Anal. ($C_8H_{14}N_4O \cdot 0.4H_2O$) C, H, N. **33**: 30%; mp 144–146 °C. Anal. ($C_9H_{13}N_3O \cdot HCl$) C, H, N. **35**: 17%; mp 118–119 °C. Anal. ($C_8H_{12}N_4O \cdot 0.05H_2O$) C, H, N. **36**: 66%; mp 205–206 °C. Anal. ($C_8H_{11}N_3O \cdot HCl$) C, H, N. **37**: 16%; mp 216–218 °C. Anal. ($C_7H_{10}N_4O \cdot HCl$) C, H, N.

5-[(*N*,*N*-Dimethylamino)methyl]-3-methyl-1,2,4-oxadiazole Hydrochloride (38). *N*,*N*-Dimethylglycine sodium salt (1.14 g, 9.1 mmol) suspended in CH_2Cl_2 (30 mL) was treated with ethyl chloroformate (1.0 mL, 10.4 mmol) for 0.5 h. Acetamide oxime (1.0 g, 13.5 mmol) was added and the mixture stirred for 2 h then diluted with CH_2Cl_2 and washed with aqueous K_2CO_3. The organic layer was dried and concentrated in vacuo and the residue heated under reflux in dioxane for 2 h. The solution was concentrated and the residue treated with ethereal HCl to give the title compound as a white solid (0.56 g, 35%): mp 150–151 °C; MS *m*/*z* 142 (FAB)$^+$, (M + H)$^+$ free base; ^{1}H NMR ($CDCl_3$) δ 2.48 (3 H, s, CH_3), 3.01 (6 H, s, $N(CH_3)_2$), 4.57 (2 H, s, CH_2). Anal. ($C_6H_{11}N_3O \cdot HCl$) C, H, N.

5-[(*N*,*N*-Dimethylamino)methyl]-3-methyl-1,2,4-oxadiazole Methiodide (39). **38** (0.14 g, 1.0 mmol) in Et_2O (10 mL) was treated with MeI (0.25 mL) for 16 h. The precipitate was filtered and washed with Et_2O to give **39** (0.14 g, 49%): mp 180 °C; MS *m*/*z* 156 (FAB)$^+$, (M^+); ^{1}H NMR (D_2O) δ 2.50 (3 H, s, CH_3), 3.35 (9 H, s, $N(CH_3)_3$), 5.01 (2 H, s, CH_2). Anal. ($C_7H_{14}IN_3O \cdot 0.5H_2O$) C, H, N.

Piperazinyl- and 1,4-Diazabicyclooctyloxadiazoles 42–48. 2-Carbethoxypiperazine **40** was prepared according to literature procedure.[27] Reaction of **40** with 1,2-dibromobutane and NEt_3 gave 2-carbethoxy-1,4-diazabicyclo[2.2.2]octane (**41**) (27%).

The following piperazinyl and 1,4-diazabicyclo[2.2.2]octane oxadiazoles were prepared using the standard procedures. **42**: 40%; hydrogen oxalate; mp 156–158 °C; R_f 0.9 in CH_2Cl_2/MeOH (95:5); MS *m*/*z* 195 (M + H)$^+$ free base; ^{1}H NMR (D_2O) δ 2.43 (3 H, s, CH_3), 3.00–3.22 and 3.32–3.50 (2 H and 6 H, each m, 5-CH_2, 6-CH_2, 7-CH_2 and 8-CH_2), 3.77 (1 H, ddd, J = 1.8, 7.7, and 13.0 Hz, 3-CH), 3.84–3.92 (1 H, m, 3-CH), 4.92 (1 H, t, J = 8.2 Hz, 2-CH). Anal. ($C_9H_{14}N_4O \cdot C_2H_2O_4$) C, H, N. **43**: 25%; mp 238–240 °C. Anal. (M^+ = 195.1115, $C_8H_{13}N_3O$ requires M^+ = 195.1120). **44**: 50%; mp 74–75 °C; R_f 0.4 in CH_2Cl_2/MeOH (95:5) on alumina; MS *m*/*z* 168 (M^+); ^{1}H NMR (D_2O) δ 1.95 (2 H, brs, NH_2), 2.41 (3 H, s, CH_3), 2.81–3.11 (5 H, m, 3-CH, 5-CH_2, and 6-CH_2), 3.32–3.35 (1 H, m, 3-CH), 4.12–4.16 (1 H, m, 2-CH_2). Anal. ($C_7H_{12}N_4O$) C, H, N. **45**: 10%; mp 115–117 °C. Anal. ($C_6H_{11}N_5O$) C, H, N. **46**: 30%; mp 180–181 °C. Anal. ($C_8H_{14}N_4O \cdot 1.55C_2H_2O_4$) C, H, N. **47**: 30%; mp 102–104 °C. Anal. ($C_7H_{13}N_5O$) C, H, N. **48**: 10%; mp 172–174 °C. Anal. ($C_8H_{15}N_5O \cdot 0.2H_2O$) C, H, N.

Acknowledgment. The authors would like to thank Dr. Roger Snow for helpful discussions.

Supplementary Material Available: Tables of detailed analysis of the ^{1}H NMR spectra of methyloxadiazoles **15a** and **15b** and microanalytical data for novel compounds (3 pages). Ordering information is given on any current masthead page.

Substituted 1,3-Dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-ones as Potential Antiinflammatory Agents

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A series of analogues based on the 1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one ring system have been synthesized and shown to possess oral antiinflammatory activity in both the reverse passive Arthus reaction (RPAR) pleural cavity assay in rats and in the adjuvant-induced arthritic rat model (AAR). Several members of this series additionally exhibit an inhibitory effect on the in vivo production of prostaglandin- and leukotriene-derived products or arachidonic acid metabolism although these compounds exhibit no significant inhibitory activity against the cyclooxygenase and 5-lipoxygenase enzymes in vitro. Structure–activity relationships in this series are discussed.

The *acidic* nonsteroidal antiinflammatory drugs (NSAID's) are well-known for thier antiinflammatory, analgesic, and antipyretic properties. The antiinflammatory activity of these classical agents has been attributed to inhibition of the production of inflammatory prostaglandin products arising from metabolism of arachidonic acid via the cyclooxygenase (CO) dependent pathway.[1] Despite the significant antiinflammatory potency exhibited by the NSAID's in clinical use today, these drugs tend to have limited efficacy in altering the course of diseases, such as rheumatoid arthritis, and are used only as palliative treatments.

Rheumatoid arthritis is a complex disease involving an interactive relationship between antibody (humoral) mediated and cellular-mediated mechanisms of inflammatory reactions. In addition, these inflammatory reactions can involve the synergistic interplay between a number of chemically distinct and diverse inflammatory mediators. For example, in addition to the cyclooxygenase-dependent pathway of arachidonic acid metabolism leading to the prostaglandins, arachidonic acid can also be metabolized by the 5-lipoxygenase (5-LO) dependent pathway to the proinflammatory leukotrienes, including leukotriene B_4 (LTB_4), a potent chemoattractant for neutrophils.[2] The leukotrienes possess the ability to increase capillary permeability[3] and thereby cause edema, as well as the capability to stimulate neutrophil degranulation.[4] Neutrophil degranulation in turn releases lysosomal enzymes and reactive oxygen species, such as superoxide radical anion, singlet oxygen, hydroxyl radical, and hydrogen peroxide. Consequently, an ideal antiinflammatory agent may have to exhibit some degree of nonspecificity, in the sense of being able to block more than one target enzyme, receptor, or inflammatory process, in order to elicit a disease-modifying antiinflammatory effect.

As both cyclooxygenase- and 5-lipoxygenase-dependent pathways of arachidonic acid metabolism lead to formation of putative mediators of inflammation, agents that inhibit both of these metabolic pathways, *dual inhibitors*, may offer some advantage in the treatment of inflammatory diseases over the *classical* nonsteroidal antiinflammatory drugs, which affect only the cyclooxygenase-dependent pathway of arachidonic acid metabolism. Since gastroin-

