

Synthesis of 5'-Methylspiro[3*H*-indole-3,2'-thiazolidine]-2,4'(1*H*)-diones

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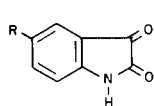
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The title compounds have been prepared, by the cyclocondensation of thiolactic acid with isatin-3-imines. 5'-Methyl-3'-phenylspiro[3*H*-indole-3,2'-thiazolidine]-2,4'(1*H*)-dione has been subjected to the Mannich condensation to give 1-substituted derivatives. With one exception, all of the products were inactive in an anti-convulsant screen.

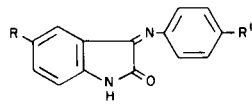
J. Heterocyclic Chem., **21**, 289 (1984).

The diverse biological activity associated with isatin derivatives [1] and 4-thiazolidinones [2] is well known. In view of the fact, that both exhibit anticonvulsant activity, we synthesized a number of 5'-methylspiro[3*H*-indole-3,2'-thiazolidine]-2,4'(1*H*)-diones in order to investigate their potential as anticonvulsants. The general synthetic approach involves the preparation of isatin-3-imines, which then are subjected to cyclocondensation with thiolactic acid.

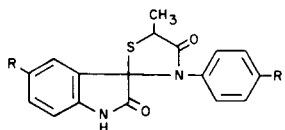
Reaction of isatin (**1**) and substituted isatins **2-4** with a number of aromatic amines gave the previously reported [3-7] Schiff bases (**5a-g, i, j, l, m**) in quantitative yields. Condensation of *p*-bromoaniline with 5-bromoisatin (**2**) and 5-nitroisatin (**3**) in ethanol/water gave the previously unreported products **5h** and **5k**.



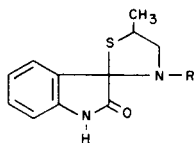
- 1 R = H
 2 R = Br
 3 R = NO₂
 4 R = CH₃



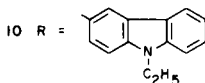
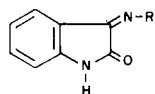
- 5
 a R = H, R' = H
 b R = H, R' = OCH₃
 c R = H, R' = Br
 d R = H, R' = Cl
 e R = H, R' = OH
 f R = Br, R' = H
 g R = Br, R' = OCH₃
 h R = Br, R' = Br
 i R = Br, R' = Cl
 j R = NO₂, R' = OCH₃
 k R = NO₂, R' = Br
 l R = NO₂, R' = Cl
 m R = CH₃, R' = Cl



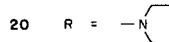
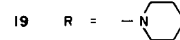
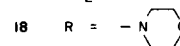
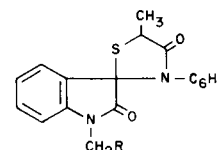
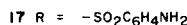
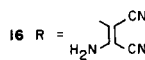
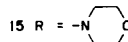
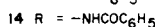
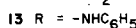
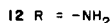
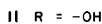
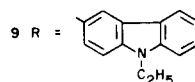
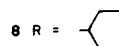
6a-m



7 R =



10 R =

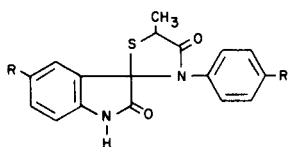


Following a procedure similar to that of Joshi *et al.*, [8] the isatin-3-imines **5a-m** were condensed with thiolactic acid in toluene under reflux, with azeotropic removal of the water formed, to give, as shown in Table I, spiro compounds **6a-m**. Similarly, the 3'-cyclopentyl analog **7** was obtained from the imine **8** [9] and the Schiff base **9** [9] gave the spiro compound **10** as anticipated.

Attempts to synthesize the analogs of **6**, where R = H and the nitrogen atom in the 3' position is connected to another heteroatom, were not successful. When isatin-3-oxime **11** [10], -hydrazone **12** [11], -phenylhydrazone **13** [12] and -benzoylhydrazone **14** [13] were refluxed with thiolactic acid in benzene, toluene or absolute ethanol for 20 hours, the starting material was recovered, even when anhydrous zinc chloride was used as a condensing agent. Compounds **15** [14] and **16** [15] behaved similarly, whereas, **17** [16] yielded a deep red gummy product, which was difficult to purify. The condensation reaction of **12** and **13** with mercaptoacetic acid has been reported [17] to give analogous spiro thiazolidinones in 16-18% yield; the anomalous behavior with thiolactic acid is not completely clear.

