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1. *Hydropteridines. Part IV.** 5 : 6 : 7 : 8-*Tetrahydropteridine.*

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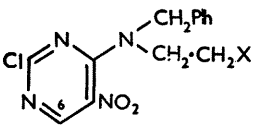
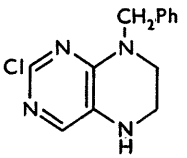
The route to 5 : 6 : 7 : 8-tetrahydro-4-methylpteridine [1] has been extended for the preparation of 5 : 6 : 7 : 8-tetrahydropteridine.

The use of 2 : 4-dichloro-5-nitropyrimidine in condensation with *N*-2-chloroethylbenzylamine, followed by reduction of the product (I; X = Cl), has given 8-benzyl-2-chloro-5 : 6 : 7 : 8-tetrahydropteridine (II), further characterised by a *N*-nitroso-derivative. The material from the reduction, in ethanol, was extremely sensitive to air and heat, and rapidly darkened even in an atmosphere of coal-gas. Absence of a 6-methyl group in the pyrimidine derivative has previously produced a similar sensitivity.[2]

The difficult nature of the reduction and the small yield of product led to the alternative condensation with 2-benzylaminoethanol. Purified material (I; X = OH) was at once



(I)



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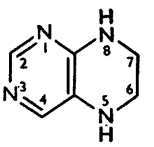

(III)

reduced and the resulting 5-amino-2-chloro-4-(*N*-2-hydroxyethylbenzylamino)pyrimidine was best cyclised by phosphoryl chloride. Treatment of the benzylchloropteridine (II) with sodium in liquid ammonia gave 5 : 6 : 7 : 8-tetrahydropteridine (III) by removal of the chlorine atom and the benzyl group. The former was removed more easily than the latter since a shorter reaction time gave 8-benzyl-5 : 6 : 7 : 8-tetrahydropteridine.

On treatment with formic acid containing acetic anhydride, 5 : 6 : 7 : 8-tetrahydropteridine gave a monoformyl derivative, adjudged to be the 5-substituted compound from

Basic strengths and light absorption of tetrahydropteridines.

5 : 6 : 7 : 8-Tetrahydropteridine	pK_a	Concn.	$\lambda_{max.}$ (mμ) ($\varepsilon \times 10^{-4}$)
Unsubstituted			268 (0·489); 306 (0·648)
cation.....	6·63 ± 0·02	M/100	208 (1·49); 304 (0·781)
2-Chloro-8-ethyl-4-methyl			292 [b] (0·780); 307 (0·875)
cation.....	3·80 ± 0·07 [a]	—	225 (1·60); 316 (1·08)
5-Formyl.....			260 (0·750); 302 (0·615)
cation.....	5·00 ± 0·02	M/400	218 (1·31); 276 (1·09)

[a] Determined spectroscopically. [b] Inflection.

the similarity of its ultraviolet absorption spectrum to that of 5-acetyl-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine.[1] Acetic anhydride converted the tetrahydropteridine into a diacetyl compound, and with methyl iodide a methiodide was formed without further *N*-methylation.

At a Ciba Foundation Symposium, Dr. E. C. Taylor, jun., described the preparation

* Part III, *J.*, 1955, 896.

[1] Brook and Ramage, *J.*, 1955, 896.
[2] Ramage and Trappe, *J.*, 1952, 4410.

of 5 : 6 : 7 : 8-tetrahydropteridine, by reduction of pteridine with lithium aluminium hydride or from 2 : 4 : 6 : 7-tetrachloropteridine, without experimental details although the formation of a monoacetate, a monohydrochloride, and a picrate was reported.[3] He has kindly established that the ultraviolet absorption spectrum of our sample of tetrahydropteridine is identical with that of his product.[4]

Further evidence that reduction of simple pteridines with lithium aluminium hydride yielded 5 : 6 : 7 : 8-tetrahydro-compounds was obtained when such a reduction of 4-methylpteridine gave 5 : 6 : 7 : 8-tetrahydro-4-methylpteridine, identical with that previously prepared.[1]

The likelihood that 8-glycosyl derivatives of pteridines exist in Nature has been discussed by Forrest, Hull, Rodda, and Todd [5] who devised some approaches to model compounds. More recently, Wright [6] has isolated pteridine co-enzymes, which contain a phosphorylated pentose group and are related to the *Leuconostoc citrovorum* factor. It is possible that the sugar unit is attached to the 8-position of a 5 : 6 : 7 : 8-tetrahydropteridine. The present route to 8-benzyltetrahydropteridines seemed capable of modification to afford other 8-substituted pteridines, and in this way 2-chloro-8-ethyl-5 : 6 : 7 : 8-tetrahydro-4-methylpteridine has been prepared.

