

[CONTRIBUTION FROM THE CHEMICAL LABORATORY, UNIVERSITY OF CALIFORNIA]

The Preparation and Asymmetric Reduction of β -Methylcinnamic Acid

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H. Erlenmeyer¹ brominated the hydrocinchonine and glucamine salts of cinnamic acid and found that the cinnamic acid dibromide was optically active. The glucamine salt was brominated using only the solid salt, but the hydrocinchonine salt was brominated in chloroform solution as well, under which condition activity of the isolated dibromo acid corresponding to 8% asymmetric synthesis was observed. These experiments have been repeated by us and the results verified.

It is apparent that in chloroform solution the amine and acid are united in such a way as to produce a coupling of the electrical fields of both molecules which extends beyond the three atoms, $-N-H-O-$, involved in a possible hydrogen bond and includes the asymmetric center of the base and the olefinic bond of the acid. This is not surprising in view of the associated character of such salts in chloroform, but it indicates that the mutual electrical inductions in such salts may be as strong as the intramolecular induction in esters.² Vavon and Jakubowicz³ studied the platinum-catalyzed hydrogenation of six optically active esters of β -methylcinnamic acid. They found that the β -phenylbutyric acid isolated after saponification had a specific rotation in benzene ($\lambda = 5461 \text{ \AA.}$) varying from $+13.3$ to -6.1° , corresponding to as much as 19% asymmetric synthesis.

The present paper describes improved syntheses of β -methylcinnamic and β -(α -naphthyl)-cinnamic acids, and their asymmetric reduction as hydrocinchonine salts.

Preparation of β -Methylcinnamic Acid.—The method of Stoermer, Grimm and Laage⁴ has been modified to ensure reproducibility and greater purity of product. Acetophenone (240 g.), 20–30 mesh granulated zinc (196 g.) and sodium-dry benzene (850 ml.) were placed in a 3-liter three-necked flask fitted with a reflux condenser, mercury-sealed stirrer and a dropping funnel. All outlets to the air were

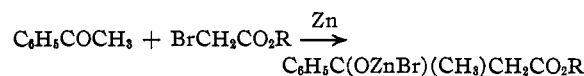
(1) H. Erlenmeyer, *Helv. Chim. Acta*, **13**, 731 (1930).

(2) The fact that racemic acids are resolved through fractional crystallization of their salts with active bases gives no evidence as to the molecular forces present in the individual molecules, as no resolution is found unless a crystalline phase separates.

(3) Vavon and Jakubowicz, *Compt. rend.*, **196**, 1614 (1933); *Bull. soc. chim.*, [4] **53**, 1111 (1933).

(4) Stoermer, Grimm and Laage, *Ber.*, **50**, 965 (1917). See also Rupe, *Ann.*, **369**, 321 (1909), and Nieuwland and Daly, *This Journal*, **53**, 1842 (1931).

closed by drying tubes. The mixture was heated to gentle refluxing on a steam-bath and then the addition of 234 g. of freshly distilled ethyl bromoacetate dissolved in 150 ml. of dry benzene started. This addition was carried out over a period of ten to twelve hours, with continual refluxing and stirring; the heating and stirring were then continued for another six hours. Under these conditions one mole of zinc reacts per mole of the other reagents.



A competing condensation reaction using one-half this amount of zinc, producing succinic ester, is inhibited by keeping a low concentration of bromoacetic ester and through the use of a large excess of zinc. Similarly reaction of the intermediate zinc derivatives with the ester group likewise is retarded by the slow addition of the ester.

The cooled reaction mixture was decanted from the unused zinc and washed with 400 ml. of 6 *N* hydrochloric acid and 200 ml. of water. Without drying, the mixture was then refluxed by means of an oil-bath in a 3-liter flask fitted with a Dean and Stark⁵ tube which was equipped with a stopcock to remove water collected from the reflux. When the water level in the tube had remained constant for half an hour, the water was drawn off and 5 ml. of phosphorus oxychloride added to the flask. Refluxing was then continued until the water collected was again constant (about one-half hour). This portion of water represents the water formed in the catalytic dehydration of the ester and is a good indication of the eventual yield. The benzene was now allowed to distill off, taking care that the oil-bath did not rise above 130° and that prolonged distillation was avoided.

The ester residue was hydrolyzed by adding two liters of 1 *N* methanolic potassium hydroxide and 45 ml. of 40% aqueous potassium hydroxide and refluxing for one and one-half hours. The methanol was then removed by steam distillation and the cooled aqueous residue extracted with ether to remove alkali-insoluble by-products. The latter represented a large portion of the reaction products and contained little acetophenone as such. The aqueous layer was added to one liter of ether and then acidified with 450 ml. of ice-cold 6 *N* sulfuric acid. Two additional ether extracts of 200 ml. each were made and the combined ether extracts dried and the ether distilled off. The crude β -methylcinnamic acid was distilled at 1 mm. pressure, or less, using a 500-ml. Claisen flask with a wide side arm: b. p. (0.6 mm.) $124-127^\circ$; b. p. (1 mm.) $135-136^\circ$ uncorr.; yield 133.6 g. or 41%.

The vacuum distilled product was a slightly yellowish, crystalline solid containing a considerable amount of low-melting material, probably a solid solution of *cis* and *trans* isomers. To remove this, the product was placed in a 500-ml. wide-mouthed flask fitted with a reflux condenser and thermometer whose bulb rested on the bottom of the flask.

(5) Dean and Stark, *Ind. Eng. Chem.*, **12**, 486 (1920).

