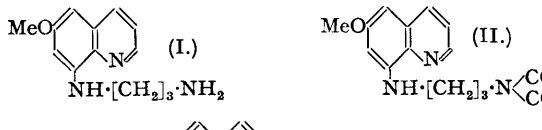
244. *Contributions to the Chemistry of Synthetic Antimalarials. Part IV. Hydrazine Hydrolysis and Radical Exchange Reactions of* N-*Substituted Phthalimides in Relation to the Constitution of the Antimalarial R.*63.

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

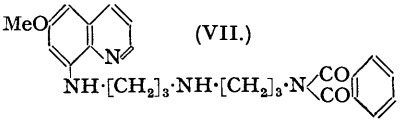
Hydrazine hydrolysis of *N*-substituted phthalimides has been shown to give the *phthalylhydrazide* salts of the liberated primary amines. Facile radical exchange reactions have been observed between *N*-substituted phthalimides and substituted aliphatic primary amines. The special case of 8-γ-phthalimidopropylamino-6-methoxyquinoline (II) has been studied in detail. The bearing of these reactions on the composition of R.63 is discussed. The antimalarial activity of R.63 can be accounted for on the basis of the 8-γ-aminopropylamino-6-methoxyquinoline (I) dihydrochloride it contains.

Early in 1944, we required 8-γ-aminopropylamino-6-methoxyquinoline (I) in quantity for part of our antimalarial research programme. In preparing this, we encountered certain side reactions relevant to the constitution of the synthetic antimalarial known as R.63 (Robinson and Tomlinson, *J.*, 1934, 1524). This subject had just been reopened by Robinson and his collaborators (*J.*, 1943, 555, 557, 561), who showed that the original constitution ascribed to R.63 was untenable and that most of the feasible alternatives were also excluded. Here was a synthetic drug of confirmed high antimalarial activity (Index 1/64) but of unknown constitution. The hypothesis that the activity was due to the presence, as an impurity, of a small proportion of a still more highly potent antimalarial was an attractive one. The discovery of the side reactions referred to above encouraged this view and indicated the nature of the impurities which might be expected. While our results do not provide absolute proof of the complete composition of R.63 and the source of its activity, they afford strong circumstantial evidence that it is a mixture of a number of products in which the dihydrochloride of (I) is present in sufficient quantity to account for the biological results obtained.

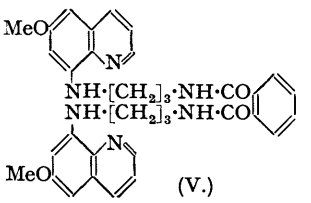


(I.)

(II.)

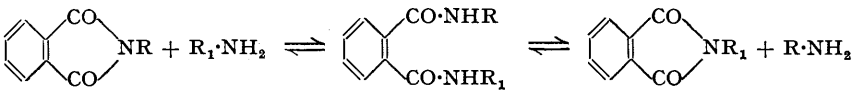


(VII.)



(V.)

In the synthesis of " antimalarial side chains " by phthalimido-alkylation reactions with substituted aliphatic amines, the following scheme of facile radical exchange has been established:

(*A*.) 

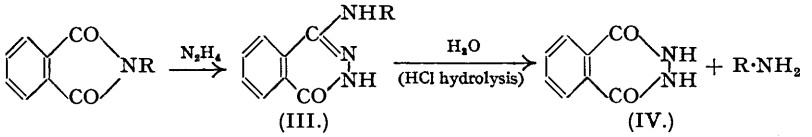
The main factors which determine the end products will be the electronic characteristics of R and R_1, and such relevant properties of their derivatives as solubility in the reagents used or

volatility at the reaction temperature. Examples of (*A*) where R and R_1 = Me, Et, or H have been described recently by Spring and Woods (*J.*, 1945, 625).

The importance to R.63 of the scheme (*A*) first became apparent while studying the hydrazine hydrate hydrolysis of 8-γ-phthalimidopropylamino-6-methoxyquinoline (II).

A number of workers (Baldwin, *J.*, 1929, 2962; Magidson and Bobishev, *J. Gen. Chem. Russia*, 1938, **8**, 912; Beer, *ibid.*, 1939, **9**, 2158; Quin and Robinson *J.*, 1943, 555) had previously used this reaction to prepare (I), their method being based on that of Ing and Manske (*J.*, 1926, 2349) who formulated the hydrolysis as follows:

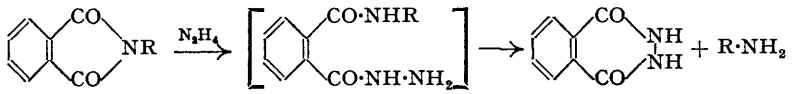
(*B.*)



(III.) (IV.)

