Synthesis of Potential Anticonvulsants: Condensation of Isatins with Acetone and Related Ketones

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Abstract □ Substituted isatins were condensed with acetone and other ketones to give analogs of 3-hydroxy-3-acetonyloxindole. Some of these alcohols were dehydrated. Several compounds with anticonvulsant activity were obtained.

Keyphrases □ Anticonvulsants, potential—condensation products of isatins with acetone and related ketones, synthesis and evaluation for activity □ Isatins—condensation products with acetone and related ketones, evaluation for anticonvulsant activity

A previous report (1) stated that 3-hydroxy-3-phenacyloxindole (I) (2) and 3-hydroxy-3-acetonyloxindole (II) (3) exhibited anticonvulsant activity in the maximal electroshock seizure (MES) test[1]. At that time, it was reported (1) that although I was active at 100 mg/kg in the MES test[2], all analogs prepared from substituted isatins and substituted acetophenone-type compounds were, with the exception of III and the 1-piperidylmethyl analog of I, inactive at 300 mg/kg in both the MES test and the pentylenetetrazol seizure threshold (Met) test[1]. Dehydration of I to IV and subsequent reduction to V (2) also led to inactive compounds (1).

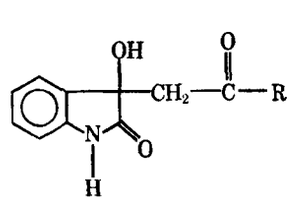
The product (II) derived from isatin and acetone exhibited even greater anticonvulsant activity than I. Compound II had an ED_{50} of 40 mg/kg and a TD_{50} of 490 mg/kg for a protective index of over 12 in the MES test[1]. Compound II also exhibited activity at 300 mg/kg in the Met test. This report describes the synthesis and anticonvulsant activity of various analogs of II.

DISCUSSION

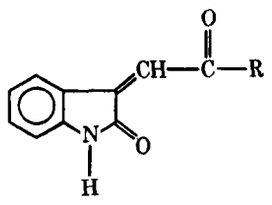
A number of substituted isatins were condensed with an excess of acetone to give analogs of II substituted in the 1-, 4-, 5-, 6-, and 7-positions of the oxindole system (Table I). None of these analogs was as active as II in the MES screen, although the compounds derived from 7-chloroisatin (XX), 4-chloro-7-methylisatin (XXIV), and 5,7-dichloroisatin (XXVI) were active in the MES screen at 100 mg/kg. Further screening of XXIV and the product from 7-methylisatin indicated ED_{50} values of 56 and 118 mg/kg and protective indexes of 3 and 4, respectively, in that screen.

Several of these analogs were more active than II in the Met screen. The compounds from 5-bromoisatin (XIV), 5-nitroisatin (XXVII), 6-chloroisatin (XIX), and 7-methylisatin (XXI) all were active at 100 mg/kg in the Met screen. Both XIV and XVII were inactive in the MES screen at 600 mg/kg. Compound XXI had ED_{50} values of 118 and 115 mg/kg and a protective index of 4 in the MES and Met screens, respectively.

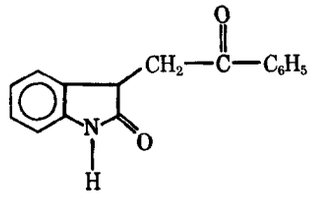
Several other ketones were condensed with isatin to give the products listed in Table II. Compound VIII, which has both a benzoyl and an acetyl group, thereby combining the features of I and II, was inactive in the MES screen but was more active than I and II in the Met screen. Compound XXIX, derived from isatin and isopropyl methyl ketone, had relatively good ED_{50} values of 76 and 159 mg/kg in the MES and Met screens, respectively, but it was one of the most toxic compounds in the series (TD_{50} of 216 mg/kg).



