THE JOURNAL OF Organic Chemistry®

VOLUME 46, NUMBER 25

DECEMBER 4, 1981

Synthesis of Ketamine Metabolites I and II and Some Anomalous Reactions of 6-Bromoketamine

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Received March 10, 1981

Two metabolites of the drug ketamine, 2-(2-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride (1),[1a] have been synthesized. They are the *N*-demethyl compound, metabolite I (13), and the *N*-demethyl-5,6-dehydro analogue, metabolite II (15). Three bromo ketones derived from ketamine have also been synthesized and their relative configurations assigned. In addition, attempted dehydrohalogenation of axial 2-bromoketamine (2a) with sodium amide in liquid ammonia has produced a novel entry into the 6-azabicyclo[3.2.0]heptane ring system. The structure of the rearrangement product (3) has been confirmed by unequivocal synthesis. Other unusual reactions include the reduction of an *N*-alkylazetidinone to an *N*-alkylazetidine and an acid-catalyzed *N*-alkyl cleavage of a β-lactam.

One of the isolated metabolites of the drug ketamine, 2-(2-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride (1),[1a] is the *N*-demethyl-5,6-dehydro analogue metabolite II (15).[2] This product arises during metabolism by demethylation of the methylamino functionality followed by the introduction of a double bond into the 2,3-position of the cyclohexanone ring.[3] We undertook the unequivocal synthesis of this compound to confirm the proposed structure and to prepare a sample for pharmacological studies.

Since ketamine was readily available to us,[1b] is was decided to use it as a model compound, and α-bromination followed by dehydrohalogenation appeared to be the most direct method to introduce the double bond.

Bromination of 1 in 48% hydrobromic acid afforded a good yield of the bromo ketone (2a) as the hydrobromide salt. This material was satisfactory for use in most reactions; however, preparative thick-layer chromatography revealed the presence of approximately 4–7% of 2,2-dibromo-6-(2-chlorophenyl)-6-(methylamino)cyclohexanone (4) and a trace of the epimeric bromo ketone 2e (Scheme IV). From the intrepretation of infrared and proton magnetic resonance spectra, it was determined that the bromine in compound 2a is axial and that of the epimer (2e) is equatorial.[4]

Table I. Carbonyl Absorption Data of 2a,b,e and Ketamine (Free Base 1) under Various Infrared Sample Conditions

		λ_{max}, cm^{-1}			
no.	conditions	2a	2b	2e	1 (free base)
1	liquid film	1704	1732		
2	chloroform	1706	1733		1714
3	carbon tetrachloride	1712	1740		
4	potassium bromide			1704	
5	chloroform			1734	1714

Since the steric relationship of the functionalities in the unbrominated ketone had been previously established for several substituted phenyl analogues,[5] the relative configurations assigned to the two isomeric bromo ketones has the methylamino functionality cis to the bromine in 2a and trans to the bromine in 2e.

(1) (a) Stevens, C. L. U. S. Patent 3 254 124; *Chem. Abstr.* **1968**, *65*, 5414. (b) Ketamine is marketed by Parke-Davis and Co. under the trade name Ketalar.

(2) Chang, T.; Dill, W. A.; Glazko, A. J. *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **1965**, *24*, 268. Chang, T.; Savory, A.; Albin, M.; Goulet, R.; Glazko, A. J. *Clin. Res.* **1970**, *18*, 597.

(3) The isolation of both the 5- and 6-hydroxymethyl compounds as metabolites indicates that the double bond is introduced by dehydration. Glazko, A. J.; et al., unpublished toxicity study on file at Warner-Lambert/Parke-Davis Pharmaceutical Research Laboratories, Ann Arbor, MI.

(4) Infrared references, 4a–d; NMR references, 4e–g; combined IR and NMR references for 2-bromo-6-phenylcyclohexanones 4h. (a) Corey, E. J.; and Burke, H. J. *J. Am. Chem. Soc.* **1955**, *77*, 5418. (b) Allinger, J.; Allinger, N. L. *Tetrahedron* **1958**, *14*, 64. (c) Allinger, J.; Allinger, N. L. *J. Am. Chem. Soc.* **1958**, *80*, 5476. (d) Hanack, Michael, Ed. "Conformation Theory"; Academic Press: New York, 1965; p 153. (e) Garbisch, E. W., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 1780. (f) Baretta, A.; Zahra, J. P.; Waegell, B.; Jefford, C. W. *Tetrahedron* **1970**, *26*, 15. (g) Wellman, K. M.; Bordwell, F. G. *Tetrahedron Lett.* **1963**, 1703. (h) Miller, B.; Wong, H. S. *Tetrahedron* **1972**, *28*, 2369.

