

[CONTRIBUTION FROM THE INSECTICIDE DIVISION, BUREAU OF CHEMISTRY AND SOILS]

**TOXICAROL. IV. CONCERNING THE STRUCTURE OF TOXICAROL**

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Toxicarol when refluxed with 5% alcoholic potassium hydroxide solution loses the elements  $C_6H_6$  and yields a colorless phenolic substance,  $C_{18}H_{16}O_7$ . This new compound, which has been named apotoxicarol, has the following properties. It contains a grouping having two hydrogen atoms that are readily removed by gentle oxidation, forming a dehydro derivative,  $C_{18}H_{14}O_7$ . It contains no readily reducible double bond; it has one more phenolic hydroxyl group than its precursor, toxicarol; and, upon oxidation with alkaline hydrogen peroxide, two acids are obtained, the structure of which can be deduced from facts now available.

The experimental evidence upon which the foregoing statements are based is as follows. When oxidized with iodine in hot alcoholic potassium acetate solution, apotoxicarol formed an iodo compound which, when treated with zinc dust and boiling acetic acid, was readily dehalogenated, forming dehydroapotoxicarol,  $C_{18}H_{14}O_7$ . The transformation is exactly analogous to the one which occurs when toxicarol is similarly treated<sup>1</sup> and indicates that the grouping responsible for the change is the same in both substances.

The readily reducible double bond present in toxicarol is absent in apotoxicarol, as shown by the latter's failure to absorb hydrogen when treated with this reagent in the presence of an active platinum catalyst.

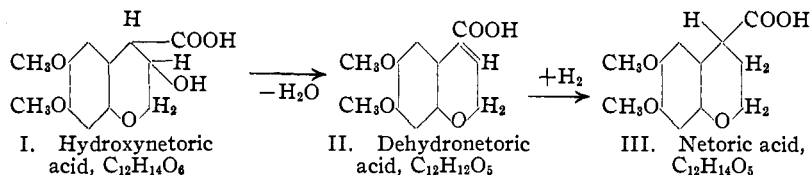
It has been shown that acetylation of toxicarol with boiling acetic anhydride and sodium acetate yields a diacetyl derivative,<sup>1</sup> but methylation, irrespective of the methods employed, has consistently given negative results. Apotoxicarol, however, when subjected to acetylation and methylation, as employed for toxicarol, gave, respectively, a triacetyl derivative and a monomethyl ether. It thus follows that the reaction involved in the formation of apotoxicarol consists of the loss from toxicarol of the elements  $C_6H_6$ , and the generation of a new hydroxyl group. It also shows that the double bond existing in toxicarol is undoubtedly associated with the grouping eliminated. These facts may be explained in several ways, but because there is not yet sufficient evidence available on which to base a decision, no interpretation of the reaction will be made at this time.

The oxidation of apotoxicarol with alkaline hydrogen peroxide, however, has yielded products which materially clarify the problem of the structure of toxicarol.

<sup>1</sup> Clark, THIS JOURNAL, 53, 2264 (1931).

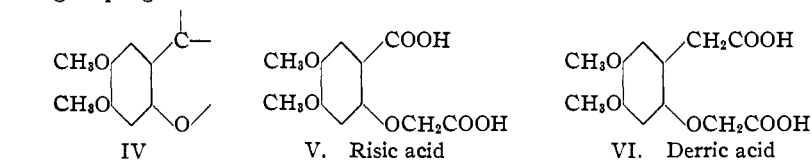
When apotoxicarol dissolved in aqueous alkali was treated with hydrogen peroxide, a vigorous reaction occurred, and two monocarboxylic acids were formed. One was a colorless substance whose molecular composition was  $C_{12}H_{14}O_6$ . The second acid was a brownish-yellow crystalline material,  $C_{12}H_{12}O_5$ . It was possible by regulating the conditions of the reaction to obtain dominantly either one or the other substance; furthermore, the first acid could be readily converted to the second by treatment with acetic anhydride.

The second acid,  $C_{12}H_{12}O_5$ , contained a double bond which was readily reduced, and the dihydro derivative thus formed was shown by comparison with an authentic sample to be netoric acid.<sup>2</sup> The yellow acid,  $C_{12}H_{12}O_5$ , was therefore dehydronetoric acid, whereas the white acid,  $C_{12}H_{14}O_6$ , was hydroxynetoric acid. The structure of netoric acid has not been determined, but evidence now available indicates that, as LaForge, Haller and Smith<sup>3</sup> have already suggested, it may be represented by III. Dehydro- and hydroxynetoric acid would then be represented, respectively, by II and I.



The reasoning involved in these statements is as follows. It has been shown in the third communication of this series<sup>4</sup> that permanganate oxidation of dehydrotoxicarol yields 2-hydroxy-4,5-dimethoxybenzoic acid and risic acid (V), which is 2-carboxy-4,5-dimethoxyphenoxyacetic acid. It was also shown that treatment of dehydrotoxicarol with alcoholic alkali yields a non-crystallizable acidic material probably consisting essentially of a compound analogous to derric and deguelic acids.

