

NOTES

The Synthesis of β -(3-Substituted-4-acetamidobenzoyl)acrylic AcidsC. S. PANDE*¹ and S. K. GANDHI

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The study of the structural features of many natural and synthetic substances possessing antibiotic activity led Geiger and Conn to believe that the $-\text{CH}=\overset{\text{I}}{\text{C}}-\text{CO}-$ group was responsible for such activity in these compounds.¹⁾ It has since been discovered that β -aroylacrylic acids have a pronounced *in vitro* activity against many gram-negative organisms and several strains of *Staphylococcus aureus*. Many of them have also been reported to possess a fungistatic activity *in vitro*.²⁾

β -Aroylacrylic acids are very useful intermediates for the synthesis of pyridazones and asymmetric malein-type dyes and as dienophiles in Diene synthesis. The introduction of an amino group into the aromatic nucleus increases their versatility even further.

The reaction was carried out at low temperatures in a carbon disulfide medium. It was observed that, with ortho-substituted acetanilides, the reaction proceeded smoothly, whereas the corresponding meta- and para-substituted compounds failed to react. One possible explanation is that, in the latter cases, the carbon atom of benzene rings likely to be attacked is, to some extent, sterically hindered. Substitution always took place at the para-position to the acetamido group.

The position of the substitution was ascertained by oxidising the products with alkaline potassium permanganate. I gave the known 4-acetamidoisophthalic acid, while II and III produced 3-methoxy and 3-ethoxy 4-acetamidobenzoic acids. On hydrolysis and deamination, these gave the known *m*-anisic acid and *m*-ethoxybenzoic acid respectively, thus proving their structures. In analogy with I and otherwise, there is no likelihood of the side chain being at the position ortho to the acetamido group (a condition not covered by the above reaction).

All the acids are yellow and form a deep yellow

solution in alkali. They are sparingly soluble in cold ethanol and methanol, but readily so in hot.

Experimental

The melting points are uncorrected. The yields reported are for single experimental runs and are not the maximum obtainable.

β -(3-Methyl-4-acetamidobenzoyl)acrylic Acid (I). 23.3 g of anhydrous aluminum chloride were added to 100 ml of dry carbon disulfide in a three-necked flask fitted with a mechanical stirrer and other accessories as for carrying out a Friedel-Crafts reaction. The flask was cooled in an ice bath, and to it there was gradually added a fine-ground mixture of 6 g of maleic anhydride and 7.5 g of aceto-*o*-toluidide, followed by 50 ml of carbon disulfide. After half an hour the ice bath was removed and the flask was allowed to come to room temperature. The reaction mixture turned yellow and viscous. After 20 hr the contents were decomposed with ice and hydrochloric acid. Yellow powder was filtered out, dissolved in 5% sodium carbonate, reprecipitated with hydrochloric acid, and recrystallized from hot ethanol in the form of light yellow crystals; mp 222°C; yield, 35%.

Found: C, 63.0; H, 5.31; N, 5.70%. Calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_4$: C, 63.16; H, 5.26; N, 5.67%.

The Oxidation of I. 0.5 g of I was oxidised with alkaline potassium permanganate at room temperature. A white crystalline acid was thus obtained, mp 295°C, it was identified as 4-acetamidoisophthalic acid.

β -(3-Methoxy-4-acetamidobenzoyl)acrylic Acid (II). It was prepared with the same method as I with the modification that the mixture in carbon disulfide was refluxed for half an hour before it was allowed to stand overnight at room temperature. The acid was recrystallized from hot ethanol in the form of yellow crystals; mp 223–224°C; yield, 30%.

Found: C, 59.18; H, 5.10; N, 5.38%. Calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_5$: C, 59.3; H, 4.94; N, 5.32%.

The Oxidation of II. 0.5 g of II was taken in alkali and oxidised with potassium permanganate. The product was an almost colorless acid which was sparingly soluble in hot ethanol, methanol and acetone. The crystals obtained from hot ethanol had a faint yellow color, giving a colorless solution in alkali, mp 283–285°C (with a red melt).

Found: C, 57.36; H, 5.30; N, 6.66%; neutral. equiv., 212. Calcd for $\text{C}_9\text{H}_9\text{NO}_2\text{-COOH}$: C, 57.42; H, 5.26; N, 6.7%; neutral. equiv., 209.

The acid was refluxed with aqueous methanolic

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1) W. B. Geiger and J. E. Conn, *J. Am. Chem. Soc.*, **67**, 112 (1945).

2) D. Papa, E. Schwenk, F. Villan and E. Klingsberg, *ibid.*, **70**, 3356 (1948).

sodium hydroxide for half an hour, at the end of which the methanol was distilled out and the solution made acidic with hydrochloric acid. The solution of amine hydrochloride was diazotized and deaminated with formaldehyde according to the method of Brewster and Poje.³⁾ The resulting compound, on purification, melted at 105°C and did not depress the melting point of a pure sample of *m*-anisic acid.

β -(3-Ethoxy-4-acetamidobenzoyl)acrylic Acid (III). It was prepared by the method described for II. The acid was obtained in the form of yellow crystals from hot ethyl acetate, in which it was sparingly soluble, mp 203°C; yield, 25%.

Found: C, 60.71; H, 5.50; N, 4.93%. Calcd for $C_{14}H_{13}NO_5$: C, 60.64; H, 5.41; N, 5.05%.

3) R. Q. Brewster and J. A. Poje, *ibid.*, **61**, 2418 (1939).

The Oxidation of III. 0.5 g of III was oxidised in the same manner as II. The resulting acid was a colorless, crystalline solid, slightly soluble in hot ethanol and methanol, mp 269°C.

Found: C, 59.30; H, 5.77; N, 6.34%; neutral. equiv., 230. Calcd for $C_{10}H_{12}NO_2-COOH$: C, 59.2; H, 5.83; N, 6.28%; neutral. equiv., 223.

The acid was hydrolysed and deaminated similarly. The product, melting at 137°C, was identified as *m*-ethoxy benzoic acid.

The Attempted Friedel-Crafts Reaction of Maleic Anhydride with Meta- and Para-acetotoluides, Anisidides and Phenetidides. The reaction was performed under the same conditions as have been described for aceto-orthotoluidide. The reaction mixture did not turn yellow or viscous, and the acetylated amines were recovered unchanged.