The Synthesis of Compounds with Potential Anti-folic Acid Activity. Part V. 4 : 7-Diamino- and 2 : 4 : 7-Triamino-pteridine and its Derivatives.*

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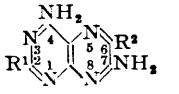
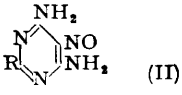
Unequivocal syntheses of 4 : 7-diamino-, 2 : 4 : 7-triamino-, and 4 : 7-diamino-2-methylthiopteridine-6-carboxylic acids and their carboxyamides from 4 : 6-diamino-, 2 : 4 : 6-triamino-, and 4 : 6-diamino-2-methylthio-5-nitrosopyrimidines with cyanoacetic acid and cyanoacetamide are reported. 4 : 7-Diamino- and 2 : 4 : 7-triamino-pteridine were obtained by decarboxylation of the corresponding acids. Sodium alkoxides were effective catalysts for the condensations.

In Part I (*J.*, 1954, 2887) an unequivocal synthesis of 6-aryl-7-aminopteridines was described, but only two pteridines have hitherto been reported which carried a 7-amino-group and were unsubstituted in the 6-position. One compound, 7-aminopteridine (Albert, Brown, and Wood, *J.*, 1954, 3832) was synthesised from 7-hydroxypteridine *via* the 7-mercapto-compound with subsequent amination, and the other, 7-amino-1 : 2 : 3 : 4-tetrahydro-1 : 3-dimethyl-2 : 4-dioxopteridine (Blicke and Godt, *J. Amer. Chem. Soc.*, 1954, **76**, 2798), by the reaction of 5 : 6-diamino-1 : 2 : 3 : 4-tetrahydro-1 : 3-dimethyl-2 : 4-dioxopyrimidine with hydrogen cyanide and formaldehyde, followed by ring closure with potassium hydroxide in methanol and oxidation with hydrogen peroxide. In the latter compound the position of the amino-group is not conclusively proved. Since no 7-amino-6-arylpteridines examined disclosed outstanding anti-folic activity we wished to ascertain the effect of absence of the aryl substituent. By extending the reaction of *o*-aminonitroso-compounds with cyanoacetic acid and amide described by us (*Chem. and Ind.* 1954, 405) to the pyrimidine series we obtained 4 : 7-diamino- (I; $R^1 = R^2 = H$) and 2 : 4 : 7-triamino-pteridine (I; $R^1 = NH_2$, $R^2 = H$) and several of their derivatives.

(I) 

 (II)

4 : 6-Diamino-, 2 : 4 : 6-triamino-, and 4 : 6-diamino-2-methylthio-5-nitrosopyrimidine were readily prepared by nitrosation of the corresponding pyrimidines unsubstituted in the 5-position. 4 : 6-Diamino-5-nitrosopyrimidine (II; R = H) in boiling 2-ethoxyethanol containing 2 mols. of sodium 2-ethoxyethoxide with cyanoacetic acid yielded 4 : 7-diaminopteridine-6-carboxylic acid (I; $R^1 = H$, $R^2 = CO_2H$). Prolonged treatment of the acid with boiling quinoline caused decarboxylation to 4 : 7-diaminopteridine (I; $R^1 = R^2 = H$). Similarly the diamine (II; R = H) with cyanoacetamide under the same conditions gave 4 : 7-diaminopteridine-6-carboxyamide (I; $R^1 = H$, $R^2 = CO{\cdot}NH_2$). 2 : 4 : 6-Triamino-5-nitrosopyrimidine (II; $R = NH_2$) similarly afforded 2 : 4 : 7-triaminopteridine-6-carboxylic acid (I; $R^1 = NH_2$, $R^2 = CO_2H$) and its amide. Prolonged boiling of the acid in quinoline in the presence of copper bronze yielded a small amount of 2 : 4 : 7-triaminopteridine (I; $R^1 = NH_2$, $R^2 = H$) together with dark amorphous material, probably a decomposition product. Treatment of the triaminopteridinecarboxyamide with hot acetic anhydride yielded the triacetamido-derivative. 4 : 6-Diamino-2-methylthio-5-nitrosopyrimidine (II; R = MeS) gave 4 : 7-diamino-2-methylthiopteridine-6-carboxylic acid (I; $R^1 = MeS$, $R^2 = CO_2H$) and its amide. The latter with hot acetic anhydride yielded the diacetamido-derivative.

