agents useful in asymmetric synthesis reactions employing organometallic reagents. The chemistry of these systems is under active investigation and will be reported on in due course.

Experimental Section

General Methods. VPC analyses were made on a Varian Aerograph Series 200 gas chromatograph equipped with a thermal-conductivity detector and a 3.3-m, 10% KOH–10% Carbowax 20M on 60/80-mesh Chromosorb W column. Optical rotations were determined on a Perkin-Elmer Model 141 polarimeter using a 1-dm jacketed cell. *d*- and *l*-tartaric acids were J. T. Baker reagent grade and were used as received. Amine product recovery by continuous extraction was conducted under a nitrogen atmosphere.

General Procedure for the Separation/Optical Resolution of *trans*-1,2-Diaminocyclohexane (*trans*-1; Run 1). A 59.0-g portion of an amine mixture having a composition of about 28% *trans*-1, 31% 2-(aminomethyl)cyclopentylamine, and 41% 1,6-hexanediamine by VPC analysis was dissolved in 177 mL of water. To stirred solution was added 22.2 g (147.7 mmol) of *d*-tartaric acid which corresponds to the amount of *trans*-1 present in the amine mixture. To the solution was then added 42 mL (731 mmol) of glacial acetic acid, and the temperature of the reaction mixture increased to 60 °C. A few crystals of (*R,R*)-(−)-*trans*-1·*d*-tartrate were added to the hot reaction mixture, and it was allowed to cool to ambient temperature over a 4-h period. A crop of white crystals separated which was recovered by filtration and dried (11.2 g). The crystals were transferred to a liquid–liquid extractor, excess 20% NaOH solution was added to liberate *trans*-1 from the tartrate salt, and the mixture was continuously extracted with benzene for 5 h. The benzene extract was evaporated under vacuum, leaving a solid crude product which was optically active (*R,R*)-(−)-*trans*-1. The crude product displayed $[\alpha]^{25}_{589}$ −36.0° (*c* 5.0, benzene) which corresponds to 86% optical purity. The weight of the crude product (4.48 g) corresponds to a 46% optical yield based on the amount of (*R,R*)-(−)-*trans*-1 isomer contained in the starting amine mixture and with correction of the product optical purity to 100%.

Runs 2–13 were done in the same manner with the following exceptions. The reaction mixture in run 2 was cooled to 2 °C. Run 6 deposited no tartrate salt upon cooling of the mixture to 2 °C. Therefore, it was concentrated on a vacuum rotary evaporator until solid deposited, this was heated to 80 °C, and enough H_2O was added to redissolve all solids while hot (total solution weight 9.17 g) and the mixture was finally allowed to cool to ambient temperature. Run 13 employed *l*-tartaric acid. Table I records the quantities of all reagents used in the various experiments.

Acknowledgment. The author thanks Mr. William J. Mykytka for his excellent technical assistance and Dr. Arthur W. Langer, Jr., for stimulating discussions on some aspects of this work.

Registry No. (±)-*trans*-1, 41013-43-8; (*R,R*)-(−)-*trans*-1, 20439-47-8; (*R,R*)-(−)-*trans*-1 *d*-tartaric acid salt, 39961-95-0; (*S,S*)-(+)-*trans*-1, 21436-03-3; (*S,S*)-(+)-*trans*-1 *l*-tartaric acid salt, 67333-70-4; *d*-tartaric acid, 8769-4; *l*-tartaric acid, 147-71-7; *cis*-2-(aminomethyl)cyclopentylamine, 74684-84-7; *trans*-2-(aminomethyl)cyclopentylamine, 74684-85-8; 1,6-hexanediamine, 124-09-4.

Synthesis and Properties of Unsymmetrical Aryl Glucosyl Disulfides: Models for a New Class of Cleavable Nonionic Detergents

