of mp 261–262 °C (79% yield). Anal. ($C_{17}H_{15}NO_4 \cdot 0.25H_2O$) C, H, N.

79. A suspension of 4′-[9-[4-[(4-nitrophenoxy)carbonyl]-acridinyl]amino]methanesulfon-*m*-anisidide[5] (6.0 g, 0.01 mol) and 6-aminohexan-1-ol (1.5 g, 0.013 mol) in DMF (20 mL) was stirred at room temperature until a homogeneous solution resulted when Et_3N (1.8 mL, 0.014 mol) was added, and the mixture stood until TLC monitoring indicated completion of reaction (15 min). Solvent was then removed in vacuo, the product was dissolved in excess EtOAc, the resulting solution was washed with ice-cold 10% $KHCO_3$ and H_2O and dried (Na_2SO_4), and the solvent was removed. The remaining base was crystallized from 1:1 EtOH–H_2O at low temperatures. A sample of this TLC-homogeneous base was dissolved in the minimum necessary volume of hot 1 N HOAc. To the hot, clarified solution was added 0.10 volume of 20% aqueous NaCl. After thoroughly cooling the solution, the crystalline hydrochloride was collected and washed with a little ice-cold H_2O, mp 106–107 °C. Anal. ($C_{28}H_{32}N_4O_5S \cdot HCl \cdot H_2O$) C, H, N, Cl.

A solution of the foregoing base (2 g, 3.7 mmol) was prepared in refluxing pyridine (8 mL) and then thoroughly cooled in an ice–salt mixture while stirring vigorously. Methanesulfonyl chloride (0.84 g, 7.4 mmol) was then added in dropwise fashion, so the temperature remained below −5 °C. Reaction was allowed to proceed at this temperature until TLC monitoring demonstrated complete conversion of starting material to the more polar product. Light petroleum (25 mL) was then added with shaking, and the precipitated thick red gum was washed with successive quantities of light petroleum by decantation. Ice-cold EtOAc (250 mL) was then added, followed by excess cold aqueous 10% $KHCO_3$, and vigorous stirring was continued until all solids had dissolved. To the washed (H_2O) and dried (Na_2SO_4) EtOAc solution light petroleum was added until turbid, and then dry HCl was passed through the solution with ice cooling. The precipitated hydrochloride was dissolved in the minimum necessary volume of dry *n*-BuOH by stirring at room temperature and then the clarified solution was stored at refrigerator temperatures until turbid. Scratching and occasional deep-freeze cooling of a small sample finally produced seed crystals. Back seeding of the bulk solution and final cooling at −15 °C then provided TLC-homogeneous product. A further crystallization from MeOH–H_2O provided pure product as deep red crystals of mp 66–67 °C (yield 1.41 g, 61%). Anal. ($C_{29}H_{34}N_4S_2O_7 \cdot HCl \cdot 0.5H_2O$) C, H, N.

Methods of elaboration of substituted acridones to the desired products have been earlier well described.[1-8]

$t_{1/2}$ Values for Thiolytic Cleavage. Formerly,[16] half-lives for drug decay in the presence of thiol were determined in 50% MeOH–H_2O solution. In contrast, drug dissociation constants have been determined spectrophotometrically in 20% DMF–H_2O solution. To obtain $t_{1/2}$ values under conditions comparable to those used in pK_a determinations, the reaction rates assays were repeated under the following conditions. Agents were dissolved in 40% DMF–H_2O to provide 50 μM solutions. The freshly prepared buffered thiol solution contained equal volumes of 0.140 M KH_2PO_4 and 0.06 M Na_2HPO_4 and 2-mercaptoethanol to provide a 0.50 M solution. Equal volumes of temperature-equilibrated drug and thiol solutions were rapidly mixed in the cuvette of a Shimadzu UV-200 double-beam spectrophotometer having thermostated cell holders maintained at 37 ± 0.1 °C. The concentration of reagents are such that the final reaction mixture is 20% in DMF and has a pH of 7.00, as measured by a glass electrode. Absorbance (A) of the reaction mixture was monitored at an appropriate wavelength (350–500 nm) as a function of time. The slope of plots of log A against time provided values of the pseudo-first-order rate constants (k) for drug disappearance and $t_{1/2}$ values were then calculated as $0.69/k$.

Necessary values (min) recorded for this study were: **22** (Table I), 13.2; **30**, 23.6; **37**, 13.4; **48**, 1.12; **55**, 1.90; **62**, 2.52.

