Chemistry of Seven-Membered Heterocycles. II. Synthesis and Reactions of 6,7-Dihydro-8-aryl-8H-[1]benzothiepino-[5,4-d]thiazolo[3,2-a]pyrimidino-10(11H)-one 5,5-dioxides

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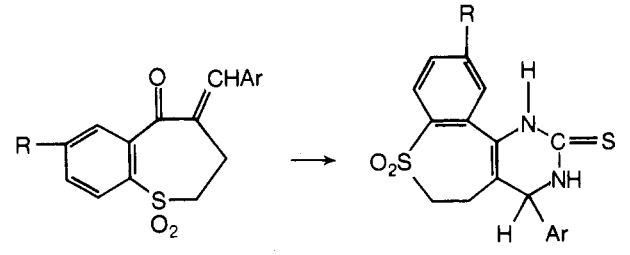
1-Benzothiepino[5,4-d]pyrimidine-10-thione 5,5-dioxides (II) were prepared by fusion of 4-arylmethylene-3,4-dihydro[1]benzothiepin-5(2H)-one 1,1-dioxides with thiourea. Compounds II reacted with chloroacetic acid to yield the title compounds III. The 11-arylmethylene and 11-arylhydrazono derivatives of III were prepared.

There appears to be an increasing interest in fused thiazolones, for example: 2,3-dihydroimidazo[2,1-b]thiazol-3-ones (*14*),* 2,3-dihydrobenzimidazo[2,1-b]thiazolone (*3, 11, 13*), 5,6,7,8-tetrahydro-2H-thiazolo[3,2-a][1,3]diazepin-3-one (*4*), 2,3,5,10-tetrahydrothiazolo[3,2-b][2,4]benzodiazepin-3-one (*7*), 2,3,5,6-tetrahydrothiazolo[2,3-b][1,3]benzodiazepin-3-one (*8*), and 2,3-dihydrothiazolo[3,2-a]perimidin-3-one (*5*).

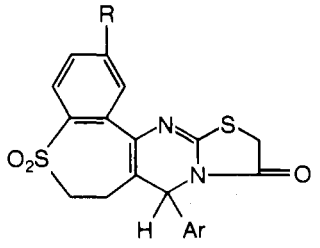
To prepare a benzothiepin system which contains a fused thiazolone ring, 4-arylmethylene-3,4-dihydro-1-benzothiepin-5(2H)-one 1,1-dioxides (*1*) were reacted with thiourea to provide the —N—C(=S)—N moiety necessary for annealing the thiozolone ring.

Thiourea reacts with α,β-unsaturated ketones to give 2-thiopyrimidine derivatives (*9, 10, 12, 15–17*). Thus, when 4-arylmethylene-3,4-dihydro-1-benzothiepin-5(2H)-one 1,1-dioxides (I) were fused with thiourea at about 200°, they formed 1-benzothiepino[5,4-d]pyrimidine-10-thione 5,5-dioxides (II).



Ia. R = H; Ar = C_6H_5
b. R = H; Ar = $C_6H_4OCH_3$
c. R = CH_3; Ar = C_6H_5

IIa. R = H; Ar = C_6H_5
b. R = H; Ar = $C_6H_4OCH_3$
c. R = CH_3; Ar = C_6H_5



IIIa. R = H; Ar = C_6H_5
b. R = H; Ar = $C_6H_4OCH_3$
c. R = CH_3; Ar = C_6H_5

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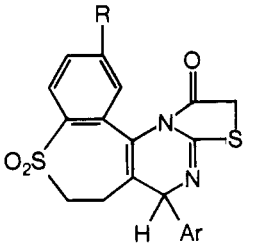
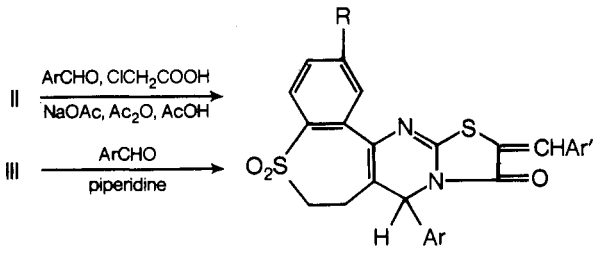
When II were treated with chloroacetic acid and fused sodium acetate in refluxing acetic acid, 6,7-dihydro-8-aryl-8H-[1]benzothiepino[5,4-d]thiazolo[3,2-a]pyrimidin-10(11H)-one 5,5-dioxides (III) were obtained. The ir spectra of IIIa,c show CO absorption at about 1730 cm^{-1}.

