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STEREOCHEMICAL STUDIES ON 7- and 9-SUBSTITUTED 3-AZABICYCLO[3.3.1]NONANES (3-ABNs)

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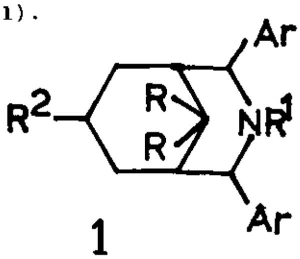
Abstract - The conformations and configurations of some 3-azabicyclo[3.3.1]nonane (3-ABN) derivatives are discussed employing C-13 nmr spectral data. The monothioketal of 2,4-diphenyl-3-ABN-9-one exists in chair-chair conformation and has the oxygen axial to the piperidine ring. The product of Reformatsky reaction of the same ABN-9-one has the OH at C-9 to the side of the piperidine ring. The chair-boat conformation is assigned to one of the isomers of 7-methyl-2,4-diphenyl-3-ABN-9-one. The conformations of a few other ABNs are also discussed.

Several 3-azabicyclo[3.3.1]nonanes (3-ABN)[1] with 2,4-diaryl substituents (1) have been synthesized[2,3] and their conformations were studied by a variety of methods[4-6] and finally established by Carbon-13 nmr spectroscopy.[7] The configurations of the epimeric 9-hydroxy-3-ABNs have been realized by the gamma-gauche effects[8,9] of the 9-substituents on the C(2,4) and C(6,8) atoms. We report in this paper the synthesis of a few new 3-ABNs and their stereochemistry by the application of C-13 nmr spectral data (Table 1).



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R=H, OH, OAc
R^1=H, Me
R^2=H, t-Bu

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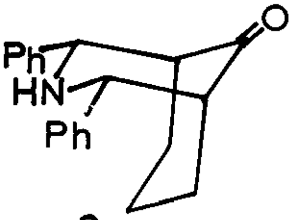
During the course of our investigations on the stereochemistry of 3-ABNs we prepared the ethylene monothioketal (**3**) from 2,4-diphenyl-3-ABN-9-one (**2**) by the reaction with 2-mercaptoethanol in the presence of boron trifluoride in ether - acetic acid mixture. Only one isomer could be isolated from this reaction. Comparison of the chemical shifts at C(6,8) with those of the diastereomeric ethylene monothioketals of 4-tert-butylcyclohexanone[10] helped assign the configuration of **3**. Relative to the corresponding carbon in tert-butylcyclohexane (27.44 ppm[11]) the upfield shift of C(3) in the isomer with the axial sulfur (**4**) is 1.60 ppm and in that with axial oxygen (**5**) it is 2.85 ppm. The upfield shift of C(6,8) in **3** relative to the corresponding carbons in the hydrogen analogue 3-azabicyclo[3.3.1]nonane (**6**) is 0.36 ppm in better agreement with a configuration involving sulfur axial to the cyclohexane ring. On the other hand, the shift of C(2,4) relative to the hydrogen analogue **6** is 5.35 ppm, in better agreement with the oxygen being axial to the heterocyclic ring. The two results agree in pointing to the configuration shown in formula 3.



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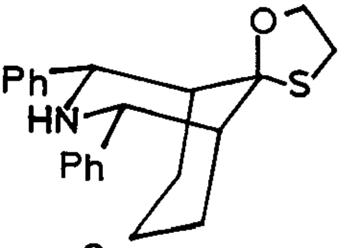

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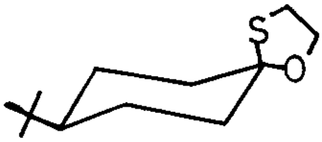

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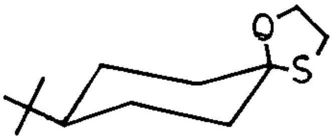

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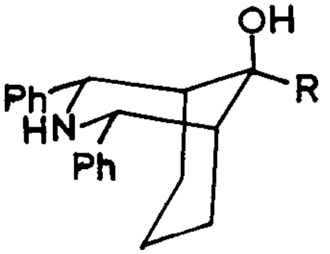
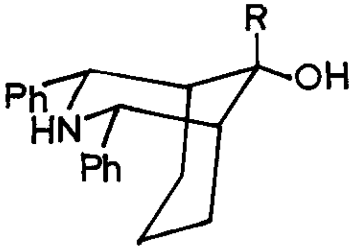
^{13}C Nmr also served to assign the configuration of the Reformatsky product (**7**) obtained from the ketone (**2**).[12] Comparison of the signals of C(2,4) and C(6,8) with those of the alcohols (**8a–d**) suggests the configuration indicated, which is the one resulting from the approach of the Reformatsky (organozinc) reagent to the less hindered side of the ketone.

