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Received May 3, 1984

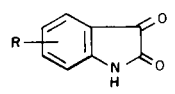
The title compounds have been prepared by the cyclocondensation of 3-mercaptopropanoic acid with isatin-3-imines. The 1-benzyl derivatives have been synthesized by simultaneously reacting 1-benzylisatin, substituted anilines and 3-mercaptopropanoic acid. Mannich condensation of the spiro thiazanones with secondary amines gave the corresponding 1-aminomethyl derivatives.

J. Heterocyclic Chem., **22**, 93 (1985).

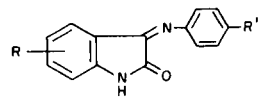
We have earlier reported [1] that isatin-3-imines reacted with 2-mercaptopropanoic acid to give 5′-methylspiro[3*H*-indole-3,2′-thiazolidine]-2,4′(1*H*)-diones. In continuation with our studies on the cyclocondensation of mercaptoacids with isatin-3-imines, we have found that 3-mercaptopropanoic acid reacts similarly to give the isomeric spiro-[3*H*-indole-3,2′-tetrahydro-1,3-thiazine]-2,4′(1*H*)-diones.

The preparation of a number of 2,3-substituted-tetrahydro-4*H*-1,3-thiazin-4-ones have been reported in the literature. Most of the 4-metathiazanones reported have been prepared from substituted benzaldehydes [2-4] and simple ketones [5] on treatment with lower amines and 3-mercaptopropanoic acid. It has also been reported [6] that certain aldehydes react with mercaptopropionamides to give 4-methathiazanones. Recently, Nakanishi and coworkers have reported [7] the preparation of spirothiazinones starting from *N*-substituted piperidones. It was of interest, therefore, to examine the feasibility of synthesizing spirothiazinones from isatins.

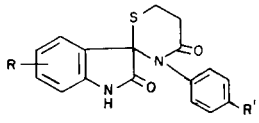
The general synthetic approach involves the preparation of isatin-3-imines, which then are subjected to cyclocondensation with 3-mercaptopropanoic acid. Reaction of



1 R = H
2 R = 5-NO_2
3 R = 7-CH_3



4a R = H R′ = OCH_3
b R = H R′ = CH_3
c R = H R′ = C_2H_5
d R = 5-NO_2 R′ = OCH_3
e R = 7-CH_3 R′ = OCH_3
f R = H R′ = H
g R = H R′ = Br



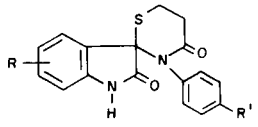
5a-g

isatin (**1**) and substituted isatins **2, 3** with aniline and substituted anilines gave the Schiff bases **4a-g** in quantitative yields.

Following the general procedure described earlier [1], the isatin-3-imines **4a-g** were then condensed with 3-mercaptopropanoic acid in toluene under reflux, with azeotrop-

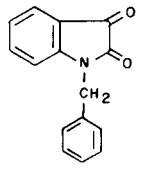
Table 1

Spiro[3*H*-indole-3,2′-tetrahydro-1,3-thiazine]-2,4′(1*H*)-diones



5	R	R′	Mp, °C [a]	Yield %	Formula	Analyses % Calcd. C	Calcd. H	Found C	Found H
a	H	OCH_3	269-271	66	$C_{18}H_{16}N_2O_3S$	63.51	4.74	63.58	4.76
b	H	CH_3	253 [b]	44	$C_{18}H_{16}N_2O_2S$	66.64	4.97	66.66	5.00
c	H	C_2H_5	249-250 [c]	60 [d]	$C_{19}H_{18}N_2O_2S$	67.43	5.36	67.26	5.39
d	5-NO_2	OCH_3	275 dec	26	$C_{18}H_{15}N_3O_5S$	56.09	3.92	56.15	4.00
e	7-CH_3	OCH_3	244-245	33	$C_{19}H_{18}N_2O_3S$	64.38	5.12	64.37	5.05
f	H	H	211-212	25	$C_{17}H_{14}N_2O_2S$	65.78	4.55	65.83	4.57
g	H	Br	240-241	28	$C_{17}H_{13}BrN_2O_2S$	52.45	3.36	52.42	3.51

[a] Recrystallized from ethanol. [b] Recrystallized from absolute ethanol. [c] Recrystallized from toluene. [d] Obtained in 49% yield on simultaneously refluxing isatin, *p*-ethylaniline and 3-mercaptopropanoic acid in toluene.



