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THE SYNTHESIS OF SPIRO AND BICYCLIC NUCLEOSIDES FROM RIBOSE ADDUCTS OF DIAMINOMALEONITRILE

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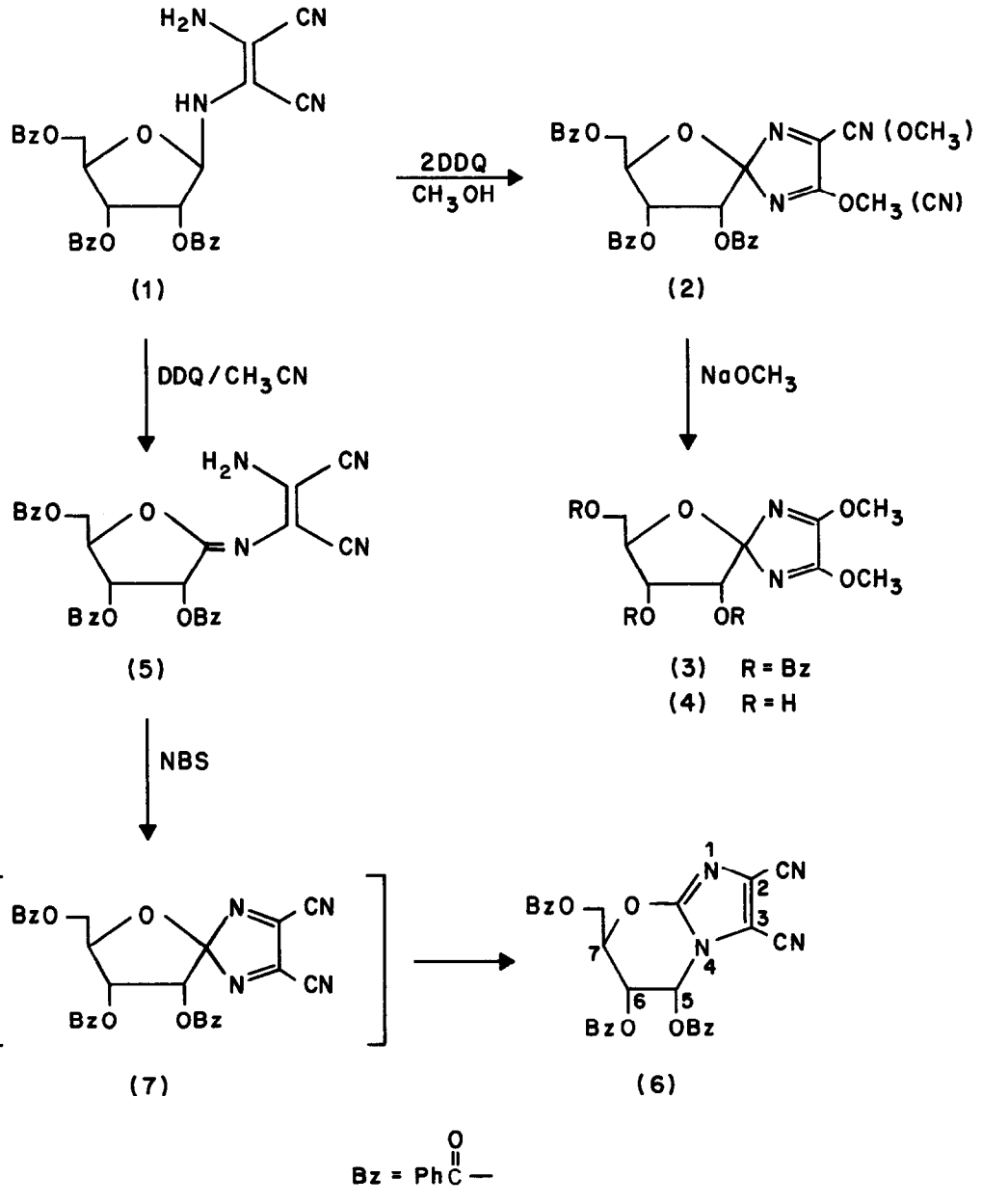
Abstract. The synthesis of a new spiro nucleoside structural type (2) and two new bicyclic nucleoside structural types (6, 10, 11) is described.

