2-[(Phenylthio)methyl]pyridine Derivatives: New Antiinflammatory Agents[1]

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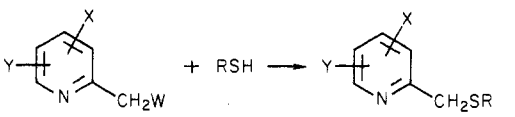
2-[(Phenylthio)methyl]pyridine derivatives (**1a–e**) inhibited the dermal reverse passive Arthus reaction (RPAR) in the rat. In the same model, indomethacin was inactive, and hydrocortisone was active. Compounds **1a–d** also significantly reduced exudate volume and white blood cell accumulation in the pleural RPAR. This pattern of activity was similar to that of hydrocortisone and different from that of indomethacin.

Immune complexes have been implicated in the pathogenesis of rheumatiod arthritis.[2-4] The Arthus reaction represents an acute model of imune complex induced inflammation and tissue injury and was chosen as a screening method for potential antiarthritic agents. The reverse passive Arthus reaction (RPAR) was elicited in the rat at two sites: the skin and pleural cavity. Indomethacin was inactive in these RPAR models, whereas hydrocortisone was a potent inhibitor. From systematic screening and chemical modification, the 2-[(phenylthio)methyl]pyridine series (**1a–e**) was identified, and this series was active in both the rat dermal and pleural RPAR and in the rat carrageenin pleural test.

Synthesis. Chemical modifications of compound **1b** were carried out separately at five sites of the molecule: (1) substitution of the phenyl ring, (2) substitution of the pyridine ring, (3) modificaton of the mercaptomethylene bridge, (4) modification of the pyridine ring, and (5) replacement of the phenyl ring by other heterocyclic rings.

Compounds **1a–r**, **2a–j**, **4a–f**, and **5a–d** were prepared, as described in Scheme I, by the reaction of 2-picolyl chloride or 2-(hydroxymethyl)pyridine with the mercaptol either in 48% hydrobromic acid under reflux or in the presence of sodium ethoxide in ethanol at room temperature. Compounds **3a–n** were prepared by straightforward chemical methods.

Scheme I



W = Cl, OH

Biological Results and Discussion

In the dermal and in the pleural RPAR, indomethacin was inactive despite the relatively high (with respect to toxicity) doses tested. In our laboratory, similar observations were made with other nonsteroidal antiinflammatory (NSAI) agents. 2-[(Phenylthio)methyl]pyridine (**1b**) was active in the dermal RPAR. Its potency was one-third (on a molar basis) that of hydrocortisone (Table I). Various substituents at the para position of the phenyl ring of **1b** caused reduction in activity. Generally, compounds containing electron-withdrawing groups, such as halogens and nitro, were more active than lipophilic or polar groups, such as methyl, *tert*-butyl, methoxy, acetamido, amino, and hydroxy. No preference for substitution position was observed. The *o*-, *m*-, and *p*-chloro derivatives **1o,l,c** had comparable activity. Substitution of the pyridine ring by methyl, methoxy, chlorine, hydroxy, or phenyl caused loss of activity (Table II). The sulfoxide, sulfone, and *N*-oxide of **1a** had similar activity to that of the parent compound (Table III). Other modifications of the mercaptomethylene bridge led to reduction of activity. Changing the linkage of the side chain from postion 2′ of the pyridine ring to the 3′ and the 4′ carbons caused complete loss of activity. The *N*-methylpiperidine analogue **4d** was active in the range of the parent compound **1a** (Table IV). Compounds **5b,e,f** containing pyrimidine, pyridine, and quinazolone in place of the phenyl ring were active (Table V).

In the pleural RPAR test, **1a** significantly reduced exudate volume and white blood cell accumulation at a dose of 82 and 73 μmol/kg, respectively. Its potency was about one-half (on a molar basis) that of hydrocortisone (Table VI). In the pleural carrageenin test, **1a** inhibited both exudate volume and cell accumulation. Hydrocortisone also affected both parameters, while indomethacin had an effect on exudate volume only (Table VII).

