Photochemical Reaction at 3-*O*-Functional Group of Methyl 4,6-*O*-Cyclohexylidene-2-deoxy-2-methoxycarbonylamino-α-D-glucopyranoside Derivatives

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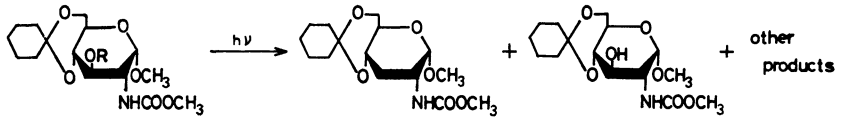
3-*O*-Acetyl, 3-*O*-thiocarbonyl, and 3-*O*-sulfonyl derivatives of the titled compound have been irradiated in aqueous HMPT. Conversion of the 3-*O*-acetyl derivative to the corresponding 3-deoxy compound was most effective. 3-*O*-Dimethylthiocarbamoyl-, 3-*O*-(methylthio)thiocarbonyl- and 3-*O*-(1-imidazolyl)thiocarbonyl derivatives were found to give the 3-deoxy compound accompanied by 3-hydroxy compound, whereas the 3-*O*-phenyl(thiocarbonyl) derivative did not give the 3-deoxy compound. 3-*O*-Methylsulfonyl and 3-*O*-tolylsulfonyl derivatives gave the 3-hydroxy compound. Under low-energy irradiation, the (1-imidazolyl)thiocarbonyl derivative gave the 3-deoxy compound in moderate yield.

Deoxygenation of the hydroxyl group at C-3 of sugars and its application to aminoglycoside antibiotics[1] are of current interest, due to the marked activities of 3′-deoxy derivatives such as 3′-deoxykanamycin A,[2] 3′,4′-dideoxykanamycin B,[3] and 3′-deoxybutirosins[4] against resistant bacteria. In α-D-glucopyranosides, however, deoxygenation at C-3 is difficult[5] since the S_N2 process at this position is hindered in the majority of cases. Barton *et al.*[6] recently solved this problem by treating *O*-thiocarbonyl derivatives with tributylstannane and have synthesized the corresponding deoxy compounds in good yields. Pete *et al.*[7] succeeded in deoxygenation of the position by acetylating the 3-hydroxyl group followed by irradiation of the solution of the *O*-acetyl derivative in aqueous hexamethylphosphoric triamide (HMPT). Horton *et al.*[8] prepared the 2- and 3-deoxy sugars by irradiation of the methanol solution of 2- and 3-*O*-dimethylthiocarbamoyl derivatives. The present studies have been undertaken to investigate the photochemical treatment of several 3-*O*-thiocarbonyl and 3-*O*-sulfonyl sugars.

The starting materials, the 3-*O*-thiocarbonyl derivatives of methyl 4,6-*O*-cyclohexylidene-2-deoxy-2-methoxycarbonylamino-α-D-glucopyranoside[10] (**1**), namely, 3-*O*-dimethylthiocarbamoyl (**4**), 3-*O*-[(methylthio)thiocarbonyl] (**5**), 3-*O*-[(1-imidazolyl)thiocarbonyl] (**6**), and 3-*O*-phenyl(thiocarbonyl) (**7**) derivatives were prepared. In addition, the 3-*O*-acetyl derivative (**3**) was prepared.

In order to select the solvent for the photochemical reaction, compound **6**, a model compound, was dissolved in several solvents and each solution irradiated (with 2537 Å lamp) for 1.5 h in the manner described in the experimental. Photochemical reactions conducted in tetrahydrofuran, dioxane, methanol, ethanol, 2-propanol, 1-butanol, acetone, acetonitrile, dimethyl sulfoxide (all including the reactions in neat solvents and aqueous solvents=5: 95), *t*-butyl alcohol, benzene or sulforane gave the starting material (**6**) together with the formation of a slight amount of the 3-hydroxy compound (**1**). The low yield of the 3-deoxy compound (**2**) was found in the reactions in 2-propanol, 1-butanol,

TABLE 1. THE YIELDS (%) OF **2** AND **1** BY IRRADIATION OF **3**—**10** IN AQUEOUS HMPT (5: 95)



