[Contribution from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service]

The Reaction of Certain 1-Thioaldose Derivatives with the Silver Salts of Carboxylic Acids. Synthesis of 1-*O*-Mesitoyl-α-D-glucopyranose

By Christian Pedersen and Hewitt G. Fletcher, Jr.

Received November 16, 1959

When treated with silver benzoate in boiling acetonitrile D-glucose diethyl dithioacetal is converted in low yield to 2-*O*-benzoyl-D-glucose, isolated as its tetraacetate. A similar treatment of ethyl 1-thio-β-D-glucopyranoside gave, after acetylation, 1,3,4,6-tetra-*O*-acetyl-2-*O*-benzoyl-α-D-glucose and 2,3,4,6-tetra-*O*-acetyl-1-*O*-benzoyl-β-D-glucose. With silver mesitoate in boiling acetonitrile ethyl 1-thio-β-D-glucopyranoside gives 1-*O*-mesitoyl-α-D-glucopyranose and its anomer (isolated as the tetraacetate). The identity of 1-*O*-mesitoyl-α-D-glucopyranose was established through its conversion to 2,3,4,6-tetra-*O*-acetyl-1-*O*-mesitoyl-α-D-glucose and to 2-*O*-mesitoyl-β-D-glucose, both substances which had been prepared in earlier researches.

In earlier work in this Laboratory[1] the two anomeric 2,3,4,6-tetra-*O*-acetyl-1-*O*-mesitoyl-D-glucopyranoses[2] were synthesized. Owing to the relative stability of the mesitoyl group, compared to the acetyl group, no difficulty was experienced in deacetylating the β-anomer IX either with methanolic ammonia[1] or sodium methoxide,[3] 1-*O*-mesitoyl-β-D-glucopyranose (V) being obtained in normal fashion. Subsequently[4] the deacetylation of the α-anomer VIII with methanolic ammonia was shown to give 2-*O*-mesitoyl-D-glucose (VII), the relatively inert mesitoyl group having migrated to the nearest *cis*-hydroxyl even under these comparatively mild conditions. Such a migration of a 1-*O*-acyl group in an aldose to a *cis* position at carbon two had previously been established by Ness and Fletcher[5] who showed that mild alkali (such as aqueous pyridine) readily converts 1,3,5-tri-*O*-benzoyl-α-D-ribose to 2,3,5-tri-*O*-benzoyl-D-ribose. Other, less clear-cut examples of this type of ester migration are known.[4,6] In contrast, 1-*O*-acylaldoses having a hydroxyl at at carbon two *trans* to the substituent at carbon one (such as 1-*O*-benzoyl-β-D-glucopyranose[7] and 1-*O*-benzoyl-α-D-talopyranose[8]) exhibit the normal stability of sugar esters. As far as the present authors are aware, no well-established example of a *cis*-1-*O*-acylaldose, otherwise unsubstituted, has been reported.[9] We wish now to describe a new route to the synthesis of 1-*O*-acylaldoses which has led to the synthesis of the *cis* structure, 1-*O*-mesitoyl-α-D-glucopyranose.

In preliminary experiments, D-glucose diethyl dithioacetal (I) was dissolved in hot acetonitrile and the solution treated with an excess of silver benzoate. The finely divided white salt partly dissolved, the solution became pale yellow and the appearance of the suspended material changed. After removal of the silver ions and benzoic acid, a sirupy product was obtained which paper chromatography showed to contain glucose and at least two other components. Acetylation led to the isolation in very low yield (7%) of 1,3,4,6-tetra-*O*-acetyl-2-*O*-benzoyl-α-glucose (II), a substance which had been described by Brigl and Zerrweck.[10] Thus the reactivity of 1-ethylthio groups toward silver acylates was demonstrated. The elucidation of the complete mechanism of the transformation awaits further work; doubtless a $C_1 \rightarrow C_2$ migration of the benzoyl group is involved.

