THERAPEUTIC SUBSTANCES DERIVED FROM UNSYMMETRICAL DIPHENYL COMPOUNDS I.*

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SOME MERCURY DERIVATIVES OF 2- AND 4-HYDROXYDIPHENYL.

The studies of diphenyl compounds in this laboratory have included the preparation of a number of mercury derivatives of the following types, (*a*) from nitrated hydroxy-diphenyls, (*b*) from brominated hydroxy-diphenyl, (*c*) from diphenyl-phenolphthalein.

The compounds were tested for their activity against bacteria and were shown to have valuable bactericidal properties. Table I illustrates the activity against *B. Typhosus*, the second column giving the minimum concentration at which the organism is killed in five minutes. The mercury compound was dissolved in the smallest excess of NaOH which would give a clear solution at 1–500, and diluted with distilled water immediately prior to the test.

TABLE I.

Germicide.	Dilution Killing *B. Typhosus* in 5 Minutes.
2-Acetoxy-mercuri-3-nitro-4-hydroxy-diphenyl	1–2000
4-Acetoxy-mercuri-3,5-dinitro-2-hydroxy-diphenyl	1–1000
4-Anhydro-mercuri-5-acinitro-3-nitro-2-hydroxy-diphenyl	1–1000
4,6-Diacetoxy-mercuri-3,5-dinitro-2-hydroxy-diphenyl	1–2500
Diacetoxy-mercuri-4′-nitro-2-hydroxy-diphenyl	1–2500
Hydroxy-mercuri-3,3′-diphenyl-5,5′-dibromo-phenolphthalein	1–1250
Diacetoxy-mercuri-3,3′-diphenyl-5,5′-dinitro-phenolphthalein	1–2500
Monoacetoxy mercuri-3,3′-dinitro-phenolphthalein	1–1000
Diacetoxy-mercuri-3,3′-dinitro-phenolphthalein	1–500
2-Phenyl-4-bromo-6-acetoxy-mercuri-phenoxy-acetic acid	1–100

The mercury derivatives of nitrophenolphthalein were prepared for comparison with the corresponding derivatives of diphenyl-phenolphthalein, and it will be noted that the introduction of the phenyl groups considerably raises the germicidal activity. In addition to the compounds contained in the above table, the mercury derivatives of condensation products of 2-hydroxy-diphenyl with isatin were studied. These will be dealt with in a separate communication.

The preparation of the mercury derivatives offered few difficulties. Mercuration was carried out by treating a boiling alcoholic solution of the suitable intermediate with an aqueous solution of mercuric acetate acidified with acetic acid, and refluxing until a filtered test portion showed absence of ionic mercury when tested with aqueous NaOH or ammonium sulphide. The mercury derivatives were thus obtained as alcohol-insoluble powders which were purified by reprecipitation from filtered alkaline solutions by means of acetic acid. They were in all cases insoluble in the common organic solvents but some were slightly soluble in boiling glacial acetic acid. In no case was a melting point observed, complete decomposition without melting taking place at temperatures above 300° C. The solubility in aqueous alkalies showed wide variations, the mercury derivative of 5-bromo-2-hydroxy-diphenyl being completely insoluble even in a large excess of boiling NaOH.

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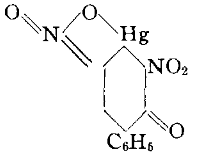
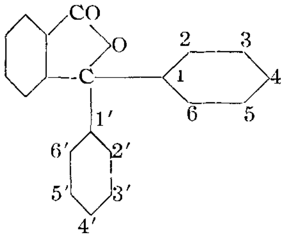
The mercury derivatives of the nitro-hydroxy-diphenyls and of the diphenyl-phenolphthaleins, however, were readily soluble in a moderate excess of alkali.

While the mercuration of 3,5-dinitro-2-hydroxy-diphenyl in alcohol solution proceeds normally, an attempt to mercurate this compound in aqueous acetic acid led to the formation of the anhydro-acinitro compound:



This dissolved in alkalies only on prolonged boiling. The structure was assigned on solubility in alkali, the analytical results and the strong orange color of the solid substance, both the mono- and dimercury derivatives of 3,5-dinitro-2-hydroxy-diphenyl being pale yellow.

