PYRAZOLE N- AND C-β-D-RIBOFURANOSYL NUCLEOSIDES. SYNTHESIS OF SOME β-D-RIBOFURANOSYL-4,7-METHANOINDAZOLES AND PYRAZOLO[1,5-*a*]AZEPINES

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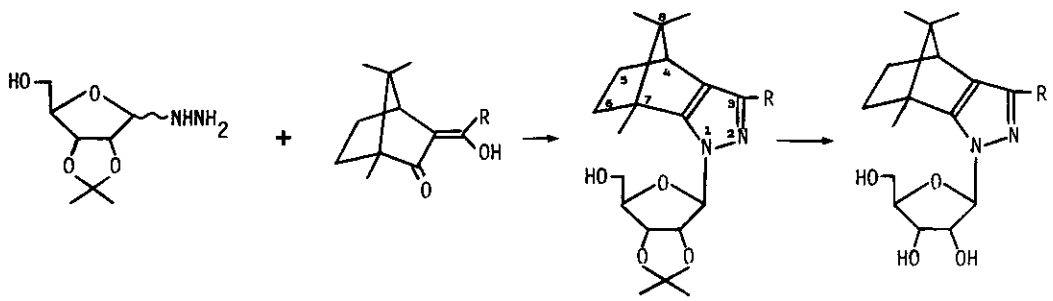
Abstract——— Condensation of *O*-isopropylidene-D-ribosylhydrazine (1) with (1*R*,4*S*)-3-hydroxymethylenebornan-2-ones (2a-b) led to selective N-1 ribosylation of pyrazole ring to provide (4*S*,7*R*)-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazoles (3a-b), and deprotected 4,7-methano-1*H*-indazole (4) after treatment with methanolic HCl. Structure determination including anomeric configuration assignment was discussed based on ^{1}H-NMR spectroscopy. 1,3-Dipolar cycloaddition of diazoketone (5) with β-D-ribofuranosyl-propiolate (8) followed by [1,5]sigmatropic rearrangement was used as a key reaction step in a novel synthesis of pyrazole C-ribofuranoside, (4*S*,7*R*)-3-(2,3-*O*- isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-8-oxo-4,7-methano-8*H*-pyrazolo[1,5-*a*]azepine (11). The protective groups of 11 were easily removed by methanolic HCl to give 3-(β-D-ribofuranosyl)-8*H*-pyrazolo[1,5-*a*]azepine (12).

We have recently prepared a series of optically active (4*S*,7*R*)-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazoles and elucidated their appreciable pharmacological activities such as stimulatory action on nerve-muscle preparation of bullfrog,[1] anticholinergic action,[2] and central nervous system stimulant activity in mice.[3]

Since it has been well known that β-D-ribofuranosyl moiety was a structural unit common to numerous pharmacologically active nucleosides, we considered that the introduction of β-D-ribofuranosyl group into the pyrazole ring of (4*S*,7*R*)-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazole might bring about interesting biological activity change. We now describe the convenient synthesis of a new class of

pyrazole N- and C-β-D-ribofuranosides.

The pyrazole N-β-D-ribofuranosides were synthesized as follows. Condensation of (1*R*,4*S*)-3-hydroxymethylenebornan-2-one (2a) with 2,3-*O*-isopropylidene-D-ribosylhydrazine (1)[4] in refluxing methanol and subsequent loose layer chromatography[5] afforded (4*S*,7*R*)-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazole (3a)[6] as a single product in 72 % yield. Similarly, (1*R*,4*S*)-2-oxobornaneglyoxylic acid (2b) was treated with hydrazine (1) and worked up as described in the preparation of 3a to give (4*S*,7*R*)-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazole-3-carboxylic acid (3b)[7] in 85 % yield.



1 **2a** : R=H, **b** : R=CO_2H **3a** : R=H, **b** : R=CO_2H **4** : R=H

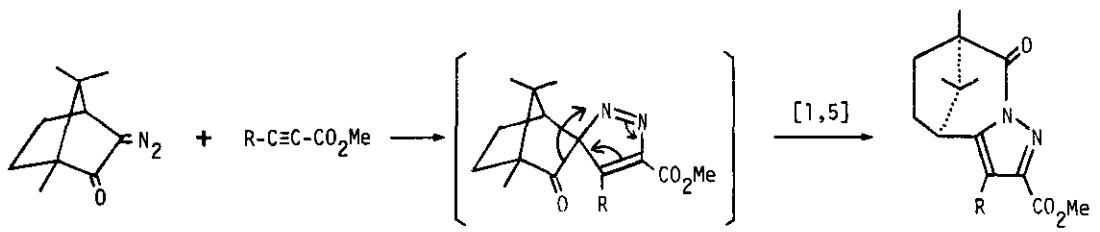
Assignment of D-ribofuranosyl groups of both 3a and 3b to N-1 position of the pyrazole ring was confirmed by ^{1}H-NMR spectral data. Namely, the anomeric protons of 3a and 3b appeared at δ 5.90 and 5.91 respectively. This chemical shift of 3b is appropriate for an anomeric proton not deshielded by the adjacent C-3 carboxylic group; the anomeric proton of 3b would show a fairly downfield shift compared with 3a if the D-ribofuranosyl moiety was bonded to N-2 position of the pyrazole ring. This assignment also agrees with our previous work[1,2] which clarified the higher electrophilic property of the C-enolized hydroxy group of 2 than the strained five-membered carbonyl group, resulting in the exclusive formation of the N-1 substituted pyrazoles in the condensation reaction with monosubstituted hydrazines.

