

127° to 128° because of similarity of m. p. The acetate obtained upon recrystallization melted at 120° to 121°.

The material marked "III A" by Clark was recrystallized. Beautiful almost transparent leaflets were obtained which melted at 135°. Even after drying at 100° over P₂O₅ in a vacuum the melting point was not changed.

The remainder of the unsaponifiable material which amounted to 53 Gm. was treated with digitonin in the manner previously described. The sterol thus obtained exhibited the same physical properties as that obtained before, *i. e.*, the free sterol melted at 138°, and the acetate melted at 131° to 132°.

A mixed melting point was made with the sterol obtained from digitalis seed and no change in the melting point could be noticed. Evidently the two sterols are identical.

The sterol acetate was saponified with alcoholic potassium hydroxide (half normal) by refluxing for one and one-half hours. The excess alkali was back titrated with half normal hydrochloric acid. The values thus obtained indicate that the sterol has the composition C₂₆H₄₃OH.

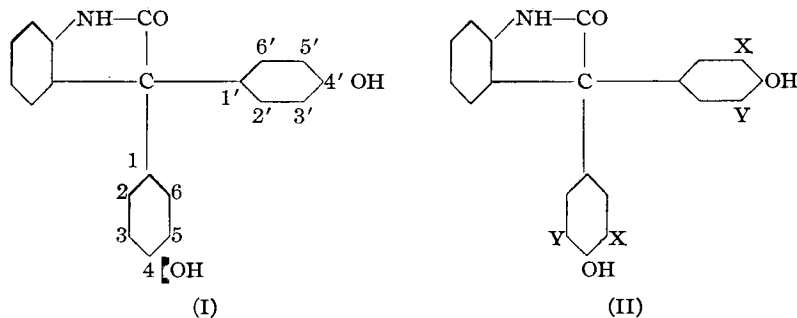
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MERCURATED SUBSTITUTION PRODUCTS OF DIPHENOL ISATIN.*

BY S. E. HARRIS AND W. G. CHRISTIANSEN.

The results obtained during our study of mercury derivatives of phthaleins derived from *o*-hydroxy diphenyl (I) suggested that therapeutically valuable mercury compounds should be found among compounds of similar general structure. Diphenol isatin (I) was selected as the parent substance for the investigation and a number of mercury derivatives of the substituted products (II) (Y = NO₂ or Br; X = H, C₆H₅, CH₃, NO₂ or Br) were prepared.



* Scientific Section, A. PH. A., Toronto meeting, 1932.

All of the compounds studied possessed considerable bactericidal properties and the results obtained when they were tested against *B. Typhosus* in aqueous alkaline solution are shown in Table I.

TABLE I.

Diphenol Isatin Derivative.	Highest Dilution Which Kills <i>B. Typhosus</i> in 5 Minutes.
Acetoxy mercuri 3,3', 5,5' tetrabromo-	1-10,000
Diacetoxy mercuri 3,3' dibromo-	1-500
Acetoxy mercuri 3,3' dinitro-	1-30,000
Diacetoxy mercuri 3,3' dinitro-	1-10,000
Acetoxy mercuri 3,3' dibromo 5,5' dimethyl-	1-500
Diacetoxy mercuri 3,3' dinitro 5,5' dimethyl-	1-1,000
Acetoxy mercuri 3,3' dibromo 5,5' diphenyl-	1-1,500
Diacetoxy mercuri 3,3' dibromo 5,5' diphenyl-	1-1,500
Diacetoxy mercuri 3,3' dinitro 5,5' diphenyl-	1-1,000
Diacetoxy mercuri 3,3' dibromo-diresorcin isatin	1-500
Hydroxy mercuri 3,3' dinitro-diresorcin isatin	1-1,000

The preparation of the intermediates was carried out by introducing the substituent into diphenol isatin prepared by the method of Baeyer and Lazarus (2), in which one molecule of isatin is condensed with two molecules of phenol by adding a small quantity of concentrated H_2SO_4 to a mixture of the two compounds. 5,5'-dimethyl- and 5,5'-diphenyl-diphenol isatin were prepared in the same manner by condensing, respectively, *o*-cresol and 2-hydroxy diphenyl with isatin. It was found that diresorcin isatin could not be prepared in this way, since the high temperature required to melt the resorcin led to an extremely violent reaction with formation of tars. Condensation proceeded smoothly in glacial acetic acid solution, the product being formed without the usual elimination of water between two hydroxyl groups. It was subsequently observed that substitution under mild conditions, *e. g.*, in glacial acetic acid, bromination could be effected without closing the oxonium ring at positions 6 and 2', whereas nitration in concentrated sulphuric acid led to the elimination of water.

