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Arbeitsvorschriften und Meßwerte · Procedures and Data

Unusual Variant of the Favorsky Rearrangement. Formation of α–Keto Acetals.

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Dedicated to Ekkehard Winterfeldt with all Good Wishes on the Auspicious Occasion of his 65th Birthday

During work directed toward the synthesis of neuroleptics related to maprotiline (ludiomil®) [1] we studied the reaction of polycyclic α-bromo ketones and also α,α'-dibromo ketones with nucleophiles and bases. Starting materials were 9,10-dihydro-9,10-propanoanthracen-12-ones, which are conveniently accessible by cycloaddition of metal oxyallyl cations to anthracene [2, 3].

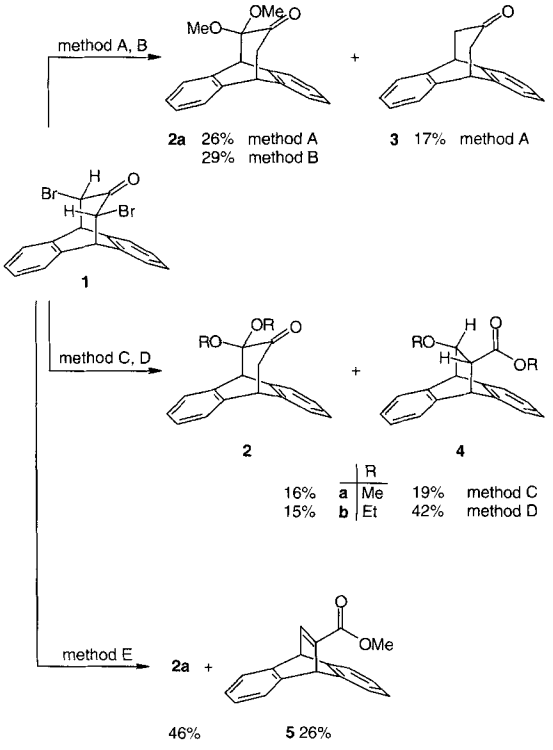
The reaction of *trans*-dibromo ketone **1** [2d] with *p*-toluenethiolate afforded not only the parent ketone **3** (17%), but also α-keto acetal **2** (26%). Products of S_N2 displacement of bromine were not observed. Since the formation of an α-keto acetal was unexpected, we decided to investigate the reactions of α,α'-dibromo ketone **1** under a variety of conditions, using alcohols and different bases.

The standard procedure for inducing the Favorsky rearrangement [4] (EtOH, KOH, 80 °C) gave the highest yield of Favorsky ester **4b** (42%). Treatment of **1** with MeOH and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), which is a comparatively weak base, furnished β-methoxy ester **4a** and, again, α-keto acetal **2a** (Scheme 1).

By increasing the strength of the base (MeOH, KOH, 60 °C) the yield of α-keto acetal was increased to 29%. Finally, on lowering the temperature to room temperature and using MeOH/MeONa, we obtained α-keto acetal **2a** in 46% yield. Another product was 11-methoxycarbonyl-9,10-dihydro-9,10-eth-11-enoanthracene (**5**), which had previously been prepared by Diels–Alder reaction of methyl 2-propynoate to anthracene [5].

Formation of the α-keto acetal involves an intramolecular oxidation-reduction reaction. Deprotonation of **1** is thought to furnish a bromoallylic bromide (cf. **A**), which undergoes an S_N1-like heterolysis to give the resonance-stabilized (metal) oxyallyl cation (**B** ↔ **C**). Recombination with methanol provides α-bromo ether **D**, which on regioselective methanolysis and ketonization furnishes α-keto acetal **2a** (Scheme 2) [6].

