It is often difficult to ascribe proton chemical shifts to specific structural features of a molecule. If the deshielding of $H_{B'}$ is indeed due to steric compression, one would expect to see an upfield shift in the ^{13}C NMR signal for the methyl group involved. With this in mind we have measured the ^{13}C spectrum of ketone **13** and assigned the methyl signals with the aid of off-resonance decoupling. The positions of the methyl groups ($\delta_{\mathrm{Me_4Si}}$ 21.0 and 22.1) are comparable to those of similarly situated groups in norbornanes.[8] This result is consistent with a moderate steric effect for each methyl group, but the near identity of the chemical shifts of these two signals fails to provide evidence for an unusually severe steric interaction of one methyl group with the one-carbon bridge. It is then not certain that the deshielding of $H_{B'}$ is simply the consequence of steric compression.

Before obtaining and comparing all these data, we found some of our early spectra puzzling and some assignments of sterochemistry uncertain. These ambiguities were removed, however, on examination of the entire set of results. We believe that these observations make a useful addition to those spectral correlations already available and that they should facilitate future stereochemical assignments in related bicyclo[2.1.1]hexanes.

Experimental Section

The spectra of **4–7** and **9–13** were recorded for dilute CCl_4 solutions of samples purified by vapor-phase chromatography and with a Varian Model HR-220 (220 MHz, Fourier transform mode), a Varian Model T-60, or the 600-MHz spectrometer at Carnegie-Mellon University.[3,9]

Registry No. 1, 20441-29-6; 2, 32426-60-1; 3, 32426-61-2; 4, 72867-93-7; 5, 72867-94-8; 6, 72904-13-3; 7, 72867-95-9; 8, 72867-96-0; 9, 72867-97-1; 10, 6040-45-5; 11, 72867-98-2; 12, 72904-14-4; 13, 72904-15-5.

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(6) Haywood-Farmer, J.; Malkus, H.; Battiste, M. *J. Am. Chem. Soc.* **1972**, *94*, 2209 and references cited therein.

(7) Our cursory comparison of reported chemical shift data for exo protons in various norbornanes and bornanes has revealed no consistent pattern in the effect of similar methyl substitution in the bicyclo[2.2.1]heptane system.

(8) Grutzner, J. B.; Jautelat, M.; Dence, J. B.; Smith, R. A.; Roberts, J. D. *J. Am. Chem. Soc.* **1970**, *92*, 7107.

(9) This research was supported by grants from the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society. We thank Dr. D. H. Live and Mr. W. M. Wittbold, Jr., for expert assistance.

4-(Dichloromethyl)-4-methyl-2,5-cyclohexadien-1-one Phenylhydrazone. Reaction with Bases and Conversion to 5-Methyl-2-phenyl-2*H*-indazole

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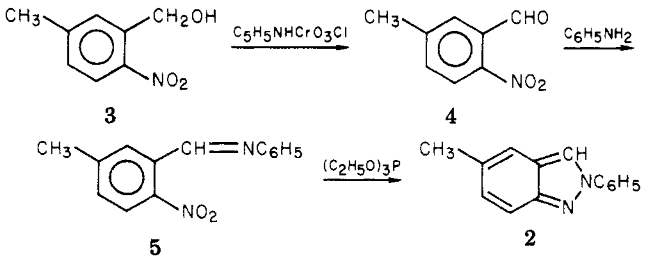
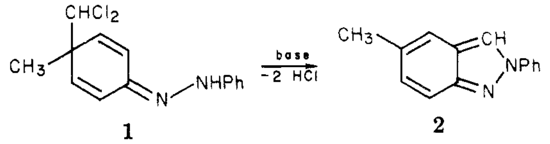
Received July 6, 1979

