Synthesis of 3-Hydroxy-3-phenacyloxindole Analogs

F. D. POPP ˣ and B. E. DONIGAN

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Abstract □ Substituted isatins and substituted acetophenones were condensed to give analogs of 3-hydroxy-3-phenacyloxindole. These alcohols were dehydrated, and the alkene was reduced. None of the products had the level of anticonvulsant activity exhibited by the parent compound.

Keyphrases □ 3-Hydroxy-3-phenacyloxindole analogs—synthesized as potential anticonvulsants □ Isatins, substituted—condensed with substituted acetophenones to give 3-hydroxy-3-phenacyloxindole analogs, screened for anticonvulsant activity □ Acetophenones, substituted—condensed with substituted isatins to give 3-hydroxy-3-phenacyloxindole analogs, screened for anticonvulsant activity □ Anticonvulsant activity—screening of 3-hydroxy-3-phenacyloxindole analogs

3-Hydroxy-3-phenacyloxindole (I) (1) and the related Compound II (2) were synthesized by condensation of isatin with the appropriate methyl ketones. Both I and II exhibited anticonvulsant activity in the maximal electroshock seizure test[1]. This paper reports on the synthesis and screening of various analogs of I.

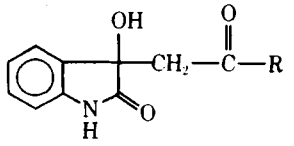
DISCUSSION

With the procedure of Lindwall and coworkers (1, 2), a number of isatin derivatives were condensed with a number of acetophenones to give 3-hydroxy-3-phenacyloxindoles (Table I) of type III. Dehydration of III gave 3-phenacylidene-2-indolinones (Table II) of type IV, which were reduced to 3-phenacyl-2-indolinones (Table III) of type V.

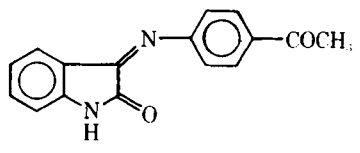
Although I (1 in Table I) was active at both 100 and 300 mg/kg in the maximal electroshock seizure test, all other compounds in Tables I–III, except 3 and 14, were inactive at 300 mg/kg in both that screen and the pentylenetetrazol seizure threshold test[1]. Compounds 14, formed from isatin and 2-acetylpyridine, and 3, formed from 1-piperidylmethylisatin and acetophenone were both active at 300 mg/kg in the maximal electroshock seizure test.

The Schiff base (VI) derived from isatin and 4-aminoacetophenone was also inactive as an anticonvulsant.

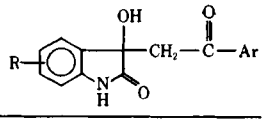
Some of the compounds submitted for other screening were found to be inactive[1]. Compounds 2, 5, 6, and 18 were inactive at 640 mg/kg in an antimalarial screen; 1 and 25 were inactive in an antitrypansomiasis



I: R = C_6H_5
II: R = CH_3



VI



[1] Anticonvulsant and anticancer screenings were carried out through the National Institutes of Health and antimalarial and antitrypansomiasis screenings were carried out through the Walter Reed Army Medical Center. The standard protocols of these groups were followed.

Table I—Reaction of Isatins with Methyl Aryl Ketones (Type III)

Compound	R	Ar	Melting Point[a]	Yield, %	Formula		Analysis, % Calc.	Found	IR (KBr), cm^{-1}
1	H	C_6H_5	173–175°[b]	80	$C_{16}H_{13}NO_3$		—	—	3350, 1710, 1680
2	1-CH_3	C_6H_5	173–175°[c]	84	$C_{17}H_{15}NO_3$	N	4.98	4.84	—
3	1-$CH_2C_5H_{10}N$	C_6H_5	143–145°	71	$C_{22}H_{24}N_2O_3$	C	72.50	72.19	3300, 1685–1695
						H	6.64	6.45	
4	5-Br	C_6H_5	220–221°	79	$C_{16}H_{12}BrNO_3$	N	4.05	4.02	3250, 1680–1705
5	5-CH_3	C_6H_5	189–190°	81	$C_{17}H_{15}NO_3$	N	4.98	4.92	3325, 1710, 1670
6	5-NO_2	C_6H_5	230–232°	63	$C_{16}H_{12}N_2O_5$	N	8.97	8.91	3250, 1705, 1675
7	5,7-$(CH_3)_2$	C_6H_5	181–182°	68	$C_{18}H_{17}NO_3$	N	4.74	4.67	3300, 1705, 1665
8	6-Cl	C_6H_5	209–211°	48	$C_{16}H_{12}ClNO_3$	C	63.69	63.63	3300, 1710, 1680
						H	4.01	4.07	
9	H	4-$NO_2C_6H_4$	185–186°	68	$C_{16}H_{12}N_2O_5$	C	61.54	61.41	3200–3400, 1720, 1690
						H	3.87	3.74	
10	H	4-$C_5H_{10}NC_6H_4$	209–211°	90	$C_{21}H_{22}N_2O_3$	C	71.98	71.95	3375, 1700, 1660
						H	6.33	6.37	
11	H	4-$CH_3C_6H_4$	189–192°[d]	88	$C_{17}H_{15}NO_3$		—	—	3350, 1710, 1670
12	H	4-$CH_3OC_6H_4$	184–186°[e]	94	$C_{17}H_{15}NO_4$		—	—	3360, 1700, 1665
13	H	4-ClC_6H_4	197–199°[f]	97	$C_{16}H_{12}ClNO_3$		—	—	3350, 1665–1700
14	H	2-Pyridyl	159–160°	57	$C_{15}H_{12}N_2O_3$	C	67.17	67.01	3250, 1680–1710
						H	4.51	4.55	
15	H	3-Pyridyl	144–146°	17	$C_{15}H_{12}N_2O_3$	C	67.15	67.20	3275, 1705, 1690
						H	4.51	4.42	
16	H	3-Indolyl	180°	61	$C_{18}H_{14}N_2O_3$	C	70.58	70.65	3250–3300, 1695–1710
						H	4.61	4.65	
						N	9.15	8.88	
17	H	Ferrocenyl	190°	93	$C_{20}H_{17}FeNO_3$	C	64.02	64.01	3350, 1700, 1650
						H	4.57	4.65	
						N	3.73	3.66	

