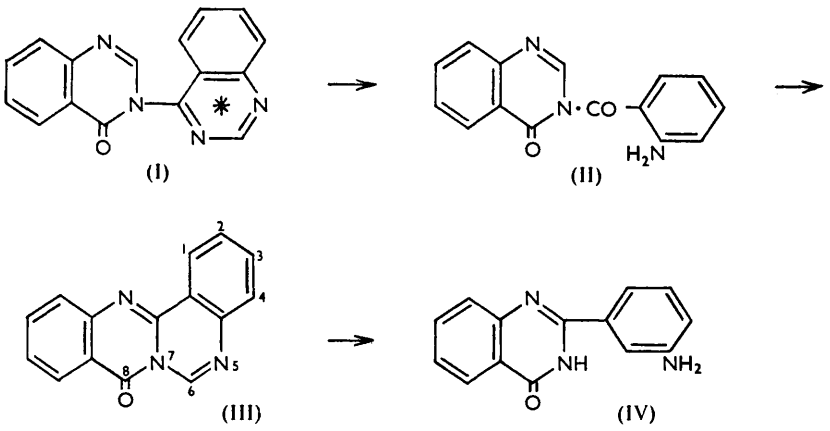
807. *Syntheses in the Quinazolone Series. Part III.* The Formation of Quinazo*[4,3-b]*quinazol-8-one and 2-o-Aminophenylquinazol-4-one by the Hydrolysis of 3-4′-Quinazolinylquinazol-4-one.*

By (Mrs.) T. Stephen and Henry Stephen.

A new method for the preparation of 3-4′-quinazolinylquinazol-8-one (I) and its hydrolysis to quinazo[4,3-*b*]quinazol-8-one (III) and subsequently 2-*o*-aminophenylquinazol-4-one (IV) are described; the conversion of the last compound into 6-substituted derivatives of (III) by acylation is also reported.

3-4′-Quinazolinylquinazol-4-one (I), which is readily obtained by condensation of 4-chloroquinazoline with quinazol-4-one, yields quinazo[4,3-*b*]quinazol-8-one (III) on hydrolysis with 0·1N-hydrochloric acid. Either compound with 2N-hydrochloric acid gives 2-*o*-aminophenylquinazol-4-one (IV), m. p. 241°. A base, m. p. 244°, was obtained by Tomisek and Christensen [1] on hydrolysis of the quinazolone (I) with concentrated hydrochloric acid, but they did not identify it.

Suitable treatment of the product from the action of phosphorus oxychloride on quinazol-4-one yields either the tetracyclic compound (III) or the quinazolone (IV), and formation of the latter can be explained by assuming that quinazol-4-one is partially



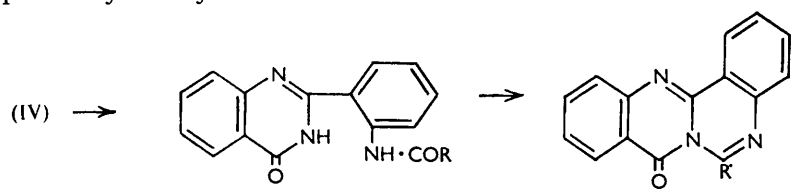
converted into 4-chloroquinazoline which condenses with unchanged quinazolone to give (I). The same explanation will account for the formation of (IV) when 4-chloroquinazoline is partially hydrolysed by water.

Hydrolysis of the compound (I) probably involves the formation of 3-*o*-aminobenzoylquinazol-4-one (II) (not isolated) and elimination of hydrogen cyanide, which is supported by the identification of formic acid and ammonia after hydrolysis of (I). This suggests that the ring marked with an asterisk undergoes fission, subsequent ring closure giving the tetracyclic compound (III). The latter on further hydrolysis yields formic acid and the 2-substituted compound (IV) which on treatment with anhydrous formic acid is reconverted into (III) [which has been independently synthesised [3]]. The product (IV) has been synthesised in this laboratory in another way which will be published later.[2] Condensation of the product (IV) with acetic anhydride gives a mixture of 2-*o*-acetamidophenylquinazol-4-one (V; R = Me) and 6-methylquinazo[4,3-*b*]quinazol-8-one (VI; R = Me), and the former may be converted into the latter by treatment with dilute hydrochloric acid or

* Part II, preceding paper.