Ultraviolet absorption spectra of 4 : 7-diaminopteridine and the 6-carboxylic acid and its amide in acid solution are given in the Experimental section.

* Part IV, preceding paper.

Experimental

4 : 7-*Diaminopteridine*-6-*carboxylic Acid*.—4 : 6-Diamino-5-nitrosopyrimidine (3·2 g.) and cyanoacetic acid (2·0 g.) were added to a solution of sodium (1·1 g.) in 2-ethoxyethanol (200 ml.), and the mixture was boiled for 15 min. during which a thick brown precipitate was deposited. After filtration, the precipitate was acidified with acetic acid and the buff material thus obtained was recrystallised several times from water (charcoal), to yield 4 : 7-*diaminopteridine*-6-*carboxylic acid* (2·1 g.) as yellow irregular plates, m. p. 292° (effervescence) (Found, in material dried at 180° : C, 41·2; H, 2·9; N, 40·0. $C_7H_6O_2N_6$ requires C, 40·8; H, 2·9; N, 40·8%). Absorption in 4½% H·CO_2H : max. at 269 and 369 mμ (ε 21·4 and 11·3 × 10^3); min. at 302 mμ (ε 2·0 × 10^3).

4 : 7-*Diaminopteridine*.—4 : 7-Diaminopteridine-6-carboxylic acid (1·0 g.) was boiled with quinoline (25 ml.) for 1 hr. On cooling, a brown crystalline precipitate was deposited which was removed and washed with light petroleum (b. p. 40—60°). Several crystallisations from water (charcoal) yielded 4 : 7-*diaminopteridine* as pale yellow needles, m. p. > 300° (Found, in material dried at 180° : C, 45·1; H, 3·4; N, 51·5. $C_6H_6N_6$ requires C, 44·5; H, 3·7; N, 51·8%). Absorption in 4½% H·CO_2H : max. at 255, 285, and 343 mμ (ε 14·8, 4·4, and 12·5 × 10^3); min. at 272 and 300 mμ (ε 3·8, 3·8 × 10^3).

4 : 7-*Diaminopteridine*-6-*carboxyamide*.—To a solution of sodium (0·15 g.) in 2-ethoxyethanol were added 4 : 6-diamino-5-nitrosopyrimidine (0·7 g.) and cyanoacetamide (0·85 g.), and the mixture was boiled under reflux for 2 min., during which a yellow precipitate was formed. After filtration the material was recrystallised from water to yield 4 : 7-*diaminopteridine*-6-*carboxyamide* (0·87 g.), pale yellow needles, m. p. > 300° (Found : C, 40·8; H, 3·55; N, 46·1. $C_7H_7ON_7$ requires C, 41·0; H, 3·4; N, 47·3%). Absorption in 4½% H·CO_2H : max. at 271 and 374 mμ (ε 22·7 and 10·6 × 10^3); min. at 304 mμ (ε 1·5 × 10^3).

2 : 4 : 7-*Triaminopteridine*-6-*carboxylic Acid*.—Finely powdered 2 : 4 : 6-triamino-5-nitrosopyrimidine (4·62 g.) and cyanoacetic acid (2·8 g.) were heated in a solution of sodium (1·5 g.) in 2-ethoxyethanol (250 ml.) for 2½ hr. After cooling in ice, the yellowish-brown precipitate was removed and recrystallised from 30% formic acid. Further purification of the material by several dissolutions in dilute ammonia solution followed by reprecipitation with dilute acetic acid yielded 2 : 4 : 7-*triaminopteridine*-6-*carboxylic acid* as needles, m. p. >300° (Found : C, 35·2; H, 3·75; N, 40·7. $C_7H_7O_2N_7,H_2O$ requires C, 35·15; H, 3·8; N, 41·0%).

