**459.*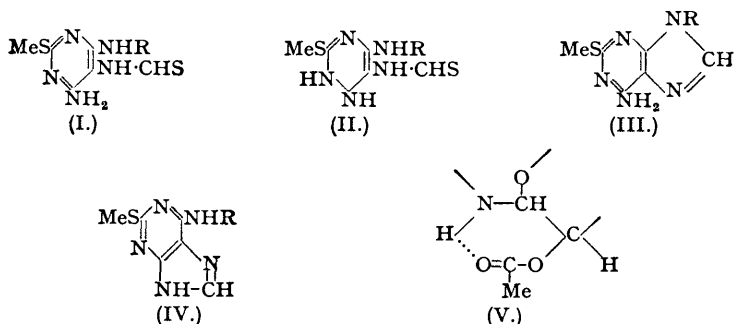* *Infra-red Spectroscopic Measurements of Substituted Pyrimidines. Part I.   The Presence of Hydrogen Bonding in 4-Triacetyl-*D-*xylosidaminopyrimidines.*

By I. A. BROWNLIE, G. B. B. M. SUTHERLAND, and A. R. TODD.

Infra-red methods have been used to demonstrate the presence of hydrogen bonding in certain 4-triacetyl-D-glycosidaminopyrimidines; the results substantiate a chelation hypothesis previously put forward on chemical evidence (Kenner, Lythgoe, and Todd, *J.*, 1944, 652; 1946, 852; Howard, Lythgoe, and Todd, *J.*, 1945, 556). Where hydrogen bonding is absent, the band due to the stretching vibration of the acetoxy >C=O groups is centred at 1750 cm.$^{-1}$, but where the C$'_2$ acetoxy-carbonyl is bonded to the glycosidic NH group, an additional >C=O band at 1725 cm.$^{-1}$ is present.

FOLLOWING the demonstration by Baddiley, Lythgoe, McNeil, and Todd (*J.*, 1943, 383) that cyclisation of 6-amino-4-methylamino-5-thioformamidopyrimidines, *e.g.* (I; R = Me), yielded exclusively the corresponding 9-methyladenines, unaccompanied by 6-methylaminopurines, a general method for the synthesis of 9-glycosidoadenine derivatives was developed, involving as a final stage, cyclisation of 6-amino-4-glycosidamino-5-thioformamidopyrimidines it being assumed that the glycosidic residue could be regarded as analogous to the methyl group in the above model experiments. It was suggested that the thioformamido-compounds exist in form (II; R = Me or glycosido) and that, accordingly, base-catalysed ring closure would not readily proceed by intervention of the imino-group at position 6. Application of this synthetic method has led to the successful synthesis of a variety of 9-glycosidoadenine derivatives, but the expectation that these would be the sole products has not been invariably fulfilled. Kenner and Todd (*J.*, 1946, 852) have reviewed a number of these cases and discussed the mechanism of the final cyclisation process in detail. Briefly, it has been found that, whereas 6-amino-4-glycosidamino-5-thioformamidopyrimidines do in fact behave like the 4-alkylamino-compounds and yield only 9-glycosidopurines, the corresponding acetylated glycosides normally give a mixture of 9-glycosidoadenine and 6-glycosidaminopurine derivatives on cyclisation. To quote a specific example, cyclisation of 6-amino-4-D-xylopyranosidamino-5-thioformamido-2-methyl-thiopyrimidine (I; R = D-xylosido) gives only 9-D-xylopyranosido-2-methylthioadenine (III; R = D-xylosido), whereas the corresponding triacetylthioformamidoglycoside (I; R = triacetyl-D-xylosido) cyclised under conditions which prevent deacetylation gives a mixture of the 9-glycoside (III; R = triacetyl-D-xylosido) and 6-triacetyl-*d*-xylopyranosidamino-2-methylthiopurine (IV; R = triacetyl-D-xylosido) (Howard, Lythgoe, and Todd, *J.*, 1945, 556). To explain these results, it was postulated (Kenner, Lythgoe, and Todd, *J.*, 1944, 652; Howard, Lythgoe, and Todd, *loc. cit.*; Kenner and Todd, *loc. cit.*) that a chelate ring may be formed in acetylated 4-glycosidaminopyrimidines as shown in (V) through a hydrogen bond between the

2-acetyl group in the sugar residue and the hydrogen atom of the glycosidic NH-group. The effect of such chelation would be to induce negative charge on the glycosidic nitrogen atom, thus increasing its basicity and also indirectly that of the nitrogen attached to position 6. As a result, the reactivity of the whole molecule would be increased and cyclisation might occur in either direction, to give an acetylated 9-glycosidoadenine or an acetylated 6-glycosidamino-purine. This hypothesis accorded well with the observed facts but was not readily susceptible of proof by chemical methods.

