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Cyclic Hydroxamic Acids Derived from Indole

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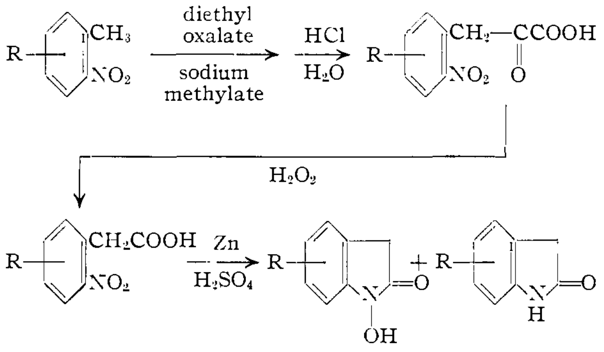
A series of oxindoles and 1-hydroxyoxindoles has been prepared by the zinc and sulfuric acid reduction of the appropriate *o*-nitrophenylacetic acids. It has been observed that halogenated oxindoles may be prepared by heating 1-methoxyoxindoles or 1-hydroxyoxindoles with hydrobromic or hydrochloric acid. A number of benzaloxindoles are also described.

Recent investigators have shown that cyclic hydroxamic acids derived from pyrazine,[1] pyridine,[2] pyrimidine,[2a] quinoline[2] and quinazoline[2b] have antibacterial activity. Interest in this class of compounds was first stimulated by the discovery that the antibiotic aspergillic acid is a cyclic hydroxamic acid.[1a,3] It has since been postulated by Lott and Shaw[2a] that the activity of this class of compounds is due to their ability to combine with and remove from the field of action metabolically essential metals such as iron by their chelating action.

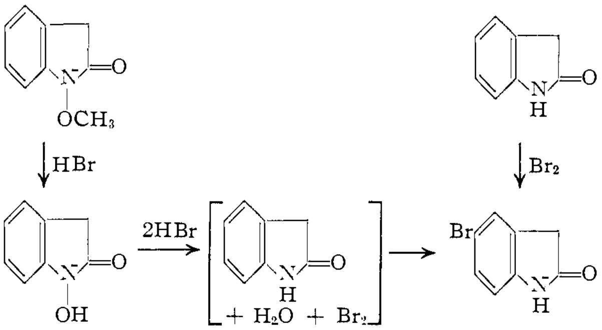
We have prepared a number of 1-hydroxyoxindoles (Table III). These were obtained by the method of Reissert[4] which consists of reducing an *o*-nitrophenylacetic acid with zinc and sulfuric acid to obtain the 1-hydroxyoxindole, often along with the oxindole as a by-product. The *o*-nitrophenylacetic acids were prepared from the *o*-nitrotoluenes through the pyruvic acids[5] as illustrated below.



The best yields of the acetic acids were obtained when the solution of crude *o*-nitrophenylpyruvic acid was treated directly with hydrogen peroxide, as appreciable material was lost in the isolation of the more soluble pyruvic acids. However, when the acetic acids were prepared from isolated pyruvic acids, these could be reduced directly without isolation and in fact better over-all yields were often obtained by this process. As most of the substituted phenylpyruvic and phenylacetic acids are unknown in the literature these are reported in Tables I and II.

In an effort to improve the yield of 1-hydroxyoxindole, a few attempts were made to reduce *o*-nitrophenylacetic acid with (a) zinc and calcium chloride and (b) calcium sulfhydrate. In the first case the maximum yield obtained was 15%; in the second, no 1-hydroxyoxindole was obtained. The zinc and calcium chloride reduction of 2-chloro-6-nitrophenylacetic acid gave even poorer results.

1-Methoxyoxindole was easily prepared by treating 1-hydroxyoxindole with dimethyl sulfate. When this compound was treated with aqueous hydrogen bromide, a monobromoöxindole was formed. The same compound was obtained when 1-hydroxyoxindole was treated with hydrogen bromide and both of these products were identical by melting point, mixed melting point and infrared spectra with a sample of 5-bromoöxindole prepared by the direct bromination of oxindole.[6] It appears likely that oxidation–reduction occurs between 1-hydroxyoxindole and hydrogen bromide and that the bromine which is formed halogenates the intermediate oxindole.



