[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PRINCETON UNIVERSITY]

A CONTRIBUTION TO THE STRUCTURE OF CITRININ

ALFRED H. FRYE, EVERETT S. WALLIS AND GREGG DOUGHERTY

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The antibiotic, citrinin, is a metabolic product of various species of molds (*Penicillium citrinin* Thom, *Aspergillus candidus*). A structure for this substance was first proposed by Coyne, Raistrick and Robinson (1); however, subsequent investigations (2, 3) yielded evidence that that structure was incorrect. It was therefore of interest to reopen the subject with a view of arriving at a more suitable formulation. Three other groups of workers (4, 5, 6) have also engaged in this reinvestigation and their conclusions have appeared in recent publications. What follows constitutes the contribution of the present writers to this problem.

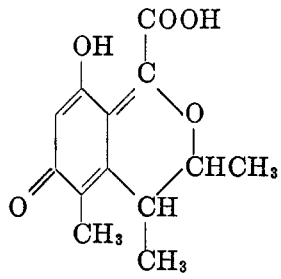
Citrinin (I, $C_{13}H_{14}O_5$) upon acid hydrolysis yields two isomeric substances, IIA and IIB, of the formula $C_{11}H_{16}O_3$. Hetherington and Raistrick (7) assumed IIB to be the optically inactive stereoisomer of IIA. Alkali fusion of IIA produces III, ($C_9H_{12}O_2$), which Cram (4) has shown to be identical with 4-methyl-5-ethylresorcinol by synthesis of that compound. At the time of publication of Cram's work we were engaged in the synthesis of 4-methyl-5-ethylresorcinol by a different route and we concur with Cram that III is identical with that synthetic substance. We have also synthesized 4-methyl-3,5-dihydroxyacetophenone in a manner which parallels our synthesis of 4-methyl-5-ethylresorcinol.

Cram proposed for the structure of IIA that of 4-methyl-5-(1-methyl-2-hydroxy)-propylresorcinol on the basis of a terminal methyl analysis of that substance indicative of three methyl groups, and on its reported coupling (2) with two moles of 2-methoxy-5-nitrobenzenediazonium chloride. This structure has two centers of asymmetry and consequently two pairs of racemates should be possible. Since only one racemate, IIB, has been reported, we undertook a further investigation of IIA and IIB. We have found that under the conditions of the acid hydrolysis of citrinin, IIA can be converted to IIB in seventy per cent yield. From the residual syrup we were unable to isolate any other substance. That IIB is actually a racemic compound of IIA and its optical antipode was shown by the partial resolution of its triacetylated derivative by the method of inoculation. Hetherington, *et al.* (7), reported that acetylation of IIA with acetic anhydride and pyridine yielded only a diacetate, while with acetic anhydride and sodium acetate they obtained the triacetate. We found that a triacetate of IIA (m.p. 88.2–89.5°, $[\alpha]_D$ +10.4°) was readily obtained with acetic anhydride and pyridine.

Confirmatory evidence that IIA has two free nuclear positions *ortho* and *para* to the phenolic hydroxyl groups as reported by Gore, *et al.* (2), was obtained by treatment of that substance with bromine water which yielded a dibromo derivative. Citrinin yields a positive test in the iodoform reaction. That the functional group responsible for this is retained in the dimethylated derivative of

IIA, ($[\alpha]_D$ −40.5°), was shown by subjecting that substance to Fuson and Tullock's (8) modification of the iodoform reaction which yielded a small but definite quantity of iodoform. Though our efforts to isolate the acid moiety from this reaction were inconclusive, a colored oil exhibiting a pronounced positive rotation was obtained. Conclusive proof of Cram's proposed structure for IIA was provided by subjecting levorotatory dimethyl IIA to the Oppenauer oxidation with aluminum isopropoxide. A dextrorotatory ketone was obtained as a colorless oil and was converted to its optically active semicarbazone derivative.

On the basis of this and other evidence we can assume with Gore, *et al.* (5) that the structure of citrinin can be represented by I, or if we assume that citrinin can couple with diazonium salts on an active C—H, formula IA is possible.



