Table III. Effects of Indapamide and of Some Isoindoline Derivatives on Water and Electrolyte Excretion by Water-Loaded Rats[a]

compd	urine vol as a % of oral water load	urine Na^+, mequiv	urine K^+, mequiv	urine Na^+/K^+ ratio
4a	127.0 ± 4.457[b]	0.6927 ± 0.0504[b]	0.2398 ± 0.0278[b]	3.110 ± 0.3012[b]
4c	106.0 ± 7.199[b]	0.2629 ± 0.0452[b]	0.1657 ± 0.0213[b]	1.638 ± 0.2337[b]
4d	87.1 ± 5.453[b]	0.1090 ± 0.0302	0.1305 ± 0.0264	0.855 ± 0.1953
indapamide	130.6 ± 5.706[b]	0.7052 ± 0.0619[b]	0.2686 ± 0.0289[b]	2.757 ± 0.2452[b]
drug vehicle	68.3 ± 6.493	0.0780 ± 0.0180	0.1031 ± 0.0167	0.738 ± 0.0868

[a] The data refer to protocol B. Mean plus or minus standard errors are reported for the cumulative urinary excretion measured in the 4 h following oral administration of the drug tested. The data were obtained on five male and five female rats. All drugs were tested at a dose of 5 mg/kg. [b] $p < 0.05$ for statistical testing with respect to control group.

1-(Hydroxymethyl)-2-(4-chloro-3-sulfamoylbenzamido)-isoindoline (4c). A solution of 5.64 g (0.0137 mol) of **4b** in dry THF (80 mL) was added dropwise to a stirred suspension of 0.6 g (0.027 mol) of $LiBH_4$ in 50 mL of dry THF at 0 °C. The stirred mixture was refluxed for 2 h and then cooled to 0 °C during the slow addition of 35 mL of H_2O. The inorganic precipitate was filtered and thoroughly washed with THF. The filtrates were collected, dried with Na_2SO_4, and concentrated to dryness in vacuo to give 4 g of crude **4c**. Anal. ($C_{16}H_{16}N_3O_4ClS$) C, H, N, Cl, S.

1-Carboxy-2-(4-chloro-3-sulfamoylbenzamido)isoindoline (4d). A solution of 6 g (0.0146 mol) of **4b** in 60 mL of 1 N NaOH (1:1 H_2O–EtOH) was stirred for 2 h at room temperature. After the EtOH was removed under reduced pressure, the aqueous layer was acidified with 2 N HCl. The resulting precipitate was then collected by filtration, yielding 4.65 g of crude **4d**. Anal. ($C_{16}H_{14}N_3O_5ClS·H_2O$) C, H, N, Cl, S.

Pharmacology. Experiments were performed on male (200–250 g) and female (160–220 g) Wistar rats, after 16 h of fasting. Three different protocols were used. In protocol A-1, male animals were fed by gastric tubing with a dose of 5 mg/kg of the agent tested in 1% saline. In protocol A-2, an identical dose was given, again 7 h later. Urine was collected for 18 h following drug administration. Protocol B was performed on both male and female rats. It consisted of an oral load of 50 mL/kg of tap water containing the drug to be tested. The urine was collected for 4 h following loading. Control animals received only the drug solvent. Sodium and potassium were measured by a Radiometer KBH flame photometer. Means and standard errors were calculated. Differences between means were tested for significance by Student's t test.

Nonsteroidal Antiinflammatory Agents. 3.[1] Synthesis of the Positional Isomers of 4'-Chloro-5-methoxy-3-biphenylylacetic Acid and Their Antiinflammatory and Analgesic Activities

Yasumitsu Tamura,

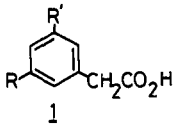
Faculty of Pharmaceutical Sciences, Osaka University, 133-1, Yamada-kami, Suita, Osaka, Japan

Yoshihiko Yoshimoto,* Shin-ichi Tada, Katsutoshi Kunimoto, Shingo Matsumura, Masao Murayama, Yoshihisa Shibata, and Hiroshi Enomoto

Research Laboratories, Nippon-Shinyaku Co. Ltd., 14, Nishinosho-Monguchi-cho, Kisshoin, Minami-ku, Kyoto, Japan.
Received August 29, 1980

The positional isomers **3a–i** of 4'-chloro-5-methoxy-3-biphenylylacetic acid [1 (DKA-9), R = 4-ClPh; R' = MeO] which is a newly developed nonsteroidal antiinflammatory agent, have been prepared and evaluated for antiinflammatory and analgesic activities using both the carrageenan-induced rat paw edema and AcOH writhing assays. The 3- and 4-biphenylylacetic acids **3a,d**, which closely resemble 1 (R = 4-ClPh, R' = MeO) structurally, showed, by far, excellent activities compared with the other isomers in these assays. However, none of the compounds tested was more active than 1 (R = 4-ClPh; R' = MeO). In this series of compounds, structural requirements for good antiinflammatory activity seemed to be parallel to those for analgesic activity.

