184. *Experiments on the Synthesis of Purine Nucleosides. Part XIV. An Interpretation of Some Interconversion Reactions of N-Glycosides.*

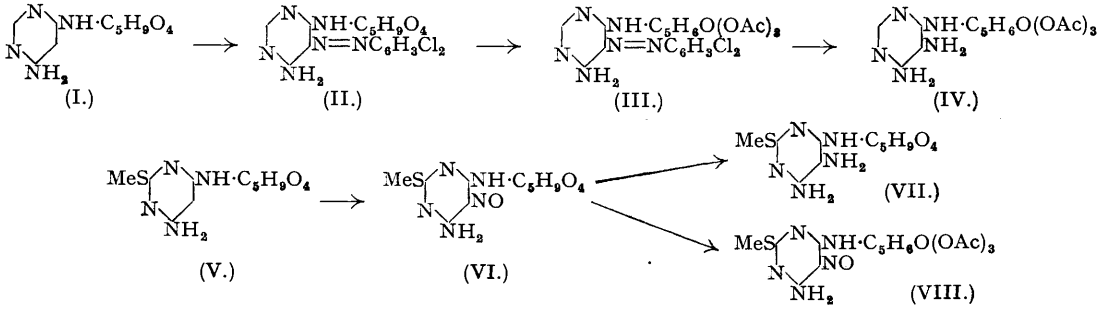
By G. A. Howard, G. W. Kenner, B. Lythgoe, and A. R. Todd.

Reinvestigation of the anilineribosides described in recent patent specifications (Lee *et al.* of Hoffmann–La Roche Inc., U.S.PP. 1945, 2,384,102—2,384.104) has provided for the first time clear evidence of the occurrence in the *N*-glycoside series of furanoside $\rightleftarrows$ pyranoside changes. Aniline-*d*-ribopyranoside is isomerised by boiling in alcohol to aniline-*d*-ribofuranoside. Aniline-α-*d*-ribofuranoside is partially converted in moist pyridine into the β-isomer without change in lactol ring structure, but in pyridine containing acidic catalysts it gives an equilibrium mixture of the α- and β-pyranosides. The bearing of these findings on the problem of the lactol ring structure of the 6-amino-4-*d*-xylosidaminopyrimidine derivatives described in Parts IX and XI (*J.*, 1944, 652; 1945, 556) is discussed; consideration of all the relevant evidence strongly favours the view already expressed, *viz.*, that they all possess, like the 9-*d*-xylosidopurines into which they can be converted, the pyranoside structure. The isomerism existing between xylosides of Series I and Series II (*loc. cit.*) is therefore of the αβ-type.

In terms of this view a reasonable interpretation is provided of the remarkable changes described in Parts IX and XI (*locc. cit.*) when only one form of a 4-*d*-xylosidaminopyrimidine derivative is produced from each of two isomers. It is suggested that xylosides of the latter type (*i.e.*, those existing in two stable forms) fail to show αβ-interconversion because the velocity of such change is too small, whilst in xylosides of the former type (*i.e.*, those isolable in only one stable form) αβ-interconversion is easy, but the equilibrium concentration of one of the forms is too small to permit its isolation; the interconversion reactions are therefore best regarded as mutarotations. In considering the influence of the structure of a 4-*d*-xylosidaminopyrimidine derivative in determining the ease of its mutarotational change, and hence in deciding to which of the above types a xyloside shall belong, it is pointed out that the determining factor appears to be the electron availability at the atom attached glycosidically to C_1 of the sugar residue, and the way in which this factor is affected by the presence of different substituents in the pyrimidine nucleus and by acetylation of the hydroxyls of the sugar residue is discussed.

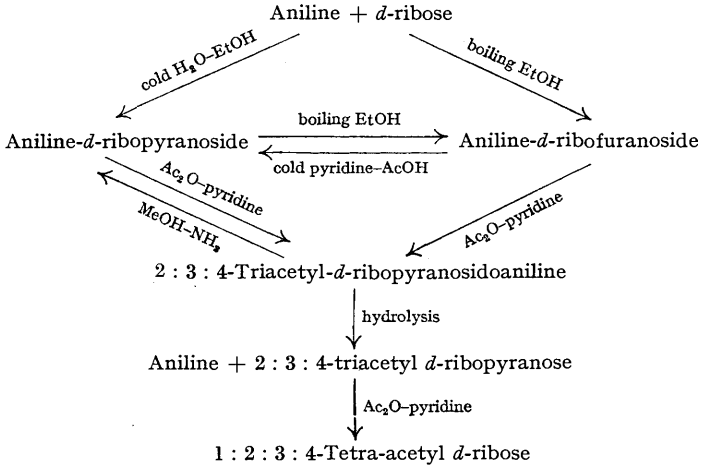
In compounds where isomerisations both of the αβ-type and of the closely related furanoside $\rightleftarrows$ pyranoside type are theoretically possible, some factors affecting the relative velocities of the two changes are considered, and the behaviour of aniline-α-*d*-ribofuranoside is shown to be in harmony with mechanisms proposed for mutarotational changes in *O*- and *N*-sugar derivatives.

