Synthesis of a Thionobenzoate in the Polyhydroxytetrahydropyran Series

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Although little investigated, thiono esters [RC(=S)-OR'] are normally prepared either through treatment of imino ethers with hydrogen sulfide[2,3] or by reaction of a chlorothionoformate with a Grignard reagent.[2] Owing the the labilities of many masking groups which are normally used in the carbohydrate field, both of these procedures are subject to limitations in the synthesis of thiono esters of the sugar series. In the course of studies of the rearrangement of esters[4] it became desirable to synthesize certain thionobenzoates of polyhydroxytetrahydropyrans (1,5-anhydroglycitols) and we therefore sought a method for the preparation of thionobenzoates which would be suitable for use in the carbohydrate field. Thiobenzoylation with thiobenzoyl chloride in pyridine solution proved to be satisfactory. However, while the reagent is readily preparable from dithiobenzoic acid as described in the literature,[5,6] the standard preparation of dithiobenzoic acid from phenylmagnesium bromide and carbon disulfide[5-7] proved troublesome in our hands. Methyl dithiobenzoate, a distillable red oil which is stable on storage, may readily be prepared from thiobenzomorpholide methiodide[8] and serves as a reliable source of dithiobenzoic acid as the latter is required. Simple treatment of the methyl ester with sodium hydrogen sulfide in dry methanol, followed by acidification gives dithiobenzoic acid which need not, however, be isolated and can be converted directly to thiobenzoyl chloride.

The desired ester, 1,5-anhydro-3,4-di-O-benzoyl-2-O-thiobenzoyl-D-arabinitol was synthesized in the following fashion. 1,5-Anhydro-D-arabinitol[9] was condensed with acetone,[10] the sirupy product, 1,5-anhydro-3,4-O-isopropylidene-D-arabinitol, being characterized as its crystalline 2-O-benzoyl derivative. Benzylation of 1,5-anhydro-3,4-O-isopropylidene-D-arabinitol afforded the 2-O-benzyl ether from which the isopropylidene group was removed by acid hydrolysis. The dibenzoate of the product, 1,5-anhydro-3,4-di-O-benzoyl-2-O-benzyl-D-arabinitol, was hydrogenated to give 1,5-anhydro-3,4-di-O-benzoyl-D-arabinitol; thiobenzoylation of this diester afforded the desired 1,5-anhydro-3,4-di-O-benzoyl-2-O-thiobenzoyl-D-arabinitol.

Possessing the C=S chromophore, thionobenzoates are characteristically yellow in color,[5] a fact which markedly facilitates the chromatography of these substances.

Experimental[11]

Thiobenzomorpholide.—The substance was made from benzaldehyde (42.5 g., freshly distilled), morpholine (52.0 g.), and powdered sulfur (19.2 g.) as described in "Method A" of Peak and Stansfield,[8] and the powdered, crude product was extracted in a Soxhlet apparatus with *ca.* 750 ml. of ethanol, the contaminating sulfur being left behind. On cooling the ethanolic solution, the product separated as large prismatic needles: 78.2 g. (94%), m.p. 137–138°.

Methyl Dithiobenzoate.—Thiobenzomorpholide (91.0 g.) was dissolved in 900 ml. of hot, anhydrous acetone, and the solution was cooled rapidly under the tap. Methyl iodide (40 ml.) was added through an efficient reflux condenser, and the solution was rewarmed at gentle reflux with vigorous stirring. After about 5 min., a yellow solid rapidly separated from the solution; the suspension was heated for a further 30 min., cooled, diluted with 150 ml. of dry pyridine, and stirred while a gentle stream of hydrogen sulfide was passed in. The reaction mixture turned orange and then to the red color characteristic of methyl dithiobenzoate, the yellow solid gradually being replaced by a colorless one.[12] A slow stream of hydrogen sulfide into the reaction mixture (at room temperature) was maintained overnight and the solution was then filtered, the solid being washed with absolute ethanol until colorless. The combined filtrate and washings were concentrated *in vacuo* (50° bath) to remove the acetone, ethanol, and the major part of the pyridine, solid separating toward the end of the concentration. After cooling in ice, the magma was acidified with an excess of ice-cold 5 *N* hydrochloric acid and the aqueous suspension was extracted with ether (a total of 500 ml.) until no more color was removed. The combined ethereal extracts were washed thoroughly with water and, finally, aqueous sodium bicarbonate solution. Moisture was removed with magnesium sulfate and the solution was concentrated *in vacuo*, the residue being distilled at 90° and 0.6 mm.[13] to give 67.3 g. (91%) of methyl dithiobenzoate as a mobile red oil. Until required, the substance was stored in stoppered, dark-colored bottles at room temperature.