We have found that the sparingly soluble intermediate which separates from the reaction mixture has not the structure (III) ascribed to it tentatively by Ing and Manske, but is in fact the *salt* of the acidic phthalylhydrazide (IV) with the liberated amine. It is more probable that the course of the reaction is:

(*C.*)



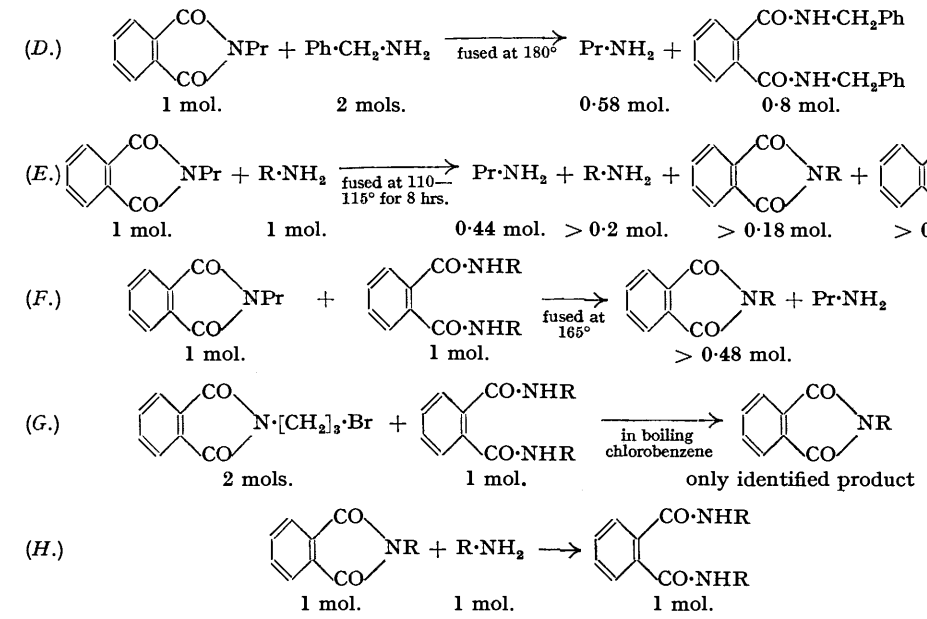
It is clear that this revised conception of the nature of the intermediate (III) suggests modified methods of isolating amines produced by the hydrazine reaction and thus broadens the scope of the method. It is no longer correct to regard the final stage of warming with acid as a hydrolysis of an intermediate such as (III), but as the simple decomposition of a salt by acid. This decomposition can also be effected by alkali, by solvent extraction, or by thermal dissociation. Incidentally, the last procedure provides a ready method of obtaining anhydrous volatile amines where their isolation from the aqueous solutions normally obtained is a matter of some difficulty; application to the laboratory preparation of anhydrous hydrazine will be recorded in a future note.

The intermediate salt we obtained by hydrazine hydrolysis of (II) was dissociated into its components by chloroform extraction and by basification. It was always contaminated by a proportion (dependent on the molar proportion of hydrazine, see Table I) of a secondary product, *phthalobis-[γ-(6-methoxy-8-quinolylamino)propyl]amide* (V). This arose by interaction [scheme (*A*)] between unchanged (II) and free primary amine (I), derived from the partial dissociation in the reaction mixture of its phthalylhydrazide salt. We have studied the acid hydrolysis of the phthalamide (V) under various conditions (Table II) to ascertain the fate of this impurity at the final stage of the Ing and Manske hydrolysis. Under typical conditions complete conversion into an equimolar mixture of (I) and (II) occurred. Thus in a hydrolysis of 1·0 mol. of (II) by the method of scheme (*B*) using 1·0 mol. of hydrazine hydrate, it can be deduced from Tables I and II that the only impurity present in the reaction product would be approximately 0·075 mol. of the phthalimide (II). This would be removed, together with the phthalylhydrazide, from the aqueous solution of the hydrochloride of the product (I) in the normal course of working up the reaction. The formation of the secondary product (V) can be eliminated by treating (II), dissolved in chloroform–alcohol, with two molar proportions of hydrazine hydrate at room temperature; (I) is then the only product obtained.

We next demonstrated the ready formation of the phthalamide (V) directly from (I) and (II), both in boiling alcohol and by fusion. The facile nature of these changes suggested that similar considerations would apply to the fusion of 8-γ-aminopropylamino-6-methoxyquinoline (I) and phthalo-γ-bromopropylimide—the first stage in the synthesis of R.63. Model experiments with some phthalimides and amines, selected for readier separation of the reaction products, confirmed scheme (*A*). These experiments are summarised in the following schemes in which R = γ-(6-methoxyquinolyl-8-amino)propyl.

