Reactions of Piroxicam with Alkyl Iodides

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Alkylation of piroxicam with a homologous series of alkyl iodides gave reversibly formed *O*-alkyl products **1** as well as unexpected, irreversibly formed zwitterionic compounds **2**, alkylated on the pyridine nitrogen, and *O,N*-bis-alkyl products **3**. Proof of structure was accomplished by nmr and X-ray crystal analysis. Product distribution ratios were determined by hplc and are explained by the Hard-Soft Acid-Base principle.

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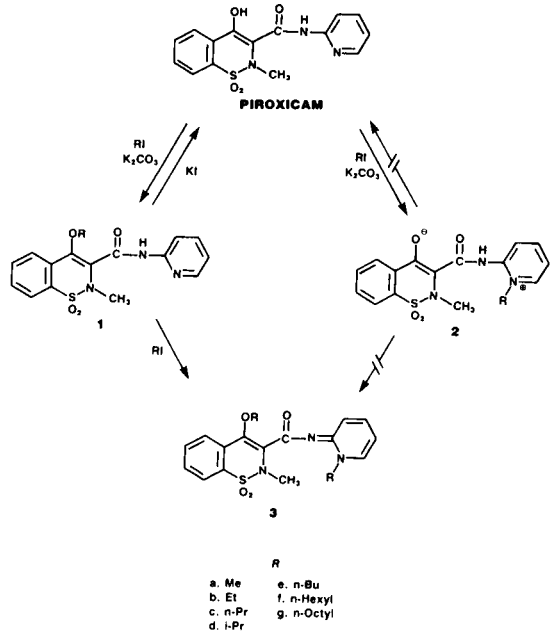
During the course of exploring the chemistry of the anti-inflammatory drug [1,2] piroxicam and related 1,2-benzothiazines [3-7], a series of alkylation reactions were carried out under heterogeneous reaction conditions employing alkyl iodides in acetone containing potassium carbonate. The reaction mixtures, were separated into their individual components by column chromatography. In addition to the expected *O*-alkylated products **1a-g**, a group of structurally novel, zwitterionic compounds alkylated on the pyridyl nitrogen **2a-g**, and the *O,N*-bis-alkylated derivatives **3a-d**, were isolated (Scheme I). Proof of structure for each group of compounds was accomplished by nmr and X-ray crystallography and is discussed below. The product ratios from the reactions with four homologous alkyl iodides were determined by hplc, and are given in Table I. Isolated yields from a more extended series of reactions are given in Table II.

Scheme I



Reaction of piroxicam with the lower alkyl iodides produces a mixture of products, the yields of which are influenced by the fact that *O*-alkylation is apparently reversible whereas the *N*-alkylation is not. This was demonstrated by treating pure, isolated samples of either **1a-b** or **2a-b** with potassium iodide in acetone and determining (by hplc) that piroxicam was formed from **1a-b** but not from **2a-b**. Significant amounts of **2a-b** were also detected, (see Table III for amounts of products with time), when **1a-b** was reacted with potassium iodide, indicating that the rates between reversible and irreversible

Table I

Product Ratios by HPLC

	R	1	2	3
a	Me	<1 (25) [a]	>99(75) [a]	trace
b	Et	85	15	trace
c	*n*-Pr	59	7	34
d	*i*-Pr	94	0	6

[a] These numbers represent the ratios when 50% of the starting piroxicam, remains. With time, decomposition and realkylation occur to give N:O ratios greater than 99% by the end of the reaction, as evidenced by the disappearance of piroxicam.

