Tricyclic Thiazolo[3,2-*a*]thiapyrano[4,3-*d*]pyrimidines and Related Analogs as Potential Anti-inflammatory Agents

George Rovnyak, Virginia Shu and Joseph Schwartz*

The Squibb Institute for Medical Research, P. O. Box 4000, Princeton, New Jersey 08540

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A series of novel tricyclic thiazolo[3,2-*a*]thiapyrano[4,3-*d*]pyrimidines and related oxa, aza and carbo analogs of general formula **1** were prepared by a convenient addition-cyclization reaction involving 2-amino-2-thiazoline (**4**) and bisarylidene ketones of formula **3**. Some of these compounds demonstrated anti-inflammatory activity.

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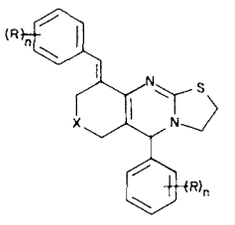
We wish to communicate the preparation of novel tricyclic thiazolo[3,2-*a*]thiapyrano[4,3-*d*]pyrimidines and related oxa, aza and carbo analogs of general formula **1** (1). Our work parallels, to some degree, the preparation of a similar tricyclic system reported recently by Hamman (2).



1

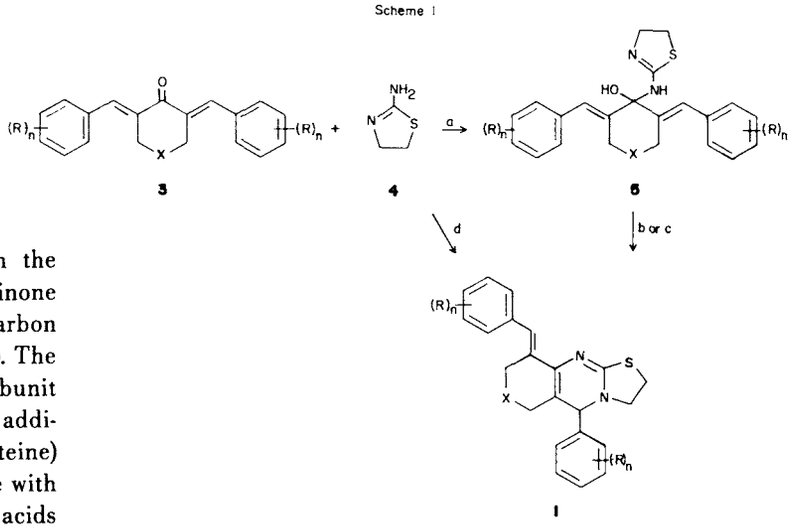
X = S, SO_2, O, NR', CH_2
R = H, alkyl, alkoxy
R' = Alkyl, acyl
n = 1–3

Our interest in these heterocycles derives from the diverse biological activities reported for quinazolinone derivatives (3) and for molecules containing an sp^2 carbon atom bonded to three (or two) heteroatoms as in **2** (4). The central carbon atom of molecules containing a subunit such as **2** would be expected to undergo electrophilic addition (5) by nucleophiles such as sulfhydryl (as in cysteine) and hydroxyl (as in serine) and, as a result, interfere with normal enzymatic reactions involving these amino acids (*e.g.*, serine proteases). This concept is central to our rationale for expecting molecules containing a subunit such as **2** to be biologically active.

2

The preparation of compounds of formula **1** (Table II) was achieved by reaction of the bis-benzylidene ketones **3** (6,8) (several novel bis-benzylidene ketones **3** are reported in Table III) with 2-amino-2-thiazoline (**4**). In some cases the initial addition product, aminol **5**, was isolated and characterized (Table I). Cyclo-dehydration of intermediate **5** could be accomplished simply by raising the temperature of the reaction. Complete reaction in refluxing acetone or chloroform solution generally required one to three days, while reaction was essentially complete in one hour in refluxing 1-butanol/DMSO (3:1) solution. Cyclodehydration of preformed aminol **5** in toluene at room temperature by the addition of titanium tetrachloride appeared to be rapid, also, although the mixture was heated at reflux temperature for one hour to insure complete reaction. Scheme I illustrates these reactions.

Scheme I



Scheme I

(a) Acetone at reflux temperature for 24 hours. (b) Chloroform at reflux temperature for 24-72 hours. (c) Titanium tetrachloride in toluene at room temperature, then at reflux for 1-2 hours. (d) 1-Butanol/DMSO at reflux temperature for 1 hour (lower boiling solvents require longer times).

