

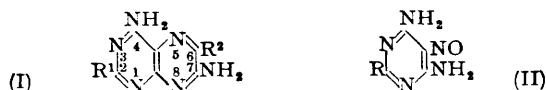
2036 *Osdene and Timmis: The Synthesis of Compounds with**The Synthesis of Compounds with Potential Anti-folic Acid Activity. Part V.* 4:7-Diamino- and 2:4:7-Triamino-pteridine and its Derivatives.*

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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-dioxypyrimidine 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.



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. $C_7H_6O_2N_4$ requires C, 40.8; H, 2.9; N, 40.8%). Absorption in 4½% $H\cdot CO_2H$: max. at 269 and 369 $m\mu$ (ϵ 21.4 and 11.3×10^3); min. at 302 $m\mu$ (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. $C_6H_6N_4$ requires C, 44.5; H, 3.7; N, 51.8%). Absorption in 4½% $H\cdot CO_2H$: max. at 255, 285, and 343 $m\mu$ (ϵ 14.8, 4.4, and 12.5×10^3); min. at 272 and 300 $m\mu$ (ϵ 3.8, 3.8×10^3).

4 : 7-Diaminopteridine-6-carboxamide.—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-carboxamide (0.87 g.), pale yellow needles, m. p. > 300° (Found : C, 40.8; H, 3.55; N, 46.1. $C_7H_7ON_4$ requires C, 41.0; H, 3.4; N, 47.3%). Absorption in 4½% $H\cdot CO_2H$: max. at 271 and 374 $m\mu$ (ϵ 22.7 and 10.6×10^3); min. at 304 $m\mu$ (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. $C_7H_7O_2N_7\cdot H_2O$ 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-carboxamide.—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-carboxamide (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. $C_7H_8ON_8\cdot \frac{5}{8}H_2O$ requires C, 36.3; H, 4.0; N, 48.4%). Treatment of the amide with hot acetic anhydride yielded the *triacyl derivative* which was crystallised from aqueous dimethylformamide (Found, in material dried at 150° : C, 44.5; H, 4.3; N, 30.8. $C_{13}H_{14}O_4N_8\cdot \frac{1}{2}H_2O$ 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-nitroso-pyrimidine** (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. $C_8H_6ON_7S$ 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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