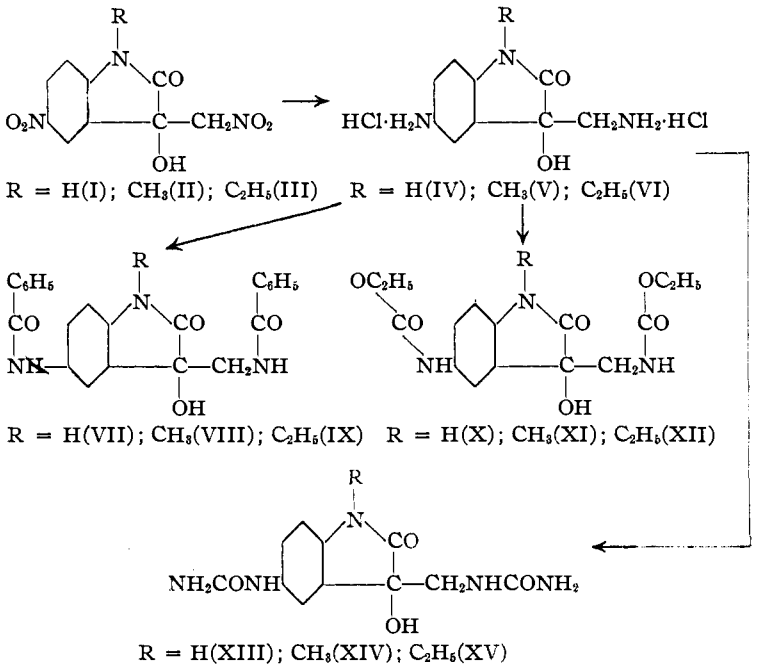
[CONTRIBUTION FROM NICHOLS LABORATORY OF NEW YORK UNIVERSITY]

Ethanolamines of the Oxindole Series

BY RAYMOND B. CRAWFORD[1] AND H. G. LINDWALL

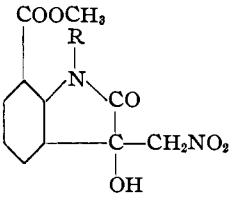
It has been reported previously[2] that isatin and N-alkylated isatins will condense with nitromethane to yield products of the type 3-hydroxy-3-nitromethyl-oxindole; these products, upon reduction, yield the respective 3-hydroxy-3-aminomethyl-oxindoles. That work has now been extended in order to obtain similar compounds containing salt-forming groups in the benzenoid ring of the oxindole structure.

CHART I



Isatin, 1-methylisatin, and 1-ethylisatin were nitrated in the 5-position by the method of Calvery, Noller and Adams.[3] The resulting nitroisatins were then condensed with nitromethane using diethylamine as the catalyst.[2] All three of these condensation products were reduced to the corresponding di-amino compounds readily, by the action of tin and hydrochloric acid (see Chart I). These di-amino compounds upon treatment with benzoyl chloride, ethyl chloroformate, and potassium cyanate, formed, respectively, the corresponding di-benzoyl, diurethan, and di-urea derivatives.

A similar study of derivatives of 7-carboxy-isatin was made. The 7-carboxy-isatin has been prepared by Sandmeyer[4] and by Rupe and Guggenbuhl[5] from anthranilic acid by the chloral hydrate and hydroxylamine method. Since Waldmann[6] has shown that a purer product can be obtained by using methyl anthranilate as the starting material, his procedure was followed in preparing the 7-carboxy-isatin and the 1-methyl- and 1-ethyl-analogs. The 7-carboxy-isatins thus obtained were then esterified and the esters were used in the condensation reactions with nitromethane. In this way the following compounds were obtained



Of these condensation products, compound XVI was subjected to treatment with tin and concentrated hydrochloric acid, and yielded 3-hydroxy-3-aminomethyl-7-carboxy-oxindole hydrochloride (XIX). Compound XIX formed benzoyl (XX), urethan (XXI), and urea (XXII) derivatives.