This acidic material when oxidized with aqueous permanganate also yields risic acid, but if it is oxidized with alkaline hydrogen peroxide, derric acid (2-carboxymethyl-4,5-dimethoxyphenoxyacetic acid, VI) is formed. These reactions prove that in the methoxylated portion of dehydrotoxicarol the grouping IV exists.



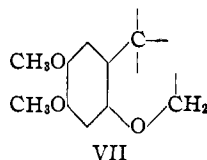
<sup>2</sup> Smith and LaForge, *THIS JOURNAL*, **52**, 4595 (1930).

<sup>3</sup> LaForge, Haller and Smith, *ibid.*, **53**, 4402 (1931).

<sup>4</sup> Clark, *ibid.*, **54**, 1600 (1932).

It is now evident that the methylene group in the  $\text{—O—CH}_2\text{COOH}$  complex in risic acid (V) must have existed as such in dehydrotoxicarol, for there is no conceivable reaction whereby permanganate oxidation could cause two hydrogen atoms to be added to or exchanged for other substituents upon the carbon atom under discussion. It will also be shown later that the  $\text{—O—CH}_2$  portion of the oxyacetic acid radical in derric acid (VI) was likewise present in dehydrotoxicarol.

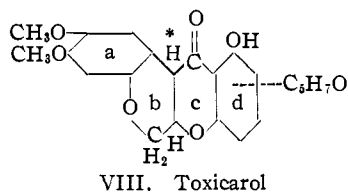
From what has just been presented it follows that in dehydrotoxicarol there exists the atomic grouping VII consisting of  $\text{C}_{10}\text{H}_{10}\text{O}_3$ . The difference between this formula and that of netoric acid,  $\text{C}_{12}\text{H}_{14}\text{O}_6$ , after deducting a carboxyl group, is  $\text{CH}_3$ . This must of necessity form a saturated ring, and the conclusion therefore emerges that netoric acid is represented by III or by the isomeric form in which the carboxyl group is attached to the carbon atom  $\beta$  to the oxygen of the pyran ring.



That formula I is undoubtedly the correct interpretation follows from facts previously published together with some new observations which will now be considered.

All direct attempts to prove the presence of a carbonyl group in toxicarol by securing characteristic derivatives such as oximes or semicarbazones have failed, but evidence of a different character definitely indicates the presence of a carbonyl group in toxicarol. The facts to be considered in this connection also indicate that the phenolic hydroxyl group in toxicarol is ortho to the carbonyl group and that one of the hydrogen atoms which is readily removed by mild oxidation in the dehydro formation is attached to a carbon atom adjacent to the carbonyl group.

In order conveniently to present the evidence in support of the statements just made, a formula which is provisionally submitted as representing the structure of toxicarol (VIII) will be used.



Previously recorded information concerning the acyl derivatives of toxicarol<sup>1</sup> is as follows. Toxicarol when treated with benzoyl chloride in pyridine forms a monobenzoyl derivative; but when it is acetylated with acetic anhydride and sodium acetate, a diacetate is obtained. The diacetate is more reactive toward oxidizing agents than is toxicarol, and it is capable of reduction to monoacetyldihydrodesoxytoxicarol.

These data when considered together with other reactions to be subsequently discussed may be explained on the basis of a keto-enol mechanism.

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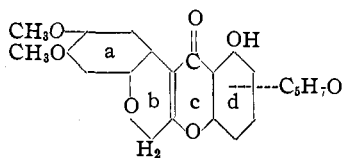
Benzoylation of toxicarol in the manner in which the reaction was conducted affected only the hydroxyl group on the benzene ring *d*; but

acetylation with boiling acetic anhydride and sodium acetate caused the acetylation not only of the phenolic hydroxyl group but also of the enol formed by the migration of the hydrogen marked with the asterisk to the carbonyl group. Reduction of the enol-acetate to monoacetyldihydro-desoxytoxicarol is in harmony with the results recently recorded by Roll and Adams<sup>5</sup> in which they show that enol-acetates are reduced to desoxy compounds with the elimination of the acetoxyl group. According to the mechanism here proposed, diacetyltoxicarol would be an enol compound with a double bond in ring *c* and consequently would be more susceptible to oxidation than would toxicarol.

In order to supplement these deductions the results obtained by hydrolyzing diacetyltoxicarol are also presented. When rapidly hydrolyzed with sodium methylate, a product was obtained differing from toxicarol in crystalline habit and in having a lower melting point (160–170°). Upon several rapid recrystallizations of this material, the low-melting rods changed to plates whose melting point was 220°, which is characteristic of toxicarol. This phenomenon may be accounted for by the fact that an enol form of toxicarol is liberated which upon recrystallization reverts to the keto form.

Dehydrotoxicarol is characterized by its ability to enter into reactions which yield the several acids mentioned before, and forms only one acetyl derivative. It undergoes the Dakin reaction<sup>6</sup> when treated with alkaline hydrogen peroxide, in which process the linkage between the carbonyl group and the benzene ring to which it is attached is split, with the formation of carboxyl and a new phenolic hydroxyl group.