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References and Notes

(1) G. J. Atwell, B. F. Cain, and R. N. Seelye, *J. Med. Chem.*, **15**, 611 (1972).
(2) B. F. Cain, R. N. Seelye, and G. J. Atwell, *J. Med. Chem.*, **17**, 922 (1974).
(3) B. F. Cain, G. J. Atwell, and W. A. Denny, *J. Med. Chem.*, **18**, 1110 (1975).
(4) B. F. Cain and G. J. Atwell, *J. Med. Chem.*, **19**, 1124 (1976).
(5) B. F. Cain, G. J. Atwell, and W. A. Denny, *J. Med. Chem.*, **20**, 987 (1977).
(6) G. J. Atwell, B. F. Cain, and W. A. Denny, *J. Med. Chem.*, **20**, 1128 (1977).
(7) W. A. Denny, G. J. Atwell, and B. F. Cain, *J. Med. Chem.*, **20**, 1242 (1977).
(8) W. A. Denny, G. J. Atwell, and B. F. Cain, *J. Med. Chem.*, **21**, 5 (1978).
(9) D. D. Von Hoff, D. Howser, P. Gormley, R. A. Bender, D. Glaubiger, A. S. Levine, and R. C. Young, *Cancer Treat. Rep.*, **62**, 1421 (1978).
(10) B. F. Cain and W. A. Denny, *J. Med. Chem.*, **20**, 515 (1977).
(11) W. A. Denny and B. F. Cain, *J. Med. Chem.*, **21**, 430 (1978).
(12) W. A. Denny, G. J. Atwell, B. C. Baguley, and B. F. Cain, *J. Med. Chem.*, **22**, 134 (1979).
(13) R. A. Scherrer and S. M. Howard, *J. Med. Chem.*, **20**, 53 (1977).
(14) H. Kubinyi, *J. Med. Chem.*, **20**, 625 (1977).
(15) Y. C. Martin and J. J. Hackbarth, *J. Med. Chem.*, **19**, 1033 (1976).
(16) B. F. Cain, W. R. Wilson, and B. C. Baguley, *Mol. Pharmacol.*, **12**, 1027 (1976).
(17) R. L. Cysyk, D. Shoemaker, and R. H. Adamson, *Drug Metab. Dispos.*, **5**, 579 (1977).
(18) W. R. Wilson, B. F. Cain, and B. C. Baguley, *Chem.-Biol. Interact.*, **18**, 163 (1977).
(19) S. M. Sherlin, G. I. Braz, A. Y. Yakubovich, E. I. Vorob'eva, and F. E. Rabinovich, *J. Gen. Chem. USSR*, **8**, 898 (1938).

Potential Antiinflammatory Compounds. 1. Antiinflammatory Phenylpiperidine Derivatives

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The syntheses of a number of amines and their derivatives, based on the phenylpiperidine nucleus, are described. Their activities on the rat paw carrageenan test are also reported. Activities comparable to that of phenylbutazone were obtained for some of the amines, notably 4-piperidino-β-methylphenethylamine.

Patent literature reports for the antiinflammatory compound fenoprofen (I, Z = CO_2H) and its close relatives have shown that antiinflammatory activity is also found in the corresponding alkanes (e.g., I, Z = Me),[1] alcohols (I, Z =

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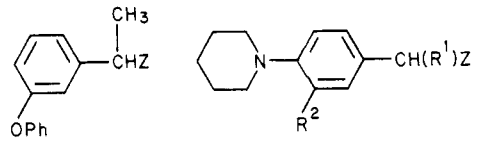


I II

CH_2OH),[2] and amines (I, Z = CH_2NH_2, etc.).[2] We have therefore investigated the antiinflammatory activities of analogous compounds with parent carboxylic acids represented by II (Z = CO_2H; R^1 = H, Me; R^2 = H, Cl).[3,4]

Chemistry. The compounds were prepared by standard methods of organic chemistry. Further details are available in Table I and the Experimental Section.

Antiinflammatory Activity. The tests for antiinflammatory activity were adapted from the rat paw edema test of Winter et al.[5] and carried out as described in the second paper of ref 5: The doses of test compounds used were 2 × 50 or 2 × 100 mg/kg. Usually, about one-fourth of the approximate oral LD_{50}, previously determined in groups of two mice given doses of 100–1600 mg/kg, was given. This procedure was adopted to minimize the occurrence of unwanted toxic effects. Groups of four female Wistar rats, bred in these laboratories and weighing 140–170 g, were dosed orally with the compounds 3 and 0.5 h prior to the injection of 0.1 mL of a 1% suspension of carrageenan (Gelozone ST-1, Whiffen and Son Ltd., Loughborough) in 0.9% saline into the plantar surface of the right hind foot of each rat. The injected (right) and noninjected (left) foot volumes were measured with a mercury-displacement plethysmograph 2.5 h after carrageenan injection, and the difference was taken to reflect the degree of inflammation produced. The mean increase in volume for each group was calculated, and the results were expressed as a percent inhibition of swelling, compared to a control group of ten rats dosed with saline and tested concurrently. A Student's t test was carried out, and compounds showing a significant reduction in swelling ($p < 0.02$) were selected for further testing (but not reported in this paper).

Representative results for compounds tested are collected in the Table I. Four "parent" carboxylic acids, **26–29**, are included for comparison. The alkane **1** was much less active than its corresponding acid **28**, but the alcohols **2** and **3** showed activities comparable to their corresponding acids **26** and **28**, while the tertiary alcohol **4** was inactive. Of the primary amines, the majority (**5–7**, **13–15**, and **18–20**) had activities comparable to their parent acids. Three primary amines (**17**, **23**, and **25**) were weakly active. Increasing the alkyl chain length of primary amines (**13–15**) did not reduce activity. Secondary and tertiary amines (**8**, **9**, and **21**) were active, as were amides (**10**, **12**, and **22**) of primary amines, but an amide (**11**) of a secondary amine was inactive. Compound **18** was resolved into its enantiomers without improvement of activity. The α-deuterated analogue **19** had somewhat reduced activity. A considerable amount of further biological work was carried out on compound **18**, with a view to progressing it toward clinical evaluation. This work was terminated when **18** was found to be lethal to dogs at 150 mg/kg, a dose less than eight times the possible clinical dose.

