*Hydropteridines. Part III.** 5 : 6 : 7 : 8-*Tetrahydro-4-methylpteridine.*

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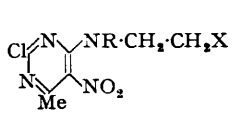
Reduction and simultaneous ring-closure of 4-(*N*-benzyl-2-chloroethylamino)-2-chloro-6-methyl-5-nitropyrimidine (I; R = CH_2Ph, X = Cl) has made available 8-benzyl-5 : 6 : 7 : 8-tetrahydro-4-methylpteridines (II; R = CH_2Ph, X = H, OH, or Cl). Reduction of the 2-chloro-compound gave 5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (II; R = X = H).

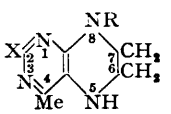
In an attempt to synthesise 5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (II; R = X = H), Ramage and Trappe (*J.*, 1952, 4410) showed that 4-2′-chloroethylamino-5-nitropyrimidines (*e.g.*, I; R = H, X = Cl) were reasonably stable in the absence from the 2-position of a group capable of initiating tautomerism. Either the introduction of such a group, *e.g.*, hydroxyl in place of the 2-chloro-group in (I; R = H, X = Cl), or reduction of the 5-nitro- to a 5-amino-group, allowed cyclisation involving the pyrimidine nitrogen atom and gave glyoxalinopyrimidines, *i.e.*, (III; X = OH, Y = NO_2; or X = Cl, Y = NH_2 respectively).

4-(*N*-Benzyl-2-chloroethylamino)-2-chloro-6-methyl-5-nitropyrimidine (I; R = CH_2Ph, X = Cl) has been prepared, and its reduction and subsequent ring-closure have been studied since the cyclisation to a tetrahydropteridine was expected to be facilitated by the *N*-benzyl group.

2 : 4-Dichloro-6-methyl-5-nitropyrimidine in chloroform was condensed with *N*-benzyl-2-chloroethylamine, the latter being conveniently prepared from 2-benzylaminoethanol by the action of thionyl chloride, rather than hydrochloric acid as used by Goldschmeidt and Jahoda (*Monatsh.*, 1891, **12**, 83). The amine (I; R = CH_2Ph, X = Cl) was obtained as a stable solid which showed no tendency to cyclise in the absence of moisture. Ether, as an alternative solvent in the condensation, gave the same product together with the hydrochloride of the bicyclic compound (IV). It was considered that the latter was formed by cyclisation of the product derived from the amine (I; R = CH_2Ph, X = Cl) by hydrolysis of the reactive 2-chloro-group by moisture in the solvent, and this was supported by its ready formation from the same amine with hydrochloric acid, or with moist ethanol, at the boil. The cyclisation was comparable with that of the non-benzylated compound (I; R = H, X = Cl) (Ramage and Trappe, *loc. cit.*).



(I)



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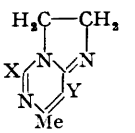

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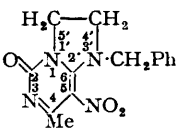

(IV)

Catalytic reduction of the chloro-amine (I; R = CH_2Ph, X = Cl) with Raney nickel in ethanol gave 8-benzyl-2-chloro-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (II; R = CH_2Ph, X = Cl) contaminated with a nickel salt. Cyclisation involving the 5-amino-group must have occurred rapidly after reduction, and the action of the resulting hydrochloride on the catalyst would explain the contamination.

The new mode of cyclisation to a benzyltetrahydropteridine proceeded readily and was evidently favoured by the presence of the benzyl group which removed any possibility of tautomerism. In contrast, the alternative ring closure from the secondary base (I; R = H, X = Cl) leading to a glyoxalinopyrimidine had required refluxing in ethanol (*idem, loc. cit.*).

