Biologically Oriented Organic Sulfur Chemistry. 22. 2-(3-Chloropropyl)-5-chloropentanol as a Prototype for Synthesis of Functionalized Polysulfides and Prodrugs[1]

Gary T. Bowman and Lamar Field*

Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235

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A synthetic approach based on 2-(3-chloropropyl)-5-chloropentanol (5) is reported that permits synthesis of trisulfides containing either Cl or four other groups. The carbinol 5 was prepared by converting diethyl bis-(3-chloropropyl)malonate (2) with Me_3SiI to the malonic acid, which was decarboxylated (with some remediable lactonization to 6), followed by reduction. The carbinol 5 was converted via the triflate (11) to a thiosulfonate, which thioalkylated Na_2S to give a trisulfide containing four Cl atoms (7). Replacement of the four Cl atoms of the carbinol 5 with $PhCH_2S$ groups, followed by formation of the tosylate (14; the triflate polymerized) and then of the thiosulfonate (13), permitted synthesis of a tetrakis(benzylthio) trisulfide (12) that illustrates tetrafunctionalization. Several intermediates are potential progenitors of prodrugs, although an effort to use bis(quaternary ammonium salts) prepared from 5 in this way was unpromising owing (chiefly) to very sparing solubilities.

Di- and trisulfide sulfinates typified by structure 1 are

$$NaO_2SRS_nRSO_2Na$$
1

promising antiradiation agents that are significantly atypical in lacking nitrogen.[2] In order to delineate the structural requirements for radioprotective activity with such compounds, we have thus far increased n of S_n beyond 3[3] and have used ArS, ArS(O),[4] and S(O)OMe[5] in lieu of SO_2Na.

This paper reports a flexible synthetic approach that permits doubling the number of functional groups associated with the S_n linkage and should also permit introduction of a considerable variety of functional groups. Scheme I shows an application of this approach to synthesis of a tetrafunctionalized trisulfide (12), where $(CH_2)_3$ and $PhCH_2S$ respectively are prototypes for the chain and functional groups. Reference compounds exemplified by 7 will permit assessment of the radioprotective effect of the S_n linkage by itself, and compounds exemplified by 12 will permit assessment of the effect of introducing four other functions.

Lending another element of interest to Scheme I is the likelihood that several of the intermediates may be useful progenitors of prodrugs.[6] Examples of functional groups of drugs that might be modified by using various intermediates are OH (with 4), CO_2H (with 5, 10, 11, 15), SH (with 4, 8, 13), and NH (with 4). Nucleophilic displacement of Cl before or after the prodrug linkage is established should permit introducing a wide variety of functional groups into the prodrug. Furthermore, in view of the "high frequency of chemically symmetrical drugs",[7] advantages may accrue from the symmetry of such prodrugs.

Initially, entry into the approach of Scheme I was attempted with use of the butylene homologue of 2, i.e., with diethyl bis(4-chlorobutyl)malonate, sought by alkylating malonic ester with 4-chlorobutyl tosylate.[8] These efforts were thwarted by cyclization of the (chlorobutyl)malonate to diethyl cyclopentane-1,1-dicarboxylate (characterized by spectra, refractive index, and conversion to the known diacid). We therefore turned instead to the propyl homologue 2 as a prototype; 2 is conveniently available from alkylation of diethyl malonate with 1-bromo-3-chloropropane.[9]

In a procedure based on one of Jung and Lyster,[10] Me_3SiI smoothly converted the malonate 2 to the malonic acid 3 (83% yield); NMR monitoring of EtO to EtI showed the reaction of the malonate to be much slower than is typical of monocarboxylates. Saponification, acid-catalyzed hydrolysis, or transesterification[11] were unsatisfactory for converting 2 to 3 or 4, the less expensive reagent Me_3SiCl–NaI led chiefly to the bis(iodopropyl)malonate,[12] and attempted conversion of 2 to the monocarboxylate, for reduction to 5, by using Me_2SO–NaCl was unpromising (probably because of reaction of a chloroalkyl group with the intermediary carbanion presumably involved).[13]

Decarboxylation of the malonic acid 3 gave the monoacid 4 (52% yield). However, a considerable amount of product was insoluble when the 4 was extracted into aqueous bicarbonate for purification. NMR indicated this material to be the lactone and/or polymeric linear ester formed by loss of HCl (collectively termed 6); indeed, when 4 itself was heated at 150–170 °C for 9 h, NMR indicated about 29% conversion to 6. Extracting a solution of 6 with 5% aqueous KOH removed nearly all of the 6 (presumably saponifying it to the hydroxy acid salt, since acid regenerated 6); KOH therefore is not an alternative to $NaHCO_3$ for extracting 4. Fortunately, reaction of the bicarbonate-insoluble product with $SOCl_2$–$ZnCl_2$ and then H_2O converted it into 4 (63% yield). Borane–methyl

(1) (a) Paper 21: Heimer, N. E.; Field, L.; Neal, R. A. *J. Org. Chem.* **1981**, *46*, 1374. (b) The Ph.D. Dissertation of G.T.B., from which this paper is abstracted, can be consulted for further details (Vanderbilt University, Aug 1981).

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(10) Jung, M. E.; Lyster, M. A. *J. Am. Chem. Soc.* **1977**, *99*, 968.

(11) Loev, B. *Chem. Ind. (London)* **1964**, 193.

(12) (a) Morita, T.; Okamoto, Y.; Sakurai, H. *J. Chem. Soc., Chem. Commun.* **1978**, 874. (b) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.

