125. *Contributions to the Chemistry of Synthetic Antimalarials. Part II. Tetrahydropamaquin.**

By H. J. Barber and W. R. Wragg.

The synthesis of 8-(4′-*diethylamino*-1′-*methylbutyl*)*amino*-6-*methoxy*-1 : 2 : 3 : 4-*tetrahydroquinoline*, hereinafter referred to as tetrahydropamaquin, and of some allied compounds, is described. Tetrahydropamaquin appears to be better absorbed and about four times less toxic than pamaquin, while possessing a comparable schizonticidal activity against *P. gallinaceum* and *P. lophuræ*.

No attempts at systematic modification of the quinoline nucleus of the pamaquin molecule have been recorded, and in this and the following paper the aim has been to confine the modification to a single simple step at a time, to determine how far the heterocyclic ring could be altered without loss of activity.

Tetrahydropamaquin thus had a double interest. First, it was a possible trace impurity in commercial pamaquin (prepared by a synthesis involving catalytic reductions) and clearly a knowledge of its toxicity and activity was of some importance. Secondly, the reduction of the quinoline nucleus to the tetrahydro derivative would convert the pyridine ring into one of aliphatic character, without appreciably altering the structure or complexity of the entire molecule.

Few tetrahydroquinolines have figured in the chemotherapy of malaria and even the parent substance,

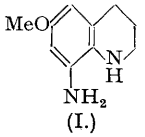
* Much of the work described here forms the subject of B.P. Application 3340/43. Since this paper was submitted, (I) above has been described, together with its picrate and iminazole derivatives, in a note by Price and Herbrandson (*J. Amer. Chem. Soc.*, 1946, **68**, 910).

8-*amino*-6-*methoxy*-1 : 2 : 3 : 4-*tetrahydroquinoline* (I), had not hitherto been described. Two routes to tetrahydropamaquin were possible; direct reduction of pamaquin, or the introduction of the side chain into the parent tetrahydroquinoline. The latter method was preferred in the first place. The separation of tetrahydropamaquin from any unreduced pamaquin would not have been expedient since bases of this type are all high-boiling viscous liquids not characterised by crystalline salts. Moreover, many of the normal methods of reducing quinolines to tetrahydroquinolines would remove the side chain. All the tetrahydroquinolines described were preserved in an oxygen-free atmosphere, as they discoloured rapidly in contact with air.

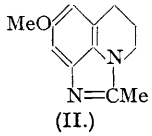
The catalytic reduction of 8-nitro-6-methoxyquinoline was studied in detail, since the presence of the tetrahydro-compound as an impurity in technical 8-amino-6-methoxyquinoline concerned the first object of this work. Most previous workers recorded melting points for 8-amino-6-methoxyquinoline between 41° and 42°, except Tschitschibabin and Hoffmann (*Compt. rend.*, 1939, **208**, 525), who gave 52°. Reduction with ammonium sulphide (or its equivalent), iron and acid, and stannous chloride has commonly been used in the preparation of this intermediate. Catalytic reduction in acetic acid solution was employed by Rothmann (D.R-P. 567,923, 1931), and recently Crum and Robinson (*J.*, 1943, 561), using Raney nickel catalyst in methanol, obtained a product, m. p. 41°. Further, Mosher (Pennsylvania State College, Ph.D. Thesis, 1942) reported that catalytic reduction of the corresponding 6-ethoxy-compound using Raney nickel was unsatisfactory, yielding a mixture of products. Our preliminary catalytic reductions of 8-nitro-6-methoxyquinoline in ethyl acetate with Raney nickel gave products which rapidly discoloured and partly decomposed on distillation. This was traced to over-reduction, and the readily oxidisable tetrahydroquinoline (I) was isolated (<1% when the reduction temperature remained <75°). The optimum reduction temperature was found to be 60—65°.

