performed. β_2-Adrenergic blocking activity was estimated with spirally cut tracheal segments. The segment of trachea was placed in a Krebs solution at 37 °C and gassed with 5% CO_2 in O_2. Contractions were recorded isotonically with a 2-g preload. The preincubation time of the antagonists was 3 min. Calculation of the classical parameters indicating possible activity (pA_2, pD_2') was performed according to the technique of Van Rossum.[26]

SHR Test for Antihypertensive Activity. Thirty-one spontaneously hypertensive male rats, 35 to 39 weeks of age, were used. They were anesthetized with pentobarbital (45 mg/kg intraperitoneally). Blood pressure was measured in the carotid artery and was recorded with a Statham pressure transducer. The drugs were injected intravenously in increasing doses until an antihypertensive effect of at least 20-min duration was observed. A 60-min period was observed between two consecutive doses. The maximal variations of both diastolic and systolic blood pressure under the influence of the drugs are calculated in percentages of the initial values before treatment. Since usually three rats were used in each group, no statistical evaluation was performed.

(26) Van Rossum, J. M. *Arch. Int. Pharmacodyn. Ther.* **1963**, *143*, 299-330.

Notes

2-(Arylmethyl)arylacetic Acids as Potential Antiinflammatory Agents

Giovanni Brancaccio,[1] Angelo Larizza, Guglielmo Lettieri,[1]

Research Laboratories of Richardson-Merrell S.p.A., Naples, Italy

and Pietro Monforte*

Istituto di Chimica Farmaceutica e Tossicologica, Università Contrada SS. Annunziata, 98100 Messina, Italy.
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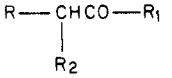
The title compounds **2** have been synthesized and tested for antiinflammatory activity. The synthetic method, consisting of the chemical sequence 3-aryl-1*H*-indenes (**4**) → 2-(aroyl)arylacetic acids (**5**) → **2**, appears to be of value because of its simplicity and generally acceptable yields. The synthesized compounds showed low pharmacological activity.

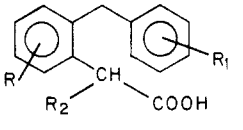
A research area of continuous and ever-growing development is that of nonsteroidal antiinflammatory agents. Derivatives of arylacetic acids[2a] of formula **1** probably



1, R = aryl, heteroaryl; R_1 = OH, NHOH, NH_2; R_2 = H, alkyl

represent the class in which the greatest research effort has occurred. This class has produced many pharmacologically interesting compounds, several of which have been clinical candidates.[2b]

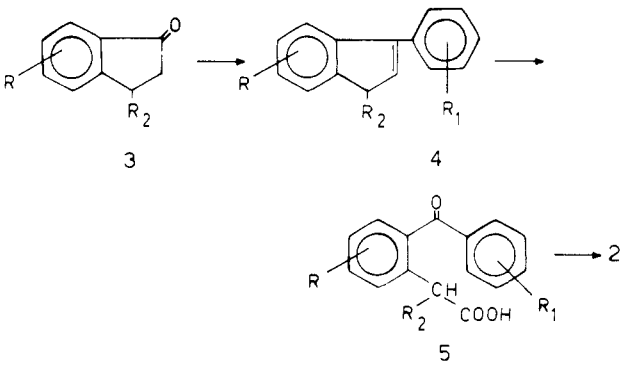
Therefore, we were interested in synthesizing a new series of 2-(arylmethyl)arylacetic acids (**2**), in order to investigate their antiinflammatory properties.



2, R = H, Cl, CH_3, OCH_3; R_1 = H, Cl, CH_3, OCH_3; R_2 = H, CH_3

Chemistry. 2-(Arylmethyl)arylacetic acids (**2**) can be prepared by the procedures of Leonard et al.[3] and Rigaudy and Nedelec.[4] These methods, however, are rather troublesome, require the use of carefully handled reagents, and, therefore, are unsuitable for large-scale preparations. We have prepared compounds **2** by the reaction sequence shown in Scheme I.

Scheme I



The starting indanones, **3**, were treated with the appropriate Grignard reagent, and the resulting alcohols were dehydrated to the indenes. Previously unreported compounds are reported in Table IV.