Conclusion

2-[(Phenylthio)methyl]pyridine derivatives **1a–d** were effective inhibitors of immune complex induced inflammation as represented by the rat reverse passive Arthus reaction. In the same reaction the representative NSAI agent indomethacin was inactive. Derivative **1a** also inhibited both exudate formation and cellular accumulation in the more conventional carrageenin pleural test; indomethacin inhibited only exudate volume in this model. In conclusion, the studies presented suggest that 2-[(phenylthio)methyl]pyridine compounds represent a new class of antiinflammatory agents working by a mechanism different from that of the classical NSAI agents.

Experimental Section

All melting points were taken on a Thomas-Hoover apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 521 spectrophotometer, ^{1}H NMR spectra on a Varian T-60 in Me_2SO-d_6, and mass spectra on an AEI-10 90-MHz spectrometer with Fabritek 1070/PDP-8 Fourier transform accessory. All new compounds had NMR and IR spectra consistent with their structures and also gave satisfactory C, H, and N analyses in the range of ±0.3% from the calculated values. 2-Phenylpyridine (**3k**) and 2-(*p*-chlorobenzyl)pyridine (**3i**) were purchased from Aldrich Chemical Co., Milwaukee, WI. All the organic phases were dried over anhydrous Na_2SO_4.

(1) This paper has been presented: see "Abstracts of Papers", 182nd National Meeting of the American Chemical Society, New York, Aug 23–28, 1981, American Chemical Society, Washington, DC, 1981, Abstr MEDI 61.
(2) N. J. Zvaifler, *Adv. Immunol.*, **16**, 265 (1973).
(3) M. Ziff, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **32**, 131 (1973).
(4) N. J. Zvaifler, *Arthritis Rheum.*, **17**, 297 (1974).
(5) D. H. Campbell, J. S. Garvey, N. E. Cremer, and D. H. Susdorf, "Methods in Immunology", W. A. Benjamin, New York, 1963, p 215.
(6) C. G. Cochrane in "The Inflammatory Process", B. W. Zweifach, L. H. Grant, and R. T. McClusky, Eds., Academic Press, New York, 1968, p 613.
(7) L. Bauer and L. A. Gardella, *J. Org. Chem.*, **28**, 1320 (1963).
(8) O. Makovcova, L. Sindelar, and P. Vaculik, *Biol. Plant.*, **10**, 354 (1968); *Chem. Abstr.*, **70**, 10543*p* (1969).

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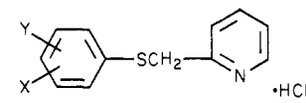
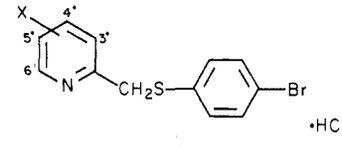
Table I. Effect of 2-[(Phenylthio)methyl]pyridine Derivatives and Reference Agents on the Rat Dermal RPAR



