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WORK ON THE SYNTHESIS OF ANTIMALARIAL DRUGS IN THE USSR

by

Professor V. I. Stavrovskaya and
A. F. Bekhli, Candidate of Medical Sciences

Synthetic Drugs Department, Martsinovskiy Institute of Medical Parasitology
and Tropical Medicine of the USSR Ministry of Health, Moscow*

Work on the synthesis of antimalarial compounds began in the USSR in 1929 and as early as 1933 the Soviet-manufactured drugs Plasmocide** (6-methoxy-8- $\sqrt{3}$ '-diethylaminopropyl]-aminoquinoline) and Acriquine (3-chloro-7-methoxy-9- $\sqrt{4}$ '-diethylamino-1-methylbutyl]-aminoacridine) were being widely used for malaria treatment.

The following drugs were synthesized later:

Bigumal: N¹-p-chlorophenyl-N⁵-isopropylbiguanide (1947)

Haloquine (Cycloquine): 7-chloro-4 $\sqrt{3}$ '5'bis(diethylaminomethyl)-4'oxyphenyl]-aminoquinoline (1955)

Quinocide: 6-methoxy-8-(4'-aminopentyl)-aminoquinoline (1956), and

Chloridine: 2,4-diamino-5-p-chlorophenyl-6-ethylpyrimidine (1957)

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** The following recommended international non-proprietary names correspond to the Soviet names of the quoted drugs:

Plasmocide	-	Fourneau 710
Acriquine	-	Mepacrine
Bigumal	-	Proguanil
Haloquine	-	Amodiaquine
Quinocide	-	Primaquine
Chloridine	-	Pyrimethamine

It should be stressed that in some instances (acriquine, haloquine, quinocide, plasmocide) the Soviet compounds are not identical with the corresponding drugs but should be regarded as their equivalents.

This work made it possible to ensure the wide development of mass curative and prophylactic measures in malaria control and thus to speed up malaria eradication in the USSR.

Research work on the synthesis of antimalarial compounds has been carried out in the main in three scientific establishments, i.e. the Synthesis Laboratory of the Academy of Sciences (L.A.S.I.N.), the All-Union Institute for Chemopharmaceutical Research (V.N.I.K.h.F.I.) and the Institute of Malaria and Medical Parasitology (now the I.M.P.I.T.M.). Certain subjects of research were dealt with in other institutes, for example, in the Institute of Precision Chemical Technology.

The search for new and more effective antimalarial compounds has been carried out in various directions but particularly thorough research was done on derivatives of 9-aminoacridine, 4- and 8- aminoquinoline, the biguanides, the sulfonamides and the pyrimidines. The aim of the research was (1) the synthesis of highly effective antimalarial drugs on the basis of study of the relationship between chemical structure and effectiveness; (2) the working out of new and more practical methods of producing a number of antimalarials commonly used for treatment of malaria; (3) determination of the structure of highly effective drugs used abroad and their production.

1. Derivatives of 8-aminoquinoline.

The structure of plasmoquine was established in 1931 by Knunyants, Topchiyev & Chelintsev.¹ In 1941 Topchiyev & Braude^{2,3,4} worked out an original method of obtaining plasmoquine. The ready availability of the initial materials and the high yields at all stages of synthesis indicate the great advantages of this method over other methods of production known at that time.^{5,6}

The synthesis and industrial production of plasmocide were due to the work of Magidson & Strukov.⁷ The method of synthesizing plasmocide is simpler than in the case of plasmoquine.

At the same time it was found that the use of plasmocide in conjunction with acriquine is perfectly permissible from the point of view of side effects, whereas the plasmoquine-acriquine combination may cause serious complications.

Study of the link between the structure and the antimalarial effectiveness of 8-aminoquinoline derivatives led to the discovery that the length and degree of branching of the side chain affect the effectiveness of a compound against malaria.^{8,9,10,11} It was found that the form of the link between the nucleus and the side chain is of importance in regard to antimalarial activity in 8-aminoquinoline derivatives. Thus it became obvious that if a secondary amino group is replaced by a tertiary¹⁰ amino group or other groups (as ether linkage¹² or a carbonyl¹³ or ketone¹⁴ group) the compounds lose their antimalarial effect almost entirely.

