216. *Polyazanaphthalenes. Part III.* Some Derivatives of 1 : 3 : 5- and 1 : 3 : 8-Triazanaphthalene.*

By V. Oakes, R. Pascoe, and H. N. Rydon.

A number of derivatives of 1 : 3 : 5- and 1 : 3 : 8-triazanaphthalene have been prepared from the 2 : 4-dihydroxy-compounds, the structures of which are discussed. The chlorine atoms in the 2 : 4-dichloro-compounds differ markedly in their reactivity towards bases, the 4-chlorine being the more reactive in both series. Catalytic hydrogenation of 2 : 4-dichloro-1 : 3 : 5-triazanaphthalene yields 1 : 3 : 5-triazanaphthalene, which proved too unstable to be isolated as the free base; by contrast, hydrogenation of 2 : 4-dichloro-1 : 3 : 8-triazanaphthalene yields the 5 : 6 : 7 : 8-tetrahydro-compound.

Periodate oxidation of 2-aminonicotinic hydrazide yields the corresponding aldehyde but similar oxidation of 3-aminopicolinic hydrazide yields only the amide.

This paper is concerned with an exploratory study of the chemistry of the 1 : 3 : 5- and 1 : 3 : 8-triazanaphthalenes about which there was, until very recently, little published information. Only four derivatives of 1 : 3 : 5-triazanaphthalene, *viz.*, the 4-hydroxy-, 2 : 4-dihydroxy-, 4-hydroxy-2-mercapto-, and 2-amino-4-hydroxy-compounds, have been recorded.[1,2] Before 1955, published information on 1 : 3 : 8-triazanaphthalene was also very meagre, being restricted to the 4-hydroxy-, 2 : 4-dihydroxy-, and 4-hydroxy-2-methyl compounds and certain of their derivatives.[3,4] Since the completion of our work,[5] however, Robins and Hitchings [6] have published an extensive investigation of the 1 : 3 : 8-triazanaphthalenes which, in many respects, duplicates and supplements our findings.

The most convenient starting material for the preparation of 1 : 3 : 5-triazanaphthalene derivatives is 3-aminopicolinic acid, which we prepared from quinolinimide by a modification of Sucharda's method;[7] substitution of sodium hypobromite for the hypochlorite in this preparation markedly increases the yield of 3-aminopicolinic acid at the expense of that of the unwanted by-product, 2-aminonicotinic acid. Contrary to our experience with 2-aminonicotinic hydrazide (see p. 1048), treatment of 3-aminopicolinic hydrazide with periodate afforded, not the expected aldehyde, but only 3-aminopicolinamide; amides have been prepared from hydrazides by treatment with nitrous acid [8] and with Raney nickel,[9] but these are hardly good analogies for this curious reaction.

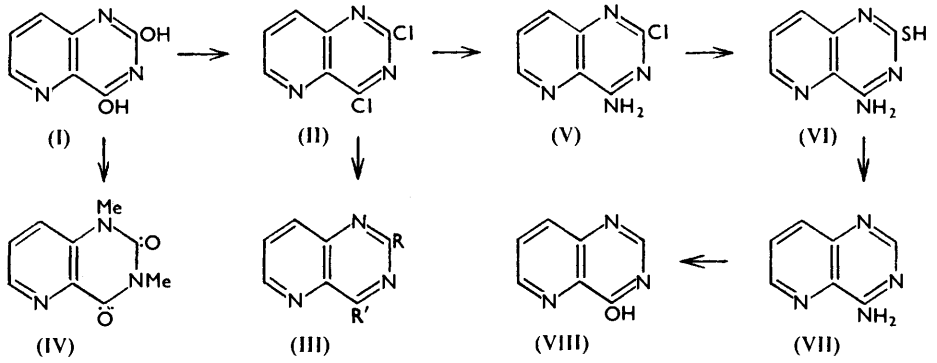
The starting point for the major part of our work in this series was 2 : 4-dihydroxy-1 : 3 : 5-triazanaphthalene [2] (I), which is most easily prepared by fusing 3-aminopicolinic acid with urea. Considerable difficulty was experienced in replacing the two hydroxyl groups by chlorine. Reaction with phosphorus oxychloride alone gave a grey solid, containing chlorine, nitrogen, and phosphorus, from which none of the required dichloro-compound (II) could be isolated. Somewhat better results were obtained by working in the presence of dimethylaniline [10] but the yields obtained by this procedure were variable, as also were those obtained in the presence of diethylaniline. Reproducible yields were finally obtained by carrying out the reaction with phosphorus oxychloride in the presence

* Part II, Landor and Rydon, *J.*, 1955, 1113.

[1] Price and Curtin, *J. Amer. Chem. Soc.*, 1946, **68**, 914.
[2] Korte, *Chem. Ber.*, 1952, **85**, 1012.
[3] Klisiecki and Sucharda, *Roczniki Chem.*, 1923, **3**, 251.
[4] McLean and Spring, *J.*, 1949, 2582.
[5] Pascoe, Thesis, London, 1952; Oakes, Thesis, Manchester, 1955.
[6] Robins and Hitchings, *J. Amer. Chem. Soc.*, 1955, **77**, 2256.
[7] Sucharda, *Ber.*, 1925, **58**, 1728.
[8] Stoll and Hofmann, *Helv. Chim. Acta*, 1943, **26**, 922; Olsen and Enkemeyer, *Chem. Ber.*, 1948, **81**, 359.
[9] Ainsworth, *J. Amer. Chem. Soc.*, 1954, **76**, 5774.
[10] Cf. Kenner, Lythgoe, Todd, and Topham, *J.*, 1943, 574.

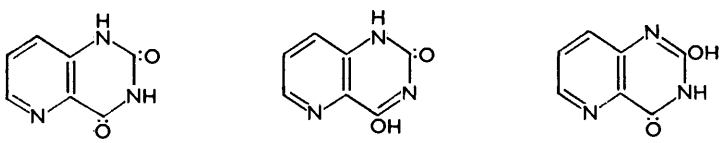
of triethylamine;[11] no evidence was obtained of the formation as by-products of the diethylamino-derivatives encountered by the American workers, although 2-chloro-4-(*N*-ethylanilino)-1 : 3 : 5-triazanaphthalene (III; R = Cl, R′ = NEtPh) was obtained on one occasion from the reaction in presence of diethylaniline.

