of 3,4-anhydro-D-talosane $<1,5>\beta<1,6>$ (IV) appears probable. This structure is assumed by



analogy on the general grounds that the alkaline detosylation of sugar derivatives in which the tosyl group occupies a *trans* position with respect to a free or potential hydroxyl group on a vicinal carbon atom is attended by a Walden inversion about that carbon atom carrying the tosyl group, and the formation of a *cis* ethylene oxide type of ring.⁴ The configuration of a 3,4-anhydro-D-allosane $<1,5>\beta<1,6>$ for the substance to which we assign formula (IV) seems excluded because the Walden inversion would have to occur at carbon 3 rather than at carbon 4, for which there is no known analogy among tosyl esters. Where Walden inversions are known with tosyl esters it is the configuration about the carbon to which the tosyl group is attached that undergoes the inversion, the ester apparently breaking at the valence bond between carbon and oxygen.⁵

Since ethylene oxide rings upon cleavage by suitable reagents undergo Walden inversion and yield mixtures of the two possible *trans* isomers,

(4) Robertson and Griffith, *J. Chem. Soc.*, 1193 (1935).

(5) Ferns and Lapworth, *ibid.*, 101, 273 (1912); Phillips, *ibid.*, 123, 44 (1923); Cohen and Schneider, *This Journal*, 63, 3382 (1941).

it was anticipated that hydrolytic rupture of 3,4-anhydro-D-talosane $<1,5>\beta<1,6>$ (IV) would yield as end-products D-mannose and D-idose. The anhydro compound was accordingly converted to a mixture of hexose acetates by allowing it to stand for some time in an acid acetylating mixture, which opens both the 3,4 and the 1,6 rings. The resulting hexose (D-mannose and D-idose) acetates were extracted from the acetylating solution with chloroform and the extract was treated with sodium methylate to deacetylate the acetates. The sugar solution was reduced with hydrogen and Raney nickel and upon concentration it yielded a mixture of crystalline D-mannitol and sirupy D-iditol. The sirupy alcohol was acetylated and the resulting crystalline acetate, after purification, proved to be D-iditol hexaacetate (m. p. 121–122°; $[\alpha]^{20}_D$ in chloroform, +25.3°). Because of the similarity of these physical constants to those of D-mannitol hexaacetate (m. p. 123–124°; specific rotation in chloroform, +25.0°), which could of course be present, the D-iditol hexaacetate was examined by optical crystallographic measurements through the kind assistance of Mr. G. L. Keenan, of the Food and Drug Administration of the Federal Security Agency, and it was found to be the enantiomorph

of an authentic specimen of L-iditol hexaacetate. The anhydro compound IV therefore yields D-mannose and D-idose when its rings are opened, as has been assumed from the views advanced by Robertson and Griffith.⁴

We express our appreciation to Dr. A. T. Ness for performing the microchemical analyses in connection with this study.

Experimental

4-Tosyl-D-mannosan $<1,5>\beta<1,6>$ (III) from 2,3-Isopropylidene-4-tosyl-D-mannosan $<1,5>\beta<1,6>$ (II).—A suspension of 30.0 g. of finely powdered 2,3-isopropylidene-4-tosyl-D-mannosan in 300 cc. of 20% acetic acid was boiled under reflux until the suspended solid dissolved completely (two hours). The solution was cooled and the crystalline 4-tosyl-D-mannosan which deposited (25.3 g., 95%) was separated by filtration and recrystallized from 10 parts of 50% alcohol. The compound formed needles which melted at 168° (cor.) and showed a specific rotation $[\alpha]^{20}_D$ of -80.3° (*c*, 1.08; *l*, 4) in absolute alcohol. These values were unchanged after two further recrystallizations. The substance was only slightly soluble in chloroform and may be recrystallized from 100 parts of this solvent.

Anal. Calcd. for $C_{12}H_{18}O_7S$: C, 49.36; H, 5.10; S, 10.14. Found: C, 49.24; H, 5.10; S, 10.07.