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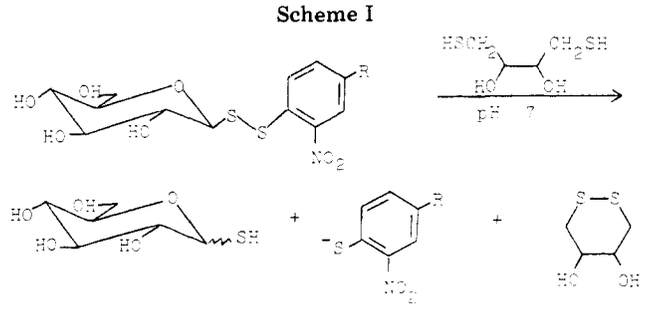
The purpose of this study was the synthesis and evaluation of the first members of a new series of unsymmetrical aryl glucosyl disulfides. Such cleavable molecules are potentially useful as solubilizing agents for membrane proteins. Unsymmetrical disulfides **6a–d** were prepared as follows. The corresponding phenol was converted into the *N,N*-dimethylcarbamothioic acid ester (e.g., **2a**) which was rearranged thermally to the thioester (e.g., **3a**). Hydrolysis gave the corresponding thiophenol (e.g., **4a**) which was then converted into the sulfenyl chloride (e.g., **5a**) by treatment with SO_2Cl_2. The key step was reaction of the sulfenyl chloride with β-D-thioglucose sodium salt in dry acetonitrile in the presence of 15-crown-5 to give the desired unsymmetrical disulfides (e.g., **6a**). Cleavage of **6c** at 25 °C (pH 7–9) with dithioerythritol was rapid and quantitative, as determined by UV–visible spectroscopy. However, these particular unsymmetrical disulfides have the limitation of low water solubility. Other unsymmetrical disulfides with larger polar headgroups should improve the water solubility, and these are under investigation.

The isolation, purification, characterization, and reconstitution of integral membrane proteins[1] such as cytochrome oxidase[2,3] and Na,K-ATPase[4,5] is currently an area of intensive biochemical investigation. Detergents[5-7] are necessarily used in the isolation and purification of membrane proteins. Reconstitution of the purified proteins into a controlled lipid environment involves the replacement of the solubilizing detergent molecules by phospholipids, for example.[8] Sometimes it is very difficult to remove the

Scheme I



(1) Singer, S. J. In "Structure and Function of Biological Membranes"; Rothfield, L., Ed.; Academic Press: New York, 1971; Chapter 4.
(2) Decuyper, M.; Joniau, M., *Eur. J. Biochem.* **1980**, *104*, 397–405.
(3) Yu, C.-A.; Yu, L.; King, T. E. *J. Biol. Chem.* **1975**, *250*, 1383–1392.
(4) Dahl, J. L.; Hokin, L. E. *Annu. Rev. Biochem.* **1974**, *43*, 327–356.
(5) Brotherus, J. R.; Jost, P. C.; Griffith, O. H.; Hokin, L. E. *Biochemistry* **1979**, *18*, 5043–5050.
(6) Helenius, A.; Simons, K. *Biochim. Biophys. Acta* **1975**, *415*, 29–79.
(7) Tanford, C.; Reynolds, J. A. *Biochim. Biophys. Acta* **1976**, *457*, 133–170.

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Table I. Ultraviolet Spectra Associated with Studies of the Cleavage of Mixed Disulfide 6c by Dithioerythritol (DTE)

substr	solvent	λ_{max}, nm (log ϵ)
4c	95/5 EtOH/H_2O	363 (3.52), 265 (4.12)
4c	95/5 EtOH/6.6 M NaOH	419 (3.19), 264 (4.24)
4c	pH 8.8 buffer[a]	419 (3.20),[b] 259 (4.24)[c]
4c	20/80 EtOH/pH 7.0 buffer[d]	423 (3.20), 258 (4.23)
6c	95/5 EtOH/H_2O	366 (3.53), 235 (4.16)
6c	pH 8.8 buffer[a]	365 (3.55),[b] 230 (4.11)[c]
6c	20/80 EtOH/pH 7.0 buffer[d]	368 (3.53), 232 (4.02)
6c + DTE	95/5 EtOH/H_2O	366 (3.53),[e] 235 (4.16)[f]
6c + DTE	95/5 EtOH/H_2O plus trace of NaOH	423 (3.18),[e] 264 (4.24)[f]
6c + DTE	pH 8.8 buffer[a]	417 (3.17),[b,e] 259 (4.23)[c,f]
6c + DTE	20/80 EtOH/pH 7.0 buffer[d]	424 (3.18),[e] 262 (4.24)[f]

[a] 12.5 mM borate buffer. [b] Because 4c and 6c were introduced into the buffer as stock solutions in 95% ethanol, the buffer solution consists of ~3% ethanol (v/v). [c] The buffer solution consists of ~0.3% ethanol (v/v) (see note b). [d] 50 mM phosphate buffer. [e] $[DTE]_{final}$ = 1.3 mM; $[6c]_{final}$ = 0.35 mM. [f] $[DTE]_{final}$ = 0.16 mM; $[6c]_{final}$ = 0.041 mM.

detergent molecules completely, owing to tight binding to sites on the protein.[6]