Mercuration was in general effected by the method previously described (1), but in a number of cases this led to the formation of mixtures of mono, di- and tri-mercury derivatives which we were unable to separate, the compounds being characterized by complete insolubility in organic solvents. Other means of mercuration were adopted in such cases. The compounds obtained were all readily soluble in a slight excess of aqueous alkali. In no case was a melting point observed, the compounds decomposing without melting when heated. The position of the mercury has not been determined. There is ground for belief, however, that in some cases the mercury enters the isatin residue while in others it enters the phenol residue. This, as in the case of the phthalein, is based on the readiness with which disubstitution occurs in certain nitro derivatives, while we have been unable to introduce a second mercury into 3,3',5,5'-tetrabromo diphenol isatin. This indicates that in acetoxy tetrabromo diphenol isatin a single mercury enters the isatin residue, and that in diacetoxy mercuri 3,3'-dinitro diphenol isatin we have mercury substitution at the 5 and 5' positions. The high-mercury analyses reported in the experimental part indicates that in the latter compound there is some formation of the triacetoxy mercuri derivative, with the third mercury entering the isatin residue.

Analysis for mercury was carried out by the method of Whitmore (3), but with somewhat unsatisfactory results. As stated elsewhere (1) the method of Tabern and Shelberg (4) is now used in this laboratory.

EXPERIMENTAL.

3,3'-Dibromo Diphenol Isatin.—3.17 Gm. diphenol isatin (2) was suspended in 40 cc. glacial acetic acid and a solution of 3.2 Gm. bromine in 10 cc. glacial acetic acid added dropwise with stirring. The reaction product was isolated by dilution with water, and recrystallized from benzene as a fine white powder.

Melting point—144–145° C.

Yield—88%.

Analysis (Parr bomb) Br—Found 33.92%; 33.24%. Calc. for $C_{20}H_{13}NO_3Br_2$ —33.83%.

Diacetoxy Mercuri 3,3'-Dibromo Diphenol Isatin.—General method of mercuration in alcohol solution: 3.5 Gm. of dibromo diphenol isatin was dissolved in 35 cc. alcohol and the boiling solution treated with a solution of 4.7 Gm. of mercuric acetate in 15 cc. water acidified with acetic acid. Stirring and boiling was continued until a side test with NaOH showed absence of ionic mercury. The precipitated mercury derivative was then filtered off and washed with alcohol and ether. It formed a pale yellow sandy powder insoluble in the common organic solvents, readily soluble in dilute alkalis.

Yield—Quantitative.

Hg—Found 41.3%. Calc. for $C_{24}H_{17}NO_7Br_2Hg_2$ —42.5%.

3,3',5,5'-Tetrabromo Diphenol Isatin.—48 Gm. diphenol isatin was suspended in 480 cc. glacial acetic acid and 97 Gm. bromine added dropwise with stirring. The mixture was allowed to stand for an hour and then poured into 3 liters of water. A fine greenish precipitate formed which was filtered off, washed with water and recrystallized from alcohol.

Yield—Quantitative. M. p. decomposes above 275° C.

Br (Parr bomb)—Found 50.82%; 50.87%. Calc. for $C_{20}H_{13}NO_3Br_4$ —50.56%.

Acetoxy Mercuri 3,3',5,5'-Tetrabromo Diphenol Isatin.—91 Gm. tetrabromo diphenol isatin was dissolved in 144 cc. 2 N NaOH and 150 cc. of water. To the boiling solution a hot solution of 46 Gm. mercuric acetate in 20 cc. N acetic acid and 150 cc. of water were added, and heating and stirring continued for a few minutes after the addition was complete. The mercury derivative was precipitated as a bluish gelatinous mass, to which 2 liters of water and sufficient NaOH to dissolve the product were added. After filtering off a small insoluble impurity the mercury derivative was regenerated, by the addition of acetic acid, as a thick gelatinous mass, very difficult to filter and wash.

Yield—Quantitative.

Hg—Found 24.3%. Calc. for $C_{22}H_{14}NO_6Br_4Hg$ —22.5%.

3,3'-Dinitro Diphenol Isatin.—3.17 Gm. diphenol isatin was suspended in 25 cc. glacial acetic acid and 1.5 cc. HNO_3 (Sp. Gr. 1.4) was added dropwise with stirring. After warming a short time on the water-bath to complete the reaction, the solution was poured into 400 cc. water and the precipitate recrystallized from dilute alcohol.

