306. *Pyrimidines. Part II.*

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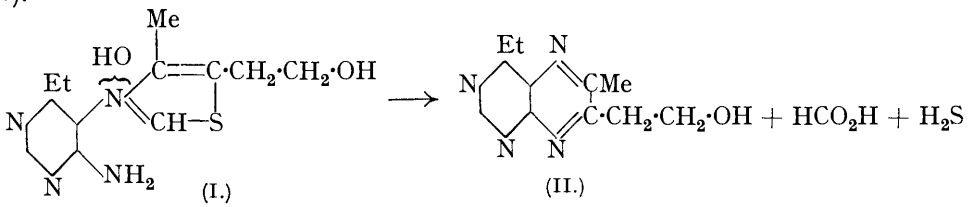
The object of the present experiments is the eventual synthesis of analogues of vitamin-B_1 which Professor R. A. Peters requires in connexion with his studies of the relation between physiological action and chemical constitution in the group.

As the result of a brilliant investigation, Williams and his co-workers (*J. Amer. Chem. Soc.*, 1935, **57**, 229, 536) have advanced the view that the expression (I) represents the constitution of the vitamin and, although the full details have not yet been disclosed, this formula is certainly in good agreement with the behaviour of the substance. Thus, although vitamin-B_1 appears to be unimpaired in activity after treatment with nitrous acid in acid solution (Peters, 1923 and private communication; von Veen, *Rec. trav. chim.*, 1932, **51**, 279), the existence of the quaternary ammonium group may greatly reduce the effective basic function of the free amino-group, especially as the spatial proximity of the two groups would favour the inhibition contemplated.

The formula is also resourceful in connexion with the formation of various pyrimidazine degradation products. The action of alkaline agents might proceed as shown below and account for one of the fluorescent substances encountered by Peters (*Nature*, 1935, **135**, 107).



(I.) (II.)

In the hope of synthesising a pyrimidazine of the type (II), we have prepared 4 : 5-*diamino*-6-*ethylpyrimidine* (III), following a method devised by Gabriel and Colman (*Ber.*, 1907, **34**, 1266) for the lower homologue.

6-Ethyluracil (Wheeler and Bristol, *J. Amer. Chem. Soc.*, 1905, **33**, 446), obtained originally from ethyl-ψ-thiourea, cannot be prepared by the condensation of ethyl propionylacetate and urea; it was, however, accessible from 6-*ethyl*-2-*thiouracil* (IV) by interaction with hot dilute nitric acid.

(III.) (IV.) (V.) (VI.)

5-*Nitro*-6-*ethyluracil* (V) was converted into 2 : 4-*dichloro*-5-*nitro*-6-*ethylpyrimidine* (VI), and then into 2-*chloro*-5-*nitro*-4-*amino*-6-*ethylpyrimidine* (VII) by the action of ammonia. The corresponding diamine condenses with benzil to (VIII), so the chlorine atom in position 4 is the more reactive (compare Gabriel and Colman, *loc. cit.*). The elimination of the chlorine atom in position 2 was effected by means of hydrazine in the presence of palladised strontium carbonate, and the base (III) obtained.

(VII.) (VIII.)

Experimental.

6-*Ethyl*-2-*thiouracil* (IV).—Ethyl propionylacetate (43·3 g.) (Willstätter and Clarke, *Ber.*, 1916, **47**, 298) and thiourea (22·8 g.) were dissolved in alcoholic sodium ethoxide (7·0 g. of sodium

in 150 c.c.) and the solution was refluxed for 2 hours and then evaporated. On addition of acetic acid to an aqueous solution of the residue, *ethylthiouracil* separated. It crystallised from water in colourless prisms (31 g.), m. p. 228° (Found: C, 45·8; H, 5·2. $C_6H_8ON_2S$ requires C, 46·2; H, 5·1%). The condensation was also accomplished in cold alcoholic solution in the presence of hydrogen chloride.

When ethylthiouracil (2 g.) was gently heated with nitric acid (25 c.c. of 2·5*N*), a brisk evolution of nitrous fumes occurred and the solid passed into solution. Ammonia was added until present in excess and the liquid was evaporated to dryness on the steam-bath. The residue was washed by trituration with water and then crystallised from water. The ethyluracil separated in colourless prisms, m. p. 205° (yield, 50—55%) (Found: C, 51·1; H, 6·0. Calc. for $C_6H_8O_2N_2$: C, 51·4; H, 5·7%). Methyluracil was obtained from methylthiouracil by a similar procedure.

