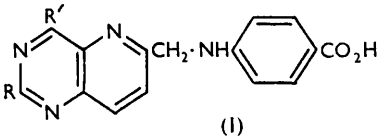
853. *Polyazanaphthalenes. Part IV.*[1] *Further Derivatives of* 1 : 3 : 5- *and* 1 : 3 : 8-*Triazanaphthalene.*

By V. Oakes and H. N. Rydon.

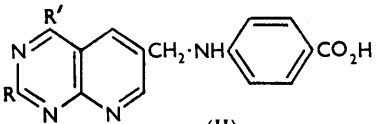
Several 2- and 4-substituted derivatives of 6-methyl-1 : 3 : 5-triazanaphthalene have been synthesised; the 4-hydroxy- and 2 : 4-dihydroxy-compounds have been converted into the corresponding pteroic acid analogues by side-chain bromination, followed by condensation with *p*-aminobenzoic acid. 2 : 4-Dihydroxy- and 2 : 4-dichloro-6-methyl-1 : 3 : 8-triazanaphthalene have also been synthesised but attempts to convert them similarly into pteroic acid analogues were not successful.

A theoretical explanation is given for the preferential reactivity of the 4-chlorine atom in the 2 : 4-dichloro-derivatives of quinazoline, 1 : 3 : 5-triazanaphthalene, and 1 : 3 : 8-triazanaphthalene.

The work described in this paper had as its objective the synthesis of pteroic acid analogues of the general types (I) and (II), containing the 1 : 3 : 5- and the 1 : 3 : 8-triazanaphthalene ring system, respectively, in place of the pteridine (1 : 3 : 5 : 8-tetrazanaphthalene) ring system present in pteroic acid itself. The general chemistry of these two ring systems, and convenient synthetic routes to them, have been described in Part III of this series.[1] The route envisaged for the synthesis of the required pteroic acid analogues involved synthesis of appropriately 2- and 4-substituted 6-methyl compounds, followed by side-chain bromination and condensation with *p*-aminobenzoic acid.[2]



(I)

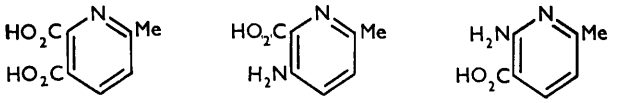


(II)

The most convenient starting material for the synthesis of derivatives of 6-methyl-1 : 3 : 5-triazanaphthalene is 8-hydroxy-2-methylquinoline.[3] Nitric acid oxidation by the procedure used by Sucharda [4] for the oxidation of 8-hydroxyquinoline was unsatisfactory but in carbon tetrachloride gave satisfactory yields of 6-methylquinolinic acid (III). Some difficulty was encountered in the conversion of this acid into its imide; fusion of the ammonium salt resulted in extensive decomposition, while reaction of the anhydride with acetamide [4] gave very variable yields. The best yields were finally obtained by heating the diamide just below its melting point; [5] actual fusion of the diamide resulted in a

[1] Part III, Oakes, Pascoe, and Rydon, *J.*, 1956, 1045.
[2] Cf. Boothe *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 27.
[3] Doebner and Müller, *Ber.*, 1884, **17**, 1706.
[4] Sucharda, *Ber.*, 1925, **58**, 1728.
[5] Cf. Engler, *Ber.*, 1894, **27**, 1788.