When 1-methoxyoxindole was treated with concentrated hydrochloric acid an 18% yield of a monochloroöxindole melting at 195–196° was obtained. This is presumed to be 5-chloroöxindole.

Bromination of 1-methoxyöxindole resulted in a 64% yield of a monobromo derivative; by analogy with literature studies of the bromination of oxindoles,[6,7] the bromine atom is assigned to the 5-position and the product is 5-bromo-1-methoxyoxindole. When this compound was refluxed with concentrated hydrochloric acid, a compound believed to be 5-bromo-7-chloroöxindole was obtained in 40% yield.

The oxindoles reacted with benzaldehydes in the presence of a piperidine catalyst to form 3-benzaloxindoles,[8] usually in nearly quantitative yields. A number of these are described in Table IV.

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(1) (a) J. D. Dutcher and O. Wintersteiner, *J. Biol. Chem.*, **155**, 359 (1944); (b) G. Dunn, *et al.*, *Nature*, **164**, 181 (1949); (c) S. R. Safir and J. H. Williams, *J. Org. Chem.*, **17**, 1298 (1952).

(2) (a) A. Lott and E. Shaw, THIS JOURNAL, **71**, 70 (1949); (b) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1864 (1948).

(3) (a) J. D. Dutcher, *J. Biol. Chem.*, **171**, 321 (1947); (b) G. Dunn, G. T. Newbold and F. S. Spring, *Nature*, **162**, 779 (1948).

(4) A. Reissert, *Ber.*, **41**, 3921 (1908).

(5) (a) F. J. DiCarlo, THIS JOURNAL, **66**, 1420 (1944); (b) F. Mayer and G. Balle, *Ann.*, **403**, 188 (1914).

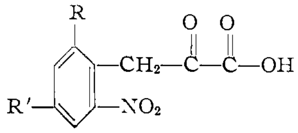
(6) W. C. Sumpter, M. Miller and L. N. Hendrick, THIS JOURNAL, **67**, 1656 (1945).

(7) R. Stolle, *J. prakt. Chem.*, **128**, 1 (1930).

(8) A. Wahl and P. Bagard, *Compt. rend.*, **149**, 132 (1909).

TABLE I

2-NITROPHENYLPYRUVIC ACIDS

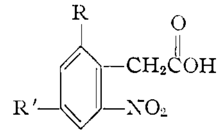


R	R′	Yield, %	M.p., °C.	Formula	Carbon, %		Hydrogen, %		Chlorine, %		Nitrogen, %	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
H	H	51	119–120[a]									
H	Cl	39	137–139	$C_9H_6ClNO_5$	44.4	44.5	2.49	2.59	14.6	14.4	5.75	5.85
Cl	H	35	104–106[b]	$C_9H_6ClNO_5$	44.4	44.3	2.48	2.65	14.6	14.4	5.75	5.67
CH_3	H	32	125–126	$C_{10}H_9NO_5$	53.8	54.0	4.06	3.95			6.28	6.25

[a] Ref. 5a reported, m.p. 119–120°. [b] F. C. Uhle, THIS JOURNAL, 71, 763 (1949), reported m.p. 114–115°.