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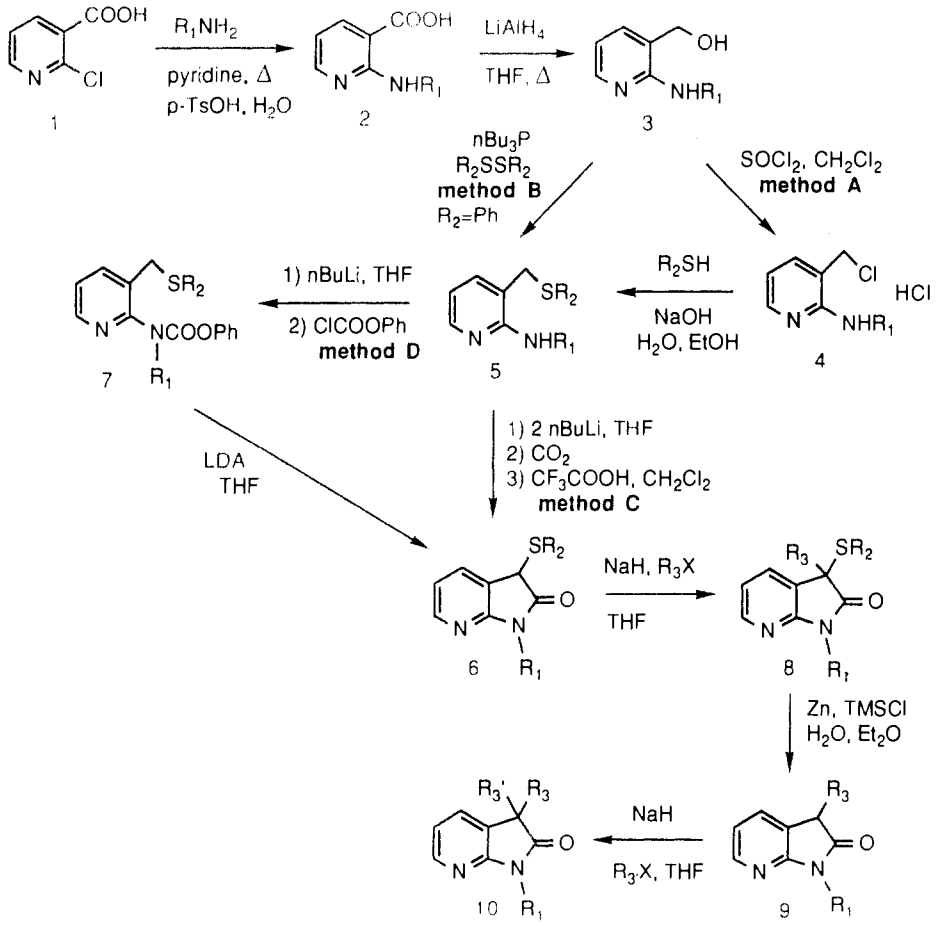
Scheme I



testinal side effects of cyclooxygenase inhibition may limit the dose used in the clinic and thereby prevent a disease modifying action, dual inhibitors may negate this effect.[5]

During the course of screening selected compounds in our antiinflammatory assays, 1,3-dihydro-3,3-dimethyl-1-phenyl-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (**10a**), a *nonacidic* agent, was identified as a lead structure of interest. While **10a** exhibited no significant inhibitory activity against the cyclooxygenase and 5-lipoxygenase enzymes in vitro,[6] it exhibited significant in vivo antiinflammatory activity in acute (RPAR pleural cavity assay) and chronic models (AAR models) of inflammation following oral administration. Compound **10a** exhibits an inhibitory effect on the in vivo production of prostaglandin (TxB_2) and leukotriene (LTE_4) derived products of arachidonic acid metabolism following oral administration, in contrast to its lack of in vitro inhibitory activity against the enzymes that produce these mediators. It may be possible that compound **10a** is inhibiting at an earlier step in cell activation prior to cyclooxygenase/5-lipoxygenase activity.

Development of the structure–activity relationships in this series led to the selection of 1-(4-chlorophenyl)-1,3-dihydro-3,3-dimethyl-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (**10s**) for preclinical toxicologic evaluation.

Chemistry

The pyrrolo[2,3-*b*]pyridin-2-ones (**10**) were generally prepared by the synthesis illustrated in Scheme I. Condensation of 2-chloronicotinic acid (**1**) and primary amines yielded the substituted nicotinic acids (**2**) according to the procedure of Kermack and Weatherhead.[7] Reduction of **2** with lithium aluminum hydride provided alcohols **3**, which were converted by thionyl chloride into the chlorides **4**. Displacement of the chlorine by a thiol anion gave sulfides **5** (method A). When this conversion was problematic, i.e. when R_1 was sensitive to thionyl chloride treatment, reaction of **3** with tri-*n*-butylphosphine and diphenyl sulfide[8] produced **5** directly (R_2 = phenyl) (method B). Formation of the 1,3-dihydropyrrolo-2-one ring could be accomplished in one step by quenching the dianion[9] of **5** with solid carbon dioxide (dry ice) followed by acid-catalyzed cyclization (method C). In instances where this procedure was not successful, a two-step method of first forming the carbamate **7**, followed by base-catalyzed ring closure, was used (method D). Selective introduction of two different substituents at the 3-position in **10** was achieved by alkylation of **6** (Table I), followed by treatment of the monoalkyl intermediate with zinc and trimethylsilyl chloride[10] in order to remove the sulfide group, before the second alkyl group was introduced.

From research efforts in related projects, other synthetic routes toward the pyrrolo[2,3-*b*]pyridin-2-one ring system were available to us. The synthesis of **10o,z,bb** is described in Scheme II. Oxidation of commercially available 3-pyridylacetonitrile (**11**) with peracetic acid gave *N*-oxide

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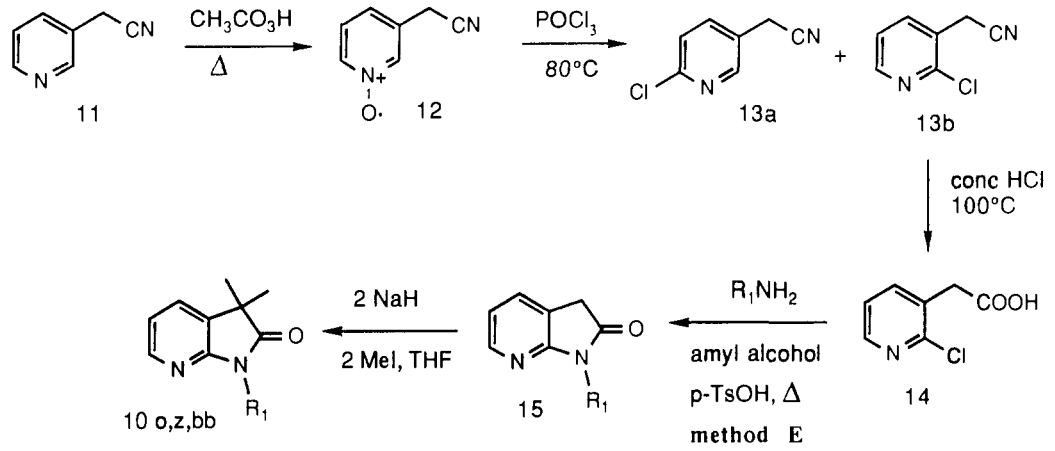
Table I. Substituted 1,3-Dihydro-3-(thio)-2*H*-pyrrolo[2,3-*b*]pyridin-2-ones

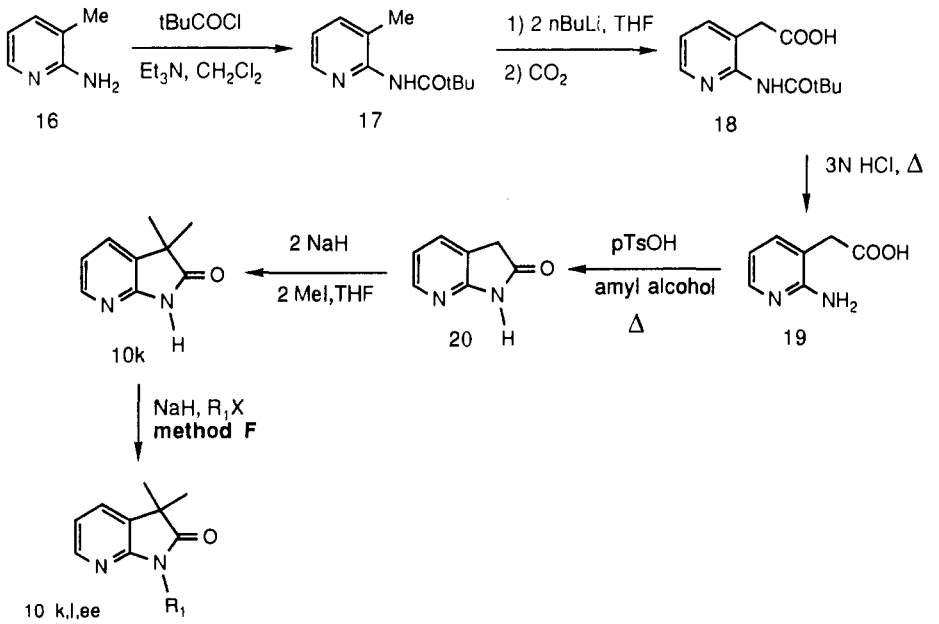
compd	R_1	R_2	method of synthesis	mp, °C	chromatography solvent	recrystn solvent	formula	anal.
6a	Ph	Me	A, C	150–152	EtOAc–CH_2Cl_2 (3:97)	iPrOAc	$C_{14}H_{12}N_2OS$	C,H,N
6b	Ph	Ph	A, C	163–165		iPrOAc	$C_{19}H_{14}N_2OS$	C,H,N
6c	Me	Ph	A, C	83–84		Et_2O	$C_{14}H_{12}N_2OS$	C,H,N
6d	iPr	Ph	A, C	121–122		Et_2O–pet. ether	$C_{16}H_{16}N_2OS$	C,H,N
6e	tBu	Ph	B, C	65–66		CH_2Cl_2–hexane	$C_{17}H_{18}N_2OS$	C,H,N
6f	4-$iC_3H_7C_6H_4$	Ph	A, C	152–154		CH_2Cl_2–Et_2O	$C_{22}H_{20}N_2OS·HBr·0.5H_2O$	C,H,N
6g	3-ClC_6H_4	Ph	A, C	117–118		iPr_2O–pet. ether	$C_{19}H_{13}ClN_2OS$	C,H,N
6h	3,4-$Cl_2C_6H_3$	Ph	A, C	113–115		iPr_2O	$C_{19}H_{12}Cl_2N_2OS$	C,[a]H,N
6i	2-CH_3, 3-ClC_6H_4	Ph	A, C	150–152		CH_2Cl_2–hexane	$C_{20}H_{15}ClN_2OS·0.25H_2O$	C,H,N
6j	3-$CF_3C_6H_4$	Ph	A, C	86–87	EtOAc–CH_2Cl_2 (5:95)	hexane	$C_{20}H_{13}F_3N_2OS$	C,H,N
6k	CH_2Ph	Ph	A, C	91–92	EtOAc–CH_2Cl_2 (5:95)	iPrOAc–iPr_2O	$C_{20}H_{16}N_2OS$	C,H,N

[a] Calcd: C, 58.92. Found: C, 58.47.