Clearly in the first stage of the preparation of R.63, where phthalo-γ-bromopropylimide (VI) is substituted for phthalo-*n*-propylimide in equation (*E*), the products of the reaction may be very complex and their separation has proved extremely difficult. The yields of isolated and purified substances must therefore represent much less than the quantities formed in the reaction. From the product of fusing (I) and (VI) by the method of Glen and Robinson (*J.*, 1943, 557) we isolated *in a pure state* the following: 8-γ-phthalimidopropylamino-6-methoxyquinoline

(II) in 5% of the theoretical quantity, 8-γ-aminopropylamino-6-methoxyquinoline (I) in 10% recovery, and a small quantity of 8-γ′-phthalimidopropyl-γ-aminopropylamino-6-methoxyquinoline (VII) monohydrobromide. Since our object was to identify the highly active component responsible *ex hypothesi* for the activity of R.63, we did not attempt quantitative separation of the mixture but turned our attention instead to the synthesis of compounds deduced from the application of scheme (*A*).



(II) doubtless appeared as the result of a reaction, type (*E*), from which we inferred that the highly reactive bifunctional compound, γ-bromopropylamine (VIII), was liberated simultaneously with (II). (VIII) could undergo self-condensation to 1 : 5-diaza*cyclo*octane dihydrobromide (IX) or react in many ways with the various components of the melt. However both the hydrobromide of (VIII) (Gabriel, *Ber.*, 1888, **21**, 2669) and (IX) (Buhle, Moore, and Wiselogle, *J. Amer. Chem. Soc.*, 1943, **65**, 29) have been found devoid of antimalarial activity.

As molecular proportions of the reagents (I) and (VI) are used in this fusion, the recovery of 10% of unchanged (I) indicated that a similar quantity of phthalo-γ-bromopropylimide (VI) might remain unchanged in the fusion product. This would react during the second stage of the preparation of R.63 (treatment of the crude fusion melt with alcoholic hydrazine hydrate followed by warm dilute hydrochloric acid) giving a variety of products. Accordingly, pure (VI) was submitted to the sequence of hydrazine treatment (using various molar proportions of hydrazine) and acid " hydrolysis ", but the total basic product derived was always inactive.

Lastly the identification of the " normal " product (VII) of the fusion reaction of (I) and (VI) in the crude melt indicated that some 8-γ′-aminopropyl-γ-aminopropylamino-6-methoxyquinoline trihydrochloride would appear in R.63.

Being impressed by the fact that most of the physical change in the fusion reaction took place during the first few minutes, we studied the rate at which the free amino-group of (I) reacted. Table III summarises the results of some Van Slyke nitrogen determinations and shows their relation to the quantities of the various products proved to be present in the melt after various times of fusion. It is noteworthy that the proportion of primary amine (Van Slyke) drops to approximately 30% of its initial value in the first five minutes of fusion and remains at this value even after the seven hours specified by Glen and Robinson (*loc. cit.*).

The complex nature of the first reaction in the preparation of R.63 made it apparent that alcoholic hydrazine hydrate treatment of the crude product could only add to its complexity. We did not therefore proceed to attempt to separate R.63 into its components. However, on the evidence submitted here R.63 would obviously contain at least 10% of unchanged (I), together with a further proportion of (I) (> 5%) formed when the phthalimide (II) present in the melt was treated with hydrazine hydrate. If the Van Slyke figure for N were taken as a

measure of the amine (I) present in the fusion product, a reasonable assumption, then the final R.63 could be calculated to contain > 35% of the possible quantity of the amine (I).

Results obtained in the Biological Laboratories, May & Baker Ltd., indicate that the antimalarial activity and toxicity of R.63 are in general accord with the chemical evidence that upwards of 30% of (I) is present. It should be emphasised, however, that extreme caution is necessary in interpreting the results obtained on a mixture, since the biological properties may be far from additive. The presence of a small proportion of a highly active substance is still not definitely excluded. A fuller discussion of the biological results will appear elsewhere in due course, together with a report on the antimalarial evaluation of phthalobis-[γ-(6-methoxy-8-quinolylamino)propyl]amide (V) and 8-γ-*phthalamidopropylamino*-6-*methoxyquinoline*.

Addendum.—Publication of this work has been delayed largely because British Patent Application 17071/44, covering the preparation of the phthalamide (V), was placed on the secret list. An independent investigation of the constitution of R.63 has been described recently by Mosher (*J. Amer. Chem. Soc.*, 1946, **68**, 1565). We had, however, followed a somewhat different approach to the problem and overlap in results is restricted to the following points:

Mosher is in agreement that R.63 (as prepared by Robinson and his co-workers) contains considerable 8-γ-aminopropylamino-6-methoxyquinoline (I) dihydrochloride (R.36) and some 4% of 8-γ-phthalimidopropylamino-6-methoxyquinoline (II), although he does not explain how the latter compound was formed. He has demonstrated the presence of a larger proportion (> 20%) of 8-γ′-aminopropyl-γ-aminopropylamino-6-methoxyquinoline trihydrochloride (R.120) than that reported here. Lastly, Mosher foreshadows our elucidation of the nature of the intermediate which separates in the hydrazine hydrolysis of *N*-substituted phthalimides.