Research on the character of the terminal amino group in the side chain led to the synthesis of a highly effective new drug, quinocide (Stavrovskaya & Braude^{15,16}) which ensured radical cure of P. vivax malaria in 97-99 per cent. of cases. (See Appendix II.) The wide use of quinocide in the terminal phase of malaria eradication programme in the USSR sharply reduced the time needed for eradicating the residual foci and decreased the consumption of DDT and BHC residual insecticides.

2. Derivatives of 4-aminoquinoline

The foundation for the synthesis of highly active antimalarial compounds derived from 4-aminoquinoline was laid by the work of Magidson & Rubtsov,¹⁷ who obtained derivatives of 6-methoxy-4-dialkylamino-alkylaminoquinoline which possess antimalarial properties.¹⁸

Research on the replacement of side-chain aliphatic amines by amino-alkylarylamines led to the synthesis of a new highly active drug, Haloquine (Cycloquine) (Stavrovskaya^{19,20}).

The great therapeutic value of 4-aminoquinoline derivatives (chloroquine, haloquine, amodiaquine) gave impetus to the search for new methods of synthesizing them, since the methods already described were complicated and required the use of expensive initial products.^{21,22}

In the Soviet Union a new method of synthesizing 4-aminoquinoline derivatives, and particularly chloroquine, was worked out which had some important advantages over the other methods available (Bekhli,^{23,24,25}). This method is based on the use of cheap initial raw material, is easy to carry out and gives consistent yields at every stage of synthesis, which makes it easy to use it industrially. (See Appendix I.)

3. Derivatives of 9-aminoacridine.

The structure of mepacrine was established in 1933 (Knunyants, Chelintsev et al.^{26,27} and was confirmed by synthesis of the drug. The synthesis and industrial methods of production of this drug were worked out by members of the staff of the All-Union Institute for Chemopharmaceutical Research (Magidson, Grigorovski et al.^{28,29}). Large-scale industrial production of acriquine was developed in 1937. By that time the drug had been studied in experiments on birds, under clinical conditions and in extensive field trials in various zones of the USSR and methods of using it for chemotherapeutic and chemoprophylactic purposes had been worked out and tested in practice.

A number of chemists and biologists studied the link between the structure of acriquine analogues and their effectiveness against malaria. Research was carried out in two directions: (1) the effect of changes in the side chain; (2) the effect of substitution in the acridine nucleus. It was established that changes in the side chain (length and degree of branching of the chain, the character of the terminal amine, the introduction of a hydroxyl group) affect the antimalarial activity of a compound.^{30,31,32,33}

Study of the effect of substitution in the acridine nucleus showed that the introduction of certain substituents (e.g. a halogen) is of essential importance for the antimalarial activity of 9-aminoacridine derivatives.^{31,34,35,36,37} Some acriquine analogues were synthesized which possessed greater antimalarial activity than acriquine itself.^{36,37,38,39}

The importance of the methoxyl group in the acriquine molecule, as the group reducing the toxicity of the compound was discovered.³⁵

The replacement of the aliphatic side chain in 9-aminoacridine derivatives by a cyclic substituent leads to highly active compounds.^{40,41}

4. Derivatives of biguanide

In 1946, Soviet chemists had worked out independently a method of obtaining biguanide (Bekhli, Ufimtsev and Topchiyev) and its industrial production was started in 1949. The drug was produced under the name of bigumal and was widely used for the treatment of P. vivax malaria and particularly in the course of eradication of P. falciparum malaria.

5. Derivatives of pyrimidines

The great effectiveness of pyrimethamine against malaria attracted the attention of Soviet chemists. Magidson & Volkova⁴³ worked out a method of industrial production.

In 1959 production of pyrimethamine under the name of chloridine, began on an industrial scale.