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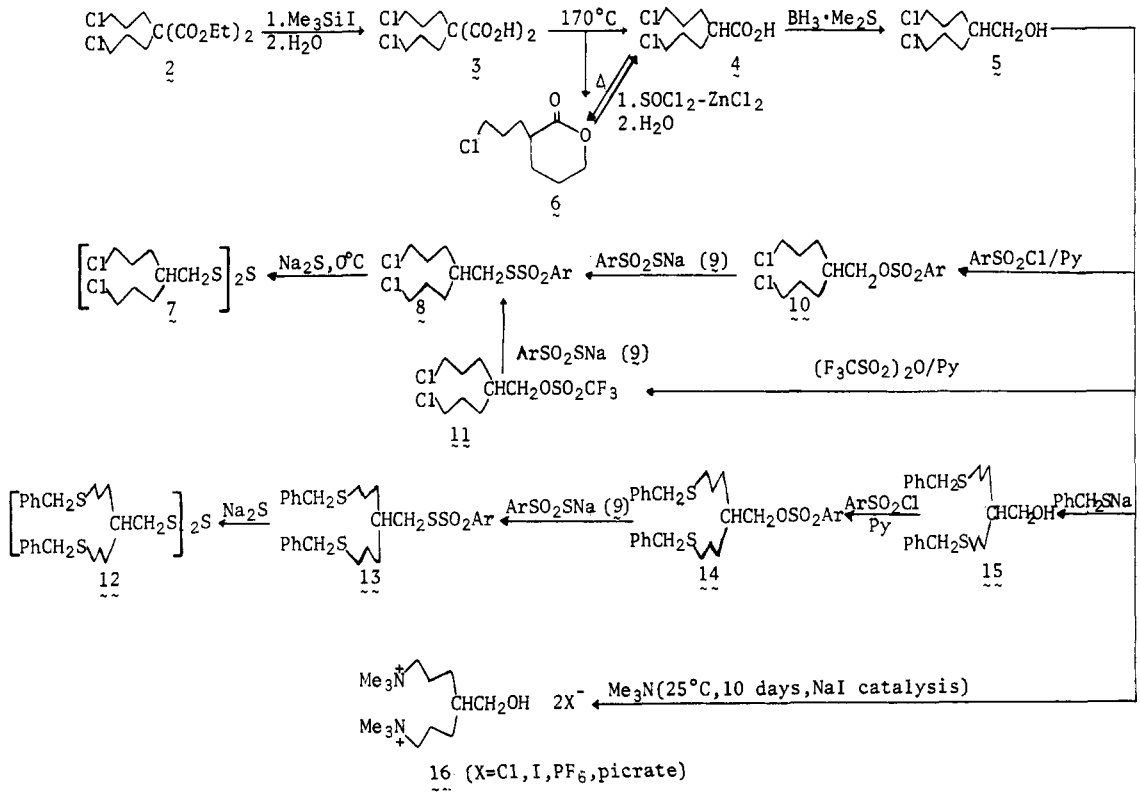
0022-3263/82/1947-0222$01.25/0

Scheme I[a]



[a] Ar = *p*-$CH_3C_6H_4$; Py = pyridine.

sulfide reduced the acid **4** to the carbinol **5**.

For the synthesis of the trisulfide **7**, the carbinol **5** first was converted to the tosylate **10** (tosyl chloride–pyridine). Efforts to obtain the thiosulfonate **8** by using the thiosulfonate **9** to replace the tosylate moiety of **10** evidently succeeded in large part, since reaction of **9** and **10** at 60 °C for 24 h in DMF gave a product estimated to contain 86% of thiosulfonate linkages by the method of Barnard and Cole.[14] However, NMR spectra indicated partial replacement of Cl, as well as of tosylate, and a variety of conditions failed to obviate this problem. The triflate **11** therefore was prepared. When the reaction of **11** was attempted with the thiosulfonate **9** in DMF, the **11** reacted exothermically with the DMF, and none of the thiosulfonate **8** could be isolated. In sulfolane on the other hand, the triflate **11** reacted rapidly with **9** at 25 °C, although the yield of **8** was only 26–30% (after chromatography), perhaps partly because of loss of elemental sulfur from **9** and formation of the sulfone counterpart of **8**. Sodium sulfide converted the thiosulfonate **8** to the nearly pure trisulfide **7** in 87–99% yield.

The preparation of a tetrafunctionalized trisulfide is illustrated by conversion of the dichlorocarbinol **5** to **12**. In the first step, alkylation of phenylmethanethiolate ion by **5** replaced both of the chlorine atoms of **5** with $PhCH_2S$ to give **15** (80% yield). In related preliminary work, Cl also was replaced by SH in good yield and practicable purity by alkylating sodium trithiocarbonate with **5** and acidifying the resulting trithiocarbonate, i.e., $[NaSCS_2(CH_2)_3]_2CHCH_2OH$, by a method based on one of Martin and Greco;[15] this supplement to Scheme I should permit synthesis of polysulfides (or other carbinol-derived products) containing a variety of functional groups of sulfur derived from the thiol moieties.

In the next step toward **12**, efforts to prepare the triflate of **15** analogously to **11** led to polymerization, presumably because of displacement of triflate by benzylthio moieties (the product had a molecular weight of ca. 1059 by vapor-pressure osmometry). Fortunately, the enhanced reactivity of the triflate necessitated by the competition of chlorine as a leaving group in the preparation of **8** was unnecessary. The tosylate **14** could be prepared in good yield and then converted to the thiosulfonate **13** (62% yield). The thiosulfonate **13** thioalkylated Na_2S to give **12** (87% yield).

