tion of 2-bromocholestanone with this reagent, and recrystallizing from ethanol–chloroform (gelatinous solution); m. p. 166–177° (dec.).

Anal. Calcd. for $C_{34}H_{50}O_4N_4$: C, 70.55; H, 8.71; N, 9.68. Found: C, 70.23; H, 8.55; N, 9.57.

Methyl 2-bromo-3-ketoetio*allo*cholanate as well as 2,2-dibromocholestanone could be dehydrobrominated in a similar manner, but the products gave analytical figures which were always 2% too low in carbon content.

Reaction of 2-Bromocholestanone with Semicarbazide Hydrochloride.—A solution of 230 mg. of 2-bromocholestanone in 5 cc. of glacial acetic acid was heated with 60 mg. of finely crushed semicarbazide hydrochloride for six minutes. After dilution with water and recrystallization from ethanol–chloroform, there was obtained 170 mg. (78%) of Δ^1-cholestenone semicarbazone with m. p. 233–235°, undepressed on admixture with an authentic specimen; the derivative showed the typical maximum at 266 mμ, log E 4.41 (chloroform). The product gave a negative Beilstein test and was cleaved almost instantaneously with dioxane–43% sulfuric acid to yield 86% of Δ^1-cholestenone. It should be noted that while dinitrophenylhydrazones are usually isolated and purified more readily than the corresponding semicarbazones, the latter are very easily split into their components.[25]

Summary

The dehydrobromination of steroidal bromo ketones with dinitrophenylhydrazine, first discovered by Mattox and Kendall[11] in the case of 4-bromo-3-ketosteroids, has been examined critically. In addition to the 4-bromo ketones, the method is applicable to the dehydrobromination of 2-bromo- and 2,2-dibromo-3-keto*allo*steroids as well as 2-bromo- and 6-bromo-Δ^4-3-ketosteroids. The last two compounds both yield the hydrazone of the $\Delta^{4,6}$-dien-3-one. A mechanism for the reaction is suggested which employs a cyclic imonium compound as the key intermediate.

The regeneration of the unsaturated carbonyl compounds from the dinitrophenylhydrazones was examined and was found to be feasible from a preparative standpoint only in the case of the Δ^1- and Δ^4-3-ketones, thus imposing somewhat of a limitation on the Mattox–Kendall reaction.

SUMMIT, NEW JERSEY RECEIVED SEPTEMBER 30, 1948

[CONTRIBUTION NO. 152 FROM THE RESEARCH LABORATORIES OF HOFFMANN–LA ROCHE, INC.]

Synthesis of 5,5′-Dibromosalicil and Related Compounds

BY JACOB FINKELSTEIN AND SEYMOUR M. LINDER

In reports distributed by the Office of The Publication Board, No. 20,466 (Bios Final Report No. 219) it was revealed that Kuhn, in 1943, at Heidelberg had prepared 2,2′-dihydroxy-5,5′-dibromobenzil (3065) and claimed it to be the first compound found to be effective against Rickettsia and Influenza virus strain A employing mice as test animals. The I.G. Laboratories at Elberfeld found this substance to be tolerated by man in ten-gram doses. However, they were disappointed in its action in bacterial infections when compared to the sulfa drugs of choice. The substance is extremely insoluble. Therefore, the solubilized form prepared in borax and soda was tested and showed a fatal dose in the mouse of 30 mg./kg. Nevertheless, the claim by another I.G. Laboratory of its activity against virus organisms served as a stimulus to prepare the substance for testing in our chemotherapeutic laboratories. Although we were unable to confirm Kuhn's chemotherapeutic findings for the compound, we continued the investigation by synthesizing closely related substances. However, none of the compounds prepared was active *in vivo*, but the chemistry involved is interesting and forms the subject of this paper.

The methods of synthesizing the dibromosalicil are rather straight-forward. Kuhn, *et al.*[1] employed two closely related procedures. In one they started with 1,1′-dimethoxybenzil which was previously reported by Schonberger and Kraemer[2] and Irvine.[3] The compound was smoothly demethylated by aluminum chloride and then brominated in acetic acid. The other method by Perkin[4] starts with 2-methoxy-5-bromobenzaldehyde undergoing the benzoin condensation to produce the bromomethoxybenzoin. Another synthesis was outlined in the Department of Commerce Publication paralleling the latter method starting with 2-methoxymethoxy-5-bromobenzaldehyde (I). This methoxymethoxy substituent is ultimately removed by extremely mild conditions to produce the dibromosalicil.

For our investigation, the last method discussed was selected and the compound at each intermediate stage isolated and chemotherapeutically tested. In extending the problem to the preparation of closely related compounds, different compounds from those expected were isolated in several instances.

The first compound in the series capable of variation, 2,2′-di-(methoxymethoxy)-5,5′-dibromobenzoin (II), was subjected to hydrolysis for two minutes to produce the 2,2′-dihydroxy derivative (III). However, under identical conditions and with the reaction time increased to thirty minutes, the expected phenolic compound was readily acetylated to form 2,2′-diacetoxy-5,5′-dibromobenzoin (IV). The structure of this compound was proven by a negative color reaction with ferric chloride and conversion to III by hydrolysis with 10% sodium hydroxide.

(1) Kuhn, *et al.*, *Ber.*, **76**, 900 (1943).
(2) Schonberger and Kraemer, *ibid.*, **55**, 1184 (1922).
(3) Irvine, *J. Chem. Soc.*, **79**, 670 (1901).
(4) Perkin, *Ann.*, **145**, 304 (1868).

