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A CONVENIENT SYNTHESIS OF XANTHURENIC ACID

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The main obstacle to the continued research with xanthurenic acid, the abnormal metabolic product of tryptophan in pyroxidine-deficient diets, is its unavailability in sufficient quantities. Although detected in the urine of rats (1), dogs (2), monkeys (3), and even man (4), it has been isolated from these urines only in milligram yields. From the published synthetic method it can be obtained in decigram yields (5); however, the drawback to this method is that the main starting material, dimethyl oxalacetate, requires a number of steps for its synthesis.

This paper describes a convenient synthesis of xanthurenic acid starting with readily available chemicals. The method comprises condensing ethyl oxalacetate (liberated *in situ* from its sodium salt) with *o*-anisidine to form diethyl α-(*o*-methoxyanil)succinate, cyclizing this to ethyl 8-methoxy-4-hydroxyquinaldate, and finally simultaneously cleaving the methyl ether and hydrolyzing the ethyl ester by the Stone and Schechter (10) method of refluxing the ether ester in a solution of potassium iodide in 95% phosphoric acid. In the final step, the yield of crystalline xanthurenic acid is quantitative. All other methods commonly used for cleaving ethers either failed or resulted in only minute amounts of final product. The spectrum of the compound and its crystal data are given.

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EXPERIMENTAL

Ethyl oxalacetate (sodium salt). This compound is available commercially.

Diethyl α-(o-methoxyanil)succinate. To a mixture of 250 ml. of water and 500 ml. of benzene was added 105 g. (0.5 mole) of sodium ethyl oxalacetate. Without delay and while stirring rapidly, 84 ml. (0.15 mole) of 6 *N* sulfuric acid was added over a 5-minute period. [On longer standing the ester polymerized (6).] The yellow-colored benzene solution was separated and washed with two 150-ml. portions of water. Approximately 60 g. of anhydrous sodium sulfate (7) and 98.4 g. (89.4 ml., 0.8 mole) of *o*-anisidine were added to the benzene solution. The mixture was refluxed for 1 hour, cooled, filtered, washed twice with 100-ml. portions of 3 *N* sulfuric acid and finally with 500 ml. of water. As the anil hydrolyzed in acid, these washings lowered the yield but aided in the production of an anil free of excess *o*-anisidine; the latter is necessary for the condensation but is detrimental in the cyclization step (8). Most of the benzene was removed by distillation, and the concentrated solution was cooled in an ice-bath and stirred until crystallization seemed complete. The solid was recrystallized from ether. Yield of yellow crystals was 50%; m.p. 60°.

Anal. Calc'd for $C_{15}H_{19}NO_5$: C, 61.44; H, 6.53; N, 4.78.

Found: C, 61.55; H, 6.60; N, 4.78.

Note: A slight improvement in the yield was obtained when condensation catalysts

were used, or when the method of Surry and Hammer (8) of isolating the free ester before condensation was tried.

Ethyl 8-methoxy-4-hydroxyquinaldate. To 30 ml. of refluxing Dowtherm A was added 9 g. of recrystallized succinate. After 10 minutes the contents were cooled, diluted with 75 ml. of petroleum ether, placed in an ice-salt bath until crystallization was complete, filtered, and washed with petroleum ether. The solid was recrystallized from water. Yield of white crystals 65.6%; m.p. 100°.

