Esters of 3-Nitrocumic Acid*

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Experimental data concerning a number of esters of 3-nitrocumic acid are presented. A number of physical constants are included. An attempt was made to prepare 3-hydroxy-2-carboxy-4-isopropylbenzoic acid.

Although terpene chemistry is one of the oldest branches of organic chemistry, its present-day importance continues to attract research workers. This is particularly true in the naval stores industry which is yielding a variety of commercial products including perfume materials. During the last twenty-five years the production of terpene products has been increased considerably in turpentining operations, from stumps, wood waste, and as by-products from kraft pulp mills.

During the last decade, more research has been applied to the monocyclic terpenes than the bicyclic terpenes with the result that this class of compounds has now acquired a distinguished place in industry. The structural relationship of the monocyclic terpene hydrocarbons to *p*-menthane and cymene can be readily seen. The conversion of these terpene hydrocarbons to cymene and the conversion of *p*-cymene to cymene acids is being carried out successfully on a commercial scale. One of these cymene acids is cumic acid. The fact that cumic acid (*p*-isopropyl benzoic acid) is a homolog of benzoic acid further increases its interest to the pharmaceutical chemist.

With these facts in mind the preparation of a number of esters of cumic acid and 3-nitrocumic acid was undertaken with a view to their possible value in flavors, cosmetics, and other pharmaceutical products. Another report from this laboratory is being submitted by Carkhuff and Gramling. It deals with esters of cumic acid whereas this report is limited to derivatives of 3-nitrocumic acid. 3-Nitrocumic acid has been prepared by several methods (1, 2).

The 3-nitrocumic acid was prepared using fuming nitric acid as the nitrating agent because the time involved in the nitration was relatively short (thirty to thirty-five minutes). The possibility of obtaining dinitro and trinitro derivatives was lessened. This method was further justified by higher yields and ease of purification. Ethyl alcohol was found to be the crystallizing solvent of choice. Using this method of nitration and one crystallization from ethyl alcohol, pure 3-nitrocumic acid was obtained in yields of ninety per cent.

The 3-nitrocuminoyl chloride was prepared by using two different reagents—thionyl chloride and phosphorous pentachloride. The reaction proceeded smoothly with both reagents. Refluxing was necessary in the case of thionyl chloride and when the reaction had gone to completion the excess thionyl chloride was removed under reduced pressure. An excess of phosphorous pentachloride was used after which the phosphorous trichloride was removed under reduced pressure. Attempts to purify the 3-nitrocuminoyl chloride by distillation at atmospheric pressure and at a pressure of 1 mm. failed. At atmospheric pressure decomposition was almost complete with the evolution of hydrogen chloride gas and the deposition of a black residue in the distilling flask. At a pressure of 1 mm., decomposition was also excessive and a loss of fifty per cent was experienced in attempting to purify the 3-nitrocuminoyl chloride in this manner. The method finally adopted was that of removing the excess reagent under reduced pressure, avoiding any further heating after the removal of the excess reagent. Using the 3-nitrocuminoyl chloride obtained in this manner, esters were prepared in good yields and purified.

Due to the difficulty in obtaining purified 3-nitrocuminoyl chloride, it was thought advisable to attempt esterification by other means also. Thus two other methods were used. Esterification was carried out in the presence of dry hydrogen chloride gas and in the presence of phosphorous trichloride.

With the exception of one ester, all the esters prepared were liquids. The one solid ester, the methyl ester, was purified by recrystallization from ethyl alcohol.

The liquid esters of 3-nitrocumic acid could not be purified by distillation at atmospheric pressure.

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All distillations of these liquid esters were carried out at pressures of 1–3 mm. Even at these pressures some decomposition was evident, especially when distilling esters of higher molecular weight. It seems evident from this work that the introduction of the nitro group in the aromatic nucleus decreases stability and increases the rate of decomposition in these compounds at elevated temperatures. At pressures of 1–3 mm., esters with boiling points above 160–165° showed definite signs of decomposition on distillation.

