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Short Communications

Electron-impact Induced and Thermal Decomposition of Dithranol Derivatives, II[1]:

Multiple H-Rearrangements in 10-Benzylthio-dithranol Radical Cations

Elektronenstoß-induzierter und thermischer Zerfall von Dithranol Derivaten, 2. Mitt.[1]: Mehrfache H-Umlagerungen in den Molekülionen des 10-Benzylthio-dithranols

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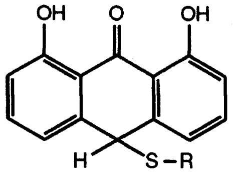
10-Alkylthio- and 10-arylthio-derivatives of dithranol (anthralin; 1,8-dihydroxy-9-anthrone) are of interest in search for new anti-psoriatic agents[2,3]. By working out ms procedures for unequivocal identification of trace amounts of these compounds[4] it was established that in case of 10-phenylthio-dithranol putative by-products, especially one giving rise to ions at m/z = 226 (dithranol), are artefacts of thermal reaction in the mass spectrometer[1]. In the EI-MS of those 10-substituted dithranols containing a S-CH_2R chain, however, these ions (m/z = 226) arise from $M^{+\bullet}$ as well. Scope and mechanism of their formation was examined by analyzing compound **1** and its D-labelled derivatives **2** and **3**.



1 : R = $CH_2C_6H_5$
2 : R = $CD_2C_6H_5$
3 : R = $CD_2C_6D_5$

In the standard EI mass spectra of **1** (Exp. Part), ions at m/z = 226 appear with various intensities depending on inlet-system, ion-source conditions and crucible materials due to thermal decomposition of **1** before ionization[1]. Therefore, only those fragment ions which are derived from metastable molecular ions of **1** decomposing in the 1st field free region (B/E = const. linked scans) were examined (Table 1).

In addition to the loss of $H^\bullet$ (→ m/z 347), three fragmentation pathways can be postulated: two of them initiated by single bond cleavage giving rise to ions at m/z = 257 (M - $^\bullet C_7H_7$) and m/z = 225 (M - $^\bullet S\text{-}CH_2C_6H_5$), and one proceeding with H-rearrangement (m/z = 226; $C_{11}H_{10}O_3$) resulting in ionized dithranol or an isomer thereof. By lowering excess energies of $M^{+\bullet}$ (70 eV → 12 eV), these fragmentation processes gain intensity as compared to $H^\bullet$-loss, as expected in case of rearrangements and fission of the relatively weak C-S bond[5].

From the data of Table 2, further mechanistic conclusions can be derived:

- The hydrogen atom migrating into the "dithranol" moiety of $M^{+\bullet}$ prior to or in the course of the C(10)-S bond breakage originates mainly from the benzylic position of the side chain. Accordingly, m/z = 226 is shifted to m/z = 227 in the spectra of **2** and **3**.
- The deuteriated analogues of $\mathbf{1}^{+\bullet}$ yield still a remarkably high amount of m/z = 226 ions, even in case of **3**. So, an exchange of the H-atoms of the "dithranol" part and the benzylthio-group must take place.
- A minor percentage of the "anthrone" part contains two D-atoms (m/z 228).
- The ions at m/z = 257 (**1**) are partly shifted to m/z = 258 (**2**; **3**) with a strong increase of % Σ-values comparing **2** and **3**. So, one D-atom migrates from the benzylic CD_2-group (**2**) as well as from the aromatic nucleus (**3**) into

Table 1: MI-MS of **1** (m/z 348) (m/z; % rel. int.)[a)]

70eV	347(100)	257(35)	226(20)	225(28)
12eV	347(100)	257(70)	226(75)	225(80)

a) average of 10 runs.

Table 2: MI-MS of **1-3**; % Σ (225-229) and % Σ (257-258) (70/12 eV)[a)]

No. / m/z	225	226	227	228	229	257	258
1	58/52	42/48	-	-	-	100/100	-
2	60/50	10/10	28/38	2/2	-	84/75	16/25
3	71/61	8/8	18/27	2/3	~1/~1	70/62	30/38

a) average of 10 runs.