Experimental Section

Melting points are uncorrected. Microanalyses were carried out by Mr. G. Maciak and associates, Eli Lilly and Co., Indianapolis, Ind., and microanalytical results were within 0.4% of the theoretical values. IR (Perkin-Elmer 457 spectrophotometer) and NMR (Varian A-60A spectrometer) spectra were obtained for all of the compounds and were consistent with the given structures. Typical examples of the various methods are given below. As the methods used were derived from well-known procedures used in organic chemistry, only brief accounts are given. Further details of the compounds are noted in the Table I. All temperatures are in degrees centigrade.

Method 1. (4-Isopropylphenyl)piperidine Hydrochloride (1). Hydrogenation of 4-piperidino-α-methylstyrene hydrochloride [Anal. ($C_{14}H_{20}ClN$) C, H, N; prepared by dehydration of compound **4** in EtOH with gaseous HCl at 0 °C (quinol present)] in EtOH over 10% Pd/C at STP or at 60 psi yielded compound **1**.

Method 2. 2-(4-Piperidinophenyl)ethanol (2). Ethyl (4-piperidinophenyl)acetate (see method 6) was reduced to give the alcohol **2** using sodium dihydrobis(2-methoxyethoxy)aluminate in C_6H_6. This method was also used to prepare **3** from ethyl methyl(4-piperidinophenyl)acetate (see method 6).

Method 3. α,α-Dimethyl-4-piperidinobenzyl Alcohol (4). This compound was prepared from 4′-piperidinoacetophenone by the action of MeMgI at 0 °C.

Method 4. *N*-(4-Piperidinophenyl)ethylpiperidine (9). Compound **5** in DMF with $Br(CH_2)_5Br$, K_2CO_3, CuI, and KI was refluxed (4.5 h). Treatment of the cooled mixture with H_2O yielded **9**.

Method 5. (4-Piperidinophenyl)acetic Acid (26). The thiomorpholide from 4′-piperidinoacetophenone, sulfur, and morpholine was hydrolyzed with refluxing 10% NaOH in EtOH (24 h). Acidification to pH 5 yielded the acid **26**. The method was used to prepare **27** from the thiomorpholide derived from 3′-chloro-4′-piperidinoacetophenone [bp 158–160 °C (0.7 mm); n^{25}_D 1.5920] prepared by the Sandmeyer reaction on 3′-amino-4′-piperidinoacetophenone [Anal. ($C_{13}H_{18}N_2O$) C, H, N], which was obtained by reduction of 3′-nitro-4′-piperidinoacetophenone.

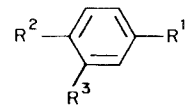
Method 6. Methyl(4-piperidinophenyl)acetic Acid (28). (4-Piperidinophenyl)acetic acid (**26**) was esterified to give ethyl (4-piperidinophenyl)acetate: yield 58%; bp 127–130 °C (0.05 mm); n^{22}_D 1.5403. Anal. ($C_{15}H_{21}NO_2$) C, H, N. Ethyl (4-piperidinophenyl)acetate was converted to ethyl methyl(4-piperidinophenyl)acetate by the method of ref 6: yield 64%; bp 147–149 °C (1.6 mm). Anal. ($C_{16}H_{23}NO_2$) C, H, N. This method was used to prepare the ethyl ester of **29** [yield 70%; bp 132–134 °C (0.1 mm); n^{28}_D 1.5330. Anal. ($C_{16}H_{22}ClNO$) C, H, N] from the ethyl ester of compound **27**: bp 139–144 °C (0.2 mm). Anal. ($C_{15}H_{20}ClNO_2$) C, H, Cl, N. These esters were hydrolyzed to their corresponding acids **28** and **29** by KOH in refluxing EtOH.

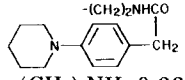
Method 7. 2-(4-Piperidinophenyl)ethylamine Dihydrochloride (5) and Hydrogen Carbonate (6). Hydrogenation of 4-piperidinobenzyl cyanide [mp 70–72 °C. Anal. ($C_{13}H_{16}N_2$) H, N; C: calcd, 78.0; found, 77.12], prepared from 4-aminobenzyl cyanide by method 4, in 12% NH_3 in EtOH over Raney Ni W-5 at 60 psi for 18 h gave 2-(4-piperidinophenyl)ethylamine: bp 117–120 °C (0.15 mm). The amine was converted to **5** using HCl in Et_2O–EtOH. Compound **6** was prepared by adding an aqueous solution of **5** to aqueous $NaHCO_3$. Method 7 was also used for the preparation of compound **13** from 4-(4-piperidinophenyl)-butyronitrile [bp 150 °C (0.1 mm)], prepared from 4-(4-aminophenyl)butyronitrile by method 4, and of compound **16** from 3-piperidinobenzyl cyanide [bp 135–136 °C (0.05 mm). Anal. ($C_{13}H_{16}N_2$) C, H, N], prepared from 3-aminobenzyl cyanide.

