ester, 96866-17-0; 2-amino-*N*-(3-methylbutyl)acetamide, 87429-13-8; *N*-[3(*RS*)-[*N*-(benzyloxy)-*N*-formylamino]-1-oxo-2-benzylpropyl]glycine isopentylamide, 96866-18-1; *N*-[3(*RS*)-[*N*-(benzyloxy)-*N*-formylamino]-1-oxo-2-benzylpropyl]glycine benzylamide, 96866-19-2; 3-(ethoxycarbonyl)-2-benzylidenepropanoic acid, 87439-00-7; glycine *tert*-butyl ester, 6456-74-2; *N*-[3-(ethoxycarbonyl)-2-benzylidene-1-oxopropyl]glycine *tert*-butyl ester, 87439-01-8; *N*-(3-carboxy-2-benzylidene-1-oxopropyl)glycine *tert*-butyl ester, 87439-02-9; *N*-[3-[[(benzyloxy)amino]carbonyl]-2-benzylidene-1-oxopropyl]glycine *tert*-butyl ester, 96866-20-5; *N*-[3-[[(benzyloxy)amino]carbonyl]-2-benzylidene-1-oxopropyl]glycine, 87438-57-1; *N*-[3-(ethoxycarbonyl)-2-benzylidene-1-oxopropyl]glycine isopentylamide, 96866-21-6; *N*-(3-carboxy-2-benzylidene-1-oxopropyl)glycine isopentylamide, 96866-22-7; *N*-[3-[[(benzyloxy)amino]carbonyl]-2-benzylidene-1-oxopropyl]glycine isopentylamide, 96866-23-8; L-alanine *tert*-butyl ester, 21691-50-9; *N*-[3-(ethoxycarbonyl)-2-benzylidene-1-oxopropyl]-L-alanine *tert*-butyl ester, 96896-87-6; *N*-(3-carboxy-2-benzylidene-1-oxopropyl)-L-alanine *tert*-butyl ester, 96896-88-7; *N*-[3-[[(benzyloxy)amino]carbonyl]-2-benzylidene-1-oxopropyl]-L-alanine *tert*-butyl ester, 96896-89-8; *N*-[3-[[(benzyloxy)amino]carbonyl]-2-benzylidene-1-oxopropyl]-L-alanine, 96896-90-1; EC 3.4.24.11, 82707-54-8; aminopeptidase, 9031-94-1; dipeptidylaminopeptidase, 9032-67-1.

5,6-Diaryl-2,3-dihydroimidazo[2,1-*b*]thiazoles: A New Class of Immunoregulatory Antiinflammatory Agents

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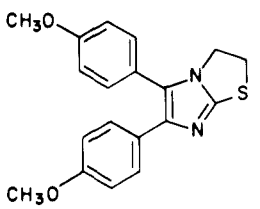
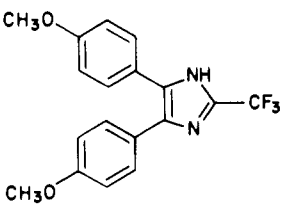
A series of substituted 5,6-diaryl-2,3-dihydroimidazo[2,1-*b*]thiazoles were synthesized and evaluated in the rat adjuvant-induced arthritis and mouse oxazolone-induced contact sensitivity assays to determine the potential of these compounds for use as immunoregulatory antiinflammatory agents. This class of compounds was derived by combining salient structural features of the antiinflammatory agent flumizole and the immunoregulatory drug levamisole. Unlike the latter two, a number of compounds in the target series were found to possess the desired combination of activities. Exploration of structure–activity relationships in the adjuvant-induced arthritic rat assay revealed that optimal potency was exhibited by symmetrically substituted 5,6-diaryl compounds having one of the following alkyl heteroatom or halogen functions at the para position: methoxy, ethoxy, methylthio, *N*-ethyl-*N*-methylamino, fluoro, or chloro. Scrambling of these two substituent classes to yield the unsymmetrically substituted 5,6-diaryl compounds resulted in potent activity only with the 5-alkyl heteroatom, 6-halo-substituted regioisomers. However in the oxazolone-induced contact sensitivity assay, no consistent relationship of variation in activity with structural change was apparent. The initial target compound 5,6-bis(4-methoxyphenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (1) was compared with its progenitors in additional models of inflammation and immunoregulation.

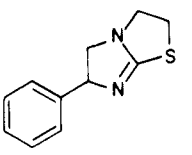
Rheumatoid arthritis, a systemic disease characterized by inflammation and progressive joint destruction, continues to be treated primarily symptomatically.[1] Although of unknown etiology, this disease is characterized by a variety of immune abnormalities, including excess immunoglobulin production, the presence of autoantibodies, and an impairment in thymic derived lymphocyte function.[2a–d] The search for an improved agent to treat rheumatoid arthritis and other inflammatory diseases with immunological abnormalities has gone in two major directions: the investigation of nonsteroidal antiinflammatory drugs (NSAIDs) possessing diminished ulcerogenic properties and the study of immunomodulating agents.[3] Fusion of both sets of properties into a single drug that could reduce the arthritic inflammation, restore immune function to normal, and provide protection from tissue destruction would be therapeutically advantageous. By combining closely related pharmacophoric structures of the potent antiinflammatory agent flumizole[4a,b] with the biological response modifier levamisole,[4c] compound 1 was designed and synthesized as our first such hybrid.[4d] Although many antiinflammatory flumizole analogues and immunomodulatory levamisole analogues have been reported,[3,4a,5–7] hybrid molecules possessing such a combined profile are not well-known.



1



flumizole



levamisole

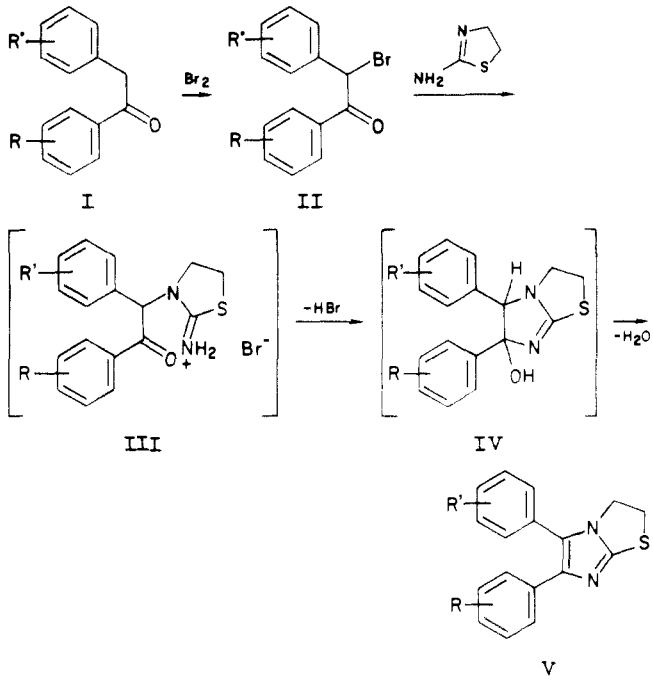
Compound 1 stimulated mouse subliminal oxazolone-induced contact sensitivity in a manner analogous to le-

† Department of Medicinal Chemistry.
‡ Department of Immunology.
§ Department of Synthetic Chemistry.

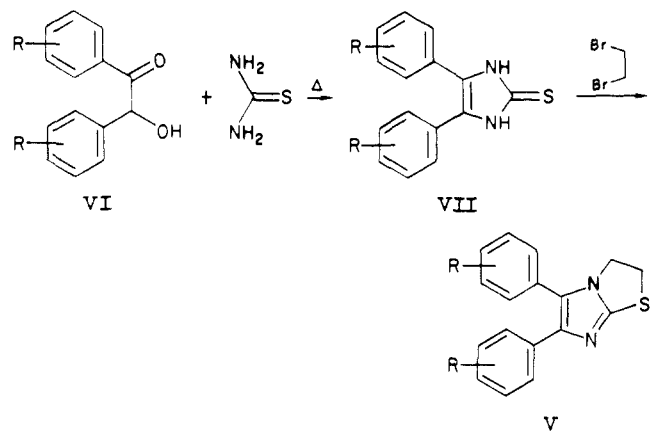
(1) Hart, F. D.; Huskisson, E. C.; Ansell, B. M. In "Drug Treatment of the Rheumatic Diseases"; Hart, F. D., Ed.; ADIS Press: New York, 1982; Chapter 2.
(2) (a) Raeman, F.; DeCock, W.; Debeukelaar, T.; Decree, J.; Verhaegen, H.; *Clin. Exp. Immunol.* **1981**, *45*, 475. (b) Meijer, C. J. L. M.; Lafeber, G. J. M.; Cnossen, J.; Damsteeg, M. G. M.; Cats, A. *J. Rheumatol.* **1982**, *9*, 18. (c) Veys, E. M.; Hermanns, P.; Schindler, J.; Kung, P. C.; Goldstein, G.; Symoens, J.; Van Wauwe, J. *Ibid.* **1982**, *9*, 25. (d) Veys, E. M.; Hermanns, P.; Verbruggen, G.; Schindler, J.; Goldstein, G. *Ibid.* **1982**, *9*, 821.
(3) Lombardino, J. G. In "Annual Reports in Medicinal Chemistry"; Hess, H.-J., Ed.; Academic Press: New York, 1981; Chapter 18.

0022-2623/85/1828-1169$01.50/0

Scheme I



Scheme II



vamisole and exhibited good antiinflammatory and antiarthritic activity in the rat adjuvant-induced arthritic model (see Table IV). With this novel biological profile providing encouragement, analogues were prepared to investigate structure–activity relationships and **1** was compared to its progenitors in additional assays of inflammation and immunoregulation.