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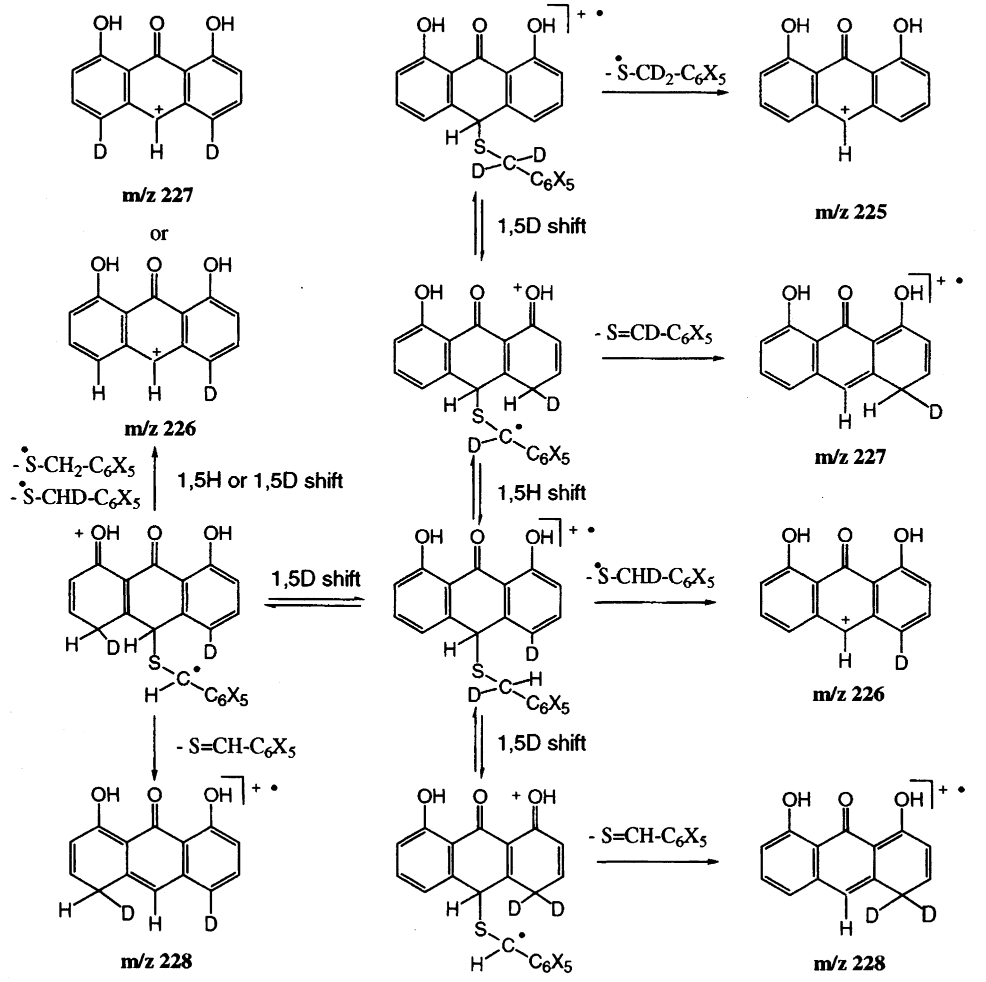
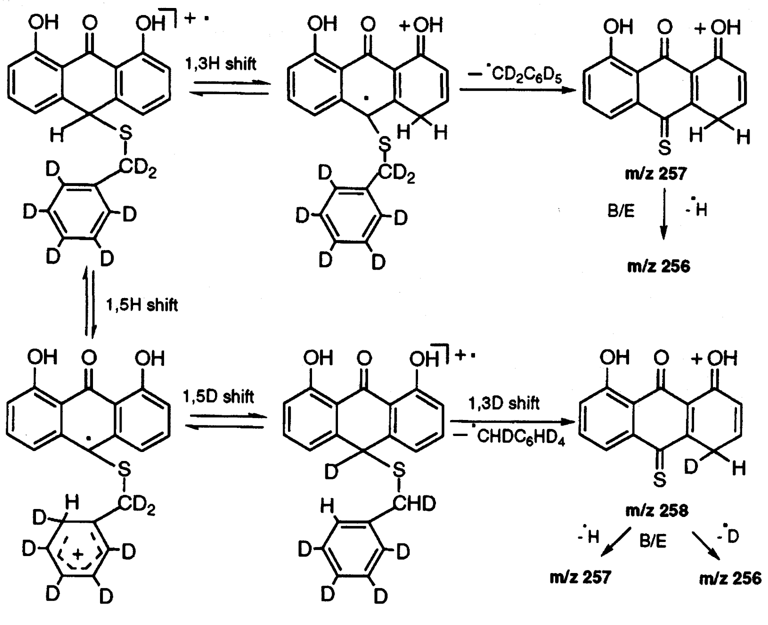