Previously, we prepared a series of 3-biphenylylacetic acids (1)[1,2] and found that 4'-chloro-5-methoxy-3-biphenylylacetic acid [1 (DKA-9), R = 4-ClPh; R' = MeO] showed excellent antiinflammatory and analgesic activities[2,3] with less tendency to cause irritation in the gastrointestinal tract than ibuprofen, indomethacin, and flufenamic acid. At that time we were interested in the effect on potency caused by structural variations. The present paper describes the synthesis of nine positional isomers (**3a–i**) of 1 (R = 4-ClPh; R' = MeO), which are obtainable by moving the methoxy and 4-chlorophenyl groups on the benzene ring of the phenylacetic acid moiety of 1 (R = 4-ClPh; R' = MeO), and their biological activities.



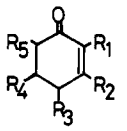
1

Chemistry. Synthetic routes to the acetic acids **3a–i** are illustrated in Schemes I–VI (see paragraph at the end of this paper concerning supplementary material). The routes shown in Schemes I–IV involve the preparation of the cyclohexenones **8a–f**, **9**, and **11** (Table I) and the

(1) For the second paper of this series, see Tamura, Y.; Yoshimoto, Y.; Kunimoto, K.; Tada, S.-I.; Matsumura, S.; Murayama, M.; Shibata, Y.; Enomoto, H. *J. Med. Chem.* **1981**, *24*, 43.
(2) Tamura, Y.; Yoshimoto, Y.; Kunimoto, K.; Tada, S.-I.; Tomita, T.; Wada, T.; Seto, E.; Murayama, M.; Shibata, Y.; Nomura, A.; Ohata, K. *J. Med. Chem.* **1977**, *20*, 709.
(3) Shibata, Y. *Arzneim.-Forsch.* **1977**, *27*, 2299.

0022-2623/81/1824-1006$01.25/0

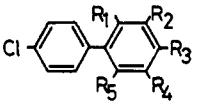
Table I. Cyclohexenones for Aromatization



no.	R_1	R_2	R_3	R_4	R_5	mp (recrystn solvent)[a] or bp (mm), °C	yield, %	formula	anal.
8a	H	CH_2CO_2Me	H	H	4-ClPh	66-68 (A)	72[b]	$C_{15}H_{15}O_3Cl$	C, H, Cl
8b	H	CH_2CO_2Me	4-ClPh	H	H	190-192 (3)	58[c]	$C_{21}H_{19}N_4O_6Cl$[g]	C, H, N, Cl
8c	H	4-ClPh	CH_2CO_2Me	H	H	91-93 (B)	90[d]	$C_{15}H_{15}O_3Cl$	C, H, Cl
8d	CH_2CO_2Me	4-ClPh	H	H	H	103-106 (A)	27[e]	$C_{15}H_{15}O_3Cl$	C, H, Cl
8e	H	4-ClPh	H	H	CH_2CO_2Me	84-86 (B)	51[e]	$C_{15}H_{15}O_3Cl$	C, H, Cl
8f	4-ClPh	CH_2CO_2Me	H	H	H	63-65 (A)	59[f]	$C_{15}H_{13}O_3Cl$	C, H, Cl
9	H	H	H	H	4-ClPh	61-62.5 (A)	98[b]	$C_{12}H_{11}OCl$	C, H, Cl
11	H	H	4-ClPh	H	H	138-141 (1)	69[c]	$C_{18}H_{15}N_4O_4Cl$[g]	C, H, N, Cl

[a] A = i-Pr_2O; B = MeOH. [b] Yield from 7a. [c] Yield from 10. [d] Yield from 13. [e] Yield from 15. [f] Yield from 19. [g] In cases of 8b and 11, analyses of the elements were carried out on the corresponding 2,4-dinitrophenylhydrazone (2,4-DNP). 2,4-DNP of 8b, mp 134-136 °C; 2,4-DNP of 11, mp 200-202 °C.