On the other hand, the assignment of anomeric β-configuration of the carbohydrate moieties of 3a and 3b was based on the following ^{1}H-NMR spectral data; (a) the observed $J_{1',2'}$ values of 3a and 3b were both 0 Hz. (b) the chemical shift

differences ($\Delta\delta$) between the two methyl signals of the isopropylidene groups of 3a and 3b were 0.22 and 0.23 respectively, which were in excellent agreement with the value characteristic of β-configuration. Consequently, these compounds were assigned as the structure 3a and 3b.

Deisopropylidation of 3a with methanolic HCl gave a good yield of the corresponding (4*S*,7*R*)-7,8,8-trimethyl-1-(β-D-ribofuranosyl)-4,5,6,7-tetrahydro-4,7-methano-1*H*-indazole (4)[8] without cleavage of a linkage between the sugar and heterocyclic moieties. The structure of 4 was confirmed by spectral data. Attempted deprotection of 3b with a variety of reagents, however, was unsuccessful.

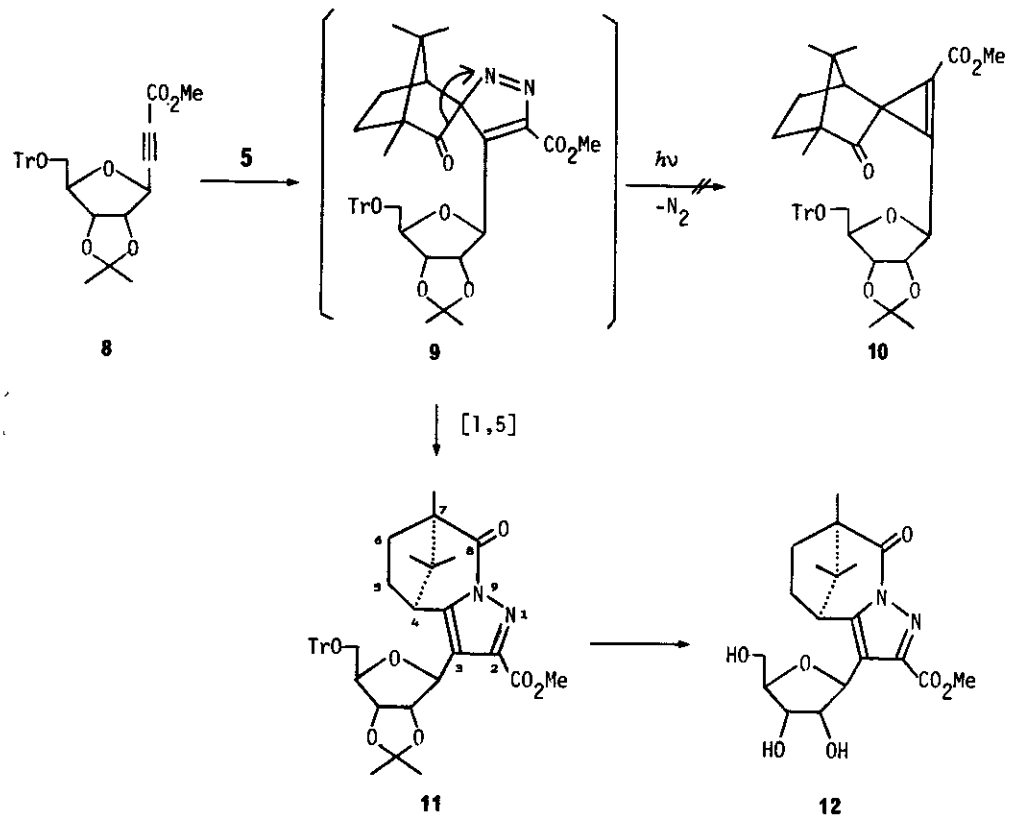
We next investigated a novel synthesis of pyrazole C-β-D-ribofuranosides. Our earlier studies[9] indicated that the reaction of (1*R*,4*S*)-3-diazobornan-2-one (5) with methyl propiolate (6: R=H) gave spiropyrazole, whose a [1,5]sigmatropic rearrangement of acyl group afforded methyl (4*S*,7*R*)-4,7-methano-8*H*-pyrazolo[1,5-*a*]azepine-2-carboxylate (7a).