These reactions become intelligible if the formation of dehydrotoxicarol



IX. Dehydrotoxicarol

is explained by the elimination of the two hydrogen atoms attached to the carbon atoms common to the two pyran rings. The removal of these two hydrogen atoms generates a double bond between the carbon atoms under discussion so that dehydrotoxicarol would be represented by IX.

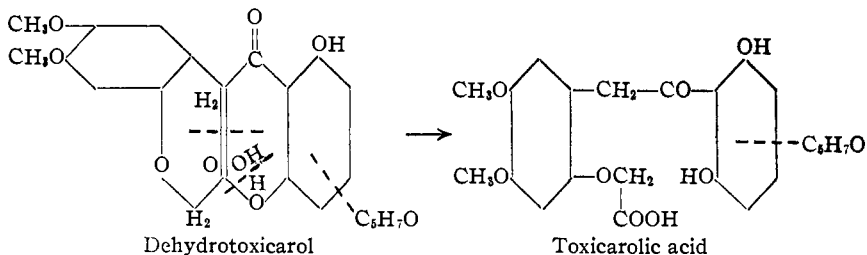
A compound of this structure would be expected to undergo the reactions given as characteristic of dehydrotoxicarol. For example, in considering the methoxylated portion of the molecule, it would be anticipated that permanganate would attack the double bond first, forming a diol which, as the reaction proceeded, would be further oxidized to risic and then to 2-hydroxy-4,5-dimethoxybenzoic acid. The two latter products, as stated before, are invariably formed when dehydrotoxicarol is treated with permanganate. Dehydrotoxicarol, according to the structure postu-

<sup>5</sup> Roll and Adams, *THIS JOURNAL*, **53**, 3469 (1931).

<sup>6</sup> Dakin, *Am. Chem. J.*, **42**, 477 (1909).

lated for it, no longer contains a hydrogen atom capable of migrating to the carbonyl oxygen to form an enol. Consequently it is only possible, as found experimentally, to form a monoacetyl derivative.

The splitting of dehydrotoxicarol with alcoholic alkali to form an acid analogous to derrisic and deguelic acids may also be explained on the basis of the structure represented by IX. This reaction is in all probability a simple hydrolysis which occurs at a double bond adjacent to a carbonyl group.<sup>7</sup> It may be represented thus



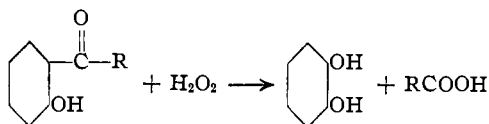
As pointed out before, no crystalline material corresponding to toxicarolic acid has been obtained, doubtless due to the lability toward alkali of the  $C_6H_7O$  group. However, when dehydrodihydrotoxicarol<sup>1</sup> was treated with alcoholic alkali, there was obtained in very good yield a crystalline monocarboxylic acid which analyzed for dihydrotoxicarolic acid. When treated with boiling acetic anhydride, this acid underwent a reaction which was the reverse of that by which it was formed, yielding a monoacetyl dehydrodihydrotoxicarol. This process is analogous to the way in which derrisic and deguelic acids, respectively, revert to dehydrorotenone and dehydrodeguelin. It was possible, however, to block the condensation by esterifying the carboxyl group. When this was done and the hydroxyl groups were acetylated with acetic anhydride and pyridine, a diacetyl-dihydrotoxicarolic acid ester was produced, showing that in the formation of the acid a new phenolic hydroxyl group was developed which, according to the equation given above, was due to the breaking of the oxygen bridge in ring *c*. This reaction is exactly analogous to the one which occurs with dehydrorotenone<sup>8</sup> and dehydrodeguelin.<sup>9</sup>

The Dakin reaction to which previous reference has been made is of unusual importance when applied to dehydrotoxicarol and its derivatives. It may be described as the oxidation of ortho- and para-hydroxy derivatives of benzaldehyde, acetophenone and related substances to polyphenolic compounds and an acid. The reaction may be illustrated by the equation

<sup>7</sup> Houben, "Die Methoden der org. Chem.," III auf., 1925, p. 1021.

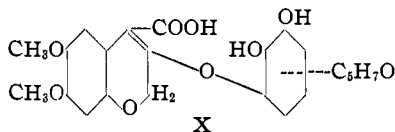
<sup>8</sup> Butenandt, *Ann.*, **464**, 272 (1928).

<sup>9</sup> Clark, *THIS JOURNAL*, **53**, 2369 (1931).



The formation of derric acid by alkaline hydrogen peroxide oxidation of toxicarolic and dihydrotoxicarolic acids, when considered in relation to the reaction above, furnishes more direct evidence that the structures assigned the last-named acids are probably correct.

When the same reaction was applied to dehydrotoxicarol a similar split occurred at the carbonyl group and gave an acid,  $\text{C}_{23}\text{H}_{22}\text{O}_9$  (X).