Chemistry. The majority of the 5,6-diaryl-2,3-dihydroimidazo[2,1-*b*]thiazoles and related analogues employed in this study (see Tables I and II) were prepared by one of two synthetic routes. In method A (Scheme I), a substituted α-bromodesoxybenzoin (II) is prepared by bromination of the corresponding desoxybenzoin (I). Condensation of II with 2-aminothiazoline presumably proceeds through the ring-alkylated intermediate III,[5] which is deprotonated and cyclized in the presence of excess base to give alcohol IV. This alcohol is subsequently dehydrated either spontaneously or upon acidic workup to afford the aromatic imidazole-containing product V. Thus, in one step this route transformed II regiospecifically into the single isomer V. In method B (Scheme II), the substituted imidazole-2-thione VII (see Table III) was first elaborated by heating thiourea with the substituted benzoin VI in dimethylformamide or refluxing hexanol and then cycloalkylated with a 1,2-dihaloethane to afford the fused thiazoline ring product V.[8] The thiazine **46** was prepared in a similar fashion using 1,3-dibromopropane.[9]

The nonregiospecific nature of this latter ring closure resulted in nearly equal amounts of regioisomers when unsymmetrical imidazolethiones were used.[10] Therefore, this route was employed only to prepare the symmetrically substituted 5,6-diaryl products.

Additional analogues were synthesized by further modification of compounds obtained via Schemes I and II. Demethylation of **1** catalyzed by boron tribromide afforded the phenol **14**, while O-alkylation of the disodium salt of phenol **14** with allyl bromide or 2,2,2-trifluoroethyl triflate gave ethers **23** and **33**, respectively. Amines **31** and **36** were obtained via acid-catalyzed hydrolysis of the acetamides **20** and **34** respectively (Method C). N-alkylation of the secondary amine **36** with excess iodomethane afforded the tertiary amine **40**. Acylation of phenol **14** to the acetate **15** was accomplished with acetic anhydride and potassium carbonate, while acylation of the amine **31** to the pivalamide **32** was achieved by refluxing **31** in a mixture of pivalic acid and pivalic anhydride. The 2,3-dihydroimidazo[2,1-*b*]thiazoles were most conveniently oxidized to their sulfoxides and sulfones by treatment with 1 or 2 equiv of *m*-chloroperbenzoic acid in methylene chloride (Methods E and D, respectively).

The *N*-alkyl-2-(thioalkyl)imidazole products **50** and **52** were obtained by dialkylation of the imidazole-2-thione **54** with the iodoalkane and potassium carbonate. The monoalkylated 2-(thioalkyl)imidazole **49** was similarly prepared with 1 equiv of iodomethane.[11] However, **51** was synthesized by condensation of the *S*-ethyl thiouronium salt with α-bromodesoxyanisoin in the presence of base.

The required benzoins (VI) were prepared either by the classical benzoin condensation[12] or by the Stetter modification.[13] Oxidation of 4,4′-bis(methylthio)benzoin with *m*-chloroperbenzoic acid afforded the 4,4′-bis(methylsulfinyl)benzoin intermediate. Synthesis of the precursor desoxybenzoins (I) was accomplished by either reduction of the benzoins with tin, Friedel–Crafts acylation, or Curtius rearrangement of the substituted stilbenecarbonyl azides.[14] The α-bromodesoxybenzoins (II) were prepared

(4) (a) Lomardino, J. G.; Wiseman, E. H. *J. Med. Chem.* **1974**, *17*, 1182. (b) Wiseman, E. H.; McIhenny, H. M.; Bettis, J. W. *J. Pharm. Sci.* **1975**, *64*, 1469. (c) Janssen, P. A. J. *Prog. Drug. Res.* **1976**, *20*, 347. (d) During the course of this research **1** was described in the following U.S. patents: Baetz, J. L. E. U.S. Patent 4 110 460, 1978. Bender, P. E. U.S. Patent 4 263 311, 1981. Cherkofsky, S. C.; Sharp, T. R. U.S. Patent 4 064 260, 1977.

(5) Raeymaekers, A. H. M.; Allewijn, F. T. N.; Vandenberk, J.; Demoen, P. J. A.; Van Offenwert, T. T. T.; Jansen, P. A. J. *J. Med. Chem.* **1966**, *9*, 545.

(6) Cherkofsky, S. C.; Sharpe, T. R. U.S. Patent 4 190 666, 1980.

(7) Niedballa, U.; Klose, W.; Bottcher, I. *Arch. Pharm.* **1983**, *316*, 934.

(8) Markova, Y. V.; Kusmina, K. K.; Peresleni, E. M.; Shchukina, M. N. *Zh. Org. Khim.* **1965**, *1*, 1475; *Chem. Abstr.* **1965**, *64*, 2080*h*.

(9) Gupta, R. P.; Pujari, H. K. *Indian J. Chem., Sect. B.* **1978**, *16B*, 329; *Chem. Abstr.* **1978**, *89*, 129450*p*.

(10) Lantos, I.; Bender, P. E.; Razgaitis, K. A.; Sutton, B. M.; DiMartino, M. J.; Griswold, D. E.; Walz, D. T. *J. Med. Chem.* **1984**, *27*, 72.

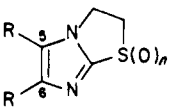
(11) Zauer, K.; Zauer-Csullog, I.; Lempert, K. *Chem. Ber.* **1973**, *106*, 1628.

(12) Ide, W. S.; Buck, J. S. In "Organic Reactions"; Adams, R., Ed.; Wiley: New York, 1948; Chapter 5.

(13) Stetter, H.; Ramsch, R. Y.; Kuhlmann, H. *Synthesis* **1976**, 733.

(14) Hill, D. T.; Stringer, O. D. Presented at the 13th Mid-American Regional Meeting of the American Chemical Society March 1979; ORG 21.

Table I. 2,3-Dihydroimidazo[2,1-*b*]thiazoles[a]



no.	5-R	6-R	*n*	mp, °C	method[b]	yield, %	recryst solvent[c]	formula[d]
1	4-$MeOC_6H_4$	4-$MeOC_6H_4$	0	154–156	A, B	66	G–H	$C_{19}H_{18}N_2O_2S$
2	C_6H_5	C_6H_5	0	184.5–188	A	72	B–H	$C_{17}H_{14}N_2S$
3	4-MeC_6H_4	4-MeC_6H_4	0	258–260	A	21	E	$C_{19}H_{18}N_2S$·HBr
4	3-$MeOC_6H_4$	3-$MeOC_6H_4$	0	212–213	A	15	I	$C_{19}H_{18}N_2O_2S$·HBr
5	C_6H_5	4-$MeOC_6H_4$	0	273–274	A	19	W	$C_{18}H_{16}N_2OS$·HBr
6	2-$MeOC_6H_4$	2-$MeOC_6H_4$	0	238–240	A	31	I	$C_{19}H_{18}N_2O_2S$·HBr·0.5H_2O
7	4-ClC_6H_4	4-ClC_6H_4	0	289–290	A	61	M–F	$C_{17}H_{12}Cl_2N_2S$·HBr
8	4-$EtOC_6H_4$	4-$EtOC_6H_4$	0	214–215	A	30	I	$C_{21}H_{22}N_2O_2S$·HBr
9	4-$BuOC_6H_4$	4-$BuOC_6H_4$	0	149–151	A	30	E–F	$C_{25}H_{30}N_2O_2S$·H_2SO_4
10	4-$MeOC_6H_4$	C_6H_5	0	228–231	A	39	I	$C_{18}H_{16}N_2OS$·HBr
11	C_6H_5	3,4-$(MeO)_2C_6H_4$	0	224–225	A	35	E	$C_{19}H_{18}N_2O_2S$·HBr
12	4-$MeOC_6H_4$	4-$MeOC_6H_4$	2	231–232	D	26	A	$C_{19}H_{18}N_2O_4S$
13	3,4-$(MeO)_2C_6H_3$	3,4-$(MeO)_2C_6H_3$	0	227–229	A	11	A–F	$C_{21}H_{22}N_2O_4S$·HBr
14	4-OHC_6H_4	4-OHC_6H_4	0	341–350	*b*	52	M–F	$C_{17}H_{14}N_2O_2S$·HBr
15	4-$AcOC_6H_4$	4-$AcOC_6H_4$	0	172–173	*b*	64	G–P	$C_{21}H_{18}N_2O_4S$·0.25H_2O
16	3,4,5-$(MeO)_3C_6H_2$	3,4,5-$(MeO)_3C_6H_2$	0	243–245	B	22	M	$C_{23}H_{26}N_2O_6S$·HBr
17	3,4-$CH_2O_2C_6H_3$	3,4-$CH_2O_2C_6H_3$	0	278–280	B	56	M	$C_{19}H_{14}N_2O_4S$·HBr
18	3,4-$(MeO)_2C_6H_3$	C_6H_5	0	244–245	A	21	E	$C_{19}H_{18}N_2O_2S$·HBr
19	4-FC_6H_4	4-FC_6H_4	0	280–282	A	45	M	$C_{17}H_{12}F_2N_2S$·HCl
20	4-$AcNHC_6H_4$	4-$AcNHC_6H_4$	0	292–295	B	54	M	$C_{21}H_{20}N_4O_2S$·0.5CH_3OH
21	4-$CF_3C_6H_4$	4-$CF_3C_6H_4$	0	314–315	*e*	40	B	$C_{19}F_{12}F_6N_2S$·HBr
22	4-$MeSC_6H_4$	4-$MeSC_6H_4$	0	270	B	34	C–F	$C_{19}H_{18}N_2S_3$·HBr
23	4-CH_2=$CHCH_2OC_6H_4$	4-CH_2=$CHCH_2OC_6H_4$	0	135–137.5	*b*	16	G–H	$C_{12}H_{23}H_{32}N_2O_2S$
24[f]	H	4-$MeOC_6H_4$	0	210–214	A	27	M–I	$C_{12}H_{12}N_2OS$·1.5HBr
25	3-MeC_6H_4	3-MeC_6H_4	0	118–119	B	18	F	$C_{19}H_{18}N_2S$
26	4-$MeOC_6H_4$	4-$MeOC_6H_4$	1	190–191	*b*	64	A	$C_{19}H_{18}N_2O_3S$
27	3-FC_6H_4	3-FC_6H_4	0	145.5–146.5	B	86	C–F	$C_{17}H_{12}F_2N_2S$
28	3-F-4-$MeOC_6H_3$	3-F-4-$MeOC_6H_3$	0	185–187	A	57	none	$C_{19}H_{16}H_2N_2S$
29	3-Me-4-$MeOC_6H_3$	3-Me-4-$MeOC_6H_3$	0	221–222	A	61	I	$C_{21}H_{22}N_2O_2$·$HClO_4$·0.25H_2O
30	4-BrC_6H_5	4-BrC_6H_5	0	208–210	*b*	18	M	$C_{17}H_{12}Br_2N_2S$[g]
31	4-$NH_2C_6H_4$	4-$NH_2C_6H_4$	0	205–206.5	C	13	A	$C_{17}H_{16}N_4S$[h]
32	4-$Me_3CCONHC_6H_4$	4-$Me_3CCONHC_6H_4$	0	211–215	*b*	48	C	$C_{27}H_{32}N_4O_2S$·0.5H_2O
33	4-$CF_3CH_2OC_6H_4$	4-$CF_3CH_2OC_6H_4$	0	164–166	*b*	65	G–H	$C_{21}H_{16}F_6N_2O_2S$
34	4-Ac(Et)NC_6H_4	4-Ac(Et)NC_6H_4	0	170.5–171.1	B	15	J	$C_{25}H_{28}N_4O_2S$·H_2O
35	4-$MeSOC_6H_4$	4-$MeSOC_6H_4$	0	95	B	18	none	$C_{19}H_{18}N_2O_2S_3$·1.5H_2O
36	4-$EtNHC_6H_4$	4-$EtNHC_6H_4$	0	168–169	C	69	C–H	$C_{21}H_{24}N_4S$·0.25H_2O
37	4-FC_6H_4	4-FC_6H_4	1	198–200	E	60	T	$C_{17}H_{12}F_2N_2OS$
38	4-FC_6H_4	4-$MeOC_6H_4$	0	187.5–188	A	30	G–H	$C_{18}F_{15}FN_2OS$
39	4-$MeSC_6H_4$	4-FC_6H_4	0	252–254	A	9	E	$C_{18}H_{15}FN_2S_2$·HCl
40	4-Et(Me)NC_6H_4	4-Et(Me)NC_6H_4	0	168.5–171.5	*b*	15	none	$C_{23}H_{28}N_4S$
41	4-$MeSOC_6H_4$	4-$MeSOC_6H_4$	1	foam	E	44	none	$C_{19}H_{18}N_2O_3S_3$·H_2O[i]
42	4-FC_6H_4	4-FC_6H_4	2	258–260	D	24	M	$C_{17}F_{12}F_2N_2O_2S$
43	3-$MeOC_6H_4$	3-$MeOC_6H_4$	1	135–136.5	E	71	G–F	$C_{19}H_{18}N_2O_3S$
44	4-$MeOC_6H_4$	4-FC_6H_4	1	199.5–200	E	48	C–H	$C_{18}H_{15}FN_2O_2S$·0.25H_2O
45	4-FC_6H_4	4-$MeSC_6H_4$	0	264–270	A	21	M	$C_{18}H_{15}FN_2S_2$·HCl

