## 21. *Pteridines. Part I. An Unambiguous Synthesis of 7 : 8-Dihydro-6-hydroxypteridines.*

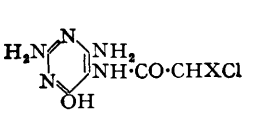
By W. R. Boon, W. G. M. Jones, and G. R. Ramage.

Condensation of 4-chloro-5-nitropyrimidines with an α-amino-acid ester readily yields 5-nitro-4-pyrimidylaminoacetic acid esters. Reduction of these compounds followed by loss of alcohol from the resultant 5-amino-compounds offers an unambiguous route to the synthesis of a large number of 7 : 8-dihydro-6-hydroxypteridines.

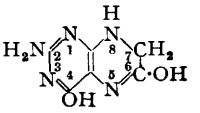
Nearly all the methods available for the synthesis of pteridine derivatives involve the condensation of 4 : 5-diaminopyrimidines with α-diketones, α-keto-acids, α-ketols, or related substances. (For a review of the earlier literature see *Ann. Reports*, 1946, **43**, 250; 1948, **45**, 226.) Unless a symmetrical α-diketone is employed in such syntheses there is always an element of ambiguity about the structure of the resulting products. When 2 : 4 : 5-triamino-6-hydroxypyrimidine is used as the starting material it is frequently possible to check the constitution of the product by degradation to 2-amino-4-hydroxypteridine-6- or -7-carboxylic acid, both of which were prepared and characterised unambiguously by degradation during the determination of the structure of pteroylglutamic acid (Mowat *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 14). In other cases degradation to a pyrazine derivative has been employed (Weijlard, Tishler, and Erickson, *ibid.*, 1945, **67**, 802; Cain, Mallette, and Taylor, *ibid.*, 1948, **70**, 3026). Neither of these methods of orientation is readily extended to other classes of pteridine derivatives since, in many cases, it would prove difficult to obtain the necessary reference compounds by unambiguous synthesis.

There appear to be only two syntheses of pteridine derivatives by cyclisation of pyrimidine derivatives. Purrmann (*Annalen*, 1941, **546**, 98) condensed 2 : 4 : 5-triamino-6-hydroxypyrimidine with dichloroacetic acid and heated the silver salt of the resulting dichloroacetamide (I; X = Cl) with silver carbonate to obtain xanthopterin. In a similar manner Hitchings and Elion (*J. Amer. Chem. Soc.*, 1949, **71**, 467) treated the chloroacetamide (I; X = H) with sodium hydrogen carbonate and obtained a product to which they assign the structure (II) but which is different from the dihydroxanthopterin obtained by the reduction of xanthopterincarboxylic acid (Purrman, *Annalen*, 1941, **548**, 284), leucopterin (Totter, *J. Biol. Chem.*, 1944, **154**, 105), or xanthopterin (O'Dell, Vandenbelt, Bloom, and Pfiffner, *J. Amer. Chem. Soc.*, 1947, **69**, 250), and to which structure (II) has hitherto been assigned.

Timmis (*Nature*, 1949, **164**, 139) has described a method for the unambiguous synthesis of pteridine derivatives by condensation of 4-amino-5-nitrosopyrimidines with ketones, but only a few such pyrimidines can be prepared readily (Lythgoe, Todd, and Topham, *J.*, 1944, 315).



(I.)



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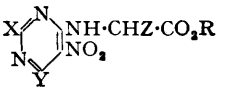


(III.)

This paper describes a method, first disclosed in B.P. 619,915, for the preparation of 7 : 8-dihydro-6-hydroxypteridines of unambiguous structure involving the reduction and subsequent cyclisation of α-(5-nitro-4-pyrimidylamino)-acid esters of type V. Waldmann (*J. pr. Chem.*, 1915, [ii], **91**, 193) has recorded a similar reaction in the preparation of 6-amino-1 : 2-dihydro-3-hydroxyquinoxaline by reduction of *N*-(2 : 4-dinitrophenyl)glycine or its ethyl ester. More recently Polonovski and Jérôme (*Compt. rend.*, 1950, **230**, 392), using essentially the procedure described in the above patent, prepared 2-amino-7 : 8-dihydro-6-hydroxy-4-methylpteridine from ethyl 2-amino-4-methyl-5-nitro-6-pyrimidylaminoacetate. The present paper describes a more extensive investigation of the scope of the method. Part II will record similar syntheses of other pteridine derivatives in which the first step is the condensation of an α-amino-ketone with a 4-chloro-5-nitropyrimidine (cf. B.P. 635,582; also Polonovski, Pesson, and Puister, *Compt. rend.*, 1950, **230**, 2205).

