Nonsteroidal Antiinflammatory Agents. 1. 5-Alkoxy-3-biphenylylacetic Acids and Related Compounds as New Potential Antiinflammatory Agents

Yasumitsu Tamura,

Faculty of Pharmaceutical Sciences, Osaka University, 133-1, Yamada-kami, Suita, Osaka, Japan

Yoshihiko Yoshimoto,* Katsutoshi Kunimoto, Shinichi Tada, Toshio Tomita, Toshiyuki Wada, Eisuke Seto, Masao Murayama, Yoshihisa Shibata, Akira Nomura, and Katsuya Ohata

Research Laboratories, Nippon Shinyaku Co., Ltd., 14, Nishinosho-Monguchi-cho, Kisshoin, Minami-ku, Kyoto, Japan.
Received March 15, 1976

A series of 5-alkoxy-3-biphenylylacetic acids and related compounds was prepared as potential antiinflammatory agents. Among them, 4'-chloro-5-methoxy-3-biphenylylacetic acid (**6p**) (DKA-9) showed excellent antiinflammatory and analgesic activities in biological tests. Structure–activity relationships are discussed.

Recently many aryl- and heteroarylacetic acids having potent antiinflammatory activities have appeared in the literature.[1] Our own efforts in this area have led to the synthesis of the title compounds which exhibit antiinflammatory activity. We first prepared 5-methoxy-3-biphenylylacetic acid (**6f**) and observed that it suppressed considerably carrageenan-induced edema in the rat paw. On the basis of this observation, we have prepared a series of the title compounds and examined them for antiinflammatory and analgesic activities. Among them, 4'-chloro-5-methoxy-3-biphenylylacetic acid (**6p**) showed excellent activities and was selected as a candidate for clinical trials. In this paper, we describe the synthesis of the title compounds and discuss the structure–activity relationships on the basis of the screening data.

Results and Discussion

Chemistry. The synthetic route of compounds of type **6** is outlined in Scheme I. For example, 4'-chloro-5-methoxy-3-biphenylylacetic acid (**6p**) was prepared as follows. Condensation of 4-chlorobenzaldehyde with acetone in the presence of 1% sodium hydroxide gave a 91% yield of 4-chlorobenzalacetone (**1h**). Condensation of **1h** with diethyl malonate in methanol containing an equimolar amount of sodium methoxide, followed by hydrolysis and decarboxylation, gave 5-(4-chlorophenyl)cyclohexane-1,3-dione (**2i**) in 95% yield. Chlorination of **2i** with phosphorus oxychloride in toluene in the presence of sodium carbonate gave 3-chloro-5-(4-chlorophenyl)-2-cyclohexen-1-one (**3i**) in 84% yield. Treatment of **3i** with sodium methylacetoacetate in toluene resulted in condensaton and thermal decarboxylation[2] to give methyl 3-oxo-5-(4-chlorophenyl)-1-cyclohexen-1-ylacetate (**4i**) in 79% yield. Aromatization and simultaneous O-methylation[2] of **4i** with Br_2 in benzene containing methanol gave methyl 4'-chloro-5-methoxy-3-biphenylylacetate (**5i**) in 62% yield. Hydrolysis of **5i** with aqueous methanolic sodium hydroxide gave **6p** in 89% yield. These experimental procedures were shown to be widely applicable for other compounds of type **6**.

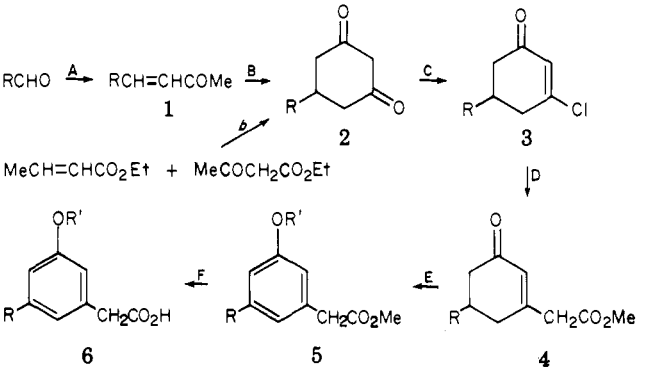
Modifications were made on the acidic group of **6p** as outlined in Scheme II.

Pharmacology. The compounds **6a–m**, **6o–w**, and **20** shown in Table III and **7**, **8a,b**, **9**, **12–17**, **19**, and **5i** in Table IV were tested for antiinflammatory and analgesic activities and acute toxicities by the methods described in the Experimental Section (see Pharmacological Testing).

As to the antiinflammatory activity, 3-methoxyphenylacetic acid (**20**), which is considered to be a parent skeletal compound, showed no significant activity. Substitution at position 5 of **20** with methyl, isopropyl, cyclohexyl, *p*-tolyl, and 4-methoxyphenyl groups resulted in no improvement of the activity (cf. **6a,d,e,l,m**). On the other hand, introduction of phenyl and halogenated phenyl groups into position 5 of **20** markedly increased the activity (cf. **6f,o,p,v,w**), and 4'-chloro-5-methoxy-3-biphenylylacetic acid (**6p**) (DKA-9) showed the highest activity with an ED_{50} of 11 mg/kg and a comparatively low toxicity among the compounds tested. On the basis of these observations we suggest that position 5 of **20** requires a lipophilic group and that 4-chlorophenyl is the best. Concerning the 5-methoxy group and the 3-acetic acid group of **6p**, changing the former to hydroxy, ethoxy, *n*-propoxy, *n*-butoxy, isobutoxy, and *n*-pentyloxy groups (cf. **7**, **6q–u**) and the latter into methyl ester, ethyl ester, ethanol, carboxylic acid, propionic acid, carboxamide, and hydroxamic acid groups (cf. **5i**, **15**, **9**, **19**, **12**, **13**, **14**) caused a decrease or destruction in activity.