[a] All compounds exhibited IR, NMR, and mass spectra consistent with structures. [b] See the Experimental Section for general methods and specific compound synthesis. [c] Solvents: A = CH_3CN; B = benzene; C = $CHCl_3$; D = DMF; E = EtOH; F = Et_2O; G = CH_2Cl_2; H = hexane; I = 2-propanol; J = EtOAc; K = HOAc; M = MeOH; P = petroleum ether; T = toluene; W = water; X = hexanol. [d] All compounds gave C, H, and N analyses within ±0.4% of the theoretical values. [e] Reference 14. [f] Reference 53. [g] C: calcd, 46.81; found, 46.27. [h] C: calcd, 66.21; found, 66.69. [i] C: calcd, 52.27; found, 51.69.

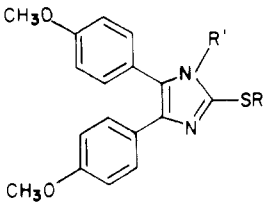
by treatment of the desoxybenzoins with bromine.

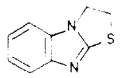
Structure–Activity Relationships. Compounds **1–35** and **37–53** were tested for antiarthritic activity in the rat adjuvant-induced arthritis model[15] and for immunoregulatory activity in the mouse subliminal oxazolone-induced contact sensitivity assay.[16a] The data obtained from these assays are displayed side by side in Table IV for comparison. While changes in activity in the mouse contact sensitivity assay appear unrelated to structural variation, examination of the rat adjuvant arthritis data reveals a number of structural correlations.

Maximum activity was achieved in symmetrically substituted 5,6-diaryl compounds having the following halogen or alkyl heteroatom functions at the para position of both phenyl rings: fluoro (**19**), chloro (**7**), bromo (**30**), methoxy (**1**), ethoxy (**8**), methylthio (**22**), methylsulfinyl (**35**), *N*-ethyl-*N*-methylamino (**40**). A significant reduction in the activity of **1** was observed on substitution of both 4-methoxy substituents with 2-methoxy (**6**); a 3-substituent such as 3-methoxy (**4**), 3-fluoro (**27**), or 3-methyl (**25**); multiple substituents such as 3,4-dimethoxy (**13**), 3,4-methylenedioxy (**17**), or 3,4,5-trimethoxy (**16**); a 4-alkoxy substituent longer than a two-carbon atom chain such as 4-allyloxy (**23**) or 4-butoxy (**9**); a nonalkylated heteroatom substituent such as 4-hydroxy (**14**), 4-amino (**31**), 4-acylamino (**20, 32, 34**), or 4-acetoxy (**15**); or hydrogen (**2**). In contrast with these findings, an antiarthritic SAR study of flumizole analogues has shown reduced potency of both

(15) Orman, C. G. V.; Bohidar, N. R. In "New Drugs: Discovery and Development"; Rubin, A. A., Ed.; Marcel Dekker: New York, 1978; Chapter 1.
(16) (a) Griswold, D. E.; Walz, D. T. *Inflammation* **1982**, *6*, 55. (b) Griswold, D. E.; Walz, D. T. *Inflammation* **1978**, *3*, 111.

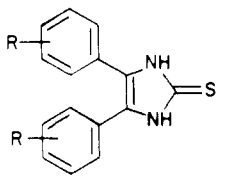
Table II. Substituted 2-Thioimidazoles[a]



no.	R	R'	yield,[b] %	mp, °C	recrystn solvent[c]	formula[d]
46[e]	$-CH_2CH_2CH_2-$		40	185-187	M	$C_{20}H_{20}N_2O_2S$
47[f]	$-CH_2CO-$		36	190-191	J	
48[g]	$-CH=CH-$		39	155.5-158	B-H	$C_{19}H_{16}N_2O_2S$
49[h]	Me	H	58	132-134	M	
50	Me	Me	12	114.5-115	M	$C_{19}H_{20}N_2O_2S$
51[i]	Et	H	25	109-129		$C_{19}H_{20}N_2O_2S \cdot 0.5CH_3OH$
52	Et	Et	12	106-108	C-F	$C_{21}H_{24}N_2O_2S$
53[j]				215-217	E	

[a-d] See corresponding footnotes in Table I. [e] Reference 9. [f] Reference 18. [g] Reference 17. [h] Reference 11. [i] Reference 6. [j] Reference 54.

Table III. Imidazole-2-thiones[a]



no.	R	mp, °C	reaction solvent[b,c]	recrystn solvent[c]	yield, %	formula[d]
54[e]	4-MeO	268	X	E	53	
55[f]	4-MeS	296	X	D, E	61	$C_{17}H_{16}N_2S_3$
56	3,4-OCH_2O	282-283	X	D	33	$C_{17}H_{12}N_2O_4S$[g]
57	3,4,5-$(MeO)_3$	252-253	X	X	53	*h*
58	4-MeSO	261-262	X	M	28	*h*
59	4-Br	288-294	X	J	41	*h*
60	3-F	244-253	D	I	45	$C_{17}H_{12}F_2N_2S$
61	4-AcNH	368-382	X	M	46	$C_{19}H_{18}N_4O_2S \cdot 0.5H_2O$

[a-d] See corresponding footnotes in Table I. [e] Reference 55. [f] Reference 56. [g] H: calcd, 8.23; found, 7.42. [h] Product used directly without further purification.

the 4-fluoro and 4-methylthio analogues and a lack of activity of the 4-ethoxy derivative relative to the parent compound.[4a]

In unsymmetrically substituted analogues possessing one 4-fluorophenyl and one 4-(methylthio)phenyl or 4-alkoxyphenyl ring, significant antiarthritic activity on day 16 was observed only with one regioisomer; the active isomer is the one in which the 4-fluorophenyl substituent is at the C-6 and the 4-(methylthio)phenyl or 4-methoxyphenyl moiety is at the C-5 position of the imidazo[2,1-*b*]thiazole ring (**39** and **44** relative to **45** and **38**). Thus, there appears to be regiospecificity with respect to adjuvant rat antiarthritic activity in these isomers.

