Carbohydrate Research, 30 (1973) 225–227

Preliminary communication

A facile synthesis of nucleoside derivatives of 1,4-oxathiane

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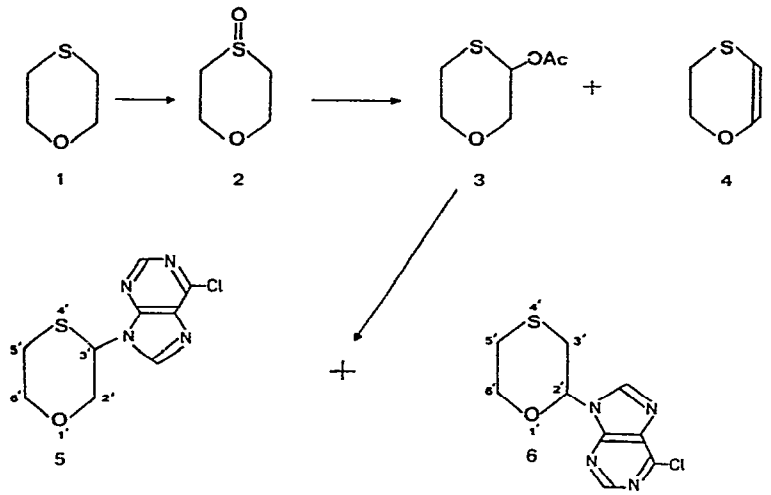
(Received July 18th, 1973; accepted July 31st, 1973)

Certain compounds obtained by condensation of periodate-oxidized nucleosides with isonicotinic acid hydrazide have antitumor activity and are useful for blocking the autoimmune processes in warm-blooded animals[1]. The compounds have substituted morpholine structures; for example, periodate-oxidized adenosine affords *N*-[2-(9-adenyl)-3,5-dihydroxy-6-(hydroxymethyl)morpholino]isonicotinamide. It is known[2] also that many 9-(tetrahydropyran-2-yl)-9*H*-purines[3] exhibit significant antitumor activity. These results prompted synthesis of nucleoside analogs containing 1,4-oxathiane; the present Communication describes a facile synthesis of such compounds. Interestingly, several organophosphorus derivatives of 1,4-oxathiane display[4] insecticidal and acaricidal activity.

Foster and coworkers[5] have converted suitably protected glycopyranosides into derivatives of 2-hydroxy-1,4-oxathiane. In the present work; nucleoside-base derivatives of 1,4-oxathiane were synthesized from a non-carbohydrate precursor, namely, 1,4-oxathiane (**1**) itself, by way of a Pummerer reaction[6]. McCormick and McElhinney[7] have previously employed the Pummerer reaction in a synthesis of carbohydrate derivatives in which the ring oxygen atom is replaced by sulfur.

1,4-Oxathiane (**1**) was converted into the hygroscopic sulfoxide 2 in 80% yield by oxidation with sodium metaperiodate by the method of Leonard and Johnson[8]. Treatment of 2 with 1.5 equiv. of acetic anhydride in boiling benzene containing a trace of *p*-toluenesulfonic acid monohydrate for 3.5 h afforded the chromatographically separable Pummerer-reaction product **3**, and a small proportion of 1,4-oxathiene (**4**). Compound 4 had b.p. 58°/20 torr (lit.[9] b.p. 54°/20 torr), and the n.m.r.-spectral data accorded with literature values[10]. The acetate 3 was isolated as a colorless liquid, λ_{max}^{film} 5.75 μm (OAc).

An intimate mixture of compound 3, 6-chloropurine (1.1 equiv.), and a trace of *p*-toluenesulfonic acid monohydrate was heated for 20 min on a steam bath. The brown reaction-mixture was extracted with hot ethyl acetate, and the extracts were concentrated to an orange syrup. T.l.c. on silica gel [1:1 (v/v) ethyl acetate–benzene] showed six components. Preparative t.l.c. afforded the two major ones, 6-chloro-9-(1,4-oxathian-3-yl)-9*H*-purine (**5**, R_F 0.40) and 6-chloro-9-(1,4-oxathian-2-yl)-9*H*-purine (**6**, R_F 0.52), in approx-



