Table II shows the dissolution rates for the batches representing various manufacturers. The batch results are not corrected for aspirin hydrolysis. Only three of the seven batches showed significant amounts of dissolution in the 3–4 hr period. A physical inspection of the residues from batches C_1, D_1, D_2, and D_3 revealed that the tablets were still firm and 90% intact. Batch D_3, which gave one of the lowest percentage rates, was analyzed again at a paddle speed of 100 rpm. There was no increase in dissolution. The percentages were almost identical to the results obtained at 50 rpm. No sample showed signs of dissolution in the 1-hr pretreatment with gastric fluid.

Both batch A_1 and D_1 gave similar salicylate blood level concentrations[12]. Therefore, this dissolution test, in its present form, is not satisfactory for predicting bioavailability.

Suppository Validation Test—Portions of a composite prepared from a commercial 324-mg suppository were analyzed by the USP XX and the dilute-and-read procedures. The result for the USP procedure was 102.5% of declared and 104.9% for the proposed procedure. The UV curves obtained from the standard and sample solutions were nearly identical and showed very little background interference from the suppository excipients. The results obtained for the content uniformity determination of aspirin and the salicylic acid concentrations in suppositories are given in Table III. Three batches from Manufacturer E exceeded the USP XX limit for salicylic acid.

Salicylic Acid Limit Test Validation by TLC—A linear calibration curve was obtained for salicylic acid when concentrations from 0 to 800 ng/μl were spotted. The fluorescent readings were made by scanning the chromatogram with the spectrodensitometer in the reflectance mode at a fluorescence excitation wavelength of 310 nm and an emission wavelength of 410 nm. Table IV shows the data obtained by the TLC and USP XX (5) procedures on commercial samples. Salicylic acid has a relative R_f value of 1.7 compared to aspirin. In addition, five batches of enteric coated tablets (A_1, A_2, B_1, C_1, and D_2) were analyzed for aspirin-related impurities by the HPLC method described previously (3). Table V shows the amounts of impurities found in these batches. Suppository samples were not tested for impurities.

[12] R. D. Kirchhoefer, unpublished data.

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NOTES

Potential Anticonvulsants IV: Condensation of Isatin with Benzoylacetone and Isopropyl Methyl Ketone

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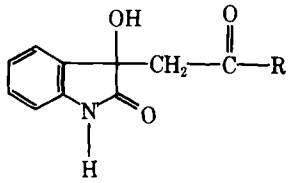
Received June 8, 1981, from the *Department of Chemistry, University of Missouri-Kansas City, Kansas City, MO 64110.* Accepted for publication November 16, 1981.

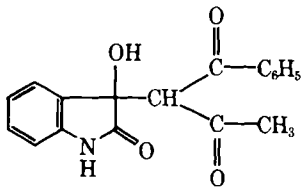
Abstract □ A series of new 3-hydroxy-3-substituted oxindoles were prepared and screened for anticonvulsant activity. A number of these 3-hydroxyoxindoles had activity in the maximal electroshock seizure test.

Keyphrases □ Anticonvulsants—condensation of isatin, benzoylacetone, isopropyl methyl ketone □ Isatin—anticonvulsants, condensation, benzoylacetone, isopropyl methyl ketone □ Benzoylacetone—anticonvulsants, condensation of isatin, isopropyl methyl ketone □ Isopropyl methyl ketone—anticonvulsants, condensation of isatin, benzoylacetone

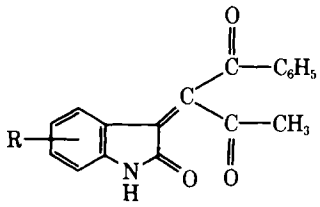
The anticonvulsant activity[1] of 3-hydroxy-3-phenacyloxindole (I) (1) and 3-hydroxy-3-acetonyloxindole (II) has been reported previously. In a study of analogs of I and II (2) it was found in initial screening that III, derived from isatin and benzoylacetone and having features of both I and II, was inactive at 600 mg/kg in the maximal electroshock seizure test (MES)[1] but was active at 100 mg/kg in the pentylenetetrazol seizure threshold test (Met)[1]. Compound IV related to II and derived from isatin and isopropyl methyl ketone, was active at 100 mg/kg in the MES test and inactive in the Met test. This report de-



I R = C_6H_5
II R = CH_3
IV R = $CH(CH_3)_2$



III



V

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

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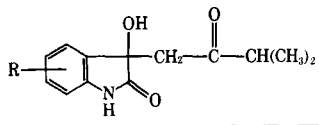
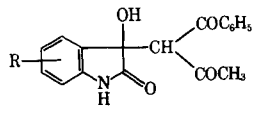
Table I—Reaction of Isatins with Isopropyl Methyl Ketone



