eine wäßrige Glucoselösung ad libitum zur Verfügung. In das Auffanggefäß wurde etwas NaF zur Bakteriostase gegeben. Der gesammelte 24-h-Urin (zusammen ca. 25 ml) wurde nach standardisierten Verfahren aufgearbeitet[2, 4].

Die Identifizierung der Metabolite erfolgte mit der computergestützten GC-MS-Kopplung[2]. GC: HP 5970 A, mit Massenspektrometer MSD HP 5970 A und Workstation 59970 A. GC-Bedingungen: Hochleistungskapillare 12 × 0.2 mm, gepackt mit Methylsilikon (cross linked), Filmdicke: 0.33 µm; Temp.-Programm von 100–310°, 30°/min, 5 min Nachlauf; Einspritzblocktemp.: 270°; Trägergas: Helium, 1 ml/min. Open split, 260°. MS-Bedingungen: Ionisierungsenergie: 70 eV; Ionenquellentemp.: 220°; Scangeschwindigkeit: 1 scan/s.

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Phenanthrylalkanoic Acids I:

Syntheses and Biological Activities of 1-Phenanthryl Derivatives

Ana Eirín, Franco Fernández*), Generosa Gómez, Carmen López, and Ana Santos

Departamento de Quimica Orgánica, Facultad de Farmacia, Universidad de Santiago, 15706-Santiago de Compostela, Spain

José M. Calleja, Dolores de la Iglesia, and Ernesto Cano

Departamento de Farmacologia. Facultad de Farmacia. Universidad de Santiago. 15706-Santiago de Compostela, SPAIN

Received 23. February 1987

0365-6233/87/1111-1110 $ 02.50/0

Reformatsky reactions between 3,4-dihydro-1(2*H*)-phenanthrenone **(5)** and ethyl α-bromoacetate or propanoate yield several unsaturated esters which, upon aromatization followed by saponification, lead to the 1-phenanthrylacetic **(1)** and 2-(1-phenanthryl)propanoic **(2)** acids, whose analgesic and anti-inflammatory properties were measured and found comparable to those of Fenbufen.

Phenanthrylalkansäuren I. Synthese und biologische Wirksamkeiten von 1-Phenanthrylderivativen

Reformatsky Reaktionen zwischen 3,4-Dihydro-1(2*H*)-phenanthrenon **(5)** und Ethyl-α-bromacetat oder -Propionat produzieren verschiedene ungesättigte Ester, die nach Aromatisierung und Verseifung 1-Phenanthrylessigsäure **(1)** und 2-(1-Phenanthryl)propansäure **(2)** liefern. Die schmerzstillenden und entzündungshemmenden Eigenschaften dieser Säuren sind gemessen worden; sie sind vergleichbar mit den Eigenschaften des Fenbufens.

Several simple derivatives of biphenyl- and naphthalenealcanoic acids are known as useful antiinflammatory agents. In as much phenanthrene may be regarded as an analogue of both biphenyl and naphthalene systems, our attention has been drawn to the preparation and testing of antiinflammatory properties of phenanthrenealcanoic acids. Our work on the 1-phenanthrylacetic acid **(1)** and 2-(1-fenanthryl)propanoic acid **(2)** is here reported.

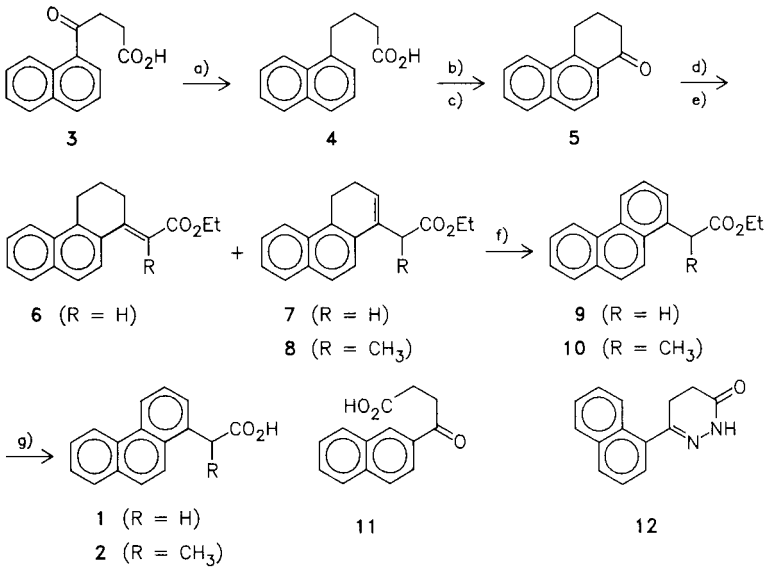
We have synthesized **1** and **2** by the route shown in Scheme 1. Acetic acid derivatives had once been prepared by *Hoch* [1a], though in a "bad yield", using a similar approach, and more recently by *Harmon* et al.[2] starting from the 1-methylphenanthrene. Compound **2** has not yet been reported.