compd	X	Y	synth method	yield, %	formula	mp, °C	ED_{40},[a] μmol/kg po
1a	4-Br	H	A	60	$C_{12}H_{11}BrClNS$	194-196	151 (106, 232)
1b	4-H	H	A	60	$C_{12}H_{12}ClNS$[b]	133-135	101 (63, 236)
1c	4-Cl	H	A	80	$C_{12}H_{11}Cl_2NS$	190-192	186 (115, 439)
1d	4-F	H	A	79	$C_{12}H_{11}ClFNS$	184-186	159 (87, 554)
1e	4-NO_2	H	A	90	$C_{12}H_{11}ClN_2O_2S$	219-221	233 (120, 2026)
1f	4-$C(CH_3)_3$	H	A	73	$C_{16}H_{20}ClNS$	163-165	34%
1g	4-CH_3	H	A	82	$C_{13}H_{14}ClNS$	189-190	NA
1h	4-OCH_3	H	B	75	$C_{13}H_{14}ClNOS$	125-127	23%
1i	4-NH_2	H	A	43	$C_{12}H_{14}Cl_2N_2S$	220-221	25%
1j	4-$NHCOCH_3$	H	B	84	$C_{14}H_{15}ClN_2OS$	178-180	30%
1k	4-OH	H	Ex[c]	60	$C_{12}H_{12}ClNOS$	145-150	NA
1l	3-Cl	H	A	85	$C_{12}H_{11}Cl_2NS$	152-154	223 (121, 1127)
1m	3-OCH_3	H	B	76	$C_{13}H_{14}ClNOS$	108-110	273 (163, 869)
1n	3-CF_3	H	B	79	$C_{13}H_{11}ClF_3NS$	143-145	307 (158, 2343)
1o	2-Cl	H	A	62	$C_{12}H_{11}Cl_2NS$	144-146	300 (153, 3205)
1p	2-Br	H	A	85	$C_{12}H_{11}BrClNS$	140-142	282 (144, 3368)
1q	3-Cl	4-Cl	A	80	$C_{12}H_{10}Cl_3NS$	208-210	402 (240, 1177)
1r	2-CH_3	4-$C(CH_3)_3$	A	51	$C_{17}H_{22}ClNS$	148-150	30%
hydrocortisone							33 (25, 47)
indomethacin							NA[d]

[a] The dose estimated to produce 40% inhibition with 95% confidence limits in parentheses; calculated by least-squares regression analysis. Compounds that produce <40% at the highest dose (350 μmol/kg) are listed as the percent obtained or NA for no significant activity ($p \leq 0.05$). [b] Reference 7. [c] Ex = experimental procedure described. [d] The highest dose tested for indomethacin was 56 μmol/kg.

Table II. Effect of 2-[(Phenylthio)methyl]pyridine Derivatives in the Rat Dermal RPAR



compd	X	synth method	yield, %	formula	mp, °C	% inhibn[a] at 350 μmol/kg
2a	3'-OH	A	25	$C_{12}H_{11}BrClNOS$	148-149	NA
2b	6'-$CH_2SC_6H_4$-4-Br	A	45	$C_{19}H_{16}Br_2ClNS_2$	174-175	NA
2c	6'-CH_3, 3'-OH	A	14	$C_{13}H_{13}BrClNOS$	202-203	NA
2d	3'OCH_3	Ex[b]	33	$C_{13}H_{13}BrClNOS$	200-201	26
2e	6'-CH_3	A	54	$C_{13}H_{13}BrClNS$	190-193	28
2f	5'-CH_3	Ex	60	$C_{13}H_{12}BrNS$[c]	69-72	NA
2g	3'-CH_3	Ex	60	$C_{13}H_{13}BrClNS$	198-200	25
2h	6'-Cl	Ex	44	$C_{12}H_9BrClNS$[c]	49-50	NA
2i	4'-Cl	Ex	25	$C_{12}H_{12}BrCl_2NOS$[d]	178-180	NA
2j	4'-C_6H_5	Ex	42	$C_{18}H_{15}BrClNS$	190-192	NA

[a] Represents the percent inhibition obtained at the highest dose tested (350 μmol/kg). NA stands for no significant activity ($p \leq 0.05$). [b] Ex = experimental procedure described. [c] Isolated as free base. [d] Isolated as monohydrate.

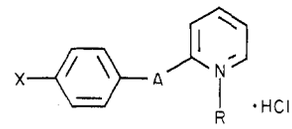
General Synthetic Methods for the Preparation of 2-[(Phenylthio)methyl]pyridine Derivatives. A. A suspension of the pyridylcarbinol (60 mmol) and the mercaptol (66 mmol) in 48% hydrobromic acid (75 mL) was heated under reflux for 24 h. The reaction mixture was cooled to 0 °C, and the precipitate was filtered, washed with ice–water, and dried to give the product as its hydrobromide salt. The salt was dissolved in saturated sodium bicarbonate, and the solution was extracted with ether. The extracts were dried and concentrated in vacuo. The residue was treated with ethereal hydrogen chloride to give the product as the hydrochloride salt.