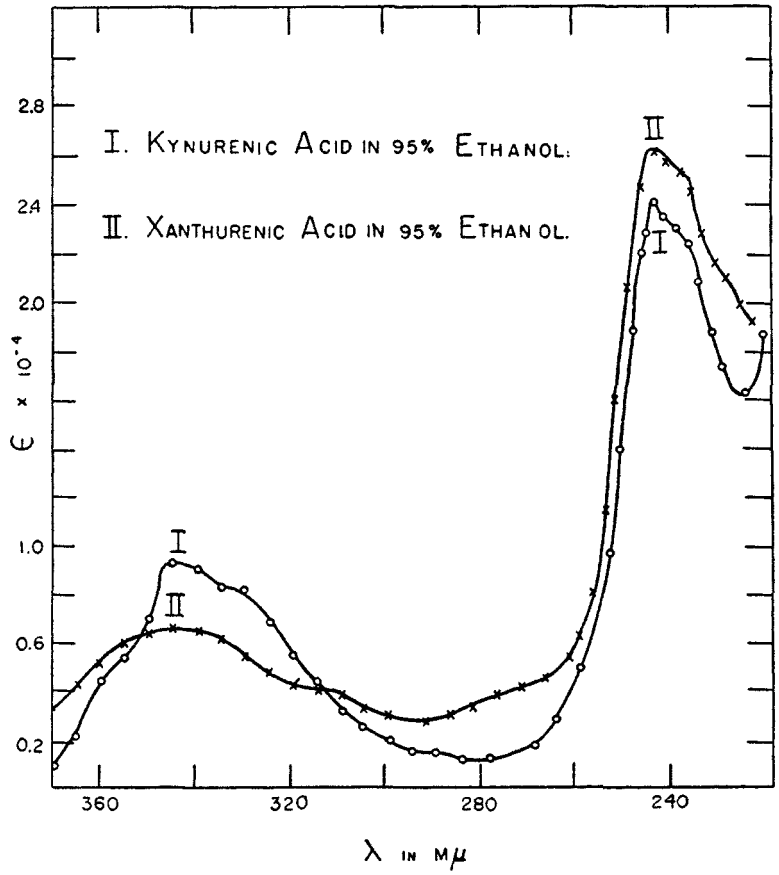

FIGURE 1. ULTRAVIOLET ABSORPTION SPECTRUM OF KYNURENIC ACID AND XANTHURENIC ACID.

Anal. Calc'd for $C_{13}H_{13}NO_4 \cdot 0.5\ H_2O$: C, 60.80; H, 5.09; N, 5.47.
Found: C, 60.33; H, 5.37; N, 5.28.

Note: When the cyclization step was done in mineral oil at 250°, too much decomposition was noted (9). Other media tried were diphenyl ether, diphenyl, and mixtures of these. When 1-g. samples were cyclized, yields of 85.5% were obtained; when more than 9-g. batches were used, the yields were markedly lower.

4,8-Dihydroxyquinaldic acid (Xanthurenic acid). A mixture of 4.3 g. (0.016 mole) of the cyclized product, 10.6 g. (0.064 mole) of potassium iodide, and 12 g. (0.112 mole) of 95% phosphoric acid (10) was refluxed for 3 hours. The solution was cooled, and about 75

ml. of water was cautiously added. On cooling, yellow crystals were obtained in quantitative yields; m.p. 284° (uncorr.).

Anal. Calc'd for $C_{10}H_7NO_4$: N, 6.83. Found; N, 6.90.

All color tests reported for xanthurenic acid were positive.

Note: None of the usual methods of ether-splitting——*e.g.*, hydrogen iodide, *sp. gr.* 1.7; hydrogen bromide, *sp. gr.* 1.48 in glacial acetic acid; iodine in 85% phosphoric acid—— were found satisfactory.

Optical properties. 1. Anisotropic; 2. Habit: diamond-shaped plates, some triangles; 3. First order colors, strong birefringence; Pleochroic: color changes from deep lemon yellow to light lemon yellow; 5. Parallel extinction for the views most often incurred; 6. Interference figures: biaxial, optic axial angle about 54°; 7. Indices of refraction: $\alpha = 1.545 \pm 0.001$, $\beta = 1.5659 \pm 0.0002$; 8. Fluorescence: the compound fluoresces ruby red in ultraviolet light (maximum emission, 3650 Å).

Spectrum. The ultraviolet absorption spectrum is identical with that of xanthurenic acid which was synthesized by the method of Musajo and Minchilli (5). For comparison the spectrum of kynurenic acid is given in Figure 1.

SUMMARY

An improved, convenient synthesis of xanthurenic acid has been described, starting with commercially available sodium ethyl oxalacetate and *o*-anisidine. Crystallographic and ultraviolet spectrophotometric data are given for this compound.

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