BIGINELLI TYPE REACTION WITH TETROSES DERIVATIVES

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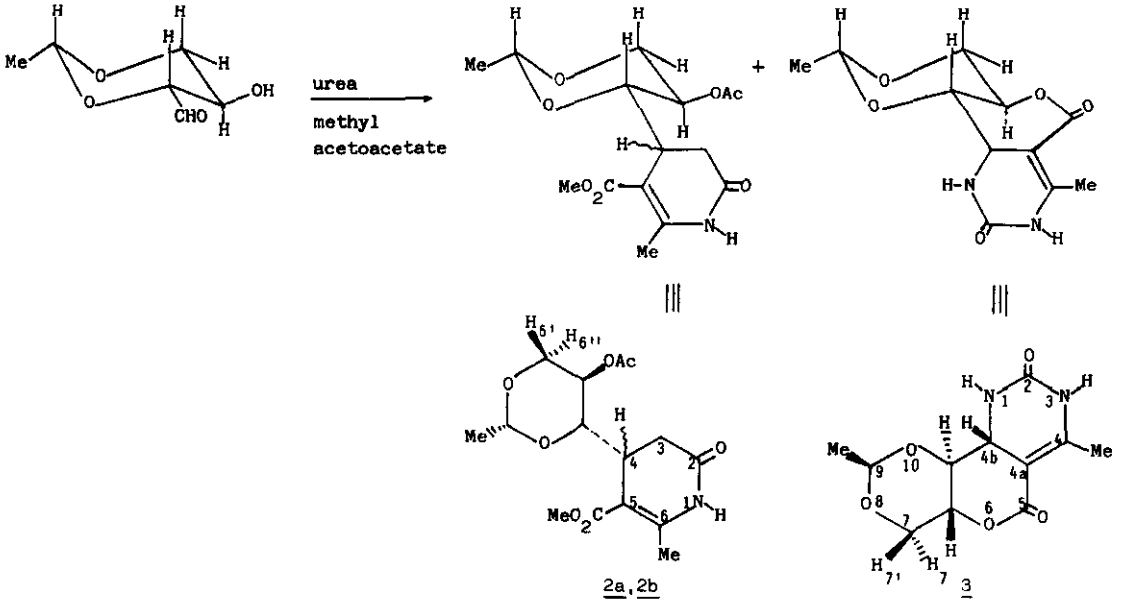
Abstract - The reaction of 2,4-O-ethylidene-D-erythrose and -threose with methyl acetoacetate and urea, or thiourea, under the conditions of the Biginelli type reaction, gives as principal reaction products C-polyhydroxyalkylpyrimidines derivatives.

In continuation of our study on the Biginelli type reaction[1,2,3] with sugar derivatives for the preparation of C-nucleosides and analogues, we wish to report a further extension of our previous work, with tetrose derivatives. With these compounds we tried to check the role that the presence of the free 3-OH and its different configurations of sugar, plays in the course and the results of this reaction.

When the 2,4-O-(1R)-ethylidene-D-erythrose[4] (1 dimeric cyclic acetal) was made to react with urea and methyl acetoacetate in conditions similar to those previously described[3], a mixture of products was yielded. By column chromatography, we have isolated the two major products, characterized as: 4-(5R-acetoxy-2R-methyl-1,3-dioxan-4S-yl)-5-methoxycarbonyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyridine (2) (37.5%) and (4bR, 6aR, 9R, 10aS)-4,9-dimethyl-2,5-dioxo-1,2,3,4b-tetrahydro-oxan|3,2-d|-1,3-dioxane|8,7-d|pyrimidine (3) (20.2%).

