[Contribution from the Department of Chemistry, the State University of Iowa]

THE PREPARATION OF TIGLIC AND ANGELIC ACIDS AND ESTERS[1]

ROBERT E. BUCKLES and GENE V. MOCK

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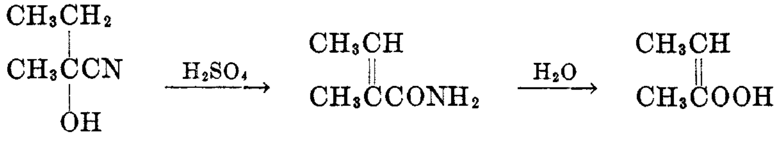
The methods of preparation most commonly applied to the synthesis of the isomeric α,β-dimethylacrylic acids, tiglic (I) and angelic (II) acids, involve the elimination of water from α-hydroxy-α-methylbutyric acid (1, 2, 3) or the elimination of acetic acid from β-acetoxy-α-methylbutyric acid (4). These methods were investigated but were found to be relatively unsatisfactory because of difficulties in separating the isomeric acids and because of low yields. It was desirable, therefore, to develop methods of preparation in which the acids could be isolated in the pure state in relatively high yields.

It was found that pure tiglic acid, the stable isomer, could be prepared in relatively large amounts by the action of 100% sulfuric acid on α-hydroxy-α-methylbutyronitrile (III) followed by hydrolysis to tiglic acid (I). This procedure is analogous to that used for the preparation of methacrylic acid and its derivatives (5, 6). The resulting tiglic acid (m.p. 61–64°) was easily isolated by steam-distillation from the reaction mixture. Yields of 40–53% based on 2-butanone were obtained in experiments involving 10 moles of ketone. If the acid was prepared by this method from α-hydroxy-α-methylbutyronitrile free of appreciable amounts of unchanged ketone, it was not contaminated with angelic acid. In some preparations of tiglic acid where unchanged ketone was present in the cyanohydrin large amounts of oily mixture were isolated along with lowered yields of tiglic acid. Tiglic acid and a small amount of angelic acid were isolated with some difficulty from one such oily mixture.

Tiglic acid (I) was converted by a three-step process to its labile isomer, angelic acid (II) in 33% yield. The addition of bromine to tiglic acid gave an 86% yield of α,β-dibromo-α-methylbutyric acid (IV) (7, 8), which in turn was treated with 25% methanolic potassium hydroxide to yield (62.5%) β-bromoangelic acid (V) (9). Reduction of the bromo acid with 9% sodium amalgam in water gave 61% yield of angelic acid (m.p. 44–46°) (10, 11). This synthesis represents an improvement over the methods reported in the literature. The angelic acid obtained was uncontaminated by tiglic acid and thus was easily purified.



$$\begin{array}{c}CH_3CH_2\\ |\\ CH_3CCN\\ |\\ OH\end{array} \xrightarrow{H_2SO_4} \begin{array}{c}CH_3CH\\ \|\\ CH_3CCONH_2\end{array} \xrightarrow{H_2O} \begin{array}{c}CH_3CH\\ \|\\ CH_3COOH\end{array}$$

II I

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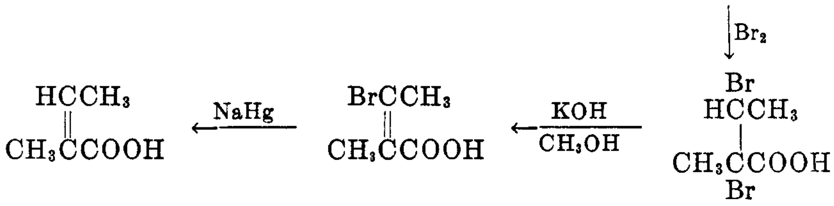
[1] Abstracted from a thesis presented by Gene V. Mock to the Graduate College of the State University of Iowa in partial fulfillment of the requirements for the Ph.D. degree, February 1949. Du Pont Predoctoral Fellow, 1947–1948. Present address: E. I. du Pont de Nemours and Company, Wilmington, Delaware.