As to the analgesic activity, most of the compounds tested were found to be weak (**6m,o**; ED_{50} = 165 and 195 mg/kg, respectively) or inactive (ED_{50} > 200 mg/kg) except for **6p** (ED_{50} = 38 mg/kg) and ibuprofen [ED_{50} (95% confidence limits) = 69 (35–135) mg/kg].

Scheme I. Synthetic Route of 5-Alkoxy-3-biphenylylacetic Acids and Related Compounds[a]

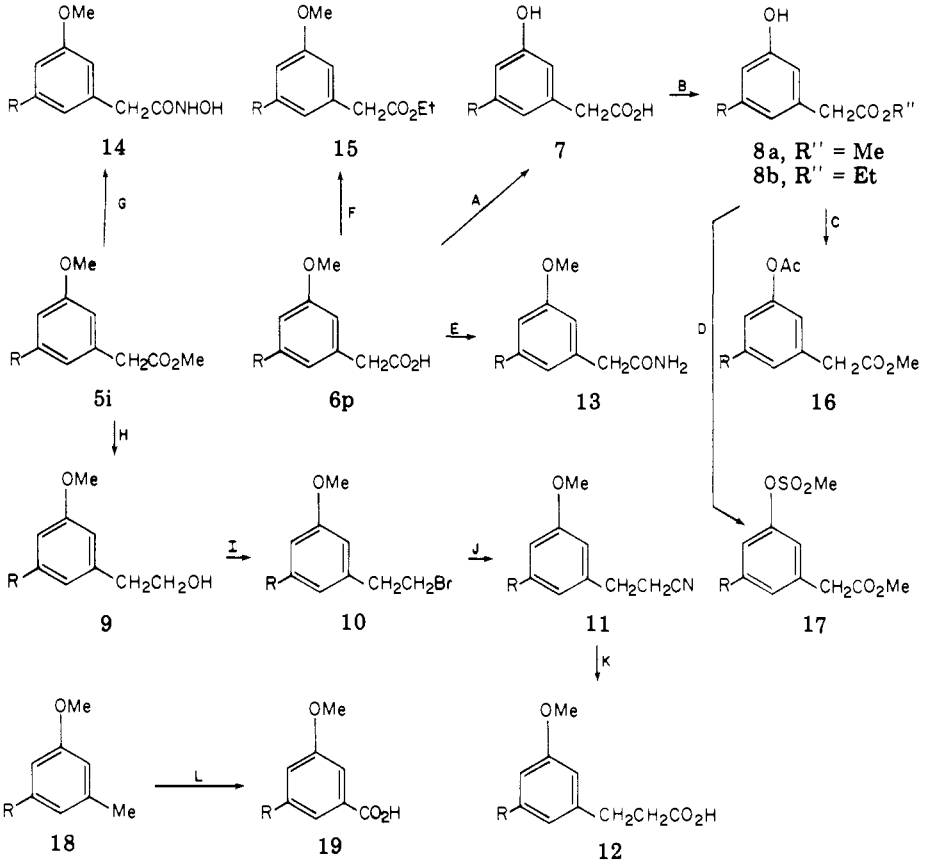


[a] Reagents for method A, 1% NaOH, Me_2CO, H_2O; B, $CH_2(COOEt)_2$, Na, MeOH; C, Na_2CO_3, $POCl_3$, toluene or PCl_3, $CHCl_3$; D, Na, $MeCOCH_2COOMe$, toluene; E, Br_2, R'OH, C_6H_6; F, NaOH, H_2O, MeOH. [b] Only 5-methylcyclohexane-1,3-dione (2a) was prepared by this method.

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 were within ±0.4% of the calculated values. IR spectra were obtained with a Hitachi 215 spectrometer. NMR spectra were

Scheme II. Preparation of Derivatives of 4'-Chloro-5-methoxy-3-biphenylylacetic Acid[a,b]



[a] Reagents for method A, 48% HBr, AcOH; B, H_2SO_4, C_6H_6, MeOH (or EtOH); C, Ac_2O, pyridine; D, $MeSO_2Cl$, pyridine; E, $SOCl_2$, C_6H_6, 28% NH_3; F, H_2SO_4, EtOH, C_6H_6; G, Na, $NH_2OH \cdot HCl$, MeOH; H, $LiAlH_4$, ether; I, PBr_3, CCl_4; J, NaCN, EtOH, H_2O; K, H_2SO_4, AcOH, H_2O; L, $KMnO_4$, H_2O, pyridine. [b] R = 4-chlorophenyl.

determined on a Nichiden-Varian Model NEVA A-60D spectrometer. The IR and NMR spectra of all new compounds were consistent with their structures.

4-Substituted 3-Buten-2-ones (1a–j). 5-Methyl-3-hexen-2-one (1a) and 4-cyclohexyl-3-buten-2-one (1b) were prepared by the known method.[3,4] Compounds 1c–j were prepared from the corresponding aldehyde by a similar method to that described for 4-chlorobenzalacetone (1h) below.