Schiff bases derived from 4-(dichloromethyl)-4-methyl-2,5-cyclohexadien-1-one undergo a reaction with primary amines in which the dichloromethyl group is cleaved from the molecule, and the remaining moiety is converted to a secondary amine.[1] The azine undergoes loss of both dichloromethyl groups and is converted to *p,p'*-azotoluene when heated with diglyme.[2] Similar loss of the dichloromethyl group occurs when the parent ketone itself is heated with secondary amines, a tertiary amine being the chief product.[3] The dienone also reacts with alkalies to give tars from which a very small yield of 5-methylsalicylaldehyde has been isolated.[4] We now report an unusual reaction of 4-(dichloromethyl)-4-methyl-2,5-cyclohexadien-1-one phenylhydrazone (**1**) with certain bases in which the dichloromethyl group is not cleaved but is rearranged. The net reaction involves the loss of two molecules of hydrochloric acid and the formation of 5-methyl-2-phenyl-2*H*-indazole (**2**). The product mixture is complex and tarry, and the conversion of **1** to **2** is moderate at best, exceeding 30% only in the most favorable case, i.e., with hydroxide ion under phase-transfer-catalysis conditions. Yields of 10% can be isolated by crystallization.

Scheme I





The indazole **2**, previously undescribed, was identified by its spectral properties and elemental analysis. Of particular use in the structure determination was the marked downfield shift of the proton at position 3, a characteristic noted in the NMR spectra of other 2*H*-indazoles.[5] An independent synthesis starting from 5-methyl-2-nitrobenzyl alcohol (**3**, Scheme I) confirmed the assigned structure.

The influence of various bases and conditions on the conversion of **1** to **2** was studied by using an analytical method for **2** based on isolation of the neutral (to 5% hydrochloric acid) reaction products by extraction, separation of the components by thin-layer chromatography, and estimation of the quantity of **2** present by fluorescence densitometry directly on the TLC plate with a Kontes K-495000 densitometer.[6,7] This procedure, while not highly refined, was accurate enough for the estimation of product yields.

Hydroxide ion, a strong base, is effective in converting **1** to the indazole **2** particularly under the conditions for phase-transfer catalysis where a relatively low temperature and short reaction time gave the maximum conversion obtained. Weaker bases, e.g., the primary amines aniline and phenethylamine and the secondary amine 2-(benzylamino)ethanol, are also effective in converting **1** to **2** at temperatures of 185–200 °C. On the other hand, the reaction was not promoted by tertiary amines (Bu_3N or

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(1) T. G. Miller, *J. Org. Chem.*, 31, 3178 (1966).

(2) J. R. Merchant, *Curr. Sci.*, 43, 719 (1974).

(3) N. Nagarajan and A. Venkateswarlu, *Tetrahedron Lett.*, 293 (1967).

(4) J. Leitich, *J. Org. Chem.*, 27, 1081 (1962).

(5) J. Elguero, A. Frachier, and R. Jacquier, *Bull. Soc. Chim. Fr.*, 2075 (1966).

(6) Kontes Glass Co., Vineland, NJ 08360.

(7) For a general discussion of TLC densitometry, see J. C. Touchstone and J. Sherma, Eds., "Densitometry in Thin Layer Chromatography, Practice and Applications", Wiley, New York, 1979.

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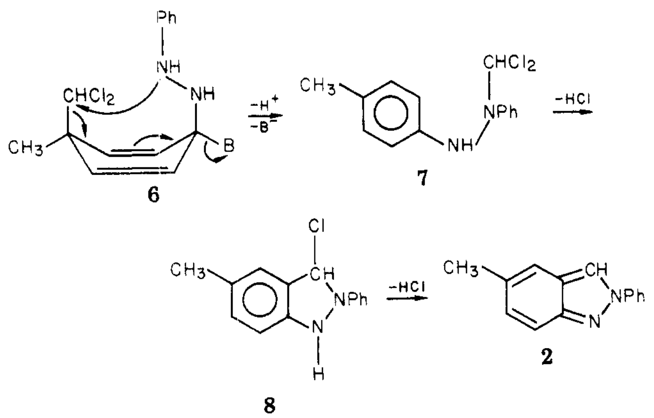
Scheme II



$PhNMe_2$) or a polar solvent in the absence of added base [2-(2-methoxyethoxy)ethanol].