Hydrogenolysis of the dichloro-compound (II) over Adams catalyst, with or without added magnesium oxide, proceeding smoothly, yielding 1 : 3 : 5-triazanaphthalene (III; R = R′ = H), isolated as its picrate, m. p. 191°. The free base, a low-melting waxy solid, was very unstable, decomposition and oxidation or polymerisation to red or brown insoluble materials attending all attempts at purification by crystallisation or distillation.



The chlorine atoms in (II) are very reactive, exposure to moist air being sufficient to bring about hydrolysis to the dihydroxy-compound (I), and they can be replaced by a variety of other groups; owing to its ready hydrolysis, all reactions with the dichloro-compound (II) must be carried out in anhydrous media. Reaction with thiourea, followed by treatment of the resulting bisthiuronium salt with hot water, afforded the dithiol (III; R = R′ = SH), while reaction with sodium ethyl sulphide yielded the diethylthio-compound (III; R = R′ = SEt); both of these compounds, on desulphurisation with Raney nickel, afforded the parent base (III; R = R′ = H), isolated as its picrate.

Treatment of the dichloro-compound (II) with sodium methoxide and ethoxide afforded the 2 : 4-dimethoxy- (III; R = R′ = OMe) and 2 : 4-diethoxy-compound (III; R = R′ = OEt); the former is not identical with the isomeric dimethyl derivative, obtained by treating the dihydroxy-compound (I) with dimethyl sulphate and alkali, which must therefore be the *N*-methyl derivative (IV) (cf. the similar *N*-methylation of 2 : 4 : 7-trihydroxypteridine [12]). Light-absorption curves for the dihydroxy-compound (I) and the two dimethyl derivatives are shown in Fig. 1; the similarity of the curve for the dihydroxy-compound to that for the *O*-methyl derivative (III; R = R′ = OMe), rather than to that for the *N*-methyl derivative (IV), suggests that its structure is indeed (I), rather than the



alternative diketo-structure (IX), although the monoketo-structures (X) and (XI) cannot be excluded. This conclusion is in interesting contrast to the conclusions reached, on similar evidence, concerning the structures of 2-, 4-, and 2 : 4-hydroxylated pyrimidines.[13]

[11] Cf. Robins and Christensen, *J. Amer. Chem. Soc.*, 1952, **24**, 3624.
[12] Tschesche and Korte, *Chem. Ber.*, 1951, **84**, 801.
[13] (*a*) Marshall and Walker, *J.*, 1951, 1004; (*b*) Boarland and McOmie, *J.*, 1952, 3716; (*c*) Brown and Short, *J.*, 1953, 331; (*d*) Brown, Hoerger, and Mason, *J.*, 1955, 211.

Treatment of the dichloro-compound (II) with ammonia in boiling phenol [14] yielded the diamino-compound (III; R = R′ = NH_2), whereas treatment with ammonia in cold dioxan gave an amino-chloro-compound; the chlorine in the latter compound was remarkably resistant to hydrolysis, the compound surviving boiling with water for several hours but being completely hydrolysed to the dihydroxy-compound (I) with hot 2N-sodium hydroxide. This amino-chloro-compound was shown to be 4-amino-2-chloro-1 : 3 : 5-triazanaphthalene (V) by conversion into the 4-amino-2-mercapto-compound (VI), also

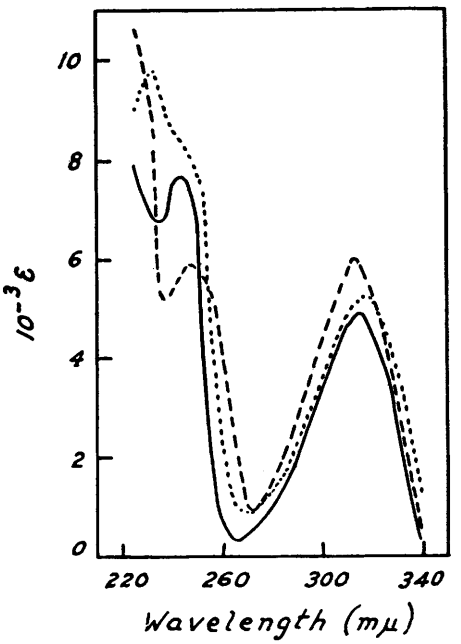


FIG. 1.

Light absorption, in ethanol, of 2 : 4-*dihydroxy*-1 : 3 : 5-*triazanaphthalene* (I) (——), 2 : 4-*dimethoxy*-1 : 3 : 5-*triazanaphthalene* (III; R = R′ = OMe) (– – – –), *and* 1 : 2 : 3 : 4-*tetrahydro*-1 : 3-*dimethyl*-2 : 4-*dioxo*-1 : 3 : 5-*triazanaphthalene* (IV) (. . . .).

obtained by the action of ammonia on the dithiol (III; R = R′ = SH), followed by Raney nickel desulphurisation to the 4-amino-compound (VII), which was finally converted, by acid hydrolysis, into the 4-hydroxy-compound (VIII), identical with material prepared from 3-aminopicolinic acid and formamide.[1] Similar preferential reactivity of the 4-chlorine atom in (II) has also been observed towards diethylamine and 3-diethylaminopropylamine.