The formulation of the cyclized product as III is tentatively favored over the isomeric structure III' An analogous choice has been made in the case of 2,3,5,6-tetrahydrothiazolo[2,3-b][1,3]benzodiazepin-3-one (*8*).



III'

Compounds III contain an active methylene group. They condensed with aromatic aldehydes in the presence of piperidine to yield 11-arylmethylene-6,7,10,11-tetrahydro-8-aryl-8H-[1]benzothiepino[5,4-d]thiazolo[3,2-a]pyrimidin-10-one 5,5-dioxides IV.

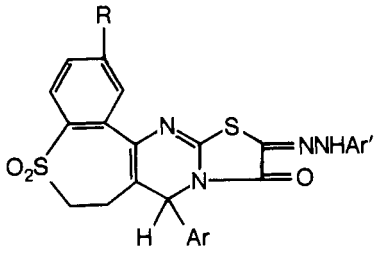


IV

However, the arylmethylene derivatives IV were prepared directly from II by the action of chloroacetic acid, the aromatic aldehyde, and sodium acetate in the presence of acetic acid and acetic anhydride.

The ir spectra of IVa,i show CO absorption at 1700 cm^{-1}. This shift to lower frequency is due to conjugation with the exocyclic double bond (*2*). The uv spectrum of IVa shows two maxima at 315 nm (ϵ 11,700) and 367 nm (ϵ 16,900).

Compounds III coupled with aryldiazonium salts in pyridine to give 6,7,10,11-tetrahydro-8-aryl-8H-[1]benzothiepino[5,4-d]thiazolo[3,2-a]pyrimidine-10,11-dione 5,5-dioxide 11-arylhydrazones (V).



V

The ir spectrum of Va shows CO absorption at 1710 cm^{-1}. The uv spectra of Vc,d show a maximum band at about 400 nm. Monophenylhydrazones exhibit a strong absorption band at a wavelength higher than 320 nm (*6, 18*). These spectral data support the arylhydrazone structure assigned to the coupling products V.

Experimental

1-Benzothiepino 5,4-d pyrimidine-2-thione S,S-dioxides (II): general procedure. A mixture of 5 grams of 4-arylmethylene-3,4-dihydro-1-benzothiepin-5(2H)-ones (Ia,b,c), and 1.5 grams of thiourea was heated in a metal bath at 170° (bath temperature), whereat the mixture melted. The viscous mass was stirred with a glass rod, and the temperature of the bath was allowed to rise to 195° whereat it solidified. The temperature was raised to 210°, and heating was continued for 15 min. The product was collected and crystallized from ethanol.

Compound IIa was obtained as white crystals, mp 260°C; yield 96%.

Anal. Calcd $C_{18}H_{16}N_2O_2S_2$ (356.4) requires: C, 60.64; H, 4.52; N, 7.86; S, 17.99%. Found: C, 60.70; H, 4.60; N, 7.90; S, 18.10%.

Compound IIb was obtained as very pale yellow crystals, mp 250°; yield 98%.

Anal. Calcd $C_{19}H_{18}N_2O_3S_2$ (386.5) requires: C, 59.03; H, 4.69; N, 7.25; S, 16.59%. Found: C, 59.10; H, 4.80; N, 7.10; S, 16.60%.

Compound IIc was obtained as white crystals, mp 280°; yield 98%.

Anal. Calcd $C_{19}H_{18}N_2O_2S_2$ (370.5) requires: C, 61.60; H, 4.89; S, 17.31%. Found: C, 61.57; H, 4.95; S, 17.40%.

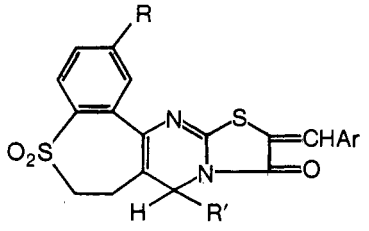
6,7-Dihydro-8-aryl-8H-[1]benzothiepino[5,4-d]thiazolo-[3,2-a]pyrimidin-10(11H)-one S,S-dioxides (III): general procedure. A mixture of 9 grams of each of IIa,b,c, 5 grams of monochloroacetic acid, and 10 grams of fused sodium acetate in 100 ml glacial acetic acid was refluxed for 4 hr, allowed to cool, and then poured into water. The solid formed was collected, washed with water, and crystallized. The products were insoluble in sodium carbonate or sodium hydroxide solution.

Compound IIIa was crystallized from ethanol as very pale brown crystals, mp 250°; yield 90%.

Anal. Calcd $C_{20}H_{16}N_2O_3S_2$ (396.5) requires: C, 60.60; H, 4.07; N, 7.07; S, 16.17%. Found: C, 60.62; H, 4.18; N, 7.20; S, 16.00%.

