287. *Attempts to find New Antimalarials. Part X.* 8-*Amino*-6-γ-*aminopropoxyquinoline and Some Related Substances.*

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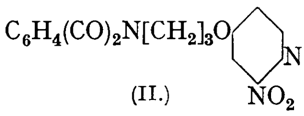
The object of the present investigation was the preparation of bases of plasmoquine type (compare Barger and Robinson, J., 1929, 2947) in which the aminoalkyl side chain should be attached to the oxygen atom in position 6 of the quinoline nucleus rather than to the nitrogen atom in position 8; an extension, combining the two types, was also contemplated.

The alkylation of 6-hydroxyquinolines is difficult, and it was found necessary to apply the Skraup reaction to suitable aniline derivatives already containing the desired substituents. Some interesting points were encountered in the course of the preparation of these intermediates and in their conversion into quinoline derivatives.

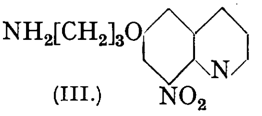
The scheme of synthesis worked out as the result of exploratory trials is the following : *p*-Acetamidophenol is converted into its *γ-phthalimidopropyl ether*,

$$NHAc{\cdot}C_6H_4{\cdot}O[CH_2]_3N(CO)_2C_6H_4 \text{ (I)},$$

and the latter nitrated in the *o*-position to the acetamido-group. On hydrolysis by means of hot concentrated hydrochloric acid, 2-*nitro*-4-*γ-phthalimidopropoxyaniline* (II) is obtained, and this undergoes the Skraup reaction, with arsenic acid as the oxidising agent, to form 8-*nitro*-6-*γ-aminopropoxyquinoline* (III) in good yield.



(II.)



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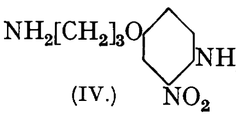


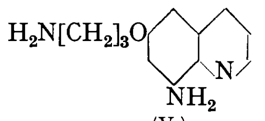
(IV.)

Although the phthalimido-group is detached in the course of this process, it is certain that the quinoline ring is closed in the first stage, *i.e.*, before and not after the hydrolysis. The base (IV) was recovered largely unchanged when it was submitted to the conditions that sufficed for the conversion of (II) into (III). Similarly the phthalamic acid related to (II) remains unaffected when treated in the same way. The explanation in the case of (IV) is probably to be sought along the lines discussed below, and, although the inactivity of the phthalamic acid is unexpected, it may be due to a betaine-type constitution which would intensify the positive electrical field over the aromatic nuclei. Attention may be drawn to striking contrasts in the relative ease of hydrolysis of some related phthalimide derivatives by acids.

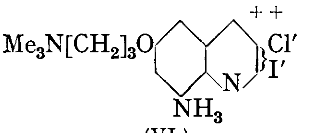
According to Lohmann (*Ber.*, 1891, **24**, 2632), *γ*-phenoxypropylphthalimide, $PhO[CH_2]_3N(CO)_2C_6H_4$, is somewhat readily hydrolysed by acids, but we find that its *p*-amino-derivative, $NH_2{\cdot}C_6H_4O[CH_2]_3N(CO)_2C_6H_4$, is unchanged after treatment with boiling concentrated hydrochloric acid during many hours. The nitro-derivative (II) is slowly hydrolysed under these conditions, and the phthalo-derivative of (III) is very readily hydrolysed as already inferred and confirmed by direct experiment.

Inspection of the formulæ of these substances shows that the inhibiting factor is a basic centre, and as this is weakened, first by introduction of a nitro-group and again by the conversion of the substituted aniline into a substituted quinoline, the faculty of hydrolysis is restored.

