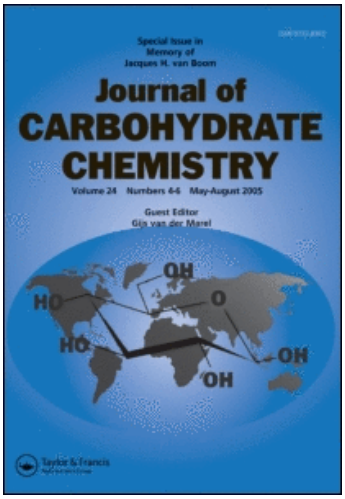


Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

A Novel Approach for the Synthesis of *C*-Nucleoside Analogs by Constructing Benzoxazine Rings Linked to a Carbohydrate Moiety

El Sayed H. El Ashry[a]; Nagwa Rashed[a]; Ahmed Mousaad[a]
[a] Department of Chemistry Faculty of Science, Alexandria University, Alexandria, Egypt

To cite this Article Ashry, El Sayed H. El , Rashed, Nagwa and Mousaad, Ahmed(1987) 'A Novel Approach for the Synthesis of *C*-Nucleoside Analogs by Constructing Benzoxazine Rings Linked to a Carbohydrate Moiety', Journal of Carbohydrate Chemistry, 6: 4, 599 — 607
To link to this Article: DOI: 10.1080/07328308708058889
URL: http://dx.doi.org/10.1080/07328308708058889

J. CARBOHYDRATE CHEMISTRY, 6(4), 599-607 (1987)

A NOVEL APPROACH FOR THE SYNTHESIS OF C-NUCLEOSIDE ANALOGS BY CONSTRUCTING BENZOXAZINE RINGS LINKED TO A CARBOHYDRATE MOIETY[1]

El Sayed H. El Ashry,* Nagwa Rashed, and Ahmed Mousaad

Department of Chemistry
Faculty of Science
Alexandria University
Alexandria, Egypt

Received September 11, 1986 - Final Form July 17, 1987

ABSTRACT

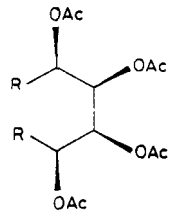
Dehydrative cyclization of the condensation product of 2,3,4,5-tetra-O-acetyl-galactaryl chloride with anthranilic acid gave 1,2,3,4-tetra-O-acetyl-1,4-bis(4H-benzoxazin-4-one-2-yl)-galacto-tetritol. Its reaction with aniline in the presence of phosphorus trichloride afforded 1,4-bis(3-phenylquinazolin-4-one-2-yl)-1,2,3,4-tetra-O-acetyl-galacto-tetritol.

INTRODUCTION

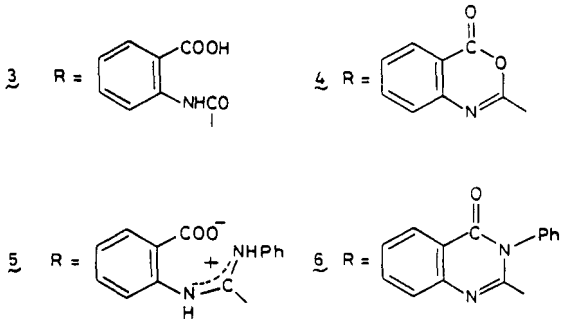
Benzoxazines are a well-known class of organic compounds which can be transformed into other nitrogen heterocyclic compounds,[2 - 6] some of which may have potential physiological activity[7 - 10] or may be useful as components of thermostable polymers.[11,13] As a continuation of our work for developing new syntheses for C-nucleoside analogs[14,15] and heterocycles from carbohydrate precursors,[16,17] we report the details[18] of the synthesis of a new acyclic C-nucleoside analog possessing a benzoxazine ring, which is the first example of a benzoxazine in the carbohydrate series. Its rearrangement to quinazolones was also investigated, as the later heterocyclic ring system has the potential for pharmacological activity.[19 - 25]

RESULTS AND DISCUSSION

2,3,4,5-Tetra-O-acetyl galactaric acid (**1**, Scheme 1) was selected as a model starting material for the synthesis of this type of C nucleoside analog. Condensation of its dichloride **2** with anthranilic acid afforded a colorless crystalline product **3** whose elemental analysis indicated that reaction had occurred between 2 and two equivalents of anthranilic acid. Its infrared (IR) spectrum showed the CO and OH of the carboxylic acid group at 1690 and 3400 cm^{-1}, respectively, the OAc groups at 1760 cm^{-1}, and the newly formed amide linkage at 1680 cm^{-1}. These data agreed with the structure 2,3,4,5-tetra-O-acetylgalactaric 1,6-bis[(o-carboxyphenyl)amide] (**3**).