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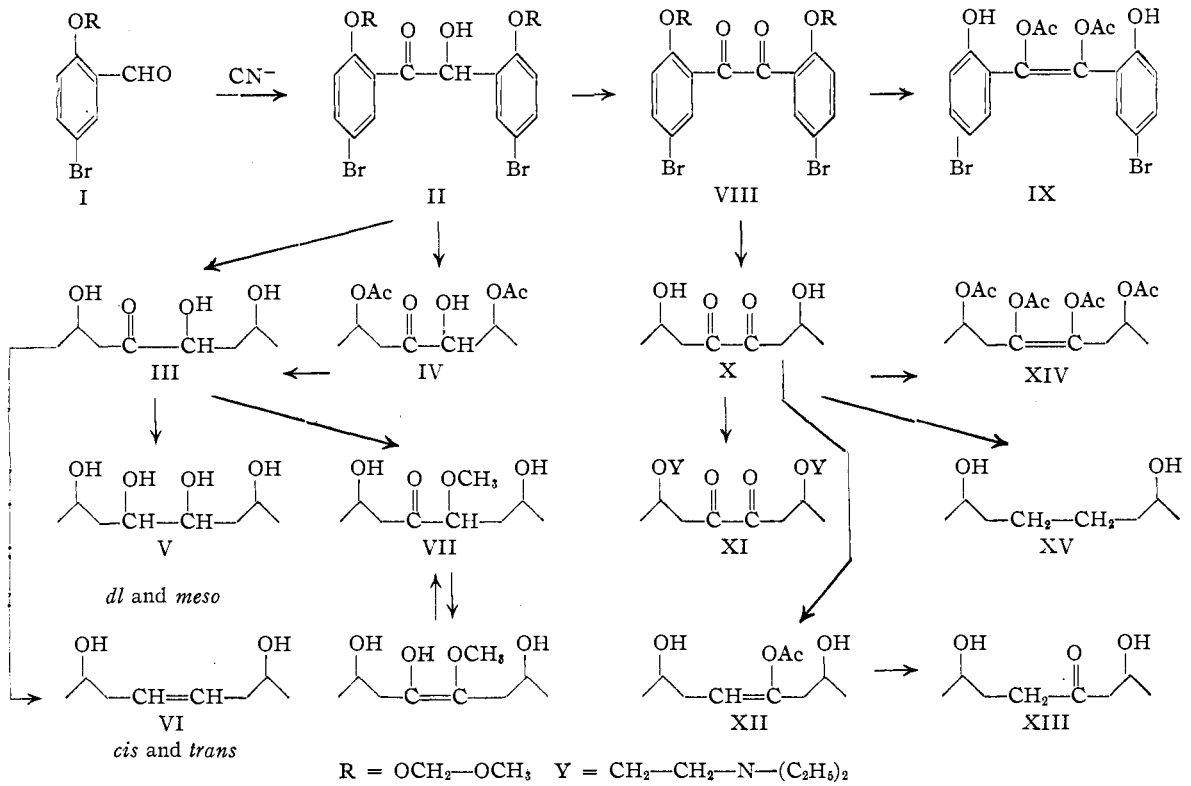


R = $OCH_2—OCH_3$ Y = $CH_2—CH_2—N—(C_2H_5)_2$

From the dihydroxybenzoin (III), five additional compounds were prepared. By reduction with sodium amalgam in wet ether in the manner of Irvine and Weir[5] as applied to benzoin, we were able to isolate the two possible hydrobenzoins (V), the *dl* and *meso* forms.

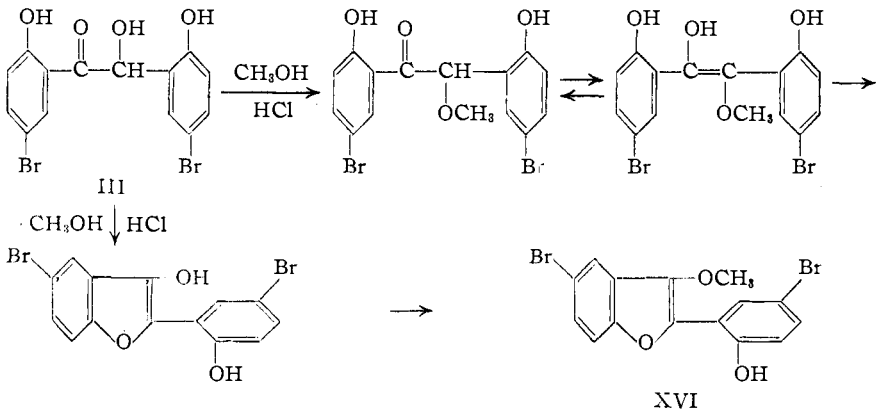
The stilbene derivative, 2,2′-dihydroxy-5,5′-dibromostilbene (VI) was prepared from the benzoin analog following the method of Ballard and Dehn[6] for the conversion of benzoin into stilbene. The two possible isomers were obtained.

Clemmensen[7] was able to convert benzoin or benzil to α,β-diphenylethane by reduction with zinc amalgam in dilute hydrochloric acid. Upon attempting to prepare 2,2′-dihydroxy-5,5′-dibromo-α,β-diphenylethane (XV), from the corresponding benzoin (III), a substance was obtained which is believed to be 2,2′-dihydroxy-5,5-dibromomethoxybenzoin monohydrate (VII). To account for such a substance, it would not be unreasonable to postulate the replacement of the alcoholic hydroxy group by a chlorine atom which when treated with methanol, as worked up, would produce the methyl ether. The location of the methoxy group was established by the negative reaction of the compound to Fehling solution.

