Methanol–water (52.1% w/w) and phosphate (pH 8.21) and carbonate (pH 11.32) buffers were made up according to procedures of standard source.[20] Phosphate buffer (pH 8.21): 0.01000 mol of KCl, 0.002752 mol of KH_2PO_4, 0.002757 mol of Na_2HPO_4 in 52.1% w/w methanol–water solvent mixture. Carbonate buffer (pH 11.32): 0.01000 mol of KCl, 0.002771 mol of $NaHCO_3$, 0.002771 mol of Na_2CO_3. Intermediate pH buffers were obtained by different mixtures of these two. Attention was made to keep a constant ionic strength.

An accurate quantity of compound was dissolved in an accurate volume of 52.1% w/w methanol–water mixture to allow a concentration of about 5×10^{-4} M. This was diluted with buffers to a concentration of 1×10^{-5} M. pH and spectra were recorded. Relative pK_a values were calculated by using the relationship

$$pK_a = pH - \log ([A^-]/[HA])$$

$[A^-]$ and [HA] were calculated from visible spectral data.

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Registry No. **1a**, 58346-32-0; **1b**, 91178-47-1; **1c**, 91178-48-2; **1d**, 91178-49-3; **1e**, 91178-50-6; **1e**·$HClO_4$, 91178-52-8; 4-picoline, 108-89-4; 4-hydroxybenzaldehyde, 123-08-0; 3,5-dimethyl-4-hydroxybenzaldehyde, 2233-18-3; 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde, 1620-98-0.

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Synthesis of (*Z*)- and (*E*)-6-Hydroxyketamine

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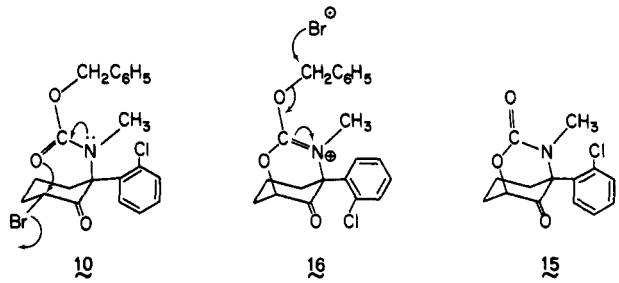
(*Z*)- and (*E*)-6-hydroxyketamine, potential metabolites of the dissociative anesthetic agent ketamine [(±)-2-(*o*-chlorophenyl)-2-(methylamino)cyclohexanone], have been prepared by oxidation of the trimethylsilyl enol ether of *N*-(methoxycarbonyl)ketamine with *m*-chloroperoxybenzoic acid. The relative stereochemistry of these diastereoisomers was established via the cyclic carbamate formed from the thermal cyclization of (*E*)-6-bromo-2-(*o*-chlorophenyl)-2-[(benzyloxycarbonyl)methylamino]cyclohexanone which, upon base hydrolysis, yielded (*Z*)-6-hydroxyketamine. Confirmation of this assignment was achieved by the selective cyclization of (*E*)-2-(*o*-chlorophenyl)-2-[(methoxycarbonyl)methylamino]-6-(tosyloxy)cyclohexanone, a reaction which the corresponding *Z* isomer did not undergo.

The anesthetic agent ketamine (**1**) is biotransformed to a variety of metabolites, some of which may have biological activity.[1,2] In order to further our knowledge of the metabolism of ketamine (Chart I), we have undertaken the synthesis of (*Z*)- and (*E*)-6-hydroxyketamine (**2** and **3**, respectively), two compounds which, on the basis of mass spectral evidence, are potential metabolites of the parent drug.[3]

Of several possible approaches to these α-hydroxy ketones[4-8] we examined first the α-bromination of *N*-benzoylketamine (**4**) with phenyltrimethylammonium tribromide.[9] A poor yield of a pure α-bromo derivative of **4** was obtained which displayed a well-defined ABX system[10] for the C_6-methine ^1H NMR signal, consistent with the 6_{eq}-bromo structures **5** and **6**. A modified pathway involving the reaction of the lithium enolate **8** of *N*-(benzyloxycarbonyl)ketamine (**7**) with bromine[11] gave a much improved yield of a pure α-bromo ketone which displayed an ^1H NMR spectrum consistent with the 6_{eq}-bromo structures **9** and **10**.

Reaction of **9**/**10** with potassium acetate in acetic acid yielded two products, neither of which proved to be the desired α-acetoxy ketones **11** and **12**. The less polar compound displayed spectral characteristics consistent with the elimination product 3-(*o*-chlorophenyl)-2-hydroxycyclohex-2-enone (**13**). Reaction of **13** with *o*-phenylenediamine gave, as expected for a potential 1,2-dione, the tetrahydrophenazine **14**.[12] Mass spectral and elemental analyses established the empirical formula of the second product as $C_{14}H_{14}NO_3Cl$, which differs from that of the starting material **9**/**10** by the elements of benzyl bromide.

Scheme I



10 **16** **15**

†Department of Medicinal Chemistry, School of Pharmacy, University of Washington, Seattle, Washington 98195

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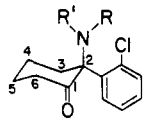
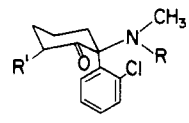
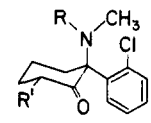
Chart I



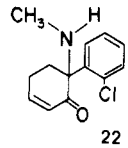
1 : R = CH_3; R' = H
4 : R = CH_3; R' = COC_6H_5
7 : R = CH_3; R' = $COOCH_2C_6H_5$
26 : R = CH_3; R' = $COOCH_3$



2 : R = H; R' = OH
5 : R = COC_6H_5; R' = Br
9 : R = $COOCH_2C_6H_5$; R' = Br
11 : R = $COOCH_2C_6H_5$; R' = $OOCCH_3$
17 : R = H; R' = Br



3 : R = H; R' = OH
6 : R = COC_6H_5; R' = Br
10 : R = $COOCH_2C_6H_5$; R' = Br
12 : R = $COOCH_2C_6H_5$; R' = $OOCCH_3$
18 : R = H; R' = Br



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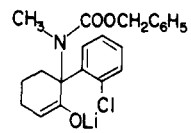
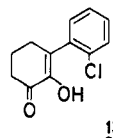
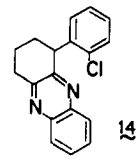