Scheme II



Scheme III



12, which rearranged upon treatment with phosporus oxychloride into 2-chloropyridines **13a** and **13b**. The isomers **13a** and **13b** were separated by recrystallization from diethyl ether. Acidic hydrolysis of **13b** produced the intermediate **14**.[11] Condensation of **14** and primary amines produced **15** (method E). Bismethylation using sodium hydride and methyl iodide gave **10o,z,bb**.

Compounds **10k,l,ee,ff,gg** were synthesized by the alternative route described in Scheme III. Derivatization of 2-aminopyridine (**16**) into the corresponding amide **17** allowed carbonylation of the methyl group to afford acid **18**.[12] Acidic hydrolysis of **18** gave **19**, which cyclized to **20** when treated with *p*-toluenesulfonic acid in *n*-amyl alcohol.[11] Alkylation of **20** using sodium hydride and methyl iodide gave **10k**. Various R_1 groups were introduced by N-alkylation of **10k** (method F).

Modification of the carbonyl group or the pyridine ring in **10** necessitated specific transformations. Lawesson's

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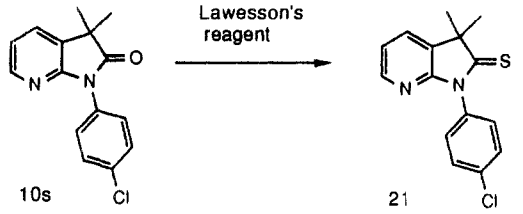
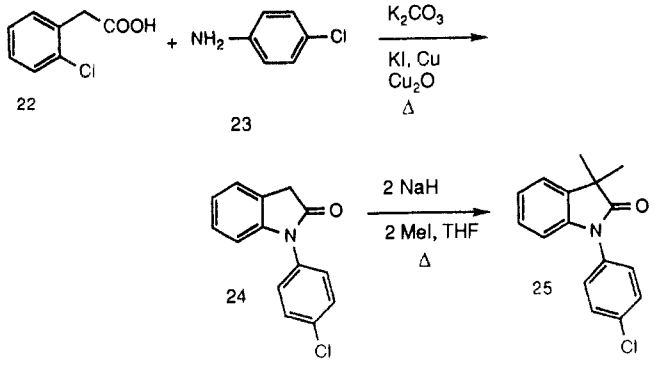
reagent[13] converted **10s** directly into the thiocarbonyl analogue **21**. Compound **25**, the indolone analogue of **10s**, was obtained by treating commercially available 2-chlorophenylacetic acid (**22**) with 4-chloroaniline[14] to give the intermediate indol-2-one **24**. Bismethylation of **24** using sodium hydride and methyl iodide gave **25**.



Methods A and D illustrated in Scheme I were used to obtain **26**, the 6-bromo analogue of **10s**, from 5-bromo-2-chloronicotinic acid.



Biological Test Methods

Activity was assessed by several different assays.

The primary in vitro biochemical screen was evaluation of 5-lipoxygenase (5-LO) enzyme inhibition in human polymorphonuclear (PMN) cells by measurement of 5-hydroxy-6,8,11,14-eicosatetraenoic acid (5-HETE) production and determination of cyclooxygenase (CO) enzyme inhibition in human platelets by measurement of 12-hydroxyhepta-5,8,10-trienoic acid (HHT) formation.[6]

The primary in vivo screen was a reverse passive Arthus reaction (RPAR) induced in the pleural cavity of rats.[15] In the RPAR pleural cavity model, inflammation was induced by the intravenous injection of bovine serum albumin followed by the intravenous injection of antibovine serum albumin into the pleural cavity. The percentage reduction, relative to control, of both neutrophil number and edema volume in the pleural cavity of rats was the indicator for antiinflammatory activity.

Compounds that exhibited activity in either primary screen were studied in secondary assays which included determining 5-lipoxygenase (5-LO) and cyclooxygenase (CO) products in the pleural cavity of rats[16] (in vivo 5-LO/CO assay) and chronic antiinflammatory activity in the prophylactic and therapeutic variants of the adjuvant arthritic rat (AAR) model.[17]

In the in vivo 5-LO/CO assay, the effect of the compound on prostaglandin and leukotriene mediator production in the rat pleural cavity was assessed concomitantly with measurement of the inhibition of cell influx and fluid volume as described above. 5-LO enzyme inhibition was determined by the level of LTE_4 produced, while CO enzyme inhibition was evaluated by the level of thromboxane B_2 (TxB_2) formed relative to control. Several compounds exhibited significant inhibition of mediator production in the rat pleural cavity in vivo, but failed to inhibit mediator production when tested in the enzyme assay in vitro.

Hind paw edema was induced in the AAR models by injection of complete Freunds' adjuvant. The compounds were orally administered either before edema stimulation (prophylactically) or after edema formation (therapeutically). Antiinflammatory activity was assessed by the extent that edema formation was inhibited in both the injected (primary) and noninjected (secondary) paws of the rat.

Results and Discussion

1,3-Dihydro-3,3-dimethyl-1-phenyl-2*H*-pyrrolo[2,3-*b*]-pyridin-2-one (**10a**) was initially selected as a compound of interest since it appeared to be a dual inhibitor of in vivo production of prostaglandin- and leukotriene-derived products of arachidonic acid metabolism even though it lacked in vitro inhibitory activity against these enzymes. The oral potency (ED_{50}) of **10a** in the RPAR pleural cavity assay was 21.9 mg/kg against cells and 35.1 mg/kg against fluid. In contrast, **10a** exhibited a complete absence of inhibition against CO and 5-LO enzymes in vitro at 15 μM (Table II). Compound **10a** was also orally active in a chronic model of inflammation, exhibiting 24% inhibition in the secondary paw at 25 mg/kg in the prophylactic AAR assay (Table III). A structure–activity relationship study (SAR) was initiated in order to identify a more potent analogue in this series.

Structure–Activity Relationships. The primary biological activity of the 1,3-dihydro-2*H*-pyrrolo[2,3-*b*]-pyridin-2-ones **10** is summarized in Table II. Trends in the SAR were based on the biological activity determined at a single oral dose, 25 mg/kg, in the RPAR pleural cavity assay. Compounds that were determined active at this dose were then evaluated by using a dose–response analysis in the RPAR pleural cavity assay in order to estimate their potency (ED_{50}) and their effect on mediator production. The most potent compounds were also further tested for inhibition of eicosanoids in vivo and for activity in a chronic model of inflammation, the AAR model.

R_3 and $R_{3'}$ Substituents. Increasing the size of the alkyl groups R_3 and $R_{3'}$ (**10d–j**) did not improve antiinflammatory activity in the RPAR pleural cavity assay. The steric requirement at this position appears to be quite strict and small groups appear to be optimal. Replacement of one of the alkyl groups with a hydrogen (**10b**) or fluorine (**10c**) atom also did not enhance biological activity. Therefore, both alkyl substituents appear to be necessary.

R_1 Substituent. The pendant R_1 group is an important structural substituent. The most dramatic effect on antiinflammatory activity is observed with changes at this position. Replacement of the phenyl moiety with a benzyl (**10dd**, **10ee**) group results in analogues that exhibit a significant decrease in antiinflammatory activity. Introduction of electron-donating groups, such as isopropyl, methoxy, or methylthio (**10n**, **10o**, **10p**) into the phenyl ring also did not enhance antiinflammatory activity. However, the introduction of electron-withdrawing substituents (**10q–cc**) at different positions in the aryl group