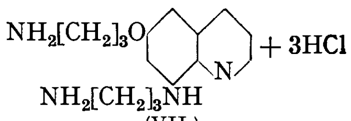
One of us has already commented on the theoretical aspect of this phenomena (J., 1923, **123**, 534 ; *Proc. Roy. Soc.*, 1931, **130**, 452), which may be described as a particular example of the general deactivating influence of a positive charge or field on anionoid reactivity. Hydrolysis of an amide by acids is probably initiated by proton attack of the amide, *i.e.*, by salt formation ; but the more powerful basic centre (the amino-group in this case) will be the more prone to accept the first available proton, and this will enormously diminish, by the simple mechanism of electrostatic repulsion, the proton avidity of the amide group, feebly developed as this is without any such handicap. It is analogous to the familiar disproportion between the first and the second ionisation constants of acids and bases exaggerated by the very unequal strengths of the molecular centres as bases. The base (III) was reduced to (V), and also methylated and reduced to (VI) ; further, by reduction of its phthalimido-derivative, introduction of a second phthalimidopropyl group, and removal of the phthalic acid residues, (VII) was obtained. These three substances were isolated as *hydrochlorides*.



(V.)



(VI.)



(VII.)

EXPERIMENTAL.

p-*γ-Phthalimidopropoxyacetanilide* (I).—The following prescription is the best of nine variations (yields, 35—60%). An intimate mixture of finely powdered *γ*-bromopropylphthalimide (50 g.), *p*-acetamidophenol (40 g.), and potassium carbonate (40 g.) was slowly heated to 140°, vigorous reaction first occurring at 120° and lasting for 10 minutes. After 1 hour at the higher temperature (with frequent shaking), the cooled mass was powdered, extracted and washed with water, and crystallised from alcohol (300 c.c.); white needles, m. p. 157° (Found : C, 67·4; H, 5·2; N, 8·3. $C_{19}H_{18}O_4N_2$ requires C, 67·4; H, 5·3; N, 8·3%).

γ-p-*Nitrophenoxypropylphthalimide.*—A mixture of *p*-nitrophenol (6 g.), γ-bromopropylphthalimide (10 g.), potassium carbonate (8 g.), and xylene (100 c.c.) was refluxed for 5 hours. The hot filtered solution deposited the new *ether* on cooling; the crystals were collected, washed with acetone, and crystallised from acetic acid; long, white needles, m. p. 183° (yield, 7 g.) (Found : C, 59·0; H, 4·6; N, 8·5. $C_{17}H_{14}O_5N_2,H_2O$ requires C, 59·3; H, 4·6; N, 8·1%). The substance is sparingly soluble in boiling alcohol and, being unchanged by treatment with hot dilute hydrochloric acid, is probably not a phthalamic acid.

p-γ-*Phthalimidopropoxyaniline.*—(*a*) The foregoing nitro-compound (4 g.) may be reduced by an application of West's method (J., 1925, **127**, 494), using alcohol (100 c.c.), concentrated hydrochloric acid (6 c.c.), and iron filings (3 g.). The product was isolated by extraction, of the crude material precipitated by ammonia, with acetone, and crystallised from alcohol in slender, orange-tinted needles, m. p. 92—94° (Found : N, 9·4. $C_{17}H_{16}O_3N_2$ requires N, 9·4%). The *amine* is readily soluble in acetone, chloroform, or acetic acid, sparingly soluble in cold alcohol and in light petroleum; it was proved to be diazotisable. On hydrolysis by means of hydrazine, followed by treatment with hydrochloric acid, *p*-γ-aminopropoxyaniline was obtained, but not quite pure (m. p. 124—127°). This diamine is readily soluble in alcohol, chloroform, and water, sparingly soluble in ether and light petroleum.

(*b*) The acetyl derivative (I; 10 g.) was refluxed for 5 hours with concentrated hydrochloric acid (600 c.c.), and the amine (5 g.) was then isolated. Boiling for 1 hour with hydrochloric acid (300 c.c.) effected the hydrolysis of only 12% of the material. When the amine was heated with acetic acid and acetic anhydride, the acetyl derivative was produced and identified with the specimen obtained from *p*-acetamidophenol.

p-γ-(o-*Carboxybenzamido*)*propoxyacetanilide.*—*p*-γ-Phthalimidopropoxyacetanilide (3 g.) was suspended in aqueous potassium hydroxide (100 c.c. of 3%), which was rapidly brought to the boil and filtered. The cooled solution was acidified, and the precipitated phthalamic *acid* was purified by repeated solution in aqueous alkali and reprecipitation (yield, 2·2 g.; m. p. 177·5°) (Found : C, 63·9; H, 5·7; N, 8·1. $C_{19}H_{20}O_5N_2$ requires C, 64·0; H, 5·6; N, 7·9%). This acid is freely soluble in alcohol, and attempts to crystallise it from aqueous alcohol failed owing to gradual ring closure. It is interesting that this reaction does not occur in boiling anhydrous alcohol.

