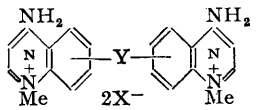
495. *Cinnolines and Other Heterocyclic Types in Relation to the Chemotherapy of Trypanosomiasis. Part VI.* Synthesis of Quaternary Salts of Dicinnolyl- and Diquinolyl-ureas, -thioureas, and -guanidines.*

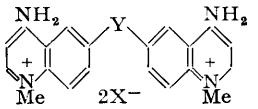
By J. S. Morley and (the late) J. C. E. Simpson.

The hypothesis that structures consisting of two quaternised amino-heterocyclic units joined by a linking group are likely to exhibit trypanocidal properties has been further explored by the synthesis of a series of compounds in which two quaternised cinnoline or quinoline nuclei are joined by urea, thiourea, and guanidine linkages. No activity against *T. congolense* infections in mice is shown by quaternary salts containing a thiourea residue or by cinnoline compounds containing a 3-methyl substituent, but N^1N^3-di-(4-amino-6-cinnolyl)guanidine dimethiodide is highly active and exhibits a chemotherapeutic index of the same order as that of " Antrycide."

Following our conception that the principal structural features of a possible new class of trypanocidal compound may be represented by the general formula (I) (Keneford, Lourie, Morley, Simpson, Williamson, and Wright, *Nature*, 1948, **161**, 603; Part I, *J.*, 1952, 2595) and our investigation of azo-compounds (Y = ·N:N·) (preceding papers) we now describe the synthesis of a series of compounds in which pairs of quinoline, cinnoline, and 3-methylcinnoline units are joined by urea, thiourea, and guanidine residues.

The choice of these linking groups was determined by a number of factors, of which the most important from the practical aspect was the wish to introduce the linkage at the latest possible stage in the synthesis; we thus hoped to minimise the manipulative difficulties which, from experience with the azoquinolines and azocinnolines (*loc. cit.*), are seemingly associated with " double-ended " heterocyclic molecules of this type. The methods employed in the present work involved the condensation of 4 : 6-diamino-quinoline, -cinnoline, and -3-methylcinnoline, or their quaternary salts, with carbonyl chloride or thiocarbonyl chloride. It was expected that the 4-amino-group in these compounds would escape reaction, and trial experiments with thiocarbonyl chloride and 4-aminoquinoline or its methochloride confirmed this.


(I)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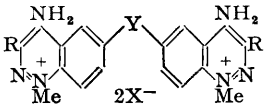
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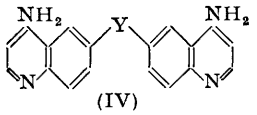
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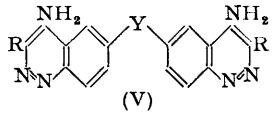
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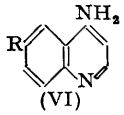
(VI)

Treatment of two molecular proportions of the appropriate base with one of thiocarbonyl chloride in boiling aqueous acetone yielded *NN'*-di-(4-amino-6-quinolyl)- (IV; Y = NH·CS·NH), *NN'*-di-(4-amino-6-cinnolyl)- (V; R = H, Y = NH·CS·NH), and *NN'*-di-(4-amino-3-methyl-6-cinnolyl)-thiourea (V; R = Me, Y = NH·CS·NH) as hydrochlorides. These salts and the free bases were somewhat unstable, showing a tendency to evolve hydrogen sulphide in warm aqueous solution, and methanethiol was evolved when (IV; Y = NH·CS·NH) and methyl toluene-*p*-sulphonate were heated at 140°. Interaction between equimolecular proportions of thiocarbonyl chloride and 4 : 6-diaminoquinoline likewise gave (IV; Y = NH·CS·NH) as main product, but a small amount of 4-amino-6-quinolyl *iso*thiocyanate (VI; R = ·NCS) was also formed, identified by conversion into (IV; Y = ·NH·CS·NH) on fusion with 4 : 6-diaminoquinoline. Desulphurisation of these dihydrochlorides by means of methanolic ammonia and mercuric