Attention was now turned to the behavior of ethyl 1-thio-β-D-glucopyranoside (III) with silver benzoate.[11] Here again, the treatment with silver benzoate in hot acetonitrile afforded an amorphous product. Acetylation led to the isolation in low yield of 1,3,4,6-tetra-*O*-acetyl-2-*O*-benzoyl-α-D-glucose (II) and 2,3,4,6-tetra-*O*-acetyl-1-*O*-benzoyl-β-D-glucose (IV).[7,12,13] The formation of these compounds suggests that, while a 1-*O*-benzoyl-β-D-glucopyranose may be stable under these reaction conditions, the *cis* anomer undergoes acyl migration. With the ester of a sterically hindered acid, having less tendency to migrate, one might expect to obtain an α-1-ester. Accordingly, ethyl 1-thio-β-D-glucopyranoside (III) was heated in boiling acetonitrile with silver mesitoate. A crystalline mono-*O*-mesitoyl-D-glucose, differing in melting point and rotation from the previously known mono-*O*-mesitoyl-D-glucoses, was obtained. On acetylation it was converted to 2,3,4,6-tetra-*O*-acetyl-1-*O*-mesitoyl-α-D-glucose (VIII), a substance which had been made in earlier work[1] through fusion of α-D-glucopyranose pentaacetate with mesitoic acid in the presence of zinc chloride. The identity of the new monoester as VI was confirmed through its rearrangement, using methanolic ammonia, to 2-*O*-mesitoyl-β-D-glucose (VII).

Acetylation of the mother liquor from the treatment of ethyl 1-thio-β-D-glucopyranoside (III) with silver mesitoate led to the isolation of 2,3,4,6-tetra-*O*-acetyl-1-*O*-mesitoyl-β-D-glucose (IX); both anomeric 1-*O*-mesitoyl-D-glucoses (V and VI) had, therefore, been formed from the 1-thio glucoside. Applications of this reaction to structural problems

---

(1) H. B. Wood, Jr., and H. G. Fletcher, Jr., This Journal, **78**, 207 (1956).

(2) Mesitoyl = 2,4,6-trimethylbenzoyl.

(3) F. Micheel and G. Baum, *Chem. Ber.*, **88**, 2020 (1955).

(4) H. B. Wood, Jr., and H. G. Fletcher, Jr., This Journal, **78**, 2849 (1956).

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

(6) R. K. Ness and H. G. Fletcher, Jr., *ibid.*, **80**, 2007 (1958).

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

(8) H. B. Wood, Jr., and H. G. Fletcher, Jr., This Journal, **79**, 3234 (1957).

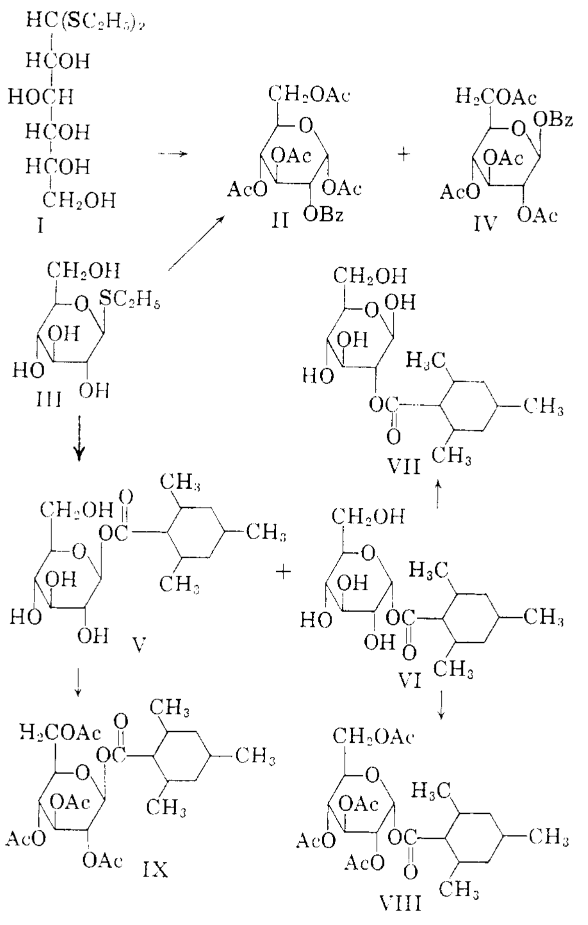
(9) A possible exception, "α-glucogallin" (1-*O*-galloyl-α-D-glucopyranose), has been reported by O. Th. Schmidt and J. Herok [*Ann.*, **587**, 63 (1954)]. Significantly, these authors report that α-glucogallin mutarotates in aqueous solution, an observation which may be due to acyl migration followed by normal anomerization at carbon one.

(10) P. Brigl and W. Zerrweck, *Z. physiol. Chem. Hoppe-Seyler's*, **229**, 117 (1934).

(11) It may be noted that the tetraacetate of ethyl 1-thio-β-D-glucopyranoside appeared to be unattacked when heated in acetonitrile with silver benzoate.

(12) G. Zemplén and E. D. Laszlo, *Ber.*, **48**, 915 (1915).