Method 8. 2-(3-Chloro-4-piperidinophenyl)ethylamine Hydrochloride (7). 3-Nitro-4-piperidinobenzaldehyde[7] was reduced to give 3-amino-4-piperidinobenzaldehyde as an impure solid, mp 230 °C dec. The amino compound was converted by the Sandmeyer reaction in 34% yield to 3-chloro-4-piperidinobenzaldehyde: bp 146 °C (0.27 mm); n^{24}_D 1.6069. Anal. ($C_{12}H_{14}ClNO$) C, H, Cl, N. Reaction of this aldehyde with $MeNO_2$ in boiling benzene in the presence of n-$BuNH_2$ and AcOH with elimination of H_2O gave 3-chloro-4-piperidino-β-nitrostyrene as an oil; this was reduced using $LiAlH_4$ in Et_2O to give 2-(3-chloro-4-piperidinophenyl)ethylamine: bp 163–164 °C (3 mm); n^{20}_D 1.5620. This was converted to **7** using HCl in Et_2O. This method was also used to prepare **17** from 4-piperidino-β-methyl-β-nitrostyrene, mp 52–54 °C. Anal. ($C_{14}H_{18}N_2O_2$) H, N; C: calcd, 68.26; found, 68.9.

Method 9. *N*-(4-Piperidinophenethyl)-2,2,2-trifluoroacetamide (10), *N*-Methyl-*N*-(4-piperidinophenethyl)-2,2,2-trifluoroacetamide Hydrochloride (11), and *N*-Methyl-2-(4-piperidinophenyl)ethylamine Succinate (8). 2-(4-Piperidinophenyl)ethylamine (from **5**) was converted to **10** according to the

Table I[a]



no.	R¹	R²	R³	mp or bp (mm), °C	method	recrystn solvent	yield, %	formula	anal.	antiinflammatory act.[b]	LD_{50} in mice, po
1	*i*-Pr·HCl	piperidino	H	200–207	1	EtOAc–EtOH	75	$C_{14}H_{22}ClN$	C, H,[c] Cl, N	*30/50	1200
2	$-(CH_2)_2OH$	piperidino	H	59–66 134–138 (0.4)	2		37.6	$C_{13}H_{19}NO$	C, H, N	*51/100	1200
3	$-CHMeCH_2OH$	piperidino	H	134–135 (0.4)	2		67	$C_{14}H_{21}NO$	C, H, N	*71/100	1600
4	$-CMe_2OH$	piperidino	H	72–74	3	P(60)[d]	80	$C_{14}H_{21}NO$	C, H, N	N	600
5	$-(CH_2)_2NH_2·2HCl$	piperidino	H	233–235	7	EtOH	56	$C_{13}H_{22}Cl_2N_2$	C, H, Cl, N	*55/100	1200
6	$-(CH_2)_2NH_2·H_2CO_3$	piperidino	H	91–95	7		49	$C_{14}H_{22}N_2O_3$	C, H, N	*54/100	800
7	$-(CH_2)_2NH_2·HCl$	piperidino	Cl	198–200 (dec)	8	EtOH	47	$C_{13}H_{21}Cl_3N_4$	C, H, Cl, N	*58/1 × 100	800
8	$-(CH_2)_2NHMe·(CH_2CO_2H)_2$	piperidino	H	132–133	9	EtOH	35	$C_{18}H_{28}N_2O_4$	C, H, N	*33/50	600
9	$-(CH_2)_2$-c-NC_5H_{10}	piperidino	H	42–44 163–166 (0.6)	4		23	$C_{18}H_{28}N_2$	C, H, N	*46/50	400
10	$-(CH_2)_2NHCOCF_3$	piperidino	H	110–112	9		57.5	$C_{15}H_{19}F_3N_2O$	C, H, N	*60/100	1600
11	$-(CH_2)_2NMe$-$COCF_3HCl$	piperidino	H	178–180	9	Et_2O-HCl	70	$C_{16}H_{22}ClF_3N_2O$	C, H, N	38/100	1600
12		piperidino	H	156–158	11	EtOH	70	$C_{26}H_{35}N_3O$	C, H, N	*22/100	1600
13	$-(CH_2)_4NH_2·0.33H_2CO_3$	piperidino	H	93–94	7		86	$C_{15}H_{24}N_2·0.33H_2CO_3$	C, H, N	*54/100	600
14	$-(CH_2)_6NH_2·(CH_2CO_2H)_2$	piperidino	H	143–145	12	EtOH	53	$C_{21}H_{34}N_2O_4$	C, H, N	*57/100	1200
15	$-(CH_2)_4NH_2·(CH_2CO_2H)_2$	piperidino	Cl	147–149.5	12	EtOH	33	$C_{19}H_{29}ClN_2O_4$	C, H, Cl, N	*71/100	1600
16	$-(CH_2)_3NH_2·2HCl$	H	piperidino	218–220	7	EtOAc-*i*-PrOH	78	$C_{13}H_{22}ClN_2$	C, H, Cl, N	*39/50	600
17	$-CH_2CHMeNH_2·(CH_2CO_2H)_2$	piperidino	H	170–171	8	EtOH	17	$C_{18}H_{28}N_2O_4$	C, H, N	*33/50	600
18	$-CHMeCH_2NH_2·2HCl$	piperidino	H	226–229	13	EtOH–AcOEt	58	$C_{14}H_{24}Cl_2N_2$	C, H, Cl, N	*57/50	600
19	$-CHMeCD_2NH_2·2HCl$	piperidino	H	231–235	14	EtOH–Et_2O	61	$C_{14}H_{20}D_2Cl_2N_2·0.25H_2O$	C, H, (D), N	*47/50	600
20	$-CHMeCH_2NH_2·2HCl$	piperidino	Cl	216–225	15	EtOH–HCl–Et_2O	44	$C_{14}H_{23}Cl_3N_2$	C, H, N	*39/50	600
21	$-CHMeCH_2NMe_2·2HCl$	piperidino	H	240–243	10	*i*-PrOH–Et_2O–AcOEt	32	$C_{16}H_{28}Cl_2N_2$	C, H, N	*70/100	600
22	$-CHMeCH_2NHCOCF_3$	piperidino	H	84–87	9	aq MeOH	72	$C_{16}H_{21}F_3N_2O$	C, H, N	*32/50	600
23	$-CH(CO_2H)CH_2NH_2$	piperidino	H	265 (dec)	16	AcOH–EtOH	17	$C_{14}H_{20}N_2O_2$	C, H, N	*40/100	>1600
24	$-CHMeCH_2NH_2·(CH_2CO_2H)_2$	H	piperidino	141–142	12	EtOH	76	$C_{18}H_{28}N_2O_4$	C, H, N	N	600
25	$-CMe_2CH_2NH_2·(CH_2CO_2H)_2$	piperidino	H	155–161	17	EtOH–MeOH	64	$C_{19}H_{30}N_2O_4$	C, H, N	*34/50	400
26	$-CH_2CO_2H$	piperidino	H	118–119[e]	5	Et_2O-P(40)	70	$C_{13}H_{17}NO_2$	C, H, N	*51/100	800
27	$-CH_2CO_2H$	piperidino	Cl	120–122[f]	5	aq EtOH	59	$C_{13}H_{16}ClNO_2$	C, H, Cl, N	*43/100	800
28	$-CHMeCO_2H$	piperidino	H	86–88[g]	6	P(60)-EtOAc	55	$C_{14}H_{19}NO_2$	C, H, N	*68/50	800
29	$-CHMeCO_2H$	piperidino	Cl	89–92[h]	6	P(60)	44	$C_{14}H_{18}ClNO_2$	C, H, Cl, N	*53/100	1200

