229. *The Synthesis of Compounds with Potential Antifolic Acid Activity. Part VII.*[1] *Styryl-pteridines and -purines.*

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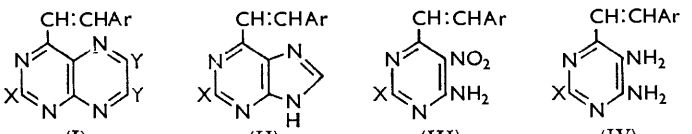
4-Dialkylaminostyryl derivatives of aminopurines and aminopteridines have been synthesised, and the ethylene groups have been hydrogenated.

In continuation of our search for compounds with antifolic acid activity for the treatment of experimental malignancies, we have prepared and examined various pteridine derivatives. Many were active, most markedly derivatives of 2,4-diaminopteridine; but since, in general, compounds with antifolic activity are poor tumour-inhibitors, special modifications were introduced. Because of the growth-inhibiting activity of *p*-dialkylamino-stilbenes and -quinolines,[2] we prepared the pteridine (I) and purine analogues (II).



Ar = *p*-$R_2N{\cdot}C_6H_4$ here and below.

Another reason for adding the dimethylaminostyryl group was the conversion *in vivo* of dimethylaniline into *o*-aminophenol[3] and the inhibition of adenosine triphosphate phosphorylase by the latter. This enzyme controls the function of adenosine triphosphate which, like folic acid, is essential for biosynthesis of nucleic acid. Our styryl compounds would, we hoped, be metabolised to derivatives of *o*-aminophenol and thus cause additional interference with this biosynthesis.

To date only two styrylpteridines have been reported;[4] benzaldehyde was condensed with 4-methyl-5-nitrouracil in piperidine and the product converted into its 2,6-dichloro-derivative which on amination, reduction, and ring closure gave the pteridines. However, replacement of the 2-chloro-atom requires working under pressure and this causes fission of the ethylenic bond.[4]

As most of the derivatives we required had a 2-amino- or substituted 2-amino-group a less vigorous method was needed. This basic group was introduced into the 4-methyl-5-nitropyrimidine, and the resulting 2,6-diamino-4-methyl-5-nitropyrimidines condensed with the aldehydes in ethanol containing a small amount of hydrochloric acid (piperidine was ineffective as catalyst).

In view of the physiological importance of the amino-group in the styryl moiety, the amino- and dialkylaminostyryl-nitropyrimidines (III) were prepared.

Previous preparations of 4-aminostyryl derivatives[4,5] have utilised the stable and readily available *p*-nitrobenzaldehyde but this is unsatisfactory as the zinc chloride fusion required to effect condensation gives rise to products contaminated with inorganic matter. The use of *p*-aminobenzaldehyde has perhaps been discouraged by claims of its readiness to polymerise. We find this aldehyde[6] to be stable for some weeks in the dark. It readily condensed in ethanolic hydrochloric acid.

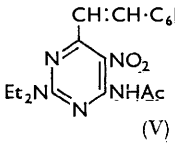
A "nitrogen mustard" aldehyde [*p*-di-(2-chloroethyl)aminobenzaldehyde][7] has also

[1] Part VI, Osdene and Timmis, *J.*, 1955, 2214.
[2] Haddow, Harris, Kon, and Roe, *Phil. Trans. Roy. Soc.*, 1948, *A*, **241**, 147; Hughes, Bates, Bahner, and Lewis, *Proc. Soc. Exp. Biol. Med.*, 1955, **88**, 230; Bahner, *Proc. Amer. Assoc. Cancer Res.*, 1957, **2**, No. 3.
[3] Horn, *Z. physiol. Chem.*, 1936, **238**, 84; **242**, 23.
[4] Ross, *J.*, 1948, 1128.
[5] Brown and Kon, *J.*, 1948, 2147.
[6] Beard and Hodgson, *J.*, 1944, 4.
[7] Anker and Cook, *J.*, 1944, 489.

been condensed with a methylnitropyrimidine, but the product (III; R = $CH_2 \cdot CH_2Cl$, X = Et_2N) was not converted into a pteridine.

The nitrostyrylpyrimidines (III) were reduced by stannous chloride or hydrogen over Raney nickel to the triamines (IV) which were usually difficult to crystallise. In one case, 2,4,5-triamino-6-methylpyrimidine was isolated as a hydrolytic product.

