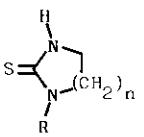
REACTION OF GLYCOSYLISOTHIOCYANATES WITH 2–CHLOROETHYLAMINE

M. Avalos González[a], R. Babiano Caballero[a], P. Cintas Moreno[a], J. Fuentes Mota[b], J.L. Jiménez Requejo[a], and J.C. Palacios Albarrán[a]*

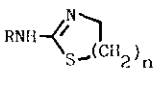
Department of Organic Chemistry, University of Extremadura, 06071–Badajoz, Spain[a], and Department of Organic Chemistry, Faculty of Chemistry, University of Seville, 41071–Seville, Spain[b].

Abstract – The products formed in the reaction of per–*O*–acyl–glycosylisothiocyanates with ω–haloalkylamines are shown to be glycosylamino– and *N,N'*–bis–glycosyl–heterocycles.

Per–*O*–acyl–glycosylimidazolidine–2–thiones (1) are starting materials for the preparation of some mesoionic nucleosides[1] related to biologically active natural products[2]. In 1981, Ogura[3] claimed an efficient synthesis of *N*–nucleoside derivatives of imidazolidine–2–thione (1) and hexahydropyrimidine–2–thione (2). Among the data reported by these authors there, an unassignable absorption appears in the infrared spectrum at 1625 cm^{-1} which is in disagreement with these structures, and it suggests that the products formed are glycosylaminoheterocycles (3 or 4)[4].



1 n=1
2 n=2

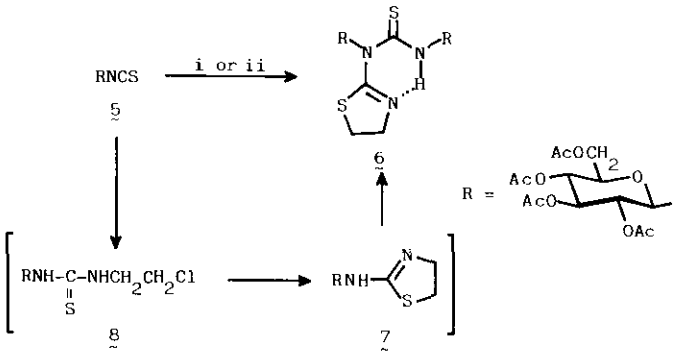


3 n=1
4 n=2

R = sugar moiety

On treatment of 2,3,4,6–tetra–*O*–acetyl–β–D–glucopyranosylisothiocyanate (5) with 2–chloroethylamine hydrochloride under the same conditions described by Ogura[3], a new product is isolated which was confirmed the structure of *N,N'*–bis(2,3,4,6–tetra–*O*–acetyl–β–D–glucopyranosyl)–*N*–(2–thiazolin–2–yl)thiourea (6)[5] by ^{13}C–nmr spectroscopy. Thus, all glycosidic signals are duplicated in the ^{1}H– and ^{13}C–nmr spectra, showing the existence of two sugar moieties. The presence of the thiourea linkage in 6 was indicated by a signal at δ 181.97 ppm and the large upfield position at δ 165.76 ppm is in agreement with a C=N bond, but not with a C=S signal of an imidazolidine–2–thione moiety. Finally, the two different resonances at δ 54.61

and 24.85 ppm for CH_2–N= and CH_2–S–, respectively, are congruent with carbon–heteroatom linkages of different electronegativity[6].

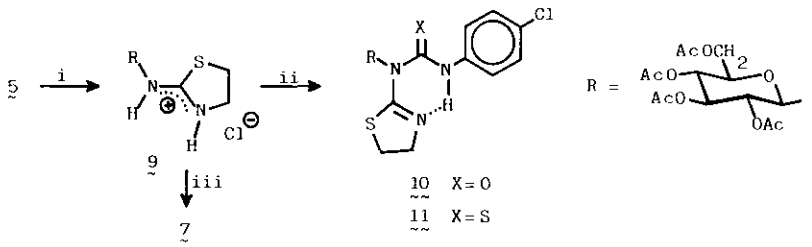


i) $ClCH_2CH_2NH_2.HCl$, py, r.t., 2h

ii)$ClCH_2CH_2NH_2.HCl$, NaOAc, $CHCl_3$, r.t., 2h

The formation of **6** should occur *via* addition of **5** to the glycosylaminothiazoline **7** (not isolated), which proceeds by spontaneous intramolecular cyclization of 2–chloroethylthiourea **8**, formed in the first step by reaction of **5** with 2–chloroethylamine.

The alternative synthesis of **7**, however, has been achieved by addition of **5** to an ethereal solution of 2–chloroethylamine, which leads to the hydrochloride intermediate **9**. Its further treatment with aqueous sodium hydrogen carbonate in chloroform afforded the free base **7**, which was additionally characterized *via* unequivocal preparation of compounds **10** and **11** by reaction with 4–chlorophenyliso(thio)cyanate in pyridine[7].



i) $ClCH_2CH_2NH_2$, ether; ii) 4–ClC_6H_4NCX, py, r.t.

iii) $NaHCO_3$, $CHCl_3/H_2O$

Compounds **6**, **10**, and **11** show a strongly chelated structure[8] as shown by both the large downfield shift of

NH signals in the ^{1}H–nmr spectra (12–14 ppm) and the lower frequencies of bonded NH in the ir spectra (<3000 cm^{-1}). These compounds constitute a special class of *N*–nucleosides, in which intramolecular hydrogen bonding closes a "heterocyclic moiety". The structure of clytocine has been reported[9] recently being the first nucleoside isolated from natural sources, with such a characteristic. Other analogous compounds have been isolated in the interaction between DNA and carcinogenic amines[10].