An attempt has been made to produce 3-hydroxy-2-carboxy-4-isopropylbenzoic acid. The possibilities of such a compound with respect to its properties as an antiseptic or insect repellent, as compared to cumic acid, was the reason for attempting this synthesis.

The synthesis of 3-hydroxy-2-carboxy-4-isopropylbenzoic acid involved the use of thymol as a starting material, the first step being the introduction of the carboxyl group in position 2, then oxidation of the 1-methyl to a carboxyl group.

The production of the *o*-thymotinic acid was carried out by the method (4), of dissolving the thymol in dry xylene, treating with metallic sodium and dry carbon dioxide at atmospheric pressure and at the temperature of refluxing xylene.

The oxidation of the 1-methyl group to a carboxyl was the next step in the synthesis. Three possible methods were available. In order to obtain the exclusive oxidation of the 1-methyl group, two methods were eliminated. The acid-permanganate oxidation results in the oxidation of both the methyl and the isopropyl groups. Alkaline permanganate oxidizes the methyl group almost exclusively but will also introduce a hydroxyl group in the isopropyl group, replacing the hydrogen on the tertiary carbon. Since the methyl group of *p*-cymene can be oxidized almost exclusively, to produce cumic acid, by catalytic air oxidation of *p*-cymene (3), it was thought advisable to try this method. The *o*-thymotinic acid was dissolved in benzene and the oxidation attempted by passing air through the solution in the presence of a catalyst consisting of equal parts of anhydrous manganese and lead acetates, two per cent by weight of the *o*-thymotinic acid. The air oxidation was allowed to proceed for seventy-two hours. At the end of this time the benzene was removed and the solid obtained was crystallized from ethyl alcohol twice. On checking the melting point and the neutral equivalent it was concluded that the product was *o*-thymotinic acid and that the oxidation had not taken place. Thus the compound 3-hydroxy-2-carboxy-4-isopropylbenzoic acid was not obtained.

EXPERIMENTAL

The cumic acid available was of technical grade and was purified by recrystallizing from methyl or ethyl alcohol. These two solvents proved the most satisfactory from the standpoint of yield and purity of the product.

3-Nitrocumic Acid.—Five-grams cumic acid (m. p. 116–117°) was dissolved in 15 Gm. concentrated sulfuric acid and cooled on ice. The mixture was stirred vigorously while 4 Gm. of fuming nitric acid was added slowly in small portions over a period of fifteen minutes. After thirty minutes from the start of the reaction, stirring was stopped and the reaction mixture was poured into ice water. The mixture was then stirred for a period of ten to fifteen minutes. The precipitate of 3-nitrocumic acid was collected on a suction filter and washed with distilled water until the filtrate was clear. The washed and dried 3-nitrocumic acid was crystallized once from ethyl alcohol. The yield of purified 3-nitrocumic acid (m. p. 156–157°) was 5.7 Gm.

3-Nitrocuminoyl Chloride.—Thirty-grams purified thionyl chloride was added to 50 Gm. of 3-nitrocumic acid. The mixture was refluxed on a water-bath for two hours and at the end of that time the solution was a clear red color. The excess thionyl chloride was removed at a pressure of 15 mm. The resulting liquid was placed in a vacuum desiccator over calcium chloride and dried under reduced pressure.

Attempts to purify this compound by distillation at a pressure of 1 mm. proved unsatisfactory as heating caused serious decomposition. The 49 Gm. of 3-nitrocuminoyl chloride, obtained from 50 Gm. of 3-nitrocumic acid, was used to produce esters and the impurities were removed in the purification of the esters.

Esters of 3-Nitrocumic Acid.—The methyl and thymyl esters were prepared by reacting together a molecular equivalent weight of 3-nitrocuminoyl chloride with molecular equivalent weights of methyl alcohol and thymol, respectively. The excess 3-nitrocuminoyl chloride was hydrolyzed with 5% aqueous potassium hydroxide. The residue was then washed with distilled water until neutral. The methyl ester was twice crystallized from ethyl alcohol. The liquid thymyl ester was purified by distillation at reduced pressure. The reaction in the case of the thymyl ester was carried out using benzene as a solvent.

