area obtained in the control group to the individual lesion areas obtained in the treatment groups. An average activity of 18% or greater denotes significant inhibition using one-way analysis of variance and Duncan's[12] multiple range test ($p < 0.05$). Lower responses were considered inactive.

Rat Pleural Reverse Passive Arthus Test (Pleural RPAR). Groups of eight to ten rats weighing 160–200 g were injected iv with 3 mg/kg of BSA in 0.9% w/v saline (2 mL/kg). Approximately 1 h later, 0.2 mL of anti-BSA preparation was injected intrapleurally (ipl). Test compounds at four dose levels or control vehicle was administered 30 min prior to the ipl injection. Four hours after the ipl injection, the rats were sacrificed with carbon dioxide, and the pleural cavity was opened. The volume of exudate fluid and the number of exudate white blood cells (WBC) present were determined by a phenol red dye dilution technique.[13] Percent inhibition of exudate volume and cellular accumulation were calculated by comparison of mean control group values to individual values in the treatment groups.

Rat Pleural Carrageenin Test. The rat pleural carrageenin test (modified from the method described by Vinegar et al.[14]) was performed in groups of eight to ten rats weighing 160–200 g. The procedure was essentially that described for the pleural Arthus test with the exception that carrageenin (125 μg/0.2 mL of saline) was injected ipl in place of antibody, and no intravenous BSA was administered. Test compounds at four dose levels or control vehicle were given 30 min prior to carrageenin, and the animals were sacrificed 4 h after the ipl injection. The inflammatory exudate was assessed by the dye dilution technique as in the pleural Arthus test.

Registry No. **1a**, 83782-10-9; **1a**·HCl, 83782-11-0; **1b**, 71897-63-7; **1b**·HCl, 81850-99-9; **1c**, 81851-17-4; **1c**·HCl, 81851-02-7; **1d**, 83782-12-1; **1d**·HCl, 81851-08-3; 1e, 83782-13-2; **1e**·HCl, 83782-14-3; **1f**, 83782-15-4; **1f**·HCl, 83782-16-5; **1g**, 33984-18-8; **1g**·HCl, 83782-17-6; **1h**, 83782-18-7; **1h**·HCl, 83782-19-8; **1i**, 69751-36-6; **1i**·HCl, 83782-20-1; **1j**, 83782-21-2; **1j**·HCl, 83782-22-3; **1k**, 83782-23-4; **1k**·HCl, 83782-24-5; **1l**, 83801-83-6; **1l**·HCl, 83782-25-6; **1m**, 83782-26-7; **1m**·HCl, 83782-27-8; **1n**, 81851-18-5; **1n**·HCl, 81851-13-0; **1o**, 83782-28-9; **1o**·HCl, 83782-29-0; **1p**, 83782-30-3; **1p**·HCl, 83782-31-4; **1q**, 83782-32-5; **1q**·HCl, 81851-05-0; **1r**, 83782-33-6; **1r**·HCl, 83782-34-7; **2a**, 83782-35-8; **2a**·HCl, 83782-36-9; **2b**, 83782-37-0; **2b**·HCl, 83782-38-1; **2c**, 83782-39-2; **2c**·HCl, 83782-40-5; **2d**, 83782-41-6; **2d**·HCl, 83782-42-7; **2e**, 83782-43-8; **2e**·HCl, 83782-44-9; **2f**, 83782-45-0; **2g**, 83782-46-1; **2g**·HCl, 83782-47-2; **2h**, 83782-48-3; **2i**, 83782-49-4; **2i**·HCl, 83782-50-7; **2j**, 83782-51-8; **2j**·HCl, 83782-52-9; **3a**, 83782-53-0; **3b**, 83782-54-1; **3c**, 16173-72-1; **3c**·HCl, 83782-55-2; **3d**, 31309-57-6; **3d**·HCl, 83782-56-3; **3e**, 83782-57-4; **3e**·HCl, 83782-58-5; **3f**, 83782-59-6; **3f**·HCl, 83782-60-9; **3g**, 83782-61-0; **3g**·HCl, 83782-62-1; **3h**, 83782-63-2; **3h**·HCl, 83782-64-3; **3i**, 4350-41-8; **3i**·HCl, 6320-64-5; **3j**, 83782-65-4; **3j**·HCl, 83782-66-5; **3k**, 1008-89-5; **3l**, 2116-62-3; **3l**·HCl, 19337-88-3; **3m**, 83782-67-6; **3m**·HCl, 83782-68-7; **3n**, 83782-69-8; **4a**, 83782-70-1; **4a**·HCl, 83782-71-2; **4b**, 83782-72-3; **4b**·HCl, 83782-73-4; **4c**, 83782-75-6; **4d**, 83782-76-7; **4d**·HCl, 83782-77-8; **5a**, 83782-78-9; **5a**·HCl, 83782-79-0; **5b**, 83782-80-3; **5b**·HCl, 83782-81-4; **5c**, 83782-82-5; **5c**·HCl, 83782-83-6; **5d**, 83782-84-7; **5d**·HCl, 83782-85-8; **5e**, 83782-86-9; **5e**·2HCl, 83782-87-0; **5f**, 83782-88-1; 2-picolyl chloride, 4377-33-7; 2-(hydroxymethyl)pyridine, 586-98-1; sodium thiophenolate, 930-69-8; picolyl chloride hydrochloride, 6959-47-3; 2-(chloromethyl)-5-methylpyridine hydrochloride, 71670-70-7; *p*-bromothiophenol, 106-53-6; 2-(chloromethyl)-3-methylpyridine, 4377-43-9; 2-methyl-6-chloropyridine *N*-oxide, 52313-59-4; 2-methyl-6-chloropyridine, 18368-63-3; 2-(hydroxymethyl)-6-chloropyridine hydrochloride, 83782-89-2; 2-(hydroxymethyl)-4-chloropyridine, 63071-10-3; 2-methyl-4-chloropyridine, 3678-63-5; 2-methyl-4-phenylpyridine, 15032-21-0; 2-(hydroxymethyl)-4-phenylpyridine, 55218-73-0; 2-pyridinecarboxaldehyde, 1121-60-4; *p*-bromoaniline, 106-40-1; 2-vinylpyridine, 100-69-6; 2-chloromethyl)piperidine, 56098-50-1; 2-(chloromethyl)-1-methylpiperidine, 49665-74-9.

