

88. *The Chemistry of Simple Heterocyclic Systems. Part I. Reactions of 6- and 7-Nitro-4-hydroxyquinazoline and their Derivatives.*

By J. S. MORLEY and J. C. E. SIMPSON.

The preparation is described of 6- and 7-nitro-4-amino-, -4-acetamido-, -4-phenoxy-, and -4-anilino-quinazoline, starting from the appropriate hydroxy-compounds (I and II; R = OH), the properties of which are briefly compared with those of 6-nitro-4-hydroxycinnoline (III).

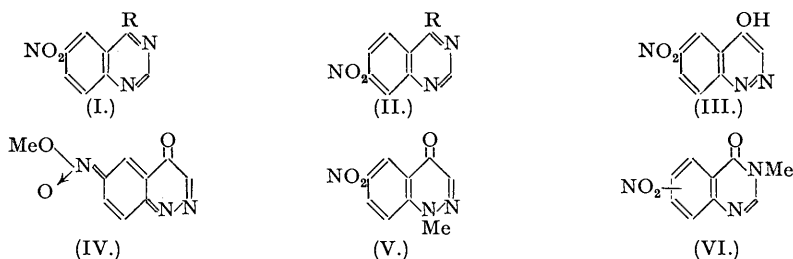
Conversion of the 4-anilino-isomers into stable quaternary salts proceeds normally, but with the 4-phenoxy- and 4-acetamido-compounds the reaction leads to fission of the 4-substituents and to production of 6- and 7-nitro-1-methyl-4-quinazolone, the constitutions of which have been proved by a study of their facile alkaline hydrolysis. 6-Nitro-3-methyl-4-quinazolone and its 7-nitro-isomer are similarly hydrolysed and oriented, and a common mechanism is proposed for these alkaline hydrolyses and those of the -4-amino- to the -4-hydroxy-quinazolines; according to this mechanism, the quinazolones and aminoquinazolines are regarded as, respectively, cyclic and semi-cyclic amidines, and the initial step in the hydrolyses is an attack on the amidine double bond.

Reference is also made to the reactivity of the 4-substituted quinazolinium salts, and to the probable non-identity of the sites of substitutive alkylation and of proton-acceptance in 4-hydroxyquinazolines; the former is N³, and it is concluded tentatively that the latter is N¹.

THE present communication deals with reactions of 6- and 7-nitro-4-hydroxyquinazoline (I and II; R = OH) and their derivatives. The chemistry of these hydroxy-compounds has received little attention despite the fact that they are easily accessible and have been known for many years. The 7-nitro-derivative was first prepared from 4-nitroanthranilic acid by the Niementowski reaction (Bogert and Klaber, *J. Amer. Chem. Soc.*, 1908, **30**, 807); (I; R = OH) was prepared similarly [Bogert and Scatchard, *J. Amer. Chem. Soc.*, 1919, **41**, 2052; Magidson and Golovchinskaya, *J. Gen. Chem. Russia*, 1938, **8**, 1797 (*Chem. Abs.*, 1939, **33**, 4993)], and also by nitration of 4-hydroxyquinazoline (Bogert and Geiger, *J. Amer. Chem. Soc.*, 1912, **34**, 524). The amine obtained by reduction of (I; R = OH) has been described (Bogert and Geiger, *loc. cit.*; Magidson and Golovchinskaya, *loc. cit.*), and the chloro-compounds (I and II; R = Cl) have also been prepared [U.S.P. 1,880,447 (*Chem. Abs.*, 1933, **27**, 998); Magidson and Golovchinskaya, *loc. cit.*].

The compounds (I and II; R = OH) show important qualitative differences from 6-nitro-4-hydroxycinnoline (III). Thus the hydroxyquinazolines failed to react with acetic anhydride under conditions which result in quantitative acetylation of (III) and other 4-hydroxycinnolines (*J.*, 1945, 512; 1946, 1035; this vol., p. 354); replacement of the hydroxyl group by chlorine also occurs less readily with (I and II; R = OH) than with (III). Again, (I and II; R = OH)

have slight basic properties in addition to their acidic nature, whereas (III) is devoid of basic character. Furthermore, alkylation of (III) with methyl sulphate is notably different from



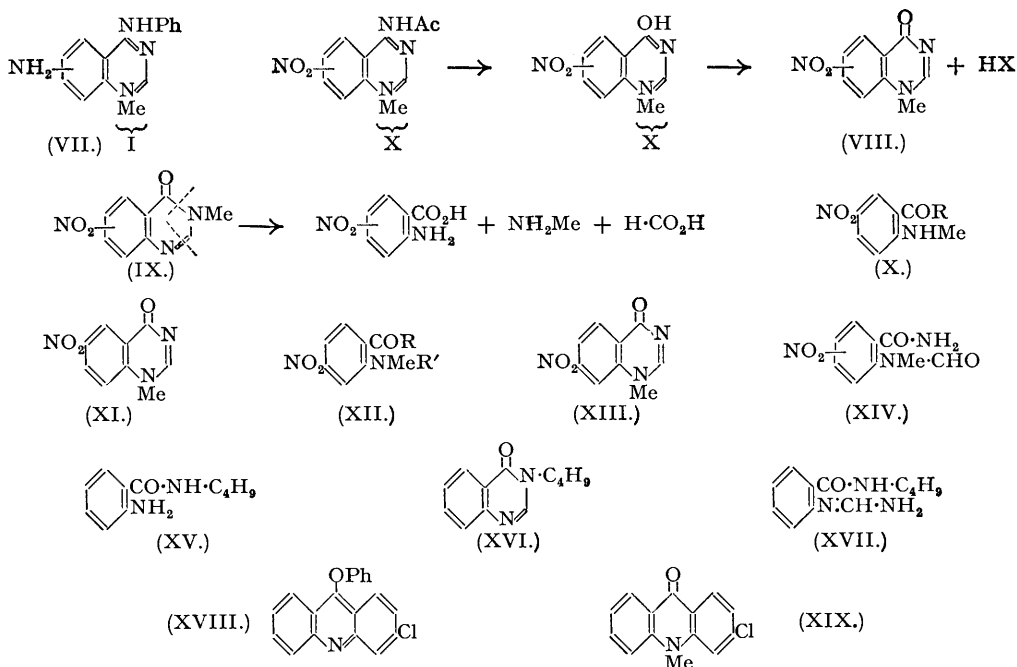
that of (I and II; R = OH); (III) gives a mixture of (IV) and (V) (Schofield and Simpson, *J.*, 1945, 512), but, as is shown later, (I and II; R = OH) give as sole isolable products the corresponding 3-methyl-4-quinazolones (as VI).