MeS⟨N⟩NHR NH·CHS NH₂ (I.)　　MeS⟨N⟩NHR HN NH·CHS NH (II.)　　MeS⟨N⟩ NR CH NH₂ N (III.)

MeS⟨N⟩NHR N NH-CH N (IV.)　　N—CH O=C-O Me (V.)

The same hypothesis was used by Howard, Kenner, Lythgoe, and Todd (*J.*, 1946, 855) to explain certain interconversion reactions of 4-glycosidaminopyrimidines. Whereas, for example, the α- and β-isomers of 5-nitroso-6-amino-4-D-xylopyranosidamino-2-methylthiopyrimidine are stable and do not show mutarotation, acetylation of either gives rise to one and the same triacetyl derivative; it was suggested by these authors that the increased basicity of the glycosidic nitrogen in the acetylated compounds so facilitates configurational change at the glycosidic carbon that as a result one of the acetylated nitroso-compounds undergoes a rapid and complete mutarotation to its more stable isomer.

The present investigation was undertaken in order to determine by infra-red spectroscopy whether hydrogen bonding of the type postulated could be detected in suitable acetylated 4-glycosidamino-pyrimidines.

There are at least two ways in which the formation of such a hydrogen bond might be expected to affect the vibration spectrum of compounds of this type. The weak link between the oxygen of the CO group and the hydrogen of the NH group should (*a*) cause a lowering of the C꞊O stretching frequency, normally near 1760 cm.⁻¹, similar to that found in the carboxylic acids by association (Davies and Sutherland, *J. Chem. Physics*, 1938, **6**, 767) and (*b*) produce a corresponding lowering of the NH stretching frequency normally near 3400 cm.⁻¹. It might also be expected to increase the NH deformation frequency, but as the location of this frequency is not so well established, we decided to concentrate our attention on the first two effects. The general method was to compare the spectra of compounds in which hydrogen bonds were suspected to exist with those of the nearest analogue in which a hydrogen bond could be definitely excluded.

<center>EXPERIMENTAL.</center>

Since substituted 4-D-glycosidaminopyrimidines are, in general, soluble only in solvents which absorb strongly in the region 2 μ (5000 cm.⁻¹) to 15 μ (667 cm.⁻¹), they were examined as a capillary layer, between rock-salt plates, as a fine suspension in " Nujol." As the work formed part of a larger pro-gramme, the substances were examined from 2 to 15 μ on a double-beam spectrometer (Sutherland and Thompson, *Trans. Faraday Soc.*, 1945, **41**, 174) fitted with a 30° rock-salt prism of the Littrow type and a Hilger–Schwarz vacuum thermopile. The compounds were further examined from 2 to 6 μ on a special spectrometer of very high resolving power (cf. Sutherland, Blackwell, and Fellgett, *Nature*, 1946, **158**, 873) fitted with a lithium fluoride prism.

Results and Discussion.—The results for the region of the C꞊O stretching frequency are summarised in the table and illustrated in Figs. 1—5; the complete results for the region 2—15 μ will appear in a further paper on a series of substituted pyrimidines (Brownlie and Sutherland, in preparation). The evidence obtained from the 3 μ region was not clear-cut, since the absorption frequency of the glycosidic NH group is complicated by the absorption of other substituents in the pyrimidine ring, especially that due to the NH₂ group. The full discussion of the region is reserved for the comprehensive paper.

