183. *Experiments on the Synthesis of Purine Nucleosides. Part XIII. An Improved Method for the Cyclisation of 4-Glycosidamino-5-thioformamidopyrimidines.*

By G. W. Kenner and A. R. Todd.

As anticipated on theoretical grounds alcoholic alkoxide solutions have proved effective reagents for the cyclisation of 4-glycosidamino-5-thioformamidopyrimidines to 9-glycosidopurines. Both 6-amino-4-*d*-xylopyranosidamino-5-thioformamido-2-methylthiopyrimidine (I; R = MeS; R_1 = *d*-xylosido) and its triacetyl derivative (I; R = MeS; R_1 = triacetyl-*d*-xylosido) give exclusively 9-*d*-xylopyranosido-2-methylthioadenine by this method, whereas the triacetyl derivative heated with a mixture of potassium acetate and acetic acid in methyl cyanide solution gives 6-triacetyl-*d*-xylopyranosidamino-2-methylthiopurine. The results obtained with acetylated compounds are interpreted in terms of a chelation hypothesis.

The cyclisation of 4-amino-5-thioformamidopyrimidines to yield purine derivatives, first observed by Todd, Bergel, and Karimullah (*J.*, 1936, 1557) was extended by Baddiley, Lythgoe, McNeil, and Todd (Part I; *J.*, 1943, 383) and utilised for the synthesis of 9-alkylpurines in excellent yield. In subsequent papers of this series (Parts VI, IX, X, XI; *J.*, 1944, 318, 652, 657; 1945, 556) analogous syntheses of 9-glycosidopurines have been effected by cyclisation of 4-glycosidamino-5-thioformamidopyrimidines in boiling pyridine solution. In this important field, however, the yields obtained were frequently low and isolation of the products was complicated by extensive decomposition during the reaction. These defects in the final stage of the method were especially serious in studies now in progress on the synthesis of 9-glycofuranosidoadenines where the pyrimidine intermediates were likely to be at once less accessible and less stable than those employed in the syntheses of 9-glycopyranosidoadenines already described. Accordingly the cyclisation procedure has been re-examined with the object of practical improvement.

We consider that the mechanism of the cyclisation reaction is satisfactorily represented by Scheme 1. In it the function of the base *B* in promoting the initial prototropic change and the final ring-closure was presumably fulfilled in earlier experiments (*loc. cit.*) by the solvent employed (water, pyridine, quinoline). It appeared noteworthy that Howard, Lythgoe, and Todd (Part XI; *loc. cit.*) observed ready cyclisation of 6-amino-4-*d*-xylopyranosidamino-5-thioformamido-2-methylthiopyrimidine * in aqueous alkali, although considerable quantities of the corresponding 5-formamido-compound were simultaneously formed. It was therefore expected that the use of alcoholic sodium alkoxide solutions as cyclisation media might prove successful, and this was borne out by experiment; cyclisation of 6-amino-4-*d*-xylopyranosidamino-5-thioformamido-2-methylthiopyrimidine by this method proceeded smoothly giving 9-*d*-xylopyranosido-2-methylthioadenine. From a series of experiments using methanol, ethanol, and *n*-propanol it appeared that best results were obtained by refluxing the thioformamido-compound in ethanol with one mol. of sodium alkoxide. Under these conditions the thioformamido-compound dissolved slowly and yields of *ca.* 63% were obtained; if the amount of alkoxide was increased immediate dissolution of the thioformamido-compound occurred but the yield of product was somewhat lower. Reactions in *iso*propanol and *tert.*-butanol were accompanied by considerable darkening and were less successful. A point of interest in these experiments is that, although

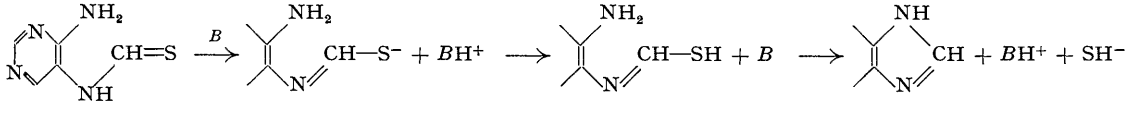
* In previous papers of this series the term pyranoside has been applied only to glycosides in which the lactol ring structure has been rigidly established. In view of the virtual certainty of the ring-structure of this and other pyrimidine glycosides mentioned in this paper and to avoid confusion in later recording studies on furanosides we have assumed the pyranoside structure in naming them.

in one case a small amount of 6-amino-4-*d*-xylopyranosidamino-5-formamido-2-methylthiopyrimidine was formed as a by-product, no 6-*d*-xylopyranosidamino-2-methylthiopurine was ever isolated.

