Tetrahedron Letters No. 25, pp. 2353-2356, 1971. Pergamon Press. Printed in Great Britain.

SINGLE CRYSTAL X-RAY STRUCTURE OF CHEMOTHERAPEUTIC AGENTS IV, THE STRUCTURE OF 6-CHLORO-9-(3,4-DI-O-ACETYL-2-DEOXY-β-D-RIBOPYRANOSYL)PURINE (1)

Donald J. Abraham, Robert D. Rosenstein and Todd G. Cochran
Departments of Medicinal Chemistry and Crystallography
University of Pittsburgh, Pittsburgh, Pennsylvania, U.S.A.
and
Eldon E. Leutzinger and L. B. Townsend
Department of Biopharmaceutical Science and Department of Chemistry
University of Utah, Salt Lake City, Utah, U.S.A.

(Received in USA 12 April 1971; received in UK for publication 24 May 1971)

The direct acid-catalyzed fusion of 6-chloropurine with 3,4-di-O-acetyl-D-arabinal has been reported (2) to furnish a mixture of the α and β anomers of 6-chloro-9-(3,4-di-O-acetyl-2-deoxy-D-ribopyranosyl)purine. The anomer with mp 205-207° was assigned the α configuration and the anomer with mp 159-160° was assigned the β configuration on the basis of double resonance studies at 60 MHz. However, at this frequency, certain relevant decouplings (H3-H4) were precluded because of inadequate chemical shift difference between signals, and a recent communication (3) has indicated, on the basis of 100 MHz studies, that the anomeric assignments should be reversed. In order to solve this problem unambiguously we initiated an X-ray crystallographic analysis of one of these anomers.

Single crystal data was collected on a metastable crystal form of the higher melting anomer. These crystals had a melting point of 173-175° . However, when they were crushed between glass plates, the resulting fragments softened near 190° and melted at 200-205°, indicating that this material is readily transformed to the more stable crystal form, melting at 205-207° . Thin layer chromatography of both crystalline forms was identical in three different solvent systems. The cell dimensions were a = 8.412 Å, b = 17.057 Å, c = 10.955 Å and the space group, as determined by systematic absences, was $P2_12_12_1$ with four molecules in the unit cell. A total of 1356 independent reflections was measured using a Picker FACS 1

diffractometer with Ni filtered Cu Kα radiation. The data was processed in the usual manner to produce a set of normalized E factors, and the structure was solved using the tangent formula (4). The first E map revealed the locations of all 24 atoms heavier than hydrogen and several cycles of least squares refinement reduced the R factor (anisotropic) to 11.8% for all reflections. Bond distances and angles are given in Figure 1, and the atomic coordinates are listed in Table 1.

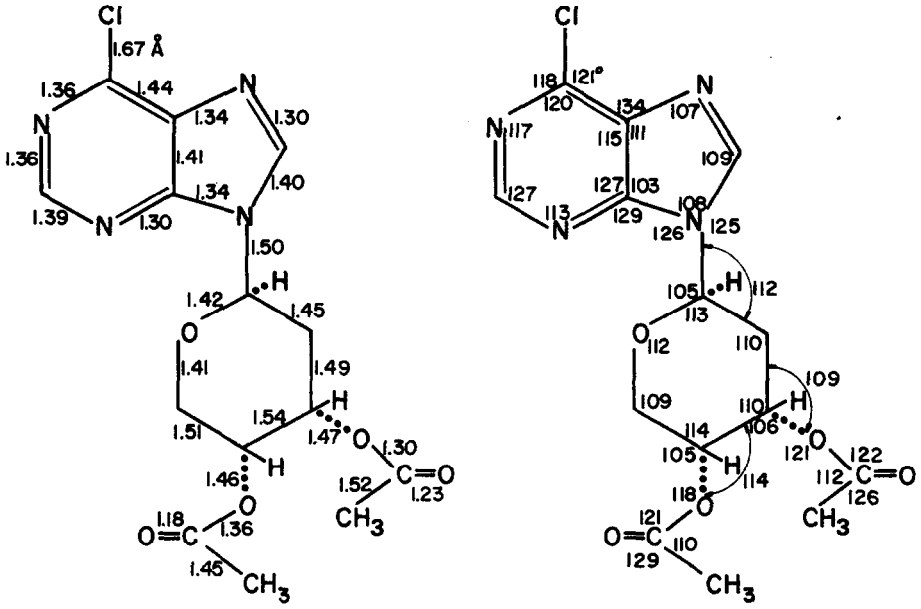

FIGURE I. Bond Distances and Angles
(In Ångstroms) (In Degrees)

The structure was found to be that of the β anomer. Therefore, the anomer melting at 205-207° (and 173-175°) should be assigned the structure 6-chloro-9-(3,4-di-O-acetyl-2-deoxy- β-D-ribopyranosyl)purine while the anomer melting at 159-160° should be assigned the structure 6-chloro-9-(3,4-di-O-acetyl-2-deoxy- α-D-ribopyranosyl)purine.

It is of considerable interest that the 6-mercaptopurine derivative (NSC #111362) of the anomer melting at 159-160° has demonstrated sufficient antitumor activity (5) (leukemia L-1210) to be assigned a test status code of 11 while the 6-mercaptopurine derivative (NSC #111361) of the other anomer was absolutely devoid of any activity in the same test system. Therefore,

contrary to the usual trend in nucleosides, in this case the α -anomer rather than the β -anomer exhibited antitumor activity.

TABLE 1. List of Atomic Coordinates

Atom Identification (6)	X	Y	Z
Cl	0.1507	0.3555	0.2242
N 1	0.3345	0.2511	0.3240
N 3	-0.0485	0.2387	0.4706
N 7	0.2209	0.4320	0.4924
N 9	-0.1219	0.1201	0.3688
O 1'	-0.1245	0.1745	0.1750
O 3'	0.2507	0.0990	0.1071
O 4'	-0.4051	0.3518	0.1054
O 6'	-0.4751	0.4571	0.2107
O 8'	-0.1258	0.4714	0.0336
C 2	0.4254	0.2247	0.4178
C 4	-0.1216	0.1715	0.4615
C 5	0.2802	0.3640	0.4507
C 6	0.2632	0.3215	0.3379
C 8	-0.2213	0.0572	0.3992
C 1'	-0.0289	0.1276	0.2530
C 2'	0.0095	0.0517	0.2000
C 3'	0.0953	0.0629	0.0818
C 4'	0.0046	0.1216	0.0010
C 5'	-0.0447	0.1956	0.0670
C 6'	-0.3968	0.3996	0.2045
C 7'	-0.2960	0.3645	0.2967
C 8'	0.3791	0.0758	0.0512
C 9'	-0.4714	0.1139	0.1026

References and Footnotes.

1. This work was supported by Contract PH 43-67-1186 and PH 43-65-1041 with the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, U.S. Public Health Service and by the University of Pittsburgh Computer Center for unsponsored computing time.

2. E. E. Leutzinger, W. A. Bowles, R. K. Robins and L. B. Townsend, J. Amer. Chem. Soc., 90, 127 (1968).

3. M. Fuertes, G. Garcia-Munoz, R. Madronero, M. Stud, and M. Rico, Tetrahedron, 26, 4823 (1970).

4. S. R. Hall (1967), adapted to the IBM 7090 by H. Berman (1969), revised by R. Shiono, University of Pittsburgh, unpublished report (1970).

5. These testing data were obtained from the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, U.S. Public Health Service.

6. The atom identification numbering system is that shown below: