about 18 hr. at room temperature protected from moisture, the solvent was removed *in vacuo*. The residue was suspended in 10 ml. of water and extracted with chloroform (two 30-ml. portions). Combined extracts were washed with water, dried with magnesium sulfate, and evaporated to dryness *in vacuo;* yield, 480 mg. (67% from VI) of oily XIX that could not be crystallized; ν_{max}^{film} 3550 (OH); 1255, 1210, 1065 (C—O—C) and no acetate C=O at 1740 cm.$^{-1}$.

To a stirred solution of 1.04 g. (3 mmoles) of a similar preparation of XIX in 6 ml. of reagent pyridine was added 490 mg. (3.5 mmoles) of benzoyl chloride with ice cooling. After 24 hr., the mixture was processed in the usual way[1,3] to give 0.95 g. of an oil showing benzoate C=O at 1710 cm.$^{-1}$. A solution of this crude XX in 20 ml. of benzene was poured onto a column of about 65 g. of neutral alumina (Brockmann activity III). Elution with 50 ml. of benzene, then 50 ml. of 1:1 chloroform–benzene gave 50 mg. of material with weak benzoyl absorption at 1710 cm.$^{-1}$ and was rejected. Further elution with 200 ml. of chloroform afforded 0.75 g. (56%) of pure XX as an oil that could not be crystallized; $[\alpha]^{25}D$ +18 ± 1° (0.2%); ν_{max}^{film} 1710 (ester C=O); 1260, 1200, 1070 (C—O—C); 715 cm.$^{-1}$ (benzoyl CH).

Anal. Calcd. for $C_{24}H_{34}O_8$: C, 64.0; H, 7.55. Found: C, 64.1; H, 7.73.

4-O-Benzoyl-1,2:5,6-di-O-isopropylidene-D-talitol (IVa).—Depyranylation of 200 mg. (0.44 mmole) of XX, as described for depyranylation of VIII, afforded 135 mg. (83%) of a syrup. Crystallization from ethyl acetate–petroleum ether slowly occurred over 2 days at −5° giving 20 mg. (12%) of the 3-benzoate (IVb), m.p. 123–124°, that was identical with the material previously prepared from II.[3] Spin evaporation of the mother liquor *in vacuo* gave the remainder of the product as the sirupy 4-benzoate (IVa) (115 mg., 71%) which had ν_{max}^{film} 3550 (OH); 1710, 710 (benzoate); 1260, 1080 cm.$^{-1}$ (C—O—C) and which was debenzoylated (description follows).

1,2:5,6-Di-O-isopropylidene-D-talitol (XXII).—The preceding sirupy 4-benzoate (IVa) was debenzoylated as described for the preparation of IX. Crystallization from petroleum ether gave 45 mg. (37% based on XX), m.p. 62–63°, that was identical with an authentic sample.

3,4-Di-O-benzoyl-1,2:5,6-di-*O*-isopropylidene-D-talitol (XXI).—Benzoylation of 115 mg. of syrupy benzoate (IVa) with 60 mg. of benzoyl chloride in 1.5 ml. of reagent pyridine, then work-up as usual,[1,3] gave 60 mg. of XXI, m.p. 144°, that was identical with an authentic sample.[3]

3-Benzamido-3-deoxy-1,2:5,6-di-O-isopropylidene-4-O-(2-tetrahydropyranyl)-D-altritol (XV).—A mixture of 0.85 g. (2 mmoles) of VI, 0.39 g. (6 mmoles) of sodium azide, and 10 ml. of dimethylformamide was refluxed for 6 hr. The solvent was removed by spin evaporation *in vacuo* on a boiling water bath. The residue was suspended in 20 ml. of ice–water and extracted with chloroform (three 20-ml. portions). Dried with magnesium sulfate, combined extracts were evaporated to residue *in vacuo;* yield, 0.66 g. (89%) of crude azide (XIII); ν_{max}^{film} 2125 (—N_3); 1255, 1210, 1065 cm.$^{-1}$ (C—O—C).

To a stirred suspension of 230 mg. (6 mmoles) of lithium aluminum hydride in 40 ml. of reagent ether was added a solution of 1.01 g. (2.73 mmoles) of crude azide (XIII) in 10 ml. of reagent ether at such a rate that gentle reflux was maintained. After being refluxed for 1 hr., the excess hydride was decomposed by the careful addition of 1 ml. of ethyl acetate followed by 0.35 ml. of water. The mixture was filtered and the salts washed with ether. The filtrate was decolorized with charcoal, then spin evaporated *in vacuo;* yield, 0.797 g. (90%) of 3-aminodeoxy-1,2:5,6-di-O-isopropylidene-4-O-(2′-tetrahydropyranyl)-D-altritol that could not be crystallized and had ν_{max}^{film} 3400 (NH); 1260, 1080 (C—O—C); and no azide absorption at 2125 cm.$^{-1}$.

