salt was obtained. The analysis of the sulphonic acid and its salts will be reported upon later.

A new lot of *Calycanthus glaucus* seeds has been ordered and the work is to be continued.

NORTHWESTERN UNIVERSITY SCHOOL OF PHARMACY.

DERIVATIVES OF TRIMETHYLPARACONIC AND OF CAMPHORONIC ACIDS.[1]

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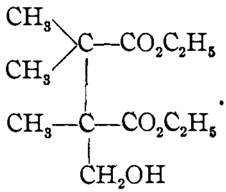
IN THE last paper on this subject published by one of us,[2] a brief account has been given of attempts to secure a synthesis of a derivative of camphor by the aid of trimethylparaconic acid. Such a synthesis has not been obtained, but, although results in this direction are negative, since we can no longer continue the work together it seems desirable to give a brief account of what has been done.

It had been shown by Noyes and Patterson[3] that when the diethyl ester of trimethylitamalic acid is treated with phosphorus tribromide, ethyl bromide is split off and trimethylparaconic ester is formed. As the ester used by them was not pure and was not at all thoroughly examined, it seemed advisable to repeat the experiment, using the dimethyl ester instead of the diethyl ester, principally because of the fact that the percentages of carbon and hydrogen in the diethyl ester of trimethylitamalic acid and in the ethyl ester of trimethylparaconic acid are so nearly the same that analysis would not serve to distinguish between them.

Dimethyl Ester of Trimethylitamalic Acid,



$$\begin{array}{l} \begin{array}{l}CH_3\\CH_3\end{array}\!\!>C-CO_2C_2H_5 \\ \qquad\quad | \\ CH_3-C-CO_2C_2H_5 . \\ \qquad\quad | \\ \qquad\quad CH_2OH \end{array}$$

—Three times the calculated quantity of methyl iodide was put into a small flask, which was so arranged as to be easily connected

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[1] This investigation was carried out by means of a grant from the Carnegie Institution, partly in the laboratories of the Johns Hopkins University and partly in those of the Bureau of Standards, Washington, D. C. We desire to express our thanks to each of these institutions for the assistance rendered.

[2] *Am. Chem. J.*, **33**, 356.

[3] *Ibid.*, **28**, 232.

with a return condenser by means of a short piece of rubber tubing which slipped over the neck of the flask and the end of the condenser tube, the latter passing inside the neck of the flask. Silver trimethylitamalate[1] was then added in small portions. After each addition the flask was quickly attached to the condenser until the reaction was finished. At first the reaction was a little slow, but after a few portions of the silver salt had been added the action became quite vigorous, so that it had to be controlled by dipping the flask into cold water. After all the silver salt had been added, the flask was warmed for two hours on the water-bath. The silver iodide was filtered from the liquid and washed repeatedly with ether. The filtrate was dried with calcium chloride, filtered, and distilled under diminished pressure. After the ether had been removed a yellow oil remained which boiled at 122–127° under 12 to 14 mm. pressure and at 261–265° under atmospheric pressure. The analysis gave: C, 55.82, 55.81; H, 7.99, 7.74. Calculated for $C_{10}H_{18}O_5$, C, 55.05; H, 8.26. The methyl ester of trimethylparaconic acid contains; C, 58.02, H, 7.59.

Attempts were made repeatedly and under a considerable variety of conditions to replace the hydroxyl of the ester with bromine by treatment with hydrobromic acid or phosphorus tribromide. In some cases products were obtained containing 1 or 2 per cent. of bromine, but in every case there was either only a very trifling replacement of the hydroxyl or the bromine at once split off as methyl bromide, giving the methyl ester of trimethylparaconic acid, as the ethyl ester had done before.

Attempts to prepare an acetyl or a benzoyl derivative by the use of acetyl chloride, benzoyl chloride, or acetic anhydride were also unsuccessful. Even heating the ester with acetic anhydride in a sealed tube at 165–180° was not effective. It seems probable that the failure to react is due to the manner in which the hydroxyl group is related to the rest of the molecule, in space or otherwise.[2] That the hydroxyl group may react with acetic anhydride under favorable conditions has been shown by the preparation of the acetyl derivative of trimethylitamalic anhydride.[3]

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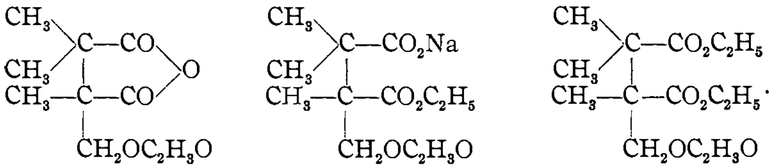
[1] *Am. Chem. J.*, **28**, 230.

[2] Endemann (*Am. Chem. J.*, **33**) has recently drawn the conclusion that abietic acid does not contain two hydroxyl groups from the fact that it takes only one acetyl group when heated with acetic anhydride in a sealed tube. This inference is probably correct but in the light of our experience the evidence cannot be considered as conclusive.