Several of the products will be tested for physiological activity.

Experimental Part

Compounds I, II, and III.—5-Nitro-isatin (or 1-methyl-5-nitro-isatin or 1-ethyl-5-nitro-isatin) (15 g.) was suspended in absolute ethyl alcohol (15 cc.) containing 10 g. of nitromethane, and the mixture was cooled to −15°. Then diethylamine (15 drops) was added with stirring. After standing at −15° for two hours, 1 cc. of glacial acetic acid was added and the solvent was partially removed

(1) From the dissertation presented by Raymond B. Crawford to the Faculty of the Graduate School of New York University in candidacy for the degree of Doctor of Philosophy, June, 1938.

(2) Conn and Lindwall, THIS JOURNAL, **58**, 1236 (1936).

(3) Calvery, Noller and Adams, *ibid.*, **47**, 3059 (1925).

(4) Sandmeyer, *Helv. Chim. Acta*, **2**, 234 (1919).

(5) Rupe and Guggenbuhl, *ibid.*, **10**, 926 (1927).

(6) Waldmann, *J. prakt. Chem.*, **147**, 338 (1937).

TABLE I

PROPERTIES AND ANALYSES OF COMPOUNDS

	Derivative	Crystals and color	Crude yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found.	Chlorine Calcd.	Chlorine Found	Water Calcd.	Water Found
3-Hydroxy-3-nitromethyl-5-nitro-oxindoles															
I	...	...	57	145–147	$C_9H_7O_6N_3$	42.70	42.85	2.79	3.11	...	...	...	...	...	...
II	1-Methyl-	Light yel. prisms	82	153	$C_{10}H_9O_6N_3$	44.95	44.78	3.39	3.58	...	...	...	...	...	...
III	1-Ethyl-	Stout yel. prisms	72	134–135	$C_{11}H_{11}O_6N_3$	46.98	47.23	3.94	4.21	...	...	...	...	...	...
3-Hydroxy-3-aminomethyl-5-amino-oxindole di-hydrochlorides															
IV	...	White glossy plates	72	>300	$C_9H_{13}O_2N_3Cl_2$	40.62	40.32	4.92	4.95	15.79	15.72	26.64	26.40	...	...
	Picrate of IV	Yel. prisms	...	198 dec.	...	...	...	..	..	...	...	...	...	...	...
V	1-Methyl-	...	80	170–173	$C_{10}H_{15}O_2N_3Cl_2$	...	...	..	..	...	...	25.31	28.18	...	...
	Picrate of V	Yel. brown plates	...	201–203 dec.	...	...	...	..	..	...	...	...	...	...	...
VI	1-Ethyl-	Needles	40	137–137.5	$C_{11}H_{17}O_2N_3Cl_2 \cdot 2H_2O$	40.01	40.15	6.41	6.64	12.73	12.53	21.47	21.48	10.91	10.78
	Picrate of VI	Yel. plates	...	179–180	...	...	...	..	..	...	...	...	...	...	...
3-Hydroxy-3-benzoylaminomethyl-5-benzoylamino-oxindoles															
VII	...	White needles	100	200–201	$C_{23}H_{19}O_4N_3$	68.82	68.58	4.77	5.28	...	...	...	...	...	...
VIII	1-Methyl-	White needles	100	249–251	$C_{24}H_{21}O_4N_3$	69.38	69.01	5.09	5.46	10.11	9.53	...	...	...	...
IX	1-Ethyl-	White needles	100	227–227.5	$C_{25}H_{23}O_4N_3$	69.92	70.66	5.40	5.26	...	...	...	...	...	...
3-Hydroxy-3-ethylcarbamidomethyl-5-ethylcarbamido-oxindoles															
X	...	White prisms	100	154	$C_{15}H_{19}O_6N_3$	...	...	..	..	12.46	12.21	...	...	...	...
XI	1-Methyl-	White needles	100	171–172	$C_{16}H_{21}O_6N_3$	54.69	54.83	6.02	6.14	...	...	...	...	...	...
XII	1-Ethyl-	White needles	100	183	$C_{17}H_{23}O_6N_3$	55.88	55.92	6.34	5.87	...	...	...	...	...	...
3-Hydroxy-3-uramidomethyl-5-uramido-oxindoles															
XIII	...	White needles	90	Chars	$C_{11}H_{13}O_4N_5$	47.31	47.34	4.99	5.00	...	...	...	...	...	...
XIV	1-Methyl-	White needles	90	213–214	$C_{12}H_{15}O_4N_5$	...	...	..	..	23.88	23.92	...	...	...	...
XV	1-Ethyl-	White needles	90	224–225	$C_{13}H_{17}O_4N_5$	50.81	50.46	5.58	5.82	...	...	...	...	...	...
3-Hydroxy-3-nitromethyl-7-carbomethoxy-oxindoles															
XVI	...	White silky	...	159–161.5	$C_{11}H_{10}O_6N_2$	49.62	49.32	3.79	3.65	10.52	10.34	...	...	...	...
XVII	1-Methyl-	White prisms	80	138–139	$C_{12}H_{12}O_6N_2$	51.43	51.18	4.31	4.36	10.00	9.99	...	...	...	...
XVIII	1-Ethyl-	White prisms	60	96–97.5	$C_{13}H_{14}O_6N_2$	53.06	52.87	4.80	4.62	...	...	...	...	...	...
3-Hydroxy-3-aminomethyl-7-carboxy-oxindole hydrochloride															
XIX	...	White needles	80	187–188	$C_{10}H_{11}O_4N_2Cl$	46.43	46.26	4.38	4.03	10.86	10.53	13.71	13.85	...	...
3-Hydroxy-3-benzoylaminomethyl-7-carboxy-oxindole															
XX	...	White prisms	53	240–241	$C_{17}H_{14}O_6N_2$	62.63	62.75	4.33	4.39	8.60	8.18	...	...	...	...
3-Hydroxy-3-ethylcarbamidomethyl-7-carboxy-oxindole															
XXI	...	White needles	45	217–218	$C_{13}H_{14}O_6N_2$	53.06	53.03	4.80	4.85	9.52	9.42	...	...	...	...
3-Hydroxy-3-uramidomethyl-7-carboxy-oxindole															
XXII	...	White	42	218–219	$C_{11}H_{11}O_5N_3$	49.81	49.57	4.48	4.92	15.84	15.90	...	...	...	...