imately equal proportions (25% combined yield from 3). Compound 5 had m.p. 108–109°; λ_{max}^{EtOH} 265 nm (ϵ 7,960), $\lambda_{max}^{0.1\ M\ HCl}$ 265 nm (ϵ 7,960), $\lambda_{max}^{0.01\ M\ NaOH}$ 266 nm (ϵ 8,340); λ_{max}^{KBr} 6.3, 6.4, and 6.7 μm (purine ring); n.m.r. data*: τ 1.17, 1.25 (1-proton singlets, H-2,8), 4.43 (1-proton, broad peak, $J_{3',2'} + J_{3',2''} \sim 6$ Hz, H-3'), 5.0–6.3 (4 protons, $-H_2COCH_2-$), and 6.5–7.8 (2 protons, $-SCH_2-$). Compound 6 had m.p. 137–138°; λ_{max}^{EtOH} 265 nm (ϵ 9, 710), $\lambda_{max}^{0.1\ M\ HCl}$ 264 nm (ϵ 9,430), $\lambda_{max}^{0.01\ M\ NaOH}$ 264 nm (ϵ 9,430); λ_{max}^{KBr} 6.3, 6.4, and 6.7 μm (purine ring); n.m.r. data: τ 1.23, 1.63 (1-proton singlets, H-2,8), 3.95 (1-proton doublet of doublets, $J_{2',3'} + J_{2',3''} = 11.5$ Hz, H-2'), 5.3–6.3 (2 protons, $-OCH_2-$), and 6.5–7.9 (4 protons, $-H_2CSCH_2$). Both nucleosides gave satisfactory elemental analyses: the maximal u.v. absorption at 264–266 nm in neutral, acid or basic solution is in agreement[11] with a 9-substituted purine. The structural differentiation of the two nucleosides was made tentatively, on the basis of n.m.r.-spectral data. It has been found[10,12] that, in the spectrum of 1,4-oxathiane in carbon tetrachloride, the OCH_2 multiplet resonates at lower field (τ6.12) than the SCH_2 multiplet (τ7.43). Accordingly, the nucleoside whose n.m.r. spectrum showed a 4-proton multiplet at τ5.0–6.3 and a 2-proton multiplet at τ6.5–7.8, was assigned the 3-substituted 1,4-oxathiane structure (5), and the nucleoside whose spectrum showed a 2-proton multiplet at τ5.3–6.3 and a 4-proton multiplet at τ6.5–7.9, was assigned the 2-substituted 1,4-oxathiane structure (6). If it is assumed that the 1,4-oxathiane rings of the nucleosides 5 and 6 adopt chair conformations, then the value (~6 Hz) obtained for $J_{3',2'} + J_{3',2''}$ from the n.m.r. spectrum of 5 indicates a preponderance in chloroform-*d* of the conformer having the purine moiety in an axial orientation, whereas the value (11.5 Hz) obtained for $J_{2',3''} + J_{2',3''}$ for 6 indicates a preponderance of the equatorial form (compare Ref. 13).

The isolation, from the condensation reaction, of the nucleoside 6, in addition to the expected product 5, is noteworthy. The formation of 6 is presumed to occur by the

* N.m.r. spectra were recorded at 60 MHz in chloroform-*d* with tetramethylsilane as the internal standard.

acid-catalyzed addition of 6-chloropurine to 1,4-oxathiene (4) [compare Refs. 3 and 9] produced during the condensation reaction.

ACKNOWLEDGMENTS

The authors are grateful to Professor J.K.N. Jones for his constant interest and encouragement, and the National Research Council of Canada for their financial support of this work.

REFERENCES

1 W. Dvonch and H. E. Alburn, *Abstr. Papers Amer. Chem. Soc. Meeting*, 155 (1968) C56; *Chem. Eng. News*, 46[17] (1968) 41; U.S. Patent 3,542, 776, Nov. 24, 1970; *Chem. Abstr.*, 74 (1971) 31760.
2 R. K. Robins, *J. Med. Chem.*, 7 (1964) 186.
3 R. K. Robins, E. F. Godefroi, E. C. Taylor, L. R. Lewis,and A. Jackson, *J. Amer. Chem. Soc.*, 83 (1961) 2574.
4 A. H. Haubein, *J. Amer. Chem. Soc.*, 81 (1959) 145.
5 K. W. Buck, F. A. Fahim, A. B. Foster, A. R. Perry, M. H. Qadir,and J. M. Webber, *Carbohyd. Res.*, 2 (1966) 14.
6 L. Horner and P. Kaiser, *Ann.*, 626 (1959) 19; W. E. Parham and L. D. Edwards, *J. Org. Chem.*, 33 (1968) 4150.
7 J. E. McCormick and R. S. McElhinney, *Chem. Commun.*, (1969) 171.
8 N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, 27 (1962) 283.
9 W. E. Parham, I. Gordon,and J. D. Swalen, *J. Amer. Chem. Soc.*, 74 (1952) 1824.
10 N. de Wolf, P. W. Henniger and E. Havinga, *Rec. Trav. Chim. Pays-Bas*, 86 (1967) 1227.
11 E. E. Leutzinger, W. A. Bowles, R. K. Robins,and L. B. Townsend, *J. Amer. Chem. Soc.*, 90 (1968) 127; L. B. Townsend, R. K. Robins, R. N. Loeppky,and N. J. Leonard, *J. Amer. Chem. Soc.*, 86 (1964) 5320.
12 W. B. Smith and B. A. Shoulders, *J. Phys. Chem.*, 69 (1965) 579.
13 N. S. Zefirov, V. S. Blagoveshchensky, I. V. Kazimirchik,and N. S. Surova, *Tetrahedron*, 27 (1971) 3111