Synthesis, X-Ray Crystal Structure Determination and Antiinflammatory Activity of the Regioisomers: 5-Phenyl-6-(4-pyridyl)-2,3-dihydroimidazo[2,1-*b*]thiazole and 6-Phenyl-5-(4-pyridyl)-2,3-dihydroimidazo[2,1-*b*]thiazole. A Structural Reassignment

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A regiospecific synthesis of 6-phenyl-5-(4-pyridyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (**2**) was accomplished by treatment of 6-phenyl-2,3-dihydroimidazo[2,1-*b*]thiazole (**10**) with the reactive complex of pyridine and ethyl chloroformate followed by oxidation with chromium(VI) oxide. Reaction of 4-phenyl-5-(4-pyridyl)imidazole-2-thione (**12**) with 1,2-dibromoethane in the presence of base also gave **2** together with its regioisomer **3**. The structures of **2** and **3** were confirmed by X-ray crystallography. Evaluation, on oral administration, in a one hour arachidonic acid-induced mouse ear inflammation assay, showed the inhibition of edema by **2** (48%) and **3** (34%) to be less than that of the 6-(4-fluorophenyl) analog **1** (SK&F 86002) (69%), a known antiinflammatory agent.

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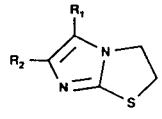
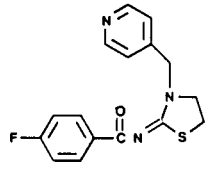
Because of their antiarthritic and antiinflammatory activity, 5,6-diarylimidazo[2,1-*b*]thiazoles have been of interest in our laboratories for some time [2]. Of special note is 6-(4-fluorophenyl)-5-(4-pyridyl)-2,3-dihydroimidazo[2,1-*b*]thiazole, (**1**, SK&F 86002). This compound, the antiarthritic properties of which were first reported by Lantos *et al* [3] has been the subject of an extensive biological evaluation [4]. Recently, Klose described the synthesis of the des-fluoro congener of **1**, 6-phenyl-5-(4-pyridyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (**2**) and its regioisomer **3** [5]. Although the yield and ^{1}H nmr chemical shift assignments of **2** were reported, additional data in support of the assigned structures was not given. The synthesis of **2** was accomplished stepwise by the displacement of the 2-bromine of 2-bromo-2-phenyl-1-(4-pyridyl)-1-ethanone hydrobromide (**4**) by the exocyclic nitrogen of 2-aminothiazoline (**5**) followed by cyclization and dehydration (Scheme I). While the nature of the resulting products formed in a reaction sequence of this type may be influenced by solvent effects or *p*H, the regiochemistry reported for this synthesis of **2** runs counter to that generally observed for such alkylation-cyclocondensation reactions of **5** [6,7,8]. Further, our own earlier efforts to use a similar route to prepare **1** led to the imidazole ring-opened thiazoline **6** as the only isolated product [3].



#	R_1	R_2
1	4 - C_5H_4N	4 - FC_6H_4
2	4 - C_5H_4N	C_6H_5
3	C_6H_5	4 - C_5H_4N
8	4 - FC_6H_4	4 - C_5H_4N
9	H	4 - FC_6H_4
10	H	C_6H_5
11	N - (EtO_2C) - 4C_5H_5N	C_6H_5
16	4 - C_5H_4N	4 - $CH_3OC_6H_4$
17	4 - $CH_3OC_6H_4$	4 - C_5H_4N



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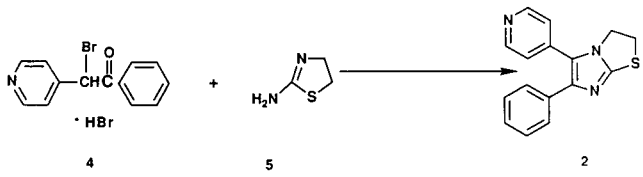
As part of our investigation of the antiinflammatory activity of this general class of compounds, supplies of **2** and **3** were needed for structure-activity relationship (SAR) studies. We now report the synthesis of these two compounds using alternate synthetic routes from that employed by Klose [5]. A comparison of the physical and spectroscopic properties of **2** and **3** prepared by us with those properties reported previously [5] for these compounds reveals significant differences. Confirmation of the structures assigned to **2** and **3** was obtained by X-ray crystallography.

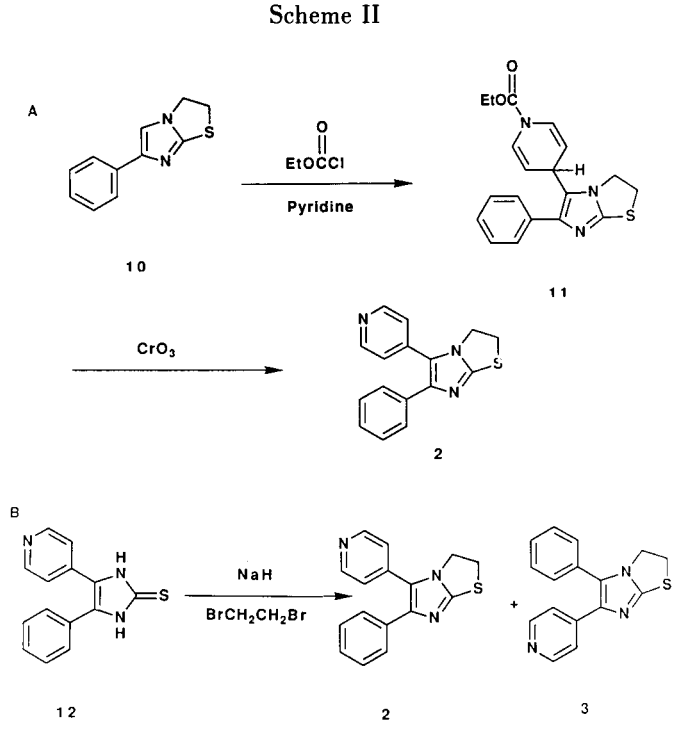
Scheme I



Synthesis.

