Nonsteroidal Antiinflammatory Agents. 2.[1] Synthesis of 4',5-Disubstituted 3-Biphenylylacetic Acids and Their Derivatives with Antiinflammatory and Analgesic Activities

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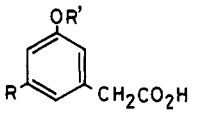
A series of 4',5-disubstituted 3-biphenylylacetic acids (**5a–n**) and several α-methyl derivatives (**5o–v**) were prepared as analogues of a newly developed nonsteroidal antiinflammatory agent, 4'-chloro-5-methoxy-3-biphenylylacetic acid [1 (DKA-9), R = 4-ClPh; R' = Me], and evaluated for antiinflammatory and analgesic activities using both carrageenan rat paw edema and AcOH writhing assays. Among them, 5-fluoro-3-biphenylylacetic acid (**5m**) showed the highest antiinflammatory activity, while 2-(3-biphenylyl)propionic acid (**5o**) showed the highest analgesic activity. However, they were less potent than 1 (R = 4-ClPh; R' = Me) in these assays.

Although many different types of nonsteroidal antiinflammatory agents are reported in the literature of the past 2 decades, the search continues for more effective compounds.[2] In the previous paper[1] we reported the synthesis of 5-alkoxy-3-biphenylylacetic acids (1), among which 4'-chloro-5-methoxy-3-biphenylylacetic acid [1 (DKA-9), R = 4-ClPh; R' = Me] was demonstrated to have excellent



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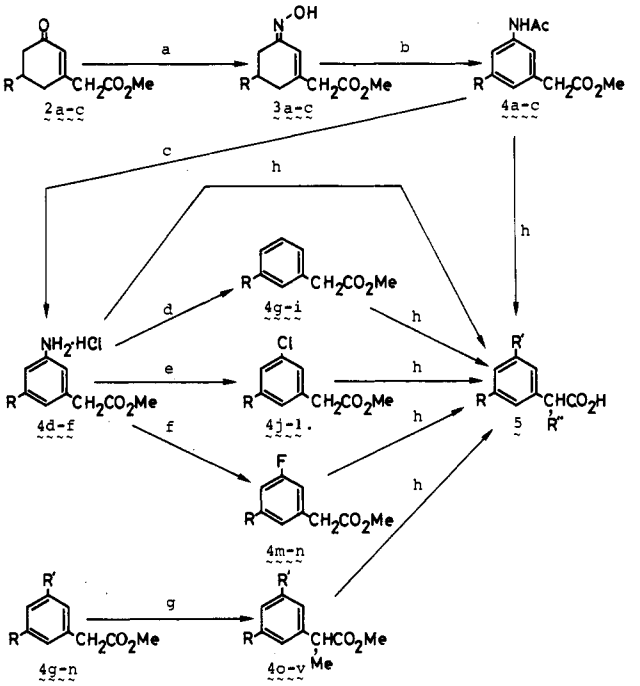
antiinflammatory and analgesic activities.[3] On the other hand, *m*-halogenophenylacetic acids, such as 4-(allyloxy)-3-chlorophenylacetic acid (Alclofenac),[4] 2-(3-fluoro-4-biphenylyl)propionic acid (Flurbiprofen),[5] and 2-(3-chloro-4-cyclohexylphenyl)propionic acid,[6] have been shown to have potent antiinflammatory activity, and the former two are now on the market in some countries. It was therefore of interest to examine the antiinflammatory activity of the title compounds **5**, because they are structurally related to the above compounds. Variants at position 5 of **1** were also prepared as an extension of our earlier work.[1] The compounds were evaluated using both carrageenan-induced rat paw edema and AcOH writhing assays. In this paper, the synthesis and antiinflammatory and analgesic activities of the title compounds **5** will be described.

Chemistry. To prepare **5** effectively, we selected a synthetic route via Semmler–Wolff aromatization of the oximes **3a–c** of methyl 3-oxo-5-substituted-1-cyclohexen-1-ylacetates **2a–c**[1] as shown in Scheme I. The Semmler–Wolff aromatization of **3c** under known conditions,[7a–c] such as AcOH–Ac_2O–HCl or PPA, resulted in failure; this transformation was achieved using **3c**, pyri-

Scheme I. Synthetic Routes to 4',5-Disubstituted 3-Biphenylylacetic Acids and Their Derivatives[a,b]



[a] Reagents for a: NH_2OH·HCl, NaOAc, MeOH; b: (i) Ac_2O, pyridine, (ii) AcCl; c: concentrated HCl–MeOH; d: (i) aqueous $NaNO_2$, concentrated HCl, (ii) H_3PO_2, DMF–H_2O; e: (i) aqueous $NaNO_2$, concentrated HCl–acetone, (ii) Cu_2Cl_2; f: 43% HBF_4, aqueous $NaNO_2$; g: *n*-Bu_4N^+-HSO_4^-, NaOH, CH_2Cl_2–H_2O, MeI; h: NaOH, H_2O–MeOH. [b] R, a = Ph, b = 4-MeOPh, c = 4-ClPh; R'' = H, Me; R' = H, Cl, F in 4o–v; NHAc, NH_2, H, Cl, F in 5.