Ring-closures with α-diketones to the pteridines (I) were carried out in ethanol from which the products were precipitated. The products (IV; X = NH_2 or NEt_2, R = H) with glyoxal gave maroon solids which could not be crystallised, were insoluble in most solvents, and gave unsatisfactory analyses, and it seemed that the *p*-aminostyryl group was also involved in the reaction. To obviate this *p*-acetamidobenzaldehyde was treated with the methylpyrimidine but reaction was slow and produced only the deacetylated styrylpyrimidine. It seemed that deacetylation of the benzaldehyde was necessary before condensation could take place. Acetylation of the styrylpyrimidine (III; R = H, X = NEt_2) produced the derivative (V) which on catalytic reduction gave the 8-methylpurine (VI). The ready solubility of this purine in dilute alkali precluded the possibility that acetylation had produced a *NN*-diacetylamino-pyrimidine as this on ring closure would have given rise to an insoluble 9-acetylpurine.



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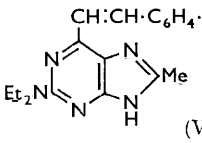


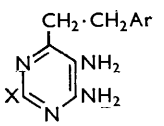
(VI)

The styrylpteridines were unstable in acid solution, this being expected since electron-attracting substituents reduce the stability of simple pteridines.[8] They were also relatively insoluble in water, the effect increasing with the number of primary amino-groups; associated with this was readiness to form hydrates, a notable characteristic of 2-amino-pteridines, although the anhydrous bases were generally obtained by drying.

Variations were made on the groups at the 2-, 6-, and 7-positions in an exploration of their effect on solubility and stability towards acid. The 2-position was substituted by diethylamino-, benzylamino-, cyclohexylamino-, and furfurylamino-, and the 6- and the 7-position were substituted by isopropyl, phenyl, and phenanthryl groups. Solubility was decreased by the 6- and 7-substituents but stability was not appreciably increased by the electron-releasing isopropyl group.

No identifiable product was obtained on attempted preparation of the purine (II; R = Et, X = NEt_2, Y = H). The product was gummy as were the pyrimidine intermediates, the combined diethylamino-groups giving a low-melting and very soluble pteridine.

Attempts to condense aldehydes with 4-methyl-, 2-amino-4-methyl-, and 2-acetamido-4-methyl-pteridine led to destruction of the pteridine nucleus. In attempts to cause 4-methyl-5-nitropyrimidines to react with dimethylaminocinnamaldehyde under various conditions, only starting materials were recovered.



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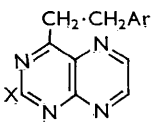
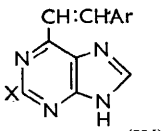


(VIII)



(IX)

A further modification made was reduction of the ethylenic bond. Direct hydrogenation of styrylpteridines was unsatisfactory. However hydrogenation of nitrostyryl-pyrimidines (III) with palladium–charcoal in ethanol gave compounds (VII) which were readily converted into aminophenethylpteridines (VIII) by the usual means.

[8] Albert, *Quart. Rev.*, 1952, **6**, 216.

The synthesis of some 6-styrylpurines is included in this paper because they were readily obtained from the intermediates prepared for the pteridines. They may also have antifolic acid action and, in any case, they may affect adenosine triphosphate in the way postulated for the styrylpteridines.

The appropriate 4,5-diaminopyrimidines (IV) or (VII) (or their hydrochlorides) were heated in formamide containing hydrochloric acid at 170—180° and the products were isolated by the addition of water or dilute ammonia solution. Compound (IX; R = Me, X = NH_2) was isolated as a hydrated monoformyl derivative.

Purines in which the ethylenic bond has been reduced show the same hypsochromic colour shift as known for the pteridines.

Of the styrylpteridines examined, the compound (I; X = NH_2, Y = H, R = Me) has fairly marked activity as a folic acid antagonist.[9]

Experimental

Products were dried at 110° for analysis unless otherwise stated. M. p.s were determined on a Kofler block.