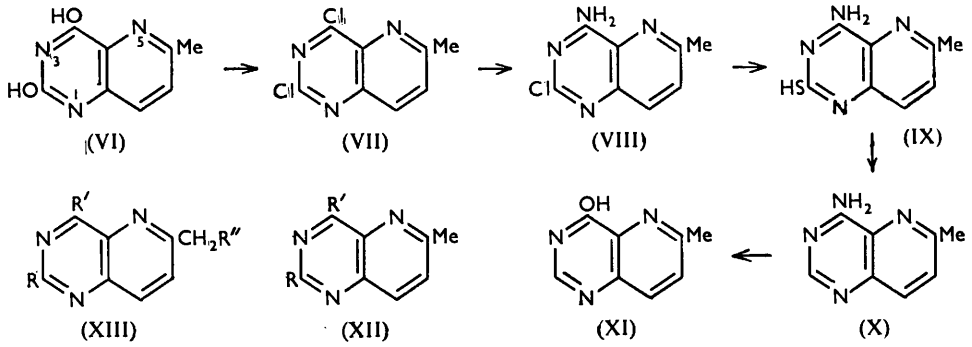
considerably diminished yield. Treatment of 6-methylquinolinimide with sodium hypobromite might yield either the desired 3-amino-6-methylpicolinic acid (IV) or the isomeric 2-amino-6-methylnicotinic acid (V), the former being the more probable product by analogy



(III) (IV) (V)

with the course of the similar reaction with quinolinimide.[1] That the reaction took the expected, and desired, course was shown by decarboxylation, which gave a product, m. p. 95°, which was clearly 5-amino-2-picoline (lit.,[6] m. p. 96°) and not the 6-amino-compound (lit.,[7] m. p. 41°).

2 : 4-Dihydroxy-6-methyl-1 : 3 : 5-triazanaphthalene (VI) was readily prepared by fusion of 3-amino-6-methylpicolinic acid (IV) with urea and converted into the 2 : 4-dichloro-compound (VII) in satisfactory yield by treatment with phosphorus oxychloride in the presence of triethylamine.[1,8] As with the unmethylated compound,[1] the two chlorine atoms in (VII) differed markedly in reactivity towards nucleophilic reagents, that in position 4 being the more reactive. Thus, treatment with ammonia in cold dioxan yielded the 4-amino-2-chloro-compound (VIII) which, on treatment with thiourea, afforded the 4-amino-2-mercapto-compound (IX); Raney nickel desulphurisation of the last-named compound gave the 4-amino-compound (X) which was converted by boiling dilute acid into 4-hydroxy-6-methyl-1 : 3 : 5-triazanaphthalene (XI), identical with material prepared by fusing 3-amino-6-methylpicolinic acid with formamide, this identity confirming the structures assigned to (VIII), (IX), and (X). Treatment of the dichloro-compound (VII) with ammonia in boiling phenol [1,9] yielded, not the expected diamine, but the 4-amino-2-



(VI) (VII) (VIII) (IX)

(XIII) (XII) (XI) (X)

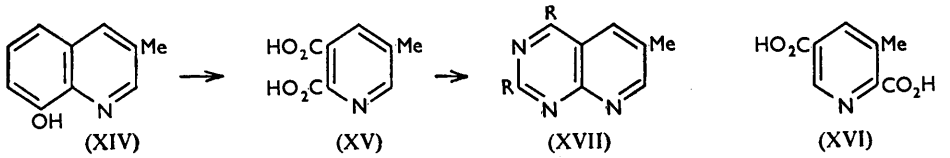
phenoxy-compound (XII; R = PhO, R′ = NH_2), the structure of which was established by its preparation from the amino-chloro-compound (VIII) and phenol. 2 : 4-Diamino-6-methyl-1 : 3 : 5-triazanaphthalene (XII; R = R′ = NH_2) was finally obtained in excellent yield by heating the dichloro-compound (VII) or the amino-chloro-compound (VIII) at 170° with ethanolic ammonia.[10]

Side-chain bromination of the 4-hydroxy- (XI) and the 2 : 4-dihydroxy-compound (VI) gave smoothly the corresponding 6-bromomethyl compounds (XIII; R″ = Br); these resisted attempted purification but the presence of the side-chain bromine in the 2 : 4-dihydroxy-compound (XIII; R = R′ = OH, R″ = Br) was confirmed by its conversion into the 2 : 4-dihydroxy-6-hydroxymethyl compound (XIII; R = R′ = R″ = OH) by