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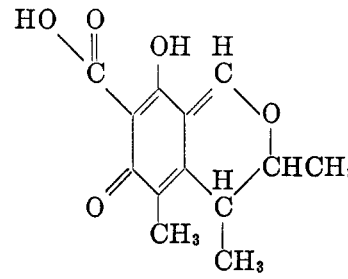

Ia

EXPERIMENTAL

2-Methyl-3,5-dinitrobenzoyl chloride. To 113 g. of 2-methyl-3,5-dinitrobenzoic acid (m.p. 207.5–208°) was added 105 g. of phosphorus pentachloride and the mixture was shaken to insure homogeneity. When the initial vigor of the reaction had subsided, the reaction was completed by heating for 2.5 hours on a hot water-bath and the phosphorus oxychloride was removed under reduced pressure over the course of three hours. Upon cooling, the material solidified to a cream-colored mass. This was purified by evaporation onto a cold finger in high vacuum at 80–90° to yield 108.5 g. (88.7%) of almost colorless crystals. Upon recrystallization from absolute ether tiny white needles, m.p. 63.5–64.0°, were obtained.

Anal. Calc'd for $C_8H_5ClN_2O_6$: C, 39.26; H, 2.10.
Found: C, 39.33; H, 2.15.

4-Methyl-3,5-dinitrobenzoyl chloride. When 113 g. of 4-methyl-3,5-dinitrobenzoic acid (m.p. 161.2–162.0°) was reacted with phosphorus pentachloride in the same manner used on the isomeric acid, a yield of 112.2 g. (91.6%) of the acyl chloride was obtained, which crystallized as colorless rhombs; m.p. 56.5–57.0°.

Anal. Calc'd for $C_8H_5ClN_2O_6$: C, 39.26; H, 2.10.
Found: C, 39.14; H, 2.08.

Ethyl 2-methyl-3,5-dinitrobenzoylacetoacetate. A solution of sodium ethoxide was prepared by treating 12 g. (0.52 atom) of freshly cut sodium with 150 cc. of absolute ethanol. The reaction was completed by heating the mixture on a steam-bath and then sufficient absolute ethanol was added to bring the volume of the solution up to 200 cc. Meanwhile 61 g. (0.25 mole) of 2-methyl-3,5-dinitrobenzoyl chloride was dissolved in sufficient absolute ether to give a volume of 1200 cc. In a three-necked flask, immersed in an ice-water bath and fitted with a mechanical stirrer and two dropping funnels, was placed 34 g. (0.261 mole) of ethyl acetoacetate. From one of the funnels 100 cc. of the sodium ethoxide solution was introduced into the flask and after fifteen minutes, 600 cc. of the benzoyl chloride solution was added slowly in a thin stream. The solution was allowed to react for an hour, stirring

being continuously maintained, and then a second portion of 50 cc. of sodium ethoxide solution was added, followed by a second portion of 300 cc. of the benzoyl chloride solution. In this portion-wise manner the entire quantities of the two reagents were combined with the acetoacetic ester, one hour being allowed to pass between the addition of one pair of the reagents and the subsequent addition of the following pair. The various portions used were:

Sodium Ethoxide	*2-Methyl-3, 5-dinitrobenzoyl Chloride*
cc.	*cc.*
100.00	600.0
50.00	300.0
25.00	150.0
12.50	75.0
6.25	37.5
6.25	37.5

When the last portion had been added, the mixture was allowed to stand for 48 hours in a cold water bath. The precipitated product was collected by filtration, washed several times with ether, and dissolved in 10 l. of cold water and filtered from any insoluble material. Dissolution was slow and was aided by stirring. The filtrate was acidified with 1 *N* sulfuric acid and a precipitate was formed upon standing. The product was purified by recrystallization from methanol to yield 72.6 g. (85.9%) of pale flesh-colored prisms; m.p. 95–96°.

Anal. Calc'd for $C_{14}H_{14}N_2O_8$: C, 49.71; H, 4.17.
Found: C, 49.74; H, 4.09.