R	Melting Point[a]	Formula	Analysis Calc.	Analysis Found	Anticonvulsant Activity, mg/kg MES	Anticonvulsant Activity, mg/kg Met
H[b]	128–130°	$C_{13}H_{15}NO_3$	—	—	100[c]	NA[c]
4-Cl-7-CH_3	149–150[d]	$C_{14}H_{16}ClNO_3$	C 59.68	59.29	300	600
			H 5.72	5.62		
			N 4.97	4.87		
4-Cl-7-OCH_3	139–140	$C_{14}H_{16}ClNO_4$	C 56.48	56.74	NA[e]	600
			H 5.42	5.38		
			N 4.71	4.62		
1-$C_6H_5CH_2$	155–156[f]	$C_{20}H_{21}NO_3$	C 74.28	74.38	NA[e]	300
			H 6.55	6.51		
			N 4.33	4.27		
5-NO_2	261–263	$C_{13}H_{14}N_2O_5$	C 56.11	56.00	NA[e]	NA[e]
			H 5.07	4.97		
5-Br	240–241	$C_{13}H_{14}BrNO_3$	C 50.14	49.95	NA[e]	600
			H 4.53	4.29		

[a] Recrystallized from ethanol unless otherwise noted, melting point uncorrected, spectral data consistent with structure. [b] Described in Reference 2. [c] Additional screening indicated an ED_{50} of 151.8 in the MES test, an ED_{50} of 242.9 in the Met test, and a TD_{50} of 843.6. [d] Recrystallized from chloroform. [e] Not active at 600 mg/kg. [f] Recrystallized from ethyl acetate.

Table II—Reactions of Isatins with Benzoylacetone



R	Melting Point[a]	Formula	Analysis Calc.	Analysis Found	Anticonvulsant Activity, mg/kg MES	Anticonvulsant Activity, mg/kg Met
H[b]	184–185	$C_{18}H_{15}NO_4$	—	—	NA[c]	100
1-CH_3	158–159	$C_{19}H_{17}NO_4$	C 70.57	70.52	NA[c]	NA[c]
			H 5.30	5.19		
			N 4.33	4.40		
1-C_6H_5-CH_2	136–137	$C_{25}H_{21}NO_4$	C 75.20	75.43	NA[c]	NA[c]
			H 5.26	5.33		
			N 3.51	3.58		
5-Br	187–189	$C_{18}H_{14}BrNO_4$	C 55.68	55.38	NA[c]	100
			H 3.64	3.37		
			N 3.61	3.81		
5-Cl	190–192	$C_{18}H_{14}ClNO_4$	C 62.89	62.81	NA[c]	600
			H 4.10	4.16		
			N 4.08	4.07		
5-CH_3	173–174	$C_{19}H_{17}NO_4$	C 70.57	70.16	NA[c]	NAc
			H 5.30	5.71		
			N 4.33	4.06		
5-NO_2	215–217	$C_{18}H_{14}N_2O_6$	C 61.01	60.92	NA[c]	NA[c]
			H 3.98	3.97		
			N 7.91	7.95		
6-Cl	200–201	$C_{18}H_{14}ClNO_4$	C 62.89	62.52	NA[c]	300
			H 4.10	4.11		
			N 4.08	3.80		
4-Cl-7-CH_3	200–201	$C_{19}H_{16}ClNO_4$	C 63.78	63.74	NA[c]	300
			H 4.51	4.63		
			N 3.91	3.86		
4-Cl-7-OCH_3	190–191	$C_{19}H_{16}ClNO_5$	C 61.05	61.24	NA[c]	NA[c]
			H 4.32	4.39		
			N 3.75	3.73		

[a] Recrystallized from ethanol, mp uncorrected, spectral data consistent with structure. [b] Reference 2. [c] Not active at 600 mg/kg.

scribes the synthesis and anticonvulsant activity of analogs of III and IV and related compounds.

RESULTS AND DISCUSSION

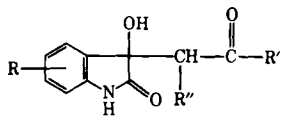
A number of substituted isatins were condensed with isopropyl methyl ketone to give the analogs of IV shown in Table I. None of these compounds were as active as II. Benzoylacetone was also condensed with a number of substituted isatins to give the analogs of III shown in Table II. None of these compounds were active in the MES test and only the 5-bromo analog of III was as active as III in the Met test. Subsequent screening of IV has shown an ED_{50} of 151.8 in the MES test, 242.9 in the Met test, and 211.8 in the subcutaneous picrotoxin test with a TD_{50} of 843.6. This compound gave a maximum protection of 62.5% at 200 mg/kg in the subcutaneous bicuculline test.