4-Chlorobenzalacetone (1h). A mixture of 4-chlorobenzaldehyde (281 g, 2 mol), acetone (319.4 g), and H_2O (405 mL) was heated with stirring at 65 °C. To the mixture 1% NaOH (500 mL) was added dropwise at such a rate that the temperature was maintained at 65 °C. After the addition, the mixture was heated at this temperature for 2.5 h, then cooled, and neutralized with 10% HCl. A yellow oil which separated was extracted with benzene. The extracts was washed with saturated NaCl, dried over $MgSO_4$, and concentrated. The residual oil (361 g) was distilled to give 1h as a pale yellow oil (324 g, 90%): bp 145–147 °C (5 mm), which on standing solidified as pale yellow crystals, mp 55–57 °C (lit.[10] mp 59–59.5). Yields and boiling points (or melting points) of other compounds of type 1 were as follows: **1c**, R = Ph,[5] bp 122–124 °C (8 mm) (88%); **1d**, R = 4-MePh,[6] bp 152–154 °C (16 mm) (92%); **1e**, R = 4-MeOPh,[7] bp 175–176 °C (13 mm) (91%); **1f**, R = 3,4-methylenedioxyphenyl,[8] mp 109–110 °C (88%); **1g**, R = 2-ClPh,[9] bp 150–152 °C (10 mm) (87%); **1i**, R = 2,4-Cl_2Ph, bp 155–157 °C (5 mm), mp 82–83 °C (77%); **1j**, R = 4-FPh, bp 101–104 °C (5 mm) (83%).

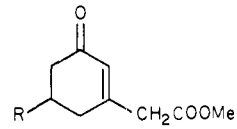
5-Substituted Cyclohexane-1,3-diones (2a–k). 5-Methylcyclohexane-1,3-dione (**2a**) was prepared by the known method.[11] Compounds **2b–k** were prepared from **1a–j** by a similar method to that described below for **2i**.

5-(4-Chlorophenyl)cyclohexane-1,3-dione (2i). Sodium metal (4.6 g, 0.2 g-atom) was dissolved in absolute MeOH (75 mL). To this solution was added dropwise diethyl malonate (33.3 g, 0.208 mol) at 15–25 °C and then 1h at 60 °C. The reaction mixture was refluxed with stirring for 4 h, diluted with H_2O (100 mL), concentrated to half volume, and made alkaline with aqueous NaOH (17.6 g of NaOH in 70 mL of H_2O). The alkaline solution was warmed at 80 °C for 40 min and, after cooling, washed with benzene. To this solution concentrated HCl (70 mL) was added under reflux when a violent CO_2 evolution was observed. A precipitated pale yellow powder was washed with acetone to give **2i** (42.2 g, 95%): mp 193–194 °C (lit.[12] mp 197–199 °C). Yields and melting points of other compounds of type 2 were as follows: **2b**, R = *i*-Pr,[13] mp 62–64 °C (66%); **2c**, R = cyclohexyl,[14] mp 154–156 °C (67%); **2d**, R = Ph,[15] mp 187–189 °C (93%); **2e**, R = 4-MePh, mp 165–167 °C (67%); **2f**, R = 4-MeOPh,[16] mp 177–178.5 °C (67%); **2g**, R = 3,4-methylenedioxyphenyl, mp 174–176 °C (88%); **2h**, R = 2-ClPh, mp 153–154 °C (97%); **2j**, R = 2,4-Cl_2Ph, mp 179–181 °C (68%); **2k**, R = 4-FPh, mp 181–185 °C (88%).

3-Chloro-5-substituted 2-Cyclohexen-1-ones (3a–k). 3-Chloro-5-methyl-2-cyclohexen-1-one (**3a**), 3-chloro-5-isopropyl-2-cyclohexen-1-one (**3b**), and 3-chloro-5-cyclohexyl-2-cyclohexen-1-one (**3c**) were prepared by the known method.[17] Compounds **3d–k** were prepared from **2d–k** by a similar method to that described for **3i** below.

3-Chloro-5-(4-chlorophenyl)-2-cyclohexen-1-one (3i). To a stirred suspension of **2i** (66.6 g, 0.33 mol) and Na_2CO_3 (10.6 g, 0.33 mol) in toluene at 90–100 °C was added dropwise $POCl_3$ (15.3 g, 0.1 mol) and stirring was continued for a period of 4.5 h, during which time Na_2CO_3 (10.6 g) and $POCl_3$ (15.3 g) (after 1.5 h) and further $POCl_3$ (3.9 g) (after 2.5 h) were added. Stirring was continued for an additional 2 h. To the cooled reaction mixture H_2O (300 mL) was added. The organic layer was separated, washed with 2% NaOH and then H_2O, dried over $MgSO_4$, and concentrated. The reddish brown oil was distilled to give **3i** (60.6 g, 84%), bp 166 °C (2 mm), as a colorless oil. Anal. ($C_{12}H_{10}OCl_2$) C, H, Cl. Yields and boiling points of other compounds of type 3 were as follows: **3d**, R = Ph,[18] bp 152–154 °C (6 mm) (87%); **3e**, R = 4-MePh, bp 167–168 °C (6 mm) (68%); **3f**, R = 4-MeOPh,[19] bp 185–188 °C (5 mm) (83%); **3g**, R = 3,4-methy-

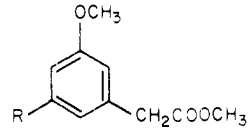
Table I. Methyl 3-Oxo-5-substituted 1-Cyclohexen-1-ylacetates



Compd no.	R	Mp or bp (mm), °C	Yield, %	2,4-DNP,[a] mp, °C	Analyses[b]
4a	Me	165–170 (4)	53	109–112	C, H, N
4b	*i*-Pr	141–144 (5)	91	100–102	C, H, N
4c	Cyclohexyl	172–178 (6)	82	113–114	C, H, N
4d	Ph	197–205 (3)	83	158–160	C, H, N
4e	4-MePh	62–63	87		C, H
4f	4-MeOPh	73–74	80		C, H
4g	3,4-Methylenedioxyphenyl	220–230 (5)	79	152–153	C, H, N
4h	2-ClPh	200–208 (5)	83	148–150	C, H, N, Cl
4i	4-ClPh	76–78.5	79		C, H, Cl
4j	2,4-Cl_2Ph	77–77.5	70		C, H, Cl
4k	4-FPh	178–182 (3)	76	152–153	C, H, N, F

[a] 2,4-DNP = 2,4-dinitrophenylhydrazone. [b] Analyses of the elements were determined on the corresponding 2,4-DNP when the product was an oil.