* Part V, preceding paper.

oxide furnished the corresponding guanidines [IV; Y = NH·C(:NH)·NH] and [V; R = H and Me, Y = NH·C(:NH)·NH], isolated as trihydrochlorides. The free bases were readily converted into the dimethiodides [II; X = I, Y = NH·C(:NH)·NH] and [III; R = H and Me, X = I, Y = NH·C(:NH)·NH], by reaction with methyl iodide in boiling methanol or ethanol. The quinoline quaternary salt was isolated directly, but the primary products from the two dicinnolylguanidines appeared to be quaternary salt complexes containing two and one extra molecules respectively of methyl iodide which dissociated in aqueous solution and yielded the normal dimethiodides.

NN'-Di-(4-amino-6-quinolyl)thiourea dimethiodide (II; X = I, Y = NH·CS·NH) was prepared from 4 : 6-diaminoquinoline methiodide (2 mols.) and thiocarbonyl chloride (1 mol.) in boiling aqueous acetone, but similar treatment of 4 : 6-diaminocinnoline methiodide gave the thiourea dimethochloride (III; R = H, X = Cl, Y = NH·CS·NH); this salt underwent hydrolysis during attempted conversion into the dimethiodide, and 4 : 6-diaminocinnoline methiodide was recovered in 70% yield. The 3-methyl analogue (III; R = Me, X = Cl, Y = NH·CS·NH) was prepared from 4 : 6-diamino-3-methylcinnoline methochloride and thiocarbonyl chloride in boiling aqueous acetone.

Condensation of the same three bicyclic quaternary salts with carbonyl chloride in aqueous acetone gave, respectively, *NN'*-di-(4-amino-6-quinolyl)urea dimethiodide (II; X = I, Y = NH·CO·NH), *NN'*-di-(4-amino-6-cinnolyl)urea dimethochloride (III; R = H, X = Cl, Y = NH·CO·NH), and *NN'*-di-(4-amino-3-methyl-6-cinnolyl)urea dimethochloride (III; R = Me, X = Cl, Y = NH·CO·NH); the first two reactions were notably more vigorous than those with thiocarbonyl chloride, but that with 4 : 6-diamino-3-methylcinnoline methochloride was sluggish, and buffering with sodium acetate was necessary. The quinoline salt (II; X = I, Y = NH·CO·NH) was also prepared by direct quaternisation of the urea base (IV; Y = NH·CO·NH). This base was obtained from 4 : 6-diaminoquinoline by condensation with carbonyl chloride and also by fusion with urea; a by-product in the latter reaction was 4-amino-6-quinolylurea (VI; R = $NH{\cdot}CO{\cdot}NH_2$), which on fusion with 4 : 6-diaminoquinoline was converted into the diquinolylurea (IV; Y = NH·CO·NH).

The biological activity of the quaternary salts of types (II) and (III) has been examined in the Department of Pharmacology, Oxford, by Dr. E. M. Lourie and Dr. J. M. Walker. The results are described elsewhere (Lourie, Morley, Simpson, and Walker, *Brit. J. Pharmacol.*, 1951, **6**, 643), but are summarised here. They were obtained by subcutaneous injection of aqueous solutions into mice infected with *T. congolense*. The three thiourea compounds were inactive, as also were the guanidine salts containing quinoline and 3-methylcinnoline rings and the 3-methylcinnoline urea salt. Temporary clearance of the blood from trypanosomes, followed by relapse, was observed with the quinoline and cinnoline urea salts. The guanidinocinnoline salt (which we designate for convenience as " 528 "), on the other hand, showed considerable activity. On a weight-for-weight basis, " 528 " is both less active and less toxic than antrycide methyl sulphate, but the chemotherapeutic indices (LD_{10}/CD_{90}) of the two drugs are very similar, *viz.*, 11·6 and 12·5 respectively.