[a] More than one reaction type may be described under a method number. [b] Results marked with an asterisk are percentage reductions of swelling which are significant ($p < 0.02$) at the given dose level; e.g., 43/50 means 43% reduction at 2 × 50 mg/kg (see text). Measurements (on treated animals) shown as N (for negative) and without an asterisk were not significantly different from measurements on controls; drug doses for compound 24 were 2 × 100 mg/kg and for 4 were 2 × 50 mg/kg. Control compounds used were phenylbutazone, which gave 50–70% reduction at 2 × 100 mg/kg ($p < 0.001$), and hydrocortisone, which gave 35–70% reduction at 2 × 50 mg/kg ($p < 0.001$). [c] H: calcd, 8.83; found, 9.28. [d] P(40) and P(60) refer to light petroleum of bp 40–60 and 60–80 °C. [e] Reference 3 gives mp 189–193 °C for the hydrochloride. [f] Reference 4 gives mp 105–106 °C. [g] Reference 3 gives mp 211–214 °C for the hydrochloride. [h] Reference 4 claims the preparation of this compound but fails to quote a melting point.

method of ref 8. Similarly, the free base of 18 was converted to 22. Compound 10 was then methylated according to the method of ref 8, but the procedure failed to remove the trifluoroacetyl group; a sample of the product was converted to the hydrochloride 11. The rest of the product was hydrolyzed in refluxing KOH–EtOH (3.4 h), and the resulting amine was converted to the succinate 8.

Method 10. β,N,N-Trimethyl-2-(4-piperidinophenyl)ethylamine Dihydrochloride (21). β-Methyl-2-(4-piperidinophenyl)ethylamine (from 18) was refluxed (8 h) in 90% HCO_2H containing 40% CH_2O solution. The resulting amine was converted to 21.

Method 11. N-(4-Piperidinophenethyl)(4-piperidinophenyl)acetamide (12). This was prepared from the ethyl ester of 26 (see method 6) and 4-piperidinophenethylamine (from 5) by the method of Openshaw and Whittaker.[9]

Method 12. 6-(4-Piperidinophenyl)hexylamine Succinate (14), 4-(3-Chloro-4-piperidinophenyl)butylamine (15), and 2-Methyl-2-(4-piperidinophenyl)ethylamine (24). (i) Adipic anhydride (prepared by refluxing 146.14 g (1 mol) of adipic acid and 400 mL of Ac_2O together for 6 h) was dissolved in refluxing PhF (384.4 g, 4 mol), cooled to 0 °C, and treated cautiously with $AlCl_3$ (308 g, 2.3 mol) with stirring. After adding further PhF (170 mL) and refluxing for 1 h, the mixture was cooled, added to ice (1 L) and concentrated HCl (500 mL), and extracted with $CHCl_3$. The $CHCl_3$ was evaporated to dryness and the residue treated with NaOH solution. The residue from the latter was filtered off and was identified as 1,4-bis(*p*-fluorobenzoyl)butane, [mp 165–167 °C. Anal. ($C_{18}H_{16}F_2O_2$) C, H, F], while the filtrate was acidified to give 5-(4-fluorobenzoyl)hexanoic acid, mp 96–98 °C. Anal. ($C_{12}H_{13}FO_3$) C, H, F.