Crystallisation of the slightly water-soluble hydrochloride of 8-amino-6-methoxyquinoline (cf. Tschitschibabin and Hoffmann, *loc. cit.*) separated this base from the more soluble hydrochloride of the unstable tetrahydro-base. The regenerated base then proved quite stable in air, was almost white, and had m. p. 50—51°.

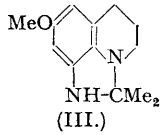
When the preparation of (I) by catalytic reduction of 8-amino-6-methoxyquinoline was attempted it was found that reaction with the solvent, ethyl acetate, in the presence of Raney nickel at 110°/40 atmospheres led to the formation (40% yield) of 5-*methoxy*-2-*methyl*-1 : 7-*trimethylenebenziminazole* (II), together with the required product (I). This was attributed to the catalytic effect of an impurity in the ethyl acetate since under



(I.)



(II.)



(III.)

apparently identical conditions, but with different batches of materials, smooth reduction to (I) alone resulted. Contamination of (I) by side reaction with the solvent was eliminated when dioxan was substituted. The iminazole (II) was prepared directly from (I), the latter being further characterised as its *dibenzoyl* derivative. Acetone condensed with (I) to form a well-defined but somewhat unstable *anhydro*-compound (III).

The 5-diethylaminopentan-2-one used in this work was purified *via* its diethyl acetal. 5-Diethylamino-2 : 2-diethoxypentane (IV) was prepared from the purified ketone in 95% yield compared with the 60% yield obtained with crude ketone. This acetal underwent thermal decomposition in the presence of ammonium chloride at temperatures above 140° with the elimination of one molecule of alcohol from each molecule of acetal, leaving 5-*diethylamino*-2-*ethoxypent*-2-*ene* (V).

$CH_3 \cdot C(OEt) \cdot CH \cdot CH_2 \cdot CH_2 \cdot NEt_2$ (V.)

$CH_2 \cdot C(OEt) \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot NEt_2$ (VI.)

Ozonolysis gave no formaldehyde, thus excluding a terminal methylene group as in (VI).

The acetal (IV) condensed in the presence of ammonium chloride with the tetrahydroquinoline (I) to form the *anil* (VII). The monoethoxy base (V) condensed similarly and the product, on reduction, yielded *tetrahydropamaquin*. Hydrogenation of the anil (VII) failed in the presence of Raney nickel and platinum on charcoal catalysts. Sodium in ethyl alcohol produced only incomplete reduction, but a 60% yield of tetrahydropamaquin was realised with sodium in amyl alcohol. Tetrahydropamaquin has also been prepared directly from pamaquin by the catalytic method and by means of sodium in amyl alcohol, the product being identified by refractive index, analysis, and boiling point.

It was found that pamaquin was not acetylated by treatment with acetic anhydride in pyridine. Under these conditions, therefore, the 1 position of tetrahydropamaquin alone should have acetylated. However, the reaction product proved complex, the iminazole (II) being isolated as picrate in 10% yield together with an unidentified demethylated compound of totally unexpected properties in *ca.* 10% yield.

Dr. A. O. Seeler, of the Merck Institute for Therapeutic Research, Rahway, N.J., U.S.A., has kindly furnished the following biological data obtained from his initial examination of our product :

" The activity of the isethionate of tetrahydropamaquin was compared with that of the isethionate of pamaquin against certain avian malaria infections. Both drugs were administered as aqueous solutions into the crops of the birds once daily. Tetrahydropamaquin was found to be approximately two and a half times as active as pamaquin against the schizonts of *Plasmodium gallinaceum* in chicks and about equally as active as

pamaquin against the schizonts of *P. lophuræ* in ducklings. Both tetrahydropamaquin and pamaquin prolonged the incubation period of sporozoite induced *P. gallinaceum* infections when administered at the highest tolerated dose levels for three days after the inoculation of the chicks.

" Determinations of the blood concentrations in groups of rats three hours after the oral administration of 10 mg. per kg. of tetrahydropamaquin and of 10 mg. per kg. of pamaquin, gave average blood values of 260 micrograms per l. of tetrahydropamaquin and 100 micrograms per l. of pamaquin. Neither drug could be detected in the blood twenty-four hours after a single oral dose of 10 mg. per kg.