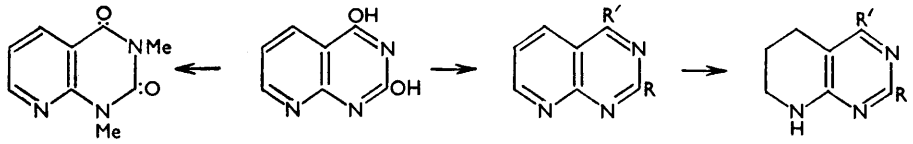
The great reactivity of the 4-, as compared with the 2-, chlorine atom in (II) is in marked contrast to the approximately equal reactivities of the two chlorine atoms in 2 : 4-dichloropyrimidines [15] and recalls the enhanced reactivity of the 4-chlorine in 2 : 4-dichloro-5-nitropyrimidines [16] and in 2 : 4-dichloroquinazoline.[17] Curd, Landquist, and Rose [17] explain this enhanced reactivity on the basis of inductive electron-withdrawal from the 4-position by the neighbouring nitro-group or benzene ring and a similar explanation probably applies also in our case. The presence of the pyridine nitrogen does not seem to be of great importance since a similar enhanced reactivity of the 4-chlorine is also observed in 2 : 4-dichloro-1 : 3 : 8-triazanaphthalene (see below and ref. 6).

Distillation of the dihydroxy-compound (I) with zinc dust afforded a crystalline product, $C_6H_5N_3$, m. p. 152°; this appears to be 1 : 3 : 4-triazaindene.[18]

The starting material for our work in the 1 : 3 : 8-triazanaphthalene series was 2-aminonicotinic acid, which was prepared from quinolinic monoamide by the method of Phillips.[19]

[14] Cf. Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 753.
[15] Gabriel, *Ber.*, 1905, **38**, 1689; Hilbert and Johnson, *J. Amer. Chem. Soc.*, 1930, **52**, 1153.
[16] Gabriel and Colman, *Ber.*, 1901, **34**, 1234; Isay, *Ber.*, 1906, **39**, 252.
[17] Cf. Curd, Landquist, and Rose, *J.*, 1947, 775.
[18] Petrow and Saper, *J.*, 1948, 1389.
[19] Phillips, *Annalen*, 1895, **288**, 253.

Periodate oxidation [20] of 2-aminonicotinic hydrazide or, better, of its *iso*propylidene derivative (acetone 2-aminonicotinoylhydrazone), yielded 2-aminonicotinaldehyde which, however, gave no isolable 1 : 3 : 8-triazanaphthalene with formamide.



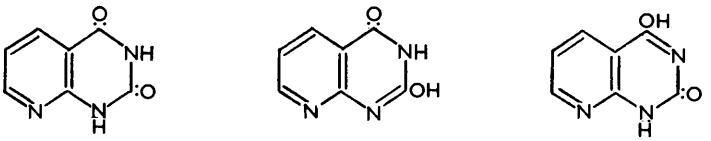
(XV) (XII) (XIII) (XIV)

2 : 4-Dihydroxy-1 : 3 : 8-triazanaphthalene (XII) was conveniently prepared by fusing 2-aminonicotinic acid with urea.[6] As in the 1 : 3 : 5-series, we experienced some difficulty in establishing a satisfactory preparation of the dichloro-compound (XIII; R = R′ = Cl), the procedure of McLean and Spring [4] being often unsuccessful in our hands. A simple procedure, which we have found to give reproducible yields, is described in the Experimental section; the addition of a tertiary base in the reaction between the dihydroxy-compound (XII) and phosphorus oxychloride appears to be without advantage.

On catalytic hydrogenation over Adams catalyst, with or without added magnesium oxide, the dichloro-compound (XIII; R = R′ = Cl) underwent, not hydrogenolysis, but hydrogenation, yielding a tetrahydro-derivative. This is formulated as the 5 : 6 : 7 : 8-tetrahydro-compound (XIV; R = R′ = Cl), rather than the 1 : 2 : 3 : 4-tetrahydro-compound, mainly on the basis of the relative unreactivity of the chlorine atoms; the compound is unaffected by boiling for 10 minutes with N-sodium hydroxide and yields the corresponding dimethoxy-compound (XIV; R = R′ = OMe) on prolonged heating with methanolic sodium methoxide. This view of the structure of the hydrogenation product is supported by consideration of the light-absorption data (solutions in ethanol) collected in the annexed Table, which indicate that the hydrogenation product is a chlorinated 4-aminopyrimidine, rather than a chlorinated 2-aminopyridine which would be expected to absorb at longer wavelengths.

Compound	$\lambda_{max.}$ (mμ)	$\log_{10} \varepsilon$
2 : 4-Dichloro-1 : 3 : 8-triazanaphthalene (XIII; R = R′ = Cl)	252, 307	3·95, 4·03
Hydrogenation product (XIV; R = R′ = Cl)	252, 290	4·17, 3·89
2-Aminopyridine [21]	290	3·58
4-Aminopyrimidine [13b]	236, 272	4·30, 3·71
4-Amino-2 : 6-dichloropyrimidine [22]	248, 284	4·30, 3·71

McLean and Spring [4] showed that methylation of the dihydroxy-compound (XII) with dimethyl sulphate afforded the *N*-methyl derivative (XV), whereas the action of sodium methoxide on the dichloro-compound (XIII; R = R′ = Cl) yielded the isomeric *O*-methyl compound (XIII; R = R′ = OMe). Light-absorption curves for ethanolic solutions of



(XVI) (XVII) (XVIII)

these two compounds and the dihydroxy-compound (XII) are shown in Fig. 2. As in the 1 : 3 : 5-series the comparison supports the dihydroxy-structure (XII) rather than the diketo-structure (XVI), although it does not completely exclude the mono-keto-structures (XVII) and (XVIII).

[20] Cf. Wingfield, Harlan, and Hanmer, *J. Amer. Chem. Soc.*, 1952, **74**, 5796.
[21] Spiers and Wibaut, *Rec. Trav. chim.*, 1937, **56**, 573.
[22] Calc. from the data for 4-aminopyrimidine by the method of Boarland and McOmie, ref. 13*b*.