Certain 6-amino-4-glycosidaminopyrimidine derivatives prepared by the method described in Part III (*J.*, 1943, 571) have been shown to display an isomerism the seat of which is the sugar residue (Parts IX and XI, *loc. cit.*); thus 6-amino-4-*d*-xylosidaminopyrimidine (I) and its 2-methylthio-derivative (V) each appear to exist in two forms, only one of which in each case has so far been obtained crystalline. The two forms of (I) can be converted into well-defined isomeric 5-arylazo-derivatives (II) and triacetyl-5-arylazo-derivatives (III); both isomers of (III) give on catalytic reduction the same triacetyl-5-amino-derivative (IV). Similarly the two forms of (V) yield isomeric 5-nitroso-derivatives (VI), reduction or acetylation of which is accompanied by loss of isomerism to give only one form of the 5-amino-derivative (VII) or the triacetyl-5-nitroso-derivative (VIII). On account of its possible importance for the chemistry of the *N*-glycosides some explanation of these remarkable reactions seems called for, since they do not appear at first sight to find any parallels in the *O*-glycoside series. The present paper provides an interpretation of these changes, together with an account of some closely related reactions which we have observed amongst the simpler *N*-glycosides of aromatic amines.



General experience of sugar chemistry suggested the provisional view expressed in Part XI (*loc. cit.*) that the isomerism was of the αβ-type and that the 4-*d*-xylosidaminopyrimidines possess a pyranoside structure; this structure has been established for the 9-*d*-xylosidopurine derivatives into which they can be converted, but rigid proof for the *d*-xylosidaminopyrimidines by a direct determination of the ring structures of both members of an isomeric pair has not so far been obtained. It might therefore be argued that at least one member of such a pair might be a furanoside, particularly if any weight were to be attached to the claim of Kuhn and Ströbele (*Ber.*, 1937, **70**, 773) that such a structure is present in their *o*-nitroanilinepentosides, which show a striking formal similarity to our 4-glycosidaminopyrimidines and are produced under identical reaction conditions. The grounds on which these authors base their claim, however (formation of trityl derivatives), are known to be insecure, and in some experiments to clarify this point it has been found in this laboratory (with Mr. N. W. Bristow) that at least one of the pentosides of the Heidelberg workers (*viz.*, *o*-nitroaniline-*l*-arabinoside, the only compound so far investigated) is in fact a pyranoside; these investigations will be described in a later paper.

The *o*-nitroanilinepentosides therefore provide no support for the view that the method described in Part III (*loc. cit.*) gives rise to furanosides. That such structures may sometimes be obtained by condensation of amines with pentoses is clear from recent patent specifications of Hoffmann–La Roche, Inc., which have attracted our attention on these and other grounds. Lee, Solmssen, and Berger (U.S.P. 1945, 2,384,102) described a method of condensing aromatic amines and pentoses in aqueous alcoholic solution at room temperature and pH *ca.* 4 to give *N*-pentosides to which the pyranoside structure was ascribed, and showed that in many cases condensation of the components by refluxing their alcoholic solutions yielded isomeric *N*-pentosides which they considered to be furanosides. The mutarotation behaviour of these isomeric pentosides shows that the isomerism is not due to αβ-differences, but no convincing proof was presented of the correctness of the lactol ring structures ascribed, and the results contrast strikingly with those obtained in the formation of *O*-glycosides where methanolic hydrogen chloride is known to react with aldoses in the cold to give furanosides, and at higher temperatures to give pyranosides. In view of this, and of possible applications of the methods described to the production of 4-glycosidaminopyrimidine derivatives, we have reinvestigated and extended some of the work of the American authors.



We found that, as they reported, aniline and *d*-ribose condense in the cold to give aniline-α-*d*-ribopyranoside; the isomeric aniline-α-*d*-ribofuranoside we obtained both by direct condensation of the components in boiling alcohol and by isomerisation of the pyranoside in the same solvent. We observed that mutarotation of both isomerides was arrested in dry pyridine, and took place only after addition of a small quantity of water; further, it appears that isomerisation of the pyranoside to the furanoside in boiling alcohol is dependent upon some factor(s) as yet unknown, since although we were sometimes successful in effecting the change, in other experiments, conducted with pure materials and under apparently identical reaction conditions, only unchanged starting material could be isolated.

