Synthesis of Some Pyrazolo[4,3-*e*][1,2]- and Thiazolo[4,5-*e*][1,2]thiazine 1,1-Dioxide Derivatives

Robert Bellemin and Didier Festal*

LIPHA, Centre de Recherches, 34, rue Saint-Romain,
BP 8481 Lyon Cedex 08, France

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The synthesis of various 2-methylpyrazolo[4,3-*e*]- and thiazolo[4,5-*e*][1,2]thiazine 1,1-dioxide derivatives is described.

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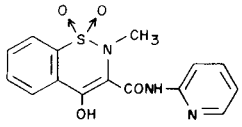
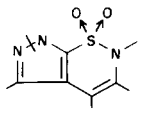
A number of 3-carboxamides of 2-alkyl-4-hydroxy-2*H*-[1,2]benzothiazine 1,1-dioxides have been reported [1] as being potent anti-inflammatory agents in various animal models and the 2-methyl-*N*-(2-pyridyl) derivative known as "Piroxicam" [2] is now used in the treatment of several inflammatory conditions in humans.

Our continued interest in the chemistry of heterocyclic sulfonamides and the fact that many molecules with a thiazole or a pyrazole moiety in their structure have been found to exhibit significant anti-inflammatory activity [3], led us to investigate the related new pyrazolo[4,3-*e*]- and thiazolo[4,5-*e*][1,2]thiazine ring systems, **1** and **2**.



Piroxicam



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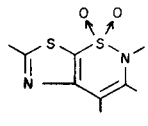

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We describe here the synthesis of various methyl-3-carboxylates and 3-carboxamides of 2-methyl-2*H*,6*H*-(or 7*H*)-pyrazolo[4,3-*e*][1,2]thiazine 1,1-dioxides and 2-methyl-2*H*-thiazolo[4,5-*e*][1,2]thiazine 1,1-dioxides **7-12** (see Scheme I).

Thus, diazotation of the appropriate amino ester **3** in a mixture of acetic and formic acid followed by addition of the resulting diazonium salt to a solution of sulfur dioxide in acetic acid in the presence of cupric chloride provided sulfonic acid chlorides **4**. These were then reacted with methyl glycine ester and potassium carbonate in tetrahydrofuran to obtain sulfonyl diesters **5**, which on treatment with sodium methylate in dimethylsulfoxide (DMSO), underwent a Dieckmann type cyclisation to **6**. Subsequent alkylation with methyl iodide either in aqueous ethanol (**6a**, **6b** and **6f**) or in dimethylformamide (**6c**, **6d**) in the presence of one equivalent of sodium bicarbonate yielded 2-methylthiazines **7a-d** and **7f**. Compound **7e** was prepared by hydrogenolysis of the corresponding 7-benzyl derivative **7d** by means of 10% palladium on carbon in a mixture of chloroform-methanol. Finally carboxamides **8-12** were obtained by reacting the parent compound **7** with amines **14** in refluxing xylene.

Sulfonyl chlorides **4b**, **4d** and **4f** were used for the next step without purification. These were identified by their spectral properties as well as by conversion to the corresponding primary sulfonamides **13** upon treatment with 34% aqueous ammonia in tetrahydrofuran at a temperature below 15°.

The structure of the various 2-methylthiazines prepared according to Scheme I are based on correct elemental analysis and spectroscopic data (see Tables I, II and III).

All of these compounds were completely enolized as indicated by ir spectra (no band in the carbonyl region above 1670 cm^{-1} for the esters **7** or 1640 cm^{-1} for the carboxamides **8-12**) and nmr spectra (enol OH at δ 11-13). These results were quite similar to the findings of Lombar-

