SYNTHESIS OF 6-METHOXY-8-(4'-AMINOPENTYLAMINO)QUINOLINE (QUINOCIDE) DIHYDROCHLORIDE

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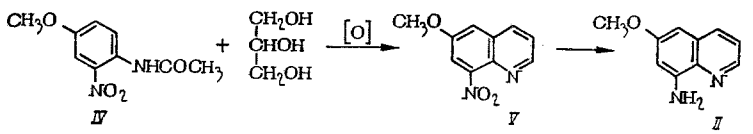
The dihydrochloride of 6-methoxy-8-(4'-aminopentylamino)quinoline [(I), quinocide], an antimalarial preparation, was described for the first time in 1955-1956 [1, 2]. A characteristic feature of (I) is its effect on the tissue forms of inducers of three- and four-day malaria: (I) is used for preventing relapses of the disease during these forms of malaria. The main starting materials for preparing (I) are 6-methoxy-8-aminoquinoline (II) and 4-aminopentanol (III).

The synthesis of (II), the N-alkyl derivatives of which have been studied widely and some of which have been introduced into medicinal practice as antimalarial preparations [3], is expressed by the following scheme:



2-Nitro-4-methoxyacetanilide (IV) with glycerin in the presence of an oxidizing agent is transformed by the Skraup reaction into 6-methoxy-8-nitroquinoline (V), which is reduced further into (II). During the preparation of (V) arsenic pentoxide was used as the oxidizing agent. Because of the high toxicity of arsenic pentoxide and the process occurring violently with it, sometimes with ejections and strong tarring, we developed another method of obtaining (V), in which m-nitrobenzenesulfonic acid [4] was the oxidizing agent. Complete safety of the process was attained as a result and the yield of (V) increased from 52 to 62%.

The second stage of synthesis of (II) (reduction), according to literature data, can be achieved by various methods. Chemical methods [5-10], not requiring special apparatus, have obtained wide distribution, together with catalytic methods. Thus, for example, reduction of (V) with iron filings in aqueous acetic acid in the presence of chlorobenzene was used to obtain (II) in the industrial synthesis of the preparation "plasmocide." However, because of the complexity of the technological formulation of the process and the large number of operations to separate (II) involved in this method, it seemed more expedient to us to achieve the catalytic reduction of (V). It is known that the nitro group in (V) can be reduced in the presence of platinum [7], palladium [9], and nickel [10] catalysts. In the last case the process is carried out at 60°C and a pressure over hydrogen of 80 atm. However, as our investigations showed, under these conditions hydrogenation does not stop after absorption of 3 moles of hydrogen, but proceeds further, evidently due to reduction of the pyridine portion of the quinoline ring. Hydrogenation of (V) at room temperature and use of a methanol solution of (II) instead of separating (II) by high-vacuum distillation made it possible for us to create a technological method of obtaining (V).

The second starting compound for the synthesis is (III). Two methods of obtaining (III) are described in the literature: a) condensation of nitroethane with ethyl acrylate and subsequent reduction of the ethyl ester of γ-nitrovaleric acid with lithium aluminum hydride; yield 29.7%, calculated on ethyl acrylate [2];

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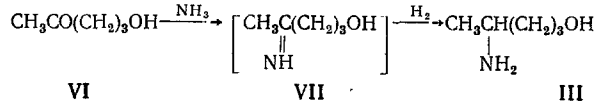
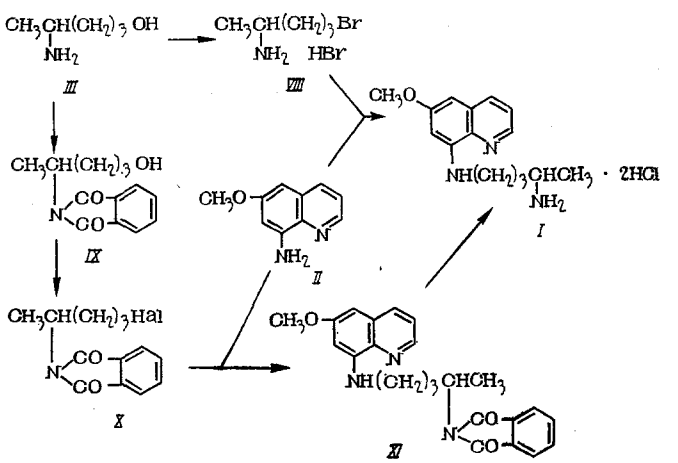
b) reductive amination of γ-acetopropyl alcohol (VI) in the presence of Raney nickel at room temperature; yield 43.4% [11]. Because of the use of a large collection of reagents and the unsafety of the process the first method is not acceptable for the preparation of any significant amounts of (III). It was found upon a careful study of the more promising second method that, although the method makes it possible to obtain (III) is a yield above that indicated (up to 65%), the formed (III) contains about 20% of a nitrogen-free compound, not separable by distillation.