[6] Graf, *J. prakt. Chem.*, 1932, **133**, 19.
[7] Meyer, *Rec. Trav. chim.*, 1925, **44**, 323.
[8] Cf. Robins and Christensen, *J. Amer. Chem. Soc.*, 1952, **74**, 3624.
[9] Cf. Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 353.
[10] Cf. Robins and Hitchings, *J. Amer. Chem. Soc.*, 1955, **77**, 2256.

boiling water. Condensation of the crude 6-bromomethyl compounds with *p*-aminobenzoic acid [2] afforded two pteroic acid analogues containing the 1 : 3 : 5-triazanaphthalene skeleton, *viz.*, (I; R = H, R′ = OH) and (I; R = R′ = OH).

These two pteroic acid analogues were kindly tested for anti-folic acid activity by Dr. O. R. Bird of Messrs. Parke, Davis & Co. of Detroit, to whom we express our best thanks; both were inactive (inhibition index for *Streptococcus faecalis* greater than 75,000).



(XIV) (XV) (XVII) (XVI)

8-Hydroxy-3-methylquinoline (XIV), the most convenient starting material for the synthesis of derivatives of 6-methyl-1 : 3 : 8-triazanaphthalene, was prepared in very poor yield by the Skraup reaction between *o*-aminophenol and α-methylacraldehyde. Oxidation with fuming nitric acid [4] gave a good yield of 5-methylquinolinic acid (XV), m. p. 181°. Durkopf and Göttsch [11] assigned (XV) as one of two possible structures to the methylpyridinedicarboxylic acid, m. p. 223°, obtained [12] by oxidation of 2-ethyl-3 : 5-dimethylpyridine; the non-identity of the melting points establishes (XVI) (3-methylpyridine-2 : 5-dicarboxylic acid) as the structure of this oxidation product. Treatment of the diamide of (XV) with sodium hypobromite [1,13] afforded 2 : 4-dihydroxy-6-methyl-1 : 3 : 8-triazanaphthalene (XVII; R = R′ = OH) which was readily converted into the dichloro-compound (XVII; R = R′ = Cl); as with the unmethylated compound [1] hydrogenation failed to remove the nuclear chlorine atoms, giving, in this case, a dihydro-compound. Not unexpectedly, neither the dihydroxy- nor the dichloro-compound (XVII) could be halogenated in the side-chain, although several methods were tried; further work in this series was therefore abandoned.

In Part III [1] the greater reactivity towards nucleophilic reagents of the 4-chlorine, as compared with the 2-chlorine atom, in 2 : 4-dichloro-1 : 3 : 5- and -1 : 3 : 8-triazanaphthalenes was accounted for by extension of the explanation advanced by Curd, Landquist, and Rose [14] for the similar preferential reactivity of the 4-chlorine atom in 2 : 4-dichloroquinazoline. A more satisfying explanation results by applying the simplified Longuet-Higgins quantum-mechanical treatment [15] which has been extended to several other halogeno-polyazanaphthalenes by Chapman.[16] The results of these calculations are given in the following Table, in which δ^{N}, δ^{Cl}, and δ^{Me} represent the perturbations in charge-