The synthetic routes selected for the synthesis of **2** and **3** were based on our experience in preparing **1** [2,3]. Initially, **1** was prepared by treatment of 4-(4-fluorophenyl)-5-(4-pyridyl)imidazole-2-thione (**7**) with sodium hydride in dimethylformamide followed by addition of 1,2-dibromoethane [3]. This route affords **1** and an equal amount of the biologically less interesting regioisomer **8**. The structure of **1**, established by comparison of its ^{1}H nmr spectrum with that of **8**, was confirmed by X-ray crystal structure determination [3]. In order to avoid separation of the isomers by chromatography, a more efficient, regiospecific synthesis of **1** was developed starting from 6-(4-fluorophenyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (**9**) [9]. The 4-pyridyl moiety was introduced at the 6-position by treatment of **9** with the reactive complex of pyridine and ethyl chloroformate formed *in situ*, followed by oxidation with sulfur in mesitylene or potassium *t*-butoxide and air to give **1** in 92% and 85% yield respectively. This methodology has been used in the synthesis of a variety of substituted phenyl analogs [9] and was chosen for the initial synthesis of **2** as outlined in Scheme IIA.

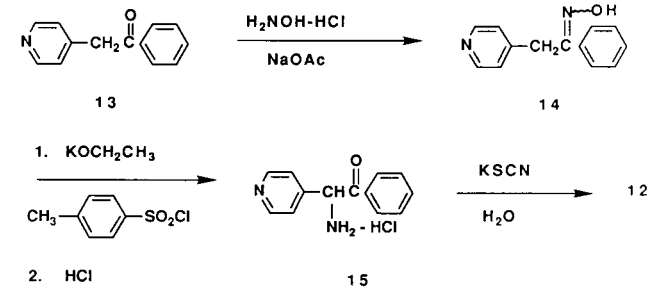
Scheme II



Thus ethyl chloroformate was added to a solution of pyridine and 6-phenyl-2,3-dihydroimidazo[2,1-*b*]thiazole (**10**) [9] in methylene chloride kept at 0-5°. After warming to ambient temperature overnight the mixture was again cooled to 0° and a second portion of pyridine and ethyl chloroformate added. Quenching in water, followed by extraction and chromatography gave the ethoxycarbonyl-1,4-dihydropyridine (**11**) in 85% yield after crystallization. Oxidation of **11** with chromium(VI) oxide in pyridine gave **2** in 19% yield after workup, chromatography and recrystallization.

The route to **3** is shown in Scheme IIB and is modelled upon our first approach to the synthesis of the fluoro congeners **1** and **8**. The imidazole-2-thione **12** was required as an intermediate and its synthesis starting from the known 1-phenyl-2-(4-pyridyl)ethanone (**13**) [10,11,12] is outlined in Scheme III. Conversion of the ketone **13** to the oxime **14** was carried out in standard fashion. The oxime **14** was treated sequentially first with sodium ethoxide, then *p*-toluenesulfonyl chloride followed by the addition of potassium ethoxide to give the α-amino ketone **15** formed *via* the Neber rearrangement [13]. Isolated as the hydrochloride, the unstable **15** was converted immediately, in low yield (6.6 %) to the thione **12** on treatment with aqueous potassium thiocyanate. Treatment of **12** with sodium hydride and 1,2-dibromoethane gave **2** together with the desired **3** which were separated by chromatography.

Scheme III



For comparison, the ^{1}H nmr and ir spectral data as well as the melting points of **2** and **3** are listed in Table 1 together with the corresponding data of compounds assigned these structures (**3c** and **4b**, respectively) in the previous report [5]. Both **2** and **3** were obtained as high melting crystalline solids. In contrast, Klose reported his compound assigned structure **2** (**3c**) to be a yellow oil and the compound assigned structure **3** (**4b**) to have a considerably different melting point (105°) than that observed by us (155°). Differences also are observed in the ^{1}H nmr spectra both with respect to chemical shifts and splitting patterns.

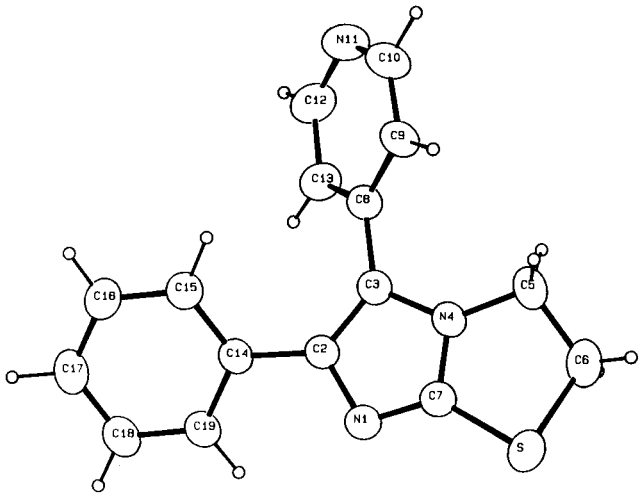


Figure 1. ORTEP drawing of **2** with thermal ellipses at the 50% probability level; H atoms as spheres of arbitrary size.