(1) Part 1 of this series: Y. Tamura, Y. Yoshimoto, K. Kunimoto, S. Tada, T. Tomita, T. Wada, E. Seto. M. Murayama, Y. Shibata, A. Nomura, and K. Ohata, *J. Med. Chem.*, **20**, 709 (1977).
(2) J. G. Lombardino, *Annu. Rep. Med. Chem.*, **13**, 167 (1978).
(3) Y. Shibata, *Arzneim.-Forsch.*, **27**, 2299 (1977).
(4) G. Lambelin, J. Roba, C. Gillet, and N. P. Buu-Hoi, *Arzneim.-Forsch.*, **20**, 610 (1970).
(5) (a) S. S. Adams, K. F. McCullough, and J. S. Nicholson, *Arzneim.-Forsch.*, **25**, 1786 (1975); (b) I. M. Chalmers, B. J. Cathcart, E. B. Kuwar, W. C. Dick, and W. W. Buchanan, *Ann. Rheum. Dis.*, **31**, 319 (1972).
(6) C. G. Van Arman, R. P. Carlson, E. A. Risley, R. H. Thomas, and G. W. Nuss, *J. Pharmacol. Exp. Ther.*, **175**, 459 (1970).
(7) (a) AcOH–Ac_2O–HCl: G. Schröether, A. Gluschke, S. Götzky, J. Huang, G. Irmisch, E. Laves, O. Schrader, and G. Stier, *Chem. Ber.*, **63**, 1308 (1930). (b) PPA: E. C. Horning, V. L. Stromberg, and H. A. Lloyd, *J. Am. Chem. Soc.*, **74**, 5153 (1952). (c) PPA: Y. Tamura, Y. Kita, and J. Uraoka, *Chem. Pharm. Bull.*, **20**, 876 (1972).

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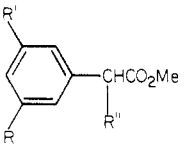
Table I. Methyl 4′,5-Disubstituted 3-Biphenylylacetates and Their Derivatives



no.	R	R′	R″	mp (recrystn solvent)[a] or bp (mm), °C	yield, %	formula	anal.
4a	Ph	NHAc	H	viscous oil	69[d]	$C_{17}H_{17}NO_3$	C, H, N
4b	4-MeOPh	NHAc	H	106-108 (B)	71[d]	$C_{18}H_{19}NO_4$	C, H, N
4c	4-ClPh	NHAc	H	126-127.5 (E)	69[d]	$C_{17}H_{16}NO_3Cl$	C, H, N, Cl
4d[b]	Ph	NH_2	H	204-207 (A)	70[e]	$C_{15}H_{16}NO_2Cl$	C, H, N, Cl
4e[b]	4-MeOPh	NH_2	H	216-218.5 (A) dec	90[e]	$C_{16}H_{18}NO_3Cl$	C, H, N, Cl
4f[b]	4-ClPh	NH_2	H	201-202 (C)	60[e]	$C_{15}H_{15}NO_2Cl_2$	H, N, Cl; C[h]
4g	Ph	H	H	146-147.5 (1)	66[f]	$C_{15}H_{14}O_2$	C, H
4h	4-MeOPh	H	H	87.5-88.5 (D)	82[f]	$C_{16}H_{16}O_3$	C, H
4i	4-ClPh	H	H	180-185 (2)[c]	79[f]	$C_{15}H_{13}O_2Cl$	C, H, Cl
4j	Ph	Cl	H	172-175 (2)	48[f]	$C_{15}H_{13}O_2Cl$	C, H, Cl
4k	4-MeOPh	Cl	H	56.5-58 (A)	47[f]	$C_{16}H_{15}O_3Cl$	C, H, Cl
4l	4-ClPh	Cl	H	180-190 (2)[c]	70[f]	$C_{15}H_{12}O_2Cl$	C, H, Cl
4m	Ph	F	H	156-158 (3)	39[f]	$C_{15}H_{13}O_2F$	C, H, F
4n	4-ClPh	F	H	175-185 (2)[c]	30[f]	$C_{15}H_{12}O_2ClF$	C, H, Cl, F
4o	Ph	H	Me	156-157 (2)	66[g]	$C_{16}H_{16}O_2$	C, H
4p	4-MeOPh	H	Me	181-182 (1)	78[g]	$C_{17}H_{18}O_3$	C, H
4q	4-ClPh	H	Me	175-180 (2)[c]	88[g]	$C_{16}H_{15}O_2Cl$	C, H, Cl
4r	Ph	Cl	Me	173-176 (2)	70[g]	$C_{16}H_{15}O_2Cl$	C, H, Cl
4s	4-MeOPh	Cl	Me	184-186 (1)	63[g]	$C_{17}H_{17}O_3Cl$	C, H, Cl
4t	4-ClPh	Cl	Me	173-180 (2)[c]	90[g]	$C_{16}H_{14}O_2Cl_2$	C, H, Cl
4u	Ph	F	Me	152-160 (2)[c]	75[g]	$C_{16}H_{15}O_2F$	C, H, F
4v	4-ClPh	F	Me	165-170 (2)	91[g]	$C_{16}H_{14}O_2ClF$	C, H, Cl, F