This material has been designated as dehydrotoxicarol monocarboxylic acid. In the formation of this material, according to the Dakin reaction, the oxygen linkage of ring *c* remained intact, thus forming an ether. The compound was hydrogenated to a dihydro derivative, indicating that the double bond adjacent to the carboxyl group was not affected. In support of this contention an excess of hydrogen peroxide in a boiling strongly alkaline solution oxidized the ether to risic acid.

When the monocarboxylic acid was acetylated by the method of Chatta-way,<sup>10</sup> only a monoacetyl derivative was formed, whereas a diacetate was to be expected. Attempts to obtain a diacetyl compound by more drastic methods of acetylation only resulted in material which would not crystallize. However, the presence of a free hydroxyl group in the monoacetyl derivative was indicated by a faint ferric chloride test.

The formation of dehydrotoxicarol monocarboxylic acid by means of the Dakin reaction is significant as it shows that the phenolic hydroxyl group in ring *d* of dehydrotoxicarol and consequently of toxicarol is either ortho or para to the carbonyl group. However, the results relative to the failure to methylate toxicarol, reported earlier in this discussion, are sufficient proof that the position of the OH group is ortho to the carbonyl, for it is well known that an hydroxyl ortho to an carbonyl group is refractory to methylation.<sup>11</sup>

It follows from what has preceded that apotoxicarol may be represented by VIII with the  $\text{C}_6\text{H}_7\text{O}$  group replaced by an hydroxyl. From this structure it is possible to decide which of the two configurations proposed for netoric acid (III) is correct. The Dakin reaction applied to apotoxicarol

<sup>10</sup> Chatta-way, *J. Chem. Soc.*, 2495 (1931).

<sup>11</sup> Gomm and Nierenstein, *THIS JOURNAL*, 53, 4408 (1931), and references quoted therein.

should cause ring *c* to be split, converting the carbonyl group to a carboxyl group. With the substituents on ring *d* differing from those in toxicarol, the reaction proceeds with the elimination of ring *d* in such a manner that the oxygen atom in ring *c* forms an hydroxyl group on the carbon atom ortho to the methylene group of ring *b*. Thus hydroxynetric acid (I) is formed, and this, as pointed out, loses the elements of water, forming dehydronetric acid (II). The latter upon reduction yields netoric acid (III). It follows from this series of reactions that the position of the carboxyl group in netoric acid is as represented in III.

With the exception of optical activity, all available experimental data relative to the structure of toxicarol are in agreement with formula VIII. In this formula there are two optically active centers, namely, the carbon atoms common to rings *b* and *c*. In preparing toxicarol, however, it is necessary to treat with alkali the non-crystallizable extractives in which it is found and this process undoubtedly causes complete racemization. It would certainly occur at the carbon atom containing the hydrogen adjacent to the carbonyl group because alkali has been shown to cause a keto-enol change. No importance, therefore, is attached to the fact that toxicarol is optically inactive.

The reactions involved in the foregoing discussion which are presented for the first time are summarized in the accompanying chart.

### Experimental

**Apotoxicarol.**—A mixture of 5 g. of toxicarol, 100 cc. of absolute alcohol and 10 cc. of a 50% aqueous potassium hydroxide solution was refluxed for three hours. The resulting liquid was then diluted with 1 liter of water and treated with 100 cc. of a 7.5% solution of calcium chloride. The resulting precipitate was removed by means of a folded filter, and the filtrate was acidified to Congo red with hydrochloric acid.

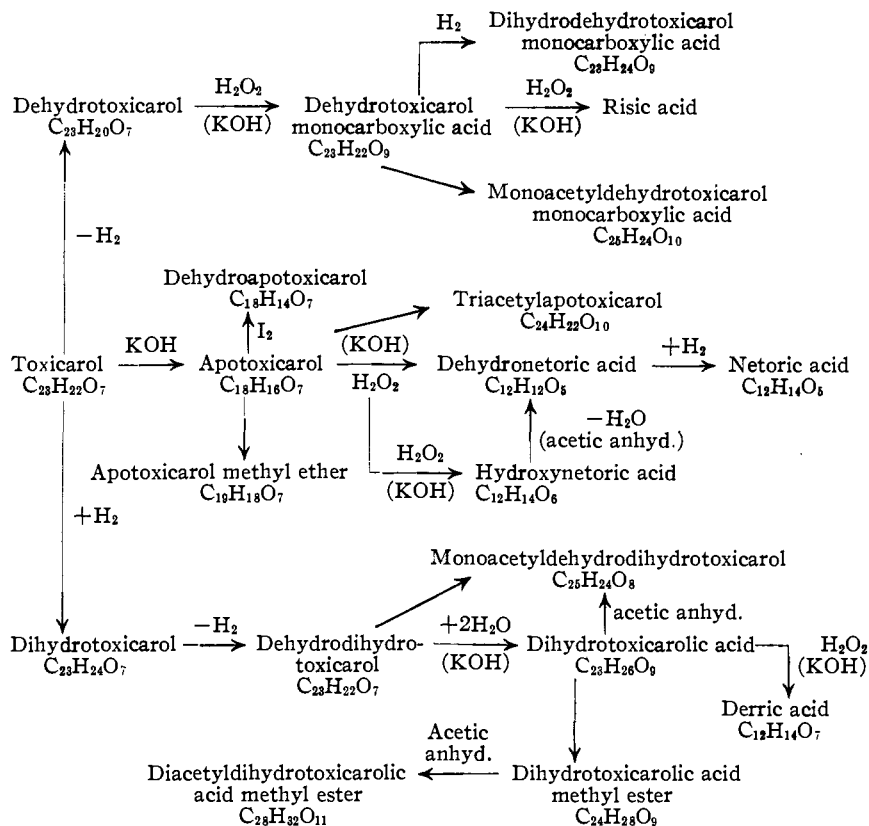
The flocky precipitate thus formed was allowed to settle, and the greater part of the supernatant solution was decanted. The remaining liquid with the precipitate was transferred to a separatory funnel and shaken with ether. The aqueous liquid was discarded, and the ether with the insoluble precipitate was shaken with fresh water, which in turn was discarded. The solid material suspended in the ether was collected upon a filter and dried.