Insufficient evidence is available to support any conclusions about the mechanism for conversion of 1 to 2. It does seem significant, however, that even the very weak base aniline promotes the reaction and that tertiary amines of greater base strength do not. Such a dramatic difference seems difficult to justify on the basis of any presumed steric influence on an acid-base reaction,[8] and it thus appears probable that the base also functions as a nucleophile. We offer for speculation the possibility of a transannular transfer of the dichloromethyl group in an addition product, 6 → 7, followed by ring closure of the hypothetical Vilsmeier-type intermediate, 7 → 8[9,10] (Scheme II).

Experimental Section

4-(Dichloromethyl)-4-methyl-2,5-cyclohexadien-1-one Phenylhydrazone (1). To a solution of 10 g (0.052 mol) of 4-(dichloromethyl)-4-methyl-2,5-cyclohexadien-1-one[11] in 100 mL of methanol was added water to incipient cloudiness, followed by 13 g (0.090 mol) of phenylhydrazine hydrochloride and 15 g (0.11 mol) of hydrated sodium acetate. The mixture was heated to 40 °C for 10 min, during which time a yellow oil separated. Methanol was added until the oil dissolved, and the solution was allowed to cool slowly and was chilled to give the phenylhydrazone as yellow prisms. After recrystallization from methanol and water the yield was 11.7 g (80%): mp 97–97.5 °C;[12] IR (CCl_4) 1608, 1558, 1508, 1256, 1143, 909, 692 cm^{-1}; UV max (CH_3OH) 369 nm (log ϵ 4.4), 294 (4.0), 253 (4.1); NMR ($CDCl_3$) δ 1.38 (s, 3 H), 5.5–7.9 (m, 11 H). Anal. Calcd for $C_{14}H_{14}Cl_2N_2$: C, 59.79; H, 5.02; N, 9.96. Found: C, 59.91; H, 5.20; N, 9.78.

Reaction of 4-(Dichloromethyl)-4-methyl-2,5-cyclohexadien-1-one Phenylhydrazone (1) with Bases. Isolation of 5-Methyl-2-phenyl-2*H*-indazole (2). Reactions with amines were typically run with the amine used in excess as both reactant and solvent as follows. A solution of 3.0 g (10.7 mmol) of 1 and 7 mL of aniline was added dropwise, with stirring, over a 10-min period to 7 mL of boiling aniline. The black tarry mixture was stirred an additional 5 min at reflux and was then poured into 100 mL of 3 N hydrochloric acid. The acid mixture was extracted with ether (3 × 15 mL), and the organic layer was dried over potassium carbonate. Evaporation of the ether gave a brown oil (1.2 g) which solidified after standing several days in air. The solid was crushed on a clay plate and then crystallized from methanol-water to give 0.25 g (11%) of the indazole, mp 110.5–111.5 °C, which was fluorescent (blue) under short-wavelength ultraviolet light, insoluble in 5% hydrochloric acid, and soluble in concentrated hydrochloric acid: IR (CCl_4) 1601, 1521, 1507, 1372, 1209, 1053, 962, 692 cm^{-1}; NMR ($CDCl_3$) δ 2.40 (s, 3 H), 7.0–7.9 (m, 8 H), 8.20 (s, 1 H); UV max (CH_3OH) 294 nm (log ϵ 4.50), 237 (4.70); mass spectrum (70 eV), *m/e* (relative intensity) 208 (M^+, 100), 39 (38), 77 (36), 51 (29), 207 (26), 29 (25), 31 (23), 44 (17), 209 (M + 1, 15.7), 27 (14). Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.81; H, 5.82; N, 13.40.