Scheme 1

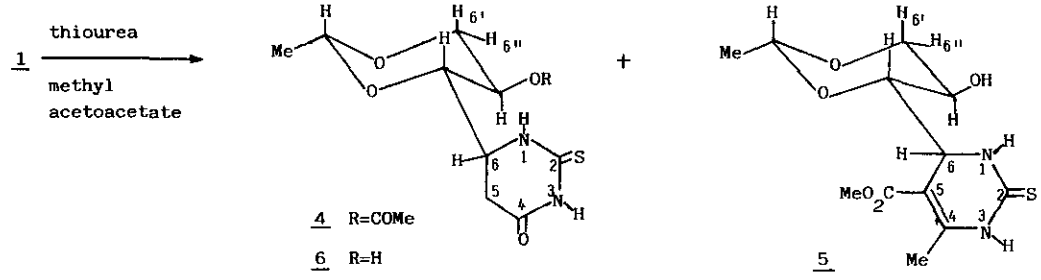


From the pyridine derivative 2 (which has incorporated in its structure two units of methyl acetoacetate) we have isolated the two C-4 epimers 2a and 2b (10:1 ratio). The protons H-5', H-3 and H-4 of isomer 2a, are shown by ^{1}H-nmr to be very different from those of the isomer 2b. In the major isomer 2a, the geminal protons of the heterocyclic ring show a chemical shift at 2.70 ppm (J 16.5 and 8.0 Hz) and 2.45 (J 16.5 and 1.5 Hz), and the proton H-4 at 3.38 ppm (J 8.0, 1.5 and 3.0 Hz). The proton H-5' has a chemical shift at 4.46 ppm. In the minor isomer 2b, these protons appear at 2.77 (J 16.7 and 0 Hz), 2.44 (J 16.7 and 7.9 Hz), 3.08 (J 7.9 and 3.6 Hz) and 4.81 ppm respectively. Two dimensional ^{1}H-nmr measurements were carried out to verify the assignments (COSY, NOESY), nevertheless they are not sufficient to assign the absolute configuration in C-4.

The tetrahydropyrimidine derivative 3 is the expected product of Biginelli condensation, but this compound has experienced a process of hydrolysis and further lactonization of the ester group on C-5, with the free hydroxyl of sugar moiety. We have isolated only one C-4b epimeric form of 3, to which we have assigned the (R)-configuration, on the basis of the Nuclear Overhauser Enhancement Spectroscopy Spectrum. This spectrum showed strong cross peaks with the signals at 4.48 ppm for the H-4b proton, and at 4.08 ppm for the H-6a proton, which could only arise if the H-4b possessed a R-configuration. The NOESY interactions between MeCH of the ethylidene group and the H-10a and H-7 protons also confirm the conformation of sugar moiety.

The reaction of 1 with thiourea and methyl acetoacetate, under our experimental conditions, gave the next pyrimidine derivatives: 6-(5R-acetoxy-2R-methyl-1,3-dioxan-4S-yl)-4-oxo-2-thiohexahydropyrimidine (4, 26.3%), 6-(5R-hydroxy-2R-methyl-1,3-dioxan-4S-yl)-5-methoxycarbonyl-4-methyl-2-thio-1,2,3,6-tetrahydropyrimidine (5, 27.15%) and 6-(5R-hydroxy-2R-methyl-1,3-dioxan-4S-yl)-4-oxo-2-thiohexahydropyrimidine (6, 12.2%). All the products of these condensations present similar values of coupling constants of carbohydrate moiety by ^{1}H-nmr, indicating the same preferential conformation.