It was purified by recrystallization from a hot saturated acetic acid solution by the addition of two volumes of methanol. The yield from 50 g. of toxicarol was usually 6 g. of crude material. Upon recrystallization this gave 4 g. of apotoxicarol whose melting point was 244°. For analysis it was recrystallized until it had a constant melting point of 246–247°. It consisted of small white rods, which frequently occurred in rosetts, and it gave a deep reddish-violet color with ferric chloride.

*Anal.* Calcd. for  $C_{18}H_{16}O_2$ : C, 62.78; H, 4.69;  $OCH_3$  (2), 18.1. Found: C, 62.91; H, 4.81;  $OCH_3$ , 18.3.

**Dehydroapotoxicarol.**—One gram of apotoxicarol and 1.5 g. of potassium acetate were dissolved in 50 cc. of absolute ethanol and treated portion-wise with 20 cc. of an absolute ethanolic solution of 1 g. of iodine. The reaction mixture was allowed to stand for a day, after which the yellow crystalline iodo compound (0.65 g.) was removed by filtration. The substance evolved iodine at approximately 200°, but it did not melt

## NEW REACTIONS OF TOXICAROL AND SOME OF ITS DERIVATIVES



even when heated to  $310^\circ$ . When the iodo compound was boiled for one and one-half hours with 25 cc. of acetic acid and 1 g. of zinc dust, dehalogenation occurred, yielding 0.2 g. of dehydroapotoxicarol. When treated with water, the mother liquors from which the crystalline iodo compound was obtained gave an amorphous precipitate. This material after having been dried was treated with zinc dust and acetic acid as above, yielding 0.1 g. of dehydroapotoxicarol.

For analysis the dehydroapotoxicarol was crystallized from a hot phenol solution by adding two volumes of methanol. It separated as light greenish-yellow rods and needles, which upon heating gradually darkened and sintered and finally melted at  $298^\circ$ . In parallel polarized light (crossed nicols) the extinction was straight and the elongation was negative. The polarization colors were brilliant. No interference figures were observable in convergent polarized light (crossed nicols), but the substance appeared to be biaxial:  $\eta_\alpha$ , 1.543 (lengthwise);  $\eta_\beta$ , 1.685 (crosswise);  $\eta_\gamma$ ,  $> 1.740$  (crosswise). Some rods, however, matched a liquid of  $\eta$  1.740; all  $\approx 0.003$ .<sup>12</sup>

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{14}\text{O}_7$ : C, 63.15; H, 4.12;  $\text{OCH}_3$  (2), 18.1. Found: C, 63.10; H, 4.28;  $\text{OCH}_3$ , 18.3.

<sup>12</sup> The optical data reported in this communication were determined by George L. Keenan of the Food and Drug Administration, U. S. Department of Agriculture.



**Triacetylaptotoxicarol.**—A mixture of 0.5 g. of aptotoxicarol, 4 cc. of acetic anhydride and 0.1 g. of anhydrous sodium acetate was boiled for fifteen minutes. The condenser was then removed, and three-fourths of the anhydride was boiled away. When the residue was treated with water the acetyl compound became solid. The yield was 0.6 g. The crude material was purified by dissolving it in 15 cc. of hot acetic acid, filtering the solution through norit and then adding two volumes of methanol.

The pure acetyl compound (0.3 g.) separated as colorless square micaceous plates which melted at 206°. The plates extinguished sharply in parallel polarized light (crossed nicols), precluding satisfactory interference figures. However, the material appeared to be biaxial when examined in convergent polarized light (crossed nicols):  $\eta_{\alpha}$ , 1.547 (common);  $\eta_{\beta}$ , indeterminate;  $\eta_{\gamma} > 1.740$ ; an intermediate value  $\eta_i$ , 1.645 is commonly found; all  $\approx 0.003$ .