A brief summary of the present paper appeared in *Nature* (**1946**, **158**, 514). Spring and Woods have since added further evidence for scheme (*A*) (*ibid.*, p. 754).

Experimental.

(Melting points are corrected.)

8-γ-*Phthalimidopropylamino*-6-*methoxyquinoline* (II).—8-Amino-6-methoxyquinoline (696 g.) (Barber and Wragg, *J.*, 1946, 612) was refluxed with 0·5 molar proportion of phthalo-γ-bromopropylimide (536 g.) in chlorobenzene (2 l.) for 12 hours. After a short delay, 8-amino-6-methoxyquinoline hydrobromide commenced to separate. This salt (404 g.; 76%) was collected from the cold reaction mixture and the filtrate diluted with alcohol (6 l.); 8-γ-phthalimidopropylamino-6-methoxyquinoline then separated as yellow felted needles. The product was collected after 24 hours, washed with light petroleum (2 l.)–alcohol (750 c.c.), and dried at 40°/11 mm., giving 403 g. (56%), m. p. 99—101°. The chlorobenzene–alcohol liquors were treated with excess of concentrated hydrochloric acid, and the precipitated orange hydrochloride was removed and washed with alcohol (500 c.c.). The damp salt (344 g.) was suspended in boiling alcohol (5 l.) and treated with a small excess of concentrated ammonia. 8-γ-Phthalimidopropylamino-6-methoxyquinoline (104 g.) crystallised, making a total yield of 70%. No 8-bis-(γ-phthalimidopropyl)amino-6-methoxyquinoline was obtained as a by-product under these conditions (cf. Glen and Robinson, *loc. cit.*; Mosher, *loc. cit.*).

8-γ-*Aminopropylamino*-6-*methoxyquinoline* (I).—(a) *Hydrolysis of* (II) *in cold chloroform–alcohol using 2·25 mols. of hydrazine hydrate.* 8-γ-Phthalimidopropylamino-6-methoxyquinoline (7·22 g.) dissolved in chloroform (50 c.c.) and alcohol (50 c.c.) was treated with hydrazine hydrate (4·5 c.c., 50% w/v aqueous solution). After 3 hours at room temperature a gelatinous white precipitate began to separate. After 4 days the solvents were removed at 40°/20 mm. and the residue shaken mechanically (2 hours) with a mixture of 2N-ammonia (30 c.c.), water (40 c.c.), and chloroform (70 c.c.). A small quantity of insoluble material (*ca.* 0·5 g.) was dissolved separately by warming with chloroform–ammonia solution and returned to the main bulk. The chloroform layer (*A*) was extracted with four portions of N-acetic acid (20 c.c.) which were bulked, basified with concentrated ammonia, and then exhaustively extracted with ether. This extract on distillation in a bulb tube (air-bath at 180°) at 0·01 mm. gave 8-γ-aminopropylamino-6-methoxyquinoline (4·1 g., 89%), $n_D^{24°}$ 1·637, converted into carbamate derivative, m. p. 113—116°. The chloroform (*A*) was evaporated to dryness, leaving a negligible dark red residue (0·2 g.). The aqueous ammoniacal layer, precipitated with concentrated hydrochloric acid, yielded 2·98 g. (92%) of phthalylhydrazide, m. p. 342—344°.

(b) *Hydrolysis of* (II) *in boiling alcohol with various proportions of hydrazine hydrate.* Hydrazine hydrate (40 c.c., 50% w/v aqueous solution; 0·8 mol.) was added to a solution of 8-γ-phthalimidopropylamino-6-methoxyquinoline (180 g.) in boiling alcohol (1·5 l.) and the mixture refluxed for 3 hours. The alcohol was removed under reduced pressure from the suspension of cream insoluble product, and the residue vigorously shaken with 2N-ammonia (500 c.c.), diluted with water (1 l.), and chloroform (2·5 l.). The aqueous alkaline layer was separated and acidified with concentrated hydrochloric acid; phthalylhydrazide separated (56 g.), m. p. 342—344°.

