902. *Polyazanaphthalenes. Part VII.*[1] *Some Derivatives of Quinazoline and* 1,3,5-*Triazanaphthalene.*

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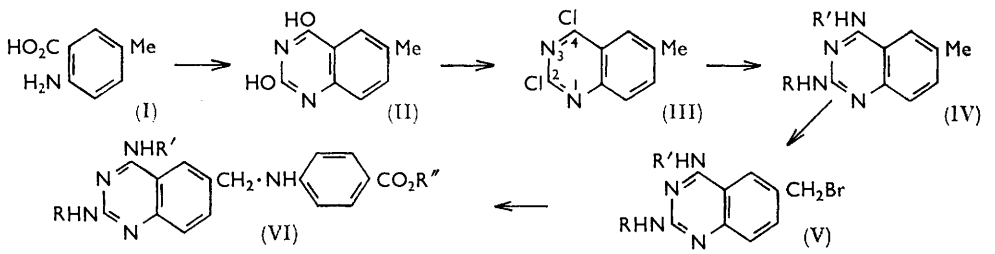
2,4-Diamino-6-methylquinazoline has been synthesised and converted, by side-chain bromination of its dibenzoyl derivative, condensation with ethyl *p*-aminobenzoate, and removal of the benzoyl and ester groups, into the pteroic acid analogue (VI; R = R′ = R″ = H). A similar procedure has led to the successful synthesis of pteroic acid analogues derived from 2,4-diamino- and 2-amino-4-hydroxy-1,3,5-triazanaphthalene.

The expected preferential reactivity of the 4-chlorine atom in 2,4-dichloro-6-methylquinazoline is exhibited in its reactions with ammonia, hydrazine, and benzylamine, but not in that with aniline.

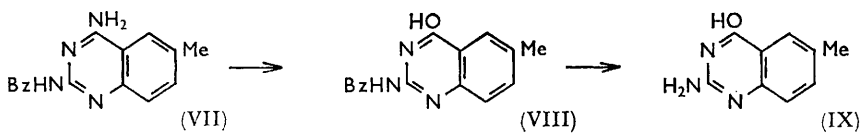
The general objective of this series of papers is the synthesis of a series of analogues of pteroic acid in which one or more of the ring-nitrogen atoms are replaced by methine groups; the present paper is concerned mainly with the synthesis of the analogue (VI; R = R′ = R″ = H), based on the quinazoline ring system.

The annexed synthetic route was employed.



The starting material, 2-amino-5-methylbenzoic acid (I), is readily obtained[2] by oxidation of 5-methylisatin. Fusion with urea gave the required 2,4-dihydroxy-6-methylquinazoline (II) and this with phosphorus oxychloride gave 2,4-dichloro-6-methylquinazoline (III) which, by reaction with ammonia, best in boiling phenol,[3] yielded 2,4-diamino-6-methylquinazoline (IV; R = R′ = H).

As in the case of the corresponding quinoline derivative,[4] no pure product could be obtained by treatment of the diamine (IV; R = R′ = H) with *N*-bromosuccinimide, and it was clearly necessary to protect the amino-groups before bromination. The diamine was, accordingly, converted into the dibenzamido-compound (IV; R = R′ = Bz) by the action of benzoyl chloride in the presence of triethylamine; pyridine, a weaker base than the diamine, is unsatisfactory for this purpose.



When the dibenzamido-compound (IV; R = R′ = Bz) was treated with bromine in chloroform it gave, in theoretical yield, not the expected bromomethyl compound, but a hydrobromide, analysis of which showed that one benzoyl group had been lost. This

[1] Part VI, Oakes and Rydon, *J.*, 1958, 209.
[2] Mayer, Schäfer, and Rosenbach, *Arch. Pharm.*, 1929, **267**, 571.
[3] Backeberg and Marais, *J.*, 1942, 381.
[4] Rydon and Undheim, *J.*, 1962, 4689.

product was shown to be the hydrobromide of the 2-benzamido-compound (VII) by conversion into 2-amino-4-hydroxy-6-methylquinazoline (IX) by reaction with nitrous acid and then sodium ethoxide. The end-product was identified by comparison with an authentic specimen prepared by heating 2-amino-5-methylbenzoic acid (I) with guanidine carbonate. Surprisingly, the amino-hydroxy-compound (IX) with benzoyl chloride and triethylamine yields, not the expected *N*-benzoyl derivative (VIII), but the isomeric *O*-benzoyl derivative. The ready removal of one of the benzoyl groups from compound (IV; R = R′ = Bz) during the attempted side-chain bromination is presumably due to the action of hydrogen bromide, arising from bromination of the solvent, and illustrates the lability of the dibenzamido-compound towards acid; the preferential removal of the 4-benzoyl group is a further instance of the generally greater reactivity of 4- than of 2-substituents in the quinazoline series.[5] The required 6-bromomethyl compound (V; R = R′ = Bz) was finally obtained, in good yield, by treatment of the dibenzamido-compound (IV; R = R′ = Bz) with 1,3-dibromo-5,5-dimethylhydantoin in boiling carbon tetrachloride, under the catalytic influence of benzoyl peroxide and light.