[a] A = MeOH; B = MeOH-Et_2O; C = 10% HCl-MeOH; D = i-Pr_2O; E = ethyl acetate. [b] HCl salt. [c] Bath temperature. [d] Overall yields from 2a-c. [e] Yields from 4a-c. [f] Yields from 4d-f. [g] Yields from 4g-n. [h] C: calcd, 57.70; found, 57.29.

dine, Ac_2O, and AcCl[8] in a ratio of 1:1:2:2. The yields of methyl 5-acetamido-4′-substituted-3-biphenylylacetates **4a–c** by this method were 69, 71, and 69%, respectively. Conversion of the compounds **4a–c** to **4d–n** were carried out by conventional methods given under Experimental Section. The esters **4a–n** were hydrolyzed to the acetic acids **5a–n** under basic media. Of the esters prepared, the compounds **4g–n** were treated with methyl iodide in CH_2Cl_2–H_2O in the presence of NaOH and tetrabutylammonium hydrosulfate, and the resulting α-methyl esters **4o–v** were hydrolyzed to the α-methylacetic acids **5o–v**.

Pharmacology. The compounds **5a–v** (Table II) were tested for antiinflammatory and analgesic activities and acute toxicities by the methods described under Experimental Section. All compounds were administered orally in a dose of 50 mg/kg in these assays. Where 30% inhibition or more was found, the compound was further tested at 20 and 10 mg/kg.

As to antiinflammatory activity, the compounds bearing the acetamido or amino groups at position 5 or the methoxy group at position 4′ (cf. **5a–f,h,k**) lacked activity. The known compound **5g**[9] had comparable activity to **1** (R = 4-ClPh; R′ = Me) at 50 mg/kg but was much less active at 20 mg/kg. Compound **5i**, which is the demethoxylated compound of **1** (R = 4-ClPh; R′ = Me), showed about half the activity of **1** (R = 4-ClPh; R′ = Me) even at 20 mg/kg. This observation suggests that the high potency of **1** (R = 4-ClPh; R′ = Me) is due to a great extent to the 4′-chloro-3-biphenylylacetic acid moiety, and the methoxy group at position 5 plays an important role in enhancing the activity of **5i**. Most of the 5-halogeno-3-biphenylylacetic acids showed moderate or excellent activity at 50 mg/kg (cf. **5j, l–n**). The highest activity was exhibited by 5-fluoro-3-biphenylylacetic acid (**5m**) with 45 (at 20 mg/kg) and 26% (at 10 mg/kg) inhibitory activity, but it was less active than **1** (R = 4-ClPh; R′ = Me). On the other hand, α-methylation of the compounds **5g–n** resulted in no enhancement of the activity. Compound **5u**, which is not only a positional isomer of flurbiprofen but also closely resembles it structurally, was much less active than the parent acetic acid **5m**.

As to analgesic activity, most of the compounds tested were found to be inactive (ED_{50} > 50 mg/kg) except for **5q** [ED_{50} = 45.0 (30.0–67.5) mg/kg], the known **5o**[10a,b] [ED_{50} = 26.8 (11.7–61.6) mg/kg], **1** (R = 4-ClPh; R′ = Me) [ED_{50} = 16.1 (8.9–30.0) mg/kg)] and indomethacin [ED_{50} = 3.1 (1.5–6.5) mg/kg].