TABLE II

2-NITROPHENYLACETIC ACIDS

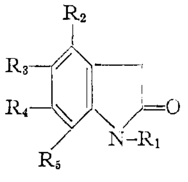


R	R′	M.p., °C.	Yield, %		Formula	Carbon, %		Hydrogen, %		Halogen, %		Nitrogen, %	
			a	b		Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
H	H	140–141[c]	50	93									
H	Cl	166–168	4		$C_8H_6ClNO_4$	44.6	44.6	2.81	2.83	16.5	16.3	6.50	6.35
Cl	H	196–197	51	93	$C_8H_6ClNO_4$	44.6	44.7	2.81	2.82	16.5	16.3	6.50	6.45
H	*i*-Propyl	132–133	42		$C_{11}H_{13}NO_4$	59.2	59.4	5.87	5.78			6.28	6.12
H	CH_3	171–172	34		$C_9H_9NO_4$	55.4	55.5	4.65	4.48			7.18	7.08
CH_3	H	192–193	62	94	$C_9H_9NO_4$	55.4	55.5	4.65	4.53			7.18	7.06

[a] Prepared directly from the *o*-nitrotoluene. [b] Prepared from the substituted pyruvic acid. [c] Ref. 5b reported m.p. 141°.

TABLE III

DERIVATIVES OF OXINDOLE



R_1	R_2	R_3	R_4	R_5	Yield, % From nitrophenyl- Acetic	Yield, % From nitrophenyl- Pyruvic	M.p., °C.	Formula	Carbon, %		Hydrogen, %		Halogen, %		Nitrogen, %	
									Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
OH	H	H	H	H	22 15[a]	47	199–201[b]	$C_8H_7NO_2$	64.4	64.3	4.73	4.56			9.39	9.35
OH	Cl	H	H	H	18–25 16[a,c]	38–41	230–232	$C_8H_6ClNO_2$	52.3	52.4	3.30	3.36	19.3	19.6	7.63	7.56
OH	H	H	Cl	H		33	241–242	$C_8H_6ClNO_2$	52.3	52.4	3.30	3.14	19.3	19.0	7.63	7.71
OH	Me	H	H	H	5[c]		219–220	$C_9H_9NO_2$	66.2	66.4	5.56	5.46			8.58	8.66
OH	H	H	*i*-Pro	H	18[c]		165–167	$C_{11}H_{13}NO_2$	69.2	69.2	6.86	7.00			7.33	7.10
H	Cl	H	H	H	25–39	16	217–218	C_8H_6ClNO	57.3	57.4	3.61	3.44	21.2	21.1	8.36	8.27
H	Me	H	H	H	62		211–212	C_9H_9NO	73.5	73.6	6.16	6.19			9.52	9.61
H	H	Br	H	H		21[d]	218–220	C_8H_6BrNO	45.3	45.2	2.85	3.06	37.7	37.6	6.61	6.63
H	H	Cl	H	H		18[e]	195–196	C_8H_6ClNO	57.3	57.3	3.61	3.82	21.2	21.3	8.36	8.57
H	H	Br	H	Cl		40[f]	252–253	$C_8H_5BrClNO$	39.0	38.8	2.04	1.88	[g]		5.68	5.83
OMe	H	H	H	H		65[h]	84–86[c]	$C_9H_9NO_2$	66.2	66.3	5.56	5.52			8.58	8.54
OMe	H	Br	H	H		64[e]	118–120	$C_9H_8BrNO_2$	44.7	44.6	3.33	3.34	33.0	32.9	5.79	5.77

[a] From zinc and calcium chloride reduction. [b] Reference 5a reported m.p. 198–199°. [c] Crude yield. [d] From 1-hydroxyoxindole. [e] From 1-methoxyoxindole. [f] From 5-bromo-1-methoxyoxindole. [g] Bromine: calcd. 32.4, found 32.6. Chlorine: calcd. 14.4, found 14.6. [h] From 1-hydroxyoxindole; ref. 4 reported m.p. 86.5°.

Experimental

***o*-Nitrophenylpyruvic Acids** (Table I).—All of the *o*-nitrophenylpyruvic acids were prepared by the same general method as described below:

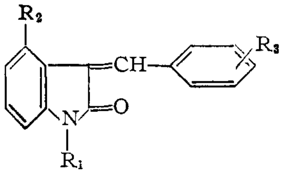
A cooled solution of 1 mole of diethyl oxalate and 1 mole of the *o*-nitrotoluene was added to a cooled solution of 1 mole of sodium methylate in about 300 ml. of anhydrous ethanol. The reaction mixture was stirred for one-half hour at room temperature and then heated on the steam-bath for one-half hour. It was then cooled to 60° or lower and about 600 ml. of water was added. The mixture was again refluxed for one hour and then steam distilled for one hour or longer if necessary to remove the unreacted nitrotoluene. After clarification with activated carbon, the clear filtrate was acidified with hydrochloric acid and the precipitate which separated was either used directly or recrystallized from water.