Fusion of the bromomethyl compound (V; R = R′ = Bz) with ethyl *p*-aminobenzoate gave the ester (VI; R = R′ = Bz, R″ = Et), from which the benzoyl groups were removed by treatment with ethanolic sodium ethoxide; careful saponification of the resulting ester (VI; R = R′ = H, R″ = Et) gave the desired pteroic acid analogue (VI; R = R′ = R″ = H).

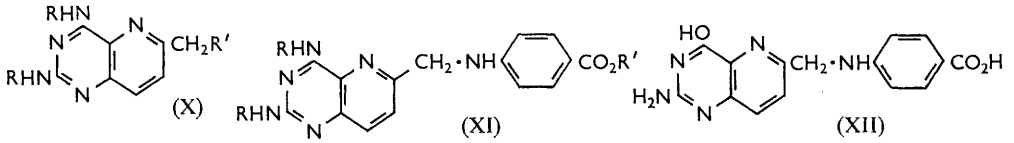
It is to be expected, on both theoretical [6] and experimental [5] grounds, that the 4-chlorine atom in 2,4-dichloro-6-methylquinazoline (III) would be considerably more reactive towards nucleophiles than the 2-chlorine; this expectation is borne out in practice. Thus, the dichloro-compound (III) reacts smoothly with ammonia, hydrazine, and benzylamine in dioxan to give the 4-replacement products, 4-amino-, 4-hydrazino-, and 4-benzylamino-2-chloro-6-methylquinazoline in almost theoretical yield; vigorous conditions are required to bring about replacement of the 2-chlorine atom in these products by a second amino- or benzylamino-group. Strangely, however, this marked differential reactivity is not exhibited in the reaction of 2,4-dichloro-6-methylquinazoline (III) with aniline; even if only one equivalent of aniline is used, the dianilino-derivative (IV; R = R′ = Ph) is the sole product; a somewhat similar phenomenon has been observed [7] with 2,4-dichloro-1,5-naphthyridine. Advantage was taken of this reactivity of the 2-chlorine atom towards aniline to prepare 4-amino-2-anilino-6-methylquinazoline (IV; R = Ph; R′ = H) from the dichloro-compound (III), by treating this first with ammonia and then with aniline.

4-Hydroxy-6-methylquinazoline was readily obtained by refluxing 2-amino-5-methylbenzoic acid (I) with formamide. Treatment with phosphorus oxychloride gave 4-chloro-6-methylquinazoline, the chlorine atom in which showed the expected reactivity towards nucleophiles, reaction with ammonia, hydrazine, and aniline yielding 4-amino-, 4-hydrazino- and 4-anilino-6-methylquinazolines, respectively.

The preparation of 2,4-diamino-6-methyl-1,3,5-triazanaphthalene (X; R = R′ = H) was described in an earlier paper; [6] side-chain bromination followed by condensation with *p*-aminobenzoic acid gave [8] the pteroic acid analogue (XI; R = R′ = H), but the yields were poor and the product not pure. We now describe a much improved procedure, based on that employed in the quinazoline series. Benzoylation of the diamino-compound (X; R = R′ = H) gave the dibenzamido-derivative (X; R = Bz, R′ = H) which was satisfactorily brominated, with 1,3-dibromo-5,5-dimethylhydantoin, to the bromomethyl compound (X; R = Bz, R′ = Br). Fusion of the latter with ethyl *p*-aminobenzoate gave the ester (XI; R = Bz, R′ = Et) which was readily debenzoylated by sodium ethoxide to the diamino-ester (XI; R = H, R′ = Et). Saponification of this was more difficult

[5] Curd, Landquist, and Rose, *J.*, 1947, 775.
[6] Oakes and Rydon, *J.*, 1956, 4433.
[7] Oakes and Rydon, *J.*, 1958, 204.
[8] Oakes and Rydon, B.P. 838,015; U.S.P. 2,924,599.

than in the case of the quinazoline analogue, owing to the ease with which the 4-amino-group underwent hydrolysis; however, by interrupting the saponification before it was complete, the required analogue (XI; R = R′ = H) was obtained. If the saponification



was allowed to proceed further, deamination occurred, undoubtedly in the 4-position, to give the true 1,3,5-triazanaphthalene analogue (XII) of pteroic acid.

Experimental

Ultraviolet absorption spectra were measured with a Unicam S.P. 500 instrument; results are reported as maxima, in mμ, followed by ε in parentheses.

