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DL-4-ACETAMIDO-4-HYDROXY-2-BUTENOIC ACID γ -LACTONE

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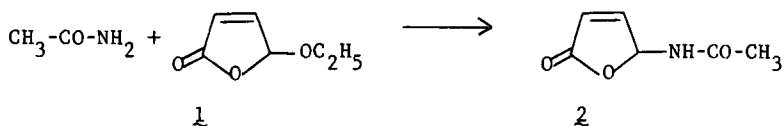
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DL-4-ACETAMIDO-4-HYDROXY-2-BUTENOIC ACID γ -LACTONE¹

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The title compound (2) has been isolated from *Fusarium* molds^{2,3} and implicated as a causative agent in "fescue foot" of cattle.² The method described here is based on the reported small-scale synthesis from acetamide and malealdehydic acid in dilute hydrochloric acid,^{3,4} but has several significant differences. Malealdehydic acid was replaced by its pseudo ester 1 and concentrated hydrochloric acid was used instead of dilute acid. These modifications made larger scale synthesis feasible. Although malealdehydic acid could be an intermediate, it is not isolated.

Experimental

4-Ethoxy-4-hydroxy-2-butenic Acid γ -Lactone.-- This compound was prepared photochemically from furfural, oxygen, and ethanol in the presence of eosin and vanadium pentoxide, by the method of Schenck.⁵ Crude product was found to be best removed from the reaction mixture by distillation in a rotary evaporator at 0.2 to 0.5 mm from a water bath at 75° and with the receiver immersed in ice water. Three redistillations through a Vigreux column gave pure pseudo ester 1, bp 54-6° at 0.4 mm.

GRATZ, COOK, AND WALL

The pseudo ester (85 g, 0.67 mole) was dissolved in 25 ml of 12N hydrochloric acid. Acetamide (60 g, 1.02 mole) was added, and the mixture was heated on a steam bath for 15 min, whereupon it turned black. Tlc [acetone/CCl₄ (1/2)] indicated about 50% conversion with only a small amount of malealdehydic acid present. More acetamide (50 g, 0.85 mole) and 5 ml of water were added and the mixture warmed again until tlc showed no ester remaining. Tetrahydrofuran was added to the reaction mixture and an inorganic precipitate filtered off.⁶ The filtrate was evaporated, and the residue was chromatographed on a total of 1200 g of Florisil. Ether eluted an oil. Ethyl acetate then eluted a mixture of acetamide and 2, which was dissolved in chloroform. Addition of 2-3 volumes of ether precipitated fine crystals which were filtered and subjected to sublimation at 75° and 0.5 mm to remove acetamide. The residue was recrystallized from chloroform to give 24 g of 2, mp 115.0-5.5° (reported² mp 115.5-7.5°), with infrared, nuclear magnetic resonance, and ultraviolet spectra identical to those reported.^{2,3}

References

1. This work was carried out under a contract with the Northern Utilization Research and Development Division, Agricultural Research Service, United States Department of Agriculture.
2. S. G. Yates, H. L. Tookey, J. J. Ellis, and H. J. Burkhardt, *Tetrahedron Letters*, 621 (1967); *Phytochem.*, 7, 139 (1968).
3. E. P. White, *J. Chem. Soc.*, 346 (1967).
4. Another synthesis was reported by H. J. Burkhardt, R. E. Lundin, and W. H. McFadden, *Tetrahedron*, 24, 1225 (1968).
5. G. O. Schenck, *Ann. Chem.*, 584, 156 (1953).
6. This is presumably NH₄Cl from hydrolysis of acetamide.
7. We thank Dr. Ivan Wolff for a sample of genuine 2.

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