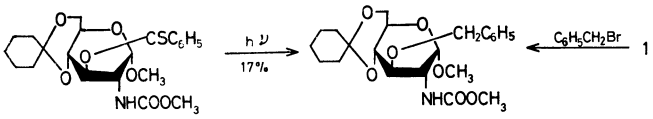
3-10 2 1

Compound	R	2537 Å Lamp Time/h	2	1	St. m. and other products	3000 Å Lamp Time/h	2	1	St. m. and other products
3	CH_3CO–	1.5	88	0	0	14	0	0	100[a] (**3**)
4	$(CH_3)_2NCS$–	14	72	10	0	14	0	0	100(**4**)
5	CH_3SCS–	2	57	12	14(**5**)	14	0	0	100(**5**)
6		1.5	54	17	5(**4**)	4	51	26	8(**4**)
7	C_6H_5CS–	3	0	≈30	>7(**7**) >17(**11**)	4	0	9	b)
8	$(CH_3)_2NSO_2$	4	0	0	100[a] (**8**)	14	0	0	100(**8**)
9	CH_3SO_2–	6	trace(?)	86	9(**9**)	14	0	0	100(**9**)
10	*p*-$CH_3C_6H_4SO_2$–	4	0	91	0	14	0	0	100(**10**)

a) The figure 100 indicates that no product other than the starting material (st. m.) was produced. b) A large amount of unidentified product was formed, but the formation of **11** was not observed.

sulforane, and dimethyl sulfoxide (all including the reactions in neat solvents and in aqueous solvents= 5: 95). In the reaction in *N,N*-dimethylformamide and aqueous *N,N*-dimethylformamide (5: 95), **6** was converted to the dimethylthiocarbamoyl derivative (**4**). The reaction mechanism is thought to that **6** reacts with dimethylamine produced from *N,N*-dimethylformamide during the irradiation. **1** and **2** were however formed in trace amounts. The solution of **6** however in aqueous HMPT (5: 95) when irradiated produced the 3-deoxy compound (**2**) in 54% yield.

On the basis of these results **3**—**7** were treated photochemically (2537 Å lamp) in aqueous HMPT, the results of which are summarized in Table 1. The acetyl derivative (**3**) gave the best result, the deoxy compound (**2**) being formed exclusively. In the case of **4**, **2** was formed in good yield, but the reaction required a longer period and the product was contaminated by the 3-hydroxy compound (**1**). In the cases of **5** and **6**, **2** and **1** were formed but in the case of **7** the expected **2** was not formed, the 3-hydroxy compound (**1**) and an unidentifiable product being formed. Interestingly the 3-*O*-benzyl product (**11**) was found to be formed in this reaction. This product was proved by synthesis from **1** and α-bromotoluene.



Under low-energy irradiation (3000 Å lamp), only the (1-imidazolyl)thiocarbonyl compound (**6**) was converted to the 3-deoxy compound (**2**) in moderate yield, but other compounds except **7** were all stable after 14 h irradiation (Table 1). This demonstrates that low-energy irradiation, only the (1-imidazolyl)-thiocarbonyl group can be removed to give the deoxy compound in the presence of acetyl, dimethylthiocarbamoyl), (methylthio)thiocabonyl, methylsulfonyl, and *p*-tolylsulfonyl groups.

The deoxygenation at C-3 of α-D-glucopyranosides by treatment of the 3-*O*-dimethylsulfamoyl derivatives with sodium metal in liquid ammonia has been reported.[10] The mechanism of photochemical reaction and the reaction with sodium metal are both considered to be radical reactions and consequently the photochemical treatment of the 3-sulfonic esters (**8**—**10**) of **1** in aqueous HMPT (5: 95) were examined. On photochemical treatment of the 3-*O*-dimethylsulfamoyl derivative[10] (**8**), however, no deoxy compound was formed and the starting material was recovered (Table 1). In the cases of the 3-*O*-methylsulfonyl (**9**) and 3-*O*-(*p*-tolylsulfonyl) derivative (**10**), the 3-hydroxy compound (**1**) was formed in good yield. The ready removal of the 3-*O*-tosyl group of **10** offers a facile method for detosylation. Zen *et al.*[11] reported the photochemical detosylation of sugar tosylates in methanol containing sodium methoxide.