2 : 4-Dichloro-compound of	Nucleophilic substitution of	$\Delta U - \Delta U_0$	$\Delta U_{4Cl} - \Delta U_{2Cl}$
Quinazoline	2-Cl	$0{\cdot}63\delta^{N} + 0{\cdot}08\delta^{Cl}$	$0{\cdot}10\delta^{N} + 0{\cdot}16\delta^{Cl} + \delta'$
	4-Cl	$0{\cdot}73\delta^{N} + 0{\cdot}24\delta^{Cl}$	
1 : 3 : 5-Triazanaphthalene	2-Cl	$0{\cdot}71\delta^{N} + 0{\cdot}08\delta^{Cl}$	$0{\cdot}08\delta^{N} + 0{\cdot}16\delta^{Cl} + \delta'$
	4-Cl	$0{\cdot}79\delta^{N} + 0{\cdot}24\delta^{Cl}$	
6-Methyl-1 : 3 : 5-triazanaphthalene	2-Cl	$0{\cdot}71\delta^{N} + 0{\cdot}08\delta^{Cl} - 0{\cdot}13\delta^{Me}$	$0{\cdot}08\delta^{N} + 0{\cdot}16\delta^{Cl} + 0{\cdot}04\delta^{Me} + \delta'$
	4-Cl	$0{\cdot}79\delta^{N} + 0{\cdot}24\delta^{Cl} - 0{\cdot}09\delta^{Me}$	
1 : 3 : 8-Triazanaphthalene	2-Cl	$0{\cdot}75\delta^{N} + 0{\cdot}08\delta^{Cl}$	$0{\cdot}07\delta^{N} + 0{\cdot}16\delta^{Cl} + \delta'$
	4-Cl	$0{\cdot}82\delta^{N} + 0{\cdot}24\delta^{Cl}$	

density distribution in the transition state at the point of substitution for a ring-nitrogen atom, a chlorine atom, and a methyl group, respectively, that for the last-named being opposite in sign from those for the other two. The values of $\Delta U - \Delta U_0$ (third column) are measures of the calculated differences in the activation energies, at 0° K, of the reactions

[11] Durkopf and Göttsch, *Ber.*, 1890, **23**, 1111.
[12] *Idem, ibid.*, p. 688; Durkopf and Schlaugk, *Ber.*, 1888, **21**, 834.
[13] McLean and Spring, *J.*, 1949, 2582.
[14] Curd, Landquist, and Rose, *J.*, 1947, 775.
[15] Longuet-Higgins, *J. Chem. Phys.*, 1950, **18**, 283.
[16] Chapman, *Chem. Soc. Spec. Publ.*, No. 3, 1955, p. 155; Chapman and Russell-Hill, *J.*, 1956, 1563.

of the chlorine atoms indicated with nucleophilic reagents and the corresponding reactions of the reference compounds, *viz.*, 1- and 2-chloronaphthalene for the 4- and 2-chloroheterocycles, respectively. The differences, $\Delta U_{4Cl} - \Delta U_{2Cl}$ (last colmun), are then measures of the calculated differences in activation energy between the reactions of the 4- and the 2-chlorine atoms in the four dichloropolyazanaphthalenes with a given nucleophilic reagent, the additional term, δ', representing the (relatively small) differences in activation energy between the corresponding reactions of the two reference chloronaphthalenes; the major effect will, without doubt, be that due to the ring nitrogen atoms (*i.e.*, the δ^N term). It will be seen that, in all cases, the calculated activation energy for the reaction of the 4-chlorine is less than that for the reaction of the 2-chlorine atom (δ being negative), leading to a predicted preferential reactivity of the former, in agreement with the experimental observations.

Experimental

1 : 3 : 5-*Triazanaphthalene Derivatives.*

6-*Methylquinolinic Acid* (III).—8-Hydroxy-2-methylquinoline [3] (20 g.), in carbon tetrachloride (50 ml.), was added dropwise, with ice-cooling and vigorous mechanical stirring, to fuming nitric acid (100 ml.). After being stirred for a further 30 min., the mixture was concentrated on the steam-bath to 50 ml. Water (300 ml.) was then added and the filtered solution evaporated to dryness; treatment of the resulting gum with a little ethanol gave the *acid* (10 g., 44%) which crystallised from ethanol in needles, m. p. 164° (Found : C, 52·9; H, 4·0; N, 7·6. $C_8H_7O_4N$ requires C, 53·0; H, 3·9; N, 7·7%).

