SYNTHETIC METHODS AND DRUG PRODUCTION TECHNOLOGY

HYDROXYETHYLATION OF PHENYLACETONITRILE

M. I. Mostova, D. V. Ioffe, I. L. Mal'ko,
A. S. Vitvitskaya, M. A. Argitti,
and I. A. Karpinskaya

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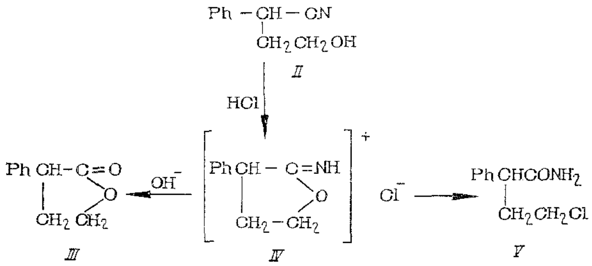
The first stage in the manufacture of the Soviet preparation pyrroxan is the conversion of phenylacetonitrile (I) to 1-phenyl-3-hydroxybutyronitrile (II). The hydroxyethylation of I can be carried out under various conditions. Alkali-metal amides in liquid ammonia [1], phenyllithium in ether [2], or potassium hydroxide in aprotic solvents [3] can be used as metalating agent and ethylene oxide or ethylene halohydrin as alkylating agent [1-3]. In the commercial process for pyrroxan, II is prepared by reaction of the potassium salt of I with ethylene chlorohydrin in DMF. Satisfactory yields of the technical product can be obtained by using a fivefold excess of solid potassium hydroxide with vigorous stirring of the reaction mixture. However, the content of II in the technical product varies, reaching only 20% in individual cases. Hence our intention in the work reported here was to identify the impurities in the technical product and to find the conditions of their formation.

Qualitative analysis of technical II by gas-liquid chromatography (GLC) revealed that the major impurities are unreacted nitrile I and 1-phenyl-3-hydroxybutyrolactone (III). Hydroxy nitriles are readily susceptible to acid- and base-catalyzed isomerization to cyclic imino lactones and the subsequent hydrolysis of the imino lactones to lactones [4]. We have found that under the conditions of the Pinner reaction hydroxy nitrile II readily forms the unstable hydrochloride of imino lactone IV, which in acidic solution isomerizes to 1-phenyl-3-chlorobutyramide (V) [5]. Attempts to prepare the free base of the imino lactone by neutralizing the hydrochloride or by isomerization of II in alkaline solution did not give positive results. The rate of hydrolysis of the imino lactone in alkaline solution apparently exceeds the rate of its formation, and so we could detect only the lactone and not the imine in the reaction mixture.



The GLC analysis of technical II also revealed the presence of high-boiling impurities. These compounds have high retention times and are not sharply eluted, which made their direct identification by GLC difficult. However we identified two of them from the mean spectra.

Among the high-boiling impurities we detected a compound with molecular weight 234, which corresponded to the dimerization product of I, 1,3-diphenyl-2-iminobutyronitrile (VI). Compound I is known to be readily susceptible to base-catalyzed condensation, forming the dimer and trimer [6].

Mass spectrometry also revealed the presence in technical II of a compound with molecular weight 205, corresponding to the bishydroxyethylation product of I. We isolated this compound from the reaction mixture as the picrate and identified it by comparison with authentic 2-imino-3-phenyl-3-(2-hydroxyethyl)tetrahydrofuran picrate (VII). Finally we found another possible cause of the low yield of the desired product. Compound II can decompose under conditions similar to those of hydroxyethylation. When it is heated in DMF solution in the presence of potassium hydroxide cleavage of II begins even at 60°C, forming the starting I.

Thus the hydroxyethylation of I is accompanied by several side and secondary reactions:

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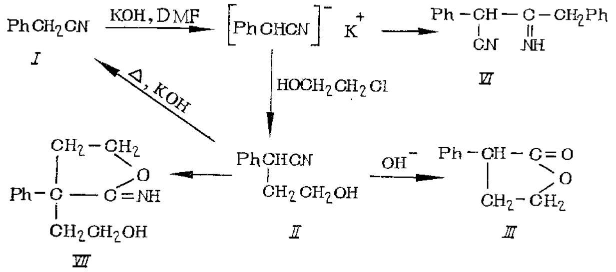
TABLE 1. Effect of Temperature and Reaction Time on Yield of the Desired Product

Base	Hydroxyethylation		Decomposition		Yield, %		
	temp., °C	time, h	temp., °C	time, h	II	I	III
Potassium hydroxide, 5 mole/mole I	25	5	10	0,5	54,0	18,7	traces
Same	50	2	10	0,5	79,2	4,0	6,7
"	50	5	10	0,5	80,5	9,7	8,7
"	50	2	10	18	21,5	8,1	traces
"	50	2	35	0,5	64,7	8,0	9,2
Sodium hydroxide							
5 mole/mole I	50	2	10	0,5	65,9	15,1	1.5
8 mole/mole I	50	2	10	0,5	79,3	11,2	traces



We used our own method for quantitative GLC analysis of the reaction mixture to examine the effect of varying individual parameters on the yield of II (Table 1). A satisfactory yield of II can be obtained only in a comparatively narrow temperature range. Hydroxyethylation of I at 20°C for 5 h gives 54% yield; increase in temperature to 50°C promotes the reaction and after only 2 h the yield reaches 80%. Further increase in the reaction time scarcely increases the yield of II; a slight increase in the content of I in the reaction mixture can be detected and may be due to the partial cleavage of II.