About 35 ml. of pentane was added and refluxed until the boiling point was constant. After cooling, the liquid phase was removed through an immersion filter and the pentane extraction repeated several times until successive extracts had the same boiling point. The remaining solid (the *trans* isomer) was dissolved in ligroin (b. p. 90–100°), using 225 ml. of solvent per 100 g. of acid, charcoal treated, and recrystallized; m. p. 98.4–98.7° corr.; yield, 89 g. or 27%. To remove any possible catalyst poison the product was recrystallized from aqueous methanol, 560 ml. of methanol and 720 ml. of water per 100 g. of acid.

None of the acid fractions gave the lemon-yellow color or intense violet color in concentrated sulfuric acid noted by the above authors and attributed to the stable and labile acids, respectively.

Preparation of β -(α -Naphthyl)-cinnamic Acid.—This acid was prepared by essentially the same procedure as used for the methyl derivative, substituting α -naphthyl phenyl ketone prepared by the method described by Fieser⁶ for the acetophenone. The crude yield varied from 55–72%, and it is significant that the alkali-insoluble saponification product was nearly pure α -naphthyl phenyl ketone. The yield of acid was virtually 100% based on the ketone actually consumed. It was purified by crystallization from carbon tetrachloride, acetic acid or absolute ethanol; m. p. 213.1–214.0° corr.

Hydrocinchonine was prepared by catalytic hydrogenation of cinchonine, using palladium chloride as catalyst;⁷ crystallization was from dioxane, m. p. 275° corr. (dec.); $[\alpha]_D^{25} + 214^\circ$ (0.0223 *M* hydrocinchonine in 0.024 *M* aqueous HCl).

Reduction of Hydrocinchonine β -Methylcinnamate by Hydrogen.—The first reduction was carried out in an 0.0434 *M* solution of the salt in absolute ethanol, using 0.076 g. of Adams platinum oxide per each 100 ml. of solution. The catalyst was forty-eight days old. Hydrogen was introduced at a pressure of 41 lb. (3 atm.) per square inch, with vigorous shaking; the reaction was complete in four and one-half hours at room temperature. Special care was used to remove the dextrorotatory hydrocinchonine from the acid. After removing the ethanol by vacuum distillation, the residue was treated with benzene and excess dilute sulfuric acid at room temperature. Three successive acid extracts eventually showed no optical activity nor a test for alkaloid with KBiI_4 . The optical activity of the benzene solution, assuming a quantitative reduction and recovery, indicated $[\alpha]_{461}^{25} + 5^\circ$. An alkaline extract of the benzene solution, using 0.1 *N* NaOH, gave an observed rotation of $+0.062^\circ$, corresponding to $[\alpha]_{461}^{25} + 3^\circ$. Finally the free acid was recovered in benzene again and the benzene evaporated. The residue at constant weight amounted to 1.07 g. of sirupy liquid; dissolved in benzene at a dilution of 0.065 g./ml., $\alpha = +0.629^\circ$ in a 2-dm. tube or $[\alpha]_{461}^{25} + 4.5^\circ$. This corresponds to about 8–9% asymmetric synthesis.

A second reduction was made under approximately the same conditions except that the hydrogen pressure was 760 mm., the temperature 25.0°, and using a catalyst twenty-four days old. The recovered β -phenylbutyric acid had an activity of $[\alpha]_{461}^{25} + 0.64^\circ$ in benzene.

(6) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1935, pp. 192–196.

(7) Haidelberger and Jacobs, THIS JOURNAL, 41, 817 (1919).

Reduction of Hydrocinchonine β -(α -Naphthyl)-cinnamate.—The reduction was carried out in 0.05 *M* ethanol solution using 0.106 g. of catalyst in 100 ml. of solution. The temperature was 25.0° and the pressure of hydrogen 760 mm. The recovered reduced acid had an activity corresponding to $[\alpha]_{461}^{25} - 0.5^\circ$ in chloroform solution.

Discussion

The poor and sometimes erratic yields in the Reformatsky reaction employed in these preparations may be attributed to condensations of the bromoacetic ester with itself, producing eventually water-soluble products after saponification. This is clearly indicated in the condensation using α -naphthyl phenyl ketone, in which the unsaponifiable fraction was largely unchanged ketone. The yield of desired condensation product was quantitative on the basis of used ketone, with complete disappearance of the bromoacetic ester and the quantitative consumption of zinc. In the case of acetophenone further side reactions are self-condensation to *sym*-triphenylbenzene (recovered in some experiments) and possibly Claisen-type condensation with the bromoacetic ester to form ketonic products. In this case the alkali-insoluble saponification product was not simply unused ketone, and the yields are uniformly poorer than in the condensation with the purely aromatic ketone. The slow addition of bromoacetic ester to the reaction mixture produces a consistent and apparently nearly maximum yield; the procedure is employable on any scale of operation.

The fact that heterogeneous hydrogenation of these alkaloid salts in alcohol solution leads to partial asymmetric synthesis of the reduced acids indicates that adsorption of these polar substances has not prevented the molecular inductions responsible for the specificity.

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Summary

A procedure for the Reformatsky condensation of aromatic ketones and bromoacetic ester leading to maximum yields and applicable to any scale of operation is given.

The hydrocinchonine salts of β -methylcinnamic acid and β -(α -naphthyl)-cinnamic acid are catalytically reduced in ethanol solution by hydrogen to produce optically active β -phenylbutyric acid and β -(α -naphthyl)-hydrocinnamic acid, respectively.