Table II

Isolated Product Yields and Melting Points

		O-Alkyl **1**		*N*-Alkyl **2**	
Compound	R	Yield (%)	MP (°C)	Yield (%)	MP (°C)
a	Me	29	203-205	75	255-257
b	Et	50	135-137	7	223-224
c	*n*-Pr	21	122-123.5	3	189-191
d	*i*-Pr	63	123-125	0	-
e	*n*-Bu	53	95-96.5	4	209-210
f	*n*-Hexyl	39	72-74	4	177-178
g	*n*-Octyl	34	103-104	<1	168-169

Table III

Products Formed With Time Upon Degradation of **1**

	Time (hours)	% **1** (OR)	% **2** (NR)	% Piroxicam
a R = CH_3	0.5	88.9	10.0	1.1
	57	3.6	78.7	17.7
b R = C_2H_5	23	97.3	2.7	0
	144	85.7	12.5	1.8

reactions are competitive. The reverse reaction for the methyl derivative **1a** to form piroxicam occurs at a much faster rate than for the higher alkyl iodides. In order to obtain an optimum yield of **1a** when piroxicam is alkylated with methyl iodide, the reaction must be interrupted at approximately 50% consumption of piroxicam. At this point, a 25:75 mixture of **1a:2a** (O:N) is formed. If the reaction is continued until the complete consumption of piroxicam (*ca.* 10 hours), the ratio changes to a >99% preponderance of **2a**. The reactions with higher alkyl iodides showed no significant shifts in product ratios during the period when piroxicam was still present.

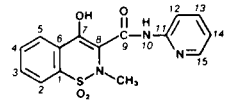
Dialkylation to form the *O,N*-bis compounds **3a-d** occurred minimally with methyl and ethyl iodide and to a significant extent with propyl and isopropyl iodides. That the dialkyl products originated from further reactions of the *O*-alkylated compounds **1** and not the *N*-alkyl compounds **2** was substantiated by subjecting samples of **1** and **2** to further reaction with the appropriate alkyl iodide and potassium carbonate and monitoring by hplc. Compounds **3a** and **3c** were the only dialkyl compounds that could be isolated pure. Compound **3d** could not be isolated, but its identity was inferred by the presence of a low level (<1%) hplc peak with the expected retention time. Compound **3d** was obtained as a mixture with **1d** and could not be purified by column chromatography or fractional crystallization. Its identity was established by hplc retention time, and the correct mass spectra molecular ion. The overall reaction sequence is shown in Scheme I.

Proof of Structures.

The original determination of the zwitterionic *N*-alkyl structure was accomplished by nmr spectroscopy. The end product from the reaction with methyl iodide was first presumed to be **1a**, [6] but the correct isomeric structure **2a** was established by means of its ^{13}C and ^{1}H nmr spectra in dimethyl sulfoxide-d_6. The chemical shift observed for the exchangeable proton (16.2 ppm), was higher than expected for amides (10.3 ppm in **3a**). The formal proof of structure required three prior steps: (1) correlating the shifts of directly bonded ^{13}C, ^{1}H pairs through two dimensional experimental methods [8]; (2) grouping the =CH- units thus assigned into two sequences of four each on the basis of H, H spin couplings [9] (done by single one-dimensional spin decoupling experiments); (3) identifying and ordering the pyridyl ring sequence based on the predictably large $^{1}J_{C,H}$ (188 Hz) fine splitting in the unit attached to the pyridyl nitrogen. The coupled ^{13}C spectrum also revealed a 3.8 Hz hyperfine splitting in one of the methyl carbon signals, which was shown to result from the α-hydrogen on the pyridyl ring by selective heteronuclear decoupling. This can occur over the normal spin-coupling

