Potential Anticonvulsants VI: Condensation of Isatins with Cyclohexanone and other Cyclic Ketones

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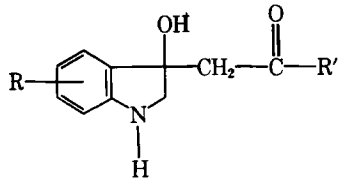
Abstract □ Cyclohexanone, substituted cyclohexanones, and other cycloalkanones have been condensed with isatin and substituted isatins to give a series of new 3-hydroxy-3-substituted oxindoles. A number of these 3-hydroxyoxindoles possess anticonvulsant activity.

Keyphrases □ Anticonvulsants—potential, condensation of isatins with cyclohexanone and other cyclic ketones □ Isatins—condensation with cyclohexanone and other cyclic ketones, potential anticonvulsants □ Cyclohexanones—condensation of isatins, potential anticonvulsants

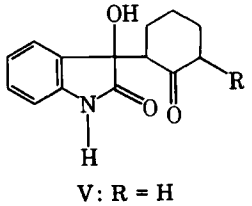
It has been reported (1, 2) that I exhibited anticonvulsant activity in the maximal electroshock seizure test[1] with an ED_{50} of 102 mg/kg and a protective index of ~4 and that II had an ED_{50} of 40 mg/kg and a protective index of 12 in that same test. The 3-hydroxyoxindole derivative, II, was also active at 300 mg/kg in the pentylenetetrazol seizure threshold test[1]. Compound III had an ED_{50} of 56 with a protective index of 3 in the maximal electroshock seizure test, while IV had an ED_{50} of ~115 and a protective index of ~4 in both tests (2).

Compound V was derived from isatin and cyclohexanone and was active in the maximal electroshock seizure (MES) screen (2). Dehydration to VI resulted in an increase in activity. This latter observation is in contrast to the observation that the dehydration products of I and II were inactive. A number of products from isatin and cyclic ketones (3) were prepared, and it was found that VII had an ED_{50} of 171 and a protective index of 8 in the MES screen and that VIII was active in both screens.

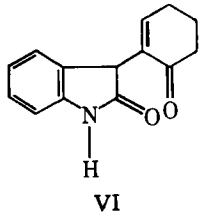
The present investigation reports on the condensation of various alicyclic ketones with isatins to give additional analogs of V–VIII.



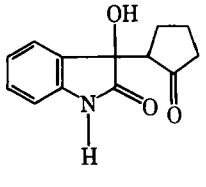
I: R = H, R′ = C_6H_5
II: R = H, R′ = CH_3
III: R = 4-Cl-7-CH_3, R′ = CH_3
IV: R = 7-CH_3, R′ = CH_3



V: R = H
VII: R = CH_3



VI



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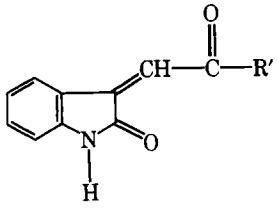

IX

EXPERIMENTAL[2]

Condensation of Isatin with Ketones—The compounds in Tables I–IV were prepared, as previously described (1–3, 5, 6), by heating on a steam bath a solution of the isatin and the appropriate ketone in absolute ethanol containing a few drops of diethylamine.

Dehydration of 3-Hydroxyoxindoles—The compounds in Table V were prepared, as previously described (1, 2, 5), by heating the 3-hydroxyoxindoles on a steam bath in acetic acid containing a small amount of hydrochloric acid.

DISCUSSION

Cyclohexanone was condensed in the presence of diethylamine with a variety of substituted isatins to give compounds of type V. These products are included in Table I. With the exception of the product derived from 4-chloro-7-methoxyisatin, none of these derivatives were as active as V in the MES screen. In contrast, a considerable number of these analogs were active in the pentylenetetrazol seizure threshold test (Met) screen. Worthy of particular note were those products formed from 7-methyl-, 4-chloro-7-methoxy-, and 6-chloro-7-methylisatin. 5-Chloro-, 5-methyl-, and 5-nitroisatin also led to compounds active in the Met test.

In view of the activity of VIII (3), a number of cycloalkanones of various ring sizes were condensed with isatins to give the compounds shown in Table II. With the exception of a high degree of Met test activity in the product from 5-bromoisatin and cyclopentadecanone, none of the compounds, including several from cyclopentanone and substituted isatins, were as active as VIII.