The dichloro-compound (XIII; R = R′ = Cl) is less susceptible to hydrolysis than its isomeride in the 1 : 3 : 5-triazanaphthalene series but nevertheless undergoes replacement reactions readily. Reactions with sodium ethyl sulphide afforded the 2 : 4-diethylthio-compound (XIII; R = R′ = SEt); an attempt to obtain 1 : 3 : 8-triazanaphthalene by Raney nickel desulphurisation of this compound was unsuccessful. Reaction of the dichloro-compound (XIII; R = R′ = Cl) with ammonia [6] afforded the 2 : 4-diamino-

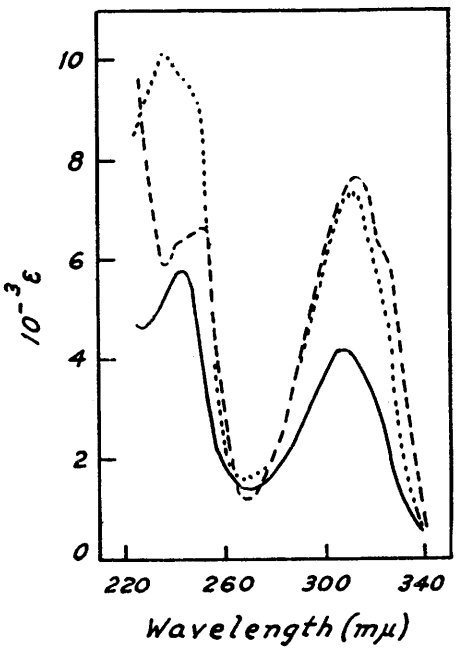


FIG. 2.
Light absorption, in ethanol, of 2 : 4-dihydroxy-1 : 3 : 8-triazanaphthalene (XII) (——), *2 : 4-dimethoxy-1 : 3 : 8-triazanaphthalene* (XIII; R = R′ = OMe) (– – – –), and *1 : 2 : 3 : 4-tetrahydro-1 : 3-dimethyl-2 : 4-dioxo-1 : 3 : 8-triazanaphthalene* (XV) (. . . .).

compound (XIII; R = R′ = NH_2) or the 4-amino-2-chloro-compound (XIII; R = Cl; R′ = NH_2) according to the severity of the reaction conditions. Alkaline hydrolysis converts all these compounds into the parent dihydroxy-compound (XII).

Like Robins and Hitchings,[6] we, too, prepared 4-hydroxy-1 : 3 : 8-triazanaphthalene (XIII; R = H, R′ = OH) both by heating 2-aminonicotinic acid with formamide (cf. Klisiecki and Sucharda [3]) and by Raney nickel desulphurisation of the 4-hydroxy-2-mercapto-compound (XIII; R = SH; R′ = OH), obtained from 2-aminonicotinic acid and thiourea.

As in the pteridines,[23] so also in the 1 : 3 : 5- and 1 : 3 : 8-triazanaphthalenes, the presence of groups capable of hydrogen bonding markedly raises the melting point and lowers the solubility. This is well brought out in the annexed Table of melting points.

Substituents 2-	Substituents 4-	1 : 3 : 5-Triazanaphthalene	1 : 3 : 8-Triazanaphthalene *	Substituents 2-	Substituents 4-	1 : 3 : 5-Triazanaphthalene	1 : 3 : 8-Triazanaphthalene *
OH	OH	>380°	361° (365°)	Cl	NH_2	265°	>360° (>310°)
SH	OH	>360	360 (355—356)	H	NH_2	224	(299—301)
H	OH	345	256 (258)	Cl	Cl	173	160 (158—159)
SH	SH	340	(>360)	OMe	OMe	138	144
NH_2	NH_2	318	342 (356)	SEt	SEt	56	76
$NH{\cdot}NH_2$	$NH{\cdot}NH_2$	266	(348—350)				

* Melting points in parentheses are those recorded by Robins and Hitchings.[6]

A curious feature is the apparent tendency for 1 : 3 : 5-triazanaphthalenes with a hydroxyl-group in the 4-position to melt considerably higher than, and those with an

[23] Albert, Brown, and Cheeseman, *J.*, 1951, 474; 1952, 4219.

amino-group in this position considerably lower than, the corresponding 1 : 3 : 8-triazanaphthalenes; this may, perhaps, be connected with a tendency for 4-hydroxyl, but not 4-amino-, groups to form hydrogen bonds with a ring-nitrogen atom at position 5.

In view of the useful antituberculosis activity of *iso*nicotinic hydrazide [24] the action *in vitro* of 2-aminonicotinic, 3-aminopicolinic, and 3-amino*iso*nicotinic hydrazides on *Mycobacterium tuberculosis* was investigated by Dr. M. W. Fisher, to whom our thanks are due, in the laboratories of Messrs. Parke, Davis, and Company in Detroit; all three compounds showed activity, the most active of them being 3-amino*iso*nicotinic hydrazide which was, however, only about half as active as *iso*nicotinic hydrazide itself.

Experimental

1 : 3 : 5-*Triazanaphthalene derivatives.*

3-*Aminopicolinic Acid and its Derivatives.*—Aqueous sodium hypobromite (from bromine, 56 g., and ice-cold 15% sodium hydroxide solution, 350 ml.) was added to a solution of quinolinimide [7] (50 g.) in ice-cold 10% sodium hydroxide solution (1 l.). The mixture was kept at room temperature for an hour and then at 85° for a further hour; after cooling, the pH was brought to 5 with 50% sulphuric acid and the mixture kept at 2° for 48 hr. A small amount of 2-aminonicotinic acid was removed by filtration and the filtrate treated with copper acetate (20 g.) in hot water (400 ml.) containing acetic acid (10 ml.). The precipitated copper salt was collected by filtration, washed with water, and resuspended in water (400 ml.), and the suspension saturated with hydrogen sulphide; copper sulphide was removed by filtration and the filtrate concentrated. 3-Aminopicolinic acid (26 g.; 56%), m. p. 210°, separated on cooling; a further crop (13 g.; 28%) of less pure material could be obtained from the mother-liquor by evaporation to dryness.