(5) Stevens, C. L.; Hanson, H. T.; Taylor, K. G. *J. Am. Chem. Soc.* **1966**, *88*, 2769. Stevens, C. L.; Thuillier, A.; Daniher, F. A. *J. Org. Chem.* **1965**, *30*, 2962.

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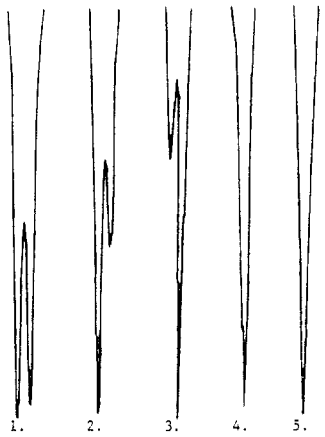
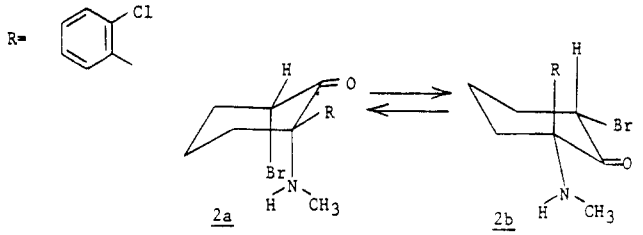


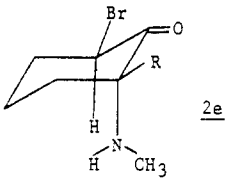
Figure 1. Carbonyl absorption bands for **2a,b** in liquid film, chloroform and carbon tetrachloride and the carbonyl absorption of **2e** in KBr and chloroform.

In order to relieve the unfavorable *cis*-1,3-diaxial interaction between the 6-methylamino and 2-bromo substituents, a solvent dependent equilibrium is established between the axial and the equatorial bromo ketones **2a** and **2b**.[6] The infrared carbonyl absorptions and frequencies



for **2a** and **2b** as a liquid film, in chloroform, and in carbon tetrachloride are shown in Figure 1 and Table I. For the liquid film, the relative carbonyl absorptions are approximately equal (Figure 1-1) while the more polar solvent chloroform favors the equatorial configuration for bromine (Figure 1-2). On the other hand, the less polar solvent carbon tetrachloride favors the axial configuration (Figure 1-3).

The assignment of the designated configuration to the equatorial bromo ketone **2e** produces a structure without an unfavorable 1,3-diaxial interaction as shown by a single shifted carbonyl in both KBr and chloroform (Figure 1 and Table I).

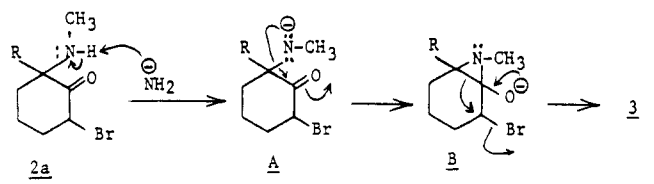


After several of the standard methods for dehydrohalogenation failed to produce the desired model compound (**11**), elimination of hydrogen bromide from **2a** was accomplished by employing the bicyclic base 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in acetonitrile (Scheme IV).

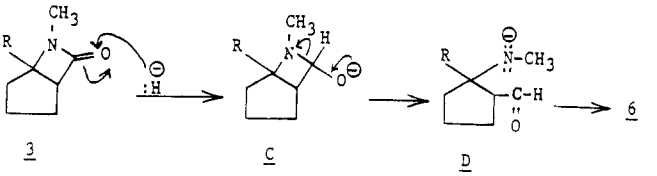
The synthesis of metabolite I (**13**) proceeded smoothly (Scheme VI) with the hydroxy imine **12** being formed in good yield (90%) by the action of liquid ammonia on 1-bromocyclopentyl 2-chlorophenyl ketone.[1] The thermal rearrangement of the hydrochloride salt of **12**, in Dowtherm-A at 200 °C, produced metabolite I (**13**) in 88% yield. Bromination of **13** in 48% hydrobromic acid provided the

(6) A similar equilibrium carbonyl mixture has been observed for the two conformers of 2-bromocyclohexanone (see ref 4b).

