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N, N-BIS(2-CHLOROETHYL) AMIDES AND N, N-BIS(2-CHLOROETHYL) HYDRAZIDES OF CARBOXYLIC ACIDS OF THE FURAN SERIES

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Reaction of N, N-bis(2-chloroethyl)amine hydrochloride with chloroanhydrides of carboxylic acids of the furan series, in chloroform in the presence of pyridine gives N, N-bis(2-chloroethyl)amides of furan carboxylic acid, furylacrylic acid, 5-nitrofuran carboxylic acid, and 5-nitrofurylacrylic acid.

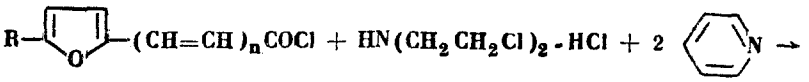
N, N-bis(2-chloroethyl)hydrazides of furan carboxylic acid, furyl carboxylic acid, 5-nitrofuran carboxylic acid, and 5-nitrofurylacrylic acid were obtained in 78-88% yields by reacting N, N-bis(2-chloroethyl)hydrazine hydrochloride with the chloroanhydrides of the appropriate acids in chloroform in the presence of pyridine. The last two hydrazides were prepared in 31% and 56% yield, respectively, using anhydrous sodium acetate in place of pyridine.

Recently research workers have turned their attention to seeking all the possible transport forms of N, N-bis(2-chloroethyl)amine, i.e., for compounds which under the action of body enzymes liberate an active principle with an anti-tumor action. The acyl derivatives of N, N-bis(2-chloroethyl)amine [1-5] and N, N-bis(2-chloroethyl)hydrazine [6, 7] function as such transport forms. The nature of the acyl radical [8, 9] plays an important part in the selective action of such compounds: on it depends the rate of enzymatic splitting, and hence of the final anti-tumor action.

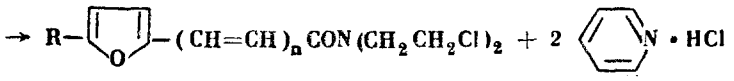
In this connection positive interest attaches to the present synthesis of N, N-bis(2-chloroethyl)amides and N, N-bis-(2-chloroethyl)hydrazides of carboxylic acids of the furan series. Such compounds are usually obtained by the action of thionyl chloride on the corresponding 2-hydroxyethyl derivatives [1, 7]. However, in the case of derivatives of carboxylic acids of the furan series the method does not give identifiable products.

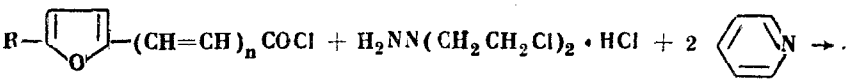
N, N-bis(2-chloroethyl)amides and N, N-bis(2-chloroethyl)hydrazides of acids can also be obtained by the action of chloroanhydrides of acids on N, N-bis(2-chloroethyl)amine and N, N-bis(2-chloroethyl)hydrazine or their salts, in benzene in the presence of an acceptor for hydrogen chloride N, N-bis(2-chloroethyl)amine [10] itself, hydroxides [8, 11] and carbonates of potassium or sodium [9], pyridine, and triethylamine [3, 4, 9, 12, 13], or without an acceptor [7]. In preparing 5-nitrofuran series derivatives, use cannot be made of alkalies as condensing agents, because of the known sensitivity of the 5-nitrofuran ring towards them. We have shown that using carbonates of potassium and sodium also leads to resinification of the reaction product. The chloroanhydrides of 5-nitrofuran carboxylic acid and 5-nitrofuranacrylic acid could be condensed with N, N-bis(2-chloroethyl)hydrazine in the presence of anhydrous sodium acetate in chloroform. However, this method did not afford satisfactory results with the chloroanhydrides of furan carboxylic and furylacrylic acids.

A general method for obtaining the N, N-bis(2-chloroethyl)amides and N, N-bis(2-chloroethyl)hydrazides of carboxylic acids of the furan series was found to be reaction of chloroanhydrides of the acids with the amine (I) or hydrazine (II) hydrochloride in chloroform in the presence of a small excess of pyridine.

