

was treated with sulfur dioxide the bromoarsine formed melted at 63–64°<sup>16</sup> after recrystallization from absolute alcohol. The bromoarsine was converted into tetra-(4-methoxyphenyl)-arsyl oxide when it was warmed for a short time with ammonia water; the oxide melted at 132–134°<sup>16</sup> after recrystallization from petroleum ether (90–100°).

**3,3' - Dinitro - 4,4' - dimethoxydiphenylarsinic Acid.**— Twelve grams of 4,4'-dimethoxydiphenylarsinic acid was nitrated in the same manner as the corresponding dihydroxy acid; yield 12.6 g. of the dinitro acid. The compound was recrystallized from acetic acid; when heated it softened about 220° and melted at 231° with decomposition.

*Anal.* Calcd. for C<sub>14</sub>H<sub>10</sub>O<sub>6</sub>N<sub>2</sub>As: As, 18.18. Found: As, 17.73.

**3,3' - Diamino - 4,4' - dimethoxydiphenylarsinic Acid.**— Ferrous hydroxide was prepared by the addition of 9.5 g.

(15) Prepared by a different method Blicke and Smith<sup>14</sup> found the melting point to be 60–62°.

(16) Michaelis and Weitz [*Ber.*, **20**, 50 (1887)] obtained the oxide by a different procedure and recorded the melting point as 130°.

of 70% sodium hydroxide, dissolved in 36 cc. of water, to 23 g. of ferrous sulfate, dissolved in 66 cc. of water; 2 g. of the dinitro acid, dissolved in 20 cc. of water and 1.6 g. of sodium hydroxide, was added. After several hours the mixture was filtered, the filtrate shaken with charcoal, filtered and the filtrate acidified with acetic acid; yield 1.4 g.; the glistening crystals melted at 183–184° with decomposition after recrystallization from water.

*Anal.* Calcd. for C<sub>14</sub>H<sub>17</sub>O<sub>4</sub>N<sub>2</sub>As: As, 21.28. Found: As, 21.27.

### Summary

A detailed study has been made of tetra-(3-amino-4-hydroxyphenyl)-diarsyl.

The preparation of 4,4'-dimethoxydiphenylarsinic acid and of 3,3'-diamino-4,4'-dihydroxydiphenylarsinic acid and some of their derivatives has been described.

ANN ARBOR, MICHIGAN

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[CONTRIBUTION FROM THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, UNITED STATES DEPARTMENT OF AGRICULTURE]

## Quassin. I. The Preparation and Purification of Quassin and Neoquassin, with Information Concerning their Molecular Formulas

BY E. P. CLARK

The bitter and presumably the physiologically active constituent of quassia wood or Surinam wood (*Quassia amara*) is known as quassin. This material was first obtained in crystalline form by Winckler<sup>1</sup> in 1835. Although it has since been investigated by others, little information of value concerning its nature has emerged; in fact, instead of clarifying the problem, these investigations have tended to confuse it.

The principal contributions to the subject have been made by Wiggers,<sup>2</sup> Christensen,<sup>3</sup> Oliveri and Denaro,<sup>4</sup> Oliveri,<sup>5</sup> and Massute.<sup>6</sup> As Christensen and Massute give comprehensive reviews of the subject, the present discussion will present only a résumé of the essential claims concerning the material.

Wiggers, the first to analyze quassin, found it to have 65.8% carbon and 6.94% hydrogen (recalculated on the basis of present atomic weight values). Christensen, who undoubtedly

had a pure material, recorded its melting point as 205°, [ $\alpha$ ]<sub>D</sub><sup>18</sup> as +37.8° (C, 4.22 in chloroform), and its analysis according to the average of three combustions as 66.9% carbon and 7.44% hydrogen. He proposed the molecular formula C<sub>31</sub>H<sub>42</sub>O<sub>9</sub> for the material, and showed conclusively that it was not a glucoside. Finally, by boiling quassin for twelve hours with 3% sulfuric acid, he obtained a product which melted at 237° and gave upon combustion 66.87% carbon and 6.72% hydrogen.