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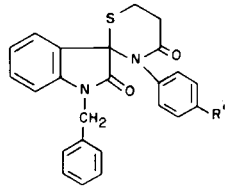
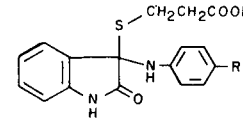
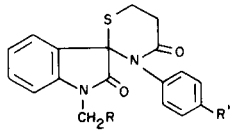


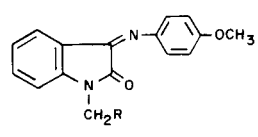
7a R' = OCH_3
b R' = CH_3
c R' = C_2H_5
d R' = n-C_4H_9
e R' = H
f R' = Cl
g R' = Br



11a R' = CH_3
11b R' = H
11c R' = Br



8a R = N(O) R' = OCH_3
b R = N R' = OCH_3
c R = N R' = OCH_3
d R = N(O) R' = C_2H_5
e R = N R' = C_2H_5
f R = N R' = C_2H_5



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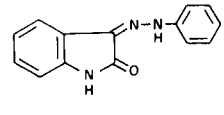
9a R = N(O)
b R = N



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ic removal of the water formed, to give, as shown in Table 1, the spiro compounds **5a-g**. It was found that a fifty percent excess of 3-mercaptopropanoic acid gave the spiro products in better yields. The spiro compound **5c** was also obtained by simultaneously refluxing isatin, *p*-ethylaniline and 3-mercaptopropanoic acid.

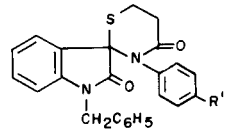
Compound **5a**, when stirred at room temperature with sodium hydride and benzylbromide in DMF gave the 1-benzyl derivative **7a** in low yield. Owing to the low yield of **7a** by the above procedure, attempts were made to prepare **7a** starting from 1-benzylisatin (**6**). Equimolar amounts of *p*-anisidine and **6**, and excess 3-mercaptopropanoic acid, when refluxed in toluene with azeotropic removal of water, gave **7a** in much better yields. Similarly, 1-benzylisatin, 3-mercaptopropanoic acid and a number of substituted anilines were cyclocondensed to give compounds **7b-g**, as shown in Table 2, without isolating the Schiff base initially formed.

Compounds **5a** and **5c** were also subjected to the Mannich condensation. A mixture of **5a** (or **5c**), 37% formaldehyde solution and the appropriate secondary amine, was refluxed in absolute ethanol to give the 1-substituted-aminomethyl derivatives **8a-f** shown in Table 3.

Compound **4a**, when subjected to the Mannich condensation with morpholine and piperidine gave the reported [8] products **9a** and **9b** respectively. Attempts to prepare the spiro products **8a** and **8b** by the cyclocondensation of the Schiff bases **9a** and **9b** with 3-mercaptopropanoic acid were not successful. In both cases, a dark and viscous gum-

Table 2

1-Benzylspiro[3*H*-indole-3,2'-tetrahydro-1,3-thiazine]-2,4'(1*H*)-diones

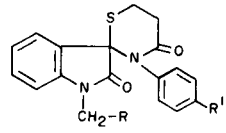


7	R'	Mp, °C [a]	Yield %	Formula	Analyses % Calcd. C	Calcd. H	Found C	Found H
a	OCH_3	198-200 [a]	63 [d]	$C_{25}H_{22}N_2O_3S$	69.74	5.15	69.58	5.11
b	CH_3	230-231 [b]	66	$C_{25}H_{22}N_2O_2S$	72.43	5.35	72.51	5.39
c	C_2H_5	203-204 [a]	67	$C_{26}H_{24}N_2O_2S$	72.87	5.64	72.78	5.69
d	n-C_4H_9	160-161 [c]	65	$C_{28}H_{28}N_2O_2S$	73.65	6.18	73.60	6.15
e	H	214-215 [c]	62	$C_{24}H_{20}N_2O_2S$	71.97	5.03	71.78	5.06
f	Cl	175-176 [e]	27	$C_{24}H_{19}ClN_2O_2S$	66.27	4.40	66.44	4.51
g	Br	193-194 [a]	26	$C_{24}H_{19}BrN_2O_2S$	60.13	3.99	60.16	4.12

[a] Recrystallized from ethanol. [b] Recrystallized from toluene. [c] Recrystallized from absolute ethanol. [d] Compound **7a** was obtained in 31% yield on treating **5a** with sodium hydride and benzyl bromide in DMF. [e] Recrystallized from toluene-hexane.