To a stirred solution of 0.70 g. (2 mmoles) of the amine in 7 ml. of reagent pyridine cooled in an ice bath and protected from moisture was added 326 mg. (2.3 mmoles) of benzoyl chloride. After being stirred for 3 hr. in the ice bath and 18 hr. at room temperature, the mixture was processed in the usual manner.[1,3] Crystallization from ethyl acetate–petroleum ether gave 504 mg. (56%, or 40% from VI) of XV, m.p. 140°. Recrystallization from chloroform–petroleum ether afforded white needles, m.p. 141°; $[\alpha]^{25}D$ +8.2 ± 0.6° (0.8%); ν_{max}^{Nujol} 3325 (NH); 1640, 1525 (amide); 1250, 1210, 1065 (C—O—C); 705 cm.$^{-1}$ (benzoyl CH).

Anal. Calcd. for $C_{24}H_{35}NO_7$: C, 64.2; H, 7.78; N, 3.11. Found: C, 64.3; H, 7.99; N, 3.34.

3-Benzamido-4-O-benzoyl-3-deoxy-1,2:5,6-di-O-isopropylidene-D-altritol (XVIII).—Depyranylation of 150 mg. of XV as described for the depyranylation of VIII gave 110 mg. (90%) of crude XVI, which was benzoylated with 64 mg. of benzoyl chloride in 2 ml. of reagent pyridine in the usual manner.[3] Recrystallization of the product from ethyl acetate–methanol afforded 90 mg. (67%) of XVII, m.p. 202–203°, which was identical with an authentic sample prepared by a different route.[1]

Acknowledgment.—We wish to thank the Cancer Chemotherapy National Service Center, National Cancer Institute, and Starks Associates, Inc., for large scale preparation of certain intermediates, mediated by contract no. SA-43-ph-4346.

Synthetic Nucleosides. LVII.[1] Facile Displacement Reactions in the D-Mannitol Series. IV. Investigation of Thiourethane Derivatives[2]

B. R. BAKER AND H. S. SACHDEV

Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo 14, New York

Received February 11, 1963

Reaction of the monosodium salt of 1,2:5,6-di-O-isopropylidene-D-mannitol (V) with phenyl isothiocyanate did not form the expected phenylthiourethane derivative (VI). Instead, a facile cyclization took place to give a cyclic carbonate (XIV), a thionocarbonate (IX), or a phenyliminocarbonate (X) derivative of V, depending upon the work-up conditions. Additional evidence to support a proposed mechanism for these reactions also is presented.

Possible routes to synthesis of sugars containing a *cis*-mercapto alcohol system (I) such as that in the 2-mercapto-2-deoxy-D-ribose or 3-mercapto-3-deoxy-D-ribose of Baker and co-workers[3–5] has been under investigation for several years; nucleosides containing such sugars might afford interesting biological properties.[3] Although thio sugars with a *trans* relationship of OH and SR groups (IV) are readily synthesized by ring opening of sugar epoxides (III) with mercaptides,[6] successful routes to *cis* compounds with a *cis* relation-

(1) For the previous paper in this series, see B. R. Baker and H. S. Sachdev, *J. Org. Chem.*, **28**, 2132 (1963).

(2) This work was generously supported by grant CY-5845 of the National Cancer Institute, U. S. Public Health Service.

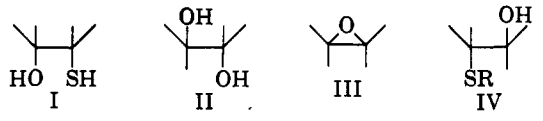
(3) B. R. Baker, K. Hewson, L. Goodman, and A. Benitez, *J. Am. Chem. Soc.*, **80**, 6582 (1958).

(4) L. Goodman, A. Benitez, C. D. Anderson, and B. R. Baker, *ibid.*, **80**, 6582 (1958).

(5) E. J. Reist, J. H. Osiecki, A. Benitez, L. Goodman, and B. R. Baker, *J. Org. Chem.*, **26**, 3554 (1961).

(6) (a) C. D. Anderson, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **81**, 3967 (1959); (b) C. D. Anderson, L. Goodman, and B. R. Baker, *ibid.*, **81**, 898 (1959); (c) J. Davoll, B. Lythgoe, and S. Tripett, *J. Chem. Soc.*, 2230 (1951); (d) R. Jeanloz, D. A. Prins, and T. Reichstein, *Helv. Chim. Acta*, **29**, 371 (1946); (e) W. Pigman, "The Carbohydrates," Academic Press, Inc., New York, N. Y., 1957.