An alternative route to the pteridine (II; R = CH_2Ph, X = Cl) from the hydroxy-amine (I; R = CH_2Ph, X = OH) was also used. The latter compound was prepared by the condensation of 2-benzylaminoethanol with 2 : 4-dichloro-6-methyl-5-nitropyrimidine, and on reduction with Raney nickel gave 5-amino-4-(*N*-benzyl-2-hydroxyethylamino)-2-chloro-6-methylpyrimidine, without nickel contamination. Ready cyclisation to the

* Part II, *J.*, 1954, 4109.

pteridine (II; R = CH_2Ph, X = Cl) occurred on treatment with phosphoryl chloride followed by alkali. Hydrogenolysis of the benzyl group in this product was attempted by the use of palladised charcoal in acetic acid (Baltzly and Buck, *J. Amer. Chem. Soc.*, 1943, **65**, 1984), but only the 2-chloro-group was removed. Treatment with constant-boiling hydrobromic or hydrochloric acid hydrolysed the 2-chloro-group and gave the 2-hydroxypteridine (II; R = CH_2Ph, X = OH). Both the chloro- and the benzyl group were, however, reduced off by sodium in liquid ammonia and 5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (II; R = X = H) was obtained. 1-Benzylglyoxaline derivatives, which contain a similar " amidine " arrangement of nitrogen atoms, have been debenzylated in this way (Du Vigneaud and Behrens, *J. Biol. Chem.*, 1937, **117**, 27). An attempt merely to effect only debenzylation with a shorter reaction time showed that the chlorine was preferentially attacked, as in hydrogenolysis, and the benzyltetrahydromethylpteridine was again obtained.

5 : 6 : 7 : 8-Tetrahydro-4-methylpteridine was treated with formic acid in the presence of acetic anhydride and gave a monoformyl derivative which, by analogy with the work on reduced pteroylglutamic acid (May, Bardos, Barger, Lansford, Ravel, Sutherland, and Shive, *J. Amer. Chem. Soc.*, 1951, **73**, 3067), was considered to be a 5-formyl derivative. Acylation with acetic formic and diacetic anhydride, however, gave respectively a diformyl and a diacetyl derivative which showed that both the 5- and the 8-position were reactive; so an unambiguous synthesis of the 5-formyl derivative was attempted.

Formylation of the benzylpteridine (II; R = CH_2Ph, X = Cl), in which the 8-position was occupied, definitely established 5-formylation, but treatment of this product with sodium in liquid ammonia caused simultaneous removal of the chloro-, benzyl, and formyl groups, yielding tetrahydro-4-methylpteridine. The formyl group was removed more easily than the benzyl group, since 8-benzyl-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (II; R = CH_2Ph, X = H) was obtained with a shorter reaction time. However, a similar series of reactions *via* the 5-acetyl derivative was successful and gave 5-acetyl-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine.

The similarity of the ultra-violet absorption spectrum (cf. Table) of the monoformyl derivative of tetrahydro-4-methylpteridine (II; R = X = H) to that of the 5-acetyl derivative confirmed location of the formyl group also in the 5-position. In addition, the basic strengths of these derivatives and of 4-aminopyrimidine were comparable (cf. Albert, Goldacre, and Phillips, *J.*, 1948, 2240).

For the diacetyl compound, it was found that the basic strength (cf. Table) was appre-

Basic strengths and ultra-violet absorption spectra.[2]

5 : 6 : 7 : 8-Tetrahydro-4-methylpteridines	pK_a in water and concn. (20°) [1]	$\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$	$\lambda_{min.}$ (mμ)	log $\varepsilon_{min.}$
(II; R = X = H) ...	—	211, 300	4·18, 3·82	241, 274 *	3·21, 3·68
cation	6·74 (±0·02) M/100	213, 305	4·12, 3·93	251	3·00
5-Acetyl-8-benzyl- ...	—	217, 263	4·17, 4·11	238, 287 *	3·73, 3·79
cation	5·49 (±0·02) [3] —	205, 281	4·31, 4·23	245	3·84
8-Benzyl-5-formyl- ...	—	217, 266	4·26, 4·12	240, 290 *	3·79, 3·85
cation	5·46 (± 0·03) [3] —	207, 282	4·25, 4·22	247	3·70
5-Formyl-	—	216, 253, 288	4·14, 3·93, 3·70	235, 276	3·82, 3·68
cation	5·45 (±0·02) M/100	211, 272	4·07,4·06	246	3·74
5-Acetyl-	—	217, 248, 287	4·06, 3·94, 3·69	233, 274	3·84, 3·64
cation	5·26 (±0·01) M/100	210, 271	4·02, 4·01	247	3·76
5 : 8-Diacetyl- [4]	—	219, 241, 265, 284	4·18, 4·02, 3·97, 3·92	233, 260, 277	4·00, 3·97 3·91
cation [5]	2·15 (±0·01) M/100	—	—	—	—

