Preparation of a DSCG-Like Bisbenzofuran

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The preparation of 6,6'-[(2-hydroxy-1,3-propanediyl)*bis*(oxy)]*bis*(3-hydroxy-2-benzofurancarboxylic acid) diethyl ester trisodium salt trihydrate (**6**), a compound structurally related to disodium cromoglycate (DSCG), is described.

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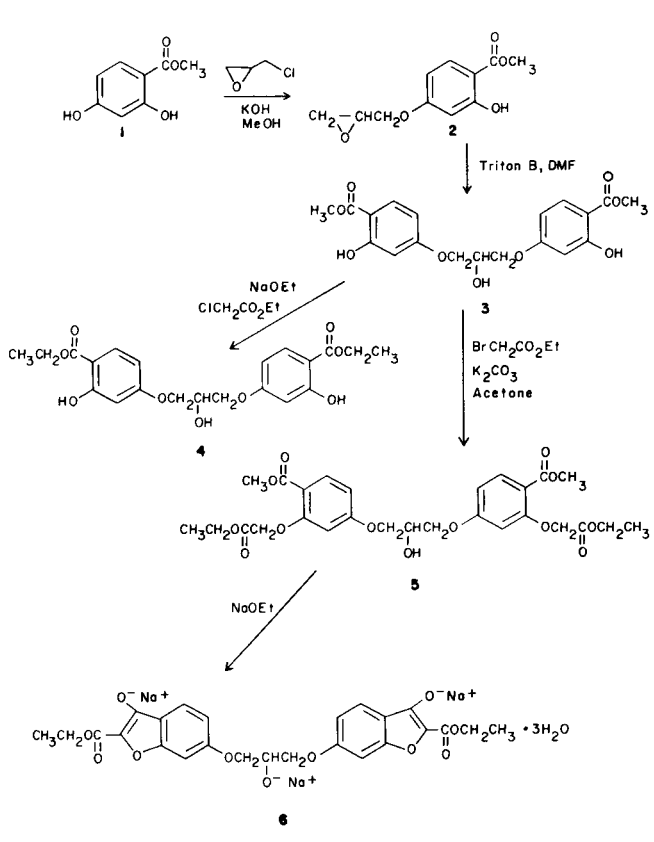
Since the discovery of disodium cromoglycate (DSCG), a drug which is useful in the treatment of human asthma, several isoteric or structurally related *bis* heterocyclic systems have been synthesized (1-3).

We have recently prepared a *bis*benzofuran compound related to DSCG, whose synthesis we wish to report. The preparation of 6,6'-[(2-hydroxy-1,3-propanediyl)*bis*(oxy)]-(3-hydroxy-2-benzofurancarboxylic acid) diethyl ester trisodium salt trihydrate (**6**) is described in Scheme 1.

Scheme I



Treatment of methyl 2,4-dihydroxybenzoate (**1**) with epichlorohydrin and potassium hydroxide gave methyl 2-hydroxy-4-(oxiranylmethoxy)benxoate (**2**) in 40% yield, after purification by distillation. *Bis* compound **3** was then prepared, in 81% yield, by treating **2** with **1** in the presence of benzyltrimethylammoium hydroxide (Triton B) in dimethylformamide at reflux. Attempted alkylation of **3** with ethyl chloroacetate in ethanol, employing sodium ethoxide as the base, was not successful. These conditions resulted only in ester interchange, and diethyl ester **4** was isolated (4). However, treatment of **3** with ethyl bromoacetate in acetone, using potassium carbonate as the base, gave the dialkylated product **5** in 67% yield, as a viscous oil. Purity of this material as isolated was good as indicated by spectral data and by comparison with an aliquot which was purified by preparative thick layer chromatography on silica gel.

Treatment of **5** with sodium ethoxide resulted in an 84% yield of **6**. The nmr spectrum of diethyl ester **6** showed the absence of a methyl ester signal, and the infrared spectrum was consistent with that of a β-ketoester sodium salt. Elemental analysis indicated a trisodium salt trihydrate. As would be predicted from its structure, *bis*-benzofuran **6** was very water soluble.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with a Perkin-Elmer Model 727B Spectrophotometer, nmr spectra with Varian T-60 and Varian EM360A spectrometers, and mass spectra with a Finnigan gc/ms Model 3000D (electron impact and chemical ionization) mass spectrometer at 70 eV. Combustion analyses for C, H and N were performed by Dow Analytical Laboratories, Midland, MI, and Midwest Microlab, Ltd., Indianapolis, IN.

