Phenanthrylalkanoic acids, II: Syntheses and Antiinflammatory Activity of 2-, 3- and 9-Phenanthryl- and 9-Chloro-3-phenanthrylacetic Acids

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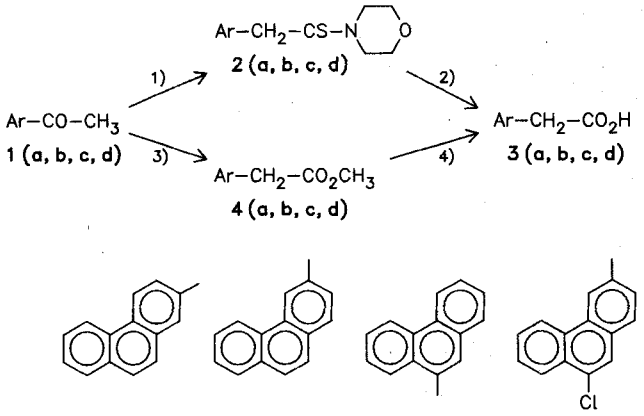
Application of *Willgerodt-Kindler* reaction to the phenanthryl ketones **1a–d** led to the thiomorpholides **2a–d**, hydrolysis produced the acids mentioned in the title. An alternative route, of much better yield, was based on the oxythallation of **1a–d** to give the methyl arylacetates **4a–d**, which were saponified to **3a–d**. Among these four acids, only **3b** showed an antiinflammatory activity approaching that of Fenbufen.

Phenanthrylalkansäuren, II: Synthese und entzündungshemmende Wirksamkeiten von 2-, 3- und 9-Phenanthryl- und 9-Chlor-3-phenanthrylessigsäuren

Willgerodt-Kindler Reaktionen der Phenanthrylketone **1a–d** liefern die Thiomorpholides **2a–d**, durch Hydrolyse entstehen die Titelverbindungen. Eine andere Methode, die auf der Oxythallierung von **1a–d** basiert, führt mit wesentlich besseren Ausbeuten zu den Methyl-arylacetaten **4a–d**, welche zu den Säuren **3a–d** verseift werden. Nur die Säure **3b** zeigte eine mit der des Fenbufens vergleichbare entzündungshemmende Wirkung.

Our interest for the exploration of the antiinflammatory properties of phenanthrylalkanoic acids[1] led us to perform the synthesis and pertinent pharmacological tests of the 2-phenanthrylacetic **(3a)**, 3-phenanthrylacetic **(3b)**, 9-phenanthrylacetic **(3c)** and 9-chloro-3-phenanthrylacetic **(3d)** acids.

For the preparation of these compounds the clasical *Willgerodt-Kindler* reaction[2], was first taken into consideration (Scheme 1), since the acetyl derivatives **1a–d** needed as starting materials would be commercially available and/or can be prepared easily[3].



1) S, HN O, 130°. 2) H_3O^+, 95°. 3) $Tl(NO_3)_3$, $HClO_4$, CH_3OH.
4) KOH, 50–60°; H_3O^+.

None of the crude products from the *Willgerodt-Kindler* reactions of **1a–d** solidified spontaneously and generally failed to crystallize from any solvent. Once purified by column-chromatography they gave TLC homogeneous materials that had to be recrystallized several times until sharp melting samples could be got. Only the thiomorpholide **2a** had been previously reported by *Gore* et al.[4]; they quoted for it a m. p. 32 °C lower than that obtained by us. Identity and purity of our product **2a** was undoubtfully checked by analytical and spectroscopic means (IR, NMR, MS); the product referred to by *Gore*[4] as **2a**, if pure, could only be a polymorphism of ours. The barrier of the rotation around the C–N bond in simple thioamides can be as high as 25 Kcal/mol[5], giving rise even to *Z/E* isomerism at room temp. in certain cases[6], but such a situation is prevented here by the symmetry of the morpholine ring.