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Table II. Substituted 1,3-Dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-ones

compd	R_1	R_3	$R_{3'}$	method of synthesis	mp, °C	chromatography solvent	recrystn solvent	formula	anal.	% inhibition: in vitro 5-LO/CO assay (15 μM) HHT	% inhibition: in vitro 5-LO/CO assay (15 μM) 5-HETE	% inhibition: RPAR pleural cavity assay (25 mg/kg)[a] cells	% inhibition: RPAR pleural cavity assay (25 mg/kg)[a] fluid
10a	Ph	Me	Me	A, C	122–124	CH_2Cl_2	iPr_2O–pet. ether	$C_{15}H_{14}N_2O$	C,H,N	0	0	ED_{50} = 21.9[f]	ED_{50} = 35.1[g]
10b	Ph	Me	H	A, C	63–65	EtOAc–hexane (1:1)	iPr_2O–pet. ether	$C_{14}H_{12}N_2O$	C,*H*,N		0	29	18
10c	Ph	Me	F	A, C	83–85	EtOAc–hexane (30:70)	iPr_2O–pet. ether	$C_{14}H_{11}FN_2O$	C,H,N		0	50	35
10d	Ph	Me	SMe	A, C	87–89	EtOAc–CH_2Cl_2 (5:95)	iPr_2O	$C_{15}H_{14}N_2OS$	C,H,N		21	34	53
10e	Ph	Me	Et	A, C	84–85	CH_2Cl_2	CH_2Cl_2–pet. ether	$C_{16}H_{16}N_2O$	C,H,N		13	36	12
10f	Ph	Et	Et	A, C	88–89	CH_2Cl_2	iPr_2O–pet. ether	$C_{17}H_{18}N_2O$	C,H,N		12	13	0
10g	Ph	Me	nBu	A, C	oil	EtOAc–hexane (1:2)		$C_{18}H_{20}N_2O$	C,H,N		13	21	5
10h	Phe	Me	$SCH_2CH_2OCH_3$	A, D	oil	EtOAc–hexane (1:2)		$C_{17}H_{18}N_2O_2S·H_2O$	C,H,[c]*N*		0	26	23
10i	Ph	Me	CH_2Ph	A, C	62–64	EtOAc–hexane (1:3)	iPr_2O–pet. ether	$C_{21}H_{18}N_2O$	C,H,N		17	9	0
10j	Ph	Me	SPh	A, C	113–114	EtOAc–hexane (1:6)	EtOAc–hexane	$C_{20}H_{16}N_2OS$	C,H,N			0	0
10k	H	Me	Me	F	169–172	EtOAc	iPrOAc–hexane	$C_9H_{10}N_2O$	C,H,N			46	38
10l	Me	Me	Me	F	48–50	EtOAc	pet. ether	$C_{10}H_{12}N_2O$	C,H,N			69	53
10m	iPr	Me	Me	A, C	oil	CH_2Cl_2		$C_{12}H_{16}N_2O·H_2O$	C,H,[d]*N*		6	34	14
10n	4-$iC_3H_7C_6H_4$	Me	Me	A, C	81–82	CH_2Cl_2	pet. ether	$C_{18}H_{20}N_2O$	C,H,N		0	29	6
10o	4-$CH_3OC_6H_4$	Me	Me	E	108–109		iPrOAc–pet. ether	$C_{16}H_{16}N_2O_2$	C,H,N		11	63	42
10p	4-$CH_3SC_6H_4$	Me	Me	A, C	102–103		iPr_2O–pet. ether	$C_{16}H_{16}N_2OS$	C,H,N		23	29	37
10q	4-$CH_3SOC_6H_4$	Me	Me	A, C	133–134	MeOH–CH_2Cl_2 (10:90)	iPr_2O–pet. ether	$C_{16}H_{16}N_2O_2S$	C,H,N		11	39	0
10r	4-$CH_3SO_2C_6H_4$	Me	Me	A, C	180–181	EtOAc	CH_2Cl_2–pet. ether	$C_{16}H_{16}N_2O_3S$	C,H,N		13	42	0
10s	4-ClC_6H_4	Me	Me	A, C	100–101	CH_2Cl_2	Et_2O–iPr_2O	$C_{15}H_{13}ClN_2O$	C,H,N	47	13	ED_{50} = 4.5[h]	ED_{50} = 27.9[i]
10t	3-ClC_6H_4	Me	Me	A, C	120–122	CH_2Cl_2	CH_2Cl_2–iPr_2O	$C_{15}H_{13}ClN_2O$	C,H,N	0	3	51	49
10u	2-ClC_6H_4	Me	Me	B, C	117–118	EtOAc–CH_2Cl_2 (5:95)	CH_2Cl_2–iPr_2O	$C_{15}H_{13}ClN_2O$	C,H,N		0	14	3
10v	4-FC_6H_4	Me	Me	A, C	101–103		iPr_2O–pet. ether	$C_{15}H_{13}FN_2O$	C,H,N	0	2	ED_{50} = 4.5[j]	ED_{50} = 29.5[k]
10w	4-BrC_6H_4	Me	Me	A, D	135–137	CH_2Cl_2	iPr_2O–pet. ether	$C_{15}H_{13}BrN_2O$	C,H,N		11	46	55
10x	3-$CF_3C_6H_4$	Me	Me	A, C	110–111	CH_2Cl_2	iPr_2O	$C_{16}H_{13}F_3N_2O$	C,H,N		34	35	10
10y	3,4-$Cl_2C_6H_3$	Me	Me	A, C	111–112	CH_2Cl_2	iPr_2O	$C_{15}H_{12}Cl_2N_2O$	C,H,N	0	0	26	25
10z	3,5-$Cl_2C_6H_3$	Me	Me	E	138–139		hexane	$C_{15}H_{12}Cl_2N_2O$	C,H,N			49	33
10aa	2,4-$Cl_2C_6H_3$	Me	Me	A, C	94–95	CH_2Cl_2	iPr_2O	$C_{15}H_{12}Cl_2N_2O$	C,H,N		20	16	8
10bb	2,4-$F_2C_6H_3$	Me	Me	E	91–92		hexane	$C_{15}H_{12}F_2N_2O$	C,H,N		7	61	19
10cc	2-CH_3-3-ClC_6H_3	Me	Me	A, C	129–130	EtOAc–CH_2Cl_2 (3:97)	iPr_2O	$C_{16}H_{15}ClN_2O$	C,H,N		7	14	0
10dd	CH_2Ph	Me	Me	A, C	92–93		iPr_2O	$C_{16}H_{16}N_2O$	C,H,N		2	12	12
10ee	CH_2-4-ClC_6H_4	Me	Me	F	111–113	EtOAc–hexane (1:1)	iPr_2O–pet. ether	$C_{16}H_{15}ClN_2O$	C,H,N		26	6	0
21				A, C	146–148	CH_2Cl_2	iPr_2O–pet. ether	$C_{15}H_{13}ClN_2S$	C,H,N		17	41	42
25					131–132		Et_2O	$C_{16}H_{14}ClNO$	C,H,N			0	0
26				A, D	190–192	EtOAc–hexane (1:4)	iPr_2O	$C_{15}H_{12}BrClN_2O$	C,[e]*H*,N		34	29	0
27					240–245			$C_{15}H_{14}ClN_2O_2$·Na·0.75H_2O	C,H,N	28	0	ED_{50} = 11.3[l]	ED_{50} = 9.6[m]

[a] ED_{50} are reported in milligrams/kilogram. Values in parentheses are confidence intervals determined at 95%, $p = 0.05$. [b] Calcd: C, 74.97. Found: C, 74.50. [c] Calcd: H, 6.08. Found: H, 5.37. [d] Calcd: H, 8.16. Found: H, 7.21. [e] Calcd: C, 51.23. Found: C, 53.04. Calcd: H, 7.97. Found: H, 8.61. [f] ED_{50} = 21.9 (13.5–34.1). [g] ED_{50} = 35.1 (25.1–51.5). [h] ED_{50} = 4.5 (0.38–19.0). [i] ED_{50} = 27.9 (14.4–79.9). [j] ED_{50} = 4.5 (1.3–11.5). [k] ED_{50} = 29.5 (estimate). [l] ED_{50} = 11.3 (5.6–24.8). [m] ED_{50} = 9.6 (6.8–13.7).

Table III. Antiinflammatory Activity of Substituted 1,3-Dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-ones in Secondary Models

				in vivo 5-LO/CO assay in the RPAR pleural cavity					adjuvant arthritic rat			
					% inhibition				% inhibition			
				dose,					dose,	prophylactic		therapeutic	
compd	R_1	R_3	$R_{3'}$	mg/kg	cells	fluid	LTE_4	TxB_2	mg/kg	1° paw	2° paw	1° paw	2° paw
10a	Ph	Me	Me	40	70	60	54	54	25	0	24		
10l	Me	Me	Me	25	69	53	62	17					
10o	4-$CH_3OC_6H_4$	Me	Me	25	63	42	0	34	25	0	0		
10s	4-ClC_6H_4	Me	Me	25	73	83	87	78	25	13	65	31	54
10t	3-ClC_6H_4	Me	Me	25	51	49	59	62	25	0	31		
10v	4-FC_6H_4	Me	Me	20	70	43	36	53	25	0	48		
10y	3,4-$Cl_2C_6H_3$	Me	Me	25	26	25	46	44					
27				25	62	71	76	81	25	14	34		
iodomethacin				1.0	48	24	0	100	2.0		70		88

R_1 appears to improve activity (except for **10u**, **10aa**, **10cc**). The biological data described in Table II suggest the following trend in antiinflammatory activity: 3-trifluoromethyl (**10x**) = 3,4-dichloro (**10y**) < 3,5-dichloro (**10z**) < 4-bromo (**10w**) = 3-chloro (**10t**) < 4-chloro (**10s**) = 4-fluoro (**10v**). Compounds **10s** and **10v** exhibit the highest level of antiinflammatory activity in the RPAR pleural cavity assay with respective oral ED_{50} of 4.5 and 4.5 mg/kg in cells and oral ED_{50} of 27.9 and 29.5 mg/kg in fluid.

Skeletal Framework. The necessity of retaining the 1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one ring system was also examined. The thiocarbonyl analogue **21** of **10s** exhibited modest antiinflammatory activity in the RPAR pleural cavity assay: 41% inhibition of cells and 42% inhibition of fluid. Antiinflammatory activity was found to decrease in the bromopyridine analogue (**26**): 29% inhibition of cells and 0% inhibition of fluid. Most importantly, when the pyridine nitrogen atom is removed, as in the benzene analogue (**25**) of **10s**, antiinflammatory activity is completely lost. These results suggested that the pyridine ring is of significance.