(12) D. B. Duncan, *Biometrics*, 11, 1 (1955).
(13) G. W. Carter, P. R. Young, M. K. Martin, and K. W. Mollison, *J. Pharm. Pharmacol.*, **34**, 66 (1982).
(14) R. Vinegar, J. F. Truax, and J. L. Selph, *Proc. Soc. Exp. Biol. Med.*, **143**, 711 (1973).

Nonsteroidal Antiinflammatory Agents. 2.[1] [(Heteroarylamino)phenyl]alkanoic Acids

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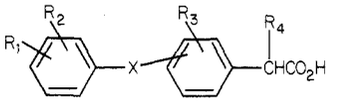
A series of [(heteroarylamino)phenyl]alkanoic acids having pyridine, quinoline, or pyrimidine as the heteroaryl moiety was prepared as potential antiinflammatory agents. Among them, 2-[4-(2-pyridylamino)phenyl]propionic acid (**14b**) showed excellent antiinflammatory and analgesic activities with less tendency to cause gastric side effects. Structure–activity relationships are discussed.

Several arylalkanoic acids[2] are clinically used as antiinflammatory agents. However, almost all of them have some undesirable side effects, such as gastric irritation. Many attempts have been made to prepare better antiinflammatory agents with little or no gastric side effect. Since compounds of structure **1**, which includes 2-(3-benzoylphenyl)propionic acid (ketoprofen) and [2-(2,6-dichloroanilino)phenyl]acetic acid sodium salt (diclofenac sodium), have been reported to possess useful antiinflammatory properties,[3] we were interested in synthesizing a new series of [(heteroarylamino)phenyl]alkanoic acids in order to investigate their biological activities. Consequently, it was found that 2-[4-(2-pyridylamino)phenyl]-propionic acid (**14b**) possessed excellent antiinflammatory and analgesic activities in laboratory models with far less tendency to cause gastric ulcers in rodents than ibuprofen.



1, X = O, CO, NH; R_1, R_2, R_3 = H, CH_3O, halogen; R_4 = H, CH_3

(1) Y. Nagai, A. Irie, H. Nakamura, K. Hino, H. Uno, and H. Nishimura, *J. Med. Chem.*, **25**, 1065 (1982).
(2) (a) S. S. Adama, K. F. McCullogh, and J. Nicholson, *Arch. Int. Pharmacodyn. Ther.*, **178**, 115 (1969). (b) L. Julou and J. C. Guyonnet, *J. Pharmacol.*, **2**, 259 (1971). (c) A. Roszkowski, W. H. Rooks, A. J. Tomolonis, and L. M. Miller, *J. Pharmacol. Exp. Ther.*, **179**, 114 (1971). (d) S. Wong, J. F. Gardocki, and T. P. Pruss, *ibid.*, **185**, 127 (1973).
(3) P. F. Juby, in "Antiinflammatory Agents", Vol I, R. A. Sherrer and M. W. Whitehouse, Eds., Academic Press, New York, 1974, p 91.