Table II. Methyl 5-Methoxy-3-biphenylylacetates and Related Phenylacetates



Compd no.	R	Mp or bp (mm), °C	Yield, %	Formula	Analyses
5a	Me	126–127 (9)	53	$C_{11}H_{14}O_3$	C, H
5b	*i*-Pr	120–124 (3)	52	$C_{13}H_{18}O_3$	C, H
5c	Cyclohexyl	164–168 (5)	73	$C_{16}H_{22}O_3$	C, H
5d	Ph	195–200 (5)	76	$C_{15}H_{14}O_3$	C, H
5e	4-MePh	34.5–35.5[a]	75	$C_{17}H_{18}O_3$	C, H
5f	4-MeOPh	220–221 (5)	79	$C_{17}H_{18}O_4$	C, H
5g	3,4-Methylenedioxyphenyl	214–217 (3)	48	$C_{17}H_{16}O_5$	C, H
5h	2-ClPh	195–202 (7)	74	$C_{16}H_{15}O_3Cl$	C, H, Cl
5i	4-ClPh	54.5–56[a]	62	$C_{16}H_{15}O_3Cl$	C, H, Cl
5j	2,4-Cl_2Ph	201–204 (3)	80	$C_{16}H_{14}O_3Cl_2$	C, H, Cl
5k	4-FPh	178–180 (5)	75	$C_{16}H_{15}O_3F$	C, H, F

[a] Recrystallized from methanol.

lenedioxyphenyl, bp 200–201 °C (5 mm) (17%); **3h**, R = 2-ClPh, bp 171–176 °C (8 mm) (65%); **3j**, R = 2,4-Cl_2Ph, bp 205–207 °C (10 mm) (78%); **3k**, R = 4-FPh, bp 101–103 °C (4 mm) (65%).

Methyl 3-Oxo-5-substituted 1-Cyclohexen-1-ylacetates (4a–k). Compounds 4a–k were prepared from **3a–k** by a method similar to that described for methyl 3-oxo-5-(4-chlorophenyl)-1-cyclohexen-1-ylacetate (**4i**) below.

To a stirred suspension of sodium metal (10.2 g, 0.44 g-atom) in absolute toluene (200 mL) was added dropwise methyl acetoacetate (102 g, 0.87 mol) at such a rate that the solvent was maintained at gentle reflux. To this, **3i** (52.5 g, 0.44 mol) was rapidly added, and the mixture was heated at 90 °C for 3 h and cooled. To the reaction mixture was added AcOH (20 g) and H_2O (100 mL). The organic layer was separated, washed with H_2O, saturated $NaHCO_3$, and then H_2O, dried over $MgSO_4$, and concentrated. The residual reddish brown oil crystallized when its MeOH solution was kept in the freezer at −20 °C. The crystals were collected, washed with a small amount of MeOH, and dried to afford white crystalline **4i** (34.5 g), mp 74.5–77 °C. The mother liquor and the MeOH washing were combined and concentrated. Distillation of the residual oil gave a pale yellow oil (18 g), bp 200 °C (2 mm), whose MeOH solution on standing at −20 °C gave an additional crop of **4i** (13 g): mp 70–73 °C; total yield 47.5 g (79%). Recrystallization of **4i** from MeOH afforded an analytical sample, mp 76–78.5 °C. Anal. ($C_{15}H_{15}O_3Cl$) C, H, Cl. Yields and boiling points (or melting points) of compounds of type **4** are listed in Table I.

Methyl 5-Methoxy-3-biphenylylacetates and Related Phenylacetates (5a–k). Compounds **5a–k** were prepared from **4a–k** by a similar method to that described below for methyl 4′-chloro-5-methoxy-3-biphenylylacetate (**5i**).

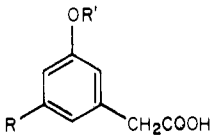
To a stirred mixture of **4i** (100 g, 0.36 mol), MeOH (50 mL), and benzene (500 mL) was added dropwise Br_2 (63 g, 0.397 mol) at such a rate that the temperature was maintained at 0–5 °C. The reaction mixture was stirred for an additional 1 h at room temperature and then washed with H_2O, 2% NaOH, and then H_2O, dried over $MgSO_4$, and concentrated. The resulting reddish brown oil was distilled to give a pale yellow oil (80.3 g), bp 210–211 °C (2 mm), which solidified on standing at −20 °C. Recrystallization from MeOH gave **5i** (64.8 g, 62%), mp 54.5–56 °C as white crystals. Anal. ($C_{16}H_{15}O_3Cl$) C, H, Cl. Yields and boiling points (or melting points) of compounds of type **5** are listed in Table II.

When the above aromatization of **4a,d,i** was carried out in the presence of primary and secondary alcohols other than MeOH, the corresponding 3- (or 5-) alkoxy derivatives were obtained. However, an ester exchange reaction occurred in these cases giving a mixture of methyl ester and the ester corresponding to the alcohol used. Therefore, the product was hydrolyzed to the corresponding acetic acids (**6b,c,g–i,k,q–u**) without further purification.

5-Alkoxy-3-biphenylylacetic Acids and Related Phenylacetic Acids (6a–w). Compounds **6a–w** were prepared by a method similar to that described below for 4′-chloro-5-methoxy-3-biphenylylacetic acid (**6p**).

