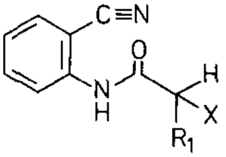
THE SYNTHESIS, SEPARATION AND STRUCTURE DETERMINATION OF TWO CONFORMERS OF 2,2-DIMETHYL-5-PHENYL-1,2-DIHYDRO-3H-1,4-BENZODIAZEPIN-3-ONE

Jan Bergman and Anna Brynolf
Department of Organic Chemistry, Royal Institute of Technology,
S-100 44 Stockholm, Sweden

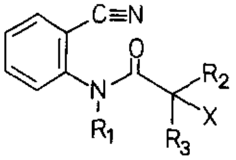
Karl-Wilhelm Törnroos, Bengt Karlsson and Per-Erik Werner
Institute of Physical, Inorganic and Structural Chemistry, Arrhenius Laboratories,
S-106 91 Stockholm, Sweden

Abstract - 3,3-Dimethyl-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-3-one has been synthetized by interaction of C_6H_5MgBr with α-bromo-α,α-dimethyl-2-cyanoacetanilide. Two conformers of the product were isolated and their structures determined by X-ray crystallography.

As reported in the preceding paper addition of RMgX or RLi to N-acylated anthranilonitriles of the general structure 1 will result in the formation of quinazolines and/or 1,4-benzodiazepines. If the acidic protons indicated in formula 1 are, partially or completely, removed by substitution (as exemplified in formula 2) different outcome of the interaction with the organometallic reagents might be expected and in this paper the results of the addition of C_6H_5MgBr to 2a will be reported.



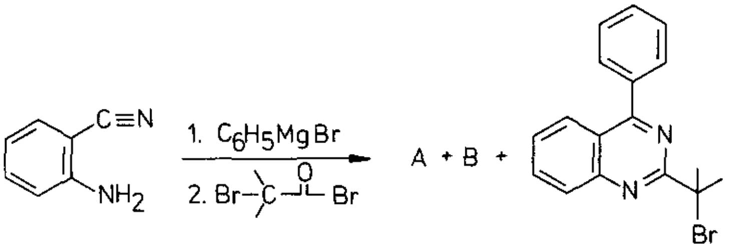
1



2 a $R_1 = H, R_2 = R_3 = CH_3$
b $R_1 = R_2 = R_3 = CH_3$

Addition of C_6H_5MgBr to 2a in ether resulted in the formation of two yellow products (A and B in the rough proportion 10:1) with identical composition ($C_{17}H_{16}N_2O$). The IR spectra were quite different[1] (A IR(KBr): 1658, 1605 cm^{-1}) (B IR(KBr): 1685, 1615 cm^{-1}). Further studies revealed that A could be completely converted into the more stable product B by reflux in CH_3CN for 30 min or by standing in solution of DMSO at 25 °C for 24 h.

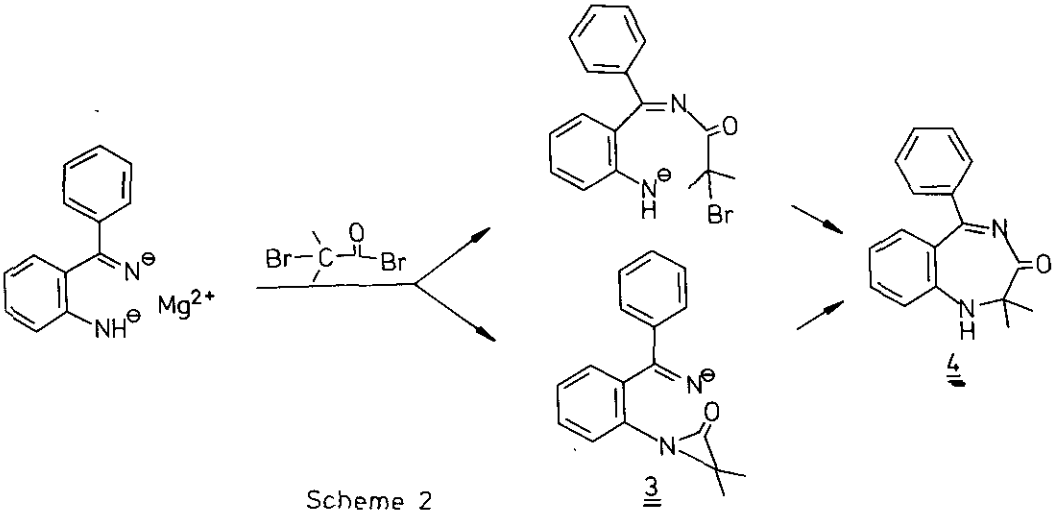
Later it was found that compounds A and B could be similarly prepared in a high combined yield (∿ 80%, relative porportion A to B ≈ 1:1) by the procedure outlined below. In addition a colourless quinazoline was formed (Scheme 1).



Scheme 1

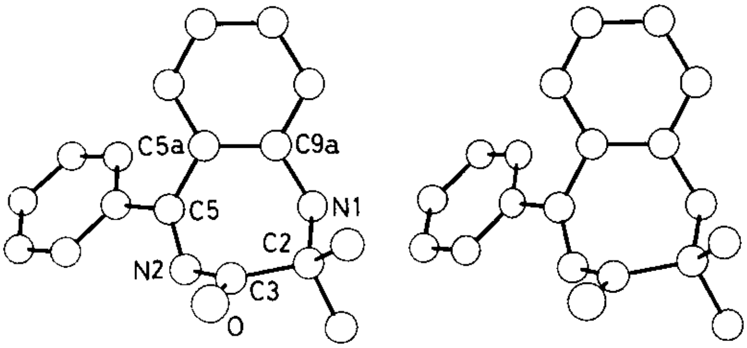
Many structures were considered and discussed for A and B and the problem was finally solved by X-ray crystallography. As can be seen from the stereopictures A and B are two conformers of 2,2-dimethyl-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-3-one rather than structural isomers. The isomer 3,3-dimethyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one was not formed at all in the described reactions (*Cf* ref. 2).