* Inflection. [1] Determinations by the procedure of Albert, Brown, and Cheeseman (*J.*, 1951, 481). [2] Spectra of all bases, except the diacetyl compound, were determined in 0·1N-NaOH, and those of the cations in 0·1N-HCl. [3] Determined spectroscopically. [4] Spectrum in water at pH 6·10; aged samples of the solid showed no peak at 241 mμ. [5] Unstable in N-HCl.

ciably lowered by the 8-acetyl group, although the pK_a value still exceeded that of pyrimidine. In N-hydrochloric acid, after 4 hours at room temperature, the diacetyl derivative had been hydrolysed to the 5-acetyl compound, as was established by the spectra.

Experimental

The spectrographic work was done on a Unicam S.P. 500 quartz spectrophotometer (kindly lent by the Wool Textile Research Council).

N-Benzyl-2-chloroethylamine.—Thionyl chloride (30 c.c.) was added during 20 min. to a stirred solution of 2-benzylaminoethanol (30 g.) in chloroform (150 c.c.), and the mixture was refluxed for 6 hr. Ether (400 c.c.) was added to the cooled chloroform solution, which was then left in the refrigerator overnight. *N*-Benzyl-2-chloroethylamine hydrochloride was filtered off, and on crystallisation from ethanol (charcoal) gave plates (30·5 g.), m. p. 192°.

4-(N-Benzyl-2-chloroethylamino)-2-chloro-6-methyl-5-nitropyrimidine (I; R = CH_2Ph, X = Cl).—(*a*) *N*-Benzyl-2-chloroethylamine hydrochloride (10·3 g.) was gradually added with shaking to a mixture of 2 : 4-dichloro-6-methyl-5-nitropyrimidine (10·4 g.) (Baddiley and Jopham, *J.*, 1944, 678; cf. Albert, Brown, and Wood, *J.*, 1954, 3832) in chloroform (150 c.c.) and sodium hydrogen carbonate (9 g.) in water (30 c.c.), and shaking was continued for a further 20 min. The chloroform layer was separated, washed with water (20 c.c.), and dried (Na_2SO_4), and the chloroform was removed under reduced pressure. The residue, crystallised from methanol, gave *4-(N-benzyl-2-chloroethylamino)-2-chloro-6-methyl-5-nitropyrimidine* (14·8 g.) as yellow plates, m. p. 95—96° (Found: C, 49·7; H, 4·2. $C_{14}H_{14}O_2N_4Cl_2$ requires C, 49·3; H, 4·1%).

(*b*) A similar preparation with ether (300 c.c.), instead of chloroform, gave 7·5 g. of product, m. p. 95°. Concentration of the methanolic mother-liquor gave *3′-benzyl-2′ : 3′ : 4′ : 5′-tetrahydro-4-methyl-5-nitroglyoxalino-(1′ : 2′-1 : 6)pyrimid-2-one hydrochloride* (2·0 g.) which crystallised from dilute hydrochloric acid as pale yellow prisms, m. p. 230° (decomp.) (Found: C, 52·0; H, 4·5; Cl, 11·4. $C_{14}H_{15}O_3N_4Cl$ requires C, 52·2; H, 4·7; Cl, 11·0%). The hydrochloride, boiled with water or treated with sodium hydrogen carbonate, gave the *base* (IV) which crystallised from water as yellow plates, m. p. 171—172° (Found: C, 58·8; H, 5·0. $C_{14}H_{14}O_3N_4$ requires C, 58·7; H, 4·9%).

