Electron-Impact Induced and Thermal Decomposition of Dithranol Derivatives, III [1]:

Fragmentations of 10-Alkoxy- and 10-Benzyloxydithranol Radical Cations*)

Elektronenstoß-induzierter und thermischer Zerfall von Dithranol-Derivaten, 3. Mitt. [1]: Fragmentierungen der Molekülionen von 10-Alkoxy- und 10-Benzyloxy-dithranol

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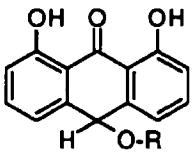
Derivatives of dithranol [anthralin; 1,8-dihydroxy-9(10*H*)-anthracenone] with substituents at C-10 are of interest in the search for antipsoriatic remedies [2]. While a wealth of compounds with a C-10 carbon bond was tested [3], only little is known about substituted anthralins with side-chains bound by hetero-atoms directly to C-10 [4 - 7]. Our studies on 10-alkylthio- and 10-arylthio-1,8-dihydroxy-9(10*H*)-anthracenones [1, 6, 8] caused us to synthesize *i.a.* the dithranol ethers **1**–**3** and their deuterium-labelled analogues **1a** and **3a**–**3c**.



R=	**1**	CH_3
	1a	CD_3
	2	C_2H_5
	3	$CH_2C_6H_5$
	3a	$CD_2C_6H_5$
	3b	$CH_2C_6D_5$
	3c	$CD_2C_6D_5$

Scheme 1

Under standard electron-impact ionization conditions (70/12 eV), *ipso*-cleavage [9] processes dominate dissociations in the ion source, in the case of **1** – **3** giving rise to strong ions at m/z 241 (M – $^{\bullet}$R) and m/z 225 (M – $^{\bullet}$OR), while in particular molecular ions of **3** additionally decompose to rearrangement ions at m/z 240, 226, and 92 (Table 1).

In the spectra of **1**, **1a**, and **2** m/z 240 ions arise by loss of $H^{\bullet}$ from m/z 241; m/z 226 ions come directly from the molecular ions by ejecting CH_2O (**1a**: CD_2O, → m/z 227) or CH_3CHO, respectively, as confirmed for metastable $M^{+\bullet}$ (B/E = const. linked scans). α-Cleavage (M – $^{\bullet}CH_3$) and elimination of C_2H_4, preponderant features of ionized ethyl ethers [9], could not be detected. Metastable $M^{+\bullet}$ of **3** decompose to m/z 331 (– $H^{\bullet}$), m/z 241 (– $^{\bullet}C_7H_7$), m/z 240 (–C_7H_8), m/z 226 (– C_6H_5CHO), and m/z 92 ($C_7H_8^{+\bullet}$) (Table 2).

Table 2: MIMS of **3** (m/z 332) (m/z; % rel. int.)[a)].

70 eV	331 (100)	254 (2)	241 (80)	240 (5)	226 (65)	92 (3)
12 eV	331 (100)	254 (3)	241 (95)	240 (2)	226 (70)	92 (5)

[a)] average of 10 runs

Table 1: Partial EIMS (70/12 eV; % rel. int.) of **1** – **3** (^{13}C corr.)[a)].

m/z No.	332	331	270	269	256	255	242	241	240	226	225	197	92	91
1 (256)	–	–	–	–	66/ 100	2/4	–	49/ 11	8/5	15/ 12	100/ 36	49/-	–	–
2 (270)	–	–	36/ 100	1/1	–	1/-	2/3	65/ 12	20/ 14	51/ 52	100/ 23	30/-	–	–
3 (332)	3/4	<1/ <1	–	–	–	–	–	47/ 27	100/ 66	98/ 100	49/ 7	34/-	25/ 18	34/ 10

[a)] average of 20 runs.

The data of the specifically deuterated ethers **3a** – **3c** support the concept of multiple H-migrations in their molecular ions before or in the course of fragmentation (Table 3):

m/z 226 ions are shifted mainly to m/z 227 in the MIMS of **3a** and **3c**, they keep their position in the case of **3b**. However,

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Table 3: MIMS (70/12 eV) of **3**, **3a**, **3b**, and **3c**; %Σ(m/z 226 to m/z 229) and %Σ(m/z 240 to m/z 243)[a].