Yield—3 Gm. M. p. decomposes at 225° C.

N—Found 10.54%; 10.86%. Calc. for $C_{20}H_{18}N_3O_7$ —10.37%.

Diacetoxy Mercuri 3,3'-Dinitro Diphenol Isatin.—Mercuration was carried out by the general method. The product was a bright yellow powder.

Yield—Quantitative.

Hg—Found 47.1%; 48.1%. Calc. for $C_{24}H_{17}N_3O_{11}Hg_2$ —43.5%.

All methods of preparation gave products with a high and variable mercury content.

Diresorcin Isatin.—5.6 Gm. isatin and 8.2 Gm. resorcin were suspended in 50 cc. glacial acetic acid, and conc. H_2SO_4 added drop by drop with good stirring till the isatin color disappeared and a homogeneous solution resulted. On pouring into 500 cc. water and standing, a fine white powder was precipitated. A suitable solvent for recrystallization was not found.

Yield—6 Gm. M. p. decomposes above 270° C.

Found	C	68.9	H	4.2	N	3.89
		68.8		4.5		4.08.
Calc. for $C_{20}H_{16}NO_5$	C	68.8	H	4.3	N	4.01%.

3,3'-Dibromo Diresorcin Isatin.—7 Gm. diresorcin isatin in 50 cc. glacial acetic acid was treated with 6.3 Gm. bromine dissolved in 10 cc. glacial acetic acid. The product was isolated by dilution with water, and recrystallized from alcohol.

M. p. 250–255° with decomposition.

Diacetoxy Mercuri 3,3'-Dibromo Diresorcin Isatin.—2 Gm. of the dibromo compound was mercurated by the general method with 2.5 Gm. mercuric acetate.

Yield—90%.

Hg—Found 38.4%. Calc. for $C_{24}H_{16}NO_8Br_2Hg_2$ —39.2%.

3,3'-Dinitro Diresorcin Isatin.—5 Gm. diresorcin isatin was dissolved in 30 cc. conc. H_2SO_4 and cooled to 0° C. To this solution a mixture of 2.8 cc. HNO_3 and 3 cc. H_2SO_4 was added drop by drop, keeping the temperature at 0° C. After stirring for a further period of 30 minutes the reaction mixture was diluted with 5 volumes of water, the precipitate filtered off and washed. The brown reaction product was very soluble in alcohol and glacial acetic acid but did not separate in a crystalline form on evaporation or dilution. It was insoluble in ether, benzene and chloroform. Decomposed without melting at 220° C.

Yield—Practically quantitative.

N—Found 10.16%; 10.65%. Calc. for $C_{20}H_{18}N_3O_8$ 9.97%.

Hydroxymercuri 3,3'-Dinitro Diresorcin Isatin.—4.2 Gm. 3,3'-dinitro diresorcin isatin was dissolved in 50 cc. *N* NaOH and a hot solution of 6 Gm. mercuric acetate in 25 cc. water acidified with acetic acid added. After standing a short time the mercury derivative was precipitated by adding dilute H_2SO_4 , filtered off and washed with water, alcohol and ether.

Hg—Found 32.8%; 32.0%. Calc. for $C_{20}H_{10}N_3O_9Hg$ 31.5%.

Yield—Practically quantitative.

3,3'-Diphenyl-Diphenol Isatin.—20 Gm. 2-hydroxy diphenyl was melted and 5 Gm. isatin suspended in the molten mass, maintaining the temperature at about

60° C. 2 cc. conc. H_2SO_4 was added dropwise and stirring continued until the reaction mixture set to a solid cake. This was then broken up and boiled with water to remove traces of 2-hydroxy diphenyl. The product was purified by recrystallization from alcohol and water or by solution in NaOH and reprecipitation with dilute acid. It forms a white powder, m. p. 183–185° C.

Found	C	82.3	H	4.95	N	2.87; 2.95
Calc. for $C_{32}H_{23}NO_3$	C	81.9	H	4.90	N	3.00%

3,3'-Diphenyl 5,5'-Dibromo Diphenol Isatin.—31 Gm. 3,3'-diphenyl diphenol isatin, dissolved in 300 cc. alcohol or glacial acetic acid, was treated with 20.5 Gm. bromine dropwise. After standing for a short time the product was isolated by dilution with 1.5 liters water, and recrystallized from dilute acetic acid.

Yield—96%. M. p. 115° C.