^{1}H-NMR spectra of all our thioamides showed the presence of four groups of signals, each for every methylene group of the morpholine moiety, occasionally seen as four slighty distorted triplets, though often the two central ones were mixed and are given as a multiplet. Differences in chemical shifts between these signals are attributed to the fact of methylene groups being α- with regard to the N or O atom, and *s-cis* or *s-trans* with regard to the arylmethyl moiety, while virtual multiplicity and coupling constants point out to the near equivalence of both protons of each methylene group, thus meaning a fast chair-chair interconversion. On the other hand, MS of both **2a** and **2b** were very similar, indicating that their most important fragmentation patterns are due to their common aliphatic moiety. Fragmentations giving rise to their most prominent peaks are depicted in Scheme 2.

Acid hydrolysis of the thiomorpholides **2a–d** led to the corresponding acids **3a–d**, with low to moderate yields (alkaline hydrolysis of **2b** gave a poorer yield of **3b**): these yields are referred to the products isolated after a first recrystallization or a reprecipitation from an alkaline extract.

Each acid showed a wide melting range (8–10 °C) and had to be recrystallized several times in order to get the sharp melting materials used

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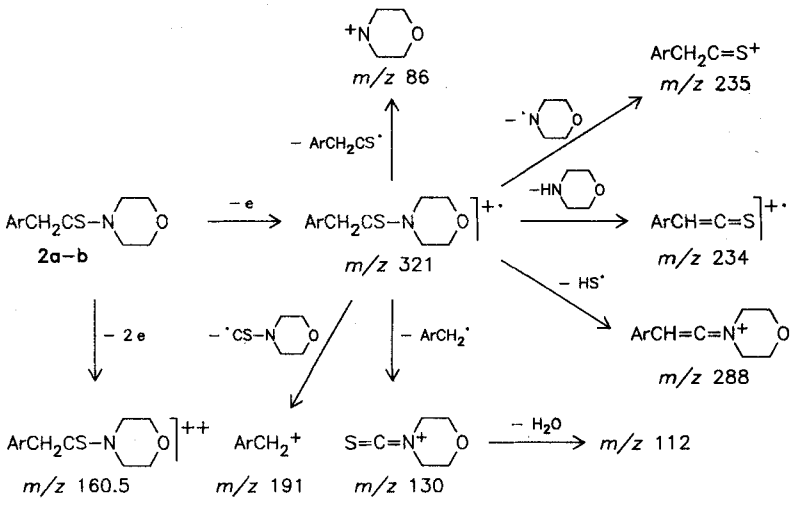

for the pharmacological tests. Thus, presence of small amounts of impurities lowers very much the m. p. of these acids (IR and NMR spectra of wide range and sharp melting samples of the same substance were virtually superimposable); this fact may account for the wide variety of m. p. attributed to some of them in the literature[4, 7-13].

Due to the insatisfactory yields obtained in the preparation of the acids **3a–d** by the *Willgerodt-Kindler* route, we had to achieve the transformation of the ketones **1a–d** by a better method. Oxythallations are a familiy of reagent-related processes which, when applied to unsaturated substrates (including enolizable ketones), give rise to several synthetically usefull transformations[14]. One of them is the reaction between an aryl methyl ketone and thallium trinitrate (TTN) in acidic methanol, which affords, in good to very good yields, the corresponding methyl arylacetates, thus providing in some cases[15] a usefull alternative to the *Willgerodt-Kindler* route for the preparation of arylacetic acids. To our knowledge, this process had not been tried previously on a phenanthrenic substrate.

We first ruled out a competitive oxythallation at the olefin-like 9,10-region of the aromatic nucleus, by observing that phenanthrene itself proved to be unreactive towards TTN during 72 h under standard conditions of the reaction used for acetophenones. In fact, when the oxythallation process was applied to the ketones **1a–d**, the methyl phenanthrylacetates **4a–d** were clean and smoothly obtained in very good yields. Moreover, saponification of the crude products from oxythallation afforded the acids **3a–d** nearly quantitatively, which were much easier to purify than those proceeding from the *Willgerodt-Kindler* route.

