Tetrahedron Letters No. 13, pp 1177 - 1180, 1977. Pergamon Press. Printed in Great Britain.

NUCLEOPHILIC DISPLACEMENT REACTIONS WITH THIOBENZOATE. NEW SYNTHESES OF DEOXY-THIOADENOSINE DERIVATIVES STARTING FROM ADENOSINE.

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(Received in UK 6 February 1977; accepted for publication 21 February 1977)

Modifications of the carbohydrate moiety of adenosine have led to compounds such as 3'-amino-3'-deoxyadenosine, cordycepin (3'-deoxyadenosine) and 4'-thioadenosine[1], which show cell growth inhibitory activity. These findings also prompted the interesting synthesis of 3'.deoxy-3'-thioadenosine (6), which was prepared previously by Goodman et al.[2] as follows: methyl-3,5-di-O-tosyl-α-D-xylofuranoside was converted to the 2-thionobenzoate on reaction with thiobenzoylchloride. Some 2-benzoate was also formed. Neighbouring group participation resulted in intramolecular 3-sulfonate displacement, and further steps yielded 1-O-acetyl-3-S-benzoyl-3-thio-ß-D-ribofuranose. The latter was converted in 18 % yield to 6 by the chloromercury procedure.

We were interested in 6 as starting material for the preparation of the 3'-thio analog of c-AMP, and in the following report we describe a more convenient route to this compound.

Direct displacement reactions of the functionalized secondary hydroxyl groups of furanoses are generally considered to be difficult[3], but recent examples have been described[4]. 3'-Deoxy-3'-iodo-xylofuranosyladenine (3) can be prepared from adenosineriboepoxide (2)[5], which is readily available from adenosine (1)[6]. When 3 was reacted with sodium thiobenzoate in DMF at 100°C, two main products were formed. The major one (50 % yield) was readily identified as the 3',4'-unsaturated compound 5[7]. The second compound (40 %) contained a S-benzoyl as well as an O-benzoyl group. The analytical and spectroscopic data are in agreement with structure 4. (Mass spectrum: M^+ = 491 m/e, n.m.r. see table 1).

Jnder the employed reaction conditions O-benzoylation at the 2'-OH also takes place, as was indicated by the low field shift of $C_{2'}$-H in the n.m.r.. Upon catalytic hydrogenation, compound 4 yielded 2'-O-benzoyl-3'-deoxyadenosine (7), which with sodium methoxide gave 3'-deoxyadenosine (8). With adenosine, xyloadenosine and 3'-deoxyadenosine O-benzoylation did not occur with sodium thiobenzoate. Therefore we assume that after the nucleophilic displacement, 3'-S ⟶ 2'-O benzoyl migration has occurred, followed by benzoylation of the 3'-SH group[8]. This explanation is supported by the reaction of 6 with thiobenzoate to yield 4. Compound 6 was obtained on treating 4 with sodium methoxide in the presence of nitrogen to avoid disulfide formation. The mass spectrum of 6 was identical with the one previously published[9]. The physical data differed slightly from the reported[2]: m.p. 204 - 206°C[10]; $[\alpha]_D^{25} = -18^\circ$ (c = 0,20 in H_2O). The SH-determination with "Ellman's Reagent" [5,5'-dithiobis-(2-nitrobenzoic acid)][11] gave the correct value.

In the n.m.r. spectrum the coupling constant $J_{1'-2'}$ (2,0 Hz) of 6 was found to be similar to that of xyloadenosine ($J_{1'-2'}$ = 2,0 Hz)[6].

For comparison the corresponding xylo-thioadenosine (10) was prepared. Adenosineriboepoxide (2) was selectively ring opened with thiobenzoic acid, yielding 9. Catalytic hydrogenation of 9 with Pd/C gave 3'-deoxyadenosine (8), which proves the ring opening has taken place at the 3'-position. Sodium methoxide treatment of 9 under nitrogen gave 10. The $J_{1'-2'}$ coupling constant of the xylo-derivative 10 was similar to that of adenosine ($J_{1'-2'}$ = 6,1 Hz). When 10 was reacted with sodium thiobenzoate, the SH-group was selectively benzoylated yielding 9. This is consistent with trans arrangement of the 3'-SH and 2'-OH group, which excludes 3'-S ⟶ 2'-O-benzoyl migration.

