

carbazone and ethyl mercaptal of the above aldehyde have been synthesized in crystalline form.

3. The free aldehyde form of fucose tetraacetate is similar to the corresponding compound

of galactose in its ability to form stable carbonyl addition compounds with water and alcohol.

4.  $\alpha$ -*l*-Fucose tetraacetate has been synthesized in crystalline condition.

COLUMBUS, OHIO

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

## Toxicarol. V. 7-Hydroxytoxicarol and Related Compounds

BY E. P. CLARK

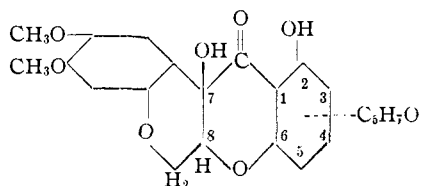
Recently Butenandt and Hilgetag<sup>1</sup> described a substance, designated as toxicarol hydrate, which they obtained by the action of alcoholic alkali upon toxicarol. It was characterized as yellow prisms which melted at 223.5° and gave a green color with ferric chloride. It was stable toward alcoholic alkali, but when boiled with alcoholic hydrochloric acid it was readily converted to dehydrotoxicarol. The authors tentatively assumed, as the name implies, that toxicarol reacted additively with a molecule of water to form the compound  $C_{23}H_{24}O_8$ .

Continuing their study of the substance, they hydrogenated the reaction mixture with palladium-charcoal and hydrogen and obtained a new compound which melted at 217.5°. The same material was also obtained by treating dihydrotoxicarol with alcoholic alkali. From analogy, this should have the formula  $C_{23}H_{26}O_8$ . Strangely enough, however, they suggested  $C_{21}H_{24}O_7$  as its formula, notwithstanding that a methoxyl determination would have given decisive information as to which was correct.

Finally, in a more recent communication<sup>2</sup> in which they again reported the preparation and analysis of the compound and designated the substance as dihydrotoxicarol hydrate, two formulas,  $C_{23}H_{26}O_8$  and  $C_{23}H_{24}O_8$ , were proposed. In this case their analytical data definitely agreed with the latter formula. Thus, from these preparatory statements it is evident that the nature of the two compounds is greatly in need of clarification.

Information necessary for this purpose is available, largely as a result of work already reported or in progress, and consists of a correlation of studies involving the preparation of the compounds by different methods and a consideration

of their reactions. The conclusion derived from these data is that toxicarol hydrate is 7-hydroxytoxicarol,<sup>3</sup>  $C_{23}H_{22}O_8$ , represented by formula I, and dihydrotoxicarol hydrate is 7-hydroxydihydrotoxicarol,  $C_{23}H_{24}O_8$ .



I 7-Hydroxytoxicarol

The evidence supporting this statement follows. In addition to clarifying the point under consideration it is also important because of its bearing upon the structure of toxicarol.

The reaction described by Butenandt and Hilgetag is undoubtedly one of atmospheric oxidation and is the same as that described by Takei, Miyajima and Ono<sup>4</sup> in which tephrosin and isotephrosin are formed from deguelin. As evidence of this the following is pertinent. The action of alcoholic alkali upon toxicarol produces 7-hydroxytoxicarol (toxicarol hydrate) as reported, but the yields and the purity of the product vary with the conditions of the experiment. For example, occasionally shaking the alkaline reaction mixture results in larger yields and a purer product than is obtained when this is not done. From the preparative standpoint, a better procedure is to stir rapidly an alkaline benzene-99% alcoholic solution of toxicarol for five hours, then allow it to stand until the next day. These conditions give some dehydrotoxicarol and a good yield of 7-hydroxytoxicarol, but because of the insolubility of the dehydro compound it may be separated readily from the main product.

(3) The numbering system is that previously employed in considering deguelin and tephrosin [THIS JOURNAL, 54, 3000 (1932)].