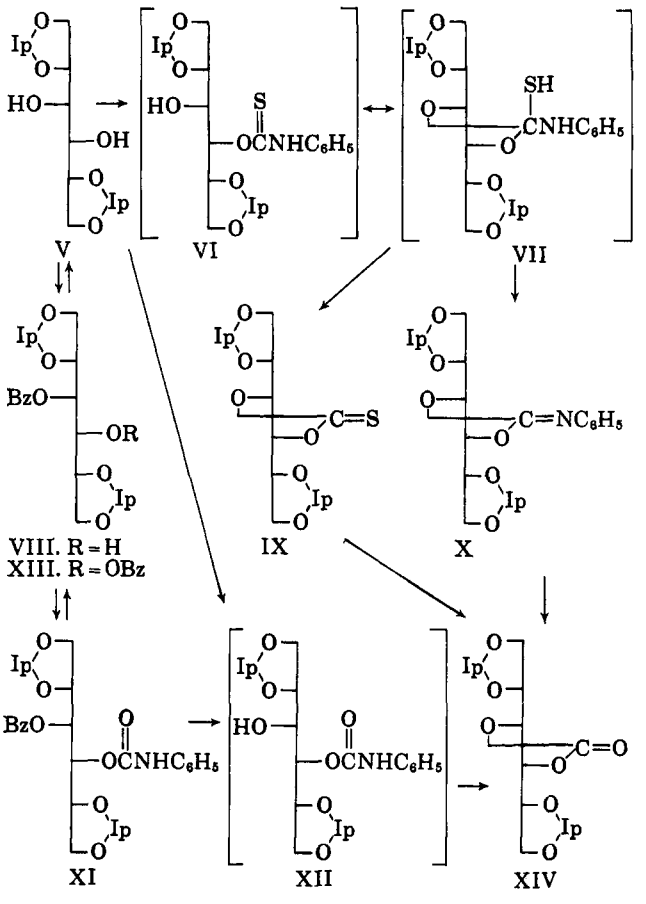
ship (I) have so far been elusive. Terminal thio functions readily can be introduced into the sugar molecule by displacement reactions,[6e] but the displacement of a ring secondary tosylate by mercaptide ion has been uniformly unsuccessful due to the weak electrophilic character of these sugar ring tosylates[7]; therefore, our attention has been directed primarily to the introduction of a *cis*-mercapto group by anchimeric assistance of a neighboring group where the energy barrier is considerably reduced and reactions are accelerated a thousandfold compared to the SN2 type.[8]



That the *cis*-mercapto alcohol system in a ring can be synthesized by utilization of the neighboring phenylthiocarbonyl group has been established in the cyclopentane series. Although the appropriate thiocarbonyl derivative in a pentofuranose[5] and a hexopyranose[3] could be synthesized, their conversion to the *cis*-mercapto alcohol system of type I failed primarily due to the difficulty of removing an isopropylidene blocking group in the furanose case, and the instability of a benzylidene blocking group in the second case. Since we have been undertaking a study of reactions of 1,2:5,6-di-O-isopropylidene-D-mannitol (V) for synthesis of sugars containing a new functional group in place of a hydroxyl,[7,9] this compound (V) appeared to be an attractive one to study the introduction of sulfur by the neighboring phenylthiocarbamyl group; although this approach so far has been unsuccessful in its ultimate goal, the unusual nature of the reactions encountered has prompted this paper.

Similar to methyl 4,6-O-benzylidene-α-D-glucopyranoside,[3] but in contrast to 1,2-*trans*-cyclopentanediol,[4] 1,2:5,6-di-O-isopropylidene-D-mannitol (V) failed to react with phenyl isothiocyanate in boiling toluene; therefore, the more strenuous conditions employed for the glucopyranoside,[3] *i.e.*, formation of the sodium alcoholate with sodium hydride in dimethylformamide, then reaction with phenyl isothiocyanate, was investigated. Surprisingly, none of the desired phenylthiourethane (VI) was obtained, but either the tricyclic product, XIV, or a mixture of IX and X could be obtained depending upon how the reaction mixture was processed.

When the reaction mixture was acidified with glacial acetic acid then diluted with water as previously described for the glucopyranoside,[3] diphenylthiourea was isolated in 33% yield; from the mother liquor was obtained 30% of a crystalline mixture of the cyclic carbonate (XIV) and the cyclic thionocarbonate (IX). These two compounds were difficultly separable by fractional crystallization, but were obtained pure; the two compounds were readily distinguishable by their infrared spectra and the composition of a mixture of the two could be estimated since XIV had a five-membered ring carbonyl group at 1780 cm.$^{-1}$ and carbonate C–O–C at 1260 and 1065 cm.$^{-1}$, whereas IX showed additional carbonate C–O–C bands at 1325 and 1300 cm.$^{-1}$ and no carbonyl absorption. When the organic material was quickly separated from the aqueous solution by extraction, the product was primarily the thionocarbonate (IX) and little hydrolysis to XIV took place. The thionocarbonate (IX) was converted to the carbonate (XIV) in 80% yield by reaction with silver carbonate in methanol. That no change of configuration had taken place during the conversion of V to XIV *via* VI was shown by synthesis of the carbonate, XIV, from V with methyl chlorocarbonate in 55% yield under conditions that could not cause inversion.[10,11]



Bz = benzoyl; Ip = isopropylidene

Some insight into the possible mechanism of formation of the thionocarbonate (IX) from the supposed thiourethane (VI) was gained when the dimethylformamide solution of the sodium salt of VI was processed without addition of glacial acetic acid; in this case neither diphenylthiourea nor the thionocarbonate (IX) were formed; instead a new compound containing nitrogen and no sulfur was obtained in about 30% yield. That this crystalline compound was the phenyliminocarbonate (X) was shown by the presence of five-membered ring exocyclic C=N absorption at 1690 cm.$^{-1}$, monosubstituted benzene absorption at 700 cm.$^{-1}$, lack of NH absorption near 3303 cm.$^{-1}$, and by hydrolysis with dilute acetic acid to the cyclic carbonate (XIV).

