Research Laboratories, Indianapolis, for helpful correspondence and data in advance of publication on the relevant patents.

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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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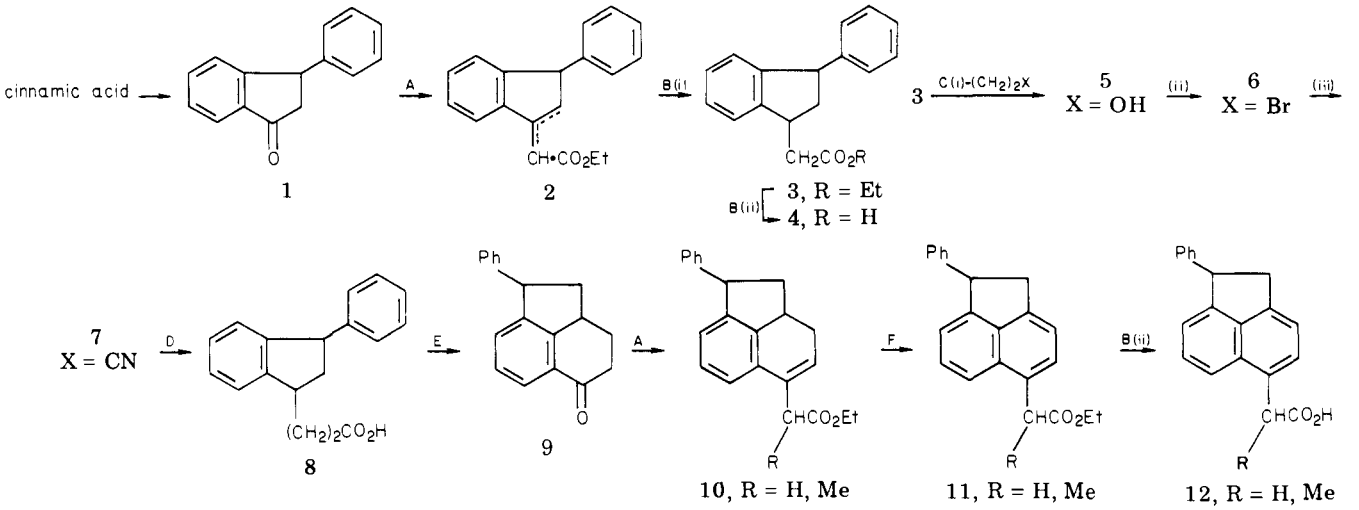
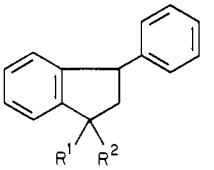
Scheme I. Preparation of Compounds in the Acenaphthene Series[a]

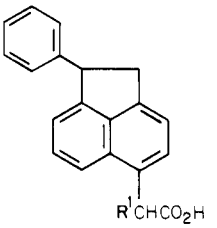


[a] Reagents for method A: Zn, $BrCH(R)CO_2Et$ (R = H, Me); B (i) (for 3), H_2, Pd/C, EtOH, 1 h; B (ii), 2 N NaOH reflux 3.5 h, H^+; C (i), $LiAlH_4$ on 3; C (ii), 49% HBr on 5; C (iii), NaCN on 6; D, concentrated HCl; E, PCl_5 in C_6H_6; F, Pd/C, 200 °C; F (i), 2 N NaOH, reflux 3.5 h, H^+.

Table I. Intermediates 1, 4, and 8 of the Acenaphthene Series and Acenaphthenes 12



1, 4, 8



12

no.	R^1	R^2	mp, °C	method	yield, %	purifn proced[a]	formula	anal.	antiinflam[b] act. vs. carrageenan: dose, mg/kg po × 2	antiinflam[b] act. vs. carrageenan: % redn	ca. LD_{50} in mice, mg/kg po
1	$R^1 + R^2 = O$		71–72[j]	*j*	61	I	$C_{15}H_{12}O$	C, H	100	*48[c,h]	1600
4	H	CH_2CO_2H	126–129	A–B'	84	II	$C_{17}H_{16}O_2$	C, H	100	0[d]	1600
8	H	$(CH_2)_2CO_2H$	124–125	C–D	75	II	$C_{18}H_{18}O_2$	C, H	25	0[e]	300
12	H		200	B'	45	III	$C_{20}H_{16}O_2$	C, H	100	*53[f,h]	400
12	Me		199–200	B'	18	IV	$C_{21}H_{18}O_2$	C, H	100	*44[g,h]	1600