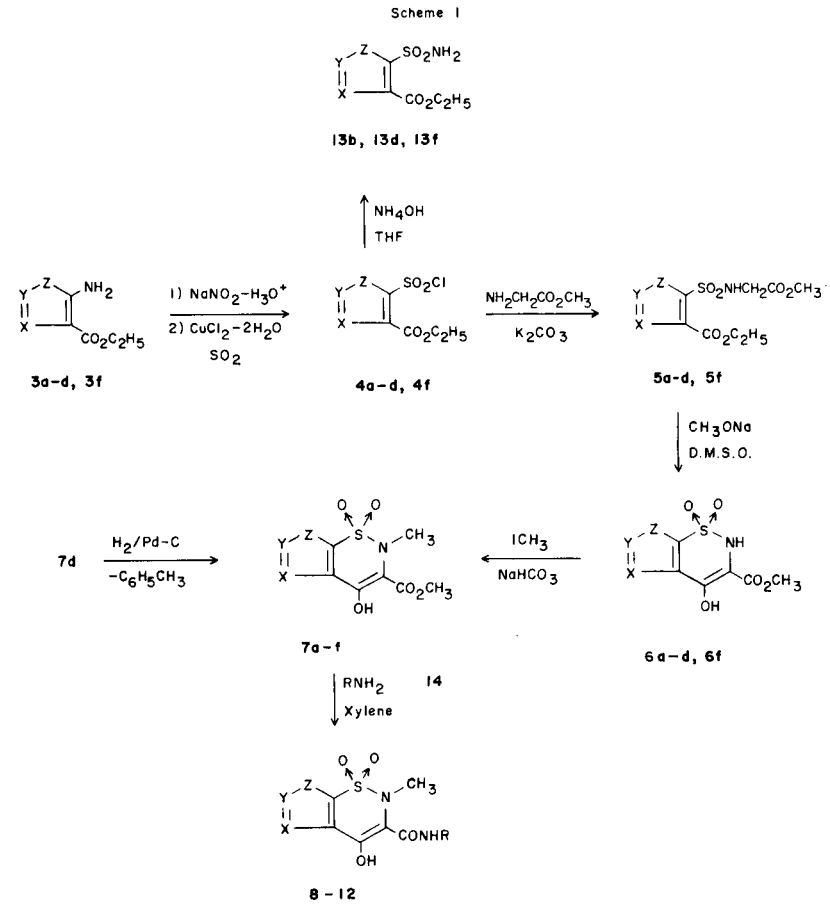
Table I

Compounds **7**

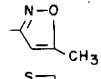
Compound No.	Mp °C (crystallization solvent)	Yield %	Molecular formula	Analyses % Calcd. C	H	N	S	Found C	H	N	S
7a	164 [a]	70	$C_9H_{11}N_3O_5S$	39.55	4.06	15.38	11.73	39.32	4.15	15.50	11.90
7b	158-160 (ethanol)	71	$C_{10}H_{13}N_3O_5S$	41.80	4.56	14.63	11.16	41.94	4.28	14.42	11.11
7c	182-184 (ethyl acetate)	85	$C_9H_{11}N_3O_5S$	39.55	4.06	15.38	11.73	39.70	3.92	15.45	11.88
7d	158-160 (acetonitrile)	96	$C_{15}H_{15}N_3O_5S$	51.57	4.33	12.03	9.18	51.35	4.27	12.10	9.23
7e	206-208 (ethanol-water) (1:1)	87	$C_8H_9N_3O_5S$	37.06	3.50	16.21	12.37	37.13	3.39	16.41	12.12
7f	179-181 (ethyl acetate)	76	$C_9H_{10}N_2O_5S_2$	37.23	3.47	9.65	27.56	37.35	3.62	9.63	27.37

[a] Inst. mp.

Scheme I



	X	Y	Z
a	CH	N	NCH_3
b	CCH_3	N	NCH_3
c	CH	NCH_3	N
d	CH	N	$NCH_2C_6H_5$
e	CH	N	NH
f	N	CCH_3	S

	R
8	
9	
10	
11	$-C_6H_5$
12	

dino [4] and Zinnes [5] for the benzo series.

Compounds **8-12** were generally less active than "Piroxicam" in anti-inflammatory-primary screening.

EXPERIMENTAL

All melting points were determined on a Gallenkamp apparatus (capillary method) and are uncorrected. Nuclear magnetic resonance spectra were obtained with a Varian T-60 instrument operating at 60 MHz, and chemical shifts are reported in δ units relative to TMS as the internal standard and J in Hz. The abbreviations, br, s, d, t, q, m, refer to broad, singlet, doublet, triplet, quartet, multiplet. Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer, samples were examined as potassium bromide pellets. Microanalyses were performed by "Analytische Laboratorien Malissa and Reuter" Grummersbach-1-Elbach (West Germany) and by "Le Service Central d'Analyses du C. N. R. S." Vernaison, France. All starting amino esters **3** were prepared according to published procedures [6] and amines **14** were commercially available.

