N-(2,3-EPOXYPROPYL)-α-PYRROLIDONE: A NEW REAGENT FOR THE SYNTHESIS OF DRUGS

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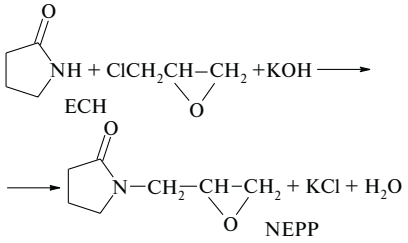
The presence of a pyrrolidone ring in the structure of organic compounds usually is associated with an increase in the hydrophilicity and ability for complex formation and a decrease in toxicity, and it favors some other properties useful for pharmacologically active substances [1]. This circumstance had an important role in the synthesis of some drugs containing pyrrolidonyl radicals [2]. However, the set of reagents to which these radicals can be added is rather limited, including primarily N-vinylpyrrolidone [1], N-(β-hydroxyethyl)-, N-(chloroalkyl)-, and N-(mercaptoethyl)-pyrrolidones [3, 4]. In this context, it was of interest to study the properties of N-(2,3-epoxypropyl)-α-pyrrolidone (NEPP) – a highly reactive compound [5 – 8] that is a new promising reagent for the synthesis of therapeutically active (in particular, radioprotector) substances [7].

NEPP was originally synthesized [9, 10] using a reaction of epichlorohydrin (ECH) with potassium pyrrolidone in an organic solvent (diethyl ether or methylene chloride). Potassium pyrrolidone was preliminarily prepared by interaction of pyrrolidone and metallic potassium. Later [11], we developed a single-stage NEPP synthesis based on the reaction of α-pyrrolidone with ECH in the presence of an alkaline agent (potassium or sodium hydroxides).

The purpose of this work was to study the single-stage synthesis of NEPP from α-pyrrolidone and ECH in the presence of potassium hydroxide in more detail.

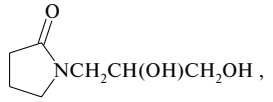


The reaction proceeds even at room temperature, but the best conditions are provided by heating to 50 – 60°C. The optimum ratio of pyrrolidone, ECH, and the alkaline agent is 1 : 6 : 1.15. Water formed as a result of this reaction is removed in an azeotropic form with excess ECH at a residual pressure of 110 – 120 Torr (ECH can be regenerated and used repeatedly). The reaction duration varies from 60 to 90 min at 50 – 60°C to four days at room temperature. The final pyrrolidone conversion is about 60%.

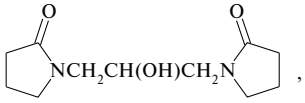
Attempts at increasing the reaction temperature and duration lead to the following side reactions:

(a) heterocycle opening with the formation of a potassium salt of γ-aminobutyric acid $NH_2(CH_2)_3COO–K^+$,

(b) water addition with glycol formation



(c) NEPP interaction with the initial pyrrolidone, leading to N-(2-hydroxy-3-N-pyrrolidonylpropyl)-2-pyrrolidone



(d) NEPP polymerization in the presence of alkali, leading to resinification of the reaction mixture.

We have attempted to inhibit the resin formation caused by NEPP polymerization, which probably took place during the product isolation from the reaction mass, by adding agents of an acidic character (hydrochloric acid, $CoCl_2$, $MgSO_4$, KU-2 resin in H^+ form). However, these additives only slightly reduced the amount of resinous products. From this we inferred that polymerization of the reaction mass components takes place immediately in the course of syntheses.

We have also studied single-stage synthesis in the presence of an interphase transfer catalyst, triethylbenzylammonium chloride (TEBAC) and sodium hydroxide. In this case,

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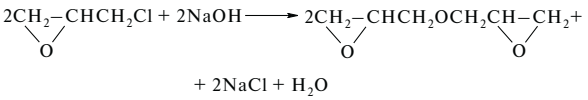
TABLE 1. Single-Stage Synthesis of N-(2,3-Epoxypropyl)-α-pyrrolidone (NEPP) Using an Interphase Transfer Catalyst (TEBAC)

Experiment	Weight of reaction components, g (mole)				Solvent (volume, ml)	Vacuum distillation conditions			NEPP yield, %
	α-Pyrrolidone	NaOH	ECH	TEBAC		B.p., °C	Residual pressure, Torr	Bottom residue weight, % of charge	
1	12.8 (0.15)	50.1 (1.30)	83.2 (0.90)	0.75 (0.003)	–	78 – 80	0.02	14.6	88
2	12.8 (0.15)	8.4 (0.21)	83.2 (0.90)	0.75 (0.003)	–	95 – 96	0.40	8.5	90
3	76.6 (0.9)	50.4 (1.26)	250 (2.70)	2.25 (0.01)	Toluene (210)	103 – 105	1.00 – 1.50	17.0	75
4	269 (3.16)	177 (4.42)	1850 (20.0)	7.9 (0.03)	–	115 – 120	4.00 – 5.00	34.0	66

Notes. In experiments 1 and 2, alkali was added in the form of a 50% aqueous solution.

the NEPP yield increases up to 90% and the reaction product contains virtually no initial pyrrolidone. However, not less than five impurities appear instead, of which only the major one (diglycidyl ester) was isolated and identified.



The results of some experiments on NEPP synthesis in the presence of TEBAC are listed in Table 1.

EXPERIMENTAL PART

The ^{13}C NMR spectra were measured on a Bruker AC-200 spectrometer operated at a working frequency of 200 MHz, using $CDCl_3$ as a solvent and TMS as an internal standard.

N-(2,3-Epoxypropyl)-α-pyrrolidone (NEPP). To a mixture of 34.3 g (0.4 mole) of α-pyrrolidone and 236 g ECH in a flat-bottom three-neck flask equipped with thermometer, stirrer, capillary, and reflux cooler were added with intensive stirring 24.8 g of powdered or granulated potassium hydroxide. The mixture exhibited self-heating to 30 – 35°C. The azeotropic water – ECH mixture was distilled off at 60 – 63°C/110 – 120 Torr. The reaction mixture was filtered, and the residue (containing predominantly potassium chloride) was washed several times with ECH. The filtrates were combined, and ECH was distilled on a rotary evaporator. By the ^{13}C NMR data, the residual liquid was a NEPP mixture with the initial reagents. NEPP was purified by chromatography on a column filled with SiO_2 (L 40/100) eluted with a chloroform – acetone (5 : 1) mixture; NEPP yield, 22.6 g (40%).

Pure NEPP is a colorless transparent liquid with a slight characteristic odor, which acquires a slight yellowish tint upon prolonged storage. NEPP is soluble in water, alcohols, acetone, benzene, and chloroform and insoluble in hydrocarbons; b.p., 101 – 103°C/2.5 Torr, 92 – 93°C/1.5 Torr; n_D^{20}, 1.4860; d_4^{20}, 1.1362; ^{13}C NMR spectrum in $CDCl_3$ (δ, ppm): 174.89 (C-2), 30.31 (C-3), 17.70 (C-4), 44.34 (C-5 + C-6), 49.88 (C-7), 47.99 (C-8).

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