4-Amino-2-benzylamino-6-methyl-5-nitropyrimidine.—To a stirred solution of 4-amino-2-chloro-6-methyl-5-nitropyrimidine (1·9 g.) in chloroform (80 ml.) was added dropwise benzylamine (2·5 ml.) in chloroform (30 ml.) in 20 min. After refrigeration the benzylamine hydrochloride was filtered off and the chloroform solution washed three times with water and dried (Na_2SO_4). Evaporation left a yellow oil which quickly crystallised. *4-Amino-2-benzylamino-6-methyl-5-nitropyrimidine* recrystallised from methanol as cream needles (2·1 g., 81%), m. p. 142—143° (Found: C, 55·5; H, 5·2; N, 26·8. $C_{12}H_{13}O_2N_5$ requires C, 55·6; H, 5·1; N, 27·0%).

4-Amino-2-cyclohexylamino-6-methyl-5-nitropyrimidine.—The chloropyrimidine (2·85 g.) and cyclohexylamine (3·8 ml.) were treated as above. *4-Amino-2-cyclohexylamino-6-methyl-5-nitropyrimidine* (3·3 g., 88%) crystallised from aqueous methanol as lemon-yellow prisms, m. p. 141—142° (Found: C, 52·8; H, 6·8; N, 28·0. $C_{11}H_{17}O_2N_5$ requires C, 52·6; H, 6·8; N, 27·9%).

4-Amino-2-furfurylamino-6-methyl-5-nitropyrimidine was similarly obtained (yield 56%) as buff crystals, m. p. 132—133° (from methanol) (Found: C, 48·3; H, 4·4; N, 28·1. $C_{10}H_{11}O_3N_5$ requires C, 48·2; H, 4·5; N, 28·1%).

2-Acetamido-4-methylpteridine.—2-Amino-4-methylpteridine [10] (0·9 g.) was heated on a water-bath for 30 min. with acetic anhydride. When the solution was evaporated to half-volume and cooled *2-acetamido-4-methylpteridine* (0·85 g., 75%) was obtained; it gave fawn needles, m. p. 181—183°, from ethanol (Found: C, 53·7; H, 4·1; N, 34·3. $C_9H_9ON_5$ requires C, 53·2; H, 4·5; N, 34·5%).

4-Amino-5-nitro-6-styrylpyrimidines (Table 1).—The preparation of *2,4-diamino-5-nitro-6-4′-dimethylaminostyrylpyrimidine* (III; R = Me, X = NH_2) is given as an example.

TABLE 1. *Compounds* (III).

				Yield	Found (%)				Required (%)		
X	R	M. p.	Solvent	(%)	C	H	N	Formula	C	H	N
NH_2	H	279°	Aq. Me_2N·CHO	60	53·0	4·7	30·5	$C_{12}H_{12}O_2N_6$	52·9	4·4	30·9
NH_2	Me	279	Aq. Cellosolve	51	56·0	5·1	27·5	$C_{14}H_{16}O_2N_6$	56·0	5·4	28·0
NH_2	Et	221	Aq. dioxan	40	58·5	6·3	25·5	$C_{16}H_{20}O_2N_6$	58·5	6·1	25·6
NEt_2	H	204	Aq. Me_2N·CHO	52	58·1	5·8	25·4	$C_{16}H_{20}O_2N_6$	58·5	6·1	25·6
NEt_2	Me	159	EtOH	49	60·9	6·9	23·4	$C_{18}H_{24}O_2N_6$	60·7	6·8	23·6
NEt_2	CH_2·CH_2Cl	186	EtOAc	73	53·6	5·9	18·4	$C_{20}H_{26}O_2N_6Cl_2$	53·4	5·8	18·5
NH·C_7H_7	Me	210	Aq. Cellosolve	61	64·2	5·6	21·4	$C_{21}H_{22}O_2N_6$	64·6	5·7	21·5
NH·C_6H_{11}	Me	170	Aq. acetone	34	63·0	6·9	21·6	$C_{20}H_{26}O_2N_6$	62·8	6·9	22·0
NH·C_5H_5O	Me	181	Aq. acetone	35	60·3	4·9	22·6	$C_{19}H_{20}O_3N_6$	60·0	5·3	22·1

2,4-Diamino-6-methyl-5-nitropyrimidine (1·5 g.) in ethanol (100 ml.) containing hydrochloric acid (*d* 1·16; 1 ml.) and water (8 ml.) were heated with *p*-dimethylaminobenzaldehyde (1·65 g.) for 3 hr. The solution was concentrated to half-volume, then cooled, and the purple-black crystals of the hydrochloride were filtered off. Trituration under ammonia solution (*d* 0·88) gave *2,4-diamino-6-4′-dimethylaminostyryl-5-nitropyrimidine* which crystallised from aqueous

[9] Collier, personal communication, 1958.
[10] Lister, Ramage, and Coates, *J.*, 1954, 4109.

