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A CONVENIENT SYNTHESIS OF α-SULFO-β-AMINO ACIDS

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Although β-sulfo-alanine (cysteic acid) has been extensively studied, the isomeric α-sulfo-β-amino acids have been almost neglected. DL-α-Sulfo-β-alanine (I) was prepared by Gabriel (1) by the oxidation of isocysteine, prepared in low overall yield by multistep procedures (2) (3). Recently it was reported from this laboratory (4) that I and DL-α-sulfo-β-amino isobutyric acid (II) were obtained in low yield from the reaction of acrylonitrile or methacrylonitrile respectively with fuming sulfuric acid. Further work has shown that I is obtained in high yield by the direct sulfonation of β-alanine(5).

In continuation of this work, we wish to report a convenient general synthesis of α-sulfo-β-amino acids. This synthesis is based on a modified Ritter reaction (6). α,β-Unsaturated carboxylic acids, their esters or amides are reacted with nitriles such as acetonitrile in the presence of fuming sulfuric acid. It is known that the reaction of nitriles with unsaturated carboxylic acids in the presence of concentrated sulfuric acid leads to the formation of N-acyl-β-amino acids (7) and under the present conditions, α-sulfonation by the fuming sulfuric acid takes place as well (5), leading to the formation of N-acyl-α-sulfo-β-amino acids. These products, which were not isolated, gave on subsequent acid hydrolysis, α-sulfo-β-amino acids in high yields. The respective β-amino acids formed by the normal Ritter reaction are usually present in small amounts as byproducts.

Thus, a mixture of acrylic acid (7.2 g, 0.1 mole) and acetonitrile (12.3 g, 0.3 mole) was added dropwise with stirring under anhydrous conditions onto oleum (33% SO_3) (40 ml) cooled in an ice-salt bath. At the end of the addition, the cooling bath was removed, the mixture was stirred at room temperature for 30 min, heated on a boiling water bath for another 30 min, and left at room temperature for 3 days. Water (85 ml) was added cautiously, and the mixture was boiled for 24 h to affect hydrolysis of the N-acyl groups. On cooling the mixture overnight, I precipitated out, and was recrystallized from a small volume of water; yield 15.1 g (89.3%). The amino acid was identified by comparison of its ir spectrum and R_f with that of an authentic sample (5) and by elemental analysis. (Calculated values for $C_3H_7NO_5S$: C, 21.29; H, 4.17; N, 8.28; S, 18.95. Found: C, 21.52; H, 4.10; N, 8.19; S, 18.71).

Under similar conditions using methyl acrylate, I crystallized out in 70% yield; and the mother liquor contained another 24.5% of I, as seen from quantitative paper chromatography (8) carried out on the neutralized solution (barium hydroxide).

In the reaction of methacrylic acid with acetonitrile, II crystallized out from the acid solution after hydrolysis in 46.9% yield and the filtrate contained another 27.8% of II (quantitative paper chromatography). On using a higher concentration of oleum (43% SO_3) (60 ml) and omitting the heating on a water bath, higher yields of II were obtained (49.1% crystallized out and 43.6% remained in the mother liquor).

The amino acid (II) was recrystallized from dilute ethanol (mp. with decomposition, 280°) and was identified by comparison of its ir spectrum and R_f with that of an authentic sample (4) and by elemental analysis. (Calculated values for $C_4H_9NO_5S$: C, 26.22; H, 4.95; N, 7.64; S, 17.50. Found: C, 25.92; H, 5.13; N, 7.42; S, 17.67).

Further investigations of the "amino sulfonation" of unsaturated carboxylic acids, as well as the preparation of N-acyl derivatives of α-sulfo-β-amino acids, are under way.

REFERENCES

1. S. Gabriel, Ber., **38**, 642 (1905).
2. S. Gabriel, ibid, **38**,637 (1905).
3. A Schöberl and H. Braun, Ann., **542**, 274 (1939).
4. A. Zilkha, I. Barzilay, J. Naiman, and B.A. Feit, J. Org. Chem., **33**, 1686 (1968).
5. D. Wagner, D. Gertner and A. Zilkha, Tetrahedron Letters, in press.
6. J.J. Ritter and P.P. Minieri, J. Amer. Chem. Soc., **70**, 4045 (1948).
7. L.W. Hartzel and J.J. Ritter, J. Amer. Chem. Soc., **71**, 4130 (1949).
8. J.P. Greenstein, and M. Winitz, " Chemistry of the Amino Acids", Wiley and Sons, New York, 1961 p. 1309.