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SYNTHESIS AND STRUCTURAL ANALYSIS OF SOME NEW SATURATED SIX-MEMBERED RING HETEROCYLIC COMPOUNDS OBTAINED FROM TERPENOIDS

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ABSTRACT. The synthesis, structural analysis and the stereochemistry of some new six-memebered ring heterocyclic derivatives obtained by the ketalisation reaction of some mono- and bicycloterpenoids are reported. The structural analysis of the compounds was carried out using NMR investigations and the anancomeric structure of the compounds and the influence of the chirality introduced in the molecule by the terpenoidic structure were revealed.

Keywords:

INTRODUCTION

Many spiro and polispiro compounds with saturated six-membered rings were studied in connection with their structural behavior.[1-10] The investigations of these compounds revealed the helical chirality of the spirane skeleton and the anancomeric or flipping conformational behavior of the compounds in correlation with the nature of the substituents located in positions 2 and 4 of the spirane skeleton.[1-4,10] Many spiro 1,3-dioxane derivatives were synthesized for various applications in material sciences,[11] as chiral reagents,[12] and drugs[13].

In this context we considered of interest to investigate new spiro 1,3-dioxanes obtained starting from terpenoids.

RESULTS AND DISCUSSIONS

New six membered heterocyclic compounds were synthesized by the condensation reaction of some terpenoids with 1,3-diols (when 1,3-dioxanes were obtained) (Scheme 1). The acetalization reaction being of equilibrium leads to the more stable structure in which the substituents located at the heterocycle exhibit an equatorial orientation.

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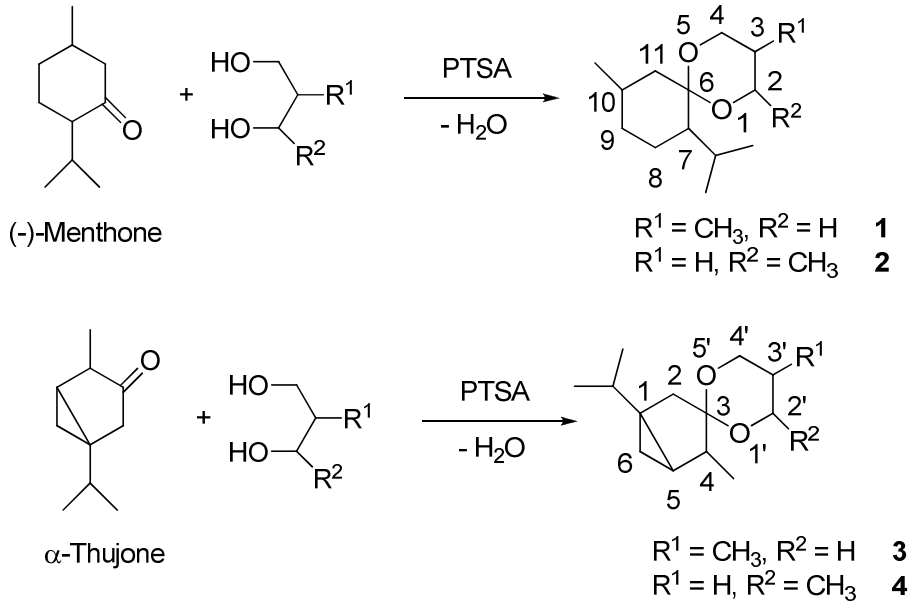
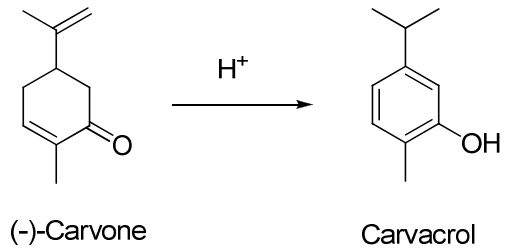


Scheme 1

Trying to use (-)-carvone for the ketalisation reaction in the same conditions (acidic catalysis) instead of the 1,3-dioxane compound, the characteristic side reaction[14] to carvacrol took place as main process (Scheme 2). Also the ketalisation reaction of (*1S*)-camphor or (*1R*)-verbenone did not worked in the typical procedures and the corresponding 1,3-dioxane derivatives could not be obtained.



