

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 LiBH₄ 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 H₂O. The inorganic precipitate was filtered and thoroughly washed with THF. The filtrates were collected, dried with Na₂SO₄, and concentrated to dryness in vacuo to give 4 g of crude **4c**. Anal. (C₁₆H₁₆N₃O₄ClS) 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 H₂O-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. (C₁₆H₁₄N₃O₅ClS) C, H, N, Cl, S.

H₁₄N₃O₅ClS·H₂O) 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-biphenylacetic Acid and Their Antiinflammatory and Analgesic Activities

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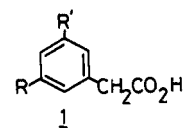
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The positional isomers **3a-i** of 4'-chloro-5-methoxy-3-biphenylacetic acid [**1** (DKA-9), R = 4-ClPh; R' = MeO] which is a newly developed nonsteroidal antiinflammatory agent, have been prepared and evaluated for antiinflammatory and analgesic activities using both the carrageenan-induced rat paw edema and AcOH writhing assays. The 3- and 4-biphenylacetic 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-biphenylacetic acids (**1**)^{1,2} and found that 4'-chloro-5-methoxy-3-biphenylacetic 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

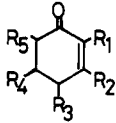
present paper describes the synthesis of nine positional isomers (**3a-i**) of **1** (R = 4-ClPh; R' = MeO), which are obtainable by moving the methoxy and 4-chlorophenyl groups on the benzene ring of the phenylacetic acid moiety of **1** (R = 4-ClPh; R' = MeO), and their biological activities.



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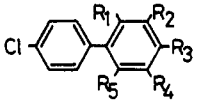
Chemistry. Synthetic routes to the acetic acids **3a-i** are illustrated in Schemes I–VI (see paragraph at the end of this paper concerning supplementary material). The routes shown in Schemes I–IV involve the preparation of the cyclohexenones **8a-f**, **9**, and **11** (Table I) and the

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 ₂ CO ₂ Me	H	H	4-ClPh	66-68 (A)	72 ^b	C ₁₅ H ₁₅ O ₃ Cl	C, H, Cl
8b	H	CH ₂ CO ₂ Me	4-ClPh	H	H	190-192 (3)	58 ^c	C ₂₁ H ₁₉ N ₄ O ₆ Cl ^g	C, H, N, Cl
8c	H	4-ClPh	CH ₂ CO ₂ Me	H	H	91-93 (B)	90 ^d	C ₁₅ H ₁₅ O ₃ Cl	C, H, Cl
8d	CH ₂ CO ₂ Me	4-ClPh	H	H	H	103-106 (A)	27 ^e	C ₁₅ H ₁₅ O ₃ Cl	C, H, Cl
8e	H	4-ClPh	H	H	CH ₂ CO ₂ Me	84-86 (B)	51 ^e	C ₁₅ H ₁₅ O ₃ Cl	C, H, Cl
8f	4-ClPh	CH ₂ CO ₂ Me	H	H	H	63-65 (A)	59 ^f	C ₁₅ H ₁₃ O ₃ Cl	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 ₄ O ₄ Cl ^g	C, H, N, Cl

^a A = *i*-Pr₂O; 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. Biphenylacetates and Biphenyls^a