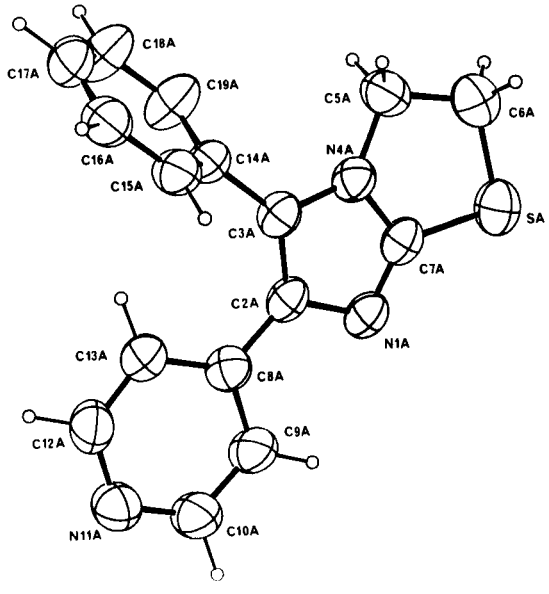


Figure 2. ORTEP drawing of one of the two independent molecules (A) of **3**. The water molecule has been omitted. Thermal ellipses are drawn at the 50% probability level; H atoms as spheres of arbitrary size.

Examination of the ^{1}H nmr chemical shift data of **2** in comparison with the chemical shifts for Klose's analogous compound with the same regiochemical assignment (**3c**) indicates significant differences (Table 1). For example, the chemical shift of the α-pyridyl protons differ by 0.2 ppm and is reported to be a doublet of doublets for **3c** while **2** is observed at higher field strength to be only a doublet. Differences also are seen between the corresponding 2-CH_2 and 3-CH_2 for the two compounds. However, if one assumes the regiochemical assignment of **3c** is reversed, as expected based on the regiochemistry of the alkylation-cyclocondensation of **5**, comparison of the chemical shifts of **3c** with those we observed for **3** reveals a close correspondence. A similar observation also is seen upon comparing Klose's ^{1}H nmr chemical shifts for **4b** and the chemical shifts for **2**. Thus the ^{1}H nmr chemical shift comparisons suggest that the regiochemistry assignments of **3c** and **4b** in Klose's report [5] should be reversed. This reassignment in regiochemistry would be consistent with expectations for the alkylation-cyclocondensation reactions of 2-aminothiazoline (**5**) cited earlier [6,7,8].

X-Ray Crystal Structure.

The structures of **2** and **3** were confirmed by X-ray crystallography. Figures 1 and 2 display the structure of **2** and **3**, respectively. For **3** there are two crystallographically independent molecules per asymmetric unit but only one is displayed. Both molecules have the same constitution, but differ in conformational detail. The X-ray analysis unequivocally establishes the regioisomerism of the two molecules. Bond distances and angles for the three molecular structures are given in Table 2.

Table 1

Spectral Data for **2** and **3** and Klose's **3c** and **4b** [a]

Compound #	MP (°C)	Spectral Data
2	206.5-208.5	^{1}H nmr: [b] 8.60 (d, 2H, J = 5.93 Hz, α-pyridyl H), 7.49-7.47 (m, 2H, aromatic), 7.28-7.23 (m, 5H, aromatic), 4.20 (t, 2H, J = 7.22 Hz, CH_2), 3.86 (t, 2H, J = 7.22 Hz, CH_2) ir: (cm^{-1}, chloroform) 2960, 1595, 1440, 1330, 1255, 835
3	154-155	^{1}H nmr: [b] 8.35 (bd, 2H, α-pyridyl H), 7.41-7.28 (m, 7H, aromatic), 4.00 (t, 2H, J = 7.20 Hz, CH_2), 3.76 (t, 2H, J - 7.20 Hz, CH_2)
3c	oil	^{1}H nmr: [b] 8.41 (dd, 2H, J = 5 Hz, 2 Hz, α-pyridyl H), 7.45-7.20 (m, 7H, aromatic), 4.00 (d, 2H, J = 7 Hz, CH_2), 3.80 (d, 2H, J = 7 Hz, CH_2)
4b	105	H nmr: [b] 8.55 (dd, 2H, J = 5 Hz, 2 Hz, α-pyridyl H), 7.60-7.05 (m, 7H, aromatic), 4.10 (d, 2H, J = 7 Hz, CH_2), 3.85 (d, 2H, J = 7 Hz, CH_2)

[a] See reference 5 for assigned structures. [b] Chemical shifts measured in ppm in deuteriochloroform at 400 MHz for **2** and **3**, at 60 or 80 MHz for **3c** and **4b**.

Table 2
Principal Bond Distances (Å) and Angles (°)