Oliveri and Denaro had a material that melted at 210–211°, but in view of information which will be presented later they obviously had a mixture of several crystalline substances. They proposed the molecular formula C<sub>32</sub>H<sub>42</sub>O<sub>10</sub> or C<sub>16</sub>H<sub>22</sub>O<sub>5</sub> for their quassin, and claimed the formation of several anhydrides as the result of the action of dilute sulfuric acid and of acetic anhydride and sodium acetate upon their material. By heating quassin with concentrated hydrochloric acid in a sealed tube, they obtained methyl chloride and a crystalline material to which they assigned the formula C<sub>28</sub>H<sub>38</sub>O<sub>6</sub>(COOH)<sub>2</sub>, and which they called quassic acid. On the basis

(1) F. L. Winckler, *Repert. pharm.*, [2] **4**, 85 (1835); **15**, 74 (1838).

(2) A. Wiggers, *Ann.*, **21**, 40 (1837).

(3) A. Christensen, *Arch. Pharm.*, **220**, 481 (1882).

(4) V. Oliveri and A. Denaro, *Gazz. chim. ital.*, **14**, 1 (1884); **15**, 6 (1885).

(5) V. Oliveri, *ibid.*, **17**, 570 (1887); **18**, 169 (1888).

(6) F. Massute, *Arch. Pharm.*, **228**, 147 (1890).

of these findings and some incomplete work, they stated that quassin had four hydroxyl groups, two carboxymethyl groups and two ketonic groups, and that the molecule had an anthraquinone skeleton.

Massute separated his crude quassin into several fractions having different melting points and assumed them to be homologs differing by various multiples of  $\text{CH}_2$ , as  $\text{C}_{32}\text{H}_4\text{O}_1(\text{CH}_2)_3$  and  $\text{C}_{32}\text{H}_4\text{O}_1(\text{CH}_2)_5$ . He made no molecular weight determinations, although methods were then available. He repeated some of the work previously reported, but none of the results were helpful.

On the basis of the foregoing work the chemical information concerning quassin may be summarized as follows: (1) it is an extremely bitter, neutral substance or mixture of substances composed of carbon, hydrogen and oxygen, which contains methoxyl groups; (2) it is not a glucoside; and (3) in general, derivatives are not easily obtained from it.

The work to be reported here is concerned with (1) a practical method for the preparation of quassin, (2) the purification of the crude product, which has been shown to be essentially a mixture of two isomers, and (3) the determination of the molecular formula of these materials.

Of the two main fractions, the one corresponding to Christensen's quassin has been further studied, and some derivatives of it have been prepared and their properties recorded. The information thus obtained is as follows: crude quassin consists essentially of two isomeric compounds having the formula  $\text{C}_{22}\text{H}_{37}\text{O}_6$ . One melts at  $205\text{--}206^\circ$  and is undoubtedly the material studied by Christensen. The other isomer melts at  $225\text{--}226^\circ$  and has properties other than its melting point which distinguish it from the first. It is proposed to retain the name "quassin" for the first isomer and call the second "neoquassin." Both compounds have two methoxyl groups.

When treated with boiling 3.5% hydrochloric acid, quassin loses one methoxyl group and yields a compound,  $\text{C}_{21}\text{H}_{28}\text{O}_6$ , which is insoluble in carbonates and bicarbonates but is freely soluble in alkali hydroxides and in many organic solvents. If, however, constant-boiling hydrochloric or hydrobromic acid is used, the quassin loses two methoxyl groups and two hydrogen atoms and yields a compound,  $\text{C}_2\text{H}_{24}\text{O}_6$ , which is freely soluble in alkalis but relatively insoluble in metha-

nol or ethanol. This material melts at  $263^\circ$  with decomposition. Doubtless the substance is that called quasside or quassic acid by earlier workers. It is proposed to designate this compound as "quassinol." Acetylation of quassinol yields a monoacetyl derivative.