Ethyl 4-methyl-3,5-dinitrobenzoylacetoacetate. When 34 g. of ethyl acetoacetate was benzoylated with 61 g. of 4-methyl-3,5-dinitrobenzoyl chloride in the method detailed above, a yield of 73.7 g. (87%) of ethyl 4-methyl-3,5-dinitrobenzoylacetoacetate was obtained, crystallizing as almost colorless tiny needles; m.p. 81.0–81.5°.

Anal. Calc'd for $C_{14}H_{14}N_2O_8$: C, 49.71; H, 4.17.
Found: C, 50.06; H, 4.35.

2-Methyl-3,5-dinitroacetophenone and 2-methyl-3,5-dinitrobenzoylacetone. A mixture of 84.5 g. of ethyl 2-methyl-3,5-dinitrobenzoylacetoacetate and 8.5 liters of 40% sulfuric acid was refluxed with continuous stirring for eighteen hours. It is important that the stirrer employed be particularly effective so as to keep the oil suspended in the aqueous phase as fine droplets. Upon cooling the oil solidified and was collected. This product was triturated repeatedly with 2% sodium hydroxide until the decanted alkaline solution was colorless. The red-colored alkaline extract was immediately acidified with dilute sulfuric acid to precipitate the crude 2-methyl-3,5-dinitrobenzoylacetone, while the alkali insoluble acetophenone derivative was freed from remaining traces of 2-methyl-3,5-dinitrobenzoylacetone by dissolving it in ether and washing the ether solution with 2% sodium hydroxide. Evaporation of the ether solution yielded the crude 2-methyl-3,5-dinitroacetophenone which was purified by recrystallization from alcohol. The yield of this product was 82%. Further purification from petroleum ether, in which it was difficultly soluble, gave colorless needles melting at 71.5–72.5°.

Anal. Calc'd for $C_9H_8N_2O_5$: C, 48.67; H, 3.59.
Found: C, 48.59; H, 3.88.

The 2-methyl-3,5-dinitrobenzoylacetone was purified by two recrystallizations from 95% ethanol to yield 5.3 g. (8.1%) of colorless, long fine needles; m.p. 90.0–90.5°.

Anal. Calc'd for $C_{11}H_{10}N_2O_8$: C, 49.62; H, 3.78.
Found: C, 50.05; H, 3.92.

4-Methyl-3,5-dinitroacetophenone and 4-methyl-3,5-dinitrobenzoylacetone. Under the conditions of hydrolysis employed upon ethyl 2-methyl-3,5-dinitrobenzoylacetoacetate, 84.5 g. of ethyl 4-methyl-3,5-dinitrobenzoylacetoacetate yielded 44.8 g. (84.2%) of 4-methyl-3,5-dinitroacetophenone; m.p. 68–69°.

Anal. Calc'd for $C_9H_8N_2O_5$: C, 48.67; H, 3.59.
Found: C, 48.72; H, 3.28.

The yield of 4-methyl-3,5-dinitrobenzoylacetone was 3.5 g. (5.3%), which crystallized as very pale flesh-colored needles; m.p. 144.0–144.5°.

Anal. Calc'd for $C_{11}H_{10}N_2O_6$: C, 49.62; H, 3.78.
Found: C, 49.41; H, 3.65.

2-Methyl-3-nitro-5-aminoacetophenone and 2-methyl-3-amino-5-nitroacetophenone. A solution of 67 g. (0.35 mole) of anhydrous stannous chloride in 470 cc. of absolute methanol was saturated with dry hydrogen chloride while being chilled in a salt-ice bath. This solution was then slowly added, accompanied by stirring, to a solution of 26.43 g. (0.118 mole) of 2-methyl-3,5-dinitroacetophenone in 2 liters of absolute methanol, the temperature of which was maintained below 5°. After standing over night and allowing it to come to room temperature, the solution was slowly warmed in a water-bath and then refluxed for one-half hour. The clear light-yellow solution was concentrated to about 100 cc. under reduced pressure and then poured into a liter of water which produced a turbidity. This was exhaustively extracted with ether and the aqueous solution set aside for later treatment. After drying the ether extract with potassium carbonate, hydrogen chloride was passed in to precipitate the amine hydrochloride which was collected by filtration. The ether mother liquor was washed with water and then with sodium carbonate solution. Evaporation to dryness of this ether solution left a solid residue which was recrystallized from methanol to yield 5.9 g. (0.026 mole) of unchanged starting material. The amine hydrochloride was added to 300 cc. of water, whereupon the free base immediately separated. This was recrystallized from 95% ethanol to yield coral-colored crystals, presumably the alcoholate, which became bright yellow upon drying in a vacuum desiccator over sulfuric acid. Yield, 9.25 g. (51.8%) of product; m.p. 110.5–111.0°.