Scheme 2

The structural analysis of **1**-**4** was carried out using NMR investigations. The spectra of compounds **1-3** exhibit different signals for the axial and equatorial protons of the 1,3-dioxane rings (Table 1) and prove the anancomeric structure of these compounds. On the other side for compounds **1** and **3**,

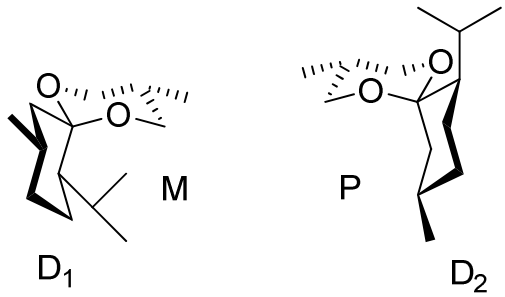
positions 2 and 4 are diastereotopic as a consequence of the chirality of the molecules (helical chirality of the spirane unit and chiral centers of the terpenoid moiety).

Table 1. NMR data (300 MHz, C_6D_6, δ ppm) for compounds **1**-**3***

Compound	2(2')-H		4(4')-H	
	ax.	eq.	ax.	eq.
1	3.40	3.95	3.17	3.70
2	2.81	-	3.76	3.52
3	3.22	3.57	3.19	3.57

*The NMR spectrum of **4** exhibit overlapping of the investigated signals and their assignment could not be carried out properly.

For compounds **1** and **3** two diastereoisomers are possible ($\mathbf{D_1}$ and $\mathbf{D_2}$, Scheme 3). In $\mathbf{D_1}$ (exhibiting the *M* configuration of the spirane skeleton) the *i*-Pr group is oriented "inside" referred to the 1,3-dioxane unit. This orientation determines an important hindrance and it is instable. In $\mathbf{D_2}$ (with *P* configuration of the spirane skeleton) the *i*-Pr group is oriented "outside" relatively to the 1,3-dioxane unit, the steric hindrance is diminished and this conformer is considerably more stable. The synthesis of **1** and **3** is running under thermodynamic control so the reaction leads mainly to the $\mathbf{D_2}$ isomer.



Scheme 3

The methyl group at position 3 of the spirane exhibits an equatorial preference in agreement with the high conformational enthalpy of the methyl substituents located at position 5 of the 1,3-dioxane rings[15-17].

In the case of compound **2** and **4**, the methyl group located in position 4 also prefers the equatorial orientation, the possible equilibrium run during the acetalization reaction being totally shifted towards this isomer. On the other hand as in the previously shown case (for 1 and 3), for compounds 2 and 4 two diastereoisomers are possible. In this case too, the major (representative) diastereoisomer exhibits the methyl group of position 4 oriented "outside" the 1,3-dioxane ring.

CONCLUSIONS

New spiro compounds were obtained starting from terpenoids and substituted 1,3-propanediols. The NMR investigations revealed the preference for the formation of the less hindered diastereoisomers and the anancomeric conformational behavior of these ones.

EXPERIMENTAL

^{1}H-NMR (300 MHz) spectra were recorded at *rt* in C_6D_6 on a Bruker 300 MHz / 400MHz spectrometer, using the solvent line as reference.

Chemicals were purchased from Aldrich or Acros and were used without further purification.

*General procedure for the synthesis of compounds **1-4***

0.1 mol of 1,3-diol and the corresponding quantities of terpenoids (0,1 mol) with catalytic amounts of *p*-toluenesulphonic acid (0.1 g) were solved in 200 mL benzene. The mixture was refluxed and the water produced in the reaction removed using a Dean-Stark trap. When 80 % of the water had been separated, the mixture was cooled to room temperature and the catalyst was neutralized (under stirring 0.5 h) with sodium acetate powder in excess (0.2 g), then washed with water (2 x 100 mL) and dried on anhydrous Na_2SO_4 After filtration, the solvent was removed and the crude products were purified by vacuum distillation (0.5 -1 mmHg).