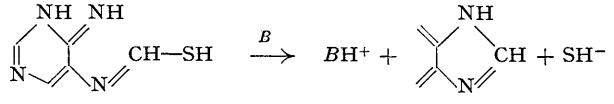
Baddiley, Lythgoe, and Todd (Part VI; *loc. cit.*) prepared 6-amino-4-*d*-xylopyranosidamino-5-thioformamido-2-methylpyrimidine (I; R = Me; R_1 = *d*-xylosido) but were unable to cyclise it by boiling it in pyridine solution; the corresponding triacetyl compound (I; R = Me; R_1 = triacetyl-*d*-xylosido), however, yielded, under similar conditions, a mixture of 9-triacetyl-*d*-xylopyranosido-2-methyladenine (II; R = Me, R_1 = triacetyl-*d*-xylosido) and 6-triacetyl-*d*-xylopyranosidamino-2-methylpurine (III; R = Me; R_1 = triacetyl-*d*-xylosido) in moderate yield. Application of the alkoxide method to (I; R = Me; R_1 = *d*-xylosido) gave the 9-substituted purine (II; R = Me; R_1 = *d*-xylosido) in a yield of *ca.* 20% while the same product was obtained in 63% yield by heating the corresponding triacetyl derivative with 1 mol. of sodium methoxide in ethanol under anhydrous conditions. The preparation of 9-*d*-xylopyranosidoadenine and 9-*d*-ribopyranosidoadenine from the appropriate triacetylthioformamido-compounds was effected with equal ease. Whether the low yield in the case of 6-amino-4-*d*-xylopyranosidamino-5-thioformamido-2-methylpyrimidine is to be ascribed to the low solubility of this compound or to a structural difference from the product of deacetylation of 6-amino-4-triacetyl-*d*-xylopyranosidamino-5-thioformamido-2-methylpyrimidine is not at present clear.

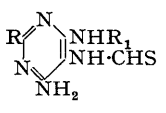
In none of the above experiments was any 6-glycosidaminopurine obtained, in contrast to the general production of such compounds when acetylated thioformamidoglycosides are cyclised by heating in pyridine solution. Since deacetylation is very rapid in hot sodium alkoxide solution (Zemplén and Pacsu, *Ber.*, 1929, **62**, 1613) all the experiments with acetylated glycosides should be regarded as effectively ring-closures of acetyl-free glycosides; indeed, the behaviour of 6-amino-4-*d*-xylopyranosidamino-5-thioformamido-2-methylthiopyrimidine in ethanolic sodium methoxide is indistinguishable from that of its triacetyl derivative. The present results are thus in agreement with the observation recorded in Part XI (*loc. cit.*) that no 6-glycosidaminopurine is obtained on cyclising 6-amino-4-*d*-xylopyranosidamino-5-thioformamido-2-methylthiopyrimidine and with the views expressed in Part I (*loc. cit.*), where it was shown that almost quantitative yields of 2 : 9-dimethyladenine and 2-methylthio-9-methyladenine are obtained, to the exclusion of the 6-methylaminopurines, by cyclising the corresponding 6-amino-4-methylamino-5-thioformamidopyrimidines. It was suggested that such thioformamido-compounds exist in form (IV) rather than (V), and it was implied that ring-closure occurred by the mechanism shown in Scheme 1 and not by that in Scheme 2, which involves the intervention of an imino-group and elimination of a proton from elsewhere in the molecule.

Scheme 1 :

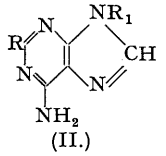


Scheme 2 :

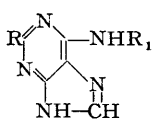




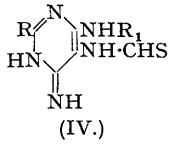
(I.)



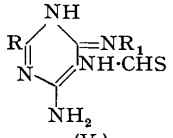
(II.)



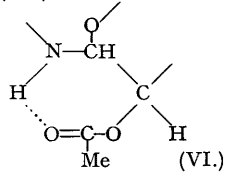
(III.)