under vacuum at 30°, the product separated and recrystallized from ethyl alcohol (I), or (II and III) from glacial acetic acid.

Compounds IV, V, and VI from I, II, and III, respectively.—Compound I (or II or III) (25.3 g.) was suspended in 100 cc. of concentrated hydrochloric acid and mossy tin (41.6 g.) was added slowly, keeping the temperature below 60°. In one-half hour all of the nitro compound had gone into solution. Then 50 cc. of concentrated hydrochloric acid and 41.6 g. of mossy tin were added and the mixture was boiled for twenty hours. The unused tin was then filtered off, the solution was diluted to 1600 cc. with water, and tin was removed as the sulfide. The product was obtained by evaporation to dryness on the steam-bath. Purification of IV was by dissolving in water and saturating with hydrogen chloride; of VI by crystallization from alcohol; V could not be recrystallized.

The Benzoyl Derivatives of IV, V, and VI (VII, VIII, and IX).—Compound IV (or V or VI) (0.5 g.) was dissolved in 10 cc. of water and 1 g. of sodium carbonate and 1.5 g. of benzoyl chloride were added. The product separated after standing two hours at room temperature; recrystallized from ethyl alcohol.

The Urethan Derivatives of IV, V, and VI (X, XI, and XII).—Compound IV (or V or VI) (0.5 g.) was dissolved in 10 cc. of water and 1 g. of sodium carbonate and 0.7 g. of ethyl chloroformate were added. The products were crystallized from ethyl alcohol.