Infrared spectra were measured, in potassium bromide discs, with a Hilger H100 instrument and a rock-salt prism; owing to hydrogen-bonding, sharp bands were not obtained in the 3000 cm.$^{-1}$ region. The principal bands, down to 1360 cm.$^{-1}$, with suggested assignments, are listed below; for further details see Undheim.[9]

Chromatograms were run, by the descending technique, on Whatman No. 1 filter paper with either butan-1-ol–pyridine–water (39 : 21 : 39 v/v) (R_{FPy}) or butan-1-ol–acetic acid–water (100 : 16·7 : 37·5 v/v) (R_{FAc}). Spots were revealed either by viewing in ultraviolet light or by the chlorine–starch–iodide method.[10]

Quinazoline Derivatives

2,4-*Dihydroxy*-6-*methylquinazoline* (II).—An intimate mixture of 2-amino-5-methylbenzoic acid [2] (40 g.) and urea (27 g.) was fused at 195° for 1 hr. The finely ground, cooled product was dissolved in an excess of 2N-sodium hydroxide and a small amount of insoluble material removed by filtration. Saturation of the filtrate with carbon dioxide afforded the *dihydroxy-compound* (26·5 g., 57%) as a cream precipitate, which crystallised from water in prisms, m. p. 316° (Found: C, 61·3; H, 4·3; N, 15·3. $C_9H_8N_2O_2$ requires C, 61·4; H, 4·6; N, 15·9%).

2,4-*Dichloro*-6-*methylquinazoline* (III).—2,4-Dihydroxy-6-methylquinazoline (20 g.) was heated under reflux for 3 hr. with phosphorus oxychloride (300 ml.). The resulting solution was evaporated to dryness under reduced pressure and the residue treated with ice-cold saturated sodium hydrogen carbonate solution; the insoluble material was collected, dried, and sublimed at 160°/0·02 mm., yielding the *dichloro-compound* as long needles, m. p. 140° (Found: C, 50·6; H, 3·0; N, 12·9. $C_9H_6Cl_2N_2$ requires C, 50·7; H, 2·8; N, 13·1%).

2,4-*Diamino*-6-*methylquinazoline* (IV; R = R′ = H).—2,6-Dichloro-6-methylquinazoline (5 g.) was dissolved in boiling phenol (50 g.), and gaseous ammonia passed through the boiling solution for 8 hr. The solution was then cooled to 60°, treated with an excess of 15% sodium hydroxide, and refrigerated for 1 hr.; two volumes of 40% sodium hydroxide were then added and the mixture refrigerated for a further 3 hr. The precipitated *diamino-compound* (4·0 g., 98%) was collected and washed with water; it crystallised from water in needles, m. p. 256° (Found: C, 62·7; H, 6·0. $C_9H_{10}N_4$ requires C, 62·1; H, 5·8%), and was chromatographically homogeneous (R_{FPy} 0·72, R_{FAc} 0·62). Titration of a 0·005M-solution in 5% ethanol at 20° with N-hydrochloric acid showed the base to have pK_{a1} 8·02 and pK_{a2} *ca.* 2·5. The base had $\nu_{max.}$ 3436 and 3352 (NH stretching), 3076 (aromatic CH stretching), 1670 (NH deformation), 1625, 1573, 1509, and 1469 (aromatic CC or CN), 1453 (methyl CH deformation), 1427 and 1399 (not assigned) cm.$^{-1}$. Addition of nitric acid to an aqueous solution of the base precipitated the *mononitrate*, m. p. 293° (Found: C, 45·8; H, 5·0; N, 29·0. $C_9H_{10}N_4,HNO_3$ requires C, 45·6; H, 4·7; N, 29·5%).

2,4-*Dibenzamido*-6-*methylquinazoline* (IV; R = R′ = Bz).—Benzoyl chloride (8 ml.) was added in portions in 10 min. to a refluxing, stirred solution of 2,4-diamino-6-methylquinazoline

[9] Undheim, Ph.D. Thesis, Exeter, 1959.
[10] Rydon and Smith, *Nature*, 1952, **169**, 922.

(5 g.) in anhydrous dioxan (150 ml.) containing triethylamine (20 ml.). After a further 20 minutes' refluxing and stirring, triethylamine hydrochloride was removed by hot filtration. The product (5·5 g.) crystallised on cooling and was collected by filtration; the filtrate was evaporated to dryness under reduced pressure and the residue dissolved in hot ethanol and treated with charcoal, yielding, on cooling, a further crop of the product (3·5 g.). The *dibenzamido-compound* (9·0 g., 82%) so obtained recrystallised from ethanol in needles, m. p. 198° (Found: C, 72·6; H, 4·7; N, 14·4. $C_{23}H_{18}O_2N_4$ requires C, 72·3; H, 4·8; N, 14·7%), $\nu_{max.}$ 3437 (NH stretching), 3057 (aromatic CH stretching), 2925 and 2878 (methyl CH stretching), 1674 (amide C=O), 1616 and 1575 (aromatic CC or CN), 1542 (amide NH), 1472 (aromatic CC or CN), 1402 (not assigned), 1358 (methyl CH deformation).