6-*Methylquinolinimide*.—(*a*) 6-Methylquinolinic acid (15 g.) was refluxed with acetic anhydride (50 ml.) for 6 hr.; the resulting clear solution was evaporated to dryness under reduced pressure and the residue heated at 125—130° for 8 hr. with acetamide (15 g.). The mixture was cooled, poured into water, and filtered and the filtrate extracted continuously with ether for 4 hr. The product obtained by evaporation of the extract was added to the solid obtained by filtration, and the mixture recrystallised from ethyl acetate, affording the *imide* (6 g., 46%), m. p. 244° (Found : C, 58·8; H, 3·6. $C_8H_6O_2N_2$ requires C, 59·2; H, 3·7%); the yield was very variable.

(*b*) 6-Methylquinolinic acid (4 g.) was refluxed on the steam-bath for 4 hr. with ethanol (10 g.) and sulphuric acid (10 g.). The cooled product was poured on ice, basified with aqueous ammonia, and extracted with ether. The crude ester obtained by evaporating the extract was suspended in aqueous ammonia solution (*d* 0·880; 40 ml.) and ammonia passed through the suspension for 5 hr. 6-*Methylquinolindiamide* separated (1·8 g., 46%) and crystallised from water in needles, m. p. 210° (Found : C, 53·4; H, 4·8. $C_8H_9O_2N_3$ requires C, 53·6; H, 5·0%).

This amide (20 g.) was heated at 210—215° until evolution of ammonia ceased. The product was cooled, crushed, and recrystallised from ethyl acetate, affording the imide (18 g., 99·5%), prisms, m. p. 244°.

3-*Amino*-6-*methylpicolinic Acid* (IV).—Aqueous sodium hypobromite (from bromine, 5·6 ml., and ice-cold 2N-sodium hydroxide, 120 ml.) was added to a solution of 6-methylquinolinimide (16 g.) in ice-cold 2N-sodium hydroxide (300 ml.), and the mixture kept at room temperature for an hour and then at 80° for a further hour. After cooling, the pH was brought to 5 with 50% sulphuric acid, and the mixture kept at 2° for 24 hr. The small amount of precipitate was filtered off and the filtrate treated with copper acetate (6 g.), in hot water (150 ml.) containing acetic acid (6 ml.). The precipitated copper salt was collected, washed with water, and resuspended in water (150 ml.); the suspension was then saturated with hydrogen sulphide. Copper sulphide was removed and the filtrate decolorised with charcoal and evaporated to dryness. The resulting *acid* (7·5 g., 50%) crystallised from ethanol in pale yellow prisms, m. p. 205° (Found : C, 55·4; H, 5·2. $C_7H_8O_2N_2$ requires C, 55·3; H, 5·3%).

This acid (200 mg.) was heated in a long tube at 230° for 10 min. and then at 270° for 20 min. The distillate was crystallised from benzene–light petroleum (b. p. 60—80°), yielding 5-amino-2-picoline as plates, m. p. 95° (lit.,[6] m. p. 96°).

2 : 4-*Dihydroxy*-6-*methyl*-1 : 3 : 5-*triazanaphthalene* (VI).—3-Amino-6-methylpicolinic acid (5 g.) was intimately mixed with urea (3 g.), heated slowly to 190—200°, and kept at this temperature for an hour. The cooled product was dissolved in 2N-sodium hydroxide (50 ml.) and decolorised with charcoal. Saturation with carbon dioxide precipitated the *dihydroxy-compound* (2·2 g., 38%) which crystallised from water in needles, m. p. >270° (Found : C, 54·7; H, 3·6. $C_8H_7O_2N_3$ requires C, 54·2; H, 3·95%).

2 : 4-*Dichloro*-6-*methyl*-1 : 3 : 5-*triazanaphthalene* (VII).—The dihydroxy-compound (VI) (500 mg.) was heated under reflux for 6 hr. with phosphorus oxychloride (15 ml.) and triethylamine (1 ml.). The product was evaporated to dryness under reduced pressure and the residue heated at 100°/12 mm. for an hour. The cooled residue was treated with ice-water (15 ml.), and the insoluble portion collected, dried at the pump, and sublimed at 140° (bath)/0·1 mm. The resulting *dichloro-compound* (300 mg., 50%), recrystallised from light petroleum (b. p. 80—100°), had m. p. 138° (Found : C, 45·1; H, 2·5. $C_8H_5N_3Cl_2$ requires C, 44·8; H, 2·3%).