Compound IIIb was obtained as pale orange crystals from acetic acid, mp 240°; yield 84%.

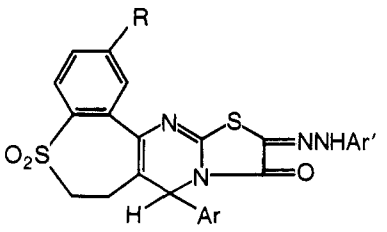
Table I. 11-Arylmethylene-6,7,10,11-tetrahydro-8-aryl-8H-[1]-benzothiepino[5,4-d]thiazolo[3,2-a]pyrimidin-10-one 5,5-dioxides (IV)



Compound	Ar	Yield, %	Mp, °C	Solvent	Formula	MW	Analysis: Calcd C	H	N	S	Found C	H	N	S
					R = H; R′ = C_6H_5									
IVa	C_6H_5	90	245	A[a]	$C_{27}H_{20}N_2O_3S_2$	484.6	66.92	4.16	5.79	13.23	66.82	4.24	6.00	13.40
b	$C_6H_4OCH_3$-*p*	95	250	A	$C_{28}H_{22}N_2O_4S_2$	514.6	65.34	4.31	5.45	12.47	65.40	4.20	5.28	12.30
c	C_6H_4Cl-*p*	95	310	A	$C_{27}H_{19}ClN_2O_3S_2$	519.0	62.44	3.69	5.40	12.35	62.57	3.90	5.33	12.55
d	$C_6H_4NO_2$-*p*	89	270	A	$C_{27}H_{19}N_3O_5S_2$	529.6	61.22	3.62	7.94	12.11	61.14	3.67	7.96	12.10
e	$C_6H_4NMe_2$-*p*	93	230	A	$C_{29}H_{25}N_3O_3S_2$	527.6	66.02	4.78	7.96	12.15	66.02	4.74	7.76	12.18
f	$C_6H_3(OMe)_2$-3,4	88	170	B[b]	$C_{29}H_{24}N_2O_5S_2$	544.6	63.95	4.44	5.15	11.77	64.03	4.64	5.00	11.80
g	$C_6H_5CH{=}CH$	80	280	C[c]	$C_{29}H_{22}N_2O_3S_2$	510.6	68.21	4.35	5.49	12.56	68.13	4.63	5.44	12.33
					R = H; R′ = $C_6H_4OCH_3$-*p*									
h	C_6H_5	90	170	A	$C_{28}H_{22}N_2O_4S_2$	514.6	65.34	4.31	5.45	12.47	65.30	4.42	5.50	12.61
i	$C_6H_4OCH_3$-*p*	92	150	B	$C_{29}H_{21}N_2O_5S_2$	544.6	63.95	4.43	5.15	11.77	63.75	4.38	5.00	11.60
j	C_6H_4Cl-*p*[d]	95	260	A	$C_{28}H_{21}ClN_2O_4S_2$	549.0	61.24	5.85		11.68	61.07	4.02		11.71
k	$C_6H_4NMe_2$-*p*	70	233	A	$C_{30}H_{27}N_3O_4S_2$	557.7	64.62	4.87		11.50	64.70	5.00		11.53
l	$C_6H_5CH{=}CH$	90	250	A	$C_{30}H_{24}N_2O_4S_2$	540.6	66.65	4.47		11.86	66.52	4.28		11.90
					R = CH_3; R′ = C_6H_5									
m	C_6H_5	90	275	A	$C_{28}H_{22}N_2O_3S_2$	498.6	67.45	4.45		12.86	67.54	4.50		13.00
n	$C_6H_4OCH_3$-*p*	95	268	A	$C_{29}H_{24}N_2O_4S_2$	528.6	65.89	4.58		12.14	65.85	4.80		11.92
o	C_6H_4Cl-*p*[e]	92	282	A	$C_{28}H_{21}ClN_2O_3S_2$	533.0	63.08	3.97		12.03	63.02	3.96		11.88
p	$C_6H_3(OMe)_2$-3,4	70	220	A	$C_{30}H_{26}N_2O_5S_2$	558.6	64.51	4.49		11.48	64.38	4.55		11.29
q	$C_6H_5CH{=}CH$	90	275	A	$C_{30}H_{24}N_2O_3S_2$	524.6	68.69	4.61		12.21	68.49	4.59		11.98

[a] Dioxane. [b] Ethyl alcohol. [c] Acetic acid. [d] Calcd: Cl, 6.45; Found: Cl, 6.60%. [e] Calcd: Cl, 6.65; Found: Cl, 6.70%.