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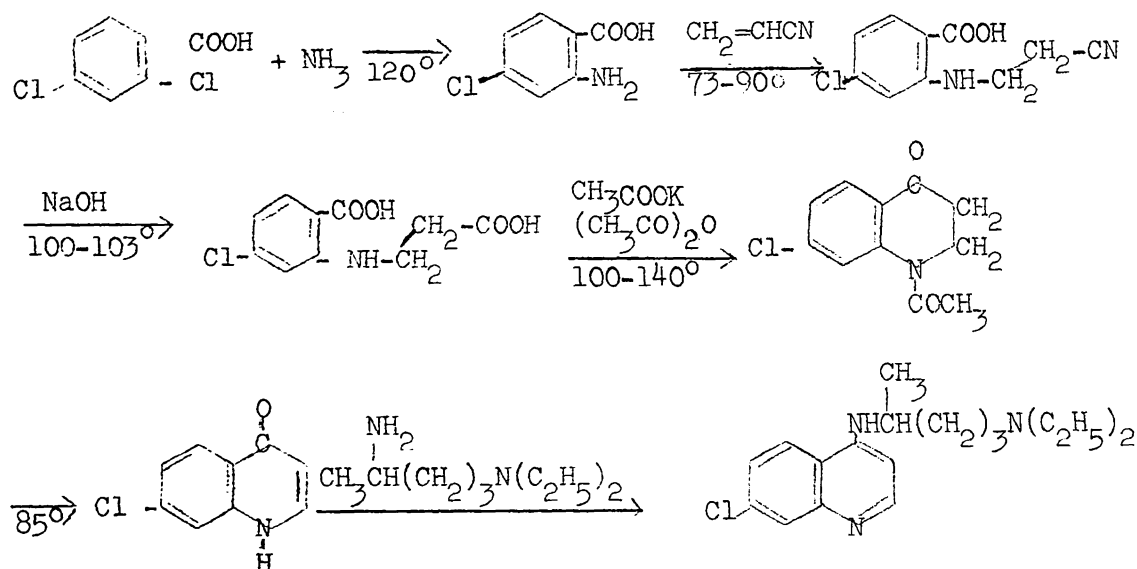
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A NEW METHOD OF SYNTHESIZING 4-AMINOQUINOLINE DERIVATIVES

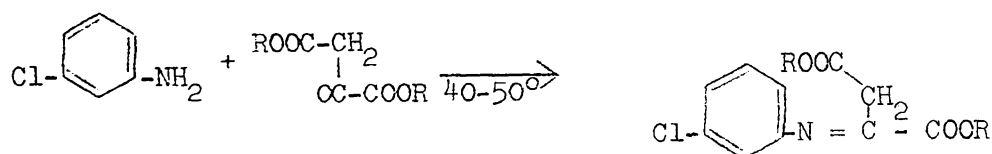
The advantage of the new method of synthesis over those now used (the Surrey-Hammer²¹ and Price-Roberts²² methods) resides in the fact that a cheap initial raw material is used (acrylonitrile and 2,4-dichlorobenzoic acid) instead of the expensive material used in the other methods described (ethoxymethylenemalonic ester or oxalo-acetic ester and m-chloraniline).

In the new method synthesis takes place at not too high a temperature (100-170°) whereas in the other methods mentioned high temperatures (up to 275°) are required and this complicates industrial production.

