Phenanthrylalkanoic Acids, IV[1]:

Syntheses and Antiinflammatory Activity of 2-, 3-, and 9-Phenanthryl- and 9-Chloro-3-phenanthryl Derivatives of Propanoic Acid

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The phenanthrylethanols **2a-d** were obtained by reduction of the acetyl derivatives **1a-d** and converted, through the phenanthrylethyl halides **3a-d** and **4b**, into the nitriles **5a-d**, whose acid hydrolysis afforded the acids of the title, **6a-d**. The antiinflammatory activity of these acids was measured on the carrageenin-induced edema and found as 1/3 (**6a**), 1/43 (**6b**), 1/5 (**6c**), and 1/7 (**6d**) of that of fenbufen.

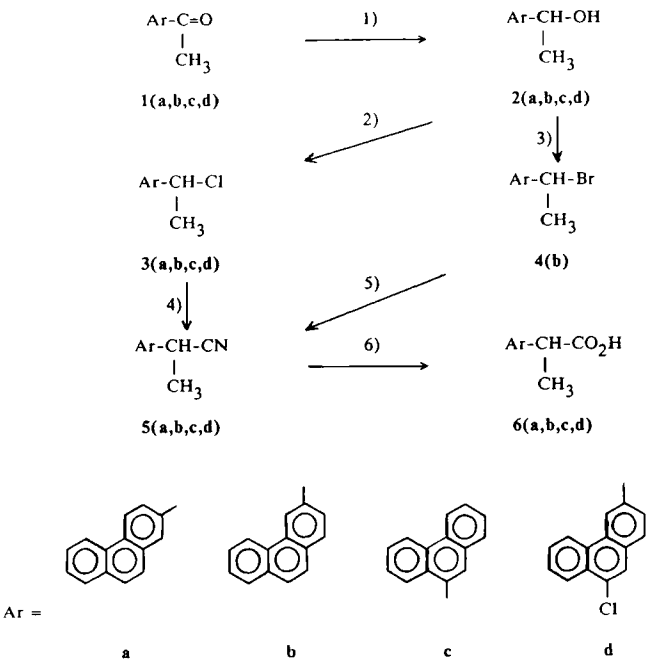
Phenanthrylalkansäuren, 4. Mitt.: Synthese und entzündungshemmende Wirkung von 2-, 3- und 9-Phenanthryl- und 9-Chlor-3-phenanthrylderivativen der Propionsäure

Durch Reduktion der Acetylderivate **1a-d** wurden die Phenanthrylethanole **2a-d** gewonnen, welche über die Phenanthrylethylhalogenide **3a-d** und **4b** in die Nitrile **5a-d** umgesetzt wurden, deren saure Hydrolyse die Titelsäuren **6a-d** lieferte. Es wurde die entzündungshemmende Wirkung dieser Säuren auf das durch Karragenin hervorgerufene Ödem gemessen, wobei sich rund 1/3 (**6a**), 1/43 (**6b**), 1/5 (**6c**) und 1/7 (**6d**) der entspr. Wirkung des Fenbufens ergaben.

We have reported the evaluation of the antiinflammatory properties of several phenanthrylalkanoic acids[1]. As a continuation of that work, here is reported the synthesis and pertinent pharmacological testing of the 2-(2-phenanthryl)propanoic (**6a**), 2-(3-phenanthryl)propanoic (**6b**), 2-(9-phenanthryl)propanoic (**6c**) and 2-(9-chloro-3-phenanthryl)propanoic (**6d**) acids.

For the preparation of these compounds, the acetyl derivatives **1a-d** (Scheme 1) were selected as starting materials since they are commercially available and/or can be easily prepared[2]. Direct "reductive cyanation" of ketones by means of tosylmethyl isocyanide (TosMIC)/Bu^{t}OK was first tried on two of them (**1a-b**). However, using the conditions reported by *van Leusen* et al.[3] for the p-bromoacetophenone (results not described in the experimental part), the reaction did not progress any longer than a mere 3%, while only about 50% of the starting materials were recovered in pure form.

Such disappointing results turned us to the classical, longer route depicted in Scheme 1. Alcohols **2** and arylethyl chlorides **3** were obtained in very high or quantitative yields. The conversion of crude halides **3** (only **3d** was purified for analytical and spectroscopic characterization) into nitriles **5**, by means of NaCN in DMSO, was the less satisfactory of all the steps, as it could never been carried to completion. Use of more drastic conditions, while promoting the total consumption of **3**, did not improve the yield in **5**.