The substituted 3-aryl-1*H*-indenes **4** were oxidized to the corresponding 2-(aroyl)arylacetic acids **5**, which in turn could be reduced to the expected 2-(arylmethyl)arylacetic acids **2**. The conversion[5] of **4** into **5** was usually accomplished by $K_2Cr_2O_7$ in H_2SO_4 solution at 55 °C.

(1) Consorzio Regionale Farmaceutico Ospedaliero Via Manzoni 249, Napoli, Italy.

(2) (a) P. F. Juby in "Antiinflammatory Agents", Vol 1, R. A. Scherrer and M. W. Whitehouse, Eds., Academic Press, New York, 1974, p 91. (b) P. F. Juby, ref 2a, p 99. *Drugs Today*, **15**, 43 (1979); **15**, 91 (1979). *Drugs Future*, **3**, 924 (1978); **4**, 373 (1979).

(3) N. J. Leonard, A. J. Kresge, and M. Oki, *J. Am. Chem. Soc.*, **77**, 5078 (1955).

(4) J. Rigaudy and L. Nedelec, *Bull. Soc. Chim. Fr.*, 638 (1959).

(5) C. F. Koelsch and C. D. Le Claire [*J. Org. Chem.*, **6**, 516 (1941)] reported the oxidation of 1,1-dimethyl-3-phenylindene to 2-benzoyl-α,α-dimethylbenzeneacetic acid. However, it must be noted that this last compound, in contrast to compounds of structure **5**, is resistant to further oxidation.

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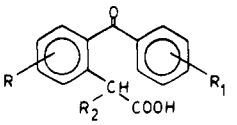
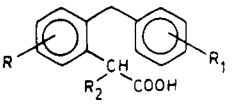
Table I. Substituted 2-(Aroyl)arylacetic Acids



no.	R	R_1	R_2	% yield[a] (procedure)	mp,[b] °C	formula	anal.
1	H	H	H	65 (A), 46 (B), 4 (C)	124-126[c]	$C_{15}H_{12}O_3$	C, H
2	H	2'-CH_3	H	14 (A), 5 (B), 22 (D)	94-97	$C_{16}H_{14}O_3$	C, H
3	H	3'-CH_3	H	48 (A), 62 (B)	127-129	$C_{16}H_{14}O_3$	C, H
4	H	4'-CH_3	H	30 (A), 58 (B)	134-136[d]	$C_{16}H_{14}O_3$	C, H
5	H	4'-Cl	H	27 (A), 61 (B)	152-155	$C_{15}H_{11}ClO_3$	C, H, Cl
6	H	4'-Br	H	48 (A), 51 (B)	149-151	$C_{15}H_{11}BrO_3$	C, H, Br
7	H	4'-OCH_3	H	40 (B)	143-145[e]	$C_{16}H_{14}O_4$	C, H
8	4-Cl	H	H	59 (A), 63 (B)	141-144	$C_{15}H_{11}ClO_3$	C, H, Cl
9	4-OCH_3	H	H	18 (A)	151-152	$C_{16}H_{14}O_4$	C, H
10	5-OCH_3	H	H	22 (A)	124-126	$C_{16}H_{14}O_4$	C, H
11	3,6-$(CH_3)_2$	H	H	37 (A), 41 (B)	138-141	$C_{17}H_{16}O_3$	C, H
12	4-Cl	3'-CH_3	H	43 (A)	94-96	$C_{16}H_{13}ClO_3$	H, Cl; C[f]
13	H	H	CH_3	21 (E)	102-104	$C_{16}H_{14}O_3$	C, H

[a] The yields refer to uncrystallized, chromatographically pure, products directly employed for the next step. [b] Determined on a crystallized sample. [c] L. Legrand and N. Lozac'h, *Bull. Soc. Chim. Fr.*, 1787 (1964), reported mp 128 °C. [d] Legrand and Lozac'h, (footnote *c*) reported mp 123 °C. [e] A. Horeau and J. Jacques, *Bull. Soc. Chim. Fr.*, 53 (1948), gave mp 151-152 °C. [f] C: calcd, 66.55; found, 67.02.