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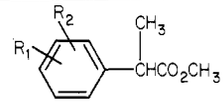
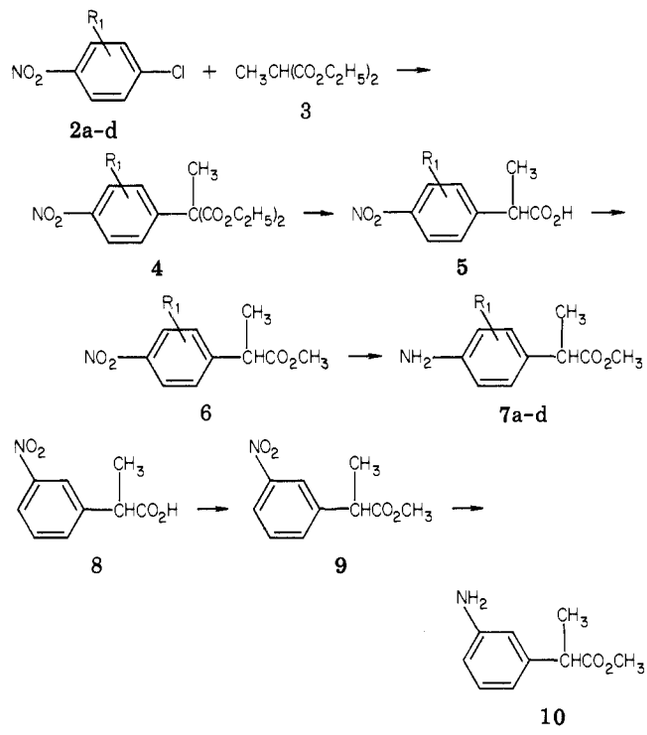
Table I. Chemical Data of Various Intermediates



compd	R_1	R_2	yield, %	bp, °C (mm)	formula[a]
6a[b]	4-NO_2	H	85	151 (7)	$C_{10}H_{11}NO_4$
6b	4-NO_2	2-Cl	58	179-183 (7)	$C_{10}H_{10}ClNO_4$
6c	4-NO_2	3-Cl	34	viscous oil	$C_{10}H_{10}ClNO_4$
6d	4-NO_2	3-CH_3	13	viscous oil	$C_{11}H_{13}NO_4$
7a[c]	4-NH_2	H	94	165-170 (4)	$C_{10}H_{13}NO_2$
7b	4-NH_2	2-Cl	85	viscous oil	$C_{10}H_{12}ClNO_2$
7c[c]	4-NH_2	3-Cl	52	168-172 (1)	$C_{10}H_{12}ClNO_2$
7d	4-NH_2	3-CH_3	70	viscous oil	$C_{11}H_{15}NO_2$
9	3-NO_2	H	84	viscous oil	$C_{10}H_{11}NO_4$
10	3-NH_2	H	88	170-175 (1)	$C_{10}H_{13}NO_2$

[a] All compounds were analyzed for C, H, N, and halogen; analytical results were within ±0.4% of the theoretical values. [b] J. H. Schauble, G. J. Walter, and J. G. Morin, *J. Org. Chem.*, 39, 755 (1974); bp 116 °C (0.15 mm). [c] B. Dumaltre, A. Fouquet, C. Perrin, P.-J. Cornu, A. Boucherle, C. Plotra, G. Domage, and G. Streichenberger, *Eur. J. Med. Chem.*, 14, 207 (1979). 7a: bp 144-145 °C (2.5 mm). 7c: bp 126-128 °C (0.4 mm).

Scheme I[a]



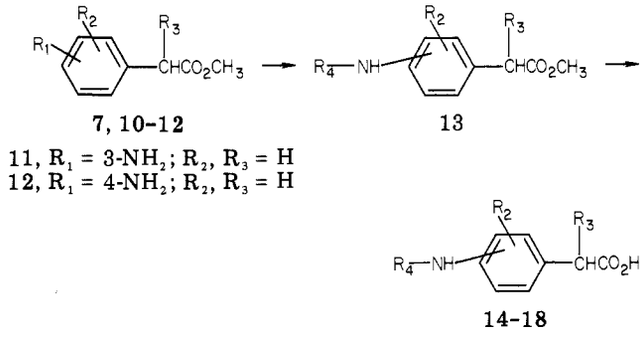
[a] For compounds 2-7, a, R_1 = H; **b**, R_1 = 2-Cl; c, R_1 = 3-Cl; d, R_1 = 3-CH_3.

Chemistry. The requisite intermediate methyl 2-(4-aminophenyl)propionates (**7**) were easily synthesized by the route shown in Scheme I. Thus, reaction of 4-nitrophenyl chlorides (**2**) with diethyl methylmalonate (**3**) in the presence of sodium hydride gave diethyl 4-nitrophenylmethylmalonates (**4**), which were then treated with aqueous sodium hydroxide to give 2-(4-nitrophenyl)-propionic acids (**5**). Esterification of **5** and subsequent hydrogenolysis on palladium/carbon gave the required methyl 2-(4-aminophenyl)propionates (**7**).

Another intermediate, methyl 2-(3-aminophenyl)-propionate (**10**), was synthesized by esterification of 2-(3-nitrophenyl)propionic acid (**8**),[4] followed by catalytic reduction of the nitro group.