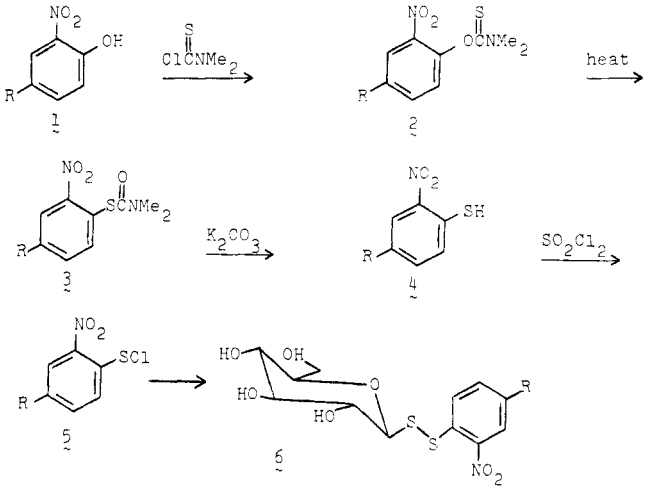
As an approach to the solution of this problem we envisaged the synthesis of a new class of cleavable detergents that could be selectively chemically modified into easily removable fragments after protein solubilization. It is not yet possible to predict with a high degree of certainty whether or not some randomly chosen amphipathic molecule will be a useful, biologically compatible detergent. Thus, our target molecules **6a–d** have structures similar to that of the superior membrane protein detergent *n*-octyl-β-D-glucoside,[9-11] while also incorporating a disulfide linkage (see Scheme I). This serves as a site for chemical cleavage by mild protein-compatible reducing agents such as dithioerythritol (DTE). The thioglucose and 4-alkyl-2-nitrothiophenol ($pK_a \approx 5$[12]) produced in the cleavage reaction should be readily removed by dialysis, for example. The chromophoric alkylnitrophenol group may also prove useful in monitoring removal of the detergent and cleavage by UV-visible spectroscopy.

Results and Discussion

The synthesis of unsymmetrical disulfides **6a–c** is outlined in Scheme II. The procedure of Newman and Karnes[13] was used for the conversion of 4-alkyl-2-nitrophenols **1a–c** into the corresponding 4-alkyl-2-nitrothiophenols **4a–c** by way of intermediates **2a–c** and **3a–c**. For example, 4-*tert*-octyl-2-nitrophenol (**1a**) was treated with sodium hydride in *N*,*N*-dimethylformamide (DMF) followed by dimethylthiocarbamoyl chloride, producing *O*-aryl thiocarbamate **2a** in 48% yield. This substance was then rearranged thermally (190 °C) to give the *S*-aryl thiocarbamate **3a** in nearly quantitative yield. Hydrolysis of **3a** with hot aqueous methanolic potassium carbonate for 30 min led to 4-*tert*-octyl-2-nitrothiophenol (**4a**) in 79% yield (~90% based on recovered **3a**). Longer reaction times or use of stronger bases gave lower yields of **4a**, accompanied by several unidentified side products.

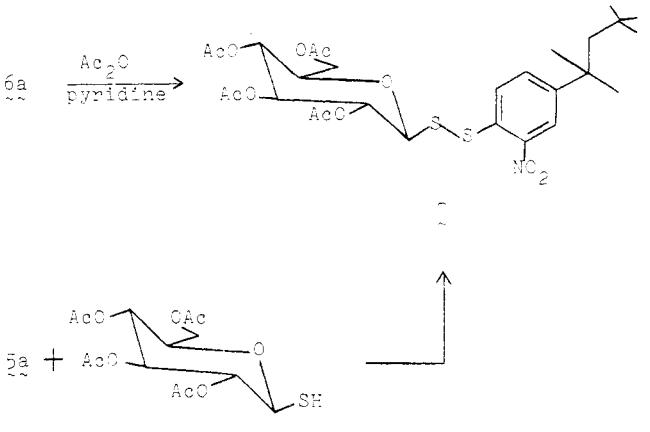
Of the many methods available for the synthesis of unsymmetrical disulfides,[14] we chose to utilize the reaction

Scheme II



[a] a, R = *tert*-octyl; b, R = *tert*-butyl; c, R = *sec*-butyl; d, R = H.