4-*Amino*-2-*chloro*-6-*methyl*-1 : 3 : 5-*triazanaphthalene* (VIII).—Ammonia was passed for 15 min. through a solution of the dichloro-compound (VII) (190 mg.) in anhydrous dioxan (20 ml.). The product was evaporated to dryness under reduced pressure; treatment of the residue with water (15 ml.), filtration, and washing with water afforded the *amino-chloro-compound* (150 mg., 87%) which crystallised from benzene in needles, m. p. 261° (Found : C, 49·7; H, 3·7; N, 28·8. $C_8H_7N_4Cl$ requires C, 49·2; H, 3·6; N, 28·6%).

4-*Amino*-2-*mercapto*-6-*methyl*-1 : 3 : 5-*triazanaphthalene* (IX).—The amino-chloro-compound (VIII) (150 mg.) was refluxed for 5 hr. with thiourea (150 mg.) in ethanol (25 ml.). The *amino-mercapto-compound* (90 mg., 61%) was slowly deposited from the resulting solution as yellow prisms, m. p. >400° (Found : N, 29·0. $C_8H_8N_4S$ requires N, 29·1%).

4-*Amino*-6-*methyl*-1 : 3 : 5-*triazanaphthalene* (X).—The amino-mercapto-compound (IX) (90 mg.) and Raney nickel (1 g.), suspended in ethanol (40 ml.) and aqueous ammonia (*d* 0·880; 10 ml.), were heated under reflux for 2 hr. The cooled product was filtered and the solid washed with hot ethanol (3 × 10 ml.); evaporation of the filtrate and washings under reduced pressure, followed by recrystallisation from benzene–light petroleum (b. p. 60—80°), afforded the *amine* (50 mg., 67%), m. p. 184° (Found : C, 60·3; H, 4·8; N, 34·9. $C_8H_8N_4$ requires C, 60·0; H, 5·0; N, 35·0%). This amine was heated for an hour with 5N-hydrochloric acid; concentration and addition of sodium carbonate afforded the 4-hydroxy-compound (IX) (see below), m. p. and mixed m. p. 296—297°.

4-*Hydroxy*-6-*methyl*-1 : 3 : 5-*triazanaphthalene* (XI).—3-Amino-6-methylpicolinic acid (1·5 g.) and formamide (1 g.) were heated together at 125° for 2·5 hr. and then at 180° for 2·5 hr. On cooling, the *hydroxy-compound* (700 mg., 44%) was deposited as needles which were washed with ethanol and recrystallised from water, yielding plates, m. p. 299° (Found : C, 59·7; H, 4·5; N, 26·2. $C_8H_7ON_3$ requires C, 59·6; H, 4·4; N, 26·1%).

4-*Amino*-6-*methyl*-2-*phenoxy*-1 : 3 : 5-*triazanaphthalene* (XII; R = PhO, R′ = NH_2).—(*a*) Ammonia was passed for 2 hr. through a solution of the dichloro-compound (VII) (250 mg.) in boiling phenol (10 g.). The cooled product was treated with an excess of 10% sodium hydroxide solution, and the precipitated amino-phenoxy-compound (90 mg.) collected by filtration and recrystallised from methanol in needles, m. p. and mixed m. p. 231°.

(*b*) The amino-chloro-compound (VIII) (50 mg.) was heated for 3 hr. in boiling phenol (2·5 g.). The cooled product was treated with excess of 10% sodium hydroxide solution, and the insoluble *amino-phenoxy-compound* (50 mg., 77%) collected and recrystallised from benzene–light petroleum (b. p. 60—80°), forming prisms, m. p. 231° (Found : C, 67·5, 67·5; H, 4·7, 4·6; N, 22·8. $C_{14}H_{12}ON_4$ requires C, 66·8; H, 4·7; N, 22·2%).