In contrast with the statements of Lee and Berger (U.S.P. 1945, 2,384,104) that both furanoside and pyranoside forms of aniline-*d*-riboside can be acetylated to give the corresponding 2 : 3 : 5- and 2 : 3 : 4-triacetyl derivatives, we found that during acetylation of aniline-*d*-ribofuranoside a change in ring structure takes place. The resulting triacetyl derivative, $[\alpha]_D^{18°} = +30{\cdot}7 \pm 1{\cdot}3°$ ($c = 4$ in chloroform), is identical with that obtained by acetylation of aniline-α-*d*-ribopyranoside, into which in fact it is converted by deacetylation with methanolic ammonia. The triacetyl derivative obtained from either source yielded, on hydrolysis with hot aqueous acetic acid by the method described by Lee and Berger (*loc. cit.*), aniline and a syrupy product identified as 2 : 3 : 4-triacetyl ribopyranose since it yields on further acetylation 1 : 2 : 3 : 4-tetra-acetyl ribose; these facts provide support for the pyranoside structure ascribed by Lee, Solmssen, and Berger to the product of cold condensation of aniline and *d*-ribose. Further investigation showed that the change in ring structure

which occurs during the acetylation of aniline-α-*d*-ribofuranoside is due to the rapid conversion of this compound into the isomeric pyranoside which takes place in pyridine in presence of acids (*e.g.*, acetic acid); the mutarotation curve of the furanoside in such solutions shows an end value identical with that of the pyranoside in moist pyridine or in pyridine containing acetic acid. These changes are summarised in the scheme on opposite page.

They provide what we believe to be the first clear evidence of the occurrence in *N*-glycosides of changes in lactol ring structure, although it seems probable that the behaviour of the aniline glucosides studied by Irvine and Gilmour (*J.*, 1908, **93**, 1429), and believed by them to be due to αβ-isomerisation, is really to be ascribed to changes in ring structure analogous to those described above for the aniline ribosides. They obtained by cold condensation of the compounds a *d*-glucosidoaniline, $[\alpha]_D = +10{\cdot}7°$ (probably a furanoside), which in methanol at room temperatures underwent conversion (strongly catalysed by acids) into a more stable form, $[\alpha]_D = -52{\cdot}3°$ (probably a pyranoside), the change being partially reversed on refluxing the latter in methanol. Such alterations in ring structure are of course known to occur in *O*-glycosides, *e.g.*, in the conversion of methyl-*d*-ribopyranoside into 1 : 2-monoacetone methyl-*d*-ribofuranoside (Levene and Stiller, *J. Biol. Chem.*, 1934, **106**, 421); the acid catalysed isomerisations of both α- and β-forms of 3 : 6-anhydro-methyl-*d*-glucopyranoside into the corresponding furanoside derivatives, discovered by Haworth, Owen, and Smith (*J.*, 1941, 88), and shown by them to be possible because of the considerable strain existing in the 1 : 5-lactol ring, provide particularly interesting examples.

The demonstration that in many cases condensation of an amine and a pentose at room temperature gives a pyranoside whereas condensation in boiling alcohol gives the furanoside prompts the question as to whether such a distinction is of general validity, since if it were some doubt might be cast on the pyranoside nature of the products obtained by the method described in Part III (*loc. cit.*). We have found, however, that there is often no such distinction, even where aromatic amines are used. Thus aniline and *d*-xylose gave the same aniline-*d*-xyloside by both methods of condensation, and in the course of other work in this laboratory a similar finding has been made for *o*-nitroaniline and *d*-ribose. Neither 4 : 6-diaminopyrimidine nor its more reactive 2-methylthio-derivative could be brought into reaction with *d*-ribose under the conditions of cold condensation described by Lee, Solmssen, and Berger (*loc. cit.*). These results offer no opposition to the view that, especially in the case of weakly basic amines such as the derivatives of *o*-nitroaniline and 4 : 6-diaminopyrimidine, condensation in hot alcohol in presence of acidic catalysts may give rise completely or almost completely to pentopyranosides. That our 6-amino-4-*d*-xylosidaminopyrimidine derivatives do in all probability possess this structure is supported by the following considerations. If, for example, one of the isomers of the triacetyl-5-arylazo-derivative (III) were a furanoside, it would follow that during catalytic hydrogenation to the triacetyl-5-amino-derivative (IV) simultaneous migration of an acetyl group and change in lactol ring structure takes place. Migration of acetyl groups in partly substituted sugar compounds is known to occur occasionally, and the behaviour of the aniline ribosides described above shows that furanose–pyranose changes in *N*-glycosides cannot be considered as excluded, but a transformation of this type, where both glycosidic centre and all hydroxyl groups capable of providing alternative positions for ring closure are blocked by substitution, is quite without parallel and seems to us most unlikely. Moreover it will be shown in another paper that the relevant optical data are in accord with the view that members of an isomeric pair of 4-*d*-xylosidaminopyrimidine derivatives stand in αβ relationship to each other.

