of **1b**: mp 98–99 °C (*n*-hexane); colorless needles; IR ($CHCl_3$) 1755 cm^{-1}; mol wt (by vapor pressure osmometry in $CHCl_3$) 226 (calcd 224). Anal. Calcd for $C_{12}H_{20}N_2O_2$: C, 64.25; H, 8.99; N, 12.49. Found: C, 64.52; H, 9.07; N, 12.51. The liquid fraction consisted mainly of **7b** and small amounts of **1b**.

1,7-Diisocyanatoheptane (7c) was obtained in 84% yield [11.5 g; bp 75–78 °C (0.01 mm); identical on IR comparison with an authentic sample prepared according to a published procedure[17]] from 16.45 g (0.525 mol) of **6c** and 20 g (0.2 mol) of triethylamine in 200 mL of chloroform within 18 h at room temperature.

Registry No. 1a, 79568-33-5; **1b**, 79568-34-6; **4a**, 72995-04-1; **4b**, 79568-35-7; **4c**, 6543-91-5; **5a**, 79568-36-8; **5b**, 79568-37-9; **5c**, 79568-38-0; **6a**, 79568-39-1; **6b**, 79568-40-4; **6c**, 79568-41-5; **7a**, 78980-33-3; **7b**, 4538-39-0; **7c**, 18020-78-5.

Synthesis and Structural Assignments for ("1*R*-*anti*")- and ("1*R*-*syn*")-1-(2-Chlorophenyl)-6-methyl-6-azabicyclo[3.1.1]heptan-7-ol

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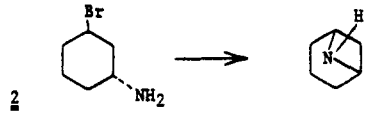
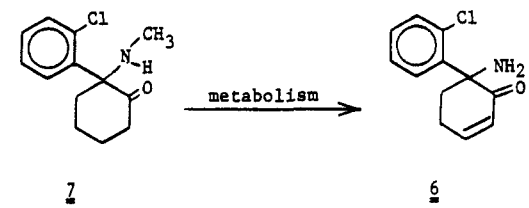
The only reported example of the 6-azabicyclo[3.1.1]-heptane ring system is the parent compound 1 reported by von Braun et al. in 1928.[1] It was prepared by an intramolecular displacement of bromine from *trans*-3-bromocyclohexanamine (2, eq 1).



2 1 (1)

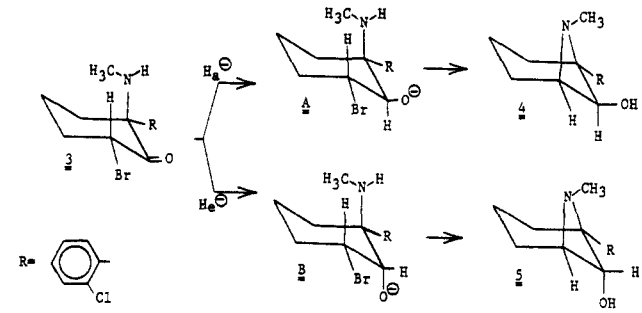
As part of our attempt to synthesize metabolite II (6)[6] of ketamine (7,[2] Scheme I), a sodium borohydride reduction was carried out on 2-bromo-6-(2-chlorophenyl)-6-(methylamino)cyclohexanone (3). This reaction gave a mixture of the title compounds (4 and 5). The bromine substituent of 3 had been previously established as having the equatorial conformation.[3] Therefore, the delivery of a hydride ion axial or equatorial at the carbonyl carbon

Scheme I



7 6

Scheme II

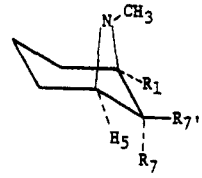


leads to the formation of the alkoxide anions A and B, respectively (Scheme II). The resulting change in hybridization at C-1 from sp^2 to sp^3 alters the overall conformation of the molecule, allowing the electrons on nitrogen to displace bromine in an intramolecular S_N2 reaction. Subsequent protonation of the anions afforded a mixture of the two isomers (4 and 5) which were separated by fractional crystallization.

Initial structural assignments can be made by analogy with the bicyclo[3.1.1]hept-2-ene[4] and bicyclo[3.1.1]heptane[5] ring systems which have been previously described. These workers have established that the coupling constant for $H_{5,7}$ is very small ($J \simeq 0$ Hz) while that of $H_{5,7'}$ is comparatively large ($J \simeq 6$ Hz). The parameters describing the pertinent protons of the two aza isomers of the bicyclo[3.1.1]heptane ring system are summarized in Table I.

