# METHOD FOR THE PREPARATIVE OF PIPERAZINEDIONE-2,6

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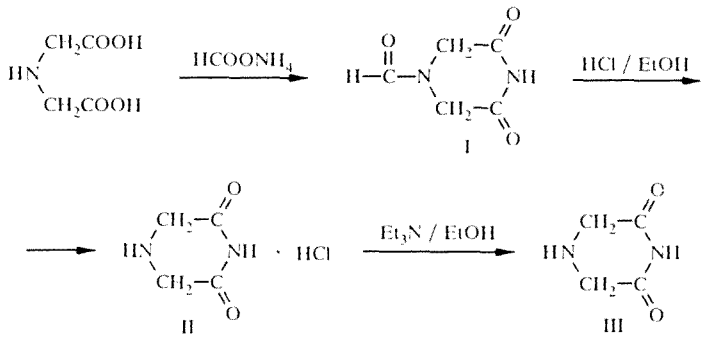
*A method has been developed for the preparation of piperazinedione-2,6. It consists in the cyclization of iminodiacetic acid with ammonium formate. The dependance of the yield of the final product on the reaction temperature, the ratio of the components, and the choice of the solvent has been investigated.*

The derivatives of piperazinedione-2,6 display a relatively wide spectrum of biological activities [1-5]; some of them are being used in technology and in the industry [6-8].

Since it is the simplest compound of this class, piperazinedione-2,6 (III) can be used as the key compound for the synthesis of many derivatives; however, the fact that the synthesis consists of many stages, the low yields (10-15%) [7, 9], and the need for expensive raw materials [10] limit its use. The search for effective methods for the preparation of this compound represents therefore an acute task.

Iminodiacetic acid has been chosen as the starting material for the synthesis. N-Substituted iminodiacetic acids cyclize to form the piperazinedione ring when heated with ammonia or with compounds that liberate ammonia when decomposed (urea, formamide, acetamide) [11, 12]. However, this approach did not give the desired compound; ammonium formate was therefore used as the source of ammonia.




The optimum conditions for the condensation were established. Data showing the influence of the reaction temperature, the ratio of the components, the solvent, and the synthesis method on the yield of the final product are presented in Table 1. The optimum temperature interval for the reaction was found to be 150-170°C, at which a moderate decomposition of the ammonium formate and the condensation itself took place.

It is known that a high temperature enhances decarboxylation of dicarboxylic acids. The N-formyliminodiacetic acid, formed in the condensation of iminodiacetic acid with ammonium formate, is stronger than the iminodiacetic acid or its N-alkyl or N-aryl derivatives, due to the I-effect of the aldehyde group; it underwent decarboxylation at a higher reaction temperature, which prevented an increase in the yield of the final product (to more than 59-60%). After heating of the N-formyl-iminodiacetic acid for 4 h at 150-170°C, the dark-brown residue contained no starting acid. (The N-formyliminodiacetic acid was prepared by refluxing iminodiacetic acid with excess formic acid.)

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TABLE 1. Conditions for the Cyclization

| Molar ratio of reactants, AF | Temperature, °C | Duration of cyclization, h | Yield of final product, % | Molar ratio of reactants, AF | Temperature, °C | Duration of cyclization, h | Yield of final product, % |
|---|---|---|---|---|---|---|---|
| 1 | 120 | 3 | — | 3 | 110...175 | 3 | 23,9 |
| 1 | 150...170 | 4,5 | 9,7 | 3 | 140...175 | 3 | 44,1 |
| 1,5 | 150...170 | 3 | 15,7 | 3 | 150...170 | 4 | 57,3*[2] |
| 1,5 | 150...170 | 6,3 | 16,2 | 3 | 160...180 | 5 | 58,1 |
| 2 | 140 | 4 | 12,6 | 4 | 140...170 | 4,5 | 26,2 |
| 2 | 150 | 3,5 | 19,4 | 5 | 140...170 | 4,5 | 34,8 |
| 2 | 130...160 | 4 | 30,3 | 7 | 140...170 | 4,5 | 35,0 |
| 2 | 130...160 | 6,5 | 30,3 | 10 | 140...170 | 4,5 | 37,2 |
| 2 | 170 | 3 | 41,2*[2] | 2 | 120...160 | 5 | 15,3 |
| 2 | 140...170 | 7 | 35,1 | 3 | 150...170 | 3 | 5,6 |
| 2 | 170...185 | 3,5 | 36,7 | 3 | 180...185 | 2,5 | Resin |
| 2 | 160...180 | 2,5 | 33,4 | 2 | 150...160 | 5,5 | 40,5*[3] |
| 2 | 145 | 6 | 9,7 | 3 | 145 | 4,5 | 44,7*[3] |
| 3 | 150...170 | 4 | 2,3* | 3 | 150...160 | 3,5 | 34,1*[3] |
| 3 | 150...170 | 4 | 51,9 | 3 | 150...180 | 3 | 55,9*[3] |

*Cyclization performed without removal of the water and formic acid (with reflux condenser).

