126. *Contributions to the Chemistry of Synthetic Antimalarials. Part III. An Open Ring Analogue of Tetrahydropamaquin.*

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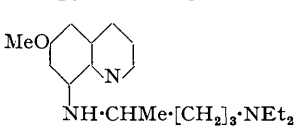
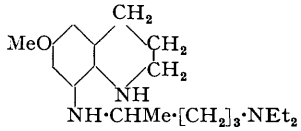
4-n-*Propylamino*-3-(4′-*diethylamino*-1′-*methylbutyl*)*aminoanisole*, a compound of strong structural similarity to tetrahydropamaquin [8-(4′-diethylamino-1′-methylbutyl)amino-6-methoxy-1 : 2 : 3 : 4-tetrahydroquinoline], has been prepared, and its hydrochloride shown to have only slight antimalarial activity against *P. gallinaceum* and to be ineffective against *P. relictum*. An interesting reaction involving the

replacement of a nitro-group by a hydrogen atom was observed during the acid hydrolysis of 3-*nitro*-4-(N⁴-*acetyl*-N¹-n-*propylsulphanilamido*)*anisole*, and also of the corresponding *p*-toluenesulphonamide.

In Part II (preceding paper) it was shown that antimalarial activity was retained when the pyridine ring of the pamaquin (I) molecule was reduced to the tetrahydro-derivative (II). The next step in this line of research was the examination of the closely analogous compound (III), differing in structure only by the opening of the reduced pyridine ring.



(I.)



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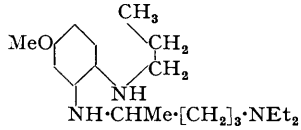
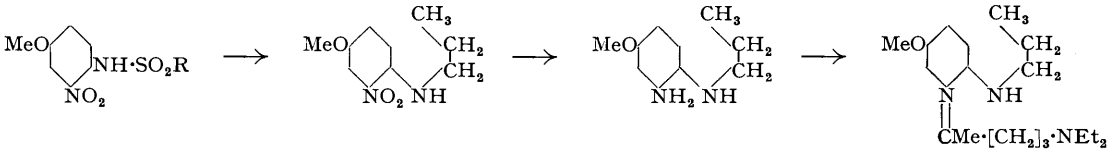


(III.)

This modification resulted in almost entire loss of antimalarial activity. Only three other active benzenoid derivatives appear to have been described in the literature (Fourneau *et al.*, *Ann. Inst. Pasteur*, 1930, **44**, 503); one of these showed definite activity in canaries, but was without effect in man.

Two compounds similar to our product have been described. Simonov (*J. Gen. Chem. Russia*, 1940, **10**, 1588) reported the preparation of 3-amino-4-(3′-diethylaminopropyl)aminoanisole by a route similar to that described here for 3-*amino*-4-n-*propylaminoanisole* (VI). Since this work was first completed Clemo and Swan (*J.*, 1944, 274) have described 4-amino-3-(5′-diethylamino-2′-pentyl)aminoanisole [the corresponding 4-nitro-compound having been described previously by Topeijev (*Compt. rend. Acad. Sci. U.R.S.S.*, 1935, **4**, 201) but not conclusively orientated] and the isomer, 3-amino-4-(5′-diethylamino-2′-pentyl)aminoanisole. The former compound contains the basic side chain in the same position relative to the methoxyl group as pamaquin, but it has not the close formal resemblance to it as has the compound (III).

Any route to (III) which involves successive direct alkylation reactions for the introduction of the two side chains is almost certain to give rise to mixtures. The following unambiguous synthesis was therefore devised :



(IV.) (V.) (VI.) (VII.)

3-Nitro-4-aminoanisole was converted into a *sulphonamide* (IV). It was found preferable to use the 4-N^4-acetylsulphanilamide rather than the 4-*p*-toluenesulphonamide, as on acid hydrolysis the former rapidly yields the sulphanilyl derivative which, being soluble in acid, is more readily hydrolysed to the free amine. The sulphonamide (IV) by alkylation with propyl bromide followed by drastic acid hydrolysis, gave the *nitroamine* (V). This hydrolysis was not uncomplicated, since partial elimination of the nitro-group occurred, and about 12% of 4-n-*propylaminoanisole* (VIII) was isolated.