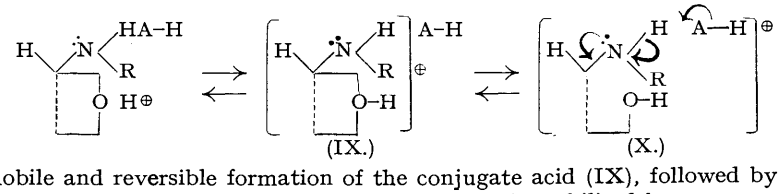
In terms of this view, we suggest that those reactions of our 4-*d*-xylosidaminopyrimidine derivatives in which only one isomer is produced from each of two different isomers are best interpreted as involving interconversion reactions of essentially the same sort as those concerned in mutarotations; specifically, that the acetylation of 5-nitroso-6-amino-4-*d*-xylosidamino-2-methylthiopyrimidine-II (VI) to give 5-nitroso-6-amino-4-triacetyl-*d*-xylosidamino-2-methylthiopyrimidine-I (VIII) (Part XI, *loc. cit.*) is to be regarded as due to the tendency of the unknown 5-nitroso-6-amino-4-triacetyl-*d*-xylosidamino-2-methylthiopyrimidine-II first produced in the reaction to undergo a facile and complete mutarotation to its αβ-isomer. Since mutarotation in the sense of an observable change in rotation due to equilibration of α- and β-forms has not hitherto been recorded for any of our glycosidaminopyrimidine derivatives, an initial difficulty may attach to this conception. This is resolved on realisation that constitutional features may decide in two ways whether a sugar derivative shall exhibit mutarotation in the strict sense, either by affecting the velocity with which αβ-change takes place or by controlling the final position of the equilibrium between the two forms. The two forms of *o*-nitroxylidine-*l*-arabinoside (Kuhn and Ströbele, *loc. cit.*) are presumably compounds where the velocity of αβ-change is too low to be measurable under ordinary conditions; examples of the opposite type are α-acetochloroglucose and tetra-acetyl-*d*-glucosido-*p*-toluidine, which show no mutarotation in the accepted sense because each represents the more stable member of a pair of compounds of widely differing stabilities. That compounds of these structures are capable of αβ-isomeric change is shown by the behaviour of their αβ-isomers, which on dissolution in alcohol undergo rapid and virtually complete αβ-change (Schlubach and Gilbert, *Ber.*, 1930, **63**, 2292; Kuhn and Dansi, *Ber.*, 1936, **69**, 1745). We suggest that the 4-*d*-xylosidaminopyrimidine derivatives existing in isomeric forms, *e.g.*, (I), (II), (III), (V), and (VI), show no mutarotation because the velocity of αβ-change is too small, and that in derivatives of structures (IV), (VII), and (VIII) αβ-change is facile, but because the two possible forms are of widely differing stabilities the equilibrium mixture obtained contains no isolable quantity of the less stable form. What structural features are responsible for this disparity in the stabilities of two αβ-isomers, and how these determine, for example, that in the acetohalogeno-

sugars it is usually the α-form which is the more stable, whilst in the 5 : 6-diamino-4-glycosidaminopyrimidines it is, as will be shown in a further paper, the β-form which is usually the more stable, are questions to which at present no answer can be given. It is, however, possible in the light of what is already known of the influence of structural features on ease of mutarotational changes to understand why compounds of structures (IV), (VII), and (VIII) show, in contrast to the other xylosidaminopyrimidines, the high tendency to αβ-changes which causes them to appear in only a single form.