The action of acetic anhydride and sodium acetate upon quassin itself produces at least three substances. One is an anhydro compound,  $\text{C}_{22}\text{H}_{28}\text{O}_6$ , m. p.  $196^\circ$ , which represents a loss of a molecule of water from quassin; the second is a dehydro compound,  $\text{C}_{22}\text{H}_{28}\text{O}_6$ , m. p.  $256^\circ$ , containing two less hydrogen atoms than the starting material; and the third is an isomer of quassin, m. p.  $214\text{--}215^\circ$ , which is identical with a substance that has been isolated from the wood of *Picraena excelsa*. This is probably one of the picrasmins reported by Massute.<sup>6</sup> Work upon this phase of the problem is in progress and will be reported separately.

The action of chromic acid upon quassin is unusual. When an acetic acid solution of sodium dichromate is allowed to act upon quassin, a slow reaction occurs, and at the end of a week the dichromate is completely reduced. From this mixture is obtained about a 50% yield of a white crystalline material, m. p.  $221^\circ$ , which is isomeric with the starting material.

Attempts to obtain the material by allowing an acetic acid solution of quassin to stand, as in the chromic acid experiment, failed, and only the original material was obtained.

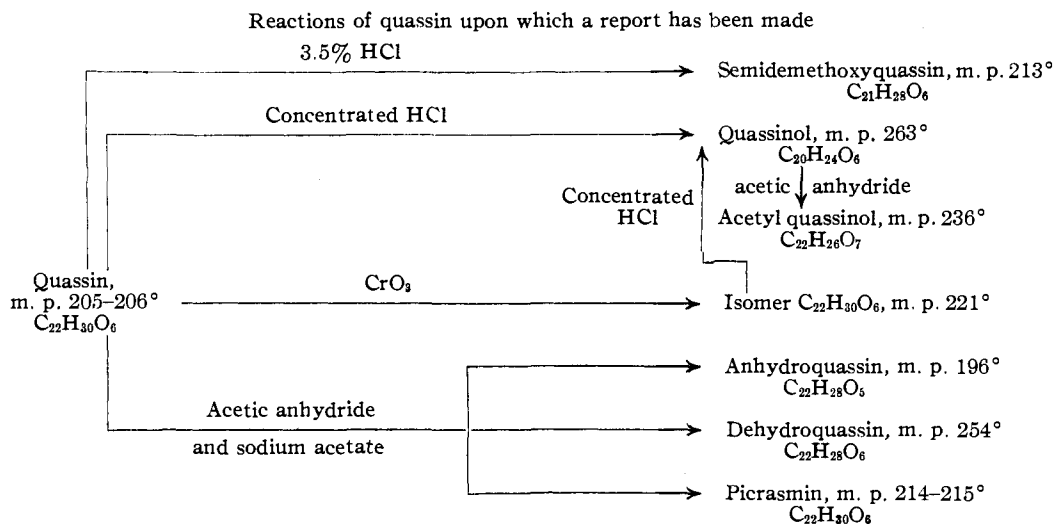
The reactions that have been discussed are represented diagrammatically in the accompanying chart.

### Experimental

**Preparation of Quassin.**—Quassia chips (20 kg.) were extracted by allowing them to stand in hot water for three hours. The decoction was decanted, and the process was repeated three times. Approximately 70 liters of extract was obtained from each treatment. Each extract was treated with a solution of normal lead acetate until further addition failed to give a precipitate; then, without removal of the separated material, sufficient activated carbon (Carbex) was added to adsorb the quassin. Complete adsorption was determined by the absence of a bitter taste in a filtered test portion.

The quantities of lead acetate and carbon necessary for each of the four extracts were

Extract no.	Carbon, g.	Lead acetate, g.
1	600	150
2	400	100
3	200	50
4	150	50



The carbon was removed from each of the extracts and air-dried. It was then mixed, divided into two portions, and each portion was thoroughly percolated with chloroform. Each chloroform extract (representing 10 kg. of quassia chips) was concentrated to dryness under reduced pressure and then dissolved in 150 cc. of methanol. To this solution 950 cc. of hot water (*ca.* 60°) was added, and the turbid liquid was filtered through a thin layer of norit on a Büchner funnel.