Table II. Biphenylylacetates and Biphenyls[a]



no.	R_1	R_2	R_3	R_4	R_5	mp (recrystn solvent)[b]	yield, %
2a	MeO	H	H	CH_2CO_2Me	H	54-56 (A)	79[c]
2b	H	H	MeO	CH_2CO_2Me	H	86-87 (A)	38[c]
2c	MeO	H	CH_2CO_2Me	H	H	68-70 (A)	72
2d	H	MeO	CH_2CO_2Me	H	H	68-68.5 (A)	69
2e	MeO	H	H	H	CH_2CO_2Me	180-185[d] (2)	23
2f	H	MeO	H	H	CH_2CO_2Me	184-190[d] (3)	83
2g	H	H	MeO	H	CH_2CO_2Me	66-68 (A)	62
2h	H	H	H	MeO	CH_2CO_2Me	165[d] (2)	47.5
20	MeO	H	H	H	H	52-53[e]	52
21	H	H	MeO	H	H	113-114	86

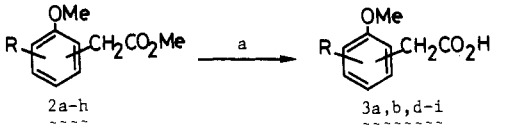
[a] Compounds 2a-h: Anal. ($C_{16}H_{15}O_3Cl$) C, H, Cl. Compounds 20 and 21: Anal. ($C_{13}H_{11}OCl$) C, H, Cl. [b] A = MeOH, B = n-hexane. [c] Yield from the acetophenones 26a and 22. [d] Bath temperature. [e] Literature[22] mp 58 °C. [f] Literature[22] mp 116 °C.

successive aromatization[4] as their essential steps. The intermediary cyclohexenones, other than **8c** and **9**, were prepared by the use of literature procedures (Schemes I–III). An initial attempt to prepare **8c**, starting from p-chloroacetophenone (**14**) according to the procedure of Nasipuri et al.,[5] was unsuccessful, but it was achieved by treatment of ethyl 3-(4′-chlorobenzoyl)propionate (**12**) with methyl vinyl ketone in the presence of DBU in toluene followed by esterification of the resulting 4-oxocyclohexen-1-ylacetic acid **13**, as shown in Scheme II.

Attempts to prepare cyclohexenone **9** from β-chlorocyclohexenone **7a** under known conditions, such as Zn–KI–MeOH,[6] Zn–Ag–MeOH,[7] or Zn–Cu–THF–H_2O,[8] resulted in failure, but this transformation was achieved quantitatively using Zn–Cu in MeOH.

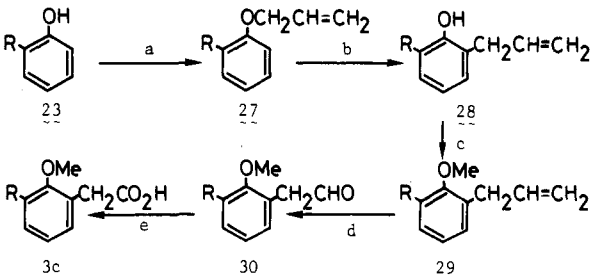
Aromatization and simultaneous O-methylation of the cyclohexenones **8a–f**, **9**, and **11** with iodine in MeOH[4] gave the esters **2c–h** and the biphenyls **20** and **21** (Table II). The biphenyls **20** and **21** were transformed into the methyl esters **2a** and **2b** by the methods shown in Scheme IV. Basic hydrolysis of the esters **2a–h** gave the acetic acids

Scheme V[a,b]



[a] Reagents for a: NaOH, H_2O, and MeOH. [b] R = 4-ClPh.

Scheme VI[a,b]



[a] Reagents for a: CH_2=$CHCH_2Br$, K_2CO_3, acetone; b: N,N-dimethylaniline; c: $(MeO)_2SO_2$, K_2CO_3, acetone; d: OsO_4, KIO_4, dioxane–H_2O; e: $AgNO_3$, 6% KOH, EtOH. [b] R = 4-ClPh.

(4) Tamura, Y.; Yoshimoto, Y. *Chem. Ind. (London)* **1980**, 888.
(5) Nasipuri, D.; Choudhury, S. R. Roy; Bhattacharya, A. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 1451.
(6) Frank, R. L.; Hall, H. K. Jr. *J. Am. Chem. Soc.* **1950**, *72*, 1645.
(7) Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1974**, *39*, 3658. *Ibid.* **1976**, *41*, 636.
(8) Blankenship, R. M.; Burdett, K. A.; Swenton, J. S. *J. Org. Chem.* **1974**, *39*, 2300.

