Hydrophilic Derivatives of Dithranol

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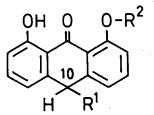
The syntheses of dithranol derivatives with ω-carboxyalkyl side chains at C-2 (and C-7) or ω-methoxycarbonylacyl-substituents at C-10, respectively, are described.

Hydrophile Dithranolderivate

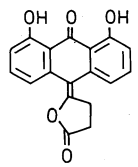
Die Herstellung von Dithranolderivaten mit ω-Carboxyalkyl-Seitenketten an C-2 (und C-7) bzw. mit ω-Methoxycarbonylacyl-Substituenten an C-10 wird beschrieben.

We have reported a) upon the inhibition of glucose-6-phosphate-dehydrogenase by dithranol **(1)**[1], b) upon the UV-spectra of **1** and its anion[2] and c) upon the active oxygen species generated by **1**-C-10-anion[3]. These experiments were hampered by the low degree of solubility of **1** in aqueous buffer systems.

Here we describe the syntheses of hydrophilic derivatives of **1** which will be used as model compounds for further experiments in the context of the problems a)–c) mentioned above.



1: $R^1 = R^2 = H$
2: R^1 = n-CO-C_3H_7, $R^2 = H$
3: $R^1 = CO-(CH_2)_2-COOCH_3$, $R^2 = H$
4: $R^1 = CO-(CH_2)_3-COOCH_3$, $R^2 = H$
5: $R^1 = H$, $R^2 = CO-(CH_2)_3-COOCH_3$



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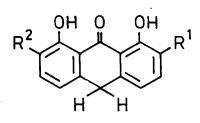
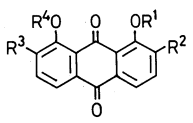
A) C-10-Acylated Dithranol Derivatives

C-10-acylated derivatives of **1** have been investigated thoroughly by *Mustakallio* et al.[4] mainly under clinical aspects, butantrone **(2)** being the most potent compound of this series. Unfortunately **2** is not suitable for our purposes. So we converted **1** into the esters **3** and **4**, respectively, by acylation with ω-methoxycarbonyl-propionyl chloride[5] or the homologous ω-methoxycarbonyl-butyryl chloride.

Besides the main components **3** and **4** the phenyl ester **5** arose as a side product. – **1** reacted with succinyl chloride yielding the lactone **6**.



7: $R^1 = CH_2-CH_2-COOH$, $R^2 = H$
12: $R^1 = R^2 = CH_2-COOH$
15: $R^1 = CH_2-COOH$, $R^2 = H$



8: $R^2 = CH_2-CH(COOC_2H_5)_2$, $R^4 = CH_3$, $R^1 = R^3 = H$
9: $R^1 - R^4 = H$
10: $R^2 = R^3 = CH_2-COOH$, $R^1 = R^4 = H$
11: $R^2 = R^3 = CH_2-COOCH_3$, $R^1 = R^4 = CH_3$
13: $R^4 = CH_3$, $R^1 - R^3 = H$
14: $R^2 = CH_2-COOH$, $R^4 = CH_3$, $R^1 = R^3 = H$

**) Herrn Prof. Dr. Zymalkowski, Bonn, in Verehrung zum 75. Geburtstag gewidmet.

B) C-2 (and C-7) Substituted Dithranol Derivatives

2-(2-carboxyethyl)-dithranol **7** was obtained by ether cleavage, saponification, decarboxylation, and reduction of the anthraquinone **8**[6] with $SnCl_2$ in a one-pot-reaction according to *Auterhoff*[7].

Chrysazin **(9)** when being treated with an excess of $(HO)_2$CH-COOH/NaOH/Na-dithionite according to *Marschalk*[8] yielded the bis-(carboxymethyl)-dihydroxyanthraquinone **10** as a very polar, crude material which was methylated to **11** for characterization. Under *Auterhoff's* reductive conditions[7] **11** was converted to 2,7-bis-(carboxymethyl)-dithranol **12**.

Analogously to the reaction of chrysazin **(9)** its mono-methyl ether **13**[6] was converted with $(HO)_2$CH-COOH to the mono-carboxymethyl-derivative **14**, which was reduced to the carboxymethyldithranol **15** with concomittant ether cleavage.