Oxidation of the thiazoline ring sulfur of **1**, **19**, and **35** to the sulfoxides resulted in analogues **26**, **37**, and **41** with similar potency. However, further oxidation of the sulfoxides (**26**, **37**) to the sulfones (**12**, **42**) resulted in compounds of reduced potency. Formal opening of the thiazoline ring to give the 2-(alkylthio)imidazoles **49** and **51** or the 1-methyl-2-(methylthio)imidazole **50** resulted in adjuvant arthritic activity comparable to **1**. However, lengthening the alkyl chains of **50** by a methylene (**52**), inserting a methylene into the C2–C3 bond of **1** to give the ring-expanded thiazine **46**, introduction of a double bond at C2–C3 (**48**),[17] and oxidation of C3 to a carbonyl (**47**)[18] all significantly reduced activity, suggesting narrow steric requirements for antiarthritic activity.

Eight representative 5,6-diaryl-2,3-dihydroimidazo[2,1-*b*]thiazoles were evaluated further for antiinflammatory activity in the carrageenan-induced rat paw edema assay. These data are presented in Table V. Both **1** and its closest analogue **22**, where a sulfur atom is substituted for each oxygen atom, are active in all three assays. In contrast, compound **19**, active in both earlier assays, compounds **4** and **21**, active in the oxazolone-induced contact sensitivity model, and compound **41**, active in the adjuvant-induced arthritis assay, did not show significant activity in this carrageenan-induced inflammatory model.

Comparative Pharmacology of Compound 1. The lead compound (**1**), because of its activity in all three model systems, was examined in additional pertinent assays of inflammation, arthritis, and immunoregulation in order to better characterize and compare its pharmacological actions with those of levamisole and flumizole. The resulting data are exhibited in Table VI.

Compound **1** inhibited both the primary (nonimmune, L3) and secondary (immune, R16) inflammatory lesions in rat adjuvant-induced arthritis with a potency that falls between that of its parent flumizole and levamisole. A comparison of the antiinflammatory activity exhibited by

(17) Lednicer, D. U.S. Patent 3 455 924, 1969.

(18) Mustafa, A.; Ali, M. I.; Abou-State, M. A.; Hamman, A. E. G. *J. Prakt. Chem.* **1972**, *314*, 785.

Table IV. Analogues of I: Antiarthritic and Immunoregulatory Activity

	rat adjuvant-induced arthritis[a]						mouse contact sns[b]	
	L-3		L-16		R-16			
no.	% chg	sig[c]	% chg	sig[c]	% chg	sig[c]	% chg	sig[c]
1	-24	***	-34	***	-21	*	211	***
2	-12	**	-4	NS	-4	NS		NS
3	-6	NS	0	NS	-7	NS	86	NS
4	0	NS	-4	NS	-16	*	166	***
5	-5	NS	-10	*	1	NS	26	*
6	0	NS	-5	NS	-7	NS	95	**
7	-18	***	-35	***	-38	***	43	NS
8	-22	***	-34	***	-32	***	150	***
9	5	NS	2	NS	2	NS	130	**
10	-15	*	-11	*	-6	NS	112	**
11	8	NS	-1	NS	-6	NS	82	*
12	-11	*	-12	*	-7	NS	95	**
13	0	NS	-2	NS	5	NS	48	NS
14	-9	*	-7	NS	9	NS	122	**
15	-16	***	-12	*	-17	NS	101	*
16	-2	NS	0	NS	-19	*	75	NS
17	-18	**	-23	***	-27	*	16	NS
18	5	NS	1	NS	11	NS	69	NS
19	-39	***	-36	***	-49	***	79[d]	**
20	3	NS	-1	NS	12	NS	78	*
21	0	NS	12	***	1	NS	89[e]	***
22	-25	***	-36	***	-38	***	73	**
23	-2	NS	-2	NS	-21	**	71	NS
24	-3	NS	-10	NS	-16	NS	132	***
25	-14	**	-13	*	-5	NS	38	NS
26	-24	***	-29	***	-32	**	76[e]	**
27	-1	NS	-1	NS	3	NS	22	NS
28	1	NS	0	NS	-3	NS	88	**
29	-16	***	-20	**	-19	NS	30	NS
30	-25	***	-42	***	-46	***	71[f]	**
31	-15	**	-10	NS	0	NS	36	NS
32	-4	NS	-3	NS	-1	NS	15	NS
33	-13	**	-20	**	-3	NS	26	NS
34	-4	NS	-1	NS	-10	NS	43	**
35	-25	***	-27	***	-19	NS	117	***
37	-31	***	-41	***	-44	***	67	**
38	11	*	-4	NS	6	NS	103	**
39	-16	**	-30	***	-30	***	122	***
40	-31	***	-41	***	-36	***	69	*
41	-27	***	-44	***	-47	***	38	NS
42	-6	NS	-17	***	-34	***	20	NS
43	4	NS	9	NS	7	NS	59	**
44	-35	***	-39	***	-39	***	65	*
45	-14	**	0	NS	6	NS	44	**
46	-2	NS	-4	NS	-20	*	30	NS
47	-4	NS	4	NS	0	NS	25	NS
48	-6	NS	-9	*	0	NS		NS
49	-29	***	-45	***	-38	***	52	*
50	-24	***	-31	***	-35	***	150	***
51	-31	***	-42	***	-37	***	119	**
52	-6	NS	-9	NS	-8	NS	65	NS
53	-18	***	-2	NS	7	NS	51	*

[a] Dose 50 mg/kg; 100% survival except compound 21 which had 87.6% survival. [b] Dose 25 mg/kg except where noted. [c] Statistical significance: *, ≤0.05; **, ≤0.01; ***, ≤0.001; NS, not statistically significant. [d] Dose 1 mg/kg. [e] Dose 10 mg/kg. [f] Dose 50 mg/kg.

the three agents in carrageenan-induced inflammation demonstrates that adrenalectomy abrogated levamisole's activity while both 1 and flumizole retained their activity. This suggests that the antiinflammatory activity shown by levamisole is adrenal mediated and unrelated mechanistically to that of both 1 and flumizole.

Hemagglutination titers to sheep red blood cells (SRBCs) injected into adjuvant-induced arthritic rats on day 8 (post adjuvant treatment) can be "normalized" (19S raised and 7S lowered) toward nonadjuvant control levels when dosed on days 1–16 with antiinflammatory agents such as indomethacin. Although these agents are not effective in animals dosed on days 6–10, immunoregulating agents such as levamisole will significantly lower hyperimmune IgG (7S) under these conditions.[19] As seen in Table VI, compound 1 suppressed 7S titer to SRBCs in this modified assay in a manner comparable to a levamisole, while indomethacin was ineffective.

Table V. Carrageenan-Induced Paw Edema[a]

	50 mg/kg		100 mg/kg	
no.	% chg	sig[b]	% chg	sig[b]
1	-63	***		
2	-9	NS	-7	NS
4			-3	NS
19	-9	NS	6	NS
21			4	NS
22	-33	***		
41	10	NS		
42	3	NS		

[a] See the Experimental Section for pharmacological assays. [b] See footnote c of Table IV.

Further evidence suggesting an immunoregulatory action of compound 1 is its stimulation of subliminal oxazolone-induced contact sensitivity and its ability to restore methotrexate-suppressed oxazolone-induced contact sensitivity to a degree comparable with that achieved by levamisole. The inactivity of flumizole in these same assays effectively discriminates between flumizole-like antiinflammatory activity and levamisole-like immunoregulatory activity. These assays reliably detect the characteristic ability of levamisole to stimulate day-2 contact sensitivity, which does not appear to be appreciably modulated by T suppressor cells.[16a,b] Additionally, it should be noted that 1 did not inhibit antibody production in normal rats like the immunosuppressive drugs cytoxan and methotrexate, suggesting that it does not possess immunosuppressive activity.

It is apparent from this comparative evaluation that 1 possesses the desired hybrid antiinflammatory–immunoregulatory profile predicted for this fused flumizole–levamisole type structure. The antiinflammatory activity is clearly seen in the inhibition of inflammation in both the primary lesion of the arthritic rat as well as paw edema in the carrageenan assay. The immunoregulatory behavior of 1 is evidenced by its ability to (1) alter the secondary (immune) lesions in adjuvant-induced rats, (2) normalize the 7S hemagglutination titer to SRBC, (3) stimulate oxazolone-induced contact sensitivity, and (4) restore oxazolone-induced contact sensitivity in the methotrexate-immunosuppressed mouse. The secondary lesion is an immunologically driven inflammatory response arising from disseminated adjuvant arthritis. Adjuvant accelerates the humoral response, i.e. shift to 7S antibody production. The oxazolone contact sensitivity assay reflects the response to sensitized T effector cells. These assays, taken together, provide a measure of a compound's immunoregulatory activity and reveal a profile of activity of 1 comparable to that of levamisole.

In conclusion, hybridization of structural elements of flumizole with those of levamisole has resulted in a number of compounds possessing major aspects of the antiinflammatory and immunoregulatory activities of both. Of these, compound 1 was shown to possess one of the most advantageous profiles of activity. It was well tolerated in rats; the acute LD_{50} exceeded 2000 mg of base/kg po, and the subacute LD_{50} was in excess of 400 mg of base/kg po.

Experimental Section

Chemistry. Melting points were determined on a Thomas-Hoover Unimelt or, when >250 °C, on an Electrothermal capillary

(19) DiMartino, M. J.; Kropp, J.; Laydon, J.; Walz, D. T. *Fed. Proc.* 1981, *41*, 1031.