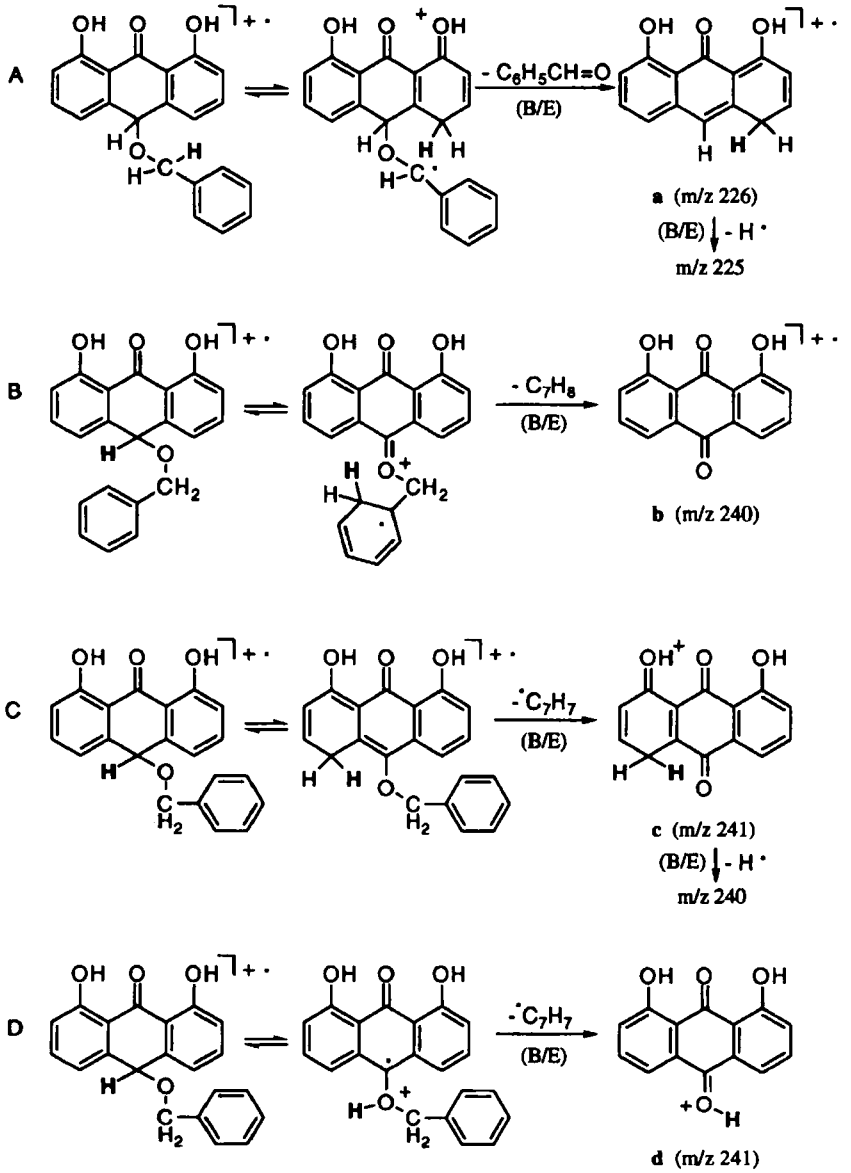
No./ m/z	226	227	228	229	240	241	242	243
3 (332)	100/100	–	–	–	5/7	95/93	–	–
3a (334)	–	95/94	5/6	–	11/9	85/80	3/8	1/3
3b (337)	81/76	15/18	4/6	–	10/6	50/45	35/41	5/8
3c (339)	2/3	87/79	8/13	3/5	8/7	54/50	33/36	5/7

[a] average of 10 runs

signals of minor to medium intensity at m/z 226 (**3c**), m/z 227 (**3b**), and m/z 228 and 229 (**3b**, **3c**) substantiate partial exchange of H-atoms of the 'dithranol' moiety and the benzyloxy group.

The ions at m/z 241 are partly shifted to m/z 242 and 243 (**3a–3c**) with a strong increase of %Σ-values (m/z 242) in the case of **3b** and **3c** as compared with **3a** due to D-atom migration from the benzylic CD_2-group (**3a**, **3c**) and to a higher extent from the aromatic nucleus (**3b**, **3c**) into the 'dithranol' part.

A mechanistic rationalization is given by equations **A** – **D** in Scheme 2, where reversible H-exchange between the positions C - 4/5 and C - 10, the benzylic methylene and the phenyl group is depicted.