1) $NaBH_4$, EtOH, 20°.
2) $SOCl_2$, C_6H_6, 80°, or $CCl_4/P(C_6H_5)_3$, 65°.
3) HBr/AcOH, 20°.
4) NaCN, DMSO, 70-75°.
5) NaCN, TEBACl, CH_2Cl_2, 20°.
6) H_3O^+, AcOH, 105°.

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Variable amounts of ketones **1** were formed in all these processes, probably as a result of a side reaction mechanistically related to the conversion of benzylic halides into aromatic aldehydes by $NaHCO_3$/DMSO[4,5a] and to the *Pfitzer-Moffatt* oxydation of secondary alcohols to ketones[5b]. Almost clear-cut separations of the corresponding crude products into their **1**, **3** and **5** components could be achieved by column chromatography and yields in isolated nitriles **5** ranged between 38% and 54%.

Some alternatives were tried for the preparation of **5b**. First, bromide **4b**, also obtained in nearly quantitative yield, was subjected to nucleophilic displacement in the heterogeneous solid $NaCN/CH_2Cl_2$ system, with TEBA chloride as phase transfer catalyst. A very long reaction time was required to achieve a fair degree of conversion of **4b** into **5b** and the need of chromatographic separation of **5b** was not avoided. Secondly, the "one pot" procedure of transformation of alcohols into nitriles reported by *Brett* et al.[6] was tried for the conversion **2b** → **5b**, but proved to be of no use for our substrate. Though the virtually quantitative formation of **3b** could be checked after the first part of the process, it was later on transformed into a polymer looking, non volatile residue plus only traces of **5b**.

Compounds **1**, **3**, **4**, and **5** had in GLC very characteristic and reproducible retention times (which are given taking that of ketone **1** as the reference for each phenanthrenic substrate), thus allowing an easy monitoring of reactions and separation procedures. On the other hand, alcohols **2** had all the same retention time as the corresponding ketone **1**, though it could be checked by other means (IR and/or NMR spectroscopies) that they never coexisted in any final reaction mixture.

Acid hydrolysis of the nitriles **5a-d** finally led to the acids **6a-d** in good to very good yields. However, as it happened before with their acetic homologues[1b], several recrystallizations of these racemic acids were needed in order to get the pure, sharp melting materials used for the pharmacological tests. Optical resolutions of acids **6** were not attempted.

Pharmacology

Anti-inflammatory activity: Carrageenin-induced edema of the rat paw

A modification of the method of *Winter* et al.[7] was applied. Each dose group consisted of 8 male Wistar rats (170-190 g). Diet was stopped 18 h before the experiment. Test-drug solutions or vehicle control were administered perorally by gavage, at 20 mL/kg body weight, 1 h before 0.05 mL 1% carrageenin in saline was injected into the plantar surface of the right hindpaw. Edema was evaluated by the difference between plethysmographically measured volumes of the injected paw, before and 3 h after carrageenin injection. Drug activity was expressed as % inhibition of edema formation compared to controls not treated with the drug. Antiedema ED_{50} values were calculated by a least square analysis. Results: Tab. 1.

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Table 1: Anti-inflammatory Activity

Compound	Oral Dose (mg/kg)	% Inhibition (3 h) (Mean ± se)	ED_{50} (mg/kg)
	25.0	40.3 ± 5.2	
6a	50.0	55.6 ± 4.8	37.6
	100.1	74.5 ± 5.3	
	25.0	14.1 ± 3.2	
6b	50.0	21.6 ± 4.0	491
	100.1	31.0 ± 4.3	
	25.0	36.6 ± 3.7	
6c	50.0	47.0 ± 4.7	55.1
	100.1	60.5 ± 5.2	
	28.5	30.1 ± 3.7	
6d	56.9	41.9 ± 3.6	82.6
	113.9	56.3 ± 5.2	
	25.4	59.0 ± 5.2	
Fenbufen	50.8	67.1 ± 5.2	11.4
	101.7	74.7 ± 5.9	

Experimental Part

MP: Kofler Thermopan Reichert, uncorr.- Elementary Analysis: Microanalysis Service, University of Santiago.- IR Spectra: Perkin-Elmer 297 and Perkin-Elmer 681, film (liquids) or KBr disk (solids).- ^{1}H-NMR Spectra: Varian FT-80A, in $CDCl_3$ unless otherwise stated/TMS int.stand.- Column Chromatography: Silica gel (230 mesh, Merck).- Gas Liquid Chromatography: Hewlett Packard 5710A, FID, H-P 3380S integr.; column: 2 m, 1/8", 10% OV-101/Chromosorb W-HP; N_2, 20 mL/min, 250°C.