3a,b,d–i (Scheme V). Synthesis of **3c** by a similar route, i.e., through conversion of the acetophenone **26b** into the corresponding phenyl acetate by Taylor's procedure,[9] failed, but it was accomplished starting from the phenol **23** by the methods outlined in Scheme VI.

Pharmacology. The acetic acids **3a–i**, together with 1 (R = 4-ClPh; R′ = MeO) and Indomethacin, were tested for antiinflammatory activity using the carrageenan-induced rat paw edema method,[10] for analgesic activity by the AcOH writhing method,[11] and for acute toxicity (see Experimental Section). The test results are summarized in Table III.

Results and Discussion

As to the antiinflammatory activity, all the 2-biphenylylacetic acids **3f–i** were inactive. Among the 3- and 4-biphenylylacetic acids **3a–e**, two isomers (**3a,d**) which closely resemble 1 (R = 4-ClPh; R′ = MeO) structurally showed good activity. In contrast with **3a,d** and 1 (R = 4-ClPh; R′ = MeO), **3b,c,e** had little or weak activity. The results suggest that in this series of compounds substitution of the position adjacent to the acetic acid group with a methoxy or 4-chlorophenyl group causes a decrease or destruction in activity. Among the active compounds **3a,d** and 1 (R = 4-ClPh; R′ = MeO), 1 (R = 4-ClPh; R′ = MeO) had the highest activity. The activity of 1 (R = 4-ClPh; R′ = MeO) can be explained as follows. The high activity of 1 (R = 4-ClPh; R′ = MeO) is due to a great extent to the parent skeleton 1 (R = 4-ClPh; R′ = H) which recently has been shown to possess about half the activity of 1 (R = 4-ClPh; R′ = MeO) at 20 mg/kg.[1] Thus, we suppose that in the molecule of 1 (R = 4-ClPh; R′ = MeO) the methoxy group at position 5 plays an important role in enhancing the activity of 1 (R = 4-ClPh; R′ = H). The present results reflect that, although a molecule must possess the requisite geometry to interact with the receptor, other factors are also very important in determining activity.

As to the analgesic activity, **3a,d** and 1 (R = 4-ClPh; R′ = MeO) showed, by far, excellent activities compared to the other isomers. Therefore, it is suggested that the structural requirements for analgesic activity seem to be parallel to those for antiinflammatory activity.

In conclusion, the studies carried out have verified that among the isomers evaluated 1 (R = 4-ClPh; R′ = MeO) demonstrates the highest antiinflammatory and analgesic activities.

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 ±0.3% of the calculated values. IR spectra were recorded on a Hitachi EPI-G3 spectrometer. NMR spectra were obtained on a Nichiden-Varian NEVA A-60D spectrometer. Mass spectra were obtained on a Hitachi RMU-6MG spectrometer. The spectral data for all new compounds were consistent with the assigned structures.

4-(4-Chlorophenyl)cyclohexane-1,3-dione (6) was prepared in 88% yield by heating methyl 4-(4′-chlorophenyl)-5-oxohexanoate, prepared from 4-chlorobenzaldehyde by the procedure of Bergmann et al.,[12] with an equimolar amount of *t*-BuOK in *t*-BuOH, mp 150–153 °C (ethyl acetate). Anal. ($C_{12}H_{11}O_2Cl$) C, H, Cl.

Table III. Chemical and Pharmacological Data for the Positional Isomers of 4′-Chloro-5-methoxy-3-biphenylylacetic Acid[a]

compd	R_1	R_2	R_3	R_4	R_5	mp (recrystn solvent),[b] °C	yield,[c] %	inhib act. on carrageenan paw edema[f]: dose, mg/kg po	inhib act. on carrageenan paw edema[f]: % inhibn at 3 h	inhib act. on AcOH writhing: ED_{50}, mg/kg po[g]	acute toxicity: LD_{50}, mg/kg ip[g]
3a	MeO	H	H	CH_2CO_2H	H	144.5–146 (B)	94	50	49***	26.7 (11.1–64.1)	673 (477–949)
								20	19**		
3b	H	H	MeO	CH_2CO_2H	H	185–186 (A)	95	50	0	>50	566
3c	H	H	H	CH_2CO_2H	MeO	122.5–124.5 (C)	50[d]	50	16	>50	283
3d	MeO	H	CH_2CO_2H	H	H	144.5–146.5 (B)	70	50	38**	35.1 (13.5–91.3)	238 (168–336)
								20	27**		
3e	H	MeO	CH_2CO_2H	H	H	185–186 (A)	81	50	27**	>50	400 (245–653)
3f	MeO	H	H	H	CH_2CO_2H	146–147 (C)	40	50	0	>50	566
3g	H	MeO	H	H	CH_2CO_2H	110–111 (B)	83	50	0	>50	566
3h	H	H	MeO	H	CH_2CO_2H	123–125 (C)	53	50	13	>50	566
3i	H	H	H	MeO	CH_2CO_2H	151–153 (C)	88	50	0	>50	476 (336–673)
1 (DKA-9),[e] R = 4-ClPh; R′ = MeO								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] Compounds 3a–i. Anal. ($C_{15}H_{13}O_3Cl$) C, H, Cl. [b] A = MeOH; B = benzene, C = *i*-Pr_2O. [c] Yields from the esters 2a–h, except for 3c. [d] Yield from 29. [e] See ref 2. [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.