Interaction of the chloronitroquinazolines (I and II; R = Cl) with phenol and solid potassium hydroxide gave 6- and 7-nitro-4-phenoxyquinazoline (I and II; R = OPh) in moderate yield. The use of ammonium carbonate instead of potassium hydroxide gave the same compounds mixed with 6- and 7-nitro-4-aminoquinazoline (I and II; R = NH₂), and in the reaction with (I; R = Cl) the 4-aminoquinazoline was the main product under these conditions. On the other hand, the phenol-ammonium carbonate method, which is the standard procedure for making 5-amino- from 5-chloro-acridines (cf. Albert and Gledhill, *J. Soc. Chem. Ind.*, 1942, 61, 159), gives phenoxy-compound and little or no amino-derivative when applied to nitro-4-chlorocinnolines (this vol., pp. 356, 358). The amines (I and II; R = NH₂) were also prepared easily and in good yield by the method described elsewhere (this vol., p. 358) of fusing the phenoxycompounds with ammonium acetate, and we also found that 6- and 7-nitro-4-aminoquinazoline can be obtained (the 6- more readily than the 7-isomer) from the chloro-compounds and cold ammonia solution (cf. Tomisek and Christensen, *J. Amer. Chem. Soc.*, 1945, 67, 2112). The nitro-4-aminoquinazolines, like 4-aminocinnolines (this vol., p. 358), are easily acetylated, but differ from the latter compounds in being readily hydrolysed to the 4-hydroxy-compounds in acid and in alkaline solution. The acid hydrolysis of various 4-alkylaminoquinazolines is mentioned by Tomisek and Christensen (*loc. cit.*).

One of the objects of this work was the preparation of quaternary salts of 6- and 7-amino-4-substituted quinazolines and the determination of the site of quaternary salt formation. 4-Aminoquinoline forms quaternary salts on the ring nitrogen (Claus and Frobenius, *J. pr. Chem.*, 1897, 56, 181, and confirmed in this laboratory), and the same is true of 5-aminoacridine (Albert and Ritchie, *J.*, 1943, 458) and of 6-chloro-4-aminocinnoline (and probably other 4-aminocinnolines) (*J.*, 1947, 1653). However, no well-defined product resulted when 7-nitro-4-aminoquinazoline was refluxed with methyl iodide in alcohol, and it appeared that protection of the 4-amino-group was a prerequisite to effective quaternary salt formation on the ring nitrogen. To this end, (I and II; R = Cl) were condensed with aniline in slightly acid aqueous acetone (cf. Curd, Davis, Owen, Rose, and Tuey, *J.*, 1946, 370), and the resultant 6- and 7-nitro-4-anilinoquinazoline (I and II; R = NHPh) were converted into quinazolinium salts by means of methyl *p*-toluenesulphonate. Conversion of these salts into the *iodides*, followed by reduction, yielded 6- and 7-amino-4-anilino-1-methylquinazolinium iodide (as VII). 6- and 7-Nitro-4-acetamidoquinazoline (I and II; R = NHAc) were also smoothly converted into quinazolinium salts with methyl *p*-toluenesulphonate, but, as might be expected in view of the hydrolysis, referred to above, of (I and II; R = NH₂) to (I and II; R = OH), the products obtained, after treatment of the original reaction products with hot acid, were *compounds*, m.p. 271° and 219°, which had the composition of nitromethylquinazolones, removal of the acetamido-group having occurred during either the original reaction or the subsequent working-up. Smooth reactions were likewise observed between methyl *p*-toluenesulphonate and the phenoxy-compounds (I and II; R = OPh), but phenol was eliminated in each case, and the products isolated were the *p*-toluenesulphonates of the same nitromethylquinazolones, m. p. 271° and 219°. These *p*-toluenesulphonates were authenticated by liberation of the quinazolone bases (the salt from 6-nitro-4-phenoxyquinazoline was rapidly hydrolysed in aqueous solution, but the 7-nitro-isomer was more stable), and by the preparation of the salts from the bases and *p*-toluenesulphonic acid.

It is clear that the formation of these quinazolone bases from the acetamido- and phenoxy-

compounds involves an initial quaternary salt formation, followed by hydrolysis either *in situ* (phenoxy-compounds) or possibly at a later stage (acetamido-compounds), as outlined in the formulæ below. The resultant quinazolone bases could conceivably be either the 1-methyl compounds (as VIII) or the 3-methyl isomers; it thus followed that the elucidation of the structures of the compounds, m. p. 271° and 219°, would disclose the point of quaternary salt formation, and hence the basic centre, of the parent quinazolines. This question was settled in the following way.