The chloroform layer was concentrated under reduced pressure to 700 c.c. and diluted with an equal volume of dry ether. *Phthalobis-[γ-(6-methoxy-8-quinolylamino)propyl]amide* (V) separated (44 g.), m. p. 170—174°, crystallising from chloroform–methanol as tiny brown needles, m. p. 177—179° (Found: C, 68·7; H, 6·3; N, 14·0; OMe, 11·0; *M* (ebulliscopic in chloroform), 600. $C_{34}H_{36}O_4N_6$ requires C, 68·9; H, 6·1; N, 14·2; OMe, 10·5%; *M*, 592). (V) was converted into the *hydrochloride*, m. p. 208—210° by treatment of a warm solution in chloroform–methanol with concentrated hydrochloric acid

(Found : N, 12·6; Cl, 10·6. $C_{24}H_{36}O_4N_6,2HCl$ requires N, 12·6; Cl, 10·7%). This hydrochloride was readily reconverted into the base by suspension in a large volume of cold water.

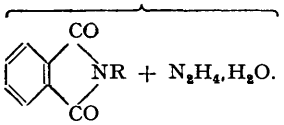
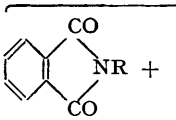
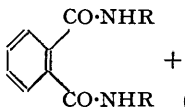
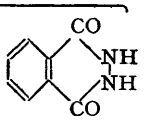
The liquors from the separation of crude (V) above were evaporated to dryness under reduced pressure and the oily residue taken up in dry ether (1 l.). Carbon dioxide was passed, very slowly at first, into the filtered bright ethereal solution, precipitating the *carbamate* derived from (I) (63 g.) as a white powder, m. p. 112—114° [Found : C, 64·2; H, 7·0; N, 16·8. $(C_{13}H_{17}ON_3)_2CO_2$ requires C, 64·0; H, 6·76; N, 16·6%]. When a solution of the carbamate in warm methanol was treated with a small excess of concentrated hydrochloric acid the corresponding *dihydrochloride*, crystallising from methanol–ether in short orange needles, was obtained (96%). Drying over potash in a vacuum gave the anhydrous salt (cf. Beer, *loc. cit.*), m. p. 244—246° with slight previous shrinking from about 230° [Purification of many samples failed to give material, m. p. 251—252° (cf. Baldwin, *loc. cit.*; Beer, *loc. cit.*)] (Found : N, 13·7; Cl, 23·5. Calc. for $C_{13}H_{17}ON_3,2HCl$: N, 13·8; Cl, 23·4%). The free base (I) was prepared in 96% yield by dissolving the carbamate in a small excess of dilute hydrochloric acid at 80°, removing any dissolved carbon dioxide with a rapid stream of nitrogen for 10 minutes, basifying with concentrated aqueous ammonia, and extracting the liberated base with ether. Distillation of the residue on removal of the ether gave (I) as a single fraction, b. p. 160°/0·01 mm., a viscous yellow oil, $n_D^{23°}$ 1·637 (Found : C, 67·5; H, 7·4; N, 18·05. Calc. for $C_{13}H_{17}ON_3$: C, 67·5; H, 7·4; N, 18·2%), stored under an atmosphere of hydrogen. On long standing this sample solidified to a waxy solid, m. p. 37—38°.

In the experiment below where unchanged phthalimide (II) was recovered, this was isolated from the ethereal liquor after the precipitation and removal of the carbamate of (I).

The above experimental details exemplify the method of separation employed to obtain the results summarised in Table I.

TABLE I.

Reaction of the phthalimide (II) *with hydrazine hydrate.*

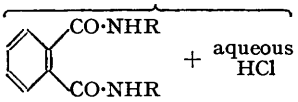
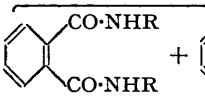
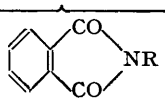
Reactants.			Products.			
 (II)	N_2H_4,H_2O.	Time in boiling alcohol.	 unchanged (II)	 (V)	+ R·NH_2 + (I), as carbamate.	 (IV)
1·0 mol.	1·0 mol.	2 hrs.	none	0·075 mol.	0·57 mol.	Theoretical quantity
1·0 mol.	0·8 mol.	4 hrs.	none	0·15 mol.	0·5 mol.	,,
1·0 mol.	0·5 mol.	10 hrs.	0·3 mol.	0·16 mol.	0·23 mol.	,,

[R = γ-(6-methoxyquinolyl-8-amino)propyl.]

The products obtained, when the phthalamide (V) was treated with aqueous hydrochloric acid under various conditions, were separated and identified by means very similar to those described in the case of Table I. These results are summarised in Table II.

TABLE II.

Reaction of the phthalamide (V) *with acid.*

Reactants.			Products.		
 (V)	+ aqueous HCl	Conditions.	 unchanged. (V)	+  (II)	+ R·NH_2. (I) as carbamate.
2 g.	90 c.c., 10%	1 hr. reflux	none	0·8 g.	trace
2 g.	30 c.c., 2N	30 mins. at 95°	none	1·05 g.	0·6 g.
2 g.	30 c.c., N	15 mins. at 95°	0·75 g.	0·57 g.	0·17 g.
2 g.	30 c.c., N	15 mins. at 70°	1·75 g.	none	trace

[R = γ-(6-methoxyquinolyl-8-amino)propyl.]