Additional Biological Properties. Selected compounds that exhibited significant potency in the primary screens were analyzed further in secondary assays, the in vivo 5-LO/CO assay and the AAR model (Table III). The target compounds **10** appear to be dual inhibitors in vivo of both CO and 5-LO products in the RPAR pleural cavity. However, they do not inhibit either the CO and 5-LO pathways in the in vitro biochemical human PMN and platelet assays. While no correlation appears to exist between our in vitro and in vivo results, the biological data described in Table III suggest a correlation between activity in the acute model, the in vivo 5-LO/CO assay, and the chronic model of inflammation. Our initial lead structure **10a** exhibits an oral ED_{50} of 21.9 mg/kg in cells and an oral ED_{50} of 35.1 mg/kg in fluid in the in vivo 5-LO/CO test and a corresponding 24% inhibition in the secondary paw in the prophylactic AAR test following oral administration. The 4-fluoro analogue **10v** exhibits improved potency with an oral ED_{50} of 4.5 mg/kg in cells, an oral ED_{50} of 29.5 mg/kg in fluid, and 48% inhibition in the secondary paw following oral administration. Compound **10s**, 1-(4-chlorophenyl)-1,3-dihydro-3,3-dimethyl-2*H*-pyrrolo[2,3-*b*]pyridin-2-one, has an oral ED_{50} of 4.5 mg/kg in cells and an oral ED_{50} of 27.9 mg/kg in fluid. Compound **10s** also exhibits the highest overall level of antiinflammatory activity in the chronic model, 65% inhibition in the secondary paw prophylactically and 54% inhibition in the secondary paw therapeutically following oral administration. On the basis of these results, compound **10s** was chosen for preclinical toxicologic studies. While assignment of the structure of **10s** was consistent with all available spectroscopic data, the structure of this novel heterocyclic system was unequivocally established by single-crystal X-ray analysis (Figure 1). The crystal structure was solved by direct methods.[18] Full-matrix least-squares refinement of atomic parameters[19] converged at $R = 0.052$ ($R_w = 0.072$)[20] over 1678 reflections.

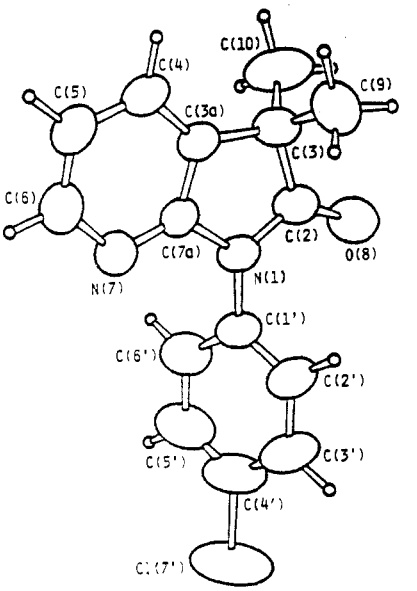
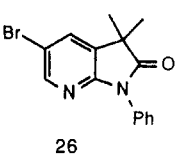
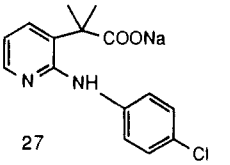


Figure 1. Structure and solid-state conformation of 1-(4-chlorophenyl)-1,3-dihydro-3,3-dimethyl-2*H*-pyrrolo[2,3-*b*]-pyridin-2-one (**10s**); small circles represent hydrogen atoms.

While **10s** is hydrolytically stable at physiologic pH, the possibility exists that **10s** could be a substrate for enzymatic hydrolysis and therefore act as a prodrug for **27**.



26



27

The carboxylic acid **27** is similar in structure to other classical NSAIDs. Although the metabolic fate and pharmacodynamic profile of **10s** have not been examined, we have investigated this possibility by preparing and determining the antiinflammatory activity of **27**. Interestingly, and possibly fortuitously, **27** exhibits antiinflammatory activity in acute and chronic models of inflam-

(18) Crystallographic calculations were performed on PDP11/44 and MicroVAX II computers by use of the Enraf-Nonius Structure Determination Package incorporating MULTAN11/82.

(19) Supplementary material, see the paragraph at the end of the paper.

(20) $R = \sum||F_o| - |F_c||/\sum|F_o|$; $R_w = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$.

mation comparable to **10s**, i.e. an oral ED_{50} = 11.3 mg/kg in cells, an oral ED_{50} = 9.6 mg/kg in fluid, and 34% inhibition in the secondary paw prophylactically following oral administration.

In conclusion, the antiinflammatory activity of a new class of substituted 1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-ones has been described. Structure–activity studies in this series have led to 1-(4-chlorophenyl)-1,3-dihydro-3,3-dimethyl-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (**10s**), which exhibits significant antiinflammatory activity in acute and chronic models of inflammation and was selected for preclinical toxicologic evaluation.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus. ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz), XL-200 (200 MHz), or XL-300 (300 MHz) spectrometer and are expressed as ppm from Me_4Si internal standard. Microanalyses were performed by the Physical and Analytical Research Department of the Schering-Plough Pharmaceutical Research Division, and carbon, hydrogen, and nitrogen results were within ±0.4% of theory, except as noted in the tables. Mass spectra were obtained with a Varian MAT CH5 spectrometer. Flash chromatography[21] was performed on silica gel supplied by E. Merck (No. 9385). All organic solutions were dried over $MgSO_4$. Unless otherwise indicated, all reagents and chemicals were obtained commercially and were used without pretreatment of further purification. All amines were obtained from Aldrich Chemical Co.

Synthesis of Alcohol 3. To acid **2** (0.10 mol) dissolved in tetrahydrofuran (500 mL) was added portionwise lithium aluminum hydride (7.7 g, 0.20 mol) under a nitrogen atmosphere. The resulting reaction mixture was refluxed for 24 h and then cooled to room temperature. Water (8 mL), 1 N NaOH (8 mL), and water (24 mL) were added carefully in sequence in order to precipitate the aluminum salts. The aluminum salts were removed by filtration and washed with dichloromethane. Evaporation of the filtrate gave the crude product as a solid which was triturated with petroleum ether to yield the final product. For R_1 = 4-chlorophenyl, 97% yield was obtained.

Synthesis of Sulfide 5. Method A. To alcohol **3** (0.10 mol) dissolved in dichloromethane (300 mL) was added thionyl chloride (29.7 g, 0.25 mol). The reaction mixture was stirred at room temperature for 16 h. The product was isolated by filtration and washed with diethyl ether to give chloride **4**. To NaOH (8.4 g, 0.21 mol) dissolved in water (50 mL) and ethanol (500 mL) was added thiophenol (11.6 g, 0.105 mol). The reaction mixture was cooled to 0 °C, and chloride **4** (0.10 mol) was added. The resulting reaction mixture was stirred at room temperature for 16 h. Water (850 mL) was added, and the precipitate was isolated by filtration. The solid was dissolved in dichloromethane, dried, and filtered. Evaporation of the solvent gave sulfide **5**. For R_1 = 4-chlorophenyl, 95% yield was obtained. ^{1}H NMR ($CDCl_3$): δ 4.08 (s, 2 H, CH_2S), 6.65 (dd, 1 H, *J* = 5, 7.5 Hz, meta H of pyridine), 7.10–7.50 (m, 10 H), 8.3 (dd, 1 H, *J* = 2.5, 5 Hz, ortho H of pyridine); MS: M^+ 325 (50.1%).

Synthesis of Sulfide 5. Method B. To phenyl disulfide (12.0 g, 0.055 mol) and alcohol **3** (0.050 mol) dissolved in dichloromethane (275 mL) was added tri-*n*-butylphosphine (12.1 g, 0.060 mol) dropwise over 15 min. The reaction mixture was stirred at room temperature for 48 h. Water (100 mL) was added, and the layers were separated. The organic solution was washed with 5% NaOH and water, dried, and filtered. Evaporation of the solvent gave the crude product which was purified by flash chromatography, eluting with dichloromethane. For R_1 = 2-chlorophenyl, 54% yield was obtained. ^{1}H NMR ($CDCl_3$): δ 4.10 (s, 2 H, CH_2S), 6.70 (dd, 1 H, *J* = 5, 7.5 Hz, meta H of pyridine), 6.90 (td, 1 H, *J* = 7.5, 2.5 Hz), 7.25 (m, 5 H), 7.38 (m, 3 H), 7.70 (s, 1 H, NH), 8.18 (dd, 1 H, *J* = 2.5, 5 Hz, ortho H of pyridine), 8.30 (dd, 1 H, *J* = 2.5, 7.5 Hz). MS: MH^+ 327.