Scheme 1: Formation of ions at m/z 225 - m/z 228 (**2**: X = H; **3**: X = D)



Scheme 2: Formation of ions at m/z 256 - m/z 258 (**3**)

the "anthrone" moiety before fragmentation comes about. Accordingly, m/z = 91 (**1**: C_7H_7) is shifted to m/z = 92 (**2**: C_7H_6D) and m/z = 97 (**3**: C_7HD_6).

These results are summarized in Schemes 1 and 2 where a series of reversible H-rearrangements, partly giving rise to isotopomers, in accordance with those published for α,ω-diphenylalkanes[6] illustrate the formation of these ions.

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Experimental Part

EI-MS (70/12 eV) and MI-MS: Finnigan MAT 95 double-focusing instrument. Samples were introduced *via* the direct insertion probe (quartz crucibles), at 100°C; ion source temp. 100-120°C. High resolution measurements with m/Δm = 15000.- Melting points: Büchi 510 melting point apparatus, uncorrected.- ^{1}H-NMR spectra: Varian EM 390 (90 MHz), TMS as internal standard.- Fourier-transform IR spectra (KBr): Nicolet 510M FTIR spectrometer.- D-content of the samples was measured by mass spectrometry.

$$C_6H_5COCl \xrightarrow{LiAlD_4} C_6H_5CD_2OH \xrightarrow{HBr} C_6H_5CD_2Br$$

$$\xrightarrow{EtOCS_2K} C_6H_5CD_2SCSOEt \xrightarrow{LiAlH_4} C_6H_5CD_2SH$$

$$C_6D_5CD_2Cl \xrightarrow{EtOCS_2K} C_6D_5CD_2SCSOEt \xrightarrow{LiAlH_4} C_6D_5CD_2SH$$

Scheme 3

[α,α-D$_2$]-Benzyl alcohol

A solution of benzoyl chloride (11.2 g, 80 mmole) in 20 ml of anhydrous ether was added dropwise with vigorous 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 the excess of reagent followed by 10% H_2SO_4 (10 ml). The solution was extracted twice with ether (2 x 100 ml). The extracts were dried (Na_2SO_4) and distilled: 8.1 g (92%).- MS: m/z = 110 (100%).

[α,α-D$_2$]-Benzyl bromide

[α,α-D$_2$]-Benzyl alcohol (8.1 g, 74 mmole) was added dropwise to a mixture of 30 g 62% HBr and 10.8 g conc. H_2SO_4. The reaction mixture was refluxed for 2 h, cooled, and extracted with ether (2 x 100 ml). The ether layer was washed successively with water, diluted HCl, and 5% $NaHCO_3$. The residue was purified by distillation: 7.5 g (60%).- MS: m/z = 172 (^{79}Br; 12%); D_2 = 99%, D_1 = 1%.

[α,α-D$_2$]-Benzyl ethylxanthate

To 1.72 g (10 mmole) of [α,α-D$_2$]-benzyl bromide in 5 ml of acetone was added dropwise with intensive agitation a solution of commercial potassium ethylxanthate (2.4 g, 15 mmole)[7] in 50 ml of acetone over a period of 30 min; the reaction mixture was then stirred for additional 3 h. After filtration of KBr, chloroform was added, the solution was washed with water, dried (Na_2SO_4), and the solvent was removed *in vacuo*: 1.5 g (70%).- MS: m/z = 214 (28%).

[α,α-D$_2$]-Benzyl thiol

[α,α-D$_2$]-Benzyl ethylxanthate (1.5 g, 7 mmole) in 20 ml of anhydrous ether was added dropwise to a suspension of 0.5 g $LiAlH_4$ in 20 ml of anhydrous ether. After stirring for 4 h, acetone was added to destroy the excess of reagent followed by 6N H_2SO_4 (10 ml). The ether layer was separated and extracted 3 times with 10% KOH. The alkaline extracts were combined and acidified with HCl. The thiol was extracted with ether (2 x 100) and the ethereal layer was washed with water and dried (Na_2SO_4). Distillation yielded 0.8 g (90%) of the product, b.p. 194-195°C.- MS: m/z 126 (37), 93 (100).