4-(1-Naphthyl)-4-oxobutanoic acid **(3)** is usually prepared by succinoylation of naphthalene. In the past, several workers[3] have reported the formation of "sensibly equal amounts" of the 1-naphthyl- **(3)** and 2-naphthylderivative **(11)** for the reaction run in nitrobenzene with ratios **3/11** of 1.2–1.3 for the pure isolated products, with a joint yield of 65–80 %.

We have been unable of duplicating such results. In fact, after having strictly followed the procedure of *Colonge* et al.[3a] but for the last recrystallizations, we finally isolated **3** and **11**, both pure (> 99.5 % by GLC of their methyl esters), in a ratio **3/11** of 0.23, for a joint yield of 74 %.

Running the reaction in 1,1,2,2-tetrachloroethane (TCE) led to a substantial increase of the ratio **3/11** in the reaction mixture; however, once the crude product was partitioned, the main fraction having a **3/11** ratio of 9.0 was impurified by much tarry material (not shown by GLC) which raised difficulties in the isolation of **3**, thus failing to improve its yield. Running the reaction in $CHCl_3$ was absolutely useless.

4-(1-Naphthyl)butanoic acid **(4)** had formerly been prepared by *Clemmensen* reduction of **3**[3a, 4] or by malonic synthesis[1,5]. We tried to reduce **3** by catalytic hydrogenolysis in conditions similar to those quoted for other ω-aryl-ω-oxoalkanoic acids[6] but the method was found unreliable. Finally **4** was obtained in 71 % yield from **3** by the *Huang-Minlon* procedure of ketone reduction[7], while in a run carried out in ethyleneglycol, 4,5-dihydro-6-(1-naphthyl)-3(2*H*)-pyridazinone **(12)** was isolated as the main product.



a) N_2H_4/KOH/DEG, 200°; b) $SOCl_2$; c) $SnCl_4$;
d) $RCHBrCO_2Et$/Zn~Hg; e) HCO_2H, 60°; f) S, 270°; g) NaOH.

Snyder's method of direct cyclization of arylalcanoic acids in PPA[8] was tried on **4**, but led to extensive resinification: even in the mildest conditions (50°, 3 hr), the non-acidic fraction (60 %) of the product was a black tarry material, from which **5**, though present (IR, GLC), could not be isolated. The procedure of *Nishimura* et al. (Ac_2O/H_3PO_4, 130°, 4 h) afforded **5** in 30 % yield, though 50 % of **4** could be recovered. Finally, **5** was obtained in a fair yield by the acid chloride-$SnCl_4$ method[10].

Reformatsky reactions between **5** and ethyl α-bromoacetate and -propionate were carried out following the procedure of *Bachmann* et al. for an isomeric substrate[10b]. In the first case, dehydration of crude hydroxy ester led in a 71 % yield to a 1:3 mixture of α, β- **(6)** and β, γ- (7) unsaturated esters, which were separated by column chromatography and undoubtedly characterized by their IR and ^{1}H-NMR spectra.