" The $L.D._{50}$ of tetrahydropamaquin after four weeks of administration to 200 gram albino rats was found to be 30 mg. per kg. while the $L.D._{50}$ of pamaquin in the same experiment was found to be about 7·5 mg. per kg.

" Two *Macacus Rhesus* monkeys were given 10 mg. per kg. of tetrahydropamaquin by stomach tube once daily for two weeks. Neither monkey showed any evidence of distress and there was no weight loss. Gross examination of the organs on autopsy revealed no evidence of pathological changes. One of the two monkeys developed a slight normocytic anæmia during the experiment. Methæmoglobin could not be detected in either monkey."

A full account of the results of subsequent biological examination in the Biological Laboratories, May & Baker Ltd., will be published elsewhere. This work suggests a somewhat modified conclusion in that the decreased toxicity of tetrahydropamaquin appears to be offset by a corresponding decrease in antimalarial activity. Tests in our own laboratories have shown that the iminazole (II) is devoid of activity against *P. gallinaceum* in chicks when administered subcutaneously.

Experimental.

8-Amino-6-methoxyquinoline.—8-Nitro-6-methoxyquinoline (150 g.) was hydrogenated in ethyl acetate (750 c.c.) at 60—65°/20 atmospheres in the presence of Raney nickel catalyst (10 g.), until a definite break in the hydrogen absorption curve was observed. The residual oil, after removal of solvent, was converted into hydrochloride and crystallised from hot water. The hydrochloride was washed free of mother liquors with cold 2N-hydrochloric acid until the washings did not deepen in colour on addition of a few drops of ferric chloride solution—a test for over-reduced product. A second crystallisation was sometimes necessary. The pure hydrochloride was dissolved in the minimum amount of water and basified with 50% sodium hydroxide. The solid base was collected, washed free of alkali, dried, and distilled as a bright yellow oil b. p. 170°/4 mm., which recrystallised in rhombs, m. p. 50—51° (102 g., 80% yield). The bright red crystalline *monoisethionate*, obtained by treating 8-amino-6-methoxyquinoline dissolved in alcohol with concentrated isethionic acid, crystallised from alcohol as rectangular rods, m. p. 153—154° (corr.), soluble in water (Found : N, 9·05. $C_{10}H_{10}ON_2,C_2H_6O_4S$ requires N, 9·3%).

Catalytic Reduction of 8-Amino-6-methoxyquinoline.—(a) *Ethyl acetate as solvent.* 8-Amino-6-methoxyquinoline (100 g.) was hydrogenated in ethyl acetate (385 c.c.) at 110°/40 atmospheres in the presence of 25% Raney nickel. After 17 hours the absorption of hydrogen ceased. Two fractions were obtained on distillation in a hydrogen atmosphere. One, b. p. 175—185°/1 mm., a yellow oil (50 g.), proved to be the required product, *8-amino-6-methoxy-1 : 2 : 3 : 4-tetrahydroquinoline* (I) (Found : C, 67·3; H, 7·87. $C_{10}H_{14}ON_2$ requires C, 67·4; H, 7·86%). The fraction, b. p. 195—200°/1 mm., crystallised to a yellow solid (25 g.), m. p. 113—116°. Purification raised this to 120—121° (corr.), mixed m. p. 120—121° (corr.) with authentic iminazole (II). The base was confirmed to be identical with (II) by preparation of the picrate, m. p. 252—254° (corr.).