4-*Amino*-2-*benzamido*-6-*methylquinazoline* (VII).—Bromine (0·08 ml.) in chloroform (15 ml.) was added dropwise during 30 min. to a refluxing solution of 2,4-dibenzamido-6-methylquinazoline (500 mg.) in chloroform (15 ml.); the mixture was irradiated with a 500-w tungsten-filament lamp. After 2½ hr. the mixture was colourless and the crystalline precipitate (470 mg., 100%) was collected; recrystallisation from acetic acid afforded the *base hydrobromide*, m. p. 249—251° (decomp.) (Found: N, 15·2; Br, 22·7. $C_{16}H_{15}BrN_4O$ requires N, 15·6; Br, 22·3%). The free *base*, liberated from the hydrobromide by the action of aqueous sodium hydroxide at 50°, crystallised from aqueous ethanol in needles, m. p. 214° (Found: N, 18·9. $C_{16}H_{14}N_4O,H_2O$ requires N, 18·9%), R_{FPy} 0·91, R_{FAc} 0·77.

2-*Benzamido*-4-*hydroxy*-6-*methylquinazoline* (VIII).—4-Amino-2-benzamido-6-methylquinazoline (1·08 g.) was dissolved in warm 6N-sulphuric acid (50 ml.), and the solution was cooled rapidly to 0° and treated with sodium nitrite (4 g.) in water (20 ml.), added dropwise during 10 min. After the mixture had been left at room temperature for 10 min. and heated at 100° for 15 min., the yellow precipitate was filtered off from the cooled mixture and re-dissolved in N-sodium hydroxide. Saturation with carbon dioxide precipitated the *hydroxy-compound* (0·44 g., 41%) which recrystallised from ethanol in plates, m. p. 205° (Found: N, 15·1. $C_{16}H_{13}N_3O_2$ requires N, 15·1%), R_{FAc} 0·94, $\nu_{max.}$ 3458 and 3198 (NH stretching), 3060 (aromatic CH stretching), 1686 (amide C=O), 1618 and 1575 (aromatic CC or CN), 1558 (amide NH), 1486 (aromatic CC or CN), 1445 (methyl CH deformation), 1410 (not assigned) cm.$^{-1}$.

2-*Amino*-4-*hydroxy*-6-*methylquinazoline* (IX).—(*a*) A mixture of 2-amino-5-methylbenzoic acid (6 g.) and guanidine carbonate (7·2 g.) was heated at 195° for 75 min. The cooled, powdered product was dissolved in 2N-sodium hydroxide, and the filtered solution treated with charcoal and saturated with carbon dioxide; the precipitated *amino-hydroxy-compound* (3·45 g., 50%), purified by recrystallisation from ethanol or sublimation at 250°/0·05 mm., had m. p. >360° (Found: N, 23·6. $C_9H_9N_3O$ requires N, 24·0%), R_{FPy} 0·86, R_{FAc} 0·70, $\lambda_{max.}$ (in 0·1N-NaOH) 228 (39), 265 (200), 272 (9160), 332 (9070) mμ, $\nu_{max.}$ 3420 and 3184 (NH stretching), 2948 and 2873 (methyl CH stretching), 2760 (not assigned), 1679 (amide C=O), 1645 (NH deformation), 1614 and 1572 (aromatic CC or CN), 1561 (amide NH), 1514 and 1485 (aromatic CC or CN), 1453 and 1387 (methyl CH deformation) cm.$^{-1}$.

This compound (290 mg.), suspended in anhydrous dioxan (40 ml.) containing triethylamine (2 ml.), was treated during 10 min., with stirring and refluxing, with benzoyl chloride (2 ml.) in dioxan (8 ml.). The mixture was heated for a further 45 min., cooled, freed from triethylamine hydrochloride by filtration, and evaporated under reduced pressure. The residual gum was extracted with ether (2 × 10 ml.) and the filtered extract evaporated to dryness. Recrystallisation of the residue from ethanol gave 2-*amino*-4-*benzoyloxy*-6-*methylquinazoline* (160 mg., 35%), m. p. 235° (Found: C, 64·7; H, 5·4; N, 13·6. $C_{16}H_{13}N_3O_2,H_2O$ requires C, 64·6; H, 5·1; N, 14·1%), R_{FPy} 0·91, R_{FAc} 0·77, $\nu_{max.}$ 3481 and 3113 (NH stretching), 3057 (aromatic CH stretching), 2953 and 2887 (methyl CH stretching), 2345 (not assigned), 1708 (ester C=O), 1679 (not assigned), 1660 (NH deformation), 1618 and 1495 (aromatic CC or CN), 1448 (methyl CH deformation), 1410 (not assigned), 1368 (methyl CH deformation) cm.$^{-1}$.

(*b*) 2-Benzamido-4-hydroxy-6-methylquinazoline (240 mg.), in anhydrous ethanol (20 ml.), was refluxed with ethanolic sodium ethoxide (from sodium, 70 mg., and ethanol, 10 ml.) for 4½ hr. The mixture was evaporated to dryness, and the residue washed with ether and water and dissolved in 2N-sodium hydroxide (20 ml.). Saturation with carbon dioxide precipitated 2-amino-4-hydroxy-6-methylquinazoline (150 mg., 57%), which after recrystallisation from ethanol had m. p. 345° (decomp.) (Found: N, 23·4%). The m. p. was raised to 350° on admixture with an authentic specimen; the ultraviolet and infrared spectra of the two preparations were identical.

