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SYNTHESIS OF 9-AZABICYCLONONANES FROM (Z,Z)-CYCLOOCTA-1,5-DIENE [1]

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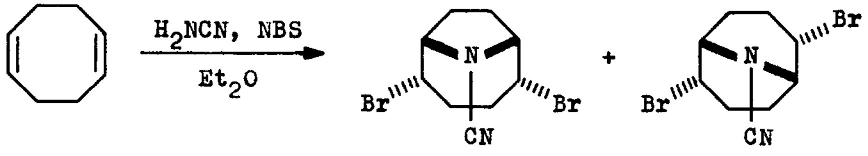
Summary: The transannular N-heterocyclization of cycloocta-1,5-diene with NBS in the presence of cyanamide is a preparative useful method for the synthesis of 9-azabicyclononanes; a mixture of endo,endo-2,5-dibromo-N-cyano-9-azabicyclo[4.2.1]nonane and endo,endo-2,6-dibromo-N-cyano-9-azabicyclo[3.3.1]nonane is obtained in high yield.

In the course of experiments designed to investigate the transannular reactivity of medium sized dienes [1,2], we got interested in the reaction of (Z,Z)-cycloocta-1,5-diene (1) with N-bromosuccinimide (NBS) in the presence of amines. But the reactions with primary aliphatic or aromatic amines were not succesful in obtaining any product of a transannular cyclization with participation of an amino group.

The formation of substituted 9-azabicyclononanes from cyclooctadiene is possible using mercury or thallium salts and primary arylamines [3-5] or N,N-dibromo-p-toluenesulfonamide in chloroform [6].

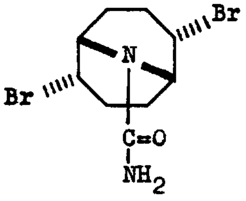
Now we found that the known [7] reaction of alkenes with cyanamide and NBS in the case of 1 (molar ratio diene/NBS 1:2) in ether at room temperature occurs with transannular participation of the initially added cyanamido group.



1 2 3

A white crystalline 50:50 mixture (80% isolated yield) of endo,endo-2,5-dibromo-N-cyano-9-azabicyclo[4.2.1]nonane (2) and endo,endo-2,6-dibromo-N-cyano-9-azabicyclo[3.3.1]nonane (3) [8,9] was obtained. Under the reaction conditions the product ratio is constant for minimal 72 h. Compound 2 (colorless needles, m.p. 107-108 °C) could be separated by several crystallizations from n-hexane, and compound 3 (colorless, fine needles, m.p. 138,5-139,5 °C) by several crystallizations of the residue from ethanol.

The stirring of the mixture of 2 and 3 (50:50) in 50% aq. sulfuric acid for 8 h at r.t. gave only one product (92% yield), the urea 4 [8] (m.p. 198-200 °C). In addition to the hydrolysis of the cyanamido group under these acidic conditions an isomerization of the 9-azabicyclo[4.2.1]nonane system to the more stable 9-azabicyclo[3.3.1]nonane system took place.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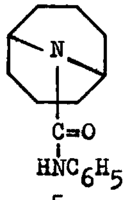
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The reduction of the mixture of 2 and 3 with $LiAlH_4$ in ether leads to an air sensitive [10] product, which could be trapped by treatment of the dried etheral solution with phenylisocyanate. An uniform product was isolated (87% yield, m.p. 193-194 °C) which was identified as the phenylurea 5 [8]. Thus, the isomerization of the 9-azabicyclo[4.2.1]nonane system also occurs in a basic medium.

References and Notes

1. Transannular Reactions of Cycloalkenes, Cycloalkadienes, and Cycloalkatrienes, Part IX. For part VIII. see G. Haufe, and M. Mühlstädt, J. Prakt. Chem. 323, 89 (1981).
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6. H. Stetter, and K. Heckel, Tetrahedron Letters 1972, 801.
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8. Satisfactory elemental analyses, MS, IR, and H-1-NMR spectra were obtained for all new compounds. Carbon-13-NMR spectra (22,63 MHz, TMS, $CDCl_3$):
   2: δ 114,0 (CN), 65,2 ($\underline{C}HN$), 51,1 ($\underline{C}HBr$), 32,2 ($\underline{C}H_2CHBr$), 27,1 ($\underline{C}H_2CHN$);
   3: δ 115,3 (CN), 55,6 ($\underline{C}HN$), 47,8 ($\underline{C}HBr$), 31,3 ($\underline{C}H_2CHBr$), 25,3 ($\underline{C}H_2CHN$);
   4 (DMSO): δ 156,4 (CO), 52,3 ($\underline{C}HN$), 49,6 ($\underline{C}HBr$), 31,4 ($\underline{C}H_2CHBr$), 25,1($\underline{C}H_2CHN$);
   5: δ 171,1 (CO), 150,4, 128,8, 122,6, 119,8 (aryl carbons, α, m, p, o), 47,2 ($\underline{C}HN$), 30,0 ($\underline{C}H_2CHN$), 20,6 (CH_2-$\underline{C}H_2$-CH_2).
9. For C-13-chemical shifts of 9-azabicyclo[4.2.1]nonane and 9-azabicyclo-[3.3.1]nonane systems cf. A. G. Anastassiou, and E. Reichmanis, J. Amer. Chem. Soc. 98, 8267 (1976); M. Barrelle, M. Apparu, and C. Gey, Canad. J. Chem. 56, 85 (1978).
10. cf. A. G. Anastassiou, and R. P. Cellura, J. Org. Chem. 37, 3126 (1972).

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