Experiments to disclose the mechanism of this structural displacement are in progress.

to those of glucose-1-methylphenyl-2-phenylosazone justifies discarding the V and V′ formulas of glucosazone as well. All the more so, as the methylation of glucosazone, as has already been pointed out,[5] invariably leads to D-glucose-1-methylphenyl 2-phenylosazone derivable from the IV and IV′ forms, and so, so far, it has proved impossible to prepare methylated D-glucosazone from the chelate structures V and V′ neither by direct methylation nor in some roundabout way. The so-called mixed osazone B, which could be supposed to possess this structure, has been proved to be D-glucosazone contaminated with mixed osazone A.[5]

Acknowledgment.—We wish to express our indebtedness to Professor G. Zemplén for valuable advice given and to thank Dr. W. Cieleszky for the determination of the ultraviolet spectra, finally, Miss Ilona Batta for the microanalyses.

(25) L. F. Fieser and M. Fieser, "Organic Chemistry," D. C. Heath & Co., Boston, Mass., 1944, p. 351.

(26) F. Ramirez and R. J. Bellet, THIS JOURNAL, **76**, 491 (1954).

BUDAPEST, HUNGARY

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

1-*O*-Benzoyl-α-D-talopyranose

BY HARRY B. WOOD, JR., AND HEWITT G. FLETCHER, JR.

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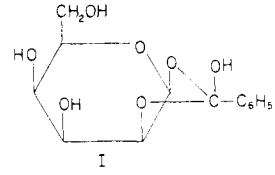
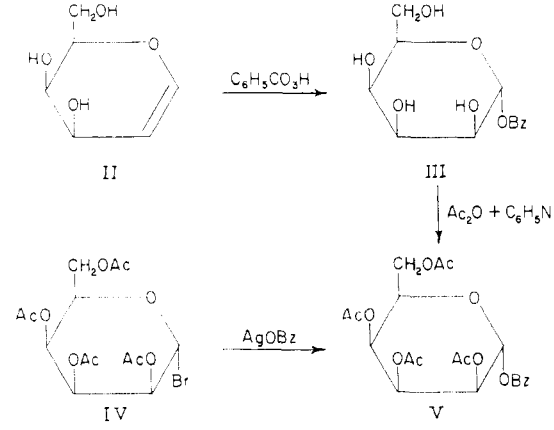
Oxidation of D-galactal with perbenzoic acid has given a new D-talose monobenzoate. Acetylation of this ester afforded an amorphous ester which is identical with 2,3,4,6-tetra-*O*-acetyl-1-*O*-benzoyl-α-D-talose synthesized from 2,3,4,6-tetra-*O*-acetyl-α-D-talopyranosyl bromide. The new substance is, therefore, 1-*O*-benzoyl-α-D-talopyranose. The possible structure of another D-talose monobenzoate, described earlier in the literature, is discussed.

In 1937, Pigman and Isbell[1] described a mono-*O*-benzoyl-D-talose which they had obtained as a by-product in the preparation of D-talose *via* the oxidation of D-galactal (II) with perbenzoic acid. Owing to the fact that the substance was stable in dilute acid solution but mutarotated in water, methanol, dilute alkali and pyridine, a cyclic orthoacid structure (I) was assigned to it.



I

The lability of this substance compared with the stability of the well-characterized 1-*O*-benzoyl-β-D-glucopyranose prepared somewhat earlier by Zervas[2] and the widespread currency of the cyclic orthoacid concept which had first been suggested by Emil Fischer,[3] combined to make such a tentative assignment of structure a reasonable one at that period.[4] However, subsequent advances in the chemistry of the sugar esters have shown (a) that acyl groups are very prone to migrate from C_1 to C_2 of an aldose when the hydroxyl at C_2 is free and spatially accessible to C_1[5,6] and (b) that cyclic orthoacid structures such as I are not likely to be sufficiently stable for isolation.[6] Furthermore, Isbell and his co-workers[7] have shown recently that the sample of D-talose monobenzoate prepared in 1937 had undergone no change in physical properties during the intervening years and was indeed a normal ester as shown by its characteristic ester carbonyl absorption in the infrared.