Potentialities of intermediates in Scheme I as progenitors of prodrugs was mentioned above. Interest in penicillamine (**17**) in relation to diseases of collagen, especially

$Me_2C(SH)CH(NH_2)CO_2H$ (**17**) $\quad Me_3\overset{+}{N}(CH_2)_n\overset{+}{N}Me_3\ 2X^-$ (**18**)

rheumatoid arthritis,[16] prompted us to explore the use of the dichloro carbinol **5** for this purpose. Since anticholinergic blocking agents of structure **18** accumulate preferentially in cartilage,[17] linkage of **18**-related structures with **17** was attempted in seeking a prodrug of **17** that might localize in connective tissue and show fewer adverse effects than **17**.[18]

Reaction of **5** with trimethylamine gave **16** (X = Cl) as a hygroscopic solid (100% yield). This chloride was convertible to iodide or hexafluorophosphate salts (**16**, X = I or PF_6) but was best characterized as the picrate [**16**, X = $(NO_2)_3PhO$]. Since anticholinergic activities would preclude use of **16** for prodrugs, it was determined that **16**

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(15) Martin, D. J.; Greco, C. C. *J. Org. Chem.* **1968**, *33*, 1275.
(16) For leading citations, see ref 5.
(17) Asghar, K.; Roth, L. J. *Biochem. Pharmacol.* **1971**, *20*, 3151.
(18) For discussion of adverse effects of 17, see: Lyle, W. H. "Distamine D(−) Penicillamine—a Review"; Dista Products Ltd.: Liverpool, 1973; pp 22–28.

(X = Cl) does not possess significant anticholinergic or neuromuscular activities.[19]

Unfortunately, quaternary salts of structure **16** proved to be unpromising choices as prodrug progenitors, chiefly because of such sparing solubility in suitable solvents that conversions and purifications were unsatisfactory (for details, see ref 1b). For example, preparation of an unsymmetrical disulfide of **17** was frustrated by inability to convert **16** (X = Cl or PF_6) to the requisite tosylate or triflate. Preparation of a thiazolidine of **17** showed promise by spectra when **16** (X = PF_6) was oxidized to the aldehyde (Me_2SO–dicyclohexylcarbodiimide), followed by reaction with **17**; however, this product seemed too sparingly soluble (and potentially too toxic) for biological use, and use of this model route failed because of the sparing solubility of **16** (X = Cl) and formation of I_2 with **16** (X = I). Conversion of the carbinol **5** through the aldehyde to the bis(3-chloropropyl)methylthiazolidine of **17**, followed by quaternization with Me_3N, was defeated by reaction of a chloropropyl group with the NH of the thiazolidine ring. Acid-catalyzed interchange of **16** (X = Cl) with the methyl ester hydrochloride of **17** gave no indication of an ester of **17** when an ethylene dichloride medium was distilled during 23 h to remove MeOH.

Experimental Section

Melting points were determined by using a Thomas-Hoover stirred-liquid apparatus and are corrected. NMR spectra, reported in parts per million (δ), were obtained with a JEOLCO Model JNM-MH-100 spectrometer using Me_4Si as an internal standard (or in D_2O with $Me_3Si(CH_2)_3SO_3Na$). IR spectra were obtained by using Nujol mulls, neat liquids, or KBr pellets with a Perkin-Elmer 727 spectrometer. Elemental analyses were performed by Galbraith Laboratories. Moist extracts were dried by using Na_2SO_4 or $MgSO_4$, and the solvent then was removed under reduced pressure by using a rotary-flask evaporator. TLC was performed on Eastman Chromagram Catalog No. 13181 by using the solvents as stated, with visualization by UV or development by I_2 vapor. Brinkmann 7729 silica gel (<230 mesh) was used for column chromatography, and Whatman PLK5F plates (1000 μm) for preparative TLC. Sodium *p*-toluenethiosulfonate dihydrate (**9**) was prepared by modifying a method of Buckman:[20] sodium *p*-toluenesulfinate (30.1 g, stated to be the dihydrate, 140.5 mmol) and sulfur (4.50 g, 140.4 mmol) were stirred well in H_2O (120 mL)–EtOH (120 mL) for 4 days at 60 °C, unreacted sulfur was removed, and the solution was concentrated to a mush; addition of 2-propanol (100 mL) and chilling gave 17.6 g (51%) of **9**·$2H_2O$ (for preparative work the dihydrate was assumed, but an excess of **9** was desired in any event). All other materials were commercial products, except when otherwise specified.