Sulfonyl Chlorides **4**. General Procedure.

The appropriate amino ester **3** (0.45 mole) was diazotized in a mixture of 10 *N* hydrochloric acid (90 ml, 0.9 mole), acetic acid (300 ml) and formic acid (90 ml) by adding dropwise a solution of sodium nitrite (32.4 g, 0.47 mole) in water (63 ml), while maintaining the temperature in the range of −8° to −6°. The diazo solution was stirred for an additional 5 minutes and then poured portionwise at 15° into a freshly prepared mixture of cupric chloride dihydrate (18 g) and acetic acid (400 ml) in which sulfur dioxide (126 g) had been dissolved at room temperature. The reaction mixture was stirred at room temperature for 15 minutes and then evaporated to dryness after removal of excess sulfur dioxide by passing a stream of air through it while heating at 40°. The residue was extracted with ether, and the extract was dried over sodium sulfate and then allowed to evaporate, leaving the compounds **4** as oils [7].

Compound **4a**.

This compound was obtained in a yield of 70%, bp 95-97°/1 mm; ir: 1740 (C=O), 1395 and 1190 cm^{-1} (SO_2); nmr (carbon tetrachloride): 1.4 (t, J = 7, CH_3 ester), 3.8-4.7 (m, CH_3N + CH_2O), 7.8 (s, CH pyraz).

Table II

Compounds **8-12**

Compound No.	Mp °C (crystallization solvent)	Yield %	Reaction Time (in hours)	Molecular formula	Analyses % Calcd. C	H	N	S	Found C	H	N	S
8a	171-172 dec (toluene)	60	2.5	$C_{13}H_{13}N_5O_4S$	46.56	3.91	20.89	9.56	46.56	3.87	21.00	9.60
8b	188 dec (toluene)	51	3	$C_{14}H_{15}N_5O_4S$	48.13	4.33	20.05	9.18	47.90	4.29	20.16	9.44
8c	205-207 dec (toluene)	60	9	$C_{13}H_{13}N_5O_4S$	46.56	3.91	20.89	9.56	46.27	3.86	20.81	9.25
8d	177 dec (toluene)	52	5	$C_{19}H_{17}N_5O_4S$	55.46	4.17	17.02	7.79	55.45	3.96	17.18	7.90
8e	203 dec (ethanol)	69	2	$C_{12}H_{11}N_5O_4S$	44.85	3.45	21.80	9.98	44.92	3.33	21.63	10.09
8f	187-188 dec (ethanol)	62	13	$C_{13}H_{12}N_4O_4S_2$	44.30	3.43	15.90	18.20	44.63	3.29	15.75	18.02
9a	187-189 dec (acetonitrile)	54	3	$C_{12}H_{13}N_5O_5S$	42.47	3.86	20.64	9.45	42.54	3.84	20.84	9.60
9b	198 dec (acetonitrile)	71	3	$C_{13}H_{15}N_5O_5S$	44.18	4.28	19.82	9.07	44.34	4.42	19.68	9.13
9c	226-228 dec (toluene)	79	9	$C_{12}H_{13}N_5O_5S$	42.47	3.86	20.64	9.45	42.62	3.85	20.52	9.15
9d	194 dec (toluene)	58	5	$C_{18}H_{17}N_5O_5S$	52.04	4.13	16.86	7.72	52.36	4.14	16.77	7.62
9f	216-217 dec (acetonitrile)	50	16.5	$C_{12}H_{12}N_4O_5S_2$	40.44	3.40	15.72	17.99	40.30	3.11	15.58	18.21
10a	259 dec (acetonitrile)	50	5	$C_{11}H_{11}N_5O_4S_2$	38.70	3.25	20.52	18.78	39.16	3.29	20.33	18.74
10c	211-213 dec (toluene)	59	9	$C_{11}H_{11}N_5O_4S_2$	38.70	3.25	20.52	18.78	39.14	3.15	20.43	18.51
10d	183 dec (toluene)	48	5	$C_{17}H_{15}N_5O_3S_2$	48.91	3.62	16.78	15.36	49.33	3.73	16.53	15.04
10f	211-212 dec (DMF)	31	5	$C_{11}H_{10}N_4O_4S_3$	36.86	2.81	15.63	26.84	37.03	2.69	15.64	26.58
11a	188-190 (toluene)	92	5	$C_{14}H_{14}N_4O_4S$	50.29	4.22	16.76	9.59	50.53	4.15	16.83	9.65
12a	242 (toluene)	35	8	$C_{12}H_{12}N_6O_4S$	42.85	3.60	24.99	9.53	42.94	3.78	24.78	9.82

Compound **4b**.