To prove that the compound obtained is 2,2′-dihydroxy-5,5′-dibromomethoxybenzoin, an attempt was made to prepare it by another method for comparison purposes. Irvine[8] prepared methoxybenzoin by passing dry hydrogen chloride into a methanol solution of benzoin without controlling the temperature. When this was done with the benzoin (III), the compound isolated was alkali soluble and did not reduce Fehling solution. Thus phenolic methylation did not occur. The empirical formula, $C_{15}H_{10}O_3Br_2$, is that of the expected compound $C_{15}H_{12}O_4Br_2$, less the elements of water indicating the formation of a cyclic compound which could be 2-(2′-hydroxy - 5′ - bromophenyl) - 3 - methoxy - 5 - bromocoumarone (XVI). The possible courses of reaction may be graphically indicated as follows.

To obtain further information as to the course of reaction, 2,2′-dihydroxy-5,5′-dibromomethoxybenzoin monohydrate (VII) was treated with dry hydrogen chloride in methanol without any cooling. Under these conditions, the coumarone was not formed but a substance melting at 119–121° was obtained as compared to 173–175° for the starting compound. It gave an analysis which indicated no change in chemical formula and no reaction with Fehling solution. It is probable, therefore, that the compound VII was the *cis* form and the halogen acid catalyzed its conversion to the *trans* form. This conversion undoubtedly takes place more readily than ring closure. The melting point relationship is reversed from the usual and since the 119–121° iso-

(5) Irvine and Weir, *J. Chem. Soc.*, **91**, 1385 (1907).
(6) Ballard and Dehn, THIS JOURNAL, **54**, 3970 (1932).
(7) Clemmensen, *Ber.*, **47**, 683 (1914).
(8) Irvine, *J. Chem. Soc.*, 670 (1901).

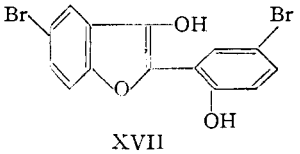


III

XVI

mer did not undergo ring closure to form a coumarone it is therefore *trans*.

Pursuing the original objective to prepare the methoxybenzoin from the benzoin compound, the above experiment was repeated keeping the reaction temperature between −15 and 10°. The compound thus obtained gave a positive Fehling reaction and was alkali soluble. The analysis also indicated the elimination of a molecule of water and analogously must be the unmethylated coumarone (XVII).



XVII

The positive Fehling test is not surprising especially since it was shown by Friedländer and Neudörfer[9] that 3-hydroxycoumarone displays such a reaction. It was also found that the hydroxycoumarone could be obtained from the methoxymethoxybenzoin II when its methanol solution was saturated at 0° with dry hydrogen chloride. In this case, the methoxymethoxy ethers are readily cleaved and ring closure follows. The compounds obtained from each source are identical.

From all these observations, compound XVI is probably prepared *via* the hydroxycoumarone intermediate rather than through the methoxybenzoin since the latter did not undergo cyclization.

However, the desired diphenylethane derivative (XV) was obtained when 2,2′-dihydroxy-5,5′-dibromobenzil was reduced by zinc and concentrated hydrochloric acid in alcohol. The compound was extremely difficult to purify. Although its melting point indicated that it may have been the lower melting stilbene isomer VI, a mixed melting point gave a depression.

For another series of compounds, 2,2′-di-(methoxymethoxy)-5,5′-dibromobenzoin II was first oxidized by Fehling solution to 2,2′-di-(methoxymethoxy)-5,5′-dibromobenzil (VIII).

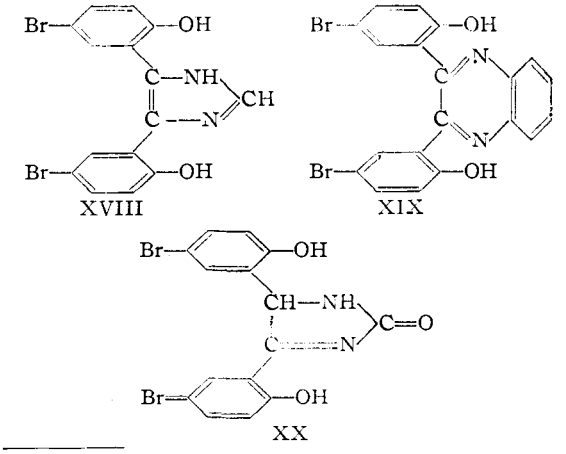
(9) Friedländer and Neudörfer, *Ber.*, **30**, 1081 (1897).

When VIII was subjected to reductive–acetylation below 40°, there was obtained 2,2′-dihydroxy-5,5′-dibromo-α,α′-diacetoxystilbene (IX).

Thus, during the reaction, the phenolic ethers were cleaved. However, when the ethers of VIII were removed by hydrolysis, 2,2′-dihydroxy-5,5′-dibromobenzil (5,5′-dibromosalicil) (X) was obtained. It agreed in all respects with the compound obtained by Kuhn. In an extension of the work several closely related compounds were synthesized. It was thought to be interesting to synthesize a derivative containing a basic water-soluble group. Therefore, 2,2′-bis-(β-diethylaminoethoxy)-5,5′-dibromobenzil (XI), was obtained as the free base and hydrochloride.