Although the products from isatin and 4-substituted cyclohexanones were inactive (3), compound VII had good MES activity. In view of this, a number of 2-substituted cyclohexanones and 3-methylcyclohexanone were condensed with isatins to give the products shown in Table III. In the case of VII the introduction of substituents in the isatin portion of the molecule or replacement of the methyl by phenyl or cyclohexyl led to a loss of activity. A single exception is the activity of the 5-nitro analogue of VII, which is active in the Met test. Replacement of 2-methylcyclohexanone by 3-methylcyclohexanone gave an active product both with isatin and with 1-methylisatin.

Although it has been reported that dehydration of I (1) and II (2) to IX causes a loss of activity, dehydration of V to VI leads to an increase of activity in the MES test. Unfortunately, dehydration of a number of analogues of V and VII resulted in a decrease or loss of activity. These dehydration products are shown in Table V.

Table IV includes a number of additional examples of compounds of type I. None of these compounds exhibited any significant anticonvulsant activity.

This series of investigations has reported (1–3, 5, 6) on the synthesis of a number of 3-substituted oxindoles with anticonvulsant activity.

[1] Anticonvulsant screenings were carried out through the Antiepileptic Drug Development Program of the NINCDS, National Institutes of Health. The standard screening protocol of that group was followed.

[2] All compounds exhibited IR spectra consistent with the structures shown and with those previously reported (1–3). Melting points are uncorrected, and analyses were carried out by Spang Microanalytical Laboratory.

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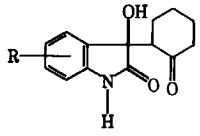
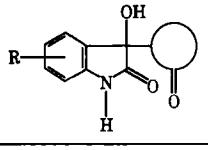
Table I—Reaction of Isatins with Cyclohexanone



Substituent	mp°[a]	Formula	Analysis, % Calc. / Found C	H	N	Anticonvulsant Activity, mg/kg[b] MES	Met
H	198–199[c]	$C_{14}H_{15}NO_3$	—	—	—	300	NA[d]
H[e]	240–241	$C_{22}H_{20}N_2O_5$	67.34 / 67.40	5.14 / 5.25	7.14 / 7.13	—	—
1-$C_6H_5CH_2$	183–185	$C_{21}H_{21}NO_3$	75.20 / 75.22	6.31 / 6.48	4.18 / 4.18	NA[f]	NA[f]
5-Br	218–219	$C_{14}H_{14}BrNO_3$	51.87 / 52.01	4.35 / 4.42	—	NA[f]	NA[f]
5-Cl	217–218	$C_{14}H_{14}ClNO_3$	60.11 / 59.91	5.04 / 5.03	—	NA[f]	100
5-CH_3	198–199	$C_{15}H_{17}NO_3$	69.48 / 69.69	6.61 / 6.79	—	NA[f]	100
5-CH_3O	162–164[g]	$C_{15}H_{17}NO_4$	—	—	—	600[h]	300[h]
5-NO_2	228–230	$C_{14}H_{14}N_2O_5$	57.93 / 57.82	4.86 / 4.87	—	NA[f]	100
6-Cl	220–222	$C_{14}H_{14}ClNO_3$	60.11 / 59.70	5.04 / 5.22	—	NA[f]	NA[f]
7-CH_3	196–198	$C_{15}H_{17}NO_3$	69.48 / 69.44	6.61 / 6.71	—	600	30[i]
4-Cl-7-CH_3	209–211	$C_{15}H_{16}ClNO_3$	61.37 / 61.53	5.49 / 5.60	4.77 / 4.74	NA[f]	NA[f]
4-Cl-7-CH_3O	153–154	$C_{15}H_{16}ClNO_4$[j]	57.38 / 57.26	6.23 / 6.16	3.94 / 3.92	300[h]	30[h]
5-Cl-7-CH_3	200–202	$C_{15}H_{16}ClNO_3$	61.33 / 61.17	5.49 / 5.46	—	NA[f]	600
5-CH_3O-6-Cl	240–241	$C_{15}H_{16}ClNO_4$	58.16 / 58.10	5.21 / 5.09	4.52 / 4.54	NA[f]	NA[f]
6-Cl-7-CH_3	207–208	$C_{15}H_{16}ClNO_3$	61.33 / 61.22	5.49 / 5.45	—	NA[f]	30