In a personal communication, Professor A. Albert stated that he had not observed the deviations from Beer's law, for solutions of 4-methylpteridine in 0·1M-sodium hydroxide, reported in Part II of our series.[7] The original sample, which had been analysed and was considered to be pure, was available and on sublimation gave a product which behaved normally. Attempts to reproduce the conditions leading to an abnormal product have failed and the evidence has shown that the impurity (6%) was responsible for the results reported. The characteristics of 4-methylpteridine given by Albert, Brown, and Wood [8] are confirmed.

Some physical data are tabulated.

Experimental

The spectrophotometric work was done on a Unicam S.P. 500 Quartz Spectrophotometer (kindly lent by the Wool Textile Research Council).

2-Chloro-4-(N-2-chloroethylbenzylamino)-5-nitropyrimidine (I; X = Cl).—*N*-2-Chloroethylbenzylamine hydrochloride (9·3 g.) was added with shaking to a mixture of 2 : 4-dichloro-5-nitropyrimidine (8·7 g.) in chloroform (150 c.c.) and sodium hydrogen carbonate (7·8 g.) in water (50 c.c.). After a further 10 minutes' shaking, evolution of carbon dioxide had ceased and the chloroform layer was separated, washed with a little water, and dried (Na_2SO_4). Removal of the chloroform and crystallisation of the residue from methanol gave *2-chloro-4-(N-2-chloroethylbenzylamino)-5-nitropyrimidine* (13·4 g.) as pale yellow plates, m. p. 119° (Found: C, 47·4; H, 3·6. $C_{13}H_{12}O_2N_4Cl_2$ requires C, 47·7; H, 3·7%).

2-Chloro-4-(N-2-hydroxyethylbenzylamino)-5-nitropyrimidine (I; X = OH).—2-Benzylaminoethanol [9] (19·1 g.) in chloroform (50 c.c.) was condensed with 2 : 4-dichloro-5-nitropyrimidine (24·5 g.) in chloroform (200 c.c.) in the presence of a solution of sodium hydrogen carbonate (6·5 g.) in water (30 c.c.) by the same method as above. *2-Chloro-4-(N-2-hydroxyethylbenzylamino)-5-nitropyrimidine* (23·9 g.) crystallised from carbon tetrachloride in pale yellow prisms, m. p. 82° (Found: C, 50·2; H, 4·1. $C_{13}H_{13}O_3N_4Cl$ requires C, 50·6; H, 4·2%).

5-Amino-2-chloro-4-(N-2-hydroxyethylbenzylamino)pyrimidine.—The corresponding 5-nitropyrimidine (7·0 g.) in ethanol (180 c.c.) was shaken with Raney nickel (12 c.c.; settled suspension) in hydrogen. Intake reached the theoretical amount for reduction of a nitro-group in 20 min. and the catalyst was filtered off and washed with a little ethanol. The combined filtrates yielded *5-amino-2-chloro-4-(N-2-hydroxyethylbenzylamino)pyrimidine* (4·5 g.) which crystallised from a little methanol in plates, m. p. 126° (Found: C, 55·7; H, 5·5. $C_{13}H_{15}ON_4Cl$

[3] Taylor, Carbon, Garland, Hoff, Howell, and Sherman, "Chemistry and Biology of Pteridines," Churchill, London, 1954.
[4] Personal communication.
[5] Forrest, Hull, Rodda, and Todd, *J.*, 1951, 3.
[6] Wright, *J. Amer. Chem. Soc.*, 1955, **77**, 3930.
[7] Lister, Ramage, and Coates, *J.*, 1954, 4109.
[8] Albert, Brown, and Wood, *J.*, 1954, 3832.
[9] Gabriel and Stelzner, *Ber.*, 1896, **29**, 2381.

requires C, 56·0; H, 5·4%). Acetylation with acetic anhydride, followed by treatment with sodium hydroxide, gave the N-*acetyl derivative*, which crystallised from water in prisms, m. p. 162° (Found : C, 55·8; H, 5·1. $C_{15}H_{17}O_2N_4Cl$ requires C, 56·2; H, 5·3%).