Chemical shift assignments in the nuclear magnetic resonance spectra of **11-24** support the tricyclic structure **1**. Selected chemical shift assignments for compounds **11-24** are reported in Table IV. The methylene between X and the carbon bearing the exocyclic benzylidene group

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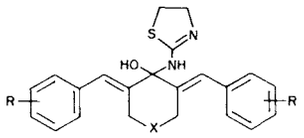
Table I

Intermediate Aminols



Compound No.	X	R	Yield (%) (1)	m.p. (°C)	Formula	Calcd. / Found C	H	N	S	m/e
6	S	H	92	171-172.5	$C_{22}H_{22}N_2OS_2$	67.17 67.01	5.64 5.59	7.12 7.05	16.25 16.38	394
7	SO_2	H	76	176-177	$C_{22}H_{22}N_2O_3S_2$	61.94 62.01	5.20 5.34	6.57 6.75	15.04 15.24	
8	S	4-CH_3	76	189-191	$C_{24}H_{26}N_2OS_2$	68.21 68.34	6.20 6.14	6.63 6.52	15.17 15.41	422
9	SO_2	4-OCH_3	97	194-196	$C_{24}H_{26}N_2O_3S_2$	59.23 58.99	5.38 5.17	5.75 5.60	13.17 13.45	
10	O	H	57(2)	—						

(1) Reaction conditions: **6**, acetone at reflux temperature for 24 hours; **7**, chloroform at reflux temperature until homogeneous solution, then at room temperature for 24 hours; **8**, acetone at reflux temperature for 32 hours; **9**, methyl ethyl ketone at reflux temperature for 1 hour; **10**, acetone at reflux temperature for 5 hours, then acetone/chloroform (6/4) trituration. (2) Not obtained analytically pure or characterized.

(structure **1**) has been assigned to lower field than the opposite methylene based 1) on analogy to related bicyclic systems (6) and 2) on the observance of allylic coupling (J = 1.5 Hz) to the benzylidene =CH in two compounds (**17** and **18**). The methine proton of the center ring appears as a distinctive singlet between δ 4.8-5.3.

The compounds prepared and reported here were variously tested for hypotensive, anti-anflammatory, anti-allergic, antibiotic and/or anti-helminthic activity. Several of these compounds demonstrated anti-inflammatory activity when administered by the intraperitoneal route; however, this activity was not sufficiently maintained after oral administration to justify further interest, a result most likely reflective of poor absorption from the gastro-intestinal tract.

EXPERIMENTAL

Melting points were taken on a Thomas Hoover capillary melting point apparatus and are uncorrected. Proton nmr spectra were obtained on a Perkin Elmer PE R12B spectrometer operating at 60 mHz and on a Varian T-60 spectrometer, using tetramethylsilane as an internal standard; chemical shifts are reported on the δ scale. Infrared spectra were obtained on a Perkin Elmer Model 621 or Infracord spectrometer. New compounds gave elemental analyses that were within 0.3% of the calculated values.

General Procedure for the Preparation of Compounds **6-10** (Table I).

A slurry of the appropriate bis-benzylidene ketone **3** and 1.1 to 1.5 equivalents of 2-amino-2-thiazoline (**4**) in the reaction solvent was heated until tlc analysis (silica gel) showed the absence of starting ketone. The reaction mixture was cooled and the product was collected by filtration.

Attempts to recrystallize these materials gave either partial reversal to starting material and/or cyclodehydration to the tricyclic systems **1**.

These conditions often led to significant cyclodehydration product **1** under conditions which were expected to yield the intermediate aminol as the major product (see, for example, **22** and **24**).

General Procedure for the Preparation of Compounds **11-24** (Table III).

Method A (from Aminol, Titanium Tetrachloride).

A slurry of 5 mmoles aminol (Table I) in 20 ml. of dry toluene under nitrogen at room temperature was treated with 12 ml. of 0.25*M* (3 mmoles) of titanium tetrachloride in toluene. The resulting suspension was heated at reflux temperature for one hour. Upon cooling, the solids were collected and partitioned between chloroform and dilute aqueous sodium hydroxide. The organic portion was washed with water, dried over anhydrous calcium chloride and concentrated on a steam bath. Methanol was added periodically to maintain volume until crystallization commenced. Upon cooling, the product was collected.

Method B (from Aminol, Thermally; Compound **16**).

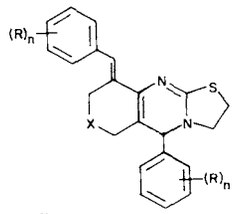
A suspension of 6.0 g. (12 mmoles) of aminol **9** in 75 ml. of 1-butanol and 25 ml. of dimethylsulfoxide was heated at reflux temperature for one hour. Concentration to one-half the volume and cooling afforded 4.7 g. of crude product: m.p. 235-240°. Crystallization from 25 ml. of dimethyl formamide gave 4.0 g. of product, m.p. 243-245°.