This hydrochloride was also prepared from the pyrimidine (I; R = CH_2Ph, X = Cl) (3·0 g.), methanol (80 c.c.), and 2·5N-hydrochloric acid (20 c.c.) at the boil for 45 min. The solution was evaporated to 20 c.c. under reduced pressure, then cooled, and the hydrochloride (2·3 g.) was filtered off.

4-(N-Benzyl-2-hydroxyethylamino)-2-chloro-6-methyl-5-nitropyrimidine (I; R = CH_2Ph, X = OH).—2-Benzylaminoethanol (6·0 g.) in ether (30 c.c.) was gradually added with shaking to a mixture of 2 : 4-dichloro-6-methyl-5-nitropyrimidine (8·25 g.) in ether (250 c.c.), and sodium hydrogen carbonate (3·5 g.) in water (10 c.c.). After a further 20 min., evolution of carbon dioxide had ceased, and the ethereal layer was washed with water (20 c.c.), and dried (Na_2SO_4). Removal of the solvent and crystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave *4-(N-benzyl-2-hydroxyethylamino)-2-chloro-6-methyl-5-nitropyrimidine* (9·4 g.) as yellow prisms, m. p. 87—88°, raised to m. p. 90° on further crystallisation (Found: C, 51·9; H, 4·4. $C_{14}H_{15}O_3N_4Cl$ requires C, 52·1; H, 4·7%).

5-Amino-4-(N-benzyl-2-hydroxyethylamino)-2-chloro-6-methylpyrimidine.—The above 5-nitropyrimidine (4·0 g.) in ethanol (50 c.c.) was shaken with Raney nickel (5 c.c.; settled suspension) in hydrogen and theoretical uptake was reached after 45 min. The catalyst was filtered off and washed with a little ethanol, and the combined filtrates on concentration gave *5-amino-4-(N-benzyl-2-hydroxyethylamino)-2-chloro-6-methylpyrimidine* (2·9 g.) which crystallised from a small volume of methanol as prisms, m. p. 129—130° (Found: C, 57·6; H, 5·9. $C_{14}H_{17}ON_4Cl$ requires C, 57·4; H, 5·9%).

8-Benzyl-2-chloro-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (II; R = CH_2Ph, X = Cl).—(*a*) 4-(*N*-Benzyl-2-chloroethylamino)-2-chloro-6-methyl-5-nitropyrimidine (3 g.) in ethanol (100 c.c.) was agitated with Raney nickel (5 c.c.; settled suspension) under hydrogen until the theoretical amount had been absorbed (3 hr.). The catalyst was filtered off and washed with ethanol, and the solvent was removed from the combined filtrates at 60° under reduced pressure. Water was added to the green resin and the solid was filtered off (the filtrate contained nickel as shown by the dimethylglyoxime test). *8-Benzyl-2-chloro-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine* (1·3 g.) crystallised from ethanol as prisms, m. p. 181° (Found: C, 61·4; H, 5·5; Cl, 12·9. $C_{14}H_{15}N_4Cl$ requires C, 61·2; H, 5·5; Cl, 12·9%).

(*b*) 5-Amino-4-(*N*-benzyl-2-hydroxyethylamino)-2-chloro-6-methylpyrimidine (1·65 g.) was dissolved in phosphoryl chloride (10 c.c.) with gentle warming and the solution kept for 12 hr. Excess of phosphoryl chloride was removed under reduced pressure and the residue, dissolved in water (50 c.c.), was made alkaline with 2N-sodium hydroxide before extraction with chloroform. The solvent was removed from the dried extracts and crystallisation of the residue yielded

8-benzyl-2-chloro-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (1·2 g.), m. p. 181°, identical with the above.

