286. *The Chemistry of Simple Heterocyclic Systems. Part III Basic Centres of 4-Substituted Quinazoline Derivatives.*

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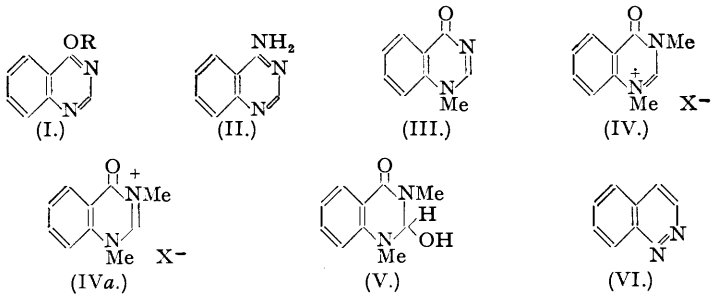
The preparation from 4-hydroxyquinazoline of 4-phenoxy- and 4-amino-quinazoline is described.

Fusion of 4-phenoxyquinazoline with methyl toluene-*p*-sulphonate yields 1-methyl-4-quinazolone *via* an unstable quaternary salt, thus disclosing $N_{(1)}$ as the basic centre in the phenoxy-compound; however, similar treatment of 4-methoxyquinazoline attacks both $N_{(1)}$ and $N_{(3)}$ with formation of the quaternary salt (IV) or (IV*a*).

Attempted conversion of cinnoline methiodide into 1-methyl-4-cinnolone results in dealkylation and formation of cinnoline in 50% yield.

It has recently been shown (Morley and Simpson, *J.*, 1948, 360) that 6- and 7-nitro-4-acetamido- and -4-phenoxy-quinazoline are converted by quaternary-salt formation and subsequent fission into 6- and 7-nitro-1-methyl-4-quinazolone, and therefore that $N_{(1)}$ is the proton-accepting centre in these quinazolines. On the other hand, the centre of basicity, as deduced from quaternary-salt formation and degradation, is $N_{(3)}$ in quinazoline itself (Gabriel and Colman, *Ber.*, 1904, **37**, 3643). It was therefore desirable to ascertain whether $N_{(1)}$ or $N_{(3)}$ is the basic centre in other 4-substituted quinazolines, and we now record our results with 4-*phenoxyquinazoline* (I; R = Ph) and 4-methoxyquinazoline (I; R = Me).



(I.) (II.) (III.) (IV.)

(IV*a*.) (V.) (VI.)

4-Phenoxyquinazoline was readily prepared from 4-chloroquinazoline by reaction with phenol and potassium hydroxide. Treatment of the chloro-compound with phenol and ammonium carbonate likewise yielded (I; R = Ph) together with some 4-*aminoquinazoline* (II), which was also obtained from 4-chloroquinazoline and concentrated aqueous ammonia at room temperature (cf. Tomisek and Christensen, *J. Amer. Chem. Soc.*, 1945, **67**, 2112) and, almost quantitatively, from the phenoxy-compound and ammonium acetate at 190°. The properties of compounds previously designated as 4-aminoquinazoline are not in good agreement with those of our material; thus Dewar (*J.*, 1944, 619) states that 4-aminoquinazoline, m. p. 259—260°, is almost non-basic and fails to react with acid chlorides under a variety of conditions, and Tomisek and Christensen (*loc. cit.*) state that it melts at 245—260° (decomp.) and yields (apparently with considerable difficulty) an acetyl derivative, m. p. 172°. In our hands, 4-aminoquinazoline prepared by each of the three methods mentioned has m. p. 267° (decomp.), readily yields 4-acetamidoquinazoline, m. p. 174—175°, and has pronounced basic properties (see Part IV, following paper).

Fusion of 4-phenoxyquinazoline with methyl toluene-*p*-sulphonate proceeded with elimination of phenol, and subsequent treatment with water yielded 1-methyl-4-quinazolone (III), isolated as the *picrate*. The structure of this base was proved by alkaline fission to *o*-methylaminobenzamide (*N*-methylanthranilamide) and also by nitration to 6-nitro-1-methyl-4-quinazolone (Morley and Simpson, *loc. cit.*). As 4-hydroxyquinazoline yields 3-methyl-4-quinazolone under ordinary conditions of alkylation (Knape, *J. pr. chem.*, 1891, **43**, 209; Bogert and Geiger, *J. Amer. Chem. Soc.*, 1912, **34**, 524), these results indicate that 4-phenoxyquinazoline is converted by reaction at $N_{(1)}$ into an unstable quaternary salt, which then undergoes decomposition to 1-methyl-4-quinazolone.

