Department of Chemistry, Stanford University

Heterocyclic Compounds. VI.

An Improved Preparation of *N*-Hydroxysuccinimide (1)

Kung-Tsung Wang (2), Donald N. Brattesani and Boris Weinstein (3)

N-Hydroxysuccinimide is an intermediate used in peptide chemistry to prepare various activated esters of acylamino acids (4, 5, 6, 7). The compound has been known for many years (8, 9, 10), but has only recently been obtained in moderate amounts by fusion of succinic anhydride either with hydroxylamine (11) or hydroxylamine hydrochloride, followed by fractional crystallization.

A simple alternative to this later procedure exists in the addition of succinic anhydride to a solution of hydroxylamine, then heating in an inert solvent such as toluene or xylene to form *N*-hydroxysuccinamic acid, followed by cyclization under forced esterification conditions to afford the desired product. The principal advantage to the modified method described here is the ability to manipulate large quantities without the need for special apparatus and temperature control.

EXPERIMENTAL (12)

N-Hydroxysuccinimide.

A freshly prepared solution of sodium (6.70 g., 0.291 g.-atom) in methanol (100 ml.) was poured into a stirred suspension of finely-ground hydroxylamine hydrochloride (22.2 g., 0.291 mole) in methanol (100 ml.). The mixture was refluxed on a steam bath for 15 minutes, chilled in an ice bath for 15 minutes, and filtered to remove precipitated sodium chloride. Succinic anhydride (29.1 g., 0.291 mole) was added in small portions over a several-minute period to the stirred hydroxylamine filtrate, and the resulting liquid was boiled for 2 hours. Excess solvent was removed by distillation, toluene (or xylene) (1200 ml.) was mixed with the viscous *N*-hydroxysuccinamic acid, and refluxing was continued for another 4 hours. During this period, a Dean-Stark trap was used to collect a mixture of methanol-toluene-water (200 ml.). The hot solvent was decanted, and on standing deposited crude *N*-hydroxysuccinimide, m.p. 86.0-92.0°. The residual solid in the reaction flask was extracted with a combination of toluene mother liquor and methyl ethyl ketone (100 ml.), and on concentration and cooling afforded a second crop of product. The analytical sample was recrystallized from ethyl acetate to give 16.5 g. (49%) of white flakes, m.p. 97.0-98.0°, identical with authentic material; infrared cm^{-1}: 3000 (broad), 1775 (s), 1700 (broad), 1420 (s), 1220 (broad), 1070 (s), and 655 (s).

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(2) On leave of absence from the Department of Chemistry, National Taiwan University, Taipei, Taiwan, Republic of China.
(3) To whom inquiries concerning this paper should be directed.
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