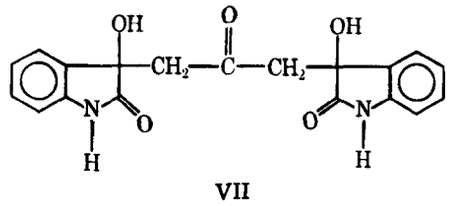
I: R = C_6H_5
II: R = CH_3
III: R = 2-pyridyl



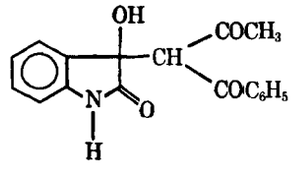
IV: R = C_6H_5
VI: R = CH_3



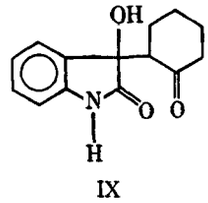
V



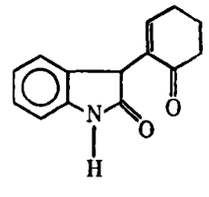
VII



VIII



IX



X

Depending on the ratio of isatin to acetone used, it also is possible to obtain VII (3) from the reaction of isatin and acetone. Several other compounds of this type were prepared (Table III), but none had any appreciable anticonvulsant activity.

As in the dehydration of I to IV (1), dehydration of II to VI was accompanied by a decrease in activity. Dehydration of VII and several other compounds (listed under *Experimental*) also produced inactive compounds. However, dehydration of the product (IX) from isatin and cyclohexanone to X (4) resulted in increased activity in the MES screen from 300 to 100 mg/kg.

In conclusion, II appears to be the most useful compound in this series in the MES screen. Several compounds are of interest in the Met screen,

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

[2] Additional screenings of I indicated an ED_{50} of 102 mg/kg in the MES screen and a TD_{50} of 414 mg/kg with a protective index of ~4.

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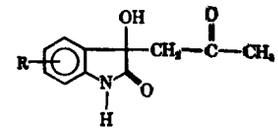

Table I—Reaction of Isatins with Acetone (Ring-Substituted Analogs of II)

Compound	R	Melting Point[a]	Yield, %	Formula		Analysis, % Calc.	Found	Anticonvulsant Activity, mg/kg MES	Met
II	H	163–166° [b]	90	$C_{11}H_{11}NO_3$		—	—	40	300
XI	1-CH_3	146–147° [c]	80	$C_{12}H_{13}NO_3$		—	—	300	300
XII	1-Piperidyl methyl	128–131° [d]	35	$C_{17}H_{20}N_2O_3$		—	—	300[e]	300[e]
XIII	4-CF_3	189–191°	60	$C_{12}H_{10}F_3NO_3$	C	52.75	52.53	100	300[e]
					H	3.69	3.72		
XIV	5-Br	205–206°	73	$C_{11}H_{10}BrNO_3$	C	46.50	46.37	NA[f]	100
					H	3.55	3.53		
					N	4.93	4.82		
XV	5-Cl	200–201°	40	$C_{11}H_{10}ClNO_3$	C	54.90	55.12	600	300
					H	4.27	4.21		
					N	5.79	5.84		
XVI	5-I	233–235°	52	$C_{11}H_{10}INO_3$	C	39.90	40.09	NA[f]	300
					H	3.04	3.11		
XVII	5-NO_2	239–240°	45	$C_{11}H_{10}N_2O_5$	C	52.80	52.70	NA[f]	100
					H	4.03	4.02		
					N	11.29	11.17		
XVIII	5-CH_3	166–168°	22	$C_{12}H_{13}NO_3$	C	65.74	65.72	600	600
					H	5.98	5.44		
					N	6.39	6.27		
XIX	6-Cl	201–203°	34	$C_{11}H_{10}ClNO_3$	C	55.12	55.08	600	100
					H	4.21	4.24		
XX	7-Cl	175–177°	32	$C_{11}H_{10}ClNO_3$	C	55.12	54.95	100	300[e]
					H	4.21	4.32		
					N	5.84	5.75		
XXI	7-CH_3	203–204° [g]	53	$C_{12}H_{13}NO_3$	C	65.74	65.68	300	100
					H	5.98	6.06		
					N	6.39	6.40		
XXII	7-CF_3	205–207° [h]	40	$C_{12}H_{10}F_3NO_3$	C	52.75	52.76	NA[f]	600
					H	3.69	3.76		
XXIII	4-Cl,7-OCH_3	216–218°	50	$C_{12}H_{12}ClNO_4$	C	53.44	53.38	300	300
					H	4.48	4.44		
XXIV	4-Cl,7-CH_3	235–237°	44	$C_{12}H_{12}ClNO_3$	N	5.22[i]	5.52	100	300[e]
XXV	4,7-Cl	223–225°	53	$C_{11}H_9Cl_2NO_3$	C	48.20	48.10	300	300
					H	3.31	3.25		
XXVI	5,7-Cl	187–188°	15	$C_{11}H_9Cl_2NO_3$	C	48.20	48.17	100	300
					H	3.31	3.30		
XXVII	6-Cl,7-CH_3	253–255°	37	$C_{12}H_{12}ClNO_3$	N	5.22[j]	5.65	NA[f]	NA[f]