[a] Recrystallized from ethanol, melting point uncorrected, spectral data consistent with structure. [b] Anticonvulsant screenings were carried out through the Antiepileptic Drug Development Program, National Institutes of Health. The standard screening protocol of the group was followed. [c] Described in ref. 2. [d] No activity at 300 mg/kg. [e] Product from reaction of 2 moles of cyclohexanone with 1 mole of isatin. [f] No activity at 600 mg/kg. [g] Reported (6) mp 168–171°. [h] Toxic at 600 mg/kg. [i] Met ED_{50} 550.23; TD_{50} > 900. [j] Analysis, sample $C_{15}H_{16}ClNO_4 \cdot C_2H_5OH$.

Table II—Reaction of Isatin with Cyclic Ketones



Substituent	Ketone Used	mp°,[a]	Formula	Analysis, % Calc. / Found C	H	N	Anticonvulsant Activity, mg/kg[b] MES	Met
H	Cyclopentanone	173–174[c]	$C_{13}H_{13}NO_3$	—	—	—	100[d]	300[d]
5-Br	Cyclopentanone	270–271	$C_{13}H_{12}BrNO_3$	—	—	4.52 / 4.91	600	300
5-NO_2	Cyclopentanone	200–201	$C_{13}H_{12}N_2O_5$	56.52 / 56.19	4.38 / 4.24	10.14 / 10.21	NA[e]	600
4-Cl-7-OCH_3	Cyclopentanone	196–198	$C_{14}H_{14}ClNO_4$	56.86 / 56.96	4.77 / 4.77	4.74 / 4.66	NA[e]	300
H	2-Ethylcyclopentanone	132–134	$C_{15}H_{17}NO_3$	69.48 / 69.29	6.61 / 6.64	5.40 / 5.54	300	NA[f]
H	Cycloheptanone	169–170	$C_{15}H_{17}NO_3$	69.48 / 69.42	6.61 / 6.50	5.40 / 5.43	300[g]	300[g]
5-Br	Cycloheptanone	220–221	$C_{15}H_{16}BrNO_3$	53.27 / 53.49	4.77 / 4.79	4.14 / 4.15	NA[e]	NA[e]
5-NO_2	Cycloheptanone	224–225	$C_{15}H_{16}N_2O_5$	59.20 / 58.94	5.30 / 5.24	9.21 / 9.02	NA[e]	NA[e]
4-Cl-7-OCH_3	Cycloheptanone	199–200	$C_{16}H_{18}ClNO_4$	59.35 / 59.44	5.60 / 5.72	4.33 / 4.31	NA[e]	NA[e]

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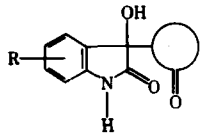
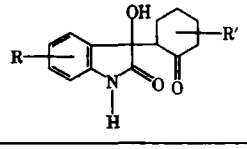
Table II—*Continued*



Substituent	Ketone Used	mp°,[a]	Formula	Analysis, % Calc. / Found C	H	N	Anticonvulsant Activity, mg/kg[b] MES	Met
H	Cyclooctanone	168–169	$C_{16}H_{19}NO_3$	70.30 / 70.33	7.01 / 6.96	5.12 / 5.16	600	NA[e]
5-Cl	Cyclopentanone	175–176	$C_{13}H_{12}CNO_3$	58.76 / 58.47	4.55 / 4.61	—	600[g]	600[g]
5-CH_3	Cyclopentanone	256–257	$C_{14}H_{15}NO_3$	68.55 / 68.20	6.16 / 5.73	—	NA[e]	300
6-Cl-7-CH_3	Cyclopentanone	206–207	$C_{14}H_{14}ClNO_3$	60.11 / 60.16	5.04 / 5.07	5.01 / 4.81	300	NA[e]
5-Br	Cyclooctanone	195–196	$C_{16}H_{18}BrNO_3$	54.56 / 55.00	5.50 / 5.19	3.98 / 4.09	NA[e]	NA[e]
5-NO_2	Cyclooctanone	147–149	$C_{16}H_{18}H_2O_5$	60.39 / 60.06	5.70 / 5.70	—	600	600
H	Cyclododecanone	185–186	$C_{20}H_{27}NO_3$	72.92 / 73.11	8.26 / 8.37	4.25 / 4.36	NA[e]	NA[e]
1-CH_3	Cyclopentadecanone	180–181	$C_{24}H_{35}NO_3$	74.76 / 74.80	9.15 / 9.25	3.63 / 3.79	NA[e]	NA[e]
5-Br	Cyclopentadecanone	213–215	$C_{23}H_{32}BrNO_3$	61.33 / 61.49	7.16 / 7.24	3.11 / 3.10	NA[e]	30[h]
5-NO_2	Cyclopentadecanone	233–235	$C_{23}H_{32}N_2O_5$	66.32 / 66.03	7.74 / 7.72	6.73 / 6.69	NA[e]	NA[e]
4-Cl-7-OCH_3	Cyclopentadecanone	223–225	$C_{24}H_{34}ClNO_4$	66.12 / 66.05	7.86 / 7.83	3.21 / 3.18	NA[e]	NA[e]