Atoms	2	3a	3b
Distances			
N1-C2	1.397(1)	1.397(3)	1.401(3)
C2-C3	1.384(1)	1.377(3)	1.385(3)
C3-N4	1.390(1)	1.374(3)	1.376(3)
N4-C5	1.458(1)	1.462(3)	1.457(3)
C5-C6	1.530(2)	1.500(4)	1.500(4)
C6-S	1.822(1)	1.821(3)	1.806(3)
S-C7	1.738(1)	1.735(3)	1.732(3)
C7-N4	1.351(1)	1.340(3)	1.349(3)
C7-N1-	1.310(1)	1.317(3)	1.314(3)
C2-C14	1.468(1)	-	-
C3-C8	1.468(1)	-	-
C2-C8	-	1.460(3)	1.463(3)
C3-C14	-	1.480(3)	1.471(3)
C8-C9	1.399(1)	1.389(3)	1.383(4)
C9-C10	1.378(2)	1.382(4)	1.368(4)
C10-N11	1.333(2)	1.327(3)	1.322(4)
N11-C12	1.334(2)	1.339(3)	1.329(4)
C12-C13	1.386(2)	1.377(4)	1.367(4)
C8-C13	1.388(1)	1.380(4)	1.380(4)
C14-C15	1.398(1)	1.389(3)	1.391(3)
C15-C16	1.383(1)	1.389(3)	1.392(4)
C16-C17	1.386(2)	1.375(4)	1.375(4)
C17-C18	1.385(2)	1.377(4)	1.367(4)
C18-C19	1.386(2)	1.379(4)	1.375(4)
C14-C19	1.400(1)	1.378(3)	1.384(3)
Angles			
C6-S-C7	89.63(5)	90.8(1)	90.5(1)
C2-N1-C7	104.4(1)	104.3(2)	104.8(2)
C3-N4-C5	136.5(1)	134.1(2)	134.9(2)
C3-N4-C7	107.0(1)	108.0(2)	108.4(2)
C5-N4-C7	116.5(1)	117.8(2)	116.7(2)
C10-N11-C12	115.8(1)	115.5(2)	115.3(3)
N1-C2-C3	110.3(1)	110.1(2)	109.9(2)
N1-C1-C14	118.4(1)	119.7(2)	119.8(2)
C3-C2-C14	131.3(1)	130.2(2)	130.2(2)
N4-C3-C2	104.9(1)	105.0(2)	104.7(2)
N4-C3-C8	122.0(1)	121.3(2)	120.9(2)
C2-C3-C8	133.1(1)	133.8(2)	134.4(2)
N4-C5-C6	104.9(1)	106.1(2)	107.0(2)
S-C6-C5	107.9(1)	110.2(2)	111.3(2)
S-C7-N1	132.8(1)	133.1(2)	133.3(2)
S-C7-N4	113.7(1)	114.1(2)	114.5(2)
N1-C7-N4	113.5(1)	112.7(2)	112.2(2)
C3-C8-C9	121.6(1)	120.7(2)	120.4(3)
C3-C8-C13	121.5(1)	123.6(2)	124.4(2)
C9-C8-C13	116.9(1)	115.7(2)	115.3(3)
C8-C9-C10	119.1(1)	120.2(2)	120.0(3)
N11-C10-C9	124.6(1)	124.3(2)	124.7(3)
N11-C12-C13	124.4(1)	124.5(3)	123.9(3)
C8-C13-C12	119.2(1)	119.8(2)	120.8(3)
C2(3)-C14-C15	122.8(1)	120.9(2)	120.8(2)
C2(3)-C14-C19	118.9(1)	120.6(2)	119.9(2)
C15-C14-C19	118.2(1)	118.5(2)	119.3(2)
C14-C15-C16	120.4(1)	120.5(3)	119.1(3)
C15-C16-C17	121.1(1)	120.2(3)	120.4(3)
C16-C17-C18	119.0(1)	120.6(3)	120.6(3)
C17-C18-C19	120.6(1)	119.4(3)	119.6(3)
C14-C19-C18	120.8(1)	121.0(3)	121.1(3)

The molecular conformations may be compared via the dihedral angles between planes defined by the imidazo ring and the substituent rings. For **2**, the dihedral angle between the phenyl and imidazo rings is -24.8(1)° while that between pyridyl and imidazo is 45.0(1)°. For **3**, the phenyl-imidazo dihedral angle is 115.5(1)° in molecule **A** and 57.5(1)° in molecule **B** while the pyridyl-imidazo dihedral angle is 7.4(5)° in **A** and 7.1(2)° in **B**.

Table 3 Inhibition of Arachidonic Acid-Induced Inflammation in the Mouse [a]

Compound #	Percent Inhibition	
	Oral	Subcutaneous
1	69*** [b]	64***
8	57***	58***
2	48***	
3	34*	31**
16	40***	52***
17	41***	

[a] Balb/c mice were treated with 50 mg/kg of test compound in an acidified saline vehicle 15 minutes prior to application of 2 mg of arachidonic acid on the left ear. One hour later the ear swelling was quantified. Vehicle control N-10 and test N-5. [b] ***, Statistically significant at a $p<0.01$. **, Statistically significant at a $p<0.01$. *, Statistically significant at a $p<0.05$ Determined as significant differences from control with use of Student's t test.

Table 4
Positional Parameters for 2 and Their Estimated Standard Deviations

Atom	x	y	z	B(AZ)
S	0.77114(6)	0.08272(3)	0.74672(3)	3.690(8)
N1	0.7034(2)	-0.04523(8)	0.8961(1)	2.79(2)
N4	0.8147(1)	0.07553(7)	0.9912(1)	2.61(2)
N11	0.9287(2)	0.1143(1)	1.4786(1)	4.38(3)
C2	0.7266(2)	-0.04915(8)	1.0277(1)	2.43(2)
C3	0.7962(2)	0.02543(8)	1.0886(1)	2.43(2)
C5	0.8840(2)	0.15868(9)	0.9825(1)	3.30(3)
C6	0.8105(2)	0.1807(1)	0.8382(2)	4.07(3)
C7	0.7565(2)	0.03018(9)	0.8805(1)	2.68(2)
C8	0.8418(2)	0.05563(8)	1.2222(1)	2.55(2)
C9	0.9975(2)	0.09850(9)	1.2858(1)	3.25(3)
C10	1.0330(2)	0.1257(1)	1.4112(2)	4.12(4)
C12	0.7813(2)	0.0728(1)	1.4174(1)	3.89(3)
C13	0.7324(2)	0.0429(1)	1.2915(1)	3.22(3)
C14	0.6831(2)	-0.12771(8)	1.0778(1)	2.47(2)
C15	0.7636(2)	-0.15260(9)	1.2079(1)	2.94(3)
C16	0.7222(2)	-0.2288(1)	1.2499(1)	3.33(3)
C17	0.6028(2)	-0.2826(1)	1.1652(1)	3.52(3)
C18	0.5239(2)	-0.2590(1)	1.0367(1)	3.51(3)
C19	0.5625(2)	-0.18242(9)	0.9937(1)	2.96(3)

Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as: (4/3) * [a2*B(1,1) + b2*B(2,2) + c2*B(3,3) + ab(cos gamma)*B(1,2) + ac (cos beta)*B(1,3) + bs(cos alpha)*B(2,3)]

Table 5
Positional Parameters for 3A and 3B and Their Estimated Standard Deviations

Atom	x	y	z	B(AZ)
SA	0.78380(9)	0.01022(5)	0.8102(1)	5.99(2)
SB	0.26992(9)	0.48081(6)	0.7901(1)	6.40(3)
O1W	0.9722(3)	0.2124(1)	0.2692(3)	7.40(8)
O2W	0.7200(3)	0.3167(2)	0.1481(3)	9.4(1)
N1A	1.0048(3)	-0.0568(1)	0.6869(3)	4.36(6)
N1B	0.4613(3)	0.5531(1)	0.7327(3)	4.76(7)
N4A	1.0154(2)	0.0585(1)	0.8158(3)	4.03(6)
N4B	0.5311(3)	0.4375(1)	0.7703(3)	4.30(6)
N11A	1.4167(3)	-0.1736(1)	0.4721(3)	5.36(7)
N11B	0.8250(3)	0.6843(2)	0.6524(3)	6.46(8)
C2A	1.1303(3)	-0.0302(2)	0.6925(3)	3.96(7)
C2B	0.6020(3)	0.5294(2)	0.7222(3)	4.28(8)
C3A	1.1376(3)	0.0416(2)	0.7724(3)	3.93(7)
C3B	0.6463(3)	0.4569(2)	0.7448(3)	3.94(7)
C5A	0.9597(4)	0.1230(2)	0.9091(4)	5.44(9)
C5B	0.5005(4)	0.3706(2)	0.7993(4)	5.97(9)
C6A	0.8106(4)	0.1063(2)	0.9002(4)	5.9(1)
C6B	0.3504(4)	0.3872(2)	0.8140(5)	7.1(1)
C7A	0.9411(3)	-0.0010(2)	0.7627(3)	4.14(7)
C7B	0.4247(3)	0.4959(2)	0.7616(3)	4.43(8)
C8A	1.2300(3)	-0.0782(2)	0.6192(3)	4.18(7)
C8B	0.6807(3)	0.5809(2)	0.6971(3)	4.41(8)
C9A	1.1924(3)	-0.1467(2)	0.5276(4)	5.15(8)
C9B	0.6101(4)	0.6500(2)	0.6660(5)	6.9(1)
C10A	1.2876(4)	-0.1916(2)	0.4589(4)	5.61(9)
C10B	0.6853(4)	0.6984(2)	0.6456(5)	7.8(1)
C12A	1.4531(3)	-0.1076(2)	0.5608(4)	5.7(1)
C12B	0.8926(4)	0.6176(2)	0.6814(4)	6.3(1)
C13A	1.3663(3)	-0.0594(2)	0.6350(4)	5.23(9)
C13B	0.8263(4)	0.5660(2)	0.7037(4)	5.64(9)
C14A	1.2443(3)	0.0960(2)	0.8156(3)	4.05(7)
C14B	0.7801(3)	0.4043(2)	0.7491(3)	4.10(7)
C15A	1.2619(3)	0.1225(2)	0.6974(3)	4.63(8)
C15B	0.8216(3)	0.3844(2)	0.6171(4)	4.88(8)
C16A	1.3645(3)	0.1724(2)	0.7390(4)	5.33(8)
C16B	0.9489(3)	0.3343(2)	0.6257(4)	5.92(9)
C17A	1.4498(3)	0.1961(2)	0.8979(4)	5.74(9)
C17B	1.0302(4)	0.3037(2)	0.7614(5)	6.2(1)
C18A	1.4322(4)	0.1700(2)	1.0152(4)	6.8(1)
C18B	0.9887(4)	0.3227(2)	0.8906(4)	6.0(1)
C19A	1.3295(4)	0.1210(2)	0.9742(4)	5.99(9)
C19B	0.8639(4)	0.3726(2)	0.8841(4)	5.21(9)

Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as: (4/3) * [a2*B(1,1) + b2*B(2,2) + c2*B(3,3) + ab(cos gamma)*B(1,2) + ac (cos beta)*B(1,3) + bs(cos alpha)*B(2,3)]

Antiinflammatory Activity.

Compounds **2** and **3**, and for SAR purposes, the 4-fluorophenyl analogs **1** and **8**, and the 4-methoxyphenyl congeners **16** and **17** prepared earlier [3,9] were evaluated for antiinflammatory activity in a one hour arachidonic acid-induced mouse ear edema assay following a published procedure [14]. This test is sensitive to a), combination 5-lipoxygenase and cyclooxygenase inhibitors, b), to 5-lipoxygenase inhibitors alone, but is relatively insensitive to selective inhibitors of cyclooxygenase and affords a measure of a compound's antiinflammatory activity [14]. The compounds were administered orally and subcutaneously in a saline vehicle at 50 mg/kg. The data are displayed in Table 3. Both **2** and **3** showed a significant inhibition of edema upon oral administration but were less active than either of the fluoro compounds **1** and **8**. Interestingly, the methoxyphenyl derivatives **16** and **17**, examples of compounds with electron-donating substituents, had activity comparable to the unsubstituted analogs **2** and **3**. Because of their lack of potency compared to **1** additional interest in **2** and **3** as antiinflammatory agents has diminished.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ^{1}H nmr spectra (400 MHz) were obtained on a Bruker AM 400 in deuteriochloroform, using tetramethylsilane as the internal standard. Infrared spectra were taken in chloroform solution on a Perkin-Elmer 283 spectrophotometer. High resolution mass spectra were obtained on a VG ZAB-1F-HF spectrometer at a resolution of 5000 by direct probe insertion.