(13) E. Fischer and M. Bergmann, *ibid.*, **51**, 1760 (1918).



in the 2-deoxy-D-ribose series are described in the paper immediately following; its use in the synthesis of nucleosides will be described in a later communication.

Experimental[14]

Reaction of D-Glucose Diethyl Dithioacetal (I) with Silver Benzoate.—One gram of D-glucose diethyl dithioacetal, dissolved in 25 ml. of acetonitrile, was treated with 3.2 g. (4 molar equivalents) of silver benzoate and the solution boiled under reflux for 5 hr. The cooled mixture was filtered, the solvent removed from the filtrate and the amorphous residue dissolved in methanol. Silver was removed with hydrogen sulfide and, after filtration, the solution was concentrated *in vacuo* to a sirup. The material was then dissolved in water and extracted with ether to remove benzoic acid. Upon reconcentration *in vacuo* there was obtained a sirup (980 mg.). A sample of this, chromatographed on paper using butanol–ethanol–water (40:11:19), was resolved into three components which were visualized with periodate–benzidine sprays. One component migrated at the same rate as glucose; another probably contained sulfur since it gave a positive test when sprayed with bromine–methyl orange.[15] The sirup was acetylated with pyridine–acetic anhydride in the usual fashion to give an amorphous product (1.32 g.). From its solution in 5 ml. of ether at +5° this deposited 110 mg. (7%) of crystalline material. Recrystallized twice from methanol this product gave 63 mg. of pure material melting at 185–186° and rotating $[\alpha]^{20}D$ +49.9° in chloroform (*c* 0.55).

Anal. Calcd. for $C_{21}H_{24}O_{11}$: C, 55.75; H, 5.35. Found: C, 55.79; H, 5.47.

Brigl and Zerrweck[10] reported m.p. 186° and $[\alpha]D$ +51.8° ($CHCl_3$) for 1,3,4,6-tetra-*O*-acetyl-2-*O*-benzoyl-α-D-glucose and observed that the various isomeric tetra-*O*-acetyl-mono-*O*-benzoyl-D-glucopyranoses are readily distinguished through these two constants.

Reaction of Ethyl 1-Thio-β-D-glucopyranoside (III) with Silver Benzoate.—Ethyl 1-thio-β-D-glucopyranoside[16] (0.5 g.) was dissolved in 20 ml. of acetonitrile and treated with 2.5 g. of silver benzoate (4.9 molar equivalents). The solution was boiled under reflux for 3 hr. and then worked up as described above in the case of D-glucose diethyl dithioacetal to give 0.5 g. of a sirup. Chromatography of a sample of this on paper with butanol–ethanol–water (40:11:19), followed by periodate–benzidine sprays revealed four components, one of which had migrated at the same rate as glucose. The material was acetylated with pyridine and acetic anhydride to give an amorphous acetate (0.70 g.) which, from 5 ml. of methanol, deposited 50 mg. (5%) of crystalline material melting at 175–180°. After recrystallization from methanol this melted at 183–184° and rotated $[\alpha]^{20}D$ +49.2° ($CHCl_3$, *c* 0.39); admixture with the 1,3,5,6-tetra-*O*-acetyl-2-*O*-benzoyl-α-D-glucose, obtained from the diethyl dithioacetal as described earlier, failed to depress its melting point.

The main mother liquors from the above preparation were concentrated *in vacuo* and the residue adsorbed on acid-washed Alorco alumina. After preliminary elution with benzene–cyclohexane (2:3), elution with benzene alone provided a fraction which was crystallized from methanol: 63 mg. (6.2%), m.p. 144–145°, $[\alpha]^{20}D$ −26.2° ($CHCl_3$ *c* 0.65). A mixed melting point with pure 2,3,4,6-tetra-*O*-acetyl-1-*O*-benzoyl-β-D-glucose, prepared through the condensation of silver benzoate with 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl bromide, was undepressed.

Reaction of Ethyl 1-Thio-β-D-glucopyranoside (III) with Silver Mesitoate.—Ethyl 1-thio-β-D-glucopyranoside (1.5 g.) and 5.7 g. (3.1 molar equivalents) of silver mesitoate were dissolved in 30 ml. of boiling acetonitrile to give a clear yellow solution from which a dark precipitate began to form after a few minutes. The suspension was boiled under reflux for 3 hr., cooled, and then filtered. Solvent was removed *in vacuo*, the residue dissolved in methanol (50 ml.) and silver ions precipitated with hydrogen sulfide. After filtration, the solution was concentrated *in vacuo* to a sirup and the residue suspended in water (50 ml.). Methylene chloride was used to extract the mesitoic acid and the solution was then concentrated to dryness. From 15 ml. of hot water the residue deposited 0.53 g. of crude crystalline **1-*O*-mesitoyl-α-D-glucopyranose** which was recrystallized twice from ethyl acetate (6–7 ml.): 380 mg. (17%), m.p. 164–166°, $[\alpha]^{20}D$ +102° (H_2O, *c* 0.18), $[\alpha]^{20}D$ +102° (CH_3OH, *c* 0.48). A further crystallization from ethyl acetate raised the melting point to 165–166° but failed to change the rotation.