[a] Recrystallized from ethanol, melting point uncorrected, spectral data consistent with structure. [b] Anticonvulsant screenings were carried out through the Antiepileptic Drug Development Program, National Institutes of Health. The standard screening protocol of the group was followed. [c] Described in ref. 3. [d] MES ED_{50} 124.4; Met ED_{50} 202.4, TD_{50} 255.4. [e] No activity at 600 mg/kg. [f] No activity at 300 mg/kg, toxic at 600 mg/kg. [g] Toxic at this dose. [h] Repeated testing indicated that the subcutaneous Met activity is variable.

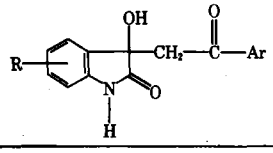
Table III—Reaction of Isatins with Substituted Cyclohexanones



Substituent	Ketone Used	mp°,[a]	Formula	Analysis, % Calc. / Found C	H	N	Anticonvulsant Activity, mg/kg[b] MES	Met
H	2-Methylcyclohexanone	199–201[c]	$C_{15}H_{17}NO_3$	—	—	—	100[d]	600[d]
1-CH_3	2-Methylcyclohexanone	160–162	$C_{16}H_{19}NO_3$	70.30 / 70.36	7.01 / 7.11	5.12 / 5.02	300[e]	NA[f]
5-Br	2-Methylcyclohexanone	228–230	$C_{15}H_{16}BrNO_3$	53.27 / 53.36	4.77 / 4.71	—	NA[f]	600
5-NO_2	2-Methylcyclohexanone	236–237	$C_{15}H_{16}N_2O_5$	59.20 / 59.22	5.30 / 5.27	—	NA[f]	30
4-Cl-7-CH_3	2-Methylcyclohexanone	229–230	$C_{16}H_{18}ClNO_3$	62.44 / 62.39	5.90 / 5.78	4.55 / 4.64	NA[f]	NA[f]
H	2-Methylcyclohexanone	187–188	$C_{20}H_{19}NO_3$	74.74 / 74.75	5.96 / 5.95	4.36 / 4.45	NA[f]	NA[f]
5-NO_2	2-Methylcyclohexanone	235–236	$C_{20}H_{18}N_2O_5$	64.50 / 64.64	6.50 / 6.53	7.52 / 7.38	NA[f]	NA[f]
5-Br	2-Cyclohexylcyclohexanone	235–236	$C_{20}H_{24}BrNO_3$	59.12 / 59.31	5.95 / 5.99	3.45 / 3.15	NA[f]	NA[f]
H	3-Methylcyclohexanone	171–172	$C_{15}H_{17}NO_3$	69.48 / 69.38	6.61 / 6.68	5.40 / 5.35	100[g]	300[e]
1-CH_3	3-Methylcyclohexanone	167–168	$C_{16}H_{19}NO_3$	—	—	5.12 / 5.36	100	600[e]
5-Br	3-Methylcyclohexanone	219–220	$C_{15}H_{16}BrNO_3$	53.27 / 53.35	4.77 / 4.82	—	NA[f]	NA[f]
5-NO_2	3-Methylcyclohexanone	228–229	$C_{15}H_{16}N_2O_5$	59.20 / 58.88	5.30 / 4.92	—	NA[f]	NA[f]

[a] Recrystallized from ethanol, melting point uncorrected, spectral data consistent with structure. [b] Anticonvulsant screenings were carried out through the Antiepileptic Drug Development Program, National Institutes of Health. The standard screening protocol of the group was followed (see Table I). [c] Described in ref. 3. [d] MES ED_{50} 171.5; TD_{50} 1380. [e] Some toxicity at this dose. [f] No activity at 600 mg/kg. [g] MES ED_{50} 83.7; TD_{50} 323.9.