This compound was obtained in a yield of 81%; ir: 1715 (C=O), 1390 and 1195 cm^{-1} (SO_2).

Compound **4c**.

This compound was obtained in a yield of 92%, mp 79-81° (ether-hexane); ir: 1725 (C=O), 1372 and 1180 cm^{-1} (SO_2); nmr (carbon tetrachloride): 1.4 (t, J = 7, CH_3 ester), 4.05 (s, CH_3N), 4.35 (q, J = 7, CH_2O), 8.1 (s, CH pyraz).

Compound **4d**.

This compound was obtained in a yield of 95%; ir: 1720 (C=O), 1390 and 1180 cm^{-1} (SO_2).

Compound **4f**.

This compound was obtained in a yield of 57%; ir: 1735 (C=O), 1385 and 1185 cm^{-1} (SO_2); nmr (carbon tetrachloride): 1.4 (t, J = 7, CH_3 ester), 2.4-3.1 (m, CH_3 thiaz), 4.4 (q, J = 7, CH_2O).

Sulfonamides **13b, 13d, 13f**. General Procedure.

To a well stirred aqueous ammoniac solution (34%, 140 ml) was slowly added a solution of compound **4b, 4f** (0.125 mole) in tetrahydrofuran, the temperature being maintained in the range of 10 to 15°. Stirring was continued for 30 minutes at room temperature, then tetrahydrofuran was evaporated off at a temperature below 40°. Addition of ether to the remaining aqueous solution afforded a precipitate which was filtered to yield analytically pure **13**. The ethereal layer was separated, then stirred a few minutes with silica (5 g) and concentrated under reduced pressure to produce a further crop of pure **13**.

Compound **13d** was prepared by following the same procedure as above but the reaction mixture was extracted with ethyl acetate (2 × 50 ml). The combined extracts were washed with a saturated aqueous sodium chloride solution, dried on sodium sulfate and evaporated *in vacuo*. The residue thus obtained was triturated with cold diisopropyloxide to yield crude **13d**, mp 113-115°.

Compound **13b**.

This compound had mp 114-116°; ir: 3350 and 3280 (NH_2), 1685 (C=O), 1355 and 1175 cm^{-1} (SO_2); nmr (deuteriochloroform): 1.4 (t, J = CH_3 ester), 2.4 (s, CH_3C pyraz), 4.1 (s, CH_3N), 4.4 (q, J = 7, CH_2O), 6.4 (s, NH_2, deuterium oxide exch).

Anal. Calcd. for $C_6H_{13}N_3O_4S$: C, 38.86; H, 5.30; N, 16.99; S, 12.97. Found: C, 38.69; H, 5.20; N, 16.91; S, 12.93.

Compound **13d**.

This compound had mp 119-121° (diisopropyloxide); ir: 1700 (C=O), 1370 and 1160 cm^{-1} (SO_2); nmr (deuteriochloroform): (t, J = 7, CH_3 ester), 4.3 (q, J = 7, CH_2O), 5.75 (s, CH_2 benz), 6.3 (s, NH_2, deuterium oxide exch), 7.3 (near s, C_6H_5), 8 (s, CH pyraz).

Compound **13f**.

This compound had mp 131-133°; ir: 3350 and 3180 (NH_2), 1710 (C=O), 1335 and 1165 cm^{-1} (SO_2); nmr (deuteriochloroform): 1.4 (t, J = 7, CH_3 ester), 2.5 (s, CH_3 thiaz), 4.5 (q, J = 7, CH_2O), 6.2 (br, NH_2, deuterium oxide exch).