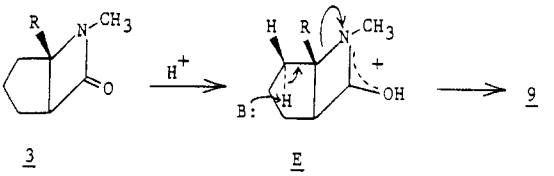
Scheme I



Scheme II



Scheme III



bromo ketone **14** which was dehydrohalogenated to metabolite II (**15**) by the procedure employed with the model compound **2a**. The infrared and proton magnetic resonance spectra of both **13** and **15** were identical with those of the compounds isolated by Glazko and co-workers.[2]

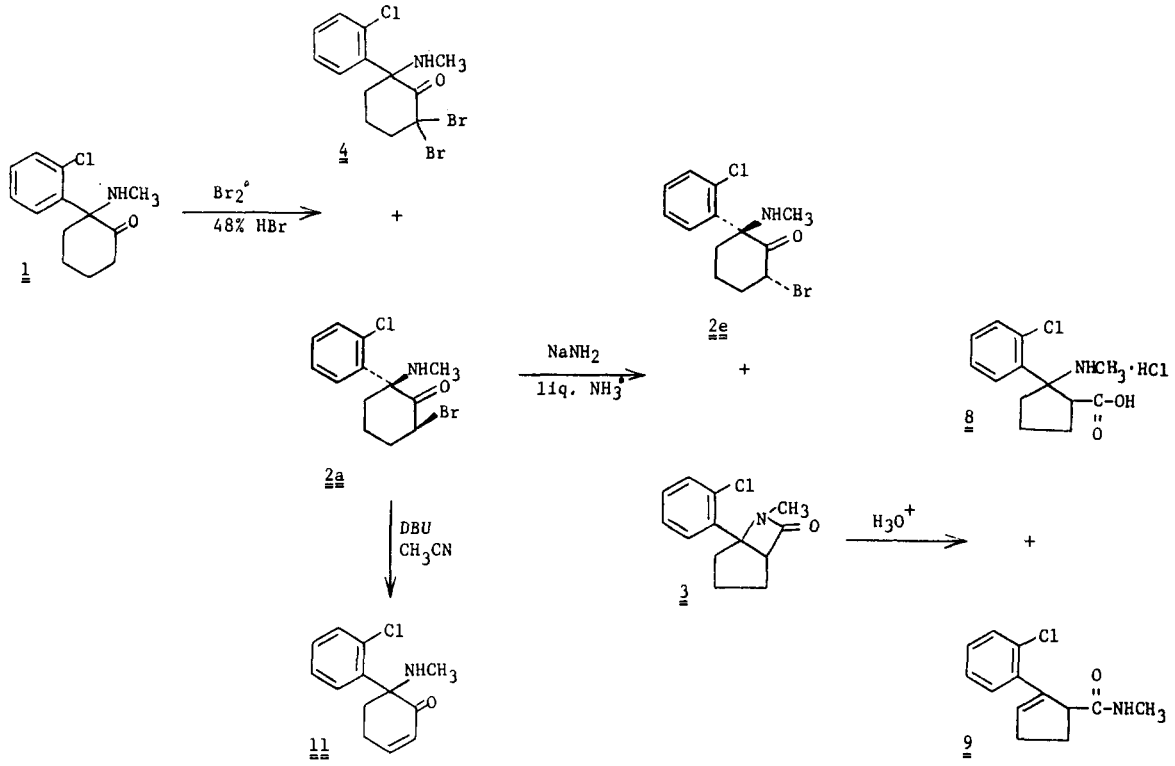
One of the attempted dehydrohalogenations of **2a** using sodium amide in liquid ammonia produced the bicyclic β-lactam **3** in a 36% yield and also epimerized the initial bromo ketone **2a** to the equatorial epimer **2e** (Scheme IV). The proposed mechanism for the formation of **3** follows a quasi-Favorskii pathway (Scheme I). Sodium amide abstracts a proton from **2a**, yielding the amide ion A which attacks the carbonyl to give the intermediate B. The re-formation of the carbonyl group to form the β-lactam causes the migration of the C_1–C_2 bond which displaces bromide ion in typical Favorskii fashion.[7]

In order to establish the structure of **3**, we performed a lithium aluminum hydride reduction which afforded the tertiary azetidine **5** and the amino alcohol **6** (Scheme V). The almost exclusive formation of **5** (>90% yield) was rather unexpected since it has been reported that the lithium aluminum hydride reduction of 1-alkyl-substituted azetidinones produces substituted aminopropanols exclusively.[8] The expected amino alcohol (**6**) was isolated in trace quantities from the distillation residue of **5**. Since 1-substituted azetidinones cannot form a ring-stabilized conjugate base with aluminum hydride, the mechanism for amino alcohol formation in this case may begin with the attack of a hydride ion on the lactam carbonyl, yielding the alkoxy ion C (Scheme II). Re-formation of the carbonyl double bond causes the breaking of the carbonyl carbon–nitrogen bond, thus forming the amide ion and the aldehyde D. The aldehyde is further reduced to the al-

(7) For a review see: Kende, A. S. *Org. React.* **1960**, *11*, 261.

