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AN UNUSUAL REDUCTIVE RING-OPENING OF THE 1,2,3,5,6,7-HEXAAZAACENAPHTHYLENE RING SYSTEM

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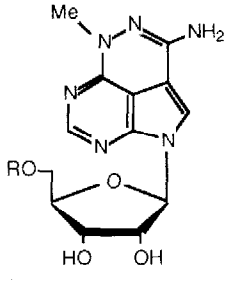
Abstract: Studies on an unexpected reaction involving a reductive cleavage of the pyridazine moiety of a tricyclic heterocycle are described. Structure assignments for the products obtained from the reductive cleavage were made using physicochemical methods.

The pro drug[1] (TCN-P, 1b) of 6-amino-4-N-methyl-8-(β-D-ribofuranosyl)-1,3,4,5,8-pentaaza-acenaphthylene[2] (TCN, 1a) is currently undergoing clinical trials under the auspices of the National Cancer Institute.[3] It is generally thought that both TCN and TCN-P are acting as adenosine analogs[4] but the exact biochemical mechanism has not yet been elucidated. It has been reported that a ring scission of the

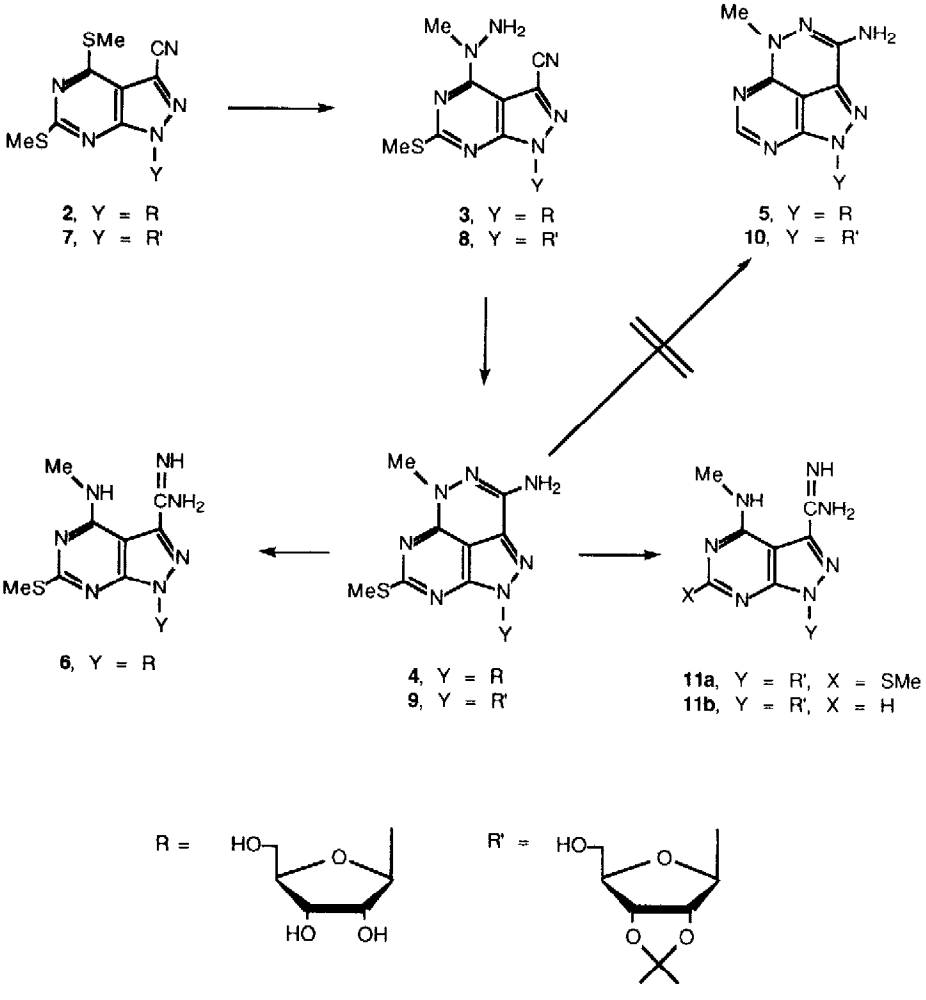


1a, R = H

1b, R = -P(=O)(OH)-OH

pyrrole ring of TCN occurs in vivo, and this prompted us to initiate a synthesis of the aza analog of TCN (5) with a nitrogen being substituted for carbon at the site of the in vivo ring scission in TCN (1a).

We elected to use 4,6-bis(methylthio)-1-(β-D-ribofuranosyl)pyrazolo[3,4-d]pyrimidine[5] (2) as our starting material. Treatment of 2 with ten equivalents of methylhydrazine afforded a good yield of a compound which was tentatively assigned the structure 3-cyano-4-N-(1-methylhydrazino)-6-methylthio-1-(β-D-ribofuranosyl)pyrazolo[3,4-d]pyrimidine (3) based on the following data: 1) a singlet (δ 2-3) in the ^{1}H NMR spectrum for one methylthio group; 2) a strong peak at 2240 cm^{-1} in the IR spectrum (CN). The displacement by methylhydrazine could have conceivably occurred in two possible ways, i.e., displacement


SMe
CN
MeS
Y
Me
NH2
NH
CNH2
X
2, Y = R
7, Y = R'
3, Y = R
8, Y = R'
5, Y = R
10, Y = R'
6, Y = R
4, Y = R
9, Y = R'
11a, Y = R', X = SMe
11b, Y = R', X = H
R =
R' =
HO
OH
O

of the methylthio group by the substituted nitrogen to give 3 or displacement by the unsubstituted nitrogen to afford the isomeric compound. The ^{1}H NMR spectrum supported the initial structure assignment, vide infra, for 3, since the signal assigned to the N-methyl function at δ 3.35 was observed as a singlet instead of a doublet. Thus, a selective displacement of the 4-methylthio function of 2 was effected without the involvement of either the 3-cyano or the 6-methylthio group.

The ring closure of 3 to 4 was accomplished with sodium methoxide. The sodium methoxide could either effect a Neff-type activation [6] of the cyano group or simply act as a base. The IR spectrum of 4 revealed the absence of a band within the 2200-2300 cm^{-1} region and the UV spectrum of 4, at pH 7, showed a 15 nm bathochromic shift relative to 3. The ^{1}H NMR spectrum also showed a downfield shift of 0.21 ppm for the N-methyl signal of 4 relative to the N-methyl signal observed for 3.

With the nucleoside 4 in hand, the desired aza analog, 8-amino-6-N-methyl-2-(β-D-ribofuranosyl)-1,2,3,5,6,7-hexaazaacenaphthylene (5), should have been easily obtained *via* a conventional dethiation reaction of 4 with Raney nickel.[7,8] However, treatment of 4 with Raney nickel under mild conditions resulted in a low yield of a compound which was not the desired tricyclic product 5. This unexpected product was assigned the structure 3-carboxamidine-4-N-methylamino-6-methylthio-1-(β-D-ribofuranosyl)pyrazolo[3,4-d]pyrimidine (6) based on the following physicochemical data: UV and ^{1}H NMR spectra and elemental analysis[9]. The UV spectrum of 6, at pH 7, showed a significant hypsochromic shift of about 15 nm relative to the UV data of 4. Furthermore, the UV spectrum of 6 was similar to the UV spectra of some structurally related substituted pyrazolo[3,4-d]pyrimidines [8a,b]. The ^{1}H NMR spectrum of 6 showed a doublet at δ 2.98 which was assigned to the N-methyl protons and upon exchange with deuterium oxide this doublet collapsed to a singlet. A singlet (3 protons) was observed at δ 2.51 which supported the presence of the 6-methylthio group.

It was presumed, a priori, that this anomalous result could possibly be due to the extreme insolubility of compound 4 in the usual organic solvents. Therefore, the 2',3'-*O*-isopropylidine derivative (9) of 4 was synthesized from 3-cyano-4,6-bis(methylthio)-1-(2,3-*O*-isopropylidine-β-D-ribofuranosyl)pyrazolo[3,4-d]pyrimidine[5] (7) *via* the same methodology as used for the synthesis of 4. Compound 9 was found to be very soluble in ethanol. However, when compound 9 was treated with Raney nickel under mild conditions, the desired tricyclic product, compound 10 was not obtained. Instead, two major products were isolated from the reaction mixture and subsequently characterized as 3-carboxamidine-4-N-methylamino-6-methylthio-1-(2,3-*O*-isopropylidine-β-D-ribofuranosyl)pyrazolo-[3,4-d]pyrimidine (11a, 31% yield) and 3-carboxamidine-4-N-methylamino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)pyrazolo[3,4-d]pyrimidine (11b, 29% yield). Both products were apparently the result of a reductive cleavage of the pyridazine ring of 9. The physicochemical data for 11a and 11b were similar to those of 6. The UV spectra of 11a and 11b showed a hypsochromic shift relative to the UV data for 9 with 11b being slightly more pronounced. The ^{1}H NMR spectra of 11a and 11b exhibited the same pattern of signals as 6 except for the isopropylidine group and a singlet at δ 8.31 in the spectrum of 11b which was attributed to the C6 aromatic proton. This was the direct result of a removal of the methylthio group (δ 2.51). After an exchange with deuterium oxide, the doublet appearing at δ 3.09, which was assigned to the NMe protons, collapsed to a singlet.

This reductive cleavage of the pyridazine ring of 4 and 9 was unexpected under the mild conditions used since numerous examples have been cited in the literature where fused pyridazines,[10a] e.g., imidazo[4,5-d]pyridazines[10b,c] or imidazo[4,5-c]pyridazines,[10d,e] have remained intact under similar conditions employing Raney nickel. After trying various other reducing reagents, e.g., tri-*n*-butyltin hydride,[11a] Raney cobalt,[11b] zinc dust,[11c] and deactivated Raney nickel,[11d] we have concluded that reductive conditions must be avoided in the dethiation of 4 or 9 due to the unexpected lability of this particular pyridazine ring.

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