B. To a solution of sodim thiophenolate, prepared by dissolving sodium (100 mg atoms) and the mercaptol (50 mmol) in ethanol (100 mL), was added a solution of the picolyl chloride hydrochloride (50 mmol) in ethanol (100 mL) over a period of 30 min. The mixture was stirred at room temperature overnight. Ethanolic hydrogen chloride solution was added, and the inorganic precipitate was filtered. The filtrate was concentrated in vacuo, and the residue was dissolved in water and washed with ether. The aqueous solution was concentrated to give the product as the hydrochloride salt.

2-[[(*p*-Hydroxyphenyl)thio]methyl]pyridine hydrochloride (1k) was obtained from the methoxy analogue **1h** upon treatment with concentrated hydrobromic acid under reflux for 6 h. The hydrobromide product was converted into the hydrochloride salt upon heating in methanolic hydrogen chloride solution.

2-[[(*p*-Bromophenyl)thio]methyl]-3-methoxypyridine Hydrochloride (2d). Sodium methoxide (1.08 g, 20 mmol) was added at room temperature to a stirred solution of **2a** (3.32 g, 10 mmol) in absolute ethanol (500 mL). The solution was refluxed for 3 h, and then dimethyl sulfate (1.26 g, 10 mmol) in ethanol (10 mL) was added. Reflux was continued for an additional 24 h. The precipitate was filtered, and the filtrate was concentrated in vacuo. The residue was taken up in chloroform, insoluble material was filtered, and the filtrate was again concentrated to give a dark oil. This was treated with ethanolic hydrogen chloride and ether. Upon cooling, **2d** crystallized. A second crystallization

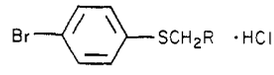
Table III. Effect of Pyridine Derivatives on the Rat Dermal RPAR

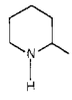
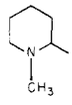


compd	A[b]	X	R	formula	mp, °C	ED_{40},[a] μmol/kg po
3a	$SOCH_2$	Br	NS[c]	$C_{12}H_{10}BrNOS$[d]	77-79	216 (149, 289)
3b	SO_2CH_2	Br	NS	$C_{12}H_{10}BrNO_2S$[d]	141-143	192 (137, 317)
3c	OCH_2	Cl	NS	$C_{12}H_{11}Cl_2NO$	137-139	39%
3d	$NHCH_2$	Br	NS	$C_{12}H_{12}BrClN_2$	182-183	NA
3e	CH_2S	Br	NS	$C_{12}H_{11}BrClNS$	158-159	36%
3f	SCH_2CH_2	Br	NS	$C_{13}H_{13}BrClNS$	125-127	NA
3g	S	Br	NS	$C_{11}H_9BrClNS$	195-198	369 (247, 727)
3h	CH_2SCH_2	Br	NS	$C_{13}H_{13}BrClNS$	110-112	31%
3i	CH_2	Cl	NS	$C_{12}H_{11}Cl_2N$	153-154	35%
3j	$SCH(CH_3)$	Br	NS	$C_{13}H_{13}BrClNS$	124-125	212 (148, 374)
3k	bond	H	NS	$C_{11}H_8N$[d]	76-77	32%
3l	CH_2CH_2	H	NS	$C_{13}H_{14}ClN$[e]	114-115	36%
3m	SCH_2	Br	O	$C_{12}H_{11}BrClNOS$	155-157	148 (93, 304)
3n	SCH_2	Br	CH_3	$C_{13}H_{13}BrINS$[f]	172-173	22%

[a] Represents the dose producing 40% inhibition with 95% confidence limits in parentheses; calculated by least-squares regression analysis. Compounds producing <40% inhibition are listed with the percentage obtained at 350 μmol/kg or as NA when no significant activity was obtained. [b] Left end of side chain A is linked to phenyl. [c] NS = nonsubstituted. [d] Free base. [e] Reference 8. [f] Isolated as the iodide salt.