When Thiele's[10] procedure for reductive–acetylation was applied to dibromosalicil, 2,2′-dihydroxy-5,5′-dibromo-α-acetoxystilbene (XII) was produced. The formation of this substance probably involved the dehydration of the intermediate di-hydroxy compound to the mono-hydroxy stilbene which was then acetylated. This compound, when hydrolyzed by 10% sodium hydroxide, yielded 2,2′-dihydroxy-5,5′-dibromodesoxybenzoin (XIII). Only by modification of the procedure for reductive-acetylation of dibromosalicil (X) could 2,2′,α,α′-tetraacetoxy-5,5′-dibromostilbene (XIV) be prepared.

Three cyclic derivatives of possible chemotherapeutic interest were also synthesized. These were 4,5-bis-(2-hydroxy-5-bromophenyl)-imidazole (XVIII), 2,3-bis-(2-hydroxy-5-bromophenyl)-quinoxaline (XIX) and 4,5-bis-(2-hydroxy-5-bromophenyl)-glyoxalone (XX). The imidazole was prepared from 2,2′-dihydroxy-5,5′-dibromobenzil



XVIII XIX XX

(10) Thiele, *Ann.*, **306**, 142 (1899).

(X) by the improved procedure of Davidson, *et al.*[11] The quinoxaline (XIX) was obtained from X and *o*-phenylenediamine. The glyoxalone (XX) was formed from 2,2'-dihydroxy-5,5'-dibromobenzoin (III) as in "Organic Syntheses."[12]

Chemotherapeutic Results.[13]—5,5'-Dibromosalicil, its water-soluble borate complex and the thirteen dibromo derivatives which constitute chemical variations of dibromosalicil were tested as to their toxicity for mice and their possible therapeutic effect in selected experimental infections.

Toxicity.—Since the majority of compounds were insoluble in water, they were administered by the oral route. Their LD50 was found to be higher than 5.0 g./kg., *i.e.*, that a 10% suspension given by gavage did not produce toxic symptoms. Compound VIII was injected by the subcutaneous route dissolved in peanut oil. A 5% solution was tolerated, corresponding to LD50 of more than 2.5 g./kg. The LD50 of 5,5'-dibromosalicil borate complex was 0.095 g./kg. for the subcutaneous injection.

Chemotherapeutic Activity *in vivo*.—All compounds were tested in experimental infections with a hemolytic streptococcus (group A, type 3), or a type 1 pneumococcus, but none of them exerted any therapeutic effect. Furthermore all compounds were tried in the infection with poliomyelitis virus (SK strain). Up to ten treatments were given during the incubation period, but no protective effect was noted. There was also no evidence of the alleged activity of dibromosalicil in experimental influenza infections of mice (intranasal infection with type A strain PR 8). Neither dibromosalicil nor its borate complex and none of the other compounds had any significant activity toward this viral infection.

Two compounds, VI, IX, were also tried in mice infected with *Trypanosoma equiperdum*. No trypanocidal effect was observed.

Anti-bacterial Activity *in vitro*.—The lack of solubility in water of most of the compounds did not allow determinations of the bacteriostatic activity *in vitro* at least not with the usual methods of the dilution test. Two compounds, the borate complex and III, were sufficiently soluble to permit *in vitro* testing. The results are shown in the Table I which gives the reciprocal figures of the minimal bacteriostatic concentrations after forty-eight hours of contact.

TABLE I

Compound	Strepto-cocci	Pneumo-cocci	*Staph. aureus*	*E. coli*	*E. typhosa*
5,5'-Dibromosalicil borate complex	25,600	25,600	1,024,000	51,200	6400
2,2'-Bis-β-diethyl-aminoethoxy-5,5'-dibromo-benzil dihydro-chloride	128,000	64,000	16,000	8,000	1000

(11) Davidson, *et al.*, *J. Org. Chem.*, **2**, 319 (1937).

(12) "Organic Synthesis," Coll. Vol. 2, p. 231.

(13) The authors are indebted to Drs. R. Schnitzer and E. Grunberg of the Chemotherapy Department for these results.

The findings, as far as the soluble borate complex of 5,5'-dibromosalicil is concerned, confirm the figures recently given by Schales and Suthon[14] particularly the specific effect on *Staphylococcus aureus*. The substituted dibromobenzil derivative XI had a more marked limitation of activity to the group of gram-positive organisms.

Experimental

Chloromethyl Ether.—This compound was prepared according to the method of Clarke, Cox and Mack.[15]

5-Bromo-2-hydroxybenzaldehyde.—This compound was prepared as per Avwers and Burger[16] by bromination of salicylaldehyde.

2-(Methoxymethoxy)-5-bromobenzaldehyde (I).—To a solution of 63.5 g. of sodium in methanol, 555 g. of 5-bromo-2-hydroxybenzaldehyde and 2.5 liters of dry toluene were added. The excess methanol was removed by distillation. After cooling to 0°, 220 g. of pure chloromethyl ether was added dropwise with stirring during one hour keeping the temperature between 0–10°. After the reaction was stirred and refluxed for one hour, the mixture was slightly acid. After cooling to room temperature, water was added to dissolve the sodium chloride and separated. The toluene layer was extracted with dilute sodium hydroxide until a test portion of the washings did not produce a precipitate upon acidification. Then, the toluene solution was washed with water until neutral and concentrated *in vacuo* from a water-bath to remove the solvent leaving a yellow oil, which was fractionated *in vacuo*. At 5 mm. the desired product was collected between 152–154°. The yield was 82%. *Anal.* Calcd. for $C_9H_9O_3Br$: C, 44.21; H, 3.70. Found: C, 43.55; H, 3.76.