(8) The reduction also fails to produce azetidines with 1-arylazetidinones. Speeter, M. E.; Maroney, W. H. *J. Am. Chem. Soc.* **1954**, *23*, 1102. Klonowski, R. S., Ph.D. Thesis, University of Michigan, 1959; "Heterocyclic Compounds with Three- and Four-Membered Rings"; Weissberger, A., Ed.; Wiley: New York, 1964; Part 2, p 947. However, $LiAlH_4$ reductions run on N-unsubstituted or *N*-acylazetidinones provides a good method for azetidine formation. Testa, E.; Bonati, A.; Pagani, G.; and Gatti, E. *Justus Liebigs Ann. Chem.* **1961**, *647*, 92. Testa, E.; Fontanella, L.; Mariani, L.; and Cristiani, G. F. *Ibid.* **1961**, *633*, 56; "Heterocyclic Compounds with Three- and Four-Membered Rings"; Weissberger, A., Ed.; Wiley: New York, 1964; pp 900, 947.

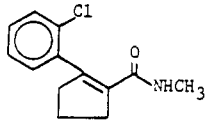
Scheme IV



cohol, and the amide ion is protonated during isolation to produce **6**.

Hydrolysis of the azetidinone **3** in concentrated hydrochloric acid (Scheme IV) led to the formation of the amino acid hydrochloride **8** and the carboxamide **9**. The relatively high yield of **9**[9] was rather unexpected since it requires the somewhat unusual *N*-alkyl cleavage which has been reported for only a few other amide systems.[10] The proposed mechanism involves protonation of the carbonyl oxygen, yielding the delocalized carbonium ion E from which **9** can be formed directly via a concerted trans elimination (Scheme III).[11]

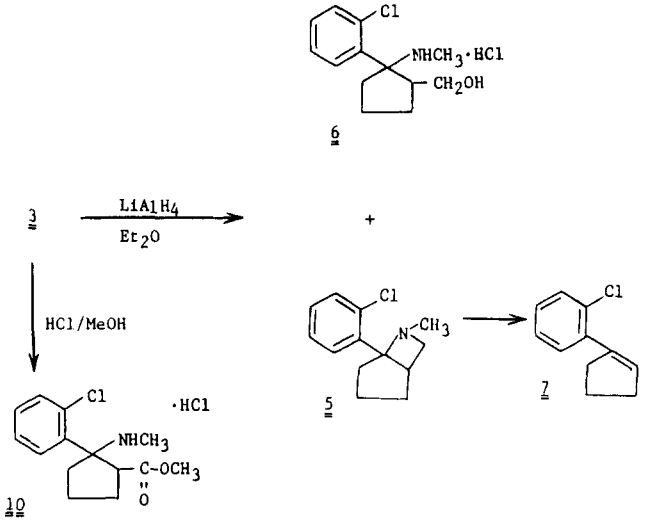
There were no other double bond positional isomers of **9** detected in the reaction mixture. Initially a structure such as **18** might seem likely since the double bond is



18

conjugated not only into the phenyl ring as in **9** but also to the carbonyl function. Structure **18**, however, requires a configuration in which the 2-chlorophenyl and carboxamide groups are cis and therefore have a bulky steric interaction.

Scheme V



Acid methanolysis of **3** (Scheme V) led to the expected amino acid ester **10**; carboxamide formation was not observed in this case probably due to the nucleophilicity and/or lower basicity of methanol. An attempt to open the azetidine ring (**5**) by using Eschweiler–Clark conditions produced an inseparable mixture of basic compounds. However, the isolation of the neutral compound 1-(2-chlorophenyl)cyclopentene (**7**),[12] which arises by fragmentation of the azetidine ring, provided further proof of structure for **5**.

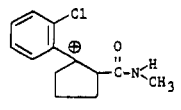
With the information obtained from the reactions of **3**, the proposed structure seemed highly probable. However, since it requires a complete skeletal rearrangement of **2a** to produce this novel structure, it was decided to attempt to synthesize **3** by an unequivocal route.

A search of the literature showed that the 1,2-dipolar cycloaddition reaction of chlorosulfonyl isocanate (CSI)

(9) The 50% yield of **9** accounted for two-thirds of the products isolated.