Anal. Calc'd for $C_9H_{10}N_2O_3$: C, 55.65; H, 5.19.
Found: C, 55.38; H, 4.98.

The aqueous solution, from which the preceding ether extract had been obtained, was heated to 90° and hydrogen sulfide passed in until the tin had been completely precipitated. After filtering off the stannic sulfide, the solution was made basic with 10% sodium hydroxide and extracted with ether. The ether extract was dried with potassium carbonate and then treated with hydrogen chloride to precipitate the amine hydrochloride. This was collected and added to 20 cc. of water whereupon the free base precipitated. Recrystallization from ethanol yielded 0.85 g. (4.8%) of tiny, bright yellow needles melting at 116.0–117.5°.

Anal. Calc'd for $C_9H_{10}N_2O_3$: C, 55.65; H, 5.19.
Found: C, 55.42; H, 5.44.

The two products are therefore the isomeric *2-methyl-3-nitro-5-aminoacetophenone* and *2-methyl-3-amino-5-nitroacetophenone*, although their particular identity has not been ascertained.

4-Methyl-3-nitro-5-aminoacetophenone. Reduction of 15.9 g. of 4-methyl-3,5-dinitroacetophenone with 40.4 g. of anhydrous stannous chloride as detailed above yielded 3.1 g. of the unreacted dinitroacetophenone and 6.2 g. (56%) of 4-methyl-3-nitro-5-aminoacetophenone as tiny orange needles melting at 158–159°.

Anal. Calc'd for $C_9H_{10}N_2O_3$: C, 55.65; H, 5.19.
Found: C, 55.47; H, 5.09.

2-Methyl-(3 or 5)-hydroxy-(5 or 3)-nitroacetophenone. To a suspension of 2.3 g. of the hydrochloride of 2-methyl-(3 or 5)-amino-(5 or 3)-nitroacetophenone (m.p. 110.5–111.0°) in 7.5 cc. of concentrated hydrochloric acid maintained at 0° there was slowly added 0.7 g. of finely powdered sodium nitrite accompanied by stirring. When the addition was complete, sufficient ice was added to give a volume of 25 cc. and then the clear yellow solution was poured into 160 cc. of 50% sulfuric acid and the solution warmed to 85° over the course of twenty-five minutes. After 1.5 hours at 85–90° the evolution of nitrogen was completed and the turbid yellow solution was cooled in an ice bath and extracted with ether. The

ether extract was evaporated to dryness and the residue crystallized from water and then benzene, in which it was difficultly soluble to yield 1.26 g. (60.3%) of colorless needles; m.p. 110.5–112°.

Anal. Calc'd for $C_9H_9NO_4$: C, 55.38; H, 4.64.
Found: C, 55.52; H, 4.48.

4-Methyl-3-nitro-5-hydroxyacetophenone. The same method of diazotization and hydrolysis was used upon 2.3 g. of the hydrochloride of 4-methyl-3-nitro-5-aminoacetophenone. A yield of 1.3 g. (62%) of the 4-methyl-3-nitro-5-hydroxyacetophenone was obtained as almost colorless needles; m.p. 152.5–153.5°.

Anal. Calc'd for $C_9H_9NO_4$: C, 55.38; H, 4.64.
Found: C, 55.17; H, 4.48.