Table IV. Effect of (Phenylthio)methyl Derivatives on the Rat Dermal RPAR



compd	R	formula	mp, °C	ED_{40},[a] μmol/kg po
4a		$C_{12}H_{11}BrClNS$	174-176	23%
4b		$C_{12}H_{11}BrClNS$	207-209	26%
4c		$C_{16}H_{20}BrNO_4S$[b]	146-147	430 (238, 1808)
4d		$C_{13}H_{19}BrClNS$	166-167	159 (109, 266)

[a] Represents the dose producing 40% inhibition with 95% confidence limits in parentheses. The percent obtained at the highest dose (350 μmol/kg) is listed for two compounds that produced <40% inhibition. [b] Isolated as the oxalate salt.

was obtained from isopropyl alcohol–ether.

2-[[(*p*-Bromophenyl)thio]methyl]-5-methylpyridine Hydrochloride (2f). 2-(Chloromethyl)-5-methylpyridine hydrochloride was prepared according to A. B. Ash et al.[9] in 25% yield. This was reacted with *p*-bromothiophenol according to method B to give **2f**.

2-[[(*p*-Bromophenyl)thio]methyl]-3-methylpyridine Hydrochloride (2g). 2-(Chloromethyl)-3-methylpyridine was prepared from 2,3-lutidine upon reaction with chlorine gas as described by Mathes and Schüly.[10] This was reacted with *p*-bromothiophenol according to method B to give **2g**.

2-[[(*p*-Bromophenyl)thio]methyl]-6-chloropyridine (2h). A solution of 2-methyl-6-chloropyridine *N*-oxide (17.8 g, 124 mmol) (prepared from 2-methyl-6-chloropyridine upon treatment with 30% hydrogen peroxide–acetic acid) in acetic anhydride (120 mL) was stirred and heated in an oil bath at 120–130 °C for 2.5 h. The reagent was removed in vacuo, and the residue was treated with 10% hydrochloric acid (100 mL) under reflux for 2 h. The solvent was evaporated, and the residue was crystallized from ethanol–ether to give 2-(hydroxymethyl)-6-chloropyridine hydrochloride (3.96 g, 16% yield), mp 137–140 °C.

A solution of 2-(hydroxymethyl)-6-chloropyridine hydrochloride (2.48 g, 13.7 mmol) in thionyl chloride (20 mL) was refluxed for 30 min. Excess reagent was removed in vacuo, and the residue was dissolved in benzene and concentrated again. The oil was dissolved in absolute ethanol (100 mL) and treated at 0 °C with a solution of *p*-bromothiophenol (2.61 g, 13.7 mmol) and sodium ethoxide (2.18 g, 28 mmol) in ethanol (50 mL). The reaction mixture was stirred at room temperature under nitrogen overnight and concentrated in vacuo. The residue was taken up in CH_2Cl_2 and washed with water. The organic phase was dried and concentrated to give a semisolid residue. This was crystallized from petroleum ether to give **2h**.

2-[[(*p*-Bromophenyl)thio]methyl]-4-chloropyridine Hydrochloride (2i). 2-(Hydroxymethyl)-4-chloropyridine was prepared from 2-methyl-4-chloropyridine by the procedure described above. This was reacted with *p*-bromothiophenol according to method A to give **2i**.

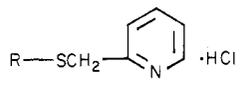
2-[[(*p*-Bromophenyl)thio]methyl]-4-phenylpyridine Hydrochloride (2j). 2-Methyl-4-phenylpyridine was prepared from 4-phenylpyridine according to Agrawal and co-workers' procedure.[11] This was converted into 2-(hydroxymethyl)-4-phenylpyridine according to the procedure described above and then reacted with *p*-bromothiophenol according to method A to give **2j**.