8-*Benzyl*-2-*chloro*-5 : 6 : 7 : 8-*tetrahydropteridine* (II).—(*a*) 2-Chloro-4-(*N*-2-chloroethylbenzylamino)-5-nitropyrimidine (3·0 g.) in ethanol (150 c.c.) was shaken in hydrogen with Raney nickel (8 c.c.; settled suspension) until intake reached the theoretical amount. The pale yellow ethanolic solution, obtained by removal of the catalyst, rapidly darkened on exposure to air and the solvent was removed under reduced pressure at 40° in an atmosphere of coal-gas. The brown residue was treated with water which removed contamination by nickel chloride, and the resulting insoluble solid (0·8 g.) was filtered off. Crystallisation from pentyl alcohol (considerable loss) gave 8-*benzyl*-2-*chloro*-5 : 6 : 7 : 8-*tetrahydropteridine* (0·35 g.) as prismatic needles, m. p. 133° raised to 136° on recrystallisation from benzene–*cyclo*hexane (Found : C, 59·4; H, 5·1. $C_{13}H_{13}N_4Cl$ requires C, 59·9; H, 5·0%). The substance slowly became yellow, a change not observed with the corresponding compound in the 4-methyl series. The N-*nitroso-derivative*, formed on treatment with nitrous acid, crystallised from a little methanol as pale yellow plates, m. p. 126° (Found : C, 54·0; H, 4·4. $C_{13}H_{12}ON_5Cl$ requires C, 53·9; H, 4·2%). The *acetyl derivative*, formed by treatment with acetic anhydride, crystallised from light petroleum (b. p. 100—120°) in plates, m. p. 113° (Found : C, 59·3; H, 4·9. $C_{15}H_{15}ON_4Cl$ requires C, 59·5; H, 5·0%).

(*b*) 5-Amino-2-chloro-4-(*N*-2-hydroxyethylbenzylamino)pyrimidine (3·0 g.) was gradually added to phosphoryl chloride (30 c.c.) maintained at room temperature by external cooling. The mixture was left overnight, the suspension dissolving. Volatile constituents were removed at 45° under reduced pressure. Chloroform (50 c.c.) and water (100 c.c.) were added to the residue, followed by sodium hydrogen carbonate, little by little with shaking, until the evolution of carbon dioxide stopped. The chloroform layer was separated, reduced to 10 c.c., and chromatographed on an alumina column with chloroform as eluant, thus giving 8-benzyl-2-chloro-5 : 6 : 7 : 8-tetrahydropteridine (2·0 g.), m. p. 136°, identical with the previous sample. A yellow impurity was retained at the top of the alumina and was shown to contain phosphorus (ammonium molybdate test) but was not characterised further.

5 : 6 : 7 : 8-*Tetrahydropteridine* (III).—Sodium (0·7 g., in pieces) was added to a suspension of finely ground 8-benzyl-2-chloro-5 : 6 : 7 : 8-tetrahydropteridine (2·0 g.) in anhydrous ammonia (150 c.c.), and the reduction was allowed to proceed for 7 min. Excess of ammonium chloride was then added and, after evaporation of the ammonia, the residue was extracted with chloroform. Chromatography of the extracts as above gave 5 : 6 : 7 : 8-*tetrahydropteridine* (0·38 g.), which crystallised from benzene–chloroform (charcoal) as needles, m. p. 146—147° not raised by sublimation at 125°/10^{-4} mm. (Found : C, 52·7; H, 5·9. $C_6H_8N_4$ requires C, 52·8; H, 5·9%).

The *picrate* crystallised from ethanol in yellow needles, m. p. 199—200° (Found : C, 39·8; H, 3·3. $C_6H_8N_4,C_6H_3O_7N_3$ requires C, 39·5; H, 3·0%). Short boiling with methyl iodide in acetone gave the *methiodide*, which crystallised from propanol in needles, m. p. 203° (Found : C, 30·75; H, 4·1. $C_6H_8N_4,CH_3I$ requires C, 30·2; H, 4·0%), and acetic anhydride with the pteridine gave a *diacetyl derivative*, which crystallised from benzene–light petroleum (b. p. 60—80°) as prisms, m. p. 82—83° (Found : C, 54·8; H, 5·4; N, 25·4. $C_{10}H_{12}O_2N_4$ requires C, 54·6; H, 5·5; N, 25·5%). Treatment with formic acid containing 20% of acetic anhydride gave the 5-*formyl derivative*, which crystallised from benzene in prismatic needles, m. p. 177° (Found : C, 51·8; H, 4·9; N, 33·7. $C_7H_8ON_4$ requires C, 51·2; H, 4·9; N, 34·1%).