Cellosolve as scarlet prisms (1·35 g., 51%), m. p. 278—279° (Found: C, 56·0; H, 5·1; N, 27·5. $C_{14}H_{16}O_2N_6$ requires C, 56·0; H, 5·4; N, 28·0%).

Reduction of 4-Amino-5-nitro-6-styrylpyrimidines.—(A) *Stannous chloride.* 4,5-Diamino-2-diethylamino-6-4′-dimethylaminostyrylpyrimidine (IV; R = Me, X = Et_2N). 4-Amino-2-diethylamino-6-4′-dimethylaminostyryl-5-nitropyrimidine (3 g.) was added slowly to hydrochloric acid (*d* 1·2; 30 ml.) and treated portionwise with stannous chloride (12 g.). After 10 minutes on the water-bath the solution was cooled and the solid filtered off and taken up with water (130 ml.). Hydrogen sulphide was passed in, the sulphides were filtered off (Filtercel), and the cake was washed with hot water. The combined washings and filtrate were evaporated to dryness, the residue was taken up in warm water (60 ml.), and the solution basified with ammonia. After cooling, the crystalline precipitate was filtered off and recrystallised from the minimum of methanol. *4,5-Diamino-2-diethylamino-6-4′-dimethylaminostyrylpyrimidine hydrochloride* (2·4 g., 75%) was obtained as lemon-yellow prisms, m. p. 217—220° (Found: N, 22·5; Cl, 9·5. $C_{18}H_{26}N_6,HCl,\frac{1}{2}H_2O$ requires N, 22·6; Cl, 9·5%). Catalytic reduction (method B) of the nitropyrimidine gave the free base, m. p. 184—186°, as yellow prisms from aqueous methanol (Found: C, 66·1; H, 7·6; N, 25·6. $C_{18}H_{26}N_6$ requires C, 66·3; H, 8·0; N, 25·8%).

(B) *Raney nickel.* 2,4,5-Triamino-6-4′-dimethylaminostyrylpyrimidine (IV; R = Me, X = NH_2). A solution of 2,4-diamino-6-4′-dimethylaminostyryl-5-nitropyrimidine (3 g.) in ethanol was hydrogenated over Raney nickel. The filtered solution was evaporated under reduced pressure and the residue crystallised from ethanol. *2,4,5-Triamino-6-4′-dimethylaminostyrylpyrimidine* (1·45 g., 54%) crystallised in yellow-brown prisms, m. p. 222—226° (Found: C, 62·1; H, 6·4; N, 31·0. $C_{14}H_{18}N_6$ requires C, 62·2; H, 6·7; N, 31·1%).

Similarly were obtained *2,4,5-triamino-6-4′-diethylamino-* (from aqueous ethanol), m. p. 190—192° (Found: C, 64·3; H, 7·4; N, 28·0. $C_{16}H_{22}N_6$ requires C, 64·5; H, 7·4; N, 28·2%), *4,5-diamino-2-benzylamino-* (48%), yellow needles, m. p. 192—195° (from aqueous methanol) (Found, for material dried at 140°: C, 70·0; H, 6·8. $C_{21}H_{24}N_6$ requires C, 70·0; H, 6·7%), and *4,5-diamino-2-cyclohexylamino-6-4′-dimethylaminostyrylpyrimidine*, lemon-yellow, m. p. 169—171° (from ethyl acetate) (Found: C, 68·1; H, 7·7; N, 23·9. $C_{20}H_{28}N_6$ requires C, 68·1; H, 8·0; N, 23·9%).

(C) *Palladium–charcoal.* 2,4,5-Triamino-6-4′-dimethylaminophenethylpyrimidine (VII; R = Me, X = NH_2). An ethanolic solution of 2,4-diamino-6-4′-dimethylaminostyryl-5-nitropyrimidine (1·8 g.) was reduced catalytically over 5% palladium–charcoal (0·2 g.). Absorption ceased after 4 hr. and the solution was filtered and evaporated. The residual brown oil was taken up in methanol, water cautiously added, and the solution cooled. *2,4,5-Triamino-6-4′-dimethylaminophenethylpyrimidine* was deposited as buff prisms (1·2 g., 71%), m. p. 154—155° (Found: C, 60·6; H, 7·4; N, 30·0. $C_{14}H_{20}N_6,\frac{1}{4}H_2O$ requires C, 60·7; H, 7·5; N, 30·4%). Drying at 130° gave the anhydrous *base* (Found: C, 61·4; H, 6·9; N, 31·4. $C_{14}H_{20}N_6$ requires C, 61·7; H, 7·4; N, 30·9%).