Anal. Calcd. for $C_7H_{10}N_2O_4S_2$: C, 33.59; H, 4.03; N, 11.19; S, 25.62; O, 25.57. Found: C, 33.58; H, 4.17; N, 11.23; S, 25.86; O, 25.55.

Compounds **5**. General Procedure.

To a stirred mixture of methyl glycine ester (12.5 g, 0.14 mole) and anhydrous potassium carbonate (9.7 g, 0.07 mole) in tetrahydrofuran (70 ml) the appropriate sulfonyl chloride **4** (0.07 mole) in tetrahydrofuran (70 ml), was gradually added, with cooling, so that the temperature did not exceed 5°. After stirring at room temperature for 3.5 hours, the reaction mixture was filtered and then evaporated to dryness. The residue was triturated with hexane to give a crystalline solid which was washed on the filter with cold ethanol followed by ether, then recrystallized from suitable solvent to yield pure **5**.

Compound **5a**.

This compound was obtained in a yield of 56%, mp 70-72° (methanol); ir: 3270 (NH), 1745 and 1725 (C=O), 1365 and 1165 cm^{-1} (SO_2); nmr (deuteriochloroform): 1.4 (t, J = 7, CH_3 Et carboxyl), 3.3-4.1 (m, CH_2N + CH_3O), 4.4 (q, J = 7, CH_2O), 7.2-7.7 (m, NH, deuterium oxide exch), 7.9 (s, CH pyraz).

Compound **5b**.

This compound was obtained in a yield of 83%, bp 180-183°/0.7 mm, mp 50-52°; ir: 3260 (NH), 1745 and 1710 (C=O), 1360 and 1175 cm^{-1} (SO_2); nmr (deuteriochloroform): 1.4 (t, J = 7, CH_3 Et carboxyl), 2.4 (s, CH_3C pyraz), 3.3-4.7 (m, CH_3N + CH_3O + CH_2N + CH_2O), 7.2-7.6 (m, NH, deuterium oxide exch).