(ii) The above acid in Me_2SO with K_2CO_3 and piperidine was stirred at 110–135 °C (4 h) and yielded 5-(4-piperidinobenzoyl)pentanoic acid: yield 66%; mp 92–93 °C. Anal. ($C_{17}H_{23}NO_3$) C, H, N. (a) Ethyl 5-(4-piperidinobenzoyl)pentanoate (from the above acid, 91% yield) had mp 72–73 °C. Anal. ($C_{19}H_{27}NO_3$) C, H, N. (b) The above ester was hydrogenated in AcOH (10% Pd/C, 3 drops of 70% $HClO_4$) to give ethyl 6-(4-piperidinophenyl)hexanoate (84%) as an oil (NMR as expected). (c) This ester was converted, by heating for 19 h in glycerol saturated with NH_3 in a sealed vessel, in 78% yield to 6-(4-piperidinophenyl)hexanamide, mp 124–127 °C. Anal. ($C_{17}H_{26}N_2O$) N. (d) The above amide was reduced using $LiAlH_4$ in C_6H_6 to yield an oil, which was converted to 14.

Method 12d was used to prepare 15 from 4-(3-chloro-4-piperidinophenyl)butyramide, mp 110–113 °C. Anal. ($C_{15}H_{21}ClN_2O$) C, H, Cl, N. The amide was prepared from the ethyl ester of 4-(3-chloro-4-piperidinophenyl)butyric acid. The acid [mp 81.5–82.5 °C. Anal. ($C_{15}H_{20}ClNO_2$) C, H, Cl, N] was prepared by Wolff–Kishner reduction of ethyl 3-(3-chloro-4-piperidinobenzoyl)propionate: bp 190–210 °C (0.25 mm); n^{25}_D 1.5628. Anal. ($C_{17}H_{22}ClNO_3$) C, H, Cl, N. This ester was prepared from 3-(3-chloro-4-piperidinobenzoyl)propionic acid [mp 140–145 °C; from PhMe. Anal. ($C_{15}H_{18}ClNO_3$) C, H, N], which was prepared using method 12 (ii) from 3-(3-chloro-4-fluorobenzoyl)propionic acid [mp 108–113 °C. Anal. ($C_{10}H_8ClFO_3$) C, H]. This acid was made from o-ClC_6H_4F and succinic anhydride using method 12 (i). Method 12d was also used to prepare compound 24 from methyl(3-piperidinophenyl)acetamide, mp 85–88 °C. Anal. ($C_{14}H_{20}N_2O$) C, H, N. The latter was prepared from 3-piperidinobenzyl cyanide via the intermediates ethyl (3-piperidinophenyl)acetate [bp 124–126 °C (0.2 mm); n^{22}_D 1.5342. Anal. ($C_{15}H_{21}NO_2$) C, H, N] and ethyl methyl(3-piperidinophenyl)acetate [bp 113–115 °C (0.02 mm); $n^{24.5}_D$ 1.5275. Anal. ($C_{16}H_{23}NO_2$) C, H, N].

Method 13. 2-Methyl-2-(4-piperidinophenyl)ethylamine Dihydrochloride (18). (a) Using method 12c, ethyl methyl(4-piperidinophenyl)acetate was converted to methyl(4-piperidinophenyl)acetamide, mp 143–146 °C. Anal. ($C_{14}H_{20}N_2O$) C, H, N. The amide was reduced with $LiAlH_4$ as in method 12d to give the ethylamine [bp 112–114 °C (0.25 mm); n^{21}_D 1.5585], which was converted to the dihydrochloride 18 by means of ethereal HCl.

(b) β-Methylphenethylamine was acetylated with Ac_2O to give *N*-acetyl-β-methylphenethylamine as an oil: yield 92%; IR 1650, 3260 cm^{-1}. This amide was nitrated with concentrated HNO_3 to give *N*-acetyl-2-methyl-2-(4-nitrophenyl)ethylamine, mp 84 °C. Anal. ($C_{11}H_{13}N_2O_3$) N. Reduction of the nitro compound with Fe filings in H_2O containing NH_4Cl at 80–90 °C (2 h) gave the corresponding 4-amino compound: yield 82%. This was converted to *N*-acetyl-2-methyl-2-(4-piperidinophenyl)ethylamine using method 4. This compound was hydrolyzed by refluxing concentrated HCl (6 h) to give 2-methyl-2-(4-piperidinophenyl)ethylamine, bp 136 °C (0.2 mm), and converted to the dihydrochloride, identical with the material obtained in "a" above.