(IV.)



(V.)



(VI.)

These considerations naturally require exclusive formation of 9-alkylpurines and, by analogy, 9-glycosidopurines when compounds of type I are cyclised. By employing base catalysis under conditions which nevertheless avoided deacetylation, we have been able to confirm that acetylation of the sugar residue alters this situation. Treatment of 6-amino-4-triacetyl-*d*-xylopyranosidamino-5-thioformamido-2-methylthiopyrimidine (I; R = MeS; R_1 = triacetyl-*d*-xylosido) with 4 mols. of potassium acetate and 2 mols. of acetic acid in boiling anhydrous methyl cyanide gave a substantial yield of 6-triacetyl-*d*-xylopyranosidamino-2-methylthiopurine (III; R = MeS; R_1 = triacetyl-*d*-xylosido). Under similar conditions 6-amino-4-triacetyl-*d*-xylopyranosidamino-5-thioformamidopyrimidine (I; R = H; R_1 = triacetyl-*d*-xylosido) was much less reactive and gave only a small amount of 9-*d*-xylopyranosidoadenine; the yield of cyclised material was too low to permit of isolation of any 6-glycoside which might have been formed. Accordingly we feel justified in reiterating the hypothesis briefly mentioned in Parts IX and XI of this series (*locc. cit.*) that a chelate ring may

be formed, as shown in (VI), through a hydrogen bond between the 2′-acetyl group in the sugar residue and the hydrogen atom of the glycosidic NH-group—a sterically feasible structure. The effect of such chelation would be to induce negative charge on the glycosidic nitrogen atom thus increasing the basicity of that atom and also, indirectly, of the 6-imino-group. As a result, the reactivity of the whole molecule in the cyclisation process would be increased and the production of 6-triacetylglycosidopurines according to Scheme 2 would be possible. Increased general reactivity in such compounds is indicated by the shorter period of heating necessary for the cyclisation of the acetylated thioformamidoglycosides in pyridine solution and by the production of considerable quantities of 9-glycosidopurines in such reactions. Explanations resting on simple steric considerations are, in our view, much less satisfactory. The question of the balance between 6- and 9-glycoside formation in individual cases is not easy to determine owing to the difficulty of quantitative isolation of reaction products.

Two other points emerge from the present work, one of theoretical and the other of practical interest. It is clear that ring-closure of the thioformamido-compounds is most rapid in those containing a 2-methylthio-substituent. The increased basicity of the 4(6)-amino group so indicated is reflected in the relatively easy glycosidisation of 4 : 6-diamino-2-methylthiopyrimidine (Baddiley, Lythgoe, and Todd, Part III; *J.*, 1943, 571) whilst a similar ease of nitrosation (Lythgoe, Todd, and Topham, Part V; *J.*, 1944, 315) is evidence of simultaneously increased electron density at C_5 in the pyrimidine nucleus. Apparently the pyrimidine ring system transmits electronic disturbance efficiently to both the 5- and the 4 : 6-positions in contrast to the *o*-*p*-selectivity displayed in benzenoid compounds.

In the course of preparative work acetylated thioformamidoglycosides are frequently obtained as gels which offer considerable (at times insuperable) resistance to direct crystallisation. The rough chromatographic purification technique described in the experimental portion is an effective method of overcoming this difficulty and is thus a useful complement to the improved cyclisation procedure in synthesising purine glycosides.

Experimental.

The m. ps. of certain purine glycosides prepared by the methods given below are somewhat higher than those recorded for materials prepared by cyclisation in pyridine solution. It has been noted in previous work that these m. ps., all accompanied by decomposition, whilst reproducible with any given specimen, vary somewhat in different preparations without noticeable alteration in analytical composition or purity.

9-d-*Xylopyranosido*-2-*methylthioadenine from* 6-*Amino*-4-d-*xylopyranosidamino*-5-*thioformamido*-2-*methylthiopyrimidine*.—(1) The thioformamido-compound (100 mg.) and sodium methoxide (16 mg.; 1 mol.) were heated in boiling methanol (5 c.c.) during 5 hours. Evaporation under reduced pressure and trituration of the residue in water gave 9-*d*-xylopyranosido-2-methylthioadenine, m. p. 293—294° (yield, 45%). The results obtained in a series of experiments are tabulated below.