Scheme III



between a sulfenyl chloride and a thiol salt[15] for construction of the requisite disulfide linkage in **6**. Thus, the thiophenols **4** were converted quantitatively into the corresponding arylsulfenyl chlorides **5** by reaction with SO_2Cl_2 in chloroform. The sulfenyl chlorides were then coupled to β-D-thioglucose sodium salt in dry acetonitrile in the presence of 15-crown-5. The coupling reaction did not proceed in the absence of the crown ether, likely owing to the low solubility of the sodium salt in acetonitrile. Unoptimized yields of yellow crystalline unsymmetrical

(8) See for example: Korenbrot, J. I. *Ann. Rev. Physiol.* **1977**, *39*, 19–49. Petri, W. A., Jr.; Wagner, R. R. *J. Biol. Chem.* **1979**, *254*, 4313–4316.
(9) Keana, J. F. W.; Roman, R. B., *J. Membr. Biochem.* **1978**, *1*, 323–327.
(10) Baron, C.; Thompson, T. E. *Biochim. Biophys. Acta* **1975**, *382*, 276–285.
(11) Stubbs, G. W.; Smith, H. G., Jr.; Litman, B. J. *Biochim. Biophys. Acta* **1976**, *426*, 46–56.
(12) Bordwell, F. G.; Andersen, H. M. *J. Am. Chem. Soc.* **1953**, *75*, 6019–6022.
(13) Newman, M. S.; Karnes, H. A. *J. Org. Chem.* **1966**, *31*, 3980–3984.
(14) See, for example: Oae, S.; Kim, Y. H.; Fukushima, D.; Takata, T. *Chem. Lett.* **1977**, 893–896; Mattes, K. C.; Chapman, O. L.; Klun, J. A. *J. Org. Chem.* **1977**, *42*, 1814–1815.
(15) See, for example: Endo, T.; Tasai, H.; Ishigami, T. *Chem. Lett.* **1975**, 813–814.

disulfides **6a–c**[16] after chromatographic purification were, respectively, 54%, 43%, and 67%. By this same procedure commercially available 2-nitrobenzenesulfenyl chloride afforded disulfide **6d** in 60% yield.

The unsymmetrical disulfide structure assignment was confirmed in the case of **6a** as follows. Acetylation of **6a** with acetic anhydride in pyridine gave tetraacetate **7** (mp 130.5–131.5 °C) in 62% yield (Scheme III). This same material was also prepared (72% yield) by treatment of sulfenyl chloride **5a** with β-D-thioglucose tetraacetate in acetone in the presence of potassium carbonate.

The ease of cleavage of the disulfide linkage in **6a–d** under physiologically compatible conditions was investigated by ultraviolet spectroscopy using **6c** as a representative of the series. Whereas **6c** was unreactive toward DTE in 95% ethanol, addition of a trace of NaOH resulted in immediate conversion to the thiophenoxide anion (Table I). More significantly, addition of DTE to a solution of **6c** in either pH 8.8 buffer or in a 20/80 mixture of ethanol and pH 7.0 buffer led to immediate and quantitative formation of the thiophenoxide anion. When the ethanol was omitted in the pH 7.0 experiment, the observed maximum was 410 nm. This was likely due to the formation of insoluble aggregates of **4c** and its anion since addition of base caused a slow return to the ~420-nm maximum. Also, when a solution of the thiophenoxide anion in pH 9 buffer was acidified to pH 6.5, the mixture became cloudy. Thus, operationally, the cleavage reaction is best conducted in solutions with pH ~8.8.

In conclusion, our results establish the concept of a chemically cleavable detergent. The disulfide linkage is a satisfactory cleavage site for such a molecule and the alkylnitrothiophenol moiety is a useful reporter group for the cleavage process. Models **6a–d** are all yellow, nicely crystalline substances which are stable toward storage at 25 °C for several months. The chief limitation of the applicability of these particular unsymmetrical disulfides is their low water solubility (**6a**, 0.16 g/L; **6c**, 0.36 g/L).[17] Unsymmetrical disulfides with larger polar headgroups are expected to overcome the solubility limitation. The synthesis and properties of such molecules are under active investigation.

Experimental Section[18]