Scheme 2

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Experimental Part

EIMS (70/12 eV) and MIMS: Finnigan MAT 95 double-focusing instrument. Samples were introduced by the direct insertion probe (quartz crucibles) at T = 100 °C; ion source temp. 100–120 °C. High resolution measurements were performed with m/Δm = 15 000.– Melting points: Büchi 510 melting point apparatus, uncorrected.– ^{1}H-NMR spectra: Varian EM 390 (90 MHz) or Bruker Spectrospin WM 250 spectrometer (250 MHz), TMS as int. standard.– Fourier-transform IR spectra (KBr): Nicolet 510M FT-IR spectrometer.– The D-content of the samples was measured by MS.

[α,α-D_2]-Benzyl alcohol [1]

A solution of benzoyl chloride (11.2 g, 80 mmole) in 20 ml of anhydrous ether was added dropwise with good stirring over a period of 30 min to a suspension of $LiAlD_4$ (1.89 g, 45 mmole) in 50 ml of anhydrous ether. After stirring for 2 h, water was added to destroy excess reagent followed by 10 % H_2SO_4 (10 ml). The solution was extracted twice with ether (2 × 100 ml). The extracts were dried (Na_2SO_4) and then distilled. Yield 8.1 g (92 %).– MS: m/z 110 (100 %); 99 % d_2, 1 % d_1.

[2,3,4,5,6-D_5]-Benzyl alcohol

A solution of [2,3,4,5,6-D_5]-benzoic acid (Aldrich) (1 g, 7.9 mmole) in 20 ml of anhydrous ether was added dropwise with good stirring over a period of 30 min to a suspension of $LiAlH_4$ (0.5 g, 13 mmole) in 20 ml of anhydrous ether. After stirring for 4 h, water was added, followed by 10 % H_2SO_4 (10 ml).– Yield 0.8 g (90 %).– MS: m/z 113 (100 %); 98 % d_5, 2 % d_4.

[α,α,2,3,4,5,6-D_7]-Benzyl alcohol

A solution of [2,3,4,5,6-D_5]-benzoic acid (Aldrich) (1 g, 7.9 mmole) in 20 ml of anhydrous ether was added dropwise with good stirring over a period of 30 min to a suspension of $LiAlD_4$ (0.5 g, 12 mmole) in 20 ml of anhydrous ether. After stirring for 4 h, water was added, followed by 10 % H_2SO_4 (10 ml).– Yield 0.8 g (88 %).– MS: m/z 115 (57 %); 97 % d_7, 2 % d_6, 1 % d_5.

10-Alkoxy and 10-Benzyloxy-1,8-dihydroxy-9-(10H)-anthracenone (**1, 2, 3, 3a, 3b, 3c**)*; General Procedure*

To a solution of 10-bromo-1,8-dihydroxy-9(10*H*)-anthracenone [10] (305 mg, 1.0 mmole) and 0.1 ml of trifluoroacetic acid in dry CH_2Cl_2 (20 ml) was added methanol (20 ml), ethanol (20 ml) or benzyl alcohol (1 g, 1.5 mmole) under N_2. The reaction mixture was stirred at room temp. for 4 h. Removal of the solvent and recrystallization of the residue from CH_2Cl_2 gave solid products.

10-Methoxy-1,8-dihydroxy-9(10H)-anthracenone (**1**)

Mp. 92–93 °C; lit.: 77–78 °C [7b].– FT-IR (KBr): 1636 (CO···HO) cm^{-1}.– EIMS (m/z; % rel. int.): 256 (66/100), 241 (49/11), 240 (8/5), 226 (15/12), 225 (100/36), 197 (49/-).– MIMS (B/E, m/z 256 ($M^{+\bullet}$)): 241 (90), 226 (35), 225 (100).

10-[D_3]-Methoxy-1,8-dihydroxy-9(10H)-anthracenone (**1a**)

Mp. 92–93 °C.– FT-IR (KBr): 1635 (CO···HO) cm^{-1}.– EIMS (m/z; % rel. int.): 259 (68/100), 241 (60/10), 240 (9/4), 227 (37/21), 225 (100/25), 197 (74/–).– MIMS (B/E, m/z 259 ($M^{+\bullet}$)): 241 (100), 227 (20), 225 (75).