In conclusion, the biological test results of the title compounds **5**, when compared with that of the control compound **1** (R = 4-ClPh; R′ = Me) did not encourage us to investigate them further.

Experimental Section

All melting points were determined in an open capillary tube on a Büchi melting point apparatus and are uncorrected. All boiling points are uncorrected. Analyses of the elements indicated

(8) F. M. Beringer and I. Ugelow, *J. Am. Chem. Soc.*, **75**, 2635 (1953). It has been recognized that the yield of **4c** depends considerably on the molar ratio of the oxime and reagents used. For example, when oxime **3c** was treated under Beringer's conditions employing **3c**, pyridine, Ac_2O, and AcCl in a ratio of 1:1.02:7.38:2.92, **4c** was obtained in 37% yield. Yields of **4c** in other molar ratios were as follows: (a) **3c**–pyridine–Ac_2O–AcCl, 1:1:1:1, 9%; (b) **3c**–pyridine–Ac_2O–AcCl, 1:2:1:4, 15%.

(9) D. L. Turner, *J. Am. Chem. Soc.*, **72**, 3823 (1950).

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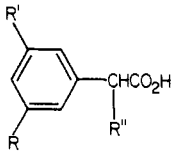
Table II. Chemical and Pharmacological Data of 4',5-Disubstituted 3-Biphenylylacetic Acids and Their Derivatives



compd	R	R'	R''	mp (recrystn solvent),[a] °C	yield, %	formula[b]	inhib act. on carrageenan paw edema[f] dose, mg/kg po	% inhibn at 3 h	inhib act. on AcOH writhing: ED_{50}, mg/kg po[g]	acute toxicity: LD_{50}, mg/kg ip[g]
5a	Ph	NHAc	H	166-168 (A)	60	$C_{16}H_{15}NO_3$	50	5	>50	>800
5b	4-MeOPh	NHAc	H	186-187 (A)	90	$C_{17}H_{17}NO_4$	50	15*	>50	>800
5c	4-ClPh	NHAc	H	211-213 (A)	82	$C_{16}H_{14}O_3Cl$	50	0	>50	476 (336-673)
5d	Ph	NH_2	H	158-160 (A)	63	$C_{14}H_{13}NO_2$	50	0	>50	566
5e	4-MeOPh	NH_2	H	179-181 (A)	73	$C_{15}H_{15}NO_3$	50	0	>50	800
5f	4-ClPh	NH_2	H	194-196 (B) dec	88	$C_{14}H_{12}NO_2Cl$	50	16*	>50	400 (268-597)
5g	Ph	H	H	133-134.5 (A)[c]	76	$C_{14}H_{12}O_2$	50	47***	>50	566
							20	0		
5h	4-MeOPh	H	H	156.5-158 (C)	78	$C_{15}H_{14}O_3$	50	11	>50	>800
5i	4-ClPh	H	H	140-142 (D)	86	$C_{14}H_{11}O_2Cl$	50	44***	>50	238 (168-336)
							20	25**		
5j	Ph	Cl	H	143-145 (A)	80	$C_{14}H_{11}O_2Cl$	50	32**	>50	283
							20	25**		
5k	4-MeOPh	Cl	H	163-166 (A)	71	$C_{15}H_{13}O_3Cl$	50	19**	>50	570
5l	4-ClPh	Cl	H	145-147 (E)	77	$C_{14}H_{10}O_2Cl_2$	50	45***	>50	283
							20	29**		
5m	Ph	F	H	96.5-97 (F)	87	$C_{14}H_{11}O_2F$	50	50***	>50	566
							20	45***		
							10	26*		
5n	4-ClPh	F	H	121-123 (F)	85	$C_{14}H_{10}O_2ClF$	50	38**	>50	283
							20	16		
5o	Ph	H	Me	64.5-65.5 (G)[d]	71	$C_{15}H_{14}O_2$	50	17	26.8 (11.7-61.6)	566
5p	4-MeOPh	H	Me	109-110.5 (F)	76	$C_{16}H_{16}O_3$	50	0	>50	566
5q	4-ClPh	H	Me	89-91 (H)	68	$C_{15}H_{13}O_2Cl$	50	35***	45.0 (30.0-67.5)	283
							20	31***		
5r	Ph	Cl	Me	92.5-93.5 (G)	84	$C_{15}H_{13}O_2Cl$	50	4	>50	168 (119-238)
5s	4-MeOPh	Cl	Me	89.5-91 (H)	65	$C_{16}H_{15}O_2Cl$	50	8	>50	283
5t	4-ClPh	Cl	Me	91-93 (H)	68	$C_{15}H_{12}O_2Cl_2$	50	41***	>50	200 (134-298)
							20	33***		
5u	Ph	F	Me	101-103 (G)	68	$C_{15}H_{13}O_2F$	50	31**	>50	566
5v	4-ClPh	F	Me	syrup[e]	67	$C_{15}H_{12}O_2ClF$	50	39**	>50	200 (134-298)
							20	26**		
1 (DKA-9)	4-ClPh	Me					50	53***	16.1 (8.9-30.0)	570 (520-624)
							20	65***		
							10	39**		
indomethacin							5	45***	3.1 (1.5-6.5)	
							2	25***		
							0.5	19*		

