Table II. Kinetic β-Deuterium Isotope Effects on the Reaction Steps for the Basic Hydrolysis of *p*-Nitroacetanilide

| rate constant[a] | $k_n^H/k_n^D$ [b] |
|---|---|
| $k_1$ | 0.938 ± 0.007 |
| $k_2$ | 0.902 ± 0.020 |
| $k_3$ | 1.000 ± 0.010 |

[a] See text for definition of rate constants. [b] Best fit values from a nonlinear least-squares fit of the $k_0^H/k_0^D$ vs. $C_m$ data (Table I) to eq 1.

Table III. Calculated Isotope Effects for Values of $k_3/k_2$

| $k_3/k_2$, $M^{-1}$ | isotope effects[a] | | |
|---|---|---|---|
| | $k_1$ | $k_2$ | $k_3$ |
| 200 | 0.936 | 0.927 | 1.012 |
| 400 | 0.937 | 0.910 | 1.003 |
| 500 | 0.938 | 0.902 | 1.000 |
| 600 | 0.938 | 0.895 | 0.999 |
| 800 | 0.939 | 0.880 | 0.997 |

[a] Calculated from nonlinear least-squares fit of the experimental data of Table I to eq 19 using the rate constants $k_1 = 4.5 \times 10^{-3}$ $M^{-1}$ $s^{-1}$ and $k_3 = 4.6 \times 10^{-2}$ $M^{-1}$ $s^{-1}$.

butions from transition states on parallel paths.

Finally, then, we see that the observed isotope effect on PNAA hydrolysis is equal to eq 19.

$$\frac{k_0^H}{k_0^D} = \frac{k_0}{k_1[HO^-]}\left(\frac{k_1^H}{k_1^D}\right) + \frac{C_{[2,3]}}{k_2[HO^-] + k_3[HO^-]^2}\left(k_2[HO^-]\frac{k_2^H}{k_2^D} + k_3[HO^-]^2\frac{k_3^H}{k_3^D}\right) \quad (19)$$

Nonlinear least-squares fit of the $k_0^H/k_0^D$ vs. $C_m$ data (Table I) to eq 1 allows the determination of the isotope effects of $k_1$, $k_2$, and $k_3$. These values are collected in Table II. (Mechanistic interpretation of the isotope effect will be presented elsewhere.[6]) It should be noted that although values for three rate constants are needed for calculation of transition-state contributions, one of these constants, $k_2$, could not be determined.[6] In the present analysis $k_2$ was assigned what we believe to be a reasonable value of $9.2 \times 10^{-5}$ $M^{-1}$ $s^{-1}$ ($k_3/k_2 = 500$ $M^{-1}$). Of course it is of interest to know how sensitive the calculated isotope effects are to $k_2$, and in Table III are collected the calculated isotope effects for several values of $k_2$. Clearly, the isotope effects, especially on $k_1$ and $k_3$, are insensitive to $k_2$ and, indeed, at the two extremes of $k_2$ which mark limits of reasonable values the isotope effects generated lead one to identical qualitative mechanistic interpretations.[6]

The procedure outlined here for the analysis of observed isotope effects on rates of complex reactions is a general one and can be applied to kinetic isotope effect data for any reaction having a virtual transition state whose structure can be varied by adjustment of some reaction parameter which influences the relative free-energy barriers of the individual reaction steps. The utility of this procedure lies in its ability to extract isotope effects for individual reaction processes from complex, observed isotope effects without precise knowledge of rate constants which may frequently be difficult if not impossible to obtain.

**Acknowledgment.** This work was supported by the National Institutes of Health (GM-20198 from NIGMS). I express may deepest gratitude to Professor Richard L. Schowen for the provision of facilities and continual assistance.