Bis(3-chloropropyl)malonic Acid (3). Diethyl bis(3-chloropropyl)malonate (**2**) was prepared essentially as described (52% yield):[9] mp 50–51 °C (lit.[9] mp 51–52 °C); NMR (CCl_4) δ 4.02 (q, 4 H), 3.37 (t, 4 H), 2.06–1.42 (m, 8 H), 1.22 (t, 6 H). Trimethylsilyl iodide (30 mL, 42.18 g, 211 mmol; prepared as described[10] and then distilled onto and stored over Cu wire at −25 °C) was added in one portion via a syringe to a solution of **2** (20.0 g, 63.8 mmol) in CCl_4 (75 mL) under N_2; care must be taken to exclude Cu because it inhibits the reaction indefinitely. The reaction mixture then was heated with stirring at 50 °C. Additional Me_3SiI (20 mL, 28.12 g, 141 mmol) was added after 2 days. After 3 more days of stirring at 50 °C, the purple solution was cooled to ca. 25 °C and then was poured carefully into H_2O (100 mL). Et_2O was added, and the aqueous layer was extracted with additional Et_2O. The combined organic layers were washed with 5% aqueous $NaHSO_3$ to remove I_2 and then were extracted with saturated aqueous $NaHCO_3$. Acidification of the $NaHCO_3$ extract caused precipitation of the diacid **3** as a white solid: yield 13.7 g (83%); mp 155–157 °C dec. Recrystallization of this **3** three times from H_2O gave **3** of constant melting point: mp 156–157 °C dec; NMR (CD_3OD) δ 3.60 (t, 4 H), 2.22–1.54 (m, 8 H); IR (KBr) 3570–2270, 1700, 1445, 1410, 1390, 1320, 1290, 1270, 1260, 1220, 1190, 890, 770, 670, 645 cm^{-1}.

Anal. Calcd for $C_9H_{14}Cl_2O_4$: C, 42.04; H, 5.50; neutralization equivalent 129. Found: C, 41.91; H, 5.45; neutralization equivalent 131.

Similar results were obtained with a 6.3-fold increase in scale.

2-(3-Chloropropyl)-5-chloropentanoic Acid (4) [and 2-(3-Chloropropyl)-δ-valerolactone (6)]. The diacid **3** (28.72 g, 112 mmol) was heated at 170 °C for 1 h. The resulting oil was cooled to ca. 25 °C and then was dissolved in Et_2O. The ethereal solution was extracted with saturated aqueous $NaHCO_3$. The organic layer after drying and concentration gave 7.61 g (39%) of presumed lactone **6** (and/or linear ester terminated by lactone) containing perhaps a trace of acid. The combined $NaHCO_3$ extracts were acidified with concentrated HCl and then extracted with Et_2O. The combined Et_2O layers were dried and concentrated to yield 12.33 g (52%) of the analytically pure acid **4** as a colorless oil: n^{26}_D 1.4798; NMR (CCl_4) δ 11.42 (s, 1 H), 3.54 (t, 4 H), 2.42 (m, 1 H) 2.06–1.54 (m, 8 H); IR (neat) 3750–2270, 1710, 1455, 1420, 1280, 1240, 1160, 1060, 940, 760, 720, 650 cm^{-1}.

Anal. Calcd for $C_8H_{14}Cl_2O_2$: C, 45.08; H, 6.63; Cl, 33.27. Found: C, 45.05; H, 6.83; Cl, 32.89.

Organic layers from several experiments conducted as described above for the preparation of **4** gave ca. 25 g of material believed to be largely the lactone **6** (if so, ca. 0.14 mol). The lactone **6** (and/or linear ester) could be converted to the acid **4** by adaptation of a procedure of Goel and Seamans for the conversion of γ-butyrolactone to esters of 4-chlorobutyric acid.[21] Thus thionyl chloride (19.0 g, 160 mmol) was added to a suspension of freshly fused $ZnCl_2$ (1.09 g, 8 mmol) in **6** (14.1 g, 80 mmol). The reaction mixture was stirred at 50 °C for 2 days and then was cooled to ca. 25 °C and poured carefully into ice–water. Et_2O was added to dissolve the precipitated oil, and the aqueous layer was extracted with additional Et_2O. The combined organic extracts were washed with H_2O and then extracted with saturated aqueous $NaHCO_3$. The $NaHCO_3$ extracts were washed with Et_2O, acidified with concentrated HCl, and extracted with Et_2O. The ethereal extracts were dried and then concentrated to yield 10.76 g (63%) of **4** (identity confirmed by NMR).

2-(3-Chloropropyl)-5-chloropentanol (5). Borane–methyl sulfide complex (15 mL of a 10 M solution, 150 mmol) was added over 30 min to a solution of the acid **4** (15.0 g, 70.4 mmol) in Et_2O (75 mL) under an atmosphere of Ar. The resulting solution was heated under reflux for 5 h, cooled to ca. 25 °C, and poured carefully into MeOH (72 mL). The methanolic solution was stirred overnight, and H_2O (100 mL) and Et_2O (25 mL) then were added. The aqueous layer was extracted with additional Et_2O (3 × 25 mL), and the combined ethereal extracts were washed with saturated aqueous $NaHCO_3$ (2 × 15 mL), H_2O (1 × 15 mL), 5% aqueous $NaHSO_3$ (1 × 15 mL), and H_2O (1 × 15 mL) and then were dried. Evaporation of Et_2O gave 13.43 g (96%) of the carbinol **5** as an oil, n^{23}_D 1.4847. A portion (2 g) of this **5**, distilled at reduced pressure by using a short-path distillation apparatus, gave 0.96 g (46%) of analytically pure **5**: bp 126–130 °C (2.2 torr); n^{25}_D 1.4836; NMR (CCl_4) δ 3.65–3.41 (m, 6 H), 2.92 (s, 1 H), 2.01–1.25 (m, 9 H); IR (neat) 3600, 3375, 2960, 2880, 1460, 1300, 1030, 720, 650 cm^{-1}.

Anal. Calcd for $C_8H_{16}Cl_2O$: C, 48.25; H, 8.11; Cl, 35.60. Found: C, 48.10; H, 7.99; Cl, 35.62.