2-*Nitro*-4-γ-*phthalimidopropoxyacetanilide.*—A mixture of nitric acid (10 c.c.; *d* 1·5) and acetic acid (50 c.c.) was added drop-wise to a vigorously stirred suspension of powdered *p*-γ-phthalimidopropoxyacetanilide (40 g.) in acetic acid (400 c.c.) and acetic anhydride (130 c.c.) cooled to below 5°. The stirring was continued for 2 hours, the temperature being kept below 10°, and a clear yellow solution resulted. Crystallisation then began in ½ hour, and after a further 12 hours, water (150 c.c.) was added, and the yellow product collected (yield, 85—90%) and crystallised twice from acetic acid (about 150 c.c.). The *nitro*-compound was so obtained in the form of large, glistening, golden-yellow leaflets, m. p. 162° (Found : C, 59·5; H, 4·3. $C_{19}H_{17}O_6N_3$ requires C, 59·5; H, 4·4%); it is easily soluble in acetone, chloroform, or hot acetic acid, and difficulty soluble in alcohol or ether.

2-*Nitro*-4-γ-*aminopropoxyaniline.*—This base was first obtained from the foregoing nitro-derivative by hydrolysis with boiling 50% aqueous potassium hydroxide, and in the form of red needles which were recrystallised from water (Found : C, 51·2; H, 6·2; N, 19·7. $C_9H_{13}O_3N_3$ requires C, 51·2; H, 6·2; N, 19·9%). The same *base*, m. p. 147°, was obtained by successive treatment of the nitro-compound with hydrazine hydrate in alcoholic solution, and with boiling dilute hydrochloric acid.

2-*Nitro*-4-γ-(2-*carboxybenzamido*)*propoxyaniline.*—A mixture of finely powdered nitrophthalimidopropoxyacetanilide (30 g.) and aqueous sodium hydroxide (500 c.c. of 3%) was heated at 80° with stirring for 15 minutes, and an almost clear solution was obtained. The filtered liquid was cooled to 0° and acidified with sulphuric acid; an immediate crystalline precipitate was observed, but at room temperature this became oily. Crystallisation from various solvents failed, and the best method was to keep a concentrated alcoholic solution for 2 days in the ice-chest. A mixture of oil and crystals separated, and when this was collected and rubbed with a glass rod the whole solidified (20 g.; m. p. of crystals, 130·5°) (Found : C, 56·6; H, 5·0; N, 11·7. $C_{17}H_{17}O_6N_3$ requires C, 56·8; H, 4·7; N, 11·6%). On boiling with aqueous alcohol (50%), ring closure occurs as in the case of the un-nitrated phthalamic acid.

2-*Nitro*-4-γ-*phthalimidopropoxyaniline* (II).—A mixture of nitrophthalimidopropoxyacetanilide (30 g.) and concentrated hydrochloric acid (750 c.c.) was boiled for 40 minutes; complete solution occurred in 20 minutes, and thereafter a colourless hydrochloride soon crystallised. Much water was added, causing decomposition of the hydrochloride, and the orange-red *base* was crystallised from methyl alcohol (yield, 93% of m. p. 172·5°) (Found: C, 59·6; H, 4·6; N, 12·3. $C_{17}H_{15}O_5N_3$ requires C, 59·8; H, 4·4; N, 12·3%). The substance is not soluble in dilute aqueous acids or alkalis, and it is very resistant to further hydrolysis by means of hot concentrated hydrochloric acid or 50% sulphuric acid. It may, however, be hydrolysed by hydrazine in alcoholic solution.

