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A NOVEL APPROACH TOWARDS THE SYNTHESIS OF THE 3,4,5-TRIHYDRO-1,3-DIAZEPIN-5-OL RING STRUCTURE

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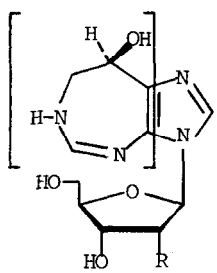
Abstract: A catalytic reduction of the nitrile portion of the trimethylsilyl cyanohydrin 7 to a primary amine has produced an in situ annulation to generate the 3,4,5-trihydro-1,3-diazepin-5-ol ring. This ring substructure has demonstrated important biological significance.[3]

Our efforts directed towards the synthesis of potential inhibitors of the enzyme adenosine deaminase have yielded a new and novel method for the formation of a 3,4,5-trihydro-1,3-diazepin-5-ol ring (Figure 1, in brackets) fused to another heterocyclic ring. A bicyclic heterocyclic ring system containing the 3,4,5-trihydro-1,3-diazepin-5-ol structure fused to an imidazole ring is shared by the nucleoside antibiotics 2'-deoxycoformycin (1, pentostatin[1]) and coformycin[2] (2), both potent inhibitors of adenosine deaminase.[3]

Figure 1.



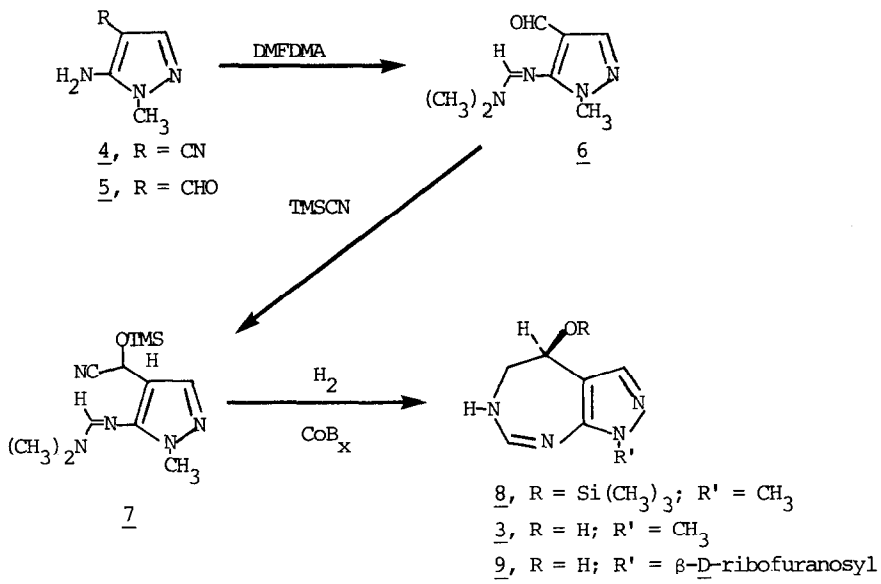
1, R = H; pentostatin

2, R = OH; coformycin

We now wish to report on the synthesis of a bicyclic heterocyclic ring system containing the 3,4,5-trihydro-1,3-diazepin-5-ol ring fused to a pyrazole ring. This synthetic route involves a new, novel and general approach towards the formation of a fused 3,4,5-trihydro-1,3-diazepin-5-ol ring.

We elected to use 5-amino-1-methylpyrazole-4-carboxaldehyde[4] (5) as the starting material for our synthesis of this new ring system. The aldehyde 5 was obtained in

high yield from the catalytic reduction[6] (Raney Nickel; 1 atm H_2) of 5-amino-4-cyano-1-methylpyrazole[5] (4) in 70% aqueous acetic acid. Evaporation of the acetic acid in vacuo, followed by trituration of the resultant residue with cold water gave the aldehyde 5 as a light yellow solid. Compound 5 was reacted with dimethylformamide dimethylacetal (DMFDMA;



4, R = CN
5, R = CHO

6

7

8, R = $Si(CH_3)_3$; R' = CH_3
3, R = H; R' = CH_3
9, R = H; R' = β-D-ribofuranosyl

CH_2Cl_2; r.t.; 3 hr) to afford a high yield of 5-[[(dimethylamino)methylene]-amino]-1-methylpyrazole-4-carboxaldehyde (6).[7,8] Whereas the aldehyde 5 was found to dimerize readily in solution, the crystalline compound 6 was very stable and allowed us to use normal recrystallization techniques (from warm absolute ethanol) for purification. The ^1H NMR (DMSO-d_6) spectrum of 6 revealed signals which could be assigned to the N,N-dimethylamino group (δ 3.10 and δ 3.00) and an absence of a resonance which could be assigned to the amino group of compound 5.[8]

Compound 6 added trimethylsilyl cyanide[13] (TMSCN, neat; N_2; r.t.; 18 hr) under the catalysis of dry, powdered zinc chloride. A removal of the excess TMSCN by evaporation was followed by a trituration of the resultant crystalline cake with anhydrous n-hexane (at room temperature) to afford an excellent yield (90%, crude) of 5-[[(dimethylamino)methylene]amino)-4-(cyano[trimethylsiloxy]methyl)-1-methylpyrazole (7).[9] Further purification of this crude compound was accomplished by using anhydrous low pressure chromatographic techniques[9] to yield compound 7 (70%) as a white amorphous powder, mp 128-130°.

