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.

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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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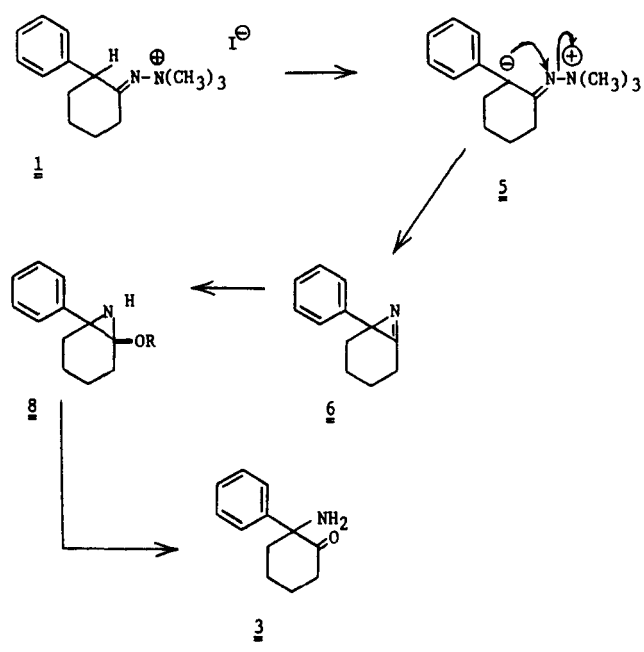
The Neber rearrangement[1] of dimethylhydrazone quaternary salts to α-amino ketones is a well-studied reaction.[2] However, when this reaction was carried out at temperatures below those of normal Neber conditions[3] by using the methiodide of 2-phenylcyclohexanone dimethylhydrazone (**1**), varying 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.

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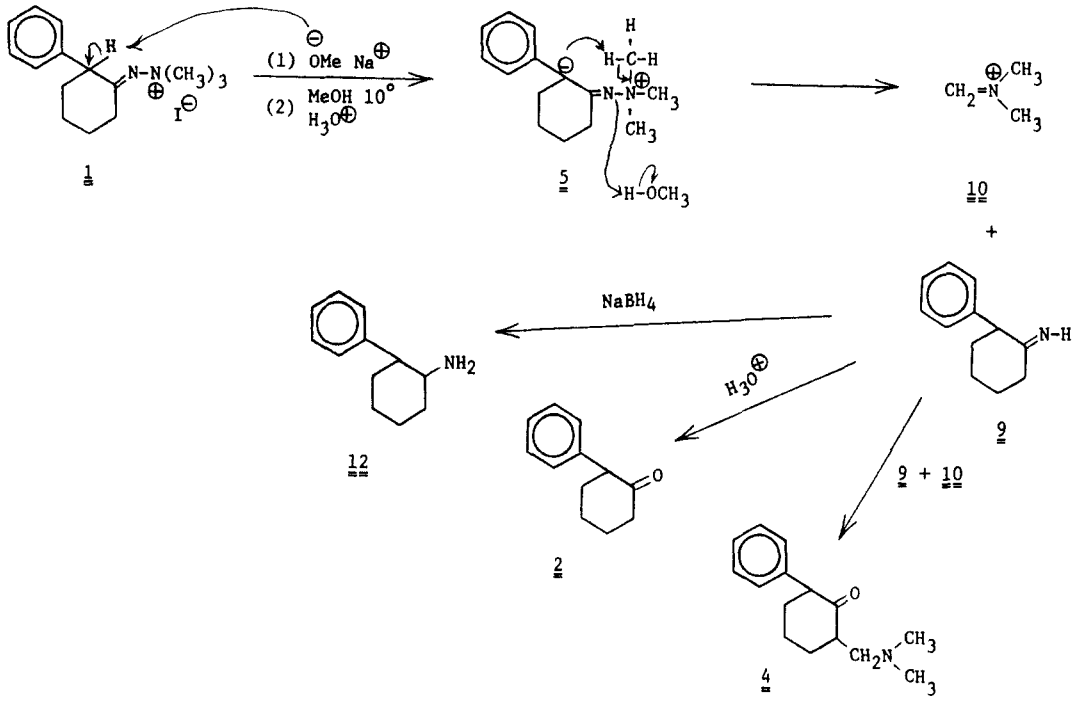
Scheme II