5-[1-(Ethoxycarbonyl)-1,4-dihydro-4-pyridyl]-6-phenylimidazo-[2,1-*b*]thiazoline (**11**).

This compound, required as an intermediate in the synthesis of **2**, was prepared in 85% yield as described [9].

6-Phenyl-5-(4-pyridyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (**2**).

A pyridine (28 ml) solution of **11** (1.0 g, 2.83 mmoles) was treated with chromium(VI) oxide (0.84 g, 8.4 mmoles) at 5° and allowed to warm to ambient temperature overnight. The reaction was filtered through silica gel with ethyl acetate and the resulting material (0.5 g) flash chromatgraghed (silica gel, ethyl acetate) to give 0.3 g. Recrystallization from ethyl acetate/hexanes gave 0.15 g (19%) of **2**, as a light yellow crystalline solid, mp 206.5-208.5°. The ^{1}H nmr and ir data are displayed in Table 1. Molecular weight calculated for $C_{16}H_{13}N_3S$: 279.0808; Found: m/z 279.0836.

Anal. Calcd. for $C_{16}H_{13}N_3S$: C, 68.79; H, 4.69; N, 15.04. Found: C, 69.09; H, 4.81; N, 15.05.

4-(4-Pyridyl)-5-(phenyl)imidazole-2-thione (**12**).

a) 1-Phenyl-2-(4-pyridyl)ethanone (**13**).

A solution of 4-picoline (18.6 g, 0.2 mole) and ethyl benzoate (47.1 g, 0.28 mole) in 1,2-dimethoxyethane (400 ml) was added under a nitrogen atmosphere to a refluxing mixture of sodium hydride (40 g of 60% dispersion in mineral oil, 1.0 mole) in 1,2-dimethoxyethane (800 ml) over 30 minutes. After refluxing 65 hours, the reaction mixture was cooled in an ice bath and acetic acid (30 ml) (**caution**: exotherm) added dropwise followed by the addition of water (300 ml). The mixture was stirred and the addition of acetic acid (30 ml) and water (300 ml) repeated. The resulting solid was removed from the biphasic system by suction filtration and the two layers separated. The aqueous layer was extracted with diethyl ether (2 x 300 ml) and the extracts and

organic layers combined, washed with water and dried (magnesium sulfate). After filtration the solvent was removed at reduced pressure to give 53.4 g of crude **13**. Recrystallization from 2-propanol/hexane give 17.8 g (45%) of **13** as a light yellow crystalline solid, mp 113-115° (lit [10] 114.0-115.5°; lit [11] 112-114°; lit [12] 112-113.4°) [15]; ir (potassium bromide): 1678 cm^{-1} (C=O stretch); ^1H nmr (deuteriochloroform): δ 4.3 (s, 2H, CH_2), 7.2 (d, 2H, J = 6.0 Hz, pyridyl-3-CH), 7.5 (m, 2H, 3-Ar), 7.6 (m, 1H, 4-Ar), 8.0 (d, 2H, J = 7.1 Hz, 2-Ar), 8.6 (d, 2H, J = 6.0 Hz, pyridyl-2-CH).

Anal. Calcd. for $C_{13}H_{11}NO$: C, 79.17; H, 5.62; N, 7.10. Found: C, 78.95; H, 5.64; N, 7.10.

b) 1-Phenyl-2-(4-pyridyl)ethanone Oxime (**14**).

A mixture of **13** (17.8 g, 0.093 mole), hydroxylamine hydrochloride (20.6 g, 0.3 mole) and sodium acetate trihydrate (55.2 g, 0.41 mole) in ethanol (200 ml) and water (200 ml) was refluxed for 2 hours. After cooling overnight the solvent volume was reduced and the resulting white solid collected, washed with diethyl ether and air dried to give 13.8 g (72%) of oxime **14** as a white solid, mp 157-158°; ir (potassium bromide): 3350-2550 cm^{-1} (OH stretch); 1605 cm^{-1} (C=N stretch); ^1H nmr (deuteriochloroform): δ 4.2 (s, 2H, CH_2), 7.27 (d, 2H, pyridyl-3-CH), 7.35 (m, 3H, ArH), 7.59 (m, 2H, ArH), 8.5 (d, 2H, pyridyl-2-CH). An analytical sample was recrystallized from ethyl acetate, mp 159-161°.

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.34; H, 5.77; N, 13.19.

c) 4-(4-Pyridyl)-5-(phenyl)imidazole-2-thione (**12**).