Kuhn and Birkofer (*Ber.*, 1938, **71**, 1535) have investigated the mutarotation of secondary (NHR–sugar) and tertiary (NR_1R_2–sugar) *N*-glycosides in its relationship to the Amadori rearrangement and to the capacity of such compounds to undergo reduction to *N*-substituted 1-aminosugar alcohols. Their results show that some tertiary *N*-glycosides may undergo mutarotation, that such changes are of the acid-catalysed variety, and that they are difficult or impossible in the glycosides of weakly basic compounds (*e.g.*, theophylline) and increasingly facile in those of the more strongly basic compounds (*e.g.*, dibenzylamine and piperidine). Parallel changes to those of the tertiary *N*-glycosides occur in some *O*-glycosides but are in general less facile, presumably because of the weaker basicity of the aglycone; examples are the isomerisation of tetra-acetyl β-methylglucoside (Pacsu, *Ber.*, 1928, **61**, 137, 1513) which takes place in boiling chloroform and requires the presence of a powerful electrophilic catalyst (*e.g.*, titanium tetrachloride), and the acid catalysed changes of 2 : 4-dimethyl 3 : 6-anhydro-α-methylglucoside (Haworth, Owen, and Smith, *loc. cit.*) and the corresponding galactoside (Haworth, Jackson, and Smith, *J.*, 1940, 620) to their β-isomers, changes promoted by the existence of strain in the lactol ring.

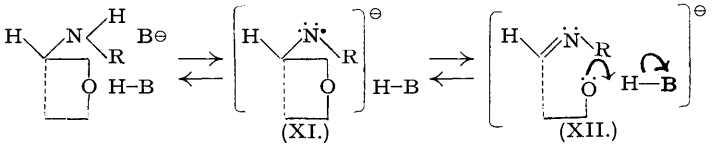
In the case of secondary *N*-glycosides, quantitative measurements have been made by Baker of the velocities of rotational change occurring in *p*-substituted anilides of tetra-acetyl glucose (*J.*, 1928, 1583) and tetramethyl glucose (*J.*, 1928, 1979); he found that in presence of acid the observed velocities ran parallel with basicity of the aglycones. In a later paper (*J.*, 1929, 1205) Baker was unable to detect mutarotation in tetra-acetyl glucosides of some secondary amines and concluded that for mutarotation due to αβ-change to take place " the original sugar derivative itself, as distinct from its cation must contain a separable hydrogen atom." Work already cited has shown that this conclusion is no longer tenable, and some reservations may be necessary regarding his interpretation of the earlier results, since, as will be shown later, complicating factors may be at work in acetylated secondary *N*-glycosides, and since the evidence given does not establish definitely that the changes in rotation observed by Baker were due completely to αβ-isomerisation. However this may be, sufficient qualitative data are available for sugar derivatives with unsubstituted alcoholic hydroxyl groups to show the broad general influence of the basicity of a group OH or NHR attached to the glycosidic centre on the facility with which mutarotation takes place. In such compounds basic catalysis of the mutarotation is possible and, where a free hydroxyl group is present at C_1, represents the main pathway of the change; in the secondary *N*-glycosides this mechanism appears to be somewhat less effective, but the acid-catalysed mechanism is very much more effective than for the oxygen analogues, and becomes increasingly so with more strongly basic aglycones; thus although many of the *N*-glycosides of aniline, *p*-toluidine, and *p*-phenetidine are known to mutarotate, such changes have not been observed in the more feebly basic *o*-nitroaniline derivatives.

These results are consistent with mechanisms of the type proposed for *d*-glucose by Fredenhagen and Bonhoeffer (*Z. physikal. Chem.*, 1938, *A*, **181**, 392) whose views are essentially similar to those expressed by Lowry (*J.*, 1925, **127**, 1371). For *N*-glycosides, the acid catalysed change, although doubtless a continuous process, may be considered in two stages, the first involving attack on the lactol ring oxygen atom by a proton



(IX.) (X.)

resulting in the mobile and reversible formation of the conjugate acid (IX), followed by a step in which the ring opens to give an activated complex of the type (X), which is stabilised by resonance between structures derived from (X) by the electronic displacements indicated. Driving force for the reaction is provided by affinity of the lactol oxygen for a proton and by incipient formation of the aldimine structure, and might therefore be expected to increase with increasing basicity of the glycosidic nitrogen atom. Incipient formation of a hydrogen bond between the hydrogen attached to this atom and a solvent molecule may provide an additional driving force, which is here of secondary importance; this factor is absent from tertiary *N*-glycosides. In consequence these do not mutarotate by a base-catalysed mechanism such as is observed amongst the secondary *N*-glycosides, and in which the main driving force is provided by the affinity of a base molecule for a proton removable from the nitrogen atom, and incipient formation of an aldimine structure :



(XI.) (XII.)

The rate is determined by the group R through the second step which in this case results in formation of an activated complex (XII) in which the lactol oxygen carries a formal negative charge, stabilisation occurring to some extent by incipient interaction with a solvent molecule HB. Here, as in the acid catalysed mechanism, additional driving force may be supplied by the existence of strain in the lactol ring.