Crystallization of crude quassin usually began at once and was completed within two days. Upon concentration, the mother liquors from the crystals gave an additional quantity of crystals. The yield from a number of experiments ranged from 0.15 to 0.18% with an average of 0.16%.

The crude material consisted principally of two isomeric compounds. One was in the form of thin, colorless plates which melted at 205-206°. The other separated from dilute methanol as dense, colorless prisms with a melting point of 225-226°.

The separation of these two isomers was accomplished in essentially the following manner.

One gram of the crude material was dissolved in 10 cc. of boiling methanol and diluted with an equal volume of hot water. The solution was then filtered through a thin layer of norit and allowed to crystallize. The substance obtained, which was approximately 50% of the starting material, consisted largely of quassin (m. p. 205-206°), with some neoquassin. The mother liquors were heated to dissolve any crystalline material, two volumes of water were added and this solution was allowed to crystallize. The crystals, which began to sinter at 205° but did not melt clear until 222°, were mainly neoquassin.

The mother liquors were then concentrated under reduced pressure, and the separated materials were removed from time to time. These fractions were shown by microscopic examination and melting point determinations to consist of both substances, but one or the other usually predominated. The fractions that consisted dominantly of quassin were combined, and the dominantly neoquassin fractions were united. Each was then dissolved in hot methanol and recrystallized by adding two volumes of

water. The mother liquors were concentrated as outlined above, and the process was repeated until quassin and neoquassin with sharp melting points and uniform crystalline habit were obtained. The proportion of quassin to neoquassin was estimated to be approximately 2 to 1.

Small quantities of lower and higher melting products were also obtained, but as difficulty was experienced in purifying them, their analysis will be reserved until sufficient material is accumulated to make their characterization certain.

**Quassin.**—Quassin separates from dilute methanol as thin, colorless rods and micaceous plates which melt at 205-206°. In parallel polarized light (crossed nicols) the rods have straight extinction and positive elongation. In convergent polarized light (crossed nicols) the plates invariably extinguish sharply, indicating that  $\eta\beta$  is more or less perpendicular to the broad base, precluding interference figures. The indices of refraction of the material are  $\eta_\alpha$  1.575;  $\eta_\gamma$  1.590.<sup>7</sup>

A solution of 122.8 mg. of quassin in 2.28 cc. of chloroform (*C*, 5.38), when placed in a 96-mm. tube at 20°, rotated the plane of polarized light 2.06° to the right. Therefore,  $[\alpha]^{20}_D$  is +39.8°. This value and those to be given subsequently were all obtained with small quantities and microapparatus. They are therefore given, not as precision measurements, but rather to indicate their order of magnitude. A duplication determination with the above sample gave a value of  $[\alpha]^{20}_D$  +41°. Active hydrogen determined by the Tschugaeff-Zerewitinoff method gave a value equivalent to one atom.

*Anal.* Calcd. for  $C_{22}H_{30}O_6$ : C, 67.67; H, 7.75;  $OCH_3$  (2), 15.9; mol. wt., 390.3; active H (1), 0.26. Found: C, 67.7, 67.8; H, 7.74, 7.73;  $OCH_3$ , 15.84; mol. wt. (Rast), 399; active H, 0.28.

**Neoquassin.**—Neoquassin separates from dilute methanol as dense, colorless six-sided prisms and quadrilateral plates which melt at 225-226°.  $[\alpha]^{20}_D$  is +46.6°; *C*, 4.92 in chloroform solution. In parallel polarized light

(7) The optical crystallographic data reported here were determined by George L. Keenan, of the Food and Drug Administration, U. S. Department of Agriculture. The values of the refractive indices are all  $\pm 0.003$ .