The apparent dystherapeutic effect of a 3-methyl group in the cinnoline nucleus is noteworthy in view of the potentiating action against trypanosome infections of a 2-methyl group in certain " double-ended," but unquaternised, quinoline compounds (Jensch, *Annalen*, 1950, **568**, 73).

Experimental

M. p.s are uncorrected.

Attempted Condensation of 4-Aminoquinoline and its Methochloride with Thiocarbonyl Chloride.—Treatment of a solution of 4-aminoquinoline in dilute hydrochloric acid with thiocarbonyl chloride at room temperature led to an 80% recovery of the base; in water alone an obscure reaction occurred, and only 15% of unchanged base could then be isolated. Treatment of a solution of 4-aminoquinoline methochloride in aqueous acetone with thiocarbonyl chloride, at room temperature or at the b. p., gave a quantitative yield of unchanged salt.

NN'-*Di*-(4-*amino*-6-*quinolyl*)*thiourea.*—(*a*) Thiocarbonyl chloride (1·3 c.c.) was added in

one portion at room temperature to a solution of 4 : 6-diaminoquinoline (5 g.) in 50% aqueous acetone (200 c.c.), and the mixture was refluxed gently for ¼ hour. The hydrochloride of the diquinolylthiourea which separated in colourless needles was collected (5·9 g.; decomposing sharply at 255° and then melting gradually up to 290°) and converted into the free base by addition of ammonia to a cold solution of the salt in 50% aqueous methanol or 50% aqueous pyridine. NN′-*Di*-(4-*amino*-6-*quinolyl*)*thiourea* separated from these solvents in pale yellow needles, which decomposed at 200—202° and then melted at 220—235°; the base was insoluble in dilute sodium hydroxide (Found: C, 58·65; H, 5·2; S, 8·6. $C_{19}H_{16}N_6S,1·5H_2O$ requires C, 58·9; H, 4·95; S, 8·3%).

(*b*) A mixture of 4 : 6-diaminoquinoline (1 g.), water (10 c.c.), concentrated hydrochloric acid (0·63 c.c.), and thiocarbonyl chloride (0·5 c.c.) was stirred for ½ hour at room temperature, after which the diquinolylthiourea hydrochloride which had separated was collected (0·82 g.). Basification of the filtrate with sodium hydroxide gave a solid (0·32 g., m. p. 255—257°) which after recrystallisation from benzene and aqueous ethanol furnished pale orange-yellow needles (0·11 g.) of 4-*amino*-6-*quinolyl* iso*thiocyanate*, decomposing at 270—275° (Found: C, 60·1; H, 3·5; N, 21·0; S, 15·5. $C_{10}H_7N_3S$ requires C, 59·7; H, 3·5; N, 20·9; S, 15·9%). Fusion of this base with 4 : 6-diaminoquinoline and crystallisation of the product from aqueous pyridine gave *NN′*-di-(4-amino-6-quinolyl)thiourea.

NN′-*Di*-(4-*amino*-6-*cinnolyl*)*thiourea*.—A solution of 4 : 6-diaminocinnoline (10 g.) in 50% aqueous acetone (200 c.c.) was refluxed with thiocarbonyl chloride (2·9 c.c.) for ½ hour; the NN′-*di*-(4-*amino*-6-*cinnolyl*)*thiourea dihydrochloride* (13 g.) which separated was collected, washed with 50% aqueous acetone, and dried in a vacuum (Found: C, 45·85; H, 4·2; Cl, 16·2; S, 6·2. $C_{17}H_{14}N_8S,2HCl,H_2O$ requires C, 45·05; H, 4·0; Cl, 15·65; S, 7·05%). The salt decomposed at 240—245° and then melted up to 270°; its solution in warm water evolved hydrogen sulphide freely, and it could not be recrystallised owing to this instability.