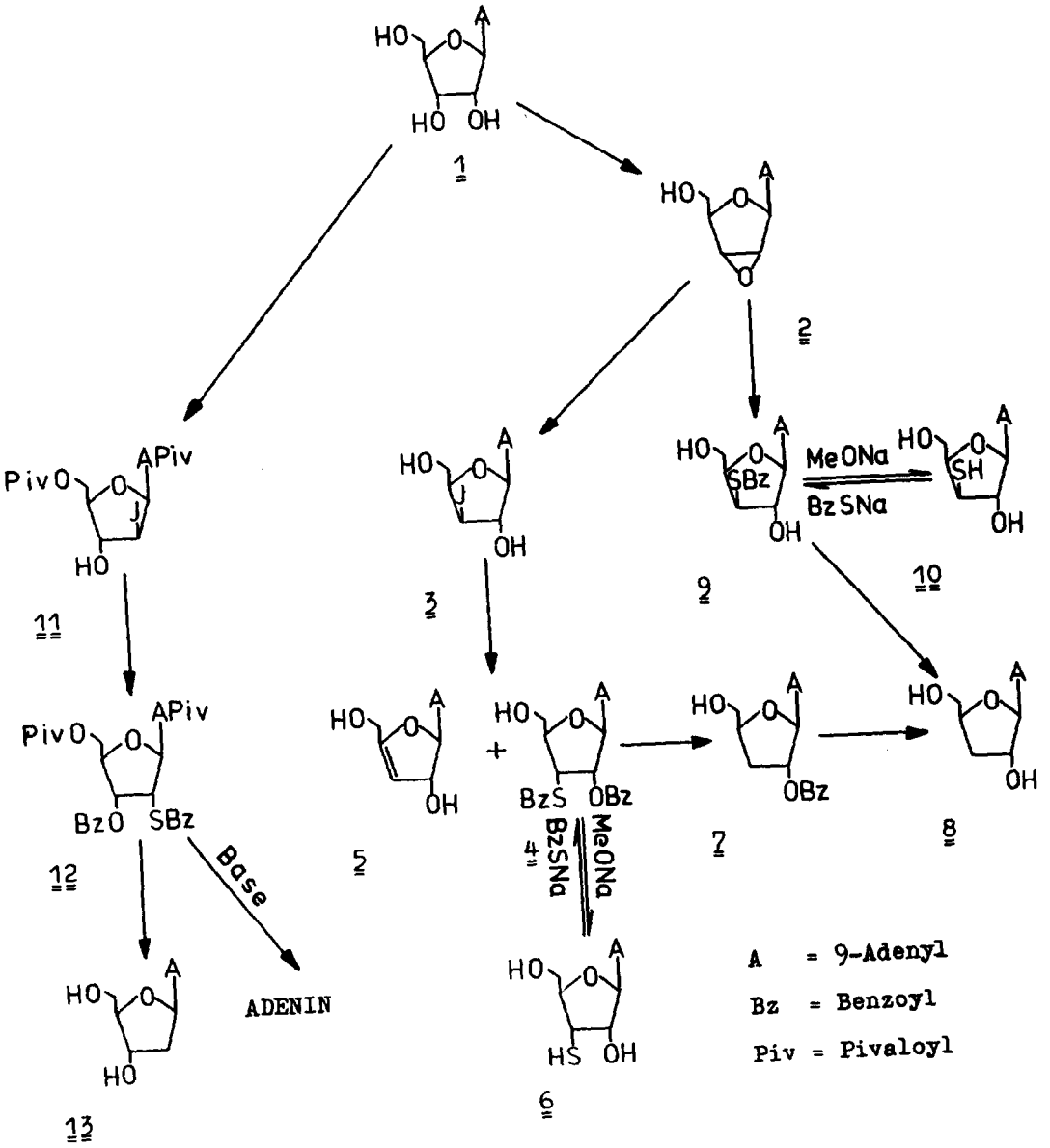
All these findings suggest that the configuration of 6 is ribo and that of 10 is xylo. The 2',3'-endo:exo ratio of the ribo and xylo-thioadenosine 6 and 10 seems to be just reversed from that of ribo and xyloadenosine as shown by NMR.

Table 1: Characteristic n.m.r. data of the substituted adenosine derivatives (δ = ppm, first order coupling constants = Hz at 100 MHz in DMSO-D_6)

	$C_{1'}$-H	$C_{2'}$-H	Others
4	6.42d $J_{1',2'}$ = 2.7	6.18q $J_{2',3'}$ = 6	7.74m, 10 protons, phenyl
6	5.98d $J_{1',2'}$ = 2.0	4.44q$^+$ $J_{2',3'}$ = 5.0	2.41 br, SH
7	6.26d $J_{1',2'}$ = 2.5	5.68m $J_{2',3'}$ = 2.5 $J_{2',3''}$ = 6	7.74m, 5 protons, phenyl
9	5.92d $J_{1',2'}$ = 6.7	4.83q$^+$ $J_{2',3'}$ = 9.2	7.77m, 5 protons, phenyl
10	5.71d $J_{1',2'}$ = 6.3	4.55q$^+$ $J_{2',3'}$ = 8.3	2.8 br, SH
12	6.70d $J_{1',2'}$ = 9.5	5.58q $J_{2',3'}$ = 5.7	6.01q $J_{3',4'}$ = 1.2 $H_{3'}$, 7.86m, 10 protons, phenyl

$^+$ = after D_2O exchange.

No. 13


HO
A
HO OH
1
2
PivO
APiv
HO
11
3
MeONa
BzSNa
SBz
SH
OH
9
10
PivO
APiv
BzO SBz
12
Base
ADENIN
5
BzS OBz
4
BzSNa
MeONa
7
OBz
8
HS
6
13
A = 9-Adenyl
Bz = Benzoyl
Piv = Pivaloyl

When we applied the thiobenzoate displacement reaction to the 2'-deoxy-2'-iodo-arabinofuranosyl adenine derivative 11[7], the reaction product again contained a S-benzoyl as well as an O-benzoyl group, as indicated by MS (M^+ = 659 m/e) and n.m.r. (see tab. 1). This product, on catalytic hydrogenation followed by sodium methoxide treatment, gave 2'-deoxyadenosine (13), suggesting structure 12. The $J_{1',2'}$ coupling constant of 9.5 Hz for compound 12 is in agreement with that assigned by Goodman et al.[12] for 6-substituted-9-purinyl nucleosides of 2'-thio-D-ribose ($J_{1',2'}$ = 9.0 - 9.5 Hz).

All attempts to remove the protecting groups from 12 with various bases, so far, have only led to isolations of adenine. A similar result has been observed by Goodman et al.[12] during the deblocking of 6-benzamido-9-(2-S-benzoyl-3,5-di-O-benzoyl-2-thio-ß-D-ribofuranosyl)-9H-purine.

This work was generously supported by the Deutsche Forschungsgemeinschaft, and the University of Konstanz.

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