[a] A = MeOH; B = EtOH; C = *i*-PrOH; D = *n*-hexane-benzene; E = benzene; F = *i*-Pr_2O; G = *n*-hexane; H = *n*-hexane-*i*-Pr_2O. [b] Analyses were obtained for C, H, and when those elements were present, for N, Cl, and F. [c] Lit.[9] mp 135-137 °C. [d] Melting point was not given in the literature.[10a,b] [e] Boiling point 195-200 °C (bath temperature) (2 mm). [f] A Student's *t* test was carried out. Results marked with asterisks are percentage reductions of swelling which are significant [* = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$] at the given dose levels, and results without an asterisk were not significantly different from measurements on controls. [g] 95% confidence limits in parentheses.

were within ±0.4% of the calculated values, unless otherwise stated. IR spectra were obtained with a Hitachi EPI G-3 spectrometer. NMR spectra were determined on a Nichiden-Varian Model NEVA A-60D spectrometer using Me_4Si as internal standard. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The IR and NMR spectra of all new compounds were consistent with their structures.

Methyl 3-Oxo-5-substituted-1-cyclohexen-1-ylacetate Oximes (3a–c). Compounds **3a–c** were prepared from the ketones **2a–c** by a similar method to that described for **3a** below.

Methyl 3-Oxo-5-phenyl-1-cyclohexen-1-ylacetate Oxime (3a). A mixture of methyl 3-oxo-5-phenyl-1-cyclohexen-1-ylacetate (**2a**;[1] 50 g, 0.205 mol), hydroxylamine hydrochloride (15.6 g, 0.225 mol), sodium acetate (16.99 g, 0.225 mol), and methanol (500 mL) was heated under reflux for 3 h and concentrated. The residue was dissolved in chloroform. The chloroform solution was washed successively with H_2O, saturated $NaHCO_3$, and H_2O and then dried over $MgSO_4$. Removal of chloroform gave **3a** (52.9 g, 100%) as an oil, which was too viscous to be distilled: IR (liquid film) 3200, 1740, 1640, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.8–2.73 (m, 4 H), 3.4–3.9 (m, 1 H), 3.68 (s, 3 H), 6.10 (s, 1 H), 7.22 (s, 5 H). Anal. ($C_{15}H_{17}O_3N$) C, H, N.

Yields and spectral data of other compounds of type **3** were as follows. **3b**: highly viscous oil (100%); IR (liquid film) 3200, 2850, 1740, 1640, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.9–2.83 (m, 4 H), 2.83–3.15 (m, 1 H), 3.18 (br s, 2 H), 3.66 (s, 3 H), 6.83 (d, 2 H, J = 9 Hz), 7.18 (d, 2 H, J = 9 Hz), 7.36 (br s, 1 H, D_2O ex-

changeable). Anal. ($C_{16}H_{19}O_4N$) C, H, N. **3c**: highly viscous oil (100%); IR (liquid film) 3250, 1725, 1630 cm^{-1}; NMR ($CDCl_3$) δ 2.16–3.0 (m, 4 H), 2.72–3.32 (m, 1 H), 3.18 (s, 2 H), 3.67 (s, 3 H), 6.13 [s, 0.6 H], 6.78 [s, 0.4 H], 7.25 (d, 2 H, J = 9 Hz), 7.40 (d, 2 H, J = 9 Hz), 8.34 (br s, 1 H, D_2O exchangeable).

Only **3c** could be separated into its *E* [mp 109–110 °C (MeOH); NMR ($CDCl_3$) 6.13 (s, 1 H). Anal. ($C_{15}H_{16}O_3NCl$) C, H, N, Cl] and *Z* isomers [mp 119.5–121.5 °C (*i*-Pr_2O); NMR ($CDCl_3$) 6.78 (s, 1 H). Anal. ($C_{15}H_{16}O_3NCl$) C, H, N, Cl] via column chromatography followed by recrystallization. Crude **3a–c** were used as starting materials in the next step.