(4) Takei, Miyajima and Ono. *Chem. Abs.* 27, 2954 (1933).

(1) Butenandt and Hilgetag, *Ann.* 495, 173 (1932).

(2) Butenandt, *ibid.*, 506, 158 (1933).

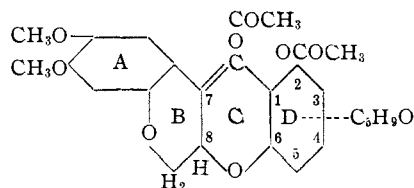
A procedure still better than the above is to stir rapidly a benzene-99% alcoholic solution of toxicarol with a liberal quantity of 2.5% sodium amalgam. Under these conditions the amalgam has no reducing action upon toxicarol, but it appears to regulate the alkalinity of the medium in such a manner that only the desired product is obtained. 7-Hydroxytoxicarol thus prepared is easily purified and may be obtained in any desired quantity. When pure it melts at 226-227°. When it reacts with acetic anhydride, acetyl dehydrotoxicarol is formed as a result of the simultaneous acetylation of the hydroxyl group on carbon 2 and the elimination of the elements of water from carbon atoms 7 and 8. The dehydro formation by this method, as well as that of boiling hydroxytoxicarol with alcoholic hydrochloric acid reported before, is the same as that which occurs in the tephrosin and isotephrosin series.<sup>5</sup>

7-Hydroxytoxicarol has also been obtained by two entirely different procedures. First, direct chromic acid oxidation of toxicarol in acetic acid gives the material, and, second, it is obtained indirectly by chromic acid oxidation of diacetyltoxicarol. Mild treatment of diacetyltoxicarol with chromic acid gives good yields of 7-hydroxymonoacetyltoxicarol. This is deacetylated when treated with alcoholic alkali and yields the same 7-hydroxytoxicarol as is obtained by the previous methods. However, when the saponification is carried out with boiling alcoholic hydrochloric acid, dehydrotoxicarol is formed as a result of the coincident saponification and dehydro formation.

Hydrogenation of 7-hydroxymonoacetyltoxicarol results in the formation of 7-hydroxymonoacetyldihydrotoxicarol, which, when deacetylated with alcoholic alkali, gives the same 7-hydroxydihydrotoxicarol as is obtained by the action of alcoholic alkali upon dihydrotoxicarol. As in the case of 7-hydroxytoxicarol, the dihydro compound is more conveniently prepared by the action of sodium amalgam upon an alcohol-benzene solution of dihydrotoxicarol. When this procedure is employed, some dehydrodihydrotoxicarol is formed, but on account of its insolubility it is readily separated from the main product. When the substance is thoroughly purified, it melts at 222-223°.

As yet no proof has been presented to show that the new hydroxyl group in the various compounds

discussed is situated on carbon 7, but this is furnished by the following experiment. Diacetyldihydrotoxicarol has been shown to be an enol acetate in which the double bond is between carbon atom 7 and the adjacent carbonyl carbon of ring C,<sup>6</sup> formula II.



II Diacetyldihydrotoxicarol

Treatment of this substance with permanganate yields the identical hydroxymonoacetyldihydrotoxicarol mentioned before. The mechanism of the reaction, which is undoubtedly classical in character, involves the formation of a diol at the double bond. There would then be two hydroxyl groups, one of which is acetylated, on the carbon atom of the original carbonyl group, and because of the instability of this structure, acetic acid is eliminated. Thus the carbonyl group originally present in dihydrotoxicarol is regenerated, leaving the remaining hydroxyl group on carbon 7. As the resulting 7-hydroxymonoacetyldihydrotoxicarol is directly related to all the hydroxy compounds previously discussed, it follows that they are all 7-hydroxy derivatives of toxicarol or dihydrotoxicarol, as the case may be.

The relationships of the various substances under consideration are diagrammatically summarized in the accompanying chart.