Method C (from Bis-benzylidene Ketone in Chloroform).

A mixture of 14 mmoles of bis-benzylidene ketone **3** and 21 mmoles of 2-amino-2-thiazoline (**4**) in 200 ml. of chloroform was heated at reflux temperature for 48-72 hours. The mixture was filtered and concentrated *in vacuo* and the residue was triturated with ethanol to give the crude product which was purified by recrystallization.

Method D (from Bis-benzylidene Ketone in 1-Butanol/Dimethylsulfoxide; Compound **15**).

Table II



Compound No.	X	R	Method	Yield (a)	Recrystallization Solvent	M.p.	Formula	Calcd. / Found C	H	N	S	m/e
11	S	H	A	73	chloroform/methanol	195-196 dec.	$C_{22}H_{20}N_2S_2$	70.17 69.98	5.35 5.41	7.44 7.55	17.03 17.09	376
12	S	4-OCH_3	C	51	chloroform/acetone	195-197	$C_{24}H_{24}N_2O_2S_2$	66.02 66.03	5.54 5.43	6.42 6.49	14.69 14.61	
13	S	4-CH_3	A	38	methanol	173-175 dec.	$C_{24}H_{24}N_2S_2$	71.25 71.08	5.98 5.74	6.92 6.95	15.85 15.68	
14	SO_2	H	A	67	chloroform/methanol	230 dec.	$C_{22}H_{20}N_2O_2S_2$	64.68 64.71	4.93 5.01	6.86 6.94	15.70 15.68	
15	SO_2	2-OCH_3	D	53	(b)	80-84 dec.	$C_{24}H_{24}N_2O_4S_2$	61.51 61.74	5.16 4.93	5.97 5.70	13.68 13.42	
16	SO_2	4-OCH_3	B	57	DMF	243-245	$C_{24}H_{24}N_2O_4S_2$	61.51 61.32	5.16 4.84	5.97 6.04	13.68 13.78	
17	O	H	A	23	chloroform/methanol	225-227 dec.	$C_{22}H_{20}N_2OS$	73.30 73.12	5.39 5.43	7.77 7.88	8.90 8.89	
18	O	4-OCH_3	C (c)	33	chloroform/methanol	167-170	$C_{24}H_{24}N_2O_3S$	68.55 68.41	5.75 5.55	6.66 6.68	7.62 7.80	420
19	O	3,4,5-$(OCH_3)_3$	C	42	acetonitrile	153-155	$C_{28}H_{32}N_2O_7S$	62.20 61.97	5.96 5.76	5.18 5.02	5.93 5.97	
20	O	4-OCH_3, 2,3-$(CH_3)_2$	C	63	DMF	235-237	$C_{28}H_{32}N_2O_3S$	70.55 70.44	6.76 6.49	5.87 5.83	6.72 6.82	
21	O	4-OCH_3, 2,5-$(CH_3)_2$	C	35	DMF/methanol	196-198	$C_{28}H_{32}N_2O_3S$	70.55 70.48	6.76 6.80	5.87 5.80	6.72 6.74	
22	NCH_3	H	C (d)	10	(e)	189-194	$C_{23}H_{23}N_3S$	73.96 73.68	6.21 6.42	11.25 11.01	8.59 8.55	
23	NAc	4-OCH_3	C (f)	78	chloroform/methanol	204-208	$C_{26}H_{27}N_3O_3S$	67.65 67.43	5.90 6.16	9.10 9.09	6.95 6.97	
24	CH_2	H	C (g)	23	chloroform/methanol	189-194	$C_{23}H_{22}N_2S$	77.06 76.84	6.19 6.13	7.81 7.82	8.94 9.23	

(a) Calculated from bis-benzylidene ketone **3**. (b) Elution with methylene chloride/toluene from silica gel column; not recrystallized. (c) 3A molecular sieves added to the reaction solution. (d) Reaction run in acetone, yielding a mixture of **22** and the corresponding intermediate aminol. Completed reaction following method A. (e) Elution with 50-100% ethyl acetate in hexane from silica gel column; trituration with hexane. (f) Reaction run in methyl ethyl ketone. (g) Reaction run in acetone/hexane (1/1), yielding a mixture of **24** and the corresponding intermediate aminol. Completed reaction following method A.