5-*Nitro*-6-*ethyluracil* (V).—Ethyluracil (1 g.) was added to a mixture of equal parts of fuming nitric and sulphuric acids (4 c.c.) at 25—30°. The solution was poured on ice and the faintly yellow, crystalline precipitate was recrystallised from water, separating in yellowish prisms, m. p. 230° (decomp.) (Found: C, 39·1; H, 3·8. $C_6H_7O_4N_3$ requires C, 38·9; H, 3·8%). The yield was almost quantitative.

2 : 4-*Dichloro*-5-*nitro*-6-*ethylpyrimidine* (VI).—A mixture of nitroethyluracil (4 g.) and phosphoryl chloride (8 c.c.) was heated in a sealed tube at 130° for 1·5 hours. The resulting brown liquid was added to ice, and the solution extracted with light petroleum. After being dried with sodium sulphate, the extract was concentrated, and the yellow residual oil was distilled in a vacuum; it then solidified to an almost colourless mass, m. p. 31° (Found: Cl, 31·3. $C_6H_5O_2N_3Cl_2$ requires Cl, 31·9%). The yield was unsatisfactory (25% or less) and variable; also the product could not be crystallised from a solution.

2-*Chloro*-5-*nitro*-4-*amino*-6-*ethylpyrimidine* (VII).—When the above dichloro-compound (2 g.) was triturated with cold aqueous ammonia (10 c.c., *d* 0·880), it became liquid but later solidified to a yellowish crystalline mass. The product (1·5 g.) crystallised from alcohol in pale yellow plates, m. p. 140—141°, which rapidly became darker on exposure to light (Found: C, 35·8; H, 3·7. $C_6H_7O_2N_4Cl$ requires C, 35·6; H, 3·5%).

2-*Chloro*-4 : 5-*diamino*-6-*ethylpyrimidine*.—The nitroamine (VII) was reduced by a method similar to that used by Gabriel and Colman (*loc. cit.*) for the corresponding methyl compound. The base (1·5 g.) was added slowly to hydrated stannous chloride (7·5 g.) in concentrated hydrochloric acid (7·5 c.c.); the solution became hot and it was placed on a boiling water-bath for 5 minutes, diluted with water, and sufficient potassium hydroxide added to precipitate the tin and redissolve the hydroxide. The solution was then extracted with ether; after the solvent had been evaporated, a colourless solid remained. This crystallised from water in fine needles, which fell to a powder, m. p. 203°, on drying (yield, 1 g.) (Found: C, 42·0; H, 5·6; N, 32·4. $C_6H_9N_4Cl$ requires C, 41·8; H, 5·2; N, 32·6%).

The Condensation of 2-*Chloro*-4 : 5-*diamino*-6-*ethylpyrimidine with Benzil*.—Equal weights of the reactants were heated together at 145° for 14 minutes. The product was rubbed with alcohol and then recrystallised from alcohol, from which 7-*chloro*-2 : 3-*diphenyl*-5-*ethylpyrimidazine* (VIII) separated in orange-yellow plates, m. p. 179—181° (Found: C, 69·5; H, 4·6. $C_{20}H_{15}N_4Cl$ requires C, 69·3; H, 4·3%). An aqueous-alcoholic solution of the substance exhibits a bluish-green fluorescence.

4 : 5-*Diamino*-6-*ethylpyrimidine* (III).—2-Chloro-4 : 5-diamino-6-ethylpyrimidine (0·5 g.) was dissolved in alcohol (100 c.c.) and fresh alcoholic potassium hydroxide (50 c.c. of 10%) together with palladised strontium carbonate (5 g. of 2%) was added. The solution was then mixed with hydrazine hydrate (40 drops) and boiled for ½ hour on a steam-bath. After filtration and washing with alcohol and water the filtrate was concentrated to remove the alcohol, diluted somewhat with water, and washed with ether, which removed a little oily matter. The aqueous solution was concentrated to a small bulk, carbon dioxide being passed in to neutralise the alkali. A precipitate, which formed on cooling, was collected and dried. It was extracted with cold acetone and the acetone solution was evaporated to dryness. The yellowish crystalline residue was recrystallised from ethyl acetate, from which 4 : 5-*diamino*-6-*ethylpyrimidine* separated in large, pale yellow prisms, m. p. 159—161° (Found: C, 52·4; H, 7·5; N, 40·3. $C_6H_{10}N_4$ requires C, 52·2; H, 7·2; N, 40·6%). The substance was soluble in water and alcohol but very sparingly soluble in ether.

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