1-(2-Phenanthryl)ethanol (**2a**)

A solution of 24.9 g **1a** (113 mmol) in 700 mL THF + 700 mL EtOH was added to a stirred solution of 5.0 g $NaBH_4$ (132 mmol) in 330 mL EtOH kept at 8-10°C and the mixture was then left stirring 12 h at room temp. Most of the solvents were removed *in vacuo*, the residue was diluted with 1 L H_2O and extracted with 3 x 300 mL Et_2O. The combined ethereal extracts were dried (Na_2SO_4) and the solvent taken off *in vacuo* to leave 25.0 g of pure (99+% by GLC) **2a**. Yield virtually quantitative. A small ammount was recrystallized from C_6H_6-hexane to give a white microcrystalline powder. M.p. 131.5-132°C (lit.[8]: 135-135.5°C).- IR: 720; 740; 815; 835; 890; 900; 940; 1000; 1010; 1020; 1070; 1140; 1155; 1170; 1250; 1285; 1305; 1390; 1425; 1600; 1620; 2960; 3350 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 1.62 (d; J = 6.5 Hz, 3H, $-CH_3$), 1.92 (broad s, D_2O exch.; 1H, -OH), 5.11 (q; J = 6.5 Hz, 1H, -CH<), 7.62 (dd; J = 8.9 Hz and 1.9 Hz, 1H, 3-H), 7.56-7.68 (m; 2H, 6,7-H), 7.73 (s; 2H, 9,10-H), 7.86 (d; J = 1.9 Hz, 1H, 1-H), 7.83-7.95 (m; 1H, 8-H), 8.61-8.72 (m; 1H, 5-H), 8.66 (d; J = 8.9 Hz, 1H, 4-H).- $C_{16}H_{14}O$ (222.3) Calc C 86.5 H 6.35 Found C 86.6 H 6.41.

1-(3-Phenanthryl)ethanol (**2b**)

From 15.40 g **1b** (69.9 mmol) in 900 mL EtOH and 2.70 g $NaBH_4$ (71.3 mmol) in 175 mL EtOH. Reaction conditions and working-up as for **2a** led to 15.1 g **2b**. Yield 97%. Recrystallized from hexane as white needles. M.p. 80.5-81°C (lit.[8]: 83-83.5°C).- IR: 620; 640; 740; 800; 820; 860; 880; 890; 910; 945; 1000; 1070; 1110; 1190; 1240; 1265; 1330; 1365; 1410; 1600; 2960; 3200 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 1.62 (d; J = 6.5 Hz, 1H, $-CH_3$), 2.03 (broad s, D_2O exch.; 1H, -OH), 5.15 (q; J = 6.5 Hz, 1H, -CH<), 7.63 (virtual d; J = 8.4 Hz, 1H, 2-H), 7.56-7.70 (m; 2H, 6,7-H), 7.72 (s; 2H, 9,10-H), 7.87 (d; J = 8.4 Hz, 1H, 1-H), 7.84-7.96 (m; 1H, 8-H), 8.66 (virtual s; 1H, 4-H), 8.67-8.78 (m; 1H, 5-H).- $C_{16}H_{14}O$ (222.3) Calc C 86.5 H 6.35 Found C 86.5 H 6.43.

1-(9-Phenanthryl)ethanol (**2c**)