NN′-*Di*-(4-*amino*-3-*methyl*-6-*cinnolyl*)*thiourea*.—(*a*) A mixture of 4 : 6-diamino-3-methylcinnoline hydrochloride (5 g.), 50% aqueous acetone (200 c.c.), and thiocarbonyl chloride (1·25 c.c.) was refluxed with mechanical stirring for 1 hour. The almost pure NN′-*di*-(4-*amino*-3-*methyl*-6-*cinnolyl*)*thiourea dihydrochloride* that had separated was collected (4 g.) and recrystallised by adding a little concentrated hydrochloric acid to a solution of the salt in tepid aqueous acetic acid; the pure salt formed a slightly gelatinous mass of yellow needles, m. p. 290° (decomp.) (Found: C, 48·95; H, 4·15; Cl, 15·65. $C_{19}H_{18}N_8S,2HCl$ requires C, 49·2; H, 4·35; Cl, 15·3%). The salt is more stable than the analogue described above, but some hydrogen sulphide is evolved when its aqueous solution is heated. The free base, obtained as a gelatinous yellow mass by addition of excess of aqueous ammonia to a solution in cold aqueous acetic acid, is soluble in dilute sodium hydroxide.

(*b*) The hydrochloride (0·55 g.) was also obtained by refluxing, for ¼ hour, of a mixture of 4 : 6-diamino-3-methylcinnoline (1 g.), 50% aqueous acetone (150 c.c.), and thiocarbonyl chloride (0·25 c.c.), followed by the addition of concentrated hydrochloric acid (25 c.c.).

N^1N^3-*Di*-(4-*amino*-6-*quinolyl*)*guanidine*.—A solution of the thiourea hydrochloride (4 g.) in methanolic ammonia (12% w/v; 250 c.c.) was stirred with yellow mercuric oxide (5 g.) for 2 hours at 35—40° under a reflux condenser. Excess of 2N-hydrochloric acid was then added, followed by aqueous sodium hydrogen sulphide, and the warm suspension was filtered. The filtrate deposited N^1N^3-*di*-(4-*amino*-6-*quinolyl*)*guanidine trihydrochloride* (2·7 g.); this crystallised from N-hydrochloric acid in colourless needles which effervesced and became orange at 295° and decomposed above 315° (Found: C, 45·4; H, 5·25; N, 18·9; Cl, 22·0. $C_{19}H_{17}N_7,3HCl,3H_2O$ requires C, 45·0; H, 5·2; N, 19·3; Cl, 21·0%). Treatment with cold sodium hydroxide gave the free base as a pale yellow granular solid, sparingly soluble in hot water, which effervesced sharply at 250° and then melted up to 260°.

N^1N^3-*Di*-(4-*amino*-6-*cinnolyl*)*guanidine*.—Finely powdered *NN′*-di-(4-amino-6-cinnolyl)thiourea dihydrochloride (5 g.; added during 10 minutes), yellow mercuric oxide (5 g.), and methanolic ammonia (12% w/v; 200 c.c.) were stirred together for 1¼ hours at 20°. The solid product was collected and digested with boiling N-hydrochloric acid (3 × 50 c.c.) and once with water (50 c.c.). The extracts were treated with hydrogen sulphide whilst hot and filtered from mercuric sulphide, and the dicinnolylguanidine trihydrochloride (3·5 g.) which separated on cooling was dissolved in water and basified with sodium hydroxide, giving N^1N^3-*di*-(4-*amino*-6-*cinnolyl*)*guanidine*; this crystallised, when ammonia was added to a solution of it in alcoholic acetic acid, as a gelatinous mass of yellow needles which effervesced and became red at 245—250° and melted with decomposition on further heating (Found: C, 50·8; H, 5·3; N, 29·4. $C_{17}H_{15}N_9,3H_2O$ requires C, 51·1; H, 5·3; N, 31·5%). The *trihydrochloride*,

prepared from the base and 2N-hydrochloric acid, formed colourless needles, m. p. 335° (decomp.), from aqueous acetone (Found: C, 45·1; H, 4·4; N, 27·4; Cl, 22·9. $C_{17}H_{15}N_9$,3HCl requires C, 44·9; H, 4·0; N, 27·7; Cl, 23·4%).