**Registry No.** *p*-Nitroacetanilide, 104-04-1.

## Isolation, Identification, and Synthesis of Compounds Cosynthesized in the Preparation of Phencyclidine[1]

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The addition of 1-piperidinocyclohexanecarbonitrile (PCC, **1**) to phenylmagnesium bromide produces 1-(1-phenylcyclohexyl)piperidine (PCP, **2**),[2] a dissociative analgesic which has become a drug of abuse[3] and is primarily self-administered by smoking PCP "doped" cigarettes.[4] Preparatory to the study of the pyrolysis products of **2** under simulated smoking conditions, we examined those compounds containing the phenyl and piperidyl groups cosynthesized in the Kalir synthesis[2] of this compound since high-pressure liquid chromatography (HPLC)[5] indicated at least 13 additional nitrogen-containing compounds were present in the crude basic fraction of this preparation. The isolation, identification, and bioassay of these cosynthetics were undertaken and the results are reported herein.

Open column chromatography on neutral alumina of the crude bases (obtained by acid–base extraction) of a Kalir[2] synthetic mixture resulted in several fractions (in addition to the PCP-containing fraction), three of which proved to consist of a single component when examined by HPLC. The first of these, eluting before **2**, was identified as 1-[1-(phenylethyl)cyclohexyl]piperidine (**3**) (average yield 0.5%). The $^1H$ NMR spectrum (see Experimental Section) showed a quartet-doublet, indicating the $CH_3CH$ unit. The mass spectrum exhibited a weak molecular ion at *m/e* 271 (2% base) and an M − $1^+$ peak at 270 (5% base).[6] Fragments of *m/e* 166 (base peak) and 105 (50% base)

(1) Presented, in part, at the Combined Regional Southeast-Southwest Meeting of the American Chemical Society, December 10–13, 1980, New Orleans, LA.

(2) A. Kalir, H. Edery, Z. Pelah, D. Balderman, and G. Porath, *J. Med. Chem.*, **12**, 473 (1969).

(3) D. C. Perry, *PharmChem. News. (Menlo Park, CA)*, **4**, 1 (1975).

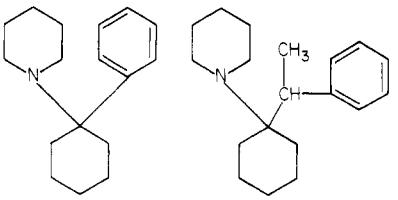
(4) (a) R. S. Burns, S. E. Lerner, R. Corrado, S. H. Jones, and S. H. Schnoll, *West. J. Med.*, **123**, 345 (1979); (b) R. S. Burns and S. E. Lerner, *Clin. Toxicol.*, **12**, 463 (1978).

(5) L. A. Jones, R. W. Beaver, and T. L. Schmoeger, in preparation.

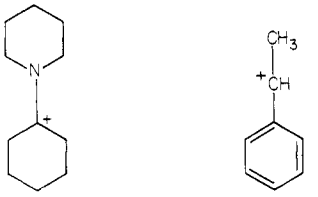
(6) The loss of a hydrogen α to nitrogen, leading to an intense (M − 1)$^+$ peak, is a facile process in piperidines and was used to confirm the presence of the piperidine ring. See H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds", Holden Day, San Francisco, 1967, pp 313–316.

0022-3263/81/1946-3330$01.25/0 

were assigned structures **4** and **5**, respectively. Interestingly, no $M - 43^+$ was observed, a particularly facile process with **2**.[7] An independent synthesis of **3** (vide infra) showed that synthetic **3** had identical $^1H$ NMR and mass spectra and retention times (GC and HPLC) with those of the isolated **3**.