(7) See B. R. Baker and A. H. Haines, *J. Org. Chem.*, **28**, 438 (1963), paper LIV of this series, for a discussion of displacement of ring tosylates by various nucleophiles, including the advantages of anchimeric assistance by a neighboring group.

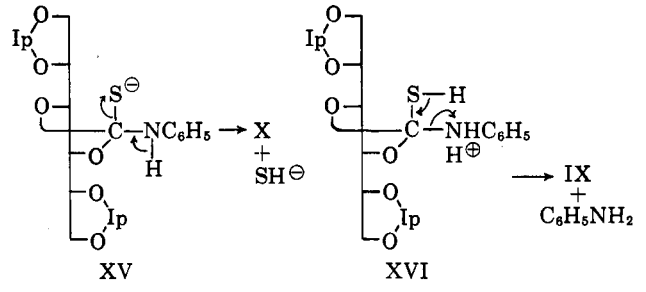
(8) S. Winstein and R. Boschan, *J. Am. Chem. Soc.*, **72**, 4669 (1950).

(9) B. R. Baker and A. H. Haines, *J. Org. Chem.*, **28**, 442 (1963), paper LV of this series.

(10) E. J. Reist, R. R. Spencer, and B. R. Baker, *ibid.*, **23**, 1958 (1958).

(11) L. Hough, J. E. Priddle, and R. S. Theobald, *J. Chem. Soc.*, 1934 (1962).

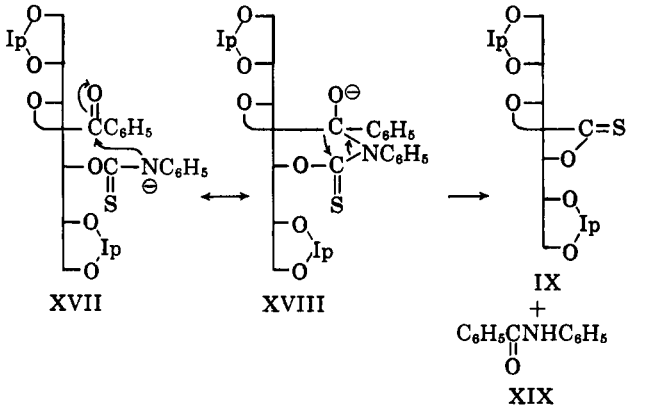
The mere addition or nonaddition of glacial acetic acid at room temperature prior to work-up giving different products suggests that the anion in dimethylformamide is not derived from the thiourethane (VI), but has structure XV derived from the cyclic structure VII; XV would be stabilized by a favorable "zig-zag" conformation.[9] Apparently, addition of water predominantly causes loss of bisulfide ion with formation of X. In contrast, when this anion (XV) is acidified with glacial acetic acid in anhydrous solution, the protonated form (XVI) readily loses aniline with formation of IX;



XV XVI

the resultant aniline then immediately forms diphenylthiourea with some unchanged phenyl isothiocyanate that is present.

Since the formation of the thiourethane (VI) was precluded by the presence of the adjacent hydroxyl group, it was clear that this hydroxyl would have to be blocked. The availability of the monobenzoate (VIII)[12] in this laboratory for other studies[7,9] suggested that an attempt be made to convert it to a phenylthiourethane; even though it was anticipated that sodium alcoholate of VIII might equilibrate to a mixture of VIII and its dibenzoate, there was a possibility that this intermolecular equilibration would be sufficiently slow to allow conversion to the phenylthiourethane derivative (XVII). Reaction of VIII with one equivalent of sodium hydride in dimethylformamide required only fifteen minutes at 50°; however, when this sodium salt was treated with phenyl isothiocyanate, a 40% yield of benzanilide along with 20% yield of a crystalline mixture of the carbonate (XIV) and thionocarbonate (IX) were obtained and none of the protonated XVII could be isolated.



XVII XVIII IX + $C_6H_5CNHC_6H_5$ (O) XIX

Although in an independent experiment, it was shown that the sodium salt of VIII could equilibrate to V, VIII, and a dibenzoate in boiling toluene, such an explanation for the formation of benzanilide and the thionocarbonate (IX) *via* VII is untenable with the isolation of the iminocarbonate (X) from VII. The anion, XV, apparently does not release aniline until acidified, conditions being too mild to allow reaction of aniline with the benzoate group of a molecule such as VIII to form benzanilide. A more tenable explanation is that the anion (XVII) is predominantly in the cyclic form, XVIII (again stabilized by the favorable "zig-zag" conformation[9]). This anion could collapse to the thionocarbonate (IX) and benzanilide (XIX) either during reaction or during work-up; further support for this explanation was obtained.