On the other hand, use of a supported reagent (TTN/K-10 montmorillonite) has been reported[16] to promote high yield conversions of acetophenones to the methyl arylacetates and even that of propiophenone to methyl α-phenylpropionate, under milder conditions than those of standard homogeneous TTN. Its use with ketone **1b**, however, led to a poor conversion **1b** → **4b**. Probably the bulky phenanthrene moiety of **1b** prevents it from penetrating to the active sites in the catalytic system, rendering the reaction possible only at the outermost centers and lowering its efficiency.

Pharmacology

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

A modification of the method of *Winter* et al.[17] was applied. Each dose group consisted of 8 male Wistar rats (170–190 g). Diet was stopped beginning 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. The 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 per cent inhibition of edema formation compared to controls. Antiedema ED_{50} values were calculated by a least square analysis. Results are given in Tab. 1.

Tab. 1: Anti-inflamatory Activity

Compound	Oral Dose (mM/kg)	% Inhibition (3 h) (Mean ± se)	ED_{50} (mM/kg)
	0.1	24.63 ± 3.82	
3a	0.2	34.03 ± 3.72	0.58
	0.4	44.68 ± 4.12	
	0.1	49.26 ± 3.06	
3b	0.2	52.29 ± 4.38	0.12
	0.4	57.48 ± 2.93	
	0.1	13.13 ± 1.92	
3c	0.2	29.23 ± 2.63	0.47
	0.4	46.23 ± 3.42	
	0.1	25.12 ± 2.71	
3d	0.2	32.68 ± 4.01	0.70
	0.4	43.06 ± 3.95	
	0.1	58.96 ± 5.23	
Fenbufen	0.2	67.14 ± 5.18	0.04
	0.4	74.72 ± 5.90	

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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.-MS: Kratos MS-25, at 70 eV. – Column Chromatography: Silica gel (230 mesh, Merck). TLC: Kieselgel 60 G Merck. – Gas Liquid Chromatography: Hewlett Packard 5710A, FID, H-P 3380S integr.; column: 2 m, ⅛″, 10 % OV-101/Chromosorb W-HP; N_2, 20 mL/min, 250°.

2-Phenanthrylacetothiomorpholide **(2a)**

A mixture of 10.0 g **1a** (45.4 mmol), 1.7 g S (53 mmol) and 15.0 g morpholine (172 mmol) was refluxed for 16 h, then diluted with 400 mL Et_2O, washed with H_2O until neutral pH, dried (Na_2SO_4) and the solvent taken off *in vacuo* to leave 16.4 g of a dark paste which was chromatographed on 300 g SiO_2, elution by C_6H_6:Et_2O: 9:1. Central fractions gave 12.7 g of solid **2a**, homogeneous in TLC, that was used as such for hydrolysis. Yield 87 %. A sharp melting point sample of **2a**, as white glistening leaflets, was obtained only after 5 recrystallizations from EtOH. M.p. 175.5–176 °C (lit.[4] 143–144 °C. – IR: 600; 675; 695; 718; 722; 760; 820; 890; 1022; 1120; 1200; 1230; 1270; 1300; 1425; 1440; 1470; 1598; 2850; 2920; 2980 cm^{-1}. – ^{1}H-NMR: δ (ppm) = 3.30–3.42 (m; 2H, morpholine), 3.64–3.82 (m; 4H, morpholine), 4.35–4.47 (m; 2H, morpholine), 4.58 (s; 2H, Ar–CH_2–CS–), 7.53 (virtual d; J = 8.3 Hz, 1H, 3–H), 7.55–7.69 (m; 2H, 6,7–H), 7.71 (s; 2H, 9,10–H), 7.83 (virtual s; 1H, 1–H), 7.80–7.92 (m; 1H, 8–H), 8.59–8.70 (m; 1H, 5–H), 8.64 (d; J = 8.3 Hz, 1H, 4–H). – MS: m/z = 323 (5.1 %, M+2), 322 (15.8, M+1), 321 (64.6, $M^{+\cdot}$), 288 (13.0), 235 (10.2), 234 (37.6), 217 (5.8), 202 (8.8), 192 (13.9), 191 (41.6), 190 (10.7), 189 (22.5), 165 (5.8), 160.5 (7.0), 132 (5.1), 131 (8.1), 130 (100), 117 (10.7), 112 (24.4), 86 (53.5). – $C_{20}H_{19}NOS$ (321.4) Calc C 74.7 H 5.96 N 4.4 Found C 74.8 H 5.86 N 4.3.