First, the preparation of 6- and 7-nitro-4-methoxyquinazoline (I and II; R = OMe) by reaction between methanolic sodium methoxide and the respective chloro-compounds eliminated these structures as possible constitutions for the compounds, m. p. 271° and 219°. It was then found that treatment of (I and II; R = OH) with methyl sulphate and alkali gave, as sole products, the known 6-nitro-3-methyl-4-quinazolone (Bogert and Geiger, *loc. cit.*) and the isomeric 7-nitro-derivative; these compounds, m. p. 197° and 211°, were likewise different from the isomers obtained from the experiments on quaternary salt formation. Independent proof of the orientation of the 6-nitro-compound, m. p. 197°, was obtained through the observation that it was rapidly hydrolysed in hot alkaline solution to 5-nitroanthranilic acid and methylamine; determination of the latter indicated that the reaction was quantitative. In similar fashion, the compound, m. p. 211°, was shown to be 7-nitro-3-methyl-4-quinazolone (as IX); in this case, formic acid was identified in addition to the other products, and the reaction was again quantitative (methylamine determination).

It thus seemed certain that N¹ is the alkylated nitrogen in the compounds, m. p. 271° and 219°, and final proof was obtained by a study of the alkaline degradation of these compounds. The former substance gave a mixture of the known 5-nitro-2-methylaminobenzoic acid (X; R = OH) and its amide (X; R = NH₂), and it must therefore be formulated as 6-nitro-1-methyl-4-quinazolone (XI). Hydrolysis of the compound, m. p. 219°, yielded, according to conditions, 4-nitro-2-methylaminobenzoic acid (XII; R = OH; R' = H), its amide (XII; R = NH₂; R' = H), and 4-nitro-2-N-methylformamidobenzoic acid (XII; R = OH; R' = CHO); the constitution of the first of these products was proved by unambiguous synthesis from methyl 4-nitroanthranilate by tosylation, methylation and two-stage hydrolysis [the ester (XII; R = OMe; R' = H) was a well-defined intermediate], and the structures of the second and third followed from their hydrolysis to the parent acid (XII; R = OH; R' = H). Representation of the compound, m. p. 219°, as 7-nitro-1-methyl-4-quinazolone (XIII) is obviously the only possible interpretation of these results.

Although purely structural arguments of the above type must be applied with caution to problems involving reactive centres, it is likely that, in 4-hydroxyquinazolines also, the basic centre is N^1 and thus does not coincide with the site of *N*-alkylation. Direct proof, depending on the isolation of quaternary salts of 4-hydroxyquinazolines, is lacking, but 4-hydroxyquinazolines are known to be not readily converted into quaternary salts (Bogert and Geiger, *J. Amer. Chem. Soc.*, 1912, **34**, 683). The importance of differentiating between the centres of basicity and of substitutive alkylation seems to have been largely unrecognised; Tomisek and Christensen (*loc. cit.*), for example, in a discussion of some reactions of 4-substituted quinazolines, have arbitrarily assigned to N^3 the function of proton-acceptance. The American workers may possibly have been influenced by the fact that quinazoline itself quaternises at N^3 (Gabriel and Colman, *Ber.*, 1904, **37**, 3643), but they do not refer to this point, and in any case its evidential value is probably very slight, owing to the decisive influence which may be exerted by 4-substituents in determining the point of maximum basicity (cf. Atkinson and Simpson, *J.*, 1947, 808; Simpson *ibid.*, p. 1653).

In the hydrolysis of the compounds (IX), the initial attack could be regarded as occurring either at N^1-C^2 (hydrolysis of a cyclic amidine) or at N^3-C^4 (hydrolysis of a cyclic amide). In the case of the hydrolysis of (XI) and (XIII), however, amidine-type hydrolysis is more plausible than alternative mechanisms; this initial step involves fission at C^2-N^3 to yield a primary product (as XIV), which by further breakdown could give rise to the various hydrolytic products isolated. Thus the fission of both the 3- and the 1-methylquinazolone may well occur *via* a common initial step, *viz.*, an attack on the amidine double bond, wherever this may be situated in the molecule. In this connexion the recent observations of Leonard and Curtin (*J. Org. Chem.*, 1946, **11**, 341) have some relevance. These workers isolated traces of *o*-aminobenz-*n*-butylamide (XV) during the preparation of 3-*n*-butyl-4-quinazolone (XVI) from 4-hydroxyquinazoline and *n*-butylamine, and consider that both products are derived from a common intermediate (XVII). We now suggest, as a more likely explanation, that (XV) arises by hydrolysis of (XVI) as a result of the amidine characteristics of the latter; further hydrolysis of (XV) to anthranilic acid, which would complete the analogy with the quinazolones (IX), was not observed, but might well be unlikely to occur under the conditions used (excess of butylamine in a sealed tube).