Scheme 2

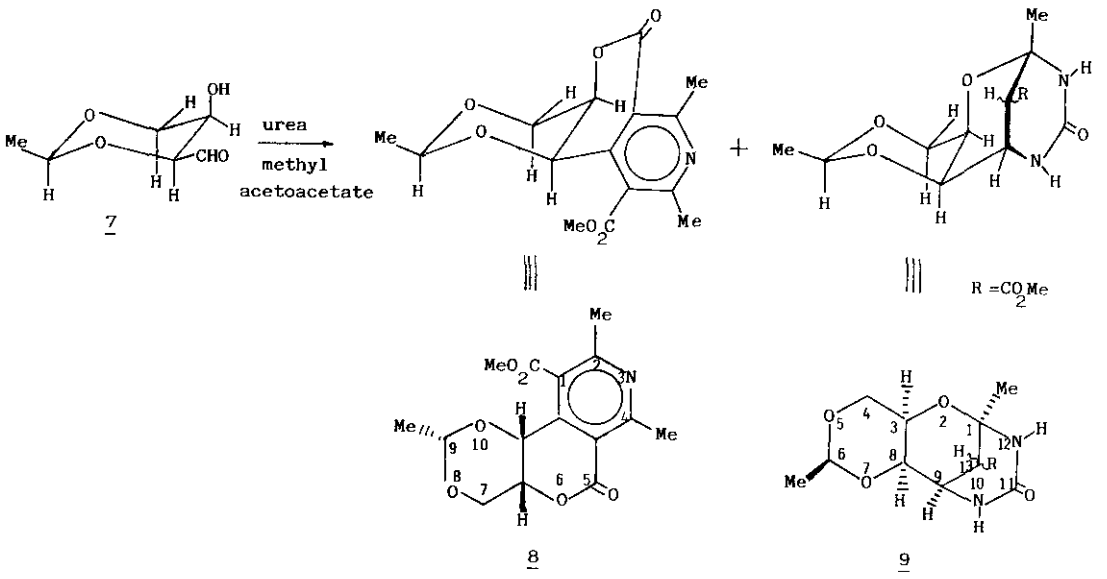


For compounds 4, 5 and 6, we have only obtained one C-6 epimer, but we have not sufficient data to assign the absolute configuration in this center.

When 2,4-O-ethylidene-D-threose [5] (7, dimeric cyclic acetal) was made to react with urea and methyl acetoacetate, a mixture of products of difficult separation was yielded. We have only characterized two compounds, a pyrimidine derivative (6aR, 9S, 10aR)-1-methoxycarbonyl-2,4,9-trimethyl-5-oxo-oxan-|3,2-d|-1,3-dioxane|7,8-c|pyrimidine (8, 3.4%) and (1S, 3R, 6S, 8R, 9S)-13-methoxycarbonyl-1,6-dimethyl-11-oxo-tricyclo|7,3,1,$0^{3,8}$|-10,12-diaza-2,5,7-trioxatridecane (9, 15.1%). Compound 8 may be

formed by a Hantzsch type synthesis and further hydrolysis and lactonization of the one ester group. In ^{1}H-nmr the upfield observed for the protons of sugar, instead of showing in compounds previously described, may be explained by the presence of an aromatic heterocycle in the structure. Compound 9 may result from a Biginelli reaction and the later addition of free hydroxyl of sugar to the double bond C_4-C_5 of the tetrahydropyrimidine ring[3].

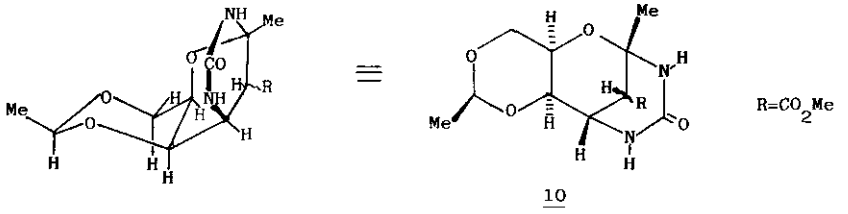
Scheme 3



7 8 9

Only one compound of the two possible reaction products 9 and 10 was isolated. We have assigned the structure 9 on the basis of the values of the coupling constant between H-8 and H-9.

Scheme 4



10

The dihedral angles H_8-C_8-C_9-H_9 expected on the basis of Dreiding models, are 60° for compound 9 and 10° for 10. The experimental value $^{3}J_{8,9}$ = 1.8 Hz are in good agreement with the dihedral angle H_8-C_8-C_9-H_9 for compound 9. Molecular mechanics geometries calculations (MMP2/85)[6] for 9 and 10 predict a H_8-C_8-C_9-H_9 dihedral angle of 65° (J = 1.29 Hz) and 18° (J = 7.45 Hz), respectively. We have not assigned the absolute configuration of C-13, however, the value of δ for H-13 and the absence of long-range coupling (W) with H-8 seem to indicate a R-configuration for this center.