(9) McKillop, A.; Swann, B. P.; Taylor, E. C. *J. Am. Chem. Soc.* **1973**, *95*, 3340.
(10) Winter, C. A.; Risley, E. A.; Nuss, G. W. *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544.
(11) Whittle, B. A. *Br. J. Pharmacol.* **1964**, *22*, 246.
(12) Bergmann, E. D.; Szmuszkovicz, J. *J. Am. Chem. Soc.* **1953**, *75*, 3226.

Similarly, **2-(4-chlorophenyl)cyclohexane-1,3-dione (16)** was obtained in 84% yield starting from ethyl 6-(4-chlorophenyl)-5-oxohexanoate, prepared from 4-chlorophenylacetonitrile by the method of Rappo et al.,[13] mp 221–223 °C (EtOH). Anal. ($C_{12}H_{11}O_2Cl$) C, H, Cl.

6-(4-Chlorophenyl)-3-chloro-2-cyclohexen-1-one (7a) and 4-(4-Chlorophenyl)-3-chloro-2-cyclohexen-1-one (7b). A mixture of **6** (15.3 g) and PCl_3 (4.7 g) in $CHCl_3$ (100 mL) was heated under reflux for 4 h. Usual workup gave an oil, which was triturated with *i*-Pr_2O to give white crystals of **7a** (10.45 g, 63%), mp 46–47.5 °C. Anal. ($C_{12}H_{10}OCl_2$) C, H, Cl. The *i*-Pr_2O layer was chromatographed on silica gel using benzene as eluent to give **7b** as an oil. Anal. ($C_{12}H_{10}OCl_2$) C, H, Cl.

Methyl 4-(4-chlorophenyl)-3-oxo-1-cyclohexen-1-ylacetate (8a) was prepared from **7a** and methyl acetoacetate by the reported procedure.[2]

6-(4-Chlorophenyl)-2-cyclohexen-1-one (9). To a stirred suspension of Zn–Cu couple (58.8 g) in MeOH (80 mL) was added **7a** (10 g) at 0 °C. Stirring was continued for 6 h at the same temperature. Zn–Cu was removed by filtration through Celite 545 and the washed (MeOH). The filtrate and MeOH washings were combined and concentrated. The residue was dissolved in ether. The ether solution was washed (10% HCl and then H_2O), dried ($MgSO_4$), and evaporated to give **9** (8.42 g, 98%), which on recrystallization gave an analytical sample of **9** as white crystals.

6-(4-Chlorophenyl)-3-isobutoxy-2-cyclohexen-1-one (10) was prepared in 75% yield by heating **7a** with an equimolar amount of *i*-BuONa in *i*-BuOH, mp 117–119 °C (*i*-Pr_2O). Anal. ($C_{16}H_{19}O_2Cl$) C, H, Cl.

Methyl 6-(4-chlorophenyl)-3-oxo-1-cyclohexen-1-ylacetate (8b) was prepared by treatment of **10** with methyl lithioacetate in THF according to the procedure of Rathke et al.[14]

4-(4-Chlorophenyl)-2-cyclohexen-1-one (11) was prepared by treatment of **10** with $LiAlH_4$ in ether according to the procedure of Stork et al.[15]

2-(4-Chlorophenyl)-4-oxo-2-cyclohexen-1-ylacetic Acid (13). To a mixture of ethyl 3-(4′-chlorobenzoyl)propionate (2.4 g) and methyl vinyl ketone (1.4 g) in dry toluene (50 mL) was added dropwise DBU (1.6 g) in dry toluene (10 mL) with stirring. The mixture was stirred for 2 h at 20 °C and then heated under reflux for 2 h. After cooling, the mixture was washed (10% HCl) and then extracted (aqueous $NaHCO_3$). The $NaHCO_3$ extracts were acidified (10% HCl) to give precipitates, which were recrystallized (EtOH) to give **13** (45% yield), mp 176–178 °C, as colorless crystals. Anal. ($C_{14}H_{13}O_3Cl$) C, H, Cl.