8



13



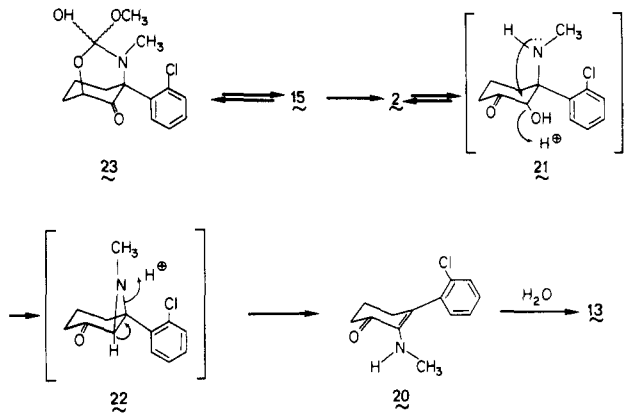
14

The IR spectrum indicated the presence of two carbonyl groups with stretching frequencies of 1750 cm^{-1} (a cyclic ketone) and 1695 cm^{-1} (a carbamate). These data suggested the cyclic carbamate **15** as the structure of this product. Consistent with this assignment, ^1H NMR analysis of a Me_2SO-d_6 solution of the starting material after 1 h of heating showed the presence of **15** and benzyl bromide in approximately equimolar concentrations. Since **15** could be obtained in good yield by simple thermolysis of the starting α-bromo ketone in DMF, we have concluded that the starting material must be the *E* isomer, compound **10**. A possible mechanism to account for the formation of **15** (Scheme I) involves an intramolecular S_N2 displacement of the bromo group of **10** by the carbonyl oxygen atom[13] followed by bromide ion attack on the resulting intermediate **16** to generate **15** and benzyl bromide.

During the course of these studies Purcell and Sanchez reported the synthesis of (*Z*)- and (*E*)-6-bromoketamine (**17** and **18**, respectively) by the direct bromination of ketamine.[14] The relative stereochemical assignments were made on the basis of analogy and IR data only. These assignments were confirmed when treatment of (*E*)-6-bromoketamine (**18**) with benzyl chloroformate was shown to yield **10**.

Treatment of **15** with trifluoroacetic acid in an attempt to cleave the carbamate ester bond while preserving the stereochemistry at C_6 led to the isolation of an unstable base which was shown to have an empirical composition corresponding to $C_{13}H_{14}NOCl$. One possible structure for this product, 5,6-dehydroketamine (**19**),[14] could be ruled out since no olefinic signals were present in the ^1H NMR spectrum. The spectral data summarized in the Experimental Section are consistent with the isomeric enamino ketone structure **20**. The smooth hydrolysis of **20** to **13** supports this assignment. A possible reaction sequence to account for these conversions (Scheme II) involves hydrolysis of **15** to (*Z*)-6-hydroxyketamine (**2**) which, via the

Scheme II



23 15 2 21 22 20 13

tautomeric α-hydroxy β-keto amine **21**, forms the bicyclo intermediate **22** leading to the required 1,2-migration step. Later we were able to document the facile acid-catalyzed conversion of **2** to **13** and **20**.

Attempted hydrolysis of **15** under mild basic conditions in aqueous methanol led to the isolation of a crystalline compound which proved to the the methanol addition product **23** of the cyclic carbamate **15**. The ^1H NMR spectrum of **23** was similar to that of **15** except for the presence of a new three-proton singlet appearing at δ 3.14 (OCH_3). A hemiketal structure could be ruled out since only one carbonyl stretch band (1750 cm^{-1}) for the cyclohexanone moiety appeared in the IR spectrum. Comparison of the properties of **23** with those of the isomeric methyl carbamates **24** and **25** (see below) eliminated these possibilities as well.

Under more vigorous base hydrolysis conditions, **15** was converted to the elimination product **13** and a second, more polar compound which was obtained in crystalline form by preparative TLC. The latter material displayed a ^{35}Cl parent ion under EIMS conditions at m/z 253 and fragment ions at m/z 235 (loss of H_2O) and m/z 225 (loss of CO). HREI mass spectral and elemental analyses established the empirical formula as $C_{13}H_{16}NO_2Cl$ as required for (*Z*)- or (*E*)-6-hydroxyketamine. ^1H NMR, ^{13}C NMR, and IR spectra all were consistent with the 6-hydroxyketamine structures. Since this product was obtained

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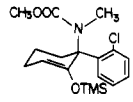
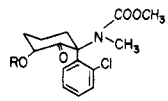
under epimerizing conditions, however, assignment of the relative stereochemistry at C_2 and C_6 was not possible.

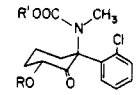
The limited success realized in the efforts described above prompted us to attempt α-functionalization of ketamine via oxidation of the protected TMS enol ether **27**.



27



24: R = H
28: R = Ts
32: R = TMS



25: R = H ; R' = CH_3
29: R = Ts ; R' = CH_3
30: R = TMS; R' = CH_3
31: R = R' = H

Treatment of *N*-(methoxycarbonyl)ketamine (**26**) with lithium diisopropylamide followed by chlorotrimethylsilane provided compound **27** as an oil. Oxidation of the TMS enol ether with *m*-chloroperoxybenzoic acid[6] led to an oily mixture from which a crystalline product separated upon addition of toluene. The CI mass spectrum of this substance displayed a ^{35}Cl-protonated molecular ion at m/z 311 and fragment ions at m/z 293 (loss of H_2O), m/z 283 (loss of CO), and m/z 248 (loss of Cl and CO), consistent with the desired *N*-(methoxycarbonyl)-6-hydroxyketamine derivatives **24** and **25**. The ^1H NMR spectrum displayed two methyl singlets at δ 3.71 (OCH_3) and δ 3.08 (NCH_3) and the IR spectrum established the presence of a ketone carbonyl group (1748 cm^{-1}) and a carbamate carbonyl group (1698 cm^{-1}). Column chromatography of the oil obtained from the filtrate led to the isolation of an oil which proved to be an isomer of the crystalline product on the basis of mass, NMR, and IR spectral data. The relative stereochemistry of these two diastereoisomers remained to be assigned. Attempts to convert either of these substances to the cyclic carbamate **15** under a variety of conditions inevitably led to the formation of the elimination product **13**.

An alternative approach to the cyclization of the *E* isomer **25** was attempted via the corresponding tosylate **29** which was expected to form the cyclic carbamate **15** in a manner similar to that already observed for the (*E*)-bromo derivative **10**. The selective conversion of the oil or the crystalline product to **15** in this way would establish the relative stereochemistry of the two compounds. The tosylates **28** and **29** were prepared (derivatization of the crystalline product required initial conversion to its lithio salt) and subjected to thermolysis. Only the tosylate derived from the crystalline carbamate led to the cyclized product **15**. On the basis of these data we assign the *E* stereochemistry (compound **25**) to the crystalline product and the *Z* stereochemistry (**24**) to the oily product.