Model Experiments.—(a) *Exemplification of scheme* (C) *where* R = *benzyl.* Phthalobenzylimide (23·7 g.) was suspended in alcohol (200 c.c.), boiling under reflux, and hydrazine hydrate (10 c.c., 50% w/v aqueous solution; 1·0 mol.) added. After 2 hours the reaction mixture was cooled and the white crystalline product collected (21·3 g.). After being dried in the steam-oven for 1 hour this material analysed for the anhydrous phthalylhydrazide (IV) *salt* of benzylamine, m. p. 326—346° (Found : C, 66·8; H, 5·4; N, 15·5. $C_8H_6O_2N_2,C_7H_9N$ requires C, 67·0; H, 5·6; N, 15·6%). 2 G. of this salt were dissociated by one crystallisation from alcohol (200 c.c.); phthalylhydrazide alone separated, m. p. 342—346° (Found : C, 59·6; H, 4·0; N, 17·5. Calc. for $C_8H_6O_2N_2$: C, 59·3; H, 3·7; N, 17·3%). Dissociation was also effected by heating the salt (5·4 g.) at 120—140°/0·05 mm. for 3 hours. The

distillate, collected in a solid carbon dioxide–acetone cooled receiver, was anhydrous benzylamine (1·66 g.; 78%) (Found: *M*, by titration, 107. Calc. for C_7H_9N: *M*, 107).

(b) *Exemplification of scheme* (*D*). Phthalo-*n*-propylimide (10 g.) and benzylamine (11·4 g.; 2 mol.) were fused in a distillation flask fitted with a Vigreux column. The melt was slowly heated to 180°. The distillate (b. p. 49°), collected in a cooled receiver, was anhydrous propylamine (1·8 g., 59%) contaminated by a small proportion of benzylamine. The residue, crystallised twice from chloroform, was phthalo-*NN'*-dibenzylamide, m. p. 176—178° (Tingle and Lovelace, *Amer. Chem. J.*, 1907, **38**, 651, give m. p. 178—179°).

(c) *Exemplification of scheme* (*E*). 8-γ-Aminopropylamino-6-methoxyquinoline (2·2 g.) was fused with phthalo-*n*-propylimide (1·89 g.) for 8 hours at 110—115°. The *n*-propylamine (44%) evolved from the melt was removed in a slow stream of hydrogen which was subsequently scrubbed with standard acid. The fusion product was dissolved in methanol (40 c.c.). On cooling, the phthalamide (V) separated, 1·06 g., m. p. 157—171°. Recrystallisation from chloroform–methanol gave 0·9 g., m. p. 176—178°; mixed m. p. with authentic material was 175—178°. On standing, the liquors from the crude phthalamide (V) precipitated the phthalimide (II) (0·64 g.) (*A*), m. p. 97—99°, characterised by mixed m. p. 100—101° with authentic material after recrystallisation from methanol. The methanol liquors from (*A*) were concentrated, and the residue dissolved in ether was treated with carbon dioxide, precipitating the carbamate of the amine (I) (0·5 g.), m. p. 112—116°.

(d) *Exemplification of scheme* (*F*). An equimolar mixture of the phthalamide (V) (5·9 g.) and phthalo-*n*-propylimide (1·9 g.) were fused at 165° for 1 hour, during which time *n*-propylamine was evolved. The fusion product was dissolved in alcohol (50 c.c.) from which 3·5 g.(48%) of bulky yellow needles separated, m. p. 84—100°. Recrystallisation from alcohol gave the phthalimide (II) (3·2 g.), m. p. 99—101°, characterised by mixed m. p. with an authentic sample.

(e) *Exemplification of scheme* (*G*). The phthalamide (V) (1·18 g.) was refluxed for 10 hours in chlorobenzene (20 c.c.) with phthalo-γ-bromopropylimide (1·07 g.). The hydrochloride precipitated from the mixture by alcoholic hydrogen chloride was crystallised twice from alcohol and then converted in aqueous methanol into the base, long bulky yellow needles from methanol (0·2 g.), m. p. 99—101°, shown to be the phthalimide (II) by mixed m. p.

(f) *Exemplification of scheme* (*H*). (i) Equimolar proportions of the amine (I) (2·31 g.) and the phthalimide (II) (3·61 g.) were refluxed for 1 hour in alcohol (70 c.c.). The total product which separated on cooling was crystallised from chloroform–ether; the phthalamide (V) (2·05 g.) was thus obtained, m. p. 173—176° (identity confirmed by mixed m. p.).

(ii) A theoretical yield of the phthalamide (V) was obtained when the above reaction was carried out by fusion for 1 hour at 115°.

