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SYNTHESIS OF 5-NITROFURYL-2- AND FURYL-2-PROPIOLIC ACID

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Nitration of methyl furyl-2-propiolate in acetic anhydride at −25° gives methyl 5-nitrofuryl-2-propiolate in good yield. Methods for preparing furyl-2-propiolic acid and its methyl ester are described.

5-Nitrofuryl-2-propiolic acid (I) is very interesting as a starting material for synthesizing antibacterial compounds of a new type containing both the nitrofuryl group and an acetylenic bond. Hitherto no satisfactory method of synthesizing this acid has existed. Recently, Kai and Ogawa [1] published a paper on the preparation of I by alkali dehydrobromination of methyl 3-(5-nitrofuryl-2)-2, 3-dibromopropionic acid in butanol solution at 50°. A check on this method showed that, because of the sensitivity of the 5-nitrofuran ring to alkalies, dehydrobromination is accompanied by resinification, and that this cuts the yield of 5-nitrofuryl-2-propiolic acid.

An attempt was made to prepare I by nitrating furyl-2-propiolic acid (II) under conditions closely resembling those used for nitrating β-(furyl-2)acrylic acid [2]. The approach is justified by the successes obtained in nitrating α, β unsaturated furan aldehydes, ketones, and carboxylic acids [2-5], as well as furylarylketones containing an acetylenic link [6], but in this case nitration of II was accompanied by extensive resinification, and it proved impossible to isolate individual products. On the other hand, nitration of methyl furyl-2-propiolate (IV) in acetic anhydride, with nitric acid and in the presence of catalytic amounts of sulfuric acid, at −25°, proceeds successfully. Methyl 5-nitrofuryl-2-propiolate (V) is obtained in about 60% yield.

Hydrolysis of V with an equimolecular amount of potassium hydroxide in butanol at 50° gives I. V and I prepared by these methods are identical with the compounds obtained by dehydrobromination of methyl 3-(5-nitrofuryl-2)2, 3-dibromopropionate [1].

Some difficulties had to be overcome in the synthesis of the starting compound II. The literature method [7] of Iotsich, carboxylation of 2-furylacetylene, is unsuitable for preparative purposes, because of the difficult nature of the method, and the low stability of the starting material. Equally ineffective was [8] debromination of 5-bromofuryl-2-propiolic acid with zinc dust [9]. It proved impossible to repeat a recently described variant of the synthesis of II, using the Wittig reaction and pyromucic chloroanhydride [10, 11]. More suitable preparatively was dehydrobromination of ethyl α-bromo-β-(furyl-2)acrylate (III), which in its turn was prepared using the Wittig reaction [12]. Successful dehydrobromination of III requires careful maintenance of optimum reaction conditions. For example, when the concentration of potassium hydroxide in the alcoholic solution is over 20%, dehydrobromination of III is accompanied by hydration and decarboxylation of the furyl-2-propiolic acid to methyl-2-furylketone. Moreover, there are certain difficulties to overcome in freeing the product from the bromo compounds which it usually contains. It was found that purification was best effected by fractionally distilling methyl furyl-2-propiolate (IV). The ester obtained in that way is pure enough for the subsequent syntheses. On saponification it gives pure acid II.

Experimental

Furyl-2-propiolic acid (II). A solution of 2.45 g (10 mmole) ethyl α-bromo-β-(furyl-2)acrylic acid (III) and 2.24 g (40 mmole) potassium hydroxide in 40 ml methanol was refluxed for 4 hr. The reaction products were neutralized and brought to pH 6-7 with dilute hydrochloric acid, the alcohol distilled off, the residue dissolved in water, made acid to congo red with hydrochloric acid, and extracted with ether. After removing the solvent there remained 0.98 g II (72%), mp 100-103°.