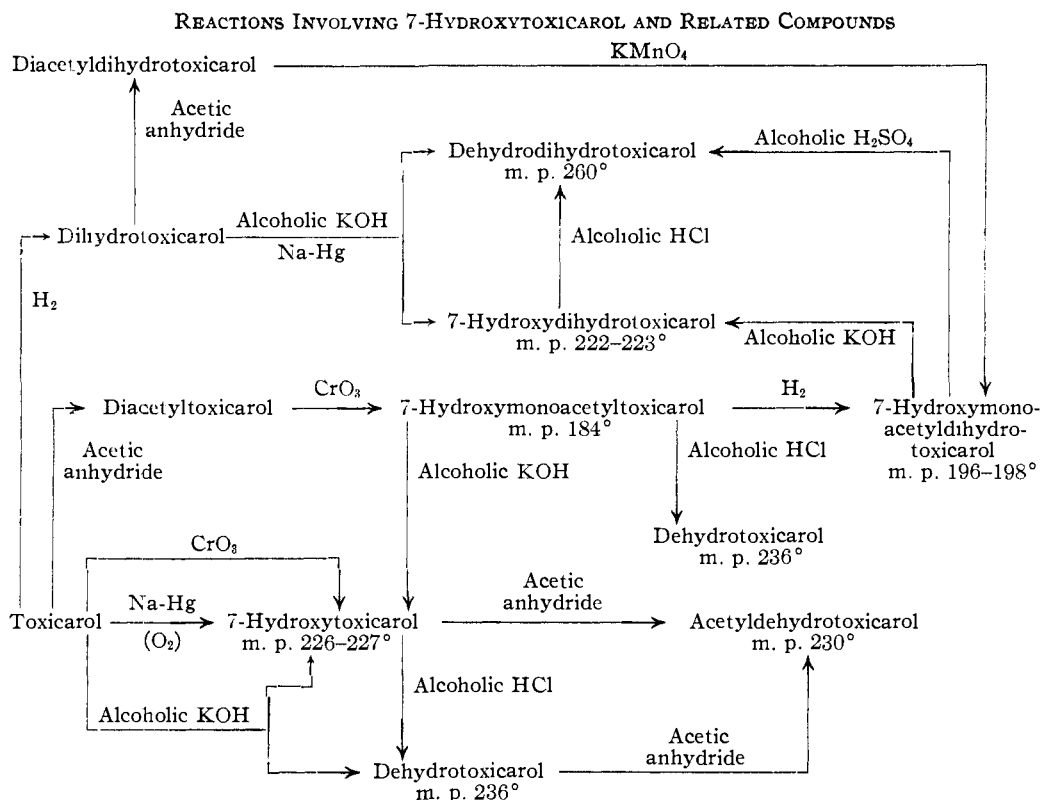
### Experimental

**Action of Alkali upon Toxicarol in an Ethanol-Benzene Solution. 7-Hydroxytoxicarol.**—A solution of 2 g. of toxicarol dissolved in 100 cc. of benzene, 25 cc. of absolute ethanol and 2 cc. of an aqueous 50% potassium hydroxide solution was mechanically stirred for five hours and then allowed to stand for a day. The solvents were largely removed by distillation under reduced pressure, then 200 cc. of water was added to the residue. The distillation was then resumed to remove the remaining benzene, after which the insoluble material was extracted with chloroform. The extract was concentrated to a small volume and treated with methanol until crystallization began. The substance which separated was identified as dehydrotoxicarol by its melting point, mixed melting point and optical properties.

The mother liquors were then further concentrated, causing most of the main reaction product to crystallize. This was 7-hydroxytoxicarol associated with a small quantity of dehydrotoxicarol. The impure material was

(5) Clark, *THIS JOURNAL*, **53**, 729 (1931); Clark and Claborn, *ibid.*, **54**, 4454 (1932).