Table VI. Comparison of the Antiarthritic, Antiinflammatory, and Immunoregulatory Activities of 1 with Levamisole and Flumizole

				carrageenan[a,b]				hemagltn tit[c]						mtx supp[e]	
	ED_{25} adjuvant arthritis,[a] mg/kg: calcd (limits)			sham		adrnlx		19S		7S		oxazo[a,d]		oxazo	
compd	L3	L16	R16	% chg	sig[f]	% chg	sig[f]	% chg	sig[f]	% chg	sig[f]	% chg	sig[f]	% chg	sig[f]
1	32.9 (12.6)[g]	18.7 (9.7-28.4)	24.4 (13.2-43.8)	-63	***	-58	***	1.2	NS	-3.7	**	211	***	156	**
levamisole	44.4 (10.3-73.4)	73.4 (37.2-112.6)	127.4 (80.9-272.1)	-55	***	-9	NS	-1.7	*	-3.3	**	230	***	163	**
flumizole	11[i]	0.45 (0.19-0.79)	0.78 (0.17-1.73)	-48	***	-47	***	h		h		-28	*	3	NS

[a] See the Experimental Section for methods. ED_{25} for levamisole was determined in Charles River Lewis rats. [b] Carrageenan-induced paw edema; percent change in paw volume in treated vs. control adrenalectomized and sham operated rats; 1, levamisole, and flumizole tested at 50, 150, and 5 mg/kg po, respectively. Lack of linear dose-response relationship of 1 with paw volume inhibition did not permit calculation of ED_{50}'s. [c] Change in 19S and 7S hemagglutination titers in treated vs. control adjuvant-induced arthritic rats. See ref 19 for description of method. Levamisole and 1 were both tested at 50 mg/kg po. [d] 1, levamisole, and flumizole tested at 50, 50, and 5 mg/kg po, respectively. [e] Percent change in paw edema in treated vs. control mice with methotrexate-suppressed oxazolone-induced contact sensitivity. See ref 16b for description of method. 1, levamisole, and flumizole were tested at 25 mg/kg po. [f] See footnote c of Table IV. [g] Zero slope of dose-response curve did not permit calculation of confidence limits. [h] Indomethacin at 2 mg/kg po exhibited no significant change on either titer.

melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian T60 spectrometer employing $(CH_3)_4Si$ as an internal standard. IR spectra were obtained on a Perkin-Elmer Model 137B Infracord spectrophotometer as Nujol mulls. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 apparatus by the Analytical Department of Smith Kline and French Laboratories.

The starting materials were prepared as described in the cited literature references. Desoxybenzoins $RPhCOCH_2Y$ (I, R, Y): Ia, 4-Me, 4-MePh;[20] Ib, 3-MeO, 3-MeOPh;[21] Ic, 4-MeO, Ph;[22] Id, 2-MeO, 2-MeOPh;[23] Ie, 4-Cl, 4-ClPh;[24] If, 4-EtO, 4-EtOPh;[25] Ig, 4-BuO, 4-BuOPh;[26] Ih, 3,4-$(MeO)_2$, Ph;[24] Ii, 3,4-$(MeO)_2$, 3,4-$(MeO)_2$Ph;[27] Ij, H, 3,4-$(MeO)_2$Ph;[28] Ik, 4-F, 4-FPh;[29] Il, 3-Me-4-MeO, 3-Me-4-MeOPh;[30] Im, 4-MeO, 4-FPh;[31] In, 4-F, 4-MeSPh;[32] Io, 4-Br, 4-BrPh;[33] Ip, 4-OH, 4-OHPh;[34] Iq, 4-CF_3, 4-CF_3Ph.[14] α-Bromoketones RPhCOCH(Br)Y (II, R, Y): IIa, 4-MeO, 4-MeOPh;[35] IIb, H, Ph;[36] IIc, 4-Me, 4-MePh;[23] IId, 4-MeO, Ph;[37] IIe, 2-MeO, 2-MeOPh;[23] IIf, 4-Cl, 4-ClPh;[38] IIg, 4-EtO, 4-EtOPh;[39] IIh, 4-BuO, 4-BuOPh;[23] IIi, H, 4-MeOPh;[40] IIj, 3,4-$(MeO)_2$, Ph;[28] IIk, 3,4-$(MeO)_2$, 3,4-$(MeO)_2$Ph;[41] IIl, 4-MeO, H;[42] IIm, 4-F, 4-MeSPh.[43] Benzoins RPhCOCH(OH)PhR (VI, R): VIa, 4-MeS;[4a] VIb, 3,4-CH_2O_2;[44] VIc, 3,4,5-$(MeO)_3$;[45] VId, 4-Br;[46] VIe, 3-Me;[47] VIf, 3-F;[23] VIg, 4-AcNH;[48] VIh, 2-MeO;[49] VIi, 3-MeO;[50] VIj, 3,4-$(MeO)_2$.[47]

Imidazo[2,1-*b*]thiazole Synthetic Methods. Method A. 5,6-Bis(4-methoxyphenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (1). A suspension of IIa (145 g, 0.433 mol), powdered 2-aminothiazoline (88.36 g, 0.865 mol), and K_2CO_3 (179.5 g, 1.3 mol) in dry CH_3CN (1 L) was stirred at room temperature for 18 h. The solvent was evaporated and the residue dissolved in CH_2Cl_2. This solution was washed with 5% aqueous Na_2CO_3 and water, dried (K_2CO_3), treated with charcoal, and filtered. Addition of hexane to the filtrate afforded a precipitate that was recrystallized (CH_2Cl_2) to give 96.6 g (66%) of 1: mp 150–153 °C; NMR ($CDCl_3$) δ 3.72 (s, 3 H, CH_3O), 3.80 (s, 3 H, CH_3O), 3.8 (m, 4 H, A_2B_2 CH_2CH_2), 7.05 (m, 8 H, aromatic). For compounds **39** and **45**, DMF was used as the reaction solvent and the bromoketone was reacted with 2–3 equiv of 2-aminothiazoline without added K_2CO_3. The mixture was poured into ice water (10 volumes) and the resulting precipitate washed with water. The HCl salt was prepared by addition of ethereal HCl to a solution of the base in EtOH and was recrystallized from the appropriate solvent. To form the HBr salt, 1 equiv of 48% w/v aqueous HBr was substituted for ethereal HCl in the above procedure. To form the H_2SO_4 salt, concentrated H_2SO_4 was substituted in the above procedure, the solvent evaporated, and the crude salt recrystallized.

Method B. 5,6-Bis(4-methoxyphenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (1). A mixture of thione **54** (4.0 g; 0.0128 mol), 1,2-dibromoethane (2.4 g, 0.0128 mol), and K_2CO_3 (2.65 g, 0.0192 mol) was refluxed in dry DMF (50 mL) for 3 h. After cooling, water (550 mL) was added and the pH adjusted to 11 with 10% aqueous NaOH. The precipitate was washed with water and dissolved in CH_2Cl_2. The organic solution was washed extensively with water, dried (K_2CO_3), and treated with charcoal. The solvent was removed and the crude product recrystallized successively (CH_3CN, $CHCl_3$–hexane, MeOH–water) to afford 0.96 g (22%) of off-white crystals of 1, mp 153–155 °C. In the preparation of compounds **16**, **17**, and **22**, the crude product was chromatographed (alumina, $CHCl_3$). Evaporation of the solvent and crystallization of the product from MeOH and 48% HBr gave the salt which was recrystallized from the appropriate solvent. To prepare compound **20**, chromatography was not necessary and the product was crystallized (MeOH) as the free base.

(20) Hutchins, W. A.; Motwani, D. C.; Mudbhatkal, K. D.; Wheeler, T. S. *J. Chem. Soc.* **1938**, 1882.
(21) Allen, I., Jr.; Buck, J. S. *J. Am. Chem. Soc.* **1930**, *52*, 310.
(22) Ney, E. *Chem. Ber.* **1888**, *21*, 2445.
(23) Bender, P. E. German Patent 2742725, 1976; *Chem. Abstr.* **1978**, *89*, 24305*s*.
(24) Pisova, M.; Soucek, M. *Collect. Czech. Chem. Commun.* **1973**, *38*, 3876.
(25) (a) Nagano, T. *J. Org. Chem.* **1957**, *22*, 817. (b) Wiechell, H. *Justus Liebigs Ann. Chem.* **1894**, *279*, 337.
(26) Tadros, W.; Sakla, A. B.; Ishak, M. S.; Armanious, E. R. *J. Chem. Soc.* **1963**, 4527.
(27) Fritsch, P. *Justus Liebigs Ann. Chem.* **1904**, *329*, 37.
(28) Kaufmann, A.; Muller, H. *Chem. Ber.* **1918**, *51*, 123.
(29) Fischer, A.; Grigor, B. A.; Packer, J.; Vaughan, J. *J. Am. Chem. Soc.* **1961**, *83*, 4208.
(30) Morgan, E. N.; Palmer, P. J.; Kruszynska, L.; Williamson, W. R. N. *J. Chem. Soc.* **1965**, 3887.
(31) Funasaka, W.; Ando, T.; Kondo, K.; Kodama, S. *Yuki Gosei Kagaku Kyokai Shi* **1959**, *17*, 717; *Chem. Abstr.* **1960**, *54*, 2248*g*.
(32) Hinkley, D. F.; Conn, J. B. U.S. Patent 3647858, 1972.
(33) Barber, H. J.; Slack, R. *J. Chem. Soc.* **1944**, 612.
(34) Zinckle, T.; Fries, K. *Justus Liebigs Ann. Chem.* **1902**, *325*, 67.
(35) Cymerman-Craig, J.; Martin, P. V.; Wailes, P. C. *Aust. J. Chem.* **1955**, *8*, 385.
(36) Szarvasi, E.; Festal, D.; Grand, M.; Depin, J. C.; Chabert, J. *Eur. J. Med. Chem.* **1976**, *11*, 115.
(37) Meisenheimer, J.; Jochelson, L. *Justus Liebigs Ann. Chem.* **1907**, *355*, 292.
(38) Koltai, E.; Nyitrai, J.; Lempert, K.; Horvath, G.; Kalman, A.; Argay, G. *Tetrahedron* **1973**, *29*, 2783.
(39) Nagano, T. *J. Org. Chem.* **1957**, *22*, 817.
(40) Padwa, A.; Dehm, D. *J. Org. Chem.* **1975**, *40*, 3139.
(41) Kubiezek, G. *Montash. Chem.* **1946**, *76*, 55.
(42) Kunckell, F.; Scheven, W. *Chem. Ber.* **1898**, *31*, 172.
(43) Bender, P. E.; Hill, D. T. U.S. Patent 4153706, 1979.
(44) Torrey, H. A.; Sumner, J. B. *J. Am. Chem. Soc.* **1910**, *32*, 1492.
(45) Richtzenhain, H. *Chem. Ber.* **1944**, *77*, 409.
(46) Van Es, T.; Backeberg, O. G. *J. Chem. Soc.* **1963**, *1371*.
(47) Shacklett, C. D.; Smith, H. A. *J. Am. Chem. Soc.* **1953**, *75*, 2654.
(48) Gee, H. L.; Harley-Mason, J. *J. Chem. Soc.* **1947**, 251.
(49) Irvine, J. C. *J. Chem. Soc.* **1901**, *79*, 668.
(50) Schonberg, A.; Malchow, W. *Chem. Ber.* **1922**, *55*, 3746.