Methyl 5-Acetamido-4′-substituted-3-biphenylylacetates (4a–c). Compounds **4a–c** were prepared from **3a–c** by a similar method to that described for **4a** below.

Methyl 5-Acetamido-3-biphenylylacetate (4a). A mixture of **3a** (52.9 g, 0.205 mol), Ac_2O (42 g, 0.41 mol), and pyridine (16.3 g, 0.205 mol) was heated with stirring at 80 °C for 0.5 h and cooled. Acetyl chloride (32.3 g, 0.41 mol) was added, and the mixture was heated at 90–95 °C for 1 h. The reaction mixture was poured onto ice. An oil which separated was extracted with ethyl acetate. The ethyl acetate solution was washed successively with H_2O, saturated $NaHCO_3$, and H_2O and then dried over $MgSO_4$. Removal of ethyl acetate afforded a reddish oil (49.5 g), which was chromatographed on silica gel using ethyl acetate as eluent to give **4a** (40 g, 69%) as a highly viscous oil: IR (liquid film) 3320, 1730, 1660, 1600 cm^{-1}; NMR ($CDCl_3$) δ 2.13 (s, 3 H), 3.62 (s, 2 H), 3.65 (s, 3 H), 7.12–7.76 (m, 8 H), 8.06 (br s, 1 H).

Methyl 5-Amino-4′-substituted-3-biphenylylacetate Hydrochlorides (4d–f). Compounds **4d–f** were prepared from **4a–c** by a similar method to that described for **4d** below.

Methyl 5-Amino-3-biphenylylacetate Hydrochloride (4d). A suspension of **4a** (35 g, 0.12 mol) in methanol (300 mL) and concentrated HCl (700 mL) was heated under reflux for 4 h and cooled. The resulting precipitate was collected by filtration and then dissolved in anhydrous 18% methanolic HCl (150 mL). The mixture was heated under reflux for 2 h and concentrated to a quarter volume, which was allowed to stand at room temperature. The precipitate was collected and dried to afford **4d** (23.3 g, 70%), which on recrystallization from methanol gave an analytical sample of **4d**, mp 204–207 °C, as pale yellow crystals: IR (KBr) 2820, 2570, 1735, 1605 cm^{-1}; NMR (Me_2SO-d_6) δ 3.61 (s, 3 H), 3.80 (s, 2 H), 5.20–6.55 (br, 2 H), 7.26–7.76 (m, 8 H).

Methyl 4′-Substituted 3-Biphenylylacetates (4g–i). Compounds **4g–i** were prepared from **4d–f** by a similar method to that described for **4g** below.

Methyl 3-Biphenylylacetate (4g). To a stirred mixture of **4d** (8.4 g, 0.03 mol), DMF (90 mL), and concentrated HCl (16 mL) was added aqueous $NaNO_2$ (2.19 g in 8 mL of H_2O) at 0 °C and then H_3PO_2 (45 mL) at 0–2 °C. The mixture was stirred for an additional 3 h at the same temperature, kept at 0–5 °C for 56 h, and diluted with H_2O (70 mL). An oil which separated was extracted with ethyl acetate. The ethyl acetate solution was washed with H_2O, dried over $MgSO_4$, and concentrated. The residual reddish brown oil (6.7 g) was dissolved in anhydrous 18% methanolic HCl (100 mL), and the mixture was heated under reflux for 1 h and concentrated. The residue was dissolved in ethyl acetate. The ethyl acetate solution was washed successively with H_2O, saturated $NaHCO_3$, and H_2O and dried over $MgSO_4$. Evaporation of ethyl acetate gave a reddish brown oil, which was chromatographed on silica gel using benzene as eluent to give **4g** (4.85 g, 71%) as a pale yellow oil. Distillation gave an analytical sample of **4g** (4.5 g, 66%), bp 146–147.5 °C (1 mm), as a colorless oil: IR (liquid film) 1735, 1600 cm^{-1}; NMR ($CDCl_3$) δ 3.68 (s, 5 H), 7–7.9 (m, 9 H).

Methyl 5-Chloro-4′-substituted-3-biphenylylacetates (4j–l). Compounds **4j–l** were prepared from **4d–f** by a similar method to that described for **4j** below.