Cleavage of the methoxycarbonyl protecting group of **24** and **25** using a variety of reagents including acid, sodium phenyl selenide,[15] and iodotrimethylsilane[16] led primarily to the formation of the elimination product **13**. To avoid overreaction, the *E* isomer **25** was converted first to its OTMS derivative **30** with BSTFA which then was treated with iodotrimethylsilane. The solid which separated displayed a ^{35}Cl parent ion under EIMS conditions at m/z 297 and a *N*-methyl ^1H NMR signal at δ 2.66 suggesting the carbamic acid structure **31**. Attempts to convert **31** to (*E*)-6-hydroxyketamine (**3**) with acid led to extensive decomposition. The filtrate obtained after separation of **31** yielded an oil from which the elimination product **13** and the desired alcohol **3** could be obtained by column chromatography. The physical and spectroscopic characteristics of **3** were similar to, but distinct from, those of the previously obtained *Z* isomer **2**. Compound **3** was easily converted to the starting methyl carbamate **25**. Furthermore, when the (*Z*)-OTMS derivative **32** was carried through the iodotrimethylsilane reaction, pure (*Z*)-6-hydroxyketamine (**2**), identical in all respects with the product isolated from the base hydrolysis reaction of the cyclic carbamate **15**, was obtained. Treatment of **2** with methyl chloroformate generated the corresponding starting methyl carbamate **24**. Finally, as expected, both **2** and **3** were converted to the elimination product **13** upon exposure to acid or base. The *E* isomer proved to be much less stable than the *Z* isomer although aqueous solutions of both compounds were stable at pH 7.4 and 37 °C (metabolic conditions).

Experimental Section

All reactions were carred out under a nitrogen atmosphere unless otherwise stated. All chemicals used were reagent grade unless otherwise specified. ^1H NMR and ^{13}C NMR spectra were obtained at 80 MHz with a Varian FT-80 spectrometer; chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (Me_4Si) in $CDCl_3$ and sodium 2,2-dimethyl-2-silapentane-5-sulfonate (SDSS) in D_2O. Spin multiplicity is given as (s) singlet, (d) doublet, (t) triplet, (q) quartet, (p) pentet, or (m) multiplet. IR spectra were taken on a Perkin-Elmer 337 grating spectrophotometer. Low-resolution EI mass spectra were obtained on a VG 70-70H mass spectrometer equipped with a VG Model 2035 data system at an electron energy of 70 eV, a source temperature of 200 °C, an emission current of 100 μA, and an accelerating potential of 4 kV. High-resolution spectra ($m/\Delta m$ 10 000) were recorded on the VG instrument at a scan rate of 10 s/decade and employed perfluorokerosene as internal mass reference. Low-resolution CI mass spectra were obtained on a modified AEI MS 902 instrument using isobutane as reactant gas. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were performed by the microanalytical laboratory, University of California, Berkeley, CA.

2-(*o*-Chlorophenyl)-2-(benzoylmethylamino)cyclohexanone (*N*-Benzoylketamine, 4). To a solution of ketamine (2.65 g, 11.1 mol) and triethylamine (5.0 mL, 35.9 mmol) in 50 mL of dry benzene was added dropwise a solution of benzoyl chloride (2.50 g, 19.8 mmol) in 15 mL of dry benzene. The reaction mixture was stirred at room temperature overnight and then was washed with H_2O, 10% HCl, 10% $KHCO_3$, and H_2O, dried over Na_2SO_4, filtered, and concentrated. The residue was crystallized from benzene to give 3.205 g (84%) of **4** as colorless crystals: mp 125–126 °C; ^1H NMR ($CdCl_3$) δ 8.08 (dd, 1 H, Ar H ortho to Ar cyclohexanone), 6.9–7.7 (m, 8 H, Ar H), 2.95 (s, 3 H, NCH_3), 1.5–3.5 (nm, 8 H, cyclohexanone); CIMS, m/z 342 and 344 (MH^+).

Anal. Calcd for $C_{20}H_{20}NO_2Cl$: C, 70.27; H, 5.90; N, 4.09. Found: C, 70.23; H, 5.95; N, 4.05.

(*Z* or *E*)-6-Bromo-2-(*o*-chlorophenyl)-2-(benzoylmethylamino)cyclohexanone (5 or 6). To a solution of **4** (462 mg, 1.4 mmol) in 6 mL of THF was added a solution of phenyltrimethylammonium tribromide (PTT, 565 mg, 1.5 mmol) in 3 mL of THF. Upon heating under reflux for 1 h, the initial orange color faded and a white precipitate formed. The reaction mixture was poured into 20 mL of H_2O from which white crystals (402 mg) were isolated. TLC analysis of the crystals showed the presence of two compounds, one of which cospoted with starting material. Recrystallization of this material from toluene/methanol gave 20 mg (3.4%) of **5/6** as pure white crystals: mp 162–163 °C; ^1H NMR ($CDCl_3$) δ 7.0–7.7 (nm, 10 H, ArH), 4.96 (dd, 1 H, methine, $J_{H_aH_e}$ = 13 Hz and $J_{H_aH_e}$ = 7 Hz), 2.99 (s, 3 H, NCH_3), 1.7–3.6 (nm, 6 H, CH_2); CIMS, m/z 420 (MH^+ ^{35}Cl, ^{79}Br), 422 (MH^+ ^{35}Cl, ^{81}Br, and ^{37}Cl, ^{79}Br), 424 (MH^+ ^{37}Cl, ^{81}Br).

Anal. Calcd for $C_{20}H_{19}NO_2ClBr$: C, 57.09; H, 4.55; N, 3.33; Cl, 8.43; Br, 18.94. Found: C, 56.84; H, 4.66; N, 3.28; Cl, 8.30; Br, 18.78.

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2-(*o*-Chlorophenyl)-2-[(benzyloxycarbonyl)methylamino]cyclohexanone (7). To a mixture of 1 (14.0 g, 59 mmol) and anhydrous sodium carbonate (13 g, 123 mmol) in 300 mL of dry benzene was added benzyl chloroformate (13 mL, 91 mmol). The reaction mixture was heated under reflux overnight and then allowed to cool to room temperature before trimethylamine (5 mL) was added. The resulting mixture was washed with H_2O, 10% HCl, 10% $KHCO_3$, and H_2O, dried over Na_2SO_4, filtered, and concentrated. Crystallization of the residue from toluene gave 20.2 g (91%) of 7 as colorless crystals: mp 120–121 °C; ^1H NMR ($CDCl_3$) δ 6.75–7.50 (nm, 8 H, Ar H), 5.13 (AB quartet, 2 H, $C_6H_5CH_2$, J_{gem} = 12.2 Hz), 3.03 (s, 3 H, NCH_3); IR (mineral oil mull) 1725 cm^{-1} (CO, ketone), 1690 cm^{-1} (CO, carbamate); EIMS m/z (relative intensity) 371 and 373 ($M^{+\cdot}$, <1), 336 [$(M - Cl)^+$, <1], 308 [$(M - Cl - CO)^+$, 50], 280 (20), 264 (5), 91 (100).