Conditions for the reaction of 1 with other bases were as follows.

Sodium Hydroxide by Phase-Transfer Catalysis. A mixture of 10 mL of 10% aqueous sodium hydroxide (27.7 mmol of NaOH), 10 mL of toluene, 0.116 g (0.398 mmol) of 1 and 0.0110 g (0.033 mmol) of tetrabutylammonium hydrogen sulfate (Aldrich) was boiled (85 °C) for 1 h. The two phases were separated, and the aqueous layer was extracted with 10 mL of ether. The combined ether and toluene layers were dried over potassium carbonate and then evaporated to dryness under a current of methane. The residue was dissolved in 25 mL of chloroform for analysis by TLC. The yield of 2 by analysis was 38%.

Sodium Hydroxide in Water-Propanol. A mixture of 10 mL of 1-propanol, 2 mL of 10% aqueous sodium hydroxide (5.5 mmol of NaOH), and 0.122 g (0.42 mmol) of 1 was refluxed for 4 h. Hydrochloric acid was added until the mixture was acidic to congo red. The solvents were then evaporated under a current of air. The residue was then partitioned between 5% hydrochloric acid (10 mL) and chloroform (20 mL). The organic layer was dried over potassium carbonate, filtered from the drying agent, and made up to 25 mL for analysis. The yield of 2 by analysis was 20%.

Analysis for 5-Methyl-2-phenyl-2*H*-indazole (2) in Crude Reaction Products. Reactions of 1 with various bases were worked up as described to isolate the neutral compounds as an oil. The oil was then dissolved in chloroform, made up to a standard volume (25 mL), and diluted volumetrically, if necessary, to give a concentration of ca. 2 $\mu g/\mu L$. A 1-μL aliquot of the solution was spotted on a 20-cm TLC plate,[13] along with two spots of solutions of known concentrations of 2,[14] and the plate was developed twice in 60:40 methylene chloride–hexane. The indazole spot could be clearly recognized, both by its R_f value compared to the standard and by its blue fluorescence under short-wavelength UV light. Quantitation of the spots was carried out by fluorescence densitometry measurements under short-wavelength UV light with a Kontes K-495000 densitometer with a baseline corrector.[6] The plates were scanned perpendicular to the direction of development for better UV lamp uniformity. Concentrations of 2 were calculated by comparing peak areas (height times width at half-height) with those of the spots from standard solutions. Peak areas from repetitive scans were reproducible within 5–10%. The concentration vs. peak area relationship was found to be linear over the range of 0.1–1.5 μg of 2, and solution concentrations were therefore adjusted so that a 1-μL spot would provide a sample size in that range.

5-Methyl-2-nitrobenzaldehyde (4). This compound, prepared previously as a mixture with the 6-nitro isomer,[15] was synthesized in 96% yield without isomer contamination by oxidation of 5-methyl-2-nitrobenzyl alcohol (Aldrich) with pyridinium chlorochromate (Aldrich).[16] After crystallization from ethanol and water the melting point was 41–42 °C (lit.[15] mp 44 °C): NMR ($CDCl_3$) δ 2.50 (s, 3 H), 7.37–8.03 (m, 3 H), 10.30 (s, 1 H).

***N*-(5-Methyl-2-nitrobenzylidene)aniline (5).** A mixture of 1.00 g (6.06 mmol) of 5-methyl-2-nitrobenzaldehyde (4), 0.564 g (6.06 mmol) of the center cut from freshly fractionated aniline, and a few crystals of aniline hydrochloride was warmed at 50–55 °C for 24 h. The crude product was allowed to stand under house vacuum (ca. 100 mm) until it had solidified (2 days), and then it was crushed on a clay plate to remove residual oils. The yield of crude product thus obtained was quite high, and the IR spectrum indicated a rather high degree of purity, but a satis-

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[8] V. Gold, *Prog. Stereochem.*, 3, 169 (1962).