Dithiobenzoic Acid.—Methyl dithiobenzoate (67 g.) was added to a solution of anhydrous, freshly prepared sodium hydrogen sulfide (25 g.) in absolute methanol (150 ml.). The mixture was stirred at room temperature until homogeneous (2 hr.) and then left overnight at room temperature. Concentration *in vacuo* (45° bath) afforded a very dark red residue which was dissolved in 200 ml. of water, and the resulting solution was extracted with dichloromethane until the extracts were virtually colorless. Ether (250 ml.) and then ice-cold 5 *N* hydrochloric acid (150 ml.) were now cautiously added to the aqueous solution, and the system was shaken until the aqueous layer was colorless. The red-violet ethereal solution was washed twice with water and then dried with sodium sulfate.[14] Dithiobenzoic acid (41 g., 67%) was obtained as a red-brown oil on concentrating the solution under nitrogen at 0°; it was characterized through the formation of its lead salt, obtained as purple-red needles, m.p. 204–205°, from toluene. The lead salt may also be used for further purification of the dithiobenzoic acid.[7,15]

(1) (a) Birkbeck College; (b) National Institutes of Health.

(2) Houben-Weyl, "Methoden der organischen Chemie," Vol. IX, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1955, p. 759; E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. IV, Chemical Publishing Co., Inc., New York, N. Y., 1962.

(3) U. Schmidt, E. Heymann, and K. Kabitzke, *Ber.*, **96**, 1478 (1963).

(4) E. J. Hedgley and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **85**, 1615 (1963).

(5) H. Staudinger and J. Siegwart, *Helv. Chim. Acta*, **3**, 824 (1920); T. Bacchetti and A. Alemagna, *Rend. Ist. Lombardo Sci. Pt. I, Classe Sci. Mat. e. Nat.*, **91**, 617 (1957); *Chem. Abstr.*, **53**, 6217 (1959).

(6) F. Bloch, *Compt. rend.*, **204**, 1342 (1937).

(7) J. Houben, *Ber.*, **39**, 3219 (1906).

(8) D. A. Peak and F. Stansfield, *J. Chem. Soc.*, 4067 (1952).

(9) H. G. Fletcher, Jr., and C. S. Hudson [*J. Am. Chem. Soc.*, **69**, 1672 (1947)] prepared this substance through the desulfurization of various aryl 1-thio-D-arabinopyranoside triacetates with Raney nickel. We have, however, found that the substance is more readily accessible through the catalytic reduction of 2,3,4-tri-O-benzoyl-β-D-arabinopyranosyl bromide, a synthetic procedure first introduced by L. Zervas and C. Zioudrou [*J. Chem. Soc.*, 214 (1956)].

(10) *p*-Toluenesulfonic acid was used as a catalyst, and Molecular Sieve, in a Soxhlet extractor, was employed as a desiccant. It is believed that this technique may have general applicability for such condensations.

(11) Melting points are corrected.

(12) Care must be taken to avoid clogging of the hydrogen sulfide delivery tube by the precipitate.

(13) Also noted were b.p. 80–85° (0.3 mm.) and b.p. 76° (0.2 mm.).

(14) It is advantageous to use this solution directly for the preparation of thiobenzoyl chloride, without isolating the dithiobenzoic acid.

(15) T. G. Levi, *Gazz. chim. ital.*, **61**, 665 (1931); *Chem. Abstr.*, **26**, 1250 (1932).

Thiobenzoyl Chloride.—Dithiobenzoic acid (37.5 g.) was dissolved in ether (50 ml.) and the solution was treated with thionyl chloride (*ca.* 40 ml.) under conditions defined by earlier workers[5,6] to give thiobenzoyl chloride (23.1 g., 61%) as a violet-red, lachrymatory liquid, b.p. 88° (3.75 mm.).