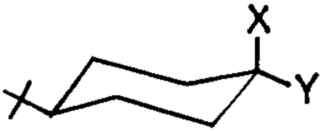


7. R=CH_2COOEt

8a. R = Ph



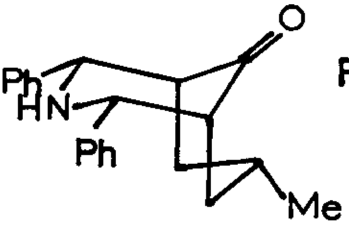
8b. R=Ph



8c. X=OH; Y=Ph

8d. X=Ph; Y=OH

The effect of an alkyl group at C(1) and C(7) position of the 3-ABN system on conformation is of interest. Introduction of a methyl substituent at the bridgehead [C(1)] position or of a *tert*-butyl group at the C(7) position does not alter the chair-chair conformation: the 3-ABN-9-ones (**2**, **10**, and **11**) are all in the chair-chair conformation. However, the 7-methyl analogue (**9**) appears to be in chair-boat form. It is interesting to note that the bulky *tert*-butyl group at C(7) does not change the conformation from chair-chair to chair-boat. The close chemical shifts of the two ketones (**2** and **10**) indicate that this does not, in fact, happen. It is of interest to note that in **11** C(1) appears at higher field (50.72 ppm) than C(5) (54.33 ppm), suggesting that the usually downfield shifting alpha-effect is reversed at the bridgehead.



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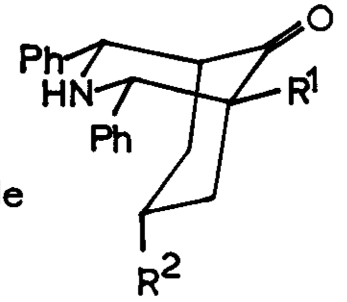
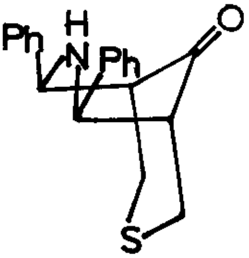


10. R^1=H; R^2=t-Bu

11. R^1=Me; R^2=H



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When a methyl group is present in the C(7) position, the lower chemical shift (213.13 ppm) of the C(9) carbonyl of the 7-methyl-3-ABN-9-one (**9**) compared with those (217.2 and 217.9 ppm) of **2** and **10** suggests that one of the two rings in **9** is in boat form causing an extra gamma-gauche effect. That it is the carbocyclic ring which assumes the boat conformation is inferred from the low field chemical shift (73.4 ppm) of the C(2,4) carbons of the 7-methyl-3-ABN-9-one (**9**) relative to the values (64.84, 64.76 ppm) of the chair-chair compounds **2** and **10**. Such a downfield shift relative to chair-chair compounds (**2** and **10**) has been seen in 7-thia-3-ABN-9-one (**12**) (after making suitable corrections for S) where the piperidine ring has been shown to exist in boat conformation (and the thianone system in chair conformation) by X-ray crystallography.[13] On the same basis if the piperidine ring existed in boat form in **9** one would expect C(6,8) at a much lower field than the observed value of 41.69 ppm. Finally the appearance of C(7) at 32.20 ppm (downfield by about 5 ppm compared to **2**, after being corrected for the alpha-effect - estimated at ca. 5 ppm - of the methyl group) may be due to the disappearance of the trans annular interaction between C(3) and C(7) when the carbocyclic ring becomes boat.

EXPERIMENTAL

The carbon-13 nmr spectra (25.16 MHz) were recorded by means of a Varian XL-100 pulsed Fourier Transform spectrometer in FT mode in 5- or 10-mm o.d. tubes in $CDCl_3$ (solvent and lock substance) containing TMS. Shift assignments (except in the case of ortho and meta carbons in the aromatic rings) were, in almost all cases, obvious from signal intensities and chemical shifts, and confirmed in some cases, from SFORD spectra.

The methods of synthesis of the azabicyclic compounds (**2**, **6**, **7**, **8a**, **8b**, and **9-12**) have been reported.[2,3,4b,12] However, an improved synthesis of the parent compound (**2**) is described here along with brief procedures for other compounds.

