A NEW METHOD FOR OBTAINING DERIVATIVES OF 4-[N', N'-BIS(2-CHLOROETHYL)HYDRAZINO]-QUINOLINE

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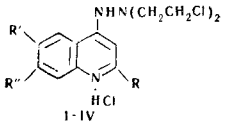
The literature contains a brief report of the synthesis of 7-chloro-4-[N', N'-bis(2-chloroethyl)hydrazino]quinoline (**I**) in the form of the hydrochloride, which was obtained by the reaction of 4-chloroquinoline with N, N-bis(2-hydroxyethyl)hydrazine and subsequent chlorination with phosphorus oxychloride with a yield of 23%; the authors did not give the concrete conditions for the preparation [1].

In a search for substances with antitumoral activity, we have developed an original method for the preparation of **I** and some new derivatives of it with the general formula



I–IV

I R = R' = H, R'' = Cl;
II R = CH_3, R' = CH_3O, R'' = H
III R = CH_3, R' = H, R'' = Cl;
IV R = CH_3, R' = R'' = H

with yields of 48–64%. The method is based on the direct reaction of N, N-bis(2-chloroethyl)hydrazine hydrochloride with 4-chloroquinoline derivatives at 110° C using glycol as solvent. This method is characterized by simplicity and comparatively high yields of the products.

The compounds obtained are crystalline substances insoluble in the usual solvents and sparingly soluble in water. The structure of compounds **I–IV** was shown by independent synthesis; by the preparation of the hydroxy derivatives and their chlorination with phosphorus oxychloride followed by isolation in the form of the hydrochlorides. Mixtures of the corresponding substances obtained by the two methods gave no depression of the melting points, and the elementary analyses were identical in the two cases.

The melting points and analyses of the compounds obtained for the first time are given in the table.

4-[N', N'-Bis(2-chloroethyl)hydrazino]-6-methoxy-2-methylquinoline (II) hydrochloride. 10 ml of glycol was added to 2.1 g (0.01 mole) of 4-chloro-6-methoxy-2-methylquinoline (**V**) and 1.94 g (0.01 mole) of N, N-bis(2-chloroethyl)hydrazine hydrochloride, and the mixture was heated at 110° C with vigorous stirring for 1 hr. Then it was left in the cold for 12 hr. The precipitate that had deposited was filtered off, washed with 20 ml of isopropanol, and dried at 90–95° C. This gave 3.4 g of the hydrochloride of **II** (64% of theory, calculated on the **V**), mp 275° C (from aqueous ethanol).

The hydrochlorides of **I, III,** and **IV** were synthesized similarly.

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1. R. M. Peck, R. K. Preston, and H. J. Creech, J. Org. Chem., **26**, 3409, 1961.

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4-[N', N'-Bis(2-chloroethyl)hydrazino]quinolines

Compound*	Mp, °C**	Empirical formula	Found, %				Calculated, %				Yield, %
			C	H	Cl	N	C	H	Cl	N	
II	275	$C_{15}H_{19}Cl_2N_3O \cdot HCl$	49.65	5.75	29.11	11.70	49.39	5.52	29.19	11.52	64
III	250	$C_{14}H_{16}Cl_3N_3 \cdot HCl$	45.53	4.84	38.73	11.68	45.55	4.64	38.41	11.38	54
IV	255—256	$C_{14}H_{17}Cl_2N_3 \cdot HCl$	50.17	5.69	31.46	12.26	50.24	5.42	31.78	12.55	48

*I mp 220–221° C (according to the literature [1], 220–222° C), yield 61.2%.
**I–IV were recrystallized from aqueous ethanol.

SIMPLIFIED METHOD FOR THE PREPARATION OF PHOSPHOROTHIOIC TRIETHYLENETRIAMIDE

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Up to the present time, phosphorothioic triethylenetriamide (**I**), which has acquired the short name "Thio-TEPA" has been obtained industrially by the reaction of anhydrous ethyleneimine (**II**) with phosphorothioic trichloride in ether or benzene with cooling to −50° C in the presence of triethylamine acting as hydrogen chloride acceptor [1–4]. In this process the yield of **I** is ~60%.