Synthesis of 1,3-Dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one 6. Method C. To sulfide **5** (0.10 mol) dissolved in dry tetrahydrofuran (300 mL) at −78 °C under a nitrogen atmosphere was added *n*-butyllithium (96.0 mL, 0.24 mol, 2.5 M in hexane). The reaction mixture was stirred at −78 °C for 3 h, warmed to −30 °C for 15 min, and then recooled to −78 °C. The dianion solution was poured onto a suspension of powdered dry ice (800 mL) in diethyl ether (1000 mL) with stirring. Evaporation of the solvent gave a solid that was dissolved in water and washed with diethyl ether. The aqueous solution was acidified to pH 3 with concentrated HCl and extracted with dichloromethane. The organic solution was dried and filtered. Evaporation of the solvent yielded an oil that was dissolved in dichloromethane (500 mL) and to which was added trifluoroacetic acid (50 mL). The reaction mixture was stirred at room temperature for 16 h, and the solvent was removed by evaporation to give an oil. The residue was partitioned between aqueous $NaHCO_3$ and dichloromethane. The aqueous solution was extracted with additional dichloromethane. The combined organic solution was dried and filtered. Evaporation of the solvent produced the crude product which was purified by flash chromatography and/or recrystallization according to the solvent systems listed in Table I. For R_1 = 4-chlorophenyl, 60% yield was obtained. ^{1}H NMR ($CDCl_3$): δ 4.70 (s, 1 H, CHS), 7.03–7.45 (m, 10 H), 7.75 (dd, 1 H, *J* = 2.5, 7.5 Hz, para H of pyridine), 8.10 (dd, 1 H, *J* = 2.5, 5 Hz, ortho H of pyridine). MS: M^+ 352 (50.1%).

Synthesis of 1,3-Dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one 6. Method D. To sulfide **5** (0.080 mol) dissolved in tetrahydrofuran (300 mL) at −78 °C under a nitrogen atmosphere was added *n*-butyllithium (33.6 mL, 0.084 mol, 2.5 M in hexane). The reaction mixture was stirred at −78 °C for 30 min, and then phenyl chloroformate (15.0 g, 0.096 mol) was added. The resulting reaction mixture was warmed to room temperature and stirred for 21 h. Evaporation of the solvent gave an oil that was dissolved in ethyl acetate. The organic solution was washed with water and brine, dried, and filtered. Evaporation of the solvent yielded the carbamate **7**, which was purified by flash chromatography, eluting with ethyl acetate–hexane. To carbamate **7** (0.070 mol) dissolved in tetrahydrofuran (150 mL) at −78 °C under a nitrogen atmosphere was added a solution of lithium diisopropylamide (0.15 mol) in tetrahydrofuran (150 mL). The reaction mixture was stirred at −78 °C for 3 h, and then 25 wt % HCl in ethanol (50 mL) was added. Water (200 mL) was added, and the organic solvent was removed by evaporation. The aqueous solution was acidified to pH = 3 with 15% HCl and extracted with ethyl acetate. The organic solution was washed with brine, dried, and filtered. Evaporation of the solvent gave the product **6**, which was purified by flash chromatography and/or recrystallization according to the solvent system listed in Table I. For R_1 = 4-bromophenyl, 59% yield was obtained. ^{1}H NMR ($CDCl_3$): δ 4.68 (s, 1 H, CHS), 7.05 (d, 2 H, *J* = 10 Hz, bromophenyl), 7.13–7.40 (m, 6 H), 7.55 (d, 2 H, *J* = 10 Hz, bromophenyl), 7.75 (dd, 1 H, *J* = 2.5, 7.5 Hz, para H of pyridine), 8.10 (dd, 1 H, *J* = 2.5, 5 Hz, ortho H of pyridine). MS: M^+ 295 (21.0%).

Synthesis of 1,3-Dihydro-3-R_3-2*H*-pyrrolo[2,3-*b*]pyridin-2-one 8. To sodium hydride (1.76 g of 60 wt % NaH in oil, 0.044 mol, washed with hexane) suspended in dry tetrahydrofuran (175 mL) at 0 °C under a nitrogen atmosphere was added 1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one **6** (0.040 mol) portionwise. The reaction mixture was stirred at room temperature for 30 min and then cooled to 0 °C. Methyl iodide (7.10 g, 0.050 mol) or other alkylating agent was added dropwise. The resulting solution was warmed slowly to room temperature and stirred for 16 h. The solvent was removed by evaporation, and the residue was partitioned between saturated aqueous $NaHCO_3$ and ethyl acetate. The aqueous solution was extracted with additional ethyl acetate. The combined organic solutions was washed with brine, dried, and filtered. Evaporation of the solvent gave a solid which was purified by recrystallization.

Synthesis of 1,3-Dihydro-3-R_3-2*H*-pyrrolo[2,3-*b*]pyridin-2-one 9. To compound **8** (0.030 mol) and zinc dust (9.81 g, 0.15 mol) suspended in tetrahydrofuran (200 mL) and water (2 mL) was added trimethylsilyl chloride (22.8 g, 0.21 mol) dropwise at less than 40 °C. The reaction mixture was stirred at room temperature for 5 h and filtered in order to remove the zinc dust. The zinc cake was washed with dichloromethane, and evaporation of the solvent from the filtrate gave an oil. The residue was dissolved in dichloromethane, washed with 1 N NaOH, and filtered to

(21) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

remove any insoluble disulfides. The organic solution was washed with brine, dried, and filtered. Evaporation of the solvent produced an oil that was purified by flash chromatography, eluting with ethyl acetate–hexane. For R_1 = 4-chlorophenyl and R_3 = H, 100% yield was obtained. ^{1}H NMR ($CDCl_3$): δ 3.69 (s, 2 H, CH_2CON), 7.00 (dd, 1 H, J = 5, 7 Hz, meta H of pyridine), 7.38–7.65 (m, 5 H), 8.11 (dd, 1 H, J = 2, 5 Hz, ortho H of pyridine). MS: M^+ 244 (92.9%).

Synthesis of 1,3-Dihydro-3-R_3-3-$R_{3'}$-2*H*-pyrrolo[2,3-*b*]pyridin-2-one 10. To sodium hydride (0.44 g of 60 wt % NaH in oil, 0.011 mol) suspended in dry tetrahydrofuran (40 mL) at 0 °C under a nitrogen atmosphere was added compound **9** (0.010 mol). The reaction mixture was stirred at room temperature for 30 min and then recooled to 0 °C. An alkylating agent (0.011 mol) was added. The resulting solution was warmed slowly to room temperature and stirred for 16 h. The solvent was removed by evaporation, and the residue was partitioned between saturated aqueous $NaHCO_3$ and ethyl acetate. The aqueous solution was extracted with additional ethyl acetate. The combined organic solutions were washed with brine, dried, and filtered. Evaporation of the solvent yielded the crude product which was purified by flash chromatography and/or recrystallization according to the solvent system listed in Table II.

Synthesis of 1,3-Dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one 15. Method E. To 2-chloro-3-pyridineacetic acid **14** (0.020 mol) and a primary amine (0.044 mol) dissolved in amyl alcohol (20 mL) was added *p*-toluenesulfonic acid (50 mg). The reaction mixture was refluxed for 18 h and cooled to room temperature. The resulting solution was partitioned between water and chloroform–ethyl acetate (1:3 by volume). The organic solution was dried and filtered. Evaporation of the solvent gave a solid that was triturated with isopropyl ether.

Synthesis of 1,3-Dihydro-3,3-dimethyl-2*H*-pyrrolo[2,3-*b*]pyridin-2-one 10. To sodium hydride (0.84 g of 60 wt % NaH in oil, 0.021 mol, washed with hexane) suspended in dry tetrahydrofuran (50 mL) at 0 °C under a nitrogen atmosphere was added compound **15** (0.010 mol). The reaction mixture was stirred at room temperature for 30 min and then recooled to 0 °C. Methyl iodide (2.98 g, 0.021 mol) was added dropwise. The resulting solution was warmed slowly to room temperature and stirred for 16 h. The solvent was removed by evaporation, and the residue was partitioned between saturated aqueous $NaHCO_3$ and ethyl acetate. The aqueous solution was extracted with additional ethyl acetate. The combined organic solution was washed with brine, dried, and filtered. Evaporation of the solvent produced the crude product which was purified by flash chromatography and/or recrystallization according to the solvent systems listed in Table II. For R_1 = 4-chlorophenyl and R_3 = $R_{3'}$ = methyl, 50% yield was obtained. ^{1}H NMR ($CDCl_3$): δ 1.53 (s, 6 H, CH_3), 7.05 (dd, 1 H, J = 5, 7.5 Hz, meta H of pyridine), 7.43–7.58 (m, 5 H), 8.18 (dd, 1 H, J = 2.5, 5 Hz, ortho H of pyridine). MS: M^+ 272 (100%).

Synthesis of 1,3-Dihydro-1-R_1-2*H*-pyrrolo[2,3-*b*]pyridin-2-one 10. Method F. To sodium hydride (0.31 g of 60 wt % NaH in oil, 7.7 mmol) suspended in dry tetrahydrofuran (30 mL) at 0 °C under a nitrogen atmosphere was added 1,3-dihydro-3,3-dimethyl-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (**10k**) (7.0 mmol). The reaction mixture was stirred at room temperature for 30 min and then recooled to 0 °C. An alkylating agent (7.7 mmol) was added. The resulting solution was warmed up slowly to room temperature and stirred for 16 h. The solvent was removed by evaporation, and the residue was partitioned between water and ethyl acetate. The aqueous solution was extracted with additional ethyl acetate. The combined organic solutions was washed with brine, dried, and filtered. Evaporation of the solvent yielded the crude product which was purified by flash chromatography and/or recrystallization according to the solvent system listed in Table II. For R_1 = 4-chlorobenzyl and R_3 = $R_{3'}$ = methyl, 76% yield was obtained. ^{1}H NMR ($CDCl_3$): δ 1.40 (s, 6 H, CH_3), 4.95 (s, 2 H, CH_2Ph), 6.95 (dd, 1 H, J = 5, 7.5 Hz, meta H of pyridine), 7.25 (dm, 2 H, J = 10 Hz, chlorophenyl), 7.38 (d, 2 H, J = 10 Hz, chlorophenyl), 7.43 (dd, 1 H, J = 2.5, 7.5 Hz, meta H of pyridine), 8.15 (dd, 1 H, J = 2.5, 5 Hz, ortho H of pyridine). MS: M^+ 286 (100%).