(crossed nicols) many fragments remain bright upon rotation of the microscope stage, while others extinguish sharply. In convergent polarized light (crossed nicols) partial biaxial interference figures are common. The refractive indices are  $n_{\alpha}$  1.575;  $n_{\beta}$  1.600;  $n_{\gamma}$  1.626.

*Anal.* Calcd. for  $C_{22}H_{30}O_6$ : C, 67.67; H, 7.75;  $OCH_3$  (2), 15.9; mol. wt., 390.3. Found: C, 67.8; H, 7.8;  $OCH_3$ , 15.5; mol. wt. (Rast), 387.

**Semidemethoxyquassin.**—A suspension of 1 g. of quassin in 20 cc. of 10% hydrochloric acid and 40 cc. of water was boiled one and a half hours. After the resulting solution cooled somewhat, it was treated with potassium hydroxide until it remained just acid to Congo red. After three days approximately 0.6 g. of crystalline material had separated. This was dissolved in ethyl acetate, filtered, concentrated to a small volume and allowed to crystallize. A poor yield (160 mg.) of dense colorless prisms, tending to be six-sided, which began to sinter at 195° and flowed at 209–211°, was obtained. A second recrystallization from ethyl acetate brought the material to a constant melting point of 213°.

In parallel polarized light (crossed nicols) the extinction is straight and the elongation negative. No interference figures were observable in convergent polarized light (crossed nicols). The refractive indices of the crystals are  $n_{\alpha}$  1.517 (common lengthwise);  $n_{\beta}$  1.585;  $n_{\gamma}$  1.613.

*Anal.* Calcd. for  $C_{21}H_{28}O_6$ : C, 67.0; H, 7.5;  $OCH_3$  (1), 8.25. Found: C, 67.1; H, 7.6;  $OCH_3$ , 8.2.

The crystals obtained from ethyl acetate may be recrystallized conveniently by dissolving them in water made slightly alkaline with potassium hydroxide and then acidifying the solution with hydrochloric acid. The resulting crystals, after thorough drying, begin to sinter at 195° and flow at 207°. This material gave the following analysis: C, 67.0; H, 7.6;  $OCH_3$ , 8.2.

**Quassinol.**—The action of constant-boiling hydrobromic or hydrochloric acid upon quassin yields quassinol, but the procedure that gave the best yields and the cleanest product is as follows. One gram of quassin dissolved in a solution of 10 cc. of acetic acid and 3 cc. of concentrated hydrochloric acid was heated in a boiling water-bath for one and one-half hours. The dark solution was diluted with four volumes of water, and the hydrochloric acid was neutralized with the calculated quantity of potassium hydroxide. The liquid was cooled with ice and allowed to crystallize. The mother liquors from the crystals were evaporated to dryness under reduced pressure, the salt was dissolved in water and the resulting mixture extracted with chloroform. The extract was dried, concentrated to a sirup and treated with a little hot methanol. Crystallization began at once. The crystalline material filtered from the original aqueous acetic acid reaction mixture was digested with hot methanol, and the resulting quassinol was added to that obtained from the chloroform extract of the mother liquors. In all 1 g. of quassin yielded 0.3 g. of quassinol, m. p. 262°. It was recrystallized by dissolving in boiling chloroform, filtering its solution through norit, concentrating the filtrate until crystallization began and then adding about five volumes of methanol. Thus obtained, it consisted of colorless rods which melted at 263° with decomposition. A solution of 114.9 mg. in 10 cc. of chloroform and observed in a 2-dm. tube

at 20° rotated the plane of polarized light 1.44° to the right [ $\alpha$ ]<sub>D</sub><sup>20</sup> is therefore +62.6°. In parallel polarized light (crossed nicols) the extinction is straight and the elongation is positive. In convergent polarized light (crossed nicols) only faint biaxial interference figures characteristic of sections perpendicular to the acute bisectrix, are shown:  $n_{\alpha}$  1.518 (crosswise);  $n_{\beta}$  1.543 (crosswise);  $n_{\gamma}$  >1.733 (lengthwise).