*Anal.* Calcd. for  $C_{24}H_{22}O_{10}$ : C, 61.26; H, 4.72;  $OCH_3$  (2), 13.2; acetyl, 27.5. Found: C, 61.38; H, 4.75;  $OCH_3$ , 13.4; acetyl, 27.8.

**Aptotoxicarol Methyl Ether.**—One gram of aptotoxicarol suspended in 10 cc. of hot methanol was dissolved by adding 10 cc. of a 10% methanolic potassium hydroxide solution. Two and five-tenths cc. of dimethyl sulfate was then added all at once, and after the reaction had subsided the mixture was again subjected to the same treatment with 10 cc. of potassium hydroxide solution and 2.5 cc. of dimethyl sulfate. The reaction was completed by boiling the mixture for five minutes, after which the product was separated by adding 10 volumes of water. Nine-tenths gram of crude material whose melting point was approximately 218° was obtained. The substance was recrystallized from a hot chloroform solution by adding two volumes of methanol. Purification by this procedure was repeated until the product had a constant melting point of 236–237°. It consisted of sheaves and rosets of fine colorless needles and gave a dark brownish color with ferric chloride. In parallel polarized light (crossed nicols) the extinction was inclined, and the elongation was negative. The crystals were apparently biaxial:  $\eta_{\alpha}$ , 1.600;  $\eta_{\beta}$ , indeterminate;  $\eta_{\gamma} > 1.740$  (both  $\approx 0.003$ ).

*Anal.* Calcd. for  $C_{18}H_{18}O_8$ : C, 63.68; H, 5.06;  $OCH_3$  (3), 26.0. Found: C, 63.75; H, 5.14;  $OCH_3$ , 25.8.

**Hydroxynetic Acid.**—Two grams of aptotoxicarol was dissolved in 35 cc. of 7.5% potassium hydroxide solution and treated portion-wise with 10 cc. of 30% hydrogen peroxide. A vigorous reaction occurred in which the color of the solution became first brown, then deep claret and finally a dark straw color. At the same time the liquid became boiling hot. After the reaction had subsided, the mixture was boiled for several minutes and then made acid to Congo red with sulfuric acid. Approximately 0.1 g. of dehydronetic acid separated (see below). This was removed by filtration, and the filtrate was allowed to evaporate to dryness in the air. The residue was extracted with acetone, and the resulting solution was concentrated to a volume of 8 cc. Upon standing, 0.35 g. of hydroxynetic acid separated. It was recrystallized from its solution in butyl ether, obtained by dissolving the acid in boiling acetone, adding two volumes of butyl ether and removing the acetone by distillation. The pure acid separated as colorless irregular-shaped plates, and occasionally rhomb-like forms, which melted at 189°. In parallel polarized light (crossed nicols) the plates extinguished sharply and showed second and third order polarization colors. In convergent polarized light (crossed nicols) the material appeared to be biaxial, although interference figures were rarely found:  $\eta_{\alpha}$ , 1.513 (common);  $\eta_{\beta}$ , indeterminate;  $\eta_{\gamma}$ , 1.660 (both  $\approx 0.003$ ).

*Anal.* Calcd. for  $C_{12}H_{14}O_6$ : mol. wt., 254.2; C, 56.67; H, 5.57;  $OCH_2$  (2), 24.4. Found: mol. wt. (titration), 258; C, 56.98; H, 5.66;  $OCH_3$ , 24.4.

**Dehydronetic Acid.**—When 10% potassium hydroxide solution was used in the procedure described above for the preparation of hydroxynetic acid, the reaction

gave exclusively dehydronetric acid. This was obtained by acidifying the reaction mixture with sulfuric acid. The yields from experiments with 2 g. of apotoxicarol were variable, ranging from 0.35 to 0.8 g. The crude acid was purified by treating with norit an aqueous solution of the potassium salt acidified with acetic acid, after which the free acid was obtained by acidifying the filtrate with sulfuric acid.

The material had a brownish-yellow color and melted at  $212^{\circ}$  with decomposition. It consisted of short isodiametric prisms, longer rod-like prisms with square ends, and still more slender forms resembling needles. In parallel polarized light (crossed nicols) the extinction was straight and the elongation was negative. The material was bi-axial, although in convergent polarized light (crossed nicols) interference figures were rarely found:  $\eta_{\alpha}$ , 1.533 (commonly shown lengthwise on rods with square ends);  $\eta_{\beta}$ , 1.678 (very common on rods crosswise);  $\eta_{\gamma} > 1.740$ . Many rods, however, matched a liquid of  $\eta$  1.740 (crosswise); all  $\approx 0.003$ .

*Anal.* Calcd. for  $C_{12}H_{12}O_5$ : mol. wt., 236.2; C, 60.99; H, 5.12;  $OCH_3$  (2), 26.27. Found: mol. wt. (titration), 233; C, 60.98; H, 5.17;  $OCH_3$ , 26.1.