Methyl 2-(4-chlorophenyl)-4-oxo-2-cyclohexen-1-ylacetate (8c) was prepared by heating **13** with dimethyl sulfate in the presence of K_2CO_3 in acetone: yield 90%.

Methyl 2-(4-chlorophenyl)-6-oxo-1-cyclohexen-1-ylacetate (8d) and methyl 4-(4-chlorophenyl)-2-oxo-3-cyclohexen-1-ylacetate (8e) were prepared from 4-chloroacetophenone via dimethyl-2-(4-chlorobenzoyl)ethylamine (**15**) by the procedure of Nasipuri et al.[5]

2-(4-Chlorophenyl)-3-chloro-2-cyclohexen-1-one (17) was prepared by the reaction of **16** with PCl_5 in chloroform: yield 51%; mp 66.5–67.5 °C (ligroin). Anal. ($C_{12}H_{10}OCl_2$) C, H, Cl.

2-(4-Chlorophenyl)-3-oxo-1-cyclohexen-1-ylacetonitrile (19) was prepared in 88% yield from **17** via ***tert*-butyl 2-(4-chlorophenyl)-3-oxo-1-cyclohexen-1-yl(α-cyano)acetate (18)** by the reported method,[16] mp 112–113 °C (benzene). Anal. ($C_{14}H_{12}ONCl$) C, H, N, Cl.

Methyl 2-(4-chlorophenyl)-3-oxo-1-cyclohexen-1-ylacetate (8f) was prepared by treatment of **19** with saturated methanolic HCl according to the reported method.[17]

Biphenylylacetates 2c–h and biphenyls 20 and 21 were prepared from **8a–f**, **9**, and **11** according to the following general procedure: To a stirred suspension of the appropriate cyclohexenone (10 mmol) in MeOH (20 mL) was added dropwise iodine (20 mmol) in MeOH (30 mL) at room temperature. The mixture was heated under reflux with stirring for 5 h and concentrated. The residue was dissolved in benzene. The benzene solution was washed successively with H_2O, aqueous $NaHCO_3$, 10% $Na_2S_2O_3$, 2% NaOH, and H_2O and dried ($MgSO_4$). Removal of the solvent gave a solid or oil, which was chromatographed on silica gel using *n*-hexane (in cases of **20** and **21**) or benzene (in cases of **2c–h**) as eluents to give the corresponding anisole derivatives, which were purified. Yields and melting points (or boiling points) of **2c–h**, **20**, and **21** are listed in Table II.

3-Acetyl-4′-chloro-4-methoxybiphenyl (22) was prepared by treatment of **21** with AcCl in the presence of $AlCl_3$ in CS_2: yield 71%; mp 71–73 °C (ligroin). Anal. ($C_{15}H_{13}O_2Cl$) C, H, Cl.

Methyl 4′-chloro-4-methoxy-3-biphenylylacetate (2b) was prepared from **22** and $Tl(ONO_2)_3$ according to the procedure of Taylor et al.[9] Similarly, compound **2a** was prepared from **26a**.

4-Chloro-2′-hydroxybiphenyl (23) was prepared in 98% yield by heating **20** with 48% HBr and AcOH, mp 47.5–49 °C (petroleum ether) (lit.[18] mp 53 °C).

2-Acetoxy-4′-chlorobiphenyl (24) was prepared in 92% yield by the reaction of **23** with Ac_2O in pyridine, mp 83.5–85 °C (ligroin). Anal. ($C_{14}H_{11}O_2Cl$).

5-Acetyl-4′-chloro-2-hydroxybiphenyl (25a) and 3-Acetyl-4′-chloro-2-hydroxybiphenyl (25b). A mixture of **24** (5.17 g) and pulverized $AlCl_3$ (3.35 g) was heated[19] at 150 °C for 30 min. After cooling, the reaction mixture was poured onto ice–water. The mixture was shaken with ether. The ether layer was extracted again with 10% KOH. Acidification gave precipitates, which on recrystallization (MeOH) gave **25a** (3.09 g, 60%), mp 165.5–167.5 °C, as colorless crystals. Anal. ($C_{14}H_{11}O_2Cl$) C, H, Cl. From the ether layer (10% KOH insoluble part) **25b**, mp 76–78 °C (ligroin), was obtained in 26% yield. Anal. ($C_{14}H_{11}O_2Cl$) C, H, Cl.