2-(3-Chloropropyl)-5-chloropentyl *p*-Toluenesulfonate (10). *p*-Toluenesulfonyl chloride (1.91 g, 10.0 mmol) was added to a solution of the carbinol **5** (1.00 g, 5.0 mmol) in pyridine (17 mL) at 0 °C. The resulting solution was kept at ca. −25 °C for 2 days. The mixture was poured into cold H_2O, Et_2O was added to dissolve the oil that separated, and the aqueous layer was extracted with additional Et_2O. The combined extracts were washed twice with 6 N HCl and once with H_2O and dried (K_2CO_3–Na_2SO_4). Removal of Et_2O gave a solid which was recrystallized from hexane/Et_2O to give 0.54 g (30%) of **10**, mp 48.5–50

(19) Rama Sastry, B. V., personal Communication, 1979. We thank Professor Sastry and his associates of the Department of Pharmacology, Vanderbilt University School of Medicine, for this evaluation (for details, see ref 1b).

(20) Buckman, J. D., Ph.D. Dissertation; Vanderbilt University, 1966, p 114.

(21) Goel, O. P.; Seamans, R. E. *Synthesis* **1973**, 538.

°C. A portion (197 mg) was recrystallized twice more to give 80 mg of **10** with a constant melting point: mp 50–51 °C; NMR ($CDCl_3$) δ 7.79 (d, 2 H), 7.36 (d, 2 H), 3.93 (d, 2 H), 3.45 (t, 4 H), 2.46 (s, 3 H), 1.87–1.23 (m, 9 H); IR (KBr) 2950, 2880, 1595, 1495, 1460, 1400, 1355, 1290, 1220, 1190, 1175, 1140, 1095, 1040, 1020, 985, 965, 940, 860, 830, 810, 715, 660 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}Cl_2O_3S$: C, 50.99; H, 6.29; S, 9.07. Found: C, 50.96; H, 6.39; S, 9.26.

Reaction of the carbinol **5** (0.96 g, 4.8 mmol) with *p*-toluenesulfonyl chloride (1.91 g, 10.0 mmol) in pyridine (17 mL) for 6 days at 5 °C gave **10**: 65% yield; mp 49–51 °C.

2-(3-Chloropropyl)-5-chloropentyl *p*-Toluenethiolsulfonate (8). The precursor, **2-(3-chloropropyl)-5-chloropentyl trifluoromethanesulfonate (11)**, was prepared by adding a solution of the carbinol **5** (5.88 g, 29.5 mmol) and pyridine (2.34 g, 29.6 mmol) in CH_2Cl_2 (30 mL) during 30 min to one of trifluoromethanesulfonic anhydride (10.0 g, 35.4 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The solution was stirred at 0 °C for 5.5 h and then was washed with H_2O (25 mL), 5% aqueous $NaHSO_3$ (15 mL), and H_2O (25 mL). The organic layer was dried and then evaporated to yield 8.86 g (91%) of the triflate **11**: NMR ($CDCl_3$) δ 4.45 (d, 2 H); 3.57 (t, 4 H), 2.07–1.35 (m, 9 H).

For conversion of the triflate **11** to the thiosulfonate **8** a solution of sodium *p*-toluenethiosulfonate (**9**; 5.66 g, 23.0 mmol) in a minimum of sulfolane (250 mL) was added over 30 min to a solution of **11** (7.0 g, 21.1 mmol) in sulfolane (30 mL). The reaction was not noticeably exothermic. The resulting solution was stirred at ca. 25 °C for 4.5 h. H_2O (1.5 L) and Et_2O (200 mL) were added, and the aqueous layer was extracted with additional Et_2O (3 × 100 mL). The combined extracts were washed with H_2O (2 × 100 mL) and dried. Removal of solvent left 5.52 g of a yellow oil, which was chromatographed on 220 g of silica gel in an 8-cm-diameter column with 2% EtOAc in pentane as eluant. The effluent volumes of 2.0–3.0 L on concentration gave 2.0 g (26%) of analytically pure **8** as an oil: n^{23}_D, 1.5488; NMR ($CDCl_3$) δ 7.82 (d, 2 H), 7.37 (d, 2 H), 3.46 (t, 4 H), 2.98 (d, 2 H), 2.47 (s, 3 H), 1.95–1.15 (m, 9 H); IR (neat) 3050 (t), 2950, 2880, 1640, 1615, 1595, 1490, 1450, 1405, 1380, 1330, 1310, 1300, 1245, 1210, 1185, 1145, 1120, 1080, 1045, 1020, 815, 720, 705, 655 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}Cl_2O_2S_2$: C, 48.77; H, 6.00; S, 17.36. Found: C, 48.95; H, 6.06; S, 17.13.