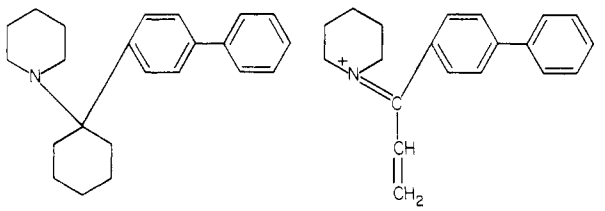


**2** **3**

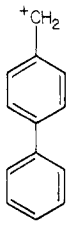


**4** (*m/e* 166) **5** (*m/e* 105)

The compound following **2** in the alumina chromatographic separation proved to be 1-[1-(1,1′-biphenyl-4-yl)-cyclohexyl]piperidine (**6**), recovered in average yields of 1%, whose $^1H$ NMR spectrum was similar to that of **2** except for the complex multiplets at $\delta$ 7.60 and 7.45 (4 H and 5 H, respectively) ascribed to the biphenyl moiety. Equally analogous to **2** was the mass spectrum of **6** which showed a molecular ion at *m/e* 319 (55% base), an $(M - 1)^+$ ion at *m/e* 318 (35% base),[6] two base peaks at *m/e* 276 and 167 (assigned structures **7** and **8**, respectively), and *m/e* 166 (45% base) (**4**). Final confirmation of the structural assignment for **6** was obtained by direct synthesis. The spectral properties and HPLC retention time[8] of synthetic **6** were identical with those of the material isolated from the Kalir synthesis.[2]



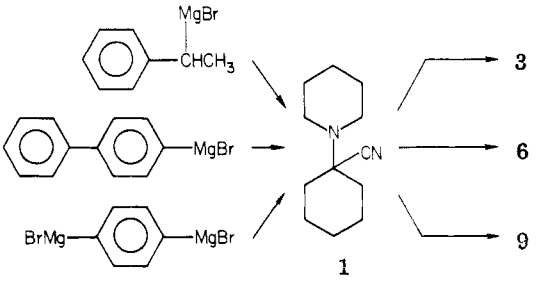
**6** **7** (*m/e* 276)

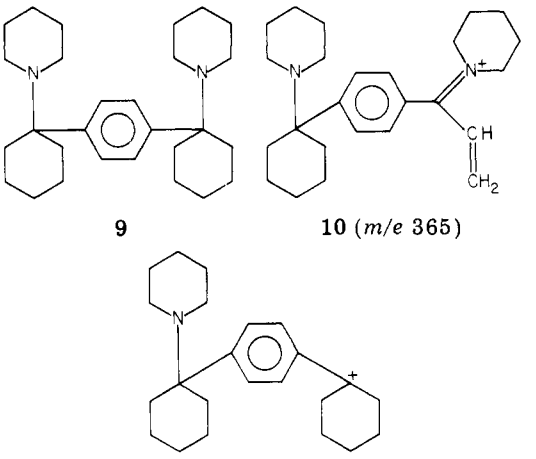


**8** (*m/e* 167)

A final compound separated from PCP (**2**) upon alumina chromatography was shown to be 1,1′-(1,4-phenylenedicyclohexylidene)bis[piperidine] (**9**), obtained in an average of 0.5% yield.

Scheme I





**9** **10** (*m/e* 365)



**11** (*m/e* 324)

Compound **9** gave a proton NMR spectrum very similar to that of **2** and, except for the slight offset of the aromatic signal and some fine structure in the aliphatic region, would appear to be identical except for the integration. Mass spectral analysis of **9** proved the key to identification. An intense molecular ion was observed at *m/e* 408 (base), an $(M - 1)^+$ ion was at *m/e* 407 (15% base,)[6] and ions at *m/e* 365 (80% base) and 324 (75% base) were assigned structures **10** and **11**, respectively. Structure **10** is once again analogous to the $(M - 43)^+$ peak reported for **2**.[7] The even mass molecular ion indicated the basic compound (the synthetic product workup eliminates nonbasic compounds; see Experimental Section) contained an even number of nitrogen atoms. Independently synthesized **9** proved to be identical with **9** isolated from the synthetic mixture as shown by HPLC retention time,[8] melting point, and $^1H$ NMR and mass spectra.