Authentic iminazole (II) was prepared from the tetrahydroquinoline (I) (20 g.) by refluxing with glacial acetic acid (20 c.c.), acetic anhydride (20 c.c.), and a few drops of concentrated sulphuric acid for 10 hours in hydrogen. *5-Methoxy-2-methyl-1 : 7-trimethylenebenziminazole* (II), liberated by excess ammonia, was extracted with chloroform, and crystallised twice from hot water (2 l.) as fluffy colourless needles (15 g.), m. p. 120—121° (corr.) (Found : C, 71·1; H, 7·15; N, 14·1. $C_{12}H_{14}ON_2$ requires C, 71·3; H, 6·93; N, 13·9%). The *picrate* crystallised from acetone in long golden needles, m. p. 253—254° (corr.) (Found : N, 16·4. $C_{12}H_{14}ON_2,C_6H_3O_7N_3$ requires N, 16·2%).

(b) Subsequent reductions as (a) above gave no iminazole on careful fractionation. The high-boiling fractions were proved to be the tetrahydroquinoline (I) by conversion in good yield to *picrate* as brown needles from alcohol, m. p. 163—164° (corr., decomp.) (Found on picrate dried over sulphuric acid at 25°/10 mm. : N, 16·5. $C_{10}H_{14}ON_2,C_6H_3O_7N_3,H_2O$ requires N, 16·5%. Found on picrate dried at 80°/10 mm. : N, 17·2. $C_{10}H_{14}ON_2,C_6H_3O_7N_3$ requires N, 17·2%). The picrate in acetone solution rapidly developed a dark green colour and decomposed on warming, whereas it could be readily crystallised from alcohol.

(c) *Dioxan as solvent.* 8-Amino-6-methoxyquinoline (106 g.) was hydrogenated in dioxan (300 c.c.) at 110—135°/40 atmospheres in the presence of 24% Raney nickel catalyst. An uptake of 110% of the theoretical for 4H was observed. The tetrahydroquinoline (I) was obtained as a bright yellow oil (87 g.), b. p. 190°/3 mm. It slowly crystallised in thick plates, m. p. 43—45° (Found : C, 67·9; H, 7·7; N, 15·7. Calc. for $C_{10}H_{14}ON_2$: C, 67·4; H, 7·86; N, 15·7%). The base was converted into the picrate, m. p. 163—164°. The *hydrochloride*, prepared by precipitation of an aqueous solution with acetone, crystallised from dry methanol–ether as thick colourless rhombs, m. p. 211—212°, which slowly became red in air (Found : C, 55·6; H, 6·99; Cl, 16·5. $C_{10}H_{14}ON_2,HCl$ requires C, 56·0; H, 7·04; Cl, 16·55%).

The tetrahydroquinoline (I) was treated with benzoyl chloride (2·2 mol.) in pyridine; the *dibenzoyl* derivative, isolated in the usual manner, crystallised from aqueous acetone as colourless elongated rhombic prisms, m. p. 205—206° (corr.) (Found : C, 74·5; H, 5·55; N, 7·4. $C_{24}H_{22}O_3N_2$ requires C, 74·6; H, 5·73; N, 7·25%).

The tetrahydroquinoline (I) (8 g.) was warmed with acetone (18 c.c.) in a nitrogen atmosphere. After 24 hours the red liquor was decanted from a crop of large reddish needles (3 g.) which were then washed free of red contamination with very small portions of acetone. They crystallised from light petroleum (b. p. 80—100°) as small colourless needles, m. p. 119° (corr.), which became red in air (Found : C, 71·6; H, 8·25; N, 12·9; OMe, 14·3. $C_{12}H_{15}N_2(OMe)$ requires C, 71·55; H, 8·25; N, 12·8; OMe, 14·25%). The compound was therefore the anhydro-condensation *product*. The formulation 5-methoxy-2 : 2-dimethyl-1 : 7-trimethylene-2 : 3-dihydrobenziminazole (III) was preferred because catalytic reduction in ethyl acetate in the presence of Adams's catalyst at 20°/1 atmosphere failed, indicating that the substance was probably not the *iso*propylidene derivative. However, hydrolysis of the product not only occurred when it was treated with cold hydrochloric acid but also when its solution in 98% alcohol was treated with alcoholic picric acid, which precipitated the picrate of the tetrahydroquinoline (I).