[a] I, recrystallization from EtOAc–light petroleum (bp 40–60°); II, recrystallization from aqueous MeOH; III, trituration with Et_2O; IV, recrystallization from EtOH. [b] An asterisk indicates that the result is significant on Student's *t* test at $p < 0.01$. [c] Control compound phenylbutazone gave 70% reduction of edema at 2 × 50 mg/kg ($p < 0.001$). [d] Hydrocortisone control: 73% reduction at 2 × 50 mg/kg ($p < 0.001$). [e] Phenylbutazone control: 40% reduction at 2 × 50 mg/kg ($p < 0.02$). [f] Phenylbutazone control: 69% reduction at 2 × 50 mg/kg ($p < 0.001$). [g] Phenylbutazone control: 51% reduction at 2 × 50 mg/kg ($p < 0.001$) (all doses po). [h] In the rat adjuvant arthritis test[12] compound 1 showed 36% reduction of the swelling in the noninjected foot using 16 daily po doses of 100 mg/kg; control compound phenylbutazone, 90% reduction at 16 × 33 mg/kg; compound 12 (R^1 = H), 0% reduction at 16 × 100 mg/kg; control compound phenylbutazone, 50% reduction at 16 × 50 mg/kg; compound 12 (R^1 = Me), 50% reduction at 16 × 50 mg/kg; control compound phenylbutazone, 90% reduction at 16 × 50 mg/kg; *p* values for the results of experiments using the adjuvant arthritis test were not calculated since only three rats could be used per drug; however, daily measurements of parameters were made and comparisons of the effects of drugs in dosed animals relative to undosed control rats were evaluated by a graphical method. [j] Reference 9 gives mp 78 °C.

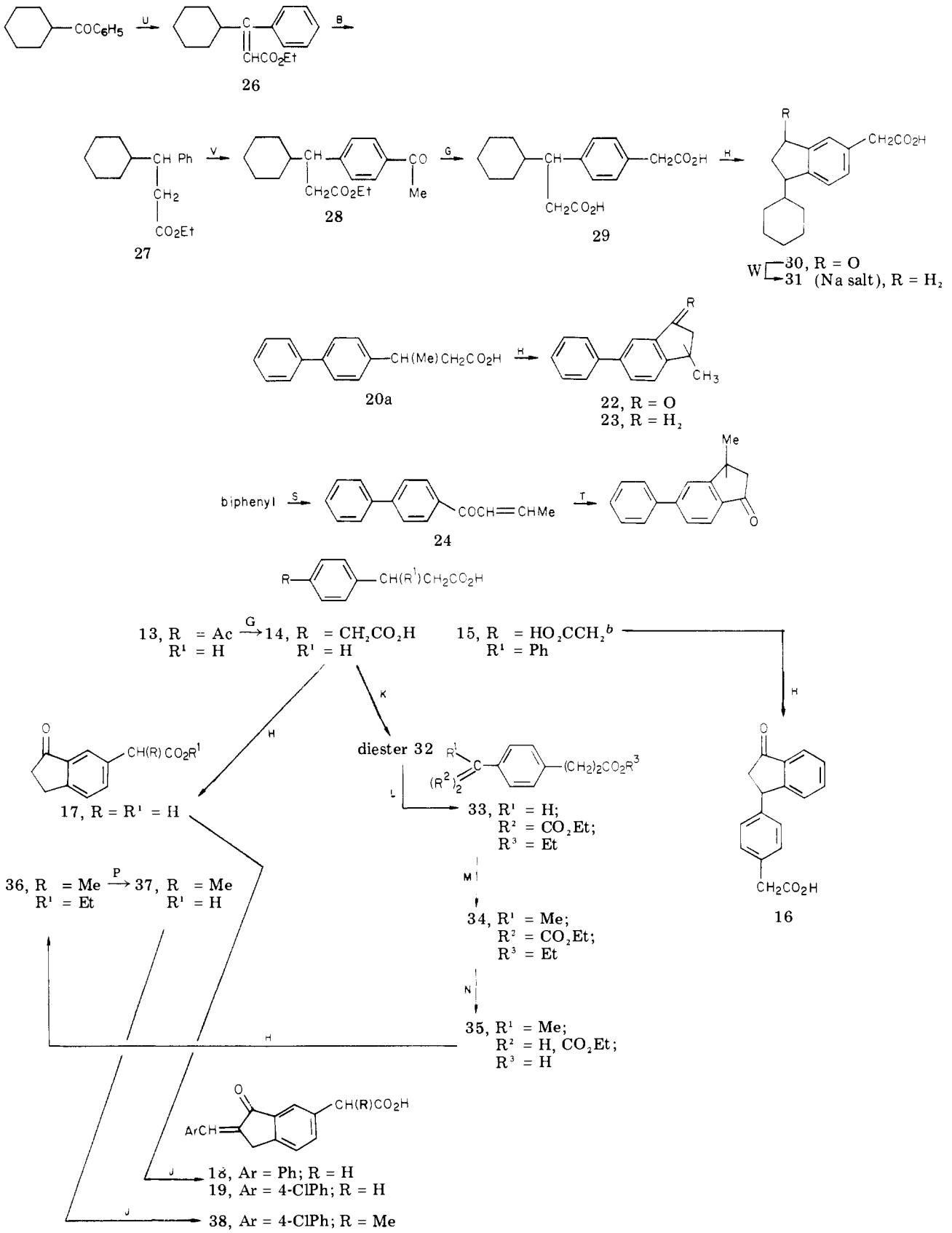
in rat adjuvant arthritis when dosed at 50 and 100 mg/kg. The magnitude of the activities of the compounds relative to those obtained using the control compounds, phenylbutazone and indomethacin, did not encourage further development of the compounds, including resolution of the diastereoisomers, or separation of the *E* and *Z* forms of the benzylidene compounds. The activity of two neutral compounds (**1** and **23**) indicates that activity in these tests is not a prerogative of acidic compounds; this has been shown before in the case of compounds such as indoxole.[2] The activity of **1** and **23** may, of course, be due to the formation of acidic metabolites.