Method C. 5,6-Bis(4-(ethylamino)phenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (36). A suspension of **34** (11.6 g, 0.0249 mol) in 6 N HCl (150 mL) was refluxed under N_2 for 2–3 h. The reaction mixture was cooled to 0 °C, made strongly alkaline with 10% aqueous NaOH, and extracted with CH_2Cl_2, and the organic layer was dried (K_2CO_3). Evaporation of the solvent gave a residue that was chromatographed in subdued light (alumina, 9:1 $CHCl_3$–CH_3CN) and recrystallized ($CHCl_3$–hexane) to afford 6.5 g (69%) of **36** as yellow crystals, mp 168–169 °C. Compound **31** was prepared in a similar manner, the alkaline solution affording a precipitate that was recrystallized directly.

Method D. 5,6-Bis(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole *S*-Dioxide (42). A solution of *m*-CPBA (85%, 11.6 g, 0.0572 mol) in CH_2Cl_2 (200 mL) was added dropwise to a solution of **19** (9.0 g, 0.0286 mol) as the free base in CH_2Cl_2 (100 mL). The reaction was stirred 24 h at room temperature. Additional *m*-CPBA in CH_2Cl_2 was added as needed until no sulfoxide remained (TLC). The mixture was filtered, and the filtrate was washed with 5% aqueous Na_2CO_3, followed by brine, and dried ($MgSO_4$). Evaporation of the solvent afforded a crude sulfone that was recrystallized from MeOH to give 2.84 g (29%) of **42**, mp 258–260 °C. To prepare compound **12**, 3.8 equiv of *m*-CPBA in absolute EtOH was used. Excess *m*-CPBA was destroyed with Na_2SO_3 and the product purified by chromatography (alumina, EtOAc).

Method E. 5,6-Bis(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole *S*-Oxide (37). A solution of **19** (9.7 g, 0.031 mol) as the free base in CH_2Cl_2 at 0 °C was treated with a solution of *m*-CPBA (6.2 g, 80–90%, 0.031 mol) in CH_2Cl_2. After 1 h at 0 °C, the solution was warmed to room temperature, washed with 5% aqueous Na_2CO_3, and dried ($MgSO_4$). Evaporation of the solvent gave white crystals that were washed with cyclohexane and then with ether and recrystallized (toluene) to give 6.14 g (60%) of **37**, mp 198–200 °C. Compounds **41**, **43**, and **44** were prepared in a similar manner; to prepare compound **41**, 3 equiv of *m*-CPBA was employed.

5,6-Bis(4-hydroxyphenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (14). A solution of boron tribromide (50.0 g, 0.199 mol) in dry CH_2Cl_2 (200 mL) was added dropwise under N_2 to a stirred mixture of **1** (39.9 g, 0.118 mol) in dry CH_2Cl_2 (500 mL) at −60 °C. After the mixture had warmed to room temperature overnight, water (750 mL) was added slowly. The crude hydrobromide was filtered off and recrystallized from MeOH–ether to afford 24 g (52%) of **14**, mp 341–350 °C.

5,6-Bis(4-acetoxyphenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (15). Compound **14** (2.2 g 0.0056 mol) was stirred with Ac_2O (15 mL, 0.136 mol) and K_2CO_3 (4.0 g, 0.029 mol) for 18 h. The viscous mixture was poured into ice and stirred until all the Ac_2O was hydrolyzed (1 h). The solid was washed with ether and recrystallized (CH_2Cl_2–petroleum ether) to afford 1.7 g (64%) of **15**, mp 172–173 °C.

5,6-Bis(4-(allyloxy)phenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (23). To a stirred solution of **14** (10.0 g, 0.026 mol) and allyl bromide (3.71 g, 0.031 mol) in DMF (100 mL) was added NaH (50% oil dispersion, 3.69 g, 0.077 mol) in small portions to maintain the solution temperature below 55 °C. When the surrounding bath temperature reached 40 °C, a second portion of allyl bromide (3.71 g, 0.031 mol) was added and the reaction heated to 60–75 °C for 1 h. The reaction was cooled and poured into water (500 mL) and the pH adjusted to 11 with 10% NaOH. The mixture was extracted into CH_2Cl_2 and the organic layer washed thoroughly with water and dried (K_2CO_3). Evaporation of the solvent, trituration with petroleum ether, chromatography (alumina, 1:1:1, ether–CH_2Cl_2–petroleum ether), and recrystallization (CH_2Cl_2–hexane) afforded 1.6g (16%) of **24** as white crystals, mp 135–137.5 °C.

5,6-Bis(4-methoxyphenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole *S*-Oxide (26). A solution of **1** (10.0 g, 0.03 mol) in MeOH (300 mL) and CH_2Cl_2 (150 mL) was added dropwise to a solution of $NaIO_4$ (7.1 g, 0.03 mol) in water (60 mL) at 0 °C. The reaction was stirred for 4 h at 0 °C. After 6 days at room temperature, water (60 mL) was added and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were back-washed extensively with water and dried (Na_2SO_4) and the solvent removed. Column chromatography of the residue (alumina, 1:1, $CHCl_3$–EtOAc) and recrystallization (CH_3CN) afforded 6.8 g (64%) of **26** as a white powder, mp 190–191 °C.

5,6-Bis(4-bromophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (30). Treatment of **IIn** (22.2 g, 0.051 mol) with 2-aminothiazoline (10.4 g, 0.101 mol) and K_2CO_3 (21.0 g, 0.152 mol) in CH_3CN (150 mL), as in method A, gave an intermediate alcohol. A suspension of this alcohol in MeOH was treated with methanolic HCl (5 equiv), and the solution was refluxed 0.5 h. The solvent was evaporated and the free base obtained by pouring a methanolic solution of the salt into ice water and adjusting the pH to 11 with 10% NaOH. Recrystallization of the precipitate ($CHCl_3$–hexane, then MeOH) afforded, after drying in vacuo, 4.6 g (18%) of **30**, mp 208–210 °C.

5,6-Bis(4-(pivalylamido)phenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (32). Compound **31** (3.2 g, 10.4 mmol) was added to a stirred solution of pivalic anhydride (4.82 g, 26 mmol) and pivalic acid (3.18 g, 31 mmol) under N_2 at 195 °C, and the solution was refluxed for 1.25 h. After cooling, a solution of the residue in $CHCl_3$ was washed with 5% aqueous Na_2CO_3 and water and dried ($MgSO_4$). Evaporation of the solvent and crystallization of the residue (MeOH–Et_2O, then $CHCl_3$) gave 2.41 g (48%) of **32** as the hemihydrate, mp 211–215 °C.

5,6-Bis(4-(2,2,2-trifluoroethoxy)phenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (33). Compound **14** (10 g, 0.0256 mol) was added to a stirred mixture of NaH (50% oil dispersion, 6.14 g, 0.128 mol) in dry THF (150 mL) under N_2, maintained below 0 °C. After stirring for 0.5 h, $CF_3SO_3CH_2CF_3$[51] (17.8 g 0.0768 mol) was added dropwise. The suspension was poured into ice water (500 mL) and the mixture extracted into CH_2Cl_2. The organic layer was washed with water and dried (K_2CO_3) and the solvent removed to afford a light tan solid. Treatment with charcoal and recrystallization (CH_2Cl_2–hexane) afforded 7.90 g (65.1%) of **33**, mp 164–166 °C.

5,6-Bis[4-(*N*-ethylacetamido)phenyl]-2,3-dihydroimidazo[2,1-*b*]thiazole (34). A stirred solution of **20** (18.6 g, 0.0470 mol) in dry DMF under N_2 was chilled to −10 °C, treated with NaH (50% oil dispersion, 6.8 g, 0.142 mol), and then warmed to room temperature to complete H_2 evolution. This mixture was chilled to −10 °C, treated dropwise with a solution of bromoethane (10.9 g, 0.10 mol) in dry DMF (10 mL), and allowed to warm to room temperature. Additional bromoethane (0.51 g, 4.7 mmol) in DMF (2 mL) was added and the mixture stirred 1 h. The reaction mixture was quenched portionwise under N_2 with ice water (1 L) and extracted with CH_2Cl_2. The extract was washed with water and dried ($MgSO_4$). Evaporation of the solvent gave a residue that was chromatographed (alumina, EtOAc) and crystallized (EtOAc) to afford 10.6 g (48%) of **34**, mp 170.5–171.5 °C.