The initial experiments in this series employed as starting material 2 : 4-dichloro-6-methyl-5-nitropyrimidine readily available by the method of Baddiley and Topham (*J.*, 1944, 678). In later experiments 2 : 4-dichloro-5-nitro-, 4 : 6-dichloro-5-nitro-, and 4 : 6-dichloro-2-methyl-5-nitro-pyrimidine were also employed, these substances being obtained in a similar manner from the corresponding dihydroxy-compounds. Condensation of 2 : 4-dichloro-5-nitropyrimidine and the corresponding 4-methyl compound with glycine methyl or ethyl ester in cold methanol gave a mixture, readily separable by crystallisation, of the mono- (III; X = Cl, Y = H or Me, Z = H, R = Me or Et) and the di-esters (III; X = $NH{\cdot}CH_2{\cdot}CO_2R$, Y = H or Me, Z = H, R = Me or Et). If, however, an ethereal solution of the chloronitropyrimidine was shaken with an aqueous solution of glycine ester hydrochloride the monosubstituted product was obtained almost exclusively. With the 4 : 6-dichloropyrimidines even the latter method invariably gave a mixture. In a similar manner ethyl aminomalonate readily condensed with 2 : 4-dichloro-5-nitropyrimidine to give ethyl 2-chloro-5-nitro-4-pyrimidylaminomalonate (III; X = Cl, Y = H, Z = $CO_2Et$, R = Et).

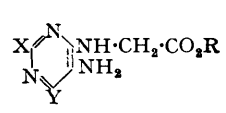
In all cases the second chlorine atom was readily replaced by an amino- or substituted amino-group, by reaction with ammonia or a primary or secondary amine. Its replacement by hydroxyl was best effected by a mild acid hydrolysis: for the 6-chloro-compounds a buffer of pH 5; for the 2-chloro-compounds N-acetic acid in presence of sodium acetate. More vigorous acid hydrolysis appeared to remove the amino-acid residue, and alkaline hydrolysis invariably gave highly coloured products.

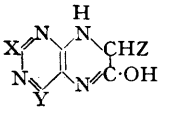
2- or 4-Amino-5-nitropyrimidylaminoacetic esters have also been made by condensation of 2- or 4-amino-6-chloro-5-nitropyrimidines with glycine ester. 2-Amino-4-chloro-6-methyl-5-nitropyrimidine was readily obtained on heating 2-amino-4-hydroxy-6-methyl-5-nitropyrimidine with an excess of phosphorus oxychloride; the required 2-amino-5-nitro-6-methylpyrimidine was obtained by the nitration of 2-amino-4-hydroxy-6-methylpyrimidine, but not purified. 4-Amino-6-chloro-5-nitro- and 4-amino-6-chloro-2-methyl-5-nitro-pyrimidine were obtained by treating the appropriate dichloronitropyrimidine with cold aqueous ammonia. While 2-amino-4-chloro-6-methyl-5-nitropyrimidine condensed readily with glycine methyl ester, no reaction occurred between 2-amino-4-chloro-6-methylpyrimidine and glycine ethyl ester either in the cold, or in boiling ethanol; this is in line with Gabriel and Colman's observation (*Ber.*, 1899, **32**, 2923) that this substance was recovered unchanged after being heated under pressure with alcoholic ammonia; evidently the greater reactivity of the amino-acid ester is insufficient to overcome the lack of reactivity of the chlorine atom (which needs to be activated by a nitro-group).

Reduction of methyl 2-chloro-5-nitro-6-pyrimidylaminoacetate (III; X = Cl, Y = Z = H, R = Me) in methanolic solution by hydrogen in presence of Raney nickel gave methyl 5-amino-2-chloro-6-pyrimidylaminoacetate (IV; X = Cl, Y = H, R = Me), which, when boiled with water preferably in an atmosphere of nitrogen, was converted into 2-chloro-7 : 8-dihydro-6-hydroxy-

H

pteridine (V; X = Cl, Y = Z = H). In the same manner ethyl 4-chloro-5-nitro-6-pyrimidylaminoacetate could also be reduced to the 5-aminopyrimidine which was subsequently cyclised to the corresponding pteridine.

(IV.) 

 (V.)

In all other cases in which X or Y was amino-, substituted amino-, or hydroxyl it was not possible readily to isolate the intermediate 5-aminopyrimidine compound on reduction. Frequently, however, in order to obtain good yields of the 6-hydroxypteridine it was necessary to heat the mixture under reflux in water.

Reduction and cyclisation of ethyl 2-hydroxy-4-methyl-5-nitro-6-pyrimidylaminoacetate gave 7 : 8-dihydro-2 : 6-dihydroxy-4-methylpteridine which however differed in both solubility and ultra-violet absorption from the substance obtained by Russell, Elion, and Hitchings (*J. Amer. Chem. Soc.*, 1949, **71**, 474).