The monobenzoate, VIII, reacted smoothly with phenyl isocyanate in boiling toluene to give the crystalline urethane (XI) in 78% yield. When XI was partially converted to the anion with 6 mole % of sodium hydride in dimethylformamide, then heated at 90–100°, 71% of the urethane residue was converted to diphenylurea, 12% of XI was recovered unchanged, and 9% yield of the cyclic carbonate (XIV) was isolated; in contrast to the breakdown of the supposed XVII, no benzanilide could be isolated although a trace could be detected by thin layer chromatography. These results are tenable with the retrogression of the anion of XI to phenyl isocyanate and the monobenzoate, VIII; the latter then equilibrates to V and a dibenzoate (XIII). The phenylurethane (XII) is then formed from V and phenyl isocyanate or by *trans*-benzoylation between V and XI; a small yield of cyclic carbonate (XIV) from the monophenylurethane (XII) is then tenable. The fact that practically no benzanilide is formed from XI, but 40% is formed from XVII certainly indicates that different mechanisms for conversion to a cyclic carbonate or thionocarbonate from XI to XVII are involved and that the retrogression mechanism *via* V and XII cannot account for benzanilide. A further argument for the formation of benzanilide *via* XVIII is that the intermediate XVIII would be more likely to form than the corresponding anion of XI since the thiourethane is a far more nucleophilic group than is the urethane.

The ease of interaction of the benzoate carbonyl with the adjacent thiourethane group in XVII is certainly unexpected. Thus to prepare a thiourethane such as VI it would be necessary to use a noncarbonyl blocking group that could be removed later, such as the tetrahydropyranyl blocking group.[1] When the sodium salt of 1,2:5,6-di-O-isopropylidene-3-O-tetrahydropyranyl-D-mannitol[1] was treated with phenyl isothiocyanate in toluene, an oil was isolated that had the proper infrared spectrum; that is, it showed NH, but no carbonyl, none of the usual by-products were obtained such as diphenylthiourea, the thionocarbonate (IX), or the cyclic carbonate (XIV). Whether or not the tetrahydropyranyl group can be removed from the oil to give VI without formation of diphenylthiourea and the tricyclic by-products is worthy of pursuit.

Experimental[13]

Reaction of 1,2:5,6-Di-O-isopropylidene-D-mannitol (V) Sodium Salt with Phenylisothiocyanate.—(A) Acetic Acid Work-Up.—To a solution of 5.20 g. (0.02 mole) of dry V in 30 ml. of di-

(12) J. M. Sugihara and G. U. Yuen, *J. Am. Chem. Soc.*, **79**, 5780 (1957).

(13) Melting points were taken in capillary tubes on a Mel-Temp block and are uncorrected. Infrared spectra were determined with a Perkin-Elmer 137B spectrophotometer. Optical rotations were measured in a 1-dm. microtube in chloroform solution at the % concentration indicated. Petroleum ether used for purification was a fraction boiling at 30–60°.

methylformamide (Spectro Grade) was added 0.873 g. (0.02 mole) of a 55% sodium hydride emulsion in mineral oil. The mixture was heated at 90° for 90 min. protected from moisture when the formation of the sodium salt was complete, and an off-white suspension was obtained. After the addition of 3.38 g. (0.025 mole) of phenyl isothiocyanate, the mixture was stirred for another 90 min. at 90–95° during which time a brown solution was formed. After being cooled to room temperature, the solution was acidified with 1.8 ml. (0.03 mole) of glacial acetic acid, stirred 5 min., then poured into 125 ml. of ice–water. A light brown oil separated which soon solidified. The material was collected on a filter and washed with a little cold water. Recrystallization from 75% ethanol afforded 1.5 g. (33%) of diphenylthiourea, m.p. 150–151°, which gave no depression in melting point when mixed with an authentic sample and which had an infrared spectrum identical with that of an authentic sample.

The mother liquor from the 1.5 g. of diphenylthiourea deposited additional crystals after standing for 2 hr. at −5°. The material was collected on a filter and washed with cold water; yield was 1.0 g. (17%), m.p. 140–141°, of a mixture of the cyclic carbonate (XIV) and the thionocarbonate (IX) as shown by its infrared spectrum. Two recrystallizations from chloroform–petroleum ether gave 0.60 g. (10%) of 2:1 mixture of IX and XIV, m.p. 149–151°.

The mother liquor from the 1.0 g. of XIV and IX was diluted with water, then kept overnight at −5° to give 0.80 g. (13%) of cyclic carbonate XIV, m.p. 135–140°. Recrystallization from ethyl acetate–petroleum ether gave 0.50 g. (8%) of pure XIV, m.p. 145–146°; this compound gave no depression in melting point when mixed with an authentic sample of XIV, prepared as described later, and their infrared spectra were identical.