[α,α,2,3,4,5,6-D$_7$]-Benzyl ethylxanthate

To a solution of potassium ethylxanthate (1.6 g, 10 mmole) in 50 ml of acetone was added dropwise a solution of [D$_7$]-benzyl chloride (1.0 g, 7.5 mmole) in acetone (5 ml). The reaction mixture was stirred for 8 h. After filtration of KBr, $CHCl_3$ was added (50 ml), the solution was washed with water, dried (Na_2SO_4), and evaporated. The residue was sufficiently pure for next step.- MS: m/z = 219 (50).

[α,α,2,3,4,5,6-D$_7$]-Benzyl thiol

MS: m/z 131 (43), 98 (100).

Preparation of 10-Benzylthio-1,8-dihydroxy-9-anthrones (**1, 2, 3**)

To a solution of 10-bromo-1,8-dihydroxy-9-anthrone[8] (305 mg, 1.0 mmole) and 0.1 ml of trifluoroacetic acid in dry CH_2Cl_2 (20 ml) was added benzyl mercaptan (0.2 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 $CHCl_3$ gave yellow crystals, mp. 155°C [Lit.[2]: 153°C].

10-Benzylthio-1,8-dihydroxy-9-anthrone (**1**)

FT-IR (KBr) 1630 (CO···HO) cm^{-1}.- ^{1}H-NMR (90 MHz, $CDCl_3$): δ (ppm) = 3.46 (s, 2H, CH_2), 5.18 (s, 1H, 10-H), 6.90 (d, J = 8.5 Hz, 2H, 2-H, 7-H), 7.00 (d, J = 8.5 Hz, 2H, 4-H, 5-H), 7.20 (m, 5 aromat. H), 7.45 (t, J = 8.5 Hz, 3-H, 6-H), 11.80 (s, 2H, 1-OH, 8-OH).- $C_{21}H_{16}O_3S$ (348.4) Calcd. C 72.3 H 4.59 Found C 72.1 H 4.53.

EIMS: m/z (70/12 eV; % rel. int.): 348 (45/100), 257 (4/1), 256 (6/12), 226 (25/58), 225 (100/81), 197 (45/-), 169 (8/), 168 (5/-), 151 (16/-), 141 (13/-), 139 (9/-), 124 (3/7), 91 (17/8).

MIMS: (B/E), (70/12 eV; % rel. int.):
m/z 348 ($M^{+\bullet}$): 347 (100/100), 257 (35/70), 226 (20/75), 225 (28/80).
m/z 257: 256 (100).
m/z 226: 225 (100).

MIMS: (B^2/E): m/z 226; 348 ($M^{+\bullet}$).

[α,α-D$_2$]-10-Benzylthio-1,8-dihydroxy-9-anthrone (**2**)

EIMS: m/z (70/12 eV; % rel. int.): 350 (56/100), 257 (5/3), 256 (1/3), 227 (5/8), 226 (26/35), 225 (100/95), 197 (38/-), 169 (6/-), 168 (3/-), 151 (12/-), 141 (10/-), 139 (7/-), 126 (4/4), 115 (5/-), 93 (19/4); d_2 = 98%, d_1 = 2%.

MIMS: (B/E), (70/12 eV, % rel. int.):
m/z 350 ($M^{+\bullet}$): 349 (100/100), 258 (7/18), 257 (38/59), 228 (1/3), 227 (14/60), 226 (5/13), 225 (30/75).
m/z 257: m/z 256 (100).

[α,α, 2,3,4,5,6-D_7]-10-Benzylthio-1,8-dihydroxy-9-anthrone (**3**)

EIMS: m/z (70/12 eV, % rel. int.) 355 (32/98), 258 (2/4), 257 (4/3), 256 (3/6), 229 (1/1), 228 (2/2), 227 (9/11), 226 (30/51), 225 (100/100), 197 (34/-), 169 (6/-), 168 (2/-), 151 (10/-), 141 (7/-), 139 (6/-), 131 (3/5), 115 (4/-), 98 (18/7); d_7 = 97%, d_6 = 2%, d_5 = 1%.

MIMS: (B/E), (70/12 eV, % rel. int.):
m/z 335 ($M^{+\bullet}$): 354 (100/100), 353 (5/8), 258 (35/40), 257 (80/65), 229 (< 0.5/~ 1), 228 (2/5), 227 (15/35), 226 (7/10), 225 (60/80).

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