Thus ν_{CO} appears at 1700 cm^{-1} (conjugated ester) for **6** while at 1730 cm^{-1} (unconjugated) for **7**. Chemical shift (δ 3.53 ppm) and multiplicity (duplet due to a small allylic splitting of 1.1 Hz) stand for the methylene α- to the ester group in **7**, while all methylene in **6** appear as triplets or multiplets. Estimation of chemical shifts of vinylic protons by means of substituent shielding coefficients[11] give values of 6.04 and 5.63 ppm respectively, both *ca.* 0.4 ppm lower than the corresponding experimental values (6.42 and 6.10 ppm). *E* configuration has been assigned to the α, β-unsaturated ester, as estimated value for its *Z*-isomer would be even lower, 5.60 ppm. On the other hand, chemical shift of allylic protons in **6** (roughly

3.25 ppm, as for benzylic ones) points out to the same stereochemical assignement, their noteworthy deshielding being due to the allylic methylene lying *cis* to the ester group. Multiplicity and coupling constants of vinylic protons in both esters also agree with proposed structures.

Same dehydration conditions applied to the hydroxy propionic derivative led only to the β, γ-unsaturated ester **8**. Besides obvious differences in the 1.0–4.0 ppm region, ^{1}H-NMR spectra show 10-H in **8** to be more deshielded than in **7**, what is attributed to the increased steric hindrance caused by the extra methyl group.

Both **6** and **7** were separatedly dehydrogenated by sulphur under standard conditions[12] to the phenanthryl derivative **9**, as well as **8** to **10**. Yields of aromatization from pure β, γ-unsaturated esters **7** and **8** were higher but, owing to the difficult separation between **6** and **7**, their mixtures were used for the preparative runs. In all cases, some 5–7 % phenanthrene was detected (GLC) in the crude products. Finally, saponification of **9** and **10** led to the desired acids **1** and **2**.

The 9, 10-H appear in the NMR spectra of **2** and **10** as a clearly recognizable AB system, what probably is due again to the deshielding steric effect caused on 10-H by the methyl group of the side chain, as such an effect is not seen for **1** nor **9**.

Pharmacology

I. *Anti-inflammatory activity*

Carragenin-induced edema of the rat paw

A modification of the method of *Winter* et al.[13] was applied. Each dose group consisted of 6 male Wistar rats (170–190 g). Diet was stopped beginning 16 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 % carregeenin 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 4 h after carrageenin injection. Drug activity was expressed as % inhibition of edema formation compared to controls. Antiedema ED_{50} values were calculated by a least square analysis. Results are given in Tab. 1.

II. *Analgesic activity*

Acetic acid writhing test

Method of *Koster* et al.[14] was followed. Male CD1 mice (22–26 g) were used in groups of 10 per dose, each experiment including a control group. Test compound or vehicle was administered by oral gavage at a volume of 10 mL/kg body weight. 15 min later each animal received an i.p. injection of 0.25 mL 1 % acetic acid solution. Mice were inmediately placed in individual glass containers and the number of writhes counted for each mouse during the 30-min observation period beginning 15 min after the i.p. injection. Analgesic effect was expresed as a percentage of protection compared

with the control group and the ED_{50} calculated as mentioned above. Results are given in Tab. 1.

Table 1

Compound	Analgesic Activity			Anti-inflammatory Activity		
	Oral dose (mM/kg)	% Protection (Mean ± se)	ED_{50} (mM/kg)	Oral dose (mM/kg)	% Inhibition (4 h) (Mean ± se)	ED_{50} (mM/kg)
1	0.1	30.8 ± 7.6	0.168	0.1	36.6 ± 2.9	0.172
	0.2	54.2 ± 9.0		0.2	53.0 ± 6.9	
	0.4	85.2 ± 5.5		0.4	71.8 ± 3.2	
2	0.1	31.2 ± 5.8	0.172	0.1	34.2 ± 5.1	0.252
	0.2	54.0 ± 8.8		0.2	46.6 ± 4.8	
	0.4	80.6 ± 5.0		0.4	57.5 ± 3.4	
Fenbufen	0.1	26.6 ± 7.7	0.197	0.1	59.0 ± 5.2	0.045
	0.2	50.5 ± 6.7		0.2	67.1 ± 5.2	
	0.4	73.9 ± 7.6		0.4	74.7 ± 5.9	

Financial support for this work and grants received by two of us (G. G. and A. S.) from Comisión Asesora de Investigación Científica y Técnica (Proyecto 0800/81) are acknowledged.