2,4-*Dibenzamido*-6-*bromomethylquinazoline* (V; R = R′ = Bz).—2,4-Dibenzamido-6-methylquinazoline (2·0 g.), 1,3-dibromo-5,5-dimethylhydantoin (0·8 g.), and benzoyl peroxide (0·15 g.) suspended in carbon tetrachloride (90 ml.) were heated, under reflux, while irradiated by a 500-w tungsten-filament lamp. An almost clear, reddish-brown, solution was obtained after 1 hr.; on further heating, the colour faded and a yellow solid was precipitated. After 1¾ hr., when the mixture was negative to starch–iodide, it was allowed to cool. The yellow precipitate was collected, washed with ether, and extracted with warm water (2 × 20 lm.); the residual *bromomethyl compound* (1·91 g., 79%), recrystallised from toluene, had m. p. 213° (Found: N, 11·7; Br, 17·3. $C_{23}H_{17}BrN_4O_2$ requires N, 12·1; Br, 17·3%), R_{FPy} 0·66, R_{FAc} 0·93, $\nu_{max.}$ 3480 (NH stretching), 3090 (aromatic CH stretching), 2360 (not assigned), 1670 (amide C=O), 1613 and 1576 (aromatic CC or CN), 1533 (amide NH), 1462 (methylene CH deformation), 1401 (not assigned) cm.$^{-1}$.

It is essential, for the success of the above preparation, for all materials to be rigorously dried. Unsatisfactory results were obtained from attempted brominations in which the dibromohydantoin was replaced by *N*-bromosuccinimide and/or the carbon tetrachloride by chloroform.

Ethyl p-(2,4-*Dibenzamidoquinazolin*-6-*ylmethylamino*)*benzoate* (VI; R = R′ = Bz, R″ = Et).—2,4-Dibenzamido-6-bromoethylquinazoline (500 mg.) and ethyl *p*-aminobenzoate (1500 mg.) were intimately mixed and fused on a boiling-water bath for 24 hr. The cooled melt was rubbed with ether (2 × 15 ml.), and the residual yellow solid dissolved in ethanol (6 ml.) and neutralised with dilute aqueous ammonia. After addition of water (10 ml.) and maintenance at 0° for 1 hr., the white precipitate was collected and washed with cold ethanol (5 ml.) and water (10 ml.). The residual *dibenzamido-ester* (500 mg., 85%) crystallised from aqueous ethanol in needles, m. p. 120—123° (decomp.) (Found: C, 67·2; H, 5·4; N, 12·1. $C_{32}H_{27}N_5O_4,1\frac{1}{2}H_2O$ requires C, 67·1; H, 5·3; N, 12·2%); this substance loses water and shrinks on drying *in vacuo* to an extremely hygroscopic product.

Ethyl p-(2,4-*Diaminoquinazolin*-6-*ylmethylamino*)*benzoate* (VI; R = R′ = H, R″ = Et).—(*a*) The dibenzamido-ester (440 mg.), dried *in vacuo* and dissolved in anhydrous ethanol (10 ml.), was heated on the water-bath for 4½ hr. with ethanolic sodium ethoxide (from sodium, 40 mg., and ethanol, 4 ml.). The mixture was kept overnight at 0° and the precipitate collected by filtration and extracted with 0·5N-sodium hydroxide (10 ml.); the residual *diamino-ester* (120 mg., 45%), recrystallised from dilute ethanol, had m. p. 162—164° (decomp.) (Found: C, 63·6; H, 5·8. $C_{18}H_{19}N_5O_2$ requires C, 64·1; H, 5·6%), $\nu_{max.}$ 3420 and 3137 (NH stretching), 3000 (aromatic CH stretching), 1684 (ester C=O),[11] 1609, 1566, 1528, and 1475 (aromatic CC or CN), 1443 (methyl CH deformation), 1396 (not assigned), 1368 (methyl CH deformation) cm.$^{-1}$. Addition of acetic acid to the sodium hydroxide washings precipitated the diamino-acid (VI; R = R′ = R″ = H), m. p. and mixed m. p. 280° (decomp.), R_{FAc} 0·66.

(*b*) The crude yellow solid obtained by fusion of 2,4-dibenzamido-6-bromomethylquinazoline (1·9 g.) and ethyl *p*-aminobenzoate (4 g.) was heated on the water-bath for 4½ hr. with ethanolic sodium ethoxide (from sodium, 0·13 g., and anhydrous ethanol, 90 ml.). The solution was neutralised with 2N-hydrochloric acid and evaporated under reduced pressure. The residue was triturated with ether (2 × 10 ml.) and N-sodium hydroxide (30 ml.) and finally recrystallised from aqueous ethanol (charcoal), affording the diamino-ester (0·77 g., 56%), m. p. 162—164° (decomp.). In this case, addition of acetic acid to the alkali washings precipitated no diamino-acid.