Diaminomaleonitrile adducts of sugars[1] are the starting points for the efficient syntheses of N-nucleoside analogs of 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide[2] and C-nucleoside analogs of the antitumor agents bredinin and pyrazomycin.[3] We describe herein the preparation of spiro and bicyclic derivatives, new nucleoside structural types, from diaminomaleonitrile adducts of ribose.

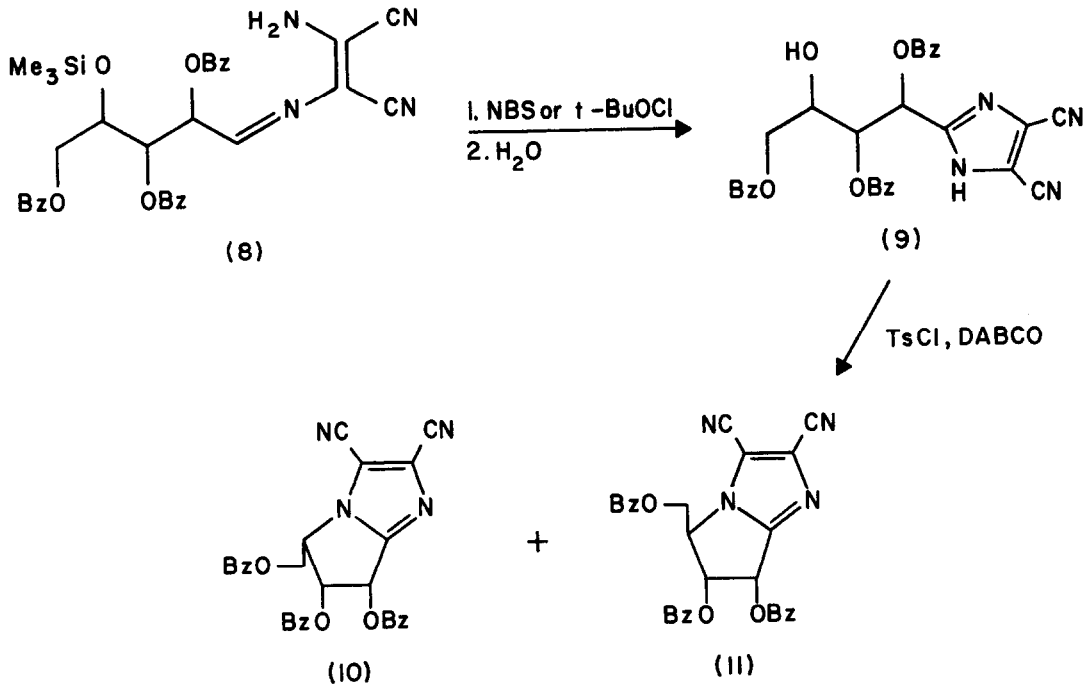
The oxidation of tribenzoylribofuranosylDAMN[2] (1) with two equivalents of dichlorodicyanoquinone (DDQ) in MeOH resulted in a 45% yield of one of the two possible regioisomers of (7R, 8R, 9R)-2(3)-cyano-3(2)-methoxy-8,9-dibenzoyloxy-7-benzoyloxymethylene-1,4-diaza-6-oxaspiro-[4,4]nona-1,3-diene (2): mp 135-137°C; [^{1}H NMR δ 4.0 (s, 3H, OMe); U.V. λ_{max} (MeOH) 229 nm (ε 40,900)]. The other regio isomer was not isolated but its presence was inferred from the presence of two OMe peaks in the ^{1}H NMR spectrum of the non-crystalline portion of the product mixture. The presence of the isoimidazole ring was established by the facile displacement of the nitrile group with one equivalent of sodium methoxide in methanol to give (3) and the observation of only weak absorption at 200 nm for the deblocked derivative (4) formed by treatment of (3) with methanolic sodium methoxide.[4]