No attempt has been made to establish the position taken by the mercury entering the molecule. In the simpler derivatives analogy with known cases has been assumed, while the diphenyl-phenolphthaleins offer a special problem. White (1) was unable to mercurate phthaleins in which 3,3′ and 5,5′ positions were all occupied



Under different experimental conditions, however, Greenbaum (2) prepared mercury derivatives of such compounds and assumed that the mercury entered the phthalic acid nucleus. We found that both 3,3′, 5,5′ tetra substituted and 3,3′ disubstituted phthaleins were mercurated with equal facility, although it was not always possible to introduce more than one mercury group, *e. g.*, into 3,3′-diphenyl-5,5′-dibromo-phenolphthalein. This would suggest that here the mercury enters the phthalic acid residue, while in the case of 3,3′-diphenyl-5,5′-dinitrophenolphthalein, which readily yielded a dimercury derivative, one or both of the mercury groups enters a phenol nucleus.

Analysis for mercury was carried out by the method of Whitmore (3). The results were not entirely satisfactory and the method has been discarded in favor of a method described by Tabern and Shellberg in a private communication through the A. D. M. A. Committee on Synthetic organic chemicals.

Experimental.—2-acetoxy-mercuri-3-nitro-4-hydroxy-diphenyl. The preparation of this compound is typical of the general method and is described in detail.

21.5 Gm. of 3-nitro-4-hydroxy-diphenyl (4) were dissolved in 200 cc. of alcohol and the solution heated to boiling under reflux. 28.7 Gm. of mercuric acetate dissolved in 200 cc. of water, acidified with 0.5 cc. glacial acetic acid were then slowly added to the boiling solution. Brisk agitation during the addition and subsequent boiling prevented the product from sticking to the sides of the flask. When a side test showed absence of ionic mercury the brick-red precipitate was filtered from the hot solution and washed with alcohol and ether. The yield was practically quantitative. On dissolving in boiling NaOH and cooling the sodium salt was thrown down as a scarlet powder, which was largely hydrolyzed when treated with water.

The analysis of this as well as the other mercury compounds is given in Table II.

TABLE II.—MERCURY DERIVATIVES.

Compound.	Analysis.	
	Found.	Calculated.
2-Acetoxy-mercuri-3-nitro-4-hydroxy-diphenyl	N 2.82	2.95
$C_{14}H_{11}NO_6Hg$	Hg 41.6	42.4
Na salt 2-AcOHg-3NO$_2$-4HO-diphenyl	Hg 42.7	44.3
$C_{14}H_{10}NO_6HgNa$		
4-AcOHg-3,5-di-NO$_2$-2-HO-diphenyl	Hg 38.7	38.7
$C_{14}H_{10}N_2O_7Hg$		
4,6-DiAcOHg-3,5-di-NO$_2$-2HO-diphenyl	Hg 51.2	51.5
$C_{16}H_{12}N_2O_9Hg_2$		
3-NO$_2$-2-anhydro-Hg-5-acinitro-2-oxy-diphenyl	Hg 43.5	43.8
$C_{12}H_6N_2O_5Hg$	N 6.18; 6.05	6.10
Di-AcOHg-4′-NO$_2$-2-HO-diphenyl	Hg 53.2	54.9
$C_{16}H_{13}NO_7Hg_2$		
3-AcOHg-5-Br-2-HO-diphenyl	Hg 35.9	38.8
$C_{14}H_{11}O_3BrHg$		
5-AcOHg-2-phenyl-4-Br-phenoxy acetic acid	Hg 31.0	35.5
$C_{16}H_{13}O_5BrHg$		
HOHg-3,3′-diphenyl-5,5′-dibromo-phenolphthalein	Hg 26.6; 26.1	23.8
$C_{32}H_{20}O_5Br_2Hg$		
Di-AcOHg-3,3′-diphenyl-5,5′-dinitro-phenolphthalein	Hg 38.2	37.3
$C_{36}H_{24}O_{12}N_2Hg_2$		
AcOHg-3,3′-dinitro-phenolphthalein	Hg 32.8; 33.0	30.1
$C_{22}H_{14}N_2O_{10}Hg$		

3-NITRO-4-ANHYDRO-MERCURI-5-ACINITRO-2-OXY-DIPHENYL.

2.6 Gm. of 3,5-dinitro-2-hydroxy-diphenyl (5) were dissolved in 31 cc. *N* NaOH and heated to boiling. 3 Gm. of mercuric acetate dissolved in 50 cc. of water and 10 cc. glacial acetic acid were added and the mixture boiled and stirred for 20 hours. The bright orange product which had gradually become granular during the reaction was filtered off and washed with water, alcohol and ether. It dissolved in NaOH only on boiling and decomposed without melting above 300° C.