5-Diethylamino-2-ethoxypent-2-ene (V).—Redistilled 5-diethylamino-2 : 2-diethoxypentane, b. p. 121—122°/22 mm. (200 c.c.), was vigorously stirred with ammonium chloride (5 g.) in a flask fitted with a short column. When the internal

temperature was raised to 140°, alcohol began to distil. The temperature was maintained at 200° for 2 hours. After 1 hour, a further quantity of ammonium chloride (5 g.) was added to ensure a complete reaction. Practically the theoretical volume of alcohol was collected. The evil-smelling residue was distilled and the fraction, b. p. 86°/13 mm. (75% yield), proved to be the unsaturated monoethoxy *base* (V) (Found : OEt, 24·5. $C_9H_{18}N(OEt)$ requires OEt, 24·4%). Hydrogenation of a 20% solution in ethanol in the presence of 8% Raney nickel at 60°/30 atmospheres resulted in 95% of the theoretical uptake for one double bond.

The monoethoxy base (V) (0·925 g.) in carbon tetrachloride (10 c.c.) was ozonolysed at −10°. No formaldehyde could be detected as its 2 : 4-dinitrophenylhydrazone.

Tetrahydropamaquin.—(a) *Condensation with 5-diethylamino-2 : 2-diethoxypentane.* 8-Amino-6-methoxy-1 : 2 : 3 : 4-tetrahydroquinoline (52 g.) was vigorously stirred with 5-diethylamino-2 : 2-diethoxypentane (79 g.) and ammonium chloride (0·4 g.) in a slow stream of hydrogen. The internal temperature was raised from 145° to 160° during one hour and from 160° to 190° during the second hour; 31 c.c. (theory, 36·5 c.c.) of alcohol distilled. Sodium bicarbonate (0·5 g.) was added to the dark yellow reaction mixture and stirring continued for 10 minutes. Ethyl acetate (350 c.c.) was added, but attempted hydrogenation of the crude anil in the presence of platinum on charcoal catalyst at 60°/32 atmospheres failed. The anil was recovered and the fraction, b. p. 180—190°/0·1 mm. (65 g.), 8-(4′-*diethylamino*-1′-*methylbutylidene*)*amino*-6-*methoxy*-1 : 2 : 3 : 4-*tetrahydroquinoline* (VII) collected (Found : C, 71·6; H, 9·8. $C_{19}H_{31}ON_3$ requires C, 71·9; H, 9·8%). Attempted reduction of this base in ethyl acetate (300 c.c.) at 60°/32 atmospheres, using 6% platinum on charcoal catalyst or 9% Raney nickel, failed.

The recovered anil was poured quickly into anhydrous amyl alcohol (1600 c.c.) at 80° to which sodium (90 g.) had just previously been added. As much of the sodium as possible was dissolved by refluxing the alcohol; the residue was dissolved by addition of methanol. An atmosphere of hydrogen was maintained over the reaction mixture during the following operations. Unchanged anil was hydrolysed by warming on the steam-bath with excess of hydrochloric acid. The amyl alcohol was removed by rapid steam distillation, after neutralisation (litmus). The residual liquors were acidified (Congo red) and ether-extracted, and then basified strongly with 50% sodium hydroxide before exhaustive ether extraction. The latter extract was dried over potassium carbonate and carefully fractionated, using an electrically heated Vigreux column, to yield 8-(4′-*diethylamino*-1′-*methylbutyl*)*amino*-6-*methoxy*-1 : 2 : 3 : 4-*tetrahydroquinoline* (*tetrahydropamaquin*) (33 g.), b. p. 175—180°/0·05 mm., $n_D^{25°}$ 1·5435 (Found : C, 71·5; H, 10·1; N, 13·1. $C_{19}H_{33}ON_3$ requires C, 71·5; H, 10·35; N, 13·2%). Tetrahydropamaquin was stored under carbon dioxide.

(b) *Condensation with unsaturated monoethoxy base* (V). The preparation of tetrahydropamaquin, using this compound instead of the acetal, gave a product identical with that above (40% yield) (Found : OMe, 9·7. $C_{18}H_{30}N_3(OMe)$ requires OMe, 9·7%).