The double-bond region of the spectrum of 5-nitroso-6-amino-4-D-xylosidamino-2-methylthio-pyrimidine is shown in Fig. 1, together with the spectrum of the corresponding triacetyl derivative. The bands between 1650 and 1500 cm.⁻¹ are known not to be due to CO groups and may be ignored; the absorption due to CO groups which appears only for the latter compound is seen to consist of a double band, the stronger component being at 1760 cm.⁻¹ and the weaker at 1725 cm.⁻¹. The former we assign to the C꞊O groups on the C₃ and C₄ atom of D-xylose, while the latter (being at a lower frequency) we assign
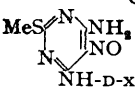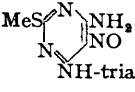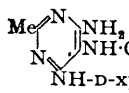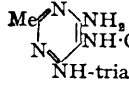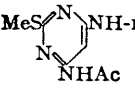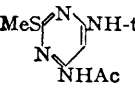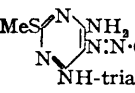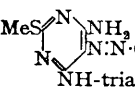
Compound.	Fig.	Remarks.

MeS—pyrimidine—NH₂, NO, NH-D-xylose

1 No bands between 1650 and 1775 cm.⁻¹.

MeS—pyrimidine—NH₂, NO, NH-triacetyl-D-xylose

1 One band at 1775 cm.⁻¹ due to $>$C$=$O stretching frequency of the OAc groups at C_3 and C_4 of D-xylose. One band at 1725 cm.⁻¹ due to bonded $>$C$=$O at C_2.

1 : 2 : 3 : 4-Tetra-acetyl D-xylose

2 One broad band at 1750 cm.⁻¹ due to $>$C$=$O stretching vibration frequency.

Me—pyrimidine—NH₂, NH·CHS, NH-D-xylose

3 No bands 1700—1775 cm.⁻¹.

Me—pyrimidine—NH₂, NH·CHS, NH-triacetyl-D-xylose

3 One band at 1750 cm.⁻¹ due to $>$C$=$O stretching frequency of the OAc groups at C_3 and C_4 of D-xylose. One band at 1725 cm.⁻¹ due to bonded $>$C$=$O at C_2.

MeS—pyrimidine—NH-D-xylose, NHAc

4 One band at 1695 cm.⁻¹ due to $>$C$=$O frequency of the 6-NHAc group.

MeS—pyrimidine—NH-triacetyl-D-xylose, NHAc

4 One band at 1745 cm.⁻¹ due to $>$C$=$O stretching frequency of the OAc groups at C_3 and C_4 of D-xylose. One band at 1710 cm.⁻¹ probably due to bonded $>$C$=$O at C_2, overlapping $>$C$=$O absorption frequency of the 6-NHAc group.

MeS—pyrimidine—NH₂, N:N·C₆H₃Cl₂, NH-triacetyl-D-ribopyranose

5 One band at 1755 cm.⁻¹ due to $>$C$=$O stretching frequency of the OAc groups. No shifted $>$C$=$O frequency present.

MeS—pyrimidine—NH₂, N:N·C₆H₃Cl₂, NH-triacetyl-L-arabopyranose

5 One band at 1750 cm.⁻¹ due to $>$C$=$O stretching frequency. No shifted C$=$O frequency present.

FIG. 1.