Bis[2-(3-chloropropyl)-5-chloropentyl] Trisulfide (7). A solution of $Na_2S·9H_2O$ (0.45 g, 1.87 mmol) in MeOH (35 mL) was added over 15 min to a solution of thiosulfonate **8** (1.44 g, 3.90 mmol) in MeOH (25 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then was concentrated. H_2O (25 mL) and CH_2Cl_2 (50 mL) were added to the residue, and the aqueous layer was extracted further with CH_2Cl_2 (2 × 25 mL) and Et_2O (2 × 50 mL). The combined organic extracts were dried. Removal of the solvent gave 0.80 g (93%) of an oil (99% with 2.5 g of **8**). An initial attempt to purify this oil by chromatography on 50 g of silica gel in a 4-cm diameter column by using 5% EtOAc in hexane did not separate minor impurities. All material (0.75 g) was recombined and chromatographed on 40 g of silica gel in a 4-cm diameter column with CCl_4 as the eluant. The effluent volumes of 0.3–0.4 L on concentration gave 0.48 g (59%) of the analytically pure trisulfide **7**: n^{24}_D 1.5515; NMR ($CDCl_3$) δ 3.55 (t, 8 H), 2.91 (d, 4 H), 2.02–1.33 (m, 18 H); IR (neat) 2930, 2860, 1445, 1410, 1365, 1330, 1310, 1280, 1240, 1040, 760, 715, 640 cm^{-1}.

Anal. Calcd for $C_{16}H_{30}Cl_4S_3$: C, 41.73; H, 6.58; Cl, 30.80; S, 20.89. Found: C, 41.69; H, 6.51; Cl, 30.99; S, 20.81.

2-[(3-Benzylthio)propyl)]-5-(benzylthio)pentanol (15) [and 2-(3-Mercaptopropyl)-5-mercaptopentanol]. α-Toluenethiol (4.97 g, 40.0 mmol) was added to a solution of sodium (0.92 g, 40.0 mmol) in MeOH (20 mL). A solution of the carbinol **5** (2.00 g, 10.0 mmol) in MeOH (7 mL) was added over 10 min to the resulting solution. The reaction mixture was stirred at ca. 25 °C for 24 h (NMR indicated disappearance of **5** by loss of CH_2Cl; δ 3.4, t) and then was diluted with H_2O (100 mL). The cloudy aqueous solution was extracted with CH_2Cl_2 (50 and 25 mL) and $CHCl_3$ (2 × 25 mL). The combined organic extracts were washed with 10% aqueous NaOH (2 × 25 mL) and H_2O (2 × 25 mL) and then were dried. Removal of the solvent gave 4.26 g of an oil, which was chromatographed on 150 g of silica gel in a 7-cm-diameter column by using 30% EtOAc in pentane as the eluant. The effluent volumes of 0.8–1.2 L on concentration gave 3.01 g (80%) of disulfide carbinol **15**: n^{23}_D 1.5801; NMR (CCl_4) δ 7.18 (s, 10 H), 3.60 (s, 4 H), 3.33 (br s, 2 H), 2.30 (t, 4 H), 1.77 (br s, 1 H), 1.64–1.12 (m, 9 H); IR (neat) 3400, 3060, 3030, 2925, 2860, 1595, 1485, 1450, 1415, 1230, 1060, 1020, 760, 695 cm^{-1}. Use of 12.9 of **5** gave **15** in 83% yield.

Anal. Calcd for $C_{22}H_{30}OS_2$: C, 70.53; H, 8.07; S, 17.12. Found: C, 70.40; H, 7.98; S, 17.24.

In work thus far, **2-(3-mercaptopropyl)-5-mercaptopentanol** has been best obtained by adding a solution of the dichloro carbinol **5** (2.00 g, 10.0 mmol) in MeOH (30 mL) during 20 min to aqueous Na_2CS_3[4] (30 mL of 2.98 M, 89 mmol) at 60 °C. The reaction mixture was stirred at 60 °C for 6 h and then was cooled to ca. 25 °C. The solution was washed with CH_2Cl_2 (1 × 100 mL). The aqueous layer was acidified with concentrated H_2SO_4 (ca. 6 mL) and then extracted with CH_2Cl_2 (1 × 100, 2 × 50 mL). The combined extracts were dried and evaporated to give 2.0 g (102%) of the dimercaptocarbinol as an oil; 0.1253 g of this oil consumed 11.7 mL of 0.0759 N KI_3, indicating 69% of the expected SH content: NMR ($CDCl_3$) δ 3.54 (d, 2 H), 2.54, (q, 4 H), 2.08 (s, 1 H), 1.84–1.24 (m, 11 H). Addition of D_2O to a NMR sample from an earlier preparation (88% yield) caused disappearance of some of the peaks of the multiplet at δ 1.84–1.24 caused by SH, the loss of the signal for OH (at δ 2.4 in this sample owing to concentration), and the collapse of the quartet for CH_2CH_2SH (at δ 2.5) to a triplet. The IR spectrum of material from this preparation had peaks at 3400 (b), 2930, 2870, 2550 (SH), 1450, 1040 cm^{-1}. The iodine titer of still another preparation (98% yield) indicated 79% of the expected SH content.

Bis[2-[3-(benzylthio)propyl]-5-(benzylthio)pentyl] Trisulfide (12). For the preparation of **2-[3-(benzylthio)propyl]-5-(benzylthio)pentyl *p*-toluenesulfonate (14), Ar = 4-MePh),** *p*-toluenesulfonyl chloride (0.19 g, 1.00 mmol) was added to a solution of the disulfide alcohol **15** (0.15 g, 0.40 mmol) in pyridine (3 mL) at 5 °C. The reaction was monitored by TLC (25% EtOAc in hexane) for the disappearance of the carbinol **15** (R_f 0.4); a new TLC spot appeared at R_f 0.6. After 23 h, only the spot at R_f 0.6 was present. The reaction mixture then was poured into H_2O (20 mL), and the cloudy aqueous layer was extracted with Et_2O (2 × 20 mL). The combined extracts were washed with 10% aqueous HCl (2 × 20 mL) and H_2O (2 × 20 mL), dried (K_2CO_3–Na_2SO_4), and evaporated to give ca. 0.2 g (95%) of the tosylate **14** as a slighly impure oil: NMR ($CDCl_3$) δ 7.75 (d, 2 H), 7.38–7.18 (m, 12 H), 4.9 (q, impurity), 3.95 (d, impurity), 3.85 (d, 2 H), 3.67 (s, 4 H), 2.42 (s, 3 H), 2.33 (t, 4 H), 2.16 (d, impurity), 1.74–1.10 (m, 9 H).