In the preparation of 2-chloro-6-nitrophenylpyruvic acid, the unreacted 2-chloro-6-nitrotoluene was very slow in distilling so the steam distillation was stopped and the upper layer was separated, clarified with activated carbon and acidified with hydrochloric acid for the desired product.

***o*-Nitrophenylacetic Acids (Table II) Prepared Directly from the *o*-Nitrotoluene.**—The aqueous solution of the crude *o*-nitrophenylpyruvic acid either after steam distillation or after separation of the upper layer was clarified with activated carbon and then adjusted to *p*H 8–9. A 3–6% solution of hydrogen peroxide was then added at 30–40° until a small sample of the reaction mixture when made alkaline

TABLE IV

BENZALOXINDOLES



R_1	R_2	R_3	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Halogen, % Calcd.	Halogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H	Cl	*o*-Cl	96	243–245	$C_{15}H_9Cl_2NO$	62.1	62.1	3.13	2.94	24.4	24.2	4.83	4.68
H	Cl	*p*-Cl	92	245–247	$C_{15}H_9Cl_2NO$	62.1	61.9	3.13	3.11	24.4	24.1	4.83	4.75
H	Cl	*o*-OH	57	182–184	$C_{15}H_{10}ClNO_2$	66.3	66.3	3.71	3.64	13.1	13.2	5.16	5.08
H	Cl	*p*-OH	67	280–283	$C_{15}H_{10}ClNO_2$	66.3	66.3	3.71	3.84	13.1	12.8	5.16	5.08
OH	H	H	72	219–221	$C_{15}H_{11}NO_2$	76.0	76.1	4.67	4.77			5.90	5.81
OH	H	*p*-Cl	55	201–205	$C_{15}H_{10}ClNO_2$	66.3	65.6	3.71	4.40	13.1	12.5	5.16	5.00
OH	H	*p*-OH	92	244–246	$C_{15}H_{11}NO_3$	71.1	71.1	4.37	4.55			5.53	5.77
OH	H	*o*-OCH_3	94	255–257	$C_{16}H_{13}NO_3$	71.9	72.1	4.90	4.89			5.24	5.02
OH	H	*p*-$(CH_3)_2N$	80	231–233	$C_{17}H_{16}N_2O_2$	72.8	73.0	5.75	5.81			9.99	10.1
OH	H	*o*-NO_2	75	244–246	$C_{15}H_{10}N_2O_4$	63.8	63.7	3.57	3.50			9.93	9.99
OH	H	*p*-NO_2	78	246–248	$C_{15}H_{10}N_2O_4$	63.8	63.8	3.57	3.58			9.93	9.95
OH	Cl	H	65	202–203	$C_{15}H_{10}ClNO_2$	66.3	66.4	3.71	3.65	13.1	12.8	5.16	5.13
OH	Cl	*o*-Cl	85	239–240	$C_{15}H_9Cl_2NO_2$	58.8	58.8	2.96	2.66	23.2	23.0	4.58	4.46
OH	Cl	*p*-Cl	79	249–251	$C_{15}H_9Cl_2NO_2$	58.8	58.8	2.96	3.16	23.2	22.9	4.58	4.78
OH	Cl	*p*-OH	85	265–267	$C_{15}H_{10}ClNO_3$	62.6	62.4	3.50	3.69	12.3	11.9	4.87	4.75
OH	Cl	*p*-CH_3CONH	89	>260	$C_{17}H_{13}ClN_2O_3$	62.1	62.1	3.99	4.03	10.8	10.8	8.53	8.56
OH	Cl	*p*-$(CH_3)_2N$	83	234	$C_{17}H_{15}ClN_2O_2$	64.9	64.9	4.80	4.83	11.3	11.2	8.90	8.77

with sodium hydroxide no longer gave the dark color characteristic of alkaline pyruvic acids. The reaction mixture was then acidified with concentrated hydrochloric acid and the product filtered off and recrystallized from dilute ethanol.