2,3-Diacetyl-4-tosyl-D-mannosan <1,5> β <1,6>.—A solution of 1.5 g. of 4-tosyl-D-mannosan in a mixture of 12.5 cc. of pyridine and 12.5 cc. of acetic anhydride was allowed to stand overnight and then poured upon crushed ice. The precipitated 2,3-diacetyl-4-tosyl-D-mannosan (1.8 g., 95%) was recrystallized from 25 parts of 50% alcohol to constant physical properties and formed elongated prisms which melted at 115–116° (cor.) and exhibited a specific rotation $[\alpha]^{20}_D$ of -103.4° (*c.* 1.24; *l.* 4) in chloroform.

Anal. Calcd. for $C_{27}H_{34}O_{10}S$: C, 61.82; H, 4.61; S, 6.11. Found: C, 61.69; H, 4.61; S, 6.03.

3,4-Anhydro-D-talosan <1,5> β <1,6> (IV) from 4-Tosyl-D-mannosan <1,5> β <1,6> (III) and Sodium Methylate.—A solution of 3.2 g. (0.01 mole) of 4-tosyl-D-mannosan in 90 cc. of warm methyl alcohol was allowed to cool to 35° and 10 cc. (0.01 mole) of *N* sodium methylate solution was added. After twenty-four hours the reaction mixture, which was neutral to litmus, was concentrated *in vacuo* to a dry crystalline residue, which was extracted with two 25-cc. portions of hot ethyl acetate and the insoluble residue of sodium *p*-toluenesulfonate (1.8 g., 95%) separated by filtration. The filtrate was concentrated by an air current to a sirup which slowly crystallized to a mass of radiating needles. The crude yield was 1.4 g. (quantitative). The compound was recrystallized by solution in 35 parts of anhydrous ether and the gradual addition of 10 parts of isopentane. It melted at 73–74° (cor.) and had a specific rotation $[\alpha]^{20}_D$ of -49.5° (*c.* 1.44; *l.* 4) in water.

Anal. Calcd. for $C_6H_{10}O_4$: C, 50.00; H, 5.60; molecular weight, 144. Found: C, 50.15; H, 5.70; molecular weight (Rast), 163.

3,4-Anhydro-D-talosan <1,5> β <1,6> from 4-Tosyl-D-mannosan <1,5> β <1,6> and Sodium Hydroxide.—A suspension of 15.8 g. (0.05 mole) of 4-tosyl-D-mannosan in a mixture of 200 cc. of water and 50 cc. (0.05 mole) of *N* sodium hydroxide was heated for one hour on the steam-bath and the resulting solution, which was neutral to litmus, was concentrated *in vacuo* to dryness. After successive addition and evaporation of two 50-cc. portions of absolute alcohol (to remove any residual water) the crystalline residue was extracted with four 25-cc. portions of boiling ethyl acetate and the extract concentrated to dryness to recover the 3,4-anhydro-D-talosan. The yield of material melting at 72–73° (cor.) was 7.2 g. (quantitative) and the substance required no further purification for synthetic use.

2-Tosyl-3,4-anhydro-D-talosan <1,5> β <1,6>.—A solution of 1.0 g. of 3,4-anhydro-D-talosan in a mixture of 15 cc. of pyridine and 1.45 g. (1.1 molecular equivalents) of *p*-toluenesulfonyl chloride was allowed to stand at room temperature for eighteen hours and then poured upon crushed ice. The crystalline precipitate (1.4 g., 67%) was separated by filtration and recrystallized from 25 parts of methyl alcohol. The compound was obtained in the form of elongated prisms which melted at 147–148° (cor.) and showed a specific rotation $[\alpha]^{20}_D$ of -19.0° (*c.* 1.08; *l.* 4) in chloroform.

Anal. Calcd. for $C_{13}H_{14}O_6S$: C, 52.34; H, 4.73; S, 10.75. Found: C, 52.53; H, 4.57; S, 10.67.