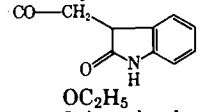
Dehydration of analogs of III derived from 5-bromoisatin and from 4-chloro-7-methoxyisatin gave compounds (V) inactive at 600 mg/kg in both the MES and Met screens.

Anticonvulsant screening results of a number of related compounds are included in Table III and further screening results on analogs of II (2) are included in Table IV.

In the 3-hydroxyoxindoles studied to date, II has the best activity and protective index in the MES test. None of the compounds in this report

Table III—3-Substituted-3-Hydroxyoxindoles



R	R′	R″	Melting Point[a]	Formula	Analysis Calc.	Analysis Found	Anticonvulsant Activity, mg/kg MES	Anticonvulsant Activity, mg/kg Met
1-$C_6H_5CH_2$	C_6H_5	H	197–198[b]	$C_{23}H_{19}NO_3$	C 77.29	77.38	NA[c]	NA[c]
					H 5.36	5.43		
					N 3.92	4.00		
1-$C_6H_5CH_2$	CH_3	H	162–163	$C_{18}H_{17}NO_3$	C 73.20	73.07	NA[c]	600
					H 5.80	5.70		
					N 4.74	4.81		
1-(4-BrC_6H_4)$NHCH_2$	CH_3	H	163–165	$C_{18}H_{17}BrN_2O_3$	C 55.54	55.40	NA[c]	NA[c]
					H 4.40	4.21		
					N 7.20	7.31		
1-(*N*-morpholino)CH_2	CH_3	H	168–169	$C_{16}H_{20}N_2O_4$	C 63.14	63.20	300	NA[c]
					H 6.62	6.64		
					N 9.21	9.11		
H	C_6H_5	C_6H_5	156–158[d]	$C_{22}H_{17}NO_3$	—	—	NA[c]	600
H	$CH_2C_6H_5$	C_6H_5	163–164	$C_{23}H_{19}NO_3$	C 77.29	77.06	NA[c]	NA[c]
					H 5.36	5.31		
					N 3.92	3.87		
6-Cl-7-CH_3	C_6H_{11} (cyclo)	H	148–150[e]	$C_{17}H_{20}ClNO_3$	C 63.45	63.31	600	600
					H 6.26	6.28		
					N 4.35	4.33		
H		H	221–223	$C_{20}H_{16}N_2O_6$	C 63.15	62.96	NA[c]	NA[c]
					H 4.24	4.25		
					N 7.37	7.32		
H	OC_2H_5	$CO_2C_2H_5$	155–157[f]	$C_{15}H_{17}NO_6$	—	—	NA[c]	NA[c]
H	2-Acetylcyclohexanone[g]		215–216	$C_{24}H_{22}N_2O_6$	C 66.35	66.38	600	NA[c]
					H 5.10	5.05		
					N 6.45	6.51		

[a] Recrystallized from ethanol unless otherwise noted. [b] Recrystallized from *n*-butanol. [c] Not active at 600 mg/kg. [d] Reported (5) mp 156–158°. [e] Recrystallized from benzene. [f] Reported (6) mp 156–158°. [g] Condensation with 2 moles of isatin.

have outstanding activity in the Met test. The effect of structure to activity in the 3-hydroxyoxindoles is still not clear, although it appears that substituents on the oxindole portion of the molecule do not enhance and generally decrease the activity. The study of the effect of substituents in the 3-position is being continued.

EXPERIMENTAL[2]

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

Dehydration of 3-Hydroxyoxindoles.—Following the procedure of Braude and Lindwall (4) the product from 5-bromoisatin and benzoylacetone was heated on a steam bath in acetic acid containing a small amount of hydrochloric acid to give V (R = 5-Br), mp 232–234° (ethanol).

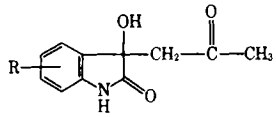
Anal.—Calc. for $C_{18}H_{12}BrNO_3$: C, 58.40; H, 3.27; N, 3.78. Found: C, 58.22; H, 3.55; N, 3.64.

In a similar manner V (R = 4-Cl-7-OCH_3), mp 225–226° (ethanol), was obtained.

Anal.—Calc. for $C_{19}H_{14}ClNO_4$: C, 64.14; H, 3.97; N, 3.94. Found: C, 64.18; H, 4.03; N, 3.86.

[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 the Spang Microanalytical Laboratory.

Table IV—Analogs of II[a]



R	MES ED_{50}	Met ED_{50}	TD_{50}
H	40	—	490
6-Cl	337.5	279.2	585.2
7-Cl	64.4	131.8	297.9
4-Cl-7-OCH_3	802.4	404.8	>1500
4-Cl-7-CH_3	90.2	211.5	615.4
4,7-Cl_2	127.8	242.8	~00

[a] Reference 2.

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