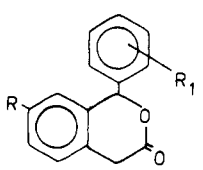
Table II. Substituted 2-(Arylmethyl)arylacetic Acids



no.	R	R_1	R_2	% yield (method)	mp, °C	formula	anal.
14	H	H	H	81 (F), 89 (G)	86-87[a]	$C_{15}H_{14}O_2$	C, H
15	H	2'-CH_3	H	77 (F)	74-77	$C_{16}H_{16}O_2$	C, H
16	H	3'-CH_3	H	64 (F)	69-72	$C_{16}H_{16}O_2$	C, H
17	H	4'-CH_3	H	84 (F)	115-117[b]	$C_{16}H_{16}O_2$	C, H
18	H	4'-Cl	H	(F)[c]	134-135[d]	$C_{15}H_{13}ClO_2$	C, H, Cl
19	H	4'-OCH_3	H	87 (F)	70-71[e]	$C_{16}H_{16}O_3$	C, H
20	4-Cl	H	H	89 (G)	150-153	$C_{15}H_{13}ClO_2$	C, H, Cl
21	4-OCH_3	H	H	71 (F)	96-98	$C_{16}H_{16}O_3$	C, H
22	5-OCH_3	H	H	72 (F), 65 (G)	83-85	$C_{16}H_{16}O_3$	C, H
23	3,6-$(CH_3)_2$	H	H	81 (F)	134-137	$C_{17}H_{18}O_2$	C, H
24	H	H	CH_3	67 (F)	92-95	$C_{16}H_{16}O_2$	C, H

[a] S. Murahashi, *Sci. Pap. Inst. Phys. Chem. Res. (Jpn.)*, **30**, 180 (1936) [*Chem. Zentralbl.*, **109** (1) 2168 (1938)] gave mp 93.5-94.5 °C. [b] J. C. Frielink, Netherlands Patent Application 6 600 710 [*Chem. Abstr.*, **65** 20066*c* (1966)] gave mp 124 °C. [c] Under the usual experimental conditions a consistent dehalogenation took place. [d] Reported mp 140 °C (footnote *b*). [e] Reported mp 70 °C (footnote *b*).

2-(Aroyl)arylacetic acids **5** (see Table I) were reduced[6] to 2-(arylmethyl)arylacetic acids **2** (see Table II) by either catalytic hydrogenolysis in the presence of 5% Pd on charcoal at 50–65 °C under 3 atm for 7 h (method F) or by heating an ammoniacal solution of the appropriate acid **5**, with excess Zn dust, in the presence of a copper salt (method G). If Zn was not in a great excess, the reduction stopped at the alcohol level, and the lactones **6** were isolated (see Table III). In one case, lactone **25** was further reduced over 10% Pd/C to the corresponding **2**.



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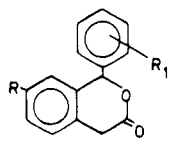
The easy accessibility of the 3-aryl-1*H*-indenes, the simplicity of the reactions, and the generally acceptable yields make the above method particularly valuable for synthesizing the substituted 2-(arylmethyl)arylacetic acids **2**.

Table III. Substituted 1-Arylisochroman-3-ones



no.	R	R_1	mp, °C	formula	anal.
25	H	H	77-79[a]	$C_{15}H_{12}O_2$	C, H
26	H	3-CH_3	83-85	$C_{16}H_{14}O_2$	C, H
27	H	4-OCH_3	104-106[b]	$C_{16}H_{14}O_3$	C, H
28	Cl	H	107-109	$C_{15}H_{11}ClO_2$	C, H, Cl

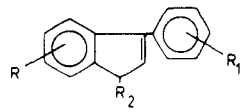
[a] A. T. Blomquist and C. G. Bottomley, *Justus Liebigs Ann. Chem.*, **653**, 67 (1962), reported mp 75 °C. [b] A. Horeau and J. Jacques, *Bull. Soc. Chim. Fr.*, 53 (1948), reported mp 107 °C, then at 120 °C after previous solidification.

Pharmacology. Compounds of Tables I and II were screened for antiinflammatory activity in the carrageenin rat foot edema assay[7] using male Wistar rats (140–170 g)

(6) In some cases, the Clemmensen method was tried but the yields were very poor.