sistent with the intermediates isolated by Parcell in his work with dimethylhydrazone quaternary salts.[2b] If the proposed mechanism is applied to our system, the formation of the normal Neber product should begin with the abstraction of the benzylic proton from 1 (Scheme I) to form the carbanion 5. This carbanion would then displace trimethylamine to produce the azirine 6. Further reaction of the azirine would presumably proceed through the previously isolated intermediates[2b] with the alkoxyaziridine 8 forming the α-amino ketone 3 upon aqueous acid hydrolysis.

By taking these previous mechanistic studies into consideration, it was felt that by varying the reaction conditions the pathway by which 2 and 4 arise could be established.

The reaction of a methanolic suspension of 1 with sodium methoxide at 10 °C afforded a 37% yield of 2. Preliminary experiments ruled out hydrolysis of the quaternary hydrazonium salt 1 to the initial ketone 2. These experiments included solution in water for 24 h, solution in aqueous methanol for 24 h, solution in aqueous acid for 24 h, and solution in anhydrous methanol with methoxide for 3 h. Hydrolysis in methanol with methoxide and a trace amount of water produced a detectable (IR) amount of hydrolysis after 0.5 h.

The acid-soluble portion from the isolation of 2, isolated as the hydrochloride salt, was not 2-amino-2-phenylcyclohexanone (3), the expected Neber product, but was instead 2-[(dimethylamino)methyl]-6-phenylcyclohexanone (4) which is the product from a Mannich reaction of 2.[6] This indicates that there must be an alternate ylide pathway which does not involve the formation of a nitrene or azirine intermediate.

One mechanism which is consistent with the observed results involves the formation of the benzyl carbanion 5 followed by the abstraction of a proton from one of the methyl groups on nitrogen in a six-centered cyclic transition state (Scheme II). Cleavage of the hydrazone nitrogen–nitrogen bond would give the imine of 2-phenylcyclohexanone (9) and the Mannich iminium salt 10. Electrophilic attack by this salt on the imine 9 or ketone 2, present from the hydrolysis of 9, leads to the formation of 4. Hydrolysis of unreacted 9 affords the initial starting material 2.

For further elucidation of the mechanism, it was decided to attempt to trap the reaction intermediates. The reaction was performed as previously described except that instead of acidification as in the previous workup, sodium borohydride was added in an attempt to reduce the proposed intermediate 9. The major compound isolated (48%) was 2-phenylcyclohexanamine (12),[7] thus establishing the imine 9 as an intermediate in the low-temperature reaction. Since 2-[(dimethylamino)methyl]-6-phenylcyclohexanamine was not observed in the reductive workup of the low-temperature reaction, it seems probable that the Mannich reaction occurs after the addition of aqueous acid either on the protonated imine or the ketone 2.

The proposed mechanism is therefore consistent with the observed results and accounts for the origin of Mannich products from an attempted Neber rearrangement.

The maximum yield (74%) of the desired Neber product (3) was achieved by heating a solution of sodium ethoxide in ethanol to reflux and adding the quaternary salt 1 portionwise as the solid. The isolated yield of neutral product 2 in this case was only 16%.

The requirement of a higher reaction temperature to obtain normal Neber products in this case may be due to the need to overcome the stereochemical integrity of the initially formed anion (5), allowing a conformation to arise which then leads to the normal Neber products.