N^1N^3-*Di*-(4-*amino*-3-*methyl*-6-*cinnolyl*)*guanidine*.—Finely powdered *NN'*-di-(4-amino-3-methyl-6-cinnolyl)thiourea dihydrochloride (4 g.) was treated as above, and the crude product extracted repeatedly with hot 2N-hydrochloric acid. Complete separation of mercuric sulphide required repeated passage of hydrogen sulphide into the hot solution, and after a single treatment a well defined mercury-containing complex separated in needles from the filtered solution; this was dissolved in fresh acid and re-treated with hydrogen sulphide. Basification (ammonia) of the combined acid solutions gave N^1N^3-*di*-(4-*amino*-3-*methyl*-6-*cinnolyl*)*guanidine* (2·75 g., 81%), which separated from aqueous-ammoniacal alcohol in pale yellow needles, m. p. 240—270° (decomp.) after effervescing at 240° (Found: C, 56·45; H, 5·55; N, 29·3. $C_{19}H_{19}N_9,2H_2O$ requires C, 55·75; H, 5·65; N, 30·8%). The *trihydrochloride* crystallised from a mixture of hydrochloric acid and acetone in colourless needles, m. p. 315° (decomp.), and was readily soluble in water (Found: C, 48·3; H, 4·9; N, 22·9; Cl, 21·1. $C_{19}H_{19}N_9$,3HCl requires C, 47·3; H, 4·6; N, 26·1; Cl, 22·05%).

N^1N^3-*Di*-(4-*amino*-6-*quinolyl*)*guanidine Dimethiodide*.—The base (0·4 g.), methyl iodide (2 c.c.), and ethanol (20 c.c.) were heated under reflux for ½ hour. Dissolution of the base was quickly followed by separation of the *dimethiodide* (0·49 g.); this crystallised from aqueous alcohol in small yellow needles which effervesced and became red at 250° and then melted at 260—295° (Found: C, 38·2; H, 4·15; N, 14·6. $C_{21}H_{23}N_7I_2,2H_2O$ requires C, 38·0; H, 4·1; N, 14·8%).

N^1N^3-*Di*-(4-*amino*-6-*cinnolyl*)*guanidine Dimethiodide*.—The base (1·5 g.), methyl iodide (15 c.c.), and dry methanol (75 c.c.) were heated under reflux for 2 hours. The clear solution was then evaporated, finally in a desiccator, yielding an orange residue [2·95 g.; m. p. 265° (decomp.)] which did not lose weight after 5 hours at 60° (Found, for material dried at 100° in a vacuum: C, 23·95, 25·5; H, 3·0, 2·6; I, 56·8. Calc. for $C_{19}H_{21}N_9I_2,2CH_3I$: C, 27·6; H, 3·0; I, 55·6. Calc. for $C_{19}H_{21}N_9I_2,2HI,2H_2O$: C, 24·75; H, 2·95; I, 55·1%). A solution of this substance (1 g.) in water (20 c.c.) slowly deposited N^1N^3-*di*-(4-*amino*-6-*cinnolyl*)*guanidine dimethiodide* (0·51 g.), which crystallised from water in small yellow needles, m. p. 270° (decomp.) (Found: C, 35·35; H, 3·7; N, 19·9; I, 39·25. $C_{19}H_{21}N_9I_2,H_2O$ requires C, 35·25; H, 3·6; N, 19·5; I, 39·2%).

The composition of the orange substance, m. p. 265° (decomp.), suggested by the analytical figures is a dihydriodide dihydrate of the above quaternary salt. Its behaviour, however, suggests that it is a complex of the quaternary salt with methyl iodide, as the original aqueous filtrate from the quaternary salt was not acid to litmus and smelt of methyl iodide.