In conclusion, in this paper the results reported by Ogura are corrected and, at the same time, an easy synthetic method of biologically active nucleosides is described. The full details of this work are currently under investigation in our laboratories.

ACKNOWLEDGEMENTS

We thank Dr. M. Rico for recording nmr spectra and Dr. J. Plumet for his helpful discussions. This research was supported by Dirección General de Investigación Científica y Técnica (Grant No. PB86–0255).

REFERENCES AND NOTES

1. R.A. Glennon and S.M. Tejany, Nucleos. & Nucleot., 1984, 3, 389.

2. a) R.H. Hall, "The Modified Nucleosides in Nucleic Acids", Columbia University Press, New York (1971). b) R.H. Hall, "Modified Nucleosides and Cancer", Ed. G. Nass, Springer–Verlag (1983).

3. H. Ogura, H. Takahashi, and O. Sato, J. Carbohydr. Nucleos. Nucleot., 1981, 8, 437.

4. This class of compounds are useful in the preparation of mesoionic xanthine nucleosides. See: R.A. Glennon, E. Schubert, and R.G. Bass, Tetrahedron Lett., 1981, 22, 2753.

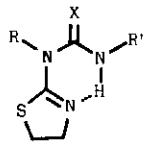
5. Compound **6** was isolated by preparative t.l.c. over silicagel plates (yield 37 %, R_f 0.42, benzene–methanol 5:1); uv (ethanol): 279 and 246 nm; ir (KBr): 3000–2840 (NH), 1730 (OAc), and 1600 cm^{-1} (C=N); ^{1}H–nmr ($CDCl_3$, 360 MHz): δ 12.47 (d, J=8.3 Hz, NH), 5.73 (dd, J=8.1 Hz, H–1B), 5.46 (t, J=10.0 Hz, H–2B), 5.40 (dd, J=10.0 Hz, H–2A), 5.24 (t, J=9.6 Hz, 2H, H–3A, H–3B), 5.07 (t, J=10.0 Hz, H–4A), 5.06 (t, J=10.0 Hz, H–4B), 5.01 (ddd, 1H, J=2.6, 7.1, and 11.2 Hz, C$\underline{H}_x$H$_y$N=), 4.35 (ddd, 1H, J=2.9, 6.8, and 11.2 Hz, CH$_x\underline{H}_y$N=), 4.34 (d, J=8.6 Hz, H–1A), 4.21 (dd, J=6.0, 11.0 Hz, H–6A), 4.17 (dd, J=5.1, 11.0 Hz, H–6B), 4.08 (dd, J=2.5, 11.0 Hz, H–6'A), 4.05 (dd, J=2.5, 11.0 Hz, H–6'B), 3.75 (m, 2H, H–5A, H–5B), 3.10 (m, 2H, CH$_2$–S), 2.01 (s, 3H, OAc), 2.00 (s, 3H, OAc), 1.99 (s, 3H, OAc), 1.98 (s, 6H, 2 OAc), 1.97 (s, 3H, OAc), 1.96 (s, 3H, OAc), and 1.95 (s, 3H, OAc); ^{13}C–nmr ($CDCl_3$, 50 MHz): δ 181.97 (C=S), 170.31, 170.25, 170.10, 169.99, 169.27, 169.14, 169.03, and 168.90 (8C, OAc), 165.76 (C=N), 89.38 (C–1A), 82.62 (C–1B), 73.58 (C–3A), 73.55 (2C, C–5A, C–3B), 72.55 (C–5B), 71.72 (C–2A), 69.46 (C–2B), 68.17 (C–4A), 68.09 (C–4B), 61.89 (C–6A), 61.84 (C–6B), 54.61

(C–N=), 24.85 (C–S), 20.68 (OAc), 20.56 (OAc), 20.51 (2C, OAc), 20.45 (2C, OAc) and 20.36 (2C, OAc).

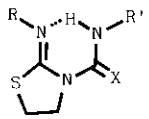
6. P. Sohár, G. Fehér, and L. Toldy, Org. Magn. Res., 1978, 11, 9.

7. All compounds reported in this paper gave spectral (uv, ir, ^{1}H–, and ^{13}C–nmr) and analytical data consistent with the assigned structures.

8. The structure **12** (exocyclic nitrogen attack), assigned to **6**, **10**, and **11**, and structure **13** (endocyclic nitrogen attack) are undistinguishable from spectral data. However, the structure **12** is preferred to **13**, on the basis of reported results by C.R. Rasmussen, F.J. Villani, Jr., M.S. Mutter, and E.A. Griffin, J. Org. Chem., 1986, 51, 1910.



13



14

9. I. Kubo, M. Kim, W.F. Wood, and H. Naoki, Tetrahedron Lett., 1986, 27, 4277.

10. B. Robillard, M.F. Lhomme, and J. Lhomme, Tetrahedron Lett., 1985, 26, 2659.

Received, 6th May, 1988