p-(2,4-*Diaminoquinazolin*-6-*ylmethylamino*)*benzoic Acid* (VI; R = R′ = R″ = H).—The diamino-ester (640 mg.) was heated on a boiling-water bath, under reflux, with potassium hydroxide (125 mg.) in ethanol (20 ml.) and water (5 ml.). Ammonia began to be evolved after 3½ hr. and the heating was then discontinued and most of the ethanol distilled off under reduced pressure. The residue was diluted with water (15 ml.) and treated with charcoal; adjustment of the pH to 7 precipitated the *diamino-acid* (470 mg., 76%), which, purified by re-solution in 0·1N-sodium hydroxide and reprecipitation with acetic acid, and recrystallised from dimethylformamide, had m. p. 283° (decomp.), R_F 0·66, $\lambda_{max.}$ 232 (44,600), 281 (25,630), and 338 mμ (4290). This substance retains water very tenaciously; an air-dried specimen appeared to be a *sesquihydrate* (Found: C, 56·8; H, 6·1; N, 21·3. $C_{16}H_{15}N_5O_2,1\frac{1}{2}H_2O$ requires C, 57·1; H, 5·4; N, 20·8%), and the water of hydration resisted removal at 100° *in vacuo* (Found, on material

[11] Cf. ethyl *p*-aminobenzoate, 1694 cm.$^{-1}$ in chloroform; Thompson, Needham, and Jameson, *Spectrochim. Acta*, 1957, **9**, 208.

dried for 4 hr.: C, 57·9; H, 6·1; N, 21·5; O, 13·9. On material dried to constant weight: C, 59·6; H, 5·7. Calc. for $C_{16}H_{15}N_5O_2,H_2O$: C, 58·7; H, 5·2; N, 21·4; O, 14·7. Calc. for $C_{16}H_{15}N_5O_2$: C, 62·1; H, 4·9; N, 22·6; O, 10·4%). The substance had $\nu_{max.}$ 3365 and 3180 (NH stretching), 2930 and 2865 (methylene CH stretching), 2354 (not assigned), 1651 (carboxyl C=O), 1600, 1524, and 1481 (aromatic CC or CN), 1415 (not assigned), 1373 (methylene CH deformation) cm.$^{-1}$.

4-*Amino*-2-*chloro*-6-*methylquinazoline*.—Ammonia was passed through a solution of 2,4-dichloro-6-methylquinazoline (2·5 g.) in cold dioxan (25 ml.) for 30 min. Next day the precipitate was collected and washed with water until the washings were chloride-free, affording the *amino-chloro-compound* (2·15 g., 95%), m. p. 272 (Found: C, 55·7; H, 4·1; N, 21·5. $C_9H_8ClN_3$ requires C, 55·8; H, 4·2; N, 21·7%).

2-*Chloro*-4-*hydrazino*-6-*methylquinazoline*.—Hydrazine hydrate (1 ml.) was added to 2,4-dichloro-6-methylquinazoline (500 mg.) in cold dioxan (25 ml.). After 30 min., the precipitate was collected and washed with water, affording the *hydrazino-compound* (450 mg., 92%), decomp. 330—335° (Found: C, 51·7; H, 3·8; N, 27·1; Cl, 17·1. $C_9H_9ClN_4$ requires C, 51·8; H, 4·3; N, 26·9; Cl, 17·0%).

4-*Benzylamino*-2-*chloro*-6-*methylquinazoline*.—Benzylamine (1 ml.) and 2,4-dichloro-6-methylquinazoline (500 mg.) were kept for 1 hr. in cold dioxan (25 ml.). The precipitated benzylamine hydrochloride (310 mg., 93%) was removed by filtration and the filtrate evaporated to dryness under reduced pressure. Trituration with water left the *benzylamino-compound* (650 mg., 96%) which crystallised from benzene–light petroleum (b. p. 60—80°) in needles, m. p. 160° (Found: C, 68·1; H, 4·8; N, 14·6. $C_{16}H_{14}ClN_3$ requires C, 67·7; H, 5·0; N, 14·8%).

The same compound was the main product in an experiment in which the reactants were heated under reflux for 6 hr. Fractional crystallisation from benzene–light petroleum gave, in addition, a small amount of 2,4-*dibenzylamino*-6-*methylquinazoline*, m. p. 147° (Found: C, 78·2; H, 5·8; N, 15·5. $C_{23}H_{22}N_4$ requires C, 77·9; H, 6·3; N, 15·8%).

2,4-*Dianilino*-6-*methylquinazoline* (IV; R = R′ = Ph).—2,4-Dichloro-6-methylquinazoline (500 mg.) and aniline (1 ml.) were kept at room temperature in anhydrous dioxan (25 ml.) for 2 days. The crystalline precipitate, collected by filtration, washed with water, and recrystallised from ethanol, was the *hydrochloride*, m. p. 313° (Found: C, 69·7; H, 5·4; N, 15·0. $C_{21}H_{19}ClN_4$ requires C, 69·5; H, 5·3; N, 15·4%). The free *base*, obtained by basification of a solution of the hydrochloride in hot water, crystallised from light petroleum (b. p. 60—80°) in plates, m. p. 125° (Found: C, 77·0; H, 5·6; N, 17·0. $C_{21}H_{18}N_4$ requires C, 77·3; H, 5·6; N, 17·2%).