From 9.04 g **1c** (41 mmol) in 500 mL EtOH and 1.56 g $NaBH_4$ (41.2 mmol) in 100 mL EtOH. Reaction conditions and working-up as for **2a** led to 9.05 g **2c**. Yield 99%. Recrystallized from C_6H_6 as white silky filaments. M.p. 135.5-136°C (lit.[8]: 135.5-136°C).- IR: 725; 750; 770; 780; 790; 860; 865; 880; 900; 950; 980; 1035; 1055; 1080; 1120; 1150; 1175; 1210; 1250; 1295; 1340; 1370; 1430; 1450; 1495; 1610; 1790; 2910; 3000; 3250 cm^{-1}.- ^{1}H-NMR (in DMSO-d_6): δ (ppm) = 1.55 (d; J = 6.1 Hz, 1H, $-CH_3$), 5.41 (broad s; 1H, -OH), 5.48 (q; J = 6.1 Hz, 1H, -CH<), 7.57-7.73 (m; 4H, 2,3,6,7-H), 7.97 (s; 1H, 10-H), 7.93-8.04 (m; 1H, 1-H), 8.18-8.30 (m; 1H, 8-H), 8.73-8.84 and 8.80-8.92 (2 m; 2H, 4-H and 5-H; assignment may be reversed).- $C_{16}H_{14}O$ (222.3) Calc C 86.5 H 6.35 Found C 86.6 H 6.30.

1-(9-Chloro-3-phenanthryl)ethanol (**2d**)

From 14.0 g **1d** (55 mmol) in 325 mL THF + 325 mL EtOH and 2.20 g $NaBH_4$ (58 mmol) in 150 mL EtOH. Reaction conditions and working-up as for **2a** led to 12.6 g **2d**. Yield 89%. Recrystallized from heptane as white leaflets. M.p. 106.5-107°C.- IR: 700; 725; 760; 780; 820; 880; 920; 940; 1010; 1070; 1090; 1115; 1165; 1195; 1210; 1240; 1280; 1320; 1375; 1420; 1450; 1505; 1570; 1600; 1760: 1920; 2870; 2940; 2970; 3070; 3350 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 1.62 (d; J = 6.4 Hz, 1H, $-CH_3$), 1.97 (d; J = 2.3 Hz, 1H, -OH), 5.14 (dq; J = 2.3 Hz and 6.4 Hz, 1H, -CH<), 7.60 (dd; J = 8.4 Hz and 1.5 Hz, 1H, 2-H), 7.64-7.76 (m; 2H, 6,7-H), 7.77 (d; J = 8.4 Hz, 1H, 1-H), 7.84 (s; 1H, 10-H), 8.32-8.44 (m; 1H, 8-H), 8.64 (virtual s; 1H, 4-H), 8.67-8.79 (m; 1H, 5-H).- $C_{16}H_{13}ClO$ (256.7) Calc C 74.9 H 5.10 Cl 13.8 Found C 74.7 H 5.12 Cl 13.7.

2-(2-Phenanthryl)propanenitrile (**5a**)

40 mL $SOCl_2$ (65.6 g; 552 mmol) were added to a stirred solution of 24.5 g crude **2a** (110 mmol) in 330 mL C_6H_6 and the mixture was refluxed for 4 h. Excess reagent and two thirds of the solvent were distilled off and the residue poured onto crushed ice and extracted with 2 x 400 mL Et_2O. The org. extracts were washed (aqueous saturated $NaHCO_3$, then H_2O) and dried (Na_2SO_4). Removal of the solvents *in vacuo* gave 25.2 g of a brownish pasty residue (98% by GLC), used as such for the next step. Crude yield in **3a** 95%.- GLC retention time: 0.53, relative to **1a**.

22.9 g of this material (95.1 mmol) in 190 mL anhydrous DMSO and 4.90 g NaCN (100 mmol) were placed in a flask fitted with a Dimroth condenser connected through a drying ($CaCl_2$) tube to a safety trap with 2N NaOH. The mixture was heated over a steam bath in a hood for 7 h, then poured on ice and extracted with 2 x 350 mL Et_2O. The org. extracts were washed with 3 x 100 mL H_2O, dried (Na_2SO_4) and the solvent was removed *in vacuo* to leave 20.2 g of a brown pasty residue, which was chromatographed on a column with 600 g SiO_2 gel. 20 x 500 mL hexane-C_6H_6 (1:2) eluted in this order, among other mixed fractions, 6.26 g **3a**, 6.15 g **5a** and 6.47 g **1a**, all pure by GLC. Yield in **5a** 38% related to unrecovered starting material. An analytical sample of **5a** was obtained by recrystallization from EtOH as white prisms. M.p. 94-95°C.- IR: 640; 680; 715; 740; 810; 830; 890; 940; 1000; 1060; 1090; 1150; 1175; 1250; 1300; 1420; 1460; 1490; 1600; 1610; 2245; 3000 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 1.76 (d; J = 7.3 Hz, 3H, $-CH_3$), 4.11 (q; J = 7.3 Hz, 1H, -CH<), 7.61 (dd; J = 8.8 Hz and 1.9 Hz, 1H, 3-H), 7.56-7.70 (m; 2H, 6,7-H), 7.75 (s; 2H, 9,10-H), 7.85 (d; J = 1.9 Hz, 1H, 1-H), 7.86-7.97 (m; 1H, 8-H), 8.60-8.71 (m; 1H, 5-H), 8.69 (d; J = 8.8 Hz, 1H, 4-H).- GLC retention time: 1.29, relative to **1a**.- $C_{17}H_{13}N$ (231.3) Calc C 88.3 H 5.66 N 6.1 Found C 88.4 H 5.60 N 6.0.