5,6-Bis(4-(methylsulfinyl)phenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (35). Thione **58** (6.09 g, 0.016 mol) in DMF (30 mL) was added dropwise to a stirred suspension of KH (24% oil dispersion, 5.5 g, 0.032 mol) in DMF (30 mL) cooled to 0 °C. After 20 min, 1,2-dibromoethane (3.04 g, 0.016 mol) in DMF (10 mL) was added. The resulting light yellow mixture was stirred an additional 30 min at 0 °C, followed by warming to room temperature over 90 min. The mixture was poured into ice water (500 mL), extracted with CH_2Cl_2 after adding brine and dried ($MgSO_4$) and the solvent removed to afford a two-phase oil. The mineral oil layer was removed and the crude product chromatographed (alumina, $CHCl_3$) to afford 1.2 g (18%) of **35** as the hydrate, mp 95 °C.

5,6-Bis[4-(ethylmethylamino)phenyl]-2,3-dihydroimidazo[2,1-*b*]thiazole (40). A mixture of **36** (10 g, 0.027 mol) and iodomethane (8.4 g, 0.059 mol) in dry MeOH (175 mL) was stirred at 100 °C in a glass bomb for 24 h. Additional iodomethane (5.2 g) was added and the mixture heated another 48 h. Removal of the solvent afforded a residue that was dissolved in CH_2Cl_2–MeOH and made alkaline with 5% aqueous NaOH. The organic layer was dried ($MgSO_4$) and the solvent removed to afford a residue that was chromatographed (alumina, $CHCl_3$) to give 1.6 g (15%) of **40** as yellow crystals, mp 168.5–171.5 °C.

2,3-Bis(4-methoxyphenyl)-5,6-dihydro[7*H*]imidazo[2,1-*b*][1,3]thiazine (46). A mixture of **54** (10.0 g, 0.032 mol), 1,3-dibromopropane (6.5 g, 0.032 mol), and K_2CO_3 (4.8 g, 0.035 mol)

(51) Hansen, R. L. *J. Org. Chem.* **1965**, *30*, 4322.

in DMF (130 mL) was refluxed 3 h under N_2. The solution was cooled and poured into water (1 L). The pH was adjusted to 9 and the solid recrystallized (MeOH) and dried in vacuo to afford 4.49 g (40%) of **46**, mp 185–187 °C.

1-Methyl-4,5-bis(4-methoxyphenyl)-2-(methylthio)imidazole (50). A slurry of **54** (9.0 g, 0.03 mol), iodomethane (9.3 g, 4.2 mL, 0.066 mol), and K_2CO_3 (8.4 g, 0.06 mol) was stirred in DMF (90 mL) at room temperature for 18 h. The reaction mixture was filtered and the filtrate evaporated to a dark yellow solid that was crystallized (ether). The crude product was recrystallized (MeOH) to afford 1.22 g (12%) of **50** as yellow crystals, mp 114.5–115 °C.

4,5-Bis(4-methoxyphenyl)-2-(ethylthio)imidazole (51). A stirred solution of IIa (10.0 g, 0.03 mol) and *S*-ethylthiuronium bromide (5.55 g, 0.03 mol) in triethylamine (6 g, 8.4 mL, 0.06 mol) and CH_3CN (90 mL) began forming a white precipitate within 10 min. After 18 h the dark red reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with water and brine, and dried (Na_2SO_4). Solvent was removed to afford a crude product that was chromatographed (silica gel, 3% ether in CH_2Cl_2). Crystallization (MeOH) gave 2.6 g (25%) of **51**, mp 109–129 °C.

1-Ethyl-4,5-bis(4-methoxyphenyl)-2-(ethylthio)imidazole (52). A slurry of **54** (50 g, 0.16 mol), iodoethane (59 g, 30 mL, 0.38 mol), and K_2CO_3 (55 g, 0.4 mol) in DMF (500 mL) was refluxed 2 h, cooled to room temperature, and poured into ice water (800 mL). The precipitate was triturated with MeOH, and the cream-colored crystals were chromatographed (silica gel, 10% ether in $CHCl_3$). Evaporation of the solvent gave a solid that was triturated with ether and recrystallized ($CHCl_3$–ether) to afford 7.3 g (12%) of **52**, mp 106–108 °C.

General Method for α-Bromination of Desoxybenzoins (I). Bromine (7.99 g, 0.05 mol) was added dropwise to a stirred solution of desoxybenzoin (0.05 mol) in CCl_4 or benzene (100 mL). A slight excess of bromine was added to obtain a persistent orange color. Irradiation with a 275-W sunlamp was employed in the case of sluggish brominations. After 1 h at room temperature, the solvent was evaporated to afford the crude product that was used directly.

General Method for Preparation of 4,5-Diarylimidazole-2-thiones (VII). A slurry of substituted benzoin (0.4 mol) and thiourea (60.8 g, 0.8 mol) in 1-hexanol (500 ml) was refluxed for 3 h with a Dean–Stark trap. The reaction mixture was then cooled to 0 °C and the precipitate washed with ether. The crude product was recrystallized from the appropriate solvent. In the preparation of compound **59**, 1.5 volumes of EtOH were added to facilitate crystallization. Conversion of benzoins VIe and VIf to the corresponding thiones was achieved by refluxing the benzoin (0.02 mol) with thiourea (3.04 g, 0.04 mol) in DMF (50 mL) for 2.5 h. The mixture was then poured into ice water and the precipitate recrystallized.

2-Bromo-1-phenyl-2-(3,4-dimethoxyphenyl)ethanone. A solution of Ij (15.4 g, 0.06 mol) in DMF (50 mL) was added dropwise to a stirred solution of trimethylsilyl chloride (7.8 g, 0.072 mol), triethylamine (14.6 g, 0.144 mol), and DMF (25 mL). The reaction mixture was refluxed 18 h, cooled to room temperature, and diluted with petroleum ether (200 mL). The organic solution was washed with 5% aqueous $NaHCO_3$, with 1.5 M HCl, and again with 5% aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated to afford 11.6 g (60%) of crude silyl enol ether as an amber oil. This oil was dissolved in CCl_4 (40 mL) and cooled to 0 °C while bromine (5.8 g, 0.036 mol) in CCl_4 (40 mL) was added dropwise. Evaporation of the solvent gave 12.0 g of crude bomoketone that was used directly in the preparation of **18**.

Bis(3-fluoro-4-methoxy)benzoin. A solution of 3-fluoro-4-methoxybenzaldehyde (15 g, 0.097 mol) and KCN (1.2 g, 0.018 mol) in EtOH (45 mL) and water (45 mL) was refluxed for 6 h. Concentration of the solution afforded, on cooling, 11.2 g (74%) of crystalline benzoin that was used below without further purification.

Bis(3-fluoro-4-methoxy)desoxybenzoin. To a solution of the above compound (16 g, 0.052 mol) in EtOH (100 mL) was added tin (12.9 g, 0.019 mol) and a solution of $CuSO_4$ (1 g, 0.006 mol) in concentrated HCl (22 mL) and water (1 mL). The mixture was refluxed 9 h and filtered and the filtrate concentrated. The residue was dissolved in $CHCl_3$, washed with 5% aqueous Na_2CO_3 and water, and dried ($MgSO_4$). Removal of solvent, followed by trituration of the residue with ether, afforded 9.1 g (60%) of crystals, mp 149–152 °C. This material was used without further purification.

4,4′-Bis(methylsulfinyl)benzoin. A solution of *m*-CPBA (85%, 42 g, 0.21 mol) in $CHCl_3$ (400 mL) was added with stirring to a slurry of VIa (30.4 g, 0.1 mol) in $CHCl_3$ (500 mL) cooled to 0 °C. The mixture was allowed to warm to room temperature over 2–3 h and was filtered; the filtrate was washed with 5% aqueous Na_2CO_3 and the organic layer dried ($MgSO_4$). Evaporation of the solvent afforded 20.0 g (59%) of a very viscous oil that was used directly in the preparation of **58**.

Pharmacology Materials and Methods. Adjuvant-Induced Arthritis Assay. Adjuvant arthritis was produced by a single intradermal injection of 0.75 mg of *M. butyricum* suspended in white paraffin oil (light N.F.) into the left hindpaw footpad of a Charles River Wistar male rat. The injected leg became inflamed and reached maximal size within 3–5 days (primary lesion). The adjuvant arthritis (secondary lesion) occurred after a delay of approximately 10 days and was characterized by inflammation of the noninjected right hind leg and further increases in the volume of the injected hind leg. Test compounds suspended in a 0.5% tragacanth vehicle were administered po daily beginning on the day of adjuvant injection, for 17 days, exclusive of days 4, 5, 11, and 12. Drug activity on the primary (left leg, day 3) and secondary (both legs, day 16) lesions was determined by comparing leg volumes of the treated group with a control arthritic (vehicle) group. Hind leg volumes were measured by immersing the leg into a mercury reservoir and recording the subsequent mercury displacement. The percent change in leg volume of eight treated animals relative to 16 nontreated controls and its significance (determined by the student's t test) was calculated for each compound. The ED_{25} value is defined as the dose that produces a 25% decrease in leg volume relative to nontreated controls. It is calculated from a minimum range of three dose levels per test and the 95% confidence limits determined using Fieller's Theorum.[52]

Oxazolone-Induced Contact Sensitivity Test. Contact sensitivity was produced by applying 0.1 mL of a 5% solution of oxazolone (4-(ethoxymethylene)-2-phenyloxazolone, Gallard-Schelessinger Chemicals) in absolute alcohol to the clipped abdomen of a male C57B1/6 mouse. Sensitization was allowed to continue for 45 h at which time the left hind leg was swabbed with the 5% oxazolone on a cotton applicator. The test compound was administered po suspended in 0.5% tragacanth, and the hind limb leg edema produced 24 h later was measured plethysmographically in a manner described for the adjuvant-induced arthritis assay. Edema was calculated as the difference in volume betweeen the oxazolone-challenged left hind leg and the untreated right hind leg. The percent change in edema for treated relative to control animals and the statistical significance (determined by using the student's t test) was calculated for each compound. Six mice were used per test and compared with eight controls.