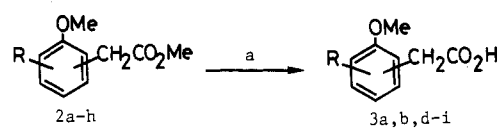
no.	R ₁	R ₂	R ₃	R ₄	R ₅	mp (recrystn solvent) ^b	yield, %
2a	MeO	H	H	CH ₂ CO ₂ Me	H	54-56 (A)	79 ^c
2b	H	H	MeO	CH ₂ CO ₂ Me	H	86-87 (A)	38 ^c
2c	MeO	H	CH ₂ CO ₂ Me	H	H	68-70 (A)	72
2d	H	MeO	CH ₂ CO ₂ Me	H	H	68-68.5 (A)	69
2e	MeO	H	H	H	CH ₂ CO ₂ Me	180-185 ^d (2)	23
2f	H	MeO	H	H	CH ₂ CO ₂ Me	184-190 ^d (3)	83
2g	H	H	MeO	H	CH ₂ CO ₂ Me	66-68 (A)	62
2h	H	H	H	MeO	CH ₂ CO ₂ Me	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. (C₁₆H₁₅O₃Cl) C, H, Cl. Compounds 20 and 21: Anal. (C₁₃H₁₁OCl) C, H, Cl. ^b A = MeOH, B = *n*-hexane. ^c Yield from the acetophenones 26a and 22. ^d Bath temperature. ^e Literature²² mp 58 °C. ^f Literature²² mp 116 °C.

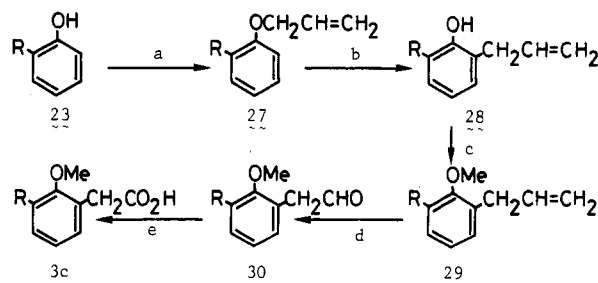
successive aromatization⁴ as their essential steps. The intermediary cyclohexenones, other than 8c and 9, were prepared by the use of literature procedures (Schemes I-III). An initial attempt to prepare 8c, starting from *p*-chloroacetophenone (14) according to the procedure of Nasipuri et al.,⁵ was 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-H₂O,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 MeOH⁴ gave the esters 2c-h and the biphenyls 20 and 21 (Table II). The biphenyls 20 and 21 were transformed into the methyl

Scheme V^{a,b}

^a Reagents for a: NaOH, H₂O, and MeOH. ^b R = 4-ClPh.

Scheme VI^{a,b}

^a Reagents for a: CH₂=CHCH₂Br, K₂CO₃, acetone; b: *N,N*-dimethylaniline; c: (MeO)₂SO₂, K₂CO₃, acetone; d: OsO₄, KIO₄, dioxane-H₂O; e: AgNO₃, 6% KOH, EtOH. ^b R = 4-ClPh.

esters 2a and 2b by the methods shown in Scheme IV. Basic hydrolysis of the esters 2a-h gave the acetic acids

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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** ($R = 4\text{-ClPh}$; $R' = \text{MeO}$) 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-biphenylacetic acids **3f-i** were inactive. Among the 3- and 4-biphenylacetic acids **3a-e**, two isomers (**3a,d**) which closely resemble **1** ($R = 4\text{-ClPh}$; $R' = \text{MeO}$) structurally showed good activity. In contrast with **3a,d** and **1** ($R = 4\text{-ClPh}$; $R' = \text{MeO}$), **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** ($R = 4\text{-ClPh}$; $R' = \text{MeO}$), **1** ($R = 4\text{-ClPh}$; $R' = \text{MeO}$) had the highest activity. The activity of **1** ($R = 4\text{-ClPh}$; $R' = \text{MeO}$) can be explained as follows. The high activity of **1** ($R = 4\text{-ClPh}$; $R' = \text{MeO}$) is due to a great extent to the parent skeleton **1** ($R = 4\text{-ClPh}$; $R' = \text{H}$) which recently has been shown to possess about half the activity of **1** ($R = 4\text{-ClPh}$; $R' = \text{MeO}$) at 20 mg/kg.¹ Thus, we suppose that in the molecule of **1** ($R = 4\text{-ClPh}$; $R' = \text{MeO}$) the methoxy group at position 5 plays an important role in enhancing the activity of **1** ($R = 4\text{-ClPh}$; $R' = \text{H}$). 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** ($R = 4\text{-ClPh}$; $R' = \text{MeO}$) 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** ($R = 4\text{-ClPh}$; $R' = \text{MeO}$) 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 $\pm 0.3\%$ 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. ($\text{C}_{12}\text{H}_{11}\text{O}_2\text{Cl}$) C, H, Cl.