2-Methyl-(3 or 5)-hydroxy-(5 or 3)-aminoacetophenone hydrochloride. Granular tin (14.23 g.) was divided into ten approximately equal portions and likewise 6.85 g. of 2-methyl-(3 or 5)-hydroxy-(5 or 3)-nitroacetophenone was divided into ten portions. To 85 cc. of 25% hydrochloric acid heated under reflux on a steam-bath was added one portion of the tin followed by a portion of acetophenone derivative. When the latter had dissolved completely, another portion of the tin and of the nitroacetophenone were added. After five portions of each of the reagents had been added in this manner, an additional 10 cc. of hydrochloric acid was added and the portionwise addition of the reagents continued. To complete the reaction, 8 g. of tin and 16 cc. of the acid were added and the mixture refluxed 3 hours longer. The solution was decanted from the unreacted tin and diluted to 1200 cc. with hot water and the tin precipitated with hydrogen sulfide. After removal of the tin sulfide, the filtrate was evaporated to dryness under reduced pressure in an atmosphere of nitrogen to yield 6.3 g. of white needles. Upon standing in air, the product took on a tannish tinge and efforts to isolate the free base indicated that that substance was unstable, so it was employed in the subsequent diazotization without further purification.

4-Methyl-3-amino-5-hydroxyacetophenone hydrochloride. By the same method of reduction, 3.1 g. of 4-methyl-3-nitro-5-hydroxyacetophenone yielded 2.8 g. of the crude hydrochloride of 4-methyl-3-amino-5-hydroxyacetophenone. Like its 2-methyl isomer, the free base is apparently unstable.

2-Methyl-3,5-dihydroxyacetophenone. To 12.5 cc. of concentrated hydrochloric acid was added 1.01 g. of the unpurified hydrochloride of 2-methyl-(3 or 5)-hydroxy-(5 or 3)-aminoacetophenone and the solution warmed to expel the hydrogen chloride which appears to have an adverse effect on the reaction. The solution was diluted with 100 cc. of cold water, cooled to 0° in an ice-bath, and then potassium nitrite solution (0.5 g. in 20 cc. of water) was introduced beneath the surface accompanied by stirring until the first permanent indication of excess nitrous acid. This required about 17 cc. of the nitrite solution. The clear diazonium solution was slowly warmed in a water-bath to 60° and maintained there for fifty minutes. The warm solution was filtered from a small amount of tar, cooled, and extracted with ether. Evaporation of the ether left a light-red oil which was dissolved in hot benzene, in which it was difficultly soluble, and refluxed with Darco. After filtering off the Darco and cooling, tan needles separated. Further purification was accomplished by dissolution in absolute ether, filtration through activated alumina, and then evaporation of the colorless filtrate to dryness. A final recrystallization from benzene yielded 0.42 g. (51%) of colorless platelets, m.p. 160.5–161.2°.

Anal. Calc'd for $C_9H_{10}O_3$: C, 65.04; H, 6.06.
Found: C, 65.02; H, 6.10.

4-Methyl-3,5-dihydroxyacetophenone. When 1.68 g. of the hydrochloride of 4-methyl-3-amino-5-hydroxyacetophenone was diazotized and hydrolyzed by the preceding method, 0.59 g. (43%) of faintly colored platelets melting at 190–191° were obtained.

Anal. Calc'd for $C_9H_{10}O_3$: C, 65.04; H, 6.06.
Found: C, 64.59; H, 5.91.

The attempted Clemmensen reduction of this compound to the desired 2-methyl-5-ethylresorcinol was unsuccessful.