N^1N^3-*Di*-(4-*amino*-3-*methyl*-6-*cinnolyl*)*guanidine Dimethiodide*.—A mixture of the base (1 g.), methyl iodide (25 c.c.), and dry methanol (50 c.c.) was treated as above and gave an orange-yellow solid (1·64 g.), m. p. 250—300° after effervescing and reddening at 230—250°, which did not lose weight on drying at 60° (Found, for material dried at 100° in vacuum: C, 34·0; H, 3·9; N, 12·75; I, 43·8. Calc. for $C_{21}H_{25}N_9I_2,CH_3I$: C, 33·1; H, 3·55; N, 15·75; I, 47·6%). A solution of this material in water was not acid to litmus, and after it had been warmed for a few minutes the odour of methyl iodide was noticeable and small yellow needles of N^1N^3-*di*-(4-*amino*-3-*methyl*-6-*cinnolyl*)*guanidine dimethiodide* (0·76 g.) gradually separated. The salt effervesced with partial melting at 251—253° and on further heating gradually decomposed up to 280° (Found: C, 38·75; H, 3·8; N, 19·1; I, 36·25. $C_{21}H_{25}N_9I_2$ requires C, 38·4; H, 3·8; N, 19·2; I, 38·6%).

NN'-*Di*-(4-*amino*-6-*quinolyl*)*thiourea Dimethiodide*.—A solution of 4 : 6-diamino-1-methylquinolinium iodide (2 g.) in 50% aqueous acetone (100 c.c.) and thiocarbonyl chloride (0·3 c.c.) was stirred and refluxed for ¼ hour. NN'-*Di*-(4-*amino*-6-*quinolyl*)*thiourea dimethiodide* (1·2 g.) separated after a few minutes as a mass of colourless needles, and, when kept, the filtrate gave a further crop in gelatinous form (0·34 g.). The salt effervesced at 235°, and then melted and darkened up to 275° (Found: C, 38·2; H, 3·4; N, 12·0; S, 2·8. $C_{21}H_{22}N_6I_2S,H_2O$ requires C, 38·1; H, 3·65; N, 12·7; S, 4·85%); it was insoluble in most organic solvents, but separated as a gelatinous mass of small needles from alcoholic phenol or aqueous alcohol. It was soluble in hot water, but the solution slowly lost hydrogen sulphide; after ¼ hour's boiling the decomposition was incomplete (Found, for recovered material: S, 2·3, 2·2%), but after 1 hour's refluxing the salt was completely hydrolysed to 4 : 6-diamino-1-methylquinolinium iodide.

NN'-*Di*-(4-*amino*-6-*cinnolyl*)*thiourea Dimethochloride*.—After 4 : 6-diamino-1-methylcinnolinium iodide (0·5 g.), thiocarbonyl chloride (0·12 c.c.), and 50% aqueous acetone (25 c.c.)

had been refluxed for ¼ hour, the slightly turbid solution was filtered and set aside. NN′-*Di*-(4-*amino*-6-*cinnolyl*)*thiourea dimethochloride* (0·23 g.) separated in small yellow needles, which effervesced at 205° and then melted gradually up to 280° (Found : C, 48·15; H, 4·65; N, 22·8; Cl, 14·9; S, 5·75. $C_{19}H_{20}N_8Cl_2S,H_2O$ requires C, 47·4; H, 4·6; N, 23·3; Cl, 14·7; S, 6·65%). In another experiment on the same scale, the filtered solution after removal of acetone on the steam-bath (reduced pressure) was treated with aqueous potassium iodide. The product which separated (0·35 g.) had m. p. 270—275° (decomp.) after crystallisation from aqueous potassium iodide, not depressed by admixture with 4 : 6-diamino-1-methylcinnolinium iodide, and gave a strong diazo-coupling reaction (Found : C, 35·8; H, 3·8; N, 21·8; I, 42·7; S, <0·1. Calc. for $C_9H_{11}N_4I$: C, 35·75; H, 3·7; N, 18·5; I, 42·05%).