A similar preparation with 2.6 g. of V, 0.873 g. of 55% sodium hydride, and 3.38 g. of phenyl isothiocyanate was processed by immediate chloroform extraction (three 50-ml. portions) after the acidified dimethylformamide mixture was added to ice–water; thus processed, no appreciable hydrolysis of the thionocarbonate (IX) to the carbonate (XIV) took place. After removal of the solvent *in vacuo*, the residue was recrystallized from ethanol to give, in three crops, 1.05 g. (35%) of thionocarbonate IX, m.p. 160–161°. A second recrystallization of the first crop from ethanol gave pure IX as white crystals, m.p. 160–161°; $[\alpha]^{25}D$ −11 ± 1° (0.3%); ν_{max}^{Nujol} 1325, 1300, 1260, 1065 (C—O—C) and a weak band at 1780 cm.$^{-1}$ from a trace amount of XIV.

Anal. Calcd. for $C_{13}H_{20}O_6S$: C, 51.3; H, 6.50; S, 10.5. Found: C, 51.6; H, 6.08; S, 10.5.

From the mother liquor of the 1.05 g. could be isolated by crystallization from benzene 1.0 g. (44%) of diphenylthiourea, m.p. 149–150°.

(B) By Alkaline Work-Up.—After 2.6 g. (0.01 mole) of V had been converted to the sodium salt with 0.436 (0.01 mole) of 55% sodium hydride, then treated with 2.02 g. (0.015 mole) of phenyl isothiocyanate as described in A, the cooled dimethylformamide solution was poured into 200 ml. of ice-cold water and extracted twice with chloroform. Fractional crystallization from ethyl acetate–petroleum ether gave first 0.5 g. (19%) of unchanged V and then 0.60 g. (20%) of pure iminocarbonate X as white needles, m.p. 111–112°; $[\alpha]^{25}D$ −6.6 ± 0.5° (1.1%); ν_{max}^{KBr} 1690 (C=N); 1590, 700 (phenyl); 1250, 1060 cm.$^{-1}$ (C—O—C).

Anal. Calcd. for $C_{19}H_{25}NO_6$: C, 62.8; H, 6.85; N, 3.87. Found: C, 63.2; H, 6.51; N, 3.77.

By further processing of the mother liquors, 0.25 g. of a crystalline mixture of iminocarbonate X and carbonate XIV was obtained which was not further separated, but which was predominantly the iminocarbonate.

1,2:5,6-Di-O-isopropylidene-D-mannitol 3,4-Carbonate (XIV).

(A) From V.—To a solution of 5.2 g. (0.02 mole) of V in 15 ml. of reagent pyridine and 20 ml. of chloroform cooled in an ice bath was added dropwise with stirring 2.07 g. (0.022 mole) of methyl chloroformate over a period of 25 min.[10] After being stirred for an additional 6 hr. at 0° and standing at 5° for 16 hr., protected from moisture, the mixture was poured into 50 ml. of ice–water and the organic layer separated.

The aqueous layer was extracted further with chloroform (three 20-ml. portions); combined extracts were washed successively with 10 ml. of saturated aqueous sodium bicarbonate and 15 ml. of cold water. Dried with magnesium sulfate, the solution was spin evaporated to dryness *in vacuo*. The semisolid residue showed a weak cyclic carbonate band at 1790 cm.$^{-1}$ and a strong linear carbonate band at 1745 cm.$^{-1}$. To a solution of this intermediate in 20 ml. of dimethylformamide was added 100 mg. of sodium methoxide and the mixture was heated at about 100° for 20 min. After removal of the solvent by spin evaporation *in vacuo*, the residue was triturated with 15 ml. of water containing 0.1 ml. of acetic acid. To a solution of the solid in 50 ml. of chloroform was added 75 ml. of petroleum ether; after 3 hr. at 0°, 1.9 g. (37%) of unchanged V was removed by filtration. The filtrate was evaporated to dryness *in vacuo* and the residue recrystallized from aqueous methanol; yield, 2.0 g. (55% based on the amount of V not recovered), m.p. 144–146°. Two recrystallizations from ethyl acetate–petroleum ether gave white needles of pure XIV, m.p. 147°; $[\alpha]^{25}D$ + 8.0 ± 0.6° (0.9%); ν_{max}^{Nujol} 1780 (cyclic carbonate C=O); 1260, 1065 cm.$^{-1}$ (C—O—C).

Anal. Calcd. for $C_{13}H_{20}O_7$: C, 54.2; H, 6.90. Found: C, 54.3; H, 7.09.

Hough, *et al.*,[11] reported the preparation of this compound by a different route after the previous experiment was completed. They report m.p. 146.5–147°; $[\alpha]^{20}D$ 14.9° (*c* 1.8, acetone); and C=O absorption at 1790 cm.$^{-1}$

(B) From the Iminocarbonate (X).—A solution of 70 mg. of X in 1 ml. of 50% aqueous acetic acid was heated on a steam bath for 20 min., then cooled, and neutralized with 5% aqueous sodium bicarbonate to pH 8. The product was collected on a filter, washed with cold water, and recrystallized from ethyl acetate–petroleum ether; yield, 25 mg. (55%) of XIV, m.p. 146–147°. A mixture with preparation A gave no depression in melting point and the two materials had identical infrared spectra. No attempt was made to obtain a second crop.