Initial attempts to prepare **3**, **6**, and **9** via a Grignard reaction (with the appropriate bromide substituted for bromobenzene) identical with that carried out for PCP (**2**) produced extremely low yields of product (<2%) in all cases. The low yield was attributed to difficult formation of the Grignard reagents (as evidenced by the large amount of unreaction Mg), since, even with vigorous stirring, a gummy film formed on the surface of the metal. It has been reported that for many organic halides which do not form Grignards readily in ether, tetrahydrofuran (THF) as a solvent produces a dramatic improvement in yield.[9] Utilizing THF as a solvent and modifying the stoichiometry substantially improved observed yields. The general reaction is shown in Scheme I.

Compound **3** could be obtained in 24% recrystallized yield by using a 6-fold excess of Mg (relative to bromoethylbenzene),[10] bringing the solution to reflux, and adding

(7) D. C. K. Lin, A. F. Fentiman, Jr., R. L. Folte, R. D. Forney, Jr., and I. Sunshine, *Biomed. Mass. Spectrom.*, **2**, 206 (1975).

(8) This compound decomposed upon contact with the hot injection port in GC analysis. PCP has also been reported to decompose at injection-port temperatures >200 °C.[7] Attempts to obtain a GC chromatogram of the compound by decreasing the injector temperature resulted in broad ill-defined peaks, suggesting that partial condensation occurred in the injector.

(9) T. Leigh, *Chem. Ind.*, 426 (1965).

THF as the ether was boiled off, followed by refluxing for an additional 2 h before the addition of PCC (1). Similarly, the yield of 6 was increased to 26% (after recrystallization) by using a 2-fold excess of Mg (relative to *p*-bromobiphenyl) and replacing the ether with THF as previously described for 3. The synthesis of 9 was best accomplished by inverse addition, i.e., the addition of 2 equiv of Mg to 1 equiv of *p*-bromobenzene in ether. After all the Mg was added and no further reaction was observed, the ether was removed by distillation while being replaced with THF and, after a 2-h reflux, 2 equiv of PCC was added and the solution refluxed for an additional 2 h. An 11% yield resulted.

To assure that the chemogenesis of 3, 6, and 9 did not result from reagent impurities, rigorous purification procedures of all starting materials were employed (see Experimental Section). Tentatively we suggest that these products arise from free-radical processes. The overall mechanism is currently under investigation.

## Experimental Section

**General Methods.** Melting points were measured in capillary tubes on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. $^1$H NMR spectra were recorded on a Varian Associates HA-100 in $CDCl_3$ with $Me_4Si$ internal standard and shifts are reported in parts per million relative to $Me_4Si$. Mass spectra were recorded on an AEI MS-12 at 70 eV. Microanalyses were performed by Atlantic Microlabs, Atlanta, GA. Analytical GC was carried out on a Hewlett-Packard 5880A equipped with a 12-m SP-2100 fused quartz capillary column and flame-ionization detector (injector temperature 250 °C, detector temperature 250 °C, and oven temperature programmed from 100 (0.5 min hold) to 250 °C at 15 °C/min). Helium at a head pressure of 70 kPa (flow rate ca. 0.5 mL/min) served as the carrier gas. Typical injection volumes were 1–2 μL of a 1–10% solution in MeOH or $Et_2O$, and injections were split 1:100. High-pressure liquid chromatography (HPLC) was carried out by using a Waters Associates ALC/GPC 244 system with UV detection at 254 nm. HPLC conditions were as follows: μBondapak C-18 column (Waters Associates); mobile phase 70:30 MeOH–$H_2O$, 5 mM in hexanesulfonate adjusted to pH 3.5 by addition of glacial acetic acid (25 mL of HOAC/L of solvent); flow rate 2.5 mL/min; peaks detected by UV absorbance at 254 nm.

