101. *Experiments on the Synthesis of Purine Nucleosides. Part II. A New and Convenient Synthesis of Adenine.*

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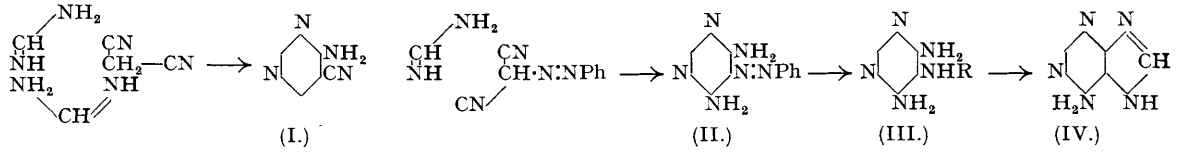
In the course of model experiments, a new synthesis of adenine has been carried out. Formamidine condensed with benzeneazomalononitrile to give 4 : 6-*diamino-5-benzeneazopyrimidine*, readily reduced to 4 : 5 : 6-*triaminopyrimidine*. The *thioformyl* derivative of this compound on boiling in aqueous or pyridine solution was converted into adenine. The overall yield of adenine was high. In the course of experiments on other methods for preparing 4 : 5 : 6-triaminopyrimidine, an interesting condensation of formamidine with malononitrile to 4-*amino-5-cyanopyrimidine* has been observed.

Before attempting to prepare a 5 : 6-diamino-4-glycosidaminopyrimidine, a necessary intermediate for the synthesis of a 9-glycosidoadenine by the route proposed in the preceding paper, we decided to prepare the parent 4 : 5 : 6-*triaminopyrimidine*, and from it to effect a synthesis of adenine. In his synthesis of adenine, Traube (*Annalen*, 1904, **331**, 64) avoided the difficulty presented by the preparation of this compound by using the more accessible 4 : 5 : 6-triamino-2-thiolpyrimidine; this was converted into 2-thioladenine and desulphurised by treatment with hydrogen peroxide in warm acid solution. The overall yield in this synthesis is poor and as a model for an adenosine synthesis it is of little value, since hydrolysis of the glycosidic linkage would almost certainly occur during desulphurisation. A convenient method for the preparation of pyrimidines unsubstituted in position 2 would therefore be essential for our purposes. Only a few pyrimidines of this type have been described in the literature. They have generally been prepared from the corresponding 2-hydroxypyrimidines by halogenation and reduction (*e.g.*, Angerstein, *Ber.*, 1901, **34**, 3957) or, less frequently, by desulphurisation of 2-thiolpyrimidines by means of hydrogen peroxide (Andersag and Westphal, *Ber.*, 1937, **70**, 2035) or decarboxylation of pyrimidine-2-carboxylic acids (Gabriel and Colman, *Ber.*, 1899, **32**, 1531). Of the aminopyrimidines containing a free 2-position, 4-aminopyrimidine and 4 : 6-diaminopyrimidine have been prepared from 2 : 4 : 6-trichloropyrimidine by Büttner (*Ber.*, 1903, **36**, 2231), but the yields were very low and the method is unsuitable for preparative purposes.

The successful use of formamidine as an intermediate in the synthesis of pyrimidines containing a free 2-position has not hitherto been reported, although alkyl- and aryl-amidines have been widely used in pyrimidine syntheses. Traube (*loc. cit.*) records a failure to isolate any product from the condensation of formamidine with ethyl cyanoacetate. We failed to effect condensation of formamidine with aminomalononitrile, but malononitrile itself condensed readily with formamidine in alcoholic solution. The product, however, was not the expected 4 : 6-diaminopyrimidine, but a substance, $C_5H_4N_4$, identical with the condensation product of thioformamide and aminomethylenemalononitrile (cf. condensation of thioacetamide with aminomethylenemalononitrile in Hoffmann-La Roche, B.P. 546,624). It is therefore 4-*amino-5-cyanopyrimidine* (I), formed by condensation of two molecules of formamidine with malononitrile. This mode of reaction is to be attributed to the reactive nature of the methylene group in malononitrile, an intermediate product being presumably aminomethylenemalononitrile. The unusual course of this reaction led us to investigate the reaction between formamidine and other compounds containing a reactive methylene group; the results will be communicated in a separate paper.

The preparation of 4 : 5 : 6-triaminopyrimidine in quantity by nitrosation and reduction of 4 : 6-diaminopyrimidine being dependent on the development of a satisfactory process for synthesising the latter compound, we turned our attention to an alternative route. Formamidine and benzeneazomalononitrile condensed smoothly to give 4 : 6-*diamino-5-benzeneazopyrimidine* (II), reduced by hydrogen in presence of Raney nickel to 4 : 5 : 6-tri-

aminopyrimidine (III; R = H). On treatment with aqueous sodium dithioformate (III; R = H) gave 4 : 6-*diamino-5-thioformamidopyrimidine* (III; R = CHS), which on boiling in aqueous or pyridine solution evolved hydrogen sulphide, yielding adenine (IV). The identity of the product was confirmed by direct comparison with adenine from natural sources. Attention is drawn to the fact that the synthesis described gives an overall yield of more than 50% (based on malononitrile), which is a marked improvement on the original Traube method, and makes adenine a readily accessible compound. Similar methods of synthesis could probably be applied in the case of other naturally occurring purines.



(I.) (II.) (III.) (IV.)

Experimental.