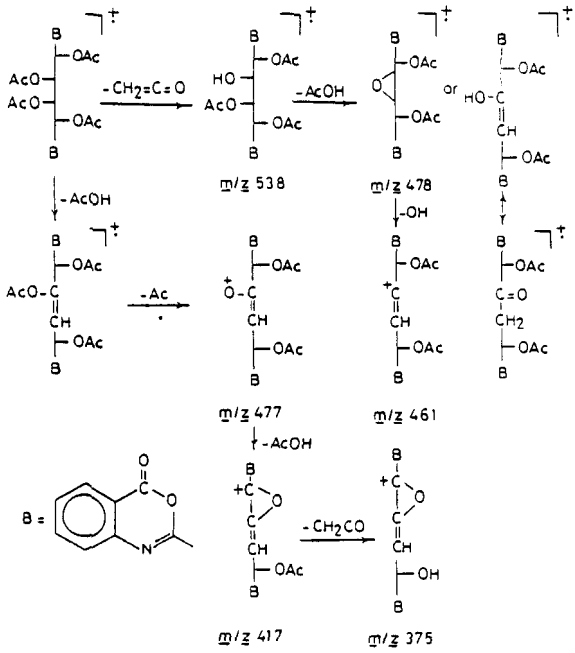


1 R = COOH 2 R = COCl



SCHEME 1

Dehydrative cyclization of 3 gave **4** whose structure was deduced from its spectroscopic data. The IR spectrum of **4** indicated the absence of bands due to the carboxylic acid and amide groups which appeared in its precursor **3**. In their place bands appeared at 1780 and 1655 cm^{-1}, respectively, attributed to the OCO and C=N of the newly formed heterocyclic ring. The ^1H NMR spectrum of **4** showed the aromatic protons of the heterocyclic rings as a multiplet and a doublet respectively at δ7.6 and 8.1, the protons of the tetritolyl residue as two singlets at δ5.58 and 5.77, and the acetoxy groups as two singlets at δ2.05 and 2.28. The ^1H NMR spectrum confirmed the symmetry existing in the molecule. The mass spectrum of **4** did not show the molecular ion peak anticipated at m/z 580; however it did show the highest mass at m/z 538, attributed to the loss of CH_2=C=O. The fragmentation pattern in general could be divided into three distinct series: The first fragmentation originates from the loss of AcOH, AcO, Ac and CH_2=C=O from the backbone