The acid (4 g.) was heated under reflux on the steam-bath with ethanol (8 g.) and sulphuric acid (8 g.) for 4 hr. The cooled product was poured on ice, basified with aqueous ammonia and extracted with ether. Evaporation of the dried extract afforded ethyl 3-aminopicolinate (2 g.; 42%), which crystallised from benzene–light petroleum in needles, m. p. 132° (lit.,[25] m. p. 131—133°) (Found : N, 16·6. Calc. for $C_8H_{10}O_2N_2$: N, 16·9%). This ester (1·6 g.) was heated on the steam-bath for an hour with hydrazine hydrate (1 g.); crystallisation of the product from ethanol afforded 3-*aminopicolinic hydrazide* (0·9 g., 61%) in needles, m. p. 103° (Found : C, 46·7; H, 5·0. $C_6H_8ON_4$ requires C, 47·4; H, 5·3%), which, on refluxing with acetone, followed by concentration, yielded *acetone* 3-*aminopicolinoylhydrazone* (71%) in plates, m. p. 172° (Found : N, 29·0. $C_9H_{12}ON_4$ requires N, 29·2%).

The hydrazide (700 mg.), suspended in water (10 ml.) and ammonia solution (*d* 0·880; 2 ml.), was slowly added to an ice-cold solution of sodium metaperiodate (1·1 g.) in water (15 ml.) and aqueous ammonia (10 ml.). After 35 minutes' shaking, barium acetate (1·2 g.), in water (5 ml.), was added and the precipitated barium salts were removed by filtration. The filtrate was brought to pH 7, saturated with sodium chloride, and extracted with chloroform. Evaporation of the extract and recrystallisation of the residue from benzene afforded 3-aminopicolinamide (350 mg., 55%) in plates, m. p. 184° (lit.,[26] m. p. 175—177°) (Found : C, 53·0; H, 5·2. Calc. for $C_6H_7ON_3$: C, 52·6; H, 5·1%); the m. p. was not depressed on admixture with a specimen of the amide prepared by passing ammonia into a mixture of ethyl 3-aminopicolinate and ammonia solution, and the identity was further confirmed by mixed m. p. of the derived picrate, needles, m. p. 214°.

2 : 4-*Dihydroxy*-1 : 3 : 5-*triazanaphthalene* (I).—A finely powdered intimate mixture of 3-aminopicolinic acid (13 g.) and urea (7 g.) was heated slowly to 190—200° and then kept at this temperature for 30 min. The cooled product was dissolved in 2N-sodium hydroxide (200 ml.); carbon dioxide was passed through the filtered solution and the precipitate (6 g., 39%) collected by filtration and recrystallised from a large volume of water as needles, m. p. above 380° (Found : C, 51·9; H, 3·3; N, 25·9. Calc. for $C_7H_5O_2N_3$: C, 51·5; H, 3·1; N, 25·8%).

The dihydroxy-compound (500 mg.) was distilled with zinc dust (5 g.). The distillate was dissolved in chloroform, and the solution evaporated to dryness after treatment with charcoal. The residue (50 mg., 14%) was recrystallised from benzene–light petroleum (b. p. 60—80°),

[24] Fox and Gibar, *J. Org. Chem.*, 1952, **17**, 1653.
[25] Gorvin, *J.*, 1949, 3304.
[26] Berrie, Newbold, and Spring, *J.*, 1952, 2042.

affording 1 : 3 : 4-triazaindene, needles, m. p. 152° (Found : C, 60·6; H, 4·2; N, 35·3. Calc. for $C_6H_5N_3$: C, 60·5; H, 4·2; N, 35·3%) (Petrow and Saper [18] give m. p. 153°).

2 : 4-*Dichloro*-1 : 3 : 5-*triazanaphthalene* (II).—(*a*) The following procedure has been found the most reliable : A mixture of 2 : 4-dihydroxy-1 : 3 : 5-triazanaphthalene (5 g.), phosphorus oxychloride (75 ml.), and triethylamine (10 ml.) was heated under reflux for 6 hr. The product was evaporated to dryness under reduced pressure and the residue heated at 100° *in vacuo* for 2 hr. The cooled residue was treated with ice-water (200 ml.), and the insoluble portion collected, dried at the pump, and sublimed at 140°/0·1 mm.; the resulting *dichloro-compound* (3·25 g., 53%), recrystallised from light petroleum (b. p. 80—100°), had m. p. 173° (Found : C, 42·4; H, 1·6; Cl, 35·7. $C_7H_3N_3Cl_2$ requires C, 42·0; H, 1·5; Cl, 35·5%).

(*b*) The same compound has been obtained in 46% yield by refluxing the dihydroxy-compound (500 mg.) for 2 hr. with phosphorus oxychloride (20 ml.) and dimethylaniline (20 ml.). The cooled product was poured on ice, the pH brought to 4—5 and the crude dichloro-compound filtered off and sublimed. The yields obtained by this procedure are variable and very low if larger quantities are used. When diethylaniline was used in place of dimethylaniline the only isolated product (100 mg., 11%) was 2-*chloro*-4-N-*ethylanilino*-1 : 3 : 5-*triazanaphthalene* (III; R = Cl, R′ = NEtPh), pale green leaflets, m. p. 168°, from light petroleum (b. p. 80—100°) (Found : C, 64·0; H, 4·7; N, 19·3; Cl, 11·9. $C_{15}H_{13}N_4Cl$ requires C, 63·3; H, 4·6; N, 19·6; Cl, 12·5%).

1 : 3 : 5-*Triazanaphthalene* (III; R = R′ = H).—2 : 4-Dichloro-1 : 3 : 5-triazanaphthalene (3 g.) was suspended in anhydrous ethanol (100 ml.) and shaken with hydrogen in the presence of Adams catalyst (300 mg.). When hydrogen uptake ceased, the mixture was filtered and the filtrate evaporated to dryness under reduced pressure. All attempts to distil, sublime, or crystallise the residue, which rapidly became red, failed. A portion was extracted with benzene, and the benzene extract treated with light petroleum (b. p. 60—80°); evaporation, under reduced pressure, of the filtrate from the brown amorphous precipitate left a yellow semi-crystalline wax, readily soluble in water, alcohol, and benzene, which resisted further attempts at purification. Addition of aqueous picric acid to the aqueous solution precipitated 1 : 3 : 5-*triazanaphthalene picrate*, which crystallised from water in needles, m. p. 191° (Found : C, 37·2; H, 3·2; N, 20·7. $C_{13}H_8O_7N_6,3H_2O$ requires C, 37·7; H, 3·4; N, 20·3%). Attempted preparation of the hydrochloride from the picrate yielded only red-brown amorphous material.