(6) Clark, *ibid.*, **53**, 2264 (1931); **54**, 2537 (1932).



dissolved in the necessary quantity of chloroform, methanol was added, and the chloroform was removed by evaporation. The dehydro compound separated and was removed, after which essentially pure 7-hydroxytoxicarol separated. Final purification was secured by recrystallization from 50% acetic acid. The material consisted of yellow prisms whose melting point was 226–227°. Its alcoholic solution gave a deep green color with ferric chloride. The crystals were frequently rhombs. In convergent polarized light (crossed nicols) partial biaxial interference figures were shown:  $\eta_{\alpha}$ , 1.580 (common);  $\eta_{\beta}$ , 1.650 (common);  $\eta_{\gamma}$ , slightly greater than 1.737 ( $\text{CH}_2\text{I}_2$ ) although many fragments matched this liquid; all  $\pm 0.003$ .<sup>7</sup>

*Anal.* Calcd. for  $\text{C}_{23}\text{H}_{22}\text{O}_8$ : C, 64.77; H, 5.20;  $\text{OCH}_3$  (2), 14.6. Found: C, 64.98; H, 5.40;  $\text{OCH}_3$ , 14.7.

The material here described is identical with the product obtained by following strictly Butenandt and Hilgetag's directions for the preparation of toxicarol hydrate. The identification consisted of comparing their melting points and their optical properties, and observing no depression of the melting point when the two substances were mixed.

**Action of Sodium Amalgam upon Toxicarol in an Ethanol-Benzene Solution.**—As stated before, 7-hydroxytoxicarol is best prepared by the action of sodium amalgam upon an ethanol-benzene solution of toxicarol. The procedure employed is as follows. Two grams of toxicarol dissolved in 100 cc. of benzene and 25 cc. of 99% ethanol

was treated during twenty-four hours with 50 g. of 2.5% sodium amalgam. The mixture was rapidly stirred for the first five hours and then allowed to stand in an open flask. The solution was then diluted with acidified water, and the organic solvents were removed by distillation under reduced pressure. The residue was dissolved in chloroform and the solution diluted with several volumes of methanol. This liquid was boiled until the chloroform was expelled after which the concentrate was allowed to crystallize. Five-tenths gram of light yellow massive prisms which melted at 224° separated. When it was recrystallized from 50% acetic acid it melted at 226–227° and was shown by comparison to be identical with the preparation recorded above.

**Action of Acetic Anhydride and of Alcoholic Hydrochloric Acid upon 7-Hydroxytoxicarol.**—A mixture of 0.1 g. of dry sodium acetate, 5 cc. of acetic anhydride and 0.5 g. of 7-hydroxytoxicarol was boiled for two hours. The excess of acetic anhydride was then removed by distillation, and ten volumes of methanol was added to the concentrate. The reaction product separated as a mat of colorless hair-like crystals which began to darken and sinter at 210° and melted at 230°. These were recrystallized from a concentrated chloroform solution upon the addition of ten volumes of methanol. The purified product melted at 230° and was shown by comparison with an authentic sample to be acetyldehydrotoxicarol.<sup>8</sup>

Dehydrotoxicarol was formed in practically quantitative yields by boiling 7-hydroxytoxicarol with 5% hydrochloric acid for fifteen minutes. The dehydro compound melted at 235° and was completely identified in the usual manner.

(7) The optical data recorded herewith were determined by George L. Keenan of the Food and Drug Administration, U. S. Department of Agriculture. Appreciation is here expressed for this cooperation.

(8) Clark, *THIS JOURNAL*, **53**, 2269 (1931).

**Action of Chromic Acid upon Toxicarol.**—A solution of 2 g. of toxicarol, dissolved in 50 cc. of hot acetic acid, was cooled and treated with 10 cc. of a 10% acetic acid solution of crystalline sodium dichromate. After twenty-four hours the liquid was diluted with water, and sodium chloride was added to flocculate the precipitate. The precipitate was dissolved in methanol and set aside for two days to crystallize. The yield was 0.85 g. It was recrystallized from 50% acetic acid as in the previous experiments. Its melting point was 226–227°, and it was shown by the usual comparisons to be 7-hydroxytoxicarol.

