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The Synthesis of Fluorinated Busulfan and Piposulfan Analogs, Including an Unsymmetrical Bis-sulfonate

Ulla Lange[a] and Alexander Senning[b,*]

[a]Kemisk Institut, Aarhus Universitet, DK-8000 Århus C, Denmark and [b]Institut for Anvendt Kemi, Danmarks Tekniske Universitet, Bygning 376, DK-2800 Lyngby, Denmark

Dedicated to Professor Lennart Eberson on the occasion of his 65th birthday

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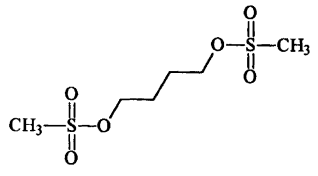
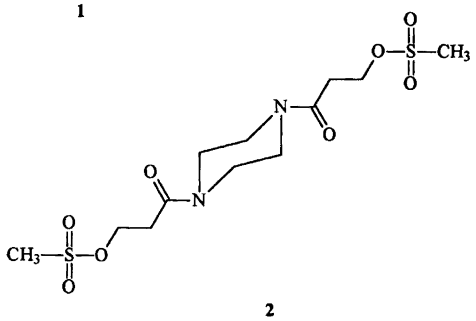
1,4-Bis(fluoromethylsulfonyloxy)butane, 1,4-bis[3-(fluoromethylsulfonyloxy)-propanoyl]piperazine and 1-(fluoromethylsulfonyloxy)-4-(methylsulfonyloxy)butane have been prepared as potential cytostatics of the busulfan type. The rate of hydrolysis of the first-mentioned has been measured.

The well established drug busulfan [1,4-bis(methylsulfonyloxy)butane] **1**[1] is a chemotherapeutic agent which has been widely used as an antineoplastic drug since its discovery in 1953.[2] It is the drug of choice for the treatment of myeloproliferative disorders such as chronic myeloid leukemia (CML),[3,4] and much effort has been devoted to the development of busulfan analogs.

The experimental drug piposulfan [1,4-bis[3-(methylsulfonyloxy)propanoyl]piperazine] **2**[5] is a busulfan analog.[6] Patients who have developed resistance against busulfan can benefit from piposulfan therapy because of the lack of cross resistance between **1** and **2**.



1



2

Modifications of **1** have been carried out, but fluoromethanesulfonic acid derivatives had to be omitted because the two key compounds fluoromethanesulfonyl chloride and silver(I) fluoromethanesulfonate were unavailable at the time. The present work was initiated to close this gap.

Results and discussion

The symmetrical busulfan and piposulfan analogs **5** and **9** were synthesized either by esterification of the appropriate diol with fluoromethanesulfonyl chloride in the presence of pyridine at room temperature [eqn. (1a)] or by heating of silver(I) fluoromethanesulfonate **6** with an alkylene diiodide in anhydrous acetonitrile [eqn. (1b)].

$$\underset{\mathbf{3}}{2\,FCH_2SO_2Cl} + \underset{\mathbf{4}}{HO(CH_2)_4OH} \rightarrow \underset{\mathbf{5}}{FCH_2SO_2O(CH_2)_4OSO_2CH_2F} + 2\,HCl \qquad (1a)$$

$$\underset{\mathbf{6}}{2\,FCH_2SO_3^-Ag^+} + \underset{\mathbf{7}}{I\text{–}X\text{–}I} \rightarrow \underset{\mathbf{5}\ \mathbf{9}}{FCH_2SO_2O\text{–}X\text{–}OSO_2CH_2F} + 2\,AgI \qquad (1b)$$

7, **5**: X = $(CH_2)_4$

8, **9**: X = $CH_2CH_2CON(CH_2CH_2)_2NCOCH_2CH_2$

$$\underset{\mathbf{11}}{CH_3SO_2Cl} + \underset{\mathbf{12}}{HO(CH_2)_4I} \rightarrow \underset{\mathbf{13}}{CH_3SO_2O(CH_2)_4I} + HCl \qquad (2)$$

$$\mathbf{6} + \mathbf{13} \rightarrow \underset{\mathbf{14}}{CH_3SO_2O(CH_2)_4OSO_2CH_2F} \qquad (3)$$

* To whom correspondence should be addressed.

Since **13** decomposes upon attempted vacuum distillation unchanged methanesulfonyl chloride could not be removed from crude **13** which was, however, satisfactory for use in step (3).

The rate of hydrolysis of the series of symmetrical alkylene bismethanesulfonates increases asymptotically with chain length to reach a constant value at C_4. This increase in chemical reactivity roughly correlates with an increase in biological activity[7] although no unambiguous relationship has been found[8] and therefore a comparison of the rates of hydrolysis was made between 1,4-bis(fluoromethylsulfonyloxy)butane **5** and related compounds, cf. Table 1. The rate of hydrolysis of **5** is only slightly greater than that of its chloro analog.