The facile alkaline and acid hydrolysis of 4-amino- to 4-hydroxy-quinazolines are readily explained by the amidine mechanism, on the assumption that such compounds react, in these hydrolyses, in the imino-dihydro- (semicyclic amidine) and not in the amine (cyclic amidine) form. By way of contrast, 4-hydroxyquinazoline and (I and II; $R = OH$) are not appreciably attacked under more drastic alkaline conditions. The difference in reactivity between the hydroxyquinazolines and the quinazolones may be regarded as the result of the fixation, by *N*-alkylation, of a non-aromatic system in the latter compounds; the amidine characteristics are thus enhanced, but are suppressed if the potential cyclic amidine group is included in, and thus subordinated to, the more stable "aromatic" system of the hydroxy-compounds. The behaviour of the 4-aminoquinazolines is consistent with the idea that the "amino-aromatic" forms are, similarly, resistant to hydrolysis under the conditions used, but that, owing to their existence in equilibrium with the non-aromatic imino-dihydro-tautomers and to the susceptibility of the latter to hydrolysis, a progressive conversion into the hydroxy-compounds occurs. According to this mechanism, the reactivity of the aminoquinazolines is to be distinguished from the superficially similar hydrolysis of the 4-acetamido- and 4-phenoxyquinazolinium compounds; here, the reactivity of the 4-substituent is engendered by electromeric shift induced by N^1 (as in heterocyclic quaternary compounds with reactive methyl groups) with accompanying entry of hydroxyl ion. In this connexion, the conversion of 2-chloro-5-phenoxy-acridine (XVIII) into 2-chloro-10-methylacridone (XIX) in 85% yield by reaction with methyl *p*-toluenesulphonate (Drozdov and Skljarov, *J. Gen. Chem. Russia*, 1944, **19**, 945) is highly relevant; the reaction is strikingly similar to that shown by 6- and 7-nitro-4-phenoxyquinazoline, and strengthens the view that the behaviour of these compounds on conversion into quaternary salts is not to be attributed to the potential amidine characteristics of the quinazoline nucleus.

EXPERIMENTAL.

(Melting points are uncorrected.)

6-Nitro-4-hydroxyquinazoline.—The following conditions were superior to those given by Bogert and Geiger (*loc. cit.*). 4-Hydroxyquinazoline (20 g.) was added during 30–40 minutes to a mixture of nitric acid (*d* 1.53, 40 c.c.) and concentrated sulphuric acid (40 c.c.), care being taken that the temperature did not exceed 95°; the solution was then heated on the steam-bath for $\frac{1}{2}$ hour and poured into water (1.5 l.); pure 6-nitro-4-hydroxyquinazoline separated, m. p. 275–277° (22.2 g., 85%).

Bogert and Scatchard (*loc. cit.*) give m. p. 286—287° (corr.); Bogert and Geiger (*loc. cit.*) give m. p. 284° (uncorr.); Magidson and Golovchinskaya (*loc. cit.*) give m. p. 275°. This compound was recovered in quantitative, and the 7-nitro-isomer (*q.v.*) in almost quantitative, yield after being refluxed for $\frac{1}{2}$ hour with 2*N*-sodium hydroxide.

7-Nitro-4-hydroxyquinazoline.—4-Nitroanthranilic acid (50 g.) and formamide (50 g.) were gently refluxed for 40 minutes; addition of water (100 c.c.) to the cooled mass and filtration, followed by washing with alcohol, gave the pure nitro-compound, m. p. 268—270° (50.5 g., 96%). Bogert and Klaber (*loc. cit.*) give m. p. 276° (corr.).

4-Chloro-6-nitroquinazoline.—An intimate mixture of the hydroxy-compound (20 g.) and phosphorus pentachloride (32.8 g.) was heated at 160° (bath temp.) for 2 $\frac{1}{2}$ hours, during which time a clear solution was formed. Ligroin (b. p. 60—80°, 750 c.c.) was added to the cold mixture, and the crude chloro-compound (19 g.) filtered off and washed with more ligroin. The pure compound could be obtained by suspension of the crude material in dilute sodium hydroxide and extraction with chloroform, from which it separated in pale, yellow-green prismatic needles, m. p. 130—131° (U.S.P. 1,880,447 gives m. p. 128°; Magidson and Golovchinskaya, *loc. cit.*, give m. p. 129°).

4-Chloro-7-nitroquinazoline.—7-Nitro-4-hydroxyquinazoline (20 g.), phosphorus pentachloride (30 g.), and phosphorus oxychloride (60 c.c.) were gently refluxed for 2 hours. Addition of ligroin (b. p. 60—80°, 750 c.c.) to the cold mixture gave the crude chloro-compound (20 g.), which, when purified in the same manner as the 6-nitro-isomer, formed almost colourless prismatic needles, m. p. 148—149° (U.S.P. 1,880,447 gives m. p. 148°).

6-Nitro-4-phenoxyquinazoline.—The crude chloro-compound from 6-nitro-4-hydroxyquinazoline (10 g.) was heated for 1 hour with a solution of potassium hydroxide (6 g.) in phenol (60 g.) at 90—95°. The melt was poured into dilute sodium hydroxide and extracted with ether, the extract washed with aqueous sodium hydroxide and water, dried, and concentrated, giving 6-nitro-4-phenoxyquinazoline (6.1 g.), which crystallised from alcohol in colourless needles, m. p. 148—149° (Found: C, 62.7; H, 3.6; N, 15.5. $C_{14}H_9O_3N_3$ requires C, 62.9; H, 3.4; N, 15.7%).

7-Nitro-4-phenoxyquinazoline.—Prepared similarly to the above isomer [using crude chloroquinazoline from 7-nitro-4-hydroxyquinazoline (15 g.), potassium hydroxide (7 g.), and phenol (70 g.)], this compound (14.7 g.) formed colourless needles, m. p. 173.5—174°, from alcohol (Found: C, 62.7; H, 3.55; N, 15.4. $C_{14}H_9O_3N_3$ requires C, 62.9; H, 3.4; N, 15.7%).