Experimental Part

Devices: Mp.: (uncorr.) apparatus according to Dr. *Tottoli* (Büchi). – UV-spectra: Shimadzu 210; 1 cm cells. – IR-spectra in KBr: Beckman Accu-lab III. – ^{1}H-NMR-spectra: Varian EM 390 (90 MHz), $CDCl_3$, 35 °C, TMS as int. stand. – MS: Varian MAT CH5, 70 eV. – NI-FAB-MS (glycerol/DMSO 1:1; Xe) Varian MAT 311A. – All the reactions were performed under N_2 and light protection.

Section A

1,8-Dihydroxy-10-(3'-methoxycarbonyl-1'-oxopropyl)-9(10H)anthracenone **(3)**

The suspension of 2.26 g (10 mmol) **1**, 1.76 g (11.7 mmol) 3-methoxycarbonyl-propionyl chloride[5] and 1.07 g (13.3 mmol) of dry pyridine in 70 ml of absol. toluene was refluxed for 4 h. – The resulting orange solution was evaporated i. vac., the residue, dissolved in a small volume of CH_2Cl_2, was purified by CC (SiO_2/Et_2O) and crystallization from Et_2O: 1.4 g (41 %) **3**, yellow crystals, m. p. 122 °C. – rf (SiO_2; Et_2O): 0.74. – $C_{19}H_{16}O_6$ (340.3) Calc. C 67.1 H 4.71 Found C 66.9 H 4.74. – UV (CH_2Cl_2): λ max (log ε) = 357 (4.01), 279 (4.00), 267 (4.02), 237 nm (3.80). – IR: 1745 (CO-OCH_3), 1725 (C=O), 1635 cm^{-1} (C=O···HO). – ^{1}H-NMR: δ (ppm) = 12.0 (s; 2 OH), 7.70–6.82 (m; 6H aromat.), 5.29 (s; 1H at C-10), 3.61 (s; 3H, CH_3), 2.42 (s; 4H, 2 × CH_2).

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1,8-Dihydroxy-10-(4'-methoxycarbonyl-1'-oxobutyl)-9(10H)anthracenone **(4)**

From 2.26 g (10 mmol) **1**, 1.92 g (11.7 mmol) 4-methoxycarbonyl-butyryl chloride (Aldrich Chemicals) and 1.07 g (13.3 mmol) of dry pyridine in toluene as described for **3**: 1.8 g (50 %) yellow crystals from Et_2O/petrol ether (40–60 °C) (1:1), m.p. 92 °C. – rf (SiO_2; Et_2O/petrol ether 1:1): 0.48. – $C_{20}H_{18}O_6$ (354.4) Calc. C 67.8 H 5.08 Found C 67.8 H 5.10. – UV (CH_2Cl_2): λ max (log ε) = 356 (4.04), 280 (4.02), 268 (4.02), 233 nm (3.92). – IR: 1735 (CO-OCH_3), 1715 (C=O), 1635 cm^{-1} (C=O···HO). – ^{1}H-NMR: δ (ppm) = 11.82 (s; 2 OH), 7.61–6.82 (m; 6H aromat.), 5.21 (s; 1H at C-10), 3.53 (s; 3H, CH_3), 2.19–1.96 (m; 4H, CH_2 at C-2' and CH_2 at C-4'), 1.77–1.54 (m; 2H, CH_2 at C-3').

1-(4'-Methoxycarbonyl-butyryloxy)-8-hydroxy-9(10H)-anthracenone **(5)**

Fractional crystallization of the mother liquors of **4** from Et_2O/petrol ether (1:1) afforded 110 mg (3.1 %) **5** as yellow crystals, m.p. 103 °C. – rf (SiO_2; Et_2O/petrol ether 1:1): 0.42. – $C_{20}H_{18}O_6$ (354.4). Calc. C 67.8 H 5.08 Found C 67.9 H 5.09. – UV (CH_2Cl_2): λ max (log ε) = 357 (3.67), 281 (4.12), 255 (4.09), 233 (3.93), 220 nm (3.47). – IR: 1765 (O-CO-R), 1735 (CO-OCH_3), 1640 cm^{-1} (C=O···H-O). – ^{1}H-NMR: δ (ppm) = 12.22 (s; 1 OH), 7.64–6.78 (m; 6H aromat.), 4.34 (s; 2H at C-10), 3.74 (s; 3H, CH_3), 2.88–2.71 (m; 2H, CH_2 (C-2')), 2.61–2.47 (m; 2H, CH_2 (C-4')), 2.29–2.03 (m; 2H, CH_2 (C-3')).