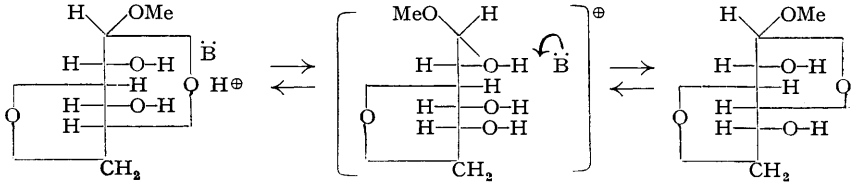
In interpreting the behaviour of the 6-amino-4-*d*-xylosidaminopyrimidines it is unnecessary to decide whether they are to be represented as secondary *N*-glycosides derived from 4 : 6-diaminopyrimidine, or whether they are in fact better formulated as secondary or tertiary *N*-glycosides derived from 6-amino-4-iminodihydropyrimidine (cf. Part III, *loc. cit.*), since in either case the argument remains qualitatively unaffected. That substances of the structures (I), (II), (V), and (VI) can exist as α- and β-forms showing little tendency to interconversion appears to be due to the circumstance that they are *N*-glycosides in which the nitrogen atoms concerned in the glycosidic linkage are very weakly basic. The introduction of the strongly basic amino-group into position 5 in the pyrimidine nucleus, *e.g.*, to give the structure (VII), may confidently be expected to produce a considerable increase in the electron availability at the glycosidic nitrogen atom; it seems probable that the increased driving force thereby available for the formation of the activated complex (X) is responsible for the promotion of αβ-isomerisation which accounts for the isolation of (VII) in only one form.

The second effect at work in the interconversion reactions of the 4-*d*-xylosidaminopyrimidine derivatives is one due to acetylation of the hydroxyl groups of the sugar residue. In Parts IX. (*loc. cit.*) and XIII it was pointed out that certain of these compounds show in quite a different connection behaviour which is most readily explained by assuming that chelation takes place between the glycosidic NH group and the carbonyl group of the acetyl residue located at C_2 in the sugar ring. The effect of such chelation would be to weaken the hold of the nitrogen atom on the hydrogen atom, thereby increasing electron availability at the former and facilitating configurational change at C_1. This effect appears to be responsible for the interconversion reaction which takes place when 5-nitroso-6-amino-4-*d*-xylosidamino-2-methylthiopyrimidine-II (VI) is acetylated to give 5-nitroso-6-amino-4-triacetyl-*d*-xylosidamino-2-methylthiopyrimidine-I (VIII). If, as seems probable, it should prove that the two *o*-nitroxylidine-*l*-arabinosides of Kuhn and Strobele (*loc. cit.*) are in fact αβ-isomers, their conversion into a common triacetyl derivative would receive a similar explanation. A further possible case of αβ-interconversion is provided by the acetylation of the isomeric 6-amino-4-*d*-xylosidaminopyrimidines and their 2-methylthio-derivatives. In each case the crystalline xyloside yields on acetylation very similar quantities of crystalline tetra-acetyl derivative to those obtained on similar treatment of the resinous xyloside mixture which has been shown (Parts IX and XI, *locc. cit.*) to consist largely of the isomeric xyloside. By analogy with the above mentioned nitroso-compounds it seems likely that the triacetyl derivatives of 6-amino-4-*d*-xylosidaminopyrimidine and its 2-methylthio-derivative show αβ-interconversion. This process would be hindered by acetylation at N_6, and it has been found that the isomeric 6-acetamido-4-triacetyl-*d*-xylosidamino-2-methylthiopyrimidines do not mutarotate in pyridine–acetic acid. In view of the behaviour of the triacetyl-5-nitroso-derivative (VIII) it may perhaps seem remarkable that the triacetyl-5-arylazo-derivative (III) should be capable of existence in α- and β-forms. A possible explanation is that the interconversion of these may be prevented by the hindering effect of the bulky 5-arylazo-substituent. When this group is removed reductively freedom of interconversion is not only restored in this way; it is further promoted by the increased electron availability due to the basic 5-amino-group, so that (IV) is isolated in only one form.

The furanose–pyranose interconversions described earlier in this paper for the aromatic amine *N*-glycosides obviously stand in a close relationship to the foregoing configurational changes, since both proceed *via* an activated complex in which the lactol ring is opened, and here again two phenomena, one involving considerations of velocity and the other those of equilibrium, are distinguishable. No satisfactory reasons can at present be given why aniline-*d*-riboside should be stable in alcohol at low temperatures as the pyranoside form, whereas at the boiling point the furanoside form appears to be the more stable, although parallel cases of the effects of temperature changes are well known : for example, Schlubach and Prochownick (*Ber.*, 1929, **62**, 1502) have shown that the amount of *d*-galactofuranose present in the equilibrium mixture in pyridine solution increases markedly with rise of temperature.