***O*-4-*tert*-Octyl-2-nitrophenyl Dimethylcarbamothioate (2a).** By use of a modification of Newman's procedure,[13] a suspension of NaH (0.391 g, 16.3 mmol) in dry DMF (20 mL) was stirred at 0 °C while a DMF (10 mL) solution of 4-*tert*-octyl-2-nitrophenol[19] (3.464 g, 13.8 mmol) was added dropwise over 1 h. Next, dimethylthiocarbamoyl chloride (Aldrich) (2.312 g, 18.7 mmol) in DMF (10 mL) was slowly added to the ice-cold, red phenoxide solution. After 4 h at 25 °C, ice–water (50 mL) was added, and the mixture was extracted with ether. The extract was washed with water, 5% aqueous NaOH (unreacted starting material may be recovered from this wash by acidification) aqueous HCl, and brine and was dried ($MgSO_4$), and the solvent was removed, yielding an orange oil which crystallized on being allowed to stand. Recrystallization from MeOH–water gave 2.239 g (48%) of **2a** as pale yellow prisms: mp 87.5–88.5 °C; NMR δ 0.74 (s, 9 H), 1.38 (s, 6 H), 1.78 (s, 2 H), 3.39 and 3.45 (2 s, 6 H), 7.16 (d, J = 4.5, 1 H), 7.67 (dd, J = 4.5, 1, 1 H), 8.09 (d, J = 4.5, 1 H). Anal. Calcd for $C_{17}H_{26}N_2O_3S$: C, 60.33; H, 7.74; N, 8.28. Found: C, 60.34; H, 7.78; N, 8.08.

***O*-4-*tert*-Butyl-2-nitrophenyl Dimethylcarbamothioate (2b).** The above procedure was applied to 4-*tert*-butyl-2-nitrophenol (Aldrich, 997 mg), affording 970 mg (67%) of **2b** as a yellow oil which was used directly in the next step: NMR δ 1.36 (s, 9 H), 3.38 and 3.46 (2 s, 6 H), 7.16 (d, J = 4.5, 1 H), 7.67 (dd, J = 4.5, 1, 1 H), 8.08 (d, J = 1, 1 H).

***O*-4-*sec*-Butyl-2-nitrophenyl Dimethylcarbamothioate (2c).** The above procedure was applied to 4-*sec*-butyl-2-nitrophenol (Aldrich, 260 mg), affording 305 mg (81%) of **2c** as a yellow oil which was used directly in the next step: NMR δ 0.84 (t, J = 3.5, 3 H), 1.27 (d, J = 3.5, 3 H), 1.64 (pentet, J = 3.5, 2 H), 2.73 (sextet, J = 3.5, 1 H), 3.39 and 3.46 (2 s, 6 H), 7.17 (d, J = 4.5, 1 H), 7.47 (dd, J = 4.5, 1, 1 H), 7.90 (d, J = 1, 1 H).

***S*-4-*tert*-Octyl-2-nitrophenyl Dimethylcarbamothioate (3a).** Thermolysis[13] of **2a** (1.368 g, 4.05 mmol) for at least 1 h gave a viscous brown oil which was purified by passage of a $CHCl_3$ solution over silica gel. There was obtained 1.341 g (98%) of **3a** as a light brown oil which was used directly in the next step: NMR δ 0.75 (s, 9 H), 1.40 (s, 6 H), 1.77 (s, 2 H), 3.05 (s, 6 H), 7.25 (s, 1 H), 7.58 (s, 1 H), 7.92 (s, 1 H).

***S*-4-*tert*-Butyl-2-nitrophenyl Dimethylcarbamothioate (3b).** Heating **2b** as above gave **3b** as a brown oil: NMR δ 1.34 (s, 9 H), 3.06 (s, 6 H), 7.60 (s, 2 H), 7.93 (s, 1 H).

***S*-4-*sec*-Butyl-2-nitrophenyl Dimethylcarbamothioate (3c).** Heating **2c** as above gave **3c** as a brown oil: NMR δ 0.81 (t, J = 3.5, 3 H), 1.20 (d, J = 3.5, 3 H), 1.58 (pentet, J = 3.5, 2 H), 2.67 (sextet, J = 3.5, 1 H), 3.04 (s, 6 H), 7.38 (dd, J = 4, 1, 1 H), 7.69 (d, J = 4, 1 H), 7.71 (d, J = 1, 1 H).

4-*tert*-Octyl-2-nitrothiophenol (4a). A MeOH (30 mL) solution of **3a** (1.368 g, 4.05 mmol), K_2CO_3 (1.115 g, 8.08 mmol), and water (7 mL) was heated at reflux for 30 min, cooled, diluted with 80 mL of 2.5% aqueous HCl, and extracted with ether. The ether was extracted with 5% aqueous NaOH (unreacted starting material remains in the ether). The aqueous extract was acidified and extracted with ether, and the ether was washed with water, aqueous HCl, water, and brine, dried ($MgSO_4$), and concentrated to give a yellow oil which crystallized on being allowed to stand. Yellow prisms of **4a** (0.854 g, 79%) were obtained by sublimation [50 °C (0.01 torr)]: mp 57.5–58.5 °C; NMR δ 0.72 (s, 9 H), 1.38 (s, 6 H), 1.76 (s, 2 H), 3.98 (s, 1 H), 7.31 (d, J = 4, 1 H), 7.96 (dd, J = 4, 1, 1 H), 8.22 (d, J = 1, 1 H). Anal. Calcd for $C_{14}H_{21}NO_2S$: C, 62.89; H, 7.92; N, 5.24. Found: C, 62.77; H, 7.68; N, 5.57.