6-Nitro-4-aminoquinazoline.—(a) Crude 4-chloro-6-nitroquinazoline (from 20 g. of hydroxy-compound) was added to a mixture of phenol (80 g.) and powdered ammonium carbonate (40 g.). After 1 hour at 90—95°, the mixture was diluted with water, excess of aqueous sodium hydroxide added, and the solid collected (20.2 g., m. p. 270—300°). This was added to ammonium acetate (100 g.) which had just been fused, and kept at 180° (bath temp.) for $\frac{1}{2}$ hour. The cold melt was diluted with water, filtered, and the crude amine dissolved in warm hydrochloric acid (0.4*N*, 250 c.c.). The filtered solution was basified with ammonia, yielding crude 6-nitro-4-aminoquinazoline, m. p. 316—319° (15.4 g.; 77% based on hydroxy-compound). The pure amine formed hair-like lemon-yellow needles, m. p. 320—320.5°, from hot water (Found: C, 51.1; H, 2.7; N, 29.2. $C_8H_6O_2N_4$ requires C, 50.5; H, 3.2; N, 29.5%). The amine was converted almost quantitatively into 6-nitro-4-hydroxyquinazoline (m. p. and mixed m. p.) after it had been heated under reflux with *N*-sodium hydroxide solution for $\frac{1}{2}$ hour, and a similar result was obtained with the 7-nitro-isomer (*q.v.*). Both amines, and also the corresponding acetamido-compounds (*q.v.*), were hydrolysed to the hydroxyquinazolines when boiled with 2*N*-hydrochloric acid for $\frac{1}{2}$ —1 hour.

(b) Pure chloro-compound (1 g.), left at room temperature under ammonia solution (*d* 0.88, 20 c.c.) for 4 days in a closed vessel, yielded unchanged material (70 mg.), and the 4-amino-compound (0.76 g., m. p. and mixed m. p. 317—319°).

7-Nitro-4-aminoquinazoline.—(a) Treatment as in (a) above of crude 4-chloro-7-nitroquinazoline (from 20 g. of the hydroxyquinazoline) gave a mixture, m. p. 265—270° (15.5 g.); fusion of this with ammonium acetate (77 g.) and purification as already described gave 7-nitro-4-aminoquinazoline (69% yield based on hydroxy-compound), which crystallised from water in long, pale yellow needles, m. p. 303—305° (Found: C, 50.9; H, 3.4; N, 29.7. $C_8H_6O_2N_4$ requires C, 50.5; H, 3.2; N, 29.5%).

(b) Extraction of the foregoing mixture, m. p. 265—270° (5.6 g.), with boiling alcohol gave 7-nitro-4-phenoxyquinazoline (1.7 g., m. p. 168—170°, identified by mixed m. p.); the alcohol-insoluble residue yielded 7-nitro-4-aminoquinazoline (1 g.), m. p. 299—300°, not depressed by admixture with authentic material.

(c) Pure 4-chloro-7-nitroquinazoline (1 g.), treated exactly as the 6-nitro-isomer with ammonia solution as described in (b) above, yielded unchanged material (0.49 g.) and 7-nitro-4-aminoquinazoline (0.37 g.).

6-Nitro-4-acetamidoquinazoline.—The amine (10 g.) and acetic anhydride (100 c.c.) were refluxed for $\frac{1}{2}$ hour; the acetamido-compound, formed in almost quantitative yield, was isolated by filtration and washing with ether. It crystallised from acetic acid in small, pale yellow needles, m. p. 262—263° (decomp.) (Found: C, 51.5; H, 3.8; N, 24.15. $C_{10}H_8O_3N_4$ requires C, 51.7; H, 3.5; N, 24.1%).

7-Nitro-4-acetamidoquinazoline.—Prepared similarly to the above compound and in similar yield, this compound separated from acetic acid in small, pale yellow needles, m. p. 240—242° (decomp.) (Found: C, 51.75; H, 3.75; N, 24.5. $C_{10}H_8O_3N_4$ requires C, 51.7; H, 3.5; N, 24.1%).

6-Nitro-4-methoxyquinazoline.—A solution of pure 4-chloro-6-nitroquinazoline (2 g.) and sodium methoxide (0.6 g.) in methyl alcohol (50 c.c.) was refluxed for $\frac{1}{2}$ hour and diluted with water, yielding 6-nitro-4-methoxyquinazoline (1.54 g., 75%) as glistening yellow prismatic needles, m. p. 118—119° after recrystallisation from 50% aqueous methanol (Found: C, 52.7; H, 3.5; N, 19.9. $C_9H_7O_3N_3$ requires C, 52.7; H, 3.4; N, 20.5%).

7-Nitro-4-methoxyquinazoline.—Prepared similarly to the above isomer, 7-nitro-4-methoxyquinazoline (yield, 90%) separated from aqueous methanol in small, soft, colourless needles, m. p. 137—138° (Found: C, 52.85; H, 3.4. $C_9H_7O_3N_3$ requires C, 52.7; H, 3.4%).

6-Nitro-4-anilinoquinazoline.—Crude 4-chloro-6-nitroquinazoline (from 10 g. of hydroxy-compound),

50% aqueous acetone (100 c.c.), aniline (5 c.c.), and concentrated hydrochloric acid (0.5 c.c.) were refluxed for $\frac{1}{2}$ hour. The mixture was then basified with aqueous ammonia, and the solid (m. p. 235—237°; 12.2 g.; 87% based on hydroxy-compound) crystallised from aqueous acetic acid, giving 6-nitro-4-anilinoquinazoline as yellow needles, m. p. 236—237.5° (decomp.) (Found: C, 63.0; H, 4.0; N, 21.5. $C_{14}H_{10}O_2N_4$ requires C, 63.15; H, 3.8; N, 21.0%).