A deuterium oxide exchange established the position of the labile hydroxy protons and their effect on the multiplicity of the other protons in the spectrum. This essentially established the structural assignments for the two isomers since the proton in 4 at δ 2.68 (d, 1 H, J = 9 Hz) was exchanged and the proton at δ 4.63 (d, 1 H, J = 9 Hz) collapsed to a singlet. This strongly indicated that the

Table I. Some ^{1}H NMR Data of the Two Aza Isomers 4 and 5



4 ($R_{7'}$ = OH, R_7 = H)		5 ($R_{7'}$ = H, R_7 = OH)	
atom	shift, δ	atom	shift, δ
H_5	3.48 (unresolved m, 1 H)	H_5	3.73 (m, 1 H)
R_7 H	4.63 (d, 1 H, J = 9 Hz)	$R_{7'}$ H	4.40 (d, 1 H, J = 6 Hz)
$R_{7'}$ OH	2.68 (d, 1 H, J = 9 Hz)	R_7 OH	2.67 (s, 1 H)

(1) van Braun, J.; Haensel, W.; Zobel, F. *Justus Liebigs Ann. Chem.* **1928**, *462*, 283. Another report (Beck, I.; Rakoczi, J.; Bolla, K.; Porszasz-Gibiszer, K. German Offen. 2 528 194; *Chem. Abstr.* **1976**, *85*, 46439) discusses (benzhydryloxy)alkylamine derivatives and cites a 9-azabicyclo[3.1.1]heptan-9-yl derivative which may be another example.
(2) Stevens, C. L.; Belgian Patent 634 208, 1963; *Chem Abstr.* **1964**, *61*, 5569*d*.
(3) Parcell, R. F.; Sanchez, J. P., submitted for publication.
(4) Kaplan, F.; Schulz, C. O.; Weisleder, D.; Klopfenstein, C. *J. Org. Chem.* **1968**, *33*, 1728.
(5) Bates, R. B.; Thalacker, V. P. *J. Org. Chem.* **1968**, *33*, 1730.
(6) Chang, T.; Dill, W.; Glazko, A. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1965**, *24*, Abstract 770.

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hydroxyl in 4 is in the 7'-positon since the J value for $H_{5,7}$ is very small. A deuterium exchange on compound **5** removed the proton at δ 2.67 (s, 1 H), with the rest of the spectrum remaining unchanged. Additional evidence for the assignments is provided by spin-decoupling experiments performed on the deuterium-exchanged samples. Irradiation of the proton at δ 3.48 (unresolved m, 1 H) in compound **4** had no effect on the proton at δ 4.63 (s, 1 H). However, irradiation of the proton at δ 3.73 (m, 1 H) in compound **5** caused the proton at δ 4.40 (d, 1 H, J = 6 Hz) to collapse to a singlet. The deuterium-exchange and spin-decoupling experiments in conjunction with the previous publications on the corresponding carbocyclic systems leads us to assign the designated structure for the two azaisomers. This is important because it not only reconfirms the conformational assignment for the bromo ketone **3** but also establishes an entry into the azabicyclo[3.1.1] ring system and shows good agreement with the NMR data previously reported for the carbocyclic system.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Digilab FTS-14 or Beckman IR9 prism grating dispersion instrument. ^1H nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM-390 or Bruker WH-90 instrument. The Bruker WH-90 was modified with a Nicolet Technology Corp. B-NC12 data acquisition system. Chemical shifts are reported in parts per million from internal tetramethylsilane. Combustion analyses were performed on a Perkin-Elmer 240 elemental analyzer. Solutions were dried with magnesium sulfate and concentrated on a rotary vaporator at 30–40 °C at pressures of 5–20 mmHg. Isolated solids were dried in a vacuum oven at room temperature and pressures of 5–20 mmHg.

[1*R*-(1α,5α,7*S)]-1-(2-chlorophenyl)-6-methyl-6-azabicyclo[13.1.1]heptan-7-ol ("1*R*-*anti*") (4).** To a stirred solution of 17.0 g (54 mmol) of 2-bromo-6-(2-chlorophenyl)-6-(methylamino)cyclohexanone (**3**),[3] 300 mL of EtOH, and 125 mL of THF was added 7.0 g (185 mmol) of $NaBH_4$. The reaction was exothermic to 40 °C for 0.5 h and was then refluxed for 2 h. The solvent was removed and the residue dissolved in Et_2O and H_2O. The aqueous layer was extracted with Et_2O, and the combined Et_2O layers were washed with H_2O, dried, filtered, and evaporated at room temperature to a semicrystalline product. The oil was dissolved away from the less soluble crystals with a minimum of Et_2O, and the crystals were removed by filtration to give 7.0 g (55%) of crystalline **4**, mp 168–172 °C. Two recrystallizations from toluene afforded the analytical sample: 6.5 g; mp 170–172 °C; IR (CCl_4) 3580 cm^{-1} (OH); NMR ($CDCl_3$) δ 2.18 (m, 6 H), 2.46 (s, 3 H), 2.68 (d, 1 H, J = 9 Hz), 3.48 (m, 1 H), 4.63 (d, 1 H, J = 9 Hz), 7.32 (m, 4 H). Anal. Calcd for $C_{13}H_{16}ClNO$: C, 65.67; H, 6.79; N, 5.89. Found: C, 65.49; H, 6.58; N, 5.94.