Styrylpteridines (Table 2).—The following is an example. 2,4,5-Triamino-6-4′-dimethylaminostyrylpyrimidine (7·1 g.) and glyoxal monohydrate (2·1 g.) were heated in ethanol under

TABLE 2. *Compounds* (I).

					Yield	Found				Required		
X	R	Y	Solvent	M. p.	(%)	C	H	N	Formula	C	H	N
NH_2	Me	H	Bu^nOH	253°	68	65·4	5·3	28·0	$C_{16}H_{16}N_6$	65·7	5·5	28·75
NH_2	Et	H	Aq. EtOH	241	47	67·2	6·0	26·1	$C_{18}H_{20}N_6$	67·5	6·3	26·2
NH_2	Me	Pr^i	Dioxan	262	35	69·9	7·4	22·0	$C_{22}H_{28}N_6$	70·2	7·5	22·3
NH_2	Me	C_6H_5	Aq. $Me_2N{\cdot}CHO$	310	42	75·4	5·7	18·9	$C_{28}H_{24}N_6$	75·7	5·4	18·9
NH_2	Me	Y + Y = Phenanthryl	Aq. $Me_2N{\cdot}CHO$	300	86	75·9	4·7	18·8	$C_{28}H_{22}N_6$	76·0	5·0	19·0
NEt_2	Me	H	EtOH	180	69	68·5	6·9	24·3	$C_{20}H_{24}N_6$	68·9	6·9	24·1
$NH{\cdot}C_7H_7$	Me	H	Aq. dioxan	252	71	72·0	5·7	21·7	$C_{23}H_{22}N_6$	72·2	5·8	22·0
$NH{\cdot}C_6H_{11}$	Me	H	EtOH	232	—	70·7	6·9	22·7	$C_{22}H_{26}N_6$	70·5	7·0	22·4
$NH{\cdot}C_5H_5O$	Me	H	Dioxan	248	29	67·9	5·7	22·3	$C_{21}H_{20}ON_6$	67·7	5·4	22·6

reflux for 20 min. After cooling, the deep maroon precipitate was filtered off and recrystallised from butan-1-ol. *2-Amino-4-4′-dimethylaminostyrylpteridine* (5·3 g., 68%) was obtained as maroon plates with a coppery lustre, m. p. 251—253° (Found: C, 65·4; H, 5·3; N, 28·0. $C_{16}H_{16}N_6$ requires C, 65·7; H, 5·5; N, 28·75%).

2-Amino-4-4′-dimethylaminophenethylpteridine (VIII; R = Me, X = NH_2).—The nitrodiamine (III; R = Me, X = NH_2) (0·5 g.) in ethanol was hydrogenated over 5% palladium–charcoal (0·1 g.). The solution was evaporated and the yellow gum heated in fresh ethanol (50 ml.) with glyoxal monohydrate (0·13 g.). The yellow product (0·25 g., 51%) was recrystallised from Cellosolve, giving *2-amino-4-4′-dimethylaminophenethylpteridine* as orange prisms m. p. 243° (Found, for material dried at 130°: C, 65·4; H, 6·2; N, 28·4. $C_{16}H_{18}N_6$ requires C, 65·3; H, 6·2; N, 28·6%).

2-Diethylamino-4-4′-dimethylaminophenethylpteridine (VIII; R = Me, X = Et_2N).—The pyrimidine (III; R = Me, X = Et_2N) (1 g.) was hydrogenated as above. The crude diamine (VII; R = Me, X = Et_2N) was obtained as white needles, m. p. 104°, from chloroform (Found: C, 57·7; H, 8·0; N, 22·8; Cl, 9·1. Calc. for $C_{18}H_{28}N_6,\frac{1}{2}H_2O,\frac{1}{3}CHCl_3$: C, 58·4; H, 7·9; N, 22·3; Cl, 9·4%). As the anhydrous material could not be obtained by drying or recrystallisation the solvate was heated in ethanol with glyoxal monohydrate (0·2 g.) for 30 min. Concentration to half-volume and cooling gave *2-diethylamino-4-4′-dimethylaminophenethylpteridine* as yellow crystals, m. p. 131—132° (Found: C, 68·4; H, 7·4; N, 23·8. $C_{20}H_{26}N_6$ requires C, 68·5; H, 7·5; N, 24·0%).