[3] This Journal, **33**, 364.

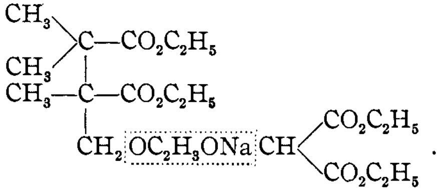
We next tried to prepare the acetyl derivative of the ester by the successive treatment of the acetyl trimethylitamalic anhydride with sodium ethylate and ethyl iodide, hoping to secure the following transformations:



An examination of the oil which was obtained demonstrated that, while the reaction may have proceeded in part as indicated, a mixture had resulted from which a pure product could not be isolated.

An attempt to hydrolyze the anhydride with a cold solution of sodium hydroxide, followed by the preparation of a silver salt and treatment of this with ethyl iodide, was equally unsuccessful.

It had been hoped that if the acetyl derivative of the ester could be secured this might be condensed directly with sodium malonic ester, thus:



Incidentally, we have shown that a similar condensation can be effected between amyl acetate and sodium malonic ester, though the yield was poor. So far as we are aware an acyl derivative has never before been used for a condensation of this type.

It was found impossible to reduce trimethylparaconic acid by the electrolytic method of Mettler,[1] using lead electrodes prepared as described by Tafel.[2] The trimethylparaconic acid was recovered unchanged.

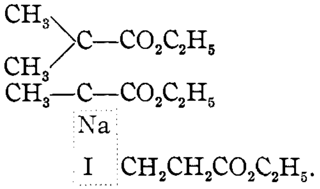
These various attempts to synthesize homocamphoronic acid by means of trimethylparaconic acid having failed, we decided to turn our attention to other methods of attacking the problem.

[1] *Ber.*, **38**, 1745.

[2] *Ibid.*, **33**, 2214.

WORK WITH TRIMETHYLSUCCINIC ACID.

It seemed possible that a sodium derivative of trimethylsuccinic ester might condense with chloracetic ester to give camphoronic ester or with β-iodopropionic ester to give homocamphoronic ester.



Condensations quite similar to this have been obtained by Michael.[1]

Eight and one-half grams of the diethyl ester of trimethylsuccinic acid were dissolved in a small amount of anhydrous ether and introduced into a tube containing 0.9 gram of finely divided sodium. Evolution of hydrogen began at once. The tube was connected with an upright condenser, the upper end of which was protected with a calcium chloride tube. The solution was heated at 50° for twenty-two hours, when the sodium had mostly disappeared. Seven grams of chloracetic ester were then added. The reaction was slow at first, but gas was evolved vigorously on heating slightly. The tube was then sealed, after the evolution of gas had ceased, and heated at 100° for six hours. The contents of the tube were dark brown in color, and a large amount of solid substance had separated. The resulting product was separated in the usual manner by means of water and ether, dried and distilled. The distillates, which came over at 105–110° and 140–150°, under low pressure were saponified and tested for camphoronic acid. No trace of camphoronic acid was found. The ammonium salt gave no precipitate with barium chloride, but gave a precipitate with calcium chloride, indicating that trimethylsuccinic acid had been recovered.

The action of sodium ethylate and chloracetic ester with the trimethylsuccinic ester gave similar results. No camphoronic acid was found, and trimethylsuccinic acid was recovered unchanged.

Attempted Condensation with Chloral.—Fittig and Miller[2]

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[1] *Ber.*, **33**, 3747.

[2] *Ann.* (Liebig), **253**, 43.

showed that anhydrous chloral condenses with sodium succinate and acetic anhydride, giving trichlormethylparaconic acid, and furthermore, this acid boiled with barium hydroxide gives the barium salt of isocitric acid.

A similar condensation of chloral with sodium trimethylsuccinate would give trichlortetramethylparaconic acid, and if this reacted with barium hydroxide in the manner described above, the resulting product should be hydroxycamphoronic acid.

Sodium trimethylsuccinate (1 mol.), acetic anhydride (1½ mols.) and anhydrous chloral (1 mol.) were brought together under varying conditions. When heated to 100–110° either in an open flask with return condenser or in a sealed tube, there was no decomposition, *i. e.*, no splitting off of chlorine. At 140° the mixture was partly carbonized, and at 180° for twenty hours it was entirely carbonized. When the substances were mixed together there was always considerable evolution of heat, and in the experiments in which there was no carbonization there was always an oil obtained which boiled at 113–115° under 20 mm. pressure and at 222° under atmospheric pressure. This oil proved to be chloral diacetate, which is easily prepared by warming acetic anhydride and chloral together. The analysis gave 42.57 per cent. Cl; calculated, 42.65 per cent

In all cases where the material was not badly carbonized, trimethylsuccinic acid was recovered unchanged, and no other definite products could be isolated.

Concentrated sulphuric acid was used instead of acetic anhydride, the mixture being heated in a sealed tube in a boiling water-bath for two days. There was some decomposition of the chloral and the trimethylsuccinic acid was recovered unchanged.