The same unstable base, yielding the same picrate, was obtained when the hydrogenation was carried out in the presence of magnesium oxide and also by refluxing 2 : 4-dimercapto- and 2 : 4-diethylthio-1 : 3 : 5-triazanaphthalene with Raney nickel in aqueous ethanol.

2 : 4-*Dimercapto*-1 : 3 : 5-*triazanaphthalene* (III; R = R′ = SH).—2 : 4-Dichloro-1 : 3 : 5-triazanaphthalene (500 mg.) and thiourea (2 g.) were refluxed together in dry dioxan (75 ml.) for 5 min. The precipitated dithiuronium salt (700 mg.; m. p. 254°) was separated from the hot solution by filtration, washed with alcohol and ether, and dried at 100°. This salt was heated in water (50 ml.) at 100° for an hour; the cooled solution deposited the *dithiol* (150 mg., 31%) as deep yellow needles, m. p. 340° (decomp.) (Found : C, 43·7; H, 3·0; N, 21·7. $C_7H_5N_3S_2$ requires C, 43·1; H, 2·6; N, 21·5%).

2 : 4-*Diethylthio*-1 : 3 : 5-*triazanaphthalene* (III; R = R′ = SEt).—2 : 4-Dichloro-1 : 3 : 5-triazanaphthalene (500 mg.) was added to sodium ethyl sulphide (from sodium, 150 mg., and ethanethiol, 20 ml.), and the mixture heated under reflux for 6 hr. Evaporation to dryness, under reduced pressure, of the filtered product afforded the *dithio-compound* (500 mg., 80%) which, recrystallised from light petroleum (b. p. 40—60°), had m. p. 56° (Found : C, 52·7; H, 5·4; S, 25·3. $C_{11}H_{13}N_3S_2$ requires C, 52·6; H, 5·2; S, 25·5%).

2 : 4-*Dimethoxy*-1 : 3 : 5-*triazanaphthalene* (III; R = R′ = OMe).—2 : 4-Dichloro-1 : 3 : 5-triazanaphthalene (250 mg.) was added to methanolic sodium methoxide (from sodium, 70 mg., and anhydrous methanol, 15 ml.), and the mixture heated under reflux for 5 hr. The product was evaporated to dryness under reduced pressure and the residue extracted with benzene. Evaporation of the extract afforded the *dimethoxy-compound* (150 mg., 63%), which crystallised from light petroleum (b. p. 60—80°) in prisms, m. p. 138° (Found : N, 22·35. $C_5H_5O_2N_3$ requires N, 22·0%).

2 : 4-*Diethoxy*-1 : 3 : 5-*triazanaphthalene* (III; R = R′ = OEt), prepared similarly in 55% yield, crystallised from light petroleum (b. p. 60—80°) in prisms, m. p. 110° (Found : C, 60·45; H, 6·2. $C_{11}H_{13}O_2N_3$ requires C, 60·3; H, 5·9%).

1 : 2 : 3 : 4-*Tetrahydro*-1 : 3-*dimethyl*-2 : 4-*dioxo*-1 : 3 : 5-*triazanaphthalene* (IV).—Dimethyl sulphate (3 g.) was shaken with a solution of 2 : 4-dihydroxy-1 : 3 : 5-triazanaphthalene (250 mg.) in 2N-sodium hydroxide (10 ml.). Next day, the solution was basified with aqueous

ammonia and extracted with chloroform. Evaporation of the extract yielded the N-*methyl* derivative (140 mg., 48%), which crystallised from ethanol in needles, m. p. 246° (Found : C, 56·3; H, 4·5. $C_9H_9O_2N_3$ requires C, 56·6; H, 4·7%).

2 : 4-*Diamino*-1 : 3 : 5-*triazanaphthalene* (III; R = R′ = NH_2).—Ammonia was passed for 3 hr. through a boiling solution of 2 : 4-dichloro-1 : 3 : 5-triazanaphthalene (1 g.) in phenol (20 g.). After cooling to 60°, most of the phenol was decanted off from the deposited product; the residue was treated with 10% sodium hydroxide solution and cooled. The *diamine* (200 mg., 25%) was collected, washed with water, and recrystallised from aqueous ethanol, forming plates, m. p. 318° (Found : C, 52·3; H, 4·35; N, 43·2. $C_7H_7N_5$ requires C, 52·15; H, 4·35; N, 43·5%). When boiled with 2N-sodium hydroxide for 30 min. this compound was converted into the dihydroxy-compound (I).

4-*Amino*-2-*chloro*-1 : 3 : 5-*triazanaphthalene* (V).—Ammonia was passed for 10 min. through a solution of 2 : 4-dichloro-1 : 3 : 5-triazanaphthalene (500 mg.) in dry dioxan (50 ml.). The precipitate was dissolved in N-nitric acid and reprecipitated with aqueous ammonia, affording the *base* (350 mg., 78%) which, crystallised from a large volume of water, had m. p. 265° (Found : N, 30·8. $C_7H_5N_4Cl$ requires N, 31·0%). This compound was recovered unchanged after 16 hours' boiling with water but was completely converted into the dihydroxy-compound (I) when boiled with 2N-sodium hydroxide for 30 min.

4-*Amino*-2-*mercapto*-1 : 3 : 5-*triazanaphthalene* (VI).—(*a*) 4-Amino-2-chloro-1 : 3 : 5-triazanaphthalene (700 mg.) and thiourea (700 mg.) were refluxed together in ethanol (50 ml.) for 4 hr. The yellow *amino-thiol* (650 mg., 94%) was collected from the hot mixture by filtration, washed with ethanol, and dried at 100°; a specimen, purified for analysis by dissolution in dilute sodium hydroxide solution and reprecipitation with acetic acid, had m. p. 344° (Found : C, 46·6; H, 3·5. $C_7H_6N_4S$ requires C, 47·1; H, 3·4%).