**General Procedures for Grignard Reactions.** Grignard reactions were carried out in three-necked round-bottomed flasks (dried overnight at >150 °C) and equipped with a reflux condenser, mechanical stirrer, and dry $N_2$ inlet. The reactions were carried out under a slow flow of dry $N_2$. In most cases, the reaction between the organic bromide and the Mg was initiated by addition of an $I_2$ crystal. Ethyl ether (anhydrous ACS reagent grade) was used without further purfication. THF (ACS reagent grade) was percolated through a column of activity I alumina to eliminate peroxides and was deemed to be suitably free from peroxides when it gave a negative test with KI solution.[11] (1-Bromoethyl)benzene was vacuum distilled (2×); 4-bromobiphenyl, *p*-dibromobenzene, and PCC (1) were recrystallized (2×) before use, and GC and mass spectral analysis indicated 99.9% purity. The bromobenzene was distilled (atmospheric pressure) three times through a 600-mm column (Kontes K502500), and the middle, constant boiling fraction collected each time. The third distillate boiled at 154.0 °C. Analysis by HPLC, GC, $^1$H NMR, and mass spectroscopy detected no impurities (estimated purity >99.9%).

**1-Piperidinocyclohexanecarbonitrile (1) and 1-(1-Phenylcyclohexyl)piperidine (PCP, 2).** These were prepared as described by Kalir.[2] The crude basic product of PCP (2), following the $NH_4Cl$ quench of the Grignard reaction,[2] was obtained as follows. The yellow ether layer was separated from the aqueous phase and extracted with successive 100-mL portions of 10% HCl until the aqueous layer was less than pH 3. The acidic aqueous layer was exhaustively extracted with $Et_2O$ to remove nonbasic organics, made strongly basic to liberate bases, and extracted with three 100-mL portions of $Et_2O$. The combined $Et_2O$ extracts were washed with saturated brine and dried ($K_2CO_3$), and the $Et_2O$ was removed under reduced pressure to yield a 72-g (74% yield based on PCP) crude basic fraction. The crude basic fraction was initially a slightly yellow oil which slowly crystallized on standing. A portion of the crude basic fraction was recrystallized successively from EtOH/$H_2O$ to yield pure PCP as white crystals: mp 45.0–45.5 °C (lit.[2] mp 44–45 °C); $^1$H NMR δ 7.32 (s (small shoulder on downfield side), 5 H), 2.25 (br distorted t, 4 H), 2.02 (br m, 4. H), 1.48 (very br m, 8 H); mass spectrum, *m/e* (% of base) 243 (75, $M^+$), 242 (40), 200 (100), 186 (40), 166 (40), 91 (80), 84 (30). Anal. Calcd for $C_{17}H_{25}N$: C, 83.89; H, 10.35; N, 5.75. Found: C, 83.86; H, 10.38; N, 5.74.

**Open Column Chromatography.** A glass chromatography column (100 × 3.5 cm) was packed by filling the column with hexane and slowly adding (with vigorous tapping) 1100 g of neutral $Al_2O_3$ (Fisher A-540, 80–200 mesh, not activated). Final depth of the $Al_2O_3$ bed was approximately 75 cm. A mixture of 40 g of the crude basic product from the PCP synthesis[2] absorbed on 40 g of alumina was carefully added to the top of the column and elution begun with 100% hexane. Fractions of 60 mL were collected with an automatic fraction collector, evaporated, and diluted to 25 mL in MeOH for HPLC examination. The eluent was changed to 0.5% $Et_2O$ in hexane at fraction 175, 1% $Et_2O$ at fraction 207, and 2% $Et_2O$ at fraction 300.