3,10-dimethyl-7-isopropyl-1,5-dioxaspiro[5.5]undecane 1

Liquid, b.p.=112-114℃ (2 mmHg), yield 60 %. $C_{14}H_{26}O_2$ (226.35, calc. 74.28 C, 11.58 H, found 73.97 C, 11.79 H. **^{1}H-NMR** (300 MHz, C_6D_6, δ ppm): 3.95 (1H, dd, *J* = 11.3 Hz, *J* = 2.7 Hz, 2-H_{eq}), 3.70 (1H, dd, *J* = 11.3 Hz, *J* = 2.7 Hz, 4-H_{eq}), 3.40 (1H, m, 2-H_{ax}), 3.17 (1H, m, 4-H_{ax}), 2.83 (1H, m, 3-H), 2.63 (2H, m, 11-H), 1.20 (3H, d, *J* = 6.9 Hz, 10-CH_3), 1.09 (3H, d, *J* = 6.9 Hz, 3-CH_3), 0.87 (6H, d, *J* = 6.6 Hz, 7-$CH(CH_3)_2$), 0.60-1.80 [7 H, overlapped peaks, 7-H, 8-H_2, 9-H_2, 10 H, 7-$CH(CH_3)_2$]

2,10-dimethyl-7-isopropyl-1,5-dioxaspiro[5.5]undecane 2

Liquid, b.p.=118-120℃ (2 mmHg), yield 58 %. $C_{14}H_{26}O_2$ (226.35), calc. 74.28 C, 11.58 H, found 74.70 C, 11.90 H. **^{1}H-NMR** (300 MHz, C_6D_6, δ ppm): 3.76 (1H, m, 4-H_{ax}), 3.52 (1H, m, 4-H_{eq}), 2.81 (1H, m, 2-H), 2.79 (1H, m, 11-H_{eq}), 2.56 (1H, d, J = 13.3 Hz, 11-H_{ax}), 2.24 (2H, m, 3-H), 1.17 (3H, d, J = 6.7 Hz, 2-CH_3), 1.05 (3H, d, J = 6.9 Hz, 10-CH_3), 0.88 (6H, d, J = 6.7 Hz, 7-$CH(CH_3)_2$), 0.70-1.10 [7 H, overlapped peaks, 7-H, 8-H_2, 9-H_2, 10 H, 7-$CH(CH_3)_2$]

3,3-(3'-methyl-1',5'-dioxapentan-1',5'-diyl)-1-isopropyl-4-methyl-byciclo[3.1.0]hexane 3

Liquid, b.p.=108-110℃ (1,4 mmHg), yield 56 %. $C_{14}H_{24}O_2$ (224.17), calc. 74.95 C, 10.78 H, found 74.60 C, 11.05 H. **^{1}H-NMR** (300 MHz, C_6D_6 , δ ppm): 3.57 (2H,overlapped peaks, 2'-H_{eq} 4'-H_{eq}), 3.22 (1H, d, *J* = 11.7 Hz 2'-H_{ax}), 3.19 (1H, d, *J* = 11.7 Hz 4'-H_{ax}), 2.56 (1H, m, 3'-H_{ax}) 2.39 (1H, d, *J* = 13.3 Hz, 2-H_{eq}), 1.79 (1H, d, *J* = 13.3 Hz, 2-H_{ax}), 1.37 (3H, d, *J* = 6.7 Hz, 3'-CH_3), 1.20 (3H, d, *J* = 6.9 Hz, 4-CH_3), 0.90 [6H, d, *J* = 6.7 Hz, 1-$CH(CH_3)_2$], 0.70-1.10 (5 H, overlapped peaks, 6-H_2, 5-H, 4 H, 1-$CH(CH_3)_2$]