1,8-Dihydroxy-10-(5'-oxo-tetrahydrofuryliden-2')-9(10H)anthracenone **(6)**

A suspension of 2.26 g (10 mmol) **1** in 40 ml of absol. toluene and 1.07 g (13.33 mmol) of dry pyridine was added to 1.6 g succinyl chloride (10 mmol) in 40 ml of absol. toluene. After refluxing for 3.5 h the orange solution thus formed was evaporated i. vac. and the residue was dissolved in a small volume of CH_2Cl_2. CC (SiO_2/CH_2Cl_2) and crystallization from CH_2Cl_2 afforded 1.1 g (36 %) **6** as yellow crystals, mp. 245 °C. – rf (SiO_2; CH_2Cl_2): 0.64. – $C_{18}H_{12}O_5$ (308.5) Calc. C 70.1 H 3.90 Found C 69.6 H 3.93. – UV (CH_2Cl_2): λ max (log ε) = 384 (4.36), 303 (sh, 4.31), 293 (4.32), 242 (4.41), 220 (4.06), 210 nm (4.05). – IR: 1810 (CO-O), 1640 cm^{-1} (C=O···HO). – ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 11.38 (s; 1 OH), 11.30 (s; 1 OH), 7.85–6.80 (m; 6 H aromat.) 3.56–3.32 (m; 2H, CH_2 (C-4')), 2.89–2.67 (m; 2H, CH_2 (C-3')). – MS: m/z = 309 (20 %), 308 (100; $M^{+\cdot}$), 280 (63), 263 (18), 253 (37), 252 (19), 238 (27), 224 (28).

Section B

3-(1,8-Dihydroxy-9(10H)-anthracenon-2-yl)-propionic acid **(7)**

10 g $SnCl_2$ in 25 ml of fuming HCl were added drop by drop to a solution of 1 g (2.3 mmol) (9,10-dihydro-1-hydroxy-8-methoxy-9,10-dioxo-2-anthryl)methyl malonic acid diethyl ester **(8)**[6] in 50 ml of boiling acetic acid (100 %). Boiling was continued for 6 h. After cooling **7** was precipitated by addition of 3–4 ml of water: 490 mg (70 %) **7**, mp. > 220° (decomp.) from CH_2Cl_2/MeOH. – rf (SiO_2; CH_2Cl_2/MeOH 9:1): 0.55. – $C_{17}H_{14}O_5$ (298.3) Calc. C 68.4 H 4.70 Found C 68.2 H 4.65. – UV (MeOH): λ max (log ε) = 357 (4.00), 291 (4.06), 257 (4.14), 207 nm (4.40). – IR: 1710 (COOH), 1620 cm^{-1} (C=O···HO). – ^{1}H-NMR (CF_3COOD): δ (ppm) = 6.99–6.77 (m; 2H aromat.), 6.47–6.18 (m; 3H aromat.), 3.55 (s; 2H, CH_2), 2.55–2.09 (m; 4H, CH_2CH_2-CO). – NI-FAB-MS: m/z = 298 (38 %; $M^{-\cdot}$), 297 [100; $(M-H)^-$], 253 (19; 297 – CO_2).

2,7-Bis-(carboxymethyl)-9,10-dihydro-1,8-dihydroxy-anthracene-9,10-dione **(10)**

A mixture of 4 g (17 mmol) **9** and 13 g (176 mmol) glyoxylic acid hydrate (Janssen Chimica) in 250 ml MeOH and 150 ml 2N NaOH was heated under N_2 to 70 °C. Na-dithionite was added in portions at this temp. until the colour changed from red violet to brown (about 3 h). Then the mixture was acidified with 2N HCl, the precipitate was filtered by suction and dried: crude material of **10**.

2,7-Bis-(methoxycarbonylmethyl)-9,10-dihydro-1,8-dimethoxy-anthracene-9,10-dione **(11)**

1 g (2.8 mmol) **10** and 2.3 g K_2CO_3 were refluxed in 40 ml dry acetone for 5 h. During this period 1.2 ml of dimethyl sulfate were added drop by drop. – After cooling and addition of 100 ml 2N HCl the mixture was extracted with CH_2Cl_2, the org. phase was washed with water, dried over Na_2SO_4 and evaporated. The residue was purified by CC (SiO_2; CH_2Cl_2): 500 mg (43 %) **11**, mp. 124 °C (CH_2Cl_2/petrol ether). – rf (SiO_2; CH_2Cl_2): 0.32. – $C_{22}H_{20}O_8$ (412.4) Calc. C 64.1 H 4.85 Found C 64.0 H 4.85. – UV (MeOH): λ max (log ε) = 356 (3.87), 255 (4.47), 218 nm (4.43). – IR: 1740 (CO-OCH_3), 1687 cm^{-1} (C=O). – ^{1}H-NMR: δ (ppm) = 8.09 (AB; 2H, H-4, H-5, J_{AB} = 7 Hz), 7.69 (AB; 2H, H-3, H-6), 4.03 (s; 6H, OCH_3) 3.86 (s; 4H, CH_2), 3.80 (s; 6H, CO-OCH_3).