(7) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962).

Table IV. Substituted 3-Aryl-1*H*-indenes



no.	R	R_1	R_2	% yield[a]	bp, °C (mmHg)	formula	anal.
29	H	2'-CH_3	H	63	105-107 (0.05)	$C_{16}H_{14}$	C, H
30	H	3'-CH_3	H	58	110-112 (0.05)	$C_{16}H_{14}$	C, H
31	H	4'-Cl	H	90	123-125 (0.05)[b]	$C_{15}H_{11}Cl$	C, H, Cl
32	H	4'-Br	H	58	140-145 (0.01)[c]	$C_{15}H_{11}Br$	C, H, Br
33	5-Cl	H	H	56	135-137 (0.05)	$C_{15}H_{11}Cl$	C, H, Cl
34	5-OCH_3	H	H	45	132-136 (0.01)	$C_{16}H_{14}O$	C, H
35	4,7-$(CH_3)_2$	H	H	40	115-118 (0.05)[d]	$C_{17}H_{16}$	C, H
36	5-Cl	3'-CH_3	H	58	136-140 (0.01)	$C_{16}H_{13}Cl$	C, H, Cl

[a] The yields are calculated from the appropriate starting indanone. [b] Melting point 60-62 °C (petroleum ether, 60-68 °C). [c] Melting point 88-90 °C (petroleum ether, 60-68 °C). [d] Melting point 57-58 °C (ethanol).

in groups of six. The compounds, suspended in 0.5% aqueous Methocel, were administered orally, at doses of 50–100 mg/kg, 1 h before eliciting the foot edema. Indomethacin was used as a reference drug. In the carrageenin test, the 2-(aroyl)arylacetic acids **5** showed weak activity (from 25 to 15% that of indomethacin), whereas 2-(arylmethyl)arylacetic acids **2** were either devoid of antiinflammatory activity or displayed a very low activity (<15% that of indomethacin).

Experimental Section

Melting points were determined on a Kofler hot plate and are uncorrected. Microanalytical results (indicated by the symbols of the elements) were within ±0.4% of the theoretical values. Structures of all the products were consistent with the IR and ^1H NMR spectroscopic data.

Substituted 3-Aryl-1*H*-indenes (4). 3-Aryl-1*H*-indenes were prepared by the reaction of indanones (indan-1-one[8] and 6-chloro-,[9] 5-methoxy-,[10] 6-methoxy,[11] 4,7-dimethyl-,[12] and 3-methyl-indan-1-one[13]) with the appropriate Grignard reagent according to the directions indicated in the literature for 3-phenyl-1*H*-indene[14] synthesis. Some prepared aryl-1*H*-indenes have been previously described: 3-phenyl-[14], 3-(4-methoxyphenyl)-,[15] 3-(4-methylphenyl)-,[16] 1-methyl-3-phenyl-, and 3-phenyl-6-methoxy-1*H*-indene.[17] New compounds are reported in Table IV.

Substituted 2-(Aroyl)arylacetic Acids (5). Procedure A. Concentrated H_2SO_4 (50 mL) was carefully added to a solution of 0.14 mol of $K_2Cr_2O_7$ in 250 mL of H_2O. The appropriate 3-aryl-1*H*-indene (0.1 mol) in 20 mL of benzene was added dropwise with vigorous stirring at 55 ± 2 °C (internal temperature). The reaction mixture was then kept at the same temperature for an additional 2–3 h. Additional benzene was added, and the organic layer was separated and shaken with H_2O and saturated K_2CO_3. The combined alkaline extracts were filtered and acidified with 6 N HCl. The precipitate collected by filtration was washed with cold H_2O and dried in vacuo. An analytical sample was crystallized from aqueous EtOH (see Table I).

Procedure B. To a mixture of 0.17 mol of $K_2Cr_2O_7$ and 270 mL of concentrated H_2SO_4 in 800 mL of H_2O was gradually added the neat 3-aryl-1*H*-indene derivative (0.01 mol) under vigorous stirring at 55 ± 2 °C (internal temperature). The reaction mixture was then heated for 2–3 h and worked up as indicated in procedure A.