4-Methyl-5-ethylresorcinol. A mixture of 10 cc. of 12% hydrochloric acid and 4.5 g. of amalgamated mossy zinc was heated under reflux on a steam-bath and 0.5 g. of 2-methyl-3,5-dihydroxyacetophenone was added in small portions over the course of 45 minutes. A quantity of tarry material was formed and floated on the surface during this period. The mixture was then refluxed for seven hours, 0.3 cc. of concentrated hydrochloric acid being added at the end of each hour. The hot solution was filtered from the tarry material and the unreacted amalgam and allowed to stand overnight, whereupon a quantity of colorless crystals separated. These were recrystallized from hot water and found to melt at 68–69°. When mixed with the monohydrate of substance III obtained by the degradation of citrinin (m.p. 68–69°), there was no depression of the melting point. Sublimation of the monohydrate of the synthetic 4-methyl-5-ethylresorcinol in high vacuum at 85° yielded the anhydrous form melting at 93–94°. When mixed with substance III, which we have found to melt at 93.4–94.2° although in the literature (7, 2) it is reported to melt at 97–99° and 98–99°, there was no depression of the melting point; hence these two substances are identical. The yield of the synthetic 4-methyl-5-ethylresorcinol was 0.21 g. (46%).

Anal. Calc'd for $C_9H_{12}O_2$: C, 71.02; H, 7.94.
Found: C, 71.10; H, 7.67.
Calc'd for $C_9H_{12}O_2 \cdot H_2O$: C, 63.51; H, 8.29.
Found: C, 63.63; H, 8.21.

Racemization of substance IIA. A solution of 0.5 g. of substance *IIA* (m.p. 127–128°; $[\alpha]_D$ −43.4° in methanol) in 20 cc. of 2 *N* sulfuric acid was refluxed for nineteen hours, at the end of which the solution was optically inactive. The mixture was allowed to cool and then filtered through a layer of Darco. The filtrate was extracted with ether and the ether extract, after drying with magnesium sulfate, was evaporated to dryness to leave a residual yellow oil. This was crystallized from 25 cc. of hot chloroform and twice from water to yield 0.35 g. (70%) of colorless, optically inactive crystals melting at 169–170°. A mixed melting point with substance IIB (m.p. 169–170°), obtained by the acid hydrolysis of citrinin, gave no depression of the melting point.

Triacetylation of substance IIA. To a mixture of 15 cc. of acetic anhydride and 4 cc. of pyridine was added 1.96 g. of substance IIA. After standing over night at room temperature, the solution was warmed to 75° for one hour and then evaporated under reduced pressure to leave a colorless syrup. This syrup was crystallized from 40% methanol to yield 2.9 g. (90%) of the triacetylated derivative, m.p. 88.2–89.5°, $[\alpha]_D^{20}$ + 10.8° in methanol.

Anal. Calc'd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.87.
Found: C, 63.25; H, 6.70.

Hydrolysis of this product with 2 *N* sulfuric acid yielded the optically active starting material.

Triacetylation of substance IIB and partial resolution of the acetylated derivative into its enantiomorphic components. Using the same method of acetylation on 0.95 g. of substance IIB a colorless, optically inactive syrup was obtained. This syrup was dissolved in 10–15 cc. of methanol and water was added until a slight permanent turbidity was produced which dissolved upon warming. The solution was allowed to cool to room temperature and then innoculated with the merest trace of optically active IIA triacetate. An hour or so later it was observed that a quantity of colorless, transparent platelets had separated. These were collected and the mother liquor set aside. These platelets melted at 83–83.5° and after a second recrystallization at 85.5–87.0°. They were optically active, $[\alpha]_D^{20}$ + 9.6°, and of the correct melting point.

Anal. Calc'd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.87.
Found: C, 63.14; H, 6.84.

Meanwhile from the original mother liquor an additional crop of crystals had separated. These were of two sorts—one variety was in the form of clusters of small, rather chunky plates, the other consisted of four unusually large and well formed thin square plates. The two types were separated manually. The large plates melted at 83–85° and when admixed

with IIA triacetate gave a pronounced depression of the melting point. A second crystallization from 50% ethanol raised the melting point to 85–86.5°. The product was optically active with $[\alpha]_D^{20}$ −9.4° in methanol.

Anal. Calc'd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.87.
Found: C, 63.33; H, 6.67.

The clusters of small chunky platelets melted at 64–69° and admixture with IIA triacetate resulted in an increase in the melting point.