[a] Recrystallized from ethanol unless otherwise noted. [b] Lit. (3) mp 166–167°. [c] Lit. (3) mp 145°. [d] Lit. (5) mp 129–131°. [e] Toxic at this dose. [f] Inactive at 600 mg/kg. [g] Lit. (6) mp 201–202°. [h] Lit. (6) mp 199–201°. [i] Calc.: Cl, 13.98. Found: Cl, 14.05. [j] Calc.: Cl, 13.98. Found: Cl, 14.05.

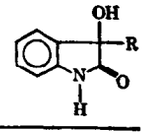

Table II—Condensation of Isatin with Ketones

Compound	Ketone	Melting Point[a]	Yield, %	Formula		Analysis, % Calc.	Found	Anticonvulsant Activity, mg/kg MES	Met
VIII	Benzoyl acetone	184–185° [b]	30	$C_{18}H_{15}NO_4$	C	69.91	69.69	NA[c]	100
					H	4.89	4.94		
					N	4.53	4.83		
IX	Cyclohexanone	198–199° [d]	55	$C_{14}H_{15}NO_3$	C	68.55	68.74	300	NA[c]
					H	6.16	6.19		
XXVIII	Acetyladamantane	189°	38	$C_{20}H_{23}NO_3$	C	73.82	73.84	NA[c]	300
					H	7.12	7.14		
XXIX	Isopropyl methyl ketone	128–130° [e]	94	$C_{13}H_{15}NO_3$		—	—	100	NA[f]

[a] Recrystallized from ethanol. [b] Lit. (7) mp 174–176°. [c] Not active at 600 mg/kg. [d] Lit. (4) mp 167–171°. [e] Lit. (6) mp 128–129°. [f] Not active at 100 mg/kg and toxic at 300 mg/kg.

and XXI is of interest in both screens. The increase in activity caused by dehydration of IX to X is under further investigation.

EXPERIMENTAL[3]

Preparation of 3-Hydroxy-3-acetonyloxindoles (II and XI–XXVII)—Following the procedure of Braude and Lindwall (3), 0.01 mole of isatin, 3 or 4 drops of diethylamine, and 50–100 ml of acetone were heated under reflux on a steam bath for 30–60 min. After standing for several days at room temperature, the products (Table I) were collected by filtration. The oxindoles (VIII, IX, XXVIII, and XXIX) (Table II) were prepared by a similar procedure, with the acetone replaced by 0.1 mole of the appropriate ketone in 25–50 ml of absolute ethanol.