2,2'-Di-(methoxymethoxy)-5,5'-dibromobenzoin (II).—A solution of 296 g. of 2-methoxymethoxy-5-bromobenzaldehyde in 320 cc. of alcohol was mixed with a solution of 31 g. of potassium cyanide in 100 cc. of water and refluxed for two hours. As much alcohol as possible was distilled off from the steam-bath and the heavy residual oil was poured into cold water. The organic product was extracted with ether which was washed with water. The small amount of solid interface was discarded. The ether solution was dried and concentrated *in vacuo*. The remaining oil was dissolved in 170 cc. of warm methanol. Upon cooling, the benzoin compound crystallized. After recrystallization it melted at 89–91°. *Anal.* Calcd. for $C_{18}H_{18}O_6Br_2$: C, 44.11; H, 3.70. Found: C, 43.87; H, 3.68.

2,2'-Dihydroxy-5,5'-dibromobenzoin (III).—To a solution of 100 g. of 2,2'-di-(methoxymethoxy)-5,5'-dibromobenzoin in 500 cc. of warm acetic acid, 40 cc. of 15% sulfuric acid was added, and the mixture then heated on the steam-bath for two minutes. It was poured into cold water and the resulting oil taken up into ether. The ethereal solution was washed with water, then with a sodium bicarbonate solution until the washings were alkaline and finally with water. After drying over sodium sulfate, the ether was distilled off. The residual oil was dissolved in benzene and the product induced to crystallize by scratching and seeding; m. p. 133–135°. This was sufficiently pure for the following reactions. Further purification when necessary was effected by several recrystallizations from benzene; m. p. 146–146.5°. *Anal.* Calcd. for $C_{14}H_{10}O_4Br_2$: C, 41.81; H, 2.51; Br, 39.74. Found: C, 41.72; H, 2.58; Br, 39.64.

2,2'-Dihydroxy-5,5'-dibromodihydrobenzoin (V).—A 5-g. solution of 2,2'-dihydroxy-5,5'-dibromobenzoin (III) was prepared in 100 cc. of wet ether. While a stream of carbon dioxide was passed through the solution, 18 g.

(14) Schales and Suthon, *Archives of Biochemistry*, **11**, 397 (1940).

(15) Clarke, Cox and Mack, THIS JOURNAL, **39**, 712 (1917).

(16) Avwers and Burger, *Ber.*, **37**, 3934 (1904).

of 3.3% sodium amalgam was added in small portions. The *p*H of the mixture was thus kept at 8 (or below). It was necessary to replace the ether lost by evaporation. Small amounts of water were added from time to time to replace that used in the reaction and to dissolve some of the salts formed. After two hours, the addition was completed. When hydrogen was no longer evolved, water was added to dissolve the sodium bicarbonate. The ether layer was separated, washed with water and dried. When the ether was removed, crystals were obtained which melted between 136–138°. When recrystallized from acetone–Skellysolve B mixture, m. p. 149–152°. This proved to be a mixture of the *dl*- and *meso*. Upon repeated crystallization, one product m. p. 225–229° was obtained and probably is the *dl* (racemic) mixture. *Anal.* Calcd. for $C_{14}H_{12}O_4Br_2$: C, 41.61; H, 2.99; Br, 39.59. Found: C, 41.60; H, 3.06; Br, 39.56.

To obtain the *meso* form, the above mother liquors were combined and concentrated to obtain a solid. Upon recrystallization from benzene, the *meso* form was obtained pure; m. p. 155–156°. *Anal.* Calcd. for $C_{14}H_{12}O_4Br_2$: C, 41.61; H, 2.99; Br, 39.59. Found: C, 41.73; H, 2.87; Br, 39.37.

2,2′-Dihydroxy-5,5′-dibromostilbene (VI).—To zinc amalgam prepared from 5 g. of mercuric chloride and 20 g. of zinc dust, a solution of 9 g. of 2,2′-dihydroxy-5,5′-dibromobenzoin (III) dissolved in 50 cc. of alcohol was added. While stirring and maintaining a reaction temperature of 15°, 40 cc. of concentrated hydrochloric acid was added dropwise over a period of two hours. After stirring for an additional hour, the mixture was diluted with a large volume of water and filtered. After washing with water, the residue was treated with ether to dissolve away the product from metal. The ether solution was dried and concentrated. The oil which was obtained soon crystallized. After three recrystallizations from xylene, the product was pure; m. p. 201–202°. This is the *trans* isomer. *Anal.* Calcd. for $C_{14}H_{10}O_2Br_2$: C, 45.41; H, 2.73; Br, 43.20. Found: C, 45.50; H, 2.64; Br, 43.03. The *cis* isomer was isolated from the xylene mother liquors and purified by recrystallization from benzene; m. p. 169–173°. *Anal.* Found: C, 45.18; H, 3.07.