Experimental Section

Melting points are uncorrected. Microanalyses were carried out by Mr. G. Maciak and associates, Eli Lilly & Co., Indianapolis, Ind., and microanalytical results were within ±0.4% of the theoretical values. IR (Perkin-Elmer 457 spectrophotometer) and NMR (Varian A 60-A spectrometer) spectra were obtained for all of the compounds and were consistent with the given structures. Examples of the methods are given below. Further details of the compounds are given in Tables I–III.

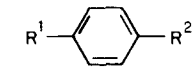
Method A. 3-Phenyl-1-indanacetic Acid (4). 3-Phenyl-1-indanone (83 g, 0.4 mol) was dried by refluxing in C_6H_6 (120 mL) with removal of the azeotroped H_2O. To this solution was added Et_2O (120 mL) and Zn wool (26.25 g, 0.4 mol). The reaction mixture was heated to near reflux and a crystal of I_2 added. Ethyl bromoacetate (110 g, 0.6 mol) was added over 2 h, the temperature being kept near reflux by heat of reaction and some external heating. After the addition of ethyl bromoacetate, the mixture was stirred and refluxed for a further 0.5 h, cooled, and poured into ice and AcOH. The mixture was extracted with Et_2O. The Et_2O was washed with 1% NH_4OH, dried (Na_2SO_4), filtered, and

Scheme II. Preparation of Compounds in the Indan Series[a]



[a] Reagents for method G, S and morpholine at 130–140 °C for 6 h, 50% NaOH, EtOH, reflux 6 h, H^+; method H, polyphosphoric acid at 95–100 °C for 0.5–1 h; method J, ArCHO–4% KOH in EtOH, 0.6–2 h, H^+; method K, EtOH–concentrated HCl, reflux 18 h; method L, NaOEt–Et_2CO_3, 100 °C; method M, NaOEt–MeI, reflux 3 h; method N, KOH–EtOH, room temperature, 96 h, H^+; method P, 10% concentrated HCl in AcOH, room temperature for 5 days; method R, H_2–10% Pd/C in EtOH, trace HCl, 60 psi; method S, MeCH=CHCOCl in CH_2Cl_2, $AlCl_3$, 1.75 h at 25 °C; method T, $AlCl_3$–NaCl at 140–180 °C, 2 min; method U, A, followed by P_2O_5–C_6H_6 reflux of product, 3.5 h; method V, AcCl–$AlCl_3$ in CH_2Cl_2, 50 min; method W, 85% $(NH_2)_2$–85% KOH in $(CH_2)_2(OH)_2$, reflux 1.5 h, 190–200 °C, 4 h, formation of Na salt. [b] Reference 8.