(iii) A 70% yield of the phthalamide (V) was similarly obtained from the fusion of the amine (I) (5·1 g.; 2 mols.) and phthalic anhydride (1·5 g.) at 115° for 1 hour.

(iv) A theoretical yield of phthalo-*NN'*-dibenzylamide was similarly obtained by fusion of equimolecular quantities of phthalobenzylimide and benzylamine at 120° for 1½ hours.

*First Stage of the Preparation of R.*63. *Separation of the Reaction Products of the Fusion of 8-γ-Aminopropylamino-6-methoxyquinoline* (I) *with Phthalo-γ-bromopropylimide* (VI).—The identification of unchanged (I) and the phthalimide (II) as products of this reaction has been confirmed at least twice, both after 15 minute and 7 hour fusions. The following are typical experiments:

(a) *Method of fusion.* Equimolar proportions of (I) (6 g.) and (VI) (7 g.) were mixed by rotation of the reaction flask, closed by a calcium chloride tube, and immersed in an oil-bath at 115°. The mixture fused to a mobile liquid which rapidly thickened to a red-brown glass.

(b) *Isolation of 8-γ-phthalimidopropylamino-6-methoxyquinoline* (II). The glassy product from a 7 hour fusion as in (a) was dissolved in glacial acetic acid (15 c.c.) with mechanical shaking (10 hours). The orange-brown precipitate which separated was filtered from the viscous red liquor, washed with three portions of glacial acetic acid (5 c.c.) and then ether, giving 1·7 g., m. p. 190—200°. This was repeatedly recrystallised from methanol until the orange hydrobromide obtained (0·98 g.), m. p. 214—220°, was sufficiently pure to yield 0·3 g. of phthalimide (II), m. p. 102—103° (identity confirmed by mixed m. p.), on treatment with ammoniacal methanol. By dilution with water and recrystallisation of the precipitate, a further 0·1 g., m. p. 100—103°, of the phthalimide (II) was isolated from the mother liquor. The original acetic acid liquors were stored at 0° (2 days) when a further 0·6 g. of orange material separated. This crystallised from methanol giving 0·35 g., m. p. 220—225°, which on conversion into the base (0·09 g.) was characterised by mixed m. p. 101—103° as the phthalimide (II).

(c) *Isolation of 8-γ-aminopropylamino-6-methoxyquinoline* (I). The fusion product from a 7 hour reaction as (a) was dissolved with mechanical shaking in chloroform (50 c.c.). The solution was shaken with 2N-ammonia (12 c.c.) and water (20 c.c.). The chloroform layer was then extracted with four 2 c.c. portions of 2N-acetic acid in water (20 c.c.) until the last extract was acid (litmus). The combined extracts were counter-extracted (chloroform) and then basified slowly with 2N-ammonia in the presence of ether (500 c.c.). The aqueous layer was then made strongly alkaline with concentrated ammonia and saturated with salt. The dried (K_2CO_3) ether layer was evaporated and distilled in a bulb tube (air-bath up to 200°) at 0·01 mm. About half the residue distilled, yielding a light brown oil, 2·0 g., $n_D^{24°}$ 1·631. This was taken up in ether and converted into the carbamate of (I) (0·7 g., 10% recovery), m. p. 100—108°, decomposing in a bulb tube to give pure (I) (0·5 g.), $n_D^{23°}$ 1·636, reconverted into carbamate derivative, m. p. 109—115° (mixed melting point with authentic material 113—116°).

(d) *Isolation of 8-γ'-phthalimidopropyl-γ-aminopropylamino-6-methoxyquinoline* (VII). The product from a 7 hour fusion, as (a) was dissolved in pyridine (25 c.c.). The brown oil precipitated with water (300 c.c.) was twice extracted by boiling with a supernatant layer of ether (100 c.c.). The residue separated by decantation was dissolved in methanol (100 c.c.) and diluted with an equal volume of ether. The precipitated gum solidified on standing. The solid was collected and recrystallised twice from methanol, forming long rectangular light brown plates, m. p. 174—177°, which proved to be *8-γ'-phthalimidopropyl-γ-aminopropylamino-6-methoxyquinoline monohydrobromide* (Found: C, 57·4; H, 5·1; N, 11·0; Br, 15·8. $C_{24}H_{26}O_3N_4$,HBr requires C, 57·7; H, 5·4; N, 11·2; Br, 16·1%). We con-

cluded that this product was not 8-γ-aminopropylamino-6-methoxy-1-γ-phthalimidopropylquinolinium bromide, or 8-γ-aminopropyl-γ-phthalimidopropylamino-6-methoxyquinoline hydrobromide, compounds of the same empirical formula, because no primary amine group could be detected in a micro-Van Slyke determination, for which we are indebted to Miss P. Garwood of Imperial College, S.W. 7.