[1] Tomisek and Christensen, *J. Amer. Chem. Soc.*, 1948, **70**, 874.
[2] T. A. Kilroe Smith, personal communication.
[3] Stephen and Stephen, preceding paper.

sodium hydroxide solution. Propionic anhydride gives 2-*o*-propionamidophenylquinazol-4-one (V; R = Et) and 6-ethylquinazo[4,3-*b*]quinazol-8-one (VI; R = Et). Benzoic anhydride, fused with (IV), gives 6-phenylquinazo[4,3-*b*]quinazol-8-one (VI; R = Ph), which has previously been synthesised.[3]



Experimental

4-Chloroquinazoline.—Quinazol-4-one (10 g.) in phosphorus oxychloride (60 c.c.) was refluxed with phosphorus pentachloride (15 g.) for 1 hr., excess of phosphorus oxychloride removed under reduced pressure, and the residue distilled at 145°/28 mm. The distillate (12·6 g.) was extracted with light petroleum (b. p. 40—60°; 3 × 150 c.c.), and the combined extracts, evaporated under reduced pressure, yielded 4-chloroquinazoline (9·5 g.), m. p. 96° (Found: equiv., by hydrolysis in aq. NaOH, 165·4. Calc. for $C_8H_5N_2Cl$: equiv., 164·5).

3-4′-Quinazolinylquinazol-4-one (I).—4-Chloroquinazoline (1 g.) was heated with quinazol-4-one (1 g.) at 100° for 15 min.; the reaction was then complete. The product was triturated with cold water, neutralised with aqueous sodium hydrogen carbonate, and filtered off; the residue was treated with boiling water to remove quinazol-4-one and crystallised from ethanol in white needles, m. p. 232° (Found: C, 70·1; H, 3·8; N, 20·3. Calc. for $C_{16}H_{10}ON_4$: C, 70·1; H, 3·6; N, 20·4%).

Conversion of the Compound (I) *into 4-Chloroquinazoline.*—A mixture of the compound (I) (1 g.) and phosphorus pentachloride (1·2 g.) in phosphorus oxychloride (10 c.c.) was refluxed until a pale yellow solution was obtained. Removal of phosphorus oxychloride gave a residue which distilled at 144°/22 mm. The distillate, after solidifying, was extracted with light petroleum (b. p. 40—60°), and yielded 4-chloroquinazoline (0·9 g.), m. p. 96°. It is probable that the amidoyl chloride is formed as an intermediate which dissociates on distillation into two mols. of 4-chloroquinazoline.

Quinazo[4,3-b]*quinazol-8-one* (III).—A solution of the compound (I) (1 g.) in ethanol (10 c.c.), boiled with 0·1N-hydrochloric acid (5 c.c.), deposited the *product* (III) as white needles, m. p. 197° (Found: C, 72·5; H, 3·8; N, 16·9. $C_{15}H_9ON_3$ requires C, 72·8; H, 3·6; N, 17·0%). Formic acid and ammonia were found in the filtrate. Ammonia was also obtained when quinazol-4-one (5 g.) was heated in phosphorus oxychloride (30 c.c.) for 1 hr.; and removal of the excess of chloride under reduced pressure gave a light brown viscous mass which was chilled in ice and neutralised with sodium hydrogen carbonate. The product was filtered off and crystallised from ethanol in needles, m. p. 197° (3·6 g., 86%).