Table III

Spectroscopic Data on 2-Methylthiazines **7-12**

Compound No.	Infrared Spectrum (cm^{-1}) ν NH/OH	ν CO max	νSO_2	NMR Spectrum (solvent)
7a	br, 3600-3300	br 1650-1670	1370-1180	3.1 (s, CH_3NSO_2), 3.9 (s, CH_3O), 4.2 (s, CH_3 pyraz), 7.8 (s, CH pyraz), 12.1 (s, OH, deuterium oxide exchangeable) (Deuteriochloroform)
7b	br, 3600-3300	1660	1360-1160	2.5 (s, CH_3C pyraz), 3.1 (s, CH_3NSO_2), 3.9 (s, CH_3O), 4.1 (s, CH_3N pyraz), 12.2 (s, OH, deuterium oxide exchangeable) (Deuteriochloroform)
7c	br, 3600-3300	1665	1350-1170	3 (s, CH_3NSO_2), 3.9 (s, CH_3O), 4.1 (s, CH_3N pyraz), 7.85 (s, CH pyraz), 11.9 (s, OH, deuterium oxide exchangeable) (Deuteriochloroform)
7d	br, 3600-3200	1665	1350-1170	3.1 (s, CH_3NSO_2), 4 (s, CH_3O), 5.6 (s, CH_2 benz), 7-7.7 (m, C_6H_5), 7.9 (s, CH pyraz), 11.9 (s, OH, deuterium oxide exchangeable) (Deuteriochloroform)
7e	3600-3240	1600	1350-1160	2.9 (s, CH_3NSO_2), 3.9 (s, CH_3O), 8.6 (s, CH pyraz) 12-14.6 (br, NH + OH, deuterium oxide exchangeable) (DMSO-d_6)
7f	br, 3600-3200	1670	1350-1180	2.9 (s, CH_3 thiaz), 3.1 (s, CH_3NSO_2), 4 (s, CH_3O), 12 (s, OH, deuterium oxide exchangeable) (DMSO-d_6)
8a	br, 3400-3330	1625	1150	2.95 (s, (CH_3NSO_2), 4.1 (s, CH_3N pyraz), 6.8-8.7 (m, pyrid + CH pyraz), 9.7-13 (br NH + OH, deuterium oxide exchangeable) (DMSO-d_6)
8b	3340	1630	1360-1150	2.6 (s, CH_3C pyraz), 3 (s, CH_3NSO_2), 4.1 (s, CH_3N pyraz), 7-8.5 (m, 4H pyrid), 8.7 (s, NH, deuterium oxide exchangeable), 13.4 (s, OH, deuterium oxide exchangeable) (Deuteriochloroform)
8c	3390	1640	1340	2.9 (s, CH_3NSO_2), 4.1 (s, CH_3N pyraz), 7-8.7 (m, pyrid + CH pyraz + NH, deuterium oxide exchangeable), OH was masked (DMSO-d_6)
8d	3340	1630	1360-1170	3 (s, CH_3NSO_2), 5.6 (s, CH_2 benz), 6.9-8.5 (m, pyrid + CH pyraz), 9 (s, NH, deuterium oxide exchangeable), 13.6 (s, OH, deuterium oxide exchangeable) (Deuteriochloroform)
8e	br, 3600-3300	1640	1350-1180	2.8 (s, CH_3NSO_2), 6.8-8.7 (m, pyrid + CH pyraz), 9-9.8 (m, NH, deuterium oxide exchangeable), 12.2-13 (br, OH, deuterium oxide exchangeable) (DMSO-d_6)
8f	br, 3600-3300	1640	1350-1170	2.8 (s, CH_3 thiaz), 2.9 (s, CH_3NSO_2), 5.8-7 (br, NH, deuterium oxide exchangeable), 7-8.6 (m, pyrid), 11.2 (s, OH, deuterium oxide exchangeable) (DMSO-d_6)
9a	3345	1630	1360-1180	2.4 (s, CH_3 isox), 3 (s, CH_3NSO_2), 4.1 (s, CH_3N pyraz), 6.7 (s, CH, isox), 8.1 (s, CH pyraz), 7.5-9 (br, NH, deuterium oxide exchangeable), 11.2 (s, OH, deuterium oxide exchangeable) (DMSO-d_6)
9b	br, 3600-3200	1620	1370-1160	2.5 (near s, CH_3 isox + CH_3C pyraz), 3.1 (s, CH_3NSO_2), 4.1 (s, CH_3N pyraz), 6.8 (s, CH isoxaz), 9.7 (s, NH, deuterium oxide exchangeable), 13.4 (s, OH, deuterium oxide exchangeable) (Deuteriochloroform)
9c	3200	1620	1350-1170	2.5 (s, CH_3 isoxaz), 2.9 (s, CH_3NSO_2), 4.1 (s, CH_3 pyraz), 6.7 (s, CH isoxaz), 8.5 (s, CH pyraz), 11.1 (s, NH or OH, deuterium oxide exchangeable 1H masked) (DMSO-d_6)
9d	3200	1620	1370-1175	2.4 (s, CH_3 isoxaz), 3 (s, CH_3NSO_2), 5.6 (s, CH_2 benz), 6.7 (s, CH isoxaz), 7.3 (s, C_6H_5), 8.2 (s, CH pyraz), 7-8.6 (br, NH, deuterium oxide exchangeable), 11.3 (s, OH, deuterium oxide exchangeable) (DMSO-d_6)
9f	3180	1620	1360-1180	2.5 (s, CH_3 isoxaz), 2.9 (s, CH_3 thiaz), 3 (s, CH_3NSO_2), 6.7 (s, CH isoxaz), 6.8-8 (m, NH, deuterium oxide exchangeable), 11.4 (s, OH, deuterium oxide exchangeable) (DMSO-d_6)
10a	br, 3310	1640	1360-1170	3 (s, CH_3NSO_2), 4.1 (s, CH_3N pyraz), 6.8-7.7 (m, CH thiaz), 7.9 (s, CH pyraz), 9.5-12.7 (br, NH + OH, deuterium oxide exchangeable) (DMSO-d_6)
10c	br, 3600-3300	1620	1350-1180	[a]
10d	3310	1630	1360	[a]
10e	br, 3600-3300	1620	1345-1180	[a]
11a	3360	1620	1360-1180	3.1 (s, CH_3NSO_2), 4.1 (s, CH_3N pyraz), 7-8 (m, C_6H_5), 8.1 (s, CH pyraz), 10.2 (s, NH, deuterium oxide exchangeable), 13-15 (br, OH, deuterium oxide exchangeable) (DMSO-d_6)
12a	br, 3600-3300	1635	1350-1180	3 (s, CH_3NSO_2), 4.2 (s, CH_3N pyraz), 7-7.4 (m, CH pyrim), 7.9 (s, CH pyraz), 8.6-8.8 (m, CH pyrim), 8.9 (s, NH, deuteriochloroform or DMSO-d_6), 13.3 (s, OH, deuterium oxide exchangeable).