(4) E. Felder, D. Pitre, L. Fumagalli, and E. Lorenzotti, *J. Med. Chem.*, **13**, 559 (1970).

Scheme II[a]



[a] For compounds **7**, **10**, **13**, and **14-18**, R_1 = NH_2; R_2 = H, Cl, CH_3; R_3 = H, CH_3; R_4 = heteroaryl.

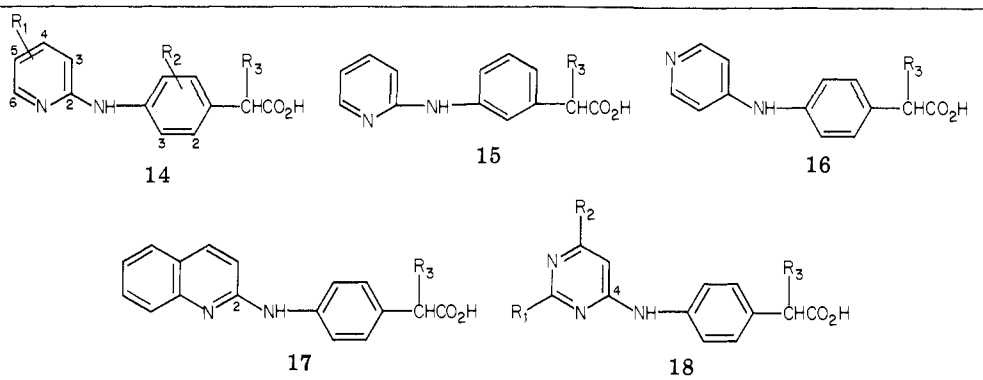
Condensation of the (aminophenyl)alkanoates (**7** and **10–12**) or their hydrochlorides with appropriate heteroaryl halides gave the (heteroarylamino)phenyl derivatives (**13**), which were then converted into the desired carboxylic acids (**14–18**) by hydrolysis (Scheme II).

Pharmacological Results and Discussion

The compounds obtained in this study were tested for antiinflammatory activity using the carrageenin-induced rat paw edema (CPE) method and for analgesic activity by the phenylquinone-induced writhing (PQW) test. Median effective doses (ED_{50}) were also determined for those compounds that initially showed some activities at 80 mg/kg in the CPE and at 100 mg/kg in the PQW tests.

As to the antiinflammatory activity, [4-(2-pyridylamino)phenyl]acetic acid (**14a**) showed potent activity. The introduction of a methyl group at the α position of the acetic acid moiety led to a more effective compound (**14b**), which was 2.5 times more potent than ibuprofen. The structural requirements for good antiinflammatory activity in this series proved rather specific, with all alterations to the structure of the parent compound **14b** proving detrimental. The introduction of a chloro or methyl group on the benzene ring of **14b** resulted in a decrease of the activity (e.g., **14c–e**), but the 3-position was less influential on antiinflammatory activity than the 2-position. Concerning the introduction of a halogeno, methyl, or nitro group on the pyridine ring of **14b**, such modification uniformly caused a marked reduction in the activity (e.g., **14f–l**). The 3-(2-pyridylamino)- and 4-(4-pyridylamino)phenyl derivatives (**15** and **16**), which are positional isomers of **14a** and **14b**, had weak activities. The replacement of the 2-pyridyl group of **14a** and **14b** with

Table II. Chemical and Pharmacological Data on [(Heteroarylamino)phenyl]alkanoic Acids