MeS—pyrimidine—NH₂, NO, NH-*triacetyl*-D-*xylose* ------

MeS—pyrimidine—NH₂, NO, NH-D-*xylose* — · · —
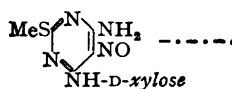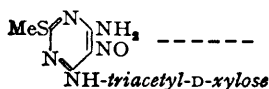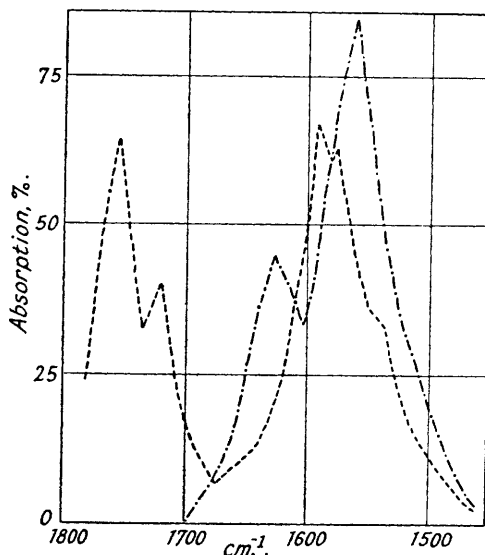
to the C=O which is bonded to the glycosidic NH group. It might be argued that the splitting does not arise from the existence of the bonded C=O group but is due to resonance between the three C=O frequencies. That this is most unlikely is proved by the spectrum of 1 : 2 : 3 : 4-tetra-acetyl D-xylose (Fig. 2) which shows a single C=O absorption band centred at 1750 cm.$^{-1}$.
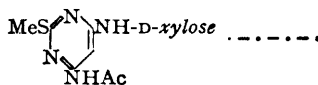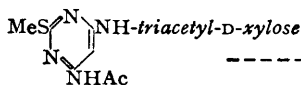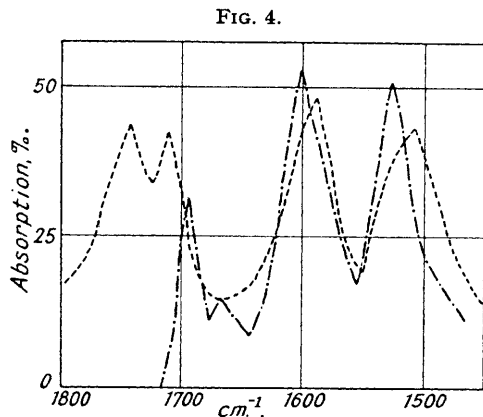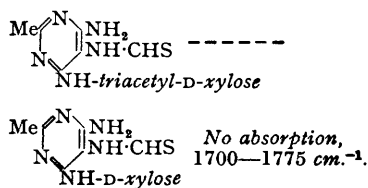
FIG. 2.

1 : 2 : 3 : 4-*Tetra-acetyl* D-*xylose.*

FIG. 3.

Me⟨N⟩NH$_2$
     NH·CHS ------
NH-*triacetyl*-D-*xylose*

Me⟨N⟩NH$_2$
     NH·CHS   *No absorption,*
NH-D-*xylose*   1700—1775 *cm.*$^{-1}$.

FIG. 4.

MeS⟨N⟩NH-*triacetyl*-D-*xylose*   MeS⟨N⟩NH-D-*xylose* .—.—.
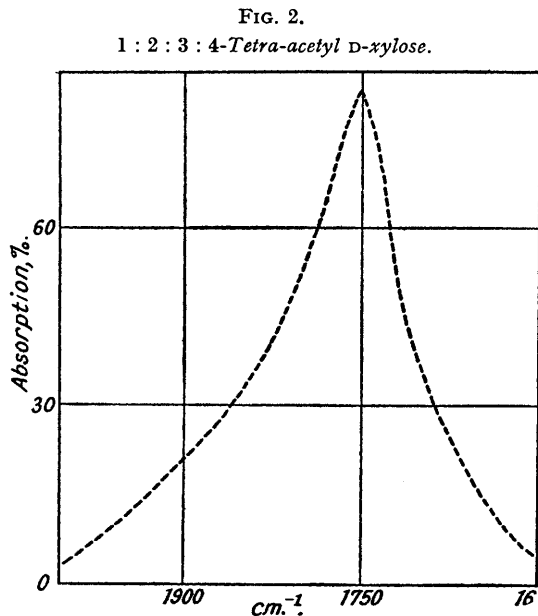   NHAc   -------   NHAc
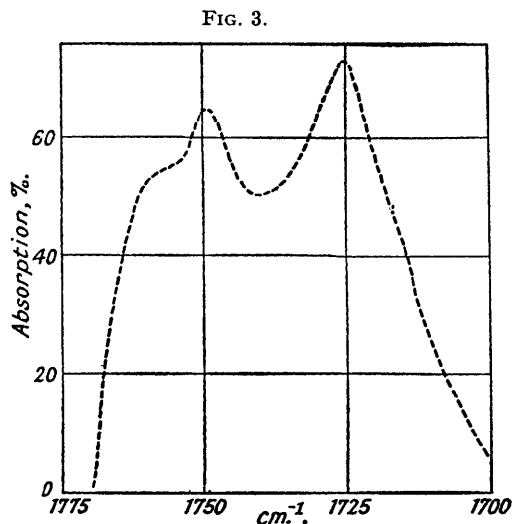
Fig. 3 shows the CO absorption from 6-amino-5-thioformamido-4-triacetyl-D-xylosidamino-2-methyl-pyrimidine. The corresponding non-acetylated compound shows no absorption in this region. Here again we find a band at 1725 cm.$^{-1}$ (the position of the bonded C=O in the analogous nitroso-compound) and a band near 1750 cm.$^{-1}$, the normal position for the CO frequency in an acetylated sugar. The band near 1750 cm.$^{-1}$ does show definite indications of further structure, but as this particular band was examined under specially high resolving power, this is not unexpected and may well arise from resonance between the two non-bonded C=O vibrations or even resonance with the overtone of some lower frequency.