Table IV

Carbon-13 (Proton) Chemical Shifts in Alkylated Piroxicams



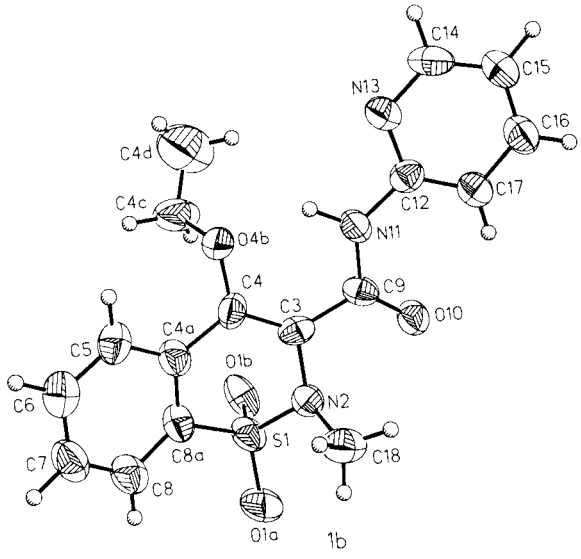
Position	*N*-alkylated [a] -Me (**2a**)	-Et (**2b**)	*O*-alkylated [b] -Me (**1a**)	-Et (**1b**)	-iPr (**1d**)	Dialkylated [b] -Me (**3a**)
1	135.4	135.4	135.6	135.4	135.7	
2	122.8 (7.73)	122.8	123.6	123.5 (7.87)	123.5	122.6 (7.87)
3	131.2 (7.72)	131.2	131.6	131.6 (7.68)	131.5	129.2 (7.55)
4	132.3 (7.78)	132.3	132.4	132.5 (7.73)	132.3	131.9 (7.64)
5	126.8 (8.08)	126.7	125.9	126.1 (7.80)	126.2	125.0 (7.80)
6	133.4	132.9	128.7	129.0	129.5	
7	165.7 [c]	165.7 [c]	151.3 [c]	150.1	148.9	
8	110.8	111.5	126.9	127.4	128.0	132.2
9	164.6 [c]	164.3 [c]	159.1	159.4	159.6	
11	151.1	151.3	151.4 [c]	151.4	151.5	
12	117.2 (8.96)	118.3	114.5	114.4 (8.32)	114.4	121.3 (8.36)
13	143.5 (8.19)	143.3	138.5	138.5 (7.72	138.4	140.3 (7.63)
14	116.5 (7.28)	116.8	120.3	120.2 (7.07)	120.1	112.4 (6.64)
15	142.5 (8.52)	141.3	148.2	148.4 (8.31)	148.5	139.3 (7.66)
$-SO_2NMe$	38.5 (2.81)	38.3	36.8	36.7 (3.06)	36.6	35.6 (3.21)
R	43.3 (4.07)	50.4 13.7	62.2	71.4 (4.13) 15.0 (1.43)	78.7 21.9	61.8 (3.82) 41.9 (3.87)
-NH-	(16.2)	(16.4)	(9.96)	(10.23)	(10.30)	

Notes: [a] Dimethyl sulfoxide-d_6. [b] Deuteriochloroform. [c] Assignments may be permuted within column.

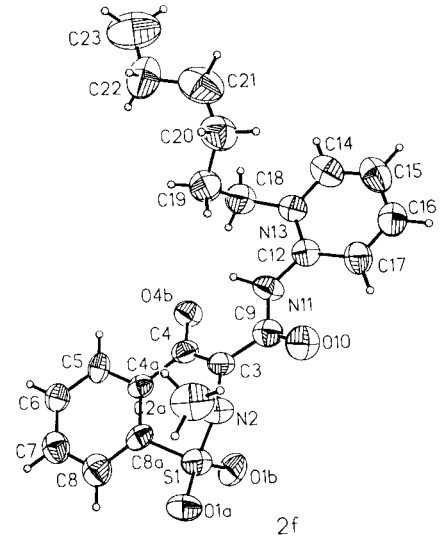
range of three bonds from **2a** only. The location of the methyl group on the pyridyl nitrogen is further confirmed by a 20% nuclear Overhauser enhancement of the α-pyridyl hydrogen from presaturation of the methyl protons whose carbon showed the hyperfine doublet splitting.

The nmr assignments for the series of compounds are summarized in Table IV. The chemical shifts within a series of homologs were consistent enough to require independent assignment in only one member. The protonated carbon assignments are based on a repetition of the preliminary steps described above, plus the ordering of benzenoid carbon assignments in **1b** and **3a**, based on nuclear Overhauser polarizations of H_5 by the *O*-alkyl protons. The assignments to positions 1 and 6 were based on selective heteronuclear decouplings of the benzenoid protons. C_8 is weakly coupled to the sulfonamide methyl protons, C_{10} is identifiable by its extensive hyperfine splitting by pyridyl protons, and C_7 in the *O*-alkylated series was assigned by its coupling to the protons on the first unit in the alkyl group.

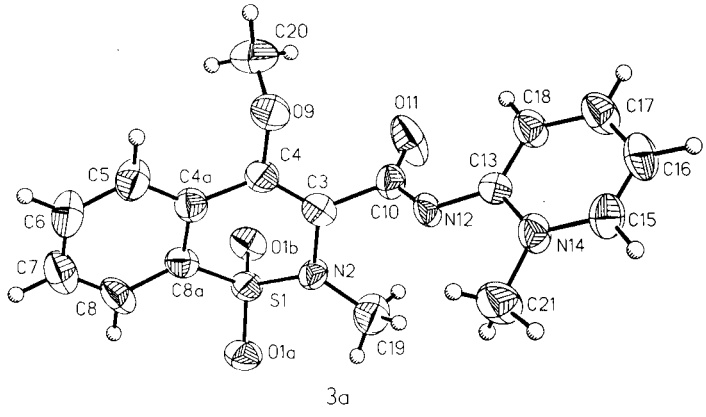
Conclusive proof of structure was subsequently obtained by X-ray crystallography for one member, **1b**, **2f** and **3a** of each class of structural types. The choice of compounds was largely dictated by the availability of a suitable crystalline product. Confirmation that a given compound was a member of the above classes was accomplished by comparison of the nmr, mass spectra, thin-layer and high performance liquid chromatography retention times. The X-ray determinations establish two additionally important points: the position of the labile proton in the *N*-alkylated **2** series, which determines their zwitterionic nature, and the nonplanarity of the bis-alkylated **3** series, which points to the importance of internal hydrogen-bonding in the formation of planar structures.



1b



2f



3a

Discussion.

The alkylation results (Table I) are an example of kinetic *vs* thermodynamic control in which (i) *O*-alkylation rates are greater than *N*-alkylation rates in all cases except methyl; (ii) *N*-alkylated products are more stable than *O*-alkylated products and (iii) *O*-alkylation is readily reversible in the case of methyl but reversibility is not a significant factor with higher alkyl groups. As Table I shows, there is a clear trend toward *O*-alkylation as the R-group increases in size or becomes more branched. These results appear to exemplify the Hard-Soft Acid-Base (HSAB) principle [10]. Pyridine is considered to be borderline between a hard and soft base, whereas oxygen, as in an alcohol or enol, is considered a hard base [11]. Correspondingly, the progression from methyl to isopropyl iodide reflects an increasing hardness in the acid strength of the alkylating agent, due to the electron-withdrawing property of alkyl groups attached to a sp3-hybridized carbon [12,13]. A harder base is expected to react with the harder alkylating agent (acid), which explains why isopropyl iodide initially reacts exclusively at the oxygen, whereas the relatively softer bases, propyl, ethyl and

methyl iodides, react to an increasingly larger extent at the pyridine nitrogen. Once the enol oxygen is alkylated, the pyridine nitrogen then becomes relatively harder due to stronger inductive effects from the amide carbonyl. After compounds of type **1** are formed, they react increasingly with the harder alkyl iodides, to give the dialkyl products, such as **3a-d**. A search for the bis-alkyl products in the reaction mixtures of the higher alkyl series was not made.

EXPERIMENTAL

All reactions were monitored by tlc on Brinkman silica gel plates (eluent: 1:1 ethyl acetate/dichloromethane) or by hplc on a LDC/Milton Roy instrument utilizing a Waters Associates C_{18} NovaPak column (Mobile Phase: 0.1*M* acetic acid (50%), methanol (30%), acetonitrile (20%) with a 1 ml/minute flowrate). A uv detector at 254 nm was used. Relative response factors (peak area/mg sample) were determined for analytical standards of the product(s) and reactants(s) by hplc. The amount of the reactant(s) and products(s) (or the extent of reaction) in the reaction mixture could then be determined by hplc peak area. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Mass spectroscopy data was determined on a Finnigan 4510 GC/MS instrument. The nmr spectra were recorded with a Bruker 250 instrument. Elemental analyses were performed by the Pfizer Central Research Analytical Department. Single crystal X-ray analysis was conducted on a Nicolet R3m/μ diffractometer.