(*b*) 2 : 4-Dimercapto-1 : 3 : 5-triazanaphthalene (50 mg.) was heated at 100° for 2 hr. with ammonia solution (*d* 0·880; 20 ml.). The precipitated aminomercaptan (40 mg., 88%) was collected and dried at 100°; it formed greenish-yellow needles, m. p. and mixed m. p. 344°.

4-*Amino*-1 : 3 : 5-*triazanaphthalene* (VII).—4-Amino-2-mercapto-1 : 3 : 5-triazanaphthalene (650 mg.) was refluxed for 3 hr. with Raney nickel (3 g.) in ethanol (200 ml.) containing ammonia solution (*d* 0·880; 40 ml.). Evaporation under reduced pressure of the filtered product afforded the *amine* (500 mg., 94%), which crystallised from water in needles, m. p. 224° (Found : C, 57·5; H, 4·1. $C_7H_6N_4$ requires C, 57·5; H, 4·1%).

4-*Hydroxy*-1 : 3 : 5-*triazanaphthalene* (VIII).—(*a*) 4-Amino-1 : 3 : 5-triazanaphthalene (50 mg.), in 5N-hydrochloric acid (8 ml.), was heated at 100° for 30 min. The solution was then concentrated under reduced pressure to 1 ml. and treated with excess of 2N-sodium carbonate. The precipitated hydroxy-compound had m. p. 342°, not depressed on admixture with a specimen prepared by method (*b*).

(*b*) 3-Aminopicolinic acid (13 g.) and formamide (8 g.) were heated together under reflux for 2½ hr. at 130° and then for a further 2½ hr. at 180°. The hydroxy-compound separated on cooling and was recrystallised from water, forming needles, m. p. 346° (9 g., 65%) (Price and Curtin,[1] who obtained only a 31% yield, record m. p. 346°).

2-*Chloro*-4-*diethylamino*-1 : 3 : 5-*triazanaphthalene* (III; R = Cl, R′ = NEt_2).—2 : 4-Dichloro-1 : 3 : 5-triazanaphthalene (150 mg.) and diethylamine (0·25 ml.) were kept at room temperature in anhydrous dioxan (15 ml.) for 15 min. Evaporation of the filtered solution, followed by crystallisation from light petroleum (b. p. 40—60°), afforded the *base* (160 mg., 90%), m. p. 82° (Found : C, 56·6; H, 5·3; N, 23·5. $C_{11}H_{13}N_4Cl$ requires C, 55·8; H, 5·5; N, 23·7%).

2-*Chloro*-4-3′-*diethylaminopropylamino*-1 : 3 : 5-*triazanaphthalene*.—2 : 4-Dichloro-1 : 3 : 5-triazanaphthalene (600 mg.) and 3-diethylaminopropylamine 390 mg.) were refluxed in anhydrous dioxan for 3 hr. On concentration to 10 ml., followed by cooling, the *base hydrochloride* (400 mg., 40%) crystallised and, recrystallised from dioxan and benzene, had m. p. 128° (Found : N, 21·5. $C_{14}H_{21}N_5Cl_2$ requires N, 21·3%).

Action of Hydrazine Hydrate on 2 : 4-*Dichloro*-1 : 3 : 5-*triazanaphthalene*.—Hydrazine hydrate (1 ml.) was added dropwise to the dichloro-compound (500 mg.) in cold dioxan (20 ml.). After 10 minutes' shaking the cream-coloured precipitate was filtered off, washed with ethanol and and ether, and dried *in vacuo*; 2(or 4)-*hydrazino*-4(or 2)-*hydroxy*-1 : 3 : 5-*triazanaphthalene* (300 mg., 68%) crystallised from ethanol in plates, m. p. 385° (decomp.) (Found : N, 39·9. $C_7H_7ON_5$ requires N, 39·6%). Addition of ethanol to the original dioxan filtrate precipitated a small amount of 2 : 4-*dihydrazino*-1 : 3 : 5-*triazanaphthalene*, plates, m. p. 266°, from ethanol (Found : N, 51·2. $C_7H_9N_7$ requires N, 51·3%).

1 : 3 : 8-*Triazanaphthalene derivatives.*

2-*Aminonicotinic Acid Derivatives.*—The following were prepared from 2-aminonicotinic acid [19] by the procedure described above for their isomerides : ethyl 2-aminonicotinate, leaflets, m. p. 96°, from water (lit.,[27] m. p. 92°) (Found : C, 58·2; H, 6·2. Calc. for $C_8H_{10}O_2N_2$: C, 57·8; H, 6·0%) ; 2-*aminonicotinic hydrazide*, needles, m. p. 176°, from ethyl acetate (Found : N, 36·7. $C_6H_8ON_4$ requires N, 36·8%) ; *acetone* 2-*aminonicotinoylhydrazone*, needles, m. p. 179°, from acetone (Found : C, 55·05; H, 6·4. $C_9H_{12}ON_4$ requires C, 55·1; H, 6·3%).

The hydrazone (700 mg.), suspended in water (10 ml.) and ammonia solution (*d* 0·880; 2 ml.), was added to an ice-cold solution of sodium metaperiodate (1·1 g.) in water (15 ml.) and ammonia solution (10 ml.). After 30 minutes' shaking, barium acetate (1·2 g.), in water (5 ml.), was added and the precipitated barium salts were filtered off; the filtrate was brought to pH 7, saturated with sodium chloride, and extracted with ether. Evaporation of the dried extract and crystallisation of the residue from light petroleum (b. p. 60—80°) afforded 2-aminonicotinaldehyde (250 mg., 56%), leaflets, m p. 98° (Found : C, 59·0; H, 4·9; N, 23·2. Calc. for $C_6H_6ON_2$: C, 59·0; H, 4·9; N, 23·0%) (Goldfarb and Karaulova [28] record m. p. 99° for a specimen obtained by ozonolysis of 2-aminometanicotine). Similar periodate oxidation of 2-aminonicotinic hydrazine gave the same compound in 30% yield.