Experimental

PMR spectra were recorded at 90 MHz with a Varian EM-390 spectrometer. Thin-layer chromatography (TLC) was performed on Wakogel B-5 using a sulfuric acid spray for detection. Silica gel (Wakogel C-200) was used for separation of the products by column chromatography.

General Procedure for Photochemical Reaction. Nitrogen was bubbled through an aqueous HMPT (5: 95, ≈10 ml) solution of the starting material (**3**—**10**, 0.04—0.05 mmol) in a quartz tube (PQV-5 or -7, 13×180 mm) for 10 min. The solution was stoppered, set in a photo-reactor (Rayonet ® RPR 208 Preparative Photochemical Reactor with MGR-100 Merry-Go-Round) and irradiated with a RUL-2537 Å or RUL-3000 Å lamp (in the latter case, a Pyrex RPV-8 tube was used instead of a quartz tube). All apparatus used was manufactured by The Southern New England Ultraviolet Company, England. The speed of reaction was influenced by both the concentration and the volume of the solution in the tube of the starting material.

Photochemical Reaction of 3 (2537 Å Lamp). A solution of **3** (55 mg) in aqueous HMPT (30 ml) was divided between three quartz tubes and, after nitrogen was bubbled through the solution, the solution was irradiated at room temperature with a 2537 Å lamp for 1.5 h. The TLC plate was prepared as follows: a small portion of the solution was poured into aqueous ether and, after shaking the mixture vigorously, the separated ethereal solution was spotted with a glass capillary on the plate and developed with benzene–ethyl acetate=5: 1. The solution showed a single spot at R_f 0.38 (**2**) (*cf.* **3**, R_f 0.2). The solution was poured into water (150 ml) and the mixture extracted with ether (150+50 ml). The ethereal solution was washed with water, dried (sodium sulfate), and concentrated. The residue was chromatographed with benzene–ethyl acetate (5: 1) to give a HMPT-free syrup of **2**, which crystallized on standing, 41 mg (88%). Recrystallization from hexane gave granular crystals; mp 118—119 °C, $[\alpha]_D^{25}$ +77° (*c* 1, chloroform); PMR ($CDCl_3$): δ 1.3—2.2 (12H), 3.40 (3H s, CH_3O), 3.72 (3H s, CH_3OCO), 4.60 (1H d, J=3.5 Hz, H-1).

Found: C, 57.28; H, 7.82; N, 4.28%. Calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44%.

Decyclohexylidenation of **2** as previously described[10] gave methyl 2,3-dideoxy-2-methoxycarbonylamino-α-D-glucopyranoside.[10]

Photochemical Reaction of 6 (2537 Å Lamp). An aqueous HMPT solution (40 ml) of **6** (73 mg) in four quartz tubes was irradiated for 1.5 h. The standard work-up as described above gave a mixture of products. The mixture showed, on TLC with cyclohexane–ethyl acetate (5: 1), spots of R_f 0.23 (major, **2**), 0.11 (trace, **4**), and ≈0.05 (minor) (*cf.* **6**, R_f 0.05). Separation by column-chromatography with cyclohexane–ethyl acetate (5: 1) as eluent gave **2** (28 mg, 54%) and **4** (3.2 mg, 5%). Further elution with ethyl acetate gave **1** (9.1 mg, 17%).

Photochemical Reaction of 6 (3000 Å Lamp). An aqueous HMPT solution (40 ml) of **6** (41 mg) in four Pyrex tubes was irradiated with a 3000 Å lamp for 4 h. The standard work-up gave **2** (14.7 mg, 51%), **4** (2.9 mg, 8%), and **1** (7.9 mg, 26%).