4′-NITRO-2-HYDROXY-DIPHENYL. (*a*) 4′-NITRO-2-AMINO-DIPHENYL.

This compound has previously been prepared (6) but the following directions give an improved yield.

167 Gm. conc. H_2SO_4 were cooled to 0° C. and 24 Gm. 2-amino-diphenyl added in small portions with good agitation. The solution was then cooled below 0° C. and a cooled mixture of 13 Gm. HNO_3 and 10 Gm. H_2SO_4 added at such a rate that the temperature remained below 0° C. Vigorous stirring was maintained during the addition and for 15–30 minutes afterward. The reaction mixture was then poured onto 200 Gm. cracked ice and allowed to stand for several hours before filtering off the 4′-nitro-2-amino-diphenyl-sulphate. It was not possible to wash the sulphate owing to rapid hydrolysis so the wet salt was suspended in water and the free base liberated by an excess of 10% NaOH. The bright orange base was recrystallized from alcohol and melted at 158–159° C. (corr.). Further confirmation of the position of the substituents was obtained by preparing the acetyl derivative m. p. 201° C. (corr.) and transforming the amine to 2-bromo-4′-nitro-diphenyl m. p. 81.5–82.5° C. (corr.). Scarborough and Waters state that 4′-ni-

tro-2-amino-diphenyl has m. p. 158° C. (corr.), 4′-nitro-2-acetamido diphenyl m. p. 199° C. (corr.), and 2-bromo-4′-nitro-diphenyl m. p. 82.5° C. (corr.).

(*b*) DIAZOTIZATION OF 2-AMINO-4′-NITRO-DIPHENYL.

18 Gm. 2-amino-4′-nitro-diphenyl were dissolved in the hot solution formed by adding 12 cc. H_2SO_4 to 120 cc. of water. The solution was heated to 90–95° C. and a solution of 5 Gm. $NaNO_2$ in 100 cc. water slowly added with stirring. The stirring was assisted by blowing in steam. When the evolution of nitrogen ceased the acid liquor was decanted, and the tarry residue extracted with boiling 2% NaOH. After treating with decolorizing carbon, the nitrophenol was precipitated by HCl and recrystallized from dilute alcohol. It formed white needles, m. p. 123–124° C., readily soluble in alcohol, ether and benzene.

Nitrogen: Found 6.2%. Calc. for $C_{12}H_9NO_3$ 6.5%.

5-BROMO-2-HYDROXY-DIPHENYL.

85 Gm. 2-hydroxy-diphenyl were dissolved in 100 cc. CS_2 or CCl_4 and the solution cooled to 0° C. Partial crystallization occurred but this appeared to have no effect on the bromination, the crystals rapidly dissolving during the early stages of the reaction. To the well-stirred, cooled solution, a solution of 80 Gm. bromine in 50 cc. CS_2 or CCl_4 was added, the reaction temperature being maintained below 5° C. by regulating the rate of addition. The solvent was then distilled off and the residue distilled under reduced pressure. B. p. 158–160/4 mm. The distillate formed a thick colorless oil which would not crystallize even on long standing. Yield—90%.

Bromine: Found 32.25%. Calc. for $C_{12}H_9OBr$ 32.13%.

2-PHENYL-4-BROMO-PHENOXY-ACETIC-ACID.

A solution of 5 Gm. of 5-bromo-2-hydroxy-diphenyl in 200 cc. *N* NaOH was boiled with 10 Gm. chloroacetic acid until the solution was neutral to litmus. It was then acidified and the gummy product dissolved in K_2CO_3 solution. After filtering the solution was acidified with dilute H_2SO_4 and the precipitate recrystallized from alcohol.

M. p.: 138–139° C. Yield—nearly quantitative.
C: Found 53.1%. Calcd. for $C_{14}H_{11}O_3Br$ 54.7%.
H: Found 3.8%. Calcd. for $C_{14}H_{11}O_3Br$ 3.6%.

ETHYL-2-PHENYL-4-BROMO-PHENOXY ACETATE.

24 Gm. of the above phenoxy acetic acid were esterified by boiling with 100 cc. absolute alcohol containing 4 Gm. HCl gas for $2^1/_2$ hours. The alcohol was then distilled off and the residual oil dissolved in ether and washed with Na_2CO_3 solution and water. After drying over $CaCl_2$ the ether was distilled off and the residue was analyzed without further purification, and mercurated.

C: Found 56.8%. Calcd. for $C_{16}H_{15}O_3Br$ 57.3%.
H: Found 4.6%. Calcd. for $C_{16}H_{15}O_3Br$ 4.5%.