Methyl 5-Chloro-3-biphenylylacetate (4j). A mixture of $CuCl_2$ (7.6 g, 0.0447 mol), Cu (3.6 g, 0.057 mol), concentrated HCl (46 mL), and H_2O (17 mL) was heated with stirring for 2 h at 90–100 °C and cooled. To the resulting dark green solution was added aqueous KCl (12.9 g in 22 mL of H_2O). To this mixture was added in small portions a solution which was prepared by adding at 0–5 °C aqueous $NaNO_2$ (3.3 g in 10 mL of H_2O) to a stirred suspension of **4d** (12 g, 0.0432 mol) in a mixture of concentrated HCl (85 mL) and acetone (85 mL). The resulting mixture was stirred for an additional 2 h at the same temperature and then was heated at 70–80 °C for 0.5 h. After cooling, the reaction mixture was shaken with chloroform (300 mL). The chloroform layer was separated, washed with H_2O, dried over $MgSO_4$, and concentrated. The resulting dark brown oil (8 g) was dissolved in anhydrous 18% methanolic HCl (200 mL), and the mixture was heated under reflux for 2 h and concentrated. The residual oil was dissolved in ethyl acetate. The ethyl acetate solution was washed successively with H_2O, saturated $NaHCO_3$, and H_2O and dried over $MgSO_4$. Evaporation of ethyl acetate afforded a reddish oil (7.4 g), which was chromatographed on silica gel using (*n*-hexane–benzene, 1:1) as eluent to give **4j** (5.7 g, 51%) as a colorless oil. Distillation gave an analytical sample of **4j**: bp 172–175 °C (2 mm); IR (liquid film) 1740, 1595 cm^{-1}; NMR ($CDCl_3$) δ 3.62 (s, 2 H), 3.68 (s, 3 H), 7.13–7.67 (m, 8 H).

Methyl 5-Fluoro-4′-substituted-3-biphenylylacetates (4m,n). Compounds **4m,n** were prepared from **4d,f** by a method similar to that described for **4m** below.

Methyl 5-Fluoro-3-biphenylylacetate (4m). A mixture of **4d** (13 g, 0.047 mol) and 43% HBF_4 (91 mL) was stirred at 0–5 °C for 10 min. To the mixture was added aqueous $NaNO_2$ (4.8 g in 19 mL of H_2O) at the same temperature with stirring. After 20 min the resulting precipitate was collected by filtration, washed with H_2O, and dried for 2 days at room temperature in a drying tube under reduced pressure using P_2O_5 as drying agent to give a fluoroborate salt (13.5 g) as pale brown crystals. On pyrolysis at 80–140 °C for 0,5 h this salt gave a black solution, which was shaken with chloroform (100 mL). The chloroform layer was separated, washed with H_2O, dried over $MgSO_4$, and concentrated. The residual black oil (8.2 g) was chromatographed on silica gel using benzene as eluent to give **4m** (5.7 g) as a pale yellow oil, which on distillation gave analytically pure **4m** (4.55 g, 39%), bp 156–158 °C (3 mm), as a colorless oil: IR (liquid film) 1745, 1615 cm^{-1}; NMR ($CDCl_3$) δ 3.63 (s, 2 H), 3.67 (s, 3 H), 6.87–7.63 (m, 8 H).

Methyl 2-(4′,5-Disubstituted-3-biphenylyl)propionates (4o–v). Compounds **4o–v** were prepared from **4g–n** by a similar method to that described for **4o** below.

Methyl 2-(3-Biphenylyl)propionate (4o). To a stirred solution of aqueous NaOH (2.3 g in 29 mL of H_2O) was added *n*-$Bu_4N^+HSO_4^-$ (9.9 g, 0.0292 mol). To this was added a mixture of **4g** (13.3 g, 0.0146 mol), methyl iodide (8.3 g, 0.0584 mol), and CH_2Cl_2 (29 mL) with vigorous stirring. The mixture was stirred for an additional 4 h at room temperature. The CH_2Cl_2 layer was separated and concentrated. To the residue was added ether, and then the precipitated *n*-$Bu_4N^+I^-$ was removed by filtration and washed with ether. The filtrate and ether washings were combined and then concentrated to give a pale yellow oil, which was a mixture of the desired **4o** and unchanged **4g** (TLC analysis). To accomplish complete α-methylation of **4g**, this mixture was again treated with the same quantity of reactants according to the method described above; workup was carried out in a similar way. The residual pale yellow oil was chromatographed on silica gel using (*n*-hexane–benzene, 1:1) as eluent to give crude **4o**, which on distillation gave pure **4o** (2.3 g, 66%), bp 156–157 °C (2 mm), as a colorless oil: IR (liquid film) 1735, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.51 (d, 3 H, J = 7 Hz), 3.62 (s, 3 H), 3.76 (q, 1 H, J = 7 Hz), 7.03–7.72 (m, 9 H). Yields and melting points (or boiling points) of compounds of type **4** are listed in Table I.

4′,5-Disubstituted 3-Biphenylylacetic Acids and Their Derivatives (5a–v). Compounds **5a–v** were prepared from **4a–v** by a similar method to that described for **5a** below.