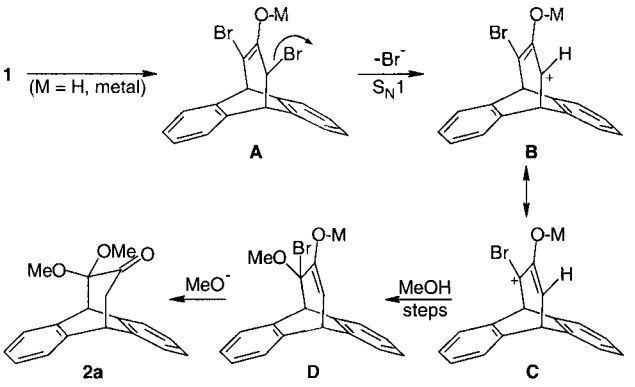
An allylic rearrangement analogous to the postulated sequence **A** → **D** was also observed for monobromo ketone **6**,



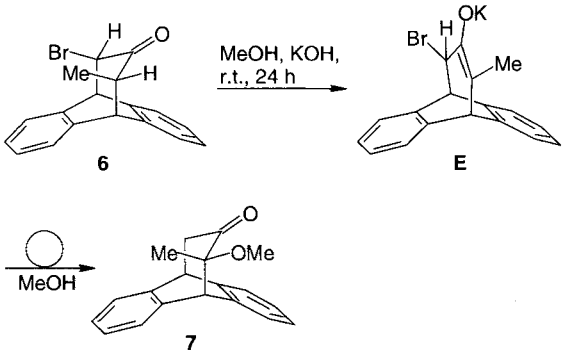
Scheme 1 Method A: *p*-$CH_3C_6H_4SH$, MeOH, KOH, *r.t.*, 5 h. Method B: MeOH, KOH, 60 °C, 3 h. Method C: MeOH, DBU, 80 °C, 3 h. Method D: EtOH, KOH, 80 °C, 5 h. Method E: MeOH, MeONa, *r.t.*, 24 h.

giving α-methoxy ketone **7** under the same conditions (Scheme 3).

In conclusion, the polycyclic framework of α,α'-dibromo ketones derived from 9,10-dihydro-9,10-propanoanthracen-12-ones, as in **1**, is probably unique in that (i) formation of a double bond at the two bridgehead positions is impossible



Scheme 2



Scheme 3

and (ii) the three-carbon atom bridge together with the two bridgehead carbon atoms are approximately in one plane, promoting allylic rearrangement in an intermediate cation **B** ↔ **C**. While the conventional Favorsky ring contraction and also the formation of dibenzobarrelene **5** are possible, they do not predominate over the formation of the α-keto acetal.

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Experimental

Column chromatography (silica gel, 0.02 – 0.63 mm, Merck) was carried out under weak positive pressure. – TLC: Precoated plates, Macherey-Nagel, Merck. – Gaschromatography: FID, N2, Varian A 1400; glass capillary column (25 m, type OV 1 CB) and SE 54 CB (25-m fused silica, widebore). – Melting points: Büchi apparatus. – IR: Electrophotometer 580 and FT spectrometer 1710, Perkin-Elmer. – ^{1}H NMR: WP 80, WH 90, WP 200 SY and AM 300, Bruker. – ^{13}C NMR: WP 200 SY, AM 300, Bruker. APT (attached proton test): spin-echo based selection of multiplicities of ^{13}C signals. Quaternary C and CH_2 carbon atoms give positive signals (+), while CH and CH_3 give negative signals (–). – MS: Spectrometer MAT 312, Finnigan. – Elementary analyses: Microanalytical laboratory of the Department of Organic Chemistry. – PE: Petroleum ether. E: Diethyl ether. CH: Cyclohexane. DCM: Dichloromethane.

11,11-Dimethoxy-9,10-dihydro-9,10-propanoanthracen-12-one (**2a**)

Method A. A mixture of dibromo cycloadduct **1** [2d] (0.26 g, 0.66 mmol), *p*-methylthiophenol (0.164 g, 1.32 mmol) and KOH (74 mg, 1.32 mmol) was stirred in methanol (20 ml) under N_2 for 5 h at room temperature. The reaction mixture was diluted with water and extracted with $CHCl_3$. The $CHCl_3$ layer was separated, dried ($MgSO_4$), filtered, and the solvent was evaporated under reduced pressure. The crude product was chromatographed (silica gel, E/PE, 1:5) to give the separable products anthraquinone (20 mg, 15%), parent cycloadduct **3** [2d] (26 mg, 17%) and α-keto acetal **2a** (50 mg, 26%).