5'-Methyl-3'-phenylspiro[3*H*-indole-3,2'-thiazolidine]-2,4'(1*H*)-dione (**6a**) was subjected to the Mannich condensation. A mixture of **6a**, 37% formaldehyde solution and the appropriate secondary amine, was refluxed in absolute

Table I

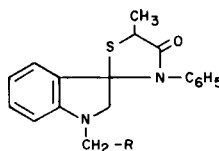
5'-Methylspiro[3*H*-indole-3,2'-thiazolidine]-2,4'(1*H*)-diones

6	R	R'	Mp °C [a]	Yield %	Formula	Analysis			
						Calcd.		Found	
						C	H	C	H
a	H	H	200-201	57	C ₁₇ H ₁₄ N ₂ O ₂ S	65.78	4.55	65.70	4.51
b	H	OCH ₃	183-184	58	C ₁₈ H ₁₆ O ₃ N ₂ S	63.51	4.74	63.70	4.86
c	H	Br	222-224	61	C ₁₇ H ₁₃ BrN ₂ O ₂ S	52.44	3.37	52.59	3.51
d	H	Cl	246-247	53	C ₁₇ H ₁₃ ClN ₂ O ₂ S	59.21	3.80	59.21	3.78
e	H	OH	306-307	59	C ₁₇ H ₁₄ N ₂ O ₃ S	62.56	4.32	62.56	4.36
f	Br	H	280-281	42	C ₁₇ H ₁₃ BrN ₂ O ₂ S	52.45	3.36	52.33	3.38
g	Br	OCH ₃	214	44	C ₁₈ H ₁₅ BrN ₂ O ₂ S	51.56	3.61	51.63	3.57
h	Br	Br	269-270	26	C ₁₇ H ₁₂ Br ₂ N ₂ O ₂ S	43.61	2.58	43.69	2.54
i	Br	Cl	282-283	54	C ₁₇ H ₁₂ BrClN ₂ O ₂ S	48.18	2.86	48.21	2.87
j	NO ₂	OCH ₃	274-275	52	C ₁₈ H ₁₅ N ₃ O ₅ S	56.09	3.92	56.05	3.88
k	NO ₂	Br	292-294	26	C ₁₇ H ₁₂ BrN ₃ O ₂ S	47.01	2.79	47.19	2.83
l	NO ₂	Cl	277 dec	38	C ₁₇ H ₁₂ ClN ₃ O ₄ S	52.38	3.10	52.51	3.22
m	CH ₃	Cl	252 [b]	54	C ₁₈ H ₁₅ ClN ₂ O ₂ S	60.24	4.21	60.34	4.14

[a] Recrystallized from ethanol unless otherwise noted. [b] Recrystallized from toluene.

Table II

Mannich Condensation Products



Compound No.	R	Mp, °C	Yield %	Formula	Analysis			
					Calcd.		Found	
					C	H	C	H
19	Morpholino-	179-180	79	C ₂₂ H ₂₃ N ₃ O ₃ S	64.52	5.66	64.63	5.67
20	Piperidino-	189-190	63	C ₂₃ H ₂₅ N ₃ O ₂ S	67.78	6.18	67.71	6.18
21	Pyrrolidino-	152-153	67	C ₂₂ H ₂₃ N ₃ O ₂ S	67.15	5.89	67.14	5.91

ethanol to give the three 1-substituted aminomethyl derivatives **18-20** shown in Table II.

The compounds **6a-m**, **10**, **18**, **19** and **20** were submitted for anticonvulsant screening [18] and, with the exception of **6b**, were all found to be inactive at 600 mg/kg, in both the maximal electroshock seizure test (MES) and the pentylenetetrazol seizure threshold test (Met). Compound **6b** was also inactive in the Met test, but was active at 600 mg/kg in the MES test. Compound **19** was also inactive (T/C = 94) at 200 mg/kg in the 3PS31 leukemia screen [19].

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 **5a-m**, **8** and **9**.

a) Compounds **5a-e,m**.

The 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 were consistent with those reported [3-5,7].

b) Compounds **5f-l**.

The isatin (0.01 mole) and the substituted aniline 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. Melting points for compounds **5f,g,i,j** and **l** were consis-

tent with those reported [6]. Compound **5h** had mp 281-283° (from ethanol), R = Br, R' = Br. Compound **5k** had mp 244-245° (from ethanol), R = NO₂, R' = Br.

c) Compounds **8** and **9** were prepared as reported [9].