*Ultra-violet light absorption of* 7 : 8-*dihydro*-6-*hydroxypteridines* (V).

| Compound no. * | X. | Y. | 0·1N-NaOH. $\lambda_{max.}$, mμ. | $\lambda_{min.}$, mμ. | ε. | 0·1N-HCl. $\lambda_{max.}$, mμ. | $\lambda_{min.}$, mμ. | ε. |
|---|---|---|---|---|---|---|---|---|
| 23 | H | H | 307 | — | 11,300 | 293 | — | 10,400 |
| | | | | 253 | 1,700 | — | 245 | 1,100 |
| 24 | Cl | H | 310 | — | 12,000 | 295 | — | 10,600 |
| | | | | 254 | 750 | — | 248 | 1,500 |
| 25 | H | Cl | 312 | — | 20,750 | 300 | — | 11,000 |
| | | | | 260 | 2,700 | — | 247 | 1,250 |
| 27 | Me | Cl | 310 | — | 6,400 | 298 | — | 6,700 |
| | | | | 257 | 375 | — | 248 | 700 |
| 28 † | Cl | H | 312 | — | 11,600 | 298 | — | 10,700 |
| | | | | 260 | 1,100 | — | 252 | 1,000 |
| 29 | $NH_2$ | H | 293 | — | 8,800 | No maximum. End absorption (ε 13,500) at 230 mμ. Infln. at 265, 295 mμ.; ε 6,800, 4,900 | | |
| | | | | 253 | 1,300 | | | |
| 30 | H | $NH_2$ | 295 | — | 10,200 | 287 | — | 11,700 |
| | | | | 257 | 3,250 | — | 252 | 1,350 |
| 32 | H | $NEt_2$ | 310 | — | 14,750 | 315 | — | 15,000 |
| | | | | 280 | 4,200 | — | 275 | 3,100 |
| 33 | Me | $NEt_2$ | 310 | — | 6,900 | 315 | — | 8,400 |
| | | | | 275 | 2,700 | — | 272 | 2,000 |
| 34 | $NEt_2$ | Me | 298 | — | 14,800 | 248 | — | 30,700 |
| | | | | 263 | 4,900 | Infl. 292 | — | 6,700 |
| 38 | $Et_2N{\cdot}[CH_2]_2{\cdot}NH$ | Me | 298 | — | 13,700 | 232 | — | 21,700 |
| | | | | 257 | 1,900 | Infl. 285 | — | 1,900 |
| 39 | OH | H | 277 | — | 10,000 | 260 | — | 10,000 |
| | | | | 258 | 4,200 | — | 285 | 3,300 |
| | | | | | | 317 | — | 6,800 |
| 40 | OH | Me | 280 | — | 9,200 | — | 243 | 6,600 |
| | | | | 257 | 4,900 | 265 | — | 9,200 |
| | | | Infl. 310 | — | 5,700 | — | 288 | 3,100 |
| | | | | | | 313 | — | 8,300 |
| 41 | H | OH | 275 | — | 6,300 | — | 245 | 2,100 |
| | | | | 253 | 100 | 272 | — | 3,800 |
| | | | | | | | 295 | 2,000 |
| | | | | | | 315 | — | 2,100 |
| 42 | Me | OH | 275 | — | 7,500 | 272 | — | 2,900 |
| | | | | 250 | 1,900 | — | — | — |

* Cf. Tables I and II. † $CO_2Et$ at position 7.

The influence of the nature of the substituents on the physical properties of the resulting pteridines is of particular interest. Compounds having a hydroxy- or an amino- or no substituent in the pyrimidine ring were, without exception, of very high melting point, insoluble in the usual organic solvents, but soluble to some extent in such high-boiling polar solvents as dimethylformamide and 2-ethoxyethanol. In a few cases the limited solubility in water per-

mitted recrystallisation for analyses but in others reprecipitation, usually by the addition of sodium acetate to a solution in dilute hydrochloric acid, was the only practicable method. In all cases drying at 120—150° over phosphoric oxide *in vacuo* was necessary if reliable analytical results were to be obtained. If the substituent in the pyrimidine portion of the molecule was 2′-diethylaminoethylamino-, the products were still fairly high melting but could be crystallised from polar solvents such as methanol and ethanol. A similar, though rather less marked, effect was brought about by the introduction of a carbethoxy-group in position 7. The presence of a diethylamino-group in the 2- and more particularly in the 4-position markedly lowered the melting point and rendered possible crystallisation from such non-polar solvents as benzene. This, no doubt, is a consequence of the greatly reduced possibilities for intermolecular hydrogen bonding.

Chlorine in the 2- or the 4-position of 7 : 8-dihydro-6-hydroxypteridines is practically inert and the compounds are similar to the unsubstituted compound; the only method so far found for the conversion of 2-chloro-7·: 8-dihydro-6-hydroxypteridine into the parent compound was reduction with hydriodic acid in presence of red phosphorus. The same product, giving an identical *X*-ray powder photograph, was obtained by a similar reduction of 4-chloro-7 : 8-dihydro-6-hydroxypteridine.

The ultra-violet light absorptions of most of the 7 : 8-dihydro-6-hydroxypteridines have been measured in solution in 0·1N-hydrochloric acid and in 0·1N-sodium hydroxide, using a Unicam photoelectric spectrophotometer (see Table).