[9] A similar intermediate was proposed for the reaction described in ref 1.

[10] For examples of electrophilic aromatic substitution by Vilsmeier complexes, see H. H. Bosshard and H. Zollinger, *Helv. Chim. Acta*, **42**, 1659 (1959).

[11] K. Auwers and G. Keil, *Chem. Ber.*, **35**, 4207 (1902).

[12] The authors of ref 11 reported that the phenylhydrazone could be prepared only as an oil.

[13] Silica gel, Quanta/Gram Q6, Quantum Industries, used without further activation.

[14] Because of possible plate-to-plate variations, internal standards were used rather than a calibration curve.

[15] F. Mayer, *Chem. Ber.*, **47**, 406 (1914).

[16] G. Glaros, *J. Chem. Educ.*, **55**, 410 (1978).

factory system for crystallizing the compound in high yield could not be found. Some crystalline material could be obtained from a hexane–petroleum ether (bp 30–60 °C) mixture, but the remainder separated as an oil. The bright yellow crystalline material melted sharply at 50 °C and turned red on exposure to light: IR (CCl_4) 1622, 1585, 1522, 1488, 1342, 831, 699 cm^{-1}; NMR ($CDCl_3$) δ 2.42 (s, 3 H), 7.07–8.07 (m, 8 H), 8.85 (s, 1 H). Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.05; H, 5.09; N, 11.41.

5-Methyl-2-phenyl-2*H*-indazole (2). A mixture of 2.60 g (10.8 mmol) of **5** in 6 mL (6.2 g, 37 mmol) of triethyl phosphite (Eastman pract) was refluxed under nitrogen for 6 h.[17] Vacuum distillation of the excess triethyl phosphite left a black residue which was chromatographed on Brockman activity 1 neutral alumina (Baker) with 4:1 benzene–chloroform as the eluent. The indazole was contained in the first 25 mL of eluent and was isolated by evaporating the solvent and crystallizing the residue from methanol–water. The yield after two crystallizations was 28%; mp 110–111 °C.

Acknowledgment. The authors are indebted to the National Science Foundation and the Lafayette College Research Fund for support of this research.

Registry No. 1, 72867-26-6; 2, 72867-27-7; 3, 66424-92-8; 4, 5858-28-6; 5, 72867-28-8; 4-(dichloromethyl)-4-methyl-2,5-cyclohexadien-1-one, 6611-78-5; aniline, 62-53-3.

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[17] J. I. G. Cadogen et al., *J. Chem. Soc.*, 4831 (1965).

N-Methyl-1,2,3,4-tetrahydropyridine

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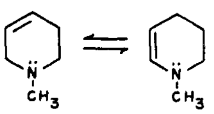
Received November 8, 1979

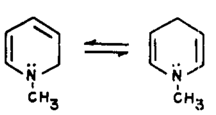
It has long been recognized that the lone pair of electrons on nitrogen interacts with an adjacent double bond. This is a very strong interaction, and this arrangement of substituents behaves as a single functional group.[1]

In spite of interest in enamines from both a theoretical and synthetic point of view, they have not been studied as extensively as dienes. For example, the enamines that have attracted the most attention have been prepared from carbonyl compounds and secondary amines such as pyrrolidine, piperidine, and morpholine.[1]

The simple enamine **2**, *N*-methyl-1,2,3,4-tetrahydropyridine, is electronically analogous to cyclohexa-1,3-diene. Because the nitrogen atom and double bond are part of the same ring in enamine **2**, molecular models indicate that the interaction between the lone pair of electrons on nitrogen and the π molecular orbitals of the double bond should be large. In spite of the interest in this simple enamine, previous attempts to prepare **2** have been unsuccessful.[2]



1 2

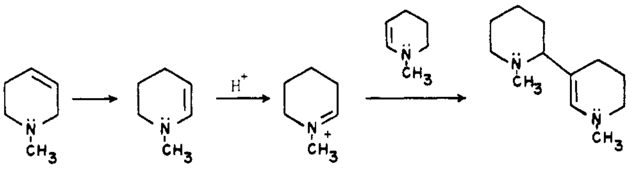


3 4

In connection with our earlier work on the base-catalyzed equilibration of the dihydropyridines **3** and **4**[3] we also studied the base-catalyzed equilibration of the allylamine **1** and the enamine **2**. The recent publication by Martinez and Joule[2b] on the base-catalyzed isomerization of **1** has prompted us to report our results on this system.