An interesting feature, however, emerges from our results with regard to the velocity phenomenon. Where change of lactol ring structure to a more stable form is possible on energetic grounds, it might be thought likely that every ring opening required to effect αβ-interconversion would also give rise to furanose–pyranose change. That this is not so is shown by the behaviour of aniline-α-*d*-ribofuranoside which in moist pyridine undergoes partial conversion into the β-form without any appreciable change in lactol ring structure; to promote conversion, addition of acetic acid is required. This point may be explained as follows. The main pathway of αβ-change in moist pyridine is most probably the base-catalysed mechanism, and the lactol oxygen atom in the activated complex (XII) carries a formal negative charge and would be expected to be more nucleophilic than that of an hydroxyl group on the adjacent carbon atom of the sugar ring; the linkage of the former oxygen to a hydrogen atom (from a solvent molecule HB) is only incipient, whereas in the latter it is complete. Closure in the lactol ring will therefore tend to involve this oxygen atom in preference to that of the adjacent hydroxyl group, and no change in lactol ring structure will take place. In the acid-catalysed mechanism which is possible in pyridine containing acetic acid the lactol oxygen atom is present in the transition state (X) as a formal hydroxyl group the oxygen atom of an adiacent hydroxyl group will therefore

compete with it for closure with C_1 on an equal footing, and in time complete furanose ⟶ pyranose change will take place. In a complete analysis of the relative rates of αβ-isomerisation and of change in lactol ring structure it is possible that in other structures account might have to be taken of factors affecting the stability of the carbonium ion in the transition state, by analogy with the considerations which determine the extent of racemisation occurring during unimolecular solvolytic hydrolysis or alcoholysis of an optically active halide $CR_1R_2R_3Br$, but no such effect need be invoked in the present case. In this connection, however, reference may be made to the results of Haworth, Owen, and Smith (*loc. cit.*), who have shown that both α- and β-forms of 3 : 6-anhydro-methyl-*d*-glucopyranoside undergo acid-catalysed conversion into the corresponding furanosides with complete retention of configuration at C_1. This behaviour is the converse of that observed for aniline-α-*d*-ribofuranoside in moist pyridine, where configurational change takes place without alteration in the ring structure. Possibly the activated complex in the anhydro-compounds is stabilised by formation of a 3-membered oxide ring as in (XIII); formation of similar 3-rings seems to be responsible for related stereochemical effects, *e.g.*, in the addition of halogens to olefins and in the replacement of halogen by hydroxyl in α-halogenocarboxylate ions (for refs. see Wheland, " The Theory of Resonance," 1944, p. 242). Since both formation and rupture of such a ring would be accompanied by inversion at C_1, the over-all effect would be a retention of the original configuration.



(XIII.)

Experimental.

Triacetyl-d-*ribopyranosidoaniline*.—(a) *From* d-*ribopyranosidoaniline*. *d*-Ribopyranosidoaniline was prepared according to Lee, Solmssen, and Berger (U.S.P. 2,384,102) and had the following characteristics: m. p. 119°; $[\alpha]_D^{17°} = +60°$ ($c = 0{\cdot}95$ in dry pyridine), constant during 30 hours; $[\alpha]_D^{17°} = +60°$ (initial value) ⟶ $+48{\cdot}4°$ (final value, after 2 days) ($c = 0{\cdot}95$ in moist pyridine); $[\alpha]_D^{18°} = +71°$ (initial value) ⟶ $+43°$ (final value, after 4½ hours) ($c = 0{\cdot}75$ in pyridine containing 10% acetic acid). A portion (1·2 g.), acetylated as described by the above authors (*loc. cit.*), gave the triacetyl derivative as an amber resin (0·9 g.), $[\alpha]_D^{18°} = +29{\cdot}4°$ ($c = 3{\cdot}57$ in chloroform); no value is available from the above patent specification for comparison purposes. When the triacetyl compound (0·5 g.) was set aside for 3 days at 0° with saturated methanolic ammonia (10 c.c.) and the solvent removed at 20—25° under reduced pressure, the residue gave on crystallisation from alcohol *d*-ribopyranosidoaniline, m. p. 110°, $[\alpha]_D^{19°} = +60°$ ($c = 0{\cdot}93$ in dry pyridine).