Method B. A mixture of dibromo cycloadduct **1** (0.16 g, 0.4 mmol) and KOH (0.05 g, 0.9 mmol) was heated at reflux in methanol (15 ml) with stirring under N_2 for 4 h. The reaction mixture was cooled, diluted with water, extracted with DCM and the extract was dried ($MgSO_4$). The filtrate was concentrated under reduced pressure and chromatographed to give colorless crystals of **2a** (35 mg, 29%).

Method C. A mixture of dibromo cycloadduct **1** (0.12 g, 0.3 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.2 ml) was heated at reflux under nitrogen in methanol (10 ml) at 80 °C for 5 h in an oil bath. The reaction mixture was diluted with HCl (0.1N), extracted with $CHCl_3$, the extract was washed with water and dried ($CaCl_2$). $CHCl_3$ was evaporated under reduced pressure and the residue was chromatographed (silica gel, E/CH, 1 : 3.5) to give ester **4a** (17 mg, 19%), followed by α-keto acetal **2a** (14 mg, 16%). Data of **2a**: *m. p.* 169 °C. – IR (KBr): ν = 2941 cm^{-1}, 2831, 1709, 1480, 1456, 1125, 1079, 1001, 715. – ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.94 (d, J = 4 Hz, 2 H, 13-H), 3.30 (s, 6 H, 2 OCH_3), 4.20 (t, J = 4 Hz, 1 H, 9-H), 4.53 (s, 1 H, 10-H), 7.18 – 7.41 (m, 8 H, arom. H). – ^{13}C NMR (50 MHz, APT, $CDCl_3$): δ 43.89 (–, C-9,10), 49.38 (+, C-13), 50.36 (–, OCH_3), 102.91 (+, C-11), 125.42–28.55 (–, arom. C), 137.30, 142.17 (+, arom. C), 202.44 (+, C=O). – MS, *m/z* (%): 294 (14) [M$^+$], 262 (6), 221 (13), 191 (23), 178 (100), 152 (5), 116 (41), 102 (1), 88 (8), 75 (8), 59 (6). – $C_{19}H_{18}O_3$: calcd. 294.1245, found 294.1256 (MS).

$C_{19}H_{18}O_3$	Calcd.:	C 77.53	H 6.16,
(294.3)	Found:	C 77.40	H 6.31.

12-Methoxy-11-methoxycarbonyl-9,10-dihydro-9,10-ethanoanthracene (**4a**)

m. p. 89–90 °C. – IR (KBr): ν = 3071 cm^{-1}, 3042, 3024, 2952, 2827, 1734, 1616, 1460, 1435, 1345, 1115, 798, 755. – ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.62 (dd like t, J = 3 Hz, 1 H, 11-H), 3.4 (s, 3 H, OCH_3), 3.64 (s, 3 H, CO_2CH_3), 4.10 (dd like t, J = 3 Hz, 1 H, 12-H), 4.56 (d, J = 3 Hz, 1 H, 10-H), 4.62 (d, J = 3 Hz, 1 H, 9-H), 7.05–7.40 (m, 8 H, arom. H). – ^{13}C NMR (200 MHz, APT, $CDCl_3$): δ 46.59, 48.42 (–, C-9,10), 52.09 (–, C-11), 52.75 (–, OCH_3), 56.75 (–, CO_2CH_3), 82.05 (–, C-12), 123.53–126.42 (–, arom. C), 139.91, 140.00, 140.75, 141.54 (+, arom. C), 172.82 (+, C=O). – MS, *m/z* (%), 219 (2), 208 (2), 202 (3), 191 (2), 178 (96), 165 (2), 152

(9), 139 (2), 111 (7), 95 (12), 85 (14), 84 (100), 77 (12), 71 (26), 65 (4), 57 (50), 47 (48). – FAB-MS, *m/z* (%): 294 (4) [M+], 263 (28), 219 (2), 203 (9), 191 (7), 178 (100), 165 (8), 154 (22), 136 (9), 120 (4), 112 (5).

$C_{19}H_{18}O_3$	Calcd.:	C 77.53	H 6.16,
(294.3)	Found:	C 77.40	H 6.31.