*Anal.* Calcd. for  $C_{20}H_{24}O_6$ : C, 66.6; H, 6.7; mol. wt., 360.3. Found: C, 66.8; H, 6.8; mol. wt. (Rast), 373.

**Acetylquassinol.**—A solution of 300 mg. of quassinol in 3 cc. of pyridine and 1.5 cc. of acetic anhydride was allowed to stand overnight. Upon dilution of the mixture with water, 300 mg. of crystalline material, m. p. 232°, separated. It was recrystallized from boiling 95% ethanol. The yield was 240 mg. and its melting point was 236° with evolution of gas.

*Anal.* Calcd. for  $C_{22}H_{26}O_7$ : C, 65.6; H, 6.5; acetyl (1), 10.7; mol. wt., 402.3. Found: C, 65.6; H, 6.6; acetyl, 11.2; mol. wt. (Rast), 422.

**Action of Acetic Anhydride and Sodium Acetate upon Quassin.**—One gram of quassin, 0.25 g. of dry sodium acetate, and 8 cc. of acetic anhydride were refluxed for one and one-half hours. The greater part of the acetic anhydride was then removed by distillation, and about 35 cc. of water was added to the mixture. Upon being stirred, the reaction product gradually crystallized, yielding 0.8 g. of material which melted between 160–170°. This was dissolved in hot methanol and an equal volume of water added. Crystallization began at once and yielded 390 mg. of a substance which melted at 190°. A second recrystallization in the same manner sufficed to yield a pure product, m. p. 196°. This was an anhydroquassin formed by the elimination of 1 mole of water from a mole of quassin.

*Anal.* Calcd. for  $C_{22}H_{28}O_5$ : C, 70.9; H, 7.6;  $OCH_3$  (2), 16.7. Found: C, 70.7; H, 7.6;  $OCH_3$ , 16.8.

The mother liquor from the first recrystallization of the crude acetylation product was diluted with three volumes of water and allowed to crystallize for a day. A small quantity of material which melted unsharply at about 235° was obtained. This was twice recrystallized from its solution in acetic anhydride by adding three volumes of *n*-butyl ether. Thus obtained, the material was pure and separated as boat-shaped crystals tending to be long hexagonal plates. Its melting point was 254°. Analysis indicated it to be a dehydroquassin.

*Anal.* Calcd. for  $C_{22}H_{28}O_6$ : C, 68.0; H, 7.3;  $OCH_3$  (2), 16.0; mol. wt., 388.3. Found: C, 67.6; H, 7.4;  $OCH_3$ , 15.6; mol. wt. (Rast), 403.

The mother liquors from the dehydro compound were concentrated under reduced pressure to a small volume, which caused a crystalline material to separate. Its melting point was 205–210°. Upon recrystallization from 25% methanol, it consisted of long rectangular plates melting at 214°. When mixed with picrasmin, m. p. 215–216°, there was no depression of the melting point.

*Anal.* Calcd. for  $C_{22}H_{30}O_6$ : C, 67.67; H, 7.75;  $OCH_3$  (2), 15.9. Found: C, 67.5; H, 7.7;  $OCH_3$ , 15.9.

**Action of Chromic Acid upon Quassin.**—Ten cubic centimeters of a 10% acetic acid solution of crystalline sodium

dichromate was added to a solution of 1 g. of quassin in 5 cc. of hot acetic acid. After a week two volumes of water was added to the solution and the mixture was concentrated under reduced pressure almost to dryness. Water was then added and the resulting crystals were collected. The yield was 0.5 g. and the material melted at 217°. One recrystallization from dilute methanol gave a pure product, m. p. 221°. It consisted of colorless rectangular rods and plates, which had optical crystallographic properties very similar to the starting material. In parallel polarized light (crossed nicols) the extinction is straight and the elongation is positive. Most of the crystals extinguish sharply (crossed nicols), although plates occasionally extinguish in a hazy, indefinite manner. In convergent polarized light (crossed nicols) these plates show a dim biaxial interference figure with both of the isogyres in the field (section perpendicular to the acute bisectrix). Owing to the dimness of the figure, the magnitude of the axial angle could not be determined definitely, but it appeared to be small. The refractive indices are:  $n_\alpha$  1.575 (common crosswise);  $n_\gamma$  1.585 (common lengthwise);  $n_\beta$  could not be determined with certainty. Its specific rotation in chloroform solution ( $C$ , 5.22) was found to be  $[\alpha]^{20}_D +35.1^\circ$ .