4-*tert*-Butyl-2-nitrothiophenol (4b). With the above procedure, **3b** (880 mg) gave **4b** (521 mg, 79%) as a yellow oil which was sufficiently pure to be used directly in the next step: NMR δ 1.34 (s, 9 H), 3.8–4.1 (br s, 1 H), 7.62 (dd, J = 4, 1, 1 H), 7.8 (d, J = 4, 1 H), 8.31 (d, J = 1, 1 H).

4-*sec*-Butyl-2-nitrothiophenol (4c). With the above procedure, **3c** (730 mg) gave **4c** (303 mg, 55%) as a pale yellow oil: bp 120 °C (0.04 torr); NMR δ 0.70 (t, J = 3, 3 H), 1.15 (d, J = 3, 3 H), 1.49 (pentet, J = 3, 2 H), 2.52 (sextet, J = 3, 1 H), 3.92 (s, 1 H), 7.15 (dd, J = 4, 1, 1 H), 7.29 (d, J = 4, 1 H), 7.94 (d, J = 1, 1 H). Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63. Found: C, 56.91; H, 6.29; N, 6.46.

4-*tert*-Octyl-2-nitrobenzenesulfenyl Chloride (5a). Reaction of **4a** (1.338 g, 5.01 mmol) and SO_2Cl_2 (1.364 g, 10.1 mmol) in $CHCl_3$ (20 mL) at 25 °C for 1 h gave **5a** (1.510 g, 99%) as a brown oil which was sufficiently pure to be used directly in the next step after removal of solvent: NMR δ 0.78 (s, 9 H), 1.45 (s, 6 H), 1.86 (s, 2 H), 7.7–8.0 (m, 2 H), 8.29 (d, J = 1, 1 H).

4-*tert*-Butyl-2-nitrobenzenesulfenyl Chloride (5b). With the above procedure **4b** (61 mg) afforded crude **5b** (70 mg, 99%)

(16) The coupling reaction is assumed to proceed without inversion at the anomeric carbon atom since alkylation, for example, of β-D-thioglucose with ethyl iodide produces the β-anomer; see: Schneider, W.; Gille, R.; Eisfeld, K. *Chem. Ber.* **1928**, *61*, 1244–1259. Confirmation of the β assignments for **6a–d** and **7** by 100-MHz spectroscopy (see: Kotowycz, G.; Lemieux, R. U. *Chem. Rev.* **1973**, *73*, 669–698) was hampered by the overlap of signals in the region of the H-1 absorption.

(17) It is possible or even likely that accessible protein SH groups, if present, may react with the disulfide linkage of the detergent to form protein–S–S–sugar linkages. Solubilization of the protein may in fact be aided by this reaction. Moreover, the linkage should undergo reversible cleavage back to the protein SH group upon treatment with DTE during the detergent-cleavage step.

(18) Melting points were obtained in a Thomas-Hoover apparatus and are uncorrected. NMR spectra were recorded on a Varian XL-100 spectrometer in $CDCl_3$ unless otherwise stated. Chemical shifts are expressed in δ units with Me_4Si as an internal standard. J values are in hertz. UV and visible spectra were measured on a Cary 15 spectrophotometer. Elemental analyses were determined at the University of Oregon by Dr. R. Wielesek. All reactions were run under a N_2 atmosphere. Solvents were routinely distilled.

(19) Nikolenko, L. N.; Karpova, E. N.; Vorozhtsov, G. N.; Sergeev, V. A.; Ivanova, M. E. *Zh. Obshch. Khim.* **1960**, *30*, 1336–1339; *Chem. Abstr.* **1961**, *55*, 426*b*.

as a dark gel suitable for the next step: NMR δ 1.38 (s, 9 H), 7.7–8.0 (m, 2 H), 8.30 (d, J = 1, 1 H).

4-*sec*-Butyl-2-nitrobenzenesulfenyl Chloride (5c). With the above procedure, **4c** (1.058 g) afforded crude **5c** (1.201 g, 98%) as a brown oil suitable for the next step: NMR δ 0.82 (t, J = 3, 3 H), 1.30 (d, J = 3, 3 H), 1.66 (pentet, J = 3, 2 H), 2.79 (sextet, J = 3, 1 H), 7.62 (dd, J = 4, 1, 1 H), 7.90 (d, J = 4, 1 H), 8.14 (d, J = 1, 1 H).

