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

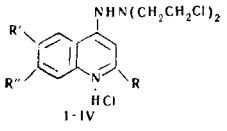
M. Yu. Lidak and N. M. Sukhova

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 3, p. 569, 1969

UDC 547.831.2.6

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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22 November 1968

Institute of Organic Synthesis
AS Latvian SSR, Riga

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

L. A. Fedotova and M. G. Voronkov

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 3, p. 570, 1969

UDC 547.717

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%.