14 15 16

17 18

compd	R_1	R_2	R_3	yield, %	mp, °C	recrystn solvent	formula[a]	ED_{50}, mg/kg po CPE[b]	ED_{50}, mg/kg po PQW[c]
14a	H	H	H	60	167-170	acetone-EtOH	$C_{13}H_{12}N_2O_2$	15.79 (7.05-37.13)[d]	>100
14b	H	H	CH_3	78	188-190	MeOH	$C_{14}H_{14}N_2O_2$	10.0 (3.87-25.90)	7.33 (2.89-18.5)
14c	H	2-Cl	CH_3	38	160-162	ether-EtOH	$C_{14}H_{13}ClN_2O_2$	⩾80	⩾100
14d	H	3-Cl	CH_3	46	154-156	acetone-ether	$C_{14}H_{13}ClN_2O_2$	13.1 (4.06-42.29)	8.62 (3.72-20.0)
14e	H	3-CH_3	CH_3	37	193	MeOH	$C_{15}H_{16}N_2O_2$	16.8	36.9 (20.6-66.0)
14f	3-CH_3	H	CH_3	35	158-160	acetone-$CHCl_3$	$C_{15}H_{16}N_2O_2 \cdot 0.25H_2O$	⩾80	⩾100
14g	4-CH_3	H	CH_3	41	168-170	ether-AcOEt	$C_{15}H_{16}N_2O_2$	>80	>100
14h	5-CH_3	H	CH_3	35	165-167	ether-AcOEt	$C_{15}H_{16}N_2O_2$	⩾80	⩾100
14i	6-CH_3	H	CH_3	36	156-158	acetone-$CHCl_3$	$C_{15}H_{16}N_2O_2 \cdot 0.5H_2O$	>80	>100
14j	5-Cl	H	CH_3	18	173-175	acetone-ether	$C_{14}H_{13}ClN_2O_2$	⩾80	⩾100
14k	5-Br	H	CH_3	47	173-175	acetone-$CHCl_3$	$C_{14}H_{13}BrN_2O_2$	⩾80	100 (35.3-283)
14l	5-NO_2	H	CH_3	78	170-172	$CHCl_3$	$C_{14}H_{13}N_3O_4$	56.61 (39.61-80.81)	⩾100
15a			H	48	180	acetone-H_2O	$C_{13}H_{12}N_2O_2$	>80	⩾100
15b			CH_3	54	208-211	AcOEt-MeOH	$C_{14}H_{14}N_2O_2 \cdot C_{12}H_{23}N$[e]	77.9 (50.5-120.0)	>100
16a			H	8	200-201	dioxane-H_2O	$C_{13}H_{12}N_2O_2 \cdot HCl$	>80	
16b			CH_3	62	123-125	EtOH-AcOEt	$C_{14}H_{14}N_2O_2 \cdot HCl \cdot 0.5C_2H_5OH$	>80	⩾100
17a			H	61	219-222	DMF-H_2O	$C_{17}H_{14}N_2O_2$	>80	⩾100
17b			CH_3	41	208-212	acetone-MeOH	$C_{18}H_{16}N_2O_2 \cdot HCl$	>80	⩾100
18a	H	CH_3	H	28	290	DMF-H_2O	$C_{13}H_{13}N_3O_2$	>80	>100
18b	H	CH_3	CH_3	45	238-240	DMF-H_2O	$C_{14}H_{15}N_3O_2$	>80	⩾100
18c	SCH_3	H	H	43	199-201	EtOH-H_2O	$C_{13}H_{13}N_3O_2S$	>80	>100
19 (PAPPA)[f]								25.52 (12.71-51.24)	>100
ibuprofen								24.3 (10.6-39.2)	50.0 (32.7-76.20)

[a] All compounds were analyzed for C, H, N, S, and halogen; analytical results were within ±0.4% of the theoretical values. [b] CPE = carrageenin paw edema. [c] PQW = phenylquinone writhing. [d] 95% confidence limits. [e] Dicyclohexylamine. [f] PAPPA = 2-[4-(phenylamino)phenyl]propionic acid.

a 2-quinolyl or 4-pyrimidyl group also decreased the potencies markedly.

As to the analgesic activity, **14b** and **14d** showed excellent activities compared to the other derivatives or to ibuprofen. Therefore, the structural requirements for the analgesic activity in general seemed to closely parallel those needed for the antiinflammatory activity.

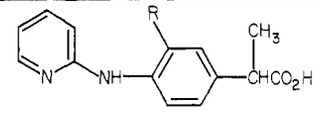
The 4-(phenylamino)phenyl analogue (**19**)[5] of **14b** was also tested for comparison. This compound exhibited antiinflammatory activity comparable to ibuprofen, but its analgesic activity was very weak.

In consideration of the efficacy in both assays, compounds **14b** and **14d** were selected for further pharmacological tests. As for the antiinflammatory activity, both compounds were evaluated for their prophylactic effects on the inflammation of adjuvant-induced arthritis in rats. Their effects at 80 mg/kg, po, were far superior than ibuprofen, and, in particular, **14b** suppressed the development of the adjuvant diseases almost completely. They were subjected to the gastric irritation test in rats, and the LD_{50} values were measured in mice. The results obtained are shown in Table III. Our results showed that compounds **14b** and **14d** tended to be far less active in causing gastric ulcers than ibuprofen; therefore, they had therapeutic ratios [UD_{50}/ED_{50} (CPE)] at least 8 times greater than ibuprofen. In addition, **14b** showed lower acute toxicity as compared to ibuprofen, whereas **14d** had higher toxicity.

On the basis of these results, **14b** seemed to be promising

(5) Rhone-Poulenc S. A., Netherlands Appl 6515071 (1966); *Chem. Abstr.*, **66**, 2379 (1971).