Anal. Calcd for $C_{21}H_{22}NO_3Cl$: C, 67.83; H, 5.96; N, 3.77. Found: C, 67.65; H, 6.13; N, 3.67.

(*E*)-6-Bromo-2-(*o*-chlorophenyl)-2-[(benzyloxycarbonyl)methylamino]cyclohexanone (10). A solution of *n*-butyllithium (41 mL of a 1.6 M solution, 60 mmol) in hexane cooled to 0 °C was added to a dry THF solution of diisopropylamine (9.6 mL, 70 mmol) by syringe. After 10 min the resulting solution of lithium diisopropylamide was cooled to −78 °C and a solution of 7 (20.28 g, 54.5 mmol) in 160 mL of dry THF was added dropwise. The mixture turned yellow and then clear, and after 1 h bromine (3.4 mL, 66 mmol) was added by syringe. After 20 min the mixture was allowed to warm to room temperature and the reaction was quenched by the addition of 150 mL of 10% Na_2SO_3. The mixture was extracted 3 times with CH_2Cl_2 and the combined CH_2Cl_2 extracts were washed with H_2O and dried over Na_2SO_4 and K_2CO_3, filtered, and concentrated. The clear oily residue was crystallized from isopropyl alcohol to give 9.4 g of colorless crystals. Recrystallization from isopropyl alcohol gave 8.2 g (18.3 mmol, 34%) of pure 10. An additional 5.8 g (12.9 mmol, 24% of pure 10) could be obtained from the mother liquors: mp 124–125 °C; ^1H NMR ($CDCl_3$) δ 6.65–7.50 (nm, 9 H, Ar H), 5.16 (s, 2 H, $C_6H_5CH_2$), 4.85 (dd, 1 H, CHBr, $J_{H_aH_a}$ = 11.9 Hz and $J_{H_aH_e}$ = 5.8 Hz), 3.03 (s, 3 H, NCH_3); IR (mineral oil mull) 1740 cm^{-1} (CO), 1690 cm^{-1} (CO); EIMS, m/z (relative intensity) 449 ($M^{+\cdot}$ <1), 414 [$(M - Cl)^+$, <1], 370 [$(M - Br)^+$, 17], 154 [$(C_8H_7N^{37}Cl)^+$, 41], 152 [$(C_8H_7N^{35}Cl)^+$, 65], 91 (C_7H_7, 100).

Anal. Calcd for $C_{21}H_{21}NO_3ClBr$: C, 55.95; H, 4.70; N, 3.10. Found: C, 56.62; H, 4.79; N, 3.05.

5-(*o*-Chlorophenyl)-4-methyl-2-oxa-4-azabicyclo[3.3.1]nonane-3,9-dione (15). A solution of 10 (4.0 g, 8.86 mmol) in 50 mL of DMF was heated under reflux for 2 h. The residue obtained after removing the solvent in vacuo was crystallized from benzene/cyclohexane to yield 2.3 g (94.3%) of the cyclic carbamate 15: mp 148.5–149 °C; ^1H NMR ($CDCl_3$) δ 7.1–7.5 (nm, 4 H, Ar H), 4.73 (t, 1 H, methine, J = 2.3 Hz), 2.56 (s, 3 H, NCH_3), 1.8–3.0 (nm, 6 H, CH_2); IR (mineral oil mull) 1750 cm^{-1} (ketone CO), 1695 cm^{-1} (carbamate CO); EIMS, m/z (relative intensity) 279 and 281 ($M^{+\cdot}$, 5), 251 [$(M - CO)^+$; 13], 235 [$(M - CO_2)^+$; 5], 222 (31), 152 (100).

Anal. Calcd for $C_{14}H_{14}NO_3Cl$: C, 60.12; H, 5.04; N, 5.01. Found: C, 59.76; H, 5.09; N, 4.98.

5-(*o*-Chlorophenyl)-3-hydroxy-3-methoxy-4-methyl-2-oxa-4-azabicyclo[3.3.1]nonan-9-one (23). A solution of the bicyclocarbamate 15 (343 mg, 1.2 mmol) in 15 mL of 0.1 M NaOH/MeOH was stirred at room temperature for 3 days. The reaction mixture was added to 25 mL of H_2O and the resulting solution was extracted with CH_2Cl_2 which in turn was washed with H_2O, dried over Na_2SO_4, and evaporated to yield 144 mg of a colorless oil. Preparative TLC (1000-μm silica gel, PLK5F, Whatman, 2% CH_3CN/CH_2Cl_2) led to the isolation of a polar component (R_f 0.05) which was crystallized from benzene/cyclohexane to give pure 23: mp 179–180 °C; ^1H NMR ($CDCl_3$) δ 7.0–7.5 (nm, 4 H, Ar H), 4.1–4.5 (nm, 1 H, methine), 3.14 (s, 3 H, OCH_3), 2.78 (s, 3 H, NCH_3); IR (mineral oil mull) 3420 cm^{-1} (OH), 1750 cm^{-1} (CO), 1735 cm^{-1} (shoulder on 1750 cm^{-1}); CIMS, m/z 312 and 314 (MH^+); EIMS (of TFA derivative), m/z (relative intensity), 407 and 409 ($M^{+\cdot}$, 5), 379 [$(M - CO)^+$, 7], 372 [$(M - Cl)^+$, 3], 167 (90), 152 (100).

Anal. Calcd for $C_{15}H_{18}NO_4Cl$: C, 57.79; H, 5.82; N, 4.49. Found: C, 57.90; H, 5.90; N, 4.36.