The most important factor responsible for the drastic reduction in the yield of II is its decomposition in the reaction mixture. It is converted to lactone III by a series of consecutive reactions. This reaction pathway apparently becomes predominant when technical II is in prolonged contact with the concentrated alkali that is formed by decomposition of the reaction mixture with water and lactone III is converted to the water-soluble 1-phenyl-3-hydroxybutyrate salt.

We attempted to reduce the production costs by replacing the expensive potassium hydroxide by sodium hydroxide but could get satisfactory yields in this case only with an eightfold excess of alkali.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer.

Hydroxyethylation of Phenylacetonitrile (I). A mixture of I (23.4 g, 0.2 mole), solid potassium hydroxide (56 g, 1 mole), and DMF (100 ml) was vigorously stirred at 20-25°C for 1 h. Ethylene chlorohydrin (19.3 g, 0.24 mole) was then added dropwise. The mixture was left to stand and then poured into (250 ml)* and extracted with benzene (4× 75 ml). The combined benzene extracts were washed with water and dried. The benzene was stripped off and the residue was analyzed by GLC. The conditions of GLC analysis were: Tsvet-101 chromatograph, flame-ionization detector, steel columns of length 3 m, diameter 3 mm, programmed heating from 165 to 300°C at 6°C/min, V_{He} = 40 ml/min, V_{H_2} = 40 ml/min, V_{air} = 400 ml/min, V_{chart} = 600 mm/h. The standard was 2-phenyl-2-hydroxybutyronitrile.

Cleavage of 1-Phenyl-3-hydroxybutyronitrile (II). A mixture of chromatographically pure II (2 g), potassium hydroxide (3.6 g), and DMF (45 ml) was heated at 60°C for 3 h. After cooling the mixture was poured into water (100 ml) and extracted with benzene. The solvent was stripped off and the residue was analyzed by GLC. The content of I was 15.2% and that of II 82.3%.

Isomerization of 1-Phenyl-3-hydroxybutyronitrile (II). Dry hydrogen chloride was passed through a solution of (II) (6.4 g) in anhydrous ether (50 ml) at −5 to 0°C for 6 h. The resulting oily precipitate of hydrochloride IV was repeatedly washed with anhydrous ether to give a compound (3 g) with mp 86-92°C. Repeated crystallization from chloroform gave V (1 g) with mp 106-108°C. IR spectrum, ν_{max}, cm^{-1}: 1700 (C=O), 3420,

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*As in Russian original – Editor.

3530 (NH_2). Found, %: C 61.02; H 6.20. $C_{10}H_{12}NOCl$. Calculated, %: C 60.76; H 6.08. To a suspension of unpurified hydrochloride in ether, derived from III (3.2 g), was added sodium bicarbonate solution (20 ml). The mixture was stirred until the evolution of carbon dioxide ceased. The layers were separated, and the ethereal layer after drying and removal of the solvent was distilled to give 2-phenyl-4-hydroxybutyrolactone (1.9 g), bp 140-141°K (2 mm Hg), n_D^{20} = 1.5420. IR spectrum, ν_{max}, cm^{-1}: 1780 (C=O).

2-Phenyl-4-hydroxybutyrolactone (VIII). Compound VIII (18 g, 0.1 mole) was heated at 100°C for 1 h with dilute hydrochloric acid (50 ml; 1:5); after cooling the product was extracted with ether. After drying and removal of the solvent distillation gave the lactone (10.1 g), bp 140-142°C (2 mm Hg), n_D^{20} = 1.5418. Found, %: C 66.87; H 6.83. $C_{10}H_{12}O_3$. Calculated, %: C 66.67; H 6.67. Literature [7]: bp 109-112°C (0.25 mm Hg), n_D^{20} = 1.5411.

2-Imino-3-phenyl-3-(2-hydroxyethyl)tetrahydrofuran (VII). To a suspension of sodium amide, derived from sodium (4.6 g, 0.2 mole) in liquid ammonia, was added I (11.8 g, 0.12 mole). The mixture was stirred for 30 min. A solution of ethylene oxide (8.8 g, 0.2 mole) in anhydrous ether (25 ml) was added dropwise to the resulting solution. After 4 h the reaction mixture was decomposed with solid ammonium chloride, the ammonia was evaporated, and the residue was dissolved in a mixture of ether (50 ml) and water (50 ml). The ethereal solution was dried and then a precipitate gradually formed. Crystallization from benzene gave VII (12.6 g, 61%), mp 128-129°C. Literature [1]: mp 130°C. Found, %: C 70.80; H 7.42. $C_{12}H_{15}O_2N$. Calculated, %: C 70.09; H 7.03. IR spectrum, ν_{max}, cm^{-1}: 1700 (C−NH).

Picrate of VII was prepared in the usual way in hot alcohol, mp 200°C (from alcohol; sublimes). The picrate prepared in the same way from technical II gave no depression to the melting point of a mixture with the picrate of VII.

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