1-Bromo-1-(3-phenanthryl)ethane (**4b**)

1.6 g crude **2b** (7.2 mmol) in 5 mL AcOH were added to 15 mL 33% HBr in AcOH and the mixture was stirred 2.5 h at room temp., poured onto crushed ice and extracted with 100 mL Et_2O. The ethereal extract was washed (aqueous saturated $NaHCO_3$, then H_2O), dried (Na_2SO_4) and evaporated *in vacuo*: 1.97 g **4b**, faintly brown, 99+% pure by GLC, oil. Yield 96%. Passage in hexane through a SiO_2 gel column rendered it colorless, without altering its spectroscopic properties.- IR: 645; 720; 755; 800; 825; 870; 890; 970; 1040; 1075; 1185; 1200; 1250; 1300; 1380; 1410; 1440; 1510; 1600; 2910; 3000; 3050 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 2.21 (d; J = 6.9 Hz, 1H, $-CH_3$), 5.50 (q; J = 6.9 Hz, 1H, -CH<), 7.59-7.72 (m; 2H, 6,7-H), 7.64 (dd; J = 8.7 and 1.3 Hz, 1H, 2-H), 7.73 (s; 2H, 9,10-H), 7.75-7.87 (m; 1H, 8-H), 7.88 (d; J = 8.7 Hz, 1H, 1-H), 8.63-8.75 (m; 1H, 5-H), 8.69 (d; J = 1.3 Hz, 1H, 4-H).- GLC retention time 0.70, relative to **1b**.- $C_{16}H_{13}Br$ (285.2) Calc C 67.4 H 4.59 Br 28.0 Found C 67.5 H 4.63 Br 27.9.

2-(3-Phenanthryl)propanenitrile (**5b**)

a) From 14.5 g crude **2b** (65.2 mmol) in 180 mL C_6H_6 and 24 mL $SOCl_2$ (331 mmol). Reaction conditions and working-up as for **3a**: 15.7 g **3b**. Yield 100%. **3b**: GLC retention time 0.66, relative to **1b**. Crude product was 99+% pure by GLC.

From 14.8 g crude **3b** (61.5 mmol) in 120 mL dry DMSO and 3.16 g NaCN (64.5 mmol), conditions and working-up as for **5a** led to 14.0 g of a residue, which was chromatographed on 450 g SiO_2 gel. Elution with 21 x 400 mL hexane-C_6H_6 (1:2) separated 1.26 g **3b**, 9.2 g enrichened (88% by GLC) **5b** and 0.90 g **1b**. Recrystallization of central fractions from EtOH led to 5.05 g pure **5a** as white needles. Yield 40% related to unrecovered starting material. M.p. 92-93°C.- IR: 620; 635; 715; 750; 785; 800; 845; 870; 885; 960; 975; 995; 1040; 1080; 1105; 1155; 1200; 1250; 1270; 1380; 1430; 1450; 1505; 1600; 2245; 2940; 2970; 3050 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 1.78 (d; J = 7.3 Hz, 1H, $-CH_3$), 4.16 (q; J = 7.3 Hz, 1H, -CH<), 7.55 (dd; J = 8.4 and 1.5 Hz, 1H, 2-H), 7.59-7.71 (m; 2H, 6,7-H), 7.73 (s; 2H, 9,10-H), 7.80-7.93 (m; 1H, 8-H), 7.89 (d; J = 8.4 Hz, 1H, 1-H), 8.64 (virtual s; 1H, 4-H), 8.64-8.75 (m; 1H, 5-H).- GLC retention time: 1.30, relative to **1b**.- $C_{17}H_{13}N$ (231.3) Calc C 88.3 H 5.66 N 6.1 Found C 88.5 H 5.54 N 6.0.