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The methyl and ethyl esters of tiglic acid were prepared most conveniently by direct esterification of the acid. The dehydration of ethyl α-hydroxy-α-methylbutyrate (12) was relatively unsatisfactory for the synthesis of ethyl tiglate. Complex mixtures, which presumably contained all the possible dehydration products as well as the starting material, were obtained. These mixtures could be separated only by careful fractionation to give ethyl tiglate in relatively low yields and of questionable purity.

Methyl angelate was prepared in 70% yield by the reaction of potassium angelate with methyl iodide as reported by Naster and Gavriloff (3). The identity of the product was established by saponification to angelic acid. One sample of the oily by-product (known to contain angelic acid) from the synthesis of tiglic acid was esterified with ethyl alcohol. The mixture of esters was fractionated carefully. The product with properties identifying it as ethyl angelate (13) yielded very impure tiglic acid when saponified. Thus, it is not possible to guarantee the identity and purity of these esters on the basis of physical properties alone.

EXPERIMENTAL

Tiglic acid (I). A mixture of 720 g. (894 ml., 10 moles) of 2-butanone and 10 ml. of a saturated aqueous solution of potassium cyanide was warmed to 30–35°, and 310 g. (11.5 moles) of anhydrous hydrogen cyanide was distilled into the mixture. The reaction was exothermic and frequently the temperature rose to 60–80° during the addition. After the reaction was complete the solution was cooled to 0° and the potassium cyanide was neutralized with a slight excess (about 10 ml.) of concentrated sulfuric acid so that the decomposition of the cyanohydrin would be suppressed.

This crude α-hydroxy-α-methylbutyronitrile was added slowly to 1470 g. (15 moles) of 100% sulfuric acid (m.p. 10.5°) maintained at 75–80°. The reaction was exothermic and required rapid stirring. The resulting mixture was usually orange-red. The mixture was heated to 125–130° for one hour while being rapidly stirred. Any foaming and blackening observed during this heating signified a lower yield of tiglic acid and the production of an oily mixture as a by-product. The reaction mixture was boiled under reflux for two hours after 720 ml. (40 moles) of water was added. To the solution 500 g. of anhydrous sodium sulfate was added, and the mixture was distilled with steam. The distillate was collected in a receiver cooled in an ice-bath. The solid tiglic acid was collected to give a 400–525-g. (40–53%) yield of product, m.p. 62–64°.

In one experiment 168 g. of the oily by-product was obtained along with 316 g. of tiglic acid. Two fractional distillations of the oil yielded 38 g. of tiglic acid, b.p. 95–97° (12 mm.) and 129 g. of an oil, b.p. 88–95° (12 mm.) from which 11.0 g. of angelic acid, m.p. 42–45°, crystallized. Thus, a 35% yield of tiglic acid and a 1.1% yield of angelic acid were obtained.

In another experiment 295 g. of crude tiglic acid and 249 g. of oily by-product were obtained. The by-product was esterified as described for the synthesis of ethyl tiglate. Fractionation yielded 60 ml. of ethyl tiglate, b.p. 152–154°, n_D^{20} 1.4340, and 73 g. of ester, b.p. 140–144°, n_D^{20} 1.4284, d_4^{20} 0.916. This latter product has the reported properties of ethyl angelate (13). Saponification of 72 g. (0.56 mole) of this ester yielded 35 g. (63%) of crude tiglic acid, m.p. 48–60°.