2-o-*Aminophenylquinazol-4-one* (IV).—The compound (I) dissolved readily in hot 2N-hydrochloric acid, and the solution on cooling deposited the *aminophenylquinazolone* as white needles which, crystallised from ethanol, had m. p. 241° (Found: C, 70·8; H, 4·8; N, 17·7. $C_{14}H_{11}ON_3$ requires C, 70·8; H, 4·6; N, 17·7%). Formic acid and ammonia were detected. Addition of platinic chloride to a solution of the product in concentrated hydrochloric acid gave a buff *platinichloride* [Found: Pt, 20·3. $(C_{14}H_{11}ON_3)_2,H_2PtCl_6,2HCl$ requires Pt, 20·4%]. The product (IV) was also obtained by refluxing quinazol-4-one (5 g.) in phosphorus oxychloride (30 c.c.) for 1 hr. The residue after removal of excess of oxychloride was boiled with water, and the yellow solution on neutralisation with ammonia gave yellow needles (3·8 g.), m. p. 241°. 4-Chloroquinazoline, moistened with water and heated, reacted vigorously and the resulting product after purification melted at 241°. The base (IV) is slightly soluble in boiling water, and soluble in hot dilute hydrochloric acid from which it crystallised on cooling. It slowly dissolved in boiling sodium carbonate solution, and immediately in cold aqueous ammonia or sodium hydroxide from which it is precipitated on acidification. A solution of the base in anhydrous formic acid, refluxed for ½ hr., cooled, and diluted with water gave the compound (III).

6-*Methylquinazo*[4,3-*b*]*quinazol-8-one* (VI; R = Me).—The base (IV) (1 g.) was refluxed with acetic anhydride (10 c.c.) for 1 hr., and on addition of water gave a mixture of 2-o-*acetamidophenylquinazol-4-one* (V; R = Me) and the base (VI; R = Me), which were separated by

treatment with cold dilute hydrochloric acid in which the latter is soluble. The insoluble portion (V; R = Me) crystallised from aqueous dioxan in needles, m. p. 177° (Found : C, 68·8; H, 48; N, 14·8. $C_{16}H_{13}O_2N_3$ requires C, 68·8; H, 4·7; N, 15·0%). The product (V) was converted into the *base* (VI; R = Me) by boiling dilute hydrochloric acid or aqueous sodium hydroxide. The filtrate, after separation of the amide, was neutralised with ammonia; the precipitate crystallised from dioxan in white needles, m. p. 276° (Found : C, 73·6; H, 4·3; N, 15·9. $C_{16}H_{11}ON_3$ requires C, 73·6; H, 4·2; N, 16·0%).

A similar reaction with propionic anhydride gave 2-o-*propionamidophenylquinazol-4-one* (V; R = Et), cream-coloured needles (from dioxan), m. p. 156° (Found : C, 69·5; H, 4·9; N, 14·4. $C_{17}H_{15}O_2N_3$ requires C, 69·6; H, 5·1; N, 14·3%), and 6-*ethylquinazo*[4,3-b]*quinazol-8-one* (VI; R = Et), white needles (from dioxan), m. p. 250° (Found : C, 74·2; H, 4·5; N, 14·8. $C_{17}H_{13}ON_3$ requires C, 74·2; H, 4·7; N, 15·0%). The former product was converted into the latter by boiling dilute hydrochloric acid or aqueous sodium hydroxide.

6-*Phenylquinazo*[4,3-b]*quinazol-8-one* (VI; R = Ph).—The base (IV) (0·5 g.) and benzoic anhydride (1 g.) were heated at 250° until reaction ceased (1½ hr.). The product, freed from benzoic acid by treatment with cold sodium carbonate solution, crystallised from dioxan in cream-coloured needles, m. p. and mixed m. p. 292° (Found : C, 77·9; H, 4·2; N, 13·1. Calc. for $C_{21}H_{13}ON_3$: C, 78·0; H, 4·0; N, 13·0%). A buff-coloured *salt* was prepared by addition of platinic chloride to a solution of the base in concentrated hydrochloric acid [Found : Pt, 13·8. $(C_{21}H_{13}ON_3)_2,H_2PtCl_6,C_{21}H_{13}ON_3,HCl$ requires Pt, 13·8%].

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