Condensation of Formamidine with Malononitrile.—To a solution of formamidine hydrochloride (3·6 g.) and malononitrile (2·0 g.) in absolute alcohol (90 c.c.), alcoholic sodium ethoxide (1·02 g. of sodium in 30 c.c. of absolute alcohol) was added, and the mixture, which evolved ammonia, left at room temperature for 24 hours. The precipitate was collected, washed with cold water to remove sodium chloride, and dried; a further quantity of the same product separated on concentration of the alcoholic mother-liquor. The combined product was sublimed in a vacuum, colourless needles of 4-*amino-5-cyanopyrimidine* (I), m. p. 250°, being obtained (yield, 45%) (Found : C, 50·0; H, 3·4; N, 46·0. $C_5H_4N_4$ requires C, 50·0; H, 3·3; N, 46·4%). The substance was soluble in hot water or dilute hydrochloric acid, but sparingly so in cold water or alcohol; its aqueous solution was neutral to litmus. The *picrate* crystallised from water in yellow needles, m. p. 189° (Found : C, 38·7; H, 2·6; N, 27·3. $C_5H_4N_4,C_6H_3O_7N_3$ requires C, 38·0; H, 2·0; N, 28·0%). Acetylation of 4-amino-5-cyanopyrimidine (0·5 g.) with boiling acetic anhydride for 15 minutes, followed by evaporation in a vacuum and crystallisation from alcohol gave colourless needles (0·5 g.), m. p. 124—125°, soluble in water and alcohol (Found : C, 51·9; H, 3·7. $C_7H_6ON_4$ requires C, 52·0; H, 3·7%). On acetylation of 4-amino-5-cyano-2-methylpyrimidine the expected 4-acetamido-compound is not obtained, the pyrimidine ring opening to give acetylacetamidinomethylenemalononitrile (unpublished observations of Dr. F. Bergel), and we therefore consider our substance, which resembles the latter in properties, to be *acetylformamidinomethylenemalononitrile*.

4-Amino-5-cyanopyrimidine was also obtained by refluxing aminomethylenemalononitrile (0·93 g.), alcoholic sodium ethoxide (0·23 g. of sodium in 10 c.c. of alcohol), and thioformamide (0·61 g.) for ½ hour. The product (0·4 g.) which separated on cooling was collected; it had m. p. 250°, undepressed on admixture with the product from formamidine and malononitrile. (This experiment was carried out by Mr. G. W. Kenner.)

4 : 6-*Diamino-5-benzeneazopyrimidine* (II).—Alcoholic sodium ethoxide (1·25 g. of sodium in 20 c.c. of absolute alcohol) was added to a solution of benzeneazomalononitrile (6·1 g.) (Hantzsch and Thompson, *Ber.*, 1905, **38**, 2266) and formamidine hydrochloride (4·3 g.) in absolute alcohol (80 c.c.), and the mixture kept for 1 hour at room temperature and then refluxed for ¾ hour. After dilution with water (300 c.c.) the red solid was collected and recrystallised from alcohol–pyridine (3 : 1). 4 : 6-*Diamino-5-benzeneazopyrimidine* separated in red-brown plates, m. p. 282—286° (decomp.). Yield, 75% (Found : C, 56·2; H, 4·5. $C_{10}H_{10}N_6$ requires C, 56·1; H, 4·7%).

4 : 5 : 6-*Triaminopyrimidine* (III; R = H).—The above azo-compound (2 g.) was dissolved in alcohol (800 c.c.) and hydrogenated (6 hours) at 100°/60 atms. in presence of Raney nickel (0·5 g.). The pale brown solution was filtered from catalyst and evaporated under reduced pressure, and the residue, freed from aniline by washing with ether, recrystallised from alcohol. 4 : 5 : 6-*Triaminopyrimidine* was thus obtained in colourless needles, m. p. 257°. Yield, 90% (Found : C, 38·6; H, 5·8; N, 55·4. $C_4H_7N_5$ requires C, 38·5; H, 5·6; N, 55·9%). The triamine was soluble in cold water and alcohol; aqueous solutions were alkaline to litmus. In one experiment the triamine was accompanied by a small amount of a less soluble substance which separated from the alcoholic reduction solution in yellow plates, m. p. 258° (Found : C, 57·6; H, 4·8; N, 36·6%); it has not yet been further investigated.

4 : 6-*Diamino-5-thioformamidopyrimidine* (III; R = CHS).—The above triamine (1 g.) was dissolved in the minimum quantity of cold water, and sodium dithioformate (2 g.) added. After 12 hours the *thioformyl* derivative was collected and recrystallised from hot water, forming colourless needles (1 g.) which had no m. p. but evolved hydrogen sulphide rapidly above 200° (Found : C, 35·9; H, 4·4; N, 41·0; S, 18·6. $C_5H_7N_5S$ requires C, 35·5; H, 4·1; N, 41·5; S, 18·9%).

Adenine (IV).—The thioformamido-compound (III; R = CHS) (1·0 g.) was suspended in water (20 c.c.), and the mixture refluxed for 12 hours. Hydrogen sulphide was evolved and the solid dissolved completely. On cooling, adenine separated in long colourless needles, m. p. 360° (yield, almost quantitative) (Found for material dried in a vacuum at 110° : C, 44·6; H, 4·0; N, 51·2. Calc. for $C_5H_5N_5$: C, 44·5; H, 3·7; N, 51·9%). The product showed the dimorphism described for adenine by Kossel (*Z. physiol. Chem.*, 1896, **20**, 253) and gave the characteristic colour in Kossel's test (*ibid.*, 1888, **12**, 252). The picrate, silky yellow needles, had m. p. 292°, undepressed by authentic adenine picrate (m. p. 292°). Comparison of the ultraviolet absorption spectrum of the synthetic product with that of authentic natural adenine showed no divergence [maximum at 2630 A. (ε 16,700) in N/20-hydrochloric acid and 2680 A. (ε 15,400) in N/100-sodium hydroxide]. The conversion of (III; R = CHS) into adenine is accomplished more rapidly by using pyridine or quinoline in place of water as a solvent.

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