Base Hydrolysis of 15 Leading to 3-(*o*-Chlorophenyl)-2-hydroxycyclohex-2-enone (13) and (*Z*)-2-(*o*-Chlorophenyl)-6-hydroxy-2-(methylamino)cyclohexanone [(*Z*)-6-Hydroxyketamine (2)]. A solution of 15 (1.6 g, 5.9 mmol) in 50 mL of 1.0 M NaOH/MeOH was heated under reflux for 3 h. After removing most of the MeOH, the residue in H_2O was extracted with CH_2Cl_2 twice and the combined organic extracts were back-extracted with 10% HCl. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to yield a solid residue which, after crystallization from benzene/cyclohexane gave 541 mg (2.4 mmol, 41%) pure 13: mp 160–161 °C; ^1H NMR ($CDCl_3$) δ 7.0–7.5 (nm, 4 H, Ar H), 6.12 (s, 1 H, exchanges with D_2O, OH), 2.67 (two overlapping t, J = 5.6 Hz, 4 H, 2 CH_2), 2.17 (m, 2 H, $CH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$) δ 195.74 (CO), 144.17, 136.96, 130.32, 130.20, 130.06, 129.70, 129.58, 127.36 (8 sp^2 C), 36.70, 30.28, 23.45 (3 sp^3 C); IR (mineral oil mull) 3383 cm^{-1} (hydrogen-bonded OH), 1665 cm^{-1} (conjugated cyclic ketone), 1642 cm^{-1} (C=C); HR-EIMS, calcd for $C_{12}H_{11}O_2{}^{35}Cl$ 222.044, found 222.0437.

Anal. Calcd for $C_{12}H_{11}O_2Cl$: C, 64.73; H, 4.98. Found: C, 64.39; H, 4.89.

The pH of the above aqueous acid layer was adjusted to 11 with 2 N NaOH, and the resulting solution was extracted 3 times with CH_2Cl_2. After washing (H_2O), drying (Na_2SO_4), and evaporating the combined CH_2Cl_2 extracts, the residue was purified by preparative TLC (1000-μm silica gel, PLK5f, Whatman, 2% CH_3CN/CH_2Cl_2). The slow moving band near the origin was isolated (CH_3OH) and crystallized from cyclohexane to yield 326 mg (1.3 mmol, 22%) of pure (*Z*)-6-hydroxyketamine (2): mp 148–150 °C; ^1H NMR ($CDCl_3$) δ 7.2–7.6 (nm, 4 H, Ar H), 4.16 (dd, 1 H, methine H), 2.8–3.2 (nm, 6 H, CH_2), 2.08 (s, 3 H, NCH_3); IR (KBr) 1725 cm^{-1} (CO); CIMS, m/z 254 and 256 (MH^+); 236 ($MH - H_2O$)$^+$; EIMS, m/z (relative intensity) 253 and 255 (M^+), 235 [$(M - H_2O)^{+\cdot}$, 4], 225 [$(M - CO)^{+\cdot}$, 60], 180 (100).

Anal. Calcd for $C_{13}H_{16}NO_2Cl$: C, 61.52; H, 6.36; N, 5.54. Found: C, 61.55; H, 6.28; N, 5.43.

1-(*o*-Chlorophenyl)-1,2,3,4-tetrahydrophenazine (14). A solution of 13 (282 mg, 1.27 mmol) and *o*-phenylenediamine (368 mg, 3.4 mmol) in 7 mL of acetic acid was heated under reflux for 6 h. The residue obtained after removal of the solvent was partitioned between 2 M NaOH and CH_2Cl_2. The organic layer was washed (H_2O, 10% HCl, H_2O), dried (Na_2SO_4), filtered, and evaporated to yield a brown oil. Preparative TLC (100-μm Whatman PLK5F, 2% CH_3CN/CH_2Cl_2) led to the isolation of a band at R_f 0.5 which, after three crystallizations from hexane, provide pure 14 (110 mg, 29%): mp 120–121 °C; ^1H NMR ($CDCl_3$) δ 6.6–8.0 (nm, 8 H, Ar H), 4.89 (t, J = 6.1 Hz, 1 H, methine H), 3.27 (t, J = 6.1 Hz, 2 H, CH_2), 1.8–2.4 (nm, 4 H, CH_2); CIMS, m/z 295 and 297 (MH^+); EIMS, m/z (relative intensity) 294 and 296 ($M^{+\cdot}$, 4), 259 [$(M - Cl)^+$, 100].

Anal. Calcd for $C_{18}H_{15}N_2Cl$: C, 73,34; H, 5.13; N, 9.50. Found: C, 72.92; H, 5.50; N, 9.64.

3-(*o*-Chlorophenyl)-2-(methylamino)cyclohex-2-enone (20). A solution of 15 (59 mg, 0.2 mmol) in 5 mL of trifluoroacetic acid was heated under reflux for 18 h. The residue after removal of the solvent was purified by preparative TLC (1000-μm silica gel, PLK5F, Whatman, 2% CH_3CN/CH_2Cl_2). The fast moving component was isolated as a viscous oil that was characterized as the rearrangement product 20: ^1H NMR ($CDCl_3$) δ 7.1–7.5 (nm, 4 H, Ar H) 4.3 (s, 1 H, exchanges with D_2O, NH), 2.56 (two overlapping t, 4 H, $2CH_2$), 2.12 (s, 3 H, NCH_3), 1.9–2.3 (nm, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 196.88 (CO), 140.66, 140.09, 133.73, 130.93, 129.95, 128.99, 127.03, 125.47 (8 sp^2 C), 37.99, 33.12, 32.31, 23.40 (4 sp^3 C); IR (neat) 3360 cm^{-1} (sharp, N–H), 1670 cm^{-1} (CO), 1620 cm^{-1} (C=C); IR ($CDCl_3$) 3360 cm^{-1} (intramolecular H bonded NH); EIMS, m/z (relative intensity) 235 and 237 ($M^{+\cdot}$, 67), 234 [$(M - H)^+$, 5], 220 [$(M - CH_3)^+$, 3], 206 [$(M - H - CO)^+$, 35], 200 [$(M - Cl)^+$, 100); EIMS (of trifluoroacetylated derivative), m/z 331 and 333 ($M^{+\cdot}$, 8), 296 [$(M - Cl)^+$, 100], 262 [$(M - CF_3)^+$, 20]; HR-EIMS gave satisfactory elemental compositions for $M^{+\cdot}$ and $(M - H)^+$ ions at m/z 235 (calcd for $C_{13}H_{14}NO^{35}Cl$ 235.0764, found 235.0728) and 234 (calcd for $C_{13}H_{13}NO^{35}Cl$ 234.0686, found 234.0682).

A solution of the above oil (15 mg, 0.1 mmol) was stirred at room temperature in 10% HCl overnight. The white solid that formed (10 mg, 70%) was shown by TLC, ^1H NMR, and mp to be identical with the elimination product 16.