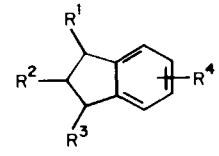
Table II. Intermediates of Indan Series[a]



no.	R¹	R²	mp or bp (mm), °C	method	yield, %	purifn proced[b]	formula	anal.
14	HO_2CCH_2	$-(CH_2)_2CO_2H$	185–187	G	64	I	$C_{11}H_{12}O_4$	C, H
15	HO_2CCH_2	$-CH(Ph)CH_2CO_2H$	159[c]	*c*	30	*c*	$C_{17}H_{16}O_4$	C, H
24	Ph	$-COCH{=}CHMe$	80–82	S	47	III	$C_{16}H_{14}O$	C, H
28	*c*-C_6H_{11}-$CH(CH_2CO_2Et)$	-Ac	178 (0.29)	V	45	IV	$C_{19}H_{26}O_3$	C, H
32	EtO_2CCH_2-	$-(CH_2)_2CO_2Et$	132–134 (0.07)	K	53	IV	$C_{15}H_{20}O_4$	C, H
33	$(EtO_2C)_2CH-$	$-(CH_2)_2CO_2Et$	170–174 (0.15)	L	70	IV	$C_{18}H_{24}O_6$	C, H
34	$(EtO_2C)_2CMe$	$-(CH_2)_2CO_2Et$	150–154 (0.2)	M	70	IV	$C_{19}H_{26}O_6$	C, H
35	$HO_2C(CH_2)_2-$	$-CH(Me)CO_2Et$	175–177 (0.25)	N	45	IV	$C_{14}H_{18}O_4$	OEt

[a] The compounds (14, 15, 24, and 39) of this table were tested on the carrageenan edema test but were inactive. [b] I, recrystallization from 50% aqueous EtOH; II, precipitated with acid, filtered, and washed with 50% EtOH; III, recrystallization from light petroleum (bp 60–80 °C); IV, distillation. [c] Reference 8 gives mp 164–165 °C.

Table III. Indan Series (Including Some Intermediates of Indan Structure)



no.	R¹	R²	R³	R⁴	mp or bp (mm), °C	method	yield, %	purifn proced[a]	formula	anal.	antiinflam act. vs. carrageenan: dose, mg/kg po × 2	antiinflam act. vs. carrageenan: % redn[b]	ca. LD_{50} in mice, mg/kg po
16	O	H_2	H, 4-$C_6H_4CH_2CO_2H$	H	151	H	56	I	$C_{17}H_{14}O_3$	C, H	100	*36[c,m]	1600
17	O	H_2	H_2	6-CH_2CO_2H	133–135	H	80	II	$C_{11}H_{10}O_3$	C, H	100	0[d]	1600
18	O	PhCH	H_2	6-CH_2CO_2H	202–204	J	60	III	$C_{18}H_{14}O_3$	C, H	100	26[e,m]	1600
19	O	4-ClC_6H_4CH	H_2	6-CH_2CO_2H	264–266	J	49	IV	$C_{18}H_{13}ClO_3$	C, H, Cl	100	0[f,m]	1600
22	O	H_2	H, Me	6-Ph	140–142 (0.2)	H	71	V	$C_{16}H_{14}O$	C, H	100	7[g]	1600
23	H_2	H_2	H, Me	6-Ph	43–45	R	34	VI	$C_{16}H_{16}$	C, H	100	*35[h,m]	1600
25	O	H_2	H, Me	5-Ph	74–75.5	T	4	V, VII	$C_{16}H_{14}O$	C, H	NT[j]		NT
30	O	H_2	H, *c*-C_6H_{11}	6-CH_2CO_2H	153–155	H	32	VIII	$C_{17}H_{20}O_3$	C, H	100	8[k]	1200
31	H_2	H_2	H, *c*-C_6H_{11}	6-CH_2CO_2Na	160	W	100	IX	$C_{17}H_{21}O_2Na{\cdot}1.7H_2O$	C, H	100	28[l]	1200
36	O	H_2	H_2	6-$CH(Me)CO_2Et$	137–144 (0.2)	H	46	V	$C_{14}H_{16}O_3$	C, H	NT		NT
37	O	H_2	H_2	6-$CH(Me)CO_2H$	109	P	42	III	$C_{12}H_{12}O_3$	C, H	NT		NT
38	O	4-ClC_6H_4CH	H_2	6-$CH(Me)CO_2H$	206–208	J	38	IV	$C_{19}H_{15}ClO_3$	C, H, Cl	NT[m]		NT

