

filtrate was acidified, an immediate heavy, white precipitate formed, which weighed 0.5 g. It did not melt below 280° and its optical properties were identical with those of 1,7-dimethyl-9-phenyl-uric acid.

Summary

1. The action of alkali on 1,3-dimethyl-9-phenyl-uric acid has been studied, and the course of the reaction and the nature of the decomposition products have been determined.

2. The primary decomposition product is 3-phenyl-isohydantoin-5-carboxylic acid methylamide. This is further decomposed by alkali to methylamine, oxalic acid, glycolic acid, formic acid and phenylurea.

3. Phenylisohydantoin-carboxylic acid methylamide is oxidized by hydrogen peroxide to 3-phenyl-5-hydroxyhydantoin-5-carboxylic acid methylamide, which is readily decomposed by alkali to mesoxalic acid, methylamine and phenylurea.

4. 1,7-Dimethyl-9-phenyl-uric acid, and the ethyl ester and methylamide of phenyl-oxaluric acid have been prepared for the first time and characterized.

5. The action of alkali on other substituted uric acids is now being investigated.

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

DERIVATIVES OF CAMPHORONIC ACID

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Introduction

Despite the fact that camphoronic acid and many of its derivatives have been known since the latter part of the nineteenth century, no direct proof for the special structures of these derivatives has ever been brought forward. Kachler² first discovered camphoronic acid in the mother liquors of a camphor-nitric acid oxidation mixture; the true structure of the acid was first suggested by Brecht³ and later confirmed by the classical synthesis of inactive camphoronic acid by Perkin and Thorpe.⁴

Of the derivatives studied in this research there are already known one anhydro acid,⁵ C₆H₁₁(CO)₂OCOOH, two isomeric anhydro acid chlorides,⁶

¹ An abstract of a thesis presented to the Graduate Faculty of the University of Illinois in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

² Kachler, *Ann.*, **159**, 288 (1871).

³ Brecht, *Ann.*, **292**, 67 (1896).

⁴ Perkin and Thorpe, *J. Chem. Soc.*, **71**, 1169 (1897).

⁵ Kachler and Spitzer, *Monatsh.*, **6**, 186 (1885).

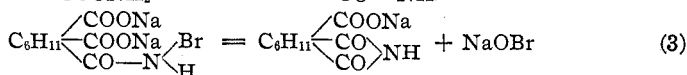
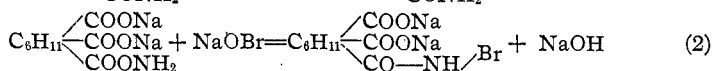
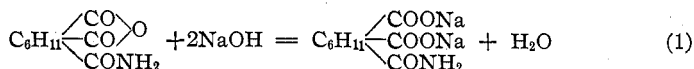
⁶ Ref. 5, p. 193.

$C_6H_{11}(CO)_2OCOC$ l, one diethyl ester,⁷ $C_6H_{11}(COOC_2H_5)_2COOH$, one mono ethyl ester,⁸ $C_6H_{11}(COOC_2H_5)(COOH)_2$, one acid imide,⁹ $C_6H_{11}(CO)_2NHCOOH$, and two isomeric anhydrobromo acid chlorides,¹⁰ $C_6H_{10}Br(CO)_2OCOC$ l, in which it is known that the bromine is on the primary carbon atom.

It was the original purpose of the present investigation to establish the structures of the various derivatives of camphoronic acid. The method of attack was planned as follows. If one of the anhydro acid chlorides were to be treated with anhydrous ammonia, the corresponding anhydroamide should be formed, which on treatment with sodium hypobromite should then yield the corresponding dibasic amino acid. This compound on treatment with nitrous acid should give a dibasic hydroxy acid. If the hydroxyl group were on the primary carbon atom, trimethyl paraconic acid, a known compound would result. If it were, however, on the carbon atom bearing the two methyl groups, an isomeric lactone should result; while if the hydroxyl group were on the central carbon atom, no lactone could be produced. In this way it was hoped that the structures of the parent substances could be proved.

Discussion

The formation of isomeric imides, when it was desired to prepare the amides from the corresponding anhydrocamphoronyl chlorides, proved, however, to be the unavoidable obstacle presented in the outline of attack set forth above. It was shown that, from the weight of ammonia absorbed and the percentage of inorganic and organic nitrogen present, both isomeric anhydro-acid chlorides of camphoronic acid, when treated with ammonia, form an anhydro amide. The failure to obtain an indication of the reaction of the latter with sodium hypobromite to produce the corresponding amino acid may be attributed to one of two causes: either the anhydro amide actually reacted with the hypobromite according to the scheme



or the anhydro amide rearranged to the more stable imidic acid structure the moment it passed into solution.