Experimental Section

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 $CDCl_3$/TMS int. stand. – *Column Chromatography*: Silica gel (230 mesh, Merck). – *Gas Liquid Chromatography*: Hewlett Packard 5710A, FID, H-P 3380S integr.; column: 50 cm, 1/8″, 10 % UCC/Chromosorb W-HP; N_2, 30 mL/min, 200°. Relative proportions and/or purity of acids **1, 2, 3, 4** and **11** were determined by GLC of their methyl esters **1a, 2a, 3a, 4a** and **11a**, quantit. prepared in $MeOH/H_2SO_4$ by the procedure of *Colonge*[3c]; **4a** also by the diazomethane method[15].

Succinoylation of naphthalene: 4-(1-naphthyl)-4-oxobutanoic acid **(3)**

a) Reaction run in $C_6H_5NO_2$ for 90 g (0.90 mol) of succinic anhydride[3c], led to a greenish insoluble solid, **A**, and a liquid mixture, **B**. From **A** were isolated 138.2 g of crude and, once recrystallized from MeOH, 123.5 g (60 %) of pure (> 99.5 %) 4-(2-naphthyl)-4-oxobutanoic acid **(11)**, m.p. 172–173° (lit. 171–173°[3a]).

Nitrobenzene and unreacted naphthalene were steam distilled off from **B** and the residue was extracted with hot aqueous Na_2CO_3 and filtered. Acidifying (HCl) of the clear alcaline solution led to 49 g of crude and – after several recrystallizations from $CHCl_3$ – 29 g (14 %) of pure (> 99.7 %) **3**. M.p. 130–131° (lit. 129–131°[3a], 126°[3c]). IR: 660; 750; 795; 1465; 1500; 1590; 1620; 1680; 1700; 2400–3250 cm^{-1}. – GLC retention times: **3a**: 7.6 min; **11a**: 9.2 min.

b) Reaction performed exactly in the same way as above but with TCE instead of $C_6H_5NO_2$, in a 1/10 of scale run, led to 4.61 g of a solid **A'**, with a **3/11** ratio of 16/84, and 7.35 g of a residue from the liquid **B'**, with a **3/11** ratio of 90/10. From this tarry material only small amounts of pure **3** could be isolated.

c) Use of $CHCl_3$ instead of $C_6H_5NO_2$ or TCE led to a black carbonaceous paste, from which neither **3** nor **11** could be isolated.

Reduction of **3**: *4-(1-Naphthyl)butanoic acid* **(4)**

a) To 8.87 g KOH (158 mmol) in 125 mL diethylene glycol (DEG) were added 21.1 g **3** (93 mmol) and 8.64 mL $N_2H_4 \cdot H_2O$ (177 mmol) and the well stirred mixture heated at 195–200° in an oil bath for 2 h. Water and hydrazine excess were then distilled off, the mixture further heated at 200° for 4 h and, once cold, diluted with 275 mL water and extracted with 2 × 100 mL Et_2O. The resulting brownish alcaline solution was acidified (HCl) and extracted with 2 × 150 mL C_6H_6, the org. layer dried (Na_2SO_4) and the solvent removed *in vacuo*. Recrystallization of the crude residue from petrol ether led to 14 g (71 %) of pure **4**. M.p. 106–107° (lit. 106–107°[3a], 109–110°[5]). – IR: 735; 775; 790; 910; 1205; 1220; 1280; 1330; 1410; 1430; 1460; 1505; 1600; 1710; 2400–3250 cm^{-1}. – ^{1}H-NMR: δ (ppm) = 1.89–2.27 (m; 2H, $-CH_2-CH_2-CH_2-$), 2.45 (t; J = 7.1 Hz, 2H, $-CH_2-CO_2H$), 3.13 (t; J = 7.4 Hz, 2H, $-CH_2-Ar$), 7.30–7.53 (m; 4H, 2′, 3′, 6′, 7′-H), 7.65–7.90 (m; 2H, 4′, 5′-H), 7.98–8.10 (m; 1H, 8′-H), 9.25 (broad s; D_2O exchang.; 1H, $-CO_2H$).