2-(o-Chlorophenyl)-2-[(methoxycarbonyl)methylamino]-cyclohexanone (26). To a mixture of 1 (43.5 g, 183 mmol) and anhydrous sodium carbonate (23.3 g, 220 mmol) in 450 mL of dry benzene was added dropwise methyl chloroformate (20 mL, 258 mmol) in 100 mL of dry benzene. The resulting mixture was heated under reflux with stirring for 4 h and after cooling was washed (H_2O, 10% $KHCO_3$, H_2O, 10% HCl, H_2O), dried (Na_2SO_4), filtered, and concentrated to give a white solid. The crude product was crystallized twice from toluene to give 33 g (112 mmol, 61%) of pure **26** as colorless crystals: mp 114–115 °C; ^1H NMR ($CDCl_3$) δ 6.8–7.5 (nm, 4 H, Ar H), 3.69 (s, 3 H, OCH_3), 3.03 (s, 3 H, NCH_3), 1.5–3.5 (nm, 8 H, CH_2); IR (mineral oil mull) 1723 cm^{-1} (CO, ketone), 1692 cm^{-1} (CO, carbamate); EIMS, m/z (relative intensity) 295 and 297 ($M^+\cdot$, 267 [$(M - CO)^+\cdot$, 6], 260 [$(M - Cl)^+$, 2], 238 (77), 232 [$(M - CO - Cl)^+$, 100], 152 (59).

Anal. Calcd for $C_{15}H_{18}NO_3Cl$: C, 60.91; H, 6.13; N, 4.74. Found: C, 60.85; H, 6.09; N, 4.71.

(Z)- and (E)-2-(o-Chlorophenyl)-6-hydroxy-2-[(methoxycarbonyl)methylamino]cyclohexanone (24 and 25, Respectively). To a solution of *n*-butyllithium (85 mL, 136 mmol, 1.6 M) in hexane cooled to 0 °C was added 100 mL of dry THF and diisopropylamine (19.2 mL, 137 mmol). The resulting mixture was cooled to −78 °C and **26** (32.2 g 114 mmol) in 300 mL of dry THF was added dropwise. The mixture was stirred at −78 °C for 1 h and then chlorotrimethylsilane (17.4 mL, 137 mmol) was added. The resulting mixture was stirred at −78 °C for 10 min and then allowed to warm to room temperature. Hexane was added and the resulting solution was washed (10% Na_2CO_3, H_2O), dried (Na_2SO_4), filtered, and concentrated to give a clear oily residue which, after bulb-to-bulb distillation (145–150 °C at 2.25 mmHg), gave 86.8 g (100 mmol, 88%) of the TMS enol ether **27** as a clear oil that was homogeneous by TLC: ^1H NMR ($CDCl_3$) δ 7.0–7.6 (nm, 4 H, Ar H), 5.7 (nm, 1 H, vinylic H), 3.64 (s, 3 H, OCH_3), 2.86 (s, 3 H, NCH_3) 1.5–3.5 (nm, 6 H, CH_2); IR (CCl_4) 1700 cm^{-1} (CO carbamate), 1658 cm^{-1} (C=C); CIMS, m/z 368 and 370 (MH^+); HR-EIMS, calcd for $C_{18}H_{26}NO^{35}ClS$ 367.137, found 367.136.

To a stirred solution of this enol ether (36.8 g, 100 mml) in hexane (400 mL) containing anhydrous Na_2CO_3 (17.0 g, 160 mmol) was added *m*-chloroperoxybenzoic acid (26.0 g, 120 mmol, 85%) in portions over 30 min. The resulting mixture was stirred at room temperature for 6 h during which time a white precipitate formed. After being heated under reflux an additional hour, the mixture was concentrated and then partitioned between ether and 10% Na_2SO_3. The aqueous layer was extracted two additional times with ether and the combined extracts were shaken with 10% HCl. After being kept in contact with the aqueous acid for 7 h, the ether layer was washed (10% $KHCO_3$, H_2O), dried (Na_2SO_4), filtered, and concentrated to give 26.3 g of a yellow oil. Treatment of the oil with toluene led to the isolation of a crystalline product which, after recrystallization from toluene, provide 2.5 g (8 mmol, 8%) of pure (E)-2-(o-chlorophenyl)-6-hydroxy-2-[(methoxycarbonyl)methylamino]cyclohexanone (**25**): mp 164–165 °C; ^1H NMR ($CDCl_3$) δ 6.7–7.5 (nm, 4 H, Ar H), 4.40 (m, 1 H, methine), 3.71 (s, 3 H, OCH_3), 3.08 (s, 3 H, NCH_3); IR (KBr) 1748 cm^{-1} (CO, ketone), 1698 cm^{-1} (CO, carbamate); CIMS m/z, 312 and 314 (MH^+); EIMS, m/z (relative intensity) 311 and 313 ($M^+\cdot$, 11), 293 [$(M - H_2O)^+\cdot$, 2], 283 [$(M - CO)^+\cdot$, 59], 212 (100), 152 (86).

Anal. Calcd for $C_{15}H_{18}NO_4Cl$: C, 57.79; H, 5.82; N, 4.49. Found: C, 57.77, H, 5.92, N, 4.36.

The above mother liquors were combined and evaporated to give 24 g of an oil. This oil was subjected to column chromatography in 5-g batches using 100 g of silica (Silicar, Mallinckrodt) per batch. Elution with 5% CH_3CN in CH_2Cl_2 led to the isolation of three fractions. The first fraction (100 mL) contained the elimination product **13** (total recovered material, 2.5 g); the second fraction (100 mL) contained N-(methoxycarbonyl)ketamine (2.0 g); the third fraction (300 mL) yielded a total of 15.5 g of an oil from which an additional 2.5 g (8 mmol, 8%) of pure **25** was obtained. The total yield of the *E* isomer **25** therefore was 16%.

Examination by ^1H NMR and TLC of the oily residue remaining after the isolation of **25** indicated that it was essentially pure (Z)-2-(o-chlorophenyl)-6-hydroxy-2-[(methoxycarbonyl)-methylamino]cyclohexanone (**24**): ^1H NMR ($CDCl_3$) δ 7.0–7.5 (nm, 4 H, Ar H), 4.1–4.6 (dd, 1 H, methine, $J_{H_aH_a}$ = 7 Hz and $J_{H_aH_a}$ = 7 Hz), 3.74 (d, 1 H, exchanges with D_2O, OH), 3.64 (s, 3 H, OCH_3), 2.80 (s, 3 H, NCH_3), 1.5–3.5 (nm, 6 H, CH_2); CIMS, 312 and 314 (MH^+); EIMS, m/z (relative intensity) 311 and 313 ($M^+\cdot$, 11), 293 [$(M - H_2O)^+\cdot$, 1], 283 [$(M - CO)^+\cdot$, 59], 212 (100), 152 (80); HR-CIMS, calcd for $C_{15}H_{18}NO_4{}^{35}Cl$ 312.098, found 312.089.