Compound **5** has been tested at the National Cancer Institute (NCI) Anti-Cancer Screening Program, but did not show confirmed activity in the first *in vitro* tests. Neither does busulfan show confirmed activity in this test system which thus does not provide conclusive evidence of anti-CML activity. In the same screen, **9** and **14** exhibited marginal *in vitro* activities in the primary tests which did not warrant further *in vivo* study by the NCI.

Experimental

Spectroscopy. ^{1}H NMR: Gemini (200 MHz); ^{13}C NMR: Gemini (50 MHz); Me_4Si and D_2O, respectively, as internal standards. IR: vs = very strong, s = strong, m = medium, w = weak.

Materials. The acetonitrile was dried according to a literature procedure.[23] All silver-containing reaction mixtures were kept in brown shaded glass vessels. The intermediates **3**,[10] **8**,[6] and **12**[11] were prepared according to literature procedures. It is possible, but not necessary, to purify **12** by passage through silica gel. All other starting materials were commercially available.

Fluoromethanesulfonic acid **10**. This preparation was based on a general procedure for the conversion of aliphatic sulfonyl chlorides into the corresponding anhydrous acids.[12] However, the reaction time was reduced from 30 h to 3 h. A mixture of 13.3 g (100 mmol) **3**[10] and 250 ml methanol was refluxed for 3 h, cooled, and evaporated *in vacuo*; yield 11.3 g (99%) crude **10** as colorless oil which was used directly for the preparation of **6**. ^{1}H NMR (CD_3CN): δ 8.82 (s, 1H), 5.11 (d, J = 46.8 Hz, 2H). ^{13}C NMR (CD_3CN): δ 88.4 (d, J = 206 Hz).

Table 1. Rates of hydrolysis of busulfan analogs in 50% aqueous acetone (37 °C).

Compound	$k_1/10^3$ min^{-1}
$FCH_2SO_2O(CH_2)_4OSO_2CH_2F$ (**5**)	5.55
$ClCH_2SO_2O(CH_2)_4OSO_2CH_2Cl$	5.30[8]
$BrCH_2SO_2O(CH_2)_4OSO_2CH_2Br$	4.33[8]
$ICH_2SO_2O(CH_2)_4OSO_2CH_2I$	2.16[8]

Silver(I) fluoromethanesulfonate **6**. This preparation was based on a general procedure for the conversion of sulfonic acids into their silver salts.[13] A mixture of 5.00 g (44.0 mmol) **10**, 40 ml methanol, and 8.70 g (30.5 mmol) silver carbonate was strirred vigorously for 40 min at room temperature. Excess silver carbonate was filtered off and extracted with hot acetonitrile. The combined organic phases were evaporated *in vacuo*, yield 7.40 g (76%) **6**, m.p. 170–172 °C. Elem. anal.: Calc. C 5.44%; H 0.91%; S 14.51%. Found: C 7.55%; H 1.48%; S 13.68%. ^{1}H NMR (D_2O): δ 5.08 (d, J = 47.0 Hz, 2H). ^{13}C NMR (D_2O): δ 92.2 (d, J = 202 Hz). IR (KBr): ν 1250vs, 1200vs, 1080m, 1020s, 790w cm^{-1}.

1,4-Bis(fluoromethylsulfonyloxy)butane **5**: *procedure (1a).* A general procedure for the synthesis of busulfan analogs was followed.[13] A mixture of 6.50 g (30 mmol) **6**, 4.60 g (15 mmol) **7**, and 30 ml anhydrous acetonitrile was stirred at room temperature for 7 h and then allowed to stand overnight. Precipitated silver iodide was filtered off and the organic phase evaporated *in vacuo*. After two recrystallizations of the residue from chloroform 0.95 g (23%) **5** was obtained, m.p. 60–62 °C. Elem. anal.: Calc. C: 25.53%; H 4.28%, S 22.72%. Found: C 24.92%; H 4.31%, S 22.69%. ^{1}H NMR ($CDCl_3$): δ 1.93 (m, 2H), 4.44 (m, 2H), 5.22 (d, J = 46.6 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 25.7 (CH_2), 72.7 (OCH_2), 88.8 (d, J = 216 Hz, FCH_2). IR (KBr): ν 3035m (CH stretch), 2960m, 1480m, 1455m (OCH_2 vibr.), 1430m, 1400s, 1375vs (SO_2 stretch, asymm.), 1340vs, 1230s, 1180vs (SO_2 stretch, symm.), 1070vs (CF), 1035s, 950vs, 920vs, 860vs, 770m, 710m cm^{-1}. MS (70 eV): *m/z* (*I*%) 281 (74) ($M^+ - H$), 140 (32) ($C_3H_6FO_3S^+$), 127 (17) ($FCH_2SO_2O^+{=}CH_2$), 57 (68) ($C_4H_9^+$), 41 (100) ($C_3H_5^+$), etc.