For conversion of the tosylate **14** to **2-[(3-benzylthio)propyl]-5-(benzylthio)pentyl *p*-toluenethiolsulfonate (13, Ar = 4-MePh),** sodium *p*-toluenethiosulfonate (**9**; 0.31 g, 1.26 mmol) was suspended in hexane, and the suspension was heated under reflux in a Dean–Stark apparatus until the distillate was clear to remove H_2O. After removal of hexane, the white solid was dissolved in DMF (5 mL). A solution of the tosylate **14** (0.20 g, 0.38 mmol) in DMF (5 mL) was added over 10 min at ca. 25 °C. The reaction mixture was stirred at 60 °C for 1 day and then was cooled to ca. 25 °C. H_2O (75 mL) and Et_2O (50 mL) were added, and the aqueous layer was extracted with additional Et_2O (2 × 50 mL). The combined extracts were washed with H_2O (3 × 25 mL), dried, and evaporated to give an oil, which was subjected to preparative TLC with 10% EtOAc in hexane as the eluant. A TLC band at R_f 0.26 contained 0.040 g (19%) of thiosulfonate **13**: NMR ($CDCl_3$) δ 7.79 (d, 2 H), 7.40–7.23 (m, 12 H), 3.85 (d, tosylate impurity), 3.68 (s, 4 H), 2.92 (d, 2 H), 2.44 (s, 3 H), 2.33 (t, 4 H), 1.67–1.11 (m, 9 H).

For the conversion of the thiosulfonate **13** to the trisulfide **12**, a solution of $Na_2S·9H_2O$ (8.6 mg, 36 μmol) in CH_3OH (2 mL) was added over 5 min to a solution of the thiosulfonate **13** (39 mg, 72 μmol) in CH_3OH (3 mL) at 5 °C. The reaction mixture was stirred at 5 °C for 30 min, diluted with H_2O, and extracted with Et_2O (3 × 15 mL). The combined extracts were dried and concentrated to give 33 mg (114%) of **12** as an oil. The NMR spectrum of this oil indicated the presence of the trisulfide **12** along with some tosylate **14**. Preparative TLC of this oil with 10% EtOAc in hexane as the eluant gave 15.0 mg (52%) of analytically pure trisulfide **12**: R_f 0.46; NMR ($CDCl_3$) δ 7.29 (s, 20 H), 3.71 (s, 8 H), 2.82 (d, 4 H), 2.41 (t, 8 H), 1.86–1.23 (m, 18 H); IR (neat) 3040, 2940, 2860, 1600, 1490, 1450, 1410, 1230, 750,

690 cm^{-1}. After 3 months at 25 °C, **12** showed a slight new TLC spot at the origin.

Anal. Calcd for $C_{44}H_{58}S_7$: C, 65.12; H, 7.21; S, 27.66. Found: C, 65.26; H, 7.24; S, 27.85.

On a larger scale (19.3 g of **15**), the yields of **14**, **13** (n^{25}_D 1.5979), and **12** (n^{25}_D 1.6090) were 103%, 62% and 87%, respectively.

2-[3-(Trimethylammonio)propyl]-5-(trimethylammonio)-pentanol Salts (16). Me_3N (16 mL, 10.7 g, 181 mmol) was allowed to vaporize, and the vapor was passed into a flask equipped with a dry ice condenser and containing a solution of the carbinol **5** (9.0 g, 45.2 mmol) and NaI (0.68 g, 4.5 mmol) in DMF (120 mL). When vaporization was complete, the flask was cooled in a dry ice–acetone bath, the dry ice condenser was removed, and the flask was stoppered tightly. The reaction mixture was stirred magnetically at ca. 25 °C for 4 days, and then additional Me_3N (16 mL, 181 mmol) was added as above. After 6 more days of stirring at ca. 25 °C, the reaction mixture (containing considerable solid) was transferred to two 250-mL centrifuge bottles, along with Et_2O rinses (total ca. 300 mL) of the reaction flask. The white solid that was collected in each centrifuge tube was washed with Et_2O (3 × 100 mL). Removal of Et_2O at reduced pressure in a vacuum desiccator over P_2O_5 left 15.0 g (100% when the weight of NaI is subtracted) of the **dichloride 16** (X = Cl) as a hygroscopic solid: NMR (D_2O) δ 3.58 (d, 2 H), 3.34 (t, 4 H), 3.13 (s, 18 H), 2.01–1.24 (m, 9 H).

A mixture of **16** (X = Cl; 0.54 g, 1.7 mmol) and KI (0.6 g, 3.6 mmol) in EtOH was warmed on a steam bath. Insoluble KCl was removed by hot filtration, and the solid that precipitated from the filtrate upon cooling was recrystallized from EtOH to give 0.47 g (55%) of the diiodide **16** (X = I): mp 180–184 °C dec; this diiodide was only slightly hygroscopic; NMR (D_2O) δ 3.55 (d, 2 H), 3.32 (t, 4 H), 3.10 (s, 18 H), 2.01–1.27 (m, 9 H).

