resistance of the sterile water increases somewhat, which may indicate the presence of current-conducting impurities in the initial water and their elimination of filtration.

The results obtained have been made the basis of the design of a semiindustrial apparatus for obtaining sterile apyrogenic water by filtration in an electric field.

LITERATURE CITED

1. P. I. Gvozdyak, T. P. Chekhovskaya, V. D. Grebenyuk, et al., in: Current Questions of Sanitary Microbiology [in Russian], Moscow (1973), p. 118.
2. P. I. Gvozdyak, T. P. Chekhovskaya, V. D. Grebenyuk, et al., Dokl. Akad. Nauk SSSR, 214, No. 2, 454 (1974).
3. F. A. Konev, in: Proceedings of an All-Union Scientific Conference on Improving the Production of Drugs and Galenical Preparations [in Russian], Tashkent (1969), pp. 90-91.
4. F. A. Konev, Farmatsiya, No. 4, 13 (1971).
5. V. V. Timofeev and F. A. Konev, Med. Prom. SSSR, No. 8, 37 (1964).

PREPARATION OF CRYSTALLINE CYANOACETIC ACID

M. G. Kostareva, A. F. Gorodilova, I. D. Ust'yantseva, and G. A. Bityutskaya

UDC 615.31:547.491.2].012.1

Cyanoacetic acid (CAA) and its salts are widely used in the vitamin and pharmaceutical chemical industry [1, 2], one of its uses being as a basic raw material in the production of theophylline.

CAA can be obtained by saponifying its ethyl ester with hydrochloric acid [3] or by isolating it from its salts obtained by the reaction of monochloroacetic acid with sodium or potassium cyanide [4].

In the synthesis of theophylline, a 25-30% aqueous solution of sodium cyanoacetate or the dry salt obtained by evaporating the solution mentioned is used. This solution contains, apart from the main substance, about 25% of inorganic salts the presence of which adversely affects the synthesis of the theophylline and also increases the pollution of the effluents. Furthermore, the storage of the salt in the form of the aqueous solution leads to its hydrolysis, which also has an adverse effect on the yield and quality of the theophylline.

All that thas been said above has induced us to investigate the possibility of extracting CAA from its aqueous solutions by organic solvents. We have tested isopropanol, butyl acetate, and ethyl acetate. The best results were obtained by using ethyl acetate.

Extraction was initially performed stepwise in flasks with mechanical stirring. The optimum temperature of the extraction process is 25-26°C. With four-stage extraction, 71-75% of the CAA passess into the solvent at a ratio of solvent to initial solution of 1:1.

We then studied the equilibrium state of the water—CAA—ethyl acetate system at a temperature of 25-26°C with aqueous solutions of CAA of various concentrations prepared from crystalline CAA of 97% purity.

It can be seen from Table 1 that the partition coefficient in the range of concentrations of CAA in the aqueous solution from 2 to 46% is not constant but varies between 1 and 1.6.

Sverdlovsk Medical Preparations Factory. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 10, No. 5, pp. 113-116, May, 1976. Original article submitted September 9, 1975.

TABLE 1. Equilibrium in the Water–CAA–Ethyl Acetate System at 25-26°C

CAA content							Partition coefficient	Degree of extraction of the CAA (in %)
initial solution		extract		raffinate				
				$\bar{y}$		x_1		
%	g	g	%	kg/kg	%	kg/kg		
2	0,4	0,22	1,166	0,1184	0,84	0,0847	1,33	55
10	1,937	1,17	5,76	0,0613	4,5	0,047	1,28	60,4
15	3,0	2,068	9,6	0,106	5,88	0,0625	1,63	68,9
20	3,91	2,725	11,98	0,136	9,18	0,102	1,3	69,5
25	5,0	3,41	13,94	0,139	11,58	—	1,2	68,2
30	6,0	4,177	16,13	0,1923	14,46	0,169	1,11	69,4
35	8,75	6,424	18,46	0,226	17,16	0,207	1,07	73,4
42,35	14,7	12,0	24,43	0,324	24,17	0,3187	1,01	81,6
46,9	6,68	6,08	23,86	0,3134	23,68	0,31	1,007	91,0