β-D-Glucopyranosyl 4-*tert*-Octyl-2-nitrophenyl Disulfide (6a). A mixture of **5a** (1.510 g, 5.01 mmol), β-D-thioglucose sodium salt (1.113 g, 5.10 mmol; Sigma Co.), and 15-crown-5 (1.106 g, 5.02 mmol) in dry acetonitrile (15 mL) was stirred at 25 °C for 10 min. The solvent was removed, and the residue was triturated with $CHCl_3$ and filtered. Chromatography over silica gel afforded, first, the orange diaryl disulfide ($CHCl_3$), second, 15-crown-5 (2% MeOH/$CHCl_3$), third, a brown unidentified oil (4% MeOH, $CHCl_3$), and finally disulfide **6a** (5% MeOH, $CHCl_3$), which crystallized upon removal of solvent. Recrystallization from ethyl acetate/hexane gave 1.233 g (54%) of **6a** as yellow crystals: mp 131–133 °C; NMR (acetone-d_6) δ 0.75 (s, 9 H), 1.43 (s, 6 H), 1.86 (s, 2 H), 2.7–4.7 (m, 12 H), 7.90 (dd, J = 4.5, 1, 1 H), 8.23 (d, J = 1, 1 H), 8.54 (d, J = 4.5, 1 H). Anal. Calcd for $C_{20}H_{31}NO_7S_2 \cdot {}^1/_2H_2O$: C, 51.04; H, 6.85; N, 2.98. Found: C, 51.27; H, 6.46; N, 2.65. The water solubility was 0.16 g/L.

β-D-Glucopyranosyl 4-*tert*-Butyl-2-nitrophenyl Disulfide (6b). With the above procedure, **5b** (70 mg) afforded **6b** (48 mg, 43%): mp 161–162 °C (acetone); NMR (CD_3OD) δ 1.40 (s, 9 H), 3.2–3.9 (m, 10 H), 4.4–4.6 (m, 1 H), 7.84 (dd, J = 4.5, 1, 1 H), 8.22 (d, J = 1, 1 H), 8.53 (d, J = 4.5, 1 H). Anal. Calcd for $C_{16}H_{23}NO_7S_2$: C, 47.39; H, 5.72; N, 3.45. Found: C, 47.21; H, 5.56; N, 3.16.

β-D-Glucopyranosyl 4-*sec*-Butyl-2-nitrophenyl Disulfide (6c). With the above procedure, **5c** (1.201 g) afforded **6c** (1.339 g, 67%): mp 125–126 °C (acetone); NMR (acetone-d_6) δ 0.84 (t, J = 3.5, 3 H), 1.28 (d, J = 3.5, 3 H), 1.63 (pentet, J = 3.5, 2 H), 2.6–2.9 (m, 2 H), 3.2–3.9 (m, 6 H), 4.2–4.8 (m, 4 H), 7.69 (dd, J = 4.5, 1, 1 H), 8.02 (d, J = 1, 1 H), 8.51 (d, J = 4.5, 1 H). Anal. Calcd for $C_{16}H_{23}NO_7S_2$: C, 47.39; H, 5.72; N, 3.45. Found: C, 47.06; H, 5.66; N, 3.11. The water solubility was 0.36 g/L.

β-D-Glucopyranosyl 2-Nitrophenyl Disulfide (6d). With the above procedure, 2-nitrophenylsulfenyl chloride (113 mg, Aldrich) afforded **6d** (122 mg, 60%): mp 77–79 °C (acetone); NMR (acetone-d_6) δ 2.80 (s, 2 H), 3.2–3.8 (m, 7 H), 4.1–5.0 (m, 3 H), 7.3–7.8 (m, 2 H), 8.05–8.2 (m, 1 H), 8.5–8.65 (m, 1 H). Anal. Calcd for $C_{12}H_{15}NO_7S \cdot {}^2/_3(CH_3)_2CO$: C, 43.32; H, 4.93; N, 3.61. Found: C, 43.18; H, 4.65; N, 3.22.