Table III. Pharmacological Data on 2-[4-(2-Pyridylamino)phenyl]propionic Acids



compd	R	ED_{50}, mg/kg po CPE[a] (rats)	ED_{50}, mg/kg po PQW[b] (mice)	gastric ulcer UD_{50}, mg/kg (rats), po	UD_{50}/ED_{50} (CPE)	acute LD_{50}, mg/kg (mice), po
14b	H	10.0 (3.87-25.90)[c]	7.33 (2.89-18.5)	>640	>64	1907 (1539-2362)
14d	Cl	13.1 (4.06-42.29)	8.62 (3.72-20.0)	545 (368-807)	41.6	729 (430-1236)
ibuprofen		24.3 (10.6-39.2)	50.0 (32.7-76.2)	124.6 (82.3-182.0)	5.1	1394 (1082-1672)

[a] CPE = carrageenin paw edema. [b] PQW = phenylquinone writhing. [c] 95% confidence limits.

as a potent antiinflammatory and analgesic agent with less liability to gastric side effects. Further studies of this compound are in progress, and the data will be published in succeeding papers.

Experimental Section

Melting points were determined on a Yanagimoto melting point apparatus and uncorrected. The IR, NMR, and mass spectral data of all compounds were consistent with structure. Organic extracts were dried over $MgSO_4$.

Methyl 2-(4-Nitrophenyl)propionates (6). General Procedure. To a suspension of 60% NaH (4.2 g, 0.105 mol) in dimethylformamide (DMF; 30 mL) was added **3** (1.74 g, 0.1 mol) under ice cooling, and the resulting mixture was warmed at 50 °C for 20 min. After being cooled, **2** (0.1 mol) was added at room temperature, and the mixture was heated at 80 °C for 15 min and then at 100 °C for 2 h. To the resulting solution was added MeOH (25 mL) under ice cooling and then a solution of NaOH (12 g, 0.3 mol) in H_2O (50 mL). The solution was warmed at 50 °C for 1 h. After being cooled, the solution was washed with $CHCl_3$ and then acidified with dilute HCl and extracted with ethyl acetate. The extract was washed with H_2O, dried, and concentrated to give crude **5**, which was used for the next step without further purification.

To a solution of crude **5** in MeOH (200 mL) was added concentrated H_2SO_4 (0.5 mL), and the resulting solution was heated under reflux for 3 h. The solution was concentrated, and H_2O was added to the residue and extracted with ether. The extract was washed with H_2O, dried and concentrated. The residual oil was purified by distillation under reduced pressure or chromatography on silica gel with $CHCl_3$.

Methyl 2-(3-Nitrophenyl)propionate (9). To a solution of **8**[4] (8 g, 0.04 mol) in MeOH (102 mL) was added concentrated H_2SO_4 (0.2 mL), and the solution was heated under reflux for 2 h. The solution was concentrated, and H_2O was added to the residue and extracted with ether. The extract was dried and concentrated. The residual oil was chromatographed on silica gel (130 g), and the fraction eluted with $CHCl_3$ gave **9** (7.2 g, 84%) as an oily product.

Methyl 2-(4-Aminophenyl)- and 2-(3-Aminophenyl)-propionate (7 and 10). General Procedure. To a solution of **6** (or **9**) (0.03 mol) in EtOH (100 mL) was added 5% Pd/C (0.5 g), and the mixture was submitted to catalytic hydrogenation under ordinary pressure. After the theoretical amount of H_2 was absorbed, the catalyst was filtered. The filtrate was concentrated, and the residual oil was purified by distillation under reduced pressure or chromatography on silica gel with $CHCl_3$.

[4-(2-Pyridylamino)phenyl]acetic or -propionic Acids (14). General Procedure. A mixture of **7** (or **12**) (0.02 mol) and the appropriate 2-pyridyl halide (0.02 mol) was heated at 160–170 °C for 1–4 h and then dissolved in MeOH (25 mL). The solution was neutralized with dilute aqueous NaOH and extracted with $CHCl_3$. The extract was dried and concentrated. The residue was chromatographed on silica gel, and fraction eluted with $CHCl_3$ gave the 4-(2-pyridylamino)phenyl derivative (**13**), which was used for the next step.

To a solution of crude **13** in MeOH (50 mL) was added 10% NaOH (40 mL), and the solution was stirred at room temperature for 1 h. Then the resulting solution was adjusted to pH 5–6 with dilute HCl, and the precipitate was collected and recrystallized from a suitable solvent.

The [(heteroarylamino)phenyl]alkanoic acids (**15**, **17**, and **18**), found in Table II, were prepared by this method from the corresponding methyl (aminophenyl)alkanoates (**7** and **10–12**) via the (heteroarylamino)phenyl derivatives (**13**).

[4-(4-Pyridylamino)phenyl]acetic or -propionic Acid (16) Hydrochlorides. A mixture of **7a**·HCl (or **12**·HCl) (0.015 mol) and 4-pyridylpyridinium chloride hydrochloride[6] (2.29 g, 0.01 mol) was heated at 180 °C for 1 h and then dissolved in MeOH (10 mL). The resulting solution was basified with dilute aqueous NaOH and extracted with ethyl acetate. The extract was dried and concentrated. The residue was chromatographed on silica gel, and the fraction eluted with $CHCl_3$–MeOH (50:1) gave the crude 4-(4-pyridylamino)phenyl derivative (**13**), which was used for the next step.