TABLE I. ^{1}H-nmr DATA (200 MHz) in $CDCl_3$

Compound	H-3a or H-5a	H-3b or H-5b	H-4 or H-6	H-4'	H-5'	H-6'	H-6''	Ethylidene CH	Ethylidene Me	Me-C=	Others
2a	2.70 (dd)	2.45 (dd)	3.38 (ddd)	3.59 (dd)	4.46 (dd)	3.21 (dd)	4.21 (dd)	4.58 (q)	1.19 (d)	2.28 (s)	7.40 (NH), 3.64 (OMe), 2.04 (OAc)
2b	2.44 (dd)	2.77 (d)	3.08 (dd)	3.58 (dd)	4.81 (dd)	3.31 (dd)	4.13 (dd)	4.56 (q)	1.20 (d)	2.31 (s)	8.01 (NH), 3.69 (OMe), 2.01 (OAc)
4	2.78 (dd)	2.90 (dd)	3.85 (ddd)	3.78 (dd)	4.80 (dd)	3.45 (dd)	4.25 (dd)	4.70 (q)	1.35 (d)	-	8.45 (NH-1), 7.40 (NH-3), 2.10 (OAc)
5	-	-	4.70 (t)	3.32 (dd)	3.77 (dd)	3.29 (dd)	4.10 (dd)	4.52 (q)	1.20 (d)	2.28 (s)	8.65 (NH-1), 7.95 (NH-3), 3.70 (OMe) 1.90 (OH)
6*	2.80 (dd)	2.97 (dd)	4.15 (m)	3.75 (dd)	3.62 (ddd)	3.48 (dd)	4.10 (dd)	4.80 (q)	1.30 (d)	-	

Compound	H-4b	H-10a	H-6a	H-7	H-7'	CH	Me	Me-C=	Others
3	4.48 (d)	3.72 (dd)	4.08 (ddd)	3.62 (dd)	4.28 (dd)	4.80 (q)	1.38 (d)	2.40 (s)	7.82 (NH), 5.55 (NH)
8	-	5.02 (d)	4.22 (ddd)	4.02 (dd)	4.38 (dd)	4.89 (q)	1.34 (d)	2.93(s) 2.65(s)	3.96 (OMe)

Compound	H-13	H-9	H-8	H-3	H-4	H-4'	CH	Me	-	Others
9	3.28 (d)	3.87 (ddd)	3.67 (dd)	3.60 (m)	3.85 (dd)	4.07 (dd)	4.70 (q)	1.32 (d)		6.60 (NH-10), 6.35 (NH-12), 3.68 (OMe), 1.60 (Me)

* D_2O

TABLE II. J values (Hz)

Compound	$J_{3a,3b}$ or $J_{5a,5b}$	$J_{3a,4}$ or $J_{5a,6}$	$J_{3b,4}$ or $J_{5b,6}$	$J_{4,4'}$ or $J_{4',6}$	$J_{4',5'}$	$J_{5',6'}$	$J_{5',6''}$	$J_{6',6''}$	$J_{ethylidene}$	Others
2a	16.5	8.0	1.5	3.0	10.0	10.0	5.4	10.0	5.0	
2b	16.7	7.9	0.0	3.6	9.7	10.5	5.4	10.5	5.0	
4	17.0	7.0	6.0	4.0	10.0	10.0	5.0	10.0	5.0	
5	-	-	-	4.0	10.0	11.0	5.5	11.0	5.0	4.0 ($J_{6,NH}$)
6	17.0	4.5	7.5	2.0	10.0	10.0	4.5	10.0	5.0	

Compound	$J_{10a,4b}$	$J_{10a,6a}$	$J_{6a,7}$	$J_{6a,7'}$	$J_{7,7'}$	$J_{ethylidene}$
3	10.0	10.0	10.0	5.0	10.0	5.0
8	-	1.7	1.6	1.7	12.9	5.0

Compound	$J_{8,9}$	$J_{8,3}$	$J_{3,4}$	$J_{3,4'}$	$J_{4,4'}$	$J_{ethylidene}$	Others
9	3.0	1.8	1.8	1.0	12.7	5.0	2.0 ($J_{9,NH}$) 1.4 ($J_{9,13}$)

In summary, the number of products obtained indicates that this reaction is more complicated than expected. Some of them can be explained by the involvement of the free hydroxyl, in the formation of δ-lactones (3, 8), the transfer of an acetyl group (2, 4) or its Michael type addition to the double bond of the heterocycle moiety (9). Loss or transfer of one acetyl group during Knoevenagel reaction of 2,4-O-ethylidene-D-erythrose has been previously reported[7]. In our case this loss or transfer before to the cyclization, would implicate the methoxycarbonyl group in the process, giving the compounds 2, 4 and 6. The reaction with the threose derivative is even more complicated, owing to the more favourable dehydration process of the starting sugar, where H-2 and HO-3 are trans-diaxial[8].