General Procedure for Preparing *O*- and *N*-Alkylated Derivatives of Piroxicam.

A combination of piroxicam [6] (8.30 g, 25.0 mmoles), potassium carbonate (6.91 g, 50.0 mmoles), alkyl iodide (150.0 mmoles) and acetone (125 ml) was stirred at reflux for 3 to 96 hours, depending upon the substituent. The reaction was cooled to room temperature, filtered to remove insoluble inorganics and the solvent removed *in vacuo* to give a yellow residue. The isomeric *O*-alkylated and *N*-alkylated products were separated by liquid chromatography on silica gel. Hplc retention times and R_f values are given in Table V.

The less polar isomer, assigned and confirmed as the *O*-alkyl derivative, was eluted from the column, the solvent removed *in vacuo* and the residue triturated with diethyl ether to give white crystals. The more polar compound, assigned and confirmed as the *N*-alkyl derivative, was similarly isolated and triturated with diethyl ether to give yellow crystals.

Mass Spectroscopy Data on *O*- and *N*-Alkylated Derivatives of Piroxicam.

The *O*- and *N*-alkylated derivatives of piroxicam can be distinguished by distinctive fragments in the mass spectrum. All *O*-alkylated derivatives have two common fragments, the loss of the alkyl group to produce a fragment of m/e 330 and the loss of -OR to produce a fragment of m/e 314. These fragments are not found in the mass spectra of *N*-alkylated products. The *N*-alkylated derivatives all have a high abundance fragment characteristic for the *N*-alkylated-2-pyridyl isocyanate fragment, which cannot occur with *O*-alkylated products.

4-Methoxy-2-methyl-*N*-(1-methyl-2(1*H*)-pyridinylidine)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (**3a**).

A mixture of piroxicam (16.5 g, 5.0 mmoles), potassium carbonate (13.8 g, 100.0 mmoles) and iodomethane (42.6 g, 300.0 mmoles) was refluxed in acetone (300 ml) for 96 hours. After cooling and filtration, the solvent

Table V

Reaction Conditions

	R	Reaction Time, hours	R_f Value on Thin-Layer Chromatography [1] O-R	R_f Value on Thin-Layer Chromatography [1] N-R	Column Chromatography Eluent O-R	Column Chromatography Eluent N-R	HPLC Retention [2] O-R minutes	HPLC Retention [2] N-R minutes
a	$-CH_3$	3, 10 [3]	0.54	0.01	[4]	[4]	6.3	1.9
b	$-CH_2CH_3$	40	0.68	0.03	[5]	[6]	4.8	2.1
c	$-(CH_2)_2CH_3$	27	0.74	*ca.* 0.07	[7]	[8]	12.8	3.1
d	$-CH(CH_3)_2$	96	0.74		[9]		12.0	
e	$-(CH_2)_3CH_3$	20	0.77	0.11	[10]	[10]		
f	$-(CH_2)_5CH_3$	23.5	0.80	0.15	[11]	[11]		
g	$-(CH_2)_7CH_3$	44 [12]	0.84	0.17	[13]	[14]		

[1] The system was 1:1 ethyl acetate:dichloromethane. Piroxicam R_f was 0.60.
[2] Mobil Phase - 50:30:20 0.1*M* acetic acid:methanol:acetonitrile.
[3] Stopping the reaction after 3 hours allowed the *O*-Me product to be isolated. When the reaction was allowed to continue until no piroxicam remained (10 hours), the *O*-Me product initially formed, was converted to the *N*-Me piroxicam derivative.
[4] The *N*-Me product was filtered off and purified by water trituration. Concentration of the filtrate gave the *O*-Me product, which was recrystallized from acetone.
[5] The system was 4:1 ethyl acetate:dichloromethane.
[6] *N*-Alkyl product was removed with methanol.
[7] The system was 95:5 dichloromethane:methanol.
[8] A second chromatography (eluent:ethyl acetate) was used to isolate the *N*-alkyl product.
[9] Only the *O*-isopropyl product was formed. The crude residue was recrystallized from ethanol.
[10] The system was 98:2 dichloromethane:methanol.
[11] The residue was triturated with diethyl ether to give crude *N*-alkylated product, which was purified by water trituration, followed by a recrystallization from benzene. The *O*-alkylated product was recrystallized from hexanes.
[12] Only 1.59 equivalents of alkyl iodide were used in this reaction.
[13] The system was 2:1 ethyl acetate:hexanes.
[14] The *N*-alkyl product was removed with ethyl acetate.