5-Acetyl-4′-chloro-2-methoxybiphenyl (26a) [mp 102–103 °C (EtOH). Anal. ($C_{15}H_{13}O_2Cl$) C, H, Cl] and **3-acetyl-4′-chloro-2-methoxybiphenyl (26b)** [mp 79–80.5 °C (petroleum ether). Anal. ($C_{15}H_{13}O_2Cl$) C, H, Cl] were prepared from **25a** or **25b** by a method similar to that described for **8c**. However, **26b** could not be transformed into methyl 4′-chloro-2-methoxy-3-biphenylylacetate by a method similar to that described for **2b**.

Acetic acids 3a,b,d–i were prepared from **2a–h** by a method similar to that described for **3a** below.

4′-Chloro-6-methoxy-3-biphenylylacetic Acid (3a). A mixture of **2a** (4.85 g), MeOH (30 mL), and aqueous NaOH (1.32 g of NaOH in 30 mL of H_2O) was heated under reflux for 1 h and then concentrated. Usual workup gave crystals, which on recrystallization (benzene) gave **3a** (4.35 g, 94%) as white crystals. Yields and melting points of the compounds **3a–i**, along with their biological data, are summarized in Table III.

2-(Allyloxy)-4′-chlorobiphenyl (27) was prepared from **23** and allyl bromide in the presence of K_2CO_3 in acetone, bp 136–138 °C (1 mm). Anal. ($C_{15}H_{13}OCl$) C, H, Cl.

3-Allyl-4′-chloro-2-methoxybiphenyl (29) was prepared from **27** via 3-allyl-4′-chloro-2-hydroxybiphenyl (**28**) according to literature procedure,[20] bp 132–135 °C (1 mm). Anal. ($C_{16}H_{15}OCl$) C, H, Cl.

4′-Chloro-2-methoxy-3-biphenylylacetic Acid (3c). Compound **29** was treated with OsO_4–KIO_4 according to literature procedure[21] to give 4′-chloro-2-methoxy-3-biphenylylacetaldehyde (**30**) [2,4-dinitrophenylhydrazone, mp 139.5–142 °C (benzene–petroleum ether). Anal. ($C_{21}H_{17}N_4O_5Cl$) C, H, N, Cl], which was treated with $AgNO_3$ and aqueous KOH in EtOH–H_2O to give **3c**.

Pharmacological Testing. Antiinflammatory Activity.[10] 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.

(13) Born, H.; Rappo, R.; Szmuskovicz, J. *J. Chem. Soc.* **1961**, 4221.
(14) Rathke, M. W. *J. Am. Chem. Soc.* **1970**, *92*, 3222. *Org. Synth.* **1973**, *53*, 66.
(15) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1975**, *38*, 1775.
(16) Tamura, Y.; Yoshimoto, Y.; Suzuki, M.; Terashima, M. *Chem. Ind. (London)* **1970**, 1410.
(17) Murayama, M.; Seto, E.; Yoshimoto, Y.; Wada, T. Japan Kokai *73*, 103 548; *Chem. Abstr.* **1974**, *80*, 70439.
(18) Colbert, J. C.; Lacy, R. M. *J. Am. Chem. Soc.* **1946**, *68*, 270.
(19) Blatt, A. H. *Org. React.* **1942**, *1*, 342.
(20) Tarbell, D. S. *Org. React.* **1944**, *2*, 1.
(21) Rappo, R.; Allen, D. S.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.
(22) Migita, T.; Morikawa, M.; Shimamura, O. *Bull. Chem. Soc. Jpn.* **1963**, *36*, 980.

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.[11] Six male STD-ddY mice were used for each group. The test compound was administered orally as a suspension in 0.5% CMC. Thrity 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 was measured for 20 min. The response of the drug-treated mouse was compared with the response using AcOH alone.

Acute toxicity, expressed as a LD_{50} value calculated by the method of Weil,[23] was determined 168 h after a single ip injection to groups of four male ddY mice.

Supplementary Material Available: Synthetic routes to intermediates **6**, **7a,b**, **8a–f**, **9–11**, **13**, **15**, **17–24**, **25a,b**, **26a,b**, and **2a–h** (Schemes I–IV) and NMR spectral data for all new compounds described in this paper (Tables IV–VIII) (8 pages). Ordering information is given on any current masthead page.

(23) Weil, C. S. *Biometrics* **1952**, *8*, 249.