The ethyl, *n*-propyl, isopropyl, *n*-butyl, *n*-amyl, and *n*-hexyl esters were prepared by passing dry hydrogen chloride gas into molecular equivalent weights of 3-nitrocumic acid and the alcohol. The reaction was carried out at the refluxing temperature of the alcohol and for a period of two hours. The excess 3-nitrocumic acid was removed as the potassium salt after which the esters were washed with distilled water until neutral. After drying over anhydrous sodium sulfate these esters were purified by distillation at reduced pressure.

The phenylethyl ester was prepared using molecular equivalent weights of 3-nitrocumic acid and phenylethyl alcohol with a slight excess of the calculated amount of phosphorous trichloride, and dry xylene as the solvent. The reaction was carried out at the temperature of refluxing xylene for a period of two hours. The xylene was then removed under reduced pressure and the residue was washed with

TABLE I.—CONSTANTS OF ESTERS OF 3-NITROCUMIC ACID

Ester of 3-Nitrocumic Acid	B.p.	M.p.	Refractive Index n^{20}	Ester Value: Calculated Theoretical	Ester Value: Average (3 Samples) Obtained
Methyl	....	64° (2)	....	247.7	245.3
Ethyl	291–292° (2), with decomp.	....	....	234.3	232.8
n-Propyl	149–150° at 1 mm.	....	1.5140	222.2	220.4
Isopropyl	147–148° at 1 mm.	....	1.5120	220.4	217.6
n-Butyl	165–166° at 1 mm.	....	1.5130	208.9	205.3
n-Amyl	181–182° at 2 mm.	....	1.5112	199.0	196.9
n-Hexyl	194–195° at 2.5 mm.	....	1.5074	189.1	186.2
Thymyl	196–198° at 1 mm.	....	1.5445	160.8	157.2
Phenylethyl	....	....	1.5310	...	...

5% aqueous potassium hydroxide, then with distilled water until neutral, and finally dried over anhydrous sodium sulfate.

SUMMARY AND CONCLUSIONS

The technical cumic acid was purified using several methods but the most satisfactory one was that of crystallizing the cumic acid from methyl or ethyl alcohol.

Three methods were used for the preparation of the 3-nitrocumic acid. The one of choice involved the use of fuming nitric acid as the nitrating agent.

Thionyl chloride was considered to be more satisfactory than phosphorus pentachloride for the production of the 3-nitrocuminoyl chloride.

The 3-nitrocuminoyl chloride obtained was used to prepare the methyl and thymyl esters with satisfactory yields. By passing dry hydrogen chloride gas through a refluxing mixture of the alcohol and the 3-nitrocumic acid, the following esters were prepared: ethyl, propyl, isopropyl, *n*-butyl, *n*-amyl, *n*-hexyl. The phenylethyl ester was prepared using phosphorous trichloride.

The following constants of these esters were found and recorded: boiling point, melting point, refractive index, and ester value. The esters prepared were all yellow, odorless, oily liquids, with the exception of the methyl ester which was a crystalline solid.

o-Thymotinic acid was prepared and air oxidation of the 1-methyl group to a carboxyl group, to produce 2-carboxy-3-hydroxycumic acid, was unsuccessful.

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WHO MAKES IT?

The National Registry of Rare Chemicals, Armour Research Foundation, 33rd, Federal and Dearborn Streets, Chicago, Ill., seeks information on sources of supply for the following chemicals:

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Vinyl iodide
Tridecamethylene bromohydrin
1,3-Dimethyl-1,3-diphenylcyclobutane
1,4-Dihydropyrazine-2,3-dione
1,2-Dihydropyridazine-3,4-dione
1,2-Dihydropyridazine-3,6-dione
Xanthotoxin
7-Hydroxy-1-H-v-triazolo-(d)-pyrimidine
7-(α)-12-(α)-Dihydroxyprogesterone
Sulfanylthiourea
Phloretin
Erythrophleine
O,N-Diacetylsalicylamide
Coniferyl aldehyde