The addition of a solution of KPF_6 (1.16 g, 6.3 mmol) in H_2O to one of the carbinol **16** (X = Cl; 1.00 g, 3.2 mmol) in H_2O caused precipitation of a white solid that was collected by filtration to give 0.70 g (41%) of the bis(hexafluorophosphate) **16** (X = PF_6); this product did not appear to be hygroscopic: mp 208–210 °C dec; NMR (Me_2SO-d_6) δ 3.40 (d, 2 H), 3.24 (t, 4 H), 3.04 (s, 18 H), 1.88–1.11 (m, 9 H); IR (KBr) 3640, 2960, 2880, 2640, 1480, 1410, 1390, 1090, 1050, 1030, 970, 840, 830, 740 cm^{-1}.

In another quaternization of the carbinol **5**, the product was isolated as a dipicrate [**16**, X = $(NO_2)_3PhO$]. Thus a mixture of the carbinol **5** (510 mg, 2.56 mmol), Me_3N (1.5 mL, 1.0 g, 16.9 mmol), and NaI (40 mg, 0.27 mmol) in DMF (10 mL) was stirred at ca. 25 °C for 8 days. After the addition of enough H_2O to effect solution, the solution was washed with Et_2O, and the solvent was evaporated to give 0.77 g (95% of **16**, X = Cl) of a pasty solid. A solution of this solid (2.4 mmol, assuming it to be **16**, X = Cl) in EtOH (10 mL) was mixed with a solution of picric acid (1.2 g, 1.1 g assuming 10% H_2O, 4.8 mmol) in 0.75 N NaOH (10 mL) to give 1.82 g of yellow solid that was collected and recrystallized from EtOH to give 0.47 g (26%, based on **5**) of analytically pure **16** [X = $(NO_2)_3PhO$]: mp 160–162 °C dec.; NMR (Me_2SO-d_6) δ 8.73 (s, 4 H), 3.13 (s, 18 H), 1.92–1.08 (m, 9 H); IR (KBr) 3410, 3370, 3090, 3040, 2960, 2930, 2870, 2650, 1640, 1610, 1560, 1550, 1475, 1435, 1370–1240, 1160, 1075, 905, 780, 740, 705 cm^{-1}.

Anal. Calcd for $C_{26}H_{38}N_8O_{15}$: C, 44.44; H, 5.45; N, 15.95. Found: C, 44.42; H, 5.65; N, 15.76.

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Registry No. **2**, 79899-30-2; **3**, 79899-31-3; **4**, 79899-32-4; **5**, 79899-33-5; **6**, 79899-34-6; **7**, 79899-35-7; **8**, 79899-36-8; **9**, 3753-27-3; **10**, 79899-37-9; **11**, 79899-38-0; **12**, 79899-39-1; **13**, 79899-40-4; **14**, 79899-41-5; **15**, 79899-42-6; **16** (X = Cl), 79899-43-7; **16** (X = I), 79899-44-8; **16** (X = PF_6), 79899-46-0; **16** (X = $(NO_2)_3PhO$), 79899-47-1; 2-(3-mercaptopropyl)-5-mercaptopentanol, 79899-48-2.

2-Amino-7-(β-D-arabinofuranosyl)pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one. Synthesis of *ara*-7-Deazaguanosine via Phase-Transfer Glycosylation

Frank Seela* and Heinz-Dieter Winkeler

Department of Chemistry, University of Paderborn, D-4790 Paderborn, Federal Republic of Germany

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2-Amino-7-(β-D-arabinofuranosyl)pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one (**2**), the 7-deaza analogue of 9-(β-D-arabinofuranosyl)guanine (ara-G, **1**) has been synthesized via phase-transfer glycosylation of 4-methoxy-2-(methylthio)-7*H*-pyrrolo[2,3-*d*]pyrimidine (**4**) with 2,3,5-tri-*O*-benzyl-1-bromo-D-arabinofuranose (**5**). The reaction was performed in a biphasic mixture of methylene chloride/50% aqueous NaOH in the presence of benzyltriethylammonium chloride as a catalyst. A regioselective N-7 glycosylation occurred to give a mixture of the anomers **6** and **7** in 84% yield. Chromatographic separation of the mixture afforded the pure β anomer **7** in 63% yield. The formation of **7** and the total yield decreased if lower NaOH concentrations were used. Treatment with acid resulted in ether cleavage of **7**, yielding **8a**, and subsequent methoxymethylation gave **8b**. The latter was converted to the protected nucleoside **8c** by nucleophilic displacement of the 2-methylthio group with acetamide/sodium hydride. After deacetylation of **8c**, the amino compound **8d** was formed. Its benzyl and methoxymethyl protecting groups were simultaneously removed by the action of boron trichloride to give crystalline 7-deaza ara-G (**2**).

The 9-β-D-arabinofuranosyl nucleosides of the naturally occurring purine and pyrimidine bases of nucleic acids have been synthesized and shown to have interesting biological activities.[1] They act as inhibitors of several enzymes such as ribonucleotide reductase or DNA polymerase.[2] Inhibitory specificity exists toward virus-induced enzymes. 9-(β-D-Arabinofuranosyl)adenine (ara-A)[3] possesses a broad spectrum of activity against herpes viruses[4] but is unfortunately deactivated by the action of adenosine deaminase.[5] The deamination can be avoided by replace-

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