A mixture of **5i** (11.6 g, 0.04 mol), MeOH (17.5 mL), and aqueous NaOH (1.75 g of NaOH in 17.5 mL of H_2O) was heated at reflux for 1 h and concentrated. The residue was taken up in H_2O (50 mL), and the aqueous solution was washed with Et_2O and acidified with 18% HCl giving crude **6p** (10.8 g), mp 148–152

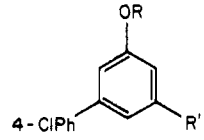
Table III. Chemical and Pharmacological Data of 5-Alkoxy-3-biphenylylacetic Acids and Related Phenylacetic Acids



Compd no.	R	R'	Mp, °C (recrystn solvent)[a]	Yield, %	Formula[b]	Inhibn of carrageenan-induced edema, ED_{50}, mg/kg po[i]	Acute toxicity, LD_{50}, mg/kg ip[i]
6a	Me	Me	87-88 (A)	55	$C_{10}H_{12}O_3$	>100	673 (477-949)
6b	Me	*n*-Bu	60-61 (A)	27[c]	$C_{13}H_{18}O_3$	>100	673 (477-949)
6c	Me	*i*-Bu	98-99 (A)	40[c]	$C_{13}H_{18}O_3$	>100	1001 (755-1325)
6d	*i*-Pr	Me	48-49 (A)	38	$C_{12}H_{16}O_5$	>100	1601 (1421-2121)
6e	Cyclohexyl	Me	64-65 (B)	40	$C_{15}H_{20}O_3$	>100	564 (448-711)
6f	Ph	Me	143-144 (F)	70	$C_{15}H_{14}O_3$	60 (29-121)	566
6g	Ph	Et	119-121 (C)	42[d]	$C_{16}H_{16}O_3$	>100	400 (268-597)
6h	Ph	*n*-Pr	86-87.5 (C-D)	51[d]	$C_{17}H_{18}O_3$	>100	475 (336-674)
6i	Ph	*n*-Bu	74-75 (D)	45[d]	$C_{18}H_{20}O_3$	>100	>1600
6j	Ph	*i*-Bu	89-90 (C-D)	30[d]	$C_{18}H_{20}O_3$	>100	566
6k	Ph	*n*-Pentyl	68-69 (D)	22[d]	$C_{19}H_{22}O_3$	>100	1131
6l	4-MePh	Me	141-142 (C)	67	$C_{16}H_{16}O_3$	>100	566
6m	4-MeOPh	Me	146-147 (C)	58	$C_{16}H_{16}O_4$	>100	636 (557-727)
6n	3,4-Methylenedioxyphenyl	Me	119-120 (C)	21	$C_{16}H_{14}O_5$	NT[h]	NT[h]
6o	2-ClPh	Me	55-57 (C-A)	7[e]	$C_{15}H_{13}O_3Cl$	39 (16-94)	252 (193-329)
6p	4-ClPh	Me	151-153 (E)	89	$C_{15}H_{13}O_3Cl$	11 (4-30)	570 (520-624)
6q	4-ClPh	Et	121-122 (C-A)	46[f]	$C_{16}H_{15}O_3Cl$	51 (23-112)	284
6r	4-ClPh	*n*-Pr	102-103 (F)	31[f]	$C_{17}H_{17}O_3Cl$	97 (58-161)	400 (268-597)
6s	4-ClPh	*n*-Bu	120-122 (E)	31[f]	$C_{17}H_{17}O_3Cl$	>100	237 (168-336)
6t	4-ClPh	*i*-Bu	87-88 (A)	44[f]	$C_{18}H_{19}O_3Cl$	>100	139 (86-227)
6u	4-ClPh	*n*-Pentyl	68-69 (D)	29[f]	$C_{19}H_{21}O_3Cl$	>100	475 (336-674)
6v	2,4-Cl_2Ph	Me	98.5-100 (D)	47	$C_{15}H_{20}O_3Cl_2$	70 (30-168)	336 (238-474)
6w	4-FPh	Me	125-125.5 (C)	55	$C_{15}H_{13}O_3F$	50 (29-85)	565
20[g]	H	Me				>100	504 (310-820)
Ibuprofen						25 (12-50)	336 (238-476)

[a] A = *n*-hexane, B = petroleum ether, C = benzene, D = ligroine, E = aqueous methanol, F = aqueous ethanol. [b] All compounds were analyzed for C, H, and halogen atom. [c] Overall yield from 4a. [d] Overall yield from 4d. [e] Recrystallization of 6o is very difficult. [f] Overall yield from 4i. [g] This compound was obtained by hydrolysis of methyl 3-methoxyphenylacetate prepared as described in ref 2. [h] Not tested. [i] 95% confidence limits in parentheses.

Table IV. Pharmacological Data of Derivatives of 4'-Chloro-5-methoxy-3-biphenylylacetic Acid



Compd no.	R	R'	Inhibn of carrageenan-induced edema, ED_{50}, mg/kg po[a]	Acute toxicity, LD_{50}, mg/kg ip[a]
7	H	CH_2COOH	>100	141
8a	H	CH_2COOMe	>100	>1600
8b	H	CH_2COOEt	>100	>1600
9	Me	CH_2CH_2OH	47 (25-89)	673 (476-951)
12	Me	CH_2CH_2COOH	>100	284
13	Me	CH_2CONH_2	>100	>1600
14	Me	$CH_2CONHOH$	>100	>1600
5i	Me	CH_2COOMe	35 (16-73)	1600
15	Me	CH_2COOEt	29 (13-64)	1130 (694-1841)
16	Ac	CH_2COOMe	>100	>1600
17	$MeSO_2$	CH_2COOMe	>100	1131
19	Me	COOH	>100	1131
Ibuprofen			25 (12-50)	336 (238-476)

[a] 95% confidence limits in parentheses.