3,3-(2'-methyl-1',5'-dioxapentan-1',5'-diyl)-1-isopropyl-4-methyl-byciclo[3.1.0]hexane 4

Liquid, b.p.=106-107℃ (1,4 mmHg), yield 42 %. $C_{14}H_{24}O_2$ (224.17), calc. 74,95 C, 10,78 H, found 74,60 C, 11,05 H. **^{1}H-NMR** (300 MHz, C_6D_6 , δ ppm): 3.70-3.60 (2H,overlapped peaks, 4'-H_{eq} 4'-H_{ax}), 2.92 (1H, m, 2'-H_{ax}), 2.49 (1H, d, *J* = 12.5 Hz, 2-H_{eq}), 2.24 (2H, m, 3-H), 1.99 (1H, d, *J* = 12.5 Hz, 2-H_{ax}), 1.37 (3H, d, *J* = 6.8 Hz, 2'-CH_3), 1.20 (3H, d, *J* = 6.9 Hz, 4-CH_3), 0.94 [6H, d, *J* = 6.7 Hz, 1-$CH(CH_3)_2$], 0.70-1.10 (5 H, overlapped peaks, 6-H_2, 5-H, 4 H, 1-$CH(CH_3)_2$]

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REFERENCES

1. Grosu I., Mager S., Plé G., Horn M., *J. Chem. Soc. Chem. Commun*. **1995**, 167.
2. Grosu I., Mager S., Plé G., *J. Chem. Soc. Perkin Trans. 2*, **1995**, 1351.
3. Grosu I., Mager S., Plé G., Mesaroş E., Gegö C., Dulău A., *Rev. Roum. Chim.*, **1999**, *44*, 467.
4. Grosu I., Mager S., Plé G., Mesaros E., *Tetrahedron* **1996**, *52*, 12783.
5. Grosu I., Plé G., Mager S., Martinez R., Mesaros C., Camacho B., *Tetrahedron* **1997**, *53*, 6215.
6. Grosu I., Mager S., Plé G., Turos I., Mesaros E., Schirger I., *Monatsh. Chem.*, **1998**, *129*, 59.
7. Opris D., Grosu I., Toupet L., Plé G., Terec A., Mager S., Muntean L., *J. Chem. Soc. Perkin Trans. 1*, **2001**, 2413.
8. Grosu I., Bogdan E., Plé G., Toupet L., Ramondenc Y., Condamine E., Peulon-Agasse V., Balog M., *Eur. J. Org. Chem*. **2003**, 3153.

9. Balog, M., Grosu, I., Plé, G., Ramondenc Y., Toupet, L., Condamine, E., Lange, C., Loutelier, C., Peulon-Agasse, V., Bogdan, E., *Tetrahedron* **2004**, *60 (22)*, 4789.
10. Cismaş, C., Terec, A, Mager, S., Grosu, I., *Curr. Org. Chem*. **2005**, *9*, 14, 1287.
11. Lemcoff, N. G., Fuchs, B., *Org. Lett*., **2002**, *4*, 731.
12. Böhm, U., Voss, G., Möller, G., Gerlach, H., *Tetrahedron*: *Asymmetry*, **1994**, *5*, 1281.
13. Séller, J., Barr, J., Ng, S. Y., Shen, H. -R., Schwach-Abdellaoui, K., Gurny, R., Vivien-Castioni, N., Loup, P. J., Baehni, P., Mombelli, A., *Biomaterials*, **2002**, *23,* 4397.
14. Raner, K. D., Strauss C. R., Vyskoc F., Mokbel L., *J. Org. Chem*. **1993**, *58*, 950.
15. Anteunis M.J.O., Tavernier D., Borremans F., *Heterocycles* **1976**, *4*, 293.
16. Kleinpeter E., *Adv. Heterocycl. Chem.*, **1998**, *69*, 217.
17. Kleinpeter E., *Adv. Heterocycl. Chem.*, **2004**, *86*, 41.