12-Ethoxy-11-ethoxycarbonyl-9,10-dihydro-9,10-ethanoanthracene (**4b**) and *11,11-Diethoxy-9,10-dihydro-9,10-propanoanthracen-12-one* (**2b**)

Method D. A mixture of dibromo cycloadduct **1** (0.17 g, 0.43 mmol) in ethanol and KOH (48 mg, 0.86 mmol) was stirred under N_2 in an oil bath at 80 °C for 5 h. The reaction mixture was worked up and chromatographed (silica gel, E/PE, 1:10) to give colorless crystals of ester **4b** (58 mg, 42%) followed by keto acetal **2b** (21 mg, 15%). Data of **4b**: *m. p.* 68 °C. – IR (film): ν = 3071 cm^{-1}, 3043, 2977, 2937, 2900, 1733, 1467, 1460, 1372, 1284, 1210, 1186, 1115, 1098, 1027, 766, 754. – ^1H NMR (200 MHz, $CDCl_3$): δ 1.10 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.20 (t, J = 7 Hz, 3 H, $CO_2CH_2CH_3$), 2.57 (dd like t, J = 3 Hz, 1 H, 11-H), 3.35–3.65 (m, 2 H, OCH_2), 4.05 (m, 2 H, CO_2CH_2), 4.18 (dd like t, J = 3 Hz, 1 H, 12-H), 4.50 (d, J = 3 Hz, 1 H, 10-H), 4.60 (d, J = 3 Hz, 1 H, 9-H), 7.00–7.40 (m, 8 H, arom. H). – ^{13}C NMR (50 MHz, APT, $CDCl_3$): δ 14.23 (–, OCH_2CH_3), 15.30 (–, $CO_2CH_2CH_3$), 46.73, 48.91, 52.99 (–, C-9,10,11), 60.77 (+, OCH_2), 64.28 (+, CO_2CH_2), 80.04 (–, C-12), 123.42–126.23 (–, arom. C), 140.17, 140.36, 140.75, 141.69 (+, arom. C), 172.41 (+, C=O). – MS, *m/z* (%), 292 (2), 248 (3), 231 (2), 219 (2), 203 (4), 191 (5), 178 (100), 165 (3), 152 (6), 139 (2), 113 (3), 99 (9), 84 (56), 77 (2), 61 (2). – FAB-MS, *m/z* (%): 322 (4) [M+], 277 (35), 219 (4), 202 (9), 191 (11), 178 (100), 165 (7), 152 (7), 136 (6), 115 (3), 102 (2).

$C_{21}H_{22}O_3$	Calcd.:	C 78.23	H 6.87,
(322.4)	Found:	C 78.09	H 6.84.

Data of **2b**: *m. p.* 126 °C. – IR (film): ν = 3030 cm^{-1}, 2975, 2929, 2896, 1704, 1479, 1456, 1112, 783, 760. – ^1H NMR (200 MHz, $CDCl_3$): δ 1.15 (t, J = 7 Hz, 6 H, 2 CH_3), 2.91 (d, J = 4 Hz, 2 H, 13-H), 3.45 (m, 2 H, OCH_2), 3.75 (m, 2 H, OCH_2), 4.20 (t, J = 4 Hz, 1 H, 9-H), 4.52 (s, 1 H, 10-H), 7.10–7.40 (m, 8 H, arom. H). – ^{13}C NMR (50 MHz, APT, $CDCl_3$): δ 15.13 (–, 2 CH_3), 43.95 (–, C-9), 49.66 (+, C-13), 51.73 (–, C-10), 58.09 (+, 2 OCH_2), 102.80 (+, C-11), 125.28–128.67 (–, arom. C), 137.06, 142.19 (+, arom. C), 202.96 (+, C=O). – MS, *m/z* (%): 322 (3) [M+], 321 (7), 307 (1), 277 (2), 265 (2), 235 (2), 203 (2), 192 (7), 178 (37), 165 (2), 152 (4), 144 (11), 121 (4), 116 (11), 103 (3), 88 (12), 86 (69), 84 (100), 76 (3), 65 (2).

$C_{21}H_{22}O_3$	Calcd.:	C 78.23	H 6.87,
(322.4)	Found:	C 77.89	H 6.84.