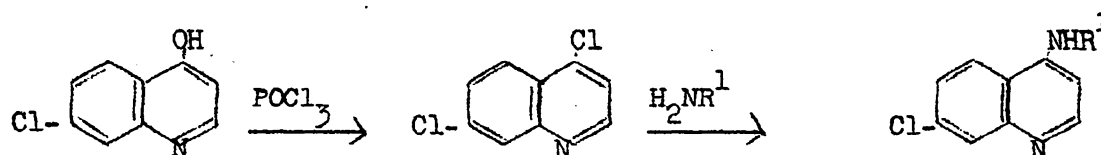
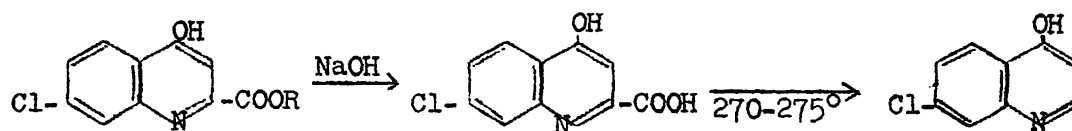
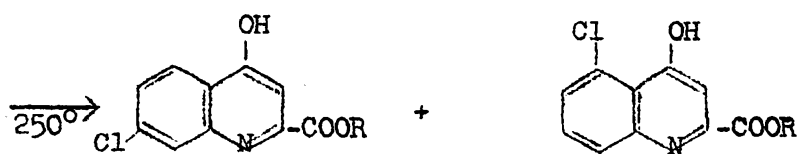
A diagram showing the new method of synthesis follows:



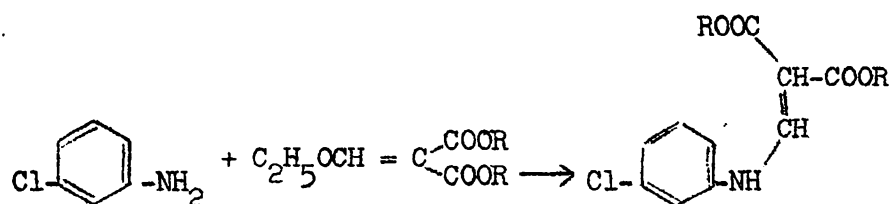
The synthesis of chloroquine by the Surrey-Hammer method can be expressed diagrammatically as follows:



Appendix I



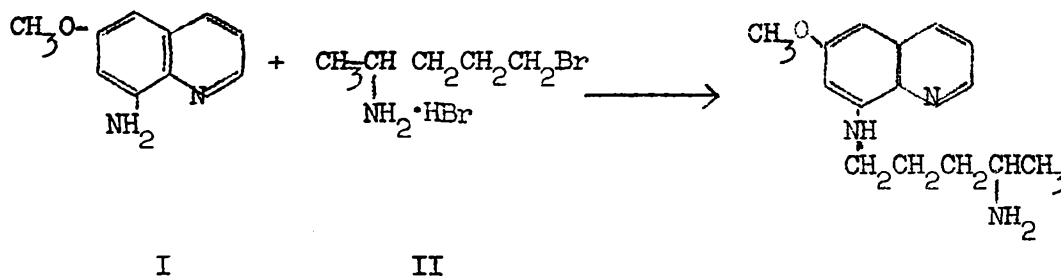
The Price-Roberts method is based on the condensation of *m*-chloraniline with ethoxymethylenemalonic ester as follows:



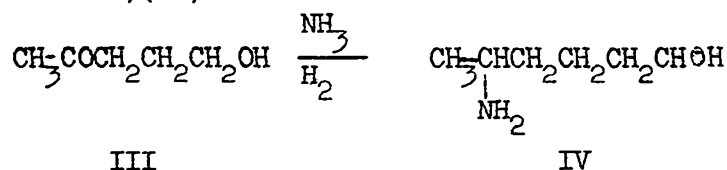
and proceeds thereafter in the same way as the Surrey-Hammer method.

THE SYNTHESIS OF QUINOCIDE

Quinocide, or 6-methoxy-8-(4-aminopentyl)-aminoquinoline is obtained by condensation of 6-methoxy-8-aminoquinoline(I) with hydrobromide of 2-amino-5-bromopentane(II).



The initial compound for obtaining the side chain is γ -acetopropyl alcohol(III) which is transformed through reductive amination into 2-amino-5-pentanol (yield 75 per cent.)(IV).



By heating with 48 per cent. hydrobromic acid the 2-amino-5-pentanol(IV) is transformed into hydrobromide of 2-amino-5-bromopentane(II) (yield 90-95 per cent.).