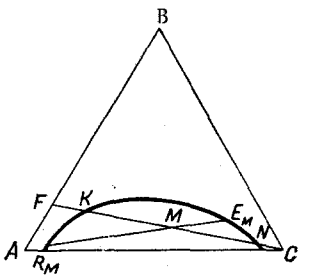

Fig. 1

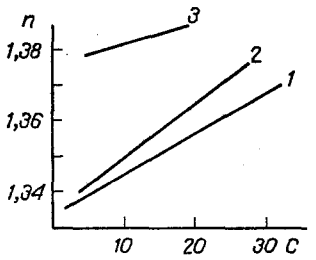

Fig. 2

Fig. 1. Triangular equilibrium diagram. F) Composition of the initial mixture; E_n) composition of the extract; R_n) composition of the raffinate; K and N) the minimum and maximum amounts of solvent, respectively.

Fig. 2. Dependence of the refractive index of a solution on the concentration of CAA in it. 1) For the initial solution; 2) for the raffinate; 3) for the extract.

A study of the influence of the time of contact of the phases on the degree of extraction in batchwise extraction with a constant volume ratio of the components (light phase/heavy phase 1:1) showed that the system reaches its equilibrium state in 15-20 min and shows no tendency to emulsification. A further increase in the time of contact does not lead to more complete extraction.

It was also found that extraction takes place more completely from concentrated solutions. Thus, with a concentration of CAA in the initial aqueous solution of 20%, the degree of extraction reaches 69%, and with an initial concentration of 46% the degree of extraction is 91% at a ratio of the light phase to heavy phase of 1:1.

According to a triangular diagram (Fig. 1), for initial aqueous solutions containing 20% of CAA the minimum and maximum amounts of solvent necessary for extraction are, respectively, 0.12 and 8.3 kg per kg of initial mixture (N, K).

Under these conditions, to achieve 92% extraction requires three theoretical equilibrium stages for a countercurrent process. Reducing the amount of solvent used to 0.7 liter per liter of initial mixture leads to an increase in the number of theoretical equilibrium stages to 8 (Table 2). In addition to this, with aqueous solutions of pure CAA and also solutions of it in ethyl acetate, we studied the dependence of the refractive index of the solution (n) on the concentration of CAA (c) in it at 20°C (Fig. 2). This dependence proved to be linear and can be used for determining the degree of passage of the CAA into the solvent in the extraction process.

TABLE 2. Determination of the Number of Theoretical Extraction Steps as a Function of the Degree of Extraction of the CAA and the Amount of Solvent

Concentration of CAA							Number of theoretical steps	Consumption of solvent (in liters per liter of initial solution)	Degree of extraction of the CAA (in %)
in the initial solution				in the extract					
before extraction		after extraction		before extraction (in kg/kg)	after extraction				
kg/kg	%	kg/kg	%		kg/kg	%			
0,25	20	0,02	1,96	0	0,25	20	8	0,7	93
0,176	15	0,02	1,96	0	0,18	15,2	5	—	88,6
0,25	20	0,0527	5	0	0,25	20	5	—	78,9
0,25	20	0,02	1,96	0	0,176	15	3	1,02	92
0,176	15	0,02	1,96	0	0,140	13	4	1,02	88,6

TABLE 3. Comparative Results of Experiments on the Production of Theophylline from Crystalline CAA and an Aqueous Solution of Its Sodium Salt

Initial system for condensation with dimethylurea	Weight of the initial substance calculated as 100% (in g)	Amount of 100% CAA in the initial material (in g)	Obtained				
			monohydrate of the nitroso compound		anhydrous theophylline		
						%	
			g	% (calculated on the sodium salt of CAA)	g	calculated on the "nitroso"	calculated on the sodium
Aqueous solution of the sodium salt	48,0	38,1	74,3	82	46,44	70,2	57,5
Crystalline CAA	37,3*	37,3	77,1	85,1	49,73	72,38	61,58

*37.3 g of crystalline CAA (100%) was obtained by extraction from an aqueous solution of the sodium salt of CAA containing 48 g of this salt calculated at 100% material.

In our experiments the efficiency of extraction was determined by the ratio of the amount of CAA passing into the extract to the amount of CAA contained in the initial solution multiplied by 100%, the amounts of CAA in the initial solution and in the extract being determined by the Kjeldahl method.