α-Hydroxy-α-methylbutyronitrile (III). To a mixture of 886 g. (1101 ml., 12.3 moles) of 2-butanone and a solution of 500 g. (9.7 moles) of sodium cyanide in 1200 ml. of water was added slowly 2100 ml. (8.5 moles) of 40% sulfuric acid. After the addition the organic layer was separated from the aqueous layer which was extracted with ether. The ether solution of cyanohydrin was dried over sodium sulfate and distilled under reduced pressure. An 878-g. yield (72%) of the cyanohydrin, b.p. 92–93° (20 mm.), was obtained. This method is similar to that used in the synthesis of acetone cyanohydrin (14). α-Hydroxy-α-methylbutyronitrile was also prepared in 70% yield by the action of a sodium cyanide-sodium bisulfite mixture on 2-butanone (2).

The pure cyanohydrin could be used in the synthesis of tiglic acid, but the yields were no better than those obtained directly from the ketone.

α,β-Dibromo-α-methylbutyric acid (IV). A mixture of 100 g. (1.0 mole) of tiglic acid in 200 ml. of anhydrous carbon tetrachloride and 160 g. (1.0 mole) of bromine was allowed to stand overnight and was then boiled under reflux until the solution was light orange. The solvent was removed by evaporation and the solid residue was crystallized from ligroin to yield 222 g. (86%) of α,β-dibromo-α-methylbutyric acid, m.p. 82–88°.

β-Bromoangelic acid (V). To a solution of 130 g. (0.50 mole) of α,β-dibromo-α-methylbutyric acid in 70 ml. of methanol was added slowly 700 g. of a 25% solution of potassium hydroxide in methanol. Anhydrous potassium carbonate (13 g.) was added to suppress decarboxylation. The temperature of the reaction mixture was raised to 55° where it was held for two hours. Excess potassium hydroxide was removed by bubbling carbon dioxide through the reaction mixture. The mixture was filtered while warm and the filtered salt was washed with 500 ml. of warm methanol. The methanol solutions were combined and most of the solvent removed by distillation. The residue was evaporated to dryness, dissolved in 100 ml. of water, and acidified to Congo Red with 6 *N* hydrochloric acid. The product was filtered, dried, and crystallized from ligroin to yield 56.4 g. (62.5%) of β-bromoangelic acid, m.p. 92–94.5°.

Angelic acid (II). To a mixture of 18 g. (0.1 mole) of β-bromoangelic acid in 135 ml. of water cooled to 5° was added in small pieces 396 g. (1.57 gram-atoms of sodium) of 9% sodium amalgam. The mixture was stirred slowly for 48 hours. The aqueous layer was separated from the mercury which was washed with 10 ml. of water. The combined aqueous solutions were acidified to Congo Red with concentrated hydrochloric acid. The precipitated product was dried, and crystallized from ligroin to yield 6.1 g. (61%) of angelic acid, m.p. 44–46°.

Ethyl tiglate. A mixture of 50 g. (0.50 mole) of tiglic acid, 92 g. (2 moles) of absolute ethanol, 234 g. of benzene, and 10 ml. of concentrated sulfuric acid was boiled for 24 hours under reflux in a Soxhlet extraction apparatus. The Soxhlet thimble contained 50 g. of calcium carbide. Excess alcohol and benzene were removed by distillation. The residue was treated with an equal volume of water and the organic product was extracted with ether. The ether extract was washed with 10% sodium bicarbonate and dried over sodium sulfate. Fractional distillation yielded 47–52 g. (74–80%) of ethyl tiglate, b.p. 153–156° (760 mm.), n_D^{20} 1.4347, d_4^{20} 0.9226. These properties check those found by von Auwers (13). This general method of esterification is that of Thielepape (15).

Dehydration of ethyl α-hydroxy-α-methylbutyrate. A sample of 150 g. (1.03 moles) of ethyl α-hydroxy-α-methylbutyrate[2] was treated with 90 g. (0.66 mole) of phosphorus trichloride at 5° according to the method of Higginbotham and Lapworth (12). After two fractional distillations 63 g. (48%) of ethyl tiglate, b.p. 71–75° (40 mm.), n_D^{20} 1.4329 was obtained.

