A New Synthesis and Crystal Structure of 2-Methyl-2-azabicyclo[3.3.1]nonan-7α-ol

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A facile, high yield synthesis of 2-methyl-2-azabicyclo[3.3.1]nonan-7α-ol **2b** from cyclohex-3-ene-1-carbaldehyde **3** is reported; an X-ray structure of **2b**·HCl established the stereochemical assignment of **2b**.

Recently, we reported that azaprophen **1a** was a novel, potent muscarinic antagonist.[1,2] Molecular modelling studies suggested that 2-methyl-2-azabicyclo[3.3.1]nonan-7α-yl diphenylpropionate **2a**, a ring homologue of azaprophen, might also be a potent muscarinic agent. The synthesis of **2a** requires 2-methyl-2-azabicyclo[3.3.1]nonan-7α-ol **2b**, a compound the synthesis of which has been previously reported.[3] In this communication, we report a new concise synthesis of **2b** that starts with readily available and inexpensive starting materials (Scheme 1). Cyclohex-3-ene-1-carbaldehyde **3** was treated with the lithium derivative of 2-trimethylsilyl-1,3-dithiane to give the ketene dithioacetal **4**. Subjection of **4** to 15% methanolic hydrogen chloride followed by basic hydrolysis gave the acid **5**. The homologation of **3** to **5** could be carried out without isolation of **4** in 80% yield.†[4] Iodination of **5** gave the iodolactone **6**‡ in 87% yield. Dehydroiodination of **6** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene provided 2-oxabicyclo[3.3.1]non-7-en-3-one **7** in 58% yield. Lactone **7** could be converted into **2c** by a procedure analogous to the synthesis we used to prepare 6-methyl-6-azabicyclo[3.2.1]octan-3-one **1b**.[5] Thus, treatment of the lactone **7** with a methanolic solution of methylamine at 100 °C gave the amide **8** in 96% yield. Lithium aluminium hydride (LAH) reduction of **8** afforded the hydroxy amine **9** in 70% yield. Allylic oxidation of **9** using activated manganese dioxide in methylene chloride solution gave the α,β-unsaturated ketone **10** that spontaneously cyclized to give the desired azabicyclo ketone **2c** in 85% overall yield from **9**.

The reduction of **2c** with sodium borohydride has been reported to give the 7α alcohol **2b**.[3] The 7α stereochemical assignment assumes that ketone **2c** is reduced in a chair–chair conformation. Molecular mechanics calculations using the MM2-87[6] program agree with this assumption and show that the chair–chair conformation is favoured by a significant amount (>4 kcal mol^{-1}; 1 cal = 4.184 J). Similar calculations swith the alcohol **2b**, however, do not suggest a clear preference for the chair–chair conformation **2bA** over the chair–boat **2bB**. As the conformational preference of analogous 7α (*endo*) substituted carbocyclic bicyclo[3.3.1]nonanes has been reported to vary depending on the substituent[7] we obtained an X-ray crystal structure of **2b**·HCl to determine its conformation and to confirm the 7α stereochemistry. A single crystal of **2b**·HCl grown from a methanol and diethyl ether

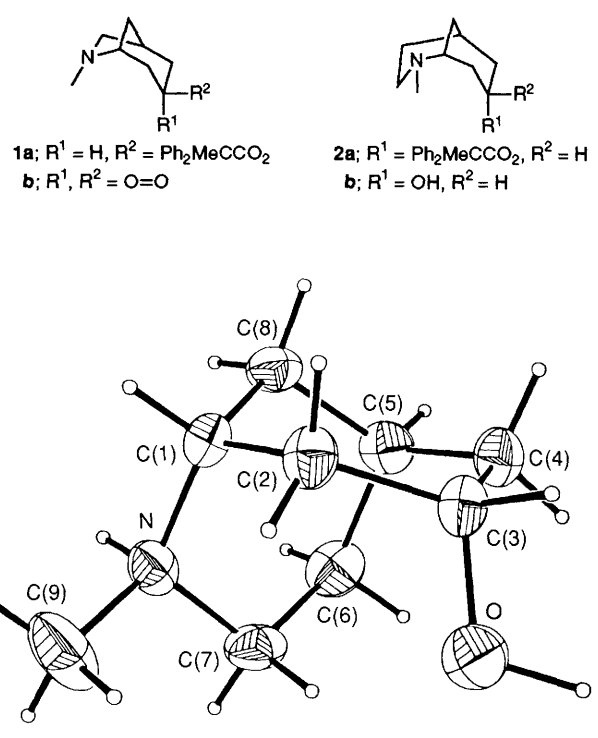
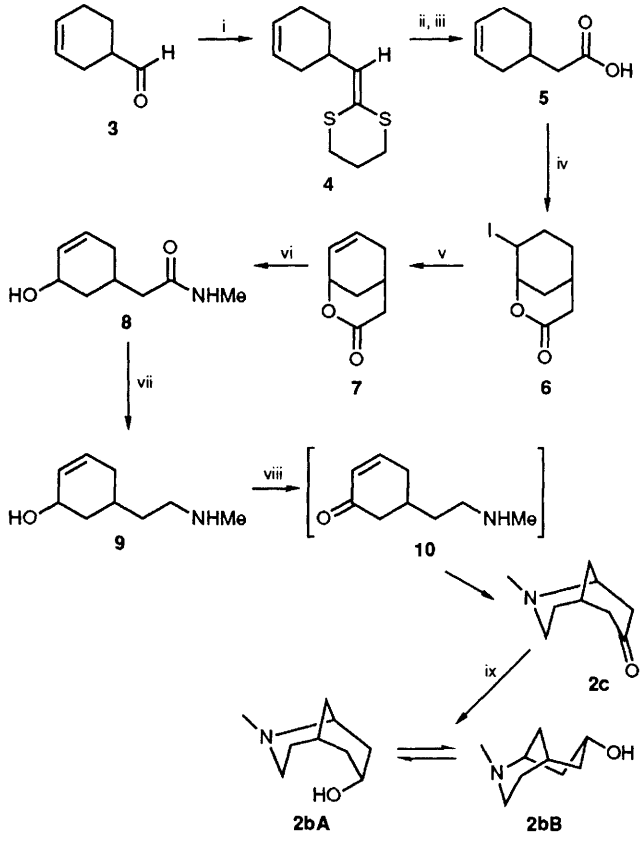