NN′-*Di*-(4-*amino*-3-*methyl*-6-*cinnolyl*)*thiourea Dimethochloride*.—When 4 : 6-diamino-1 : 3-dimethylcinnolinium chloride (0·5 g.) was treated as described above, a crystalline reaction product began to separate after ¼ hour, and was collected (0·22 g.) after a further ½ hour of refluxing. NN′-*Di*-(4-*amino*-3-*methyl*-6-*cinnolyl*)*thiourea dimethochloride* crystallised from water in small yellow needles, m. p. 313—314° (decomp.) (Found : C, 51·55; H, 4·65; N, 22·5; Cl, 14·0; S, 6·2. $C_{21}H_{24}N_8SCl_2$ requires C, 51·3; H, 4·9; N, 22·8; Cl, 14·4; S, 6·5%). No depression in m. p. was observed in admixture with 4 : 6-diamino-1 : 3-dimethylcinnolinium chloride.

NN′-*Di*-(4-*amino*-6-*quinolyl*)*urea*.—(*a*) A slow stream of carbonyl chloride was bubbled into a stirred suspension of 4 : 6-diaminoquinoline (2 g.) in water (40 c.c.) containing crystalline sodium acetate (4 g.) at 80—90° until an almost clear solution was formed (*ca.* 5 minutes). Addition of 10N-hydrochloric acid (*ca.* 10 c.c.) to the filtered solution precipitated NN′-*di*-(4-*amino*-6-*quinolyl*)*urea dihydrochloride* (1·48 g.), which formed small colourless needles, m. p. 350° (decomp.), from dilute hydrochloric acid, and was easily soluble in warm water (Found : C, 54·0; H, 4·45; N, 18·95; Cl, 17·9. $C_{19}H_{16}ON_6,2HCl$ requires C, 54·7; H, 4·35; N, 20·15; Cl, 17·0%). Basification with ammonia solution gave NN′-*di*-(4-*amino*-6-*quinolyl*)*urea*, m. p. 284—286° (decomp.), which crystallised from slightly aqueous ethanol as a gelatinous mass of small pale yellow needles, and then had m. p. 260—265° (decomp.) (Found : C, 60·9; H, 4·5; N, 22·1. $C_{19}H_{16}ON_6,1·5H_2O$ requires C, 61·4; H, 5·15; N, 22·6%). The base was sparingly soluble in aqueous ethanol, insoluble in other common solvents and in alkalis, and easily soluble in dilute acetic acid.

(*b*) (Cf. Haskelberg, *J. Org. Chem.*, 1947, **12**, 434.) A mixture of 4 : 6-diaminoquinoline (2·3 g.), urea (0·51 g.), and 10N-hydrochloric acid (1·25 c.c.) was heated at 120—130° until all the water had evaporated (¼—½ hour); the temperature of the resultant red mass was then quickly raised to 230° and kept there for ¼ hour. When cold, the mass was digested with very dilute acetic acid (35 c.c.), and the extract was filtered and basified with ammonia, yielding the above diquinolylurea (1·15 g.), m. p. (after crystallisation from aqueous ethanol) 248—253° (decomp.) alone and mixed with the foregoing specimen.

The ammoniacal filtrate from the base was treated with sodium hydroxide, and the precipitated bases (1·2 g.) were dissolved in hot water (25 c.c.); 4 : 6-diaminoquinoline [0·42 g.; m. p. and mixed m. p. 215—216° (decomp.)] first separated, followed by 4-*amino*-6-*quinolylurea* (crude, 0·3 g.), which crystallised from 2-ethoxyethanol–ether in small colourless prisms, m. p. 220—222° (effervescence) (Found : C, 59·0; H, 5·25; N, 26·55. $C_{10}H_{10}ON_4$ requires C, 59·4; H, 5·0; N, 27·7%). On fusion with 4 : 6-diaminoquinoline this base yielded *NN′*-di-(4-amino-6-quinolyl)urea, which was identified by mixed m. p. and by conversion into the dihydrochloride.