Iodoform reaction of dimethylated substance IIA. Substance IIA was methylated by the method of Hetherington and Raistrick (7). This (0.45 g.), an optically active oil ($[\alpha]_D^{20}$ −40.5°), was dissolved in 35 cc. of pure dioxane and then 5 cc. of 10% sodium hydroxide was added and the mixture thoroughly shaken. To this was then added 18 cc. of an iodine-potassium iodide solution (50 g. of iodine and 25 g. of potassium iodide dissolved in water up to 200 cc.). After shaking for five minutes at room temperature, the reaction mixture was warmed for two minutes in a water-bath at 60°, whereupon the solution became quite light in color. An additional 3 cc. of the sodium hydroxide solution was added and the mixture shaken and poured into 250 cc. of cold water which caused the formation of a small quantity of precipitate. This was collected by filtration and smelled strongly of iodoform. Steam distillation of this gummy product yielded a small but definite quantity of iodoform melting at 117–119°.

Dibromo derivative of substance IIA. A solution of 0.2 g. of substance IIA in 60 cc. of water was treated with an equal volume of freshly prepared bromine water. The bromine water was added in small portions accompanied by swirling during the course of 10 minutes. A turbid solution resulted which was clarified by the addition of 15 cc. of sodium bisulfite solution. The mixture was then extracted with ether, the ether extract dried with magnesium sulfate and filtered through a layer of activated alumina. After concentrating the ether solution to 5 cc., it was diluted with 15 cc. of petroleum ether and the mixture further concentrated on a steam-bath until the first indication of an oily precipitate was observed. Upon cooling a crystalline solid separated which was recrystallized twice from hot water to yield flat, colorless needles melting at 129–129.5°. Admixture of this substance with the starting material gave a pronounced depression of the melting point.

Anal. Calc'd for $C_{11}H_{14}Br_2O_3$: C, 37.29; H, 3.98.
Found: C, 37.44; H, 3.86.

Oppenauer oxidation of dimethylated substance IIA. To a mixture of 36 cc. of benzene and 12 cc. of acetone were added 1.97 g. (8 mmole) of dimethyl IIA ($[\alpha]_D$ −40.5°) and 1.62 g. (8 mmole) of aluminum isopropoxide. The solution was refluxed for 21.5 hours whereupon an additional 5 cc. of acetone was added and refluxing continued for another 3.5 hours. After cooling, this solution was washed twice with dilute hydrochloric acid and then dried with sodium sulfate. Filtration through a layer of activated alumina and Darco, followed by evaporation left 1.84 g. of a brown oil. This was purified by distillation in high vacuum in a molecular still. A pale-yellow oil came over between 48–55° at a pressure of 10^{-4} mm. This was optically active with $[\alpha]_D$ +45.0° in methanol, and $[\alpha]_D$ +38.5° in chloroform.

Anal. Calc'd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16.
Found: C, 69.41; H, 8.33.

Semicarbazone of the ketone obtained by the oxidation of dimethyl substance IIA. To a solution of 0.5 g. of the ketone obtained above dissolved in 10 cc. of ethanol was added a solution of 1 g. of semicarbazide hydrochloride and 1.5 g. of sodium acetate in 5 cc. of water. The mixture was refluxed for two hours and the alcohol then removed by distillation. Upon dilution with water and chilling in an ice-bath, a white solid precipitated. This was collected, dissolved in chloroform, filtered through a layer of alumina and then diluted with ether, whereupon the semicarbazone precipitated. The product melted to a clear, somewhat reddish liquid at 194.8°, with previous shrinking at 192°; $[\alpha]_D$ +43.8° in methaol.

Anal. Calc'd for $C_{14}H_{21}N_3O_3$: C, 60.19; H, 7.57.
Found: C, 60.25; H, 7.38.

SUMMARY

1. Additional evidence is presented for the structure of the antibiotic citrinin.

2. An alternative synthesis is described for 4-methyl-5-ethylresorcinol, and its identity with substance III, obtained by the degradation of citrinin, is shown, in agreement with Cram (4).

3. A parallel synthesis of 4-methyl-3,5-dihydroxyacetophenone is described.

PRINCETON, N. J.

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