3-Phenanthrylacetothiomorpholide **(2b)**

From 20.0 g **1b** (90.8 mmol), 4.17 g S (130 mmol) and 16.0 g morpholine (184 mmol), reaction and work up as for **2a**, gave 32 g of a tarry material which, by chromatography, led to 23.9 g solid **2b**, homogeneous in TLC (yield 82 %), that was used us such for hydrolysis. An analytical sample was obtained after 3 recrystallizations from EtOH, as white glistening leaflets. M.p. 174–175 °C. – IR: 675; 715; 740; 758; 820; 890; 965; 1025; 1065; 1112; 1175; 1230; 1245; 1270; 1300; 1430; 1465; 1495; 1590; 2850; 2920; 2970 cm^{-1}. – ^{1}H-NMR: δ (ppm) = 3.36 (t; J = 4.8 Hz, 2H, morpholine), 3.63–3.81 (m; 4H, morpholine), 4.40 (t; J = 4.8 Hz, 2H, morpholine), 4.56 (s; 2H, Ar–CH_2–CS–), 7.54 (virtual d; J = 7.7 Hz, 1H, 2–H), 7.57–7.71 (m; 2H, 6,7–H), 7.73 (s; 2H, 9,10–H), 7.84 (d; J = 7.7 Hz, 1H, 1–H), 7.83–7.95 (m; 1H, 8–H), 8.59 (virtual s; 1H, 4–H), 8.61–8.72 (m; 1H, 5–H). – MS: m/z = 323 (5.0 %, M+2), 322 (15.3, M+1), 321 (62.3, $M^{+\cdot}$), 288 (12.0), 235 (9.5), 234 (36.1), 217 (5.4), 202 (8.3), 192 (13.6), 191 (37.7), 190 (10.1), 189 (20.5), 165 (5.6), 160.5 (6.4), 132 (5.2), 131 (8.1), 130 (100), 117 (10.5), 112 (24.0), 86 (54.9). – $C_{20}H_{19}NOS$ (321.4) Calc C 74.7 H 5.96 N 4.4 Found C 74.9 H 5.89 N 4.3.

9-Phenanthrylacetothiomorpholide **(2c)**

From 15.0 g **1c** (68.1 mmol), 3.11 g S (97 mmol) and 9.0 g morpholine (103 mmol), as described for **2b**; 16.5 g of homogeneous **2c** (TLC) were isolated after purification by column chromatography. Yield 75 %. A constant m.p. sample was obtained after 4 recrystallizations from EtOH, as a pearl powder. M.p. 156–158 °C. – IR: 612; 720; 740; 928; 980; 1030; 1110; 1175; 1255; 1285; 1300; 1428; 1450; 1490; 1600; 2850; 2920; 2950 cm^{-1}. – ^{1}H-NMR (DMSO-d_6): δ (ppm) = 3.46–3.58 (m; 2H, morpholine), 3.66–3.86 (m; 4H, morpholine), 4.34–4.46 (m; 2H, morpholine), 4.74 (s; 2H, Ar–CH_2–CS–), 7.55–7.72 (m; 4H, 2,3,6,7–H), 7.77 (s; 1H, 10–H), 7.93–8.05 (m; 1H, 1–H), 8.01–8.13 (m; 1H, 8–H), 8.75–8.93 (m; 2H, 4,5–H). – $C_{20}H_{19}NOS$ (321.4) Calc C 74.7 H 5.96 N 4.4 Found C 74.9 H 5.90 N 4.2.