1,3-Dihydro-3,3-dimethyl-1-[4-(methylsulfinyl)phenyl]-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (10q). To 1,3-dihydro-3,3-dimethyl-1-[4-(methylthio)phenyl]-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (**10p**) (3.0 g, 0.011 mol) dissolved in dichloromethane (50 mL) at 0 °C was added *m*-chloroperoxybenzoic acid (2.4 g of 80%, 0.011 mol) portionwise. The reaction mixture was stirred at 0 °C for 1 h and then poured onto ice/water (100 mL). The resulting solution was neutralized with saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The organic solution was washed with brine, dried, and filtered. Evaporation of the solvent gave a solid that was purified by flash chromatography, eluting with ethyl acetate and then methanol–dichloromethane (1:9). The product was recrystallized from isopropyl ether–petroleum ether to yield compound **10q** (2.6 g, 78%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.53 (s, 6 H, CH_3), 2.75 (s, 3 H, $SOCH_3$), 7.08 (dd, 1 H, J = 5, 7.5 Hz, meta H of pyridine), 7.58 (dd, 1 H, J = 2.5, 7.5 Hz, meta H of pyridine), 7.78 (d, 2 H, J = 7.5 Hz, phenyl), 7.85 (d, 2 H, J = 7.5 Hz, phenyl), 8.20 (dd, 1 H, J = 2.5, 5 Hz, ortho H of pyridine). MS: M^+ 300 (28.4%).

1,3-Dihydro-3,3-dimethyl-1-[4-(methylsulfonyl)phenyl]-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (10r). To 1,3-dihydro-3,3-dimethyl-1-[4-(methylthio)phenyl]-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (**10p**) (3.0 g, 0.011 mol) dissolved in dichloromethane (50 mL) at 0 °C was added *m*-chloroperoxybenzoic acid (4.8 g of 80%, 0.022 mol) portionwise. The reaction mixture was stirred at 0 °C for 3 h and then poured onto ice/water (100 mL). The resulting solution was neutralized with saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The organic solution was washed with brine, dried, and filtered. Evaporation of the solvent gave a solid that was purified by chromatography on flash silica, eluting with ethyl acetate. The product was recrystallized from dichloromethane–petroleum ether to yield compound **10r** (2.9 g, 83%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.53 (s, 6 H, CH_3), 3.08 (s, 3, SO_2CH_3), 7.10 (dd, 1 H, J = 5, 7.5 Hz, meta H of pyridine), 7.58 (dd, 1 H, J = 2.5, 7.5 Hz, para H of pyridine), 7.95 (d, 2 H, J = 10 Hz, phenyl), 8.10 (d, 2 H, J = 10 Hz, phenyl), 8.20 (dd, 1 H, J = 2.5, 5 Hz, ortho H of pyridine). MS: M^+ 316 (100%).

1,3-Dihydro-3,3-dimethyl-1-(4-chlorophenyl)-2*H*-pyrrolo-[2,3-*b*]pyridine-2-thione (21). To 1,3-dihydro-3,3-dimethyl-1-(4-chlorophenyl)-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (**10s**) (5.00 g, 0.018 mol) dissolved in toluene (30 mL) was added Lawesson's reagent (4.45 g, 0.011 mol). The reaction mixture was refluxed for 18 h and then cooled to room temperature. The solvent was removed by evaporation, and water (100 mL) was added. The aqueous solution was extracted with dichloromethane. The organic solution was dried and filtered. Evaporation of the solvent gave an oil that was purified by flash chromatography, eluting with dichloromethane. The product was recrystallized from isopropyl ether–petroleum ether to produce compound **21** (4.3 g, 81%) as a yellow solid. ^{1}H NMR ($CDCl_3$): 1.58 (s, 6 H, CH_3), 7.13 (dd, 1 H, J = 5, 7.5 Hz, meta H of pyridine), 7.43 (d, 2 H, J = 7.5 Hz, chlorophenyl), 7.55 (d, 2 H, J = 7.5 Hz, chlorophenyl), 7.65 (dd, 1 H, J = 2.5, 7.5 Hz, para H of pyridine), 8.23 (dd, 1 H, J = 2.5, 5 Hz, ortho H of pyridine). MS: MH^+ 289.

1-(4-Chlorophenyl)-1,3-dihydro-2*H*-indol-2-one 24. To 2-chlorophenylacetic acid (**22**) (12.5 g, 0.072 mol) was added 4-chloroaniline (**23**) (20.4 g, 0.16 mol), potassium carbonate (12.9 g, 0.093 mol), potassium iodide (0.1 g), copper powder (0.1 g), and copper(I) oxide (0.5 g). The mixture was heated to a molten state at 180–190 °C for 2 h. The reaction mixture was poured into water–dichloromethane and filtered through charcoal. The filtrate was separated, and the organic solution was washed with water, dried, and filtered. Evaporation of the solvent gave a black oil which was purified by flash chromatography, eluting with ethyl acetate–dichloromethane (4:96). The product was recrystallized from ether–hexane to give the product (1.18 g, 7%). ^{1}H NMR (DMSO): δ 1.40 (s, 6 H, CH_3), 6.78 (d, 1 H, J = 7.5 Hz, phenyl), 7.10 (t, 1 H, J = 7.5 Hz, phenyl), 7.23 (t, 1 H, J = 7.5 Hz, phenyl), 7.45 (d, 1 H, J = 7.5 Hz, phenyl), 7.50 (d, 2 H, J = 7.5 Hz, chlorophenyl), 7.63 (d, 2 H, J = 7.5 Hz, chlorophenyl). MS: M^+ 271 (100%).

Sodium 2-[(4-Chlorophenyl)amino]-α,α-dimethyl-3-pyridineacetate (27). To compound **10s** (3.0 g, 11 mmol) dissolved in ethanol (100 mL) was added 40 wt % aqueous NaOH (10 mL). The reaction mixture was refluxed for 18 h and then cooled to room temperature. The solvent was removed by evaporation, and water was added. The aqueous solution was washed with diethyl ether and acidified with glacial acetic acid. The precipitate was isolated by filtration and washed with water.

This solid (1.6 g, 5.5 mmol) was stirred in 0.1 N NaOH (53 mL) for 2 min. Any remaining solids were removed by filtration, and the filtrate was lyophilized to give compound **27** (1.7 g, 52%) as a tan solid. ^{1}H NMR (D_2O): δ 1.38 (s, 6 H, CH_3), 6.85 (dd, 1 H, J = 5, 7.5 Hz, meta H of pyridine), 7.05 (d, 2 H, J = 7.5 Hz, chlorophenyl), 7.18 (d, 2 H, J = 7.5 Hz, chlorophenyl), 7.68 (dd, 1 H, J = 2.5, 7.5 Hz, para H of pyridine), 7.85 (dd, 1 H, J = 2.5, 5 Hz, ortho H of pyridine). MS: M^+ 291 (100%).

X-ray Crystal Analysis of 1-(4-Chlorophenyl)-1,3-dihydro-3,3-dimethyl-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (10s). Crystal Data. $C_{15}H_{13}ClN_2O$, M = 272.74, orthorhombic, a = 14.279 (7) Å, b = 15.692 (5) Å, c = 12.557 (7) Å, V = 2813.6 Å^3, Z = 8, D_{calcd} = 1.288 g cm^{-3}, μ(Cu Kα radiation, λ = 1.5418 Å) = 23.7 cm^{-1}. Space group $Pbca$-(D_{2h}^{15}) uniquely from the systematic absences: $0kl$ when $k \neq 2n$, $h0l$ when $l \neq 2n$, $hk0$ when $h \neq 2n$. Sample dimensions: 0.16 × 0.24 × 0.40 mm.

Crystallographic Measurements. Oscillation and Weissenberg photographs yielded preliminary unit-cell parameters and space group information. One octant of intensity data was recorded on an Enraf-Nonius CAD-4 diffractometer (Cu Kα radiation, incident-beam graphite monochromator; ω–2θ scans, θ_{max} = 67°). From a total of 2505 independent measurements, those 1678 reflections with $\sigma > 3.0s(I)$ were retained for the structure analysis. In addition to the usual Lorentz and polarization effects, an empirical absorption correction (T_{max}:T_{min} = 1.00:0.81) was also applied to the data. Refined unit-cell parameters were derived from the diffractometer setting angles for 25 reflections (41° < θ < 53°) widely separated in reciprocal space.

Structure Analysis. The crystal structure was solved routinely by direct methods.[18] Initial positions for the non-hydrogen atoms were obtained from an E map. Hydrogen atoms were all located in a difference Fourier synthesis evaluated following several rounds of full-matrix least-squares adjustment of non-hydrogen atom positional and anisotropic temperature factor parameters. Continuation of the least-squares iterations, with hydrogen atoms included at their calculated positions, led to convergence at R = 0.052 (R_w = 0.072).[20] Final atomic positional and thermal parameters are included in the supplementary material.[19] Neutral atom scattering factors used in the structure-factor calculations were taken from ref 22. In the least-squares iterations, $\sum w\Delta^2$ [$w = 1/\sigma^2(|F_o|)$, $\Delta = (|F_o| - |F_c|)$] was minimized.

