SYNTHESIS AND STUDY OF HETEROCYCLIC DERIVATIVES WITH BIOLOGICAL ACTIVITY

IX. A Study of Some Reactions in the Synthesis of Bis-β-chloroethylamines Containing a Phenazine Nucleus*

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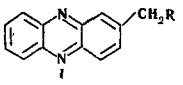
Methods for introducing the cytotoxic bis(β-chloroethyl)amino group directly into the phenazine nucleus have been studied. 2-[p-Bis(β-chloroethyl)aminobenzylideneimino]-3-hydroxyphenazine and quaternary salts of 2-(p-dimethylaminophenyl)-4,5-phenazinoimidazole, 2-(p-diethylaminophenyl)-4,5-phenazinoimidazole, and 2-[N-bis(β-chloroethyl)-aminophenyl]-4,5-phenazinoimidazole have been obtained for biological tests.

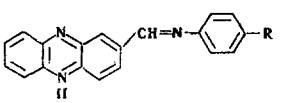
The bulk of the antitumoral materials used in practice belong to the so-called group of alkylating agents, in particular the bis(β-chloroethyl)amines. A generalization of the experimental material that has been accumulated shows that the activity of a compound is determined by the structure of the molecule to which the cytotoxic group is attached (the "carrier" of the cytotoxic group), and the greatest interest is offered by those substances in which the "carrier" is a metabolite or a residue of other biologically important natural products [1].

According to the literature, in the process of conversion, phenazine derivatives form three radicals, semiquinones, capable of catalyzing oxidation-reduction processes, which explains their physiological action [2]. In particular, it is known that 2-amino-3-hydroxyphenazine is a nonphysiological catalyst in photosynthetic phosphorylation reactions [3]. On the basis of this information, phenazine derivatives containing a bis(β-chloroethyl)amino group are of considerable interest.

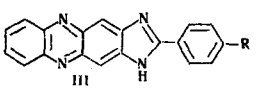
We have previously described the syntheses of bis(β-chloroethyl)aminomethylphenazine (I) and the azomethine of 2-phenazinealdehyde with p-bis(β-chloroethyl)aminoaniline (II) [4], and also a complex derivative of phenazineimidazole (III) containing a cytotoxic group [5].



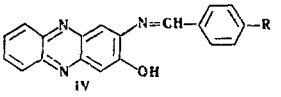
I



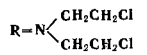
II



III

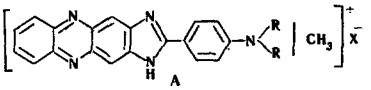


IV



The azomethine IV, in which, unlike III, the amino component is 2-amino-3-hydroxyphenazine, was obtained by the reaction with p-bis(β-chloroethyl)aminobenzaldehyde and formed dark yellow crystals not melting below 350° C.

In view of the chemical characteristics of phenazine, the preparation of derivatives in which the bis(β-chloroethyl)amino group was attached directly to the phenazine ring presented considerable difficulties. An attempt at the direct alkylation of 2-aminophenazine using ethylene chlorohydrin as the alkylating agent led only to a low yield of 2-hydroxyethylaminophenazine. The use of ethylene oxide under various conditions did not give satisfactory results. The reaction of the methyl methosulfate derivative of phenazine with diethanolamine in the oxidative amination reaction [6,7] formed an oily product contaminated with phenazine. It is possible that in this case disproportionation took place under the action of the base in the same way as described by McIlwain [8]. Alkylation of the methyl methosulfate derivative of 2-hydroxyethylaminophenazine [7] carried out under various conditions was unsuccessful. In view of the fact that a number of quaternary salts of phenazine exhibit a considerable physiological activity [9,10] and the phenazinoimidazoles obtained earlier possess a low solubility, we prepared quaternary salts of the general formula A for performing the biological tests.



A

V R=CH₃, X=CH₃SO₄⁻ VI R=C₂H₅, X=CH₃SO₄⁻ VII R=CH₂CH₂Cl, X=CH₃O₄
Va R=CH₃, X=I⁻ VIa R=C₂H₅, X=I⁻

*For part VIII, see [15].