VI VII III

We established that the poor quality of (III), obtained from commercial (VI), is associated with the presence in the latter of significant amounts (up to 30%) of cyclic compounds: 2-methyl-4,5-dihydrofuran and 2-methyl-2-(γ-acetylpropyloxy)tetrahydrofuran. These compounds are stable in aqueous ammonia solutions, do not form 4-iminopentanol (VII) [the intermediate compound during synthesis of (III)] with ammonia and remain unchanged as the impurity in (III). The method we developed for transforming the indicated cyclic compounds into (VI) without their preliminary separation [12] made it possible to obtain 97-98% (VI) and (III) from it, which primarily determined the high quality of (III). The initial hydrogen pressure and the temperature during reduction of (VII) were also found to be significant in the process of obtaining (III). Thus, while at 20° hydrogenation is drawn out for 30-50 h and virtually cannot be taken to completion, at 70° hydrogen absorption is over in 3-4 h. An initial hydrogen pressure of 50 atm should be considered most favorable. The method of obtaining (VII) virtually does not show up on the yield and quality of (III): saturation of an aqueous solution of (VI) with gaseous ammonia, or addition of liquid ammonia or a 20-25% aqueous solution of ammonia. The last method is the most technological [13].

If we start from (II) and (III) the synthesis of (I) can be achieved in two variations:



In the first variation (II) is alkylated with 1-bromo-4-aminopentane (VIII) [1]; in the second it is alkylated with 1-bromo-4-phthalimidopentane (X; Hal = Br) with subsequent removal of the phthalyl protecting group [2, 13]. The most significant disadvantage of the first method is the low yield of (I), not exceeding 20% based on (VIII), which is associated with an easily occurring side reaction, the transformation of (VIII) into 2-methylpyrrolidine. The indicated side process is predominating already at pH 4.2, i.e., during a minimal pH necessary for achievement of the alkylation reaction; at a higher pH (VIII) is virtually completely converted into 2-methylpyrrolidine. Together with the low yield, the complexity of obtaining (VIII) is an obstacle to the practical achievement of the synthesis. Compound (VIII) is formed upon heating (III) and 48% hydrobromic acid with simultaneous removal initially of dilute, and then of 48% acid, by raising the temperature of the heater to 190-200°. However, in this case the reaction does not go to completion, and the separation of (VIII) in sufficiently pure form is associated with significant losses of product.

The second of the described methods of obtaining (I) seemed more promising to us. By this method alkylation of (II) was carried out with the N-phthalimide derivative (X) (Hal = Br), instead of with bromide (VIII), to avoid cyclization of (VIII) into 2-methylpyrrolidine. To obtain (X) we transformed (III) into 4-phthalimidopentanol (IX), and the hydroxy group in the latter was replaced by a bromine using phosphorus tribromide.

In this method syntheses of (IX) and (XI), achieved by melting (III) with phthalic anhydride in one case and by melting bromide (X) with (II) in the second, were inadequate. The reaction of (X) (Hal=Br) with (II) in the presence of phosphate buffer (pH 8.3), taking 79 h, although appearing more technological, does not provide for a sufficiently high yield of (XI) [2].

Using the second variation of obtaining (I), we introduced changes into all stages of the synthesis, which made it possible to carry out the process under industrial conditions. The method we developed for obtaining (I) can be represented by the following series of transformations.