Photochemical Reaction of 7 (2537 Å Lamp). A solution of **7** (183 mg) in aqueous HMPT (90 ml) was irradiated for 3 h. The solution was poured into water (500 ml) and the mixture extracted with ethyl acetate (150 ml×2, 50 ml×3). The combined solutions were washed with water, dried (sodium sulfate) and concentrated. The residue was chromatographed on a column of silica gel with cyclohexane–ethyl acetate (5: 1). **7** (12 mg, 7%, R_f 0.46 with benzene–ethyl acetate=5: 1), a mixture of **7** and **11** (6.8 mg), and **11** (29 mg, 17%, R_f 0.33) were eluted in this order. A change of eluent to ethyl acetate gave **1** (43 mg, 32%) and to methanol gave an unidentified product (≈130 mg).

Compound **11** was purified by column chromatography with benzene–ethyl acetate (15: 1) to give colorless powder, $[\alpha]_D^{25}$ +98° (*c* 1, chloroform); IR (KBr): 1735 cm^{-1}; PMR ($CDCl_3$): δ 1.3—2.5 (10H, cyclohexylidene), 3.37 (3H s, C_1OCH_3), 3.71 (3H s, CO_2CH_3); 2H AB q centered at 4.87 (J=12 Hz, $C_6H_5C\underline{H}_2O$), 4.74 (1H d, J=4 Hz, H-1), 4.83 (1H d, J=10 Hz, NH; disappeared on deuteration), 7.40 (5H s, C_6H_5).

Found: C, 62.86; H, 7.29; N, 3.15%. Calcd for $C_{22}H_{31}NO_7$: C, 62.69; H, 7.41; N, 3.32%.

Photochemical Reaction of ***10*** *(2537 Å Lamp).* An aqueous HMPT solution (20 ml) of **10** (41.5 mg) was irradiated for 4 h in the manner described. The solution was poured into water (100 ml) and the mixture extracted with ethyl acetate (100+50 ml). The organic solution was washed with water, dried, and concentrated. The residue was chromatographed with benzene–ethyl acetate (2: 1) to give **1**, 25.7 mg (91%), $[\alpha]_D^{25}$ +78° (*c* 1, chloroform).

Methyl 3-O-Acetyl-4,6-O-cyclohexylidene-2-deoxy-2-methoxycarbonylamino-α-D-glucopyranoside ***(3)***. Prepared from **1** with acetic anhydride in pyridine gave a yield of 76%, $[\alpha]_D^{25}$ +81° (*c* 1, chloroform); UV (ethanol): λ_{max} 203 nm (ε 270); PMR ($CDCl_3$): δ 2.10 (3H, s, Ac), 3.41 (3H s, CH_3O), 3.72 (3H s, CH_3OCO), 4.72 (1H d, J=3.5 Hz, H-1), 5.10 (1H t, J=10 Hz, H-3).

Found: C, 54.72; H, 7.10; N, 3.78%. Calcd for $C_{17}H_{27}NO_8$: C, 54.68; H, 7.29; N, 3.75%.

Methyl 4,6-O-Cyclohexylidene-2-deoxy-3-O-(dimethylthiocarbamoyl)-2-methoxycarbonylamino-α-D-glucopyranoside ***(4)***. To an ice-cold solution of **1** (106 mg) in tetrahydrofuran–HMPT (1: 1, 2 ml), 50% oily sodium hydride (net wt 15 mg) was added and the mixture stirred for 10 min under an atmosphere of nitrogen. Dimethylthiocarbamoyl chloride[12] (59 mg) was added and the mixture stirred for 1 h at room temperature. The reaction mixture was poured into water and the mixture extracted with ethyl acetate. The organic solution was washed with water, dried (sodium sulfate), and concentrated to give a residue. The residue was chromatographed with chloroform–ethyl acetate (10: 1) to give a pale-yellow syrup. The solution of the syrup in hexane was concentrated *in vacuo* to give a solid, 83.3 mg (62%), $[\alpha]_D^{25}$ +32° (*c* 1, chloroform); UV (ethanol): λ_{max} 285 nm (log ε 3.00), 248 (4.18), 203 (3.95); PMR ($CDCl_3$); δ 3.14 (3H s, CH_3N), 3.41 and 3.42 (each 3H s, CH_3N and CH_3O), 3.65 (3H s, CH_3OCO), 4.79 (1H d, J=3.5 Hz, H-1), 5.99 (1H t, J=10 Hz, H-3).