2-Hydroxy-4-(oxiranylmethoxy)benzoic Acid Methyl Ester (**2**).

To a solution of 216 g. (1.28 moles) of methyl 2,4-dihydroxybenzoate (**1**) and 290 g. (3.13 moles) of epichlorohydrin in 200 ml. of methanol at reflux was added, dropwise, a solution of 79.2 g. (1.41 moles) of potassium hydroxide in 300 ml. of methanol. After 3 hours at reflux with mechanical stirring, the mixture (potassium bromide was present as a precipitate) was cooled and filtered, and the filtrate was partitioned between methylene chloride and water. The organic phase was dried (sodium sulfate) and concentrated to leave a brown, viscous oil which was purified by distillation at reduced pressure to afford 114 g. (40%) of **2**, b.p. 158-160° (0.50 mm), m.p. 54-55°; ir (Nujol): 3070 (OH), 1675 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 10.98 (s, 1H, OH), 7.63 (d, J = 9 Hz, 1H, aromatic H at 6-position), 6.56-6.18 (m, 2H, aromatic), 4.42-2.58 (m, 8H, remaining protons, with OCH_3 s at 3.88).

Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found: C, 58.70; H, 5.40.

4,4'-[(2-Hydroxy-1,3-propanediyl)*bis*(oxy)]*bis*(2-hydroxybenzoic Acid) Dimethyl Ester (**3**).

A solution of 11.2 g. (50.0 mmoles) of **2**, 8.41 g. (50.0 mmoles) of **1** and 0.836 g. (5.00 mmoles) of benzyltrimethylammonium hydroxide (2.10 g. of a 40% methanol solution) in 100 ml. of dimethylformamide was

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heated at reflux for 4 hours. The solution was cooled, diluted with water (800 ml.), and after 30 minutes of stirring the precipitate was collected and air-dried to yield 16.0 g. (82%) of **3**, m.p. 108-113°; m.p. 124-127° (ethyl acetate-hexane); ir (Nujol): 3420 (OH), 3360 (OH), 1660 (C=O) cm^{-1}; nmr (DMSO-d_6): δ 10.70 (s, 2H, both phenolic OH groups, deuterium oxide-exchangeable), 7.60 (d, J = 9 Hz, 2H, aromatic protons ortho to ester groups), 6.63-6.37 (m, 4H, remaining aromatic), 5.43 (broad s, 1H, CHO*H*, deuterium oxide-exchangeable), 4.10 (s, 5H, CH_2CHCH_2), 3.80 (s, 6H, both OCH_3 groups).

Anal. Calcd. for $C_{19}H_{20}O_9$: C, 58.16; H, 5.14. Found: C, 58.00; H, 5.04.

4,4'-[(2-Hydroxy-1,3-propanediyl)*bis*(oxy)]*bis*(2-hydroxybenzoic Acid) Diethyl Ester (**4**).

To a solution of 1.26 g. (55.0 mmoles) of sodium in 50 ml. of ethanol was added 4.91 g. (12.5 mmoles) of **3** followed by 6.74 g. (55.0 mmoles) of ethyl chloroacetate. An additional 4.91 g. (12.5 mmoles) of **3** was then added. The mixture was heated at reflux for 20 hours, cooled, and partitioned between water and methylene chloride. The organic layer was dried (sodium sulfate) and concentrated to leave 5.80 g. (55%) of **4**, m.p. 148.5-150° (methanol); ir (Nujol): 3420 and 3370 (OH), 1660 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 11.08 (s, 1H, CHO*H*, deuterium oxide-exchangeable), 7.68 (d, J = 8 Hz, 2H, protons ortho to carboethoxy groups), 6.54-6.20 (m, 4H, remaining aromatic), 4.54-3.85 (m, 9H, four OCH_2 groups and C*H*OH), 3.35 (very broad signal, 2H, phenolic OH groups, deuterium oxide-exchangeable), 1.40 (t, J = 7 Hz, 6H, both CH_3 groups); ms: (electron impact, 70 eV) m/e 420 (molecular ion).