(e) *Typical analytical experiment in outline.* The product from a 15 minute fusion, as in (a), was dissolved in alcohol (50 c.c.). The solution was slowly added to well-stirred ether (300 c.c.). The milky product was shaken with 100 c.c. water and then extracted with N-hydrochloric acid (20 c.c.). The bright ether layer was dried (K_2CO_3) and evaporated to give 1·3 g. (18% recovery) of unchanged phthalo-γ-bromopropylimide (VI), m. p. 69—72° The bulked aqueous extracts were basified with 50% sodium hydroxide and the total bases taken up into chloroform (150 c.c.) (*A*). This was extracted with 2N-acetic acid (25 c.c.) in water (50 c.c.), and the extracted material taken as base into ether. This dried (K_2CO_3) ether extract yielded the carbamate of (I) (1·0 g., 16% recovery). The chloroform (*A*) was next removed and the residue converted into hydrochloride (*B*) which was crystallised from alcohol. The insoluble hydrochloride of the phthalimide (II) (1·6 g., 15%) was first obtained. This was repeatedly crystallised from methanol, and, when sufficiently pure, converted into base confirmed to be (II) by m. p. and mixed m. p. The more soluble hydrochloride in the mixture (*B*) was crystallised from alcohol–ether many times without a pure substance being definitely characterised, although a N : Cl ratio of 2·07/1 indicated 8-γ′-phthalimidopropyl-γ-aminopropylamino-6-methoxyquinoline (VII) dihydrochloride.

The above results are summarised in Table III, together with Van Slyke estimations for primary amino-group on the products of fusions [as (a)] of varying duration.

TABLE III.

*R.*63 *fusion. Progress of reaction.*

Duration of fusion.....	Nil.	5 mins.	15 mins.	7 hrs.
Van Slyke estimation of N present as primary amino-group (%)	6·4, 6·3*	2·1	—	2·4
Proportion of amine (I) recovered unchanged (%)	—	—	16	10
Proportion of phthalimide (VI) recovered unchanged (%)	—	—	18	—
Proportion of theoretically possible phthalimide (II) actually isolated as crude hydrobromide (%)	—	—	15	22†

* Amine (I) requires 6·06%. † 5% as pure base.

*Preparation of R.*63 *for Antimalarial Test.*—The procedure of Glen and Robinson (*loc. cit.*) was exactly followed [Found on our sample of R.63 : N as primary amino-group (Van Slyke), 4·85. Calc. for amine (I) dihydrochloride, 4·6. Calc. for 8-γ′-aminopropyl-γ-aminopropylamino-6-methoxyquinoline trihydrochloride, 3·5%].

8-*Bis*-(γ-*phthalimidopropyl*)*amino*-6-*methoxyquinoline.*—8-γ-Phthalimidopropylamino-6-methoxyquinoline (20 g.) was fused with exclusion of moisture with phthalo-γ-bromopropylimide (32 g.) for 12 hours at 120°. The red glassy product was dissolved in methanol (200 c.c.), and an orange hydrobromide (20 g.) crystallised out. This was converted into base in methanol–2N-ammonia. 8-Bis-(γ-phthalimidopropyl)amino-6-methoxyquinoline crystallised from pyridine–methanol, m. p. 165—167° (13 g., 43%) (cf. Quin and Robinson, *loc. cit.*).

8-γ-*Phthalamidopropylamino*-6-*methoxyquinoline.*—8-γ-Phthalimidopropylamino-6-methoxyquinoline (20 g.) was added to a boiling solution of potassium hydroxide (13·8 g.) in alcohol (275 c.c.). After 30 minutes the mixture was cooled to 0° and almost neutralised with 2N-hydrochloric acid. The precipitated salt was just dissolved by adding water (200 c.c.) and the alcohol removed at 30 mm. The remaining liquor (charcoaled) was just acidified (litmus) cold with glacial acetic acid. The precipitated *product* was crystallised from aqueous methanol and dried over phosphoric oxide at 10 mm. (Found : C, 63·7; H, 6·1; N, 10·7; *M*, by titration, 390. $C_{21}H_{21}O_4N_3,H_2O$ requires C, 63·5; H, 5·8; N, 10·6%; *M*, 397). The loss in weight at 100° on this hydrated acid (Found : 9·2. $C_{21}H_{21}O_4N_3,H_2O$ requires 4·54%) indicated that both dehydration and ring closure had occurred, giving the phthalimide (II). This was confirmed by m. p. 101—103° and mixed m. p. 101—104° with authentic material after one crystallisation from methanol.

We are indebted to Mr. S. Bance, B.Sc., A.R.I.C., for the semi-microanlayses, and to the Directors of Messrs. May and Baker Ltd. for permission to publish these results.

RESEARCH LABORATORIES,
MAY & BAKER LTD., DAGENHAM, ESSEX.

[*Received, December 6th,* 1946.]