To the crude **13** was added concentrated HCl (20 mL), and the solution was heated under reflux for 2–10 h. The resulting solution was concentrated under reduced pressure, and the residue was recrystallized from a suitable solvent.

Pharmacology Methods. Materials. Test compounds were dissolved or suspended in 0.5% aqueous tragacanth and administered orally. All doses of the compounds are expressed as the molecular form indicated in Table II.

Statistics. ED_{50} values were calculated according to the method of Litchfield and Wilcoxon.[7]

Carrageenin-Induced Paw Edema (CPE).[8] Five to ten male rats of Wistar strain were used for each dose. Hind-paw edema was induced by a subcutaneous injection into the left hind paw. ED_{50} and 95% confidence limits were calculated from the number of positive rats showing the inhibitory rate of 25% or more in comparison with each vehicle control group at 3 h after carrageenin injection. Four to five doses were used for each drug.

Phenylquinone-Induced Writhing (PQW).[9] Five to fifteen female mice of ddN strain were used for each dose. The writhing was induced by an intraperitoneal injection of phenylquinone (0.03%), and the number of writhes was calculated for 15 min.

Prophylactic Effect on Adjuvant-Induced Arthritis.[10] Adjuvant was intradermally inoculated into the tail of female rats of Jcl:SD strain. Test compounds were administered orally once 3.5 h before and once each day for 20 days after adjuvant inoculation (0–20 days).

Gastric Ulcer Assay.[11] Male Wistar rats, fasted for 24 h,

(6) E. Koenigs and H. Greiner, *Ber Dtsch. Chem. Ges.*, **64**, 1049 (1931).
(7) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).
(8) (a) C. A. Winter, E. A. Risely, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, 111, 544 (1962). (b) M. Shimizu, H. Nakamura, S. Motoyoshi, and Y. Yokoyama, *Pharmacometrics*, **10**, 293 (1975).
(9) (a) E. Siegmund, R. Cadmus, and G. Lu, *Proc. Soc. Exp. Biol. Med.*, **95**, 729 (1957). (b) H., Nakamura and M. Shimizu, *Arch. Int. Pharmacodyn. Ther.*, **221**, 105 (1976).
(10) H. Nakamura and M. Shimizu, *J. Pharmacol. Exp. Ther.*, **211**, 20 (1979). L-2b.

were sacrificed 6 h after single oral administration of test compounds. The stomach was removed and macroscopically observed. The dose (UD_{50}) producing ulcers in 50% of the rats was calculated according to the regression line of each compound.

Acute Lethal Toxicity. LD_{50} was determined from the 7-day mortality after a single dose in Std:ddY male mice.

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Registry No. **2a**, 100-00-5; **2b**, 99-54-7; **2c**, 611-06-3; **2d**, 6627-53-8; **3**, 609-08-5; **5a**, 19910-33-9; **5b**, 83528-10-3; **5c**, 53455-85-9; **5d**, 83528-11-4; **6a**, 50415-69-5; **6b**, 83528-08-9; **6c**, 24646-28-4; **6d**, 83528-09-0; **7a**, 39718-97-3; **7a**·HCl, 83528-15-8; **7b**, 83528-13-6; **7c**, 67333-29-3; **7d**, 83528-14-7; **8**, 21762-10-7; **9**, 83528-12-5; **10**, 76980-62-6; **11**, 52913-11-8; **12**, 39552-81-3; **12**·HCl, 83528-16-9; **14a**, 76302-28-8; **14a** methyl ester, 83528-17-0; **14b**, 76302-29-9; **14b** methyl ester, 83528-18-1; **14c**, 83528-37-4; **14c** methyl ester, 83528-19-2; **14d**, 83528-38-5; **14d** methyl ester, 83528-20-5; **14e**, 76302-47-1; **14e** methyl ester, 83528-21-6; **14f**, 83528-39-6; **14f** methyl ester, 83528-22-7; **14g**, 83528-40-9; **14g** methyl ester, 83528-23-8; **14h**, 83528-41-0; **14h** methyl ester, 83528-24-9; **14i**, 83528-42-1; **14i** methyl ester, 83528-25-0; **14j**, 83528-43-2; **14j** methyl ester, 83528-26-1; **14k**, 83528-44-3; **14k** methyl ester, 83528-27-2; **14l**, 83542-58-9; **14l** methyl ester, 83542-57-8; **15a**, 83528-45-4; **15a** methyl ester, 83528-28-3; **15b**, 83528-46-5; **15b** methyl ester, 83528-29-4; **16a**·HCl, 83528-47-6; **16a** methyl ester, 83528-30-7; **16b**·HCl, 83528-48-7; **16b** methyl ester, 83528-31-8; **17a**, 83528-49-8; **17a** methyl ester, 83528-32-9; **17b**·HCl, 83528-50-1; **17b** methyl ester, 83528-33-0; **18a**, 83528-51-2; **18a** methyl ester, 83528-34-1; **18b**, 83528-52-3; **18b** methyl ester, 83528-35-2; **18c**, 83528-53-4; **18c** methyl ester, 83528-36-3; 4-pyridylpyridinium chloride hydrochloride, 5421-92-1.