Table 3

Mannich Condensation Products



						Analyses %			
			Mp,			Calcd.		Found	
8	R	R′	°C [a]	Yield %	Formula	C	H	C	H
a	Morpholino	OCH_3	193-194	86	$C_{23}H_{25}N_3O_4S$	62.85	5.73	62.97	5.61
b	Piperidino	OCH_3	195-196 [b]	66	$C_{24}H_{27}N_3O_3S$	65.88	6.22	65.71	6.11
c	Pyrrolidino	OCH_3	174-175	61	$C_{23}H_{25}N_3O_3S$	65.22	5.95	64.83	6.04
d	Morpholino	C_2H_5	158-159 [c]	64	$C_{24}H_{27}N_3O_3S$	65.88	6.22	65.85	6.24
e	Piperidino	C_2H_5	183-184	78	$C_{25}H_{29}N_3O_2S$	68.93	6.71	68.75	6.75
f	Pyrrolidino	C_2H_5	149-150	58	$C_{24}H_{27}N_3O_2S$	68.38	6.46	68.49	6.47

[a] Recrystallized form absolute ethanol. [b] Recrystallized from ethanol. [c] Recrystallized from toluene/hexane.

my product was obtained which was difficult to purify. It seems, that the better way to obtain compounds of type **8** is *via* the Mannich condensation of the spiro compounds.

When isatin-3-phenylhydrazone (**10**) was refluxed with 3-mercaptopropanoic acid in toluene or absolute ethanol for 36 hours, the starting material was recovered; a behavior similar to that with 2-mercaptopropanoic acid [1].

When the Schiff base **4b** was stirred with excess 3-mercaptopropanoic acid in anhydrous toluene, at room temperature, for 12 hours, a white product **11a** was obtained in quantitative yields on filtration. Compound **11a** readily dissolves in ethanol. The solution, on heating on a steam bath for 5 minutes, turned red and on cooling gave the starting Schiff base **4b**. Efforts to purify the intermediate by recrystallization from a wide range of solvents or by extracting with aqueous sodium bicarbonate were not successful. Compounds **11a** dissolves in 10% sodium bicarbonate to give a yellow colored solution. Extraction with chloroform and subsequent evaporation of the solvent gave **4b**. A faint smell of the mercaptoacid was detected on acidification of the aqueous portion with 10% hydrochloric acid. The intermediate **11a**, whose infrared spectrum is consistent with the structure, was purified by repeatedly washing the product with anhydrous toluene, followed by anhydrous ether. The spiro product **5b** was obtained on refluxing **11a** in toluene for 10 hours, with azeotropic removal of the water formed. Similarly, compounds **4f** and **4g** gave white products, when stirred with 3-mercaptopropanoic acid in toluene, which we believe to be **11b** and **11c**.

Compounds **5a-c,e,g, 7a,e-f**, and **8a-c,e,f** were inactive at 300 mg/Kg in the MES and Met anticonvulsant screens and **8a** was inactive at 200 mg/Kg in the 3PS31 leukemia screen.

EXPERIMENTAL

All Compounds exhibited ir spectra consistent with the structures shown. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Analyses were carried out by Spang Microanalytical laboratory.

Preparation of Isatin-3-imines **4a-g**.

a) Compounds **4a,b,c,f,g**.

Isatin (0.01 mole) and the appropriate aniline (0.01 mole) in 30-50 ml of absolute ethanol containing a drop of glacial acetic acid were heated at reflux on a steam bath for about 30 minutes. After standing for a few hours at room temperature, the products were collected in quantitative yields by filtration. Melting points for compounds **4a, 4b, 4f** and **4g** were consistent with those reported [9-12]. Compound **4c**, R = H, R′ = C_2H_5, had mp = 209-210° (from ethanol).

b) Compounds **4d** and **4e**.

The isatin (0.01 mole) and *p*- anisidine (0.01 mole) in 80 ml of ethanol-water (3:1) were heated at reflux on a steam bath for about 30 minutes. The products obtained were collected by filtration and recrystallized from ethanol. The melting point for compound **4d** was consistent with that reported [13]. Compound **4e**, R = 7-CH_3, R′ = OCH_3, had mp = 232° (from ethanol).