1,5-Anhydro-2,3,4-tri-O-benzoyl-D-arabinitol.—α-D-Arabinopyranose tetrabenzoate[16] (22.64 g.) was warmed gently with 40 ml. of a 30% solution of hydrogen bromide in glacial acetic acid until 2,3,4-tri-O-benzoyl-β-D-arabinopyranosyl bromide began to crystallize from the clear solution. The mixture was then stirred at room temperature for 2.5 hr., and the solution was decanted from the crystalline halide which was washed three times (by decantation) with petroleum ether b.p. (60–70°). Dissolved in 250 ml. of ethyl acetate, the halide was treated with 2.0 g. of 10% palladium on charcoal (presaturated with hydrogen) and 10.0 g. of triethylamine; on shaking with hydrogen, the solution absorbed the theoretical amount of hydrogen in 5.8 hr.; after removal of the catalyst by filtration, the solution was washed with aqueous sodium bicarbonate and concentrated to give 15.29 g. (86%) of 1,5-anhydro-2,3,4-tri-O-benzoyl-D-arabinitol, m.p. 119°. Recrystallization from methanol afforded pure material: m.p. 119–120°, $[\alpha]^{20}D$ −219° (*c* 0.11, $CHCl_3$). Fletcher and Hudson[9] reported m.p. 120–121° and $[\alpha]^{20}D$ −220° ($CHCl_3$) for 1,5-anhydro-2,3,4-tri-O-benzoyl-D-arabinitol.

1,5-Anhydro-2-O-benzoyl-3,4-O-isopropylidene-D-arabinitol.—1,5-Anhydro-2,3,4-tri-O-benzoyl-D-arabinitol was debenzoylated in conventional fashion using ammonia in methanol to give 1,5-anhydro-D-arabinitol as a sirup which crystallized on seeding. Without further purification, the anhydride (15.6 g.) was suspended in 200 ml. of anhydrous acetone containing 0.2 g. of *p*-toluenesulfonic acid. The solution was boiled for 16 hr. under a Soxhlet extractor holding Molecular Sieve, type 5A, and then neutralized with ammonia. After filtration, the solution was concentrated and the residue was distilled *in vacuo* to give 1,5-anhydro-3,4-O-isopropylidene-D-arabinitol as a yellow oil: b.p. 78–80°, (0.1–0.05 mm.), 19.05 g. (94%) A sample of the product was benzoylated with benzoyl chloride in pyridine to give 1,5-anhydro-2-O-benzoyl-3,4-O-isopropylidene-D-arabinitol as fine needles from ethanol: m.p. 102–103°, $[\alpha]^{20}D$ −111° (*c* 0.50, CH_2Cl_2).

Anal. Calcd. for $C_{15}H_{18}O_5$ (278.31): C, 64.76; H, 6.52. Found: C, 64.62; H, 6.76.

1,5-Anhydro-2-O-benzyl-3,4-O-isopropylidene-D-arabinitol.—1,5-Anhydro-3,4-O-isopropylidene-D-arabinitol (3.36 g.) was mixed with 50 ml. of anhydrous tetrahydrofuran, 2.2 g. of powdered potassium hydroxide,[17] and 3.65 g. of benzyl chloride, and the suspension was boiled under reflux for 12 hr. Solid carbon dioxide was added, the solution was concentrated to dryness, and the residue was extracted with acetone. The sirup obtained on concentrating the extract was distilled to give a mobile yellow oil: b.p. 110–120° (0.1 mm.), 4.5 g. (88%). A benzene solution of the crude product was passed through a short column of neutral alumina and then concentrated, the sirupy residue being distilled as before: 3.91 g., $[\alpha]^{20}D$ −57° (*c* 1.19, ethanol), $n^{20}D$ 1.5125. Attempts to obtain the product in crystalline form were unsuccessful.

Anal. Calcd. for $C_{15}H_{20}O_4$ (264.33): C, 68.16; H, 7.63. Found: C, 68.28; H, 7.50.

1,5-Anhydro-2-O-benzyl-D-arabinitol.—1,5-Anhydro-2-O-benzyl-3,4-O-isopropylidene-D-arabinitol (22.4 g.) was dissolved in 300 ml. of 50% aqueous ethanol. Amberlite IR-120(H) (5.0 g.) was added, and the solution was refluxed and stirred for 3 hr. After filtration and removal of the solvent, the product was dried by azeotroping with benzene. Crystallization was spontaneous: 18.8 g. (99%), m.p. 99–100°. After two recrystallizations from benzene, the product was obtained as fine needles: m.p. 101–102°, $[\alpha]^{20}D$ −35° (*c* 1.19, ethanol).

Anal. Calcd. for $C_{12}H_{16}O_4$ (224.25): C, 64.27; H, 7.19. Found: C, 64.44; H, 7.21.