## Experimental.

4 : 6-*Dihydroxy-5-nitropyrimidine.*—Nitration of 4 : 6-dihydroxypyrimidine (Kenner, Lythgoe, Todd, and Topham, *J.*, 1943, 389) in concentrated sulphuric acid generally gave low and variable yields. The following procedure was readily reproducible on any scale: 4 : 6-Dihydroxypyrimidine (1 mol.) was added, with stirring, at 15—20° to a mixture of 93% nitric acid (3 mols.) and glacial acetic acid (6 mols.). Stirring was continued for a further half hour and the mixture then poured on ice. After filtration, washing with water, and drying, the product (90% yield) was pure enough for further use. The *nitro*-compound crystallised from water in colourless leaflets, m. p. >300° (Found: C, 30·8; H, 2·0; N, 26·3 $C_4H_3O_4N_3$ requires C, 30·6; H, 1·9; N, 26·8%).

4 : 6-*Dichloro-5-nitropyrimidine.*—Dimethylaniline (93 g., 0·77 mol.) was added to a suspension of 4 : 6-dihydroxy-5-nitropyrimidine (78·5 g., 0·5 mol.) in phosphorus oxychloride (505 g., 3·3 mols.) and heated in an oil-bath at 125—130° for 1 hour. After removal of the excess of phosphorus oxychloride under reduced pressure, the reaction mixture was poured on ice (800 g.) and filtered. The filtrate was extracted with ether (3 × 350 c.c.), each extract being also used to extract the filter cake. The combined extracts were washed with water (500 c.c.) and dried ($Na_2SO_4$) and the ether was removed. The residual *dichloro*-compound crystallised from light petroleum (b. p. 80—100°) (yield 82·5 g., 85%) (Found: C, 24·9; H, 0·6; N, 21·8; Cl, 36·4. $C_4HO_2N_3Cl_2$ requires C, 24·7; H, 0·5; N, 21·7; Cl, 36·6%).

2-*Amino*-4-*chloro*-6-*methyl*-5-*nitropyrimidine.*—2-Amino-4-hydroxy-6-methylpyrimidine (30 g.) was added in small portions during 45 minutes and below 10° to 100 c.c. of a mixture of equal volumes of fuming nitric acid and concentrated sulphuric acid. After 15 minutes at room temperature the mixture was poured on ice, and excess of aqueous ammonia added, followed by acetic acid until the whole was acid to litmus. The product (21 g.), filtered off and crystallised from a large volume of water, had m. p. 325—327° (decomp.). Satisfactory analytical results could not be obtained with this substance. When heated under reflux with excess of phosphorus oxychloride and then freed from the excess by distillation and basification with sodium carbonate, it was converted into 2-*amino*-4-*chloro*-6-*methyl*-5-*nitropyrimidine*, which had m. p. 225° after crystallisation from ethanol or, better, sublimation (Found: C, 32·1; H, 3·2; Cl, 19·1. $C_5H_5O_2N_4Cl$ requires C, 31·8; H, 2·7; Cl, 18·8%).

4-*Amino*-6-*chloro*-5-*nitropyrimidine.*—To 4 : 6-dichloro-5-nitropyrimidine (38·8 g., 0·2 mol.) dissolved in ether (300 c.c.) a solution of ammonia (6·9 g., 0·4 mol.) in methanol (30 c.c.) was added, with stirring, during 1 hour. After further hour's stirring the solid was filtered off, washed with ether, and extracted with hot ethyl acetate (2 × 100 c.c.). The solid, 4 : 6-*diamino*-5-*nitropyrimidine*, crystallised from acetic acid, had m. p. >250° (Found: C, 31·1; H, 2·9. $C_4H_5O_2N_5$ requires C, 30·9; H, 3·2%). The united residues obtained by concentration of the ether–methanol filtrate and the ethyl acetate extract were extracted with hot light petroleum (b. p. 60—80°; 2 × 50 c.c.) to remove unchanged 4 : 6-dichloro-5-nitropyrimidine (4·3 g.). The residue, on crystallisation from benzene, gave 4-*amino*-6-*chloro*-5-*nitropyrimidine* (17·3 g., 54%), m. p. 155—156° (Found: C, 27·7; H, 1·5; N, 32·1; Cl, 20·0. $C_4H_3O_2N_4Cl$ requires C, 27·5; H, 1·7; N, 32·1; Cl, 20·3%).

4-*Amino*-6-*chloro*-2-*methyl*-5-*nitropyrimidine*, m. p. 183° (from xylene) (Found: C, 31·8; H, 2·65; N, 29·8; Cl, 18·8. $C_5H_5O_2N_4Cl$ requires C, 31·8; H, 2·7; N, 29·8; Cl, 18·8%), was obtained similarly from 4 : 6-dichloro-2-methyl-5-nitropyrimidine.