Preparation of 3′-(4-Methoxyphenyl)spiro[3*H*-indole-3,2′-tetrahydro-1,3-thiazine]-2,4′(1*H*)-dione, **5a** and Analogs **5b-g**.

a) A mixture of **5a** (0.01 mole) and 3-mercaptopropanoic acid (0.015 mole) in 100 ml of toluene was refluxed for 20 hours and the water formed was removed azeotropically. The reaction mixture was cooled, toluene evaporated *in vacuo* and the product obtained was recrystallized from ethanol to give **5a** as shown in Table 1.

b) Using the procedure described for the preparation of **5a**, the analogs **5b-g** were prepared and are shown in Table 1. In some cases an oil was obtained which was triturated in ethanol and refrigerated for 1 hour to yield the solid product.

c) A mixture of isatin (2.94 g, 0.02 mole), *p*-ethylaniline (2.42 g, 0.02 mole) and 3-mercaptopropanoic acid (3.2 g, 0.03 mole) in 100 ml of toluene was refluxed for 20 hours and the water formed was removed azeotropically. The reaction mixture was cooled, the product filtered and recrystallized from toluene to give **5c** as shown in Table 1.

Preparation of 1-Benzyl-3′-(4-methoxyphenyl)spiro[3*H*-indole-3,2′-tetrahydro-1,3-thiazine]-2,4′(1*H*)-dione, **7a** and Analogs **7b-g**.

a) Compound **7a**. Method A.

A mixture of 1-benzylisatin (0.004 mole), *p*-anisidine (0.004 mole), and 3-mercaptopropanoic acid in 50 ml of toluene was refluxed for 18 hours and the water formed was removed azeotropically. The reaction mixture was cooled, toluene evaporated *in vacuo* and the product obtained was recrystallized from ethanol to give **7a** as shown in Table 2.

Method B.

To a well stirred solution of **5a** (1.02 g, 0.003 mole) and benzylbromide (0.51 g, 0.003 mole) in 25 ml of anhydrous dimethylformamide at room temperature was added 50% sodium hydride in oil (0.24 g, 0.005 mole). After stirring for 2 hours, the mixture was poured onto ice and the product filtered. The product was washed with water and recrystallized from ethanol to give **7a**.

b) Compounds **7b-g**.

Using the procedure described (Method A) for the preparation of **7a**, the analogs **7b-g** were prepared as shown in Table 2. In some cases an oil was obtained, which was triturated in ethanol and refrigerated for 1 hour to yield the solid product.

Preparation of 1-Morpholinomethyl-3'-(4-methoxyphenyl)spiro[3*H*-indole-3,2'-tetrahydro-1,3-thiazine]-2,4'(1*H*)-dione, **8a** and Analogs **8b-f**.

a) Compound **8a**.

A mixture of **5a** (1.02 g, 0.003 mole), morpholine (0.26 g, 0.003 mole) and 37% formaldehyde solution (0.27 g) was refluxed in 50 ml of absolute ethanol for 10 hours. The reaction mixture was cooled to room temperature and the product obtained by filtration was recrystallized from absolute ethanol to give the product **8a** as shown in Table 3.

b) Compounds **8b-f**.

Using the procedure described for the preparation of **8a**, the analogs **8b-f** were obtained as shown in Table 3. In the case of **8d**, no solid was obtained on cooling. The ethanol was evaporated *in vacuo* and the oil obtained was triturated in hexane to give a solid product.

Preparation of 1-Morpholinomethyl-3-(4-methoxyphenyl)imino-1*H*-indole-2,3-dione, **9a** and Analog **9b**.

a) A mixture of compound **4a** (0.01 mole), morpholine (0.01 mole), 37% formaldehyde solution (2 ml) in 10 ml ethanol was heated on a steam bath for 5 minutes, cooled to room temperature. The product obtained was filtered to give **9a** as reported [8].

b) The compound **9b** was similarly prepared. Melting points were consistent with those reported [8].

Preparation of **11a**.

A mixture of compound **4b** (2.36 g, 0.01 mole) and 3-mercaptopropanoic acid (1.6 g, 0.015 mole) was stirred in anhydrous toluene for 12 hours. The white product obtained was filtered and washed thrice with anhydrous toluene and twice with anhydrous ether to give **11a**, mp 135-137°, in 99% yield.

Anal. Calcd. for $C_{18}H_{18}N_2O_3S$: C, 63.13; H, 5.30; N, 8.18; S, 9.37. Found: C, 63.18; H, 5.44; N, 8.06; S, 9.44.

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