Tetraacetyl-β-D-Glucopyranosyl 4-*tert*-Octyl-2-nitrophenyl Disulfide (7). Method A: A pyridine (5 mL) solution of **6a** (46.3 mg, 0.10 mmol) and acetic anhydride (170 mg, 1.7 mmol) was stirred at 25 °C for 1 h, and the solvent was removed. Recrystallization of the residue from ethyl acetate/hexane gave 39.1 mg (62%) of **7** as yellow crystals: mp 131.5 °C; NMR δ 0.69 (s, 9 H), 1.32 (s, 6 H), 1.81 (s, 2 H), 1.92, 1.98, and 2.06 (all s, 12 H), 3.45–3.7 (m, 1 H), 3.9–4.0 (m, 2 H), 4.5–5.2 (m, 4 H), 7.58 (dd, J = 4.5, 1, 1 H), 8.05–8.25 (m, 2 H). Anal. Calcd for $C_{28}H_{39}NO_{11}S_2$: C, 53.40; H, 6.24; N, 2.22. Found: C, 53.65; H, 6.10; N, 1.93.

Method B: A mixture of **5a** (45.5 mg, 0.151 mmol), β-D-thioglucose tetraacetate (55.2 mg, 0.152 mmol), and K_2CO_3 (70.9 mg, 0.525 mmol) in acetone (4 mL) was stirred at 25 °C for 50 min. Filtration followed by removal of solvent gave a yellow crystalline residue. Recrystallization from ethyl acetate/hexane gave 72.2 mg (72%) of **7** as yellow crystals, identical (melting point and NMR spectrum) with those obtained from method A (mmp 131–132 °C).

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Registry No. 1a, 46912-02-1; **1b**, 3279-07-0; **1c**, 3555-18-8; **2a**, 74752-31-1; **2b**, 74752-32-2; **2c**, 74752-33-3; **3a**, 74752-34-4; **3b**, 74752-35-5; **3c**, 74752-36-6; **4a**, 74752-37-7; **4b**, 74752-38-8; **4c**, 74752-39-9; **5a**, 74752-40-2; **5b**, 74752-41-3; **5c**, 74752-42-4; **6a**, 74752-43-5; **6b**, 74752-44-6; **6c**, 74752-45-7; **6d**, 74752-46-8; **7**, 19879-84-6; β-D-thioglucose sodium salt, 10593-29-0; dimethylthiocarbamoyl chloride, 16420-13-6.

A Novel Isothiocyanate Dimer

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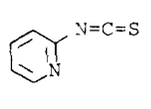
A novel type of formal isothiocyanate dimer, a 3-aryl-4-(arylimino)-1,3-thiazetidine-2-thione, has been isolated. The assignment of the structure **11** is based on physical chemical data, especially NMR and mass spectra, and is supported by an alternate synthesis.

Isothiocyanates are, in general, more stable and less reactive than isocyanates, and until 1960 no examples of dimers of isothiocyanates had been reported. At that time it was suggested[1] that the brick-red solid previously assumed[2] to be 2-pyridyl isothiocyanate (1) might be **2**. This



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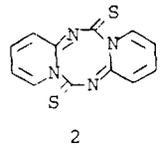

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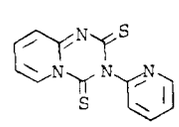

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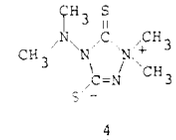
postulated structure was later shown[3,4] to be incorrect, and the correct structure for this dimer of **1** is in fact **3**. Similar dimers also involving atoms adjacent to the isothiocyanate group have been reported.[5-7] Another type of dimer involving adjacent atoms is the isolated[8] but unstable dimer, **4**, of (dimethylamino)isothiocyanate. Condensations of



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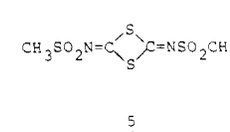

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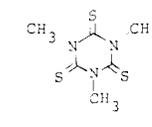

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(1) Howard, J. C.; Michels, J. G. *J. Org. Chem.* **1960**, *25*, 829–832.
(2) Fairfull, A. E. S.; Peak, D. A. *J. Chem. Soc.* **1955**, 796–802.
(3) Blatter, H. M.; Lukaszewski, H. *Tetrahedron Lett.* **1964**, 1087–1091.
(4) Nair, V.; Kim, K. H. *J. Heterocycl. Chem.* **1976**, *13*, 873–876.
(5) Goerdeler, J. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 693.
(6) Goerdeler, J.; Weber, D. *Chem. Ber.* **1968**, *101*, 3475–3490.
(7) Abraham, W.; Barnikow, G. *Tetrahedron* **1973**, *29*, 691–697.
(8) Anthoni, U.; Larsen, C.; Nielsen, P. H. *Acta Chem. Scand.* **1968**, *22*, 309–318.

0022-3263/80/1945-4219$01.00/0