The methanol solutions of fractions which were found to consist of essentially one compound (HPLC) were combined, the methanol was evaporated (reduced pressure), and the resulting solid (recrystallized from MeOH) was examined by $^1$H NMR and mass spectrometry, GC, HPLC, and bioassay.[12] Compound 3 eluted in fractions 10–16, average yield 0.5%, PCP (2) in fractions 15–180, yield 65–70%, and compound 6 in fractions 230–290, average yield 1.0%. When no further compounds were detected from fractions 300–400, the column was stripped with 500 mL of 50% $Et_2O$ in hexane. Compound 9 was isolated upon evaporation of the "strip" fraction, average yield 0.5%.

**1-[1-(1-Phenylethyl)cyclohexyl]piperidine (3).** To 6.2 g (0.30 mol) of Mg in 20 mL of $Et_2O$ was added a crystal of $I_2$ followed by 9.2 g (0.05 mol) of 1-bromoethylbenzene in 35 mL $Et_2O$ over a period of 30 minutes. The mixture was gently refluxed throughout the addition of (1-bromoethyl)benzene and for an additional 2 h upon completion. Next, 9.6 g (0.05 mol) of 1 in 50 mL of $Et_2O$ was added dropwise and the solution refluxed an additional hour. The reaction was quenched with 10% aqueous $NH_4Cl$ and the solution filtered through glass wool to remove unreacted Mg. The basic organics were isolated as described above and consisted of an oil which, when diluted with methanol, deposited white needles. Filtration yielded 2.7 g (0.01 mol, 20% yield) of 3, mp 86–87 °C. HPLC of synthetic 3 showed only one peak at $k'$ 0.75. Single peaks at $k'$ 0.75 were also obtained for isolated 3 and for a mixture of synthetic and isolated 3. GC analysis gave peaks with retention times of 9.72 min for synthetic 3, isolated 3, and a mixture of synthetic and isolated 3: NMR δ 7.14 (s with small shoulder centered at δ 7.20, 5 H, aromatic), 2.98 (q, 1 H, $J$ = 3.5 Hz, benzyl methine proton), 2.68 (br, 4 H, protons α to N in piperidine ring),[13] 2.08, 1.95, 1.82, 1.48 (all br, total 16 H, ring methylene protons), 1.20 (d, 3 H, $J$ = 3.5 Hz, methyl protons); mass spectrum, *m/e* (% of base) 271 (2, $M^+$),

(10) M. S. Malinovskii and A. A. Yavorovskii, *Ukr. Kim. Zh.*, **21**, 240 (1955); *Chem. Abstr.*, **50**, 9313a (1956).

(11) J. A. Riddick and W. B. Bunger, "Organic Solvents. Physical Properties and Methods of Purfication", 3rd ed., Wiley-Interscience, New York, 1970, pp 691–692.

(12) The pharmacological activity of the compounds isolated was determined by using trained pigeons (see C. B. Ferster and B. F. Skinner, "Schedules of Reinforcement", Appleton Century Craft, New York, 1957) and 6 produced suppressed behavior at dose levels of 20 and 40 mg/kg of body weight, but the pattern of suppression was not PCP-like. Compound 3 at dose levels up to 80 mg/kg of body weight was without effect as was 9 up to 20 mg/kg of body weight, but 9 was lethal at 40 mg/kg. With Japanese quail, however, 3 and 6 showed no disruption of normal subjective behavior up to 250 mg/kg, while 9 produced gross behavioral effects starting at 50 mg/kg of body weight (ataxia, apparent severe respiratory distress, hyperactivity, dizziness) and lethality began at 80 mg/kg of body weight, $LD_{50}$ being reached at approximately 100 mg/kg. At 120 mg/kg of body weight dose, 100% lethality was noted. The complete pharmacological study will be reported elsewhere (J. D. Leander, Jon F. Ort, and L. A. Jones, submitted for publication in *Chem. Path. Pharm.*).

270 (5), 163 (55), 162 (100), 105 (50), 91 (30), 84 (20). Anal. Calcd for $C_{19}H_{29}N$: C, 84.07; H, 10.77; N, 5.16. Found: C, 84.03; H, 10.79; N, 5.15.