**Action of Acetic Anhydride upon Hydroxynetric Acid.**—Three-tenths gram of hydroxynetric acid and 2 cc. of acetic anhydride were gently heated until the solution began to boil. The liquid was then allowed to cool for one minute, after which most of the solvent was removed by a rapid blast of air. Methanol was then cautiously added to decompose the remaining acetic anhydride, and the resulting solution was again evaporated with a current of air. When water was added to the residue, 0.25 g. of crude material was obtained, which, after recrystallization by the method given in the preceding paragraph, possessed all the properties recorded for dehydronetric acid.

**Reduction of Dehydronetric Acid.**—An ethyl acetate solution of 0.3 g. of dehydronetric acid was reduced with hydrogen and the platinum catalyst of Voorhees and Adams.<sup>13</sup> The product obtained after removing the catalyst and solvent was dissolved in 5 cc. of boiling water and purified by filtration through norit. Upon cooling, the solution rapidly crystallized. The product contained water of crystallization, which was readily lost when the material was dried at  $60^{\circ}$  in a vacuum over potassium hydroxide. The dried acid melted sharply at  $134^{\circ}$ , and when mixed with an authentic sample of netric acid, recrystallized in the same manner as the material under investigation, no depression of the melting point occurred. The reduction product was therefore netric acid.

**Dihydrotoxicarolic Acid.**—A mixture of 5 g. of dehydrodihydrotoxicarol,<sup>14</sup> 5 g. of zinc dust, 120 cc. of ethanol and 30 cc. of 50% potassium hydroxide solution was refluxed for thirty minutes. The clear solution was then separated from the zinc, diluted to 500 cc. with water and ice and carefully acidified to Congo red with sulfuric acid. The precipitate which was formed rapidly crystallized, yielding 5.2 g. of material which melted between  $110$  and  $120^{\circ}$ . When a solution of the substance in hot methanol was diluted with an equal volume of hot water, the dihydrotoxicarolic acid separated as thin, frequently elongated, hexagonal plates which melted at  $129^{\circ}$  with the evolution of gas. It gave a purple color with ferric chloride. In parallel polarized light (crossed nicols) the extinction was straight and the elongation was negative. Double refraction was extremely strong. The plates usually extinguished sharply:  $\eta_{\alpha}$ , 1.515 (common lengthwise on elongated plates);  $\eta_{\beta}$ , indeterminate;  $\eta_{\gamma}$ , 1.600 (common on elongated plates crosswise); both  $\approx 0.003$ .

<sup>13</sup> Voorhees and Adams, *THIS JOURNAL*, **44**, 1397 (1922).

<sup>14</sup> This compound may advantageously be made by oxidizing dihydrotoxicarol with iodine in potassium acetate solution in the manner recorded for the preparation of dehydrotoxicarol.<sup>1</sup> The yield is usually 75%.

*Anal.* Calcd. for  $C_{23}H_{26}O_9$ : mol. wt., 446.3; C, 61.87; H, 5.87;  $OCH_3$  (2), 13.9. Found: mol. wt. (titration), 451; C, 61.54; H, 6.13;  $OCH_3$ , 14.0.

**Monoacetyldehydrodihydrotoxicarol from Dihydrotoxicarolic Acid.**—One gram of dihydrotoxicarolic acid, 4 cc. of acetic anhydride and 0.25 g. of anhydrous sodium acetate were refluxed for fifteen minutes. The condenser was then removed and most of the anhydride was boiled away, after which 10 cc. of methanol was added to the residue. Two-tenths gram of material separated which, after it was recrystallized by treating a chloroform solution of the substance with five volumes of methanol, melted at  $238^\circ$ . The material was shown to be monoacetyldehydrodihydrotoxicarol by comparison with a sample of this compound prepared by acetylating dehydrodihydrotoxicarol according to the procedure just given.

**Dihydrotoxicarolic Acid Methyl Ester.**—One gram of dihydrotoxicarolic acid was dissolved in 25 cc. of 4% absolute methanolic solution of hydrochloric acid. After the liquid was refluxed for thirty minutes, it was poured into crushed ice, the mixture was diluted with water and the ester was removed by filtration. The yield was 0.9 g. When recrystallized from dilute methanol it consisted of thin plates and rhombs which melted at  $174^\circ$ . In parallel polarized light (crossed nicols) only partial extinction of many of the plates occurred when the microscope stage was revolved. Partial biaxial interference figures were frequently shown in convergent polarized light (crossed nicols). Double refraction was extremely strong:  $\eta_\alpha$ , 1.535 (common);  $\eta_\beta$ , indeterminate;  $\eta_\gamma$ , 1.740; both  $\pm 0.003$ .

*Anal.* Calcd. for  $C_{24}H_{28}O_9$ :  $OCH_3$  (3), 20.2. Found:  $OCH_3$ , 20.2.

**Diacetyldihydrotoxicarolic Acid Methyl Ester.**—One gram of the methyl ester dissolved in a mixture of 6 cc. of pyridine and 8 cc. of acetic anhydride was allowed to stand for three hours. The solution was then poured into 100 cc. of water, and the aqueous liquid was decanted from the yellow oil which adhered to the flask. The latter was washed several times with water and then dissolved in boiling methanol. Upon adding water to the solution until a slight turbidity was produced, 0.9 g. of the diacetate crystallized. It was recrystallized from its solution in hot methanol obtained by dissolving the material in chloroform, adding ten volumes of methanol and boiling the solution until the chloroform was removed. It separated as groups of rods, which melted at  $143$ – $144^\circ$ .