II III IV V

In all known additions to the double bond of glycals[8] the anionic portion of the adding molecule has been found attached to C_1 of the sugar and it seems reasonably certain, therefore, that the substance reported by Pigman and Isbell is a 1-*O*-benzoyl-D-talopyranose. Its failure to mutarotate in acid solution[1] and to give a phenylhydrazone[7] appear to support this assumption. The mutarotations in water, methanol, dilute alkali and pyridine reported by Pigman and Isbell[1,7] may then represent acyl migration from C_1 to C_2 or some other position. Indeed these mutarotations, which start in a *levo* direction and then turn in the *dextro* direction, suggest that an initial acyl migration frees a β-hydroxyl at C_1 and that normal equilibration of the anomeric forms then ensues. If the instability of the ester is due to a $C_1 \rightarrow C_2$ migration we must expect it to be the β- rather than the α-1-*O*-benzoyl-D-talopyranose, for such a *cis* isomer would resemble the easily rearranged 1-*O*-mesitoyl-α-D-glucose[5] and 1,3,5-tri-*O*-benzoyl-α-D-ribose[6] while the

(1) W. W. Pigman and H. S. Isbell, *J. Research Natl. Bur. Standards*, **19**, 189 (1937).

(2) L. Zervas, *Ber.*, **64**, 2289 (1931).

(3) E. Fischer, *ibid.*, **53**, 1624 (1920).

(4) *Cf.* E. Pacsu, *Advances in Carbohydrate Chem.*, **1**, 78 (1945).

(5) H. B. Wood, Jr., and H. G. Fletcher, Jr., THIS JOURNAL, **78**, 2849 (1956).

(6) R. K. Ness and H. G. Fletcher, Jr., *ibid.*, **78**, 4710 (1956).

(7) H. S. Isbell, J. E. Stewart, H. L. Frush, J. D. Moyer and F. A. Smith, *J. Research Natl. Bur. Standards*, **57**, 179 (1956).

(8) See, for instance, B. Helferich, *Advances in Carbohydrate Chem.*, **7**, 210 (1952).

α-(*trans*) isomer should be similar in stability to the well-known 1-*O*-benzoyl-β-D-glucopyranose.

On the other hand, the mechanism postulated for the oxidation of double bonds by per-acids[9,7] is such as to lead to *trans* products and this generalization has been made specifically for perbenzoic acid by Posternak and Friedli.[10] Levene and Tipson,[11] for instance, obtained 3,4,6-tri-*O*-acetyl-1-*O*-benzoyl-β-D-galactopyranose through the action of this reagent on D-galactal triacetate.[12] In the hope of throwing some light on these apparently contradictory indications[13] we have now re-examined the reaction of D-galactal with perbenzoic acid.

Preliminary experiments, following the directions which Pigman and Isbell[1] described for the aqueous oxidation of D-galactal, failed to yield us a crystalline, water-soluble product having ester carbonyl absorption. However, the second, non-aqueous oxidation procedure of these authors readily afforded a crystalline monobenzoylhexose; minor changes in the work-up procedure raised the yield to 13%. However, the physical constants of this monobenzoylhexose as shown in Table I clearly distinguish our substance from that described by the earlier authors. Not only does the new substance have an infrared absorption spectrum which distinguishes it from that reported earlier[1] but its stability is markedly greater, no mutarotation being detected in water, methanol or pyridine. All our attempts to obtain a product similar to Pigman and Isbell's have thus far failed although the oxidation produced, in addition to the new crystalline product, a large quantity of amorphous material which, upon acid hydrolysis, afforded D-talose and benzoic acid.

TABLE I

PROPERTIES OF D-TALOSE MONOBENZOATES

	Compound of Pigman and Isbell[1,7]	1-*O*-Benzoyl-α-D-talopyranose
$[\alpha]^{20}D$ in water	+21.2 (0.08 hr.) → + 5.1° (54 hr.) → 24.2° (648 hr.)	+72.4°
$[\alpha]^{20}D$ in 0.01 *N* HCl	+22.6°	+72.5°
$[\alpha]^{20}D$ in methanol	+15.4° (2.96 min.) → −33.3° (60.1 min.) → +11° (2550 min.)	+74°
$[\alpha]^{20}D$ in pyridine	+16.5° (0.1 hr.) → −12.5° (191.3 hr.) → + 4.8° (430.5 hr.)	+53°

The nature of the new monobenzoyl hexose was investigated in the following fashion. Infrared absorption measurements showed the presence of a normal ester carbonyl group. Hydrolysis with barium methoxide afforded crystalline D-talose in good yield.[14] In glacial acetic acid solution the compound consumed two moles of lead tetraacetate. Since the substance showed no mutarotation in pyridine, a sample was acetylated in this solvent. Unfortunately the product could be obtained only as a sirup, but chromatography readily gave a homogeneous fraction which had the composition of a tetra-*O*-acetyl-*O*-benzoylhexose and showed $[\alpha]^{20}D$ +84° in chloroform.