The Urea Derivatives of IV, V, and VI (XIII, XIV and XV).—Compound IV (or V or VI) (1.0 g.) was dissolved in 7 cc. of water and 1 g. of potassium cyanate dissolved in 3 cc. of water was added. The crystalline product separated after twelve hours standing in ice; in each case the product was recrystallized from water after treatment with bone coal.

Compounds XVI, XVII and XVIII.—Nitromethane (9 g.) and 7-carbomethoxy-isatin (12 g.) were placed in 12 cc. of absolute ethyl alcohol and the mixture was cooled to −15°. Diethylamine (15 drops) was added with stirring. The mixture was held at −15° for one hour, and part of the solvent was then removed to cause fairly complete separation of XVI. Compounds XVII and XVIII were prepared, respectively, by substituting 1-methyl-7-carbomethoxy-isatin and 1-ethyl-7-carbomethoxy-isatin in this procedure.

Compound XIX (from XVI).—Compound XVI (9.5 g.) was suspended in 50 cc. of concentrated hydrochloric acid and mossy tin (17 g.) was added slowly, keeping the temperature below 60°. After boiling the mixture for two hours it was diluted with water and tin was removed as the sulfide. The solution was evaporated until a solid separated; it was recrystallized from ethyl alcohol. Treatment of XIX with benzoyl chloride yielded **compound XX;** with ethyl chloroformate, **compound XXI;** with potassium cyanate, **compound XXII.**

Summary

Oxindole and N-alkylated-oxindole derivatives have been prepared in which the 3-position holds the hydroxyl and the aminomethyl groups, and the 5- or 7-position is occupied, respectively, by the amino or carboxyl group. For certain of these products benzoyl, urethan, and urea derivatives are described.

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Sulfides and Sulfones of Pyridine and Quinoline

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The similarity of therapeutic effect to sulfanilamide of the dinitro- and diaminodiphenyl sulfides and sulfones,[1,2,3] suggested the preparation of like compounds in the pyridine and quinoline series.

The chemotherapy of these diphenyl compounds[4,5] showed that while some of them possess greater activity than sulfanilamide, in general they have a greater toxicity. The introduction of the pyridine ring in sulfanilamide not only enhances the activity but also adds desirable features absent from sulfanilamide. Encouraging results were obtained with certain other pyridine compounds[6] including the dihydrobromide of 2,2′-dipyridyl sulfide. Recently, sulfonamides of some aminoquinolines have been synthesized.[7] It therefore seemed desirable to prepare pyridine and quinoline analogs of the dinitro and diamino diphenyl sulfides and sulfones.

5,5′-Dinitro 2,2′-dipyridyl sulfide (I) has been prepared by the action of sodium sulfide on 2-chloro-5-nitropyridine. This is essentially the method used by Nietzki and Bothof[8] for the preparation of the diphenyl analog. The diquinolyl sulfides (IV) and (V) (see Table I) were prepared in the same way starting with 5-chloro-8-nitro-

(1) Buttle, *Lancet*, 1331 (1937).

(2) E. Fourneau, J. and MMe. J. Trefouel, F. Nitti and D. Bovet, *Bull. acad. méd.*, **118**, 210 (1937).

(3) H. Bauer and S. M. Rosenthal, *U. S. Public Health Rpts.*, **53**, 40 (1938).

(4) A. DeM. Welch, *J. Pediatrics, II*, no. 2, 159 (1937).

(5) G. W. Raiziss, L. W. Clemence, M. Severac and J. C. Moetsch, THIS JOURNAL, **61**, 2763 (1939).

(6) J. A. Kolmer, H. Brown and G. W. Raiziss, *J. Pharmacol.*, **61**, 253 (1937).

(7) Bobranski, *Arch. Pharm.*, **277**, 75 (1939).

(8) Nietzki and Bothof, *Ber.*, **27**, 3261 (1894).