Only one equivalent of DDQ is consumed when the oxidation of (1) is performed in CH_3CN to give (5) in 50% yield: mp 84-85°C; [U.V. λ_{max} (CH_3OH) 230 nm (ε 39,940), 324 nm (ε 15,700)], ^{1}H NMR ($CDCl_3$) δ 6.37 (d, 1, H-2', $J_{2'3'}$ = 6 Hz). Reaction of (5) with one equivalent of NBS at room temperature gave a 55% yield of (6) [^{1}H NMR δ 7.4 (d, 1, H-5, $J_{5,6}$ = 3.8 Hz) U.V. λ_{max} (CH_3OH) 230 nm (ε 43,840), 266 nm (ε 26,030)]. The U.V. absorption at 266 nm is identical with that reported for 2-ethoxy-4,5-dicyanoimidazole.[5] The shift of the ^{1}H NMR signal for H-2' from 6.37 δ (5) to 7.4 δ in (6) (H-5) is consistent with the migration of C-2' from carbon to nitrogen. It is likely that (6) is formed via the initial N-halogenation of (5)[6,7], cyclization to the isoimidazole (7), and a suprafacial 1,5-shift at room temperature to give (6).[4,8] The retention of configuration at C-5 in (6) is confirmed by $J_{5,6}$ = 3.8 Hz for a H-C_5-C_6-H angle of 50° while the low temperature at which the reaction proceeds reflects the stabilization of the


H2N
CN
HN
CN
BzO
O
BzO
OBz
(1)
2DDQ
CH3OH
CN (OCH3)
OCH3 (CN)
(2)
DDQ / CH3CN
NaOCH3
(5)
RO
OCH3
OR
(3) R = Bz
(4) R = H
NBS
(7)
(6)
Bz = PhC—

developing positive charge by the unpaired electrons on the ester oxygen in the dipolar transition state leading from (7) to (6).[4]

Both t-butyl hypochlorite and NBS effected the efficient conversion of the acyclic ribose derivative (8)[2] to the 2-substituted imidazole (9): mp 92-95°C; [U.V. λ_{max} (MeOH) 230 nm (ε 41,720); 260 nm (ε 11,140)]. The pyrrolo[1,2-a]imidazole nucleoside derivatives (10): (mp 82-85°C, 47%) and (11): (mp 88-91°C, 24%), were formed in one step when (9) was heated with toluenesulfonyl chloride and 1,4-diazabicyclo[2,2,2]octane in refluxing toluene. The ^{1}H NMR spectra of (10) and (11) are very similar with the exception that $J_{5,6}$ in (10) is 7.2 Hz and 1.8 Hz in (11). The ^{3}E envelope conformation[9] is assigned to (11) in which C_6 is above the plane of the pyrroloimidazole ring, a conformation which minimizes the non-bonded repulsions between the 5-hydroxymethylene and 3-cyano groupings. The H-C_6-C_5-H dihedral angle will be in the 90-120° range in this conformation consistent with the observed $J_{5,6}$ of 1.8 Hz.[10] A similar coupling constant ($J_{3',4'}$ ca. 2 Hz) was reported for a 8,2'-cyclonucleoside hydrazone[11] which would be expected to have its sugar ring in an envelope conformation similar to that proposed for (11). The corresponding H-C_6-C_7-H dihedral angle will be in the 0-30° range consistent with the observed $J_{6,7}$ of 6.0 Hz.[10]



Compound (10) is assigned the E_3 envelope conformation since this structure minimizes the non-bonded interactions between the groups in the 3-and 5-positions. The dihedral angles between H-C_5-C_6-H and H-C_6-C_7-H will be the same in (10) and in the 0-30° range consistent with the observed $J_{5,6}$ and $J_{6,7}$ of 7.2 and 6.0 Hz respectively.[10] The difference in the two coupling constants reflects the perturbation resulting from having a nitrogen bound to C_5.[10].

The major reaction product (10) is formed by the direct displacement of the tosylate group by the imidazole ring while (11) is probably formed by the initial displacement of the tosylate by a neighboring benzoate followed by a subsequent displacement of the benzoxonium ion by the imidazole nitrogen.

The isoimidazole (2), bicyclic imidazooxazine (6) and the pyrroloimidazoles (10) and (11) represent new classes of nucleosides with the potential for useful pharmaceutical properties. The extension of these transformations to the ribopyranose adduct of diaminomaleonitrile[3] and the elaboration of these novel nucleosides into analogs of 5-amino-1-(β-D)ribofuranosyl)-imidazole-4-carboxamide is in progress.

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