Found: C, 51.65; H, 7.06; N, 6.73; S, 7.69%. Calcd for $C_{18}H_{30}N_2O_7S$: C, 51.66; H, 7.23; N, 6.69; S, 7.66%.

Methyl 4,6-O-Cyclohexylidene-2-deoxy-2-methoxycarbonylamino-3-O-[(methylthio)thiocarbonyl]-α-D-glucopyranoside ***(5)***. To a solution of **1** (365 mg) in tetrahydrofuran (4.0 ml), 50% oily sodium hydride (net wt 55 mg) and imidazole (2 mg) were added and the mixture stirred for 30 min at room temperature. Carbon disulfide (0.50 ml) was added and the reaction mixture stirred for 1 h, then methyl iodide (0.12 ml) was added and stirring continued for further 30 min. After the addition of acetic acid (1.0 ml), the mixture was poured into a mixture of ice-water and chloroform and stirred vigorously. The chloroform solution was successively washed with a 5% potassium hydrogensulfate solution, sodium hydrogencarbonate solution, and water, dried (sodium sulfate) and concentrated. The residue was chromatographed with chloroform–ethyl acetate (5: 1) to give a pale-yellow syrup, which was dissolved in hexane and concentrated to give a solid, 373 mg (80%), $[\alpha]_D^{25}$ +48° (*c* 1, chloroform): UV (ethanol): λ_{max} 281 nm (log ε 4.00), 227 (3.78), 203 (3.85): PMR ($CDCl_3$): δ 2.60 (3H s, CH_3S), 4.77 (1H d, J=3.5 Hz, H-1), 6.15 (1H t, J=9 Hz, H-3).

Found: C, 48.69; H, 6.27; N, 3.23; S, 15.49%. Calcd for $C_{17}H_{27}NO_7S_2$: C, 48.44; H, 6.46; N, 3.32; S, 15.21%.

Methyl 4,6-O-Cyclohexylidene-2-deoxy-3-O-[(1-imidazolyl)thiocarbonyl]-2-methoxycarbonylamino-α-D-glucopyranoside ***(6)***. To a solution of **1** (457 mg, 1.38 mmol) in tetrahydrofuran (5 ml), *N,N'*-thiocarbonyldiimidazole[13] (490 mg, 2.75 mmol) was added and the mixture refluxed for 4.5 h under an atmosphere of nitrogen. After the addition of chloroform (30 ml), the organic solution was washed successively with 5% potassium hydrogensulfate solution, sodium hydrogencarbonate solution, and water, dried (sodium sulfate) and concentrated to give a solid. Recrystallization from benzene–hexane gave needles, 499 mg (82%); mp 172—173 °C, $[\alpha]_D^{25}$ +62° (*c* 1, chloroform); UV (ethanol): λ_{max} 276 nm (log ε 4.08), 219 (3.70), 201 (3.70); PMR ($CDCl_3$): δ 3.46 (3H s, CH_3O), 3.61 (3H s, CH_3OCO), 4.78 (1H d, J=4 Hz, H-1), 5.10 (1H d, J=10 Hz, NH; disappeared on deuteration), 6.00 (1H t, J=10Hz, H-3); 7.09, 7.69, and 8.41 (each 1H s, imidazolyl).

Found: C, 51.95; H, 6.22; N, 9.48; S, 7.37%. Calcd for $C_{19}H_{27}N_3O_7S$: C, 51.69; H, 6.17; N, 9.52; S, 7.26%.