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Table III. Chemical and Pharmacological Data for the Positional Isomers of 4'-Chloro-5-methoxy-3-biphenylacetic Acid^a

compd	R ₁	R ₂	R ₃	R ₄	R ₅	mp (recrystn solvent), °C	yield, ^c %	inhib act. on carrageenan paw edema ^f		inhib act. on AcOH writhing: ED ₅₀ , mg/kg po ^g	acute toxicity: LD ₅₀ , mg/kg ip ^g
								dose, mg/kg po	% inhib at 3 h		
3a	MeO	H	H	CH ₂ CO ₂ H	H	144.5–146 (B)	94	50	49***	26.7 (11.1–64.1)	673 (477–949)
3b	H	H	MeO	CH ₂ CO ₂ H	H	185–186 (A)	95	20	19**	>50	566
3c	H	H	H	CH ₂ CO ₂ H	MeO	122.5–124.5 (C)	50 ^d	50	0	>50	283
3d	MeO	H	CH ₂ CO ₂ H	H	H	144.5–146.5 (B)	70	50	38**	35.1 (13.5–91.3)	238 (168–336)
3e	H	MeO	CH ₂ CO ₂ H	H	H	185–186 (A)	81	20	27**	>50	400 (245–653)
3f	MeO	H	H	H	CH ₂ CO ₂ H	146–147 (C)	40	50	0	>50	566
3g	H	MeO	H	H	CH ₂ CO ₂ H	110–111 (B)	83	50	0	>50	566
3h	H	H	MeO	H	CH ₂ CO ₂ H	123–125 (C)	53	50	13	>50	566
3i	H	H	H	MeO	CH ₂ CO ₂ H	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)
indomethacin								20	65***		
								10	39**		
								5	45***	3.1 (1.5–6.5)	
								2	25***		
								0.5	19**		

^a Compounds **3a-i**. Anal. ($\text{C}_{15}\text{H}_{13}\text{O}_3\text{Cl}$) C, H, Cl. ^b A = MeOH; B = benzene, C = *i*-Pr₂O. ^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.

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. (C₁₂H₁₁O₂Cl) 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 PCl₃ (4.7 g) in CHCl₃ (100 mL) was heated under reflux for 4 h. Usual workup gave an oil, which was triturated with *i*-Pr₂O to give white crystals of 7a (10.45 g, 63%), mp 46–47.5 °C. Anal. (C₁₂H₁₀OCl₂) C, H, Cl. The *i*-Pr₂O layer was chromatographed on silica gel using benzene as eluent to give 7b as an oil. Anal. (C₁₂H₁₀OCl₂) 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 H₂O), dried (MgSO₄), 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*-Pr₂O). Anal. (C₁₆H₁₉O₂Cl) 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 LiAlH₄ 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 NaHCO₃). The NaHCO₃ 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. (C₁₄H₁₃O₃Cl) 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 K₂CO₃ 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 PCl₅ in chloroform: yield 51%; mp 66.5–67.5 °C (ligroin). Anal. (C₁₂H₁₀OCl₂) 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. (C₁₄H₁₂ONCl) 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

Biphenylacetates 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 cyclo-

hexenone (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 H₂O, aqueous NaHCO₃, 10% Na₂S₂O₃, 2% NaOH, and H₂O and dried (MgSO₄). 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 AlCl₃ in CS₂: yield 71%; mp 71–73 °C (ligroin). Anal. (C₁₅H₁₃O₂Cl) C, H, Cl.