b) A mixture of 1.8 g **4b** (6.3 mmol) in 6 mL CH_2Cl_2, 0.98 g NaCN (20 mmol) and 500 mg TEBA was thoroughly stirred at room temp. for 5 days, diluted into 100 mL Et_2O, washed with H_2O, dried (Na_2SO_4) and the solvents were taken off *in vacuo* to leave 1.49 g of a pasty residue; GLC analysis showed a mixture of **5b** + **4b** in a 2:1 ratio. **5b** was isolated by column chromatography as above.

c) 1.5 g crude **2b** (6.75 mmol), 1.8 g dried $(C_6H_5)_3P$ (6.86 mmol) and 7 mL anhydrous CCl_4 were refluxed in a moisture protected system for 2 h, then GLC analysis showed the complete disappearance of **2b** and the only presence (equimolar amounts) of **3b** and $(C_6H_5)_3PO$ (comparison with reference standards). 7 mL of anhydrous DMSO were added to the mixture and the volatile components distilled off, 400 mg NaCN (8.16 mmol) put in and the whole heated in an oil bath at 185°C for 6 h. Standard working-up left a solid, water insoluble, organic residue; GLC analysis showed $(C_6H_5)_3PO$ as the almost only volatile component (99+%), besides traces of **3b**, **1b** or **2b** and **5b**.

2-(9-Phenanthryl)propanenitrile (**5c**)

From 8.36 g crude **2c** (37.6 mmol) in 110 mL C_6H_6 and 16 mL $SOCl_2$ (221 mmol). Reaction conditions and working-up as for **3a** led to 9.05 g **3c**. Yield 100%. **3b**: GLC retention time 0.54, relative to **1c**. Crude product was 98+% pure by GLC.

From 9.0 g crude **3c** (37.4 mmol) in 75 mL dry DMSO and 1.92 g NaCN (39.2 mmol); operating conditions and working-up as for **5a** led to 7.33 g of a residue, which was chromatographed on 170 g SiO_2 gel. Elution with 18 x 150 mL hexane-C_6H_6 (1:2) separated 0.98 g **3c**, 3.95 g **5c** and 1.92 **1c**, all pure by GLC. Yield in **5c** 51% related to unrecovered starting material. An analytical sample of **5c** was obtained by recrystallization from EtOH as white microcrystalline powder. M.p. 81-82°C.- IR: 620; 725; 755; 780;

790; 810; 825; 865; 900; 920; 975; 1030; 1095; 1150; 1200; 1255; 1370; 1390; 1450; 1490; 1600; 2240 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 1.86 (d; J = 7.2 Hz, 1H, -CH_3), 4.65 (q; J = 7.2 Hz, 1H, -CH<), 7.61-7.77 (m; 4H, 2,3,6,7-H), 7.84-8.96 (m; 2H, 1,8-H), 7.97 (s; 1H, 10-H), 8.60-8.71 and 8.71-8.83 (2 m; 2H, 4-H and 5-H; assignment may be reversed).- GLC retention time: 1.45 relative to **1c**.- $C_{17}H_{13}N$ (231.3) Calc C 88.3 H 5.66 N 6.1 Found C 88.4 H 5.69 N 6.0.

1-Chloro-1-(9-chloro-3-phenanthryl)ethane (**3d**)

From 8.45 g crude **2d** (32.9 mmol) in 130 mL C_6H_6 and 15 mL $SOCl_2$ (207 mmol). Reaction conditions and working-up as for **3a** led to 8.61 g of a yellowish solid, 98+% pure by GLC. Yield 95%. A sharp melting, analytical sample of **3d** was obtained after 3 recrystallizations from heptane, white microcrystalline powder. M.p. 88.5-89°C.- IR: 620; 660; 710; 760; 780; 785; 820; 885; 940; 970; 1145; 1235; 1280; 1290; 1380; 1425; 1450; 1500; 1565; 1600 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 1.99 (d; J = 6.8 Hz, 1H, -CH_3), 5.35 (q; J = 6.8 Hz, 1H, -CH<), 7.67 (dd; J = 8.4 Hz and 1.4 Hz, 1H, 2-H), 7.65-7.77 (m; 2H, 6,7-H), 7.79 (d; J = 8.4 Hz, 1H, 1-H), 7.85 (s; 1H, 10-H), 8.33-8.45 (m; 1H, 8-H), 8.64 (virtual s; 1H, 4-H), 8.64-8.76 (m; 1H, 5-H).- GLC retention time, 0.67, relative to **1d**.- $C_{16}H_{12}Cl_2$ (275.2) Calc C 69.8 H 4.40 Cl 25.8 Found C 70.1 H 4.52 Cl 25.9.