*[2]Toluene was used to strip off the water.

*[3]From N-formyliminodiacetic acid.

Table 1 shows that the absence of a solvent promoted decarboxylation and a strong tar formation in the reaction mass; at 180-185°C this prevented completely the formation of the final product. The optimum ratio of the iminodiacetic acid to the ammonium formate is 1:3. Increasing the excess of the cyclization agent is not expedient because it reduces the yield of the end product (from 50-58 to 26-37%). The decrease in the yield can be attributed to the accumulation of formic acid (the decomposition product of ammonium formate (AF)), which favors side reactions and which combines with the water formed.

N,N-Dimethylformamide (DMFA) is best studied; the use of other aprotic solvents (dimethylsulfoxide and sulfolane) is limited, due to difficulties in the isolation of the product.

In the condensation, formylation of the amino group, splitting off of water, and the formation of the acid anhydride take place simultaneously. By the action of ammonia the latter is converted to the monoamide of N-formyliminodiacetic acid, which, when heated, splits off one molecule of water to form 4-formylpiperazinedione-2,6 (I) and can be separated immediately after cyclization. The formyl group was removed with hydrochloric acid in ethanol; the obtained piperazinedione-2,6 hydrochloride (II) was converted to the free base: piperazinedione-2,6 (III) by treatment with triethylamine. The formylation of the imino group with formic acid is carried out relatively easily. Cyclization without removal of the water formed gave mainly N-formyliminodiacetic acid, which is also easily obtained by the refluxing of iminodiacetic acid with an excess of formic acid. The cyclization of N-formyliminodiacetic acid with ammonium formate gave the end product with yields of 40-56%.

Thus, we have developed a method for the preparation of piperazinedione-2,6, which consists in the cyclization of iminodiacetic acid by the reaction with ammonium formate at the molar ratio of the components of 1:3 in DMFA for 4-5 h at 150°C; the temperature is then gradually increased to 170°C and the water and formic acid formed is stripped off (cyclization without the removal of the water and formic acid gives only 2.3% of the end product).

## EXPERIMENTAL

The melting points of the synthesized substances were determined on a Boetius heated microstage. The PMR spectra were taken in DMSO-$D_6$ on a R-22 (90 MHz) spectrometer with HMDS as the internal standard. The progress of the reaction was followed by TLC on Silufol UV-254 plates with acetone–chloroform (3:1) as the mobile phase. A solution prepared from 1.83 g $CoCl_2 \cdot 6H_2O$, 2 g $K_2Cr_2O_7$, 10 ml glacial acetic acid, and 100 ml $H_2O$ was used to reveal the spots.

**4-Formylpiperazinedione-2,6 (I, $C_5H_6N_2O_3$).** A mixture of 13.3 g (0.1 mole) iminodiacetic acid and 18.9 g (0.3 mole) of ammonium formate in 100 ml dimethylformamide (DMFA) is heated on an oil bath for 4 h, gradually increasing the bath temperature from 150 to 170°C, and by adding 40 ml toluene to the reaction mixture in order to remove the water formed as an azeotropic mixture. The reaction mixture is then evaporated to dryness in vacuum.

The residue is treated with 30 ml methanol and cooled to 4°C. The precipitate formed is filtered and washed with 30 ml cooled methanol. Yield 7.6 g (53.5%) 4-formylpiperazinedione-2,6, cream-colored. $R_f$ 0.41. Treatment with active carbon and recrystallization from 70% methanol gives a white substance mp 218-221°C (with decomp.). PMR spectrum: 4.10 (2 H, s, $H_2$); 4.28 (2 H, s, $CH_2$); 8.07 (1 H, s, HCO); 11.25 ppm (1 H, broad s, NH).

**Piperazinedione-2,6 Hydrochloride (II, $C_4H_7N_2O_2Cl$).** A solution of 7.6 g (0.05 mole) 4-formylpiperazinedione-2,6 (I) in 100 ml ethanol and 10 ml concentrated HCl is refluxed for 3 h. The precipitate is filtered off and washed with ethanol and ether. Yield 7.5 g (98%) of grey piperazinedione-2,6, which after treatment with active carbon and recrystallization from 70% methanol has a melting point of 276-277°C. PMR spectrum: 3.88 (4 H, broad s, $CH_2$); 11.76 ppm (1 H, broad s, MH).

**Piperazinedione-2,6 (III, $C_4H_6N_2O_2$).** A mixture of 7.8 g (0.052 mole) of piperazinedione-2,6 hydrochloride (II) and 14 ml triethylamine in 100 ml ethanol is heated 1 h. The solution is evaporated to dryness in vacuum, the residue is washed with chloroform until complete removal of triethylamine hydrochloride. Yield 5.9 g (99%) of piperazinedione-2,6 (III), mp 202-205°C (with decomp., from methanol): $R_f$ 0.21. PMR spectrum: 3.18 (1 H, broad. s, NH); 3.36 (4 H, s, $CH_2$); 10.85 ppm (1 H, broad. s, NH).

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