2 : 4 : 7-*Triaminopteridine*.—2 : 4 : 7-Triaminopteridine-6-carboxylic acid (1·0 g.), redistilled quinoline (50 ml.), and a trace of copper bronze powder were boiled for 7 hr. The hot solution was filtered and on cooling deposited crystals (0·24 g.). Several crystallisations from very dilute ammonia solution yielded 2 : 4 : 7-*triaminopteridine* as straw-coloured silky needles, m. p. > 300° (Found, in material dried at 150° : C, 41·3; H, 3·6; N, 55·3. $C_6H_7N_7$ requires C, 40·7; H, 4·0; N, 55·35%).

2 : 4 : 7-*Triaminopteridine*-6-*carboxyamide*.—2 : 4 : 6-Triamino-5-nitrosopyrimidine (3·0 g.) and cyanoacetamide (1·8 g.) were heated in a solution of sodium (0·5 g.) in 2-ethoxyethanol (200 ml.) for 5 min. A further 1 g. of cyanoacetamide was added and the mixture was boiled for another 5 min. The light brown crystalline precipitate was removed and extracted three times with boiling water. Crystallisation of the residue from dilute aqueous dimethylformamide yielded 2 : 4 : 7-*triaminopteridine*-6-*carboxyamide* (2·1 g.), m. p. > 300° (Found, in material dried at 110° : C, 36·4, 36·2; H, 4·4, 4·2; N, 48·4, 48·2. $C_7H_8ON_8,\frac{5}{8}H_2O$ requires C, 36·3; H, 4·0; N, 48·4%). Treatment of the amide with hot acetic anhydride yielded the *triacetyl derivative* which was crystallised from aqueous dimethylformamide (Found, in material dried at 150° : C, 44·5; H, 4·3; N, 30·8. $C_{13}H_{14}O_4N_8,\frac{1}{2}H_2O$ requires C, 43·9; H, 4·3; N, 31·5%).

4 : 7-*Diamino*-2-*methylthiopteridine*-6-*carboxylic Acid*.—4 : 6-Diamino-2-methylthio-5-nitrosopyrimidine (1·84 g.) and cyanoacetic acid (1·0 g.) were boiled in a solution of sodium (1·0 g.) in ethanol (200 ml.) for 1 hr. The ethanol was removed and the residue was triturated with ether to give a solid material (2·4 g.) which was rapidly dissolved in boiling water (charcoal) and filtered. Acidification with dilute hydrochloric acid yielded a pink precipitate which was dissolved in hot dilute ammonia solution which was then acidified to pH 5. When scratched, the hot solution deposited unchanged nitroso-compound which was removed. The resulting yellow solution was acidified with an excess of glacial acetic acid, a pale yellow granular solid being obtained. The solid was purified by several precipitations from dilute ammonia with acetic acid to yield 4 : 7-*diamino*-2-*methylthiopteridine*-6-*carboxylic acid* as pale yellow microscopic needles, m. p. > 300° (Found, in material dried at 150° : N, 33·2. $C_8H_8O_2N_6S$ requires N, 33·3%).

4 : 7-*Diamino*-2-*methylthiopteridine*-6-*carboxyamide*.—4 : 6-Diamino-2-methylthio-5-nitrosopyrimidine (0·9 g.) and cyanoacetamide (0·5 g.) were added to a solution of sodium (0·15 g.) in ethanol (100 ml.). Raising the mixture to the b. p. gave a clear solution which then deposited a yellow precipitate. After boiling for 2 min., the mixture was cooled and the precipitate removed. Recrystallisation from acetic acid followed by one crystallisation from *n*-butanol yielded **4 : 7-*diamino*-2-*methylthiopteridine*-6-*carboxyamide*** as light yellow needles, m. p. > 300° (Found, in material dried at 150° : C, 38·6; H, 3·9; N, 38·2; S, 12·3. $C_8H_9ON_7S$ requires C, 38·2; H, 3·6; N, 39·0; S, 12·7%). Treatment of the amide with hot acetic anhydride yielded the corresponding **4 : 7-*diacetamido*-**derivative (from dimethylformamide) (Found, in material dried at 150° : C, 43·5; H, 4·0. $C_{12}H_{13}O_3N_7S$ requires C, 43·0; H, 3·9%).

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