9-Chloro-3-phenanthrylacetothiomorpholide **(2d)**

A mixture of 5.4 g **1d** (21.2 mmol), 1.0 g S (31.2 mmol) and 9.0 g morpholine (103 mmol) was refluxed for 16 h. Work up as before led to a pasty residue which was crystallized from EtOH to yield 4.68 g of **2d**, used for hydrolysis. Yield 62 %. A sample of constant m.p., as a white powder, was achieved after 4 recrystallization from EtOH. M.p. 126–128 °C. – IR: 720; 750; 790; 835; 875; 935; 980; 1030; 1105; 1170; 1200; 1285; 1305; 1430; 1490; 1590; 2830; 2850 cm^{-1}. – ^{1}H-NMR: δ (ppm) = 3.28–3.40 (m; 2H, morpholine), 3.62–3.80 (m; 4H, morpholine), 4.40 (t; J = 4.9 Hz, 2H, morpholine), 4.59 (s; 2H, Ar–CH_2–CS–), 7.57 (dd; J = 8.3 Hz, J′ = 1.3 Hz, 1H, 2–H), 7.66–7.78 (m; 2H, 6,7–H), 7.78 (d; J = 8.3 Hz, 1H, 1–H), 7.85 (s; 1H, 10–H), 8.34–8.46 (m; 1H, 8–H), 8.61 (virtual s; 1H, 4–H), 8.61–8.73 (m; 1H, 5–H). – ^{1}H-NMR (DMSO-d_6): δ (ppm) = 3.43 (virtual t; J = 4.6 Hz, 2H, morpholine), 3.67 (virtual t; J = 4.9 Hz, 2H, morpholine), 3.85 (virtual t; J = 4.6 Hz, 2H, morpholine), 4.29 (t; J = 4.9 Hz, 2H, morpholine), 4.57 (s; 2H, Ar–CH_2–CS–), 7.70 (dd; J = 8.3 Hz, J′ = 1.3 Hz, 1H, 2–H), 7.76–7.88 (m; 2H, 6,7–H), 7.97 (d; J = 8.3 Hz, 1H, 1–H), 8.11 (s; 1H, 10–H), 8.25–8.38 (m; 1H, 8–H), 8.77 (virtual s; 1H, 4–H), 8.77–8.89 (m; 1H, 5–H). – $C_{20}H_{18}ClNOS$ (355.9) Calc C 67.5 H 5.10 Cl 9.9 N 3.9 Found C 67.7 H 5.02 Cl 10.0 N 4.0.

Methyl 2-phenanthrylacetate **(4a)**

A solution of 4.94 g $Tl(NO_3)_3 \cdot 3H_2O$ (11.1 mmol) in 12 mL MeOH and 6 mL 60 % $HClO_4$ was added to 2.2 g **1a** (10 mmol) in 45 mL $CHCl_3$ and 45 mL MeOH. The initially homogeneous mixture was stirred at room temp. and soon became cloudy, then separating a white precipitate. The reaction was monitored by GLC analysis of aliquots and taken as finished when the **4a/1a** ratio was 97:3 (21 h). The mixture was filtered and the solid washed with 4 × 20 mL $CHCl_3$, all organic liquors were combined, washed (H_2O) and dried (Na_2SO_4). Removal of solvent *in vacuo* gave 2.4 g of a brownish solid, used as such for saponification. Crude yield 96 %. An analytical sample of **4a** was obtained by 2 recrystallizations from MeOH, as white needles. M.p. 79.5–80 °C (lit.[7] 78–78.5 °C. – IR: 685; 720; 735; 750; 820; 832; 875; 905; 925; 1005; 1165; 1195; 1240; 1260; 1305; 1340; 1360; 1415; 1435; 1470; 1495; 1610; 1740; 2950; 3050 cm^{-1}. – ^{1}H-NMR: δ (ppm) = 3.72 (s; 3H, $-CH_3$), 3.84 (s; 2H, $-CH_2$–), 7.51–7.68 (m; 3H, 3,6,7–H), 7.71 (s; 2H, 9,10–H), 7.77 (virtual s; 1H, 1–H), 7.82–7.93 (m; 1H, 8–H), 8.59–8.70 (m; 1H, 5–H), 8.64 (d; J = 8.1 Hz, 1H, 4–H).