Methyl 4'-chloro-4-methoxy-3-biphenylacetate (2b) was prepared from 22 and Ti(ONO₂)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 Ac₂O in pyridine, mp 83.5–85 °C (ligroin). Anal. (C₁₄H₁₁O₂Cl).

5-Acetyl-4'-chloro-2-hydroxybiphenyl (25a) and 3-Acetyl-4'-chloro-2-hydroxybiphenyl (25b). A mixture of 24 (5.17 g) and pulverized AlCl₃ (3.35 g) was heated¹⁹ 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. (C₁₄H₁₁O₂Cl) C, H, Cl. From the ether layer (10% KOH insoluble part) 25b, mp 76–78 °C (ligroin), was obtained in 26% yield. Anal. (C₁₄H₁₁O₂Cl) C, H, Cl.

5-Acetyl-4'-chloro-2-methoxybiphenyl (26a) [mp 102–103 °C (EtOH). Anal. (C₁₅H₁₃O₂Cl) C, H, Cl] and 3-acetyl-4'-chloro-2-methoxybiphenyl (26b) [mp 79–80.5 °C (petroleum ether). Anal. (C₁₅H₁₃O₂Cl) 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-biphenylacetate 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-biphenylacetic Acid (3a). A mixture of 2a (4.85 g), MeOH (30 mL), and aqueous NaOH (1.32 g of NaOH in 30 mL of H₂O) 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 K₂CO₃ in acetone, bp 136–138 °C (1 mm). Anal. (C₁₅H₁₃OCl) 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. (C₁₆H₁₅OCl) C, H, Cl.

4'-Chloro-2-methoxy-3-biphenylacetic Acid (3c). Compound 29 was treated with OsO₄–KIO₄ according to literature procedure²¹ to give 4'-chloro-2-methoxy-3-biphenylacetaldehyde (30) [2,4-dinitrophenylhydrazone, mp 139.5–142 °C (benzene-petroleum ether). Anal. (C₂₁H₁₇N₂O₅Cl) C, H, N, Cl], which was treated with AgNO₃ and aqueous KOH in EtOH–H₂O 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.

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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. 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 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 LD₅₀ 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.

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

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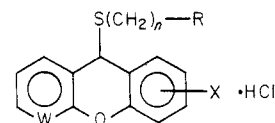
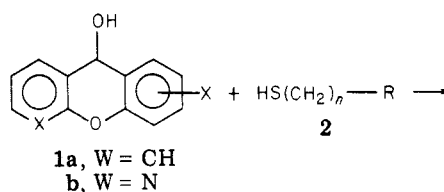
A series of 9-[(aminoalkyl)thio]-9H-xanthenes (3-6) and 5-[(aminoalkyl)thio]-5H-[1]benzopyrano[2,3-b]pyridines (7-10) possessing gastric antisecretory activity in the rat and dog is described. Many of the compounds possessed good activity in the pylorus-ligated rat and several inhibited histamine-stimulated gastric acid secretion in the dog. The mechanism of acid secretion inhibition is not related to anticholinergic or histamine (H₂) 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]-9H-xanthenes (3-6) and 5-[(aminoalkyl)thio]-5H-[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 CH₃CN. The alcohols 1a were prepared by LiAlH₄ reduction of a 9H-xanthen-9-one, while 1b was prepared by NaBH₄ reduction of 5H-[1]benzopyrano[2,3-b]pyridin-5-one³ in CH₃OH 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 rat⁴ 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-

Scheme I



- 3, W = CH; R = NH₂
- 4, W = CH; R = N(CH₃)₂
- 5, W = CH; R = c-N(CH₂CH₂)₂O
- 6, W = CH; R = c-NC₅H₁₀
- 7, W = N; R = NH₂
- 8, W = N; R = N(CH₃)₂
- 9, W = N; R = c-N(CH₂CH₂)₂O
- 10, W = N; R = c-NC₅H₁₀

stimulated gastric acid secretion in adult mongrel dogs⁵ 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.

Results and Discussion

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

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