In the reaction according to Scheme 1 it seems likely that the 1,4-benzodiazepin-3-one is formed by two path-ways, one involving a rearrangement[3,4] *via* the aziridinone 3 and the other involving a direct substitution as outlined in Scheme 2.

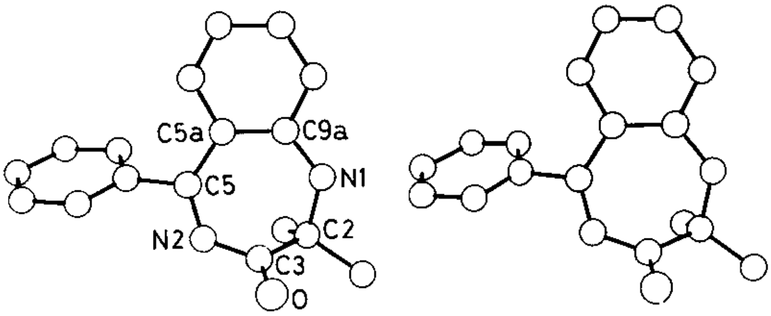


Scheme 2

Crystal data. Form A crystallizes in the orthorhombic space group $P2_12_12_1$, with the cell parameters; a = 16.600, b = 14.257, c = 5.976 Å, Z = 4, V = 1414 Å^3. Form B belongs to the monoclinic space group $P2_1$, with a = 11.645, b = 9.299, c = 6.595 Å, β = 93.16^o, Z = 2, V = 713 Å^3. Data measurements on Philips PW1100 four circle diffractometer, using graphite-monochromatized MoKα radiation, (λ = 0.7107 Å), and $\omega/2\theta$ scans. 1190 and 1935 reflections (A), $I>1.5\sigma(I)$, and (B), $I>\sigma(I)$, respectively were treated as observed. No absorption correction was applied, all measurements were carried out at room temperature. Structures were solved by direct methods using MULTAN80[5] refinement using SHELX[6] by full-matrix least-squares. All H-atoms were derived from Fourier difference maps. In Form A the non-fused benzene ring was treated as a rigid group, with individual temperature factors. H-atoms were refined riding on their respective parent atoms, all H-atoms were assigned the same isotropic temperature factor. In Form B methyls were treated as rigid groups with individual temperature factors, all nonmethyl H-atoms were refined individually. The structures[7] have been refined to R indexes of 9.3% (A), and 5.3% (B). Full details on structure determination will be published elsewhere.[8]



2,2-Dimethyl-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-3-one, conformer A.



2,2-Dimethyl-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine-3-one, conformer B.

Torsion angles[9] (°) within seven-membered ring with e.s.d.'s in parentheses

	Form A	Form B
N2-C5-C5a-C9a	43.0 (8)	22.9 (7)
C5-C5a-C9a-N1	-2.6 (8)	8.3 (7)
C5a-C9a-N1-C2	-70.5 (7)	5.6 (7)
C9a-N1-C2-C3	52.6 (6)	-54.5 (5)
N1-C2-C3-N2	34.1 (7)	83.3 (4)
C2-C3-N2-C5	-72.8 (7)	-47.6 (6)
C3-N2-C5-C5a	10.0 (8)	-14.9 (7)
C5-N2-C3-0	113.0 (8)	133.7 (7)
N1-C2-C3-0	-151.8 (7)	-98.0 (5)

REFERENCES AND NOTES

1. Conformer A IR(KBr): 3240, 3055, 2980, 1658, 1605, 1570, 1337, 1180, 760, 750 and 700 cm^{-1}; mp 195-197 °C.

   Conformer B IR(KBr): 3300, 3000, 2940, 1685, 1615, 1575, 1450, 1255, 1105, 770 and 700 cm^{-1}; mp 193-195 °C.
2. S.C. Bell, T.S. Sulkowski, C. Gochman, and S.J. Childress, *J. Org. Chem.*, **27**, 562 (1962).
3. I. Lengyel and J.C. Sheehan, *Angew. Chem. Int. Ed. Eng.*, **7**, 25 (1968).
4. A. Hassner in "Small Ring Heterocycles - Part I" in the monograph series "The Chemistry of Heterocyclic Compounds Vol. 24" Eds. A. Weissburger and E.C. Taylor, John Wiley & Sons Ltd., 1982.
5. P. Main, S.J. Fiske, S.E. Hull, L. Lessinger, G. Germain, J.P. Declercq, and M.M. Woolfson. MULTAN80, A System of Computer Programs for the Automatic Solution of Crystal Structures for X-ray Diffraction Data. Univs. of York, England, and Louvain, Belgium (1980).
6. G.M. Sheldrick. SHELX, Program for Crystal Structure Determination, Univ. of Cambridge, England (1976).
7. The atomic coordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road. Cambridge CB2 AEW, England.
8. K.W. Törnroos, B. Karlsson, P-E. Werner. To be published.
9. The angle (°) between the benzene rings is:

A	B
60.5 (3)	76.1 (4)

Received, 4th July, 1983