2-(9-Chloro-3-phenanthryl)propanenitrile (**5d**)

From 8.0 g crude **3d** (29.1 mmol) in 100 mL dry DMSO and 1.70 g NaCN (34.7 mmol), 8 h reflux and working-up as for **5a** led to 6.51 g of a residue, which was chromatographed on 140 g SiO_2 gel. Elution with 28 x 100 mL heptane-C_6H_6 (1:2) separated 0.85 g **3d**, 3.73 g **5d** and 0.29 g **1d**, all pure by GLC. Yield in **5d** 54% related to unrecovered starting material. Recrystallization from EtOH gave an analytical sample of **5d** as white leaflets. M.p. 119.5-120°C.- IR: 630; 730; 755; 780; 820; 855; 885; 960; 980; 1085; 1155; 1170; 1195; 1215; 1240; 1280; 1295; 1380; 1420; 1455; 1500; 1600; 1770; 2250; 3000 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 1.77 (d; J = 7.3 Hz, 1H, -CH_3), 4.15 (q; J = 7.3 Hz, 1H, -CH<), 7.55 (dd; J = 8.3 Hz and 1.7 Hz, 1H, 2-H), 7.67-7.79 (m; 2H, 6,7-H), 7.81 (d; J = 8.3 Hz, 1H, 1-H), 7.85 (s; 1H, 10-H), 8.34-8.46 (m; 1H, 8-H), 8.62 (virtual s; 1H, 4-H), 8.65-8.77 (m; 1H, 5-H).- GLC retention time: 1.22, relative to **1d**.- $C_{17}H_{12}ClN$ (265.7) Calc C 76.8 H 4.55 Cl 13.3 N 5.3 Found C 77.0 H 4.51 Cl 13.5 N 5.2.

2-(2-Phenanthryl)propanoic acid (**6a**)

A mixture of 4.8 g **5a** (20.7 mmol), 5 mL AcOH, 5 mL H_2SO_4 and 5 mL H_2O was refluxed for 2 h, diluted with 100 mL H_2O and extracted with 2 x 150 mL Et_2O. The org. extracts were shaken with 3 x 50 mL 2N NaOH and the alkaline phases were acidified (HCl) and re-extracted with 2 x 150 mL Et_2O. These last ethereal extracts were washed with H_2O until neutral pH, dried (Na_2SO_4) and the solvent was taken off *in vacuo* to leave 3.48 g **6a**. Yield 67%. Three recrystallizations from toluene led to 1.92 g of constant, sharp m.p. material, used for spectra and pharmacological tests.- White leaflets. M.p. 176.5-177°C (lit.[9]: 172-175°C).- IR: 680; 710; 745; 810; 860; 885; 920; 950; 1070; 1230; 1250; 1320; 1370; 1410; 1460; 1620; 1700; 2975 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 1.65 (d; J = 7.1 Hz, 3H, -CH_3), 3.98 (q; J = 7.1 Hz, 1H, -CH<), 7.55-7.68 (m; 3H, 3,6,7-H), 7.72 (s; 2H, 9,10-H), 7.82 (virtual s; 1H, 1-H), 7.81-7.93 (m; 1H, 8-H), 8.59-8.70 (m; 1H, 5-H), 8.65 (d; J = 8.8 Hz, 1H, 4-H).- $C_{17}H_{14}O_2$ (250.3) Calc C 81.6 H 5.64 Found C 81.7 H 5.59.