On treatment with nitrous acid a N-*nitroso*-derivative was obtained, which crystallised from a little methanol in yellow prisms, m. p. 102—103° (Found : C, 55·7; H, 4·7. $C_{14}H_{14}ON_5Cl$ requires C, 55·4; H, 4·6%). The 5-*acetyl* derivative was formed by short boiling with acetic anhydride and crystallised from ethanol in prisms, m. p. 151° (Found : C, 60·2; H, 5·1. $C_{16}H_{17}ON_4Cl$ requires C, 60·6; H, 5·4%); the 5-*formyl* derivative, prepared by use of formic acid and a little acetic anhydride overnight, crystallised from benzene as needles, m. p. 117° (Found : C, 59·5; H, 5·2. $C_{15}H_{15}ON_4Cl$ requires C, 59·5; H, 5·0%).

8-*Benzyl*-5 : 6 : 7 : 8-*tetrahydro*-2-*hydroxy*-4-*methylpteridine* (II; R = CH_2Ph, X = OH).—(*a*) 8-Benzyl-2-chloro-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (0·5 g.) and constant-boiling hydrobromic acid (10 c.c.) were refluxed for 1½ hr. and the excess of acid was removed under reduced pressure. The residue was dissolved in water (25 c.c.) and extracted with chloroform to remove some benzyl bromide. The aqueous solution was then neutralised with sodium hydrogen carbonate and extracted with chloroform. The residue from the extracts was crystallised from ethanol and gave 8-*benzyl*-5 : 6 : 7 : 8-*tetrahydro*-2-*hydroxy*-4-*methylpteridine* (0·18 g.) as plates, m. p. 260° (decomp.) (Found : C, 65·5; H, 6·3. $C_{14}H_{16}ON_4$ requires C, 65·6; H, 6·3%).

(*b*) In a similar reaction, but with 5N-hydrochloric acid (10 c.c.) replacing hydrobromic acid, the 2-chloro-compound (2·25 g.) gave the above 2-hydroxypteridine (0·95 g.), and no benzyl chloride was detected.

The reduction of (II; R = CH_2Ph, X = OH) by sodium in liquid ammonia produced unstable products which rapidly decomposed in solution.

8-*Benzyl*-5 : 6 : 7 : 8-*tetrahydro*-4-*methylpteridine* (II; R = CH_2Ph, X = H).—(*a*) 8-Benzyl-2-chloro-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (2·0 g.) in ethanol (100 c.c.) was shaken with 2% palladium–calcium carbonate (0·5 g.) under hydrogen. After filtration and removal of the solvent, the residue was dissolved in water (50 c.c.) and extracted with ether to remove a small amount of starting material. The aqueous layer was treated with sodium hydrogen carbonate and extracted with ether. Removal of the ether, followed by crystallisation of the residue from light petroleum (b. p. 60—80°), gave 8-*benzyl*-5 : 6 : 7 : 8-*tetrahydro*-4-*methylpteridine* (1·3 g.) as prismatic needles, m. p. 93—94° (Found: C, 70·0; H, 6·6. $C_{14}H_{16}N_4$ requires C, 69·9; H, 6·7%).

(*b*) A similar reduction of the 2-chloro-compound (1·0 g.) in acetic acid (100 c.c.) was done with 5% palladised charcoal (0·5 g.) at an initial pressure of 4 atm. of hydrogen. Treatment as in (*a*) gave the product (0·75 g.), m. p. 93—94°, as above.

(*c*) Finely ground 2-chloro-compound (2·0 g.) was added gradually to anhydrous liquid ammonia (150 c.c.) followed by sodium (about 0·3 g.; in pieces) until the reaction slowed, as judged by the rate of disappearance of the blue colour. Ammonium chloride was then added to change the solution from orange to grey and the ammonia was allowed to evaporate completely, the flask being fitted with a potassium hydroxide tube. The residue was extracted with ether (3 × 50 c.c.) and the extracts, after being washed with water (20 c.c.) to remove any debenzylated material, gave 8-benzyl-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (1·2 g.), m. p. 93—94°.

The 5-*acetyl* derivative crystallised from light petroleum (b. p. 100—120°) in plates, m. p. 121—122° (Found : C, 67·6; H, 6·5. $C_{16}H_{18}ON_4$ requires C, 68·1; H, 6·4%) : the 5-*formyl* derivative was prepared by means of formic acid and acetic anhydride at room temperature overnight, and crystallised from light petroleum (b. p. 100—120°) as prisms, m. p. 102° (Found : C, 66·7; H, 6·4. $C_{15}H_{16}ON_4$ requires C, 67·2; H, 6·0%).