2 : 4-*Diamino*-6-*methyl*-1 : 3 : 5-*triazanaphthalene* (XII; R = R′ = NH_2).—The dichloro-compound (VII) (765 mg.) or the amino-chloro-compound (VIII) (700 mg.) was heated in a sealed tube at 170° for 16 hr. with saturated ethanolic ammonia (15 ml.). The cooled product was filtered and the solid washed with water, dried, and recrystallised from benzene–ethanol, affording the *diamine* (600 mg., 95%) as needles, m. p. 241° (Found : C, 55·5; H, 4·8; N, 40·2. $C_8H_9N_5$ requires C, 54·9; H, 5·1; N, 40·0%). The *monohydrobromide* had m. p. 285° (Found : C, 38·5; H, 4·0; N, 27·3. $C_8H_{10}N_5Br$ requires C, 37·5; H, 3·9; N, 27·3%).

2 : 4-*Dihydroxy*-6-*hydroxymethyl*-1 : 3 : 5-*triazanaphthalene* (XIII; R = R′ = R″ = OH).—The dihydroxy-compound (VI) (177 mg.), bromine (0·06 ml.), and sodium acetate (100 mg.) were heated on the steam-bath, in acetic acid (30 ml.), for 2 hr. The acetic acid was then removed under reduced pressure and the residue ground and washed with water until free from inorganic matter. Recrystallisation from boiling water afforded the *hydroxymethyl compound* (110 mg., 57%) as needles, m. p. 330° (Found : C, 50·0, 49·9; H, 4·0, 3·9. $C_8H_7O_3N_3$ requires C, 49·7; H, 3·6%).

Pteroic Acid Analogues.—(*a*) 4-Hydroxy-6-methyl-1 : 3 : 5-triazanaphthalene (500 mg.), sodium acetate (250 mg.), and bromine (0·186 ml.) were heated in acetic acid (50 ml.) on the steam-bath for an hour, by which time all the bromine had reacted. *p*-Aminobenzoic acid (425 mg.) was then added and heating continued for a further 2 hr. Next day, a little *p*-aminobenzoic acid hydrobromide was filtered off and the filtrate evaporated to dryness under reduced

pressure. The residue was treated with hot water (25 ml.), and the solid collected and washed thoroughly with hot water. Reprecipitation from alkaline solution with acetic acid afforded p-(4-*hydroxy*-1 : 3 : 5-*triaza*-6-*naphthylmethylamino*)*benzoic acid* (I; R = H, R′ = OH) (50 mg., 6%) as a yellow powder, m. p. 265° (Found: C, 52·5, 52·9; H, 4·4, 4·5; N, 16·7, 16·5. $C_{15}H_{12}O_3N_4,2{\cdot}5H_2O$ requires C, 52·8; H, 5·0; N, 16·4%).

(*b*) 2 : 4-Dihydroxy-6-methyl-1 : 3 : 5-triazanaphthalene (530 mg.), sodium acetate (200 mg.), and bromine (0·18 ml.) were heated on the steam-bath in acetic acid (50 ml.) for 4 hr. Condensation with *p*-aminobenzoic acid (410 mg.), followed by working up in the usual manner, afforded p-(2 : 4-*dihydroxy*-1 : 3 : 5-*triaza*-6-*naphthylmethylamino*)*benzoic acid* (I; R = R′ = OH) (250 mg., 30%), m. p. >380° (Found: C, 52·6, 52·7; H, 4·1, 4·1; N, 16·4. $C_{15}H_{12}O_4N_4,1{\cdot}5H_2O$ requires C, 53·1; H, 4·4; N, 16·5%).