***o*-Nitrophenylacetic Acids (Table II) Prepared from the *o*-Nitrophenylpyruvic Acids.**—A mixture of the *o*-nitrophenylpyruvic acid, about 10 parts of water and enough sodium hydroxide to adjust the solution to *p*H 8–9 was treated as above with 3% hydrogen peroxide. The pure *o*-nitrophenylacetic acid was obtained on acidification and recrystallization from dilute ethanol.

1-Hydroxyoxindole by Zinc and Sulfuric Acid Reduction.—A mixture of 450 g. of *o*-nitrophenylpyruvic acid in three liters of water was made alkaline by the addition of 450 ml. of 5 *N* sodium hydroxide and 2,640 ml. of 3% hydrogen peroxide was added over a one-hour period at 28–32°. The solution was stirred for 1.5 hours longer and then clarified with activated carbon. The filtrate was acidified with 1,950 g. of 50% sulfuric acid and 340 g. of zinc dust was then added over a one-hour period. The mixture was stirred for two hours longer at 30–35° and the insoluble portion was filtered off. The product was dissolved in sodium carbonate solution and reprecipitated with hydrochloric acid. Recrystallization from water yielded 132 g. (47%) of pure 1-hydroxyoxindole, m.p. 199–201°.

When the reduction was run on *o*-nitrophenylacetic acid, the yields were only 20 and 24% in two experiments.

1-Hydroxyoxindole by Zinc and Calcium Chloride Reduction.—A mixture of 9.05 g. of *o*-nitrophenylacetic acid, 10 ml. of water, 50 ml. of anhydrous ethanol and 0.5 g. of calcium chloride was heated to 70–80° and 7.85 g. of zinc dust was added over about five minutes. The reaction mixture was refluxed for 1.25 hours and filtered hot. On working up the precipitate and filtrate, 4.2 g. of *o*-nitrophenylacetic acid was recovered and 1.1 g. (15%) of 1-hydroxyoxindole was obtained.

Attempts to Prepare 1-Hydroxyoxindole by Reduction with Calcium Sulfhydrate.—An alkaline solution of 9.05 g. of *o*-nitrophenylacetic acid in 50 ml. of water was added over a 20-minute period to 21.4 ml. of a solution containing 5.8 g. of calcium sulfhydrate. Portions were stirred for 30 minutes and for 24 hours and were then acidified with hydrochloric acid. The only product which could be isolated was *o*-nitrophenylacetic acid. Other attempts to prepare 1-hydroxyoxindole by variations of the above procedure did not yield the desired compound.

6-Chloro-1-hydroxyoxindole.—A solution of 17.3 g. of 4-chloro-2-nitrophenylpyruvic acid and 15 ml. of 5 *N* sodium hydroxide in 150 ml. of water was treated with 3% hydrogen peroxide until a small portion of the solution no longer gave a dark color when made alkaline with sodium hydroxide. The solution was acidified with 70 g. of 50% sulfuric acid. Eleven grams of zinc dust was added slowly at 35–40° and the mixture was then stirred for three hours longer and filtered. The precipitate was suspended in 200 ml. of water and the mixture was made strongly alkaline with dilute sodium hydroxide and filtered. The filtrate was neutralized and then filtered. This precipitate was dissolved in 200 ml. of 5% sodium carbonate, clarified and the filtrate again acidified until neutral and filtered. The product was recrystallized from 500 ml. of 50% ethanol. The yield of pure 6-chloro-1-hydroxyoxindole was 4.3 g. (33%), m.p. 241–242°.