The following derivatives of the above amine were obtained by conventional methods: (i) Hydrogen carbonate, mp 79–82 °C dec. Anal. ($C_{14}H_{22}N_2 \cdot 0.33H_2CO_3 \cdot 2.5H_2O$) C, H, N. (ii) (+)-Tartrate hemiethanolate, mp 156–158 °C. Anal. ($C_{18}H_{28}N_2O_6 \cdot 0.5C_2H_6O$) C, H. N. (iii) Naphthalene-β-sulfonic acid salt, mp 227–229 °C. Anal. ($C_{24}H_{30}N_2O_3S$) C, H, N, S. (iv) Fractional crystallization of the salt of the amine with 1-mandelic acid gave a levorotatory salt which yielded the optically active free base. This was converted to (−)-2-methyl-2-(4-piperidinophenyl)ethylamine hydrochloride, $[\alpha]^{22}_D$ −14.98° (*c* 0.25, EtOH). Anal. ($C_{14}H_{24}ClN_2$) C, H, N. The mother liquors from the mandelic acid salt yielded a free base, which was further reacted with *d*-mandelic acid and, as before, ultimately yielded (+)-2-methyl-2-(4-piperidinophenyl)ethylamine hydrochloride, $[\alpha]^{22}_D$ +14.38° (*c* 0.23, EtOH). Anal. ($C_{14}H_{24}ClN_2$) C, H, N.

Method 14. Dideuterio-2-methyl-2-(4-piperidinophenyl)ethylamine Dihydrochloride (19). Methyl(4-aminophenyl)acetonitrile was converted using method 4 to methyl(4-piperidinophenyl)acetonitrile: yield 74%; bp 142 °C (0.3 mm); NMR as expected. Using lithium aluminium deuteride in THF and the conditions of method 12, but using D_2O instead of H_2O for workup, α,α-dideuterio-2-methyl-2-(4-piperidinophenyl)ethylamine [yield 74%; bp 133–134 °C (0.35 mm); n^{21}_D 1.5581] was obtained and converted to its hydrochloride (19) by means of Et_2O–HCl.

Method 15. 2-Methyl-2-(3-chloro-4-piperidinophenyl)ethylamine Dihydrochloride (20). Compound 29 ethyl ester (cf. method 6) was converted in 88% yield using method 12c to its amide [mp 146–148 °C. Anal. ($C_{14}H_{19}ClN_2O$) C, H, N] and this was reduced to the amine by method 12d and converted to 20 using HCl–Et_2O.

Method 16. (Aminomethyl)(4-piperidinophenyl)acetic Acid (23). 4-Piperidinobenzyl cyanide (from 4-aminobenzyl cyanide using method 4; 20 g, 0.1 mol) was added to a mixture of NaOEt [from Na (2.4 g, 0.1 mol) and EtOH (60 mL)] and $CO(OEt)_2$ (58.4 g, 0.5 mol) in PhMe (16 mL).[10] The mixture was heated until the temperature of the distillate from it reached 112 °C (50 min). Excess $CO(OEt)_2$ was removed under vacuo, $PhCH_2OH$[11] (10.8 g, 0.1 mol) in PhMe (200 mL) was added, and the mixture was distilled again until the distillate temperature reached 110 °C. The cooled mixture of Na salt and solvent was treated with H_2O (60 mL), AcOH (8 mL), and $NaHCO_3$ (32 g) in H_2O (500 mL) and extracted with Et_2O. The extract was washed with aqueous $FeSO_4$ (100 g) containing $NaHCO_3$ until HCN could no longer be detected, washed with saturated NaCl, dried (Na_2SO_4), and evaporated to leave benzyl (cyanomethyl)-(4-piperidinophenyl)acetate as a crude oil (28.19 g). The above nitrile (25.34 g) in AcOH (100 mL) containing concentrated HCl (6.25 mL) was hydrogenated over PtO_2 (1 g) at 59 psi to give an oil in which the CN group had been reduced to CH_2NH_2 and the benzyl group had been partially removed. This oil was hydrolyzed with 2 N NaOH at room temperature to give compound 23.

Method 17. 2,2-Dimethyl-2-(4-piperidinophenyl)ethylamine, Succinic Acid Salt (25). Dimethyl(4-nitrophenyl)acetonitrile was reduced with $SnCl_2 \cdot 2H_2O$ in EtOH and concentrated HCl to give dimethyl(4-aminophenyl)acetonitrile: yield 99%; mp 40–55 °C. Anal. ($C_{10}H_{12}N_2$) C, H, N. This nitrile was converted to dimethyl(4-piperidinophenyl)acetonitrile [bp 149–154 °C (0.35 mm). Anal. ($C_{15}H_{20}N_2$) N] using method 4. This nitrile was hydrogenated using method 7 to give 2,2-dimethyl-2-(4-piperidinophenyl)ethylamine [yield 92%; bp 126–132 °C (0.15 mm), n^{20}_D 1.5562] and was converted to the succinic acid salt 25.