The known, crystalline 2,3,4,6-tetra-*O*-acetyl-D-talosyl bromide (IV)[1] was treated with silver benzoate under anhydrous conditions to give a sirup which, after chromatography, rotated $[\alpha]^{20}D$ +83° in chloroform. The infrared spectra of the sirups from the two sources (III and IV) were identical in all respects. Since such reactions of acylated glycosyl halides normally lead to products with groups on C_1 and C_2 in the *trans* relationship[15] we conclude that the product is 2,3,4,6-tetra-*O*-acetyl-1-*O*-benzoyl-α-D-talose (V) and that our monobenzoate is 1-*O*-benzoyl-α-D-talopyranose (III).

In the light of our knowledge of the behavior of 1-acyl aldoses, the relative stability of 1-*O*-benzoyl-α-D-talopyranose (III) is wholly normal; in a negative sense the evidence here adduced lends support to the supposition that the compound made by Pigman and Isbell may be, despite its origin, the β-anomer, 1-*O*-benzoyl-β-D-talopyranose.[16]

Experimental[17]

1-*O*-Benzoyl-α-D-talopyranose (III).—The procedure followed for the oxidation was modeled after that of Isbell and Pigman[1]; repeated trials led, however, to a modified method of isolation, giving higher yields of crystalline product. D-Galactal[18] (10 g.) and benzoic acid (10 g.) were dissolved in a mixture of 300 ml. of dioxane and 200 ml. of acetone. The solution was cooled to +5° and a methylene chloride solution (167 ml.) containing perbenzoic acid (18 g.)[19] added. After stirring, the solution was held at 0° for 24 hr. and then at 5° for 24 hr. Solvent was then removed *in vacuo* at less than 30° and the resulting semi-crystalline

(9) *Cf.* W. A. Waters in "Organic Chemistry," ed. by H. Gilman, John Wiley & Sons, Inc, New York, N. Y., 1953, p. 1165.

(10) T. Posternak and H. Friedli, *Helv. Chim. Acta*, **36**, 251 (1953).

(11) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **93**, 631 (1931).

(12) These authors found that further acetylation of their tri-*O*-acetyl-1-*O*-benzoyl-D-galactopyranose afforded a product identical with that which they obtained through condensation of 2,3,4,6-tetra-*O*-acetyl-α-D-galactosyl bromide with silver benzoate. As will be mentioned later, such a condensation produces *trans* products.

(13) Naturally, the identification of the parent sugar as D-talose, rather than D-galactose, is vital here. While Pigman and Isbell's evidence in this regard seemed unequivocal we have hydrolyzed a minute sample of their material and, by paper partition chromatography in a suitable solvent system, confirmed the fact that talose and only talose is present.

(14) To ensure the absence of alkali-induced rearrangements here, the reaction mixture was chromatographed on paper using a system known to separate talose and galactose. Only one spot was observed; chromatography of an acid hydrolyzed mixture gave identical results.

(15) As far as the present authors are aware, this generalization was first made by R. S. Tipson [*J. Biol. Chem.*, **130**, 55 (1939)] and first received theoretical interpretation by H. S. Isbell, *Ann. Revs. Biochem.*, **9**, 65 (1940); *J. Research Natl. Bur. Standards*, **26**, 35 (1941). It should be noted that while the high dextrorotation of tetra-*O*-acetyl-D-talopyranosyl bromide ($[\alpha]^{20}D$ +165.6° in $CHCl_3$; see ref. 1) indicates that the substance is almost certainly the α-anomer, the validity of the evidence presented here is independent of the anomeric configuration of this halide.

(16) It may be noted here that lead tetraacetate oxidation of 1-*O*-benzoyl-β-D-talopyranose and of 1-*O*-benzoyl-β-D-glucopyranose should produce the same dialdehyde and thus possibly provide a simple proof of the anomeric configuration of the D-talose monobenzoate reported by the earlier authors. Unfortunately the quantity of material available to us precluded such a test.

(17) Melting points are corrected for stem exposure.