Heating (III) with phthalic anhydride in xylene with azeotropic distillation of water forms (IX). The reactions occurs virtually quantitatively and (IX) is used for the next step without additional purification.

Replacement of the hydroxyl group in (IX) by bromine is achieved in quite good yield using phosphorus tribromide. But as a result of the absence of commercial phosphorus tribromide and also because of the higher reactivity of iodoalkanes, in comparison with bromoalkanes, we used 1-iodo-4-phthalimidopentane in the synthesis of (XI). To obtain iodide (X) (Hal=I) the hydroxy group in (IX) was replaced initially by chlorine using thionyl chloride and then 1-chloro-4-phthalimidopentane was heated with sodium iodide in acetone. Investigation of the alkylation reaction with iodide (X) (Hal=I) showed that carrying out the process in boiling toluene or xylene in the presence of dehydrohalogenating reagents having high pK_a (above 9), for example, triethylamine or sodium carbonate, makes it possible to attain quite high yields of (XI) (65%). To remove the phthalyl protecting group (XI) is heated with hydrazine hydrate in alcohol solution, and then the reaction product is treated with 35% aqueous potassium hydroxide solution. It should be noted that achievement of the second stage of hydrazinolysis, cleavage of the phthalazone derivative by heating it with hydrochloric acid as described in the literature [13], invariably led to nonqualitative dihydrochloride of (I), the appearance of a stable green tint in the preparation. The synthesis of (I), starting from (III), was carried out without separation of the intermediate compounds (IX), (X), and (XI), with stable yields of 50-52%, based on (III), which is 2-2$^1/_2$ times higher than the yield which can be attained by the first of the presented schemes on the basis of bromide (VIII).

EXPERIMENTAL

6-Methoxy-8-nitroquinoline (V). To a mixture of 33 ml of conc. sulfuric acid and 100 ml of water was added at 50-60° a solution of 54.6 g of m-nitrobenzenesulfonic acid in 100 ml of 30% sulfuric acid, then 39.6 ml of glycerin and 37.5 g of (IV) were added, and the mixture was heated for 4 h at 132-136°. The cooled mass was poured into 750 ml of water, treated with carbon, and neutralized with a 25% aqueous ammonia solution to pH 4.0-5.0. The aqueous solution was poured away from the tarry residue, and (V) was extracted from the residue with a boiling mixture of dichloroethane and water (6:1). The dichloroethane layer was separated and evaporated; the residue was mixed with methanol and filtered. We obtained 19.3 g (62%), mp 158-160°.

6-Methoxy-8-aminoquinoline (II). We mixed in an autoclave 80 g of (V), 240 ml of methanol, and 12 g of Raney nickel at room temperature and a hydrogen pressure of 50 atm. After absorption of a volume of hydrogen, necessary for reduction of the nitro group, the catalyst was filtered, and the methanol solution upon cooling was acidified with conc. hydrochloride acid to congo. The precipitated hydrochloride of (II) was filtered and washed with methanol. Yield 83.7 g (93.5%), mp 223-224°. A methanol solution of base (II) was used to obtain (XI).

4-Aminopentanol (III). A mixture of 300 g of (VI) (content 68.4%, the remainder was the cyclic compounds indicated above) and 180 ml of dilute hydrochloric acid (pH 2.5-2.8) was stirred for 18 h at 20-25° and an aqueous solution of (VI) was poured over 1 h at −3 to −5° into 670 ml of 25% aqueous ammonia solution. The reaction mass was stirred an additional 1 h, after which the aqueous ammonia solution of (VII) was subjected to hydrogenation in the presence of 30 g of Raney nickel at 70° and an initial hydrogen pressure of 50 atm. The necessary amount of hydrogen is adsorbed in 3-4 h. The catalyst was filtered, the aqueous ammonia solution of (III) was mixed with 300 ml of xylene, and water was removed by azeotropic distillation. After distillation of xylene the residue was distilled in vacuum. Yield 263 g (88.5%), bp 103-105° (7 mm).