[a] I, trituration with Et_2O; II, recrystallization from C_6H_6; III, recrystallization from 50% aqueous EtOH; IV, recrystallization from 96% EtOH; V, distillation; VI, preparative gas chromatography (D. N. B. Mallen and D. J. Osborne); VII, recrystallization from light petroleum (bp 60–80 °C); VIII, trituration with Me_2CO–light petroleum (bp 40–60 °C) (1:3); IX, evaporation of an aqueous EtOH solution. [b] An asterisk indicates that the result is significant on Student's *t* test at $p < 0.01$. [c] Control compound hydrocortisone gave 52% reduction of edema at 2 × 50 mg/kg po ($p < 0.001$). [d] Phenylbutazone control: 40% reduction at 2 × 50 mg/kg po ($p < 0.02$). [e] Phenylbutazone control: 43% reduction at 2 × 50 mg/kg po ($p < 0.05$). [f] Phenylbutazone control: 65% reduction at 2 × 50 mg/kg ($p < 0.001$). [g] Phenylbutazone control: 51% reduction at 2 × 50 mg/kg ($p < 0.001$). [h] Phenylbutazone control: 32% at 2 × 50 mg/kg ($p < 0.05$). [j] NT = not tested. [k] Phenylbutazone control: 69% reduction at 2 × 50 mg/kg ($p < 0.001$). [l] Phenylbutazone control: 53% reduction at 2 × 50 mg/kg ($p < 0.01$). [m] In the rat adjuvant arthritis test, compound 16 showed 52% reduction in swelling of the noninjected foot at 16 × 100 mg/kg and control compound phenylbutazone, 42% reduction at 16 × 33 mg/kg; compound 18 showed 25% reduction at 16 × 100 mg/kg and control compound indomethacin 57% reduction at 16 × 1 mg/kg; compound 19 showed 43% reduction at 16 × 100 mg/kg, control compound phenylbutazone, 42% reduction at 16 × 33 mg/kg; compound 38 showed 53% reduction at 16 × 100 mg/kg and control compound indomethacin, as before; compound 23 showed 32% reduction at 16 × 50 mg/kg.

evaporated, and the residue was distilled to give the esters **2**: yield 83.6 g; bp 145–155 °C (0.1 mm). Similarly prepared were the esters **10**, R = H [yield 65%; bp 255–265 °C (0.15 mm)] and R = Me [yield 73%; bp 180–190 °C (0.15 mm)], both with the ketone **9** as starting material.

Method B (i). The mixture of esters **2** was hydrogenated over 10% Pd/C (0.6 g) to give ethyl 3-phenylindan-1-acetate (84.3 g; **3**). Similarly, from the ester **26** was prepared the ester **27**: bp 100–102 °C (0.12 mm); $n^{23.5}_D$ 1.5042; NMR δ 1.02 (3 H), 0.6–2.0 (12 H), 2.5–3.0 (2 H), 3.9 (2 H), 7.15 (5 H).

Method B (ii). Ester **3** was hydrolyzed under standard alkaline conditions to give the acetic acid **4** (see Table I). Similarly prepared were the acids **12**, R = H and Me, from the corresponding esters **11**.