The comparison between the spectrum of 6-acetamido-4-D-xylosidamino-2-methylthiopyrimidine and that of the corresponding triacetylated compound is given in Fig. 4. The former shows a band at 1695 cm.$^{-1}$, which by comparison with the spectra of other pyrimidines (not shown here) must be due to the C=O bond of the 6-acetamido-group. The latter shows a double band with maxima at 1745 cm.$^{-1}$ and 1710 cm.$^{-1}$. The band at 1745 cm.$^{-1}$ again corresponds to the position for non-bonded acetyl C=O groups in the other molecules, while the maximum at 1710 cm.$^{-1}$ may reasonably be presumed to arise from an overlapping of a bonded C=O frequency at 1725 cm.$^{-1}$ with the acetamido C=O frequency at 1695 cm.$^{-1}$.

Finally in Fig. 5 are given the C=O absorption bands found in 6-amino-4-triacetyl-D-ribopyranos-amino-5-(2′ : 5′-dichlorobenzeneazo)-2-methylthiopyrimidine and the corresponding L-arabopyranose compound. Here we find in each case one strong band (with a few signs of structure) centred at 1750 cm.$^{-1}$

FIG. 5.
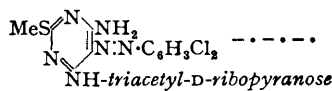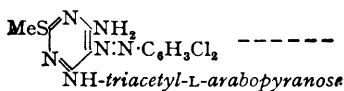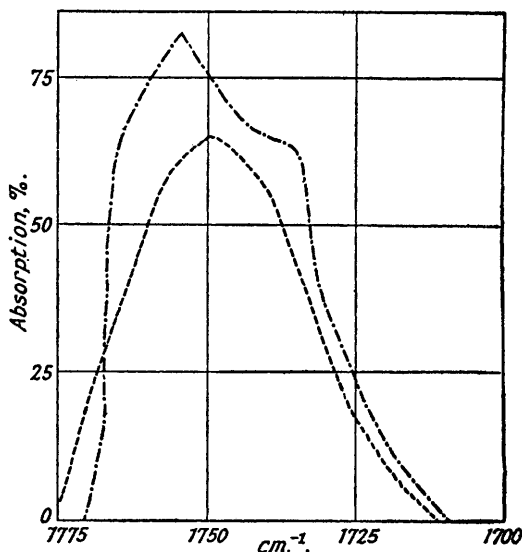
and no trace of any absorption near or below 1725 cm.$^{-1}$ (the position where a bonded CO might be expected). The absence of any evidence for hydrogen bonding in the triacetyl-5-arylazoglycosides is of considerable interest in view of its presence in the analogous 5-nitroso-compounds. This is in accord with the observed fact that, unlike the latter, the triacetyl-5-arylazoglycosides are capable of existence in both α- and β-forms.

Thus in every case where chemical behaviour has caused the introduction of the hypothesis of hydrogen bonding, a band has been found in the neighbourhood of 1710—1725 cm.$^{-1}$, whereas when chemical evidence was against chelation a single absorption has been found near 1750 cm.$^{-1}$, the normal position for an acetylated sugar. The infra-red evidence in favour of the original hypothesis of Kenner, Lythgoe, and Todd may therefore be regarded as virtually conclusive.

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