We have observed that the enamine **2** can be prepared by the treatment of allyl amine **1** with 1.0 M potassium *tert*-butoxide in dimethyl sulfoxide. If this isomerization is carried out in a 5-mm NMR tube, it can be followed by ^1H NMR spectroscopy by observing the appearance of the characteristic enamine vinyl hydrogens of **2**. The pure enamine **2** can be isolated by the addition of water to the reaction mixture, followed by extraction with pentane. However, the enamine **2** is extremely unstable and care must be exercised in this workup procedure (see the Experimental Section). The enamine **2** is stable if stored in the refrigerator (5 °C) over potassium hydroxide pellets.

Martinez and Joule[2b] also concluded that the allyl amine **1** is isomerized to the vinyl amine **2** by potassium *tert*-butoxide in dimethyl sulfoxide. However, they were unable to directly observe or isolate the vinyl amine **2**. The main product they isolated from their base-catalyzed isomerizations was *N*,*N*′-dimethyl-1,4,5,6-tetrahydroanabasine.[5]



1 2 5

Since **5** is undoubtedly produced from the dimerization of **2**, they inferred that potassium *tert*-butoxide in dimethyl sulfoxide catalyzes the isomerization of **1** to **2**. From their data they concluded that the dimerization occurs in the presence of the strong base and not in the workup procedure. This is probably not the case since under almost identical conditions we can directly observe the enamine **2** by proton magnetic resonance and we can isolate the enamine **2** if care is taken in the workup procedure.

The dihydropyridines **3** and **4** both contain the enamine function and, in principle, are capable of undergoing an acid-catalyzed dimerization analagous to that observed for **2**. We have observed qualitatively that the relative stability of these enamines with respect to dimerization in glass storage vessels is **4** > **3** > **2**. Enamine **2** is by far the most reactive. It undergoes dimerization within minutes in the absence of potassium hydroxide pellets, whereas **3** is stable for days and **4** is stable for weeks under similar conditions.

The enamine **2** is clearly more unstable with respect to acid-catalyzed dimerization than most aldimines.[1] This instability suggests that for enamine **2** there is a strong π interaction between the nitrogen lone pair of electrons and the carbon–carbon double bond. This interaction would stabilize the transition state involving electrophilic attack on the enamine double bond.

Since the treatment of **1** with potassium *tert*-butoxide in dimethyl sulfoxide results in equilibration of **1** and **2**, a measurement of the equilibrium constant of this system would allow for an estimation of enamine stabilization. Although it is generally accepted that enamines are more stable than the allyl amines there are few examples of a direct measurement of the equilibrium constant.[1,2b] We

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[1] Cook, A. G. "Enamines: Synthesis, Structure and Reactions"; Marcel Dekker: New York, 1969.

[2] (a) Leonard, N. J.; Hauck, F. P. *J. Am. Chem. Soc.* **1957**, *79*, 5279. (b) Martinez, S. J.; Joule, J. A. *Tetrahedron* **1978**, *34*, 3027.

[3] Fowler, F. W. *J. Am. Chem. Soc.* **1972**, *94*, 5926.

[4] Bates, R. B.; Carrighan, R. H.; and Staples, C. E. *J. Am. Chem. Soc.* **1963**, *85*, 3031.

[5] Libit, L.; Hoffmann, R. *J. Am. Chem. Soc.* **1974**, *96*, 1370.

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