Further experiments on extraction were performed in a column extractor with sieve plates (H = 700 mm, D = 59 mm, number of plates n = 8) by extracting the CAA from its aqueous solution with ethyl acetate. It was possible to achieve a 98% passage of the CAA into the ethyl acetate at a ratio of the light to the heavy phase of 1:1 and with a 30% excess of sulfuric acid taken for the isolation of the CAA from its sodium salt before extraction.

The subsequent distillation of the solvent from the extract and crystallization yielded white or cream-colored crystalline CAA with a melting point of 64-66°C. This was used as the initial raw material in experiments on the synthesis of theophylline. The mean results of these experiments are given in Table 3.

It can be seen from Table 3 that the yield of 4-amino-1,3-dimethyl-5-nitrosouracil and of theophylline increase considerably when crystalline CAA is used. This effect could be more pronounced with the use of continuous countercurrent extraction.

EXPERIMENTAL

Extraction of CAA by Ethyl Acetate. Over 1 h, 454.9 g of 50.4% sulfuric acid was gradually added with continuous stirring at a temperature of 20-26°C to one liter (1.3 kg) of an aqueous solution containing 405.6 g of the sodium salt of CAA. The mixture was stirred for 15 min and filtered from the precipitate of inorganic salts. This gave 1587 g (1.269 liter) of a 19.6% aqueous solution of CAA (yield of the acid 311.0 g). This solution was poured

into a sieve-plate extractor, and 6.345 liters (5713.7 g) of ethyl acetate was passed through it from the bottom to the top for 5 h. This gave 6067.7 g of extract containing 304.78 g 100% CAA, which amounts to 98% of the CAA taken for extraction, and 1150 g of raffinate containing 0.45%, or 5.17 g, of CAA. The ethyl acetate (5373 g; 80%) was evaporated from the extract in vacuum, and the residual mass (627 g) was cooled to 0°C and kept at this temperature for 5-6 h. The CAA that had crystallized out was filtered from the mother solution, giving 237.5 g (230.4 g of 100% material) of crystalline acid, which amounted to 75.6% of the amount present in the extract with a melting point of 64-66°C, and 97.5 g of mother solution in the form of a syrupy mass with a CAA concentration of 50%. The latter was again sent for extraction or was used directly in the form of the syrup in the stage of condensation with dimethylurea in the production of theophylline.

In the condensation of CAA with dimethylurea and subsequent nitrosation, 4-amino-1,3-dimethyl-5-nitrosouracil was obtained with a yield of 85.1%, calculated on the sodium salt of CAA, and this was used for obtaining theophylline.

Preparation of Theophylline. With continuous stirring over 1 h 20 min at 28-32°C, 16.7 g of zinc dust was added to a suspension of 20 g of dry 4-amino-1,3-dimethyl-5-nitrosouracil in 82.4 g of formic acid (22.8 g of 100% material); then 33.4 g of sulfuric acid (16.7 g of 100% acid) was added. The resulting mixture was stirred for 1 h and was then kept at 70°C for 40 min; after this, the formic acid was distilled off in vacuum. The residue was treated with 84.4 ml of hot water and the mixture was stirred at 50°C for 30 min and was cooled to 8-10°C. After crystallization for one hour, the precipitate of 4-amino-1,3-dimethyl-5-formylaminouracil was filtered off and washed with cold water, after which it was suspended in 150 ml of water, 9.1 g (4 g of 100% material) of a 43.8% solution of sodium hydroxide was added, and the mixture was stirred at 70-75°C for 10 min, cooled to 30-35°C, acidified with sulfuric acid to pH 3.0, the temperature not being allowed to rise above 50°C. The solution was stirred at this temperature for 1 h, cooled to 20°C, and after standing for 15 min the technical theophylline was filtered from the mother liquor and washed with cold water. The technical theophylline was recrystallized twice from an 8- to 10-fold amount of water with the addition of activated carbon. This gave 12.9 g of anhydrous theophylline corresponding to all the requirements of GFX [State Pharmacopoeia, 10th ed.].

LITERATURE CITED

1. Ref. Zh. Khim., No. 23N317P (1974).
2. L. S. Maiofis, The Chemistry and Technology of Pharmaceutical Chemicals [in Russian], Leningrad (1964), p. 603.
3. Ref. Zh. Khim., p. 11, No. 5N73P, Moscow (1973).
4. M. Ts. Robert-Niku, The Chemistry and Technology of Pharmaceutical Chemicals [in Russian], Moscow (1954), p. 151.