Potential Anticonvulsants. III. The Condensation of Isatin with Cyclic Ketones

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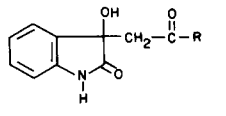
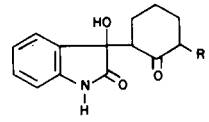
Isatin has been condensed with a series of cyclic ketones to give 3-substituted-3-hydroxyoxindoles as potential anticonvulsant agents.

J. Heterocyclic Chem., **17**, 1329 (1980).

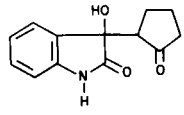
In Part I (1) and Part II (2) of this series we reported that the oxindole **1** exhibited anticonvulsant activity in the maximal electroshock seizure test (MES) (3) with an ED_{50} of 102 mg./kg. and a protective index (PI) of about 4 and that oxindole **2** had an ED_{50} of 40 mg./kg. and a PI of 12 in that same test. Oxindole **2** also was active at 300 mg./kg. in the pentylenetetrazol seizure threshold test (Met) (3). We also reported (2) that **3** was active at 300 mg./kg. in the MES test.



1 R = C_6H_5
2 R = CH_3



3 R = H
5 R = CH_3



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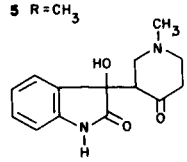

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In view of the fact that some activity was found in **3** it

Table I

Reaction of Isatin with Cyclic Ketones

Ketone Used	M.p. (a) °C	Yield, %	Formula	Analysis Calcd. / Found C	H	N
cyclopentanone	173-174	40	$C_{13}H_{13}NO_3$	67.52	5.67	—
				67.37	5.48	
1-methyl-4-piperidone	137-138	64	$C_{14}H_{16}N_2O_3$ (b)	64.60	6.20	10.76
				63.01	5.53	9.86
4-methylcyclohexanone	196-197	56	$C_{15}H_{17}NO_3$	69.48	6.61	5.40
				69.15	6.60	5.29
2-methylcyclohexanone	199-201 (c)	50	$C_{15}H_{17}NO_3$	69.48	6.61	—
				69.71	6.52	
4-*i*-propylcyclohexanone	187-188	61	$C_{17}H_{21}NO_3$	71.05	7.37	—
				70.84	7.40	
4-*t*-butylcyclohexanone	205-207	59	$C_{18}H_{23}NO_3$	71.73	7.69	4.65
				71.80	7.71	4.71
1-tetralone	221-222 (d)	88	$C_{18}H_{15}NO_3$	73.70	5.16	—
				73.71	5.13	
1,3,4,6,7,11b-hexahydro-9,10-dimethoxybenzo[*a*]quinolizin-2-one	178-179	68	$C_{23}H_{24}N_2O_5$	67.63	5.92	6.86
				67.21	5.78	6.68
3-ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxybenzo-[*a*]quinolizin-2-one	153-154	55	$C_{25}H_{28}N_2O_5$	68.79	6.47	6.42
				68.20	6.55	6.25
5-androsten-3β-ol-17-one	261-262	81	$C_{27}H_{33}NO_4$	74.45	7.64	3.22
				74.27	7.71	3.44
5α-androstan-3β-ol-17-one	254-255	60	$C_{27}H_{35}NO_4$	74.11	8.06	3.20
				74.29	8.18	3.35
5-androsten-3β-ol-17-one acetate	218-219	41	$C_{29}H_{35}NO_5$	72.93	7.39	2.93
				72.18	7.40	2.94
androstanolone benzoate	175	30	$C_{34}H_{39}NO_5$	75.39	7.26	2.59
				75.34	7.40	2.35
5α-cholestan-3-one	192-194 (e)	82	$C_{35}H_{51}NO_2$	78.75	9.63	—
				78.64	9.51	

(a) Recrystallized from ethanol, m.p. uncorrected, spectral data consistent with structure. (b) Compound is difficult to purify, see text. (c) Reported (4) m.p. 178°. (d) Reported (5) m.p. 197-198°. (e) Reported (6) m.p. 191°.

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was decided to investigate the use of other cyclic ketones. Thus isatin was condensed with a series of cyclic ketones, including steroids, in the presence of diethylamine to give the compounds of the type **3** shown in Table I. All of the compounds exhibited spectra consistent with the structure.

With two exceptions all of the compounds in Table I were inactive at 300 mg./kg. in both the MES and Met screens (3). The products derived from isatin and cyclopentanone (**4**) and 2-methylcyclohexanone (**5**), however, were both more active than **3**. Thus, **4** was active at 100 mg./kg. in the MES screen and 300 mg./kg. in the Met screen with some toxicity at 300 mg./kg., and **5** was active at 100 mg./kg. in the MES screen and 600 mg./kg. in the Met screen. Further screening of **5** indicated an ED_{50} of 171 and a PI of 8 in the MES screen (3).

The condensation of isatin with 1-methyl-4-piperidone gave a product (**6**) that was difficult to purify and of very low stability. The mass spectrum of the crude product showed a low intensity molecular ion (m/e 260), a more intense M^+-H_2O (m/e 242), but very intense peaks (m/e 147 and 113) corresponding to starting material. Attempts to dehydrate the crude product **6** with hydrochloric acid in acetic acid, a procedure that readily leads to dehydration of **1**, **2**, and **3**, gave near quantitative yields of isatin.

EXPERIMENTAL

Condensation of Isatin with Cyclic Ketones.

Isatin (0.01 mole) and the cyclic ketone (0.015-0.03 mole) in 30-50 ml. of absolute ethanol containing 3-4 drops of diethylamine were heated at reflux on the steam bath for 30-60 minutes. After standing for several days at room temperature, the products (Table I) were collected by filtration.

Attempted Dehydration of **6**.

A mixture of 0.01 mole of crude **6**, 0.5 ml. of concentrated hydrochloric acid, and 17 ml. of acetic acid was heated on the steam bath for 15-30 minutes. Addition of ethanol and standing at room temperature gave a near quantitative yield of isatin, identical in all ways with an authentic sample.

REFERENCES AND NOTES

(1) F. D. Popp and B. D. Donigan, *J. Pharm. Sci.*, **68**, 519 (1979).

(2) F. D. Popp, R. Parson, and B. E. Donigan, *ibid.*, in press.

(3) Anticonvulsant screenings were carried out through the ADD program of the NINCDS, NIH. The standard screening protocol of that group was followed. We thank them for making this service available.

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