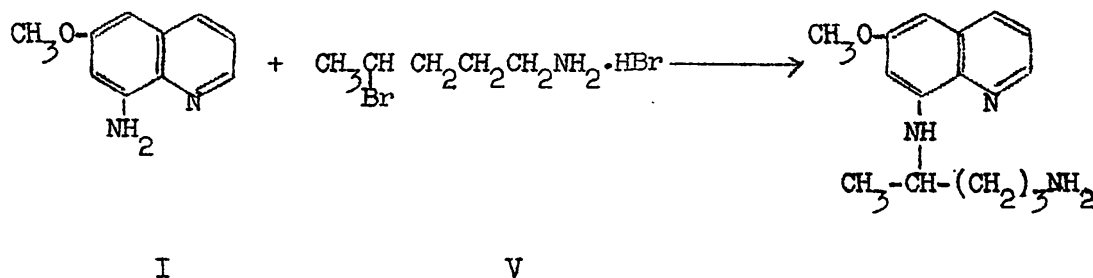
This method of obtaining quinocide has an undoubted advantage over the method of synthesizing primaquine described by Elderfield:

(1) The synthesis of quinocide is simpler in production since (a) it occurs in three stages as against the five stages required for the synthesis of primaquine, (b) the synthesis of primaquine requires the use of liquid ammonia and thionyl bromide, (c) in the synthesis of primaquine the intermediate 5-chloro-2-pentanol(VII) is unstable at room temperature.

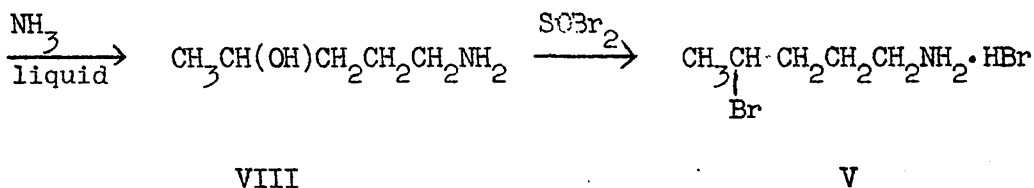
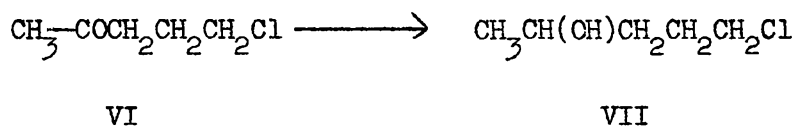
(2) The side chain in quinocide synthesis is obtained with a high yield whereas in primaquine synthesis the side chain yield is low.

Appendix II

Primaquine or 6-methoxy-8-(4-amino-1-methylbutyl)-aminoquinoline was synthesized by Elderfield in 1946 by the condensation of 6-methoxy-8-aminoquinoline(I) with 2-bromo-5-aminopentane hydrobromide (J. Amer. chem. Soc., 1946, 68, 1524 and 68, 1518).



The initial product for obtaining the side chain was γ -acetopropyl-chloride (VI) which was reduced to 5-chloro-2-pentanol(VII). The replacement of chlorine by the amino group was carried out in a liquid ammonia medium. The 5-amino-2-pentanol(VIII) which was formed was converted into 2-bromo-5-aminopentane HBr salt(V) by interaction with thionyl bromide.



When describing this synthesis Elderfield noted the instability of 5-chloropentanol at room temperature and the need to use liquid ammonia and thionyl bromide. In addition, according to published data, yields are insignificant at the amination stage (30 per cent.) and in condensation (28 per cent.).

After the synthesis of quinocide in 1952 (Chem. Abstr., 1952, 47, 277 and J. Amer. chem. Soc., 1955, 77, 4816), Elderfield published a second method of synthesizing primaquine by condensation of 6-methoxy-8-aminoquinoline with

Appendix II

2-bromo-5-phthalimidopentane. According to the published data the yield of primaquine by this method is somewhat higher than in the first method (about 40 per cent.). However, it is very difficult to calculate to what extent it is more economical than the first method described.