Methyl ester **(4a)**. By the diazomethane method[15] from **4**. Colourless liquid. IR: 780; 800; 1010; 1070; 1145; 1170; 1200; 1250; 1365; 1400; 1435; 1460; 1510; 1600; 1740; 2870; 2950; 3010; 3050 cm^{-1}. – ^{1}H-NMR: δ (ppm) = 1.86–2.23 (m; 2H, $-CH_2-CH_2-CH_2-$), 2.38 (t; J = 6.8 Hz, 2H, $-CH_2-CO_2Me$), 3.10 (t; J = 7.3 Hz, 2H, $-CH_2-Ar$), 3.64 (s; 3H, $-CO_2CH_3$), 7.28–7.51 (m; 4H, 2′, 3′, 6′, 7′-H), 7.63–7.88 (m; 2H, 4′, 5′-H), 7.98–8.10 (m; 1H, 8′-H).

b) In a similar run using ethyleneglycol instead of DEG, water added to the final cold alkaline reaction mixture precipitated a solid, which was recrystallized from EtOH to give 9.8 g (47 %) of pyridazinone **12**. M.p. 143–144°. – IR: 600; 680; 770; 800; 940; 970; 1020; 1125; 1215; 1250; 1300; 1330; 1370; 1430; 1510; 1590; 1610; 1625; 1695; 2940; 3100; 3200 cm^{-1}. – ^{1}H-NMR: δ (ppm) = 2.59–2.81 (m; 2H, $-CH_2-C(Ar)=N-$), 2.97–3.19 (m; 2H, $-CH_2-CO-$), 7.47–7.59 (m; 4H, 2′, 3′, 6′, 7′-H), 7.84–7.96 (m; 2H, 4′, 5′-H), 8.11–8.23 (m; 1H, 8′-H), 8.71 (broad s, D_2O exchang.; 1H, $-NH-$). – $C_{14}H_{12}N_2O$ (224.3) calc. C 75.0 H 5.39 N 12.5 found C 74.7 H 5.34 N 12.6.

c) Hydrogenolysis of 10 g **3** (43 mmol) in AcOH with 0.46 g 10 % Pd/C, in a shaken Parr apparatus at 56 psi and 45°, was found not to proceed significantly over a 4 h period unless 10 drops of 70 % $HClO_4$ were previously added. Removal of catalyst and solvent left a liquid residue, which was dissolved in $CHCl_3$ and extracted with 5 % NaOH. Acidification gave 9.0 g of a mixture of acids, which by recrystallization as above led only to 1.2 g of pure **4**.

3,4-Dihydro-1(2H)-phenanthrenone **(5)**

3.6 mL $SOCl_2$ (49 mmol) in 4 mL C_6H_6 were dropped into a solution of 6.0 g **4** (28 mmol) and 4 drops C_6H_5N in 40 mL C_6H_6, the mixture first stirred 90 min at room temp., then 30 min at 80°. Solvent and excess of reagent were removed under reduced pressure, the acid chloride was dissolved in 28 mL C_6H_6 and 6.9 mL anhydrous $SnCl_4$ (59 mmol) in 7 mL C_6H_6 were added to the stirred reaction mixture kept below 5°. After 30 min further stirring at this temp., the mixture was hydrolyzed with ice and dil. HCl, the org. layer separated, extracted with 10 % NH_4OH and H_2O and the solvent removed, to leave an oily residue which spontaneously solidified. Recrystallization from MeOH gave 4.2 g of pure (> 99.8 % by GLC) **5**. Yield 76 %. M.p. 95–96° (lit.[5] 94–96°). IR: 720; 755; 830; 1110; 1195; 1280; 1335; 1435; 1460; 1595; 1620; 1675; 2900; 2950; 3030; 3060 cm^{-1}. – ^{1}H-NMR: δ (ppm) = 2.12–2.46 (m; 2H, $-CH_2-CH_2-CH_2-$), 2.75 (t; J = 6.4 Hz, 2H, $-CH_2-CO-$), 3.38 (t; J = 6.2 Hz, 2H, $-CH_2-Ar$), 7.52–7.68 (m; 2H, 6,7-H), 7.76 (A part of AB system; J = 8.6 Hz, 9-H), 7.76–7.93 (m; 1H, 8-H), 8.11 (B part of AB system; J = 8.6 Hz, 10-H), 8.04–8.20 (m; 1H, 5-H). See also *Martin*[16].