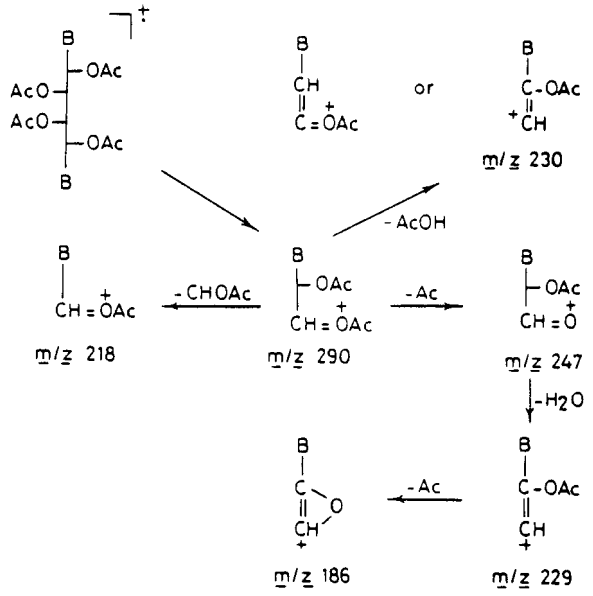


SCHEME 2

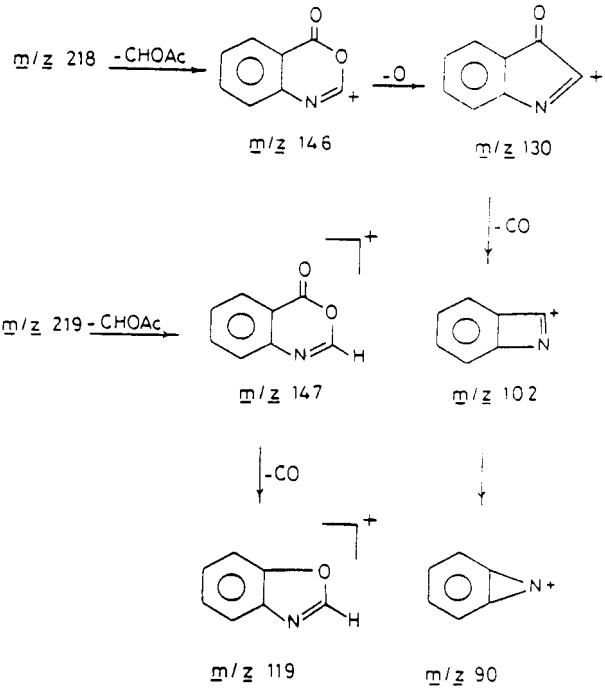
of the molecule (Scheme 2). The second series begins by a cleavage of the molecular ion into two halves to give the ion at m/z 290, which then loses CHOAc to give the ion at m/z 218. Moreover, loss of AcOH and Ac occurs from each of the principal fragments to give additional ions (Scheme 3). The third series of ions deals with fragmentations of the heterocyclic ring (Scheme 4). Structure **4** was therefore assigned to be 1,2,3,4-tetra-O-acetyl-1,4-bis(4H-benzoxazin-4-one-2-yl)-galacto-tetritol.

Reaction of **4** with aniline under any of several conditions (See Experimental Section) afforded the same product **5**. This product was found to be a result of the condensation of **4** with two molecules of aniline without elimination of water. The IR spectrum of **5** showed the COO group at 1695 cm^{-1} and OAc group at 1760 cm^{-1}, in addition to the NH group at 3190 cm^{-1}. These data confirm that aniline reacted with the benzoxazine preferentially at the carboimino center, rather than at the carbonyl group, to afford 1,2,3,4-tetra-O-acetyl-1,4-bis[N-(2-carboxyphenyl)-N'-phenylamidine]-galacto-tetritol (**5**), agreeing with reported data on simple compounds.[3]

The attempted cyclization of **5** to a quinazolone derivative using various dehydrating agents failed; however, a successful synthesis of the quinazolone could be achieved in one step by the reaction of aniline with the benzoxazine **4** in toluene in the presence of phosphorus trichloride.[26] The reaction afforded a crystalline product **6**, whose elemental analysis indicated that the condensation of **4** occurred with two molecules of aniline with the loss of two molecules of water. The structure was deduced to be 1,2,3,4-tetra-O-acetyl-1,4-bis(3-phenyl-quinazolin-4-one-2-yl)-galacto-tetritol (**6**) from the spectroscopic data. The IR spectrum showed a band at 1680 cm^{-1} for the OCN group (instead of a band at 1780 cm^{-1} for OCO group in the IR of its precursor) in addition to a band at 1755 cm^{-1} for the OAc groups. Its ^1H NMR spectrum showed the aromatic protons as a multiplet and a doublet, respectively, at δ 7.56 and 8.25, the protons of the tetritolyl residue as two singlets



SCHEME 3



SCHEME 4

at δ5.26 and 5.32, and the acetoxy groups as two singlets at δ1.62 and 2.15.

In conclusion, this model study demonstrated the successful synthesis of a benzoxazine and its transformation to a quinazolone in the carbohydrate series. The method is of potential value as the 2,5-anhydroaldonic acids are readily available starting materials for C-nucleoside synthesis.

EXPERIMENTAL

General procedures. Melting points were determined with a Kofler-block apparatus and are uncorrected. Infrared (IR) spectra were recorded with a Unicam SP 200 spectrometer, and ^{1}H NMR spectra with a Jeol-100 spectrometer (on solutions in chloroform-d), with tetramethylsilane as the internal standard. Chemical shifts are given on the δ scale. The mass spectrum was recorded with an A.E.I. MS 902 instrument. Microanalyses were performed in the Faculty of Science, Cairo University.