The mechanism of this side reaction is being more fully examined, but some of its features are recorded here. Replacement of the nitro group by a hydrogen atom took place to almost precisely the same extent during the hydrolysis of both 3-*nitro*-4-(N⁴-*acetyl*-N¹-n-*propylsulphanilamido*)*anisole* (IX) and the corresponding p-*toluenesulphonamide* derivative (X). No low-boiling fraction corresponding to (VIII) could be detected when the sulphonamide (IV; R = C_6H_4·NHAc) was hydrolysed under identical conditions. During hydrolysis of the sulphonamide (X) brown gases were evolved, and in one experiment an attempt was made to absorb them in dilute alkali. Analysis of the alkali yielded values for total nitrogen and nitrite which agreed exactly, but which accounted for only 20% of the theoretical quantity of nitrogen, calculated on the basis of the 4-*n*-propylaminoanisole actually isolated. The fact that nitrate was absent was unexpected, but sufficient evidence has accrued to confirm that the nitro-group was indeed eliminated, although the nature of the reaction is at present obscure. It may be noted that it is the 3-nitro-group of 3 : 4-dinitroanisole which reacts with amines (Topeijev, *loc. cit.*), although here the predominant influence is probably the adjacent nitro-group in the 4-position. No oxides of nitrogen could be detected during the hydrolysis of the sulphonamide (IX), but this was not unexpected as sulphanilic acid was simultaneously formed in the acid hydrolysis mixture.

The unexpected physical properties of the nitroamine (V) prompted the alternative preparation of this intermediate by a less convenient method, *viz.*, the action of propylamine on 4-bromo-3-nitroanisole, to confirm its identity. Reduction of (V) gave the diamine (VI), a very readily oxidised base, which on condensation with 5-diethylamino-2 : 2-diethoxypentane yielded the anil (VII). This was reduced catalytically or by means of sodium in dry amyl alcohol to the required 4-n-*propylamino*-3-(4′-*diethylamino*-1′-*methylbutyl*)*aminoanisole* (III), which possessed the usual properties of this type of substance, being particularly susceptible to atmospheric oxidation and not readily yielding crystalline salts.

The product (III) showed only slight schizonticidal activity when administered subcutaneously at the maximum tolerated dose to chicks infected with *Plasmodium gallinaceum*, and it was ineffective by oral administration against *P. relictum* in canaries.

Experimental.*

(Melting points are corrected.)

3-*Nitro*-4-(N⁴-*acetylsulphanilamido*)*anisole*.—*p*-Acetamidobenzenesulphonyl chloride (500 g.) was added with cooling to 3-nitro-4-aminoanisole (300 g.) in pyridine (1050 c.c.). After 24 hours the sulphonamide was precipitated by pouring the reaction mixture into water (7 l.). Dilution of a solution of the crude product in 2N-sodium hydroxide (900 c.c.) with water (8 l.) precipitated an impurity, probably the disulphonamide, which was removed. Acidification of the filtrate with 2N-hydrochloric acid precipitated the required *sulphonamide*, m. p. 173—174°, 549 g. (84% yield) (Found: N, 11·5. $C_{15}H_{15}O_6N_3S$ requires N, 11·5%).

The corresponding *p*-toluenesulphonamide, prepared in a similar manner (90% yield), formed a less soluble sodium salt. It separated from methanol as yellow rhombs, m. p. 102—103° (m. p. 103·5—104° when prepared by direct nitration; Simonov, *loc. cit.*) (Found: N, 8·9. Calc. for $C_{14}H_{14}O_5N_2S$: N, 8·7%).

3-*Nitro*-4-(N⁴-*acetyl*-N¹-n-*propylsulphanilamido*)*anisole*.—*n*-Propyl bromide (539 c.c.) was added to 3-nitro-4-(*N*⁴-acetylsulphanilamido)anisole (869 g.) dissolved in 2N-sodium hydroxide (1507 c.c.) and alcohol (550 c.c.) and the mixture was refluxed for 16 hours. It was then stirred into a mixture of water (10 l.) and 2N-sodium hydroxide (1 l.). 3-*Nitro*-4-(N⁴-*acetyl*-N¹-n-*propylsulphanilamido*)*anisole* which separated was washed with water and crystallised twice from methanol (3 l.) as light brown irregular prisms, m. p. 147—149°, 610 g. (63% yield) (Found: N, 10·4; OMe, 7·8. $C_{17}H_{18}O_5N_3S(OMe)$ requires N, 10·3; OMe, 7·6%).

