Short Communication

Aminomethylation of Bicyclo[2.2.1]heptane-2,5-dione

Maija Moilanen and Kalle Manninen

Department of Chemistry, University of Oulu, SF-90570 Oulu, Finland

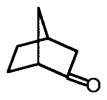
Moilanen, M. and Manninen, K., 1990. Aminomethylation of Bicyclo[2.2.1]heptane-2,5-dione. – Acta Chem. Scand. 44: 857–859.

Several methods for the aminomethylation of ketones have been reported in the literature.[1-7] A typical example is the Mannich reaction[1] of carbonyl compounds in aqueous solution of a strong acid. Thus, bicyclo[2.2.1]heptan-2-one (**1**) has been aminomethylated to 3-dimethylaminomethylbicyclo[2.2.1]heptan-2-one (**2**) in this manner.[2] The Mannich reaction of bicyclo[2.2.1]heptane-2,5-dione (**3**) gave 3,6-dimethylenebicyclo[2.2.1]heptane-2,5-dione (**4**) rather than the expected diamino diketone because amino ketones have a strong tendency to undergo deamination under these conditions.[3]

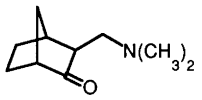
There are also more convenient methods for aminomethylation, which do not demand the presence of a strong acid. Many carbonyl compounds have been transformed into amino ketones via enaminones using amide acetals, *N,N*-dimethylformamide dimethyl acetal, bis(dimethylamino)-*t*-butoxymethane (Bredereck's reagent), or tris(dimethylamino)methane.[4] In this manner bicyclo[2.2.1]heptan-2-one (**1**) has been aminomethylated with good yield. However, bicyclo[2.2.1]hept-5-en-2-one (**5**) did not react with amide acetals, but it was successfully aminomethylated as a lithium enolate with *N,N*-dimethyl-*N*-methyleneammonium iodide (**6**).[4]

Amino ketones have been synthesized using iminium salts both directly from carbonyl compounds[5] and from their silyl enol ethers.[6] Reactions with *N,N*-dimethyl-*N*-methyleneammonium iodide (**6**) or chloride (**7**) have been used for the aminomethylation of 1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**8**), for example.[7]

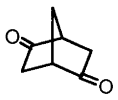
We report here the successful aminomethylation of bicyclo[2.2.1]heptane-2,5-dione (**3**) and the detailed structural analysis of the product, 3-*endo*-6-*endo*-bis(dimethylaminomethyl)bicyclo[2.2.1]heptane-2,5-dione (**9**). The compound was synthesized to serve as the starting material for the preparation of tertiary amino alcohols analogous to **10**. Many of these amino alcohols possess significant analgesic activity,[8] and they also are of interest from the point of view of structure elucidation.



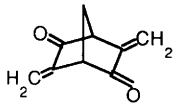
1



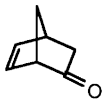
2



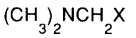
3



4

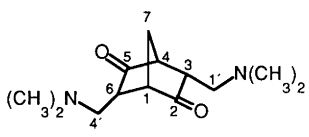


5

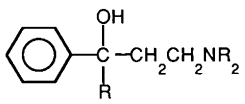


6 : X = I, 7 : X = Cl

8



9



10

Table 1. ^{1}H NMR data; chemical shifts [δ(ppm)] and couplings (*J*/Hz) of 3-*endo*-6-*endo*-bis(dimethylaminomethyl)bicyclo[2.2.1]-heptane-2,5-dione (**9**).

Proton(s)	δ_H(ppm)[a]	J_{HH}/Hz[b]
1, 4	3.18 dt	$J_{1,6} = J_{4,3} = 6.1$, $J_{1,7} = J_{4,7} = 1.6$
3, 6	2.54 m	
7	2.08 t	$J_{7,1} = J_{7,4} = 1.6$
1'A, 4'A	2.47 dd	$J_{gem} = 13$, $J_{1'A,3} = J_{4'A,6} = 3.8$
1'B, 4'B	2.13 dd	$J_{gem} = 13$, $J_{1'B,3} = J_{4'B,6} = 10$
Me	2.24 s	

[a]The data were obtained in $CDCl_3$ solution. TMS ($\delta_H = 0.00$) served as the internal chemical shift reference. [b]The signs of the coupling constants were not determined.

Table 2. ^{13}C chemical shifts [δ(ppm)] of 3-*endo*-6-*endo*-bis-(dimethylaminomethyl)bicyclo[2.2.1]heptane-2,5-dione (**9**).