Br—Found 27.49%. Calc. for $C_{32}H_{21}NO_3Br_2$ 26.69%.

Acetoxy Mercuri 3,3'-Diphenyl 5,5'-Dibromo Diphenol Isatin.—The dibromo compound on mercuration by the general method gave a brownish sandy powder in quantitative yield.

Hg—Found 22.4%. Calc. for $C_{34}H_{23}NO_3Br_2Hg$ 22.7%.

Diacetoxy Mercuri 3,3'-Dibromo 5,5'-Diphenyl Diphenol Isatin.—The bromo compound was mercurated by the general method using two equivalents of mercuric acetate. The properties resembled those of the mono-mercury derivative.

Hg—Found 36.0%. Calc. for $C_{36}H_{26}NO_7Br_2Hg_2$ 35.1%.

3,3'-Diphenyl 5,5'-Dinitro Diphenol Isatin.—4.7 Gm. 3,3'-diphenyl diphenol isatin was dissolved in glacial acetic acid and treated with 1.5 cc. HNO_3 (Sp. Gr. 1.4). The product was isolated by dilution with water, and recrystallized from alcohol. Yellow needles m. p. 148° C.

Yield—Practically quantitative.

N—Found 7.34%. Calc. for $C_{32}H_{21}N_3O_7$ 7.51%.

Diacetoxy Mercuri 3,3'-Diphenyl 5,5'-Dinitro Diphenol Isatin.—Mercuration by the general method gave a brown sandy powder assaying rather high for mercury.

Hg—Found 44.6%; 44.0%. Calc. for $C_{36}H_{25}N_3O_{11}Hg_2$ 37.3%.

As in the case of dinitro diphenol isatin, all attempts to prepare pure dimercury derivatives gave a partially trimercured mixture.

3,3'-Dimethyl 5,5'-Dibromo Diphenol Isatin.—13 Gm. di-*o*-cresol isatin (5) prepared in the same manner as diphenol isatin, was dissolved in 125 cc. glacial acetic acid and treated with 13 Gm. bromine. About 30% of the product was precipitated as a micro-crystalline powder while the remainder was obtained on dilution with water. Recrystallized from glacial acetic acid, it formed needles.

Yield—90%. M. p. decomposes 250° C.

N—Found 2.78%. Calc. for $C_{22}H_{17}NO_3Br_2$ 2.79%.

Acetoxy Mercuri 3,3'-Dimethyl 5,5'-Dibromo Diphenol Isatin.—On mercuration in alcohol solution by the general method the reaction appeared to be reversible since long boiling failed to give a negative test for inorganic mercury. The crude

product was freed from the unchanged isatin derivative by repeated extraction with boiling alcohol.

Hg—Found 26.0%. Calc. for $C_{24}H_{19}NO_5Br_2Hg$ 26.4%.

3,3'-Dinitro 5,5'-Dimethyl Diphenol Isatin.—24 Gm. di-*o*-cresol isatin (5) was dissolved in 25 cc. glacial acetic acid and treated with 10 cc. HNO_3 (Sp. Gr. 1.4). After warming on the water-bath for 15 minutes the product was precipitated by adding water and recrystallized from alcohol. Yellow micro-crystalline powder m. p. 238–240° C.

N—Found 9.68%. Calc. for $C_{22}H_{18}N_3O_7$ 9.65%.

Diacetoxy Mercuri 3,3'-Dinitro-5,5'-Dimethyl-Diphenyl Isatin.—The nitro compound when mercurated in alcohol by the general method gave a partially trimercurated product, as in the case of the other nitro derivatives.

Hg—Found 44.7%. Calc. for $C_{24}H_{18}N_3O_5Hg_2$ 43.3%.

SUMMARY.

A number of new derivatives of diphenol isatin have been prepared. The mercury derivatives of these compounds have been prepared and their bactericidal properties investigated.

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THE VALUE OF SENECIO IN MEDICINE.*¹

BY EDGAR A. KELLY AND E. V. LYNN.

In a preliminary report two years ago (3) we recorded a partial examination of senecio. Since then we have completed the study and extended it to include the pharmacology.

CHEMICAL.

The material employed was obtained in the open market and was entirely within the official requirements, but we have no knowledge of place or time of gathering.

Proximate analysis of various samples gave results as follows: moisture 6.49 to 10.92 per cent; ash 8.33 to 11.85 per cent; starch, by diastase 7.85, by acid hydrolysis 10.20 per cent; tannin 6.14 per cent.

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