(10) (a) Morrall, W. S. *J. Am. Chem. Soc.* **1960**, *82*, 5707. (b) Zalkow, L. H.; Kennedy, C. D. *J. Org. Chem.* **1963**, *28*, 852. (c) Moran, A. G.; Conley, R. T. *Ibid.* **1969**, *34*, 3259.

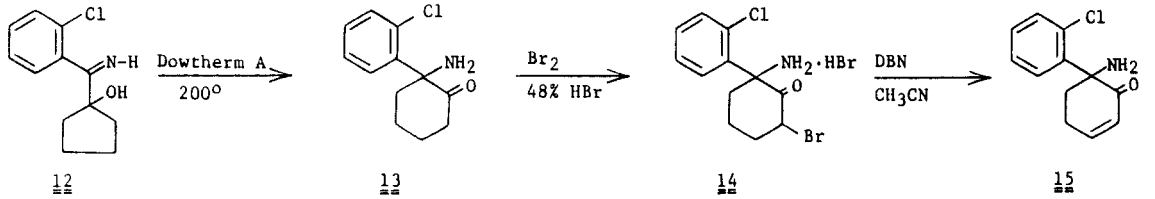
(11) In a nonconcerted mechanism, the intermediate formation of a benzyl carboniumion (F) is not only possible, but is consistent with the mechanism proposed by Moran and Conley.[10c]



F

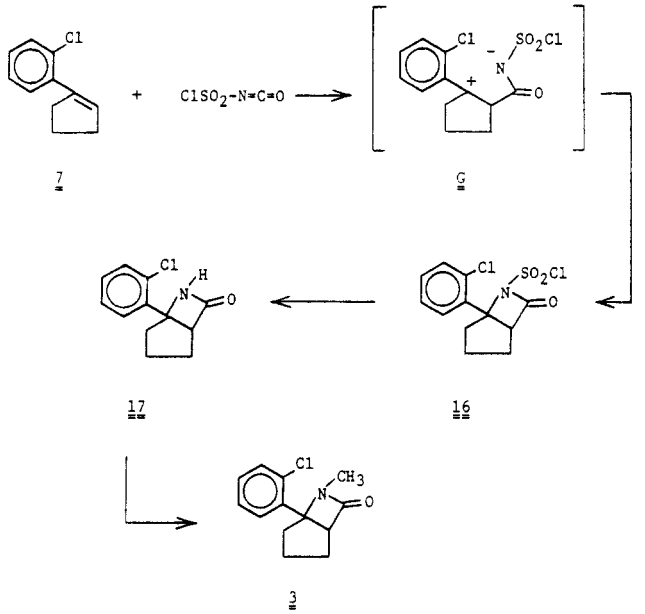
(12) Parham, W. E.; Wright, C. D. *J. Am. Chem. Soc.* **1961**, *83*, 1751.

Scheme VI



12 13 14 15

Scheme VII



7 G 17 16 3

with alkenes proceeds by a two-step mechanism with the overall result being Markovnikov addition to the double bond.[13] The addition of CSI to 1-(2-chlorophenyl)cyclopentene (7) proceeded exothermically via the proposed tertiary benzyl carbonium ion intermediate (G) to produce the *N*-chlorosulfonyl β-lactam **16** in 81% yield (Scheme VII). Hydrolysis of **16** with potassium iodide in aqueous ethanol, with the pH of the reaction being maintained between pH 7.0 and 7.4 by the addition of 10% aqueous potassium hydroxide, afforded the β-lactam **17**. Alkylation of **17** with sodium hydride in tetrahydrofuran followed by methyl iodide gave a good yield of **3** which was identical by infrared and proton magnetic resonance spectroscopy with the material produced by the action of sodium amide in liquid ammonia on **2a**. Therefore, we not only have succeeded in preparing the two ketamine metabolites (**13** and **15**) as planned but also have established a new synthetic pathway to the 6-azabicyclo[3.2.0]heptane ring system.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Digilab FTS-14 or Beckman IR 9 prism grating-dispersion instrument. ^1H nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM-390 or a Bruker WH-90 instrument. The Bruker WH-90 was modified with a Nicolet Technology Corp. B-NC12 data acquisition system. Chemical shifts are reported in parts per million from internal tetramethylsilane. Combustion analyses were performed on a Perkin-Elmer 240 elemental analyzer. Solutions were dried with magnesium sulfate and concentrated on a rotary evaporator at 30–40 °C at pressures of 5–20 mmHg. Distillations were run in vacuo at the temperatures and pressures indicated in the experimental procedures. Isolated solids were dried in a vacuum oven at room temperature and pressures of 5–20 mmHg.