6-Amino-4-anilino-1-methylquinazolinium Iodide.—6-Nitro-4-anilinoquinazoline (10 g.) and methyl *p*-toluenesulphonate (7.7 g.) were mixed and heated at 148—150° for 30 minutes; as the temperature was raised to this point, the original melt became pasty, and solidified at ca. 140°. The cold mass was digested with hot alcohol (100 c.c.), cooled, and the solid (14.6 g.; 85%; m. p. 247—248°) collected and crystallised from hot water, yielding soft, deep yellow needles, m. p. 249—250° (decomp.), of 6-nitro-4-anilino-1-methylquinazolinium *p*-toluenesulphonate (Found: C, 58.25; H, 4.6; N, 12.8; S, 7.1. $C_{22}H_{20}O_5N_4S$ requires C, 58.4; H, 4.45; N, 12.4; S, 7.1%). Addition of potassium iodide (29.2 g.) to a solution of the salt (14.6 g.) in hot water (550 c.c.) precipitated the iodide (11.6 g.; 88%); this crystallised from water in massive, yellow, prismatic needles, m. p. 247—248° (decomp.) (Found: C, 43.9; H, 3.65; N, 13.8. $C_{15}H_{13}O_2N_4I$ requires C, 44.1; H, 3.2; N, 13.7%). Occasionally a second crystalline form, m. p. 254—256° (decomp.), was obtained. A solution of the iodide (1 g.) in hot water (60 c.c.) was treated at 91—93° with iron powder (1.25 g.), added in portions during $\frac{1}{2}$ hour with mechanical stirring; after a further $\frac{1}{2}$ hour's stirring and heating, pure 6-amino-4-anilino-1-methylquinazolinium iodide (0.67 g.) separated from the filtered solution in glittering golden needles, m. p. 287—288° (Found: C, 47.7; H, 4.1; N, 15.4. $C_{15}H_{15}N_4I$ requires C, 47.6; H, 4.0; N, 14.8%). Concentration of the filtrate gave a further 0.16 g. (total yield, 89%).

7-Nitro-4-anilinoquinazoline.—Prepared similarly to the 6-nitro-isomer, this compound [9.7 g. (70%) from 10 g. of hydroxy-compound] crystallised from glacial acetic acid in stout yellow needles, m. p. 251—252° (decomp.) (Found: C, 62.7; H, 3.55; N, 21.1. $C_{14}H_{10}O_2N_4$ requires C, 63.15; H, 3.8; N, 21.0%).

7-Amino-4-anilino-1-methylquinazolinium Iodide.—This salt and its precursors were prepared as for the above 6-substituted derivatives; each salt was crystallised from water. 7-Nitro-4-anilino-1-methylquinazolinium *p*-toluenesulphonate, soft yellow needles, had m. p. 257—258° (decomp.) (yield, 92%) (Found: C, 58.6; H, 4.8; N, 12.5; S, 7.1. $C_{22}H_{20}O_5N_4S$ requires C, 58.4; H, 4.45; N, 12.4; S, 7.1%). The iodide, m. p. 256—257° (decomp.) (yield, 93%), formed lustrous, orange-red, prismatic needles (Found: C, 44.1; H, 3.8; N, 14.2. $C_{15}H_{13}O_2N_4I$ requires C, 44.1; H, 3.2; N, 13.7%). 7-Amino-4-anilino-1-methylquinazolinium iodide (yield, 90%) crystallised in brownish-yellow rectangular rods, m. p. 266—268° after melting at 210° and then resolidifying (Found: C, 45.5; H, 4.65; N, 14.9. $C_{15}H_{15}N_4I \cdot H_2O$ requires C, 45.5; H, 4.3; N, 14.2%).

Preparation and Decomposition of 6-Nitro-3-methyl-4-quinazoline.—A solution of 6-nitro-4-hydroxyquinazoline (1 part) in the minimum volume (24 parts) of 2% aqueous potassium hydroxide was stirred at 50° with methyl sulphate (0.5 part by volume); the *N*-methyl ether (yield, 75%) separated from alcohol in minute yellow needles, m. p. 196—197° [Bogert and Geiger, *loc. cit.*, give m. p. 196° (corr.)]. The use of excess of alkali gave a somewhat lower yield. Decompositions of this compound were carried out as follows:

(a) The compound (0.5 g.) was refluxed with aqueous sodium hydroxide (2N, 10 c.c.) for $\frac{1}{2}$ hour, the evolved gas being passed into water and identified as methylamine by conversion into the picrate, m. p. and mixed m. p. 205—207°. Acidification of the alkaline solution gave 5-nitroanthranilic acid (0.36 g.), m. p. and mixed m. p. 276—277° (from acetic acid) (acetyl derivative, m. p. and mixed m. p. 221—222°).

(b) In quantitative experiments, using excess of 2N-sodium hydroxide, 95.2 and 95.6% of the theoretical amount of methylamine was evolved; blank tests with known amounts of methylamine gave (mean of two) 94.7%.