⁷ Ref. 3, p. 100.

⁸ Ref. 3, p. 104.

⁹ Hess, *Ber.*, **28**, 2689 (1895).

¹⁰ Bredt, *Ann.*, **299**, 142 (1898).

It is, of course, improbable that evidence for the above reactions can be secured. On the other hand, the unusual inactivity of both isomeric imides toward even strong alkali indicates clearly the great stability of the imide structure, while the isolation of the imide instead of the anhydro-amide on extraction of the precipitate of ammonia and anhydro acid chloride with anhydrous solvents seems to leave little doubt as to the instability of the latter compound.

The results of these researches have clearly shown the futility of an attempt at the preparation of either a dibasic amide or an anhydro amide of camphoronic acid which can be made to react with sodium hypobromite. The results, furthermore, demonstrate the necessity of covering two carboxyl groups more effectively than by forming a dimetallic salt if it is desired to prepare such a compound. The great stability of the imide seemed to indicate that a most desirable "covering group" had been found. With this in mind the attempted preparation of isomeric imide-amides from the corresponding imides was undertaken, with most gratifying results. Both imide-amides have been found to react with sodium hypobromite even in the cold, and it is through these compounds that the original plan of attack set forth in the beginning of the paper, though modified, may be brought to a satisfactory conclusion.

Experimental Part

Preparation of Pure Camphoronic Acid.—In a 12-liter flask fitted with a condenser made from a glass tube slightly smaller than the neck of the flask, sealed at the bottom, and bearing an entrance and exit tube for water, was placed 2 kg. of camphor. To this was added 10 kg. of concd. nitric acid, and the mixture was gradually heated to boiling. After two weeks' continuous boiling, when the relative yield of camphoronic and camphoric acids was found to be greatest, the mixture was cooled, the camphoric acid filtered off and the mother liquor evaporated on the water-bath. The residue, which consisted of a sticky paste, was dissolved in an equal volume of hot water, the solution placed in a flask on a water-bath, and a blast of air bubbled through for two days to remove the last traces of nitric acid. (Inorganic salts, which would be formed by the neutralization of the excess of nitric acid with sodium or ammonium hydroxides, were found to inhibit materially the precipitation of barium camphoronate.) This residue was diluted with an equal volume of water and an excess of barium hydroxide, previously dissolved in water, was added. The mixture was stirred with a mechanical device and gradually heated to boiling. A cream-white, sandy precipitate of barium camphoronate resulted which was filtered off, washed, and redissolved in dil. hydrochloric acid. The solution was then boiled with 15 g. of Norite, filtered and boiled again. This was repeated eight times. The barium camphoronate was finally reprecipitated by the addition of ammonia to the neutral point, followed by boiling. Without cooling the mixture the barium salt was filtered off, washed, re-dissolved in dil. hydrochloric acid, boiled with Norite and again reprecipitated. This process was repeated four times. The final product was white barium camphoronate. The salt was again dissolved in hydrochloric acid, the barium precipitated from boiling solution by the addition of a slight excess of dil. sulfuric acid, and the filtrate evaporated to a small volume by distillation under reduced pressure. (The presence of a large excess of hydrochloric acid is desirable for it aids in the crystallization of camphoronic acid.) After standing for twelve hours the

yellow mother liquors, containing about 200 g. of camphoronic acid, were filtered from 280 g. of crystalline, snow-white camphoronic acid. Recrystallization from an equal weight of water yielded fine needles melting at 164–165° when the bath was raised 1° per second from 150°. The acid in the mother liquors was recovered, after evaporation, as its barium salt.

Anhydrocamphoronic Acid was prepared in quantitative yields by heating the pure acid under reduced pressure in a distilling bulb immersed in oil at 180°. A water-white liquid was obtained, which solidified and then melted when the bath was raised to 133°. Recrystallization from chloroform yielded snow-white crystals melting at 139°; $[\alpha]_D^{20} = +5.56^\circ$ (in chloroform).