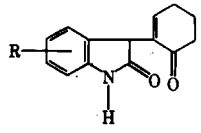
Table IV—Additional Products from Acetophenone



Substituent	Ar	mp°,[a]	Formula	Analysis, % Calc. / Found C	Analysis, % Calc. / Found H	Anticonvulsant Activity, mg/kg[b] Met
5-Cl	C_6H_5	212–213	$C_{16}H_{12}ClNO_3$	63.69 / 63.79	4.01 / 3.98	NA[c]
6-Cl-7-CH_3	C_6H_5	218–219	$C_{17}H_{14}ClNO_3$	64.66 / 64.53	4.47 / 4.42	600
7-Cl	C_6H_5	168–169	$C_{16}H_{12}ClNO_3$	63.69 / 63.57	4.01 / 4.15	600
4-Cl-7-CH_3O	C_6H_5	211–212	$C_{17}H_{14}ClNO_4$	61.54 / 61.60	4.25 / 4.23	600
H	3-$NO_2C_6H_4$	160–161	$C_{16}H_{12}N_2O_5$	61.54 / 61.59	3.87 / 3.91	600
H	2-HOC_6H_4	206–208	$C_{16}H_{13}NO_4$	67.84 / 67.91	4.63 / 4.61	NA[c]
H	4-$CF_3C_6H_4$	175–176	$C_{17}H_{12}F_3NO_3$	60.90 / 60.93	3.61 / 3.55	300

[a] Recrystallized from ethanol, melting point uncorrected, spectral data consistent with structure. [b] Anticonvulsant screenings were carried out through the Antiepileptic Drug Development Program, National Institutes of Health. The standard screening protocol of the group was followed (see Table I). All compounds were inactive at 600 mg/kg in the maximal electroshock seizure test. [c] No activity at 600 mg/kg.

Table V—Dehydration of Products (Table I) from Isatins and Cyclohexanone



R	mp°,[a]	Formula	Analysis, % Calc. / Found C	Analysis, % Calc. / Found H	Analysis, % Calc. / Found N	Anticonvulsant Activity, mg/kg[b] MES	Met
H	207[c]	$C_{14}H_{13}NO_2$	—	—	—	100[d]	NA[e]
5-Br	245–246[f]	$C_{14}H_{12}BrNO_2$	54.92 / 54.89	3.95 / 3.58	—	600	NA[g]
5-Cl	233–234[f]	$C_{14}H_{12}ClNO_2$	64.25 / 63.78	4.62 / 4.34	5.35 / 4.96	NA[g]	NA[g]
5-CH_3	211–213	$C_{15}H_{15}NO_2$[h]	72.70 / 72.87	6.86 / 6.42	5.30 / 5.14	300	NA[g]
5-NO_2	216–217	$C_{14}H_{12}N_2O_4$	61.76 / 61.65	4.44 / 4.48	10.29 / 10.22	NA[g]	NA[g]
5-CH_3O-6-Cl	265–266	$C_{15}H_{14}ClNO_3$	61.75 / 61.86	4.84 / 4.91	—	NA[g]	NA[g]
H[i]	190–192[j]	$C_{15}H_{15}NO_2$[i]	74.66 / 74.58	6.27 / 6.25	—	300	300

[a] Recrystallized from ethanol, melting point uncorrected, spectral data consistent with structure. [b] Anticonvulsant screenings were carried out through the Antiepileptic Drug Development Program, National Institutes of Health. The standard screening protocol of the group was followed (see Table I). [c] Described in ref. 2. [d] MES ED_{50} 519. TD_{50} > 1600. [e] No activity at 300 mg/kg. [f] Vε insoluble, not recrystallized, but washed with hot solvents. [g] No activity at 600 mg/kg. [h] Analysis for $C_{15}H_{15}NO_2 \cdot 0.5C_2H_5OH$. [i] Dehydration of isatin-2-methylcyclohexanone product. [j] Reported (7) mp 185–186°.

However, to date, no consistent structure to activity pattern has become evident.

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