°C, which on recrystallization from aqueous MeOH gave an analytical sample of **6p** (9.8 g, 89%), mp 151–153 °C. Anal. ($C_{15}H_{13}O_3Cl$) C, H, Cl. Yields and melting points (or boiling points) of compounds of type **6** are listed in Table III.

2-(4'-Chloro-5-methoxy-3-biphenylyl)ethanol (9). To a stirred suspension of $LiAlH_4$ (3.25 g) in absolute ether (300 mL) was added dropwise a solution of **5i** (29 g, 0.099 mol) in absolute ether at such a rate that the solvent was maintained at gentle reflux and the mixture was stirred for an additional 2 h at the same temperature. The cooled mixture was treated with H_2O (150 mL) and then with 10% H_2SO_4 (60 mL). The ether layer was separated, washed with H_2O, dried over $MgSO_4$, and concentrated

to dryness. The residual solid was recrystallized from ligroine–benzene to give **9** (23.2 g, 89%) as white crystals, mp 79–81 °C. Anal. ($C_{15}H_{15}O_2Cl$) C, H, Cl.

2-(4′-Chloro-5-methoxy-3-biphenylyl)ethyl Bromide (10). To a stirred suspension of **9** (13.2 g, 0.05 mol) in CCl_4 (60 mL) was added a solution of PBr_3 (6 g, 0.022 mol) in CCl_4 with cooling. The mixture was stirred for 2 h at room temperature and then refluxed for 30 min. The cooled reaction mixture was poured onto ice–water and extracted with ether. The ether layer was washed with H_2O, dried over $MgSO_4$, and concentrated to dryness. The residual solid was recrystallized from EtOH to give **10** (11.4 g, 61%) as white needles, mp 81–82.5 °C. Anal. ($C_{15}H_{14}OBrCl$) C, H, Br, Cl.

3-(4′-Chloro-5-methoxy-3-biphenylyl)propionitrile (11). To a solution of NaCN (0.915 g) in EtOH (30 mL) was added dropwise a hot solution of **10** (4.405 g) in EtOH. The mixture was heated at reflux for 5 h. Additional NaCN (1.2 g) was added and the mixture was heated for additional 10 h and then concentrated. The residue dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried over $MgSO_4$, and concentrated to dryness. The residual solid was chromatographed on silica gel (45 g) with (benzene–AcOEt, 4:1) to give **11** (2.15 g, 62%), mp 95–99 °C. It was recrystallized from benzene–petroleum ether to give an analytical sample, mp 99–101 °C. Anal. ($C_{16}H_{14}NOCl$) C, H, Cl.

3-(4′-Chloro-5-methoxy-3-biphenylyl)propionic Acid (12). A mixture of **11** (2 g), H_2SO_4 (2 mL), AcOH (2 mL), and H_2O (2 mL) was stirred at 100–110 °C for 14 h. The precipitates were dissolved in 5% NaOH. The alkaline solution was washed with Et_2O and acidified with 18% HCl, giving precipitates which were recrystallized from aqueous EtOH to give **12** (1.4 g, 65%) as white crystals, mp 122–122.5 °C. Anal. ($C_{16}H_{15}O_3Cl$) C, H, Cl.

4′-Chloro-5-methoxy-3-biphenylcarboxylic Acid (19). To a stirred mixture of 4′-chloro-3-methoxy-5-methylbiphenyl (**18**) [prepared from 3-methyl-5-(4-chlorophenyl)-2-cyclohexen-1-one by the procedure of Kosower[20]] (6.5 g), pyridine (110 mL), and H_2O (110 mL) was added $KMnO_4$ (17.5 g) in small portions at 90–95 °C during 4 h. The precipitated MnO_2 was removed by filtration and washed with hot acetone. The filtrate and washing were combined and concentrated. The residue was washed with Et_2O and acidified with 18% HCl. The precipitates were recrystallized from MeOH to give an analytical sample of **19** (2.4 g, 33%), mp 173–175 °C. Anal. ($C_{14}H_{11}O_3Cl$) C, H, Cl.

4′-Chloro-5-methoxy-3-biphenylylacetamide (13). A mixture of **6p** (13.85 g, 0.05 mol), $SOCl_2$ (9 g), and benzene (100 mL) was refluxed for 1 h. Excess $SOCl_2$ and benzene were removed and the resulting crude acid chloride was treated with 28% aqueous NH_3, giving crystals which were recrystallized from EtOH to give an analytical sample of **13** (9.5 g, 65%) as white crystals, mp 185–187 °C. Anal. ($C_{15}H_{14}NO_2Cl$) C, H, Cl.

4′-Chloro-5-methoxy-3-biphenylylacetohydroxamic Acid (14). Sodium metal (1.96 g, 0.082 g-atom) was dissolved in MeOH (100 mL). To this solution was added $NH_2OH{\cdot}HCl$ (5.6 g, 0.082 mol) and **5i** (5.8 g, 0.02 mol). The mixture was stirred at room temperature for 20 min, then refluxed for 30 min, allowed to stand for 2 days at room temperature, and concentrated. The residual paste was triturated with benzene giving a solid. Recrystallization of the solid from aqueous MeOH gave **14** (2.3 g, 38%), mp 149–152 °C. Anal. ($C_{15}H_{14}NO_3Cl$) C, H, N, Cl.

4′-Chloro-5-hydroxy-3-biphenylylacetic Acid (7). A suspension of **6p** (5 g, 0.018 mol) in the mixture of 48% HBr (50 mL) and AcOH (25 mL) was heated at reflux for 10 h and allowed to stand overnight at room temperature. The precipitates (4.7 g, 100%), mp 140–144 °C, were recrystallized from benzene to give an analytical sample of **7** as white needles, mp 141–143 °C. Anal. ($C_{14}H_{11}O_3Cl$) C, H, Cl.