(11) Y. Yokoyama, *H.* Nakamura and M. Shimizu, *Folia Pharmacol. Jpn*, **75**, 106p (1979).

Replacement of Aromatic or Heteroaromatic Groups in Nonsteroidal Antiinflammatory Agents with the Ferrocene Group

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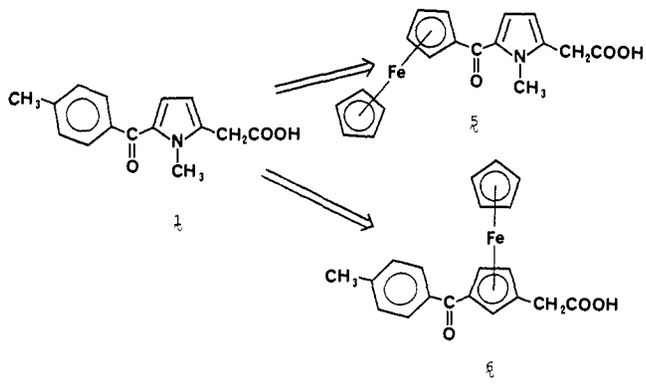
Ferrocene analogues of the antiinflammatory agents tolmetin (**1**), fenbufen (**2**), flurbiprofen (**3**), and fenclofenac (**4**) were synthesized and tested for biological activity. The derivatives exhibited little or no antiarthritic or platelet antiaggregatory activity, indicating that the ferrocene moiety is a poor bioisostere for aromatic or heteroaromatic groups in nonsteroidal antiinflammatory agents.

For many years, medicinal chemists have applied the principle of bioisosterism in drug design to improve bioactivity, reduce toxicity, and develop antagonists of know drugs.[1] In drug molecules containing aromatic rings, the introduction of heterocyclic moieties (e.g., thiophene for phenyl) is a common strategy. When considering potential analogues of tolmetin (**1**),[2] a nonsteroidal antiinflammatory agent for the treatment of arthritis, we sought an isoelectronic group to substitute for the pyrrole nucleus. A cyclopentadienide (Cp) group was an interesting possibility; however, it would be unstable by itself. Thus, a complexed formed was desired. A reasonable coordination unit, such as $Fe(CO)_3$, would afford toxicity problems, so FeCp was considered. Thus, we became intrigued with ferrocene as a bioisosteric[1c] replacement for the pyrrole unit of **1**.



Only a few ferrocene analogues of known drugs have been synthesized,[3-6] and their biological activity is generally unexciting. Nevertheless, since no systematic investigation of a therapeutic class of drugs was ever conducted, we

(1) (a) Thornber, C. W. *Chem. Soc. Rev.* **1979**, *8*, 563. (b) Korolkovas, A.; Burckhalter, J. H. "Essentials of Medicinal Chemistry"; Wiley: New York, 1976; pp 54–59. Ariens, E. J. In "Drug Design"; Ariens, E. J., Ed.; Academic Press: New York, 1971; Vol. 1, pp 241–253. (c) The concept of bioisosterism is used here in its broadest sense, as discussed by Thornber (ref 1a).

(2) Carson, J. R.; McKinstry, D. N.; Wong, S. *J. Med. Chem.* **1971**, *14*, 646. Tolmetin sodium dihydrate is sold by McNeil Pharmaceutical under the registered trade name Tolectin. For other compounds in this series, see Carson, J. R.; Wong, S. *J. Med. Chem.* **1973**, *16*, 172.

(3) Kalish, R.; Steppe, T. V.; Walser, A. *J. Med. Chem.* **1975**, *18*, 222. Loev, B.; Flores, M. *J. Org. Chem.* **1966**, *26*, 3595. Popp, F. D.; Moynahan, E. B. *J. Med. Chem.* **1970**, *13*, 1020. Popp, F. D.; Moynahan, E. B. *J. Heterocycl. Chem.* **1970**, *7*, 351.

(4) Edwards, E. I.; Epton, R.; Mars, G. *J. Organometal. Chem.* **1975**, *85*, C23. *Ibid.* **1976**, *107*, 351. *Ibid.* **1976**, *122*, C49.

(5) Hanzlik, R. P.; Soine, P.; Sione, W. H. *J. Med. Chem.* **1979**, *22*, 424.

(6) Epton, R.; Mars, G.; Rogers, G. K. *J. Organometal. Chem.* **1976**, *110*, C42.

0022-2623/83/1826-0226$01.50/0