2- *and* 4-*Chloro*-5-*nitro*-6-*pyrimidylaminoacetic Esters* (*Method* I).—The two methods which have been used for the preparation of these substances are exemplified by the following details for the preparation of *methyl* 2-*chloro*-5-*nitro*-6-*pyrimidylaminoacetate.*

(*a*) A solution of sodium methoxide [from 4·6 g. (0·2 mol.) of sodium in 120 c.c. of methanol] was added to glycine ester hydrochloride (25·1 g., 0·2 mol.) in methanol (75 c.c.). After removal of the sodium chloride by filtration the solution was added below 0°, with stirring, to 2 : 6-dichloro-5-nitropyrimidine

(19·4 g., 0·1 mol.) in methanol (50 c.c.). 15 Minutes after the addition was complete the product was filtered off; it crystallised from methanol in needles, m. p. 108° (14 g., 56·8%) (Found : C, 34·0; H, 3·0; N, 22·5. $C_7H_7O_4N_4Cl$ requires C, 34·1; H, 2·8; N, 22·7%). Some 2 : 6-*biscarbomethoxymethylamino*-5-*nitropyrimidine*, m. p. 153° (from 2-ethoxyethanol) (Found : C, 40·1; H, 4·4. $C_{10}H_{13}O_6N_5$ requires C, 40·1; H, 4·3%), was also obtained.

(*b*) To an ice-cold solution of 2 : 6-dichloro-5-nitropyrimidine (10 g., 0·05 mol.) in ether (50 c.c.) and a suspension of sodium hydrogen carbonate (16 g.) in water (50 c.c.) finely powdered glycine methyl ester hydrochloride (10 g., 0·08 mol.) was added slowly with constant shaking. The crystalline product (9 g., 73%) which separated was dried and crystallised from light petroleum (b. p. 100—120°).

In general, method (*b*) is preferred as it reduces very considerably the tendency to disubstitution; even so, the isolation of monosubstitution products from the 4 : 6-dichloro-5-nitropyrimidines is difficult. Details of the preparations are given in Table I (compounds 1—7).

2- *and* 4-*Amino-* (*and Substituted-Amino-*)5-*nitro*-6-*pyrimidylaminoacetic Esters* (*Method II*).—These were made either (*a*) by treating the appropriate chloro-5-nitro-6-pyrimidylaminoacetic ester with excess (<2 mols.) of ammonia or a base or (*b*), for the amino-compounds only, by treating a 2-amino-4-chloro-5-nitro- or 4-amino-2-chloro-5-nitro-pyrimidine with a glycine ester. In the case (*c*) where the substituted amino-group is a second aminoacetic ester residue the compounds have also been made by treating the 2 : 4- or 4 : 6-dichloro-5-nitropyrimidine with an excess of glycine ester.

*Ethyl* 2-*amino*-4-*methyl*-5-*nitro*-6-*pyrimidylaminoacetate*.—(*a*) *From ethyl* 2-*chloro*-4-*methyl*-5-*nitro*-6-*pyrimidylaminoacetate*. The chloro-ester (5·5 g., 0·02 mol.) in ethanol (30 c.c.) was cooled in ice and 6N-ethanolic ammonia (20 c.c.) added. After 1 hour the solid *pyrimidylaminoacetate* which separated was filtered off, washed with water, and crystallised from ethanol. It (4·6 g., 90%) had m. p. 187° (Found : C, 42·6; H, 5·1; N, 27·6. $C_9H_{13}O_4N_5$ requires C, 42·4; H, 5·1; N, 27·4%).

(*b*) To 2-amino-4-chloro-6-methyl-5-nitropyrimidine (3·8 g., 0·02 mol.) in ether (50 c.c.), glycine ester (2·5 g., 1·025 mol.) was added. After 1 hour the solid was collected, washed with water, and crystallised from ethanol to give the foregoing product (m. p. and mixed m. p.).

(*c*) 2 : 6-*Biscarbomethoxymethylamino*-5-*nitropyrimidine*. To 2 : 6-dichloro-5-nitropyrimidine (1·97 g., 0·01 mol.) in methanol (5 c.c.) a methanol solution of glycine methyl ester (3·5 g., 0·04 mol.) was added. The crystalline *product* which slowly separated was filtered off, washed with water, and crystallised from methanol. It (1·6 g., 55%) had m. p. 153° (Found : C, 40·1; H, 4·4. $C_{10}H_{13}O_6N_5$ requires C, 40·5; H, 4·3%). The same product was obtained from methyl 2-chloro-5-nitro-6-pyrimidylaminoacetate and glycine methyl ester in methanol.

Details of products of this type are given in Table I (compounds 8—22).

2- *and* 4-*Hydroxy*-5-*nitro*-6-*pyrimidylaminoacetic Esters* (*Method III*).—*Ethyl* 2-*hydroxy*-5-*nitro*-6-*pyrimidylaminoacetate*. Ethyl 2-chloro-5-nitro-6-pyrimidylaminoacetate (28 g., 0·1 mol.), N-acetic acid (400 c.c.), and fused sodium acetate (8·5 g.) were heated under reflux for 1 hour in a stream of nitrogen. Charcoal was then added and the whole filtered. On cooling, 7·7 g. of *hydroxy*-compound separated; a further 4·9 g. separated on concentration. Crystallised from water, it had m. p. 230—232° (decomp.) after sintering at 225° (Found : C, 40·0; H, 4·2; N, 23·3. $C_8H_{10}O_5N_4$ requires C, 39·6; H, 4·1; N, 23·2%).