2-PHENYL-4-BROMO-6-ACETOXY-MERCURI-PHENOXY-ACETIC ACID.

13 Gm. of the above ester were mercurated by the general method. The reaction mixture was then made strongly alkaline with NaOH and boiled to hydrolyze the ester. A heavy black precipitate which formed was filtered off and the filtrate acidified with acetic acid. The sticky precipitate was extracted with ether and the insoluble portion redissolved in Na_2CO_3, filtered and reprecipitated. It formed a white sandy powder, readily soluble in alkali and alkali carbonate solutions.

3,3′-DIPHENYL-PHENOL-PHTHALEIN.

10 Gm. phthalic anhydride, 36 Gm. 2-hydroxy-diphenyl and 8 Gm. conc. H_2SO_4 were heated for seven hours at 140° C. The purple melt was treated with water and boiled to remove any unreacted 2-hydroxy-diphenyl. The granular brown powder remaining was then dissolved in NaOH, filtered and reprecipitated with HCl and acetic acid. The precipitate was then dissolved in 100 cc. of alcohol, decolorized with charcoal and the alcohol solution diluted with 600

cc. of water. A small tarry precipitate was filtered off and the phthalein obtained from the filtrate by boiling out the alcohol. It formed a white fluffy powder. M. p. 234–235° C. An alkaline solution was violet-red, the color change from violet to colorless occurring between p_H 10.8–9.3.

C: Found 82.4. Calc. for $C_{32}H_{22}O_4$ 81.7%.
H: Found 5.05. Calc. for $C_{32}H_{22}O_4$ 4.7%.

3,3′-DIPHENYL-5,5′-DIBROMO-PHENOL-PHTHALEIN.

9.4 Gm. of the phthalein were suspended in 100 cc. of alcohol and 6.4 Gm. bromine added dropwise at 30–35° C. with stirring. The resulting red-colored solution was allowed to stand for some time and then poured into 500 cc. of water. The precipitate was filtered off, washed and recrystallized from dilute alcohol, m. p. 110–111° C. Yield—quantitative. An alkaline solution was deep blue with a slight red fluorescence by transmitted light. p_H range, colorless at 8.4 to red at 10.0.

Br: Found 24.98%. Calc. for $C_{32}H_{20}O_4Br_2$ 25.48%.

3,3′-DINITRO-5,5′-DIPHENYL-PHENOLPHTHALEIN.

9.5 Gm. 3,3′-diphenyl-phenolphthalein were suspended in 100 cc. glacial acetic acid and 3 cc. HNO_3 (sp. gr. 1.4) were added slowly with stirring. After warming on the water-bath for a few minutes the product was precipitated by adding 500 cc. water and recrystallized from alcohol. Yield—80–90%. Yellow needles, m. p. 135° C. after some softening at 115° C.

N: Found 5.08, 5.12%. Calc. for $C_{32}H_{20}N_2O_8$ 5.00%.

3,3′-DINITRO-PHENOL-PHTHALEIN.

20 Gm. of phenolphthalein were nitrated in exactly the same manner as the diphenyl phenolphthalein.

Yellow needles from dilute alcohol m. p. 110–111° C.
Yield—practically quantitative.
N: Found 6.59%. Calc. for $C_{20}H_{12}N_2O_8$ 6.78%.

SUMMARY.

A number of mercury derivatives of 2- and 4-hydroxy-diphenyl were prepared and their bactericidal properties investigated. The compounds mercurated were of two types, (*a*) in which a substituted hydroxy diphenyl was mercurated, (*b*) in which a phthalein prepared from hydroxy diphenyl was mercurated.

The mercury compounds have been shown to have considerable bactericidal activity.

REFERENCES.

(1) White, *J. A. C. S.*, 42 (1920), 2355.
(2) Greenbaum, *Am. J. Pharm.*, 102 (1930), 535.
(3) Whitmore, "Org. Compounds of Mercury," Chemical Catalog Co., N. Y. (1921).
(4) B. Latschinon, 6 (1872), 195.
(5) Borsche, *Ann.*, 312 (1900), 226.
(6) Scarborough and Waters, *J. C. S.*, 131 (1927), 95.

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United States Production of Coal-Tar Intermediates during 1932 totaled 218,143,000 pounds with sales of 96,960,000 pounds valued at $17,259,000, according to a United States Tariff Commission report. The 1931 output was 267,213,000 pounds with sales of 124,186 pounds, valued at $23,023,000.