2,2′-Dihydroxy-5,5′-dibromomethoxybenzoin (VII).—Zinc amalgam was prepared from 10 g. of mossy zinc, 1 g. of mercuric chloride, 0.5 cc. of concentrated hydrochloric acid and 15 cc. of water. To the amalgam, were added 5 g. of 2,2′-dihydroxy-5,5′-dibromobenzoin, 20 cc. of water and 20 cc. of concentrated hydrochloric acid. Upon refluxing, a vigorous reaction took place and, to prevent the solids from coating the flask, 5 cc. of alcohol was added. The reaction mixture was refluxed for five hours and at each hour 2 cc. of concentrated hydrochloric acid was added. After cooling, filtering and washing with water, the product was taken up in ether to separate it from the metal, and dried. Upon removal of the ether, a greenish glassy substance was obtained. It was then triturated with methanol whereupon some crystals appeared. Another crop was obtained by concentrating the methanol. The second crop was recrystallized twice from xylene; m. p. 173–175°. *Anal.* Calcd. for $C_{14}H_{12}O_2Br_2$: C, 45.20; H, 3.25; Br, 42.95. Calcd. for $C_{15}H_{13}O_4Br_2 \cdot H_2O$: C, 41.54; H, 3.22; Br, 36.86. Found: C, 41.54; H, 2.23; Br, 36.89.

2,2′-Diacetoxy-5,5′-dibromobenzoin (IV).—Eighty grams of 2,2′-di-(methoxymethoxy)-5,5′-dibromobenzoin was dissolved in 300 cc. of glacial acetic acid with warming, and 32 cc. of 15% sulfuric acid was added. The solution was heated on the steam-bath for thirty minutes and worked up as for III above. The benzene solution did not produce any crystals and so was concentrated on the steam-bath to a smaller volume. After keeping in the refrigerator, a small amount of crystals appeared. These were collected and washed with benzene; m. p. 183–187°. For Compound III the m.p. 146–146.5°. By recrystallization from methanol, the pure compound was obtained; m. p. 199–201°; no color with ferric chloride. *Anal.* Calcd. for $C_{14}H_{10}O_4Br_2$ (free phenol): C, 41.81; H, 2.51. Calcd. for $C_{16}H_{12}O_5Br_2$ (mono-acetoxy): C, 43.28; H, 2.73. Calcd. for $C_{18}H_{14}O_6Br_2$ (di-acetoxy): C, 44.46; H, 2.90. Found: C, 44.77, 44.58; H, 2.65, 2.57.

Conversion of IV to III.—One-half gram of IV and 5 cc. of 10% sodium hydroxide were mixed. The solid turned yellow and, upon heating on the steam-bath, went into solution. Upon cooling, the yellow sodium salt precipitated out. The mixture was acidified with dilute hydrochloric acid and a colorless product was obtained. It was filtered, washed and purified; m. p. 143–145°; for III crystallized several times from benzene, m. p. 146–146.5°.

2,2′-Di-(methoxymethoxy)-5,5′-dibromobenzil (VIII).—To 64.5 g. of crude 2,2′-di-(methoxymethoxy)-5,5′-dibromobenzoin in 75 cc. of alcohol, the following were added: A, 151 g. of $CuSO_4 \cdot 5H_2O$ in 600 cc. of water; B, 225 g. of $KNaC_4H_4O_6 4H_2O$ and 162 g. of potassium hydroxide dissolved in water to a volume of 860 cc. The reaction mixture was stirred at 75–80° for two hours. After cooling, the product was collected and freed from copper oxide by dissolving in hot alcohol and decolorized with Nuchar. The filtrate yielded practically colorless crystals. When recrystallized from alcohol, the compound was pure; m. p. 115–116°. A second crop can be obtained from the mother liquors. *Anal.* Calcd. for $C_{18}H_{16}O_6Br_2$: C, 44.28; H, 3.30. Found: C, 44.10; H, 3.43.

2,2′-Dihydroxy-5,5′-dibromo-α,α-diacetoxystilbene (IX).—Six grams of 2,2′-di-(methoxymethoxy)-5,5′-dibromobenzil VIII was added to 10 cc. of acetic acid previously saturated with dry hydrogen chloride. Then, 60 cc. of acetic anhydride was added, and while stirring at 30°, zinc dust was added over one-half hour in several portions until 6 g. was added. The mixture was then stirred for an additional hour and a half and poured into 500 cc. of cold water. After standing overnight, the oil was extracted with ether, washed, first with water and then sodium bicarbonate and then water again. After drying over sodium sulfate, the ether was removed and the residual oil soon crystallized. It was purified by crystallization from butanol; m. p. 121–124°. *Anal.* Calcd. for $C_{18}H_{14}O_6Br_2$: C, 44.48; H, 2.90; Br, 32.88. Found: C, 44.27; H, 3.13; Br, 32.52.

2,2′-Dihydroxy-5,5′-dibromobenzil (X).—Fifty grams of 2,2′-di-(methoxymethoxy)-5,5′-dibromobenzil (VIII) was dissolved in 250 cc. of glacial acetic acid. To the hot solution, 17 cc. of 15% sulfuric acid was added. Then, at once, 25 cc. of hot water was added and immediately crystals began to form. The heating was continued for one minute and the mixture cooled. The product was filtered, washed with methanol and dried at 90; m. p. 204–206°. Recrystallized from alcohol, the product was obtained pure; yield 95%; m. p. 209–210°; lit. m. p. 210°. *Anal.* Calcd. for $C_{14}H_8O_4Br_2$: C, 42.04; H, 2.03. Found: C, 42.44; H, 2.12.