Sodium (0.28 g, 12.2 mmoles) was added to absolute ethanol (70 ml) and stirred. Upon completion of the reaction and cooling to ambient temperature, the oxime **14** (2.12 g, 10 mmoles) was added portionwise. After 15 minutes, the milky reaction mixture was cooled in an ice bath and p-toluenesulfonyl chloride (2.38 g, 12.5 mmoles) was added in a single portion. After several minutes the reaction became exothermic warming to 15° and turning red. The mixture was stirred for 90 minutes at 5° and then a solution of freshly prepared potassium ethoxide [from 0.5 g (12.7 mmoles) of potassium and ethanol (10 ml)] was added dropwise. The mixture transformed to a semisolid mass. After 30 minutes, diethyl ether (35 ml) was added and stirring continued for an additional 30 minutes. The solid was collected and washed with diethyl ether. The filtrate was concentrated at reduced pressure and the residue redissolved in diethyl ether and extracted with 5% aqueous hydrochloric acid (2 x 30 ml). The aqueous phase was concentrated at reduced pressure to give the α-amino ketone **15** as a red oil (3.0 g). This oil was dissolved in water (30 ml) and potassium thiocyanate (1.94 g, 20 mmoles) added. After refluxing for 1 hour, the mixture was cooled and neutralized with aqueous potassium carbonate. The resulting gum-like precipitate was collected and treated with hot acetone. After cooling the solid precipitate was collected and air dried to give **12** (0.166 g, 6.6%) as a gray solid, mp >300°; ir (potassium bromide): 3100 cm^{-1} (NH), 1602 cm^{-1} (C=C), 1513 cm^{-1} (C=N), 1233 cm^{-1} (C=S); ms: 254 (M+H$^+$, 100%); ^1H nmr (DMSO-d_6): δ 7.31 (d, 2H, J = 6.0 Hz, pyridyl-3 CH), 7.44 (m, 5H, ArH), 8.50 (d, 2H, J = 6.0 Hz, pyridyl-3 CH), 12.74 (b, 2H, NH).

Anal. Calcd. for $C_{14}H_{11}N_3S$: C, 66.38; H, 4.38; N, 16.59; S, 12.66. Found: C, 65.98; H, 4.62; N, 16.05; S, 12.25.

6-Phenyl-5-(4-pyridyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (**2**) and 5-Phenyl-6-(4-pyridyl)-2,3-dihydroimidazo[2,1-*b*]thiazole (**3**).

A suspension of thione **12** (60 mg, 0.25 mmole) in dimethylformamide (2 ml) was treated with sodium hydride (18 mg) under a nitrogen atmosphere to give a red solution. After 15 minutes, 46 μl (0.53 mmole) of 1,2-dibromoethane was added and the mixture stirred for 2 hours. Additional sodium hydride (6 mg) and 1,2-dibromoethane (10 μl) were added and the mixture stirred for 1 hour. The reaction was quenched with water and extracted with methylene dichloride. The extracts were washed with dilute base, dried (magnesium sulfate), filtered and the solvent removed at reduced pressure. Flash chromatography (silica gel, 40% acetonitrile/methylene dichloride) of the residue gave 32.8 mg of **2**, eluting first, followed by 49.7 mg of **3**, mp 154-155° (recrystallized from toluene/hexanes). The gc-mass spectroscopy showed a molecular ion of 279 for **3**. The ^1H nmr chemical shift assignments for **3** are shown in Table 1.

Anal. Calcd. for $C_{16}H_{13}N_3S$ for **3**: C, 68.79; H, 4.69; N, 15.04. Found: C, 68.92; H, 4.71; N, 15.19.

X-Ray Crystallographic Analysis of **2** and **3**.

Crystals of **2** and **3** were grown by slow evaporation from solutions of toluene/methanol and water/methanol, respectively. For **2**, a block-shaped crystal of approximate dimensions 0.6 x 0.6 x 0.5 mm was mounted on a glass fiber with epoxy; for **3** the plate-shaped crystal dimensions were 0.10 x 0.20 x 0.50 mm. Analysis and data collection for both crystals was performed on an Enraf-Nonius CAD4 diffractometer equipped with graphite monochromator and, for **2**, Mo radiation (λMoK_α^- = 0.71073Å); for **3**, Cu radiation (λCuK_α^- = 1.54184Å). Data were collected for both crystals at 295 K using variable speed ω-2θ scans. Unit cell dimensions were determined from the setting angles of 25 high order reflections. For **2**, a = 8.226(4), b = 15.917(10), c = 11.038(5)Å, β = 110.87(3)°, space group $P2_1/c$, V = 1350.4(12)Å^3, Z = 4, d_{calc} = 1.374gcm^{-3}, μ = 2.211 cm^{-1}, F(000) = 584. For **3**, a monohydrate, a = 9.820(9), b = 18.802(5), c = 9.271(5)Å, α = 103.84(3), β = 114.23(6), γ = 78.49(5)°, space group $P\bar{1}$, V = 1505.6(12)Å^3, z = 4, d_{calc} = 1.312 gcm^{-3}, μ = 18.795 cm^{-1}, F(000) = 624. A total of 4175 reflections ($2\theta \leq 60°$, $0 \leq h \leq 11$, $0 \leq k \leq 22$, $-15 \leq \ell \leq 15$) were collected for **2** of which 3942 were unique after averaging (R_{int} = 1.5%). For **3** a total of 5234 reflections ($2\theta \leq 130°$, $0 \leq h \leq 11$, $-22 \leq k \leq 22$, $-10 \leq \ell \leq 10$) were collected of which 4905 were unique (R_{int} = 1.8%). Data were corrected for Lorentz and polarization effects and, in both cases, for the effect of absorption. The DIFABS procedure [16] was used for empirical absorption correction on both data sets. Correction factors were 0.600 (min) and 1.362 (max) for **2**. 0.680 (min) and 1.324 (max) for **3**. Three intensity standards monitored at the beginning, end, and every three hours of exposure time in both experiments showed no systematic variation.