Pharmacological Methods. A. Cyclooxygenase Assay with Human Platelets.[6] Human platelets (2 × 10^5 platelets/mL, 0.2 mL suspension) suspended in HEPES buffer containing 0.5 mM EGTA and 1.5 mM $CaCl_2$ were incubated with dimethyl sulfoxide (DMSO) vehicle with or without the test compound (1 mL) for 4 min. [^{14}C]Arachidonic acid (Amersham, 59 Ci/mol, 9 mM final concentration) and the calcium ionophore A23187 stimulant (Calbiochem, 1 mM final concentration) in 10 mL of water–ethanol (9:1) were added, and the mixture was incubated for another 5 min. The reaction was terminated by the addition of methanol (0.4 mL), and cellular debris was removed by centrifugation. The cyclooxygenase product, HHT, was isolated and quantitated from aliquots (100 mL) of the incubations on a Waters two pump HPLC system fitted with a Du Pont Zorbax ODS, 5 m, 4 × 80 cm Reliance Cartridge column and C18 "Guard Pak". The eluting solvent system was initially a 4:1 mixture of water–methanol–acetic acid (46:54:0.08) containing 1 mM EDTA adjusted to pH = 6.0 with ammonium hydroxide (pump A) to methanol (pump B). At 10 min, a linear gradient to reach 100% methanol (pump B) at 27 min was established. HHT eluted from this system at approximately 11 min. Results are expressed as percent inhibition of HHT production by the test compounds versus test vehicle alone.

B. 5-Lipoxygenase Assay with Human Neutrophils.[6] Human neutrophils (2 × 10^7 cells/mL, 0.2 mL suspension) suspended in HEPES buffer containing 1 mM $CaCl_2$ were preincubated with test compounds and the [^{14}C]arachidonic acid plus the calcium ionophore A23187 stimulant exactly as described for the CO assay. The 5-LO product, 5-HETE, was isolated and quantitated by the HPLC system used for the CO assay. 5-HETE eluted from this system at approximately 20 min. Results are expressed as percent inhibition of 5-HETE production by the test compounds versus test vehicle alone.

C. Reversed Passive Arthus Reaction (RPAR) Assay.[15] One hour after dosing with the test compound, groups of five male rats were injected in the penile vein with antigen (5 mg of BSA in 0.2 mL of saline per rat) and 30 min later injected in the pleural cavity with antibody (0.5 mg of antibody in the IgG fraction of rabbit anti-BSA in 0.2 mL of saline). Sham control animals were treated as RPAR animals, but did not receive BSA antigen. After 4 h, the animals were sacrificed by carbon monoxide inhalation and the pleural cavities were opened and the exudate was drained into a graduated conical glass centrifuge tube. The volume of fluid was measured. The cavity was then washed out with saline–EDTA to achieve a final volume of 5.0 mL. The number of cells (neutrophils) were determined in a Coulter counter.

D. In Vivo 5-LO/CO Assay in the Rat RPAR Pleural Cavity.[16] The same procedure as described above in C was followed with the following modifications. The exudate from the pleural cavity was drained into a graduated conical glass centrifuge tube containing indomethacin (1.8 mg) and NDGA (15 mg) to block ex vivo metabolite synthesis. The volume of fluid was recorded, and the cavity was washed out with saline–EDTA to achieve a final volume of 5.0 mL. The number of cells (95% neutrophils) was counted in a Coulter counter. The cells were centrifuged (1000g), and the supernatant was added to 4 volumes of 95% ethanol and kept on ice for 30 min. After removal of the protein precipitate by centrifugation (2500g), the ethanol extract was dried under nitrogen and stored at −20 °C. The samples were redissolved in water to a volume of 1 mL, and spiked with [^{3}H]TXB_2 and [^{3}H]LTE_4 to measure recovery. The principal eicosanoids present, determined by HPLC with RIA analysis of the fractions on the system described in procedure A (cyclooxygenase assay with human platelets), was TXB_2 and LTE_4. Production of these two eicosanoids was measured by direct RIA of sample aliquots (0.01 mL) with commercial kits (^{3}H) for TXB_2 from New England Nuclear and $LTC_4/D_4/E_4$ from Amersham.

E. Adjuvant-Induced Arthritis in Rats (AAR).[17] **(a) Prophylactic Regimen.** Heat-killed *Mycobacterium tuberculosis* (from the Ministry of Agriculture, Fisheries and Food Central Veterinary Laboratory, Weybridge, Surrey, England) was prepared by grinding to a fine powder. It was then weighed, mixed with paraffin oil (6 mg/mL), and homogenized. The animals were dosed with drug 1 h prior to challenge with adjuvant and then for 21 consecutive days. Control animals were given methylcellulose. Injection of 0.1 mL of the adjuvant was made into the left hind paw. The left and right hind paw volumes were measured immediately on a plethysmorgraph. Final measurements were taken on both paws on day 21 of the assay. Data were reported as "percent change in paw volume relative to the control".

(b) Therapeutic Regimen. The same procedure described above was followed except that the lesion was allowed to develop for 7 days before the first drug treatment. Treatment was continued for 35 days. Treatment of controls and measurements of "percent change in paw volume" were conducted as described in (a) above.

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Registry No. **2** (R_1 = 4-ClC_6H_4), 16344-26-6; **3** (R_1 = 4-ClC_6H_4), 59272-31-0; **4** (R_1 = 4-ClC_6H_4), 127555-66-2; **5** (R_1 = 2-ClC_6H_4, R_2 = Ph), 128271-14-7; **5** (R_1 = 4-ClC_6H_4, R_2 = Ph), 127555-67-3; **5** (R_1 = Ph, R_2 = Me), 128271-31-8; **5** (R_1 = Ph, R_2 = Ph), 128271-32-9; **5** (R_1 = Me, R_2 = Ph), 128271-33-0; **5** (R_1 = *i*-Pr, R_2 = Ph), 128271-34-1; **5** (R_1 = *t*-Bu, R_2 = Ph), 128271-35-2; **5** (R_1 = 4-*i*-ArC_6H_4, R_2 = Ph), 128271-36-3; **5** (R_1 = 3-ClC_6H_4, R_2 = Ph), 128271-37-4; **5** (R_1 = 3,4-$Cl_2C_6H_3$, R_2 = Ph), 128271-38-5; **5** (R_1 = 2-CH_3, 3-ClC_6H_3, R_2 = Ph), 128271-39-6; **5** (R_1 = 3-$CF_3C_6H_4$, R_2 = Ph), 128271-40-9; **5** (R_1 = CH_2Ph, R_2 = Ph), 128271-41-0; **6** (R_1 = 4-ClC_6H_4, R_2 = Ph), 127555-68-4; **6a**, 128271-21-6; **6b**, 127555-39-9; **6c**, 127555-45-7; **6d**, 127555-42-4; **6e**, 128271-22-7; **6f**·HBr, 128271-23-8; **6g**, 127555-61-7; **6h**, 127555-62-8; **6i**, 127555-46-8; **6j**, 127555-40-2; **6k**, 127555-55-9; **8** (R_1 = 4-ClC_6H_4, R_2 = Ph, R_3 = Me), 128271-15-8; **9** (R_1 = 4-ClC_6H_4, R_3 = Me), 128271-16-9; **10a**, 127555-25-3; **10b**, 127555-82-2; **10c**, 127555-23-1; **10d**, 127555-60-6; **10e**, 128271-24-9; **10f**, 127555-34-4; **10g**,

(22) *International Tables for X-Ray Crystallography*; Kynoch: Birmingham, England, 1974; Vol. IV.

128271-25-0; **10h**, 128271-26-1; **10i**, 128271-27-2; **10j**, 127555-44-6; **10k**, 109535-73-1; **10l**, 127555-22-0; **10m**, 127555-24-2; **10n**, 127555-26-4; **10o**, 127555-36-6; **10p**, 127555-30-0; **10q**, 127555-19-5; **10r**, 127555-20-8; **10s**, 127555-18-4; **10t**, 127555-27-5; **10u**, 128271-28-3; **10v**, 127555-29-7; **10w**, 127555-32-2; **10x**, 127555-31-1; **10y**, 127555-28-6; **10z**, 127555-38-8; **10aa**, 127555-33-3; **10bb**, 127555-37-7; **10cc**, 127555-35-5; **10dd**, 128271-29-4; **10ee**, 128271-30-7; **14**, 61494-55-1; **15** (R_1 = 4-ClC_6H_4), 127555-70-8; **15** (R_1 = 4-$CH_3OC_6H_4$), 127555-16-2; **15** (R_1 = 3,5-$Cl_2C_6H_3$), 127555-84-4; **15** (R_1 = 2,4-$F_2C_6H_3$), 127555-83-3; **21**, 128271-17-0; **22**, 2444-36-2; **23**, 106-47-8; **24**, 128271-18-1; **25**, 128271-19-2; **26**, 128271-20-5; **27**, 127555-63-9.

Supplementary Material Available: Tables of atomic positional and thermal parameters, interatomic distances and angles, torsion angles and displacements of atoms from selected least squares for **10s** (8 pages). Ordering information is given on any current masthead.