1-Iodo-4-phthalimidopentane (X, Hal=I). A mixture of 51.5 g of (III), 74 g of phthalic anhydride, and 300 ml of xylene was heated in an apparatus having a Dean–Stark attachment until separation of water ceased. The mass was heated with boiling for an additional 3 h, the xylene was distilled in vacuum, and the residue was dissolved in 250 ml of benzene. To the benzene solution of (IX) was added with cooling 180 g

of thionyl chloride, and the mixture was boiled for 5 h. The excess thionyl chloride and benzene were distilled in vacuum, the residue was dissolved in 400 ml of benzene, and the benzene solution was washed with an aqueous solution of sodium carbonate and water and evaporated in vacuum. To the residue was added 112 g of sodium iodide and 0.5 liter of acetone and the mixture was boiled for 40 h. The inorganic layers were filtered and the acetone solution, containing 83.4 g of (X) (Hal=I), after purification with carbon was used for alkylation of (II).

6-Methoxy-8-(4'-phthalimidopentylamino)quinoline (XI). The acetone solution of (X) (Hal=I), obtained in the preceding step, was evaporated in vacuum. To the residue was added 51.6 g of dry sodium carbonate and a methanol solution of 42.4 g of (II). The methanol was distilled in vacuum, 200 ml of xylene was added to the residue, traces of water were distilled with xylene, after which the xylene solution of a mixture of materials was boiled with energetic mixing for 20 h. The inorganic layers were filtered, the xylene was distilled in vacuum, the residue was dissolved in 1 ml of methanol, 10-12% of a methanol solution of hydrogen chloride (to an acidic reaction to congo) was added, and the reaction mass was mixed for 10 h. The residue was filtered and washed with methanol. Yield of hydrochloride of (XI) was 72 g (65%), mp 149-151°.

6-Methoxy-8-(4'-aminopentylamino)quinoline, dihydrochloride (Quinocide, I). A mixture of 80 g of (XI) hydrochloride, 21.7 g of hydrazine hydrate, and 800 ml of ethanol was boiled for 3 h. The alcohol was distilled in vacuum, 400 ml of benzene and 480 ml of a 35% aqueous solution of potassium hydroxide were added, and the mass was stirred for 30 min at 40-50°. The benzene layer was separated, and the aqueous basic layer was extracted additionally with benzene. The benzene solution was washed with water, clarified with carbon, and evaporated, and the residue was distilled in vacuum. The yield of base (I) was 42.6 g (91%), bp 195-197° (2 mm).

A solution of 41.9 g of base in 100 ml of absolute ethanol was added with stirring to a solution of 14.8 g of hydrogen chloride in 250 ml of ethanol. Heating is observed upon mixing of reagents and a transparent bright orange solution is formed, from which the precipitate of (I) dihydrochloride rapidly comes out. Yield was 52 g (95.3%), mp 227-229°.

LITERATURE CITED

1. M. B. Braude, and V. I. Stavrovskaya, Zh. Obshch. Khim., 26, 878 (1956).
2. R. C. Elderfield, E. F. Claflin, H. E. Mertel, et al., J. Amer. Chem. Soc., 77, 4819 (1955).
3. O. Yu. Magidson, I. T. Strukov, and M. D. Bobyshev, Zh. Prikl. Khim., 9, 304 (1936).
4. Yu. S. Tsizin and V. I. Shvedova, Author's Certificate No. 242900; Izobreteniya, No. 16 (1969).
5. O. Yu. Magidson and I. T. Strukov, Arch. Pharm. (Weinhaim), 271, 359 (1933).
6. R. S. Tipson and M. A. Clapp, J. Org. Chem., 11, 292 (1946).
7. F. Giral, Chem. Abstr., 40, 5052 (1946).
8. L. Haskelberg, 12, 434 (1947).
9. J. Crum, and R. Robinson, J. Chem. Soc., 561 (1943).
10. K. S. Topchiev, Dokl. Akad. Nauk SSSR, 63, 147 (1948).
11. E. E. Mikhlina, A. D. Yanina, and L. N. Yakontov, Khim.-Farmats. Zh., No. 6, 26 (1970).
12. E. E. Mikhlina, A. D. Yanina, I. A. Kuznetsova, et al., Author's Certificate No. 253074; Izobreteniya, No. 30 (1969).
13. M. B. Braude and V. I. Stavrovskaya, Med. Prom. SSSR, No. 7, 19 (1957).