Gastric Antisecretory Agents. 2. Antisecretory Activity of 9-[(Aminoalkyl)thio]-9*H*-xanthenes and 5-[(Aminoalkyl)thio]-5*H*-[1]benzopyrano[2,3-*b*]pyridines

James A. Bristol,*[1] Elijah H. Gold, Irwin Gross, Raymond G. Lovey,

Department of Chemical Research—Medicinals

and James F. Long

Department of Pharmacology, Pharmaceutical Research Division, Schering-Plough Corporation, Bloomfield, New Jersey 07003. *Received September 8, 1980*

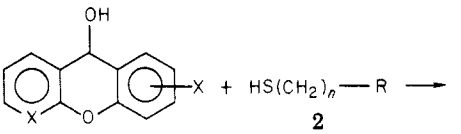
A series of 9-[(aminoalkyl)thio]-9*H*-xanthenes (**3–6**) and 5-[(aminoalkyl)thio]-5*H*-[1]benzopyrano[2,3-*b*]pyridines (**7–10**) possessing gastric antisecretory activity in the rat and dog is described. Many of the compounds possessed good activity in the pylorus-ligated rat and several inhibited histamine-stimulated gastric acid secretion in the dog. The mechanism of acid secretion inhibition is not related to anticholinergic or histamine (H_2) receptor antagonism.

As part of our efforts to identify novel compounds which inhibit gastric acid secretion,[2] we are reporting a series of 9-[(aminoalkyl)thio]-9*H*-xanthenes (**3–6**) and 5-[(aminoalkyl)thio]-5*H*-[1]benzopyrano[2,3-*b*]pyridines (azaxanthenes) (**7–10**) which represent a new class of gastric antisecretory agents. The present compounds are potent inhibitors of gastric acid secretion in the pylorus-ligated rat, and several inhibit histamine-stimulated gastric acid secretion in dogs.

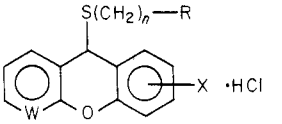
Chemistry. The [(aminoalkyl)thio]xanthenes and azaxanthenes were synthesized as shown in Scheme I from the alcohol **1** and the requisite (aminoalkyl)mercaptan hydrochloride, **2**, in CH_3CN. The alcohols **1a** were prepared by $LiAlH_4$ reduction of a 9*H*-xanthen-9-one, while **1b** was prepared by $NaBH_4$ reduction of 5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one[3] in CH_3OH at 20–25 °C.

Biological Test Methods. The compounds were evaluated for antisecretory activity in two animal models (Tables I and II). The pylorus-ligated rat[4] was used as the primary screen to assess antisecretory activity and to identify potentially toxic compounds. Compounds were administered at 40 mg/kg intraperitoneally at the time of ligation, and reduction in acid output was measured after 4 h. The secondary model was inhibition of histamine-stimulated gastric acid secretion in adult mongrel dogs[5] with surgically prepared Heidenhain pouches. Compounds were first administered at 5 mg/kg intravenously, and reduction in acid output, relative to the non-drug-treated control value in the same animal, was measured. Selected compounds were also tested at 8 mg/kg orally in the dog.

Scheme I



1a, W = CH
b, W = N



3, W = CH; R = NH_2
4, W = CH; R = $N(CH_3)_2$
5, W = CH; R = c-$N(CH_2CH_2)_2O$
6, W = CH; R = c-NC_5H_{10}
7, W = N; R = NH_2
8, W = N; R = $N(CH_3)_2$
9, W = N; R = c-$N(CH_2CH_2)_2O$
10, W = N; R = c-NC_5H_{10}

Results and Discussion

The antisecretory results for the xanthenes and benzopyrano[2,3-*b*]pyridines are shown in Tables I and II, re-

(1) Address correspondence to Warner-Lambert Co., Pharmaceutical Research Division, Ann Arbor, MI 48105.
(2) J. A. Bristol, E. H. Gold, R. G. Lovey, and J. F. Long *J. Med. Chem.*, see Articles in this issue.
(3) F. J. Villani, T. A. Mann, E. A. Wefer, J. Hannon, L. L. Larca, M. J. Landon, W. Spivak, D. Vashi, S. Tozzi, G. Danko, M. del Prado, and R. Lutz, *J. Med. Chem.*, **18**, 1 (1975).
(4) H. Shay, S. A. Komarov, S. S. Fels, D. Merance, M. Gruenstein, and H. Siplit, *Gastroenterology*, **5**, 43 (1945).
(5) J. F. Long and F. P. Brooks, *Q. J. Exp. Physiol.*, **50**, 256 (1965).

0022-2623/81/1824-1010$01.25/0