*Anal.* Calcd. for  $C_{25}H_{30}O_{11}$ : acetyl, 15.81;  $OCH_3$  (3), 17.10. Found: acetyl, 14.4;  $OCH_3$ , 17.06.

**Derric Acid from Dihydrotoxicarolic Acid.**—Dihydrotoxicarolic acid was oxidized with alkaline hydrogen peroxide according to the directions given for the preparation of derric acid from deguelic acid.<sup>15</sup> The product obtained melted at  $168^\circ$  and was shown by comparison with an authentic sample to be derric acid.

**Dehydrotoxicarol Monocarboxylic Acid.**—One gram of dehydrotoxicarol, suspended in 25 cc. of boiling ethanol, was quickly dissolved by the addition of 4 cc. of 50% aqueous potassium hydroxide solution. Four cc. of 30% hydrogen peroxide diluted with 6 cc. of water was then added at once, and the reaction was allowed to continue for *fifteen seconds*. One hundred twenty-five cc. of water was then quickly added, and the solution was filtered from a small quantity of unchanged starting material. The filtrate was then four-fifths neutralized with sulfuric acid, after which acetic acid was added until a slight turbidity resulted. The liquid was now allowed to crystallize. The yield of the acid was 0.75 to 0.9 g. The material, when recrystallized from dilute alcohol and thoroughly dried at  $75^\circ$  under reduced pressure, melted at  $230^\circ$  with the evolution of gas. It gave a dark green color with ferric chloride.

<sup>15</sup> Clark, *THIS JOURNAL*, 53, 2370 (1931).

*Anal.* Calcd. for  $C_{23}H_{22}O_9$ : mol. wt., 442.3; C, 62.43; H, 5.01;  $OCH_3$  (2), 14.03. Found: mol. wt. (titration), 448; C, 62.53; H, 5.12;  $OCH_3$ , 14.0.

**Risic Acid from Dehydrotoxicarol Monocarboxylic Acid.**—One-tenth gram of the monocarboxylic acid was dissolved in an aqueous potassium hydroxide solution and boiled with 2 cc. of 30% hydrogen peroxide until the liquid became practically colorless. Upon acidifying the solution with sulfuric acid, a crystalline precipitate formed, which melted at 262°. This material was proved, by comparison with an authentic sample, to be risic acid.

**Dihydrodehydrotoxicarol Monocarboxylic Acid.**—A solution of 2.5 g. of dehydrotoxicarol monocarboxylic acid in 250 cc. of hot ethanol was reduced with hydrogen and the platinum catalyst of Voorhees and Adams.<sup>13</sup> The resulting solution was filtered from the catalyst, evaporated to 50 cc., diluted with water until a slight turbidity resulted, and then allowed to crystallize. The yield was 2 g. The material was recrystallized from a hot acetic acid solution by the addition of two volumes of hot water. It separated as stout rods, which when dried under reduced pressure at 75° effloresced. The anhydrous material melted at 211° with the evolution of gas. It gave a purple color with ferric chloride.

*Anal.* Calcd. for  $C_{23}H_{24}O_9$ : C, 62.15; H, 5.44;  $OCH_3$  (2), 13.97. Found: C, 62.20; H, 5.54;  $OCH_3$ , 14.0.

**Monoacetyldehydrotoxicarol Monocarboxylic Acid.**—A mixture of 1 g. of free acid, 10 cc. of 5% potassium hydroxide, 10 g. of ice and 1 cc. of acetic anhydride was shaken for two minutes. The liquid was then acidified to Congo red, causing 1.1 g. of crude product to separate. This material was dissolved in 15 cc. of hot methanol. The solution was filtered through norit and then treated with 10 cc. of hot water. Crystallization began at once and yielded 0.7 g. of crystalline acetyl compound. It was recrystallized from its solution in hot methanol by adding an equal volume of hot water. It consisted of colorless rods which melted at 163°. It gave a faint greenish-yellow color with ferric chloride.

*Anal.* Calcd. for  $C_{25}H_{24}O_{10}$ : C, 61.98; H, 5.00;  $OCH_3$  (2), 12.8; acetyl, 8.88. Found: C, 61.97; H, 5.08;  $OCH_3$ , 13.1; acetyl, 8.7.

### Summary

Experimental evidence herewith presented concerning the formation and reactions of apotoxicarol, dihydrotoxicarolic and dehydrotoxicarol monocarboxylic acids, when considered in conjunction with previously published data, demonstrates that quite probably the configuration of toxicarol is that represented by formula VIII (in the text). At this time no suggestion concerning the nature of the  $C_6H_7O$  grouping or its position or positions of attachment to ring *d* will be made.

WASHINGTON, D. C.