(C) From the Thionocarbonate (IX).—A solution of 51 mg. (1.66 mmoles) of IX in 10 ml. of methanol was stirred with 46 mg. (1.66 mmoles) of silver carbonate at room temperature for 1 hr. The black precipitate was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. Recrystallization from ethyl acetate gave 40 mg. (82%) of XIV, m.p. 146–147°, that was identical with preparation A.

Reaction of 3-O-Benzoyl-1,2:5,6-di-O-isopropylidene-D-mannitol (VIII) Sodium Salt with Phenyl Isothiocyanate.—To a solution of 1.82 g. (5 mmoles) of dry VIII in 30 ml. of dimethylformamide (Spectro Grade) was added 218 mg. (5 mmoles) of a 55% dispersion of sodium hydride in mineral oil. Conversion to the insoluble gelatinous sodium salt was complete after the mixture was stirred for 15 min. at 50° protected from moisture. After the addition of 0.65 ml. (5.5 mmoles) of phenyl isothiocyanate, the mixture was stirred at 90–100° for 1 hr. Cooled to room temperature, the mixture was acidified with 0.5 ml. of glacial acetic acid, then diluted with 100 ml. of ice–water, and extracted with chloroform (three 40-ml. portions). Dried with magnesium sulfate, combined extracts were spin evaporated *in vacuo;* last of the dimethylformamide was removed at 1 mm. and 100°. The semisolid residue was triturated with 40 ml. of benzene and the white insoluble solid was collected on a filter; yield, 0.40 g. (40%) of benzanilide, m.p. 158–159°, that was identical with an authentic sample. The benzene filtrate was evaporated to dryness *in vacuo*. Recrystallization of the residue from 1:1 chloroform–petroleum ether gave 0.30 g. (20%), m.p. 145–149°, of a mixture of the cyclic carbonate (XIV) and the thionocarbonate (IX), as shown by its infrared spectrum.

3-O-Benzoyl-1,2:5,6-di-O-isopropylidene-4-O-(phenylcarbamoyl)-D-mannitol (XI).—A solution of 1.82 g. (5 mmoles) of VIII and 1.34 g. (10 mmoles) of phenyl isocyanate in 80 ml. of reagent toluene was refluxed for 20 hr. protected from moisture. The solvent was removed by spin evaporation *in vacuo* and the gummy residue triturated with 25 ml. of warm petroleum ether to remove the remaining phenyl isocyanate. Recrystallization of the insoluble solid from ethyl acetate–petroleum ether gave 1.8 g. (78%) of product in two crops, m.p. 117–118°. Recrystallization from the same solvents gave white crystals of unchanged melting point; $[\alpha]^{25}D$ +65.2 ± 0.6° (1%); ν_{max}^{Nujol} 3400 (NH); 1740 (urethane C=O); 1715 (ester C=O); 1525 (amide II); 1600, 755, 715 cm.$^{-1}$ (phenyl).

Anal. Calcd. for $C_{26}H_{31}NO_8$: C, 64.3; H, 6.39; N, 2.88. Found: C, 64.5; H, 6.47; N, 3.12.

Treatment of 3-O-Benzoyl-1,2:5,6-di-O-isopropylidene-4-O-(phenylcarbamoyl)-D-mannitol (XI) with Sodium Hydride.—To a solution of 0.97 g. (2 mmoles) of dry XI in 12 ml. of dimethylformamide protected from moisture was added 0.11 g. (2.5 mmoles) of 55% sodium hydride dispersion in mineral oil. The mixture was stirred at 90–100° for 90 min., cooled, acidified with 0.5 ml. of acetic acid, then processed as described before for the reaction of the sodium salt of V with phenyl isocyanate. The first material isolated was 150 mg. (71%) of diphenylurea,

m.p. 235°. Then 50 mg. (8.5%) of cyclic carbonate (XIV), m.p. 149–150°, and 120 mg. (12%) of unchanged XI were isolated, all three characterized by mixture melting points and comparative infrared spectra with authentic samples. The final residue (150 mg.) appeared to be mainly a mixture of the monobenzoate (VIII) and V, by its infrared spectrum.

The same results were obtained if a catalytic amount (6 mole %) of sodium hydride was employed.

3,4-Di-O-benzoyl-1,2:5,6-di-O-isopropylidene-D-mannitol (XIII).—Benzoylation of V or VIII with excess benzoyl chloride in pyridine overnight at room temperature gave an 85% yield of the dibenzoate as an oil which was free of hydroxyl absorption in the infrared. For analysis, the compound was absorbed from a benzene solution on a column of neutral alumina (Brockmann activity III), then eluted with 1:1 benzene–chloroform. The colorless oil had ν_{max}^{film} 1715 (C=O); 1260, 1100, 1080 (C—O—C); 715 cm.$^{-1}$ (benzoyl CH); $[\alpha]^{25}D$ +64.9 ± 0.7° (0.6%).

Anal. Calcd. for $C_{26}H_{30}O_8$: C, 66.4; H, 6.44. Found: C, 66.7; H, 6.24.