1,5-Anhydro-3,4-di-O-benzoyl-2-O-benzyl-D-arabinitol.—1,5-Anhydro-2-O-benzyl-D-arabinitol (18.80 g.) was benzoylated with benzoyl chloride in pyridine to give a sirup which solidified to a crystalline mass: 34.83 g. (96%). Recrystallized twice from petroleum ether (60–80°), the ester was obtained as needles: m.p. 62–63°, $[\alpha]^{20}D$ −155° (*c* 0.95, ethanol).

Anal. Calcd. for $C_{26}H_{24}O_6$ (432.45): C, 72.21; H, 5.59. Found: C, 72.28; H, 5.78.

1,5-Anhydro-3,4-di-O-benzoyl-D-arabinitol.—Palladium chloride (1 g.) was suspended in ethanol (15 ml.) and reduced with hydrogen at room pressure. 1,5-Anhydro-3,4-di-O-benzoyl-2-O-benzyl-D-arabinitol (2.16 g.), dissolved in 100 ml. of ethanol, was added to the suspended catalyst and the mixture was agitated with hydrogen until no more gas was absorbed. The catalyst was removed by filtration and the solution was concentrated *in vacuo*, finally at 80° (bath) to give 1.68 g. (98%) of crude crystalline product, m.p. 134–136°. Recrystallized from ethanol–hexane and sublimed at 135° and 0.01 mm., the ester melted at 134–135° and showed $[\alpha]^{20}D$ −212° (*c* 0.85, ethanol).

Anal. Calcd. for $C_{19}H_{18}O_6$ (342.33): C, 66.66; H, 5.30. Found: C, 66.39; H, 5.52.

1,5-Anhydro-3,4-di-O-benzoyl-2-O-thiobenzoyl-D-arabinitol.—To a solution of 3.4 g. of 1,5-anhydro-3,4-di-O-benzoyl-D-arabinitol in 15 ml. of dry pyridine (5.4 g., 3.5 molar equiv.) of thiobenzoyl chloride was added in one portion without cooling. A viscous sirup separated and the medium assumed a red-brown coloration distinct from the violet-red color of the reagent. After 12 hr., water (1 ml.) was added, then, after a further 30 min., the pyridine was removed by evaporation at 80°. The residue was dissolved in dichloromethane and the solution washed successively with dilute hydrochloric acid, water, and saturated aqueous sodium bicarbonate. After removal of moisture with sodium sulfate, the solution was concentrated to a red, viscous oil (7.1 g.). With benzene as a solvent, thin-layer chromatography on silica gel resolved the product into four components, a fast moving red fraction (R_f ~0.9), two closely associated orange and yellow fractions (R_f ~0.5), and one fraction which failed to migrate. Chromatography of 1.0 g. of the mixture on a short column of silica gel (10 g., packed as a slurry in benzene) effected an excellent resolution of the orange (0.03 g.) and yellow (0.40 g.) components. The characteristic color, optical activity, and infrared spectrum of the latter identified it as the required thionobenzoate; yield was equivalent to 62%, based on the 1,5-anhydro-3,4-di-O-benzoyl-D-arabinitol. Thin layer chromatography of the product thus isolated revealed a trace of a contaminant which fluoresced under ultraviolet light. Final purification by rapid distillation at 0.03 mm. and 220° (bath) afforded chromatographically pure material which rotated $[\alpha]^{20}D$ −140.2 ± 3.0° in ethanol (*c* 0.5): ultraviolet absorption data, λ_{max}^{EtOH} 282 mμ (ε 9680), 292 mμ (ε 9400).

Anal. Calcd. for $C_{26}H_{22}O_6S$ (462.53): C, 67.52; H, 4.79. Found: C, 67.81; H, 4.81.

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(16) H. G. Fletcher, Jr., and C. S. Hudson, *J. Am. Chem. Soc.*, **69**, 1145 (1947).

(17) Hooker Chemical Corp., Niagara Falls, N. Y.

An Improved Method for the Preparation of Methyl 6-Chloro-6-deoxy-α-D-glucopyranoside

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The only reference found in the literature to the preparation of methyl 6-chloro-6-deoxy-α-D-glucopyranoside is by Helferich, Klein, and Schaefer,[2] who report an over-all 8% yield[3] of methyl 6-chloro-6-deoxy-α-D-glu-

(1) This is a laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) B. Helferich, W. Klein, and W. Schaefer, *Ber.*, **59B**, 79 (1926).

(3) The yield reported in ref. 2 is much lower than 8%, but subsequent work by B. Helferich and H. Bredereck [*Ber.*, **60B**, 2002 (1927)] on methyl β-D-glucopyranoside improved the chlorination step, and this improvement was used in the calculation.