Procedure C. To a solution of 0.9 g (4.6 mmol) of phenyl-1*H*-indene in 20 mL of glacial AcOH was added 2.7 g (0.027 mol) of CrO_3. The mixture was stirred at room temperature for 18 h and then poured into a mixture of ice and water. The precipitate that formed was extracted into benzene, and the resulting solution was shaken several times with water and then with saturated K_2CO_3. The combined alkaline extracts were filtered and acidified with 2N HCl. The solid (0.44 g, mp 118–120 °C) was crystallized from benzene to give 0.3 g of product, mp 125–127 °C.

Procedure D. To a well-stirred mixture of 1 g (4.8 mmol) of 29 and 20 mL of H_2O was added dropwise a solution of 2.2 g (7.5 mmol) of $K_2Cr_2O_7$ and 5 mL of concentrated H_2SO_4 in 20 mL of H_2O at 55 ± 2 °C (internal temperature) over 1 h. The reaction mixture was allowed to cool to room temperature. Workup as above gave **2** (0.28 g; mp 92–95 °C).

Procedure E. 1-Methyl-3-phenyl-1*H*-indene (10.2 g, 0.05 mol) neat was added slowly to a well-stirred solution of 20.5 g (0.0692 mol) of $K_2Cr_2O_7$ and 120 mL of concentrated H_2SO_4 in 320 mL of H_2O. Temperature was kept below 34 °C, stirring was maintained for a further 2 h, and benzene was then added. The resulting organic solution was shaken with saturated K_2CO_3. After acidification of the combined alkaline extracts, **13** (2.6 g; mp 95–98 °C) was obtained. An analytical sample was crystallized from an Et_2O–petroleum ether mixture. The above organic solution was dried (Na_2SO_4) and concentrated. The oily residue solidified on trituration with Et_2O to give 1.1 g, mp 95–97 °C. The solid, after crystallization from an AcOEt–petroleum ether mixture, had mp 95–97 °C and was identified as 2-benzoylacetophenone.[18] Anal. ($C_{15}H_{12}O_2$) C, H.

Substituted 2-(Arylmethyl)arylacetic Acids (2). Method F. A solution of 0.01 mol of the appropriate 2-(aroyl)arylacetic acid in 35–40 mL of glacial AcOH was shaken under an initial 3 atm of H_2 at 50–60 °C, using 5% Pd on charcoal (0.2 g) as catalyst. After 7 h, the reaction mixture was filtered, and the filtrate, after concentration under reduced pressure, was diluted with H_2O. The crystalline precipitate was collected by filtration and dried. Purification, when required, was accomplished by crystallization from an EtOH–H_2O (see Table II).

Method G. A mixture of 0.05 mol of the appropriate 2-(aroyl)arylacetic acid, 45 mL of H_2O, 80 mL of concentrated NH_4OH, 40 g (0.61 g-atom) of Zn dust, and 1.0 mL of saturated $CuSO_4$ was heated under reflux for 3 days with vigorous stirring. After 12 h, 15 mL of concentrated NH_4OH was added. The reaction mixture was filtered, and the undissolved solid was washed several times with 15% NH_4OH. The filtrate and the washings were combined and acidified carefully with concentrated HCl. The separated solid was collected by filtration and dried.

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(11) W. S. Johnson and W. E. Shelberg, *J. Am. Chem. Soc.*, **67**, 1853 (1945).
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(13) C. F. Koelsch, H. Hockmann, and C. D. Le Claire, *J. Am. Chem. Soc.*, **65**, 59 (1943).
(14) B. Weinstein, *J. Org. Chem.*, **26**, 4161 (1961).
(15) K. N. Campbell, D. E. Rivard, and R. F. Feldkamp, U.S. Patent 2 992 231; *Chem. Abstr.*, **56**, 459*g* (1962).
(16) F. K. Beilsteins, "Handbuch der Organischen Chemie", Vol 5, Springer, Berlin, p 591.
(17) L. Novak and M. Protiva, *Chem. Listy*, **50**, 1995 (1956); *Chem. Abstr.*, **51**, 5045*b* (1957).
(18) C. F. Koelsch and P. R. Johnson, *J. Am. Chem. Soc.*, **65**, 567 (1943).