Bogert and Geiger (*J. Amer. Chem. Soc.*, 1912, **34**, 683) found that 4-methoxyquinazoline, 4-hydroxyquinazoline, and 3-methyl-4-quinazolone reacted with methyl iodide to give the same iodide, $C_{10}H_{11}ON_2I$, which must therefore be represented by one or other of the structures (IV) or (IV*a*) (X = I); its formation is thus of no value for the purpose of deciding whether $N_{(1)}$ or $N_{(3)}$

is the basic centre in 4-methoxyquinazoline. In the hope that the use of a different reagent might produce the desired result of quaternisation without further alkylation, 4-methoxyquinazoline was fused with methyl toluene-*p*-sulphonate (1 mol.), but, after conversion into the iodide, the sole product was, again, the dialkylated salt (IV or IV*a*; X = I). Treatment of this salt with cold alkali yielded an oil, the properties of which suggested that it might be the *pseudo*-base (V); however, the oil gave a *picrate*, m. p. 189°, which differed from the quaternary *picrate* (IV or IV*a*; X = $C_6H_2O_7N_3$), m. p. 198°, prepared from the iodide.

No decision, therefore, can be made as to the position of the basic centre in 4-methoxyquinazoline. The results described in this and an earlier paper (*J.*, 1948, 360), however, establish that the introduction of a phenoxy- or an acetamido-group into the quinazoline nucleus at C_4 produces a shift of the basic centre from $N_{(3)}$ to $N_{(1)}$. Particular interest thus attaches to the determination of the centre of basicity of the isomeric cinnoline (VI), inasmuch as $N_{(1)}$ has been shown to function in this capacity in 4-methyl- and 4-amino-cinnolines (Atkinson and Simpson, *J.*, 1947, 808; Simpson, *J.*, 1947, 1653). Preliminary attempts in this direction have been unsuccessful; oxidation of cinnoline methiodide with alkaline ferricyanide gave 50% of cinnoline, and no 1-methyl-4-cinnolone (Schofield and Simpson, *J.*, 1945, 512) could be detected; and treatment of the methiodide with alkali in an atmosphere of nitrogen gave no definite product.

Experimental.

Melting points are uncorrected.

4-Phenoxyquinazoline.—(*a*) 4-Chloroquinazoline (3·3 g.) was added during 10 minutes to a solution of potassium hydroxide (1·3 g.) in warm phenol (40 g.; temperature $\geqslant$ 50°). After 1 hour at 50° the melt was digested with cold 2N-sodium hydroxide and the suspension extracted with ether. The product (4·01 g.; 90%) from the washed and dried extract was crystallised from ligroin (b. p. 60—80°), yielding *4-phenoxyquinazoline* as colourless plates, m. p. 78—79° (Found: C, 75·6; H, 4·6. $C_{14}H_{10}ON_2$ requires C, 75·65; H, 4·5%).

(*b*) 4-Chloroquinazoline (1 g.) was added with powdered ammonium carbonate (4 g.) to phenol (10 g.) at 90°. After ¾ hour the product was worked up as in (*a*). It was not wholly soluble in ether, and the insoluble fraction, after dissolution in 0·5N-hydrochloric acid and reprecipitation with ammonia, yielded 4-aminoquinazoline (0·17 g.), m. p. 265—267° (decomp.) alone and mixed with the material described below. The ether-soluble portion of the reaction-product gave 4-phenoxyquinazoline (0·7 g.).