(c) *Reduction of pamaquin base.* 8-(4′-Diethylamino-1′-methylbutyl)amino-6-methoxyquinoline (36 g.) was reduced in anhydrous amyl alcohol (1300 c.c.) with sodium (100 g.), by the method described above for the reduction of the anil (VII). Tetrahydropamaquin (27·5 g.), b. p. 175—180°/0·05 mm., $n_D^{25°}$ 1·5445, was obtained (Found : C, 71·5; H, 10·0. Calc. for $C_{19}H_{33}ON_3$: C, 71·5; H, 10·35%).

8-(4′-Diethylamino-1′-methylbutyl)amino-6-methoxyquinoline (99 g.) was hydrogenated in dioxan (200 c.c.) in the presence of 20% Raney nickel catalyst at 120°/30 atmospheres until no further absorption of hydrogen took place. The crude base was dissolved in 2N-hydrochloric acid and ether-extracted. The acid liquor was basified and ether-extracted. Distillation of this extract yielded tetrahydropamaquin (85 g.), b. p. 175—180°/0·05 mm., $n_D^{20°}$ 1·5440.

Tetrahydropamaquin (15·5 g.) was converted into the hydrochloride in water (1 l.) saturated with carbon dioxide, made slightly acid (Congo red), and run with vigorous stirring, under an atmosphere of carbon dioxide, into a slightly alkaline (phenolphthalein) solution of 2 : 2′-dihydroxy-1 : 1′-dinaphthylmethane-3 : 3′-dicarboxylic acid (18·8 g.) in aqueous ammonia (3000 c.c.) containing sodium bisulphite (5 g.). The cream *salt* (31 g.) was collected, washed with air-free water containing a trace of sulphur dioxide, and dried (P_2O_5) (Found : N, 5·35. $C_{19}H_{33}ON_3,C_{23}H_{16}O_6$ requires N, 5·95%).

Acetylation of Tetrahydropamaquin.—Tetrahydropamaquin (10 g.) dissolved in dry pyridine (10 c.c.) was treated with acetic anhydride (3·5 c.c.). Next day it was heated on the steam-bath for 2 hours. The low-boiling material was removed at 0·01 mm. (up to 100°). The residue, in benzene (200 c.c.), was washed first with 2N-sodium hydroxide (50 c.c.) and then with water (25 c.c., 50 c.c.). The benzene layer was dried (Na_2SO_4) and evaporated. The residue distilled as a thick yellow oil (3 g.), b. p. 195°/0·05 mm., which was probably impure acetylated tetrahydropamaquin, and gave a picrate soluble in acetone.

The alkaline aqueous layer was neutralised, the water removed at room temperature, and the residue extracted with dry alcohol. The alcohol left a residue which distilled as a yellow oil mixed with a brown solid (4·8 g.). This mixture was dissolved in acetone (15 c.c.); light petroleum (15 c.c.) precipitated a white solid (0·9 g.) which was crystallised repeatedly from alcohol and obtained as small, colourless, irregular flat needles, m. p. 260—300° (slow decomp.) (Found : C, 58·8; H, 5·9; N, 12·2%. Repeat preparation, found : C, 58·6; H, 6·1; N, 12·25; OMe, <0·1%. The compound proved insoluble in camphor). The acetone–light petroleum liquors yielded a picrate (1·4 g.) which was recrystallised from a large volume of acetone, m. p. 249—251° (corr.). Mixed m. p. with authentic 5-methoxy-2-methyl-1 : 7-trimethylenebenziminazole picrate, 249—251° (corr.). From a separate experiment the iminazole was isolated, m. p. 115—116° (corr.). Mixed m. p. with authentic base, 115—119° (corr.) (Found : N, 13·6; OMe, 15·5. Calc. for $C_{11}H_{11}N_2(OMe)$: N, 13·88; OMe, 15·35%).

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