Stereospecific Synthesis of Nucleosides by the Fusion Reaction

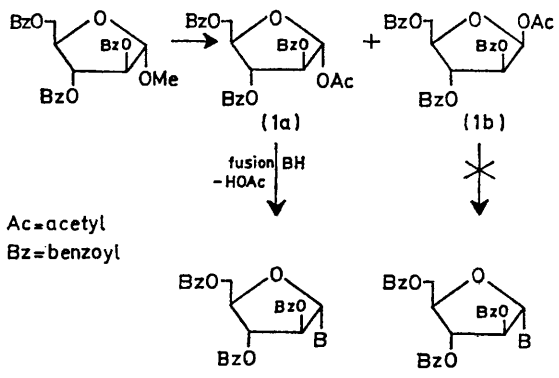
By DONALD A. BAKER, RICHARD A. HARDER, JUN., and RICHARD L. TOLMAN*
(*ICN Pharmaceuticals, Inc., Nucleic Acid Research Institute, Irvine, California* 92664)

Summary A study of the fusion of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-arabinofuranose [α/β(4:1)] with 2,6-dichloropurine or 7-methylthio-*v*-triazolo[4,5-*d*]pyrimidine to produce 9-(2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl)-2,6-dichloropurine and 1-, 2-, and 3-(2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl)-7-methylthio-*v*-triazolo[4,5-*d*]pyrimidines, respectively, revealed that the β-anomer of the starting sugar was unreactive in the fusion reaction (without acid catalyst), presumably owing to the inability of the 2-*O*-benzoyl group effectively to provide anchimeric assistance in the presence of a *cis*-OAc group at the reaction site.

THE fusion synthesis of nucleosides has been shown to be highly stereoselective[1] for the 1,2-*trans*-product when an acylated carbohydrate is employed. In a few cases both the *cis*- and *trans*-products have been observed[2] and in one case epimerization at C-2 has also been demonstrated.[3] Most of the exceptions to Baker's *trans*-rule[4] can be explained by anomalous effects of a particular aglycon employed or special instability or stereochemical properties of the carbohydrate derivative employed. It has, however, been presumed that there are no stereochemical requirements for C-1 of the carbohydrate derivative in the fusion reaction.

To test this hypothesis, 2,6-dichloropurine was fused with syrupy 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-arabinofuranose† [**1a** and **1b**], prepared by acetolysis of the corresponding α-methyl glycoside,[5] at 190° for 15 min *in vacuo* to remove HOAc formed. Chromatographic resolution of the reaction mixture gave 9-(2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosyl)-2,6-dichloropurine (**2**)‡ in 75% yield, a second unidentified nucleoside derivative (9%), plus a crystalline carbohydrate derivative (11%) identified as the β-anomer of the starting material, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-arabinofuranose (**1b**). It appears that the β-anomer of the starting sugar (**1b**) is much less reactive in the fusion reaction [the anomeric sugar mixture was determined by ^{1}H n.m.r. spectroscopy to be *ca.* 20% (**1b**) (α/β = 4:1)].

To confirm these conclusions, a second example was investigated: 7-Methylthio-*v*-triazolo[4,5-*d*]pyrimidine (6-methylthio-8-azapurine) fusion[6] at 200° with (**1a**) and (**1b**) gave a four-component mixture, which was resolved by silica gel column chromatography. Three nucleosides were characterized and identified‡ by spectral (^{1}H n.m.r., u.v.) and chemical (debenzoylation and comparison with authentic samples[6]) methods as 3- (**3a**, 37%), 2- (**3b**, 24%), and 1-α-D-arabinofuranosyl-7-methylthio-*v*-triazolo[4,5-*d*]-pyrimidine (**3c**, 5%). The fourth component was found to be unchanged starting sugar (15%) from which the β-anomer (**1b**, 11%) could be fractionally crystallized. Only 5% of the original α-anomer could be recovered but more than 50% of the original minor β-anomer was isolated.



(2) B=2,6-dichloropurin-9-yl
(3a) B=7-methylthio-*v*-triazolo[4,5-*d*]pyrimidin-3-yl (8-azapurin-9-yl)
(3b) B=7-methylthio-*v*-triazolo[4,5-*d*]pyrimidin-2-yl (8-azapurin-8-yl)
(3c) B=7-methylthio-*v*-triazolo[4,5-*d*]pyrimidin-1-yl (8-azapurin-7-yl)

Since not all of the original β-anomer was recovered in the two fusion reactions described, the pure (**1b**) was fused at 200° with 7-methylthio-*v*-triazolo[4,5-*d*]pyrimidine to test whether the unrecovered (**1b**) had reacted to form nucleoside or had decomposed. T.l.c. analysis of the reaction mixture showed only slight traces of nucleoside material (total <5%). Since the rate-controlling step of anomerization (in penta-acetyl glucopyranose) is suggested to be the breaking of the C-1–OAc bond,[7] it can be concluded that the stereospecificity[8] of this fusion reaction, and perhaps other fusions, is due to the inability of the C-2–OBz bond in (**1b**) to provide anchimeric assistance in the breaking of the C-1–OAc bond.

The cleavage of the C-1–OAc in the case of the α-anomer (**1a**) is probably assisted by participation of the *trans*-C-2–OBz.

Both of the fusion reactions described here (**1a** and **1b** with 2,6-dichloropurine or 7-methylthio-*v*-triazolo[4,5-*d*]-pyrimidine) were repeated under identical conditions except

† Satisfactory analytical and spectroscopic data have been obtained for all new compounds reported.

‡ The α-configuration of (**2**) was confirmed by ^{1}H n.m.r. comparisons of the H-1′ chemical shift and $J_{1',2'}$ with the spectral data of the known β-anomer.

that a small quantity of an acid catalyst was added (dichloroacetic acid or bis-*p*-nitrophenyl phosphate). T.l.c. analysis and column workup revealed a slight improvement in yield, but no change in the product distribution was noted, except that no unchanged sugar could be detected in either case.

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