1 : 3 : 8-*Triazanaphthalene Derivatives.*

8-*Hydroxy*-3-*methylquinoline* (XIV).—*o*-Aminophenol (50 g.), *o*-nitrophenol (25 g.), α-methylacraldehyde (40 ml.), and concentrated hydrochloric acid (100 ml.) were heated together under reflux for 90 min. The product was steam-distilled to remove excess of *o*-nitrophenol, and the residue then basified with sodium carbonate. Further steam-distillation afforded the *base* (6·5 g., 9%) which crystallised from ethanol in needles, m. p. 110° (Found: C, 75·3; H, 5·6; N, 9·2. $C_{10}H_9ON$ requires C, 75·5; H, 5·7; N, 8·8%).

5-*Methylquinolinic Acid* (XV).—8-Hydroxy-3-methylquinoline (6 g.) was treated dropwise with fuming nitric acid (20 ml.) during 2 hr. After a further hour, the mixture was heated on the steam-bath until evolution of nitrous fumes was complete. The mixture was then cooled and treated with more fuming nitric acid (30 ml.), added in a steady stream. After 3 hr. at room temperature the mixture was evaporated to dryness on the steam-bath. Treatment of the residue with water afforded the *acid* (4 g., 60%), which crystallised from ethanol in plates, m. p. 181° (Found: C, 53·1; H, 3·9. $C_8H_7O_4N$ requires C, 53·0; H, 3·9%).

5-*Methylquinolinamide*.—5-Methylquinolinic acid (3 g.) was refluxed on the steam-bath for 4 hr. with ethanol (9 g.) and sulphuric acid (5 g.). The cooled product was poured on ice and basified with aqueous ammonia. The crude ester, isolated by extraction with ether, was suspended in ammonia solution (*d* 0·880; 30 ml.), and gaseous ammonia was passed into the mixture for 5 hr. The *amide* (0·8 g., 27%) separated and crystallised from water in needles, m. p. 181° (Found: C, 53·5; H, 4·6. $C_8H_9O_2N_3$ requires C, 53·6; H, 5·0%).

2 : 4-*Dihydroxy*-6-*methyl*-1 : 3 : 8-*triazanaphthalene* (XVII; R = OH).—5-Methylquinolinamide (700 mg.) and sodium hypobromite solution (20 ml.; from bromine, 0·6 g., and 2N-sodium hydroxide, 20 ml.) were mixed and kept at room temperature for 1 hr. and then at 80° for 1 hr. After cooling, saturation with carbon dioxide precipitated the *dihydroxy-compound* (400 mg., 58%) which crystallised from water in needles, m. p. 345° (Found: C, 53·9; H, 3·7. $C_8H_7O_2N_3$ requires C, 54·2; H, 3·95%).

2 : 4-*Dichloro*-6-*methyl*-1 : 3 : 8-*triazanaphthalene* (XVII; R = Cl).—The dihydroxy-compound (250 mg.) was refluxed for 5 hr. with phosphorus oxychloride (20 ml.). The product was evaporated under reduced pressure and the residue treated with sodium hydrogen carbonate (3 g.) in water (10 ml.) and filtered. The filtrate was extracted with ethyl acetate, and the extract added to the solid from the filtration. Sublimation at 160° (bath)/0·1 mm. afforded the *dichloro-compound* (70 mg., 23%), m. p. 141° (Found: C, 44·1; H, 2·2. $C_8H_5N_3Cl_2$ requires C, 44·8; H, 2·3%).

This compound (100 mg.), in ethanol (50 ml.), was shaken in hydrogen over Adams catalyst (50 mg.); 24 ml. of hydrogen were absorbed. Filtration and evaporation afforded a 2 : 4-*dichloro*-x : y-*dihydro*-6-*methyl*-1 : 3 : 8-*triazanaphthalene* which crystallised from methanol in prisms, m. p. 234° (Found: C, 44·3; H, 3·15. $C_8H_7N_3Cl_2$ requires C, 44·4; H, 3·25%).

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