(E)-Ethyl 3,4-dihydro-1(2H)-phenanthrylideneacetate **(6)** *and ethyl 3,4-dihydro-1-phenanthrylacetate* **(7)**

To 10 g amalgamated Zn covered by 100 mL dry C_6H_6-Et_2O (1:1) a small crystal of iodine and 4.0 g **5** (20 mmol) and 4.8 mL ethyl bromoacetate (43 mmol) in 50 mL dry C_6H_6 were added. The mixture was refluxed for 3 h, while adding every 20 min further portions of 1 g amalgamated Zn and iodine, then hydrolyzed with cold dil. HCl, the org. layer was decanted and the aqueous layer extracted with C_6H_6. The combined org. extracts, after being thoroughly washed with 10 % NH_4OH and H_2O, dried (Na_2SO_4) and evaporated *in vacuo*, left 5.5 g of crude hydroxy ester [IR: 3500 (broad, OH), 1730 (CO) cm^{-1}] as an oily residue.

A solution of this Reformatsky ester in 29 mL anhydrous formic acid was heated at 60° for 1 h, diluted with H_2O and extracted with C_6H_6. The org. layer was then washed with 5 % Na_2CO_3, H_2O and the solvent removed *in vacuo*, leaving 4.1 g of an oily mixture of unsaturated esters. Analysis of this material by GLC gave 24.3 % **6** and 69.2 % **7**, the rest being two unidentified small peaks.

The first fraction of column chromatography of that mixture on 110 g SiO_2 gel, elution by C_6H_6, left a solid which was recrystallized from MeOH to afford pure **6**. The last fractions, once rechromatographied in a similar way, led to a pure sample (> 99 % by GLC) of **7**.

6: M.p. 102–103°. – IR: 760; 810; 860; 1040; 1050; 1090; 1160; 1170; 1190; 1310; 1370; 1390; 1430; 1445; 1460; 1560; 1610; 1700; 2860; 2930; 2970; 3060 cm^{-1}. – ^{1}H-NMR: δ (ppm) = 1.33 (t; J = 7.1 Hz, 3H, -O-CH_2-C<u>H</u>$_3$), 2.03 (quin; J = 6.5 Hz, 2H, -CH_2-C<u>H</u>$_2$-CH_2-), 3.16–3.36 (m; 4H, -C<u>H</u>$_2$-C=CH- + -CH_2-Ar), 4.23 (quart; J = 7.1 Hz, 2H, -O-C<u>H</u>$_2$-CH_3), 6.42 (t; J = 1.6 Hz, 1H, > C=CH-), 7.45–7.62 (m; 2H, 6,7-H), 7.70 (s; 2H, 9.10-H), 7.75–7.89 (m; 1H, 8-H), 8.00–8.14 (m; 1H, 5-H). – GLC retention time: 20.7 min.

7: Colourless liquid. – IR: 685; 710; 750; 825; 865; 1030; 1160; 1255; 1300; 1330; 1365; 1380; 1425; 1460; 1510; 1595; 1615; 1730; 2830; 2880; 2930; 2980; 3040; 3060 cm^{-1}. – ^{1}H-NMR: δ (ppm) = 1.22 (t; J = 7.1 Hz, 3H, -O-CH_2-C<u>H</u>$_3$), 2.41–2.59 (m; 2H, -C<u>H</u>$_2$-CH=C <), 3.14–3.34 (m; 2H, Ar-CH_2-), 3.53 (d; J = 1.1 Hz, 2H, -C<u>H</u>$_2$-CO_2Et), 4.14 (quart; J = 7.1 Hz, 2H, -O-C<u>H</u>$_2$-CH_3), 6.10 (dt; J = 4.6 Hz, J′ = 1.1 Hz, 1H, -CH=C <), 7.35–7.54 (m; 4H, 6,7,9,10-H), 7.77–7.91 (m; 1H, 8-H), 8.01–8.13 (m; 1H, 5-H). – GLC retention time: 13.8 min.