As trioxymethylene had given such satisfactory results with sodium trimethylsuccinate in the preparation of trimethylparaconic acid, it seemed possible that the polymeric form of chloral, polychloral, might react with sodium trimethylsuccinate in the same way. Polychloral (1 mol.), sodium trimethylsuccinate (1 mol.), and acetic anhydride (1½ mol.) were mixed in a sealing tube and, after sealing, heated to 140–160° for two hours. The polychloral was decomposed with considerable carbonization. Trimethylsuccinic acid was recovered unchanged.

Inactive Hydroxycamphoronic Acid.—In the course of the work described above, it seemed desirable to have a specimen of inactive hydroxycamphoronic acid for direct comparison with the synthetic acid which we are endeavoring to prepare. Fortunately, we had a considerable quantity of *i*-camphoronic acid which was previously prepared from synthetic *i*-camphor.[1] This served as material for the following preparations, in the general plan of which the directions of Aschan[2] in his work on the active form of the acid were followed. Since the object of this preparation was not the study of the *i*-hydroxycamphoronic acids, but the securing of a product by which to identify the acid which we hoped to synthesize, we made no study of the stereomeric forms but proceeded at once to the preparation of *i*-camphoranic acid.

Chloride of i-Bromanhydrocamphoronic Acid.—Five and one-tenth grams of *i*-camphoronic acid were brought into a sealing tube and mixed with 14.6 grams of phosphorus pentachloride, the tube being left open at one end. The mixture was warmed gently until the somewhat violent reaction was over. On cooling, the chloride of the anhydro acid crystallized from the phosphorus oxychloride. 3.75 grams of bromine were then added in a small bulb with a long capillary stem, and the tube was sealed. It was heated at 100° for six hours, the color of bromine having nearly disappeared in that time. After cooling over night the tube opened with considerable pressure. The contents of the tube were poured into cold water, and a colorless oil separated, which quickly solidified to a crystalline, white, waxy mass, which when dried on a porous plate weighed 6.6 grams. It was easily soluble in ether, and when crystallized from that solvent, melted at 123–126°. The analysis gave 38.28 per cent. Cl + Br; calculated for $C_6H_{10}O_4ClBr$, 38.80 per cent.

The Anhydride of i-Camphoranic Acid.—Five and eight-tenths grams of the chloride of bromanhydrocamphoronic acid were boiled with 100 cc. of water. The substance melted under water and gradually went into solution. The solution was evaporated to dryness, and the white, crystalline residue was dried over sulphuric acid in a vacuum desiccator. Two and nine-tenths grams of this product were heated in a distilling bulb under a pressure of 20 mm. The mass melted and lost water rapidly at

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[1] *Am. Chem. J.*, **27**, 430, and **28**, 482.

[2] *Ber.*, **28**, 20.

about 160°. It distilled at 193–194° under 20 mm. pressure. The distillate solidified in the receiver to a white crystalline mass, very difficultly soluble in ether, and melting at 119–121°. The anhydride of the active acid melts at 136–137°.[1] It dissolved readily in water, with acid reaction. Neutralized with ammonia it gave a white precipitate with silver nitrate, easily soluble in nitric acid. Warmed with ammonia and calcium chloride it gave no precipitate. Warmed with ammonia and barium chloride it gave a heavy crystalline precipitate. The free acid is not extracted from the aqueous solution by means of ether, it being almost insoluble in ether.

i-Camphoranic Acid.—One and six-tenths grams of the anhydride (the distillate described above) were boiled with a few cubic centimeters of water for a few minutes. The solution was evaporated to a small volume on the water-bath, and then allowed to stand in a vacuum desiccator over sulphuric acid for forty-eight hours. The *i*-camphoranic acid crystallized in large, square-sectioned pyramids. On heating, it partly sublimed and melted at 190–191°. The active acid melts at 209–210°.[2] Analysis: I. 0.1182 gram substance required 10.94 cc. N/10 $Ba(OH)_2$ solution for neutralization. Calculated for *i*-camphoranic acid, 10.98 cc. II. 0.1194 gram substance required 11.07 cc. N/10 $Ba(OH)_2$ solution for neutralization. Calculated, 11.05 cc. *i*-camphoranic acid acts as a dibasic acid, the lactone ring not being broken by boiling with water nor by treatment with alkalies. This agrees with the results obtained by Bredt[3] in his work on the active form.

The analysis of the anhydride was not satisfactory, probably because of the fact that *i*-camphoranic acid sublimes to some extent when heated, and we had not sufficient material to enable us to separate the two products. The analysis gave: C, 53.31, 53.17; H, 4.99, 5.05. Calculated for $C_9H_{10}O_5$, C, 54.54; H, 5.05.

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June, 1905.

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[1] Bredt: *Annalen*, **299**, 152.

[2] Bredt: *Ibid.*, **299**, 151.

[3] *Ibid.*, **299**, 131.