**7-Hydroxymonoacetyltoxicarol.**—A solution of 1 g. of diacetyltoxicarol dissolved in 30 cc. of hot acetic acid was cooled and treated with 5 cc. of a 10% glacial acetic acid solution of crystalline sodium dichromate. After twenty-four hours the liquid was diluted with water until slightly turbid and then set aside to crystallize. The crude product (680 mg.) melted at 178°, but when it was recrystallized from hot acetic acid solution to which water had been added it separated as thick rhomboidal plates which melted at 184°. They had straight extinction and the refractive indices were  $\eta_{\alpha}$ , 1.555;  $\eta_{\beta}$ , indeterminate; and  $\eta_{\gamma}$ , greater than 1.700 but less than 1.737.

*Anal.* Calcd. for  $C_{25}H_{24}O_9$ : C, 64.09; H, 5.17;  $OCH_3$  (2), 13.3. Found: C, 63.98; H, 5.17;  $OCH_3$ , 13.4.

7-Hydroxytoxicarol was obtained by alkaline hydrolysis of the above-mentioned 7-hydroxymonoacetyltoxicarol. For example, 0.9 g. of the acetyl derivative dissolved in 20 cc. of 10% alcoholic potassium hydroxide was refluxed for fifteen minutes. The solution was then cooled, diluted with water and acidified. The crude light yellow crystalline material which separated weighed 0.75 g. Its melting point was 224–225°. When purified as outlined before, it melted at 226–227° and had the other characteristic properties recorded for 7-hydroxytoxicarol.

Hydrolysis of the acetyl derivative with 5% alcoholic hydrochloric acid (refluxing for two hours) gave a quantitative yield of dehydrotoxicarol, identified by its melting point, mixed melting point and optical properties.

**Hydrogenation of the above Monoacetyl Compound.**—A solution of 100 mg. of 7-hydroxymonoacetyltoxicarol, dissolved in 5 cc. of ethyl acetate, was reduced with hydrogen and platinum dioxide. The platinum was then removed and the solution concentrated to dryness. The residue was dissolved in 5 cc. of acetone and treated with an equal volume of water. Crystallization began at once and yielded 85 mg. of the dihydro compound that melted at 196–198°. It was identified by the usual comparisons as 7-hydroxymonoacetyldihydrotoxicarol, which was prepared by the action of permanganate upon diacetyldihydrotoxicarol, to be reported upon at the conclusion of this section.

**7-Hydroxydihydrotoxicarol by the Action of Alkali and of Sodium Amalgam upon Dihydrotoxicarol.**—Dihydrotoxicarol was treated with alcoholic alkali according to Butenandt and Hilgetag's directions and also by the two procedures in which alkali and sodium amalgam in an ethanol-benzene solution was used as outlined for toxicarol. The products obtained in each case melted at 222–223° and were proved by their melting point, mixed melting point and optical properties to be identical with 7-hydroxydihydrotoxicarol obtained by permanganate oxidation of

diacetyldihydrotoxicarol, which will be considered next. In the introductory remarks attention was directed to the fact that in contrast with toxicarol, dihydrotoxicarol yields some dehydrodihydrotoxicarol when treated with sodium amalgam in an ethanol-benzene solution. Two grams of dihydrotoxicarol furnished 170 mg. of the dehydro compound and 550 mg. of pure 7-hydroxydihydrotoxicarol.