Methyl 3-phenanthrylacetate **(4b)**

a) A mixture of 2.2 g **1b** (10 mmol) in 45 mL MeOH and 4.53 g $Tl(NO_3)_3 \cdot 3H_2O$ (10.2 mmol) in 10 mL MeOH and 6 mL 60 % $HClO_4$ was stirred 5 h at room temp., GLC analysis at this point showing a **4b/1b** ratio of 93:7. Work up us for **4a** led to 2.36 g of a yellow oil, used as such for hydrolysis. Crude yield 94 %. To obtain an analytical sample, 1.18 g crude ester were chromatographed on 35 g SiO_2, elution by 18 × 25 mL C_6H_6: fractions 5–7 left 0.91 g pure (100 % by GLC) **4b** as a faintly yellowish oil, while fractions 8–12 left **4b** with increasing amounts of **1b**.

4b: – IR: 690; 710; 745; 810; 840; 950; 1010; 1160; 1205; 1260; 1435; 1455; 1510; 1605; 1740; 2960; 3010; 3030; 3070 cm^{-1}. – ^{1}H-NMR: δ (ppm) = 3.73 (s; 3H, $-CH_3$), 3.90 (s; 2H, $-CH_2$–), 7.55 (dd; J = 8.2 Hz, J′ = 1.7 Hz, 1H, 2–H), 7.56–7.70 (m; 2H, 6,7–H), 7.73 (s; 2H, 9,10–H), 7.87 (d; J = 8.2 Hz, 1H, 1–H), 7.84–7.96 (m; 1H, 8–H), 8.60 (virtual s; 1H, 4–H), 8.64–8.76 (m; 1H, 5–H).

b) 0.40 g **1b** (1.82 mmol) in 5 mL CH_2Cl_2 were mixed with a suspension of 2.8 g TTN/K-10 montmorillonite FLUKA reagent (1.96 mmol $Tl(NO_3)_3$ equivalent) and stirred 2 h at room temp. GLC analysis showed then a **4b/1b** ratio of 15:85, unchanged after 62 h additional stirring. Filtration and

remotion of solvent allowed a quantitative recovery (0.41 g) of a brown paste, mixture of **4b + 1b**.

Methyl 9-phenanthrylacetate **(4c)**

From 2.2 g **1c** (10 mmol) in 45 mL MeOH and 4.98 g $Tl(NO_3)_3 \cdot 3H_2O$ (11.2 mmol) in 10 mL MeOH and 6 mL 60 % $HClO_4$; 10 h room temp. stirring and work up as for **4b** led to 2.5 g crude **4c**, used as such for saponification. Yield 90 %. An analytical sample was obtained after 3 recrystallizations from MeOH, as white needles. M.p. 76.5–77 °C (lit. 75–75.5 °C[7], 69 °C[12], 76.2–76.8 °C[13]). – IR: 730; 750, 775, 800; 845; 890; 980; 1015; 1175; 1255; 1435; 1495; 1735; 2960; 3070 cm^{-1}. – ^{1}H-NMR: δ (ppm) = 3.70 (s; 3H, $-CH_3$), 4.12 (s; 2H, $-CH_2-$), 7.55–7.72 (m; 4H, 2,3,6,7-H), 7.68 (s; 1H, 10-H), 7.81–7.93 (m; 1H, 1-H), 7.98–8.11 (m; 1H, 8-H), 8.62–8.80 (m; 2H, 4,5-H).