D-Mannitol Hexaacetate and D-Iditol Hexaacetate from 3,4-Anhydro-D-talosan <1,5> β <1,6> (IV).—A solution of

1.4 g. (0.01 mole) of 3,4-anhydro-D-talosan in 50 cc. of acetic anhydride was cooled in an ice and salt freezing mixture and 1 cc. of concentrated sulfuric acid was added dropwise to the solution. After standing for six hours at 10°, the reaction mixture was allowed to remain for several days at 20° and then poured upon crushed ice. The solution was extracted with chloroform and the extract was washed in the usual manner and dried over anhydrous sodium sulfate. The dried chloroform extract was cooled in an ice-bath and 30 cc. of 0.4 *N* sodium methylate solution gradually added. After standing overnight, the solution was neutralized with sulfuric acid and the solvent removed by concentration *in vacuo* to dryness. The residue was dissolved in 100 cc. of water and reduced for six hours at 100° under a pressure of 167 atmospheres of hydrogen in the presence of Raney nickel. The catalyst was removed by filtration and the filtrate was concentrated to a sirup and poured into warm 80% alcohol to precipitate the sodium sulfate formed in the deacetylation. The 80% alcoholic solution was then concentrated *in vacuo* to a dry residue, which was extracted with 25 cc. of hot alcohol. The small amount of insoluble gummy solid was acetylated by warming with acetic anhydride and fused sodium acetate and yielded 0.4 g. of a mixture of hexitol hexaacetates (m. p. 106–108°). The alcoholic extract deposited 0.7 g. of fine needles (m. p. 155–157°) which upon recrystallization from alcohol yielded 0.5 g. of pure D-mannitol (m. p. 166°; mixed melting point with authentic D-mannitol, 166°; $[\alpha]^{20}_D$ -0.3° in water). No more crystalline material could be obtained directly from the alcoholic extract, so the solvent was removed and the sirupy residue was dissolved in 10 cc. of acetic anhydride and after addition of 2 g. of fused sodium acetate, the solution was heated for one hour on the steam-bath. The reaction mixture was cooled and poured into ice water and the crystalline precipitate (0.5 g.; m. p. 110–111°) was separated by filtration and recrystallized from a warm mixture of 2 cc. of alcohol and 1 cc. of water. As it cooled the solution deposited 0.2 g. of the characteristic hexagonal plates of D-iditol hexaacetate of melting point 121–122° (cor.) and specific rotation of $+25.3^\circ$ (*c.* 0.8; *l.* 4) in chloroform. Pure crystalline L-iditol hexaacetate, prepared by the acetylation of an L-iditol sirup obtained through the reduction of L-sorbose, melted at 121–122° (cor.) and gave a specific rotation $[\alpha]^{20}_D$ of -25.5° in chloroform. The melting point of the D-iditol hexaacetate from 3,4-anhydro-D-talosan was depressed to 106–107° upon admixture with D-mannitol hexaacetate, and was elevated to 160° upon admixture with authentic L-iditol hexaacetate, with which it forms a high melting racemate (see below). While the data are sufficient to characterize the D-iditol hexaacetate, it seemed desirable, in view of the similarity of the melting point and rotation of the substance (121–122°, $+25.3^\circ$) to those of D-mannitol hexaacetate (123–124°, $+25.0^\circ$) to obtain some further physical property as an aid in clearly differentiating these two compounds. Through the coöperation of Mr. G. L. Keenan it has been possible to subject the compounds to an optical crystallographic examination and completely confirm the identity of the hexitol hexaacetate as D-iditol hexaacetate.

Anal. Calcd. for $C_{18}H_{26}O_{12}$: C, 49.77; H, 6.03; CH_3CO , 59.5. Found: C, 49.81; H, 6.18; CH_3CO , 59.2.

Optical Crystallographic Properties.—(a) **L-Iditol Hexaacetate.**—*In ordinary light*, the material consists of hexagonal plates which break up into angular fragments. The crystal system appears to be hexagonal. Refractive indices (determined by the immersion method in organic oily liquids): $n_\omega = 1.505$, $n_e = 1.463$, both ± 0.002 . *In parallel polarized light (crossed nicols)*: the birefringence is strong. *In convergent polarized light (crossed nicols)*: uniaxial interference figures are frequently shown. The sign is negative.

(b) **D-Iditol Hexaacetate.**—The D-iditol hexaacetate obtained from 3,4-anhydro-D-talosane $\langle 1,5 \rangle \beta \langle 1,6 \rangle$ exhibited optical properties which were identical with those of L-iditol hexaacetate.