2,2′-Dihydroxy-5,5′-dibromodiphenylethane (XV).—To a refluxing mixture of 2 g. of 2,2′-dihydroxy-5,5′-dibromobenzil (X) dissolved in 60 cc. of alcohol, 3.5 g. of 30-mesh zinc and 5 cc. of concentrated hydrochloric acid was added. A vigorous reaction took place. At half-hour intervals, 5-cc. portions of acid were added. After one-half hour, the yellow color was discharged and after one and one-half hours, the refluxing ceased. After cooling, the solution was poured into water yielding an oil which soon crystallized. The product was filtered and dried at 100°; m. p. 153–160°. After recrystallization from benzene, the product melted at 172–173°. *Anal.* Calcd. for $C_{14}H_{12}O_2Br_2$: C, 45.20; H, 3.25; Br, 42.95. Found: C, 45.64; H, 2.54; Br, 43.22.

2,2′-Di-(β-diethylaminoethoxy)-5,5′-dibromobenzil (XI).—The disodium salt of 2,2′-dihydroxy-5,5′-dibromobenzil was prepared from 6.5 g. of the compound and 2 equivalents of sodium ethylate in alcohol and obtained dry by continuous concentration with benzene. It was then treated with excess β-diethylaminoethyl chloride in 100 cc. of dry toluene and refluxed for ten hours with continuous stirring. The sodium chloride was filtered off and the toluene solution was washed with alkali and then with water. The solution was dried over sodium sulfate and concentrated *in vacuo*. The oil soon crystallized. The free base so obtained melted at 82–84°. When recrystal-

lized from Skellysolve B, yellow crystals were obtained; m. p. 84–86°. *Anal.* Calcd. for $C_{26}H_{34}O_4Br_2N_2$: C, 52.18; H, 5.72; N, 4.68. Found: C, 52.18; H, 5.44; N, 4.72. The base was converted into the di-hydrochloride and recrystallized from isopropyl alcohol; m. p. 195–196°. *Anal.* Calcd. for $C_{26}H_{34}O_4Br_2N_2 \cdot 2HCl$: C, 46.53; H, 5.40; N, 4.17. Found: C, 46.67; H, 5.18; N, 4.36.

5,5′-Dibromo-2,2′-α,α′-tetraacetoxystilbene (XIV).—To 5 g. of 2,2′-dihydroxy-5,5′-dibromobenzil (X) dissolved in 60 cc. of acetic anhydride, 10 cc. of acetic acid previously saturated with hydrogen chloride at 15° was added with stirring and cooling. Then, at 30–40°, 6 g. of zinc dust was gradually added. The reaction mixture turned green and then black. After one hour, the reaction mixture was poured into 500 cc. of cold water. The sticky solid thus produced was filtered and dissolved in ether. The ethereal solution was first washed with water then with sodium bicarbonate and water. When dried, the solution was concentrated leaving an oil. When treated with butanol, the product crystallized. It was then recrystallized from butanol several times to constant melting point; m. p. 155–157°. *Anal.* Calcd. for $C_{22}H_{18}O_8Br_2$: C, 46.31; H, 3.18; Br, 28.02. Found: C, 45.87; H, 3.27; Br, 28.22.

2,2′-Dihydroxy-5,5′-dibromo-α-acetoxystilbene (XII).—To a suspension of 4.5 g. of 2,2′-dihydroxy-5,5′-dibromobenzil (X) in 60 cc. of acetic anhydride, with cooling, a solution of 5 cc. of concentrated sulfuric acid in 10 cc. of acetic acid was slowly added to avoid undue rise in temperature. Then, at 30–40°, 6 g. of zinc dust was gradually added with good stirring. After one hour, white crystals appeared. The reaction mixture was diluted with water and filtered. To separate the zinc, the compound was extracted in a Soxhlet extractor with ether. The ether removed, the solid was recrystallized from butanol until pure; m. p. 145–147°. *Anal.* Calcd. for $C_{16}H_{12}O_4Br_2$: C, 44.85; H, 2.80; Br, 37.40; acetyl, 10.1. Found: C, 44.74; H, 2.61; Br, 37.25; acetyl, 10.9.

2,2′-Dihydroxy-5,5′-dibromodesoxybenzoin (XIII).—A solution of 1.8 g. of 2,2′-dihydroxy-5,5′-dibromo-α-acetoxystilbene (XII) in 18 cc. of 10% sodium hydroxide was warmed for fifteen minutes on the steam-bath. After neutralization with dilute hydrochloric acid, the product crystallized. It was filtered, washed and recrystallized from benzene until it melted at 209–211°. *Anal.* Calcd. for $C_{14}H_{10}O_3Br_2 \cdot {}^1/_2H_2O$: C, 42.55; H, 2.78; Br, 40.51. Found: C, 42.24; H, 2.64; Br, 40.59.

2-(2′-Hydroxy-5′-bromophenyl)-3-methoxy-5-bromocoumarone (XVI).—A solution of 3.5 g. of 2,2′-dihydroxy-5,5′-dibromobenzoin (III) in 50 cc. of methanol was saturated with dry hydrogen chloride without any cooling. The temperature rose sufficiently to cause refluxing. After saturation and cooling, the product crystallized out. It was recrystallized from methanol, m. p. 103–104°. The Fehling test is negative. *Anal.* Calcd. for the coumarone $C_{15}H_{10}O_3Br_2$: C, 45.25; H, 2.53; Br, 40.12. Found: C, 45.78; H, 2.69; Br, 40.15.