Methyl 9-chloro-3-phenanthrylacetate **(4d)**

From 5.0 g **1d** (19.6 mmol) in 70 mL $CHCl_3$ + 50 mL MeOH and 9.1 g $Tl(NO_3)_3 \cdot 3H_2O$ (20.5 mmol) in 20 mL MeOH and 14 mL 60 % $HClO_4$, · 24 h stirring at room temp. and work up as for **4a** led to 4.94 g of crude **4d** (**4d/1d** = 92:8, by GLC), used as such for hydrolysis. Crude yield 88 %. 0.47 g of this material were chromatographed on 12 g SiO_2, elution by 15 × 10 mL C_6H_6, fractions 5–7 leaving 310 mg pure (100 % by GLC) **4d**. Recrystallization from MeOH gave white needles. M.p. 61.5–62 °C. – IR: 600; 620; 640; 700; 755; 770; 805; 880; 935; 950; 1005; 1130; 1205; 1255; 1300; 1370; 1430; 1500; 1600; 1735; 2950; 3000; 3050 cm^{-1}. – ^{1}H-NMR: δ (ppm) = 3.72 (s; 3H, $-CH_3$), 3.87 (s; 2H, $-CH_2-$), 7.53 (dd; J = 8.2 Hz, J′ = 1.5 Hz, 1H, 2-H), 7.64–7.76 (m; 2H, 6,7-H), 7.76 (d; J = 8.2 Hz, 1H, 1-H), 7.84 (s; 1H, 10-H), 8.32–8.44 (m; 1H, 8-H), 8.53 (virtual s; 1H, 4-H), 8.63–8.75 (m; 1H, 5-H). – $C_{17}H_{13}ClO_2$ (284.7) Calc C 71.7 H 4.60 Cl 12.4 Found C 71.9 H 4.53 Cl 12.6.

2-Phenanthrylacetic acid **(3a)**

a) 12.3 g **2a** (38.3 mmol) in 23 mL dioxane and 23 mL 12 M HCl were refluxed for 18 h. The mixture was poured on 300 mL $CHCl_3$, washed with H_2O until neutral pH, dried (Na_2SO_4) and the solvent was taken off *in vacuo* to leave a crude product which upon recrystallization from the minimum amount of C_6H_6 gave 4.11 g of broad melting range (185–195 °) **3a**. Yield 45 %. Three further recrystallizations from C_6H_6 led to 2.17 g of constant, very sharp m.p. material, used for spectra and pharmacological tests.

b) 2.1 g crude **4a** (8.4 mmol) in 25 mL EtOH and 2.5 mL 5 M NaOH were warmed 7 h at 50 °C. The solvent was removed *in vacuo*, the residue taken up in H_2O, extracted with Et_2O and acidified (HCl) to precipitate 1.92 g **3a**. Yield 97 %. Only one recrystallization from C_6H_6 gave 1.58 g (80 %) of the sharp melting material.

3a: White glistening leaflets. M.p. 195.5–196 °C (lit. 181–183 °C[7b], 179–183 °C[8], 187–188 °C[9], 183 °C[10], 194–195 °C[4]). – IR: 675; 720; 735; 745; 815; 920; 1225; 1240; 1260; 1305; 1340; 1405; 1470; 1695; 2925 cm^{-1}. – ^{1}H-NMR (in DMSO-d_6): δ (ppm) = 3.80 (s; 2H, $-CH_2-$), 7.60 (virtual d; J = 8.6 Hz, 1H, 3-H), 7.59–7.72 (m; 2H, 6,7-H), 7.81 (s; 2H, 9,10-H), 7.85 (virtual s; 1H, 1-H), 7.92–8.04 (m; 1H, 8-H), 8.74–8.85 (m; 1H, 5-H), 8.76 (d; J = 8.6 Hz, 1H, 4-H).

3-Phenanthrylacetic acid **(3b)**

a) 22.6 g **2b** (70.3 mmol) in 45 mL dioxane and 34 mL 12 M HCl were refluxed for 22 h. Dilution with 600 mL Et_2O and work up as for **3a** led to 16.0 g of a crude residue which was crystallized from the minimum amount of C_6H_6, giving 8.13 g of broad melting range (172–180 °C) **3b**. Yield 49 %. Four further recrystallizations from C_6H_6 led to 4.15 g of the constant, very sharp m.p. material used for spectra and pharmacological tests.

b) From 1.0 g crude **4b** (4.0 mmol) in 12 mL EtOH and 1.2 mL 5 M NaOH, as for **3a**, were obtained 0.84 g **3b**. Yield 89 %. Once recrystallized from C_6H_6 gave 0.74 g (78 %) of the sharp melting material.