Preparation and Decomposition of 7-Nitro-3-methyl-4-quinazoline.—Prepared similarly to the foregoing isomer, this compound (yield, 85%) formed small, cream-coloured needles, m. p. 210—211°, from alcohol (Found: C, 52.9; H, 3.6; N, 20.3. $C_9H_7O_3N_3$ requires C, 52.7; H, 3.4; N, 20.5%). The alkaline decomposition was carried out as above. Methylamine was identified as picrate. Acidification of the alkaline solution with phosphoric acid gave 4-nitroanthranilic acid (0.31 g.), m. p. 256—258° alone and when mixed with authentic material; the filtrate from this acid was distilled, and formic acid identified in the distillate by neutralisation, concentration, and conversion into *p*-bromoformanilide, m. p. and mixed m. p. 115—116°, in faintly acid solution. Quantitative experiments carried out under the conditions used for the 6-nitro-isomer gave 95.2 and 95.0% of the theoretical amount of methylamine (blank, 94.7%).

6-Nitro-1-methyl-4-quinazoline.—(a) An intimate mixture of 6-nitro-4-acetamidoquinazoline (5 g.) and methyl *p*-toluenesulphonate (4.2 g.) was heated in an oil-bath; reaction occurred at 160° (bath temp.), and after 10 minutes the viscous melt was cooled and extracted with hot water (100 c.c.). Concentrated hydrochloric acid (50 c.c.) was added to the aqueous solution, from which, after $\frac{3}{4}$ hour's refluxing, solvent was removed in an evacuated desiccator. Digestion of the residue with alcohol (30 c.c.) gave a crystalline mass [4.6 g., m. p. 213—216° (decomp.)]; this was dissolved in water (20 c.c.), and the filtered (charcoal) solution was treated with ammonia solution (4N, 5 c.c.), yielding crude 6-nitro-1-methyl-4-quinazoline (1.9 g., m. p. 257—259°), which on recrystallisation from water (charcoal) formed long colourless needles, m. p. 272—273° (Found: C, 53.0; H, 3.7; N, 20.6. $C_9H_7O_3N_3$ requires C, 52.7; H, 3.4; N, 20.5%).

(b) 6-Nitro-4-phenoxyquinazoline (1 g.) and methyl *p*-toluenesulphonate (0.7 g.) were heated to 125° (bath temp.). The clear orange melt then began to crystallise, and the reaction was complete after 15 minutes at 150°. The product was crystallised from alcohol-acetone, and finally from alcohol alone, yielding 6-nitro-1-methyl-4-quinazoline *p*-toluenesulphonate (1 g.) in colourless fluffly needles, m. p. 234—235° [237—238° when mixed with an authentic sample, m. p. 237—238°, prepared from an alcoholic solution of *p*-toluenesulphonic acid and the base prepared by method (a)] (Found: C, 48.6; H, 4.4; N, 10.9; S, 7.9. $C_{16}H_{15}O_6N_3S \cdot H_2O$ requires C, 48.6; H, 4.3; N, 10.6; S, 8.1%). The salt dissolved

in hot water to form a strongly acid solution, from which 6-nitro-1-methyl-4-quinazolone, m. p. 271—272° (alone and mixed with the sample described above), separated on cooling (Found: C, 53·2; H, 3·4; N, 20·3%).

Alkaline Decomposition of 6-Nitro-1-methyl-4-quinazolone.—(a) A solution of the quinazolone (0·2 g.) in hot water (21 c.c.) was treated with 2*N*-sodium hydroxide (5 c.c.); an immediate and copious crystallisation of 5-nitro-2-methylaminobenzoamide (0·2 g.) occurred; this substance formed brittle yellow needles, m. p. 218—218·5°, from water containing a little acetic acid (Found: C, 49·3; H, 4·8; N, 21·8. $C_8H_9O_3N_3$ requires C, 49·25; H, 4·65; N, 21·5%). The amide was unchanged after short boiling with 2*N*-hydrochloric acid, but was hydrolysed completely to the acid under the same conditions as those used in the following experiment.

(b) The quinazolone (1 g.), 2*N*-sodium hydroxide solution (20 c.c.), and water (30 c.c.) were refluxed for 40 minutes; ammonia was evolved, and a clear solution was gradually formed. Acidification precipitated 5-nitro-2-methylaminobenzoic acid, which formed brittle yellow needles, m. p. 263—264° (decomp.), from acetic acid. Thieme (*J. pr. Chem.*, 1891, **43**, 471) gives m. p. 259°; Blanksma (*Rec. Trav. chim.*, 1902, **21**, 269), m. p. 259°; and Keller (*Arch. Pharm.*, 1908, **246**, 1), m. p. 258°. The acid gave a negligible depression in m. p. on admixture with 5-nitroanthranilic acid, but was distinguished from the latter by its negative diazo-reaction and by its conversion into methyl 5-nitro-2-methylaminobenzoate; this ester, obtained by means of methanolic sulphuric acid, crystallised from methanol in long, pale greenish-yellow needles, m. p. 146—147° (124—126° when mixed with methyl 5-nitroanthranilate, m. p. 167—168°) (Found: C, 51·2; H, 4·9; N, 13·3. $C_9H_{10}O_4N_2$ requires C, 51·4; H, 4·8; N, 13·3%).