*Anal.* Calcd. for  $C_{22}H_{30}O_6$ : C, 67.67; H, 7.75;  $OCH_3$  (2), 15.9. Found: C, 67.8; H, 7.4;  $OCH_3$ , 15.9.

Treatment of this material with acetic and hydrochloric acids as outlined for the preparation of quassinol gave just twice the yield of quassinol that was obtained from quassin itself. The identity of the quassinol was proved by its melting point, mixed melting point and optical properties.

### Summary

A convenient method has been developed for the preparation of crude quassin. This material has been shown to consist essentially of two isomeric substances of the formula  $C_{22}H_{30}O_6$ , each containing two methoxyl groups. These have been separated, and directions are recorded for doing this. It is proposed to retain the name "quassin" for the isomer melting at 205–206° and designate the other isomer, m. p. 225–226°, as "neoquassin." A summary of the relationships between quassin and several derivatives is shown diagrammatically.

WASHINGTON, D. C.

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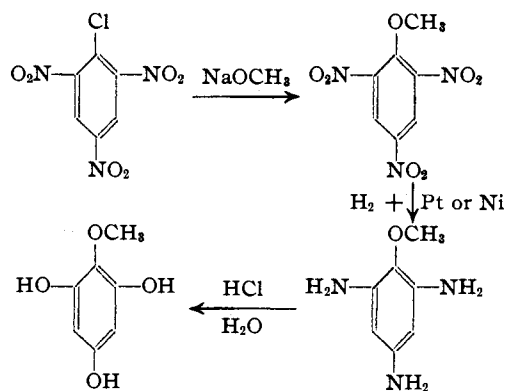
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

## A Synthesis of Iretol

BY R. E. DAMSCHRODER AND R. L. SHRINER

Iretol was first isolated by de Laire and Tiemann<sup>1</sup> as a degradation product of a glucoside obtained from *Iris florentina*. It is produced by alkaline degradation of tectorigenin<sup>2</sup> and of wogonin.<sup>3</sup> The structure of iretol as 2,4,6-trihydroxyanisole was established by conversion to phloroglucinol by de Laire and Tiemann,<sup>1</sup> and by a synthesis by Kohner,<sup>4</sup> who reduced 2,4,6-trinitroanisole with tin and hydrochloric acid to a diaminohydroxyanisole, which was then hydrolyzed to iretol. When this method was used for the preparation of iretol, it was found that the yields were very low, and that the presence of the large amounts of tin salts at the last step rendered the isolation of the product very difficult. Any procedures used for the preparation of this polyhydroxybenzene must be simple and require as short a time as possible, because aqueous solutions of the intermediate amino compound, as well as the final product, are very sensitive to oxygen of the air, and readily undergo oxidation to highly colored compounds.

A modified synthesis has been developed, using the reactions



The catalytic reduction of 2,4,6-trinitroanisole must be carried out rapidly, using a very active catalyst. A high ratio of catalyst to compound must be used. Yields of the 2,4,6-triaminoanisole as high as 81% were obtained, provided the product was isolated with the exclusion of oxygen. The final hydrolysis was accomplished with hydrochloric acid alone, no stannous chloride being necessary. Isolation of the iretol must be accomplished in a carbon

- (1) De Laire and Tiemann, *Ber.*, **26**, 2015 (1893).
- (2) Shibata, *J. Pharm. Soc. Japan*, **543**, 380 (1927).
- (3) Hattori and Hayashi, *Ber.*, **66B**, 1279–1280 (1933).
- (4) Kohner, *Monatsh.*, **20**, 933 (1899).