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References and Notes

(1) W. S. Marshall, British Patent (to Eli Lilly & Co.) 1 377 480 (1974).
(2) W. S. Marshall, U.S. Patent (to Eli Lilly & Co.) 3 600 437 (1971).
(3) Netherlands Patent (to Ciba) 6 903 273 (1969).
(4) Netherlands Patent (to Merck, A.G.) 6 810 359 (1969). We had prepared some of the compounds claimed, including **26–29**, before these patents were issued.
(5) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962); D. W. Dunwell, D. Evans, T. A. Hicks, C. H. Cashin, and A. Kitchen, *J. Med. Chem.*, 18, 53 (1975).
(6) W. G. Kenyon, R. B. Meyer, and C. R. Hauser, *J. Org. Chem.*, 28, 3108 (1963).
(7) M. D. Nair and R. Adams, *J. Am. Chem. Soc.*, 83, 3518 (1961).
(8) R. A. W. Johnstone, D. W. Payling, and C. Thomas, *J. Chem. Soc. C*, 2223 (1969).
(9) H. T. Openshaw and N. Whittaker, *J. Chem. Soc. C*, 89 (1969).
(10) E. C. Horning, A. F. Finelli, W. S. Johnson, and H. Wynberg, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, 1963, p 461.
(11) R. E. Bowman and W. D. Fordham, *J. Chem. Soc.*, 2578 (1951).

Potential Antiinflammatory Compounds. 3.[1] Compounds Derived from Acenaphthene and Indan

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Compounds having acenaphthene and indan as their parent nuclei were synthesized for antiinflammatory testing. Compounds which showed activity were 1-phenyl-5-acenaphthenylacetic acid and its α-methyl derivative (carrageenan rat paw edema) and the same α-methylacenaphthenylacetic acid and 2-(4-chlorobenzylidene)-3-oxo-5-indanacetic acid and its α-methyl derivative (rat adjuvant arthritis). None of the compounds was more active than the control compounds phenylbutazone and indomethacin.

In recent years, numerous attempts have been made to obtain compounds which could show superior antiinflammatory activities to those of the first compounds related to acetic and propionic acids to reach the clinic, indomethacin and ibufenac.[2] We chose to investigate two systems (exemplified by compounds **12**, Scheme I, and compound **31**, Scheme II) based on acenaphthene and indan. A factor in the choice of these nuclei was the activity[3] of the sulfonic acid derivatives of acenaphthene and indan as inhibitors of denaturation of protein by heat.[4]

In the indan series, we also took the opportunity of the availability of 3-oxo-5-indanacetic acid, **17**, and later α-methyl-3-oxo-5-indanacetic acid (**37**) to prepare three condensation products with aldehydes (see Scheme II, **18**, **19**, and **38**). 1-Methyl-5-phenylindan (**23**) was prepared, since it is a neutral compound which could possibly be metabolized in vivo to 5-phenylindan-1-carboxylic acid, an analogue of the active 5-cyclohexylindan-1-carboxylic acid.[6]

Chemistry. Acenaphthene Series. The route employed to the key compounds (**12**, R = H and Me) is outlined in Scheme I. The reaction sequence was partially derived from that used by Anderson and Wade[7] in their synthesis of a tetrahydro-5-acenaphtheneacetic acid.

The intermediates **2**, **3**, **5–7**, **10**, and **11** were not obtained pure but were characterized, as appropriate, by means of IR and/or NMR spectra. The intermediate **2** was a mixture of double-bond isomers (indicated in the diagram), but the tendency for exocyclic bond formation to occur in the six-membered ring analogues **10** was much less: 10% exocyclic form occurred at most. Further details of the successful routes are given in Table I and the Experimental Section.

Indan Series. Initially, we attempted the preparation of 1-phenylindan-5- and -6-acetic acids, but the cyclization of the dicarboxylic acid **15** prepared according to the method of Bruice and Bradbury[8] gave the isomer **16** rather than the required 1-phenyl-3-oxo-5-indanacetic acid (see Scheme II). After other unsuccessful routes had been abandoned, we turned to the synthesis of 1-cyclohexyl-5-indanacetic acid (**30**). The route is outlined in Scheme II. The intermediates **26–29** were not obtained pure but were characterized by IR and/or NMR spectra. Compound **26** was a mixture of double-bond isomers, but otherwise the synthesis was straightforward. The route used for the preparation of **17** and **37**, the intermediates for the condensation products **18**, **19**, and **38**, is also outlined in Scheme II. 4-Biphenylyl propenyl ketone **24** was cyclized to 3-methyl-5-phenyl-1-indanone (**25**). The indanone **25** was isomeric with 3-methyl-6-phenyl-1-indanone (**22**), which was hydrogenolyzed to give 1-methyl-5-phenylindan (**23**). Further details are given in Tables II and III and the Experimental Section.

Antiinflammatory Activity. The results of antiinflammatory testing against carrageenan-induced foot edema of Winter et al.[10] in rats, modified as indicated in ref 11, are reported in Tables I and III. The results of testing on rat adjuvant arthritis[12] for compounds **12** (R^1 = H and Me), **16**, **19**, and **38** are also given in footnotes to Tables I and III. Of the three types of acidic compounds examined, i.e., the acenaphthenes **12**, the indans **30** and **31**, and the benzylidene indanones **18**, **19**, and **38**, only the acenaphthenes were significantly active in the carrageenan-induced foot edema, while one acenaphthene (**12**, R^1 = Me) and two benzylidene indanones (**19** and **38**) showed activity

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