*Methyl* 2-*hydroxy*-4-*methyl*-5-*nitro*-6-*pyrimidylaminoacetate*, m. p. >240° (Found : C, 39·9; H, 4·4; N, 23·0. $C_8H_{10}O_5N_4$ requires C, 39·6; H, 4·1; N, 23·2%), was obtained similarly from methyl 2-chloro-5-nitro-4-methyl-6-pyrimidylaminoacetate.

*Ethyl* 4-*hydroxy*-5-*nitro*-6-*pyrimidylaminoacetate*, obtained in 45% yield by heating the chloro-compound with 0·2M-acetate buffer (pH 5) for 3 hours on the steam-bath, had m. p. 214° (decomp.) (Found : C, 39·7; H, 3·8; N, 23·3%). Methyl 2-chloro-5-nitro-6-pyrimidylaminoacetate was hydrolysed by moist air to *methyl* 4-*hydroxy*-2-*methyl*-5-*nitro*-6-*pyrimidylaminoacetate*, m. p. 230° (decomp.) (Found : C, 40·2; H, 4·1; N, 23·1%).

*Methyl* 5-*Amino*-2-*chloro*-6-*pyrimidylaminoacetate*.—Methyl 2-chloro-5-nitro-6-pyrimidylaminoacetate (6 g.) in methanol (400 c.c.) was reduced with hydrogen at room temperature and a pressure of 60 lb./sq.in. in presence of Raney nickel and calcium carbonate. After filtration, dilution with water (200 c.c.) and long storage the 5-*amino*-ester separated in fine yellow needles. Crystallised from xylene, it was obtained colourless and having m. p. 142° (Found : C, 39·3; H, 4·3; N, 25·4. $C_7H_9O_2N_4Cl$ requires C, 38·8; H, 4·2; N, 25·8%).

*Ethyl* 5-*Amino*-4-*chloro*-6-*pyrimidylaminoacetate*.—After reduction and filtration as above, the methanol was removed under reduced pressure and the residue extracted with ethyl acetate. Removal of the ethyl acetate and crystallisation of the residue first from benzene and then from hexane gave the *amino*-compound, m. p. 133° (Found : C, 41·9; H, 4·8; N, 24·0; Cl, 15·2. $C_8H_{11}O_2N_4Cl$ requires C, 42·1; H, 4·8; N, 24·3; Cl, 15·4%).

7 : 8-*Dihydro*-6-*hydroxypteridines*.—In general these substances were prepared by hydrogenation in presence of Raney nickel of the appropriate 5-nitro-6-pyrimidylaminoacetic esters in methanol. After removal of the catalyst by filtration or flotation it was sometimes necessary, particularly with the chloro-compounds, to complete the ring closure by heating the product under reflux in presence of water and in an atmosphere of nitrogen. Substances with suitable substituents, *e.g.*, diethylamino-, were reasonably soluble in organic solvents and could be purified by crystallisation. In other cases purification was effected by dissolution in dilute hydrochloric acid, treatment with charcoal, and precipitation by sodium acetate. Details and analyses are given in Table II.

7 : 8-*Dihydro*-6-*hydroxypteridine*.—2-Chloro-6-hydroxy-7 : 8-dihydropteridine (1 g.), hydriodic acid (*d* 1·7; 6 c.c.), and red phosphorus (1 g.) were heated at 160° for 1 hour. After cooling and filtration, the

TABLE I.

*5-Nitro-6-pyrimidylaminoacetic esters* (IV).