Methods C and D. 3-(3-Phenyl-1-indan)propionic Acid (8). The ester **3** (84.3 g, 0.3 mol) in THF (300 mL) was added dropwise with stirring to $LiAlH_4$ (10 g) in THF (200 mL) under N_2, and the mixture was stirred at 80 °C overnight. Processing by standard conditions yielded the alcohol **5** as an oil: yield 47.3 g; IR 3100–3600 cm^{-1} (OH). This alcohol was also obtained by reduction of the ester in THF using $LiBH_4$. The alcohol **5** (43.15 g, 0.18 mol) was refluxed overnight with 48% HBr (280 mL), cooled, and extracted with ether, which with standard processing gave the bromo compound **6** (50.8 g) as an oil. The bromo compound **6** (41.8 g, 0.14 mol) in Me_2CO (160 mL) was added to a solution of NaCN (7 g, 0.143 mol) in H_2O (40 mL), and the solution was stirred and refluxed for 64 h. The solution was evaporated to dryness and the product extracted with a mixture of AcOEt and H_2O. After drying (Na_2SO_4), filtration and evaporation of the mixture, the nitrile **7** (26.8 g) was obtained as a solid: IR 2250 cm^{-1} (CN). The nitrile **7** (24.3 g, 0.1 mol) in hot $EtOCH_2CH_2OH$ (100 mL) was treated with NaOH (24.3 g, 0.6 mol) in H_2O (40 mL), and the solution was refluxed for 6 h. It was poured into concentrated HCl (50 mL) in H_2O (250 mL) and extracted with Et_2O, and the Et_2O was extracted with 2 N NaOH. Acidification gave the acid **8**, purified as in Table I: NMR (CCl_4) δ 1.5–3.3 (7 H, CH_2), 4.12 (1 H, CH), 6.8–7.3 (9 H, Ar), 11.92 (1 H, exchangeable).

Method E. 1-Phenyl-2a,3,4,5-tetrahydro-5-acenaphthenone (9). The acid **8** (32 g, 0.12 mol) was dried by refluxing in C_6H_6 (200 mL) with removal of azeotroped H_2O. The solution was added to a stirred suspension of PCl_5 (29 g, 0.14 mol) in C_6H_6 (50 mL) and stirred for 1.5 h. The solution was added to a cooled stirred suspension of $AlCl_3$ (29 g) in C_6H_6 and stirred at room temperature for 3 h. The mixture was poured into ice and HCl and extracted with Et_2O. The Et_2O was washed ($NaHCO_3$ solution), dried (Na_2SO_4), and evaporated to give the ketone **9** [yield 25.7 g; mp 99 °C] from MeOH. Anal. ($C_{18}H_{16}O$) C, H.

Method F. Ethyl 1-Phenyl-5-acenaphthenylacetate (11, R = H). The ester **10**, R = H (18.3 g, 0.058 mol), was stirred with 10% Pd/C (1.8 g) under N_2 at 200–210 °C for 2 h. The cooled product dissolved in $CHCl_3$ was filtered and evaporated to give the ester as an oil (17.9 g). Similarly prepared was the ester **11**, R = Me, from the ester **10**, R = Me.

Method G. 4-(2-Carboxyethyl)phenylacetic Acid (14) and 4-(1-Cyclohexyl-2-carboxyethyl)phenylacetic Acid (29). The procedure of Schwenk and Papa[13] [for 4-(carboxymethyl)-phenylacetic acid] was followed exactly to obtain compound **14** from **13**.[14] Similarly, compound **29** was obtained from **28** as a brown oil: IR (film) 1708 cm^{-1}.

Method H. 1-Indanone-6-acetic Acid (17). Polyphosphoric acid (1 kg) was stirred and heated to 95–100 °C, and the acid (**14**, 100 g, 0.48 mol) was added over 10 min. The mixture was stirred for 0.5 h and poured into ice and H_2O; the product was continuously extracted with $CHCl_3$ and purified as indicated in Table III. This method was used to cyclize the acid **20a**[15] to the indanone **22**, the acid ester **35** to the indanone ester **36** (for the latter a temperature of 70–75 °C was used for the reaction), and the diacid **15** to the acid **16**.

Method J. 2-Benzylidene-3-oxo-5-indanacetic Acid (18). The acid **17** (4.94 g, 0.026 mol) was added to a stirred solution of 85% KOH (3.43 g, 0.052 mol) in EtOH (73 mL) containing PhCHO (2.76 g, 2.63 mL, 0.026 mol) at 10 °C and stirred 40 min. The K salt of the precipitated product was filtered off, dissolved in H_2O (100 mL), and acidified with concentrated HCl to give the acid **18**, which was purified as in Table III. This method was used for the acids **19** and **38**, but, instead of isolating the K salts, the products were isolated by diluting the reaction solutions with 20 times their volumes of water before acidification.