Table II. 6,7,10,11-Tetrahydro-8-aryl-8H-[1]benzothiepino[5,4-d]thiazolo[3,2-a]pyrimidine-10,11-dione 5,5-dioxide 11-arylhydrazones (V)



Compound	R	Ar	Ar'	Yield, %	Mp, °C	Solvent	Formula	MW	Analysis: Calcd C	Calcd H	Calcd S	Found C	Found H	Found S
Va	H	C_6H_5	$C_6H_4CH_3$-p[a]	70	180	A[b]	$C_{27}H_{22}N_4O_3S_2$	514.6	62.99	4.31	12.47	62.88	4.31	12.50
b	H	C_6H_5	C_6H_4Br-p[c]	72	230	A	$C_{26}H_{19}BrN_4O_3S_2$	579.6	53.88	3.31	11.06	53.71	3.18	11.05
c	H	$C_6H_4OCH_3$-p	$C_6H_4CH_3$-p	73	210	B[d]	$C_{28}H_{24}N_4O_4S_2$	544.6	61.72	4.44	11.78	61.49	4.34	11.78
d	H	$C_6H_4OCH_3$-p	C_6H_4Br-p	76	182	A	$C_{27}H_{21}BrN_4O_4S_2$	609.6	53.19	3.47	10.52	53.08	3.70	10.55
e	CH_3	C_6H_5	$C_6H_4CH_3$-p	60	213	C[e]	$C_{28}H_{24}N_4O_3S_2$	528.6	63.61	4.58	12.14	63.45	4.68	11.92

[a] N, Calcd: 10.90; Found: 10.82%. [b] Dioxane. [c] N, Calcd: 9.67; Found: 9.80%. [d] Ethanol. [e] Acetic acid.

Anal. Calcd $C_{21}H_{18}N_2O_4S_2$ (426.5) requires: C, 59.14; H, 4.25; N, 6.57; S, 15.06%. Found: C, 58.95; H, 4.30; N, 6.70; S, 15.00%.

Compound IIIc was crystallized from dioxane as very pale yellow crystals, mp 235°; yield 80%.

Anal. Calcd $C_{21}H_{18}N_2O_3S_2$ (410.2) requires: C, 61.45; H, 4.42; S, 15.63%. Found: C, 61.34; H, 4.61; S, 15.40%.

Action of sodium hydroxide on 6,7-dihydro-8-phenyl-8H-[1]-benzothiepino[5,4-d]thiazolo[3,2-a]pyrimidino-10(11H)-one S,S-dioxides (IIIa). A suspension of 3 grams of IIIa in a solution of 16 grams of sodium hydroxide dissolved in 30 ml of ethanol and 20 ml of water was refluxed on the water bath for 10 hr until dissolution occurred. The solution was cooled and acidified with hydrochloric acid. The precipitate formed was collected and thoroughly washed with water. The crude product caused effervescence with sodium carbonate solution. However, after crystallization from ethanol, the product did not react with sodium carbonate solution and was regenerated starting material.

11-Arylmethylene-6,7,10,11-tetrahydro-8-aryl-8H-[1]-benzothiepino[5,4-d]thiazolo[3,2-a]pyrimidin-10-one S,S-dioxides (IV). A mixture of 1 gram of each of IIIa,b,c, an equimolecular amount of benzaldehyde, and a few drops of piperidine was heated at 170° for ½ hr, cooled, and crystallized from the proper solvent.

A mixture of 2 grams of each of IIa,b,c, 1 gram monochloroacetic acid, 20 ml glacial acetic acid, 5 ml acetic anhydride, and an equimolecular amount of appropriate aldehyde was refluxed for 4 hr. The reaction mixture was cooled and poured into cold water. The precipitate formed was collected, washed with ethanol, and finally crystallized from the proper solvent. This method gave better yields than the previous procedure.

The compounds prepared are listed in Table I.

6,7,10,11-Tetrahydro-8-aryl-8H-[1]benzothiepino[5,4-d]thiazolo[3,2-a]pyrimidine-10,11-diene-S,S-dioxide 11-aryl-hydrazones (V). The aromatic amine (0.01 mole) was dissolved in 3 ml of concentrated hydrochloric acid and 2 ml of water, cooled to 0°, and treated with 0.7 gram of sodium nitrite in 5 ml of water.

The diazotized amine was added gradually while stirring to a cooled solution of 0.01 mole of each of IXa,b,c, in 30 ml pyridine. The reaction mixture was refrigerated for ½ hr and then diluted with water; the product obtained was filtered off, washed with water, and crystallized from the proper solvent.

The compounds obtained are listed in Table II.

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