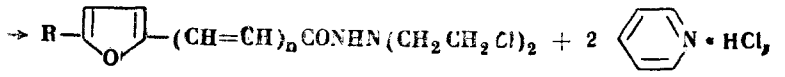


I





II



R=H, NO_2; n=0,1.

When working with 5-nitrofuran derivatives the harmful effect of an alkaline medium is avoided by adding the pyridine in two portions: only half of the necessary amount of pyridine at the beginning, and the second half of the pyridine only after all the chloroanhydride of the acide has been added. Using this method it is possible to obtain readily crystallizable products and high enough yields.

To check the amide structure, the IR spectra of the compounds prepared were determined, since the literature contains [4] indications of an amide-ester rearrangement in the case of bis(2-chloroethyl)amides of benzoic acid.

$$C_6H_5CON(CH_2CH_2Cl)_2 \xrightarrow{H_2O} [C_6H_5COOCH_2CH_2\overset{\oplus}{N}CH_2CH_2Cl]\,Cl^{\ominus}$$

However, the present IR spectra lacked the absorption maximum at 1710-1730 cm^{-1} characteristic of the ester carbonyl group, thus excluding the possibility of formation of products of the above transformation.

EXPERIMENTAL

N-(5-Nitrofuroyl)-N', N'-bis(2-chloroethyl)hydrazine

Method A. 1.75 g (0.01 mole) 5-nitrofuroylchloride, 1.93 g (0.01 mole) N, N-bis(2-chloroethyl)hydrazine hydrochloride, 4 g anhydrous sodium acetate, and 50 ml chloroform were boiled together gently for 5 hrs. The hot mixture was then quickly filtered. The residue on the filter was washed with hot chloroform, and the chloroform solution washed with 5% sodium bicarbonate solution and water, and dried over anhydrous magnesium sulfate; then the chloroform was taken off in a vacuum. Addition of ether transformed the viscous mass into crystals, which were then filtered off; the filtrate was evaporated, and the residue treated with ether to give a further quantity of product, total yield 1.65 g (56%). After a few recrystallizations from dilute alcohol the m.p. is 140-142°. Found: C 36.39; H 3.82; Cl 23.87; N 14.09%. Calculated for $C_9H_{11}Cl_2N_3O_4$: C 36.50; H 3.74; Cl 23.95; N 14.19%. IR spectra cm^{-1}: 1522, 1551, 1578, 1667.

Method B. 1.93 g (0.01 mole) N, N-bis(2-chloroethyl)hydrazine hydrochloride was suspended in 15 ml chloroform, and 0.99 g (1 ml, 0.0125 mole) pyridine added while stirring. Then a solution of 1.75 g (0.01 mole) 5-nitrofuroylchloride in 10 ml chloroform was added dropwise at a temperature of not more than 30°, together with 0.99 g pyridine. Stirring was continued at room temperature for another hour. The reaction mixture was washed with 2N hydrochloric acid, then with a saturated solution of sodium bicarbonate until the aqueous layer remained alkaline, and finally with water. Then the chloroform solution was dried over anhydrous sodium sulfate, the chloroform distilled off in a vacuum, and the residue extracted with a small quantity of hexane, giving 2.46 g product (83%) m.p. 138-140° (from alcohol + hexane). There was no depression of the m.p. on mixing with the product obtained by method A.

N-(5-nitrofurylacryloyl)-N', N'-bis-(2-chloroethyl)hydrazine was prepared by method A, from 2.01 g (0.01 mole) of the chloroanhydride of 5-nitrofurylacrylic acid, yield 1 g (31%), m.p. 159-160° (from isopropanol). Found: C 41.03; H 4.26; Cl 22.18; N 13.20%. Calculated for $C_{11}H_{13}Cl_2N_3O_4$: C 41.01; H 4.07; Cl 22.01; N 13.04%. IR spectra cm^{-1}: 1523, 1568, 1628, 1665.

Method B, starting with 2.01 g (0.01 mole) 5-nitrofurylacrylic acid chloroanhydride, gave 2.52 g (78%) of reaction product m.p. 150-155°, after crystallizing from isopropanol m.p. 159-160°.