7-Nitro-1-methyl-4-quinazolone.—(a) 7-Nitro-4-acetamidoquinazoline (5 g.) was treated exactly as already described for the 6-nitro-isomer. The product obtained by refluxing with hydrochloric acid, removal of solvent, and digestion with alcohol, crystallised from water in red-tinged plates, m. p. 252—254° (3·1 g.). Basification of a hot aqueous solution with ammonia furnished 7-nitro-1-methyl-4-quinazolone (1·27 g.), which formed massive, prismatic, flesh-coloured needles, m. p. 215—216° (Found: C, 49·7; H, 4·1; N, 19·4. $C_9H_7O_3N_3, \frac{2}{3}H_2O$ requires C, 49·8; H, 3·8; N, 19·35%).

(b) Fusion of 7-nitro-4-phenoxyquinazoline (5·2 g.) and methyl *p*-toluenesulphonate (3·8 g.) at 150° for $\frac{3}{4}$ hour gave almost colourless needles (5·8 g.) of 7-nitro-1-methyl-4-quinazolone *p*-toluenesulphonate, m. p. 247—247·5°, sparingly soluble in hot alcohol, readily in boiling water (from which it could be recrystallised without decomposition), and yielding the quinazolone (m. p. 218—219°, identified by mixed m. p.) on basification (Found: C, 48·4; H, 4·05; N, 10·3; S, 7·7. $C_{16}H_{15}O_6N_3S, H_2O$ requires C, 48·6; H, 4·3; N, 10·6; S, 8·1%). A sample of the salt prepared from the base [from method (a)] and *p*-toluenesulphonic acid in alcoholic solution had m. p. and mixed m. p. 251—252°.

Alkaline Decomposition of 7-Nitro-1-methyl-4-quinazolone.—(a) Addition of aqueous sodium hydroxide (2*N*, 5 c.c.) to a solution of the quinazolone (1 g.) in hot water (35 c.c.) produced an immediate red coloration, followed by rapid separation of 4-nitro-2-methylaminobenzoamide (0·27 g.); this substance crystallised from methanol in bundles of massive, orange prismatic needles, m. p. 188—189° (Found: C, 49·2; H, 4·6; N, 21·9. $C_8H_9O_3N_3$ requires C, 49·25; H, 4·65; N, 21·5%). The filtrate from this amide was acidified with phosphoric acid (to Congo-red), and the resultant 4-nitro-2-*N*-methylformamidobenzoic acid (0·56 g.) recrystallised from aqueous methanol, yielding light, yellow needles, m. p. 203—204° (efferv.) (Found: C, 47·8; H, 3·9; N, 13·0. $C_9H_8O_5N_2$ requires C, 48·2; H, 3·6; N, 12·5%). Distillation of the filtrate from this acid gave formic acid, identified as *p*-bromoformanilide in the manner already described.

(b) When a solution of the quinazolone (0·2 g.) in hot water (7 c.c.) and aqueous sodium hydroxide (2*N*, 5 c.c.) was refluxed for 10 minutes, ammonia was evolved, and 4-nitro-2-methylaminobenzoic acid (0·17 g.) was precipitated on acidification; recrystallisation of this from acetic acid or aqueous methanol gave glittering, orange-red, prismatic needles, m. p. 259—260° (decomp.) alone and when mixed with the synthetic acid described below (unlike the 5-nitro-isomer, a marked depression in m. p. was observed in admixture with the corresponding nitroanthranilic acid) (Found: C, 49·2; H, 4·2. $C_8H_8O_4N_2$ requires C, 49·0; H, 4·1%). The acid was also obtained by refluxing either the amide or the formamido-acid described above with excess of *N*-sodium hydroxide for $\frac{1}{2}$ hour.

Synthesis of 4-Nitro-2-methylaminobenzoic Acid.—A solution of methyl 4-nitroanthranilate (5 g.) in pyridine (50 c.c.) was treated in the cold with *p*-toluenesulphonyl chloride (7 g.) and left for 2 days. The solid which had separated (5·8 g.) was collected and recrystallised from aqueous pyridine; methyl 4-nitro-2-*p*-toluenesulphonamidobenzoate separated in long, colourless blades, m. p. 183—184° (Found: C, 51·5; H, 4·35. $C_{15}H_{14}O_6N_2S$ requires C, 51·4; H, 4·0%). A suspension of the tosyl derivative (3 g.) in alcohol (30 c.c.) was treated dropwise, with shaking, with the calculated quantity of aqueous sodium hydroxide (ca. 0·3*N*); partial solution occurred, followed by rapid separation of a yellow sodium salt. A suspension of the dry salt (3 g.) in acetone (60 c.c.) was gently refluxed with methyl iodide (12 c.c.) for 4 hours; filtration and concentration yielded methyl 4-nitro-2-*p*-toluenesulphonmethylamidobenzoate (2·75 g.), which separated from methanol in small, colourless rods, m. p. 126—128° (Found: C, 52·6; H, 4·7. $C_{16}H_{16}O_6N_2S$ requires C, 52·7; H, 4·4%). A solution of this (2 g.) in concentrated sulphuric acid (10 c.c.) was kept at 80—90° for $\frac{1}{2}$ hour and then poured into water, yielding methyl 4-nitro-2-methylaminobenzoate (1·2 g.). This ester crystallised from slightly aqueous methanol in long, soft, orange needles, m. p. 124—125° (Found: C, 51·5; H, 4·6; N, 13·3. $C_9H_{10}O_4N_2$ requires C, 51·4; H, 4·8; N, 13·3%); it was only partly hydrolysed by 5*N*-hydrochloric acid (1 hour's reflux), but was smoothly converted by *N*-sodium hydroxide ($\frac{1}{2}$ hour's reflux) into 4-nitro-2-methylaminobenzoic acid, m. p. 259—260° (decomp.) after recrystallisation from acetic acid.

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