cis-2,4-Diphenyl-3-azabicyclo[3.3.1]nonan-9-one (**2**): The ammonium acetate required for the synthesis was moistened with a small amount of cold ethanol and filtered with suction. It was dried by keeping the crystals in a descicator containing sulphuric acid. Dry ammonium acetate (7.8 g, 0.1 mol) was added to absolute ethanol (50 ml) and stirred in a partly closed vessel till the solid dissolved. A solution of benzaldehyde (21.2 g, 0.2 mol), free from benzoic acid, dissolved in ethanol (20 ml) was added followed by the addition of cyclohexanone (9.8 g, 0.1 mol). The mixture was stirred using a magnetic stirrer in a closed vessel at room temperature, till sufficient white crystals separated. If the solution became turbid while stirring, small portions (5 - 10 ml) of fairly dry ether (kept over $CaCl_2$) were added to keep the solution clear (addition of excess of ether should be avoided, since it reduces the yield due to the better solubility of the azabicyclic compound in ether). Before the yellow crystals of the dibenzylidenecyclohexanone also started appearing (10 - 18 h) the stirring was stopped. The reaction mixture was cooled to 0 - 5 °C, the crystals were filtered and washed with cold ethanol. One or two recrystallizations from ethanol (isopropanol, benzene - hexane, ether-ethanol, methylene dichloride - hexane may also be used) produced nice shining crystals of 2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-one. It melted at 184- 185 °C. The yield after recrystallisation ranged from 25 to 45 %. Dibenzylidenecyclohexanone could be obtained from the mother liquor by the addition of conc. HCl (15 ml) and stirring the mixture for 1 - 2 h. The yield of the conjugated ketone was 20 - 40 %. Tlc analysis and other analytical methods at various stages of the reaction showed that no trace of trans-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-one was formed. The recrystallized azabicyclic compound can be stored for several months without change in the purity. On long standing at room temperature the material gradually becomes yellow due to the formation of dibenzylidenecyclohexanone. Old samples are recrystallized before use and dried.

1-Methyl-3-azabicyclo[3.3.1]nonan-9-one (**11**: This ketone was prepared according to the procedure given above for **2** using 2-methylcyclohexanone instead of cyclohexanone; yield 35-40 %; mp 120-121 °C (lit.[3] mp 119-121 °C).

7-Methyl-3-azabicyclo[3.3.1]nonan-9-one (**9**): Use of 4-methylcyclohexanone for the condensation gave **9**; yield 10-15 %; mp 204-205 °C (lit.[3] mp 203-205 °C).

Monothioketal of 2,4-diphenyl-3-ABN-9-one (**3**): To a solution of the bicyclic ketone (**2**) (0.01 mol) in acetic acid (100 ml), mercaptoethanol (1.0 ml) and boron trifluoride (3 ml) in acetic acid (3 ml) were added and the mixture was kept at room temperature for two days. Excess of water containing ammonia was added till the solution was ammoniacal and the crystals separated were collected and washed with methanol. The product was recrystallized from 95 % ethanol. mp 173-175 °C; Yield 75-85 %. Anal. Calcd $C_{22}H_{25}NOS$ C:78.18; H:7.17. Found C:78.36, H:7.64. Mass spectrum m/z 351.

Ethyl 2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-acetate (**7**): To a solution of 2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-one (**2**) (15 g, 0.05 mol) purified zinc wool (8g, 0.12 mol), a bit of iodine, and ethyl bromoacetate (10 ml, 0.15 mol) were added and kept under reflux for 8-10 h. The mixture was poured into ice-sulfuric acid mixture (2N). Excess 10 % NaOH solution was added till most of the zinc hydroxide went into solution, the organic layer separated, aqueous layer extracted with benzene and the combined benzene extracts were washed with water and dried over anhydrous Na_2SO_4. The product obtained was recrystallized to obtain pure **7**; yield 35 %; mp 149-51 °C (lit.[12] mp 149-150 °C).

Table 1. Carbon-13 Nmr Chemical Shifts of 3-Azabicyclo[3.3.1]nonane derivatives

Compound	C(1)	C(2)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	Substituents
2	54.0	64.8	64.8	54.0	29.0	21.2	29.0	217.2	
3	46.9	60.1	60.1	46.9	25.8	20.4	25.8	100.8	OCH_2 69.11; SCH_2 32.55
6	35.2	65.4	65.4	35.2	26.1	22.1	26.1	37.2	
7	44.4	58.2	58.2	44.4	23.0	20.1	23.0	73.6	
8a	42.9	58.7	58.7	42.9	23.6	20.7	23.6	75.8	
8b	42.4	60.7	60.7	42.4	21.0	20.0	21.0	75.1	
9	56.8	73.4	73.4	56.8	41.7	32.2	41.7	213.1	Me 20.9
10	53.7	64.8	64.8	53.7	30.0	40.6	30.0	217.9	C 32.6; Me 27.0
11	50.7	71.2	64.9	54.3	29.0	21.4	36.8	217.1	Me 20.3
12	55.1	63.6	63.6	55.1	37.4	-	37.4	212.8	

Table 2. Carbon-13 Nmr Chemical Shifts of 4-*tert*-Butylcyclohexane Derivatives

Compound	C(1)	C(2)	C(3)	C(4)
4	97.7	40.1	26.1	47.6
5	93.8	40.0	24.5	47.7
8c	72.7	39.3	22.8	47.5
8d	73.2	38.7	24.9	47.6

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