2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride (1) was prepared by the method of Stevens:[1a] IR (KBr) 1728 cm^{-1} (C=O); IR (free base in $CHCl_3$) 1714 cm^{-1} (C=O).

6-Bromo-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone Hydrobromide (2a). To a rapidly stirred 80 °C solution of 119 g (0.50 mol) of the free base of **1** in 1.5 L of 48% aqueous HBr was added dropwise 168 g (1.05 mol) of Br_2, with a GE 500-W lamp (Type CZX) as the light source. The reaction was stirred for 10 min after the addition was complete, cooled to 20 °C and the precipitate removed by filtration. It was washed successively with 48% aqueous HBr, *i*-PrOH, and Et_2O and dried to give 195 g (98%) of **2a**, mp 252–254 °C. A small sample was recrystallized from H_2O; mp 259–261 °C. Anal. Calcd for $C_{13}H_{15}BrClNO \cdot HBr$: C, 39.27; H, 4.06; N, 3.52; Found: C, 39.02; H, 4.11; N, 3.55. The hydrobromide salt was to insoluble for solution spectra, so a small sample was converted to the free base: IR, see Figure 1 and Table I; NMR ($CDCl_3$) δ 2.02 (s, 3 H), 1.50–2.94 (m, 6 H), 4.42–4.61 (m, 1 H), 7.00–7.52 (m, 4 H).

5-(2-Chlorophenyl)-6-methyl-6-azabicyclo[3.2.0]heptan-7-one (3). To a solution of 1.13 mol of sodium amide in 2.5 L of liquid ammonia was added dropwise a solution of 444 g (1.11 mol) of the free base of **2a** in 500 mL of toluene. The reaction mixture was stirred for 2 h, the ammonia evaporated, and the residue dissolved in a mixture of 2.5 L of Et_2O and 1 L of H_2O. The mixture was decolorized with charcoal and filtered through Celite, and the layers were separated. The organic layer was washed with H_2O, dried, filtered, and concentrated, and the residue was distilled to give 81 g (36%) of **3**, bp 124 °C (0.1 mm). The distillate crystallized on being allowed to stand: mp 63–66 °C; IR (film) 1760 cm^{-1} (C=O); IR ($CHCl_3$) 1744 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.05 (m, 6 H), 2.95 (s, 3 H), 3.65 (m, 1 H); 7.35 (m, 4 H). Anal. Calcd for $C_{13}H_{14}ClNO$: C, 66.24; H, 5.99; Cl, 15.04; N, 5.94. Found: C, 66.31; H, 6.05; Cl, 15.10; N, 6.02.

6-Bromo-2-(2-chlorophenyl)-2-(methylamino)cyclohexanone (2e). The aqueous acid extracts from **3** were combined, made basic with 50% NaOH, and extracted with Et_2O. The combined Et_2O layers were washed with H_2O, dried, and filtered, and the solvent was removed to give 56 g of **2e**, mp 115–118 °C. The original charcoal–Celite filter cake from the isolation of **3** was heated in 500 mL of THF and filtered, and the solvent was evaporated to give an additional 50 g of **2e**, mp 116–119 °C. An analytical sample was recrystallized from Et_2O: mp 119–120 °C dec; IR, see Figure 1 and Table I; NMR ($CDCl_3$) δ 2.18 (s, 3 H), 1.67–2.78 (m, 6 H), 5.09–5.33 (m, 1 H), 7.05–7.37 (m, 4 H). Anal. Calcd for $C_{13}H_{15}BrClNO$: C, 49.31; H, 4.78; Br, 25.24; Cl, 11.20; N, 4.42. Found: C, 49.45; H, 4.93; Br, 25.54; Cl, 11.33; N, 4.30.

Preparative Chromatography of the Bromination Products of 1. A 1-g sample of the free base from the bromination of **1** was dissolved in cyclohexane/acetone (1:1) and streaked on two 20 × 20 cm preparative silica gel plates and developed in benzene/acetonitrile (9:1). The silica gel was scraped off, separating the three reaction products: I, R_f 0.14; II, R_f 0.41; III, R_f = 0.66. The three portions were extracted into MeOH and evaporated. The residues were dissolved in Et_2O, clarified with charcoal, filtered through Celite, and evaporated. Compound I did not crystallize as the free base. Therefore, it was converted to its hydrochloride salt, affording 570 mg of product melting at 252 °C dec. IR and TLC showed I to be the axial bromo ketone **2a**. Compound II (trace amount) was shown by IR and TLC to be the epimeric equatorial bromo ketone **2e**. Compound III crystallized as the free base and was recrystallized from Et_2O/