Carbon(s)	δ_C(ppm)[a]
1, 4	52.3
2, 5	212.6
3, 6	50.4
7	34.8
1', 4'	56.2
Me	45.6

[a]The data were obtained in $CDCl_3$ solution. TMS ($\delta_C = 0.00$) served as the internal chemical shift reference.

Results and discussion

Synthesis. Bicyclo[2.2.1]heptane-2,5-dione (**3**) was aminomethylated with *N,N*-dimethyl-*N*-methyleneammonium chloride (**7**) in dry acetonitrile.[9–11] At room temperature the reaction was very slow, but when the solution was heated, it took place rapidly and in good yield. The amino ketone was liberated from its hydrochloride with potassium carbonate. According to NMR analysis, the product was pure. The mass spectrum of the product revealed the presence of two dimethylaminomethyl groups in the molecule and a molecular weight of 238. The configurational assignment was made by means of the NMR method. Thus, the product was identified as 3-*endo*-6-*endo*-bis(dimethylaminomethyl)bicyclo[2.2.1]heptane-2,5-dione (**9**).

The formation of the *endo,endo* isomer was unexpected because in the aminomethylation of (**1**)[2] and (**8**)[7] *exo*-products are predominantly formed. To determine whether the solvent or the reagent influenced the configuration of the product, bicyclo[2.2.1]heptan-2-one (**1**) was aminomethylated with *N,N*-dimethyl-*N*-methyleneammonium chloride (**7**) in dry acetonitrile. In this case the main product was 3-*exo*-dimethylaminomethylbicyclo[2.2.1]heptan-2-one (**2**). Evidently, then, neither the solvent nor the reagent used accounts for the formation of the *endo,endo* product in the aminomethylation of **3**.

Structural analysis. ^{1}H and ^{13}C NMR spectral parameters are given in Tables 1 and 2, respectively. The 400 MHz ^{1}H NMR spectrum is presented in Fig. 1. The bridgehead protons H-1 and H-4 resonate at lowest field, as a doublet of triplets at 3.18 ppm. The mutual coupling appears to affect the shape of the resonance. The vicinal coupling to protons H-3 and H-6 is 6.1 Hz. The 1.6 Hz couplings to the bridge protons H-7 produce the triplet structure.

The methine protons H-3 and H-6 produce a multiplet at 2.54 ppm. The couplings to the methylene protons of the sidechain are 10.0 Hz and 3.8 Hz. These values are in good agreement with couplings reported earlier for an analogous structure, 3-*endo*-(dimethylaminomethyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (10.7 Hz and 4.8 Hz).[7] The coupling of 6.1 Hz from the bridgehead protons splits the resonance further. The magnitude of this coupling clearly shows that H-3 and H-6 are *exo*-protons and the sidechains are in *endo*-position. The literature values for couplings from *exo*-protons to bridgehead protons in molecules with the bicyclo[2.2.1]heptane skeleton are 3.5–6 Hz and from *endo*-protons to bridgehead protons 0–1 Hz.[12–20]

The ^{1}H NMR data confirm that the aminomethylation product of **3** is 3-*endo*-6-*endo*-bis(dimethylaminomethyl)bicyclo[2.2.1]heptane-2,5-dione (**9**).

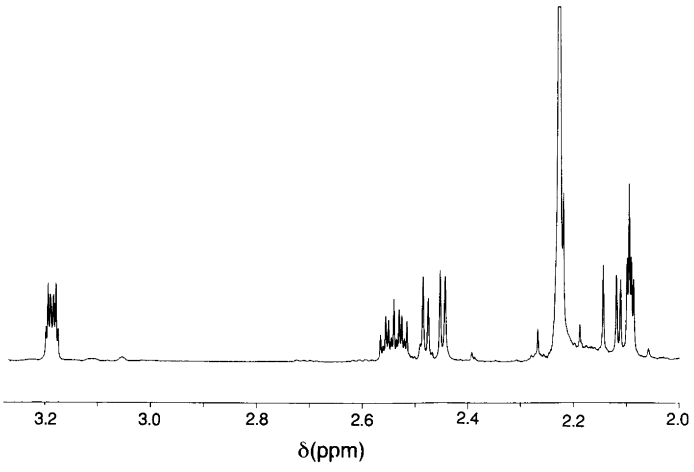


Fig. 1. 400 MHz ^{1}H NMR spectrum of 3-*endo*-6-*endo*-bis-(dimethylaminomethyl)bicyclo[2.2.1]heptane-2,5-dione.