Methyl 4′-Chloro-5-hydroxy-3-biphenylylacetate (8a). A mixture of **7** (13.0 g, 0.048 mol), MeOH (20 mL), benzene (100 mL), and H_2SO_4 (3 drops) was refluxed for 8 h and cooled. The reaction mixture was washed with saturated $NaHCO_3$ and then H_2O, dried over $MgSO_4$, and concentrated. The residue was recrystallized from benzene to give **8a** (10 g, 72%) as white needles, mp 129–131 °C. Anal. ($C_{15}H_{13}O_3Cl$) C, H, Cl.

Ethyl 4′-Chloro-5-hydroxy-3-biphenylylacetate (8b) and Ethyl 4′-Chloro-5-methoxy-3-biphenylylacetate (15). Compound **8b** [mp 94–96 °C. Anal. ($C_{16}H_{15}O_3Cl$) C, H, Cl] and **15** [bp 223–225 °C (8 mm). Anal. ($C_{17}H_{17}O_3Cl$) C, H, Cl] were prepared by a similar method for **8a** from **7** and **6p** in 86 and 84% yield, respectively.

Methyl 5-Acetoxy-4′-chloro-3-biphenylylacetate (16). To a solution of **8a** (2.76 g, 0.01 mol) in pyridine (20 mL) was added Ac_2O (1.53 g) at room temperature. The mixture was allowed to stand for 2 days. Pyridine was removed under reduced pressure and the residual oil was distilled to give **16** (2.6 g, 82%) as colorless oil, bp 238–240 °C (8 mm), which on standing solidified. The solid was recrystallized from ligroine to give an analytical sample of **16** (2.2 g), mp 82.5–84 °C. Anal. ($C_{17}H_{15}O_4Cl$) C, H, Cl.

Methyl 4′-Chloro-5-mesyloxy-3-biphenylylacetate (17). To a solution of **8a** (2.76 g) in pyridine (20 mL) was added $MeSO_2Cl$ (1.15 g) under ice cooling. The mixture was allowed to stand for 1 day. Pyridine was removed under reduced pressure. The residue was distilled to give **17** (2.5 g, 71%) as colorless oil, bp 262 °C (7 mm). Anal. ($C_{16}H_{15}O_5ClS$) C, H, Cl, S.

Pharmacological Testing. Antiinflammatory activity was examined by the method of Winter et al.[21] Ten male Wistar rats weighing 120–150 g were used for each group. The rat hind paw volume was measured by displacement in a mercury 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 edema 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, and least-squares regression lines were calculated for the probit percent response vs. log dose, and the ED_{50} (50% inhibition dose) values were calculated from the regression line constants.

Analgesic activity was evaluated by Haffner's method[22] with slight modifications. Eight male ddY mice weighing 25–30 g were used in each group. The test compound suspended in 0.5% CMC was administered ip with a threshold dose (5 mg/kg sc) of morphine hydrochloride. Compounds were examined for their ability to prevent the pseudoavoidance reflexes such as biting, squeaking, and looking backward induced by tail pinching with a forceps, and the ED_{50} was calculated by the method of Litchfield and Wilcoxon.[23]

Acute toxicity was expressed as a LD_{50} value calculated by the method of Weil.[24] It was determined 168 h after a single ip injection to groups of four male ddY mice.

References and Notes

(1) *Annu. Rep. Med. Chem., 1965–1974*, chapters on "Nonsteroidal Antiinflammatory Agents", and references cited therein.
(2) Y. Tamura, Y. Yoshimoto, M. Suzuki, and M. Terashima, *Chem. Ind. (London)*, 1410 (1970).
(3) R. Patrick and E. N. Eccott, *J. Chem. Soc.*, 905 (1930).
(4) O. Grummitt and J. Splitter, *J. Am. Chem. Soc.*, **74**, 3924 (1952).
(5) N. L. Drake and P. Allen, Jr., "Organic Syntheses", Collect Vol. I, 2nd ed, Wiley, New York, N.Y., 1956, p 77.
(6) V. Hanzlick and A. Bianchi, *Chem. Ber.*, **32**, 2282 (1899).
(7) A. Baeyer and V. Villiger, *Chem. Ber.*, **35**, 1189 (1902).
(8) P. Haber, *Chem. Ber.*, **24**, 617 (1891).
(9) K. v. Auwers and A. Kreuder, *Chem. Ber.*, **58**, 1974 (1925).
(10) R. E. Lutz, T. A. Martin, J. F. Codington, T. M. Amacker, R. K. Allison, N. H. Leake, R. J. Rowlett, Jr., J. D. Smith, and J. W. Wilson, *J. Org. Chem.*, **14**, 982 (1949).
(11) A. W. Crossley and N. Renouf, *J. Chem. Soc.*, 602 (1915).
(12) K. Schoen and I. J. Pachter, U.S. Patent 3 503 990 [*Chem. Abstr.*, **72**, P132515t (1970)].
(13) R. L. Frank and H. K. Hall, Jr., *J. Am. Chem. Soc.*, **72**, 1645 (1950).
(14) G. A. Kon, *J. Chem. Soc.*, 1792 (1926).
(15) K. W. Rosemund, H. Herzberg, and H. Schütt, *Chem. Ber.*, **87**, 1258 (1954).
(16) J. Baranowicz and W. Kirkor, *Soc. Sci. Lodz., Acta Chim.*, **9**, 159 (1964) [*Chem. Abstr.*, **63**, 4200c (1965)].
(17) (a) A. W. Crossley and H. LeSeur, *J. Chem. Soc.*, 110 (1903); (b) W. Hükel and K. Thiele, *Chem. Ber.*, **94**, 96 (1961).
(18) A. J. Boyd, P. H. Clifford, and M. E. Probert, *J. Chem. Soc.*, 1385 (1925).