(13) Graf, R. *Justus Liebigs Ann. Chem.* **1963**, *661*, 111. Moriconi, E. J.; Kelly, J. F. *J. Am. Chem. Soc.* **1966**, *88*, 3657. Moriconi, E. J.; Crawford, W. C. *J. Org. Chem.* **1968**, *33*, 370, 3036. Graf, R. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 172.

petroleum ether, affording 70 mg of 2,2-dibromo-6-(2-chlorophenyl)-6-(methylamino)cyclohexanone (4): mp 147–148 °C; IR (KBr) 1706 (C=O), 3385 cm^{-1} (NH); NMR ($CDCl_3$) δ 2.14 (s, 3 H), 1.58–2.49 (m, 4 H), 3.02–3.23 (m, 2 H), 7.02–7.64 (m, 4 H). Anal. Calcd for $C_{13}H_{14}Br_2ClNO$: C, 39.47; H, 3.57; N, 3.54. Found: C, 39.74; H, 3.52; N, 3.47.

5-(2-Chlorophenyl)-6-methyl-6-azabicyclo[3.2.0]heptane (5). A solution of 36.0 g (0.152 mol) of **3** in 200 mL of Et_2O was added dropwise to a suspension of 12.0 g (0.32 mol) of $LiAlH_4$ in 350 mL of Et_2O. The mixture was stirred for 2 h and decomposed by the consecutive dropwise addition of 12 mL of H_2O, 9 mL of 40% aqueous NaOH, and 42 mL of H_2O, titrating the final H_2O addition to give a granular precipitate. The solid was removed by filtration and washed with Et_2O. The combined filtrates were concentrated, and the residue was distilled to give 31.5 g of a mixture of **5** and **6**, bp 72–85 °C (0.1 mm). Redistillation afforded the analytical sample of **5**: 29.5 g (90%); bp 75–77 °C (0.1 mm); IR (film) 3070, 1567 (ArH), 2276 (NCH_3), 758 cm^{-1} (Cl); NMR ($CDCl_3$) δ 1.95 (m, 6 H), 2.43 (s, 3 H), 2.62 (m, 1 H), 3.08 (m, 1 H), 3.75 (t, 1 H), 7.36 (m, 4 H). Anal. Calcd for $C_{13}H_{16}ClN$: C, 70.40; H, 7.28; N, 6.32. Found: C, 70.42; H, 7.33; N, 6.28.

2-(Methylamino)-2-(2-chlorophenyl)cyclopentanemethanol Hydrochloride (6). The distillation residue (2.0 g) from **5** was converted to its hydrochloride salt by using 2-propanolic hydrogen chloride to give 2.0 g of **6**, mp 232–235 °C. One recrystallization from *i*-PrOH/Et_2O afforded the analytical sample: mp 235–237 °C; IR (KBr) 3400 (NH, OH), 1562 cm^{-1} (Ar); NMR (D_2O) δ 1.39–2.55 (m, 6 H), 2.55 (s, 3 H), 3.02 (m, 1 H), 3.98 (s, 1 H), 4.09 (d, 1 H), 7.48–7.87 (m, 4 H). Anal. Calcd for $C_{13}H_{18}ClNO{\cdot}HCl$: C, 56.53; H, 6.93;, Cl, 25.67; N, 5.07. Found: C, 56.64; H, 7.03; Cl, 25.72; N, 5.01.

2-(Methylamino)-2-(2-chlorophenyl)cyclopentanecarboxylic Acid Hydrochloride (8). A solution of 10.0 g (0.042 mol) of **3** in 60 mL of concentrated hydrochloride acid was heated at 90 °C for 1 h. The solvent was evaporated and the residue triturated with several 10-mL portions of dioxane which were also removed by evaporation. The crystals which formed were removed by filtration and washed copiously with Et_2O to give 3.0 g (24%) of **8**: mp 205–207 °C; IR (KBr) 1720 cm^{-1} (C=O); NMR (D_2O) δ 2.10 (m, 6 H), 2.58 (s, 3 H), 3.72 (m, 1 H), 4.93 (s, HDO + 3 H) 7.68 (m, 4 H). Anal. Calcd for $C_{13}H_{16}ClNO_2{\cdot}HCl$: C, 53.81; H, 5.91; N, 4.83. Found: C, 53.73; H, 5.91; N, 4.63.