Table VI

Single Crystal X-Ray Crystallographic Analysis of **1b, 2f, 3a**

A. Crystal Parameters

	1b	**2f**	**3a**
formula	$C_{17}H_{17}N_4O_3S$ (359.4)	$C_{21}H_{28}N_3O_4S$ (418.6)	$C_{17}H_{17}N_3O_4S$ (359.4)
crystallization medium	acetone	dmso	acetone and ether
crystal size, mm	0.15 x 0.15 x 0.19	0.15 x 0.15 x 0.19	0.15 x 0.15 x 0.19
cell dimensions	a = 11.575 (4)	a = 11.189 (5) Å	a = 9.485 (2) Å
γ = 90.0°	b = 12.190 (6)	b = 15.24 (1) Å	b = 7.892 (1) Å
	c = 12.215 (4)	c = 12.730 (7) Å	c = 22.789 (4) Å
	α = 90.0°	α = 90.0°	α = 90.0°
	β = 90.0°	β = 110.17 (4)°	β = 99.55 (2)°
	= 90.0°	= 90.0°	= 90.0°
	V = 1723 (1) Å^3	V = 2037 (2) Å^3	V = 1682 (1) Å^3
space group	$P2_12_12_1$	$P2_1/c$	$P2_1/c$
molecules/unit cell	4	4	4
density obsd, g/cm^3	1.36	1.37	1.42
density calcd, g/cm^3	1.39	1.36	1.42
linear absorption coefficient, cm^{-1}	18.66	16.46	19.11

B. Refinement Parameters

number of reflections	1044	2097	1700
nonzero reflections ($I > 3.0\sigma$)	930	1457	1313
R-index = $\Sigma\|\|Fo\|-\|Fc\|\|/\Sigma\|Fo\|$	0.045	0.096	0.059
GOF = $[\Sigma w(Fo^2-Fc^2)^2/(m-s)]^{1/2}$	1.56	1.12	1.30
scale factor	1.161 (2)	1.645 (6)	1.670 (4)
secondary extinction coefficient	67 (8) x 10^{-4}	none	294 (6) x 10^{-4}

Table VII

C, H, N Analyses

Compound	Formula	Calculated			Found		
1a O-Me	$C_{16}H_{15}N_3O_4S$	C 55.64	H 4.38	N 12.17	C 55.28	H 4.25	N 12.01
1b O-Et	$C_{17}H_{17}N_3O_4S$	C 56.81	H 4.77	N 11.69	C 56.54	H 4.83	N 11.66
1c O-*n*-Pr	$C_{18}H_{19}N_3O_4S$	C 57.90	H 5.13	N 11.25	C 57.95	H 5.20	N 11.22
1d O-*i*-Pr	$C_{18}H_{19}N_3O_4S$	C 57.90	H 5.13	N 11.25	C 57.73	H 5.23	N 11.23
1e O-*n*-Bu	$C_{19}H_{21}N_3O_4S$	C 58.91	H 5.46	N 10.85	C 59.08	H 5.76	N 10.85
1f O-*n*-Hexyl	$C_{21}H_{25}N_3O_4S$	C 60.70	H 6.06	N 10.11	C 60.36	H 6.13	N 9.93
1g O-*n*-Octyl	$C_{23}H_{29}N_3O_4S$	C 62.29	H 6.59	N 9.47	C 62.37	H 6.74	N 9.40
2a N-Me	$C_{16}H_{15}N_3O_4S\cdot\frac{1}{4}H_2O$	C 54.93	H 4.47	N 12.01	C 54.96	H 4.32	N 12.06
2b N-Et	$C_{17}H_{17}N_3O_4S$	C 56.81	H 4.77	N 11.69	C 56.56	H 4.95	N 11.64
2c N-*n*-Pr	$C_{18}H_{19}N_3O_4S\cdot\frac{1}{4}H_2O$	C 57.28	H 5.16	N 11.12	C 57.08	H 5.12	N 11.06
2e N-*n*-Bu	$C_{19}H_{21}N_3O_4S\cdot\frac{1}{2}H_2O$	C 57.57	H 5.59	N 10.60	C 57.55	H 5.61	N 10.71
2f N-*n*-Hexyl	$C_{21}H_{25}N_3O_4S$	C 60.70	H 6.06	N 10.11	C 61.00	H 6.22	N 9.96
2g N-*n*-Octyl	$C_{23}H_{29}N_3O_4S$	C 62.29	H 6.59	N 9.47	C 61.99	H 6.57	N 9.41
3a O, N-di-Me	$C_{17}H_{17}N_3O_4S\cdot\frac{1}{2}H_2O$	C 55.42	H 4.93	N 11.41	C 55.67	H 4.74	N 11.33
3c O, N-di-*n*-Pr	$C_{21}H_{25}N_3O_4S$	C 60.70	H 6.06	N 10.11	C 60.64	H 6.16	N 10.04