Methyl 4,6-O-Cyclohexylidene-2-deoxy-2-methoxycarbonylamino-3-O-phenyl(thiocarbonyl)-α-D-glucopyranoside ***(7)***. A mixture of carboxymethyl dithiobenzoate[14] (157 mg) and 50% oily sodium hydride (net wt 36 mg) in tetrahydrofuran (20 ml) was stirred at room temperature for 5 min. Imidazole (101 mg) was added and the mixture refluxed for 5 min. Compound **1** (245 mg) dissolved in tetrahydrofuran (3 ml) was added and the mixture refluxed for a further 5 min. The reaction mixture was poured into a mixture of ice–water and chloroform and vigorously stirred. The separated organic layer was treated similarly as described for **5** to give a syrup. Chromatography with chloroform–ethyl acetate (10: 1) gave a pale–yellow solid of **7**, 200 mg (60%). Recrystallization from hexane gave yellow needles; mp 129—131 °C, $[\alpha]_D^{25}$ +48° (*c* 1, chloroform): UV (ethanol): λ_{max} 292 nm (log ε 4.00), 253 (3.90), 217 (3.90), 202 (4.04); PMR ($CDCl_3$): δ 3.48 (3H s), 3.57 (3H s), 4.80 (1H d, J=4 Hz, H-1), 5.15 (1H d, J=8 Hz, NH), 6.35 (1H t, J=9 Hz, H-3), 7.4—8.3 (5H).

Found: C, 58.32; H, 6.35; N, 2.86; S, 6.82%. Calcd for $C_{22}H_{29}NO_7S$: C, 58.52; H, 6.47; N, 3.10; S, 7.10%.

Methyl 4,6-O-Cyclohexylidene-2-deoxy-3-O-dimethylsulfamoyl-2-methoxycarbonylamino-α-D-glucopyranoside[10] ***(8)***. Mp 136—137 °C (recrystallized from hexane), $[\alpha]_D^{25}$ +51° (*c* 1, chloroform).

Methyl 4,6-O-Cyclohexylidene-2-deoxy-3-O-methylsulfonyl-2-methoxycarbonylamino-α-D-glucopyranoside ***(9)***. Prepared in the usual manner from **1** with methanesulfonyl chloride and pyridine; mp 147.5—148.5 °C (hexane), $[\alpha]_D^{25}$ +70° (*c* 1, chloroform); UV (ethanol): λ_{max} 223 nm (ε 160), 200 (200); PMR ($CDCl_3$): δ 3.10 (3H s, Ms), 3.42 (3H s), 3.74 (3H s), 4.66 (1H t, H-3), 4.78 (1H d, H-1).

Found: C, 47.07; H, 6.50; N, 3.43; S, 7.68%. Calcd for $C_{16}H_{27}NO_9S$: C, 46.93; H, 6.65; N, 3.42; S, 7.83%.

Methyl 4,6-O-Cyclohexylidene-2-deoxy-2-methoxycarbonylamino-3-O-tosyl-α-D-glucopyranoside ***(10)***. Prepared in the standard manner from **1** with tosyl chloride and pyridine to give a solid, $[\alpha]_D^{25}$ +44° (*c* 1, chloroform); UV (ethanol): λ_{max} 223 nm (log ε 4.00), 199 (3.88); PMR ($CDCl_3$): δ 2.44 (3H s, CH_3 of Ts), 3.41 (3H s), 3.69 (3H s), 4.72 (1H d, H-1), 4.75 (1H t, H-3).

Found: C, 54.70; H, 6.53; N, 2.67; S, 6.70%. Calcd for $C_{22}H_{31}NO_9S$: C, 54.42; H, 6.44; N, 2.89; S, 6.60%.

Methyl 3-O-Benzyl-4,6-O-cyclohexylidene-2-deoxy-2-methoxycarbonylamino-α-D-glucopyranoside ***(11)***. To a solution of **1** (121 mg) in tetrahydrofuran (3 ml), 50% oily sodium hydride (net wt 17 mg) and imidazole (1 mg) were added and the mixture stirred for 15 min in an ice bath. α-Bromotoluene

(0.065 ml) was added and the mixture stirred at room temperature for 47 h. After the addition of methanol (0.2 ml), the mixture was poured into water containing sodium chloride and the mixture extracted with ethyl acetate. Concentration of the extracts gave a residue which was chromatographed on a column of silica gel with benzene–ethyl acetate (10: 1) to give **11** (59 mg, 38%), which was identical with the product obtained by photochemical reaction of **7** in all respects. Changing the eluent to ethyl acetate gave recovered **1** (48 mg, 40%).

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