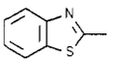
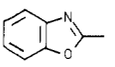
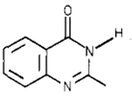
2-[[(*p*-Bromophenyl)sulfinyl]methyl]pyridine (3a) and 2-[[(*p*-Bromophenyl)sulfonyl]methyl]pyridine (3b). 2-[[(*p*-Bromophenyl)thio]methyl]pyridine hydrochloride (2.2 g, 70 mmol) was dissolved in saturated sodium bicarbonate (20 mL) and extracted with methylene chloride three times. The organic phase was dried and filtered, and the filtrate was concentrated to 50 mL. *m*-Chloroperbenzoic acid (1.2 g, 70 mmol) was added, and the mixture was stirred at room temperature for 3 h and then cooled to 0 °C. The precipitate was filtered, and the filtrate was concentrated in vacuo. The residue was chromatographed on a silica gel column. Elution with ether gave sulfoxide **3a** in 40% yield. Elution with acetone gave sulfone **3b** in 38% yield.

Compounds 3c,e,g,h,j,m were prepared by the reaction of the appropriate halide with the mercapto derivative by method B in

(9) A. B. Ash, F. A. Daniher, and B. E. Hackley, Jr., U.S. Patent 3 501 486; *Chem. Abstr.*, **72**, 121377*y* (1970).
(10) W. Mathes and H. Schüly, *Angew. Chem., Int. Ed. Engl.*, **2**, 144 (1963).
(11) K. C. Agrawal, B. A. Booth, S. M. DeNuzzo, and A. C. Sartorelli, *J. Med. Chem.*, **18**, 368 (1975).

Table V. Effect of 2-Thiopicolyl Derivatives on the Rat Dermal RPAR



compound	R	formula	mp, °C	ED_{40},[a] μmol/kg po
5a		$C_{12}H_{18}ClNS$	107-109	21%
5b		$C_{10}H_{10}ClN_3S$	173-175	283 (170, 873)
5c		$C_{13}H_{11}ClN_2S_2$	149-152	NA
5d		$C_{13}H_{11}ClN_2OS$	145-150	26%
5e		$C_{11}H_{12}Cl_2N_2S$[b]	216-218	149 (111, 215)
5f		$C_{13}H_{11}N_3OS$[c]	165-174	177 (129, 272)

[a] The dose estimated to produce 40% inhibition with 95% confidence limits in parentheses; calculated by least-squares regression analysis. Compounds producing <40% inhibition at the highest dose (350 μmol/kg) are listed as the percent obtained or NA for no significant activity ($p \leq 0.05$). [b] Dihydrochloride. [c] Isolated as the free base.

Table VI. Effect of 2-[(Phenylthio)methyl]pyridine Derivatives and Hydrocortisone on the Rat Pleural RPAR

compd	ED_{50},[a] μmol/kg po	
	exudate WBC[b]	exudate vol
1a	73 (54, 104)	82 (60, 114)
1b	252 (163, 500)	172 (122, 273)
1c	162 (125, 243)	154 (114, 235)
1d	129 (94, 188)	137 (109, 180)
hydrocortisone	50 (44, 58)	38 (33, 44)
indomethacin	NA[c]	NA[c]

[a] ED_{50} represents the dose producing 50% inhibition as calculated by least-squares regression analysis. The 95% confidence limits are in parentheses. [b] WBC = white blood cells. [c] NA = nonactive; indomethacin failed to produce a dose-related effect through 56 μmol/kg.

Table VII. Effect of 1a and Standard Agents in the Rat Pleural Carrageenin Test

compd	ED_{50},[a] μmol/kg po	
	exudate WBC[b]	exudate vol
1a	215 (155, 300)	142 (60, 221)
hydrocortisone	25 (19, 30)	33 (22, 52)
indomethacin	NA	3 (2, 5)

[a] ED_{50} represents the dose producing 50% inhibition calculated by least-squares regression analysis. The 95% confidence limits are in parentheses. NA = nonactive; indomethacin produced no significant effect at 28 μmol/kg. [b] WBC = white blood cells.

yields of 56, 23, 25, 48, 15, and 86%, respectively.