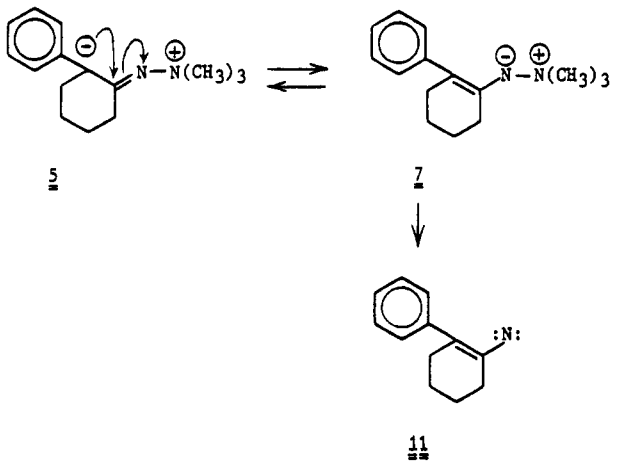
Since the anion 5 has an alternative resonance structure, 7 (Scheme III), inversion at nitrogen can give rise to either the syn or the anti configuration for the intermediate 5.

The Neber rearrangement can proceed by way of a high-temperature, concerted elimination of trimethylamine

(6) Bachmann, W. E.; Wick, L. B. *J. Am. Chem. Soc.* **1950**, *72*, 3388.

(7) Cristol, S. J.; Stermitz, F. R. *J. Am. Chem. Soc.* **1960**, *82*, 4692. Masamune, T.; Ohno, M.; Koshi, M.; Ohuchi, S.; Iwadare, T. *J. Org. Chem.* **1964**, *29*, 1419.

Scheme III



from the anion **5** in the anti configuration or via an intermediate vinyl nitrene **11** (Scheme III). The abstraction of a proton from one of the quaternary methyls by the anion **5**, in the syn configuration, would proceed as in Scheme II to produce the Mannich products. It is evident from the conditions necessary to produce the two synthetic sequences (Schemes I and II) that the concerted elimination of the neutral nucleophile, trimethylamine, is a higher energy process than the proposed route which produces the Mannich products.

Experimental Section

1,1,1-Trimethyl-2-(2-phenylcyclohexylidene)hydrazinium Iodide (1). To a solution of 389 g (1.8 mol) of 2-phenylcyclohexanone dimethylhydrazone[8] in 450 mL of CH_3CN was added 300 g (2.11 mol) of CH_3I. The reaction was exothermic to 43 °C over 2 h and was then heated to 70 °C for 3 h and cooled to room temperature. The crystalline mixture was diluted with 2 L of anhydrous Et_2O and cooled to 5 °C. The solid was removed by filtration, washed with Et_2O/CH_3CN (5:1), and dried to give 489 g (76%) of **1**, mp 165–167 °C. One recrystallization from $MeOH/Et_2O$ afforded the analytical sample, mp 166–167 °C. Anal. Calcd for $C_{15}H_{23}N_2I$: C, 50.28; H, 6.47; N, 7.82. Found: C, 50.39; H, 6.40; N, 7.85.

2-Phenylcyclohexanone (2). To a 5 °C suspension of 200 g (0.56 mol) of **1** in 400 mL of MeOH was added portionwise 0.56 mol of NaOMe in 150 mL of MeOH with the temperature maintained below 10 °C. After the addition was complete, the suspension was allowed to come to room temperature and then heated to 40 °C to complete solution. The solution was then recooled to 5 °C, and 400 mL of 3.0 M HCl was added, keeping the temperature below 10 °C. The MeOH was removed in vacuo, and the aqueous acid layer was extracted with Et_2O (3 × 250 mL). The combined Et_2O layers were dried, filtered, and evaporated to give 35.8 g (37%) of **2**, mp 54–55 °C. The IR and ^1H NMR were identical with those of an authentic sample.[9]

2-[(Dimethylamino)methyl]-6-phenylcyclohexanone (4). The aqueous acid fraction from the isolation of **2** was made basic with 50% NaOH and extracted with Et_2O (3 × 250 mL). The combined Et_2O layers were washed with H_2O, dried, and concentrated, and the residue was converted to its hydrochloride salt by using 2-propanolic hydrogen chloride. The yield of **4** was 54 g (36%), mp 164–168 °C. One recrystallization from $MeOH/Et_2O$ afforded the analytical sample, mp 165–168 °C. The IR and ^1H NMR were identical with those of an authentic sample prepared by the Mannich reaction of **2**.[6] Anal. Calcd for $C_{15}H_{21}NO\cdot HCl$: C, 67.27; H, 8.28; N, 5.23. Found: C, 67.01; H, 8.39; N, 5.07.