Carrageenan-Induced Paw Edema. Normal or where noted adrenalectomized and sham-operated Charles River Wistar Lewis rats were treated po with the test compound suspended in 0.5% tragacanth and hydrated. After 1 h, paw volume measurements were made and the rats were immediately injected with 0.5 mL of 1% carrageenan suspension in 0.9% saline into the plantar surface of the right hindpaw. After 3 h, the volume of the injected paw was measured. The percent change in right hindpaw volume of the treated relative to the control animals and the statistical significance (determined by the student's t test) were calculated.

Acknowledgment. We gratefully acknowledge E. A. Reich for the elemental analyses, J. E. Wawro and G. Roberts for the mass spectral analyses, and M. Billig, M.

(52) Finney, D. J. "Statistical Method in Biological Assay", 3rd ed.; MacMillan: New York, 1978.
(53) Andreani, A.; Rambaldi, M.; Bonazzi, D.; Lelli, G.; Bossa, R.; Galatulas, I. *Eur. J. Med. Chem.-Chim. Ther.* **1984**, *19*, 219.
(54) Ogura, H.; Itoh, T.; Shimada, Y. *Chem. Pharm. Bull.* **1968**, *16*, 2167.
(55) Anschutz, R.; Schwickerath, K.; Justus *Liebigs Ann. Chem.* **1894**, *284*, 9.
(56) Mohan, J.; Chadha, V. K.; Pujari, H. K. *Indian J. Chem.* **1973**, *11*, 747.

Garvin, S. Alessi, J. Laydon, J. Kropp, and E. Webb for technical assistance.

Registry No. 1, 64997-22-4; 2, 24736-19-4; 3, 97059-60-4; 3·HBr, 66659-52-7; 4, 97059-61-5; 4·HBr, 66659-64-1; 5, 87532-36-3; 5·HBr, 66659-77-6; 6, 97059-62-6; 6·HBr, 66659-63-0; 7, 64997-47-3; 7·HBr, 66659-53-8; 8, 66659-61-8; 8·HBr, 97059-63-7; 9, 66659-81-2; 9·HBr, 78631-68-2; 10, 64997-34-8; 10·HBr, 66659-76-5; 11, 78643-32-0; 11·HBr, 66659-97-0; 12, 65823-24-7; 13, 97059-65-9; 13·HBr, 97059-64-8; 14, 78631-67-1; 14·HBr, 66659-78-7; 15, 66659-79-8; 16, 97059-67-1; 16·HBr, 97059-66-0; 17, 78631-71-7; 17·HBr, 66660-01-3; 18, 66659-94-7; 18·HBr, 66659-95-8; 19, 97059-68-2; 19·HCl, 66659-56-1; 20, 66659-84-5; 21, 78631-69-3; 21·HBr, 66659-92-5; 22, 78631-70-6; 22·HBr, 66659-99-2; 23, 66659-87-8; 24, 92754-18-2; $24 \cdot {}^{3}/_{2}$HBr, 97059-69-3; 25, 66659-72-1; 26, 65823-25-8; 27, 66659-73-2; 28, 66659-74-3; 29, 78631-66-0; 29·$HClO_4$, 97059-70-6; 30, 66659-54-9; 31, 66659-85-6; 32, 66659-86-7; 33, 66659-88-9; 34, 66660-02-4; 35, 66660-07-9; 36, 66660-03-5; 37, 97059-71-7; 38, 97059-72-8; 39, 97059-74-0; 39·HCl, 97059-73-9; 40, 66660-04-6; 41, 97059-75-1; 42, 97059-76-2; 43, 97059-77-3; 44, 97059-78-4; 45, 97059-84-2; 45·HCl, 97059-79-5; 46, 67645-07-2; 47, 39908-38-8; 48, 23908-75-0; 49, 49855-26-7; 50, 97059-80-8; 51, 62894-32-0; 52, 97059-81-9; 53, 21224-34-0; 54, 39908-69-5; 55, 66659-98-1; 56, 66660-00-2; 57, 97059-82-0; 58, 66660-06-8; 59, 73648-78-9; 60, 66659-69-6; 61, 66659-83-4; Ia, 51490-06-3; Ib, 6266-57-5; Ic, 1023-17-2; Id, 66659-59-4; Ie, 51490-05-2; If, 2132-57-2; Ig, 38803-55-3; Ih, 3141-93-3; Ii, 4927-55-3; Ij, 29955-23-5; Ik, 366-68-7; Il, 1979-63-1; Im, 2729-19-3; In, 36187-57-2; Io, 7150-10-9; Ip, 3669-47-4; Iq, 66659-90-3; IIa, 27895-95-0; IIb, 1484-50-0; IIc, 57297-30-0; IId, 1889-77-6; IIe, 66659-60-7; IIf, 51324-24-4; IIg, 42445-10-3; IIh, 66659-80-1; IIi, 56913-16-7; IIj, 66659-96-9; IIk, 5653-07-6; III, 2632-13-5; IIm, 71006-38-7; IIn, 27895-96-1; VIa, 42445-18-1; VIb, 4720-82-5; VIc, 7467-90-5; VId, 4254-18-6; VIe, 1218-85-5; VIf, 66659-65-2; VIg, 5702-73-8; VIh, 6706-96-3; VIi, 6706-95-2; VIj, 5653-60-1; 2-aminothiazoline, 1779-81-3; 1,2-dibromoethane, 106-93-4; pivalic anhydride, 1538-75-6; 5-ethylthiourea, 2986-20-1; thiourea, 62-56-6; 2-bromo-1-phenyl-2-(3,4-dimethoxyphenyl)ethanone, 66659-93-6; α-(trimethylsilyl)oxy-β-[3,4-dimethoxyphenyl]styrene, 97059-83-1; bis(3-fluoro-4-methoxy)benzoin, 66659-67-4; 3-fluoro-4-methoxybenzaldehyde, 351-54-2; bis(3-fluoro-4-methoxy)desoxybenzoin, 1827-54-9; 4,4′-bis(methylsulfinyl)benzoin, 66660-05-7.

Acylmorphinans. A Novel Class of Potent Analgesic Agents

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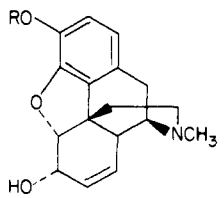
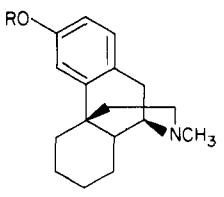
Received November 26, 1984

A series of novel 2- and 3-acylmorphinans (8–14) was synthesized in our search for a potent analgesic agent with low addiction potential. The compounds were evaluated for antinociceptive potency and receptor binding affinity. Among these compounds, the levorotatory 3-acetyl-*N*-(cyclopropylmethyl)morphinan (12) was found to be an orally active analgesic, comparable in potency to morphine (1), yet only weakly able to substitute for morphine (1) in morphine-dependent rats.

The importance of the phenolic hydroxyl group in enhancing both antinociceptive potency as well as opiate receptor affinity of morphine (1) and structurally related compounds is well-known.[1] However, substances having such a polar group often have poor oral activity, due to poor absorption and rapid metabolic inactivation via the phenolic hydroxyl group. In an attempt to reduce inactivation and prolong activity, we have already reported[2] the preparation of metabolically stable 3-*O*-*tert*-butylmorphine (3) and (−)-3-*tert*-butoxy-*N*-methylmorphinan (6). Unfortunately, these potentially interesting analogues



1. R=H
2. R=CH_3
3. R=$C(CH_3)_3$



4. R=H
5. R=CH_3
6. R=$C(CH_3)_3$

of codeine (2) and levomethorphan (5) were not only marginally active as analgesics but were also unstable under acidic conditions. In our search for novel substituents that might be able to replace the vulnerable phenolic group in morphinans and that would give stable analgesics, we focused our attention on replacement of the phenolic hydroxyl by an acyl substituent. Most importantly, it was speculated that the acyl group might interact with the opiate receptor in a mode that is different from that of the phenolic morphinans and thus eliminate or reduce the undesirable side effects common to the phenolic type of analgesics, while increasing the oral effectiveness of these compounds. In view of these assumptions, we carried out the synthesis of structurally novel 2- and 3-acylmorphinans (8–14).

Chemistry. The starting material, (−)-*N*-methylmorphinan (7), was prepared by the Grewe method.[3] Acetylation of this compound with acetyl chloride in 1,2-dichloroethane in the presence of aluminum chloride gave a mixture of isomeric morphinans (Scheme I). The major isomer was easily separated from the mixture by fractional crystallization of its tartrate salt (mp 179–181 °C, yield 36%), and the minor isomer was isolated from the concentrated mother liquors (mp 188–190 °C, yield 19%). Tentatively, structures 8 (mp 179–181 °C) and 9 (mp 188–190 °C) were assigned to these substances, respectively. Conclusive identification of the isomers proved to be difficult simply by spectroscopic methods.

The isomers 8 and 9 had similar UV and IR spectra. The 100-MHz ^{1}H NMR spectrum of 8 ($CDCl_3$) features a characteristic ABX pattern for the three aromatic protons, namely, a one-proton doublet at δ 7.87 (J = 2 Hz), a one-proton doublet of doublets at 7.67 (J = 2 and 8 Hz),

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(1) Portoghese, P. S. *J. Med. Chem.* **1965**, *8*, 609.
(2) Mohacsi, E.; Leimgruber, W.; Baruth, H. *J. Med. Chem.* **1982**, *25*, 1264.
(3) (a) Grewe, R. *Naturwissenschafen* **1946**, *33*, 33. (b) Schnider, O.; Hellerbach, J. *Helv. Chim. Acta* **1949**, *32*, 821. (c) *Ibid.* **1951**, *34*, 2218.

0022-2623/85/1828-1177$01.50/0