2-(3-Phenanthryl)propanoic acid (**6b**)

From 4.81 g **5b** (20.8 mmol) and H_2SO_4-H_2O in AcOH. Conditions of reaction and working-up as for **6a** led to 3.23 g **6b**. Yield 62%. Three recrystallizations from toluene afforded 1.47 g of constant, sharp m.p. material, used for spectra and pharmacological tests.- White prisms. M.p. 145.5-146°C (lit.[9]: 136-138°C).- IR: 630; 685; 775; 810; 840; 885; 950; 1170; 1235; 1260; 1295; 1330; 1410; 1450; 1600; 1710; 2990 cm^{-1}.- ^{1}H-NMR (in DMSO-d_6): δ (ppm) = 1.54 (d; J = 7.1 Hz, 1H, -CH_3), 4.00 (q; J = 7.1 Hz, 1H, -CH<), 7.59 (dd; J = 8.2 and 1.5 Hz, 1H, 2-H), 7.61-7.73 (m; 2H, 6,7-H), 7.81 (s; 2H, 9,10-H), 7.92-8.04 (m; 1H, 8-H), 7.94 (d; J = 8.2 Hz, 1H, 1-H), 8.71 (virtual s; 1H, 4-H), 8.75-8.87 (m; 1H, 5-H).- $C_{17}H_{14}O_2$ (250.3) Calc C 81.6 H 5.64 Found C 81.5 H 5.67.

2-(9-Phenanthryl)propanoic acid (**6c**)

From 3.35 g **5c** (14.5 mmol) and H_2SO_4-H_2O in AcOH. Conditions of reaction and working-up as for **6a** led to 2.83 g **6c**. Yield 78%. Three recrystallizations from toluene afforded 1.56 g of constant, sharp m.p. material, used for spectra and pharmacological tests.- White prisms. M.p. 183-184°C (lit.[9]: 182-184°C).- IR: 620; 660; 720; 750; 775; 795; 900; 955; 1020; 1095; 1210; 1250; 1300; 1325; 1375; 1415; 1480; 1500; 1600; 1690; 1710; 3050 cm^{-1}.- ^{1}H-NMR (in DMSO-d_6): δ (ppm) = 1.62 (d; J = 7.0 Hz, 1H, -CH_3), 4.48 (q; J = 7.0 Hz, 1H, -CH<), 7.59-7.76 (m; 4H, 2,3,6,7-H), 7.77 (s; 1H, 10-H), 7.92-8.05 (m; 1H, 1-H), 8.13-8.26 (m; 1H, 8-H), 8.74-8.86 and 8.83-8.95 (2 m; 2H, 4-H and 5-H; assignment may be reversed).- $C_{17}H_{14}O_2$ (250.3) Calc C 81.6 H 5.64 Found C 81.6 H 5.57.

2-(9-Chloro-3-phenanthryl)propanoic acid (**6d**)

From 3.21 g **5c** (12.1 mmol) and H_2SO_4-H_2O in AcOH. Conditions of reaction and working-up as for **6a** led to 3.09 g **6d**. Yield 90%. Three recrystallizations from toluene afforded 1.62 g of constant, sharp m.p. material, used for spectra and pharmacological tests.- White crystalline powder. M.p. 164.5-165°C.- IR: 600; 660; 700; 725; 760; 775; 880; 940; 1070; 1225; 1275; 1300; 1330; 1380; 1415; 1470; 1505; 1600; 1705; 2980 cm^{-1}.- ^{1}H-NMR: δ (ppm) = 1.66 (d; J = 7.1 Hz, 1H, -CH_3), 4.00 (q; J = 7.1 Hz, 1H, -CH<), 7.57 (dd; J = 8.4 Hz and J = 1.4 Hz, 1H, 2-H), 7.63-7.75 (m; 2H, 6,7-H), 7.75 (d; J = 8.4 Hz, 1H, 1-H), 7.83 (s; 1H, 10-H), 8.31-8.43 (m; 1H, 8-H), 8.55 (virtual s; 1H, 4-H), 8.62-8.74 (m; 1H, 5-H).- ^{1}H-NMR (in DMSO-d_6): δ (ppm) = 1.54 (d; J = 7.1 Hz, 1H, -CH_3), 4.02 (q; J = 7.1 Hz, 1H, -CH<), 7.63 (dd; J = 8.4 Hz and J = 1.4 Hz, 1H, 2-H), 7.76-7.88 (m; 2H, 6,7-H), 7.97 (d; J = 8.4 Hz, 1H, 1-H), 8.11 (s; 1H, 10-H), 8.25-8.37 (m; 1H, 8-H), 8.74 (virtual s; 1H, 4-H), 8.87-8.99 (m; 1H, 5-H). $C_{17}H_{13}ClO_2$ (284.7) Calc C 71.7 H 4.60 Cl 12.5 Found C 71.6 H 4.51 Cl 12.6.

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[Ph676]