Attempted Formation of the Cyclic Carbamate 15 from (Z)-2-(o-Chlorophenyl)-6-hydroxy-2-[(methoxycarbonyl)-methylamino]cyclohexanone (24). A mixture of **24** (30.9 mg, 1.0 mmol), *p*-toluenesulfonyl chloride (289 mg, 1.5 mmol), and pyridine (0.2 mL, 2.5 mmol) in 10 mL of toluene was stirred at room temperature overnight. The reaction mixture was concentrated and the crude product partitioned between CH_2Cl_2 and H_2O. The organic layer was washed with 2.0 M NaOH and H_2O, dried over Na_2SO_4, filtered, and concentrated to an oily residue. Preparative TLC (1000-μm silica gel, PLK5F, Whatman, 2% CH_3CN/CH_2Cl_2) provided the desired tosylate **28** (R_f 0.61): ^1H NMR ($CDCl_3$) δ 6.7–7.9 (nm, 8 H, Ar H), 3.61 (s, 3 H, OCH_3), 2.77 (s, 3 H, NCH_3), 2.44 (s, 3 H, tosyl CH_3); HR-CIMS gave an exact mass corresponding to $(M - H)^+$ $C_{22}H_{23}NO_6S^{35}Cl$ (calcd for 464.0935, found 464.0895); EIMS, m/z (relative intensity) 463 and 465 [$(M - 2H)^+$, 10], 428 [$(M - 2H - Cl)^+$, 10], 400 [$(M - 2H - Cl - CO)^+$, 4], 308 (50), 152 (80), 91 (100). Attempted thermal cyclization of tosylate **28** (130 °C in DMF for 5 h) led to recovery of starting material only.

Formation of the Cyclic Carbamate 15 from (E)-2-(o-Chlorophenyl)-6-hydroxy-2-[(methoxycarbonyl)methylamino]cyclohexanone (25). To a hexane solution of *n*-butyllithium (1.6 M, 0.06 mL, 0.1 mmol) cooled to −78 °C was added dropwise a solution of **25** (20 mg, 0.06 mmol) in 3 mL of THF. After 15 min, a solution of tosyl chloride (29 mg, 0.15 mmol) in 1 mL of THF was added. The reaction mixture was allowed to warm to room temperature, and the solvent was removed. The residue was partitioned between CH_2Cl_2 and H_2O, and the organic layer was washed twice with H_2O, dried (Na_2SO_4), filtered, and concentrated to yield oily **29**: ^1H NMR ($CDCl_3$) δ 6.60–7.85 (nm, 8 H, Ar H), 5.20–5.45 (dd, 1 H, methine H), 3.60 (s, 3 H, OCH_3), 3.00 (s, 3 H, NCH_3), 2.37 (s, 3 H, tosyl CH_3); HR-CIMS gave an exact mass corresponding to $(M - H)^+$ $C_{22}H_{23}NO_6S^{35}Cl$ (calcd 464.094, found 464.095); EIMS, m/z (relative intensity) 463 and 465 [$(M - 2H)^+$, 10], 428 (10), 400 (4), 308 (50), 152 (80), 91 (100). When heated for 5 h on a stream bath in DMF, tosylate **29** was converted in good yield to the cyclic carbamate **15** which was identified by ^1H NMR spectroscopy.

(Z)-2-(o-Chlorophenyl)-6-hydroxy-2-(methylamino)-cyclohexanone [(Z)-6-Hydroxyketamine (2)] from Carbamate 24. To a solution of **24** (9.7 g, 31 mmol) in 70 mL of distilled CH_2Cl_2 under argon was added *N,O*-bis(trimethylsilyl)trifluoroacetamide (13.2 mL, 50 mmol) and 2 mL of dry pyridine. The mixture was heated under reflux for 2 h and then the volatile components were removed in vacuo to yield the TMS ether **32**: ^1H NMR ($CDCl_3$) δ 3.58 (s, 3 H, OCH_3), 2.85 (s, 3 H, NCH_3), and 0.15 (s, 9 H, $Si(CH_3)_3$; EIMS, m/z (relative intensity) 383 and 385 (M^+, 3), 368 [$(M - CH_3)^+$, 4] 266 (61), 73 (100); HR-EIMS, calcd for $C_{18}H_{26}NO_4{}^{35}ClSi$ 383.1317, found 383.1335.

To a solution of **32** (11.2 g, 29 mmol) in 70 mL of distilled CH_2Cl_2 was added iodotrimethylsilane (8.2 mL, 58 mmol). The mixture was heated under reflux for 3 h, and after cooling to room temperature, MeOH (100 mL) was added. The mixture was concentrated in vacuo and the residue partitioned between H_2O and CH_2Cl_2. The CH_2Cl_2 layer was washed with 10% HCl and after adjusting the pH to 11, the aqueous layer was back-extracted with CH_2Cl_2 3 times. The CH_2Cl_2 extracts were combined and washed with H_2O, dried over Na_2SO_4, filtered, and concentrated to give 5.3 g of an amber solid. The material was sublimed and the sublimate was crystallized from benzene/cyclohexane to give 3.5 g (13.6 mmol, 47%) of pure (Z)-6-hydroxyketamine (**2**), identical in all respects with the product obtained by hydrolysis of the cyclic carbamate **15**.

(E)-2-(o-Chlorophenyl)-6-hydroxy-2-(methylamino)-cyclohexanone (3). To a solution of **25** (3.34 g, 11 mmol) in 50 mL of distilled CH_2Cl_2 under argon was added *N,O*-bis(trimethylsilyl)trifluoroacetamide (8.0 mL, 41 mmol) and 2 mL of dry pyridine. The mixture was heated under reflux for 2 h and concentrated in vacuo to yield 4.0 g (96.5%) of the pure TMS ether **30** as a colorless solid: mp 180–181 °C; ^1H NMR ($CDCl_3$) δ 3.72 (s, 3 H, OCH_3), 3.04 (s, 3 H, NCH_3), 0.14 (s, 9 H, $Si(CH_3)_3$; EIMS, m/z (relative intensity) 383 and 385 ($M^+\cdot$, 3), 368 [$(M -$

$CH_3)^+$, 4], 73 (100); HR-CIMS, calcd for $C_{18}H_{27}NO_4{}^{35}ClSi$ 384.1325, found 384.1381.

Anal. Calcd for $C_{18}H_{26}NO_4ClSi$: C, 56.31; H, 6.86; N, 3.65. Found: C, 56.29; H, 6.86; N, 3.69.