4-Chloro-1-hydroxyoxindole by Zinc and Sulfuric Acid Reduction.—A solution of 61 g. of 2-chloro-6-nitrophenylpyruvic acid in 50 ml. of 5 *N* sodium hydroxide and 500 ml. of water was treated with 300 ml. of 3% hydrogen peroxide until a portion of the solution no longer gave a dark color when made alkaline with sodium hydroxide. The solution was then acidified with 225 g. of 50% sulfuric acid and treated over a 0.5-hour period at 35–40° with 39.3 g. of zinc dust. The mixture was stirred for 3.5 hours longer at 35–40°. During this period an additional 200 ml. of water was added in order to dilute the reaction mixture for better stirring. The precipitate was filtered off, washed with water and then stirred with a solution of 35 g. of sodium carbonate in 100 ml. of water. The insoluble portion was filtered off and saved for recovery of by-product 4-chlorooxindole as described below. The filtrate was clarified with activated carbon, acidified to *p*H 7 and filtered. The crude yield of 4-chloro-1-hydroxyoxindole was 20.7 g., m.p. 228–230°. Recrystallization from 80% ethanol increased the melting point to 230–232°.

In two experiments in which 2-chloro-6-nitrophenylacetic acid was reduced by the above procedure, the yields of 4-chloro-1-hydroxyoxindole were only 18 and 25%.

4-Chloro-1-hydroxyoxindole by Zinc and Calcium Chloride Reduction.—A mixture of 10.8 g. of 2-chloro-6-nitrophenylacetic acid, 10 ml. of water, 50 ml. of ethanol and 0.5 g. of calcium chloride was heated to 70°. Zinc dust (7.85 g.) was added over about five minutes and the mixture was held at 75–80° for one hour longer and then filtered hot. The filtrate was concentrated and filtered. The two insoluble portions were combined, treated with dilute sodium hydroxide and then filtered. The filtrate was acidified and the solid which separated was filtered and then treated with sodium bicarbonate solution to dissolve any unreacted 2-chloro-6-nitrophenylacetic acid. The insoluble cake weighed

1.5 g. (16%) and was impure 4-chloro-1-hydroxyoxindole melting at about 210°.

4-Chlorooöxindole.—The sodium carbonate-insoluble portion obtained in the zinc and sulfuric acid reduction described above was recrystallized from 70% ethanol to give 4-chlorooöxindole as yellow needles which melted at 217–218°. The yield was 16%. In two reductions of 2-chloro-6-nitrophenylacetic acid, 4-chlorooöxindole was obtained in 25 and 39% yields.

1-Hydroxy-6-isopropyloxindole.—Zinc dust (15.1 g.) was added over one hour at 35–40° to a mixture of 22.3 g. of 4-isopropyl-2-nitrophenylacetic acid, 250 ml. of water and 57 ml. of 50% sulfuric acid. The reaction mixture was stirred for four hours longer. It was then filtered and the insoluble product was washed with water. The brown cake was extracted with dilute sodium hydroxide solution and the extract was acidified with hydrochloric acid. The precipitate was filtered and again treated with sodium hydroxide solution in which it was almost completely soluble. The solution was clarified and the filtrate acidified to *p*H 3. After filtration and recrystallization of the solid from dilute ethanol, 1-hydroxy-6-isopropyloxindole was obtained as white crystals, m.p. 165–167°.

1-Hydroxy-4-methyloxindole.—A solution of 19.5 g. of 2-methyl-6-nitrophenylacetic acid in 20 ml. of 5 *N* sodium hydroxide and 380 ml. of water was acidified with 65 ml. of 50% sulfuric acid, and 15.7 g. of zinc dust was added over a 45-minute period at 35–40°. The mixture was stirred at this temperature for four hours longer and then filtered. The insoluble portion was slurried in 200 ml. of 1 *N* sodium carbonate and the mixture was then filtered. The filtrate was adjusted to *p*H 7 and the insoluble product was removed by filtration. The crude yield was 0.9 g. (5%), m.p. 208°. When this material was recrystallized three times from 80% ethanol, 1-hydroxy-4-methyloxindole, m.p. 219–220°, was obtained. Acidification of the mother liquor yielded 4.1 g. of recovered 2-methyl-6-nitrophenylacetic acid.