**Permanganate Oxidation of Diacetyldihydrotoxicarol. 7-Hydroxymonoacetyldihydrotoxicarol.**—A solution of 1 g. of diacetyldihydrotoxicarol in 75 cc. of hot acetone was oxidized with 2 g. of potassium permanganate. When the reaction was completed the manganese dioxide was separated, and the acetone solution was concentrated to one-third its volume. Water sufficient to cause a slight turbidity was then added, and the liquid was set aside to crystallize. A yield of 0.6 g. of white rhomb-shaped plates which melted at 194–195° was obtained. These were recrystallized from a hot alcoholic solution to which water sufficient to produce turbidity was added. The material consisted of colorless prisms and rhombs which melted at 196° and which gave no color reaction with ferric chloride. With crossed nicols many of the rhombs did not extinguish sharply, and these showed only partial biaxial interference figures with the optic axis inclined (convergent polarized light, crossed nicols)  $\eta_{\alpha}$ , 1.550 (common);  $\eta_{\beta}$ , indeterminate;  $\eta_{\gamma}$ , 1.685 (both  $\pm 0.003$ ).

The substance was 7-hydroxymonoacetyldihydrotoxicarol and was identical with the substance reported upon above, obtained by hydrogenating 7-hydroxymonoacetyltoxicarol.

In the determination of acetyl by Perkin's method, *i. e.*, boiling the substance with alcoholic sulfuric acid,<sup>9</sup> 0.4559 g. gave 0.364 g. of dihydrodehydrotoxicarol (dehydro formation). Its identity was proved by comparison with an authentic sample of the dehydro compound. The yield of dehydrodihydrotoxicarol was 92%.

*Anal.* Calcd. for  $C_{25}H_{26}O_8$ : C, 63.82; H, 5.57;  $OCH_3$  (2), 13.2; acetyl, 9.15. Found: C, 63.84; H, 5.97;  $OCH_3$ , 13.1; acetyl, 9.77.

**Hydrolysis of the Acetyl Derivative Described above.**—A mixture of 0.5 g. of 7-hydroxymonoacetyldihydrotoxicarol in 10 cc. of a 10% alcoholic potassium hydroxide solution was refluxed for fifteen minutes. The liquid was then cooled, diluted with water and acidified with sulfuric acid, causing 0.4 g. of crude deacetylated product to separate. It was twice recrystallized from 50% acetic acid, after which it melted at 222–223°. It was identical with the product, described before, obtained by the action of alcoholic alkali and by sodium amalgam upon dihydrotoxicarol. The material (7-hydroxydihydrotoxicarol) consisted of colorless prisms, many of which were rhombohedrons:  $\eta_{\alpha}$ , 1.575 (common);  $\eta_{\beta}$ , 1.630 (common, this is apparently the  $\beta$  value although definite biaxial interference figures were obtained only with difficulty);  $\eta_{\gamma}$ , 1.695; all  $\pm 0.003$ .

*Anal.* Calcd. for  $C_{25}H_{24}O_8$ : C, 64.47; H, 5.65;  $OCH_3$  (2), 14.5. Found: C, 64.78; H, 5.70;  $OCH_3$ , 14.6.

7-Hydroxydihydrotoxicarol when boiled with 5% alcoholic hydrochloric acid gives practically quantitative yields of dehydrodihydrotoxicarol.

(9) Perkin, *J. Chem. Soc.*, **87**, 107 (1905).

### Summary

1. The substances designated by Butenandt and Hilgetag as toxicarol hydrate and dihydrotoxicarol hydrate have been shown, as a result of their formation in various ways, their reactions and their analyses, to be respectively

7-hydroxytoxicarol and 7-hydroxydihydrotoxicarol.

2. A summary of the reactions employed to demonstrate this statement is presented diagrammatically in the text.

WASHINGTON, D. C.