5 **6** **7a**: R=H **b**: R=CO_2Me

We anticipated that adaptation of this synthetic sequence should make it possible to establish a novel synthetic route to pyrazole C-β-D-ribofuranoside when methyl 3-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)propiolate (8)[10] was used in place of methyl propiolate (6). Accordingly, compound 5 was allowed to react with 8 in refluxing benzene until TLC showed the appearance of a new product. After the reaction had run for over 200 h, repeated loose layer chromatography of the reaction mixture afforded the expected methyl (4*S*,7*R*)-3-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-7,10,10-trimethyl-8-oxo-4,5,6,7-tetrahydro-4,7-methano-8*H*-pyrazolo[1,5-*a*]azepine-2-carboxylate (11)[11] in 60 % yield along with the recovery of the starting materials. However, the spectral data of 11 were not sufficient to determine whether the product was intermediate spiropyrazole 9 or compound 11. Chemical proof of the product was then made as follows; prolonged

irradiation[12] of the product resulted in recovery of the starting material, and spirocyclopentene (10) was not detected. Therefore, the structure was confirmed



as the assigned structure 11 but not as the spiropyrazole 9. The binding position of the β-D-ribofuranosyl group was also assumed as structure 11, since the 1,3-cycloaddition took place obviously in such a manner that the diazo compound 5 added with its nitrogen to the α position of ribofuranosyl propiolate (8) and with its carbon atom to the β position. This assumption was confirmed by the ^{1}H-NMR spectrum, in which the C-4 bridge head proton appeared at δ 3.15. This value was quite the same as the bridge head proton of compound 7a, while the bridge head proton of compound 7b appeared at δ 3.76 due to the deshielding effect of the adjacent methoxy carbonyl group. The β-D-ribofuranosyl structure of 11 was also strongly supported by the ^{1}H-NMR spectrum because the anomeric proton was observed at δ 5.51 as a doublet with $J_{1',2'}$ 3.0 Hz.

Removal of the isopropylidene and trityl groups in compound 11 with methanolic HCl

afforded a good yield of methyl (4*S*,7*R*)-7,10,10-trimethyl-8-oxo-3-(β-D-ribofuranosyl)-4,5,6,7-tetrahydro-4,7-methano-8*H*-pyrazolo[1,5-*a*]azepine-2-carboxylate (12)[13] in a crystalline form. The spectral data were consistent with the assigned structure.

To the best of our knowledge, this synthetic method is a novel example for C-β-D-ribofuranosyl pyrazole preparation.

Attempted 1,3-cycloaddition of compound 8 with (1*S*,4*R*,6*S*)-3-diazo-6,8-dibromobornan-2-one[14] which was an analogous compound to 5 and newly synthesized by two steps starting from (1*S*,4*R*,6*S*)-6,8-dibromobornane-2,3-dione, however, resulted in formation of (1*S*,3*S*,4*R*,7*S*)-3-bromo-7-bromomethyl-4,7-dimethyltricyclo-[2.2.1.$0^{2,6}$]hept-5-one[15] in a quantitative yield, presumably *via* a ketocarbene.

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6) 3a: $C_{19}H_{28}N_2O_4$, light yellow syrup, $[\alpha]_D^{24}$ -74.1° (*c*=0.37, $CHCl_3$) [^{1}H-NMR ($CDCl_3$) δ: 1.38 and 1.60 (6H, 2s, CMe_2), 2.78 (1H, d, *J*=3.6 Hz, H-4), 5.90 (1H, s, H-1'), 7.20 (1H, s, H-3). MS *m/z*: 348 (M^+)].

7) 3b: $C_{20}H_{28}N_2O_6$, light yellow amorphous powder, mp 105-107° (MeOH-Et_2O), $[\alpha]_D^{24}$ -8° (*c*=0.2, $CHCl_3$) [^{1}H-NMR($CDCl_3$) δ: 1.38 and 1.61 (6H, 2s, CMe_2), 3.13 (1H, d, *J*=3.5 Hz, H-4), 5.91 (1H, s, H-1'). MS *m/z*: 392 (M^+)].

8) 4: $C_{16}H_{24}N_2O_4$, light yellow amorphous powder, mp 127° (MeOH-Et_2O), $[\alpha]_D^{26}$ -17.8° (*c*=0.37, $CHCl_3$) [^{1}H-NMR($CDCl_3$) δ: 2.68 (1H, d, *J*=3.0 Hz, H-4), 5.66 (1H, d, *J*=2.0 Hz, H-1'), 7.03 (1H, s, H-3). MS *m/z*(relative intensity): 308(16, M^+), 176 (100, B+1), 133 (78, ribofuranosyl)].