| Compound no. | X. | Y. | R. | Method of prepn. | Yield, %. | Solvent.† | M. p. | Formula. | Found, %. C. | H. | N. | Required, %. C. | H. | N. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Cl | H | Me | Ia (*Ib*) | 56·8 (73) | Petrol (100—120°) | 108° | $C_7H_7O_4N_4Cl$ | 34·0 | 3·0 | 22·5 | 34·1 | 2·8 | 22·7 |
| 2 | Cl | H | Et | *Ib* | 71 | $C_6H_6$ | 101—102 | $C_8H_9O_4N_4Cl$ ‡ | 37·2 | 3·2 | 21·3 | 36·9 | 3·5 | 21·5 |
| 3 | H | Cl | Et | *Ib* | 31 | Petrol (60—80°) | 93—94 | $C_8H_9O_4N_4Cl$ ‡ | 37·1 | 3·3 | 21·4 | 36·9 | 3·5 | 21·5 |
| 4 * | Cl | H | Et | *Ib* | 52·5 | EtOH | 86 | $C_{11}H_{13}O_6N_4Cl$ | 40·0 | 3·9 | 16·7 | 39·7 | 3·9 | 16·8 |
| 5 | Cl | Me | Me | Ia (*Ib*) | 53 (75) | EtAc | (102) | $C_8H_9O_4N_4Cl$ | 37·0 | 3·6 | 21·5 | 36·9 | 3·5 | 21·5 |
| 6 | Cl | Me | Et | *Ia* | 69 | EtOH | 79 | $C_9H_{11}O_4N_4Cl$ | 39·2 | 4·1 | 20·2 | 39·3 | 4·0 | 20·4 |
| 7 | Me | Cl | Me | *Ib* | 43 | Petrol (60—80°) | 104 | $C_8H_9O_4N_4Cl$ ‡ | 36·7 | 3·2 | 21·8 | 36·9 | 3·5 | 21·5 |
| 8 | $NH{\cdot}CH_2{\cdot}CO_2Me$ | H | Me | Ia (IIc) | (55) | MeOH | 153 | $C_{10}H_{13}O_6N_5$ | 40·1 | 4·4 | — | 40·1 | 4·3 | — |
| 9 | H | $NH{\cdot}CH_2{\cdot}CO_2Et$ | Et | *Ib* | — | EtOH | 143 | $C_{12}H_{17}O_6N_5$ | 43·6 | 5·0 | 20·9 | 44·0 | 5·2 | 21·4 |
| 10 | $NH{\cdot}CH_2{\cdot}CO_2Me$ | Me | Me | IIc | 55 | MeOH | 152 | $C_{11}H_{15}O_6N_5$ | 42·1 | 4·9 | 23·0 | 42·2 | 4·8 | 22·4 |
| 11 | Me | $NH{\cdot}CH_2{\cdot}CO_2Me$ | Me | *Ib* | — | EtAc | 165 | $C_{11}H_{15}O_6N_5$ | 42·2 | 4·9 | 22·0 | 42·2 | 4·8 | 22·4 |
| 12 | $NH_2$ | H | Me | IIa | 50 | $EtO{\cdot}[CH_2]_2{\cdot}OH$ | 210 | $C_7H_9O_4N_5$ | 37·0 | 4·1 | 30·5 | 37·0 | 4·0 | 30·8 |
| 13 | $NH{\cdot}[CH_2]_2{\cdot}NEt_2$ | H | Me | IIa | 68 | $MeOH{-}H_2O$ | 108 | $C_{13}H_{22}O_4N_6$ | 47·5 | 6·5 | 25·4 | 47·8 | 6·7 | 25·8 |
| 14 | H | $NH_2$ | Et | IIa (*IIb*) | 83 | EtOH | 166 | $C_8H_{11}O_4N_5$ | 40·0 | 4·6 | 28·6 | 39·8 | 4·6 | 29·0 |
| 15 | H | $NEt_2$ | Et | IIa | 80 | Petrol (80—100°) | 78·5 | $C_{12}H_{19}O_4N_5$ | 48·8 | 6·5 | 23·6 | 48·5 | 6·4 | 23·6 |
| 16 * | $NEt_2$ | H | Et | IIa | 90 | EtOH | 98 | $C_{15}H_{23}O_6N_5$ | 48·8 | 6·4 | 19·2 | 48·8 | 6·2 | 19·0 |
| 17 | $NH_2$ | Me | Me | IIa (*IIb*) | 90 | MeOH | 187 | $C_9H_{13}O_4N_5$ | 42·6 | 5·1 | 27·6 | 42·4 | 5·1 | 27·5 |
| 18 | $NEt_2$ | Me | Me | IIa | 84 | MeOH | 100·5 | $C_{12}H_{19}O_4N_5$ | 48·5 | 6·3 | 23·7 | 48·5 | 6·4 | 23·6 |
| 19 | $NH{\cdot}[CH_2]_2{\cdot}NEt_2$ | Me | Me | IIa | 51 | Petrol (60—80°) | 83 | $C_{14}H_{24}O_4N_6$ | 49·2 | 6·7 | 24·8 | 49·4 | 7·1 | 24·7 |
| 20 | Me | $NH_2$ | Me | IIb | 65 | Dioxan | 239 | $C_8H_{11}O_4N_5$ | 40·0 | 5·0 | 29·3 | 39·8 | 4·6 | 29·0 |
| 21 | Me | $NEt_2$ | Me | IIa | 58 | Petrol (60—80°) | 77 | $C_{12}H_{19}O_4N_5$ | 48·6 | 6·3 | 23·8 | 38·5 | 6·4 | 23·6 |
| 22 | Me | $NH{\cdot}[CH_2]_2{\cdot}NEt_2$ | Me | IIa | — | Petrol (60—80°) | 82 | $C_{14}H_{24}O_4N_6$ | 49·4 | 6·8 | 24·3 | 49·4 | 7·1 | 24·7 |

* Side-chain $NH{\cdot}CH(CO_2Et)_2$ in place of $NH{\cdot}CH_2{\cdot}CO_2R$. † Petrol = light petroleum of the b. p. stated in parentheses.

‡ Found : Cl (No. 2) 13·7, (No. 3) 13·5, (No. 7) 13·3. Required : Cl, 13·6%.

TABLE II.