Methyl furyl-2-propiolate (IV).

a) A mixture of 3.4 g (25 mmole) acid II, 30 ml methanol, and 0.17 ml conc. H_2SO_4 was refluxed for 3 hr, the solvent distilled off under reduced pressure, the residue diluted with 30 ml water and extracted with ether. The extract was neutralized with a solution of sodium bicarbonate, dried, and distilled. Repeated distillation gave IV, bp 82-84° (3 mm), yield 1.5 g (40%). The product was dissolved in ether and run through an alumina column. After removal of

solvent, there were obtained crystals, mp 26-28°. Found: C 64.15; H 4.20%. Calculated for $C_3H_6O_3$: C 64.00; H 4.00%. UV spectrum in alcohol λ_{max} 280 mμ; lg ε 4.24.

b) An etheral solution of diazomethane prepared from 5 g nitrosomethylurea was added to a solution of 0.63 g (4.6 mmole) acid II in 20 ml ether. The mixture was left for 1 hr at room temperature, then washed with a solution of sodium carbonate. After drying, the ether was distilled off, and the residue then distilled under reduced pressure, when there was obtained 0.44 g IV (63.6%), bp 80-87° (3 mm).

Saponification of methyl furyl-2-propiolate (IV). A solution of 1.5 g (10 mmole) ester IV and 1.12 g (20 mmole) potassium hydroxide in 20 ml methanol was left for 12 hr at room temperature. The mixture was then neutralized with dilute hydrochloric acid, and brought to pH 6-7, the alcohol distilled off, the residue dissolved in water, the solution made acid to congo red with hydrochloric acid, and then extracted with ether. The ether solution was purified by passage through a column of alumina. After removing the solvent, there was obtained 1.04 g (76.7%) II, mp 108.5-109°. Found: C 61.85; H 3.17%. Calculated for $C_7H_4O_3$: C 61.76; H 2.94%.

Methyl 5-nitrofuryl-2-propiolate (V). A nitration mixture was prepared by adding, with exclusion of moisture, 1.9 g (30 mmole) nitric acid (d 1.52) and 0.05 ml concentrated sulfuric acid, to 7 ml acetic anhydride. It was then maintained at −25°, and a solution of 1.5 g (10 mmole) methyl furyl-2-propiolate (IV) in 3 ml acetic anhydride added. The reaction mixture turned green, then dark brown. After keeping at the same temperature for 15 min, the reaction products were poured on to 15 g ice and 15 ml water, and the whole stirred for 2 hr. A brown oil separated. The aqueous layer was twice extracted with 25 ml ether, the ether extracts and oily material were united, and washed with 10% sodium acetate solution. The ether extract was dried over anhydrous sodium sulfate, and run through a column of 5 g activated alumina, after which the solvent was distilled off. The brown oil remaining was dissolved in 3 ml acetone, a solution of 1.36 g crystalline sodium acetate in 1 ml water added, the whole held at 50° for 15 min, poured into 100 ml water, and left overnight at 0°. The pale yellow crystals which formed were filtered off with suction, washed with a small amount of water, and dried in a vacuum over P_2O_5. Yield of V 1.19 g (61%), mp 65-70°. After further purification of V by passage through an activated alumina column, followed by recrystallization from methanol, it had mp 77-78° (literature [1] mp 75-76°). Mixed mp with a specimen prepared by another method [1], undepressed. UV spectrum in alcohol, λ_{max} mμ (lg ε): 224 (3.89), 318 (4.25). IR spectrum, ν cm^{-1}: 2230 (—C≡C—), 1708 (C=O), 1508, 1362 (NO_2). UV and IR spectra found for V prepared by another method [1], were completely identical with the above.

5-Nitrofuryl-2-propiolic acid (I). 0.05 g (0.25 mmole) V was dissolved in 1 ml butanol, the solution heated to 50°, a solution of 0.014 g (0.25 mmole) potassium hydroxide in butanol added, and the whole left an hour in a refrigerator. The precipitate was filtered off with suction, dissolved in 5 ml water, 5 ml 1 N hydrochloric acid added, and the mixture extracted with 15 ml ether. The ether extract was dried over anhydrous magnesium sulfate, the solvent distilled off, and the crystals which remained recrystallized from 0.1 N hydrochloric acid, to give pale yellow crystals of I mp 130-131°. Undepressed mixed mp with I prepared from methyl 3-(5-nitrofuryl-2)-2,3-dibromopropionate. The UV spectra also proved the identity: λ_{max} 334 mμ, lg ε 4.18.

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