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A NEW SYNTHETIC ENTRY INTO THE TRICYCLO[3.3.0.0^{3,7}]OCTANE SKELETON

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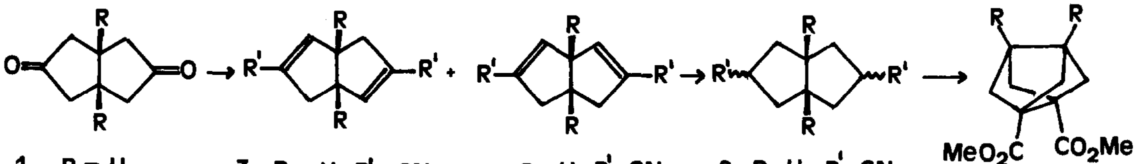
SUMMARY: A short synthesis of dimethyl tricyclo[3.3.0.0^{3,7}]octane-1,5-dicarboxylate, 13, and its 3,7-dimethyl-derivative, 14, by iodine oxidation of the bis-enolate derived from the corresponding dimethyl *cis*-bicyclo[3.3.0]octane-3,7-dicarboxylate, 11 or 12, is described.

In connection with the synthesis of polyquinanes we were interested in the preparation of dimethyl tricyclo[3.3.0.0^{3,7}]octane-1,5-dicarboxylate, 13. Some time ago, we published[1] several attempts to synthesize diester 13, and reviewed the described entries into its strained tricyclic skeleton, none of them being easily arranged for the synthesis of 13. Since then, no other new synthetic entry into this carbocyclic skeleton has been described. The recent publication by Hofmann[2] of a new access to noradamantane derivatives from the same intermediates we have used to prepare diester 13 and the corresponding 3,7-dimethyl-derivative, 14, prompt us to publish our preliminary results on this subject.

Diester 13 was readily synthesize from the easily accessible *cis*-bicyclo[3.3.0]octane-3,7-dione,[3] 1. Reaction of diketone 1 with excess KCN (5-6 mol KCN per mol diketone 1) in water gave a mixture, containing majorly the corresponding stereoisomeric bis-cyanohydrins, that was dehydrated as such by reaction with $POCl_3$ in dry pyridine under reflux to give a mixture of *cis*-bicyclo[3.3.0]octa-2,6-diene-3,7-dicarbonitrile, 3, and *cis*-bicyclo[3.3.0]octa-2,7-diene-3,7-dicarbonitrile, 4, in 54.3% overall yield, in which 3 slightly predominated over 4 (glc). Pure samples of both compounds were obtained by semipreparative hplc.[4,5] The mixture of dinitriles 3 and 4 was smoothly hydrogenated in methanol solution at 4-5 atm. using 5% Pd on charcoal as catalyst, to give majorly one of the three possible stereoisomers of *cis*-bicyclo[3.3.0]octane-3,7-dicarbonitrile,[5] 9, in quantitative yield. This stereoisomer was considered to be *endo*,*endo*-9, on the basis of its C_{2v} symmetry and the expected preferred hydrogenation by the less hindered *exo*-faces of the carbon-carbon double bonds of 3 and 4. Hydrolysis of dinitrile 9 was achieved by heating it under reflux with a 40% methanolic solution of KOH. After acidification, the crude diacid was isolated and esterified with ethereal solution of diazomethane to give dimethyl *cis*-bicyclo[3.3.0]octane-3,7-dicarboxylate, 11, in 78% overall yield, as a mixture of the three possible stereoisomers containing approximately 15% *endo*,*endo*-11, 65% *endo*,*exo*-11, and 20% *exo*,*exo*-11 (^{13}C nmr spectrum), showing that, at least, partial epimerization took place during hydrolysis. Alternatively, the mixture of dinitriles 3 and 4 was hydrolyzed (96% H_2SO_4, then aqueous NaOH) and esterified (MeOH, H_2SO_4) to give a mixture of the corresponding diesters 7 and 8, in the approximate ratio 1:1, in 50.7% yield, that was hydrogenated as described for the mixture of dinitriles 3 and 4, to give quantitatively a mixture of diesters 11, in which one of the C_{2v} stereoisomers, probably *endo*,*endo*-11, predominated. The mixture of diesters 11 was treated with 2 equiv. of lithium diisopropylamide in anhydrous THF[6] and the corresponding bis-enolate reacted with 1 equiv. iodine to give after column chromatography, the tricyclic diester 13, in 41% yield.[5]

In the same way, starting from *cis*-1,5-dimethylbicyclo[3.3.0]octane-3,7-dione,[3] 2, we obtained a mixture of dinitriles 5 and 6, in 60% yield.[7] Hydrogenation of this mixture under the