2,7-Bis-(carboxymethyl)-1,8-dihydroxy-9(10H)-anthracenone **(12)**

100 mg (0.24 mmol) **11** in 15 ml glacial acetic acid were reduced with 1.25 g $SnCl_2$ in 3 ml of fuming HCl as described for **7**. – After cooling **12** crystallized from the mixture in a pure state: 40 mg (48 %) **12**, mp. > 250 °C (decomp.) from acetic acid. – $C_{18}H_{14}O_7$ (342.3) Calc. C63.2 H 4.09 Found C 63.0 H 4.14. – UV (MeOH): λ max (log ε) = 361 (3.98), 293 (4.02), 260 nm (4.23). – IR: 1700 (COOH), 1620 cm^{-1} (C=O···HO). – ^{1}H-NMR (60 MHz, [D_6]DMSO): δ (ppm) = 12.41 (s; 2H, OH), 7.58 (AB; 2H, J_{AB} = 10 Hz), 7.02 (AB; 2H), 4.42 (s; 2H, CH_2), 3.62 (s; 4H, CH_2-CO). – NI-FAB-MS: m/z = 342 (35 %; $M^{-\cdot}$), 341 [100; $(M-H)^-$], 297 (21; 341 – CO_2), 253 (95; 297 – CO_2).

2-Carboxymethyl-9,10-dihydro-1-hydroxy-8-methoxy-anthracene-9,10-dione **(14)**

To 500 mg (1.9 mmol) **13** and 1.5 g glyoxylic acid hydrate in 100 ml MeOH and 50 ml 2N NaOH was added an excess of Na-dithionite at 60 °C under N_2. After heating for 2 h the mixture was acidified with 100 ml 2N HCl and extracted with CH_2Cl_2. After evaporation to a small volume this solution was purified bei CC (SiO_2; CH_2Cl_2/MeOH 100: 14 v/v): 220 mg (36 %) **14**, mp. > 258 °C (decomp.) (acetic acid/water 9:1). – rf (SiO_2; CH_2Cl_2/MeOH 9:1): 0.41. – $C_{17}H_{12}O_6$ + 1/2 H_2O (321.3) Calc. C 63.6 H 4.05 Found C 63.8 H 3.90. – UV (MeOH): λ max (log ε) = 416 (3.98), 258 (4.51), 225 nm (4.52). – IR: 1690 (COOH), 1665 (C=O), 1630 cm^{-1} (C=O···HO). – ^{1}H-NMR (CF_3COOH): δ (ppm) = 7.55–6.97 (m; 5H aromat.), 3.53 (s; 3H, OCH_3), 3.41 (s; 2H, CH_2CO).

(1,8-Dihydroxy-9(10H)-anthracenon-2-yl)acetic acid **(15)**

80 mg (0.26 mmol) **14** in 10 ml acetic acid were reduced as described for **12** and **7**: 50 mg (68 %) **15**, mp. > 220 °C (decomp.) from $CHCl_3$/MeOH (9:1 v/v). – rf (SiO_2; CH_2Cl_2/MeOH 9:1): 0.45. – $C_{16}H_{12}O_5$ (284.3) Calc. C 67.6 H 4.23 Found C 67.5 H 4.44. – UV (MeOH): λ max (log ε) = 355 (3.85), 289 (3.98), 258 (4.07), 209 nm (4.20). – IR: 1695 (COOH), 1623 cm^{-1} (C=O···HO). – ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 12.62 (s; 1H, OH), 12.02 (s; 1H, OH), 7.72–7.51 (m; 2H aromat.), 7.10–6.82 (m; 3H aromat.), 4.45 (s; 2H, CH_2), 3.60 (s; 2H, CH_2-CO). – NI-FAB-MS: m/z = 284 (36 %; $M^{-\cdot}$), 283 [74; $(M-H)^-$], 239 (100; 283 – CO_2).

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