2-Phenylcyclohexanamine (12). The reaction was run in a manner identical with that for the preparation of **2** to the point where the reaction was recooled to 5 °C. At this point, 21 g (0.56 mol) of $NaBH_4$ was added portionwise, with the temperature kept below 10 °C. The reaction mixture was stirred for 2 h, poured into 500 mL of 5% NaOH, and extracted with Et_2O (2 × 500 mL). The combined Et_2O layers were extracted with 5% HCl (3 × 100 mL). The neutral Et_2O layer was dried, filtered, and evaporated to give 10 g of an inseparable mixture of five compounds as indicated by TLC. The aqueous acid layers were made basic with 50% NaOH and extracted with Et_2O (4 × 150 mL). The combined Et_2O layers were washed with H_2O, dried, filtered, and evaporated, and the residue was distilled to give 46.5 g (48%) of a mixture of the cis and trans isomers of **12**, bp 70–73 °C (0.12 mm). A sample was converted to the hydrochloride salt by using 2-propanolic hydrogen chloride, mp 225–230 °C. No effort was made to separate the isomers, but two recrystallizations (from MeOH/*i*-PrOH afforded the analytical sample: mp 237–240 °C;[7] IR (KBr) 3420 cm^{-1} ($NH_2\cdot HCl$); NMR (Me_2SO-d_6) δ 1.16–2.31 (m, 8 H), 2.65–3.51 (m, 2 H), 7.10–7.28 (m, 5 H), 7.62–7.93 (s, 3 H). The broad singlet at δ 7.62–7.93 (s, 3 H) could be exchanged with deuterium oxide. Anal. Calcd for $C_{12}H_{17}N\cdot HCl$: C, 68.09; H, 8.57; N, 6.61. Found: C, 67.79; H, 8.43; N, 6.31.

2-Amino-2-phenylcyclohexanone (3).[10] To a solution of 0.66 mol of NaOEt in 500 mL of EtOH at 80 °C was added portionwise as a dry powder 209 g (0.58 mol) of **1**. The mixture was refluxed for 1 h, cooled to 15 °C, and treated portionwise with 250 mL of 4.0 M HCl, with the temperature kept below 25 °C. The reaction was concentrated in vacuo, and the residue diluted with H_2O and extracted with Et_2O. The Et_2O layer was dried, filtered, and evaporated, with the crystalline residue being recrystallized from petroleum ether to give 15.8 g (16%) of **2**, mp 54–55 °C. The aqueous acid layer was made basic with 50% NaOH and extracted with Et_2O (2 × 500 mL). The combined Et_2O layers were washed with H_2O, dried, filtered, and concentrated, and the residue was distilled to give 82 g (74%) of **3**: bp 107–110 °C (1.3 mm); IR (film) 3300, 3360 cm^{-1} (NH_2), 1716 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.44–2.17 (m, 5 H), 1.87 (s, 2 H), 2.26–2.59 (m, 2 H) 2.65–3.06 (m, 1 H), 7.14–7.58 (m, 5 H). A sample converted to its hydrochloride salt by using 2-propanolic hydrogen chloride and recrystallized from *i*-PrOH/MeOH had a melting point of 233–234 °C. Anal. Calcd for $C_{12}H_{15}NO\cdot HCl$: C, 63.85; H, 7.15. Found: C, 63.56; H, 6.96.

Registry No. **1**, 56062-76-1; **2**, 1444-65-1; **3**, 7015-50-1; **3**·HCl, 7015-20-5; **4**·HCl, 52955-93-8; **12**·HCl, 22720-50-9; *cis*-**12**, 22147-09-7; *trans*-**12**, 1011-11-6; 2-phenylcyclohexanone dimethylhydrazone, 5758-09-8.

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Ring Opening of Oxiranes by *I,I*-Bis(trifluoroacetoxy)iodobenzene

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The propensity of oxiranes to undergo ring-opening reactions is well-known.[1] We report here on the reaction of *I,I*-bis(trifluoroacetoxy)iodobenzene[2] (**2**, abbreviated

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