Experimental

Materials and methods. Bicyclo[2.2.1]heptane-2,5-dione (**3**) was prepared by oxidation of bicyclo[2.2.1]heptane-2,5-diol diformate by a known method.[5] Acetonitrile was dried over $CaCl_2$ and molecular sieves. The aminomethylating reagent, *N,N*-dimethyl-*N*-methyleneammoniun chloride (**7**), was prepared as described in the literature.[9,10]

The mass spectrum was obtained with a Kratos MS 80 RF Autoconsole mass spectrometer using electron impact (70 eV). The NMR spectra were obtained in $CDCl_3$ solution with a JEOL GX-400 FT NMR spectrometer. The chemical shifts (δ) are given in ppm relative to $SiMe_4$ (TMS) and the couplings (*J*) are given in Hz.

Aminomethylation. Bicyclo[2.2.1]heptane-2,5-dione (**3**, 4.8 g) was dissolved in 200 ml of dry acetonitrile and 9 g of the aminomethylating reagent, *N,N*-dimethyl-*N*-methyleneammonium chloride (**7**), were added. The solution was heated slowly to the boiling point with stirring and was refluxed for ca. 10 min. The mixture was stirred overnight at room temperature, after which the solid was filtered off, and 5 g of the aminomethylating reagent was added to the solution. The mixture was stirred overnight, the solid was filtered off and the solids were combined. The solid precipitate, the hydrochloride of the amine, was dissolved in a small amount of water, and saturated K_2CO_3 solution was added until the amino ketone (**9**) crystallized. It was separated by filtration and recrystallized from light petroleum (b.p. 40–60 °C). Yield 6.5 g (70 °C). M.p. 84–88 °C.

MS [IP 70 eV; *m/z* (% rel. int.)]: 238 (3, *M*), 194 (1, $[M-NMe_2]$), 193 (1, $[M-HNMe_2]$), 180 (1, $[M-CH_2NMe_2]$), 152 (2, $[M-COCH_2NMe_2]$), 148 (2, $[M-2\times HNMe_2]$), 140 (5), 113 (3), 98 (4), 91 (4), 58 (100).

References

1. Tramontini, M. *Synthesis* (1973) 703.
2. Krieger, H. *Suom. Kemistil. B35* (1962) 10.
3. Vuononvirta, P. *M.Sc. Thesis,* University of Oulu, Oulu, Finland 1974, p. 33.
4. Schuda, P. F., Ebner, C. B. and Morgan, T. M. *Tetrahedron Lett. 27* (1986) 2567.
5. Ahond, A., Cavé, A., Kan-Fan, C., Husson, H.-P., de Rostolan, J. and Potier, P. *J. Am. Chem. Soc. 90* (1968) 5622.
6. Rochin, C., Babot, O., Dunogues, J. and Duboudin, F. *Synthesis* (1986) 667.
7. McClure, N. L., Dai, G.-Y. and Mosher, H. S. *J. Org. Chem. 53* (1988) 2617.
8. Ebel, S. *Synthetische Arzneimittel,* Verlag Chemie, Weinheim 1979, p. 179.
9. Kinast, G. and Tietze, L.-F. *Angew. Chem. 88* (1976) 261.
10. Lednicer, D. and Hauser, C. R. *Org. Synth., Coll. Vol. V.* (1973) 434.
11. Böhme, H. and Hartke, K. *Chem. Ber. 93* (1960) 1305.
12. Anet, F. A. L. *Can. J. Chem. 39* (1961) 789.
13. Fraser, R. R. *Can. J. Chem. 40* (1962) 78.
14. Meinwald, J. and Meinwald, Y. C. *J. Am. Chem. Soc. 85* (1963) 2514.
15. Paasivirta, J. *Suom. Kemistil. B38* (1965) 130.
16. Laszlo, P. and Schleyer, P. v. R. *J. Am. Chem. Soc. 86* (1964) 1171.
17. Franzus, B., Baird, W. C., Jr., Chamberlain, N. F., Hines, T. and Snyder, E. I. *J. Am. Chem. Soc. 90* (1968) 3721.
18. Marchand, A. P. and Rose, J. E. *J. Am. Chem. Soc. 90* (1968) 3724.
19. Beckett, A. H., Tong Lan, N. and McDonough, G. R. *Tetrahedron 25* (1969) 5689 and 5693.
20. Hine, J. and Li, S.-W. *J. Org. Chem. 40* (1975) 289.

Received March 20, 1990.