The hydrochloride of the dianilino-compound (97% yield on aniline) was the sole product obtained when only a single equivalent of aniline was used.

4-*Amino*-2-*anilino*-6-*methylquinazoline* (IV; R = Ph, R′ = H).—4-Amino-2-chloro-6-methylquinazoline (500 mg.) and aniline (1 ml.) were refluxed for 15 hr. in anhydrous dioxan (25 ml.). The cooled solution deposited a quantitative yield of the hydrochloride, m. p. 250°, from which the free *base* was liberated in the usual manner; recrystallisation from aqueous ethanol gave needles, m. p. 190° (Found: C, 72·0; H, 5·4; N, 22·4. $C_{15}H_{14}N_4$ requires C, 72·0; H, 5·6; N, 22·4%).

4-*Hydroxy*-6-*methylquinazoline*.—2-Amino-5-methylbenzoic acid (6 g.) and formamide (4 g.) were heated together, under reflux, for 90 min. at 140° and then for 90 min. at 185°. The mixture was cooled and treated with a little alcohol. The insoluble *hydroxy-compound* (4·4 g., 69%) crystallised from water in needles, m. p. 255° (Found: C, 67·0; H, 5·2; N, 17·3. $C_9H_8N_2O$ requires C, 67·5; H, 5·0; N, 17·5%), $\nu_{max.}$: 3436 and 3134 (NH stretching), 3065 (aromatic CH stretching), 2931 and 2855 (methyl CH stretching), 2724 and 2643 (not assigned), 1690 (amide C=O), 1650 (NH deformation), 1617 and 1485 (aromatic CC or CN), 1452 (methyl CH deformation), 1398 (not assigned), 1376 (methyl CH deformation) cm.$^{-1}$.

4-*Chloro*-6-*methylquinazoline*.—4-Hydoxy-6-methylquinazoline (3 g.) and phosphorus oxychloride (50 ml.) were refluxed together for 5 hr., after which the excess of phosphorus oxychloride was distilled off under reduced pressure. The residue was treated with sodium hydrogen carbonate solution, and the insoluble material fractionally sublimed at 130°/0·001 mm., yielding recovered hydroxy-compound (1·4 g., 47%) and the required *chloro-compound* (1·5 g., 42%), m. p. 108°, which was resublimed before analysis (Found: C, 61·1; H, 4·1. $C_9H_7ClN_2$ requires C, 60·5; H, 4·0%).

4-*Amino*-6-*methylquinazoline*.—Ammonia was passed for 4 hr. through a solution of 4-chloro-6-methylquinazoline (600 mg.) in anhydrous dioxan (20 ml.). Next day, the mixture was evaporated to dryness under reduced pressure and the residue triturated with water (30 ml.) and washed free from chloride ions. Recrystallisation from water gave the *amino-compound* (420 mg., 94%), m. p. 275° (Found: C, 68·1; H, 5·5; N, 26·1. $C_9H_9N_3$ requires C, 67·9; H, 5·7; N, 26·4%).

4-*Anilino*-6-*methylquinazoline*.—4-Chloro-6-methylquinazoline (450 mg.) and aniline (0·5 ml.) were kept in anhydrous dioxan (25 ml.) for 2 days. The precipitated hydrochloride, m. p. 272° (610 mg., 100%), was filtered off and converted, as usual, into the free *base*, which crystallised from aqueous ethanol in needles, m. p. 217° (Found: C, 76·5; H, 5·7; N, 17·8. $C_{15}H_{13}N_3$ requires C, 76·6; H, 5·6; N, 17·9%).

4-*Hydrazino*-6-*methylquinazoline*.—4-Chloro-6-methylquinazoline (450 mg.) and hydrazine hydrate (1 ml.) were kept in dioxan (25 ml.) for 2 days. Recrystallisation of the precipitated *hydrazino-compound* (370 mg., 84%) from water gave needles, m. p. 162° (Found: C, 62·0; H, 5·6; N, 31·6. $C_9H_{10}N_4$ requires C, 62·0; H, 5·8; N, 32·2%).

1,3,5-*Triazanaphthalene Derivatives*

2,4-*Dibenzamido*-6-*methyl*-1,3,5-*triazanaphthalene* (X; R = Bz, R′ = H).—To a boiling, stirred, suspension of 2,4-diamino-6-methyl-1,3,5-triazanaphthalene [6] (5 g.) in anhydrous dioxan (350 ml.), containing triethylamine (20 ml.), benzoyl chloride (10 ml.) was added during 15 min. The mixture was heated for a further 45 min. and triethylamine hydrochloride removed by filtration from the still warm solution. The filtrate was evaporated to dryness under reduced pressure and the residue triturated with ether (3 × 25 ml.) and washed well with water. Recrystallisation from ethanol gave the *dibenzamido-compound* (8·77 g., 80%) as needles, m. p. 185° (Found: C, 68·8; H, 4·8; N, 18·1. $C_{22}H_{17}N_5O_2$ requires C, 68·9; H, 4·5; N, 18·3%).