2,3,4,5-Tetra-O-acetylgalactaric 1,6-bis[(o-carboxyphenyl)amide] (3). A cold solution of 2[27] (4.0 g, 9.6 mmol) in benzene (20 mL) was added dropwise to a cold and stirred solution of anthranilic acid (2.63 g, 19.2 mmol) in pyridine (10 mL) at 0 °C. The mixture was stirred for further 0.5 h, and the solvent was removed under reduced pressure. The product (4.45 g, 75% yield) was crystallized from ethanol as colorless needles: mp 283 °C (dec.); ν_{max}^{KBr} 3400 (OH), 3200 (NH), 1760 (OAc), 1690 (COO), 1680 (OCN), 1605 and 1590 cm^{-1} (C=C). Anal. Calcd for $C_{28}H_{28}N_2O_{14}$: C, 54.54; H, 4.58; N, 4.54. Found: C, 54.42; H, 4.44; N, 4.45.

1,2,3,4-Tetra-O-acetyl-1,4-bis(4H-benzoxazin-4-one-2-yl)-galacto-tetritol (4). A mixture of **3** (3.0 g, 4.9 mmol) and acetic anhydride (12 mL) was heated under reflux for 2 h, and the solvent was removed under reduced pressure. The product (2.26 g, 80% yield) was crystallized from

ethanol in colorless needles: mp 292 °C; ν_{max}^{KBr} 1780 (OCO), 1755 (OAc), 1655 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ2.05, 2.28 (2 s, 12 H, 4 $COCH_3$), 5.58 (s, 2 H, H-2,-3), 5.77 (s, 2 H, H-1,-4), and 7.6 and 8.1 (m and d 8 H, aromatic protons). Anal. Calcd for $C_{28}H_{24}N_2O_{12}$: C, 57.93; H, 4.17; N, 4.83. Found: C, 57.54; H, 3.91; N, 4.57.

1,2,3,4-Tetra-O-acetyl-1,4-bis[N-(2-carboxyphenyl)-N'-phenylamidine]-galacto-tetritol (5). a) A mixture of **4** (1.0 g, 1.7 mmol) and aniline (0.4 mL, 4.4 mmol) was fused on a water bath for 2 h. The mixture was then triturated with alcohol, and the product **5** was filtered off and dried (1.16 g, 88% yield): mp >350 °C; ν_{max}^{KBr} 3190 (NH), 1760 (OAc), 1695 (COO), 1610 cm^{-1} (C=C), in addition to a broad band for the amidine salt at 2500 - 2688 and 1579 cm^{-1}. Anal. Calcd for $C_{40}H_{38}N_4O_{12}$: C, 62.65; H, 4.99; N, 7.30. Found: C, 62.60; H, 4.90; N, 7.00.

b) A solution of **4** (1.0 g, 1.7 mmol) and aniline (0.4, 4.4 mmol) in 1,4-dioxane (20 mL) was boiled under reflux for 2 h. The product that separated out on cooling was filtered off and dried (1.22 g, 92% yield): mp >350 °C. The product was identical to that obtained from a, above.

c) A solution of **4** (0.5 g, 0.85 mmol) in aniline (1 mL, 11 mmol) was boiled under reflux for 2 h. The product that separated out on dilution with alcohol was filtered off and dried (0.56 g, 85% yield): mp >350 °C. It was identical to that obtained from a, above.

d) A solution of 4 (1.0 g, 1.7 mmol) in aniline (30 mL) was stirred for 3 h at room temperature. The reaction mixture was left overnight, and the product that separated out was filtered off and dried (1.06 g, 80% yield): mp >350 °C. It was identical to that obtained from a, above.

e) A solution of 4 (1.0 g, 1.7 mmol) and aniline (0.4 mL, 4.4 mmol) in dry benzene (100 mL) was stirred for 3 h, then left to stand overnight. The product that separated out was filtered off and dried (1.15 g, 87% yield): mp >350 °C. It was identical to that obtained from a, above.