Anhydrocamphoronyl Chlorides were prepared and separated by the method of Kachler and Spitzer. Instead of heating the mixture of phosphorus pentachloride and anhydrocamphoronic it was allowed to stand at room temperature. The α chloride (m. p., 137–138°; $[\alpha]_D^{20} = +6.25^\circ$, in chloroform) was obtained in yields of 43%. The β chloride (m. p., 38–39°; $[\alpha]_D^{20} = -4.21^\circ$, in chloroform) was obtained in yields of 48%.

Mono-ethyl Camphoronate.—The mono-ester of camphoronic acid has been prepared hitherto only from the anhydro-ester by permitting the latter to stand with water for a considerable length of time. It has been found possible to prepare this compound by the direct esterification of the acid. Camphoronic acid was treated with 1.7 times its weight of absolute alcohol. Dry hydrogen chloride was passed in until present to the extent of 3% of the total weight of the mixture. After standing for 18 hours at room temperature the mixture was diluted and evaporated, and the crystals of mono-ester were filtered off. Recrystallization from water gave transparent crystals; m. p., 139–140°; $[\alpha]_D^{20} = -30.21^\circ$, in absolute alcohol. The ester group in this compound is undoubtedly on the primary carboxyl group.

Analysis. Calc. for $C_{11}H_{18}O_6$: C, 53.61; H, 7.37. Found: C, 53.75; H, 7.24.

The diester was separated according to the method of Bredt.⁷ Its purity was ascertained by titration; $[\alpha]_D^{20} = -9.91^\circ$, in absolute alcohol.

The Bromo-anhydrocamphoronyl Chlorides.—The preparation of these compounds was carried out exactly as Bredt¹⁰ describes, except that the bromination was catalyzed by the addition of a small amount of iron filings, followed by heating for one hour. A yield of 78% of the α isomer was obtained; $[\alpha]_D^{20} = -6.29^\circ$, in chloroform.

Action of Ammonia and α -Anhydrocamphoronyl Chloride.—In an attempt to prepare the anhydro-amide of camphoronic acid 4.85 g. of α -chloride in benzene at 10° was treated with an excess of anhydrous ammonia. A precipitate resulted which, after the excess of ammonia was swept away, was filtered, dried, dissolved in water, acidified with dil. hydrochloric acid, and extracted with ether. The dried ether extract yielded 4.53 grams of solid; m. p., 196–200°. Recrystallization from hot water gave transparent crystals; m. p., 199.4–200.2°; $[\alpha]_D = -6.86^\circ$, in absolute alcohol; repeated recrystallization failed to raise the melting point.

Analyses. Calc. for $C_9H_{13}O_4N$: N, 7.03. Found: 6.99, 7.15.

Acid number. Calc. for C_9H_{11} $\begin{matrix} \diagup CO \\ \diagdown CO \end{matrix} NH$ $\begin{matrix} \diagdown COOH \\ \diagup \end{matrix}$: 281. Found: 282.

This compound was found to be identical with the imide prepared by Hess¹¹ from the anhydro acid.

To ascertain whether the acid chloride group or the anhydride group had reacted with ammonia, 0.9670 g. of α chloride was placed in a weighed bulb, dry benzene added to dissolve the chloride, the solution cooled to 10°, and anhydrous ammonia passed in

¹¹ Ref. 9. p 2687.

until no further precipitate resulted. The solvent was evaporated after the excess of ammonia was blown out with dry air, and the bulb dried to constant weight. An increase in weight of 0.1860 g. had resulted, or approximately 2.4 molecular equivalents of gas had reacted. The total percentage of nitrogen was found to be 12.05, and the ammonium nitrogen 6.80%. There was then left 5.25% of organic nitrogen. In a 1:1 mixture of anhydro amide (or acid imide) and ammonium chloride the organic nitrogen content should be 5.55%. This experiment shows conclusively that the acid chloride and not the anhydride group had reacted. The presence of 0.4 molecular equivalents' excess of ammonium nitrogen is explained by the fact that a partial rearrangement of the anhydro amide to the acid imide had occurred, which in turn reacted with more ammonia to form the ammonium salt of camphoronimide.

In the hope of securing an anhydro-amide the precipitate was placed in a dried Soxhlet thimble and extracted with anhydrous chloroform. Despite the fact that water was absent and solution resulted, rearrangement to the imide had been complete, for only an imide was recovered from the chloroform extract.

In every way the β -chloride behaved as did its isomer. With ammonia, however it yielded in benzene solution an imide which, hitherto, has not been prepared. The imide, on crystallization from water, yielded transparent crystals; m. p., 234.5–235°; $[\alpha]_D^{20} = -5.40^\circ$, in absolute alcohol.