Ethyl 1-phenanthrylacetate **(9)**

A 9 g mixture of unsaturated esters **6** (28 %) and **7** (72 %) (34 mmol altogether) and 1.2 g sulphur (37 mmol) was heated 40 min at 270°. Once cold, the crude mass was digested in Et_2O, washed (H_2O), dried (Na_2SO_4) and the solvent removed to leave a solid residue which was recrystallized from MeOH to give 5.5 g of pure **9**. Yield 61 %. M.p. 64–65°. – IR: 760; 770; 810; 820; 960; 1040; 1165; 1250; 1270; 1300; 1325; 1370; 1410; 1450; 1465; 1605; 1730; 2920; 2990; 3060 cm^{-1}. – ^{1}H-NMR: δ (ppm) = 1.21 (t; J = 7.1 Hz, 3H, -O-CH_2-C<u>H</u>$_3$), 4.12 (s; 2H, -CH_2-CO_2Et), 4.16 (quart; J = 7.1 Hz, 2H, -O-C<u>H</u>$_2$-CH_3), 7.54–7.72 (m; 4H, 2,3,6,7-H), 7.84–8.03 (m; 3H, 8,9,10-H); 8.62–8.76 (m; 2H, 4,5-H). – GLC retention time: 15.8 min.

1-Phenanthrylacetic acid **(1)**

A solution of 4.45 g **9** (16.8 mmol) in 40 mL EtOH and 6 mL aqueous 10 % NaOH was kept 4 h at 50°. Solvents were removed *in vacuo*, the residue dissolved in H_2O and washed with Et_2O. Acidulation (HCl) precipitated a white solid, which was recrystallized from C_6H_6 to give 3.35 g **1**. Yield 84 %. M.p. 190–191° (lit. 189–190°[1a], 190–191°[2]). – IR: 660; 725; 780; 800; 820; 940; 1160; 1210; 1245; 1260; 1320; 1400; 1410; 1430; 1600; 1690; 2300–3300 cm^{-1}. – ^{1}H-NMR: δ (ppm) = 4.14 (s; 2H, -C<u>H</u>$_2$-CO_2H), 7.53–7.71 (m; 4H, 2,3,6,7-H), 7.83–7.96 (m; 3H, 8,9,10-H), 8.64–8.75 (m; 2H, 4,5-H). – $C_{16}H_{12}O_2$ (236.3) calc. C 81.3 H 5.12 found C 81.1 H 5.09.

Ethyl 2-(3,4-dihydro-1-phenanthryl)propionate **(8)**

From 15 g **5** (76 mmol) and 21 mL ethyl 2-bromopropionate (162 mmol), following the same procedure as for **7**, a yellowish oily residue of 22.8 g (99 %) of crude hydroxy ester [IR: 3500 (broad, OH), 1720 (CO) cm^{-1}] was obtained. Dehydration and work up as before led to 22.6 g of a solid product, which by recrystallization from MeOH afforded 17 g pure **8**. Yield 80 %. M.p. 102–103°. – IR: 705; 750; 810; 835; 850; 1020; 1070; 1080; 1090; 1180; 1210; 1265; 1295; 1310; 1335; 1370; 1380; 1440; 1460; 1505; 1590; 1720; 2830; 2875; 2935; 2980; 3060 cm^{-1}. – ^{1}H-NMR: δ (ppm) = 1.18 (t; J = 7.1 Hz, 3H, -O-CH_2-C$\underline{H}_3$), 1.46 (d; J = 7.1 Hz, 3H > CH-C$\underline{H}_3$), 2.40 (dt; J = 8.4 Hz, J′ = 4.6 Hz, 2H, -CH_2C$\underline{H}_2$-CH=C<), 3.18 (t; J = 8.4 Hz, 2H, -C$\underline{H}_2$-CH_2-CH=C), 3.83 (dquart J = 7.1 Hz, J′ = 0.9 Hz, 1H, -CH=C-C$\underline{H}$-CH_3), 4.13 (t; J = 7.1 Hz, 2H, -O-C$\underline{H}_2CH_3$), 6.12 (dt; J = 4.6 Hz, J′ = 0.9 Hz, 1H, -CH_2-C$\underline{H}$=C-CH<), 7.36–7.57 (m; 3H, 6,7,9-H), 7.70 (d; J = 8.9 Hz, 1H, 10-H), 7.73–7.85 (m; 1H, 8-H), 8.00–8.13 (m; 1H, 5-H).