A mixture of 8.0 g. (20 mmoles) of bis-benzylidene ketone **3e** and 2.9 g. (23 mmoles) of 2-amino-2-thiazoline (**4**) in 100 ml. of 1-butanol and 40 ml. of dimethyl sulfoxide was stirred and heated at reflux temperature for one hour. The solvent was evaporated *in vacuo* and the residue was triturated with ethanol, then with ether to give 6.7 g. of crude product, m.p. 70-74° dec. Final purification by chromatography on silica gel and elution with methylene chloride/toluene (3/1) gave 5.0 g. of product, m.p. 80-84° dec. This material could not be recrystallized.

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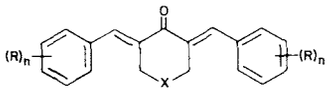
Table III

Bis-benzylidene Ketones



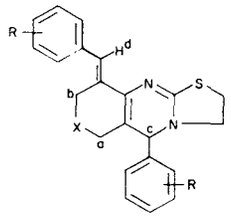
3

Compound No.	X	R	Yield (%)	m.p. (°C)	Formula or Reference	Calcd. / found C	H	N	S
3a	S	H	93	149-151	6a				
3b	S	4-CH_3	75	197.5-200.5	6b				
3c	S	4-OCH_3	66	182.5-184.5	6b				
3d	SO_2	H	82	198-200	6a				
3e	SO_2	2-OCH_3	58 (b)	198-200	$C_{21}H_{20}O_5S$	65.60	5.24		8.33
						65.33	5.32		8.34
3f	SO_2	4-OCH_3	60	188-190	8				
3g	O	H	52	185-187	8				
3h	O	4-OCH_3	55	175-177	8				
3i	O	3,4,5-$(OCH_3)_3$	44 (a)	187-189	$C_{25}H_{28}O_8$	65.77	6.18		
						65.71	6.28		
3j	O	4-OCH_3, 2,3-$(CH_3)_2$	39 (a)	225-227	$C_{25}H_{28}O_4$	76.50	7.19		
						76.45	7.30		
3k	O	4-OCH_3, 2,5-$(CH_3)_2$	39 (a)	182-184	$C_{25}H_{28}O_4$	76.50	7.19		
						76.34	7.06		
3l	NCH_3·HCl	H	73	242-244	10				
3m	NH·HCl	4-OCH_3	85 (a)	267 dec.	$C_{21}H_{21}ClNO_3$	68.01	5.70	3.77	
						67.85	5.96	3.78	
3n	NAc	4-OCH_3	74 (c)	197.5-200	$C_{23}H_{23}NO_4$	73.19	6.14	3.71	
						72.99	6.18	3.59	
3o	CH_2	H	79 (a)	117-118	11				

(a) Concentrated hydrochloric acid in ethanol. (b) Acetic acid/piperidine (2:1) in ethanol. (c) Prepared from **3n** with acetic anhydride in acetic acid; crystallized from acetic acid/water.

Table IV

Selected Chemical Shift Assignments for Compounds **11-24**



Compound No.	Solvent	- ^{1}H Hmr (δ) - a	b	c	d	Ir (Potassium Bromide, Cm^{-1})
11	deuteriochloroform	2.92 br	3.57 br	4.88	7.60	1610 (sh), 1572, 695
12	deuteriochloroform	2.90 br	3.58 br	4.82	7.53	1590, 1575, 1245, 1024
13	deuteriochloroform	2.92 br	3.58 br	4.88	7.57	1572
14	deuteriochloroform	3.35 br	3.85, 4.22 ABq, J = 15 Hz	4.90	7.97	1570 (sh), 1550, 1290, 1094
15	DMSO	buried	4.05 br	5.45	7.62	1590, 1568, 1310, 1240, 1110, 1018
16	DMSO	buried	4.17 br	5.02	7.65	1590, 1562, 1310, 1300, 1250, 1234, 1108, 1018
17	deuteriochloroform	3.72, 4.05 ABq, J = 15 Hz	4.45, 4.74 ABq, J = 14, 1.5 Hz	4.97	buried	1622, 1610, 1570
18	deuteriochloroform	buried	4.46, 4.76 ABq, J = 14, 1.5 Hz	4.91	buried	1598, 1565, 1240, 1168, 1090, 1025, 520
19	DMSO	buried	4.61 br	5.13 br	7.18	1605, 1564, 1226, 1110, 995
20	deuteriochloroform	buried	4.23, 4.51 ABq, J = 14 Hz	5.36 br	7.40	1626, 1570, 1255, 1100
21	DMSO	buried	4.32 br	5.32	buried	1605, 1566, 1240, 1088
22	deuteriochloroform	buried	2.55, 2.92 Abq, J = 16 Hz	4.95	buried	1604, 1565, 690
23	deuteriochloroform	buried	buried	4.94	buried	1637, 1600, 1565, 1242, 1023
24	deuteriochloroform	buried	buried	4.86	7.47	1570, 695

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