Analyses. Calc. for $C_9H_{13}O_4N$: N, 7.03. Found: 7.01, 7.12.

Acid number. Calc. for C_9H_{11} $\begin{matrix} \diagup CO \\ \diagdown CO \end{matrix} NH$ $\begin{matrix} \diagup \\ \diagdown \end{matrix} COOH$: 281. Found: 283.

It was hoped that the two isomeric imides could be hydrolyzed to the acid amide by alkali. Heating at 100° for 25 hours with three molecular equivalents of *N* potassium hydroxide produced, not hydrolysis to the amide, but a 2% hydrolysis to camphoronic acid in the case of the α -imide and a 20% hydrolysis in the case of the β -imide.

The Action of Anhydrous Ammonia on α -Anhydrobromo-camphoronyl Chloride.—In the hope of preparing an amide of α -anhydrobromo-camphoronyl chloride the pure crystals were treated in benzene solution at 10° with an excess of dry ammonia. After the dissolved gas had been swept away the benzene was evaporated, the residue was dissolved in dil. hydrochloric acid and repeatedly extracted with ether. A white solid was obtained, which, after recrystallization from water, melted at 220°.

Analyses. Calc. for $C_9H_{12}O_4BrN$: N, 5.03; Br, 28.76. Found: N, 5.18; Br, 28.53.

Acid number. Calc. for $C_9H_{10}Br$ $\begin{matrix} \diagup COOH \\ \diagdown CO \end{matrix} NH$ $\begin{matrix} \diagup \\ \diagdown \end{matrix} CO$: 227. Found: 239.

The Action of Sodium Hypobromite on the Reaction Product of Anhydrous Ammonia and α - and β -Anhydrocamphoronyl Chlorides.—Experiments were carried out in which both isomeric anhydro chlorides were treated at 10° in benzene solution with dry ammonia, the excess of gas was swept away and the suspended precipitate treated with six molecular equivalents of 10% sodium hydroxide solution in which was dissolved the calculated amount of bromine. In each case, after the mixture had been heated on the water-bath for one hour, acidification with hydrochloric acid produced no evolution of carbon dioxide. An ether extraction yielded an almost quantitative recovery of the corresponding imide. The aqueous layer, after evaporation to complete dryness, gave but a trace of organic matter when extracted with absolute alcohol.

The Action of Ammonia on Mono-ethylcamphoronate.—In an attempt to prepare the mono-amide of camphoronic acid, 10 g. of an absolute alcoholic solution of mono-ester was treated with 3 molecular equivalents of dry ammonia dissolved in the same solvent. The mixture was placed in a Pyrex tube, sealed, and heated for four days at 140°. At the end of this time the tube was opened, the alcohol distilled in a vacuum, and the resi-

due acidified and extracted with ether. A nitrogenous solid weighing 8.5 g. was obtained. Unchanged ester (0.5 g.) was dissolved from the pulverized solid with small amounts of chloroform. The residue was crystallized from hot water. A nitrogenous acidic solid was obtained; m. p., 199–200°. This compound proved to be identical with the imide prepared from the α -chloride.

The Action of Anhydrous Ammonia on Disodium Ethylcamphoronate.—A sample of 4.82 g. of mono-ester was heated at 140° with 1.95 molecular equivalents of sodium ethylate in a Pyrex tube for four days. A crystalline precipitate weighing 0.90 g. was filtered from the liquid portion at the end of the heating. This compound did not yield its nitrogen when heated with 10% alkali.

Analysis. Calc. for $C_9H_{11}(CO)_2NNa.COONa$: N, 5.76. Found: 6.04, 5.85.

In the belief that the disodium amide was in the mother liquors, the latter were evaporated and a crystalline precipitate weighing 4.87 g. and containing 1.69% of nitrogen was obtained. When the precipitate was treated with sodium hypobromite and alkali in proper proportions, heated for one hour, cooled and acidified, no evolution of gas was observed. An ether extract yielded 4.01 g. of solid which proved to be about 25% of imide and 75% of unchanged ester.