Method K. Ethyl **4-(2-Carbethoxyethyl)phenylacetate (32).** 4-(2-Carboxyethyl)phenylacetic acid (**14**; 20.82 g, 0.1 mol) was refluxed overnight in EtOH (416 mL) containing concentrated HCl (10.8 mL). The solvent was evaporated and the ester distilled.

Method L.[16] **Diethyl 4-(2-Carbethoxyethyl)phenylmalonate (33).** The diester **32** (340 g, 1.29 mol) was stirred in diethyl carbonate (1975.4 g, 16.7 mol) at 80–100 °C and treated with a solution of sodium (29.58 g, 1.29 mol) in EtOH (687 mL), and the mixture was stirred and distilled until the distillate temperature reached 123 °C. After storage in a refrigerator overnight, the solution was treated with AcOH (142 mL) in H_2O (567 mL) and extracted with Et_2O. The Et_2O was washed with saturated $NaHCO_3$ and saturated NaCl solutions, dried (Na_2SO_4), filtered, and evaporated, and the residue was distilled to give **33**. NMR showed that the product contained ca. 22% of **32**.

Method M. Diethyl Methyl[4-(2-carboxyethyl)phenyl]malonate (34). The tricarboxylic ester (**33**; 300 g, 0.89 mol) in EtOH (200 mL) was added to a warm solution of sodium (20.7 g, 0.9 mol) in EtOH (700 mL). Methyl iodide (322.5 g, 2.34 mol) was added, the solution was stirred and refluxed for 40 min, and further MeI (332.5 g) was added and then added again (196.1 g, 1.4 mol) after 2 h. After a total reflux for 3 h, the solution was evaporated, H_2O was added, and the mixture was extracted with Et_2O. The Et_2O solution was processed as in method L to give **34**: n^{21}_D 1.4920; NMR showed that it contained 75–77% of the required material.

Method N. Ethyl **Methyl[4-(2-carboxyethyl)phenyl]acetate (35).** The tricarboxylic ester **34** (35 g, 0.1 mol) in EtOH (400 mL) was stirred at room temperature with a solution of KOH (13.2 g of 85%, 0.2 mol) in EtOH (100 mL) for 96 h. The mixture was evaporated to dryness. The solid foam was broken up, treated with Et_2O (200 mL), and filtered. The residue was dissolved in H_2O (100 mL) and acidified with 5 N HCl to give an oil which was extracted with Et_2O. The Et_2O was dried (Na_2SO_4), filtered, and evaporated to give an oily solid. The solid was shaken with a mixture of $CHCl_3$–light petroleum (bp 40–60 °C) (100 mL of 50:50) and filtered, the residue was washed with the same solvent mixture (100 mL), and the filtrate was evaporated to leave an oil, which was distilled to give **35**.

Method P. Methyl(3-oxo-5-indan)acetic Acid (37). The ester **37** (9 g, 0.038 mol) in AcOH (90 mL) was added to concentrated HCl (90 mL) and kept at room temperature for 5 days. The solution was poured into H_2O (1 L) and extracted with Et_2O. The Et_2O was washed with saturated NaCl solution, dried ($MgSO_4$), filtered, and evaporated. The product was further purified by dissolving in saturated $NaHCO_3$ solution (100 mL), extracting with Et_2O and acidifying the aqueous phase to give **37**. A sample was recrystallized for analysis.

Method R. 1-Methyl-5-phenylindan (23). This method was the same as for method B, except that concentrated HCl (1.58 mL for 1.05 g, 10% Pd/C) was added to the hydrogenation mixture. The method was also used for preparation of the acid of the salt **31** from the keto acid **30**.

Method S. 4-Biphenylyl Propenyl Ketone (24). This method followed that given by Fieser and Herschberg for 3-crotonylacenaphthene.[17]

Method T.[18] **3-Methyl-5-phenylindanone (25).** The above unsaturated ketone **24** (10 g, 0.045 mol) was added to a finely powdered mixture of $AlCl_3$ (50 g, 0.37 mol) and NaCl (10 g) which had been stirred and heated to 140 °C. The mixture was kept at 140–180 °C for 2 min with stirring, poured into ice, and treated with concentrated HCl (15 mL). The product was extracted with $CHCl_3$, which was washed with saturated $NaHCO_3$ and saturated NaCl, dried (Na_2SO_4), filtered, evaporated, and further purified as indicated in Table III, bp 131–134 °C (0.1 min). Distillation gave a mixture of liquid and solid. The latter was separated and recrystallized.