(19) P. Chaudhuri, *J. Indian Chem. Soc.*, 21, 341 (1944).
(20) E. M. Kosower and G. S. Wu, *J. Org. Chem.*, 28, 633 (1963).
(21) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962).
(22) F. Haffner, *Dtsch. Med. Wochenschr.*, 55, 731 (1929).
(23) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, 96, 99 (1949).
(24) G. S. Weil, *Biometrics*, 8, 249 (1952).

5,6,7,8-Tetrahydroquinolines. 4.[1] Antiulcer and Antisecretory Activity of 5,6,7,8-Tetrahydroquinolinenitriles and -thioamides

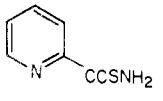
Doreen E. Beattie, Roger Crossley,* Adrian C. W. Curran, Geoffrey T. Dixon, David G. Hill, Anne E. Lawrence, and Robin G. Shepherd

Institute of Medical Research, Wyeth Laboratories, Huntercombe Lane South, Taplow, Maidenhead, Berkshire, SL6 OPH, England. *Received July 9, 1976*

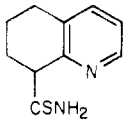
A number of 5,6,7,8-tetrahydroquinoline-8-nitriles and -8-thioamides and related compounds have been found to be potent inhibitors of basal gastric secretion in the pylorus-ligated rat and to afford protection against gastric erosions induced in rats by cold-restraint stress. Molecular manipulation has proved useful in determining factors necessary for such activity and structure–activity relationships are discussed. It has been shown that the most necessary requirements for activity are a pyridine nitrogen with its available lone pair and a primary or secondary thioamide. Also desirable is a six-membered carbocyclic ring with relative freedom from steric hinderance around the 8 position.

Although the etiology of peptic ulceration is not fully understood, it is thought to be multifactorial, and present therapy is largely concerned with the neutralization or inhibition of gastric acid secretion by use of antacids and anticholinergic agents. The main disadvantage of antacid therapy is that these agents have a very short duration of action[2] and it is well known that anticholinergic drugs have limited therapeutic value in depressing gastric secretion in peptic ulcer patients, because the doses effective in the inhibition of acid secretion cause unpleasant side actions associated with blockade of parasympathetic stimulation.[3] In recent years, a number of nonanticholinergic antisecretory agents have been reported. Among the most notable of these are pyridyl-2-thioacetamide (CMN 131),[4] 2-methoxy-*N*-methyl-2-(2-pyridyl)thioacetamide (SKF 59377),[5] 2-phenyl-2-(2-pyridyl)thioacetamide (SC 15396),[4] and the histamine H_2-receptor antagonists burimamide,[4] metiamide,[4] and cimetidine.[6]

We decided to explore a system 1 which by virtue of its shape would bear some resemblance to pyridyl-2-thioacetamide and at the same time provide a substrate for molecular manipulation in order to define more closely requirements for activity. The 5,6,7,8-tetrahydroquinoline (THQ) ring system is one such system and 5,6,7,8-tetrahydroquinoline-8-thiocarboxamide (**2**) showed a high level



1



2

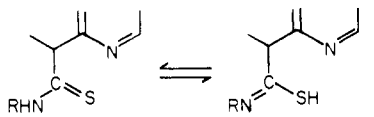
of antiulcer activity (erosion prevention in the cold-restraint rat) and antisecretory activity (pylorus-ligated rat) as shown in Table I.

There are many ways of investigating potential antiulcer activity. Acute gastric erosions can be induced in rats by imposing a stress situation, usually involving an element of immobilization,[7] or by a variety of chemical agents.[8] Various techniques are available for studying basal and chemically stimulated gastric acid secretion in both conscious and anesthetized animals.[9] The two tests described in this paper were considered the most suitable for primary screening purposes, in view of their wide acceptance and also because their nature is such that potential complications due to drug interactions are not involved. The doses used have been derived through experience, and because of the inherently more sensitive method for determining antisecretory activity these doses are one-third those used for the antiulcer test. Introduction of substituents into **2** and variation of carbocyclic ring size have enabled a series of analogues, Tables I and II, to be generated and these have been evaluated in the above two tests enabling structure–activity requirements to be delineated.

The tests used in this study may reflect different effects but they are so interrelated that separation of the effects is not possible; it may be that two independent actions of tetrahydroquinoline-8-thioamides are responsible for activity in the two screens *or* antiulcer activity may be a consequence of antisecretory activity. It is felt, however, that it is valid to consider the structure–activity relationship from the standpoint of the system having combined antiulcer–antisecretory activity especially as consideration of either one of the tests would lead to the same overall structure–activity relationships.

Replacement of sulfur by oxygen, e.g., **3** and **4**, results in a loss of activity, a feature which has been noted before[10] and which is not perhaps too surprising considering the different chemical nature of amides and thioamides.

It is when a change to secondary and tertiary thioamides is made that information about the necessity of the thioamide group becomes available. Some secondary thioamides **5–7** still retain respectable levels of activity (although slightly reduced compared with primary thioamides) so a change of primary to secondary is not undesirable per se, but the size of the substituent evidently is of importance. A change from secondary to tertiary **8** is detrimental which probably means that the thioamides need to be capable of existing at least, in some part, in the thiolimine form either by electron delocalization (**9**) or by



9

in vivo S-alkylation. Conversion of the thioamide into a thiazole **10** or imidazoline **11** or tetrahydropyrimidine **12**, features which have been associated with other antiul-