Preparation of α -Camphoronamide-imide.—A sample of α -camphoronimide weighing 14.63 g. was treated with 1.2 molecular equivalents of phosphorus pentachloride. As the mixture failed to evolve hydrogen chloride, the distilling bulb containing the two substances was heated on the water-bath for an hour. At the end of this time practically all of the phosphorus pentachloride had disappeared. The phosphorus oxychloride was distilled under a vacuum. The residue, weighing 16.36 g. and consisting of a viscous yellow oil, was dissolved in absolute ether and the solution cooled to -20° . Ligroin, at the same temperature, was added carefully. A cloud, but no crystals, appeared. One or two drops of ether were added to clear the cloud and the mixture was allowed to stand for three days at this temperature. No crystals appeared in the solution, so an excess of anhydrous ammonia was passed into the mixture. A white precipitate resulted which was filtered from the mother liquors. The latter gave only a trace of organic matter on evaporation.

The precipitate was mixed with a small amount of water and dried by suction to remove ammonium chloride. The residue was dissolved in a small amount of boiling water, the solution boiled with a little Norite, filtered, and the filtrate allowed to cool. Transparent crystals were obtained; m. p., 235–236°; $[\alpha]_{D_{41.6}}^{28.0} = +11.87^\circ$, in absolute methyl alcohol.

Analysis. Calc. for $C_9H_{11}O_2N_2$: N, 14.13. Found: 13.89.

Preparation of the Acid Chloride of β -Camphoronimide.—To 12.02 g. of β -camphoronimide, in a small distilling bulb, was added 1.2 molecular equivalents of pulverized phosphorus pentachloride, and the mixture warmed on the water-bath for one hour. At the end of this time glistening crystals, quite unlike the imide, precipitated from the mixture as it cooled. After distillation of the phosphorus oxychloride under a vacuum, the residue, weighing 14.3 g., was washed well with absolute ether; 11 g. of solid was obtained. This compound, on analysis, proved to be the acid chloride of the β imide. It was found to be very soluble in chloroform and in hot benzene. When recrystallized from the latter a beautiful solid product was obtained; m. p., 175.5–176.5°; $[\alpha]_{D_{41.6}}^{26.0} = -18.32^\circ$, in chloroform.

Analysis. Calc. for $C_9H_{10}O_2NCl$: N, 6.43; Cl, 16.31. Found: N, 6.18; Cl, 16.20.

Preparation of β -Camphoronimide-amide.—An excess of anhydrous ammonia was passed into a chloroform solution of 5.2 g. of the β -imide acid chloride, the excess of gas was swept away, the solvent evaporated, and the solid precipitate washed with a

small amount of water to remove ammonium chloride. The residue was dissolved in boiling water, the solution filtered and allowed to cool. Transparent crystals of the β -imide-amide were obtained; m. p., 205°; $[\alpha]_{541.6}^{28.0} = -13.73^\circ$, in absolute acetone.

Analysis. Calc. for $C_9H_{14}O_3N_2$: N, 14.13. Found: 13.95.

Summary

1. Anhydrocamphoronic acid has been prepared in quantitative yields.
2. Mono-ethyl camphoronate has been prepared by the direct esterification of the acid in yields of 50%.
3. Monomethyl camphoronate yields an imide on treatment with ammonia at 140°. This imide is identical with that obtained from the anhydro acid under similar treatment.
4. Anhydrous ammonia reacts with α -anhydrocamphoronyl chloride to yield first an anhydro amide and then an acid imide by rearrangement. This imide is identical with that obtained from the mono-ester.
5. Anhydrous ammonia reacts with β -anhydrocamphoronyl chloride in a similar manner to form an isomeric imide. This compound is new in the camphoronic acid series.
6. Anhydrous ammonia reacts with bromo-anhydrocamphoronyl chloride to form a bromo-imide. This compound is new in the camphoronic acid series.
7. Potassium hydroxide fails to open the ring of either α - or β -camphoronimide to yield a dibasic amide. In each case partial hydrolysis to the parent acid is the only reaction involved.
8. When the reaction product of anhydrous ammonia and α -anhydrocamphoronyl chloride, or β -anhydrocamphoronyl chloride, or disodium ethylcamphoronate is treated with sodium hypobromite the corresponding amino acid is not formed. In each case an imide is produced.
9. When α -camphoronimide is treated first with phosphorus pentachloride and then with anhydrous ammonia an imide-amide of camphoronic acid is produced. This compound is new in the camphoronic acid series. The compound reacts readily with sodium hypobromite.
10. The acid chloride of β -camphoronimide has been prepared. This compound is new in the camphoronic acid series.
11. When the acid chloride of β -camphoronimide is treated with anhydrous ammonia an amide is formed. This amide is isomeric with that prepared from the α -imide, is new in the camphoronic acid series, and reacts readily with sodium hypobromite.

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