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[2] This compound was kindly supplied by Rohm and Haas Co. Philadelphia, Pa.

The saponification of 10 g. (0.078 mole) of this ester yielded 2.0 g. (26%) of tiglic acid, m.p. 63–64°.

Similar dehydrations of ethyl α-hydroxy-α-methylbutyrate with chlorosulfonic acid, phosphorus pentoxide, phosphorus oxychloride, and thionyl chloride gave much lower yields of impure ethyl tiglate along with unidentified fractions.

Methyl tiglate. A mixture of 100 g. (1 mole) of tiglic acid, 256 g. (8 moles) of methanol, and 20 ml. of concentrated sulfuric acid was boiled under reflux for 12 hours. The ester was isolated in a manner similar to that used for ethyl tiglate. A 74.2-g. (65%) yield of methyl tiglate, b.p. 137.5–138.8° (757 mm.), n_D^{20} 1.4371, was obtained. These properties check those in the literature (3).

Methyl tiglate was also prepared by the addition of 2 l. (50 moles) of methanol and 90 ml. (5 moles) of water instead of 720 ml. of water to the cyanohydrin-sulfuric acid mixture obtained during a 10-mole preparation of tiglic acid. The methanol solution was boiled under reflux for 24 hours. All the volatile material was distilled and methyl tiglate was separated from the distillate. More crude methyl tiglate was obtained from the residue on dilution with water. Fractionation yielded 470 g. (41% based on 2-butanone) of methyl tiglate, b.p. 138–140° (760 mm.), n_D^{20} 1.4351. Saponification of 2.0 g. (0.018 mole) of this methyl tiglate yielded 1.5 g. (83%) of tiglic acid, m.p. 61–63°.

Methyl angelate. A mixture of 10.0 g. (0.10 mole) of angelic acid, 8.0 g. (0.058 mole) of anhydrous potassium carbonate, and 150 ml. of methanol was heated until the vigorous effervescence subsided. The solution was cooled somewhat and 12 ml. (21.4 g., 0.15 mole) of methyl iodide was added. The mixture was boiled gently under reflux for 28 hours, and carefully distilled until 100 ml. of methanol had been removed. Two ml. of methyl iodide was added to the residue which was heated gently for one hour. The solution was then treated with 100 ml. of water, and the ester layer was separated. The water layer was extracted with ether. The combined ether and ester solution was washed with 2% aqueous sodium bisulfite and then with a dilute silver nitrate solution. After the silver nitrate solution had been thoroughly shaken with the ether solution to remove all of the iodide ion, an excess of sodium chloride was added. The ether solution was dried over potassium carbonate and fractionally distilled. A 7.2-g. (63%) yield of methyl angelate, b.p. 127.2–128.0° (745 mm.), n_D^{20} 1.4330, d_4^{20} 0.933, was obtained. The hold-up of the fractionating column was 0.8 g. (7%). There was no residue. The properties of the methyl angelate check those reported (3).

A 2.0-g. (0.018 mole) sample of methyl angelate was dissolved in 10 ml. of methanol, and 2.0 ml. of 40% aqueous sodium hydroxide was added. The solution was allowed to stand at room temperature overnight, and then to evaporate to dryness. About 10 ml. of water was added, and the mixture was acidified to Congo Red with concentrated hydrochloric acid. A 1.4-g. (80%) yield of angelic acid, m.p. 42–44° was isolated by filtration and ether-extraction of the filtrate.

SUMMARY

1. Tiglic acid free of isomeric acids has been synthesized in 40–53% yields from 10 moles of 2-butanone. Angelic acid free of appreciable amounts of isomeric acids has been synthesized from tiglic acid in 33% yield by a three-step process.

2. Pure methyl and ethyl tiglate have been prepared by direct esterification of tiglic acid. Methyl angelate of confirmed identity has been prepared by a replacement reaction of angelate ion with methyl iodide.

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