1,2,3,4-Tetra-O-acetyl-1,4-bis(3-phenylquinazolin-4-one-2-yl)-galacto-tetritol (6). To a solution of 4 (0.7 g, 1.2 mmol) and aniline (0.28 mL) in toluene (15 mL), a solution of phosphorus trichloride (0.055 g, 0.4 mmol) in toluene (5 mL) was added dropwise. The reaction mixture was heated under reflux at 130 °C for 4 h, at the end of which time it was cooled and the toluene was decanted. The residue was washed with 10% sodium carbonate solution and water, and crystallized from alcohol (0.68 g, 77% yield) as colorless needles: mp 270 - 272 °C (dec.); ν_{max}^{KBr} 1755 (OAc) and 1680 cm^{-1} (OCN); ^{1}H NMR (CD_3Cl): δ 1.62 and 2.15 (2 s, 12 H, 4 OAc), 5.26 (s, 2 H, H-2,-3), 5.32 (s, 2 H, H-1,-4), and 7.56 and 8.25 (m and d, 18 H, aromatic protons). Anal. Calcd for $C_{40}H_{34}N_4O_{10}$: C, 65.75; H, 4.69; N, 7.67. Found: C, 65.82; H, 4.93; N, 8.13.

REFERENCES

1. Heterocycles from carbohydrate precursors, part 46.
2. L. A. Errede, J. Org. Chem., **41**, 1763 (1976).
3. L. A. Errede, J. J. McBrady, and H. T. Oien, J. Org. Chem., **41**, 1765 (1976).
4. L. A. Errede, H. T. Oien, and D. R. Yarian, J. Org. Chem., **42**, 12 (1977).
5. L. A. Errede, H. T. Oien, and D. R. Yarian, J. Org. Chem., **42**, 656 (1977).
6. H. Asakawa, M. Matano, and Y. Kawamatsu, Chem. Pharm. Bull, 27, 287 (1979).
7. J. C. Sheehan and G. D. Daves, J. Org. Chem., **29**, 3599 (1964).
8. H. Herlinger, Angew. Chem., **76**, 437 (1964).
9. G. Doleshal and K. Lambert, Tetrahedron Lett., 1195 (1963).
10. A. F. Hegarty and T. C. Bruice, J. Am. Chem. Soc., **92**, 6568 (1970).
11. I. Serlin and A. H. Markhart, J. Polym. Sci., **60**, 19 (1962).
12. B. Sillion and G. de Gaudemaris, French Pat., 1,423,631 (1965).
13. L. A. Errede, U.S. Pat., 3,367,977 (1967); 3,408,326 (1968); 3,440,228 (1969).

14. E. S. H. El Ashry, Am. Chem. Soc. Advan. Chem. Ser., **200**, 179 (1982).

15. S. Hanessian and T. H. Haskell, in W. Pigman and D. Horton (Eds.), "The Carbohydrates Chemistry and Biochemistry", 2nd edit.; Vol. IIA, Academic Press, New York, pp. 20 (1970); S. Hanessian and G. Pernet, Adv. Carbohydr. Chem. Biochem., **33**, 111 (1976).

16. E. S. H. El Ashry and Y. El Kilany, Carbohydr. Res., **80**, C8 (1980).

17. E. S. H. El Ashry, M. M. Abdel Rahman, and N. Rashed, Carbohydr. Res., **82**, 15 (1980).

18. E. S. H. El Ashry, N. Rashed, and A. Mousaad, Carbohydr. Res., **100** C39 (1982).

19. B. R. Baker, R. E. Schaub, F. J. McEvoy, and J. H. Williams, J. Org. Chem., **17**, 132 (1952).

20. M. L. Gujral, P. N. Saxona, and R. S. Tiwari, Indian J. Med. Res., **43**, 637 (1955).

21. J. R. Cummings and E. H. Stokey, Arzneim.-Forsch., **13**, 661 (1963).

22. H. J. Hers, T. H. Cronin, and A. Scriabine, J. Med. Chem., **11**, 130 (1968).

23. G. Leszkovsky and L. Tardos, Hung. Conf. Ther. Pharmacol. Res., 2nd, 1962, 415 (1964); Chem. Abstr., **62**, 16821g (1965).

24. A. H. Amin, D. R. Mehta, and S. S. Samarth, Proc. Inst. Pharmacol. Meet., 1st, **7**, 377 (1963).

25. A. H. Amin, D. R. Mehta, and S. S. Samarth, Fortschr. Arzneim.-Forsch., **14**, 218 (1970).

26. H. W. Grimmel, A. Guenther, and J. F. Morgan, J. Am. Chem. Soc., **68**, 542 (1946).

27. B. A. Lewis, F. Smith, and A. M. Stephen, Methods Carbohydr. Chem., **2**, 38 (1963).