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[CONTRIBUTION FROM THE MACKAY CHEMICAL LABORATORY OF THE UNIVERSITY OF NEVADA]

## Essential Oil in Desert Plants. IV. Examination of the Oil of *Tetrademia Glabrata*\*

BY MAXWELL ADAMS AND GREGORY R. ADAMS

The occurrence and physical properties of the essential oil of *Tetrademia Glabrata* has been given in a previous article<sup>1</sup> and the poisonous properties have been studied by Fleming, Miller and Vawter<sup>2</sup> in connection with the livestock industry of the Lahontan Basin. *Tetrademia* is known locally as "Yellow Star Sage" and as "Spring Rabbit Brush." There are six varieties identified in the intermountain region of the United States, two of which, *Glabrata* and *Spinosa* (only oil from *Glabrata* being used in this study), are found growing in the vicinity of Reno, Nevada. During the flowering period several hundred pounds of the small branches, leaves and flowers were collected near the Black Panther Mine north of Reno, Nevada, and steam distilled according to the method described for the preparation of the oil of *Chrysothamnus Nauseosus*.<sup>3</sup> One charge of twenty kilograms yielded 61 g. of oil, or about 0.03%; one small selected sample of leaves yielded more than 0.1%. The colorless oil turns yellowish-brown on standing, and if exposed to the air becomes viscous. The oil has the pungent and somewhat characteristic odor of the plant. The plant contains a poisonous principle, the exact nature of which is undetermined, but range sheep die after feeding upon it in early spring. A petroleum ether extract of the leaves when fed to rabbits produced death but the volatile oil showed no toxic effect.

Two hundred grams of the redistilled volatile oil was extracted with dilute sodium carbonate according to the usual method and the extract acidified with dilute sulfuric acid, made basic with ammonium hydroxide, and silver nitrate added. Considerable silver oxide was formed, and

from the filtrate a small yield of a salt which proved to be silver acetate, crystallized out.

The oil from which the fatty acids had been removed with sodium carbonate was now extracted with a 1% solution of sodium hydroxide. The extract thus obtained was washed with ether to remove adhering oil, made acid with sulfuric acid, and the resulting solution extracted with ether. When the ether evaporated there remained a very small yield of a thick, viscous, ill-smelling oil, which was extracted from the salt crystals with alcohol, the alcohol removed by evaporation, the residual oil treated with dilute ammonium hydroxide, and converted into the silver salt by the addition of silver nitrate. An organic silver compound was formed, which, after repeated crystallizations from alcohol, gave colorless crystals which darkened in the light, showed an indistinct melting point at 143°, and decomposed at 162°. The crystals, upon analysis, contained 14.77% silver, which indicated a compound with a molecular weight of about 616, if it is a pure substance and monovalent to silver. The sample was too small for a more detailed examination. After the removal of the acid and phenolic bodies the oil was fractionated three times at a pressure of 18 mm. using a Glinsky ball and bulb fractionating column. After the final fractionation the optical rotation was determined for each fraction, as had previously been done for the original oil.

Fraction	Dist. temp., °C.	Percentage of total	Color	Opt. rotation
Original oil			Yellowish	+17.60
No. 1	50 to 60	55	Colorless	+ 7.98
No. 2	60 to 70	20	Tinge of green	- 0.40
No. 3	70 to 80	10	Pale yellow	- .52
No. 4	80 to 105	5	Yellow	+ 2.10
No. 5	105 to 120	2	Brown	No test
Residue		8	Black	

It was found that fractions one and two could be distilled at ordinary pressure without apparent decomposition and they were further fractionated by this method. A sample which boiled at 149 to 156° at atmospheric pressure (649 mm.) was distilled over sodium and gave a small yield of pinene hydrochloride melting at 125°, and pinene nitroschloride melting at 103°, indicating the presence of  $\alpha$ -pinene. The metallic sodium combined with much of this fraction suggesting that there had been present in the original oil a considerable proportion of terpene derivatives,

\* Manuscript first received February 20, 1933.

(1) Adams, *THIS JOURNAL*, **49**, 2895 (1927).

(2) Bulletin 104, University of Nevada Agricultural Experiment Station.

(3) Adams, *THIS JOURNAL*, **54**, 2448 (1932).