Ethyl 2-(1-phenanthryl)propionate **(10)**

Aromatization of 10.1 g **8** (36 mmol) as described for **9** and recrystallization from MeOH gave 7.3 g pure **10**. Yield 73 %. M.p. 85–86°. – IR: 755; 805; 830; 870; 995; 1085; 1135; 1160; 1170; 1190; 1230; 1240; 1300; 1330; 1345; 1370; 1400; 1420; 1450; 1480; 1600; 1725; 2870; 2910; 2935; 2980; 3050 cm^{-1}. – ^{1}H-NMR: δ (ppm) = 1.16 (t; J = 7.1 Hz, 3H, -O-CH_2-C$\underline{H}_3$), 1.67 (d; J = 7.1 Hz, 3H, > CH-C$\underline{H}_3$), 4.14 (quart; J = 7.1 Hz, 2H, -O-C$\underline{H}_2$-CH_3), 4.55 (quart; J = 7.1 Hz, 1H, > C$\underline{H}$-CH_3), 7.57–7.74 (m; 4H, 2,3,6,7-H), 7.80 (A part of AB system; J = 9.1 Hz, 9-H), 7.84–7.96 (m; 1H, 8-H), 8.03 (B part of AB system; J = 9.1 Hz, 10-H), 8.60–8.76 (m; 2H, 4,5-H).

2-(1-Phenanthryl)propionic acid **(2)**

7.0 g **10** (25 mmol) in 70 mL EtOH and 4.6 mL aqueous 20 % NaOH was heated at 50° for 7 h. Usual work up and recrystallization from EtOH led to 5.7 g pure **2**. Yield 90 %. M.p. 201–202°. – IR: 630; 675; 710; 750; 785; 800; 825; 865; 885; 930; 950; 970; 995; 1045; 1080; 1090; 1175; 1220; 1250; 1310; 1325; 1375; 1395; 1415; 1450; 1600; 1705; 2300–3200 cm^{-1}. – ^{1}H-NMR: δ (ppm) = 1.70 (d; J = 7.1 Hz, 3H, > CH-C$\underline{H}_3$), 4.61 (quart; J = 7.1 Hz, 1H, > C$\underline{H}$-CH_3), 7.59–7.74 (m; 4H, 2,3,6,7-H), 7.80 (A part of AB system; J = 9.2 Hz, 9-H), 7.85–7.97 (m; 1H, 8-H), 8.05 (B part of AB system; J = 9.2 Hz, 10-H), 8.63–8.75 (m; 2H, 4,5-H). – $C_{17}H_{14}O_2$ (250.3) calc. C 81.5 H 5.64 found C 81.5 H 5.66.

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Arch. Pharm. (Weinheim) *320*, 1118–1123 (1987)

Synthesis and Calcium-Antagonist Activity of some phosphonates

Stefano Corsano*, Giovannella Strappaghetti, and Enzo Castagnino

Institute of Pharmaceutical Chemistry, University of Perugia, via del Liceo, 06100 Perugia, Italy
Received 26. February 1987

The synthesis and pharmacological evaluation of a series of phosphonates related to Fostedil, diethyl 4-(benzothiazol-2-yl)benzylphosphonate **1**, a potent calcium antogonist are reported. Among the compounds studied, only diethyl 4-(benzooxazol-2-yl)benzylphosphonate **5**, which is closely related to Fostedil, shows a low calcium-antagonist activity.

Synthese und Calcium-antagonistische Wirkung einiger Phosphonate

Synthese und pharmakologische Bewertung von Phosphonaten, die mit dem Calcium-Antagonisten Phostedyl, Diethyl-4-(benzothiazol-2-yl)-benzylphosphonat, verwandt sind, werden beschrieben.
Unter den untersuchten Verbindungen zeigt nur Diethyl-4-(benzoxazol-2-yl)-benzylphosphonat **5** das O-Analoge des Phostedyls eine niedrige Ca-antagonistische Aktivität.

Calcium-antagonists are compounds that interfere with calcium flux across cellular membranes[1]. Verapamil[2], Nifedipine[3] and Diltiazem[4] are calcium-antagonists used to treat atherosclerosis, hypertension and myocardial infarction. During researches on derivatives of dialkyl phosphonates, which show vasodilating effect[5], *Kohno* and coworkers[6] have synthesized the phosphonate **1**, named Fostedil, which shows calcium-antagonist activity comparable to that of Diltiazem.

Our object has been the synthesis of some new phosphonates in order to check if the modification of the structure of Fostedil could preserve the calcium-antagonist activity.

0365-6233/87/1111-1118 $ 02.50/0