4-Aminoquinazoline.—(*a*) 4-Phenoxyquinazoline (1 g.) was added to freshly-fused ammonium acetate (5 g.) at 160°; the temperature of the mixture was then raised to 190° and kept there for 2 minutes. When cold, the mass was dissolved in water (10 c.c.) and made alkaline with 2N-sodium hydroxide. Pure *4-aminoquinazoline* (0·64 g.; 98%) separated in colourless needles, m. p. 267—268° (decomp.), unchanged by crystallisation from alcohol; it could not be obtained anhydrous even after prolonged drying at 80° in a vacuum (Found: C, 63·8; H, 4·85; N, 28·4. $C_8H_7N_3,\frac{1}{3}H_2O$ requires C, 63·6; H, 5·1; N, 27·8%).

(*b*) 4-Chloroquinazoline (1 g.) and aqueous ammonia (50 c.c.; *d* 0·88) after 10 days at room temperature gave a crude product (0·8 g., m. p. 202—215°) which, after dissolution in warm 0·5N-hydrochloric acid, filtration, and reprecipitation, yielded fairly pure 4-aminoquinazoline (0·59 g.; 67%), m. p. 245—251° (decomp.). This (0·5 g.) was suspended in water (80 c.c.), treated with sufficient acetic acid to effect dissolution, and basified with ammonia; the solution, after filtration, in the hot, from a little gelatinous material, deposited glittering needles of pure 4-aminoquinazoline, m. p. 265—267° (decomp.).

4-Acetamidoquinazoline (60 mg.) was prepared by heating the base (100 mg.) with acetic anhydride (1 c.c.) under reflux for 2 hours, and then adding dry ether (5 c.c.) to the cooled solution; it formed fine, colourless needles, m. p. 174—175° (Found: C, 64·0; H, 4·7; N, 22·5. Calc. for $C_{10}H_9ON_3$: C, 64·15; H, 4·85; N, 22·45%).

*Reaction of 4-Phenoxyquinazoline with Methyl Toluene-*p*-sulphonate.*—A mixture of 4-phenoxyquinazoline (3·52 g.) and methyl toluene-*p*-sulphonate (3·2 g.) was fused at 150° (bath temperature) for ¼ hour; a strong odour of phenol developed and a clear orange-red melt was formed. When the mixture had cooled, water (25 c.c.) was added, and the mixture extracted with ether; the ether-soluble material was identified by conversion into tribromophenol (4·4 g.; 84%), m. p. 94—95°. Treatment of the aqueous solution with picric acid (4 g.) in hot ethanol (80 c.c.) gave *1-methyl-4-quinazolone picrate* (5·37 g.; 87%), which formed yellow needles, m. p. 249—250° (decomp.), from methanol, in which it was sparingly soluble (Found: C, 46·5; H, 3·05; N, 18·0. $C_{15}H_{11}O_8N_5$ requires C, 46·3; H, 2·85; N, 18·0%).

The free base (crude, 1·25 g.), obtained from the picrate (5·3 g.) by decomposition with ice-cold ammonia in the presence of chloroform, formed a hydrate, m. p. 65—66°, converted into the hygroscopic anhydrous base (long colourless needles, m. p. 141—142°, from chloroform–ligroin) by drying at 80—90° for 3 hours. The ammoniacal solution, after the removal of chloroform, was treated with 20% aqueous sodium hydroxide and kept for 24 hours at room temperature; extraction with benzene then yielded *o*-methylaminobenzamide (0·36 g.) (see below). Decomposition of the picrate with lithium hydroxide or sodium hydroxide gave poorer yields of the quinazolone. When a solution of the quinazolone (0·15 g.) in cold water (2 c.c.) was boiled for 2 minutes with 2N-sodium hydroxide (2 c.c.), some ammonia was evolved, and *o*-methylaminobenzamide (40 mg.) separated on cooling, m. p. 162—163° (Knape, *J. pr. Chem.*, 1891, **43**, 209, gives m. p. 159—160°), after crystallisation from aqueous alcohol (Found: C, 63·8;

H, 6·5. Calc. for $C_8H_{10}ON_2$: C, 64·0; H, 6·7%). The quinazolone (100 mg.) was added in portions to a mixture of nitric acid (0·5 c.c.; *d* 1·50) and concentrated sulphuric acid (0·5 c.c.) at 25—30°. After 20 minutes the solution was poured on ice, made just alkaline with solid potassium carbonate, and filtered, and the filtrate was evaporated under reduced pressure, yielding 6-nitro-1-methyl-4-quinazolone (30 mg.), m. p. 270—272° alone and mixed with an authentic specimen (*J.*, 1948, 360).