However, this method possesses a number of disadvantages which considerably complicate the technology of the production of Thio-TEPA and make it more expensive. These include:

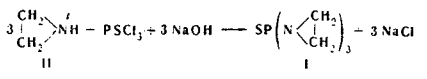
a) the necessity for using anhydrous ethyleneimine (its dehydration is an extremely laborious and unproductive process);

b) the necessity for using as hydrogen chloride acceptor the expensive and scarce triethylamine, which possesses a very unpleasant smell and also requires additional dehydration;

c) the necessity of carrying out the filtration of the reaction mixture from the precipitate of triethylamine hydrochloride which is associated with losses of valuable product and solvent.

We have developed a simple and convenient method for obtaining I. It is based on the performance in a two-phase system of the reaction of aqueous ethyleneimine and alkali (for example, NaOH) with a solution of phosphorothioic trichloride in carbon tetrachloride, chloroform, dichloroethane, or another suitable solvent.

The reaction takes place according to the equation:



The process is carried out by adding the solution of phosphorothioic trichloride in an organic solvent to a stirred mixture of the same solvent and an aqueous solution of ethyleneimine and NaOH at a temperature of from −10 to +5° C.

Compound I is separated from the organic layer by distilling off the solvent in a low vacuum and is purified by recrystallization. Its yield amounts to 62–68% of theoretical.

The proposed method has been carried out on the experimental scale in the pilot plant of the Institute of Organic Synthesis of the Academy of Sciences of the Latvian SSR.

Phosphorothioic triethylenetriamide (I). With stirring, a solution of 16.9 g (0.1 mole) of $SPCl_3$ in 25 ml of CCl_4 was added dropwise to a mixture of 50 ml of carbon tetrachloride and a solution of 13.5 g of 97–98% ethyleneimine (0.305 mole) and 13.2 g (0.33 mole) of NaOH in 50 ml of water cooled to from −10 to 0° C. After this, the reaction mixture was stirred at room temperature for another hour and at 35–40° C for 2 hr. The lower layer was separated off, dried with anhydrous magnesium sulfate (this operation is not essential but leads to a purer product), and the solvent was distilled off in a water-pump vacuum. The residue was recrystallized from petroleum ether. The yield of I with mp 52° C was 11.7–12.8 g (61.8–67.6%).

When the reactants are mixed at −10° C, the yield of I amounts to 60–67%, and at 0° C it amount to 57–61%.

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PAPERS DEPOSITED IN VINITI [All-Union Institute for Scientific and Technical Information]*; NOTES

SYNTHESIS AND REACTIONS OF FURAN DERIVATIVES

VII. Unsaturated α-Oxocarboxylic Acids of the Furan Series and Their Derivatives

N. O. Saldabol

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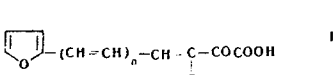
The condensation of furfural and 3-(2-furyl)acrolein with pyruvic and α-oxoglutaric acids in 3 N NaOH has given the Na salts of acids from which by the action of hydrochloric acid 2-furfurylidenepyruvic acid (I), [3-(2-furyl)allylidene]pyruvic acid (II) and β-(2-furfuryl-idene)-α-oxoglutaric acid (III), respectively, have been isolated. Compound I is also formed by the condensation of furfural with oxaloacetic acid (yield 52%). The molar ratios of aldehyde pyruvic acid NaOH = 1 : 1 : 1.25; in the case of dibasic acids, the amount of NaOH was increased.



I n = 0, R = H. II n = 1, R = H.
III n = 0, R = CH_2COOH

The following information is listed: compound, empirical formula, yield of the Na salt, %, yield of the acids, %, mp, °C, [λ_{max}, nm (log ε)]: I, $C_8H_6O_4$, 96, 52, 109–112, [239, 332 (3.40, 4.54) H_2O]: II, $C_{10}H_8O_4$, 66, 52, 126–128 [225, 360 (3.83, 4.30) ethanol]; III, $C_{10}H_8O_6 \cdot 1/2(H_2O)$, –, 86, 78–80 [238, 330 (3.25, 4.48) H_2O]. III · · $1/2(H_2O)$, is converted on drying over $CaCl_2$ into III, mp 114–116° C. Mp of the Na salt of II 320° C. Derivatives of compounds I–III at the

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