11-Methoxycarbonyl-9,10-dihydro-9,10-eth-11-enoanthracene (**5**) [5]

Method E. A mixture of dibromo cycloadduct **1** (80 mg, 0.2 mmol) and MeONa (22 mg, 0.4 mmol) was stirred in MeOH (10 ml) at room temperature under N_2 for 24 h. Work-up and chromatography (silica gel, E/CH, 1:5) gave colorless crystals of ester **5** (14 mg, 26%) followed by α-keto acetal **2a** (28 mg, 46%).

cis-11-Bromo-13-methyl-9,10-dihydro-9,10-propanoanthracen-12-one (**6**)

A mixture of anthracene (5 g, 28 mmol), Zn (7.32 g, 11.2 mmol) and CuCl (1.1 g, 1.1 mmol) in dioxane (80 ml) was sonicated at 15–20 °C for several min. A solution of 1,1,3-tribromobutanone (17.2 g, 56 mmol) in dioxane (20 ml) was added dropwise over a period of 30 min. The reaction mixture was sonicated at the same temperature under N_2 for 7 h and worked up, giving after chromatography (silica gel, acetone/CH, 1:12) colorless crystals of *cis* isomer **6** (1.25 g (14%), *m. p.* 162 °C. – IR (KBr): ν = 2938 cm^{-1}, 1695, 1478, 1455, 1287, 1153, 1119, 1087, 762, 744. – ^1H NMR (200 MHz, CD_2Cl_2): δ 1.20 (d, J = 8 Hz, 3 H, CH_3), 3.00 (ddq, J = 1.5 Hz, J = 4 Hz, J = 8 Hz, 1 H, 13-H), 4.00 (d, J = 4 Hz, 1 H, 9-H), 4.53 (d, J = 4 Hz, 1 H, 10-H), 4.67 (dd, J = 1.5 Hz, J = 4 Hz, 1 H, 11-H), 7.23 (m, 8 H, arom. H). – ^{13}C NMR (50 MHz, APT, CD_2Cl_2): δ 19.18 (–, CH_3), 50.26 (–, C-13), 51.98 (–, C-9), 55.07 (–, C-10), 57.08 (–, C-11), 126.75–129.24 (–, arom. C), 139.28, 143.10 (+, arom. C), 204.62 (+, C=O).

$C_{18}H_{15}BrO$	Calcd.:	C 66.07	H 4.62,
(327.2)	Found:	C 65.85	H 4.64.

11-Methoxy-11-methyl-9,10-dihydro-9,10-propanoanthracen-12-one (**7**)

cis Isomer **6** (0.328 g, 1.0 mmol) was stirred with KOH (84 mg, 1.5 mmol) in anhydrous methanol at 60 °C for 6 h under N_2. The reaction mixture was cooled, diluted with water und extracted with $CHCl_3$. The combined organic layers were dried ($CaCl_2$) and chromatographed (silica gel, E/CH, 1:5) to give **7** (26%). – IR (KBr): ν = 3020 cm^{-1}, 2952, 2924, 2900, 1704, 1592, 1456, 1420, 1332, 1284, 1148, 1120, 1040, 768, 728. – ^1H NMR (200 MHz, C_6D_6): δ 1.32 (s, 3 H, CH_3), 2.77 (d, J = 5 Hz, 2 H, 13-H), 2.88 (s, 3 H, OCH_3), 3.72 (t, J = 5 Hz, 1 H, 9-H), 4.00 (s, 1 H, 10-H), 7.00–7.36 (m, 8 H, arom. H). – ^{13}C NMR (50 MHz, APT, $CDCl_3$): δ 19.24 (–, CH_3), 44.06 (–, C-9), 48.42 (+, C-13), 52.05 (–, C-10), 55.70 (–, OCH_3), 84.23 (+, C-11), 124.91–129.03 (–, arom. C), 138.21–142.19 (+, arom. C), 207.54 (+, C=O). – MS, *m/z* (%): 278 (6) [M+], 264 (1), 248 (2), 246 (2), 220 (2), 204 (100), 189 (27), 178 (15), 165 (2), 152 (15), 145 (12), 131 (6), 111 (6), 97 (10), 77 (3), 73 (9), 63 (12), 51 (5), 45 (27).

$C_{19}H_{18}O_2$	Calcd.:	C 81.98	H 6.51,
(278.4)	Found:	C 81.44	H 6.20.

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