(b) *From* d-*ribofuranosidoaniline*. The furanoside, prepared according to Lee and Berger (U.S.P. 2,384,104), had the following characteristics: m. p. 126—127°; $[\alpha]_D^{17°} = +180°$ ($c = 0{\cdot}85$ in dry pyridine), constant during 30 hours; $[\alpha]_D^{17°} = +180°$ (initial value) ⟶ $+161°$ (final value, after 3 days) ($c = 0{\cdot}85$ in moist pyridine); $[\alpha]_D^{18°} = +176°$ (initial value) ⟶ $+44°$ (final value, after 2½ hours) ($c = 1{\cdot}11$ in pyridine containing 10% acetic acid). A portion (0·8 g.) was acetylated as described by Lee and Berger (*loc. cit.*) giving triacetyl-*d*-ribopyranosidoaniline (0·8 g.) as an amber resin, $[\alpha]_D^{18°} = +32°$ ($c = 4{\cdot}58$ in chloroform). When this material (0·2 g.) was deacetylated as described in (a) above aniline-*d*-ribopyranoside (73 mg.) was obtained, m. p. 113°, $[\alpha]_D^{19°} = +61°$ ($c = 0{\cdot}66$ in dry pyridine).

Conversion of Triacetyl-d-*ribopyranosidoaniline into* 1 : 2 : 3 : 4-*Tetra-acetyl Ribose*.—The resinous triacetyl compound (1·4 g., obtained as described in (a) or (b) above) dissolved in alcohol (3·5 c.c.) was added to aqueous acetic acid (40 c.c. of 5%) and the mixture distilled in steam till no more aniline passed over. After decolorisation (charcoal) the remaining solution was evaporated to dryness under reduced pressure, and the residue dried by repeated evaporation with alcohol. It was dissolved in pyridine (5 c.c.), acetic anhydride (1 c.c.) added, and set aside overnight. Excess of acetic anhydride was then destroyed by addition of alcohol, solvents were removed under reduced pressure, and the residue was crystallised from alcohol. 1 : 2 : 3 : 4-Tetra-acetyl *d*-ribose separated in good yield, m. p. 110° undepressed in admixture with authentic material.

d-*Xylosidoaniline*.—(a) To *d*-xylose (5·76 g.) in water (8 c.c.) sufficient 3N-sulphuric acid was added to adjust the pH to 4·0 and a solution of aniline (4 c.c.) in alcohol (20 c.c.) was added. After 15 minutes at 25° the solution was concentrated in a vacuum desiccator over silica gel (2 days). The separated material (2·5 g.) had m. p. 142°, $[\alpha]_D^{19°} = -87°$ ($c = 2{\cdot}37$ in pyridine). Acetylation of this material (0·5 g.) by the usual method gave *triacetyl*-d-*xylosidoaniline*, m. p. 151°, $[\alpha]_D^{13°} = +25°$ ($c = 1{\cdot}82$ in chloroform) (Found: C, 58·1; H, 6·0; N, 4·0. $C_{17}H_{21}O_7N$ requires C, 58·1; H, 6·0; N, 4·2%).

(b) *d*-Xylose (5 g.) and aniline (3·75 c.c.) were heated under reflux in alcohol (50 c.c.) for 1½ hours, and the solution was concentrated to 30 c.c. under reduced pressure. The separated xyloside was collected, washed with alcohol, and recrystallised from the same solvent. Yield, 3·5 g., $[\alpha]_D^{19°} = -87°$ ($c = 2{\cdot}37$ in pyridine). Acetylation in the usual manner gave triacetyl-*d*-xylosidoaniline identical in properties with the material described under (a) above.

6-*Acetamido*-4-*triacetyl*-d-*xylosidaminopyrimidine*.—(a) 6-Amino-4-*d*-xylosidaminopyrimidine-I (0·4 g.; Part IX, *loc. cit.*) was shaken for 15 hours with pyridine (15 c.c.) containing acetic anhydride (5 c.c.) and a few drops of acetyl chloride, and then heated to 100° for ¾ hour. After addition of alcohol, the solution was evaporated to dryness under reduced pressure and the residue extracted with boiling ethyl acetate (50 c.c.). On concentration of the extract to 5 c.c. the *tetra-acetyl* compound separated (0·13 g.). Recrystallised from alcohol it had m. p. 214—215° (Found in material dried at 110° in a vacuum over phosphoric oxide: C, 47·3; H, 5·7; N, 12·7. $C_{17}H_{22}O_8N_4,H_2O$ requires C, 47·7; H, 5·6; N, 13·1%).

(b) A portion (0·5 g.) of the resin contained in the mother-liquors from which 6-amino-4-*d*-xylosidaminopyrimidine-I separated was acetylated in the same manner, and gave a colourless crystalline solid (0·1 g.), m. p. 213—214° undepressed in admixture with the above tetra-acetyl compound.

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