To a solution of **30** (4.01 g, 10.6 mmol) in 50 mL of distilled CH_2Cl_2 was added iodotrimethylsilane (3.1 mL, 22 mmol). The mixture was heated under reflux for 3 h, and after cooling CH_3OH (50 mL) was added. The solvent was removed and the residue in CH_2Cl_2 was washed with 10% aqueous Na_2SO_3. The white precipitate (944 mg) which separated from the CH_2Cl_2 displayed properties consistent with the carbamic acid structure **34**: mp 127 °C; IR (KBr) 1705 cm^{-1} (CO); EIMS, m/z 297 and 299 ($M^{+\cdot}$), 253 $(M - CO_2)^{+\cdot}$, 235 $(M - CO_2 - H_2O)^{+\cdot}$, 225 $(M - CO_2 - CO)^{+\cdot}$. The CH_2Cl_2 filtrate obtained after removal of the precipitate was washed with 10% $KHCO_3$ and water, dried over Na_2SO_4, filtered, and concentrated to give an oily residue (1.86 g). Column chromatography of the oil on 40 g of silica gel (Silicar 7, Mallinckrodt, 5% CH_3CN/CH_2Cl_2) gave 523 mg of a solid which, following two recrystallizations from THF/hexane and isopropyl alcohol, yielded 394 mg (14.7%) of (*E*)-6-hydroxyketamine (**3**) as colorless crystals: mp 114–115 °C; ^1H NMR ($CDCl_3$) δ 7.1–7.5 (nm, 4 H, Ar H), 4.5–4.85 (nq, 1 H, methine H), 4.15 (bs, exchanges with D_2O, OH), 2.12 (s, 3 H, NCH_3); IR (KBr) 1705 cm^{-1} (CO); EIMS, m/z (relative intensity) 253 and 255 ($M^{+\cdot}$, 2), 235 $[(M - H_2O)^{+\cdot}$, 2], 225 $[(M - CO)^{+\cdot}$, 145], 180 (100), 152 (90).

Anal. Calcd for $C_{13}H_{16}NO_2Cl$: C, 61.52; H, 6.36; N, 5.54. Found: C, 61.44; H, 6.35; N, 5.20.

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Registry No. **1**, 6740-88-1; **2**, 91003-16-6; **3**, 91003-25-7; **4**, 91003-09-7; **5**, 91003-10-0; **6**, 91003-11-1; **7**, 91003-12-2; **10**, 91003-13-3; **13**, 91003-15-5; **14**, 91003-17-7; **15**, 91003-14-4; **20**, 91003-18-8; **23**, 91032-21-2; **24**, 91003-27-9; **25**, 91003-20-2; **26**, 91003-19-9; **27**, 91003-21-3; **28**, 91003-22-4; **29**, 91003-23-5; **30**, 91003-26-8; **32**, 91003-24-6; benzyl chloroformate, 501-53-1; methyl chloroformate, 79-22-1.

Thermolysis of 3-Bromo-1-nitro-1*H*-indazoles in Benzene and Toluene. Formation of 1-Phenyl-1*H*-indazoles[1]

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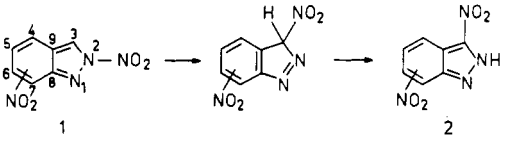
Thermolysis of the 3-bromo-1-nitro-1*H*-indazoles **5a,b** in refluxing benzene results in the evolution of bromine and NO_2 affording the 3-bromo-1*H*-indazoles **6a,b**, the dinitro-1*H*-indazoles **2a,b**, and the 1-phenyl-1*H*-indazoles **7a,b** and **8a,b**. In refluxing toluene only **6a,b** and **2a,b** are formed in addition to benzyl bromide. The structure assignments, particularly the assignment of the 1-position for the phenyl group in **7a,b** and **8a,b**, are based on ^{13}C NMR spectra. Possible mechanisms are presented for the loss of bromine and NO_2 and for the N-phenylation reaction found to occur in refluxing benzene.

The first paper in the literature reporting nitration on the nitrogen atom of indazoles[3] described the synthesis of a number of 2-nitro-2*H*-indazoles **1a–d** and their thermal rearrangement to the 3-nitro-2*H*-indazoles **2a–d** which presumably occur via an initial migration of the nitro group to the adjacent carbon atom[4] (see Scheme I). Since then,

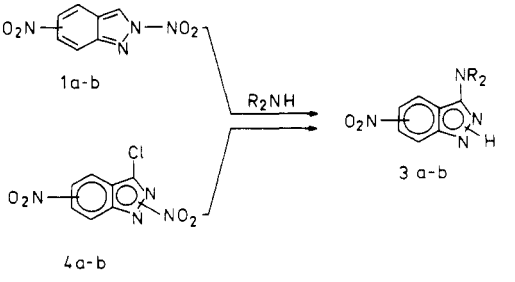
Scheme I



1 2

a, 5-NO_2; b, 6-NO_2; c, 4-NO_2; d, 7-NO_2

Scheme II



1a-b 3 a-b 4a-b

it has been shown that high yields of 3-nitro-substituted indazoles can be obtained in this way.[6,7] Moreover,

(1) Part 4 of our Indazoles Studies. For part 3 see ref 2.

(2) Waalwijk, P. S.; Cohen-Fernandes, P.; Habraken, C. L. *J. Org. Chem.*, submitted for publication.

(3) Cohen-Fernandes, P.; Habraken, C. L. *J. Org. Chem.* **1971**, *36*, 3084–3086.

(4) (a) When indazole has an unsubstituted NH group there is the possibility of tautomerism and to our knowledge 1*H*- and 2*H*-tautomers have never been isolated as separate compounds, although they may enter chemical reactions predominantly in one form. An indication that the exchange of the NH proton is so fast that the "tautomeric mixture" behaves magnetically as a single compound is evident from the proton magnetic resonance spectra of these indazoles exhibiting a one-proton signal for H-3. For indazoles designated either as 1*H*- or 2*H*-indazoles the existence and therefor the participation in reactions of the other tautomer is understood. (b) Mechanistic Studies of the analogous thermal rearrangement of 1-nitropyrazoles to 3(5)-nitropyrazoles have established that all experimental data are compatible with a rate-determining 1,5-shift of the NO_2 group to give the 3*H*-pyrazole as an intermediate, which subsequently isomerizes to the 3(5)-nitropyrazole.[5] Consequently, now we assume for the thermal isomerization of 2-nitro-2*H*-indazoles that we are dealing with an identical case, i.e., an initial rearrangement to 3*H*-indazole followed by a fast 1,5-H shift to 3-nitro-2*H*-indazole as depicted in Scheme I.

(5) Janssen, J. W. A. M.; Habraken, C. L.; Louw, R. *J. Org. Chem.* **1976**, *41*, 1758–1762 and earlier publications cited therein.

0022-3263/84/1949-3310$01.50/0