Anal. Calcd. for $C_{16}H_{22}O_7$: C, 58.88; H, 6.80. Found: C, 59.15; H, 6.57.

The aqueous mother liquor from the above preparation was concentrated to dryness and the residue acetylated with 8 ml. of acetic anhydride in 40 ml. of pyridine to yield 1.4 g. of sirup. This product was dissolved in 50 ml. of benzene and adsorbed on a column of 40 g. of neutralized Alorco alumina. Elution with benzene (600 ml.) gave 387 mg. of a sirup which, from ether–pentane, deposited 214 mg. (6.5%) of crystalline material, m.p. 137–139°. Recrystallization from benzene–pentane gave, with little loss, pure 2,3,4,6-tetra-*O*-acetyl-1-*O*-mesitoyl-β-D-glucose rotating $[\alpha]^{20}D$ +3.5° ($CHCl_3$, *c* 1.29) and melting at 139–141° either alone or in admixture with an authentic specimen prepared in earlier work[1] by the condensation of silver mesitoate with 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl bromide. The identity of the samples from the two sources was further confirmed through infrared spectra.

Elution of the alumina with benzene–ether (4:1, 400 ml.) afforded 297 mg. of a sirup which yielded 85 mg. more 2,3,4,6-tetra-*O*-acetyl-1-*O*-mesitoyl-β-D-glucose, raising the total yield of this substance to 9%.

Further elution with benzene–ether (3:2, 300 ml.), followed by ether (500 ml.) gave 161 mg. of sirup which, from ether–pentane, gave 44 mg. (1.3%) of 2,3,4,6-tetra-*O*-acetyl-1-*O*-mesitoyl-α-D-glucose melting at 119–120° and rotating $[\alpha]^{20}D$ +112° ($CHCl_3$, *c* 0.25). A mixed melting point and comparison of infrared spectra showed this

---

(14) All melting points are corrected.

(15) F. Weygand, H. J. Bestmann and H. Ziemann, *Chem. Ber.*, **91**, 1040 (1958).

(16) R. U. Lemieux, *Can. J. Chem.*, **29**, 1079 (1951).

substance to be identical with the product obtained through the acetylation of 1-*O*-mesitoyl-α-D-glucopyranose as described below.

Further elution of the alumina with acetone (500 ml.) gave 434 mg. of sirup. Neither this material nor any of the other fractions from the chromatography crystallized when seeded with 1,3,4,6-tetra-*O*-acetyl-2-*O*-mesitoyl-β-D-glucose.[4]

2,3,4,6-Tetra-*O*-acetyl-1-*O*-mesitoyl-α-D-glucose (VIII) from 1-*O*-Mesitoyl-α-D-glucose (VI).—1-*O*-Mesitoyl-α-D-glucopyranose (50 mg.) was added to a mixture of acetic anhydride (0.12 ml., 8.3 molar equivalents) and pyridine (1 ml.). The mixture was kept overnight at room temperature and then diluted with water and the product extracted with methylene chloride (2 × 10 ml.). The combined extracts were washed successively with 3 *N* sulfuric acid (2 × 10 ml.), saturated aqueous sodium bicarbonate (2 × 10 ml.) and water (2 × 10 ml.). Moisture was removed with sodium sulfate and the solution, after filtration through decolorizing carbon, concentrated *in vacuo* to dryness. From ethanol-pentane the residue yielded 42 mg. (55%) of 2,3,4,6-tetra-*O*-acetyl-1-*O*-mesitoyl-α-D-glucose melting at 119–120° either alone or in admixture with a sample made earlier[1] through the fusion of a mixture of α-D-glucopyranose pentaacetate, mesitoic acid and zinc chloride. The infrared spectra of the samples from the two sources were identical.