Fig. 1 An ORTEP drawing of **2b**. The numbering of atoms is arbitrary.



Scheme 1 *Reagents*: i, LiBu, 2-trimethylsilyl-1,3-dithiane; ii, 15% methanolic HCl (reflux); iii, 1 mol dm^{-3} NaOH (reflux); iv, I_2, KI, $NaHCO_3$, H_2O; v, DBU; vi, $MeNH_2$, MeOH, heat; vii, LAH, tetrahydrofuran; viii, MNO_2, CH_2Cl_2; ix, $NaBH_4$

† A synthesis of **5** from cyclohex-3-ene-1-carboxylic acid has been reported (ref. 4). As diazomethane was used in the reported synthesis (see ref. 4), it was not practical to scale-up the reaction.

‡ All new compounds gave satisfactory analytical and spectral data.

solution was used to determine its X-ray crystal structure.§ Fig. 1 shows an ORTEP drawing of **2b**·HCl. The figure confirms the 7α structure for **2b** and shows that, at least in the solid state, the compound possesses a chair–chair conformation with an *endo* *N*-methyl group. Compound **2a** was prepared by acylation of **2b** with 2,2-diphenylpropionyl chloride. Radioligand binding data for **2a** revealed that this compound displayed high affinity of $2.22 \pm 0.52 \times 10^{-10}$, $1.38 \pm 0.36 \times 10^{-10}$, $3.24 \pm 1.45 \times 10^{-11}$, $1.72 \pm 0.48 \times 10^{-10}$ mol dm^{-3} for rat heart, rat brain; m_1 and m_3 transfected CHO cell membrane preparations, respectively. The binding studies and data analyses were carried out as previously reported using [^{3}H]QNB (QNB = quinuclidinyl benzilate).[1,2]

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§ *Crystal data*: **2b**·HCl. $C_9H_{18}ClN_3O$, $a = 6.139(3)$, $b = 11.020(5)$, $c = 15.060(6)$ Å, $\beta = 94.22(4)°$, $V = 1016(1)$ Å^3, monoclinic space group $P2_1/c$, $M = 400.0$, $Z = 4$, $D_c = 1.25$ g cm^{-3}, $F(000) = 416$, μ(Mo-Kα) = 3.3 cm^{-1}, $R = 0.046$ ($R_W = 0.059$). Data were corrected for the Lorentz and polarization effects but not for absorption. The structure was solved by direct methods and difference Fourier techniques and refined using 1482 reflections with $I \geq 2\sigma(I)$ by block-diagonal least-squares; $\sigma(I)$ were derived from counting statistics. All calculations were performed on a Data General micro-Eclipse computer using the SHELXTL system of programs. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

References

1 F. I. Carroll, P. Abraham, S. W. Mascarella, P. Singh, C. G. Moreland, S. S. Sanker, Y. W. Kwon and D. J. Triggle, *J. Med. Chem.*, 1991, **34**, 1436.
2 D. J. Triggle, Y. W. Kwon, P. Abraham, J. B. Pitner, S. W. Mascarella and F. I. Carroll, *J. Med. Chem.*, 1991, **34**, 3164.
3 R. C. Cavestri and M. Mokotoff, *J. Med. Chem.*, 1977, **20**, 1493.
4 H. M. Schwartz, W.-S. Wu, P. W. Marr and J. B. Jones, *J. Am. Chem. Soc.*, 1978, **100**, 5199.
5 J. B. Pitner, P. Abraham, Y. J. Joo, D. J. Triggle and F. I. Carroll, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1375.
6 J. T. Sprague, J. C. Tai, Y. Yuh and N. L. Allinger, *J. Comput. Chem.*, 1987, **8**, 581.
7 N. S. Zefirov and V. A. Palyulin, in *Topics in Stereochemistry*, ed. E. L. Eliel and S. H. Whilen, John Wiley, 1991, vol. 20, pp. 171–230, and references cited therein.

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