Compound **5c**.

This compound was obtained in a yield of 75%, mp 100-102° (ethanol); ir: 3290 (NH), 1750 and 1715 (C=O), 1360 and 1180 cm^{-1} (SO_2); nmr (deuteriochloroform): 1.4 (t, J = 7, CH_3 Et carboxyl), 3.7 (s, CH_3O), 3.8-4.1 (m, CH_2N + CH_3N), 4.4 (q, J = 7, CH_2O), 6.7 (m, NH, deuterium oxide exch), 8 (s CH pyraz).

Compound **5d**.

This compound was obtained in a yield of 54%, mp 88-90° (ethanol); ir: 3230 (NH), 1745 and 1710 (C=O), 1355 and 1160 cm^{-1} (SO_2); nmr (carbon tetrachloride): 1.4 (t, J = 7, CH_3 Et carboxyl), 3.3-3.8 (m, CH_3O + CH_2N), 4.4 (q, J = 7, CH_2O), 5.8 (s, CH_2 benz), 7.3 (near s, C_6H_5 + NH), 8 (s, CH pyraz).

Anal. Calcd. for $C_{16}H_{19}N_3O_6S$: C, 50.38; H, 5.02; N, 11.02; S, 8.41; Found: C, 50.36; H, 5.04; N, 11.14; S, 8.50.

Compound **5f**.

This compound was obtained in a yield of 31%, mp 84-86° (diisopropyloxide); ir: 3260 (NH), 1740 and 1715 (C=O), 1360 and 1170 cm^{-1} (SO_2); nmr (carbon tetrachloride): 1.5 (t, J = 7, CH_3 Et carboxyl), 2.75 (s, CH_3 thiaz), 3.6 (s, CH_3O), 4 (d, J = 5, CH_2N), 4.5 (q, J = 7, CH_2O), 6.8 (t, NH, deuterium oxide exch).

Compounds **6**. Typical Procedure.

To a well stirred suspension of sodium methylate (22.7 g, 0.42 mole) in dimethylsulfoxide (80 ml) preheated at 30°, a solution of diester **5** (0.105 mole) in dimethylsulfoxide (80 ml) was added dropwise, keeping the temperature at 30-35° and stirring was continued for 10 minutes. The reaction mixture was then poured into cold water. The resulting solution was acidified by adding 3 *N* hydrochloric acid until precipitation was complete. The solid thus obtained was filtered off and washed with water and hexane to afford crude **6**.

Compound **6a**.

This compound was obtained in a yield of 60%, mp 166-168° (ethanol); ir: 3250-3220 (NH), 1675 (C=O), 1340 and 1180 cm^{-1} (SO_2); nmr (DMSO-d_6): 3.8 (s, CH_3O), 4.1 (s, CH_3N), 8 (s, CH pyraz), 9.4-11.8 (br, NH, deuterium oxide exch), 12.3 (s, OH, deuterium oxide exch).

Compound **6b**.

This compound was obtained in a yield of 71%, mp 126-128°; ir: 3210 (NH), 1670 (C=O), 1300-1380 broad and 1160 cm^{-1} (SO_2).

Compound **6c**.

This compound was obtained in a yield of 69%, mp 204-206° dec; ir: 3400-3000 broad (NH), 1670 (C=O), 1360 and 1190 cm^{-1} (SO_2).

Compound **6d**.

This compound was obtained in a yield of 60%, mp 197-199° (ethanol); ir: 3210 (NH), 1650 (C=O), 1350 and 1180 cm^{-1} (SO_2); nmr (DMSO-d_6): 3.7 (s, CH_3O), 5.4 (s, CH_2 benz), 7.2 (near s, C_6H_5), 8 (s, CH pyraz), 8.7-11.7 (br, NH, deuterium oxide exch), 12.2 (s, OH, deuterium oxide exch).