2-(2′-Hydroxy-5′-bromophenyl)-3-hydroxy-5-bromocoumarone (XVII).—A. A solution of 3 g. of 2,2′-dihydroxy-5,5′-dibromobenzoin (III) in 100 cc. of methanol was cooled to −15° and saturated with dry hydrogen chloride. During the reaction, the temperature rose to 10°, before it could be checked, and then kept at 0°. The saturated solution was poured into 500 cc. of ice-water and the resultant precipitate filtered, washed with water and dissolved in ether. The ether solution was extracted with dilute sodium hydroxide and the combined alkali extracts were acidified. The solid was collected and recrystallized from toluene, m. p. 155–156°. The Fehling test was positive. *Anal.* Calcd. for the coumarone $C_{14}H_8O_3Br_2$: C, 43.80; H, 2.10. Found: C, 44.06; H, 1.94. B. A solution of 4 g. of 2,2′-di-(methoxymethoxy)-5,5′-dibromobenzoin (II) in 100 cc. of methanol at −25° was saturated with dry hydrogen chloride keeping the temperature below 0°. The yellow precipitate obtained when the reaction mixture was poured into ice-water was collected and recrystallized from toluene; m. p. 158–159°. When mixed with the compound obtained in A, there was no depression. It also gave a positive Fehling test. *Anal.* Calcd. for $C_{14}H_8O_3Br_2$: C, 43.80; H, 2.10; Br, 41.61. Found: C, 43.96; H, 2.17; Br, 41.33.

Conversion of *cis*-2,2′-Dihydroxy-5,5′-dibromo-α-methoxybenzoin to *trans* Form.—Ninety mg. of *cis*-2,2′-dihydroxy-5,5′-dibromo-α-methoxybenzoin was dissolved in 5 cc. of methanol and saturated with dry hydrogen chloride without cooling. Then, after refluxing for fifteen minutes, it was cooled and crystals separated. After filtering and recrystallizing from methanol, it melted at 119–121°. *Anal.* Calcd. for $C_{15}H_{10}O_3Br_2$ (coumarone): C, 45.28; H, 2.53; Br, 40.12. Calcd. for $C_{15}H_{12}O_4Br_2 \cdot H_2O$ (starting compound): C, 41.50; H, 3.22; Br, 36.86. Found: C, 42.22; H, 2.79; Br, 36.83.

4,5-bis-(2-Hydroxy-5-bromophenyl)-imidazole (XVIII).—A mixture of 3.0 g. of 5,5′-dibromosalicil (X), 0.2 g. of hexamethylenetetramine, 4.5 g. of ammonium acetate and 95 cc. of glacial acetic acid was refluxed for one hour. After *dilution* with 900 cc. of water and clarification by filtration, the solution was made alkaline with ammonia. The precipitate was collected and recrystallized from dilute alcohol twice and dried at 100°; m. p. 235–237°. *Anal.* Calcd. for $C_{15}H_{10}N_2O_2Br_2$: N, 6.83. Found: N, 7.05.

2,3-bis-(2-Hydroxy-5-bromophenyl)-quinoxaline (XIX).—A solution of 4 g. of 5,5′-dibromosalicil (X), 1 g. of *o*-phenylenediamine in 125 cc. of acetic acid was refluxed for three hours and poured into ice. The crystallized product was dried by distillation of a benzene solution and recrystallized from small amounts of benzene; m. p. 216–219°. With 5,5′-dibromosalicil, the melting point was depressed. This compound does not form a hydrochloride. *Anal.* Calcd. for $C_{20}H_{12}O_2N_2Br_2$: C, 50.85; H, 2.56; N, 5.94. Found: C, 50.68; H, 2.67; N, 5.85.

4,5-bis-(2-Hydroxy-5-bromophenyl)-glyoxalone (XX).—A solution of 3 g. of 2,2′-dihydroxy-5,5′-dibromobenzoin (III), 0.81 g. of urea in 20 cc. of glacial acetic acid was refluxed for seven hours, during which time crystallization started. After standing, the product was filtered and washed with ether to remove starting material. The compound was purified by recrystallization from aqueous pyridine; m. p. 272–273°. *Anal.* Calcd. for $C_{15}H_{10}N_2O_3Br_2$: C, 42.30; H, 2.37; N, 6.58. Found: C, 42.50; H, 2.75; N, 6.41.

Acknowledgment.—The authors wish to thank Dr. John Lee for his interest, advice and helpful discussions during the course of this research and also Dr. Al Steyermark and his associates for the microanalyses.

Summary

The 2,2′-dihydroxy-5,5′-dibromosalicil (5,5′-dibromosalicil) compound of Kuhn was synthesized and his claims for its activity toward virus infections could not be substantiated.

Many closely related compounds were synthesized and tested *in vitro* against hemolytic streptococcus, pneumococcus, poliomyelitis, trypanosoma, and gram-positive organisms without revealing any marked activity.

It was shown that benzoins substituted on the adjacent carbon atom with a hydroxy group can be converted into a coumarone upon treatment with dry hydrogen chloride.

The keto-alcohol part of the substituted benzoin molecule is capable of reaction to produce a cyclic compound as a glyoxalone.

The di-keto part of the substituted benzil molecule is capable of reaction to produce cyclic derivatives as the imidazole and quinoxaline.

NUTLEY, N. J. RECEIVED SEPTEMBER 24, 1948