[1*R*-(1α,5α,7*R)]-1-(2-chlorophenyl)-6-methyl-6-azabicyclo[3.1.1]heptan-7-ol ("1*R*-*syn*") (5).** The combined mother liquors from the isolation of **4** were concentrated and crystallized to give 3.5 g (28%) of **5**, mp 105–111 °C. Two recrystallization from cyclohexane/petroleum ether afforded the analytical sample: 3.1 g; mp 110–112 °C; IR (CCl_4) 3620 cm^{-1} (OH); NMR ($CDCl_3$) δ 2.18 (m, 6 H), 2.48 (s, 3 H), 2.67 (s, 1 H), 3.73 (m, 1 H), 4.40 (d, 1 H, J = 6 Hz), 7.28 (m, 4 H). Anal. Calcd for $C_{13}H_{16}ClNO$: C, 65.67; H, 6.79; N, 5.89. Found: C, 65.39; H, 6.67; N, 5.78.

Acknowledgment. We are grateful to Dr. Forrest MacKellar and the personnel of the Physical and Microanalytical Sections for obtaining spectra and analyses and above all for the many helpful discussions.

Registry No. 3, 79466-76-5; 4, 79466-77-6; 5, 79516-84-0.

Study of the Neber Rearrangement of 2-Phenylcyclohexanone Dimethylhydrazone Methiodide. An Alternative Ylide Pathway Leading to the Formation of Mannich Products

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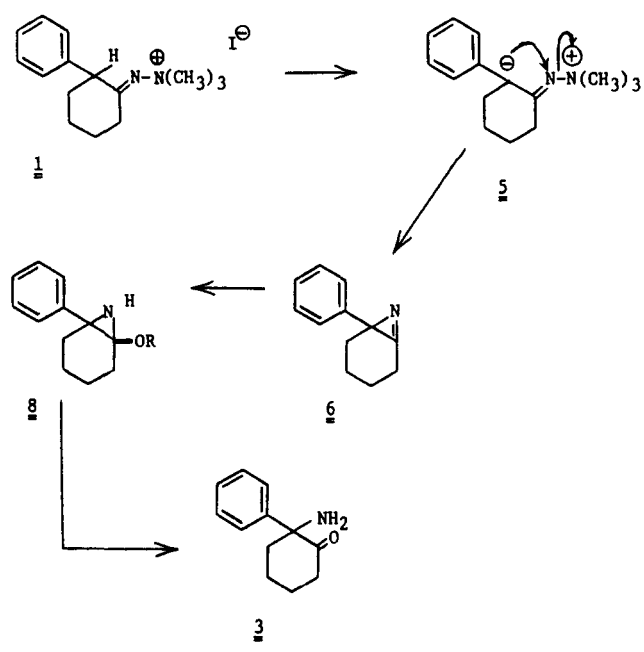
The Neber rearrangement[1] of dimethylhydrazone quaternary salts to α-amino ketones is a well-studied reaction.[2] However, when this reaction was carried out at temperatures below those of normal Neber conditions[3] by using the methiodide of 2-phenylcyclohexanone dimethylhydrazone (**1**), varying amounts of 2-phenylcyclohexanone (**2**)[4] and the Mannich product (**4**) arising from this ketone were isolated (Schemes I and II). By varying the reaction conditions, the normal Neber product could be made to predominate. This paper discusses the mechanism for the formation of these unusual products not normally observed in Neber rearrangements.

The mechanism proposed by House and Berkowitz[5] for the Neber rearrangement of oxime tosylates involves a nitrene intermediate. This proposed mechanism is con-

Scheme I



(1) Neber, P. W.; Friedolsheim, A. *Justus Liebigs Ann. Chem.* **1926**, *449*, 109 (1926). Neber, P. W.; Burgard A. *Ibid.* **1932**, *493*, 281. Neber, P. W.; Burgard, A.; Thier, W. *Ibid*, **1936**, *526*, 277. Hatch, M. J. and Cram, D. J. *J. Am. Chem. Soc.*, **1953**, *75*, 33. Hatch, M. J.; Cram, D. J. *Ibid.* **1953**, *75*, 38. O'Brien, C. *Chem. Rev.* **1964**, *64*, 81.

(2) (a) Smith, P. A. S.; Most, E. E. *J. Org. Chem.* **1957**, *22*, 358. (b) Parcell, R. F. *Chem. Ind. (London)* **1963**, 1396. (c) Morrow, D. F.; Butler, M. E. *J. Heterocycl. Chem.* **1964**, *1*, 53. (d) Morrow, D. F.; Butler, M. E.; Huang, E. C. Y. *J. Org. Chem.* **1965**, *30*, 579. (e) Leonard, N. J.; Zwanenburg, B. *J. Am. Chem. Soc.* **1967**, *89*, 4456.

(3) Neber rearrangements of dimethylhydrazone quaternary salts are normally run by adding the methiodides portionwise as a dry powder to refluxing alcohol containing excess alkoxide ion (see ref 2a–e).

(4) Morrow and co-workers have also isolated starting ketone from the Neber rearrangement of the dimethylhydrazone methiodide of pregnenolone. These workers felt that the pathway by which this ketone arises to be unclear since the use of various anhydrous alcohols made very little difference in the amount of ketone formed (see ref 2d).

(5) House, H. O.; Berkowitz, W. F. *J. Org. Chem.* **1963**, *28*, 307, 2271.

0022-3263/81/1946-5229$01.25/0