3-*Nitro*-4-(N-n-*propyl*-p-*toluenesulphonamido*)*anisole*.—3-Nitro-4-(*p*-toluenesulphonamido)anisole (644 g.) was treated with 2N-sodium hydroxide (1 l.), water (1·5 l.) and ethyl alcohol (1 l.) and the resulting suspension of sodium salt refluxed for 18 hours with propyl bromide (492 g.). 3-*Nitro*-4-(N-n-*propyl*-p-*toluenesulphonamido*)*anisole* was isolated by the addition of water (3 l.) and 2N-sodium hydroxide (1 l.), and crystallised twice from ethyl alcohol as lemon-yellow prisms, m. p. 108—109°, 562 g. (77% yield) (Found: N, 7·8; OMe, 8·7. $C_{16}H_{17}O_4N_2S(OMe)$ requires N, 7·7; OMe, 8·5%).

3-*Nitro*-4-n-*propylaminoanisole*.—(a) *Hydrolysis of* 3-*nitro*-4-(N⁴-*acetyl*-N¹-n-*propylsulphanilamido*)*anisole*. This sulphonamide (82 g.) was refluxed for 1 hour with a mixture of sulphuric acid (140 g. diluted to 200 c.c. with water) and glacial acetic acid (100 c.c.). A slow stream of nitrogen was passed through an identical hydrolysis on $\frac{1}{10}$ this scale and the effluent gas scrubbed with 2N-sodium hydroxide solution. No brown gases were evolved and the alkaline liquor in the traps gave a negative reaction for nitrate or nitrite. The dark red cold hydrolysis liquor was made alkaline (phenolphthalein) with 50% sodium hydroxide solution and the separated red oil extracted with three 1 l. portions of chloroform. The combined extracts were dried over potassium carbonate, the chloroform removed, and the residue fractionated using an electrically heated Vigreux column. Two fractions were obtained. One, a faintly red liquid, b. p. 65°/0·02 mm., $n_D^{20°}$ 1·5445, 4·0 g. (12% yield), proved to be 4-n-*propylaminoanisole* (Found: C, 72·8; H, 9·1; N, 8·8; OMe, 18·9, 18·7. $C_9H_{12}N(OMe)$ requires C, 72·7; H, 9·1; N, 8·5; OMe, 18·8%). The identity of this fraction was established by the preparation in pyridine of its p-*toluenesulphonamido*-derivative, which crystallised from light petroleum (b. p. 40—60°) in well-defined colourless rectangular rods, m. p. 53—55°, mixed m. p. 53—54° with 4-(*N*-*n*-propyl-*p*-toluenesulphonamido)anisole prepared by *n*-propylating 4-*p*-toluenesulphonamidoanisole (Reverdin, *Ber.*, 1909, **42**, 1523) (Found: C, 64·3; H, 6·9; N, 4·4; S, 10·2. $C_{17}H_{21}O_3NS$ requires C, 64·0; H, 6·6; N, 4·4; S, 10·05%). The other fraction, a deep red oily liquid, b. p. 120°/0·02 mm., 30 g. (71% yield) was 3-*nitro*-4-n-*propylaminoanisole* (Found: C, 57·0; H, 6·8; N, 13·5; OMe, 15·1. $C_9H_{11}O_2N_2(OMe)$ requires C, 57·1; H, 6·7; N, 13·3; OMe, 14·8%).

(b) *Hydrolysis of* 3-*nitro*-4-(N-n-*propyl*-p-*toluenesulphonamido*)*anisole*. This sulphonamide (91 g.) was refluxed for 1 hour with a mixture of sulphuric acid (175 g. diluted to 250 c.c. with water) and glacial acetic acid (400 c.c.). A slow stream of air was passed through the reaction mixture and then bubbled through a train of 3 absorption tubes, each containing 20 c.c. of 2N-sodium hydroxide. As the hydrolysis progressed brown gases were evolved. The apparatus was swept out with air at the end of the experiment and the bulked contents of the first two tubes analysed (total nitrogen, 0·09 g., which corresponded to 20% of the calculated quantity of nitrogen eliminated in the formation of the 5·1 g. of 4-*n*-propylaminoanisole isolated (see below). Nitrate absent. Nitrite, by permanganate titration, exactly equivalent to 0·09 g. nitrogen). Quantitative absorption of the gases evolved during the hydrolysis was not attempted.

The hydrolysis liquor was basified and extracted with chloroform as before. Fractionation of the product again yielded two fractions. One, a faintly red liquid, b. p. 65°/0·02 mm., $n_D^{22°}$ 1·5465, 5·1 g. (12% yield), analysed, as expected, for 4-*n*-propylaminoanisole (Found: N, 8·7; OMe, 18·9. Calc. for $C_9H_{12}N(OMe)$: N, 8·5; OMe, 18·8%). The high-boiling fraction, 3-nitro-4-*n*-propylaminoanisole, was obtained in 62% yield, b. p. 120°/0·02 mm.