EXPERIMENTAL

Melting points are uncorrected. Optical rotations were measured with a Perkin-Elmer polarimeter at 18-20°C. Column chromatography was performed on silica gel 60 (0.063-0.200 or 0.040-0.063 mm) (Merck). Tlc was performed on silica gel GF_{254} (Merck) with detection by sulphuric acid charring or by Uv absorption. Uv spectra were recorded in methanolic solutions on a Beckman DB-GT or Uvikon 810 spectrometers. Ir spectra (KBr disc) were taken on a Beckman Aculab IV spectrophotometer. ^{1}H-Nmr spectra were recorded for solutions in D_2O or $CDCl_3$ (internal DSS or Me_4Si) on a Bruker WP-200 SY (200 MHz) spectrometer. The ^{13}C-nmr spectrum was recorded with a Bruker WP-200 SY (50.3 MHz) spectrometer. Chemical shifts are given on the δ scale, and coupling constants in Hz. Assignments were confirmed by double resonance experiments and bidimensional correlations. Mass spectra were obtained using a Hewlett-Packard 5930-A or a Kratos MS-25 mass spectrometers. Satisfactory elemental analysis for C, H and N was obtained for all compounds.

Biginelli reaction of tetrose derivatives with methyl acetoacetate and urea or thiourea (General procedure)

Methyl acetoacetate (0.1 mol) and urea or thiourea (0.05 mol) were added to a solution of the tetrose derivative (0.05 mol) in ethanol (20-30 ml). The mixture was stirred at 70-80°C for 48-55 h and the mixture was then concentrated in vacuo and the residue was subjected to column chromatography.

Biginelli reaction of 2,4-O-(1R)-ethylidene-D-erythrose (1) with urea and methyl acetoacetate

After reaction for 50 h, the following products were obtained:

2 (40%), which was again chromatographed (preparative TLC, ether-hexane, 3:2) to obtain two epimeric compounds in C-4 (2a, 33.8% and 2b, 3.7%) and 3 (20.2%).

Compound 2a had mp 220-222 °C; $[\alpha]_D$ - 68° (c 0.1, methanol); Uv 280 nm (ε 14000); Ir 3600-3450, 1740, 1715 and 1650 cm^{-1}; ^{13}C-nmr ($CDCl_3$): δ 170.9 (COMe), 169.7 (CONH), 167.6 (COOMe), 147.9 (C-6), 101.9 (C-5), 99.2 (MeCH-O), 82.8 (C-4'), 67.6 (C-6'), 63.9 (C-5'), 51.5 (MeOCO), 34.3 (C-3), 33.3 (C-4), 20.8, 20.1 and 19.9 (MeCO, MeC=, MeCH-O). Ms m/z (rel. int.): 328 (1.5), 327 (M^+,2), 267 (3), 168 (75), 159 (36), 136 (22), 115 (100), 99 (5), 43 (49).

Compound 2b had $[\alpha]_D$ - 218° (c 0.1, acetone).

Compound 3 had mp 287-289 °C; $[\alpha]_D$ 220° (c 0.1, methanol); Uv 290 nm (ε 7800); Ir 3350, 1740, 1710 and 1680 cm^{-1}; ^{13}C-nmr ($CDCl_3$): δ 161.7 (COO), 154.7 (CONH), 153.4 (C-4), 99.7 (MeCH-O), 93.1

(C-4a), 76.0, 67.7 and 67.6 (C-10a, C-6a, C-7), 52.4 (C-4b), 20.1 and 19.3 (MeC=, MeCH-O). Ms m/z (rel. int.): 254 (M^+,2), 193 (2), 181 (4), 167 (2), 155 (100), 137 (10), 110 (25).

Biginelli reaction of 2,4-O-(1R)-ethylidene-D-erythrose with thiourea and methyl acetoacetate

After reaction for 55 h the compounds 4 (26.3%), 5 (27.1%) and 6 (12.2%) were obtained.