1,4-Bis[3-(fluoromethylsulfonyloxy)propanoyl]piperazine **9**. A general procedure for the synthesis of piposulfan analogs was followed.[14] A mixture of 1.30 g (2.9 mmol) **8**, 1.10 g (5.0 mmol) **6**, and 10 ml anhydrous acetonitrile was refluxed for 1 h with stirring. The hot reaction mixture was filtered and the solid residue washed with hot acetonitrile. The organic phase was evaporated *in vacuo* and the resulting crystals washed successively with cold water, ethanol, and ether. After recrystallization from acetonitrile 0.28 g (27%) **9**, m.p. 126–128 °C, was obtained. Elem. anal.: Calc. C 34.12%; H 4.77%, N 6.63%, S 15.18%. Found: C 34.45%; H 4.78%; N 7.02%; S 14.62%. ^{1}H NMR (CD_3CN): δ 2.82 (t, J = 6.0 Hz, 4H), 3.49 (m, 8H), 4.60 (t, J = 6.0 Hz, 4H), 5.44 (d, J = 46.0 Hz, 4H). ^{13}C NMR (CD_3CN): δ 30.9 (CH_2), 40.0 ($COCH_2$), 43.6 (NCH_2), 68.1 (OCH_2), 87.1 (d, J = 211 Hz, FCH_2), 166.9 (CO). IR (KBr): ν 2969w (CH stretch), 1645vs (tertiary amide CO), 1460w, 1445m (OCH_2 vibr.), 1380s (SO_2 stretch, asymm.), 1345w, 1225m, 1180 (SO_2 stretch, symm.), 1080m (CF), 1035w,

980m, 950m, 930m, 910m, 830w, 740w cm^{-1}. MS (70 eV): *m/z* (*I*%) 139 (21) ($C_6H_9O_2^+$), 123 (16) ($CH_3SO_2CH_2CH_2^+$), 85 (100) ($C_4H_9N_2^+$), 55 (74) ($C_3H_4O^+$), 41 (39) (C_2HO^+), 33 (22) (FCH_2^+), etc.

4-Iodobutyl methanesulfonate **13**. This procedure was based on a published synthesis of 4-chlorobutyl methanesulfonate.[15] Compound **12**, 2.00 g (10 mmol), was dissolved in a mixture of 5 ml dichloromethane and 1.30 g (11 mmol) **11**. The solution was cooled in an acetone–dry ice bath and 1.10 g (11 mmol) triethylamine in 3 ml dichloromethane was added. When the addition of triethylamine was complete the reaction mixture was allowed to warm to room temperature and poured into 5 ml water. The organic phase was separated, dried over anhydrous $MgSO_4$, and evaporated *in vacuo*; yield 1.53 g (55%) crude **13** with methanesulfonyl chloride as the main impurity. The crude product decomposed upon attempted distillation *in vacuo*. ^1H NMR ($CDCl_3$): δ 1.92 (m, 4H), 3.03 (s, 3H), 3.23 (t, J=6.5 Hz, 2H), 4.27 (t, J=6.4 Hz, 3H). ^{13}C NMR (CD_3CN): δ 29.7, 30.5, 34.3, 38.0, 69.3.

1-(Fluoromethylsulfonyloxy)-4-(methylsulfonyloxy)butane **14**. A mixture of 2.00 g (9.0 mmol) **6**, 2.50 g (9.0 mmol) **13**, and 10 ml anhydrous acetonitrile was stirred at room temperature for 1 day. Silver iodide was filtered off and the organic phase evaporated *in vacuo*. Recrystallization from ether–acetone (10:1) yielded 0.24 g (10%) **14**, m.p. 82–85 °C. Elem. Anal.: Calc. C 27.27%; H 4.96%; S 24.26%. Found: C 27.42%; H 5.16%; S 24.26%. ^1H NMR ($CDCl_3$): δ 1.94 (m, 4H), 3.03 (s, 3H), 4.29 (m, 2H), 4.47 (m, 2H), 5.24 (d, J=46.6 Hz, 2H). ^{13}C NMR (CD_3CN): δ 25.7 (CH_2), 26.1 (CH_2), 37.9 (CH_3), 69.3 (OCH_2), 73.0 (OCH_2), 88.9 (d, J=216 Hz, FCH_2). IR (KBr): ν 3020m (CH stretch), 2920m, 1470m (OCH_2 vibr.), 1445m, 1415m, 1350vs (SO_2 stretch, asymm.), 1240m, 1170vs (SO_2 stretch, symm.), 1080m (CF), 1030m, 980s, 930vs, 855s, 765m, 720w cm^{-1}. MS (70 eV): *m/z* (*I*%) 264 (5) (M^+), 169 (69) [$FCH_2SO_3(CH_2)_4^+$], 151 (39) ($CH_3SO_2O^+{=}CH_2$), 79 (53) ($CH_3SO_2^+$), 71 (62) ($C_4H_7O^+$), 51 (100) ($C_4H_3^+$), 33 (30) (FCH_2^+), etc.

Rates of hydrolysis. An acidimetric titration was carried out where the first-order rate constant k_1 for the hydrolysis was calculated in the same way as for the chloro, bromo, and iodo analogs of busulfan.[8] The hydrolyses were carried out in 50% aqueous acetone at 37 °C. The results are shown in Table 1.

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