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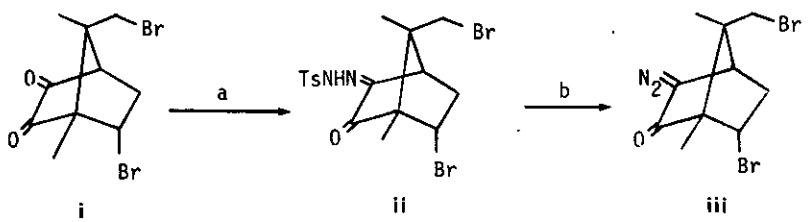
11) 11: $C_{41}H_{44}N_2O_7$, light yellow powder, mp 88° (dec) (Et_2O-petroleum ether), $[\alpha]_D^{25}$ +34.8° (*c*=1.046, $CHCl_3$) [IR($CHCl_3$) cm^{-1}: 1755 (CO_2Me), 1725 (C=O).

^{1}H-NMR($CDCl_3$) δ: 0.77, 1.07 and 1.29 (9H, 3s, 3xMe), 1.37 and 1.59 (6H, 2s, CMe_2), 3.15 (1H, d, J=6.0 Hz, H-4), 3.83 (3H, s, OMe), 5.51 (1H, d, J=3.0 Hz, H-1'), 7.18-7.41 (15H, m, trityl). MS m/z: 676 (M^+), 243 (trityl)].

12) 100W high pressure mercury lamp, Pyrex.

13) 12: $C_{19}H_{26}N_2O_7$, colorless plates, mp 114-116° (dec) (MeOH-Et_2O), $[\alpha]_D^{25}$ +21.0° (c=0.2, $CHCl_3$) [IR($CHCl_3$) cm^{-1}: 3340 (OH), 1755 (CO_2Me), 1715 (C=O). ^{1}H-NMR ($CDCl_3$-CD_3OD) δ: 0.80, 1.16 and 1.31 (9H, 3s, 3xMe), 2.88 (3H, br s, 3xOH), 3.91 (3H, s, OCH_3), 5.42 (1H, d, J=3.0 Hz, H-1'). MS m/z(relative intensity): 394 (1, M^+), 305 (100, B+44), 291 (16, B+30)].

14) (1*S*,4*R*,6*S*)-3-diazo-6,8-dibromobornan-2-one [(iii), $C_{10}H_{12}N_2OBr_2$, colorless needles, mp 218° (dec) (Et_2O). IR(KBr) cm^{-1}: 2080 (C=N_2), 1685 (C=O). ^{1}H-NMR($CDCl_3$) δ: 1.10 and 1.28 (6H, 2s, 2xMe), 3.22 and 3.38 (2H, ABq, H-8_{AB}), 4.27 (1H, dd, $J_{6\text{-}5exo}$=12.0 Hz, $J_{6\text{-}5end}$=3.0 Hz, H-6). MS m/z:338 (M^++4), 336 (M^++2), 334 (M^+), 255 (M^+-Br)] was prepared from (1*S*,4*R*,6*S*)-6,8-dibromobornane-2,3-dione (i)[16] *via* (1*S*,4*R*,6*S*)-6,8-dibromo-3-tosylhydrazonobornan-2-one [(ii), $C_{17}H_{20}N_2O_3Br_2S$, colorless needles, mp 168° (MeOH). IR(KBr) cm^{-1}: 3200 (NH), 1750 (C=O). ^{1}H-NMR($CDCl_3$) δ: 2.44 (3H, s, tosyl Me), 7.33 and 7.81 (4H, dd, J=8.0 Hz, tosyl protons). MS m/z: 494 (M+4), 492 (M^++2), 490 (M+)].



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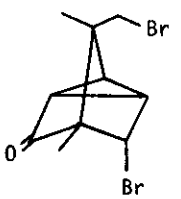
a: $TsNHNH_2$($CHCl_3$), 20°, 48h, b: basic Al_2O_3($CHCl_3$)

15) $C_{10}H_{12}OBr_2$, colorless needles, mp 97-99° (petroleum ether). IR(nujol) cm^{-1}: 1770 (C=O). ^{1}H-NMR($CDCl_3$) δ: 0.97 and 1.14 (6H, 2s, 2xMe), 1.89 (1H, t, J=6.0 Hz, H-1), 3.32 and 3.47 (2H, ABq, J=10.0 Hz, H-8_{AB}), 4.56 (1H, d, J=1.6 Hz, H-3). MS m/z: 310 (M^++4), 308 (M^++2), 306 (M^+), 291 (M^+-Me), 227 (M^+-Br).



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Received, 24th January, 1983