3b: White glistening leaflets. M.p. 183.5–184 °C (lit. 175–177 °C[7b], 174–175 °C[9]). – IR: 690, 720; 745; 750; 815; 850; 920; 1045; 1100; 1150; 1190; 1245; 1300; 1340; 1410; 1460; 1515; 1610; 1705; 3005 cm^{-1}. – ^{1}H-NMR (in DMSO-d_6): δ (ppm) = 3.86 (s; 2H, $-CH_2-$), 7.56 (dd; J = 8.0 Hz, J′ = 1.6 Hz, 1H, 2-H), 7.59–7.73 (m; 2H, 6,7-H), 7.81 (s; 2H, 9,10-H), 7.92 (d; J = 8.0 Hz, 1H, 1-H), 7.92–8.04 (m; 1H, 8-H), 8.69 (virtual s; 1H, 4-H), 8.72–8.84 (m; 1H, 5-H).

9-Phenanthrylacetic acid **(3c)**

a) 16.2 g **2c** (50.4 mmol) in 33 mL dioxane and 33 mL 12 M HCl were refluxed for 18 h. Work up as for **3b** led to a pasty residue which failed to crystallize from C_6H_6. Extraction with 300 mL 2 M NaOH and reprecipitation (12 M HCl) afforded 5.0 g of solid, broad melting range (185–195 °C) **3c**. Yield 42 %. One recrystallization from C_6H_6 and four from toluene gave 1.92 g (16 %) of constant, very sharp m.p. material, used for spectra and pharmacological tests.

b) 0.8 g crude **4c** (3.2 mmol) in 9.6 mL EtOH and 1 mL 5 M NaOH, as for **3a**, led to 0.66 g **3c**. Yield 87 %. Two recrystallizations from C_6H_6 gave 0.43 g (57 %) of the sharp melting material.

3c: White crystalline powder. M.p. 220.5–221 °C (lit. 219–221 °C[7b], 224–225 °C[11], 211–213 °C[12], 215–221 °C[13]). – IR: 665; 730; 745; 765; 800; 885; 920; 955; 985; 1150; 1190; 1210; 1225; 1250; 1290; 1335; 1410; 1450; 1495; 1695; 2940 cm^{-1}. – ^{1}H-NMR (in DMSO-d_6): δ (ppm) = 4.08 (s; 2H, $-CH_2-$), 7.59–7.75 (m; 4H, 2,3,6,7-H), 7.76 (s; 1H, 10-H), 7.88–8.01 (m; 1H, 1-H), 7.97–8.09 (m; 1H, 8-H), 8.75–8.93 (m; 2H, 4,5-H).

9-Chloro-3-phenanthrylacetic acid **(3d)**

a) 4.0 g **2d** (11.2 mmol) in 16 mL dioxane and 8 mL 12 M HCl were refluxed for 22 h. Work up as for **3b** led to 2.0 g of crude material, which upon crystallization from the minimum amount of C_6H_6 gave 1.60 g of broad melting range (194–202 °C) **3d**. Yield 53 %. Three additional recrystallizations from C_6H_6 gave 0.91 g of constant, very sharp m.p. material, used for spectra and pharmacological tests.

b) 4.47 g crude **4d** (15.7 mmol) in 60 mL EtOH and 6 mL 5 M NaOH were warmed 7 h at 60 °C. Work up us for **3a** afforded **3d** in nearly quantitative yield. One recrystallization from toluene gave 3.61 g (85 %) of the sharp melting material.

3d: White crystalline powder. M.p. 202.5–203 °C. – IR: 690; 720; 750; 780; 810; 835; 875; 920; 940; 1210; 1230; 1250; 1290; 1400; 1420; 1505; 1600; 1690; 2925 cm^{-1}. – ^{1}H-NMR: δ (ppm) = 3.89 (s; 2H, $-CH_2-$), 7.53 (dd; J = 8.2 Hz, J′ = 1.5 Hz, 1H, 2-H), 7.64–7.76 (m; 2H, 6,7-H), 7.76 (d; J = 8.2 Hz, 1H, 1-H), 7.84 (s; 1H, 10-H), 8.32–8.44 (m; 1H, 8-H), 8.53 (virtual s; 1H, 4-H), 8.62–8.74 (m; 1H, 5-H). – $C_{16}H_{11}ClO_2$ (270.7) Calc C 71.0 H 4.10 Cl 13.1 Found C 71.1 H 4.08 Cl 13.2.

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