When a reduction period shorter than 7 min. was used in the experiment above, 8-*benzyl*-5 : 6 : 7 : 8-*tetrahydropteridine* first passed down the alumina column and crystallised from benzene as plates, m. p. 95—96° (Found : C, 69·0; H, 5·9. $C_{13}H_{14}N_4$ requires C, 69·0; H, 6·2%).

2-*Chloro*-4-(N-*ethyl*-2-*hydroxyethylamino*)-6-*methyl*-5-*nitropyrimidine*.—2-Ethylaminoethanol [10] (4·7 g., 2 equiv.) in ether (60 c.c.) was added dropwise to a solution of 2 : 4-dichloro-6-methyl-5-nitropyrimidine (5·6 g.) in ether (150 c.c.), at 0°. Addition was complete in 20 min. and the 2-ethylaminoethanol hydrochloride which had separated was filtered off. The ethereal filtrate gave 2-*chloro*-4-(N-*ethyl*-2-*hydroxyethylamino*)-6-*methyl*-5-*nitropyrimidine* (5·7 g.) which crystallised from light petroleum (b. p. 60—80°) as yellow prisms, m. p. 65° (Found : C, 42·0; H, 5·0. $C_9H_{13}O_3N_4Cl$ requires C, 41·5; H, 5·0%).

5-*Amino*-2-*chloro*-4-(N-*ethyl*-2-*hydroxyethylamino*)-6-*methylpyrimidine*.—The above nitropyrimidine (1·4 g.) in ethanol (30 c.c.) was shaken with Raney nickel (7 c.c.; settled suspension) in hydrogen. Intake of hydrogen ceased in 4 min., the catalyst was filtered off, and the filtrates

[10] Knorr and Schmidt, *Ber.*, 1898, **31**, 1073.

were taken to dryness. The residue, crystallised from carbon tetrachloride, yielded **5-*amino*-2-*chloro*-4-(N-*ethyl*-2-*hydroxyethylamino*)-6-*methylpyrimidine*** (0·95 g.) as platelets, m. p. 99° (Found : C, 46·9; H, 6·7. $C_9H_{15}ON_4Cl$ requires C, 46·9; H, 6·6%).

2-*Chloro*-8-*ethyl*-5 : 6 : 7 : 8-*tetrahydro*-4-*methylpteridine*.—The above 5-aminopyrimidine (0·80 g.) was kept overnight in phosphoryl chloride (10 c.c.). Excess of reagent was removed under reduced pressure and the residue was dissolved in water (20 c.c.) with slight warming. Excess of sodium hydrogen carbonate was added and the solution was extracted with chloroform (3 × 10 c.c.). These extracts gave **2-*chloro*-8-*ethyl*-5 : 6 : 7 : 8-*tetrahydro*-4-*methylpteridine*** which crystallised from *cyclo*hexane as needles (0·5 g.), m. p. 115° (Found : C, 51·1; H, 6·3. $C_9H_{13}N_4Cl$ requires C, 50·8; H, 6·2%).

5 : 6 : 7 : 8-*Tetrahydro*-4-*methylpteridine*.—4-Methylpteridine (0·40 g.) in ether (100 c.c.) was added to lithium aluminium hydride (0·21 g., 10 × theor.) in ether (10 c.c.), the mixture being agitated and protected from air by a stream of dry nitrogen. After 1 hr., excess of hydride was decomposed by ether containing 10% of ethanol, followed by carbon dioxide. The inorganic precipitate was filtered off ("Filtercel") and the cake was washed with ethanol (4 × 50 c.c.). The combined filtrates gave 5 : 6 : 7 : 8-tetrahydro-4-methylpteridine (0·25 g.) which crystallised from benzene in needles, m. p. 145—146°, undepressed on admixture with a sample prepared by the previous route.[1] The base with picric acid gave a picrate, m. p. 263°, identical with the picrate previously obtained.

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