**1-[1-(1,1'-Biphenyl-4-yl)cyclohexyl]piperidine (6).** A solution of 7.3 g (0.031 mol) of 4-bromobiphenyl in 35 mL of $Et_2O$ was added slowly to a refluxing mixture of 1.5 g (0.063 mol) of Mg in 20 mL of $Et_2O$. THF (30 mL) was added and the $Et_2O$ distilled off. The mixture was maintained at reflux for 2 h and then 6.0 g (0.031 mol) of 1 in 30 mL of $Et_2O$ was added dropwise over 30 min. Heating was continued for an additional 1 h, the mixture was cooled, and the reaction was quenched with 10% aqueous $NH_4Cl$. After filtration through glass wool to remove excess Mg, the THF was removed (60 °C, vacuum) and the basic aqueous solution extracted as before to yield the basic organics as a heavy oil, which was diluted with 30 mL of MeOH and refrigerated. The slightly yellow crystals which deposited were filtered and recrystallized from hot EtOH to yield 2.6 g (8.2 mmol, 26%) of white crystalline **6**, mp 110–111 °C. HPLC analysis of synthetic **6**, isolated **6**, and combined synthetic and isolated **6** showed one peak at $k'$ 1.38. Attempted GC showed evidence of decomposition under conditions of analysis: NMR $\delta$ 7.60 (m, 4 H) and 7.45 (m, 5 H) (aromatic protons), 2.35 (distorted t, 4 H, $\alpha$ piperidine protons),[13] 2.18 and 1.60 (br m, 4 H and 12 H, ring methylene protons); mass spectrum, *m/e* (% of base) 319 (55, $M^+$), 318 (35), 277 (58), 276 (100), 262 (40), 223 (50), 222 (45), 167 (100), 166 (45), 138 (25), 84 (25). Anal. Calcd for $C_{23}H_{29}N$: C, 86.47; H, 9.15; N, 4.38. Found: C, 86.44; H, 9.16; N, 4.34.

**1,1'-(1,4-Phenylenedicyclohexylidene)bis[piperidine] (9).**[14] To 11.8 g (0.05 mol) of *p*-dibromobenzene in 150 mL of $Et_2O$ was added 2.4 g (0.10 mol) of Mg turnings in 0.5-g portions. The mixture was refluxed throughout the Mg addition. Portions of Mg were added only after the preceding portion had completely reacted. Portions of Mg were added only after the precedng portion had completely reacted. After all Mg was added (ca. 7 h), 50 mL of THF was added, the $Et_2O$ allowed to boil off, and the mixture allowed to reflux an additional 5 h. At this point, 19.2 g (0.10 mol) of PCC (1) dissolved in 100 mL of $Et_2O$ was added dropwise with continued external heating. As the $Et_2O$ was distilled a light tan precipitate formed in the remaining THF. Following a 1-h reflux after addition of the PCC was completed, the reaction was quenched with 100 mL of aqueous $NH_4Cl$. Extraction of the reaction mixture (as described above) yielded 50 mL of a heavy oil. The oil was diluted with 150 mL of MeOH, and, upon refrigeration, off-white crystals formed. Filtration of the crystals and recrystallization from hot toluene gave 2.2 g (5.4 mmol, 11% yield) of white crystalline **9**, mp 171–172 °C. HPLC analysis of synthetic, isolated, and mixed synthetic and isolated **9** showed only single peaks at $k'$ 0.08: NMR $\delta$ 7.26 (s with small shoulder on downfield side, 4 H, aromatic protons), 2.27 (br distorted t, 8 H, $\alpha$ piperidine protons),[13] 2.08 and 1.50 (br m, 8 H and 24 H, ring methylene protons); mass spectrum, *m/e* (% of base) 408 (100, $M^+$), 407 (15), 365 (80), 324 (75), 281 (20), 240 (20), 165 (40), 84 (30). Anal. Calcd for $C_{28}H_{44}N$: C, 82.29; H, 10.85; N, 6.85. Found: C, 82.24; H, 10.87; N, 6.82.