***N*-(2-Picolyl)-*p*-bromoaniline Hydrochloride (3d).** A solution of 2-pyridinecarboxaldehyde (5.36 g, 50 mmol) and *p*-bromoaniline (8.6 g, 50 mmol) in toluene (100 mL) was heated under a water trap for 2 h. The solvent was removed in vacuo, and the residue was dissolved in ethanol (100 mL) and treated with sodium borohydride (2.1 g, 55 mmol). The solution was stirred at room temperature for 18 h. Ethanolic hydrochloric acid solution was added to pH 1. The inorganic precipitate was filtered, and the filtrate was concentrated in vacuo. The residue was crystallized from 2-propanol to give **3d** in 26% yield.

2-[[(*p*-Bromophenyl)thio]ethyl]pyridine Hydrochloride (3f). A solution of 2-vinylpyridine (3.2 g, 31 mmol) and *p*-bromothiophenol (4.7 g, 25 mmol) in dry benzene (25 mL) was heated under reflux overnight. The solvent was removed in vacuo, and the residue was treated with ethereal hydrogen chloride. The hydrochloride salt of **3f** precipitated and was recrystallized from ethanol (94% yield).

1-Methyl-2-[[(*p*-bromophenyl)thio]methyl]pyridinium Iodide (3n). To a solution of 2-[[(*p*-bromophenyl)thio]-methyl]pyridine (4.0 g, 21 mmol) in ethanol (50 mL) was added methyl iodide (4.2 g, 30 mmol), and the mixture was heated under reflux for 20 h. While the solution cooled, **3n** crystallized (66% yield).

Compounds 4a,b were prepared from the picolyl chlorides by method A in 38 and 47% yields, respectively.

Compounds 4c,d were prepared from 2-(chloromethyl)-piperidine and 2-(chloromethyl)-1-methylpiperidine by method B in 5.5 and 18% yields, respectively.

Compounds 5a–f were prepared according to method B in yields of 69, 49, 36, 53, 46, and 40%, respectively.

Biological Testing Methods. Compound Preparation and Administration. Compounds were suspended by homogenation in a 0.2% methylcellulose vehicle just prior to use. Control vehicle or compound suspensions were administered by oral gavage at volumes of 4 mL/kg to male, Sprague–Dawley rats (King Animal Labs, Inc., Oregon, WI). The rats were deprived of food 18 h prior to dosing but allowed free access to water.

Production and Fractionation of Antiserum Used in Arthus Tests. Antibody to bovine serum albumin (BSA) was produced in rabbits. Prior to use in the Arthus tests, the antiserum was partially purified by ammonium sulfate and ethanol precipitation. The resulting γ-globulin fraction was freeze–dried. An appropriate amount of this anti-BSA preparation was dissolved in 0.9% saline and filtered through a 0.2-μm filter before use.

Rat Dermal Reverse Passive Arthus Test (Dermal RPAR). Groups of six rats weighing 140–160 g were injected intravenously (iv) via the lateral tail vein with a solution containing 0.15% weight/volume (w/v) BSA and 0.4% w/v Evans Blue dye in 0.9% saline (2 mL/kg). Approximately 1 h later, test agents were administered at three dose levles. Vehicle controls were included in each study. Thirty minutes after dosing, 0.05 mL of the anti-BSA preparation was injected intradermally (id) into the shaved dorsal skin of the rats, using a 26 gauge 0.375-in. needle. Four hours after antibody challenge, the animals were sacrificed with carbon dioxide, the dorsal skin was reflexed, and the lesions were excised. The diameters of the lesions, as outlined by the leakage of Evans Blue dye, were measured along two perpendicular axes. On the assumption that the lesions were circular, lesion area was calculated by the average of the diameters. We calculated percent inhibition of lesion area by comparing the average lesion

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.

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

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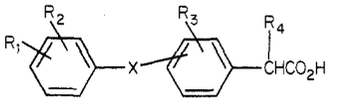
A series of [(heteroarylamino)phenyl]alkanoic acids having pyridine, quinoline, or pyrimidine as the heteroaryl moiety was prepared as potential antiinflammatory agents. Among them, 2-[4-(2-pyridylamino)phenyl]propionic acid (**14b**) showed excellent antiinflammatory and analgesic activities with less 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

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