N-(Furoyl)-N', N'-bis(2-chloroethyl)hydrazine. Method B. 1.93 g (0.01 mole) N, N-bis(2-chloroethyl)hydrazine hydrochloride was suspended in 15 ml chloroform, and 1.98 g (2 ml, 0.025 mole) pyridine added. Then a solution of 1.3 g (0.01 mole) furoyl chloride in 10 ml chloroform was added dropwise, the temperature not being allowed to rise above 25°, after which the mixture was stirred for an hour, and then worked up as in method B, to give 2.4 g (88%) of reaction product m.p. 55-67°. After freezing out of a dry ethereal solution it melts at 75-77°. Found: C 42.89; H 4.78; Cl 28.09; N 11.09%. Calculated for $C_9H_{12}Cl_2N_2O_2$: C 43.04; H 4.82; Cl 28.24; N 11.16%. IR spectra cm^{-1}: 1527, 1590, 1665.

N-(Furylacryloyl)-N', N'-bis(2-chloroethyl)hydrazine. Using method B, from 1.57 g (0.01 mole) furylacrylic chloroanhydride we obtained 2 g (71.5%) product m.p. 104-105° (after freezing out of a mixture of absolute ether and hexane). Found: C 47.67; H 5.16; Cl 25.21; N 10.05%. Calculated for $C_{11}H_{14}Cl_2N_2O_2$: C 47.67; H 5.09; Cl 25.59; N 10.11%. IR spectra cm^{-1}: 1538, 1558, 1627, 1662.

N-(Furoyl)-N, N-bis(2-chloroethyl)amine. 4.46 g (0.025 mole) N, N-bis(2-chloroethyl)amine hydrochloride in 15 ml chloroform gave (method B) with 2.61 g (0.02 mole) furoyl chloride in the presence of 3.95 g (4.1 ml, 0.05 mole) pyridine, 3.8 g (80%) reaction product, which after two recrystallizations from heptane had an m.p. 92-94°. Found: C 45.57; H 4.59; Cl 30.10; N 5.96%. Calculated for $C_9H_{11}Cl_2NO_2$: C 45.78; H 4.69; Cl 30.40; N 5.93%. IR spectra cm^{-1}: 1563, 1603; in $CHCl_3$: 1600, 1630.

N-(Furylacryloyl)-N, N-bis(2-chloroethyl)amine. 4.46 g (0.025 mole) N, N-bis(2-chloroethyl)amine and (method B) 3.13 g (0.02 mole) furylacrylic chloroanhydride with 3.95 g (4.1 ml, 0.05 mole) pyridine gave 2.7 g (52%) of product which, after freezing out of dry ether melted at 70-71°. Found: C 50.53; H 5.07; Cl 27.06; N 5.41%. Calculated

for $C_{11}H_{13}Cl_2NO_2$: C 50.40; H 5.00; Cl 27.05; N 5.37%. IR spectra cm^{-1}: 1550, 1595, 1640.

N-(5-Nitrofuroyl)-N, N-bis(2-chloroethyl)amine. 4.46 g (0.025 mole) N, N-bis(2-chloroethyl)amine hydrochloride and 3.51 g (0.02 mole) 5-nitrofuroyl chloride (method B) with 3.95 g (4.1 ml, 0.05 mole) pyridine gave 3.4 g (61%) of product, m.p. 56-58° (from dry ether). Found: C 38.30; H 3.60; Cl 25.13; N 10.16%. Calculated for $C_9H_{10}Cl_2N_2O_4$: C 38.45; H 3.59; Cl 25.23; N 9.97%. IR spectra cm^{-1}: 1502, 1532, 1572, 1623.

N-(5-Nitrofurylacryloyl)-N, N-bis(2-chloroethyl)amine. 4.46 g (0.025 mole) N, N-bis(2-chloroethyl)amine hydrochloride and 4.03 g (0.02 mole) 5-nitrofurylacrylic chloroanhydride (method B) with 3.95 g (4.1 ml, 0.05 mole) pyridine gave 4.03 g (66%) of a product m.p. 81-84° (after freezing out from dry ether). Found: C 43.28; H 4.11; Cl 22.28; N 9.06%. Calculated for $C_{11}H_{12}Cl_2N_2O_4$: C 43.10; H 3.94; Cl 23.09; N 9.12%. IR spectra cm^{-1}: 1518, 1563, 1610, 1646.

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