**Acknowledgment.** We are grateful for the generous financial support of the North Carolina Department of Crime Control and Public Safety, Division of Crime Control, and the Biomedical Research Support Grant No. RR07071.

**Registry No.** 1, 3867-15-0; 2, 77-10-1; 3, 77745-00-7; 6, 77415-81-7; 9, 76916-13-7; 1-bromoethylbenzene, 585-71-7; 4-bromobiphenyl, 92-66-0; *p*-dibromobenzene, 106-37-6.

(13) In PCP and in each of the analogues described herein, the well-separated aliphatic resonance between $\delta$ 2.25 and 2.68 (4 H) (or 8 H in the case of **9**) is assigned to the protons $\alpha$ to the nitrogen of the piperidine ring. These chemical shift values are in agreement with the values reported for the $\alpha$-hydrogens of *N*-alkyl-substituted piperidines (axial $\delta$ ~2.3; equatorial $\delta$ ~3.3). See L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed., Pergamon Press, New York, 1969, p 240.

(14) The synthesis of **9** was reported simultaneously to our report by P. Y. Johnson, R. Pan, and Q. Wen at The Combined Regional Southeast-Southwest Meeting of The American Chemical Society, December 10–13, 1980, New Orleans, LA (*J. Org. Chem.*, **46**, 2049 (1981)).

# The Question of *N*-Alkyl Nitrilium Ions from Nitriles, Alcohols, and Boron Trifluoride

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*Received February 3, 1981*

Nitrilium ions are becoming recognized as being important not only because of the role they play as intermediates in a rather large number of chemical reactions[1,2] but also because of the stereospecific manner in which they react.[3,4]

We recently formed *N*-alkyl nitrilium ions by the direct alkylation of nitriles with either triethyloxonium tetrafluoroborate or isopropyl chloride–iron(III) chloride[5] and demonstrated their reduction by trialkylorganosilicon hydrides to *N*-alkyl aldimines which yielded aldehydes upon hydrolysis (eq 1).[6]

$$RC{\equiv}N + R'X \longrightarrow RC{\equiv}\overset{+}{N}R'\ \bar{X} \xrightarrow{R''_3SiH} RCH{=}NR' \xrightarrow{H_2O} RCHO \qquad (1)$$

During the course of that study, it was found that, although *N*-alkyl nitrilium ions are reductively captured essentially quantitatively by organosilicon hydrides such as triethylsilane, incomplete alkylation of the starting nitriles by reasonable amounts of triethyloxonium tetrafluoroborate or, to a lesser extent, isopropyl chloride–iron(III) chloride reagents led to varying amounts of unreacted nitrile in the final product. In an attempt to effect a more quantitative, rapid alkylation of nitriles, we explored the system consisting of nitrile, an alcohol, and boron trifluoride. It was our expectation that this system using a Lewis acid would parallel the behavior of the usual Brønsted acid-catalyzed Ritter conditions[7] and would lead to similar formation of nitrilium ions (eq 2). This expectation was bolstered by a report that *N*-alkyl amides, the expected hydrolysis products from *N*-alkyl nitrilium ions, are formed from the reactions of nitriles and boron trifluoride with excess amounts of alcohols (eq 3).[8]

$$RC{\equiv}N + R'OH + BF_3 \longrightarrow RC{\equiv}\overset{+}{N}R'\ BF_3OH^- \qquad (2)$$

$$CH_3CN + CH_3CHOHCH_2CH_3 \xrightarrow{BF_3} \xrightarrow{H_2O} CH_3CONHCH(CH_3)\,CH_2CH_3 \qquad (3)$$

## Results and Discussion

In an initial experiment, boron trifluoride gas was passed into a dichloromethane solution containing equimolar

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