3-*Methyl-4-quinazolone.*—The method of Bogert and Geiger (*J. Amer. Chem. Soc.*, 1912, **34**, 524) gave the base in 85% yield, but the yield was somewhat lower when methyl sulphate and excess of alkali were used. The anhydrous base, m. p. 105—106° (Bogert and Geiger give m. p. 105°), readily reverted to the hydrate, m. p. 71—72° (Bogert and Geiger give m. p. 70—71°); both forms gave large depressions in m. p. when mixed with the corresponding specimens of 1-methyl-4-quinazolone. The *picrate*, m. p. 215—216° (depressed by 1-methyl-4-quinazolone picrate), formed soft, yellow needles from alcohol, in which it was much more soluble than the 1-methyl isomer (Found: C, 46·6; H, 3·05; N, 18·1. $C_{15}H_{11}O_8N_5$ requires C, 46·3; H, 2·85; N, 18·0%).

*Reaction of 4-Methoxyquinazoline with Methyl Toluene-*p*-sulphonate.*—4-Methoxyquinazoline (0·64 g.) and methyl toluene-*p*-sulphonate (0·8 g.) were heated together for a few minutes at 160°. The colourless crystalline mass obtained on cooling was dissolved in warm water (2 c.c.) and treated with a solution of potassium iodide (1 g.) in water (2 c.c.), yielding the iodide (1·01 g.; 83%) as colourless needles, m. p. 275—277° after sintering at 265° [Bogert and Geiger, *loc. cit.*, give m. p. 275° (corr.)] (Found: C, 39·75; H, 3·7; N, 9·7. Calc. for $C_{10}H_{11}ON_2I$: C, 39·75; H, 3·7; N, 9·3%). The corresponding *picrate*, obtained from the iodide and picric acid in aqueous solution, crystallised from water in soft yellow plates, m. p. 197—198° (Found: C, 47·65; H, 3·35; N, 17·35. $C_{16}H_{13}O_8N_5$ requires C, 47·65; H, 3·25; N, 17·4%). A solution of the iodide (0·2 g.) in water (5 c.c.) was treated with 2N-sodium hydroxide (5 c.c.) and left overnight. A colourless oil (insoluble in water, readily soluble in dilute acids and in ether, benzene, or chloroform) had then separated; this (0·13 g.) was isolated by extraction with ether and converted into a *picrate* (0·25 g.), which separated from alcohol in yellow needles, m. p. 188—189° (153—155° when mixed with the picrate, m. p. 197—198°, described above) (Found: C, 46·4; H, 3·85; N, 18·2, 17·9, 18·3. $C_{16}H_{13}O_8N_5,\frac{1}{2}H_2O$ requires C, 46·6; H, 3·4; N, 17·0%).

Alkaline Decomposition of Cinnoline Methiodide.—(*a*) N-Sodium hydroxide (5 c.c.) and a solution of cinnoline methiodide (0·4 g.) in water (10 c.c.) were added alternately, in small portions, to a solution of potassium ferricyanide (1·2 g.) in water (10 c.c.) during 5 minutes; the deep emerald-green solution thus formed was kept at room temperature for ½ hour with occasional shaking. Addition of excess of 20% sodium hydroxide and extraction with chloroform gave cinnoline, isolated as its picrate (0·26 g.; 49%), m. p. and mixed m. p. 196—197° (decomp.), and further authenticated by reconversion into the methiodide [m. p. and mixed m. p. 171—173° (decomp.)] with warm methanolic methyl iodide.

(*b*) Cinnoline methiodide (0·2 g.) and 0·5N-sodium hydroxide (5 c.c.) were set aside under nitrogen for ½ hour at room temperature. The deep-blue suspension was filtered into a separating funnel under nitrogen, giving a residue (A); the filtrate was treated with excess of 20% sodium hydroxide and extracted with benzene, but only a trace of oil was obtained on evaporation. The blue-green residue (A) (0·1 g., m. p. 120—125° (decomp.)) was almost insoluble in water and in benzene, but dissolved in dilute mineral acids giving pale red solutions from which it was reprecipitated by ammonia or caustic alkalis; it showed no tendency to form a picrate.

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