[a] Recrystallized from ethanol. [b] Lit. (1) mp 169–172°. [c] Lit. (1) mp 168–170°. [d] Lit. (1) mp 185–186°. [e] Lit. (1) mp 186–187°. [f] Lit. (1) mp 175–176° (material softens at 175° and melts at 197–199°).

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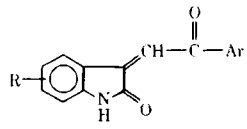

Table II—Dehydration of Dioxindoles (Type IV)

Compound	R	Ar	Melting Point[a]	Yield, %	Formula		Analysis, % Calc.	Found	IR (KBr), cm^{-1}
18	H	C_6H_5	192–194°[b]	81	$C_{16}H_{11}NO_2$		—	—	1710, 1660
19	5-Br	C_6H_5	204–205°	92	$C_{16}H_{10}BrNO_2$	C	58.56	58.72	1710, 1665
						H	3.07	3.15	
20	5-CH_3	C_6H_5	174–175°	67	$C_{17}H_{13}NO_2$	C	77.55	77.52	1705, 1655
						H	4.98	5.04	
21	5-NO_2	C_6H_5	230–231°	85	$C_{16}H_{10}N_2O_4$	C	65.30	65.36	1705, 1655
						H	3.42	3.42	
22	5,7-$(CH_3)_2$	C_6H_5	225–226°	92	$C_{18}H_{15}NO_2$	C	77.96	77.91	1705, 1670
						H	5.45	5.44	
23	6-Cl	C_6H_5	250–251°	95	$C_{16}H_{10}ClNO_2$	C	67.73	67.89	1710, 1660
						H	3.55	3.47	
24	H	3-Indolyl	294–295°	92	$C_{18}H_{12}N_2O_2$	C	74.99	74.85	1705
						H	4.20	4.31	
						N	9.72	9.65	

[a] Recrystallized from ethanol. [b] Lit. (1) mp 193–194°.

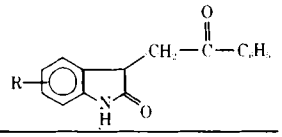

Table III—Reduction to Oxindoles (Type V)

Compound	R	Melting Point[a]	Yield, %	Formula		Analysis, % Calc.	Found	IR (KBr), cm^{-1}
25	H	173–175°[b]	90	$C_{16}H_{13}NO_2$		—	—	1695, 1670
26	5-Br	253–254°	74	$C_{16}H_{12}BrNO_2$	C	58.20	58.21	1700, 1670
					H	3.66	3.69	
27	5-CH_3	210–211°	82	$C_{17}H_{15}NO_2$	C	76.96	76.94	1670–1700
					H	5.70	5.62	
28	6-Cl	171–172°	90	$C_{16}H_{12}ClNO_2$	C	67.25	67.08	1700, 1675
					H	4.23	4.18	

[a] Recrystallized from ethanol. [b] Lit. (1) mp 177°.

screen; 1, 4, 16–19, 22, 24, and 25 were all inactive at 400 mg/kg in the L-1210 lymphoid leukemia screen; and 2–5, 11–14, 21, and VI were all inactive at 200 mg/kg in the P-388 lymphocytic leukemia screen.

Preliminary studies on analogs of II appear more promising and will be reported in detail at a later date.

EXPERIMENTAL

Preparation of 3-Hydroxy-3-phenacyloxindoles (III)—Equimolar amounts (0.01 mole) of the isatin and acetophenone in 30–50 ml of absolute ethanol, containing 3–4 drops of diethylamine, were heated at reflux on the steam bath for 30–60 min. After standing for several days at room temperature, the products (Table I) were collected by filtration.

Conversion of III to 3-Phenacylidene-2-indolinones (IV)—A mixture of 0.01 mole of III, 0.5 ml of concentrated hydrochloric acid, and 17 ml of acetic acid was heated at 95° on the steam bath for 15–30 min. Ethanol (17 ml) was added, and the mixture was allowed to stand at room temperature. The products listed in Table II were obtained.

Conversion of IV to 3-Phenacyl-2-indolinones (V)—To 1 g of IV in 25 ml of ethanol was added 2 g of sodium hyposulfite in 7 ml of water. The mixture was heated at 95° until the color disappeared and then was heated for 7 min more. After filtration, the products listed in Table III were obtained.

Synthesis of Schiff Base VI—Equimolar quantities of isatin and 4-aminoacetophenone in absolute ethanol were heated at reflux on the steam bath for 30 min. After cooling, filtration gave a 90% yield of VI, mp 257–258° (from ethanol).

Anal.—Calc. for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58. Found: C, 72.69; H, 4.54.

REFERENCES

(1) H. G. Lindwall and J. S. Maclennan, *J. Am. Chem. Soc.*, **54**, 4739 (1932).

(2) F. Brande and H. G. Lindwall, *ibid.*, **55**, 325 (1933).