5-Acetamido-3-biphenylylacetic Acid (5a). A mixture of **4a** (5 g, 0.0176 mol), methanol (50 mL), and aqueous NaOH (0.78 g in 10 mL of H_2O) was heated under reflux for 1 h and concentrated. The residue was taken up in H_2O (25 mL), and the aqueous solution was washed with ethyl acetate and then acidified with 10% HCl to give crude **5a** (3.25 g, 70%), mp 166–168 °C, which on recrystallization from methanol gave analytically pure **5a** (2.82 g, 60%): mp 166–168 °C; IR (KBr) 3300, 1710, 1630, 1595 cm^{-1}; NMR (Me_2SO-d_6) δ 2.09 (s, 3 H) 3.64 (s, 2 H), 7.18–8.0 (m, 8 H), 9.98 (br s, 1 H, exchangeable with D_2O) ~10–12 (1 H, exchangeable with D_2O).

In cases of **5d–f**, acidification of the aqueous solution was carried out by the use of AcOH. Yields and melting points (or boiling points) of compounds of type **5** are listed in Table II.

Pharmacological Testing. Antiinflammatory activity was examined by the method of Winter et al.[11] Ten male SLC–SD rats were used for each group. The rat hind paw volume was measured by displacement in a water bath, and the test compound, as a suspension in a 0.5% sodium carboxymethylcellulose solution (0.5% CMC), was administered orally. Thirty minutes later, 0.1 mL of 1% carrageenan was injected subcutaneously into the plantar surface of the hind paw. Three hours later, paw volume was measured again. The increase in paw volume of the drug-treated rat was compared with that of the control group for calculation of the percent inhibition.

Analgesic activity was evaluated by the AcOH writhing assay.[12] Six male STD-ddY mice were used for each group. The test compound was administered orally as a suspension in 0.5% CMC. Thirty minutes later, 0.1 mL/10 g of 0.6% AcOH was injected into the peritoneal cavity, and then the frequency of the repeated characteristic writhing movements were measured for 20 min. The response of the drug-treated mouse was compared with the response using acetic acid alone.

Acute toxicity, expressed as a LD_{50} value calculated by the method of Weil,[13] was determined 168 h after a single ip injection to groups of four male ddY mice.

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New Antiarrhythmic Agents. 4. 1′-(Aminoalkyl)-1,2,3,4-tetrahydronaphthalene-1-spiro-3′-pyrrolidine-2′,5′-dione Derivatives

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A series of 33 1′-(Aminoalkyl)-1,2,3,4-tetrahydronaphthalene-1-spiro-3′-pyrrolidine-2′,5′-dione derivatives was tested for antiarrhythmic and toxic effects in mice and dogs. In mice, 31 compounds produced some protection against chloroform-induced tachyarrhythmias at subcutaneous doses of 100 mg/kg, and 6 compounds produced no detectable toxicity at doses protecting 80% or more of the animals. Seven of the more potent and nontoxic derivatives were tested in dogs with surgically induced myocardial infarctions. All produced distinct antiarrhythmic effects at doses considerably lower than doses of lidocaine or tocainide producing comparable effects. The principal toxic effects observed in dogs were convulsion and depression of intracardiac conduction; they occurred generally at higher doses than those leading to antiarrhythmic effect. Several compounds also suppressed digitalis-induced arrhythmias in anesthetized dogs. Half-lives and total body clearance in dogs were determined for three compounds; two had half-lives comparable to that of tocainide, a long-acting, orally active antiarrhythmic agent, in clinical trials.

Antiarrhythmic agents are now widely used in the treatment and prevention of life-threatening cardiac arrhythmias. However, despite their widespread use, none of the presently available agents are ideal; each has its shortcoming.[1] The need for more effective and/or safer agents for treating arrhythmias is reflected in the growing list of new compounds undergoing clinical trial, for example, amiodarone, aprindine, ethmozin, mexiletine, tocainide, and verapamil.[2]

In considering possible approaches to the development of new agents, we were cognizant that many, if not all, direct-acting antiarrhythmic agents possess local anesthetic actions,[3] including quinidine, procainamide, bretylium, disopyramide, aprindine, and mexiletine. Conversely, many local anesthetic agents have antiarrhythmic effects,[4] including procaine, dibucaine, tetracaine, hexylcaine, piperocaine, prilocaine, mepivacaine, and bupivacaine. Lidocaine is a striking example of this interrelation, since it is used for both its local anesthetic and antiarrhythmic effects. The local anesthetic and antiarrhythmic effects

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