2-*O*-Mesitoyl-β-D-glucose (VII) from 1-*O*-Mesitoyl-α-D-glucopyranose (VI).—1-*O*-Mesitoyl-α-D-glucopyranose (102.7 mg.) was dissolved in 10 ml. of methanol and the solution treated with 1 ml. of 3.2 *N* methanolic ammonia. After 23 hr. at 20° the mutarotation had ceased. The solution was then evaporated to dryness and the residue crystallized from ethyl acetate–pentane to give 72 mg. (70%) of 2-*O*-mesitoyl-β-D-glucose melting at 188–190°. Two recrystallizations from ethyl acetate afforded pure material melting at 192–193°.

In earlier work[4] 2-*O*-mesitoyl-β-D-glucose was reported to melt at 180–187° and mutarotate in water (*c* 0.94) +24.0° (13.5 min.) → +45.5° (19 hr.). The sample prepared at that time was later found to melt at 188–190°. After two recrystallizations from ethyl acetate, it gave, with little loss, material melting at 192–193° and rotating $[\alpha]^{20}_{D}$ +19.8° (16 min.) → +45.4° (28 hr., constant) (H_2O, *c* 0.66). This product did not depress the melting point of that obtained as described above through the rearrangement of 1-*O*-mesitoyl-α-D-glucopyranose. The infrared spectra of the two samples were identical.

Anal. Calcd. for $C_{16}H_{22}O_7$: C, 58.88; H, 6.80. Found: C, 58.91; H, 6.52.

Acknowledgment.—Analyses were carried out in the Institutes' Analytical Services Unit under the direction of Dr. W. C. Alford.

BETHESDA 14, MD.

COMMUNICATIONS TO THE EDITOR

CHEMICAL EVIDENCE FOR A TRIPLET GROUND STATE FOR METHYLENE

Sir:

We have found what we believe to be conclusive chemical evidence that the methylene molecule possesses a triplet electronic ground state. Herzberg and Shoosmith[1] already have obtained spectroscopic evidence for a triplet state of methylene. In more recent work,[2] results were obtained which suggest that the flash photolysis of diazomethane yields methylene molecules in highly excited singlet states which are subsequently energetically degraded to the triplet ground state through collisions with inert gas molecules. The most intense spectrum for the triplet state was obtained when a large excess of nitrogen was present. On the other hand, all of the previous evidence based on the observed chemistry of methylene was consistent only with a singlet (not necessarily ground) state for this molecule.[3]

Skell, *et al.*,[3] have found that the 1,2-dimethylcyclopropane formed from methylene and *cis*- or *trans*-2-butene in the gaseous or liquid phase is almost entirely the *cis* or *trans* isomer respectively. These workers felt that this stereospecificity implied a singlet state for methylene under these conditions.

We have repeated the work of Skell and are in full agreement with his conclusions. However, we have extended the study of the photolysis of diazomethane in the gas phase to systems containing only small partial pressures of diazomethane and an alkene in the presence of a large excess of nitrogen. These are the conditions found by Herzberg to be most favorable to the formation of methylene molecules in the triplet ground state. Under these circumstances the stereospecificity of the reaction is entirely lost. In fact, in the reaction with *cis*-2-butene there is a complete reversal of the proportion in which the *cis*- and *trans*-1,2-dimethylcyclopropanes are formed.

It is evident from the data in Table I that the reaction becomes less stereospecific as the amount of nitrogen present during the decomposition is increased. This is most noticeable in the reactions with *cis*-2-butene. Our interpretation of the observations is presented. The methylene molecule when first formed is in a singlet state and thus gives rise to reactions which are almost entirely stereospecific as the two new bonds may be formed simultaneously.[3] When a large excess of nitrogen is present the methylene molecules undergo numerous collisions with the nitrogen molecules before striking an alkene. The collisions with the inert gas degrade the methylene molecules through their excited states to the ground state which in view of the loss of stereospecificity is a triplet. The combination of a methylene molecule in a triplet state ($CH_2[\uparrow\ \uparrow]$) and a butene molecule must give rise to an intermediate which is

---

[1] G. Herzberg and J. Shoosmith, *Nature*, **183**, 1801 (1959).

[2] G. Herzberg, paper presented at the R. A. Welch Foundation, Conference on Chemical Research, Nov., 1959. We are grateful to Dr. Herzberg for a copy of this manuscript prior to its publication and for further unpublished information concerning the conditions which are necessary for the observation of methylene in the triplet state.

[3] R. C. Woodworth and P. S. Skell, THIS JOURNAL, **81**, 3383 (1959); and references therein. In some substituted methylenes there is evidence of triplet states [R. M. Etter, H. S. Skovronek and P. S. Skell, *ibid.*, **81**, 1008 (1959); P. S. Skell and J. Klebe, *ibid.*, **82**, 248 (1960)]. In none of these cases has the ground state been characterized.