Characteristics of the Compounds Obtained

Compound	Mp, ° C	Empirical formula	N, % found	N, % calculated	Yield, %
Va	250	$C_{22}H_{20}IN_5$	14.55	14.20	14
VIa	230	$C_{24}H_{24}IN_5$	13.33	13.75	57
VII*	230	$C_{25}H_{25}Cl_2N_5O_4S$	—	—	50

*Found, %: Cl 12.67. Calculated, %: Cl 12.61.

The treatment of the appropriate bases with dimethyl sulfate in nitrobenzene at 110° C [11] gave the methyl methosulfates of 2-(p-dimethylaminophenyl)-4,5-phenazinoimidazole (V), 2-(β-diethylaminophenyl)-4,5-phenazinoimidazole (VI), and 2-[p-bis(β-chloroethyl)aminophenyl]-4,5-phenazinoimidazole (VII). Compounds V and VI were readily soluble in water and were easily converted into the corresponding methiodides Va and VIa by means of potassium iodide. Compound VII was insoluble in water and could not be converted into the methiodide. In view of the fact that the formation of the quaternary salts of the phenazinoimidazoles took place under the conditions of the preparation of the phenazine and that quaternary salts of benzimidazole are formed under more severe conditions (by the action of an alkyl iodide in a sealed tube or in alcoholic alkali) it may be assumed that the quaternization of the nitrogen atom in the phenazine part of the molecule took place.

EXPERIMENTAL

2-(β-Hydroxyethylamino)phenazine. A flask with a stirrer and a reflux condenser was charged with 1 mole of 2-aminophenazine[12], 4 moles of ethylene chlorohydrin, and 2 moles of sodium bicarbonate and was heated in the boiling water bath for 20 hr. The reaction mixture was diluted with anhydrous ethanol and the residue was filtered off and washed repeatedly with small portions of anhydrous ethanol. After crystallization of the residue from hot water, unchanged 2-aminophenazine with mp 273° C was obtained. The ethanolic solution was evaporated under vacuum and the residue was crystallized from hot water and a mixture of ethanol and water. Bright yellow crystals, mp 171° C. Found, %: N 17.03. Calculated for $C_{14}H_{13}N_3O$, %: N 17.57.

2-[p-Bis(β-chloroethyl)aminobenzylideneimino]-3-hydroxyphenazine (IV). A mixture of 7.2 g (0.034 mole) of 2-amino-3-hydroxyphenazine [13] and 8.65 g (0.035 mole) of p-bis(β-chloroethyl)amino benzaldehyde [14] in 70 ml of nitrobenzene was boiled for 1 hr, the reaction mass was cooled, and the product was isolated by the addition of ether. The precipitate that deposited was repeatedly washed free from nitrobenzene with ether, filtered off, and reprecipitated from chloroform with ether (five times). This gave 9.3 g (60%) of dark yellow crystals not melting below 350° C. Found, %: Cl 16.23; N 12.45. Calculated for $C_{23}H_{20}Cl_2N_4O$, %: Cl 16.14; N 12.75.

2-Hydroxyethylaminophenazine methiodide. This was obtained by a previously published method [7]. Dark red crystals, mp 256°–257° C (from water). Found, %: C 47.05; H 4.35. Calculated for $C_{15}H_{16}IN_3O$, %: C 47.25; H 4.24.

Preparation of the methyl methosulfates of phenazinoimidazoles. With heating, 0.003 mole of the initial phenazinoimidazole was dissolved in 20 ml of nitrobenzene (in the case of VII in dimethylformamide). The solution was boiled without a reflux condenser for 2 min and was cooled to 110° C. At this temperature, 0.021 mole of dimethyl sulfate was added and the mixture was kept at the same temperature for 10 min. After cooling, in the case of V a crystalline precipitate deposited which was washed with ether. The addition of ether to the mother liquor yielded more of the product. In the cases of VI and VII, ether was added to the cooled solution precipitating an oil, which could not be crystallized in the case of VI, while in the case of VII it was crystallized from ether and recrystallized from ethanol.

Preparation of the phenazinoimidazole methiodides. The methyl methosulfate derivative obtained was dissolved in a small amount of water, and the calculated amount of potassium iodide in water was added to the solution. The precipitate that deposited was filtered off and crystallized from hot water. Some properties of the compounds obtained are given in the table.

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