(c) *Alternative preparation*. 4-Bromo-3-nitroanisole (8·4 g.) (Samant, *Ber.*, 1942, **75**, 1008) was heated with *n*-propylamine (4·3 g., 2·0 mol.) in a sealed tube at 120—130° for 7½ hours. The oily product was washed with water to remove unchanged propylamine and an equal volume of concentrated hydrochloric acid was then added. Unchanged bromo-compound was removed by filtration. The filtrate was ether washed, basified, and the liberated red oil extracted with ether. The extract was dried (Na_2SO_4), evaporated, and distilled in a bulb tube at 130°/0·05 mm., yielding a dark red oil (1·5 g.). This was identified by stannous chloride reduction to 3-amino-4-*n*-propylaminoanisole, identical (mixed m. p.) with that prepared *via* the sulphonamide.

3-*Amino*-4-n-*propylaminoanisole*.—(a) *Stannous chloride reduction*. 3-Nitro-4-*n*-propylaminoanisole (37 g.) was dissolved in concentrated hydrochloric acid (56 c.c.) and treated portionwise with a solution of stannous chloride (150 g.) in concentrated hydrochloric acid (112 c.c.). The vigorous reaction was controlled by cooling. When it ceased the resultant suspension was heated until complete solution was effected, cooled, and basified with a large excess of well-cooled 50% sodium hydroxide solution while still supersaturated. The liberated base was taken up in ether and the extract evaporated, leaving a dark mobile product; 3-*amino*-4-n-*propylaminoanisole* crystallised from light petroleum (b. p. 80—100°) (charcoal) as colourless needles, m. p. 62°, 13 g. (41% yield), which, like the petroleum liquors, very rapidly developed a red colour when in contact with the atmosphere (Found: C, 66·4; H, 8·9; N, 15·6. $C_{10}H_{16}ON_2$ requires C, 66·6; H, 8·9; N, 15·55%).

(b) *Catalytic reduction*. 3-Nitro-4-*n*-propylaminoanisole (20 g.) dissolved in dioxan (200 c.c.) was hydrogenated in the presence of 5% Adams's catalyst at 20°/5 atmospheres. The product was distilled and the fraction, b. p. 110°/0·05 mm., a yellow oil, 13·5 g. (78% yield), was collected, when it crystallised; m. p. 59—61° (Found: OMe, 17·7. $C_9H_{13}N_2(OMe)$ requires OMe, 17·2%).

4-n-*Propylamino*-3-(4′-*diethylamino*-1′-*methylbutyl*)*aminoanisole*.—3-Amino-4-*n*-propylaminoanisole (13·5 g.) was condensed with 5-diethylamino-2 : 2-diethoxypentane (25 g.) in the presence of ammonium chloride (0·5 g.). The condensation mixture was stirred under an atmosphere of hydrogen, the internal temperature being raised from 130° to 190° during 2 hours. Practically the theoretical quantity of alcohol distilled. Low-boiling material up to 150° (internal temperature)/15 mm. was removed, leaving the crude anil (VII) which was dissolved in dioxan (300 c.c.) and hydrogenated in the presence of 10% Adams's catalyst at 25°/30 atmospheres. Only 60% of the theoretical uptake of hydrogen was realised, even when fresh catalyst was introduced. The partially reduced anil was recovered and reduced with sodium

* This work was first carried out in 1943 but the records were destroyed by enemy action.

(40 g.) in dry amyl alcohol (900 c.c.). An atmosphere of hydrogen was maintained in the reaction vessel during the ensuing operations. The reduction mixture was acidified (Congo red) with concentrated hydrochloric acid and warmed to hydrolyse unchanged anil. It was then neutralised (litmus) and the amyl alcohol removed by rapid steam distillation. The residue was made alkaline (phenolphthalein) and exhaustively ether extracted. The extract was dried (K_2CO_3), and fractionated by means of an electrically heated Vigreux column. The fraction, b. p. 145°/0·03 mm., was a light yellow oil (6·7 g.), which proved to be the required 4-n-*propylamino*-3-(4′-*diethylamino*-1′-*methylbutyl*)*aminoanisole* (III). It rapidly turned red in air (Found: C, 70·6; H, 10·7; N, 12·5; OMe, 9·2. $C_{18}H_{32}N_3(OMe)$ requires C, 71·0; H, 10·8, N, 13·1; OMe, 9·65%).

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