NN′-*Di*-(4-*amino*-6-*quinolyl*)*urea Dimethiodide*.—(*a*) A freshly prepared solution of carbonyl chloride (0·4 g.) in acetone (2 c.c.) was added during 5 minutes to a solution of 4 : 6-diamino-1-methylquinolinium iodide (2 g.) in 50% aqueous acetone (40 c.c.) which was stirred and kept at 0—5° throughout the experiment. After ¼ hour the solid which had separated was collected (0·91 g.), dissolved in water, and treated with aqueous potassium iodide; NN′-*di*-(4-*amino*-6-*quinolyl*)*urea dimethiodide* (0·8 g.) separated in small, pale yellow needles, m. p. 303—305° (effervescence) (Found : C, 41·4; H, 3·85; N, 13·25; I, 39·0. $C_{21}H_{22}ON_6I_2$ requires C, 40·15; H, 3·55; N, 13·4; I, 40·4%).

(*b*) Finely powdered *NN′*-di-(4-amino-6-quinolyl)urea (0·1 g.), ethyl alcohol (10 c.c.), and methyl iodide (1 c.c.) were refluxed for 1 hour. The product was collected in the cold and recrystallised first from aqueous potassium iodide and then thrice from water, whence the dimethiodide separated as small needles of the *dihydrate*, m. p. 298—300° (decomp.) alone and when mixed with the anhydrous salt (Found : C, 36·6; H, 3·8; I, 37·2. $C_{21}H_{22}ON_6I_2,2H_2O$ requires C, 37·95; H, 3·95; I, 38·2%).

NN′-*Di*-(4-*amino*-6-*cinnolyl*)*urea Dimethochloride*.—A solution of carbonyl chloride in acetone

(10 c.c. of 20% w/v) was added in portions during 2 minutes to one of 4 : 6-diamino-1-methylcinnolinium iodide (0·5 g.) in 50% aqueous acetone (10 c.c.); the temperature rose from 20° to 40—50° and a solid rapidly separated. The product was collected [0·1 g.; m. p. 289—290° (decomp.)] and recrystallised from aqueous acetone, giving small yellow needles of NN'-*di*-(4-*amino*-6-*cinnolyl*)*urea dimethochloride*, m. p. 295—297° (decomp.) (Found : C, 49·6; H, 4·9; N, 24·7; Cl, 14·9. $C_{19}H_{20}ON_8Cl_2,H_2O$ requires C, 49·05; H, 4·75; N, 24·05; Cl, 15·25%). In another experiment (on twice the scale), the filtrate was left overnight, and yielded pale yellow needles, m. p. 304—305° (decomp.), of 4 : 6-diamino-1-methylcinnolinium chloride (0·13 g.).

NN'-*Di*-(4-*amino*-3-*methyl*-6-*cinnolyl*)*urea Dimethochloride*.—Carbonyl chloride was slowly bubbled for 7 minutes into a stirred solution of 4 : 6-diamino-1 : 3-dimethylcinnolinium chloride (0·5 g.) and crystalline sodium acetate (1 g.) in water (25 c.c.) at 80°. The solid which rapidly separated (0·14 g.) was collected in the hot, washed with a little warm water, and crystallised from water, giving small yellow needles of NN'-*di*-(4-*amino*-3-*methyl*-6-*cinnolyl*)*urea dimethochloride*, m. p. 288—290° (decomp.) (Found : C, 51·75; H, 5·35; N, 21·4; Cl, 14·4. $C_{21}H_{24}ON_8Cl_2,H_2O$ requires C, 51·1; H, 5·3; N, 22·7; Cl, 14·4%). The reaction filtrate on cooling gave unchanged 4 : 6-diamino-1 : 3-dimethylcinnolinium chloride (0·3 g.), and this was the sole product if the condensation was attempted (at 0°, room, or reflux temperature) in the absence of sodium acetate.

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