2,4-*Dibenzamido*-6-*bromomethyl*-1,3,5-*triazanaphthalene* (X; R = Bz, R′ = Br).—2,4-Dibenzamido-6-methyl-1,3,5-triazanaphthalene (1 g.), 1,3-dibromo-5,5-dimethylhydantoin (0·4 g.), and benzoyl peroxide (0·08 g.) were heated in refluxing carbon tetrachloride (140 ml.) for 2½ hr. while the suspension was irradiated with a 500-w tungsten-filament lamp. Next day, the solid was collected and washed with anhydrous ether (3 × 30 ml.); the residual *bromomethyl compound* (0·85 g., 71%) crystallised from anhydrous toluene in needles, m. p. 196° (decomp.) (Found; Br, 17·9. $C_{22}H_{16}BrN_5O_2$ requires Br, 17·3%). The yield is lower if all materials are not rigorously dried before use and if carbon tetrachloride is replaced by chloroform or tetrachloroethylene.

Ethyl p-(2,4-*Diamino*-1,3,5-*triaza*-6-*naphthylmethylamino*)*benzoate* (XI; R = H, R′ = Et).—The dibenzamido-bromomethyl compound (500 mg.) was fused on the water-bath for 24 hr. with ethyl *p*-aminobenzoate (1500 mg.). The cooled melt was triturated with anhydrous ether (3 × 10 ml.), and the residual yellow solid heated on the water-bath for 4 hr. with ethanolic sodium ethoxide (from sodium, 65 mg., and anhydrous ethanol, 15 ml.). The cooled solution was neutralised with 2N-hydrochloric acid and evaporated under reduced pressure. The residue was extracted with ether (2 × 10 ml.) and N-sodium hydroxide (10 ml.) and washed with water. Recrystallisation from ethanol (charcoal) gave the *ester* (0·15 g., 29%) as a pale yellow solid, m. p. 205°, R_{FPy} 0·67, R_{FAc} 0·78 (Found: C, 57·7; H, 6·3; N, 23·3. $C_{17}H_{18}N_6O_2,H_2O$ requires C, 57·3; H, 5·7; N, 23·6%).

p-(2,4-*Diamino*-1,3,5-*triaza*-6-*naphthylmethylamino*)*benzoic Acid* (XI; R = R′ = H).—The preceding ethyl ester (470 mg.) was heated at 60° with potassium hydroxide (100 mg.) in ethanol (30 ml.) containing water (6 ml.). After 5 hr., ammonia began to be evolved and the heating was discontinued. Most of the ethanol was removed under reduced pressure and 0·5N-sodium hydroxide was added to the residue. Unchanged ester (200 mg., 43%) was removed by filtration; adjustment of the filtrate to pH 5 precipitated the *acid* (210 mg., 46%) as a yellow powder, m. p. >360° (Found: C, 51·7; H, 5·1; N, 23·4. $C_{15}H_{14}N_6O_2,2H_2O$ requires C, 52·0; H, 5·2; N, 24·2%). The product was chromatographically homogeneous (R_{FPy} 0·33; R_{FAc} 0·22) and had $\lambda_{max.}$ (in 0·1N-NaOH) 222 (31,390), 278 (27,040), and 342 (6690) mμ; $\nu_{max.}$ 3424, 3335, and 3127 (NH stretching), 2349 (not assigned), 1684 (carboxyl C=O), 1637 (NH deformation), 1604, 1576, and 1519 (aromatic CC or CN), 1448 (methylene CH deformation), 1519 (not assigned), 1373 (methylene CH deformation) cm.$^{-1}$.

p-(2-*Amino*-4-*hydroxy*-1,3,5-*triaza*-6-*naphthylmethylamino*)*benzoic Acid* (XII).—2,4-Dibenzamido-6-bromomethyl-1,3,5-triazanaphthalene (0·67 g.) and ethyl *p*-aminobenzoate (2·0 g.) were fused together on the water-bath for 24 hr. The cooled melt was triturated with anhydrous ether (3 × 15 ml.), and the residue heated on the water-bath for 4 hr. with ethanolic sodium ethoxide (from sodium, 65 mg., and ethanol, 15 ml.); water (5 ml.) was then added and heating continued for a further 2 hr., ammonia being evolved. The solution was neutralised with dilute hydrochloric acid and evaporated under reduced pressure. Dissolution of the residue in 0·1N-sodium hydroxide, treatment with charcoal, and adjustment of the pH to 5 gave the *acid* (120 mg., 24%) as a cream-coloured solid which, after one further reprecipitation and one recrystallisation from dimethylformamide, had m. p. 248° (decomp.) (Found: C, 51·2; H, 5·3; N, 20·5. $C_{15}H_{13}N_5O_32H_2O$ requires C, 51·9; H, 4·9; N, 20·2%).

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