(18) 3,4,6-Tri-*O*-acetyl-D-galactal was prepared by the method of C. Tamm and T. Reichstein [*Helv. Chim. Acta*, **31**, 1630 (1948)]; deacetylation with anhydrous, methanolic ammonia [R. Kuhn and H. H. Baer, *Chem. Ber.*, **88**, 1537 (1955)] gave D-galactal which showed $[\alpha]^{20}D$ −21.3° (MeOH, *c* 1.2) and gave satisfactory analyses for carbon and hydrogen.

(19) Perbenzoic acid was prepared by the method of G. Braun ["Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 431], the final extraction being made with methylene chloride and the extract, dried over sodium sulfate, used directly after titration of an aliquot to determine the perbenzoic acid content.

mass extracted with benzene–pentane (3 × 100 ml. of 1:2 v./v.). The mixture was dissolved in 100 ml. of water and the resulting solution extracted thrice with 1:2 benzene–pentane to remove remaining traces of acid. The aqueous solution was then extracted continuously with warm ether until no further material was removed. On concentration, the ethereal extract afforded crude crystalline product (2.6 g., 13%). Recrystallization from either ethyl acetate, acetone or 1,2-dimethoxyethane gave, with little loss, pure material melting at 165–166° and rotating $[\alpha]^{20}D$ +72.4° (H_2O, *c* 0.5), no mutarotation being observed within 1 hr. Rotations in other solvents were observed as follows: 0.01 *N* HCl, $[\alpha]^{20}D$ +72.5° (*c* 0.5); methanol, $[\alpha]^{20}D$ +74° (*c* 0.49); pyridine, $[\alpha]^{20}D$ +53° (*c* 1.1).

Anal. Calcd. for $C_{13}H_{16}O_7$: C, 54.93; H, 5.67. Found: C, 54.84; H, 5.78.

A sample (36.5 mg.) of the substance was treated with lead tetraacetate in glacial acetic acid as described by Hockett and McClenahan.[20] After 355, 1340 and 1867 minutes, analyses indicated the consumption of 1.98, 2.09 and 2.07 molar equivalents of oxidant.

D-Talose from 1-*O*-Benzoyl-α-D-talopyranose (III).—A sample (0.1616 g.) of the ester was dissolved in absolute methanol to make a total volume of 10 ml. and the rotations observed in a 1.5-dm. tube. Over a period of 8 min. at 20° no change was observed, the rotation corresponding to $[\alpha]^{20}D$ +72.8°. Four drops of 1.3 *N* barium methoxide was then added. After 43 min. the rotation had become constant at a value of +0.34°, corresponding to $[\alpha]^{20}D$ +22.7°, based on the theoretical yield of hexose. Barium ions were removed with Amberlite IR-120 and the solution concentrated *in vacuo* to a sirup. From ethanol the handsome prisms characteristic of D-talose were deposited: 0.065 g. (64%), m.p. 130–131°, $[\alpha]^{20}D$ +20.1° (H_2O, *c* 1.2). Isbell and Pigman[21] recorded m.p. 133–134° and $[\alpha]^{20}D$ +20.8° (H_2O, *c* 4) for pure D-Talose.

2,3,4,6-Tetra-*O*-acetyl-1-*O*-benzoyl-α-D-talose (V). (a) **From 1-*O*-Benzoyl-α-D-talopyranose (III).**—To a mixture of 2 ml. of pyridine and 10 ml. of acetic anhydride cooled to 0° was added 1.0 g. of 1-*O*-benzoyl-α-D-talopyranose. After 3 days at 0° the reaction mixture was poured into cold water and worked up in the usual fashion. The sirup (1.41 g., 89%) which resisted all attempts at crystallization was dissolved in 4:1 hexane–benzene and adsorbed on a column of 56 g. of alumina.[22] Successive elution with 4:1 hexane–benzene, benzene and 1:1 benzene–ether eluted no material from the adsorbent. With ether a well-defined "peak" was eluted; several of the amorphous fractions before and at the top of the peak showed $[\alpha]^{20}D$ +84° in chloroform (*c* 0.3).

Anal. Calcd. for $C_{21}H_{24}O_{11}$: C, 55.75; H, 5.35. Found: C, 56.18; H, 5.51.