2 : 4-*Dihydroxy*-1 : 3 : 8-*triazanaphthalene* (XII).—A specimen prepared by a method similar to that of Robins and Hitchings [6] had m. p. 361°, not depressed on admixture with a specimen prepared by the method of McLean and Spring.[4]

2 : 4-*Dichloro*-1 : 3 : 8-*triazanaphthalene* (XIII; R = R′ = Cl).—2 : 4-Dihydroxy-1 : 3 : 8-triazanaphthalene (5 g.) was refluxed with phosphorus oxychloride (125 g.) for 6 hr.; the mixture was evaporated to dryness under reduced pressure and the residue heated *in vacuo* at 115° for 30 min. Water (50 ml.), containing sodium hydrogen carbonate (25 g.), was then added; some dichloro-compound was collected by filtration and a further amount extracted from the filtrate with ethyl acetate. The product (2 g., 33%), purified by sublimation at 150° (bath)/10^{-3} mm., had m. p. 160° (McLean and Spring [4] give m. p. 156—157°, and Robins and Hitchings [6] m. p. 158—158·5°).

This compound (500 mg.), suspended in ethanol (50 ml.), was hydrogenated over Adams catalyst, 2 mols. of hydrogen being taken up in 1 hr. Filtration and evaporation yielded 2 : 4-*dichloro*-5 : 6 : 7 : 8-*tetrahydro*-1 : 3 : 8-*triazanaphthalene* (XIV; R = R′ = Cl) (250 mg., 49%), which, purified by sublimation at 130° (bath)/10^{-3} mm., had m. p. 165° (Found : C, 41·9; H, 3·9; N, 20·6. $C_7H_7N_3Cl_2$ requires C, 41·2; H, 3·4; N, 20·6%) ; the same compound was obtained when the hydrogenation was carried out in the presence of magnesium oxide (500 mg.). The compound was recovered unchanged after 10 minutes' boiling with 10% sodium hydroxide solution but, on refluxing with methanolic sodium methoxide for 5 hr., afforded 5 : 6 : 7 : 8-*tetrahydro*-2 : 4-*dimethoxy*-1 : 3 : 8-*triazanaphthalene* (XIV; R = R′ = OMe), needles, m. p. 166°, from light petroleum (b. p. 60—80°) (Found : N, 21·9. $C_9H_{13}O_2N_3$ requires N, 21·5%).

2 : 4-*Diethylthio*-1 : 3 : 8-*triazanaphthalene* (XIII; R = R′ = SEt).—2 : 4-Dichloro-1 : 3 : 8-triazanaphthalene (300 mg.) was refluxed for 6 hr. with sodium ethyl sulphide (from sodium, 100 mg., and ethanethiol, 15 ml.). Filtration, evaporation, and crystallisation from light petroleum (b. p. 40—60°) afforded the *thio-compound* (quantitative yield), m. p. 76° (Found : C, 52·9; H, 5·3; S, 25·4. $C_{11}H_{13}N_3S_2$ requires C, 52·6; H, 5·2; S, 25·5%).

2 : 4-*Diamino*-1 : 3 : 8-*triazanaphthalene* (XIII; R = R′ = NH_2), prepared in 72% yield as described for the 1 : 3 : 5-compound (p. 1052), crystallised from aqueous ethanol in needles, m. p. 342° (Found : N, 43·1. Calc. for $C_7H_7N_5$: N, 43·5%) (Robins and Hitchings [6] record m. p. 356°).

4-*Amino*-2-*chloro*-1 : 3 : 8-*triazanaphthalene* (XIII; R = Cl; R′ = NH_2), also prepared in the same manner as its 1 : 3 : 5-analogue, had m. p. above 360° (Found : N, 31·35. $C_7H_5N_4Cl$ requires N, 31·0%).

4-*Hydroxy*-2-*mercapto*-1 : 3 : 8-*triazanaphthalene* (XIII; R = SH, R′ = OH).—This compound was prepared by a procedure similar to method (A) of Robins and Hitchings [6] and purified by sublimation at 180° (bath)/10^{-4} mm.; the product (250 mg., 10%) had m. p. 360° (Found : N, 23·9. Calc. for $C_7H_5ON_3S$: N, 23·5%) (Robins and Hitchings [6] give m. p. 355—356°).

4-*Hydroxy*-1 : 3 : 8-*triazanaphthalene* (XIII; R = H, R′ = OH).—(*a*) A specimen prepared by a procedure similar to that of Robins and Hitchings [6] and recrystallised from aqueous methanol,

[27] Dornow and Karlson, *Ber.*, 1940, **73**, 542.
[28] Goldfarb and Karaulova, *J. Gen. Chem.* (*U.S.S.R.*), 1948, **18**, 117.

had m. p. 255—256° (Found : C, 56·9; H, 3·6; N, 28·7. Calc. for $C_7H_5ON_3$: C, 57·2; H, 3·4; N, 28·6%) (Robins and Hitchings [6] give m. p. 255—257°).

(*b*) Raney nickel (5 g.) was added to a solution of 4-hydroxy-2-mercapto-1 : 3 : 8-triazanaphthalene (200 mg.) in 2N-sodium hydroxide (50 ml.). After 16 hr., with occasional shaking, the mixture was filtered and the filtrate saturated with carbon dioxide; the precipitated phenol (50 mg., 30%) had m. p. 255°, not depressed with a specimen prepared by method (*a*).

3-*Amino*iso*nicotinic hydrazide*, prepared in 89% yield from 3-amino*iso*nicotinic acid [29] as described for its isomerides, crystallised from ethanol in feathery needles, m. p. 187° (Found : N, 36·9. $C_6H_8ON_4$ requires N, 36·8%).

Our thanks are offered to Messrs. V. V. Manohin and F. H. Oliver for the microanalyses and to Dr. A. R. Thompson for the light-absorption measurements. We are also indebted to The Anchor Chemical Company (V.O.) and to the Ministry of Education and the Cumberland Education Committee (R. P.) for maintenance allowances.

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[*Received, September* 19*th*, 1955.]

[29] Gabriel and Colman, *Ber.*, 1902, **35**, 2832.