*6-Hydroxy-7 : 8-dihydropteridines* (V).

| Compound no. | X. | Y. | Purification. | M. p.† | Formula. | Found, %. C. | H. | N. | Required, %. C. | H. | N. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 23 | H | H | $H_2O$ | >400° | $C_6H_6ON_4$ | 47·9 | 4·2 | 37·3 | 48·0 | 4·0 | 37·3 |
| 24 | Cl | H | Pptn. | >400 | $C_6H_5ON_4Cl$ | 39·3 | 3·1 | 30·4 | 39·0 | 2·7 | 30·4 |
| 25 | H | Cl | $H_2O$ | >400 | $C_6H_5ON_4Cl$ ‡ | 39·4 | 2·9 | 30·6 | 39·0 | 2·7 | 30·4 |
| 26 | Cl | Me | $EtO{\cdot}[CH_2]_2{\cdot}OH$ | >400 | $C_7H_7ON_4Cl$ § | 42·5 | 3·7 | 28·8 | 42·3 | 3·5 | 28·2 |
| 27 | Me | Cl | $H_2O$ | >400 | $C_7H_7ON_4Cl$ § | 41·5 | 3·9 | 27·6 | 42·3 | 3·5 | 28·2 |
| 28 * | Cl | H | Aq. $NH_3$ | 239 | $C_9H_9O_3N_4Cl$ | 42·2 | 3·9 | 21·8 | 42·1 | 3·5 | 21·8 |
| 29 | $NH_2$ | H | 80% $HCO_2H$ | >250 | $C_6H_7ON_5,2H_2O$ | 35·7 | 5·6 | 34·8 | 35·8 | 5·5 | 34·8 |
| 30 | H | $NH_2$ | $H_2O$ | >250 | $C_6H_7ON_5$ | 43·7 | 3·9 | 41·9 | 43·6 | 4·2 | 42·4 |
| 31 | Me | $NH_2$ | Pptn. | >400 | $C_7H_9ON_5$ | 46·5 | 5·2 | 39·2 | 46·9 | 5·0 | 39·1 |
| 32 | H | $NEt_2$ | $C_6H_6$ | 197—199 | $C_{10}H_{15}ON_5$ | 54·2 | 6·6 | 31·2 | 54·3 | 6·8 | 31·6 |
| 33 | Me | $NEt_2$ | $C_6H_6$ | 208 | $C_{11}H_{17}ON_5$ | 56·0 | 7·2 | 30·3 | 56·2 | 7·2 | 29·8 |
| 34 | $NEt_2$ | Me | MeOH | 284 | $C_{11}H_{17}ON_5$ | 56·2 | 7·1 | 29·6 | 56·2 | 7·2 | 29·8 |
| 35 * | $NEt_2$ | H | $EtO{\cdot}[CH_2]_2{\cdot}OH$ | 212 (d) | $C_{13}H_{19}O_3N_5$ | 52·9 | 6·4 | — | 53·2 | 6·5 | 23·9 |
| 36 | $MeO_2C{\cdot}CH_2{\cdot}NH$ | H | $EtO{\cdot}[CH_2]_2{\cdot}OH$ | 290 (d) | $C_9H_{11}O_3N_5$ | 45·4 | 4·9 | 29·6 | 45·6 | 4·6 | 29·5 |
| 37 | $Et_2N{\cdot}[CH_2]_2{\cdot}NH$ | H | EtOH | 204 | $C_{12}H_{20}ON_6$ | 54·1 | 7·5 | 31·9 | 54·5 | 7·6 | 31·8 |
| 38 | $Et_2N{\cdot}[CH_2]_2{\cdot}NH$ | Me | MeOH | 243 | $C_{13}H_{22}ON_6$ | 56·4 | 7·8 | 30·5 | 56·1 | 7·9 | 30·2 |
| 39 | OH | H | Pptn. | >300 | $C_6H_6O_2N_4$ | 43·6 | 3·6 | 33·8 | 43·4 | 3·6 | 33·7 |
| 40 | OH | Me | Pptn. | >300 | $C_7H_8O_2N_4$ | 46·0 | 4·6 | 30·4 | 46·6 | 4·4 | 31·1 |
| 41 | H | OH | Pptn. | >300 | $C_6H_6O_2N_4$ | 43·6 | 3·8 | 33·8 | 43·4 | 3·6 | 33·7 |
| 42 | Me | OH | $H_2O$ | >300 | $C_7H_8O_2N_4$ | 46·9 | 4·6 | 30·9 | 46·6 | 4·4 | 31·1 |

* 7-Carbethoxy-derivative. † (d) = with decomposition. ‡ Found : Cl, 18·5. Required : Cl, 19·3%.

§ Found : Cl (No. 26), 18·5, (No. 27) 17·4. Required : Cl, 17·9%.

filtrate was made strongly alkaline by 20% sodium hydroxide solution. The crystalline sodium salt which separated on cooling was dissolved in water, and acidified to Congo-red with hydrochloric acid. The whole was heated with charcoal, filtered, and reprecipitated by the addition of sodium acetate. 7 : 8-*Dihydro*-6-*hydroxypteridine* (0·7 g.) was filtered off, washed, and dried at 120° *in vacuo*; it did not melt below 300° (Found : C, 48·2; H, 3·9; N, 37·4. $C_6H_6ON_4$ requires C, 48·0; H, 4·0; N, 37·3%). The same substance was prepared similarly from 4-chloro-6-hydroxy-7 : 8-dihydropteridine (Found : C, 47·9; H, 4·2; N, 37·3%).

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