(c) **Racemic Iditol Hexaacetate.**—*In ordinary light*, this substance consists of glassy hexagonal plates which break up into angular fragments. Refractive indices (determined by the immersion method in organic oily liquids): $n_\alpha = 1.458$; $n_\beta = 1.507$; $n_\gamma = 1.515$, all ± 0.002 . All the indices are readily found. *In parallel polarized light (crossed nicols)*: the birefringence is extreme, some fragments extinguishing sharply, others remaining bright with crossed nicols. *In convergent polarized light (crossed nicols)*: partial biaxial interference figures are seen on many fragments, one optic axis being perpendicular to many of them. The sign is negative.

(d) **D-Mannitol Hexaacetate.**—*In ordinary light*, this substance consists of rather massive colorless prisms, which break up into angular fragments. The crystal system is probably monoclinic. Refractive indices (determined by the immersion method in organic oily liquids): $n_\alpha = 1.452$, $n_\beta = 1.520$, $n_\gamma = 1.526$, all ± 0.002 . All of the indices are readily found. *In parallel polarized light (crossed nicols)*: the birefringence is extreme. Fragments extinguishing sharply and others remaining bright with crossed nicols are both commonly found. *In convergent polarized light (crossed nicols)*: biaxial interference figures are frequently visible, being seen on practically all of the fragments, showing sections perpendicular to the acute bisectrix and also to an optic axis. The axial angle $2E$ is moderate in size and the sign is negative.

Racemic Iditol Hexaacetate.—A solution of a mixture of 0.055 g. of D-iditol hexaacetate and 0.055 g. of L-iditol hexaacetate in 3 cc. of boiling alcohol deposited 0.1 g. (91%) of racemic iditol hexaacetate upon cooling. The compound was recrystallized from 3 parts of boiling alcohol in the form of plates which melted at 165–166° (cor.) and showed no optical activity in chloroform solution (c , 0.8; l , 4).

Anal. Calcd. for $C_{18}H_{26}O_{12}$: C, 49.77; H, 6.03. Found: C, 49.99; H, 6.05.

Summary

The alkaline detosylation of 4-tosyl-D-mannosan $\langle 1,5 \rangle \beta \langle 1,6 \rangle$ has been shown to proceed with Walden inversion and *cis* ethylene oxide ring formation to yield an anhydro derivative which is presumably 3,4-anhydro-D-talosane $\langle 1,5 \rangle \beta \langle 1,6 \rangle$. The anhydro compound, upon treatment with an acid acetylating mixture, yields a mixture of D-mannose and D-idose pentaacetates. The hexoses present have been identified by conversion of the acetates to characteristic hexitol hexaacetates. The reactions outlined are in agreement with other reactions in the carbohydrate series involving Walden inversions with ethylene oxide ring formation and rupture, as studied especially by Robertson and his colleagues, and the present results justify the conclusion that the structure and the configuration of the anhydro compound are those of 3,4-anhydro-D-talosane $\langle 1,5 \rangle \beta \langle 1,6 \rangle$.

D- and L-iditol hexaacetates form a crystalline racemate which melts much higher than the components and differs from them in crystallographic optical properties.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Structure and Configuration of Resin Acids. Podocarpic Acid and Ferruginol

BY WILLIAM P. CAMPBELL¹ AND DAVID TODD

Podocarpic acid was first isolated in 1873 by Oudemans.² It was only recently, however, that Sherwood and Short³ studied the compound and suggested formula II as the most probable structure. The most revealing bit of evidence was the formation of 6-hydroxy-1-methylphenanthrene (III) in good yield by dehydrogenation, thus ac-

counting for all of the carbon atoms except one in a methyl group and one in the carboxyl. On the basis of this evidence the two carbon skeletons shown in formulas I and II were considered. Although formula I is similar to the resin acids, formula II was favored because the carboxyl group of podocarpic acid is much more highly hindered than that of the other resin acids.

Shortly after the appearance of this work it was pointed out by Fieser and Campbell⁴ that, if

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(2) Oudemans, *Ber.*, **6**, 1122 (1873); *Ann.*, **170**, 214 (1873); *J. prakt. Chem.*, **9**, 385 (1874).

(3) Sherwood and Short, *J. Chem. Soc.*, 1006 (1938).

(4) Fieser and Campbell, *THIS JOURNAL*, **61**, 2528 (1939).