A reduction of the nitrile functionality of 7 was effected using anhydrous p-dioxane and a

cobalt boride[10] catalyst under 15 atm of hydrogen. At 100°, this reduction was accompanied by an *in situ* annulation[11] due to a reaction between the generated aminomethylene group and the [(dimethylamino)methylene]amino group. The product which was isolated from this transformation was a mixture (4:1, approx.) of the trimethylsilyl ether 8 and the free alcohol 3 (*vide infra*: TLC analysis and inspection of the ^{1}H NMR spectrum of the mixture). Treatment of the mixture with aqueous acetic acid (1 N) in methanol effected a facile hydrolysis of the trimethylsilyl group of 8 to afford a 65% yield of 4,5,6-trihydro-1-methylpyrazolo[3,4-d][1,3]diazepin-4-ol (3) in 65% yield from 7. A 360 MHz (WM Bruker instrument) ^{1}H NMR spectrum of 3 revealed a signal at 7.62 as a broad multiplet (exchanges with D_2O, N(6)-H); the H(5) and H(5a) protons were assigned to a doublet of octets (centered at δ 3.22 and δ 3.02) consistent with their diastereotopic magnetic environments and the H(4) signal was observed as a broad sextet (δ 4.58). The vinylogous H(7) proton appears as a doublet (δ 6.86) which sharpens to a singlet on deuterium exchange of the adjacent N(6)-H. Signals for the aromatic H(3) proton (δ 7.06) and the ring N(1)-CH_3 protons (δ 3.54) appear as sharp singlets. The elemental analysis (C,H,N) and the mass spectrum (M+ 166 m/e) of this material[12] were also supportive of this structural assignment.

To test the applicability of our methodology[14] to the nucleoside area, we have used as our starting material 5-amino-4-cyano-1-(2,3-O-isopropylidene-ß-D-ribofuranosyl)pyrazole[15]. This has afforded the product 9, *via* the aldehyde and TMS cyanohydrin intermediates, as a mixture of the C(4) R,S diastereomers in good yield. The ^{1}H NMR spectrum (360 MHz DMSO-d_6) of 4,5,6-trihydro-1(ß-D-ribofuranosyl)pyrazolo]-d][1,3]diazepin-4(R,S)-ol[16] exhibits single resonances for each type of proton in the mixture, attesting to the great similarity between these diastereomers. In addition, the chemical shifts of equivalent protons in compounds 3 and 9 are very similar, e.g.: N(6)-H(m, δ 7.82); H(3)(s, δ 7.28); H(7)(d, δ 6.97); H(4)(m, 4.66); H(5,5a)(2m, δ 3.30 and 3.10).

We are currently investigating the applicability of this approach as a general route for the synthesis of other bicyclic heterocycles containing the 3,4,5-trihydro-1,3-diazepin-5-ol substructure.

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7. All compounds reported herein gave satisfactory elemental analyses (C,H,N).

8. ^{1}H NMR ($CDCl_3$): 9.42 (s, 1, CHO); 8.53 (s, 1, vinylic); 7.70 (s, 1, H(3)); 3.53 (s, 3, N(1)-CH_3); 3.00 and 2.92 (s,s; 3,3;N,N-dimethyl).

9. ^{1}H NMR ($CDCl_3$): 8.00 (s, 1, vinylic); 7.43 (s, 1, H(3)); 5.55 (s, 1, methine); 3.70 (s, 3, CH_3); 3.10 (s, 6, N,N-dimethyl); 0.20 (s, 9, $Si(CH_3)_3$. Chromatography was effected on a Lobar low pressure (size B) column which had been eluted with two void volumes (250 mL) of a 5% solution of 2,2-dimethoxypropane in ethyl acetate. Elution of the column with ethyl acetate/methylene chloride (1:1, v/v) gave 7 as an amorphous solid.

10. The cobalt boride catalyst was prepared in an analogous manner with the nickel boride catalyst, by a reduction of $CoCl_2 \cdot 6\ H_2O$ with $NaBH_4$ in water. The black flocculent precipitates which are formed from the reductions are washed with water and stored under ethanol. H.C. BROWN and C.A. BROWN, Tetrahedron, Suppl. No. 8, Part 1, 149 (1966); H.C. BROWN and C.A. BROWN, CA 68, 68529p (1968).

11. The synthesis of a benzimidazole from the reaction of DMFDMA and an ortho-phenylenediamine is an example of an equivalent annulation. See: B. STANOVNIK and M. TISLER, Synthesis, 120 (1974).

12. UV λ_{max}(nm), ($\log_{10}\varepsilon$): methanol 275(4.01); pH 1 244 (3.84); pH 11 274(4.06).

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14. In the case of nucleosides, the reaction conditions and yields of each synthetic step are very similar to those reported for the methylated bases. However, a reduction[6] of the cyano group of the nucleoside counterpart to 4 was effected using pyridine/glacial acetic acid/water (2:1:1, v/v) as solvent.

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16. The R and S mixture exhibits m.p. 185-187°. UV λ max (n,m), ($\log_{10}$); methanol, 278(3.95), 24(3.60); pH 1, 263(3.82), 235(3.77); pH 11, 277(3.97), 238(3.66).

17. The preparation, HPLC resolution and characterization of this nucleoside mixture will be published as part of a full article.

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