10-Ethoxy-1,8-dihydroxy-9(10H)-anthracenone (**2**)

Mp. 98–99 °C.– FT-IR (KBr): 1630 (CO···HO) cm^{-1}.– EIMS (m/z; % rel. int.): 270 (36/100), 241 (65/12), 240 (21/14), 226 (56/36), 225 (100/25), 197 (51/-).– MIMS (B/E, m/z 270 ($M^{+\bullet}$)): 269 (100), 255 (3), 242 (2), 241 (72), 226 (25), 225 (20).

10-Benzyloxy-1,8-dihydroxy-9(10H)-anthracenone (**3**)

Mp. 102 °C.– FT-IR (KBr): 1630 (CO···HO) cm^{-1}.– ^{1}H-NMR (250 MHz, $CDCl_3$): δ (ppm) = 4.15 (s, 2H, CH_2), 5.87 (s, 1H, 10-H), 7.00 (d, J=8.5 Hz, 2H, 2-H, 7-H), 7.23 (m, J=8.5 Hz, 7H, C_6H_5, 4-H, 5-H), 7.58 (t, J= 8.5 Hz, 3-H, 6-H), 12.18 (s, 2H, 1-OH, 8-OH).– $C_{21}H_{16}O_4$ (332.3) Calcd. C 75.9 H 4.85 Found C 75.5 H 4.83.– EIMS (m/z ; % rel. int.): 332 (3/4), 254 (1/1), 241 (47/27), 240 (100/66), 226 (98/100), 225 (49/7), 197 (34/-), 92 (25/18), 91 (34/10).– MIMS (B/E m/z 332 ($M^{+\bullet}$)): 331 (100/100), 254 (2/3), 241 (80/95), 240 (5/2), 226 (65/70), 92 (3/5).– (B/E, m/z 241) : 240 (100).

[α,α-D_2]-10-Benzyloxy-1,8-dihydroxy-9(10H)-anthracenone (**3a**)

Mp. 102 °C.– $C_{21}H_{14}D_2O_4$ Calcd. 334.1174 Found 334.1173.– EIMS: (m/z; % rel. int.): 334 (13/22), 256 (4/6), 241 (98/98), 240 (73/76), 227 (94/100), 226 (39/30), 225 (100/16), 197 (53/-), 94 (22/18), 93 (23/13), 92 (5/1).– MIMS: (B/E, m/z 334 ($M^{+\bullet}$)): 333 (30), 256 (2), 242 (4), 241 (100), 240 (15), 228 (2), 227 (40), 94 (1).– (B/E, m/z 241): 240 (100), 239 (1), 213 (1), 212 (2).– (B/E, m/z 227): 226 (100), 199 (1), 198 (1), 197 (2).

[2,3,4,5,6-D_5]-10-Benzyloxy-1,8-dihydroxy-9(10H)-anthracenone (**3b**)

Mp. 102 °C.– $C_{21}H_{11}D_5O_4$ Calcd. 337.1362 Found 337.1364.– EIMS: (m/z; % rel. int.): 337 (11/3), 254 (2/1), 242 (7/6), 241 (52/24), 240 (65/48), 227 (1/16), 226 (100/100), 225 (56/14), 197 (21/-), 97 (18/9), 96 (26/7), 95 (3/1).– MIMS: (B/E, m/z 337 ($M^{+\bullet}$)): 336 (≈1), 335 (12), 254 (1), 242 (55), 241 (75), 240 (15), 228 (2), 227 (20), 226 (100), 97 (1).– (B/E, m/z 242): 241 (100), 240 (2), 213 (2), 212 (3).

[α,α,2,3,4,5,6-D_7]-10-Benzyloxy-1,8-dihydroxy-9-(10H)-anthracenone (**3c**)

Mp. 102 °C.– $C_{21}H_9D_7O_4$ Calcd. 339.1488 Found 339.1487.– EIMS: (m/z; % rel. int.): 339 (9/19), 256 (4/4), 242 (24/26), 241 (72/53), 240 (38/36), 227 (74/100), 226 (30/19), 225 (100/20), 197 (32/-), 99 (16/20), 98 (17/3), 97 (3/1).– MIMS: (B/E, m/z 339 ($M^{+\bullet}$)): 338 (5), 256 (3), 242 (65), 241 (100), 240 (10), 228 (2), 227 (55), 226 (1), 99 (2).– (B/E, m/z 242): 241 (100), 213 (1), 212 (1).– (B/E, m/z 241): 240 (100), 213 (1), 212 (2).

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