Preparation of 5'-Methyl-3'-phenylspiro[3*H*-indole-3,2'-thiazolidine]-2,4'(1*H*)-dione (**6a**) and analogs **6b-m**, **9** and **10**.

a) A mixture of **5a** (0.01 mole) and thiolactic acid (0.01 mole) in 100 ml of toluene was refluxed for 10 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 (charcoal) to give **6a** as shown in Table I.

b) Using the procedure described for the preparation of **6a**, the analogs **6b-d**, **f-m** were prepared and are shown in Table I.

c) Using a similar procedure as mentioned above, equimolar amounts of **5e** and thiolactic acid (0.01 mole) were refluxed in 100 ml of absolute ethanol for 22 hours. The solvent concentrated *in vacuo*, and the product **6e** was recrystallized from ethanol (charcoal).

d) Using the procedure described for the preparation of **6a**, 1.5 g (0.007 mole) of **8** gave an 8% yield of **7**, mp 183-184° (from ethyl acetate over several days and then from toluene).

Anal. Calcd. for C₁₆H₁₈N₂O₂S: C, 63.55; H, 6.00. Found: C, 63.71; H, 5.92.

e) Using the procedure described for the preparation of **6a**, 2.03 g (0.006 mole) of **9** gave a 56% yield of **10**, mp 245-246° [from ethanol (charcoal), hot filtration through silica gel under vacuum].

Anal. Calcd. for C₂₂H₂₁N₃O₂S: C, 70.23; H, 4.95. Found: C, 69.95; H, 4.90.

Preparation of 1-Morpholinomethyl-5'-methyl-3'-phenylspiro[3*H*-indole-3,2'-thiazolidine]-2,4'-dione, **18** and Analogs **19** and **20**.

a) A mixture of 1.55 g (0.005 mole) of **6a**, 0.435 g (0.005 mole) of morpholine and 0.454 g of 37% formaldehyde solution 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 **18** shown in Table II.

b) Using the procedure described for the preparation of **18**, the analogs **19** and **20** were obtained as shown in Table II.

REFERENCES AND NOTES

- [1] R. S. Varma and I. A. Khan, *Def. Sci. J.*, **28**, 191 (1978).
- [2] S. P. Singh, S. S. Parmar, K. Raman and V. I. Stenberg, *Chem. Rev.*, **81**, 175 (1981).
- [3] E. Knoevenagel, *J. Prakt. Chem. [2]*, **89**, 48 (1914).
- [4] G. Jacini, *Gazz. Chim. Ital.*, **73**, 85 (1943).
- [5] G. B. Crippa and S. Pietra, *ibid.*, **81**, 195 (1951).
- [6] M. J. Kallmeyer, *Arch. Pharm.*, **308**, 742 (1975).
- [7] R. S. Varma and I. A. Khan, *Indian J. Med. Res.*, **67**, 315 (1978).
- [8] K. C. Joshi, R. Patni and P. Chand, *Heterocycles*, **16**, 1555 (1981).
- [9] F. D. Popp, *J. Med. Chem.*, **12**, 182 (1969).
- [10] Commercially available from Aldrich.
- [11] T. Curtius and K. Thun, *J. Prakt. Chem. [2]*, **44**, 188 (1891).
- [12] W. C. Sumpter, M. Miller and L. N. Hendrick, *J. Am. Chem. Soc.*, **67**, 1656 (1945).
- [13] R. S. Varma, *J. Indian Chem. Soc.*, **55**, 1052 (1978).
- [14] F. D. Popp, unpublished results.
- [15] F. D. Popp, *J. Heterocyclic Chem.*, **11**, 79 (1974).
- [16] F. D. Popp, *J. Med. Chem.*, **13**, 1017 (1970).
- [17] K. M. Hassan and Z. H. Khalil, *Z. Naturforsch.*, **34b**, 621 (1979).
- [18] Anticonvulsant screenings were carried out through the Anti-epileptic Drug Development Program, National Institutes of Health. The standard screening protocol of that group was followed and we thank them for the results.
- [19] Anticancer screenings were carried out through the National Cancer Institute, National Institute of Health. The standard screening protocol of that group was followed and we thank them for the results.