Benzoate Equilibration of 3-O-Benzoyl-1,2:5,6-di-O-isopropylidene-D-mannitol (VIII) with Sodium Hydride.—To a solution of 1.10 g. (3 mmoles) of dry VIII in 60 ml. of reagent toluene was added 130 mg. (3 mmoles) of 55% soduim hydride dispersion in mineral oil. After being refluxed for 90 min. protected from moisture, the mixture was spin evaporated to dryness *in vacuo*. The residue was suspended in 20 ml. of water containing 0.2 ml. of acetic acid; the mixture was extracted with chloroform (four 20-ml. portions). Dried with magnesium sulfate, combined extracts were evaporated to dryness *in vacuo*. Crystallization from ethyl acetate–petroleum ether gave 0.20 g. (25%) of debenzoylated product, V, identical with an authentic sample.

The filtrate was evaporated to dryness *in vacuo* leaving 0.7 g. of a semisolid. Further traces of V were removed by absorption on neutral alumina (Brockmann activity III) from a hexane solution, then elution with 8:1 benzene–methanol. The resultant 0.55 g. showed two spots on silica thin-layer chromatography with benzene–methanol (7:1) as the solvent system and iodine vapor as the detecting agent. The two spots had R_f values of 0.77 and 0.96 and moved identically with authentic samples of VIII and 3,4-di-O-benzoyl-1,2:5,6-di-O-isopropylidene-D-mannitol (XIII), respectively.

Acknowledgment.—We wish to thank the Cancer Chemotherapy National Service Center, National Cancer Institute, and Starks Associates, Inc., for large-scale preparation of certain intermediates, mediated by contract no. SA-43-ph-4346.

Notes

Nitration of Phenylcyclopropane. *ortho–para* Ratios for Nitration of Alkylbenzenes with Acetyl Nitrate[1]

ROGER KETCHAM, RICHARD CAVESTRI, AND D. JAMBOTKAR

Department of Pharmaceutical Chemistry, School of Pharmacy, University of California Medical Center, San Francisco, California

Received December 13, 1962

In connection with another study,[2] we had occasion to refer to the ultraviolet spectrum of *p*-nitrophenylcyclopropane obtained by Levina, Shabarov, and Patapov.[3] This spectrum, however, was inconsistent with data that we had accumulated[2] and was not typical of a *p*-nitroalkylbenzene. We, therefore, felt obliged to repeat their work in order to clarify the problem. Nitration at −40 to −20° with fuming nitric acid–acetic anhydride afforded a product whose ultraviolet spectrum was nearly identical with that previously published.[3] The proof of structure for the nitration product was based primarily on its oxidation with chromic acid to *p*-nitrobenzoic acid in 70% yield.[3] When our nitration product was subjected to gas chromatographic analysis, two major components in a ratio of 2:1 were observed. The smaller, slower-moving fraction crystallized on cooling (m.p. 32°) and gave an ultraviolet spectrum typical of a *p*-nitroalkylbenzene.[4] Furthermore, the infrared absorption pattern in the 5–6-μ region was typical of *p*-disubstituted benzenes.[5] The *larger*, faster-moving fraction could not be crystallized and showed a typical ultraviolet absorption spectrum for an *o*-nitroalkylbenzene.[4] In this case the infrared spectrum in the 5–6-μ region was typical of an *o*-disubstituted benzene.[5] Oxidation of the solid nitration product with chromic acid gave *p*-nitrobenzoic acid in 88% yield. The oil afforded 64% of *o*-nitrobenzoic acid under the same conditions. It is thus established that the cyclopropyl group, as expected, is an *ortho–para* director but that the major product is the *ortho* isomer.

Brown and Bonner have reported[6] *ortho–para* ratios for nitration of toluene, ethylbenzene, cumene, and *t*-butylbenzene with concentrated nitric acid–concentrated sulfuric acid at 40°. In order that our result with phenylcyclopropane could be compared directly, we have repeated the nitrations of these four alkylbenzenes with fuming nitric acid–acetic anhydride at −40°. This reagent gives results which are very similar to those from the "mixed acid" except that the yields are higher, the rate of decrease of the *ortho–para* ratio is greater, and smaller amounts of *meta* isomers were observed. When the nitrating mixture was prepared at room temperature and cooled to −40° for nitration, the *ortho–para* ratio for the branched alkylsubstituted benzene was much smaller, whereas with phenylcyclopropane the ratio was considerably higher. The nitration of phenylcyclopropane with this

(1) This work was supported, in part, by Cancer Research Funds of the University of California and by an American Cancer Society Institutional grant 1N 33D.

(2) L. A. Strait, R. Ketcham, and D. Jambotkar, paper presented at 14th Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, March, 1963.

(3) R. Ya. Levina, Yu. S. Shabarov, and V. K. Patapov, *Zh. Obschch. Khim.*, **29**, 3233 (1959); *J. Gen. Chem., USSR*, **29**, 3196 (1959).

(4) W. G. Brown and H. Reagan, *J. Am. Chem. Soc.*, **69**, 1032 (1947).

(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, pp. 67–69.

(6) H. C. Brown and W. H. Bonner, *J. Am. Chem. Soc.*, **76**, 605 (1954).