Anal. Calcd. for $C_{21}H_{24}O_9$: C, 59.99; H, 5.74. Found: C, 59.61; H, 5.65.

4,4'-[(2-Hydroxy-1,3-propanediyl)*bis*(oxy)]*bis*[2-((ethoxy)carbonyl)methyl-enoxybenzoic Acid] Dimethyl Ester (**5**).

To a solution of 39.2 g. (100 mmoles) of **3** in 450 ml. of acetone was added 32.0 g. of potassium carbonate. To the mechanically stirred mixture was added 25.4 ml. (36.8 g.; 220 mmoles) of ethyl bromoacetate and reflux was maintained for 80 hours. The mixture was filtered and the filtrate was concentrated and partitioned between chloroform and dilute sodium hydroxide solution. The organic later was dried (sodium sulfate) and concentrated to leave 40.0 g. of viscous oil. Elution through a 150-g. column of Silica Gel 60 (70-230 mesh, EM Reagents) with 9:1::chloroform-methanol gave, after concentration of the eluent, 37.8 g. (67%) of **5** as a viscous oil; ir (Nujol): 3480 (OH), 1755 (C=O), 1720 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 7.80 (d, J = 8 Hz, 2H, protons ortho to C=O groups), 6.68-6.25 (m, 4H, remaining aromatic), 4.65 (s, 4H, both $OCH_2C{=}O$ groups), 4.47-4.03 [m, 9H, $CH_2CH(OH)CH_2$ and both $O{=}COCH_2$ groups), 3.96 (s, 6H, both OCH_3 groups), 1.27 (t, J = 7.2 Hz, 6H, both CH_2CH_3 groups); ms: (70 eV, chemical ionization, methane) m/e 565 (M^+ + 1), 593 (M^+ + 29), 605 (M^+ +41).

6,6'-[(2-Hydroxy-1,3-propanediyl)*bis*(oxy)]*bis*(3-hydroxy-2-benzofuran-carboxylic Acid) Diethyl Ester Trisodium Salt Trihydrate (**6**).

To a solution of 4.10 g. (7.26 mmoles) of **5** in 50 ml. of absolute ethanol was added a solution of 0.500 g. (21.7 mmoles) of sodium in 25 ml. of absolute ethanol. A precipitate appeared. The mixture was heated at reflux for 1 hour, cooled, and the solid collected and air-dried to yield 3.76 g. (84%) of **6**, m.p. >300°; ir (Nujol): 3350 (water of hydration), 1610, 1520, 1275, 1160, 1090 cm^{-1}; nmr (deuterium oxide): δ 7.77-7.37 (m, 2H, aromatic), 6.92-6.28 (m, 4H, aromatic), 4.70 (s, 6H, water of hydration), 4.60-3.90 (m, 9H, four CH_2 groups and methine proton), 1.35 (t, J = 7 Hz, 6H, both CH_3 groups).

Anal. Calcd. for $C_{25}H_{27}Na_3O_{14}$: C, 48.39; H, 4.39. Found: C, 48.66; H, 4.36.

REFERENCES AND NOTES

(1) H. Cairns, C. Fitzmaurice, D. Hunter, P. B. Johnson, J. King, T. B. Lee, G. H. Lord, R. Minshull and J. S. G. Cox, *J. Med. Chem.*, **15**, 583 (1972).

(2) C. M. Hall, H. G. Johnson and J. B. Wright, *ibid.*, **17**, 685 (1974).

(3a) K. A. Thakar and A. B. Dumir, *Indian J. Chem.*, **B15**, 1050 (1977); (b) K. A. Thakar and A. B. Dumir, *ibid.*, **B15**, 1051 (1977); (c) K. A. Thakar and A. B. Dumir, *ibid.*, **B15**, 1053 (1977); (d) K. A. Thakar and A. B. Dumir, *ibid.*, **B15**, 1054 (1977).

(4) We also demonstrated that **4** was produced when **3** was treated with only sodium ethoxide.