5 : 6 : 7 : 8-*Tetrahydro*-4-*methylpteridine* (II; R = X = H).—(*a*) Sodium (0·7 g., 4 atomic equivs.) was added to 8-benzyl-2-chloro-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (2·0 g.) in liquid ammonia (100 c.c.) and, after 2 hr., ammonium chloride was added. The product was worked up as above (but without the water-washing) and gave 5 : 6 : 7 : 8-*tetrahydro*-4-*methylpteridine* (0·82 g.) as needles [from benzene (charcoal)], m. p. 145—146° (Found : C, 56·0; H, 6·8. $C_7H_{10}N_4$ requires C, 56·0; H, 6·7%).

The *picrate* crystallised from ethanol as deep orange prisms, m. p. 263° (Found : C, 41·1; H, 3·6. $C_7H_{10}N_4,C_6H_3O_7N_3$ requires C, 41·2; H, 3·5%), and the *methiodide* from propanol as deep cream needles, m. p. 272—274° (Found : C, 33·0; H, 4·3. $C_7H_{10}N_4,CH_3I$ requires C, 32·9; H, 4·5%). Boiling acetic acid gave the *acetate* which crystallised from benzene as prisms, m. p. 114° (Found : C, 51·9; H, 6·7. $C_7H_{10}N_4,C_2H_4O_2$ requires C, 51·4; H, 6·7%).

The tetrahydropteridine (0·2 g.) was formylated by treatment for 24 hr. with formic acid (10 c.c.) and acetic anhydride (2 c.c.) at room temperature. Excess of reagents was removed under reduced pressure and the residue was refluxed in ethanol (10 c.c.) for 10 min. After

removal of the ethanol, the *5-formyl-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine* (0·15 g.) crystallised from benzene (charcoal) as needles, m. p. 194° (Found : C, 54·5; H, 5·7; N, 32·0. $C_8H_{10}ON_4$ requires C, 53·9; H, 5·7; N, 31·5%). Formylation of the tetrahydropteridine with formic acetic anhydride at room temperature overnight gave the *5 : 8-diformyl* derivative, which crystallised from benzene as prisms, m. p. 170—171° (Found : C, 52·1; H, 4·6. $C_9H_{10}O_2N_4$ requires C, 52·4; H, 4·9%).

Boiling acetic anhydride (10 c.c.) and the tetrahydropteridine (0·5 g.) gave in 10 min. *5 : 8-diacetyl-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine* (0·4 g.) which crystallised from benzene (charcoal) as prisms, m. p. 168° (Found : C, 56·9; H, 6·0; N, 23·8. $C_{11}H_{14}O_2N_4$ requires C, 56·4; H, 6·0; N, 23·9%).

(*b*) 8-Benzyl-2-chloro-5-formyl-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (1·6 g.) was added to anhydrous liquid ammonia, followed by sodium (0·75 g., 6 atomic equivs.). After 10 min., the excess of sodium was removed by ammonium chloride, and the ammonia was allowed to evaporate. Extraction of the residue with chloroform, followed by chromatography of the extracts on alumina with the same solvent, yielded the 8-benzyltetrahydro-4-methylpteridine (0·05 g.), m. p. 93°, and then 5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (0·32 g.), m. p. 142°. No product containing a formyl group was isolated.

5-Acetyl-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine.—5-Acetyl-8-benzyl-2-chloro-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (3·2 g.) was dissolved in liquid ammonia (150 c.c.) and reduced with sodium (0·93 g.). After 20 min., excess of ammonium chloride was added and the ammonia was allowed to evaporate. The residue was extracted with chloroform, chromatographed on an alumina column, and yielded *5-acetyl-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine* (0·5 g.) which crystallised from butanone as prisms, m. p. 182° (Found : C, 56·4; H, 6·2. $C_9H_{12}ON_4$ requires C, 56·2; H, 6·3%).

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