Dehydration to 3-Acetonylideneoxindoles—Following the procedure of Braude and Lindwall (3), 0.01 mole of II, 0.5 ml of concentrated hydrochloric acid, and 17 ml of acetic acid were heated at 95° on a steam

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

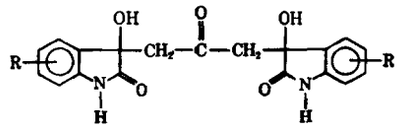

Table III—Reaction of Isatins with Acetone (Ring-Substituted Analogs of VII)

Compound	R	Melting Point[a]	Yield, %	Formula	Analysis, %	Calc.	Found
VII	H	225–227° [b]	39	$C_{19}H_{16}N_2O_5$	C	64.92	64.77
					H	4.63	4.58
					N	7.99	7.95
XXX	5,7-Cl_2	261–262°	12	$C_{19}H_{12}Cl_4N_2O_5$	C	46.56	46.56
					H	2.47[c]	2.49
XXXI	6-Cl	255–256°	8	$C_{19}H_{14}Cl_2N_2O_5$	C	54.17	54.27
					H	3.35	3.93
XXXII	5-CH_3	230–231°	6	$C_{21}H_{20}N_2O_5$	C	66.30	65.99
					H	5.30	5.33
					N	7.36	7.39
XXXIII	5-Cl	250–252°	10	$C_{19}H_{14}Cl_2N_2O_5$	C	54.17	54.19
					H	3.35[d]	3.26

[a] Recrystallized from ethanol. [b] Lit. (3) mp 212–214°. [c] Calc.: Cl, 28.94. Found: Cl, 28.88. [d] Calc.: Cl, 16.83. Found: Cl, 16.78.

bath for 15–30 min. The solution was poured over ice to give a 50% yield of VI, mp 174° [lit. (3) mp 168–171°].

By this procedure, the 7-methyl analog (XXI) was dehydrated to the 7-methyl analog of VI in a 34% yield, mp 307–309°.

Anal.—Calc. for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.36; H, 5.14; N, 6.58.

The 5-bromo analog (XIV) was dehydrated to the 5-bromo analog of VI in a 44% yield, mp 298–299°.

Anal.—Calc. for $C_{11}H_8BrNO_2$: C, 49.65; H, 3.03. Found: C, 49.47; H, 3.16.

The analog from acetyladamantane (XXVIII) was dehydrated in a 59% yield, mp 178–180°.

Anal.—Calc. for $C_{20}H_{21}NO_2$: C, 78.14; H, 6.89. Found: C, 78.08; H, 6.90.

1,3-Bis(3-hydroxy-3-oxindyl)-2-propanones (VII and XXX–XXXIII)—Following the procedure of Braude and Lindwall (3), 0.03 mole of isatin, 0.03 mole of acetone, and 3 or 4 drops of diethylamine in 25 ml of absolute ethanol were refluxed on the steam bath for 15–30 min and allowed to stand for several days. Filtration gave a 39% yield of VII, mp 225–227° [lit. (3) mp 212–214°].

Anal.—Calc. for $C_{19}H_{16}N_2O_5$: C, 64.92; H, 4.63; N, 7.99. Found: C, 64.77; H, 4.58; N, 7.95.

Additional compounds prepared by this procedure are shown in Table III.

Dehydration of VII—Compound VII was dehydrated, as described for the conversion of II to VI, in a 75% yield, mp 263–265°.

Anal.—Calc. for $C_{19}H_{12}N_2O_3$: C, 72.14; H, 3.83; N, 8.86. Found: C, 71.77; H, 3.87; N, 8.79.

1,3-Bis(3-oxindyl)-2-propanone—The dehydration product of VII (0.004 mole) was dissolved in 27 ml of warm ethanol, and 1.5 g of sodium thiosulfate in 7 ml of water was added. The mixture was heated on the steam bath for 25 min, and an additional 1 g of sodium thiosulfate in 7 ml of water was added. The mixture was allowed to stand overnight and then filtered. The filtrate was washed with hot water and recrystallized from ethanol to give a 68% yield of the reduction product, mp 255–257°.

Anal.—Calc. for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.04; N, 8.75. Found: C, 71.17; H, 4.89; N, 8.84.

Dehydration of IX to X—By the described procedure, dehydration of IX with hydrochloric acid in acetic acid gave a 50% yield of X, mp 207° [lit. (4) mp 206–207°].

Anal.—Calc. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77. Found: C, 73.85; H, 5.87.

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