Compound 4 had mp 208-210°C; $|\alpha|_D$ - 16° (c 0.1, methanol); Uv 228 nm (ε 9022) and 271 nm (ε 17182); Ir 3300, 1750, 1715 and 1590 cm^{-1}; ^{13}C-nmr ($CDCl_3$) : δ 179.7 (COMe), 169.9 (CO), 165.3 (CS), 99.4 (MeCH-O), 78.3, 63.2 (C-5', C-4'), 67.1 (C-6'), 51.8 (C-6), 29.6 (C-5), 20.9 (MeCH), 20.1 (MeCO).. Ms m/z (rel. int.) : 290 (1.3), 289 (3), 288 (M^+,17), 244 (2), 228 (3), 227 (6), 184 (5), 158 (15), 129 (15), 114 (100), 98 (47), 69 (48), 43 (50).

Compound 5 had mp 204-206°C; $|\alpha|_D$ - 3° (c 0.1, methanol); Uv 306 nm (ε 19500), Ir 3460-3400, 3220-3100, 1710-1690, 1640 and 1590 cm^{-1}; ^{13}C-nmr ($CDCl_3$): δ 176.5 (COOMe), 168.9 (CS), 148.7 (C-4), 100.0 (MeCH-O), 98.8 (C-5), 83.0 and 60.5 (C-4', C-5'), 70.5 (C-6'), 52.4 (COOMe), 51.6 (C-6), 20.4 and 17.8 (MeCH-O , MeC=). Ms m/z (rel. int.): 304 (0.4), 303 (0.3), 302 (M^+,5), 270 (15), 199 (17), 186 (60), 185 (100), 153 (58), 126 (49), 117 (3), 45 (72), 43 (71).

Compound 6 had mp 149-151°C; $|\alpha|_D$ - 24°(c 0.05, methanol); Uv 220 nm (ε 7400) and 275 nm (ε 5200); Ir 3600-3200, 1715 and 1580 cm^{-1}. Ms m/z (rel. int.): 248 (2), 247 (1), 246 (M^+,20), 203 (4.5), 187 (4.5), 130 (34), 129 (16), 117 (18), 99 (24), 73 (21), 70 (33), 45 (45), 43 (100).

Biginelli reaction of 2,4-O-(1S)-ethylidene-D-threose (7) with urea and methyl acetoacetate

After reaction for 48 h compounds 8 (3.4%) and 9 (15.1%) were obtained.

Compound 8 had mp 139-140°C; $|\alpha|_D$ - 4° (c 0.1, chloroform); Uv 210 nm (ε 7853), 230 nm (ε 4674) and 276 nm (ε 2206); Ir 1730-1715 and 1580-1570 cm^{-1}; ^{13}C-nmr ($CDCl_3$): δ 167.5 (COOMe), 164.3 (CO of lactone ring), 162.0 and 160.0 (C-2, C-4), 143.2 (C-4b), 125.1 and 117.0 (C-4a, C-1), 99.6 (MeCH-O), 70.5, 68.3 and 67.4 (C-10a, C-6a, C-7), 53.3 (OMe), 26.3, 24.2 and 21.1 (MeC-2, MeC-9, MeC-4). Ms m/z (rel. int.): 308 (1), 307 (M^+,9), 292 (3), 277 (4), 276 (3), 264 (7), 246 (12), 231 (95), 205 (12), 202 (35), 186 (3), 59 (45), 43 (100).

Compound 9 had mp 121-123°C; $|\alpha|_D$ - 34° (c 0.1, methanol); Uv 210 nm (ε 5040) and 238 nm (ε 1380); Ir 3360, 1750, 1680-1670 and 1500 cm^{-1}, ^{13}C-nmr ($CDCl_3$): δ 170.5 (COOMe), 157.2 (C-11), 98.4 (MeCH-O), 82.1 (C-1), 74.2 (C-8), 69.2 (C-4), 61.8 (C-3), 52.2 (COOMe), 50.2 (C-9), 41.8 (C-13), 25.3 (MeC-1), 21.0 (MeCH). Ms m/z (rel. int.): 287 (1.3), 286 (M^+, 7), 265 (4), 200 (70), 199 (98.5), 169 (95), 167 (98), 115 (19), 87 (37), 59 (79), 43 (100).

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