(b) **From 2,3,4,6-Tetra-*O*-acetyl-α-D-talosyl Bromide (IV).**—A mixture of 2,3,4,6-tetra-*O*-acetyl-α-D-talosyl bromide (6.5 g., m.p. 83–84°[23]), silver benzoate (10 g.) and benzene (50 ml.) was stirred at room temperature for 1 hr. and then filtered. Removal of solvent from the filtrate gave a sirup (6.5 g.) which could not be induced to crystallize. The sirupy product was, therefore, chromatographed on alumina as described in part (a) above. Elution with ether afforded a number of fractions showing $[\alpha]^{20}D$ +83° in chloroform; these were combined and rechromatographed to give a clear, colorless sirup showing $[\alpha]^{20}D$ +83° in chloroform (*c* 0.66).

Anal. Calcd. for $C_{21}H_{24}O_{11}$: C, 55.75; H, 5.35. Found: C, 55.96; H, 5.54.

Infrared absorption spectra of solutions of the products from (a) and (b) above appeared to be identical in all respects.

Acknowledgments.—We wish to express our indebtedness to Dr. H. S. Isbell for his helpful cooperation and interest in this research. We also wish to thank Mr. H. W. Diehl for the preparation of a quantity of D-galactal. Analytical determinations and absorption spectra measurements were carried out in the Institutes' microanalytical laboratory under the direction of Dr. W. C. Alford.

(20) R. C. Hockett and W. S. McClenahan, THIS JOURNAL, **61**, 1667 (1939).

(21) H. S. Isbell and W. W. Pigman, *J. Research Natl. Bur. Standards*, **18**, 141 (1937).

(22) "Alcoa" alumina, Grade F-20, mesh 80–200 manufactured by the Aluminum Company of America, Pittsburgh, Pa., was washed thoroughly with 5% hydrochloric acid and then with water until neutral. After activation at 200° the material was deliberately exposed to atmospheric humidity before use. The adsorptive capacity of alumina thus treated is inferior to that which has been kept under rigorously anhydrous conditions but its reproducibility is superior and the use of such partially hydrated alumina has the marked advantage of obviating the use of specially dried eluents.

(23) Pigman and Isbell (ref. 1) reported m.p. 84–84.5° for this substance.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES, DIVISION OF MERCK & CO., INC.]

Synthesis of Cycloserine and a Methyl Analog

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RECEIVED DECEMBER 29, 1956

DL-4-Carbomethoxy-2-phenyl-2-oxazoline (V) was converted into the corresponding hydroxamic acid VI. Dry hydrogen chloride in dioxane opened the oxazoline ring to a β-chloropropionohydroxamic acid which in aqueous alkali formed DL-4-benzamido-3-isoxazolidone (VIII). Treatment of VIII with ethanolic hydrogen chloride gave the aminoxy ester IX which cyclized in potassium hydroxide solution to DL-4-amino-3-isoxazolidone (X) (DL-cycloserine). The L-form of VIII was synthesized by the same series of reactions from L-serine. Both the benzamido (VIII) compound and DL-cycloserine were resolved. DL-4-Amino-5-methyl-3-isoxazolidone (XII) was synthesized from DL-threonine by the same series of reactions.

Cycloserine,[1] a broad-spectrum antibiotic, has been shown to be D-4-amino-3-isoxazolidone.[2,3] Preliminary reports of syntheses[3,4] of the racemate DL-4-amino-3-isoxazolidone (X) and a resolution[4] of the racemate have been published. The details of our synthesis and resolution together with the synthesis of an analog, DL-4-amino-5-methyl-3-isoxazolidone (XII), are described in this paper.

Since 3-isoxazolidone (I) had been synthesized[5]

(1) Cycloserine has been accepted as the generic name for this antibiotic. Oxamycin is now the trademark of Merck & Co., Inc., for cycloserine.

(2) F. A. Kuehl, F. J. Wolf, N. R. Trenner, R. L. Peck, E. Howe, B. D. Hunnewell, G. Downing, E. Newstead, R. P. Buhs, I. Putter, R. Ormond, J. E. Lyons, L. Chaiet and K. Folkers, THIS JOURNAL, **77**, 2344 (1955).

(3) P. H. Hidy, E. B. Hodge, V. V. Young, R. L. Harned, G. A. Brewer, W. F. Phillips, W. F. Runge, H. E. Stavely, A. Pohland, H. Boaz and H. R. Sullivan, *ibid.*, **77**, 2345 (1955).

(4) C. H. Stammer, A. N. Wilson, F. W. Holly and K. Folkers, *ibid.*, **77**, 2346 (1955).

(5) C. H. Shunk, F. W. Bachelor and K. Folkers, *J. Org. Chem.*, **22**, in press (1957).