Both structures were solved using SHELXS [17]. Refinement and analysis were performed with a locally modified version of the SDP software [18]. In the full-matrix least-squares minimization of $\Sigma w(|Fo|-|Fc|)^2$, the weights, w, were assigned as $4Fo^2/\sigma^2(I)$ with σ(I) as previously defined [19] and the instrument instability factor, p = 0.04. Non-hydrogen atoms were treated with anisotropic thermal parameters; hydrogens were located from difference Fourier maps and were refined with isotropic temperature factors. For **2**, 3059 reflections with $I \geq 3\sigma(I)$ were

used in a refinement of 234 variables which converged (max Δ/σ = 0.00) to values of $R(\Sigma||Fo|-|Fc||/\Sigma|Fo|) = 0.041$, $wR = (\Sigma w(|Fo|-|Fo|)^2/w|Fo|^2)^{1/2} = 0.060$ with G.O.F. = 2.077. An extinction coefficient [20] refined to $1.337(1) \times 10^{-6}$. Excursions in a final difference Fourier map were within $\pm$ 0.226$e_A^{\circ -3}$. For **3**, 3315 reflections with $I \geq 3\sigma(I)$ were used in a refinement of 396 variables which converged (max Δ/σ = 0.06) to values of R = 0.050 and wR = 0.063 with G.O.F. = 1.709. An extinction coefficient refined to $7.660(1) \times 10^{-7}$. Excursions in a final difference Fourier map were within $\pm$ 0.226$e_A^{\circ -3}$.

Scattering factors were from the International Tables for X-ray Crystallography [21]. Positional and equivalent isotropic thermal parameters for non-hydrogen atoms are presented in Tables 4 and 5.

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REFERENCES AND NOTES

[1a] Department of Synthetic Chemistry; [b] Department of Medicinal Chemistry; [c] Department of Immunology; [d] Department of Physical and Structural Chemistry.

[2] P. E. Bender, D. T. Hill, P. H. Offen, K. Razgaitis, P. Lavanchy, O. D. Stringer, B. M. Sutton, D. E. Griswold, M. DiMartino, D. T. Walz, I. Lantos and C. B. Ladd, *J. Med. Chem.*, **28**, 1169 (1985).

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

[4a] M. J. DiMartino, G. K. Campbell, Jr., C. E. Wolff and N. Hanna, *Agents Actions*, **21**, 303 (1987); [b] J. C. Lee, D. E. Griswold, B. Votta and N. Hanna, *Int. J. Immunopharmacol.*, **10**, 835 (1988); [c] M. J. DiMartino, C. E. Wolff, G. K. Campbell, Jr. and Hanna, *Adv. Neuroimmunol.*, **540**, 578 (1988); [d] D. E. Griswold, P. J. Marshall, E. F. Webb, R. Godfrey, J. Newton Jr., M. J. DiMartino, H. M. Sarau, J. G. Gleason, G. Poste and N. Hanna, *Biochem. Pharmacology*, **36**, 3463 (1987).

[5] W. Klose and K. Schwartz, *J. Heterocyclic Chem.*, **22**, 669 (1985).

[6] For a review see: J. P. Paolini, 5,5-Systems with a Bridgehead Nitrogen Atom, in Heterocyclic Compounds, Vol. **30**, A. Weissberger and E. C. Taylor, eds, John Wiley & Sons, Inc., New York, 1977, p 1.

[7] J. P. Paolini and L. J. Lendvay, *J. Med. Chem.*, **12**, 1031 (1969).

[8] A. H. M. Raeymaekers, F. T. N. Allewyn, J. Vandenberk, P. J. A. Demoen, T. T. T. Van Offenwert and P. A. J. Janssen, *J. Med. Chem.*, **9**, 545 (1966).

[9] I. Lantos, K. Gombatz, M. McGuire, L. Pridgen, J. Remich and S. Shilcrat, *J. Org. Chem.*, **53**, 4223 (1988).

[10] W. von E. Doering and W. E. McEwen, *J. Am. Chem. Soc.*, **73**, 2104 (1951).

[11] E. Anders, W. Will and A. Stankowiak, *Chem. Ber.*, **116**, 3192 (1983).

[12] C. Osuch and R. Levine, *J. Org. Chem.*, **22**, 939 (1957).

[13] For a review of the Neber rearrangement see: C. O'Brien, *Chem. Rev.*, **64**, 81 (1964).

[14] D. E. Griswold, E. Webb, L. Schwartz and N. Hanna, *Inflammation*, **11**, 189 (1987).

[15] Note: reference 5 reports a melting point of 237° for ketone **13**. This is considerably higher than the melting point that we and others [10,11,12] have observed for **13**. However, perhaps coincidentally, 237° corresponds very closely to the melting point we obseved (235-236°) for the α-bromo hydrobromide formed on treatment of **13** with bromine in acetic acid. Synthesis of this compound is also described in reference 5 although no melting point is reported.

[16] N. Walker and D. Stuart, *Acta Crystallogr.*, **A39**, 158 (1983).

[17] G. M. Sheldrick, SHELXS Program for Crystal Structure Determination, University of Gottingen, Federal Republic of Germany, 1986.

[18] B. Frenz, Structure Determination Package, Enraf-Nonius, Delft, The Netherlands, 1987.

[19] P. W. R. Corfield, R. J. Doedens and J. A. Ibers, *Inorg. Chem.*, **6**, 197 (1967).

[20] W. H. Zachariasen, *Acta Crystallogr.*, **16**, 1139 (1963).

[21] D. R. Cromer, International Tables for X-ray Crystallography, Vol **IV**, The Kynoch Press, Birmingham, England, 1974 (Present distributor Kluwer Academic Publishers, Dordrecht).