Anal. Calcd. for $C_{14}H_{13}N_3O_5S$: C, 50.14; H, 3.91; N, 12.53; S, 9.56. Found: C, 50.25; H, 4.02; N, 12.56; S, 9.47.

Compound **6f**.

This compound was obtained in a yield of 64%, mp 187-189° (toluene); ir; 3220 (NH), 1660 (C=O), 1360 and 1180 cm^{-1} (SO_2); nmr (deuteriochloroform): 2.8 (s, CH_3C thiaz), 3.9 (s, CH_3O), 6.6-7.2 (br, NH, deuterium oxide exch), 11.1 (s, OH, deuterium oxide exch).

Anal. Calcd. for $C_8H_8N_2O_5S_2$: C, 34.77; H, 2.92; N, 10.14; S, 23.21. Found: C, 35.07; H, 3.01; N, 10.06; S, 23.29.

Compounds **7a-d, 7f**. General Procedure.

To a solution of compound **6a-b, 6f** (0.02 mole) in ethanol (125 ml), sodium bicarbonate (1.85 g, 0.02 mole and 10%) in water (22 ml) was added, followed by methyl iodide (4.3 ml). The mixture was stirred for 48 hours at room temperature and then ethanol was evaporated off at a temperature below 35°. The resultant precipitate was successively washed with water and hexane, then dried to yield the corresponding methyl-2 thiazine **7** as a nearly pure product.

Compounds **7c-d** were prepared by following the same procedure as above but using dimethylformamide as the solvent instead of aqueous ethanol. The reaction was worked up by adding water until the precipitation was complete.

Compound **7e**.

Compound **7d** (7 g, 0.02 mole) was dissolved in a 1:1 mixture of methanol-chloroform (370 ml) in the presence of 10% palladium on carbon (14 g) and agitated at 40-45° in a hydrogen atmosphere. Additional 5 g of catalyst was added every three hours during the course of the reaction.

After 12 hours hydrogen uptake was complete. The catalyst was removed by filtration and washed on the filter with a 1:1 mixture of methanol-chloroform (3 × 150 ml). The filtrate was evaporated to dryness and the residue was triturated with hexane to yield crystalline **7e**.

Compounds **8-12**. Typical Procedure.

A mixture of methyl ester **7** (0.015 mole) and the appropriate amine **14** (0.0375 mole) in xylene (300 ml) was heated under reflux for the time given in Table II. The solvent was then removed under reduced pressure, and the residue triturated with a mixture of water-acetic acid, then washed with water followed by hexane and recrystallized from the suitable solvent to give pure compound **8-12**.

REFERENCES AND NOTES

[1] "Drugs of the Future", Vol 2, 1977, p 125 and references cited therein.

[2] Generic name.

[3] See for example: [a] A. P. Mitchell and A. Rosen, *J. Pharm. Pharmacol.*, **30**, (suppl. Brit. Pharm. Conf. 1978); [b] *Drugs of the Future*, **5**, 337 (1980); [c] *Ibid.*, **6**, 369 (1981) [d] *Ibid.*, **7**, 110 (1982).

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[5] H. Zinnes, J. C. Sircar, N. Lindo, M. L. Schwartz, A. C. Fabian, J. Shavel, Ch. F. Kasulanis, J. D. Genzer, Ch. Lutomski and G. Di Pasquale, *ibid.*, **25**, 12 (1982).

[6a] H. Dorn, G. Hilgetag and A. Zubek, *Chem. Ber.*, **98**, 3357 (1965); [b] Hori Isaburo and Igarashi Minoru, *Bull Chem. Soc. Japan*, **44**, 2856 (1971); [c] British Patent 884,851 (1961) to CIBA; *Chem. Abstr.*, **61**, 3116e (1964); [d] H. Dorn and A. Zubek, *Chem. Ber.*, **101**, 3265 (1968); [e] M. Takehiko and T. Takamitsu, Japanese Patent 7,103,972 (1971); *Chem. Abstr.*, **74**, 141756r (1971).

[7] Except for **4c** which was obtained as a semi-solid, then triturated with hexane to afford a crystalline product (mp 76-79°).