Method U. Ethyl 3-Cyclohexyl-3-phenylacrylate (26). Ethyl bromoacetate (82.55 g, 0.49 mol) and cyclohexyl phenyl ketone (91.6 g, 0.49 mol) were reacted according to method A, and the resulting β-hydroxy ester [yield 134.58 g; bp 103–109 °C (0.06 mm)] was refluxed in benzene (350 mL) for 3.5 h. Phosphorus pentoxide (50 g) was added before reflux began, and it

was again (50 and 33 g) added 1.5 and 2 h after reflux began. The cooled solution was filtered and dried (K_2CO_3), and the product was distilled: bp 105–109 °C (0.06 mm); n^{20}_D 1.5196 (not analytically pure). NMR showed that it contained 67% of the isomer designated as **26**, and the remainder was mainly the β,γ-doubly bonded ester.

Method V. Ethyl 3-Cyclohexyl-3-(4-acetylphenyl)-propionate (28). The ester **27** (56 g, 0.215 mol) was acetylated using the method which Baddeley employed for the preparation of methyl 3-(4-acetylphenyl)propionate.[14]

Method W. 1-Cyclohexyl-5-indanacetic Acid, Sodium Salt (31). The acid **30** (24.6 g, 0.09 mol) was reduced using the method [employed to prepare β-(*p*-phenoxybenzoyl)propionic acid] of ref 19 to give 1-cyclohexylindan-5-acetic acid: bp 158–162 °C (0.06 mm); n^{22}_D 1.5452. Anal. ($C_{17}H_{22}O_2$) C, H. The acid was converted to its sodium salt by adding aqueous $NaHCO_3$ to an EtOH solution of the acid, followed by evaporation.

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N-Alkylated 2-Aminotetralins: Central Dopamine-Receptor Stimulating Activity

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In order to define the structural requirements of N-substituents of 2-aminotetralins as central dopamine receptor agonists, a series of *N*-alkyl- and *N,N*-dialkyl-substituted 2-amino-5-hydroxy- and 2-amino-5-methoxytetralins have been synthesized and evaluated. The compounds were tested biochemically and behaviorally for dopaminergic activity. From the biochemical data it is concluded that an *n*-propyl group on the nitrogen is optimal for activity. The corresponding *N*-ethyl-substituted compounds are slightly less active, while the absence of *N*-ethyl or *N*-propyl groups give almost inactive compounds. It could be demonstrated that this is due to steric and not to lipophilic factors. It is suggested that a possible requirement for a potent agonist is that one of its N substituents must fit into a receptor cavity which, because of its size, can maximally accommodate an *n*-propyl but also smaller groups like ethyl or methyl. The active compounds appeared to give a similar relative pre- and postsynaptic stimulation and had also similar activities for the limbic system and for striatum. None of the compounds listed seemed to have central noradrenaline- or serotonin-receptor stimulating activity.

The high dopamine-receptor stimulating activity of apomorphine has been the basis of many structure–activity relationship studies. These include apomorphine derivatives[1,2] as well as various simplified structural analogues.[3-6] The bicyclic analogues 2-amino-5,6- and 2-amino-6,7-dihydroxytetralin and several of their N-alkylated derivatives have been shown to possess central dopamine-receptor stimulating activity.[5-12] Some of these compounds are even more potent than apomorphine.

The *N*-butyl or *N,N*-dibutyl derivatives of 2-amino-5,6-dihydroxytetralin, dopamine, or norapomorphine have very little or no dopaminergic activity, while the analogues carrying at least one *N*-ethyl or one *N*-*n*-propyl group possess high activity.[1,6,7,10-15] The results thus obtained in different investigations show that the structure of the *N*-alkylamino moiety of dopamine-related compounds is important for the dopamine-receptor stimulating activity. We have now investigated an extensive series of N-alkylated 2-aminotetralins in order to establish the influence of the N substituents upon the dopaminergic activity.

The monohydroxy derivative 5-hydroxy-2-(dipropylamino)tetralin has been reported to be almost equipotent to its 5,6-catechol analogue in producing stereotypy in rats and emesis in dogs.[16] This high potency of the 5-hydroxy derivative, together with the fact that monophenolic compounds are chemically more stable than catechols, induced us to choose the 2-amino-5-hydroxytetralin unit as the basic structure in our investigation. One could also expect

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