Styrylpurines and their Derivatives.—*6-4′-Dimethylaminostyryl-2-formamidopurine* (IX; R = Me, X = H·CO·NH). A suspension of the triaminopyrimidine (IV; R = Me, X = NH_2) as the hydrochloride (0·53 g.) was heated in formamide (8 ml.) at 170—180° for 20 min. An equal volume of 2N-ammonia was added, depositing a yellow precipitate which crystallised from the minimum of methanol. *6-4′-Dimethylaminostyryl-2-formamidopurine* formed orange crystals, m. p. 230° (Found, on material dried at 150°: C, 61·3; H, 5·3; N, 26·95. $C_{16}H_{16}ON_6,\frac{1}{4}H_2O$ requires C, 61·4; H, 5·3; N, 26·9%).

Similar preparations gave *2-diethylamino-6-4′-dimethylaminostyryl-*, m. p. 220—222° (from methanol) (Found: C, 67·7; H, 7·3; N, 25·1. $C_{19}H_{24}N_6$ requires C, 67·8; H, 7·2; N, 25·0%), and *2-amino-6-4′-diethylaminostyryl-purine*, m. p. 221—223° (from aqueous ethanol) (Found, on material dried at 135°: C, 66·6; H, 6·4. $C_{17}H_{20}N_6$ requires C, 66·2; H, 6·5%).

4-Acetamido-6-4′-acetamidostyryl-2-diethylamino-5-nitropyrimidine (V).—4-Amino-6-4′-aminostyryl-2-diethylamino-5-nitropyrimidine (0·5 g.) in acetic anhydride (15 ml.) was heated on a water-bath for 15 min. The yellow *4-acetamido-6-4′-acetamidostyryl-2-diethylamino-compound* (0·3 g., 48%) crystallised on cooling and, recrystallised from aqueous ethanol, had m. p. 243—244° (Found: C, 57·9; H, 5·8; N, 20·3; O, 15·9. $C_{20}H_{24}O_4N_6$ requires C, 58·3; H, 5·9; N, 20·4; O, 15·5%).

6-4′-Acetamidostyryl-2-diethylamino-8-methylpurine (VI).—The above diacetamidopyrimidine (0·6 g.) was hydrogenated over Raney nickel in ethanol. Evaporation left a glass which crystallised from methanol as yellow prisms of *6-4′-acetamidostyryl-2-diethylamino-8-methylpurine*, m. p. 157—159° (Found: C, 62·3; H, 6·7; N, 21·8; H_2O, 4·8. $C_{20}H_{24}ON_6,H_2O$ requires C, 62·8; H, 6·9; N, 22·0; H_2O, 4·7%). Drying to 150° gave the anhydrous *base* (Found: C, 65·8; H, 6·9. $C_{20}H_{24}ON_6$ requires C, 65·9; H, 6·6%).

2-Amino-6-4′-dimethylaminophenethylpurine.—The nitropyrimidine (III; R = Me, X = NH_2) (2 g.) in ethanol was reduced over 5% palladium–charcoal (0·2 g.). Solvent was removed and the residue heated in formamide (20 ml.) containing hydrochloric acid (*d* 1·16; 2 ml.) at 170—180° for 20 min. 2N-Ammonia (20 ml.) was added to the cooled solution, precipitating yellow *2-amino-6-4′-dimethylaminophenethylpurine* (0·81 g., 41% which was obtained from water as a yellow hydrate, m. p. 97—99° (Found: C, 60·1; H, 6·4; N, 28·2. $C_{15}H_{18}N_6,H_2O$ requires C, 60·0; N, 6·7; N, 28·0%). Drying at 100° gave the anhydrous *base*, m. p. 186—188° (Found: C, 63·8; H, 6·4. $C_{15}H_{18}N_6$ requires C, 63·9; H, 6·4%).

2-Diethylamino-6-4′-dimethylaminophenethylpurine (69%), m. p. 148—149°, was similarly prepared (Found: C, 67·4; H, 7·7; N, 24·8. $C_{19}H_{26}N_6$ requires C, 67·4; H, 7·8; N, 24·8%).

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