8-*Nitro*-6-γ-*aminopropoxyquinoline* (III).—A mixture of 2-nitro-4-γ-phthalimidopropoxyaniline (25 g.), glycerol (25 g.), sulphuric acid (25 g.), and arsenic acid (15 g.) was heated (oil-bath at 160°) under reflux for 2½ hours. The viscous mass was triturated with water (150 c.c.), then filtered through kieselguhr which was washed with water. The filtrate was rendered weakly alkaline, precipitating a dark sticky mass which was collected (filtrate A), dissolved in dilute hydrochloric acid, filtered from a little tar, and precipitated with sodium hydroxide. The precipitate was again dissolved in dilute hydrochloric acid, filtered, and the solution combined with A. The solution was rendered strongly alkaline, and the solid collected with the addition of *papier maché* to assist filtration. This crude material was dried, dissolved in alcohol, and the solution boiled for 5 minutes after the addition of rather a large amount of animal charcoal; the alcohol was then removed, after filtration, and the residual oil dissolved in dilute sulphuric acid. Careful basification of this solution with cooling and mechanical stirring afforded leaflets, which were collected, washed with ether, and dried (yield, 70%). The *base* crystallised from 30% methyl alcohol in yellow leaflets, m. p. 108° (Found: C, 58·4; H, 5·2; N, 16·2, 16·8. $C_{12}H_{13}O_3N$ requires C, 58·3; H, 5·3; N, 17·0%). It is readily soluble in alcohol and chloroform and sparingly soluble in ether and light petroleum. The hydrochloride, m. p. 211—214° (decomp.) could be crystallised from alcohol.

The failure to bring about condensation to a quinoline starting with the amine or phthalamic acid corresponding to the phthalimide was not for lack of attempts; it must be emphasised that the original bases were recovered unchanged.

8-*Nitro*-6-γ-*phthalimidopropoxyquinoline*.—Nitro-aminopropoxyquinoline (2 g.) and phthalic anhydride (1·35 g.) were heated together at 180° for 10 minutes, and the liquid then crystallised. After cooling, the mass was pulverised and extracted with hot alcohol (50 c.c.); the sparingly soluble *product* was collected (yield, 90%), and crystallised in colourless leaflets, m. p. 209°, on the addition of alcohol to a solution in chloroform (Found: C, 63·6; H, 4·0; N, 10·9. $C_{20}H_{15}O_5N_3$ requires C, 63·7; H, 4·0; N, 11·1%).

8-*Amino*-6-γ-*phthalimidopropoxyquinoline*.—Iron filings (1·3 g.) were added to a suspension and solution of the foregoing compound (2·6 g.) in alcohol (260 c.c.) and concentrated hydrochloric acid (6 c.c.); a further equal amount of iron was added after 15 mins. The mixture was refluxed until (1—2 hours) the nitroquinoline had passed into solution, and it was then concentrated to about 20 c.c., mixed with water (100 c.c.), and filtered. The residue was boiled with water (300 c.c.) for ½ hour, whereby the hydrochloride is decomposed, and the solids were again collected, and well dried at 100°. The base was then dissolved in chloroform, dried with potassium carbonate, and the solution filtered from this salt and iron filings. After concentration, the *base* was precipitated by the addition of ether in golden-yellow leaflets, m. p. 157—158° (yield, 83%) (Found: C, 69·2, 68·3, 68·3; H, 4·9, 5·1, 5·0; N, 12·1. $C_{20}H_{17}O_3N_3$ requires C, 68·4; H, 5·0; N, 12·0%). This base is soluble in hot alcohol, chloroform, or acetone, but sparingly soluble in ether and light petroleum.