Solvent.	Mols. of sodium methoxide.	Time (hours).	Yield of 9-xyloside (%).
Methanol	1	5	45
Methanol	2	5	44 *
Ethanol	1	6	63
Ethanol	2	3½	58
Ethanol	4	2	23
n-Propanol	1	2	49
*iso*Propanol	1	4	30

* The aqueous filtrate neutralised and concentrated to small bulk slowly deposited 6-amino-4-*d*-xylopyranosidamino-5-formamido-2-methylthiopyrimidine (*ca.* 2%).

When the thioformamido-glycoside was heated with sodium *tert.*-butoxide in *tert.*-butanol, severe decomposition occurred and no purine glycoside could be isolated.

Cyclisation Experiments with 6-*Amino*-4-*triacetyl*-d-*xylopyranosidamino*-5-*thioformamido*-2-*methylthiopyrimidine*.—(1) The acetylated thioformamido-compound (200 mg.) was refluxed in methanol (10 c.c.) with sodium methoxide (100 mg.; 4·2 mols.) during 6 hours. On allowing to cool, colourless needles of 9-*d*-xylopyranosido-2-methylthiopyrimidine (45 mg.) separated; a further amount (5 mg.) was obtained from the mother liquors which, however, contained no 6-*d*-xylopyranosidamino-2-methylthiopurine.

(2) The solution of the acetylated thioformamido-compound (100 mg.), anhydrous potassium acetate (81 mg.; 4 mols.), and acetic acid (0·025 c.c.; 2 mols.) in anhydrous methyl cyanide (5 c.c.) was heated under reflux for 4 hours. Potassium acetate separated on cooling and was filtered off. The filtrate was evaporated under reduced pressure and the residue triturated with ethanol (3 c.c.) giving colourless needles of 6-triacetyl-*d*-xylopyranosidamino-2-methylthiopurine (21 mg.), m. p. and mixed m. p. 251—252°. The alcoholic mother liquor contained a further small amount of the same product which was isolated, after hydrolysis with methanolic ammonia, as 6-*d*-xylopyranosidamino-2-methylthiopurine, m. p. and mixed m. p. 225—226° (total yield, 33%).

9-d-*Xylopyranosido*-2-*methyladenine*.—(1) 6-Amino-4-*d*-xylopyranosidamino-5-thioformamido-2-methylpyrimidine (50 mg.) and sodium methoxide (4·5 mg.; 1 mol.) were heated under reflux in methanol (5 c.c.) for 8½ hours. Unchanged starting material (15 mg.) separated on cooling, and from the solution 9-*d*-xylopyranosido-2-methyladenine (5 mg.) was isolated by evaporation and trituration with water (yield, allowing for recovered material, 16%). A second experiment using *n*-propanol as solvent in place of methanol gave the same product in 19% yield, and a third using 2 mols. of sodium methoxide in ethanol gave a yield of 11%.

(2) Anhydrous 6-amino-4-triacetyl-*d*-xylopyranosidamino-5-thioformamido-2-methylpyrimidine (100 mg.) and sodium methoxide (12·5 mg.; 1 mol.) were refluxed in ethanol (7 c.c.) in an atmosphere of nitrogen. A crystalline solid gradually separated and evolution of hydrogen sulphide had ceased after 4 hours. The mixture was left overnight and the 9-*d*-xylopyranosido-2-methyladenine, m. p. 291—292°, which had separated, was collected (yield, 63%). No evidence for the presence of the corresponding 6-xyloside was obtained.

In exactly similar fashion, 9-*d*-xylopyranosidoadenine (67%; m. p. 303—304°) and 9-*d*-ribopyranosidoadenine (51%; m. p. 252°) were prepared from the appropriate acetylated thioformamido-compounds.

Purification of 6-*Amino*-4-*triacetyl*-d-*xylopyranosidamino*-5-*thioformamidopyrimidine*.—A solution of the crude resinous thioformamido-compound (from 1·0 g. of the corresponding acetylated azo-compound, Part IX, *loc. cit.*) in ethyl acetate (25 c.c.) was adsorbed on neutral alumina (30 g., column 2·5 cm. diam.) and the column washed with ethyl acetate (50 c.c.) and then with chloroform (50 c.c.). Elution with pyridine (50 c.c.) gave the thioformamido-compound (500 mg.) which crystallised readily from ethanol in colourless needles.

The same technique has been applied successfully to a number of other acetylated thioformamido-glycosides.

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