1, R = H
2, R = Me

3, R = H, R' = CN
5, R = Me, R' = CN
7, R = H, R' = CO_2Me

4, R = H, R' = CN
6, R = Me, R' = CN
8, R = H, R' = CO_2Me

9, R = H, R' = CN
10, R = Me, R' = CN
11, R = H, R' = CO_2Me
12, R = Me, R' = CO_2Me

13, R = H
14, R = Me

same conditions used before for dinitriles 3 and 4, took place more slowly (approximately 24 h), giving rise quantitatively to a mixture of the three possible stereoisomers of cis-1,5-dimethylbicyclo[3.3.0]octane-3,7-dicarbonitrile, 10. It is noteworthy that Hofmann[2] was not able to catalitically hydrogenate the mixture of dinitriles 5 and 6 that was reduced with magnesium in methanol to a mixture of saturated dinitriles 10, containing approximately, 25% endo,endo-10, 45% endo,exo-10, and 30% exo,exo-10. On the basis of the Hofmann assignment, our mixture 10 contained approximately 25% endo,endo-10, 25% endo,exo-10, and 50% exo,exo-10, showing that hydrogenation of 5 and 6 takes place preferently by the endo-faces of their carbon-carbon double bonds. Hydrolysis of this mixture of saturated dinitriles 10, with 40% methanolic solution of KOH gave, after acidification, a mixture of the corresponding diacids that was esterified with ethereal solution of diazomethane to give a mixture of stereoisomers of dimethyl cis-1,5-dimethylbicyclo[3.3.0]octane-3,7-dicarboxylate, 12, in 82% yield, containing approximately 30% endo,endo-12, 40% endo,exo-12, and 30% exo,exo-12, in contrast with the acidic hydrolysis of dinitriles 10 that takes place without epimerization at C_3 and C_7.[2] The mixture of diesters 12 was transformed into the tricyclic diester 14 in 38.5% yield[5] by the same procedure described before to prepare diester 13.

Thus, a new and easy entry into functionalized tricyclo[$3.3.0.0^{3,7}$]octane derivatives, possible precursors for complex polyquinanes, from the readily available cis-bicyclo[3.3.0]octane-3,7-diones, has been developed.

References and Notes

1. P. Camps and M. Figueredo, Can. J. Chem., **62**, 1184(1984)
2. P. Hofmann, E. Beck, M.D. Hoffmann, and A. Sieber, Liebigs Ann. Chem., 1179(1986)
3. S.H. Bertz, J.M. Cook, A. Gawish, and U. Weiss, Org. Synth., **64**, 27 (1986)
4. The separation of dinitriles 3 and 4 was carried out on a Waters hplc chromatograph, model 6000A, using a 30 cm μporasil semipreparative column, and a mixture of ethyl acetate/hexane 1/4 as eluent, at 2000 psi with a flow of 1.7 ml/min. Compound 3 showed rt 23 min., and compound 4, rt 19 min.
5. Significative physical and spectroscopic data of the new single compounds. Unless otherwise stated, C-13 and H-1 nmr spectra were taken at 50 and 200 MHz, respectively, on a Varian XL 200 spectrometer, in deuterochloroform solution, using internal TMS as reference.
   3: mp 169-171°C(hexane); C-13 nmr, δ: 38.4(t), 48.5(d), 113.4(s) 115.7(s), 149.9(d)
   4: mp 128-130°C(hexane); C-13 nmr, δ: 38.5(d), 42.0(t), 59.7(d), 115.5(s), 115.7(s), 145.4(d)
   9: mp 59-61°C(ether); C-13 nmr, δ: 30.0(d), 37.5(t), 43.4(d), 121.8(s)
   13: bp 150°C(oven)/0.5 Torr; 60 MHz H-1 nmr, δ: 1.75(broad s, 8H), 2.35(broad s, 2H), 3.55 (s, 6H); C-13 nmr, δ: 37.1(d), 50.2(t), 51.7(c), 57.2(s), 173.6(s)
   14: mp 95-97°C(hexane); H-1 nmr, δ: 1.88(s, 6H), 1.70(d, J = 7.2 Hz, 4H), 1.92(d, J = 7.2 Hz, 4H), 3.67(s, 6H); C-13 nmr, δ: 16.0(c), 47.7(s), 51.6(c), 56.2(t), 58.0(s), 173.4(s)
6. T.J. Brocksom, N. Petragnani, R. Rodrigues, and H. La Scala Teixeira, Synthesis, 396(1975)
7. A similar mixture has been prepared in comparable yield by reaction of diketone 2 with "in situ generated" trimethylsilylcyanide followed by reaction of the mixture of silylated biscyanhydrins with $POCl_3$ in pyridine. H. Quast, Y. Görlach, G. Meischner, K. Peters, E.M. Peters, and H.G. von Schnering, Tetrahedron Letters, **23**, 4677(1982); H. Quast, Y. Görlach, E.M. Peters, K. Peters, H.G. von Schnering, Ll.M. Jackman, G. Ibar, and A.J. Freyer, Chem. Ber., **119**, 1801(1986). For an improved procedure based on the original method of H. Quast, see reference 2.

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