was evaporated to give a brown residue. Trituration with acetone precipitated 0.15 g (0.8%) of **3a**, mp 200-203°.

4-Propoxy-2-methyl-*N*-(1-propyl-2(1*H*)-pyridinylidine)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (**3c**).

A mixture of piroxicam (10.0 g, 30.2 mmoles), potassium carbonate (8.34 g, 60.4 mmoles) and iodopropane (32.6 g, 192 mmoles) was refluxed in acetone (150 ml) for 84 hours. After cooling and filtration the solvent was evaporated to give a brown residue. The residue was dissolved in dichloromethane and washed with water. The dried and evaporated organic layer, containing the mixture of products, was chromatographed on 300 g of 63-200 μm silica gel using methyl ethyl ketone as the eluent. This initial separation gave a mixture of **1c** and **3c**. A second chromatography using 4:1:1 isopropyl ether:dichloromethane:ethyl acetate as the eluent provided 1.30 g (10.5%) of the di(*n*-propyl) piroxicam (**3c**), mp 88-91°; ^{1}H nmr (deuteriochloroform): 0.94 (overlapping triplets, 6H, $-CH_3$), 1.64 (multiplet, 4H, $-CH_2-$), 3.24 (s, 3H, NCH_3), 3.76 (t [broad], 2H, $N-CH_2$), 4.0 (t, 2H, OCH_2), 7.06 (t, 1H, AR-H), 7.32-7.74 (multiplet, 6H, AR-H), 8.28 (s, 1H, AR-H); ms: m/e 415.1466. Calcd. for $C_{21}H_{25}N_3O_4S$: 415.1566.

Single Crystal X-Ray Analysis of **1b, 2f, 3a**.

Representative crystals were surveyed and 1 Å data sets (maximum sin θ/λ = 0.5) were collected on a Nicolet R3m/μ diffractometer. Atomic

scattering factors were taken from the International Tables for X-ray crystallography [14]. All crystallographic calculations were facilitated by the SHELXTL [15] system. All diffractometer data were collected at room temperature. Pertinent crystal, data collection, and refinement parameters are summarized in Table VI.

A trial structure was obtained by direct methods. This trial structure refined routinely. Hydrogen positions were calculated wherever possible. The methyl hydrogens and hydrogens on nitrogen and oxygen were located by difference Fourier techniques. The hydrogens parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle at least squares refinement were all less than 0.1 of their corresponding standard deviations. The final R-indices are summarized in Table VI. Final difference Fouriers revealed no missing or misplaced electron density.

The refined structures were plotted using the SHELXTL plotting package. Coordinates, distances and angles will be submitted to the Cambridge Crystallographic Data Centre, Lensfield Road, Cambridge, CB2-1EW, England.

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