8-γ-*Phthalimidopropylamino*-6-γ-*phthalimidopropoxyquinoline*.—A finely powdered mixture of the preceding compound (2 g.) and γ-bromopropylphthalimide (1·7 g.) was heated at 110—115° for 2 hours. The mass thickened after 1 hour and soon solidified; it was cooled, powdered under acetone, collected, and washed with acetone (hydrobromide, m. p. *ca.* 245°). This product was shaken with chloroform (1200 c.c.) and potassium carbonate, the solution of the base filtered, concentrated to a small volume, mixed with ether (200 c.c.), and filtered after an hour. The filtrate was mixed with light petroleum at 0°; a small quantity of tar separated (decant), followed by a yellow crystalline deposit. This was collected and purified in the same way from chloroform–ether–light petroleum, and by 8—9 recrystallisations from alcohol; the product is mixed with impurities that are difficult to remove completely (yield, 20% of yellow crystals, m. p. *ca.* 105°). The *substance* appears to be a hydrate and after drying at 100° in a vacuum the m. p. rose to 150—152° (Found: N, 10·3. $C_{31}H_{26}O_5N_4$ requires N, 10·5%).

8-γ-*Aminopropylamino*-6-γ-*aminopropoxyquinoline Trihydrochloride* (VII).—A mixture of the abovediphthalimido-compound (0·6 g.), hydrazine hydrate (1 g. of 94%), and alcohol (60 c.c.) was refluxed for 45 mins., the alcohol removed, and the residue boiled for 15 mins. with dilute hydrochloric acid. The filtered solution was basified, extracted with chloroform, and a hydrochloride precipitated from the dried extract by means of dry hydrogen chloride; the red solid was washed with chloroform, dissolved in the minimum of water, and precipitated by means of acetone at – 5°. The yellow hygroscopic powder (R 55) * obtained by several repetitions of this process was dried over phosphoric anhydride, and then melted at about 188° (Found: C, 40·3; H, 7·0. $C_{15}H_{22}ON_4,3HCl,3{\cdot}5H_2O$ requires C, 40·3; H, 7·0%). The sulphate is a similar hygroscopic salt, and the base was only obtained as an oil.

8-*Amino*-6-γ-*aminopropoxyquinoline* (V).—A mixture of 8-nitro-6-γ-aminopropoxyquinoline (2 g.), concentrated hydrochloric acid (8 c.c.), water (16 c.c.), and crystallised stannous chloride (15 g.) was heated on the steam-bath for 45 mins. After cooling, the solution was rendered strongly alkaline, and the base isolated by means of chloroform as a yellow oil, readily soluble in organic solvents. This distilled at 150—160°/ < 1 mm., and rapidly crystallised, m. p. 106—107° (Found: C, 66·3; H, 6·9; N, 19·2. $C_{12}H_{15}ON_3$ requires C, 66·4; H, 6·9; N, 19·3%). The *hydrochloride* could be crystallised in reddish-brown needles, m. p. 211—214°, by adding chloroform to its alcoholic solution (Found: Cl, 22·7. $C_{12}H_{15}ON_3,2HCl,1{\cdot}5H_2O$ requires Cl, 22·4%); it is readily soluble in water (R 54).

8-*Amino*-6-γ-*dimethylaminopropoxyquinoline Methiodide Hydrochloride* (VI).—8-Nitro-6-γ-aminopropoxyquinoline was methylated by means of methyl iodide in boiling alcoholic solution and in the presence of potassium carbonate. The salt crystallised from hot water in pale yellow prismatic needles which sintered at 212° and melted at 222° (decomp.). This methiodide (2 g.) was dissolved in alcohol (150 c.c.) and concentrated hydrochloric acid (6 c.c.), and the solution refluxed for 1½ hours after the addition of iron filings (2 g.). The alcohol was evaporated, and the residue taken up in water and rendered alkaline. The filtrate from ferric hydroxide was acidified with hydrochloric acid and evaporated to dryness under diminished pressure. The *salt* was then recrystallised from alcohol several times, forming yellow needles, m. p. 222° (decomp.) (yield, *ca.* 1 g.) (Found: C, 41·6; H, 6·0; N, 9·0. $C_{15}H_{22}ON_3I,HCl,0{\cdot}5H_2O$ requires C, 41·6; H, 5·6; N, 9·7%). The salt (R 53) was not quite free from potassium chloride, which was very difficult to remove.

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