Several attempts to improve the yield by variations of these conditions were unsuccessful.

4-Methyloxindole.—When the sodium carbonate insoluble portion mentioned in the above procedure was recrystallized from 80% ethanol, pure 4-methyloxindole, m.p. 211–212°, was obtained in 62% yield.

1-Methoxyoxindole.—When 35 ml. of dimethyl sulfate was added to a solution of 51.3 g. of 1-hydroxyoxindole in 75 ml. of 5 *N* sodium hydroxide and 500 ml. of water, a solid precipitated. The mixture was stirred for one hour longer and then heated at 50–55° for 15 minutes. It was then cooled in an ice-bath and the product was filtered and washed with water. On recrystallization from water, 36.8 g. (65%) of 1-methoxyoxindole, m.p. 83–85°, was obtained. Recrystallization once more raised the melting point to 84–86°.

5-Bromo-1-methoxyoxindole.—A solution of 24 g. of bromine and 36 g. of potassium bromide in 75 ml. of water was added over a 20-minute period at 85–90° to a solution of 24.5 g. of 1-methoxyoxindole and 12.3 g. of sodium acetate in 1,500 ml. of water. The mixture was held at 85–90° for ten minutes and then filtered hot. The insoluble portion was extracted three times with the filtrate, each time cooling to obtain the precipitated product. The total yield of 5-bromo-1-methoxyoxindole was 64%, m.p. 118–120°.

5-Bromooöxindole. Procedure A.—A mixture of 4 g. of 1-hydroxyoxindole, 20 ml. of 49% hydrobromic acid and 20 ml. of water was heated on the steam-bath for one hour. The mixture was poured into ice and water, and the precipitate was filtered, washed with water and dried. The product was recrystallized twice from anhydrous ethanol. The yield of light pinkish needles was 1.2 g. (21%), m.p. 218–220°.

Procedure B.—A mixture of 3 g. of 1-methoxyoxindole, 20 ml. of 49% hydrobromic acid and 10 ml. of water was heated on the steam-bath for 30 minutes and then poured into ice and water. The product was filtered, washed with water, dried and then recrystallized twice from anhydrous ethanol. The yield was 0.6 g. (15%), m.p. 218–220°.

Neither of these products depressed the melting point when mixed with a sample of 5-bromooöxindole prepared by the bromination of oxindole.

5-Chlorooöxindole.—A mixture of 5 g. of 1-methoxyoxindole and 5 ml. of concentrated hydrochloric acid was heated on the steam-bath for one hour and then poured into ice and water. Dilute sodium hydroxide was added to adjust the reaction to about *p*H 3 and the product was filtered, washed with water and dried. After recrystallizing twice from absolute ethanol, 0.9 g. (18%) of 5-chlorooöxindole, m.p. 195–196°, was obtained.

5-Bromo-7-chlorooöxindole.—A mixture of 10 g. of 5-bromo-1-methoxyoxindole and 100 ml. of concentrated hydrochloric acid was heated on the steam-bath for one hour and then cooled and filtered. On recrystallization of the product from 600 ml. of 80% ethanol, with activated charcoal, 4.0 g. (40%) of peach-colored needles melting at 252–253° was obtained. A second recrystallization produced white needles but did not improve the melting point.

Benzaloxindoles.—The benzaloxindoles were prepared by refluxing the oxindole with an equivalent or slight excess of the aldehyde in about 10 parts of anhydrous ethanol and with a catalytic amount of piperidine. In most cases the benzaloxindole precipitated out and was filtered and recrystallized from ethanol. In a few cases it was necessary to concentrate the reaction mixture to obtain the product. These compounds which were not alcohol-soluble were analyzed as is and generally found to be satisfactory.

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