2-(2-Chlorophenyl)-*N*-methyl-2-cyclopentene-1-carboxamide (9). The combined ether washings from the isolation of **8** were evaporated to give 5.0 g (50%) of **9**, mp 125–128 °C. Two recrystallizations from cyclohexane afforded the analytical sample: mp 129–130 °C; IR ($CHCl_3$) 1660 and 1520 (C=O), 3440 cm^{-1} (NH); NMR ($CDCl_3$) δ 2.48 (m, 4 H), 2.63 (d, 3 H), 3.93 (m, 1 H), 5.78 (m, 1 H), 6.20 (m, 1 H), 7.28 (m, 4 H). The peak at δ 5.78 (m, 1 H) was exchanged with D_2O, the rest of the spectrum remaining essentially unchanged. Anal. Calcd for $C_{13}H_{14}ClNO$: C, 66.24; H, 5.99; Cl, 15.04; N, 5.94. Found: C, 66.21; H, 5.93; Cl, 15.39; N, 5.84.

Methyl 2-(Methylamino)-2-(2-chlorophenyl)cyclopentanoate Hydrochloride (10). A solution of 10.0 g (0.042 mol) of **3** and 4.0 g (0.11 mol) of anhydrous HCl in 100 mL of MeOH was refluxed for 7 days. The solvent was removed and the residue triturated with Et_2O to give 11.0 g (85%) of **10**, mp 172–175 °C. One recrystallization from *i*-PrOH/Et_2O afforded the analytical sample: mp 173–175 °C; IR (KBr) 1730 (C=O), 3430 cm^{-1} (NH·HCl); NMR (D_2O) δ 2.05 (m, 6 H), 2.53 (s, 3 H), 3.73 (m, 1 H), 3.97 (s, 3 H), 4.86 (s, HDO), 7.68 (m, 4 H). Anal. Calcd for $C_{14}H_{18}ClNO{\cdot}HCl$: C, 55.27; H, 6.30; N, 4.61. Found: C, 55.25; H, 6.37; N, 4.53.

1-(2-Chlorophenyl)cyclopentene (7). To a 50 °C solution of 50 mL of formic acid and 15 mL of formaldehyde was added 29.5 g (0.133 mol) of **5**. The mixture was refluxed for 3 h and the solvent evaporated. The residue was diluted with Et_2O and extracted with aqueous HCl. The aqueous acid layer was made basic with 50% NaOH and extracted with Et_2O. The Et_2O layer was washed with H_2O, dried, and concentrated, and the residue was distilled to give 8.0 g of product, bp 115–120 °C (0.1 mm). NMR showed it to be a mixture of compounds although TLC in several different solvent systems showed only one spot.

The initial Et_2O layer was washed with 5% NaOH, dried, and concentrated, and the residue was distilled in vacuo to give 15.0 g (63%) of **7**: bp 68–69 °C (0.1 mm); IR and NMR spectra were identical with those of an authentic sample.[12]

6-(Methylamino)-6-(2-chlorophenyl)cyclohex-2-enone (11). A solution of 66.5 g (0.210 mol) of **2**, 34.0 g (0.224 mol) of 1,5-diazobicyclo[5.4.0]undec-5-ene, and 200 mL of CH_3CN was heated at reflux for 18 h. The solvent was removed and the residue dissolved in Et_2O and H_2O. The Et_2O layer was washed with H_2O and extracted with 5% aqueous HCl. The aqueous acid layer was decolorized with Norit, filtered through Celite, and made basic with 50% aqueous NaOH. The aqueous base fraction was extracted with Et_2O, washed with H_2O, and dried, and the solvent was evaporated to give 21 g (42%) of **11**, mp 103–120 °C. Two recrystallizations from EtOH/H_2O afforded the analytcal sample: mp 127–129 °C; IR (KBr) 3340 (NH), 1665 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.75–3.21 (m, 4 H), 1.95 (s, 1 H), 2.22 (s, 3 H), 6.02–6.31 (m, 1 H), 6.71–7.74 (m, 5 H). The singlet at δ 1.95 could be exchanged with D_2O. Anal. Calcd for $C_{13}H_{14}ClNO$: C, 66.24; H, 5.99; N, 5.94. Found: C, 65.99; H, 6.19; N, 5.97.

1-[(2-Chlorophenyl)iminomethyl]cyclopentanol (12). To 2.5 L of liquid NH_3 was added portionwise over 1 h 864 g (3.00 mol) of (1-bromocyclopentyl)(2-chlorophenyl)methanone.[1] The mixture was stirred for 4 h and the ammonia allowed to evaporate. The residue was suspended in THF, and the precipitate was removed by filtration and dried. The filtrate was concentrated and the residue triturated with petroleum ether. The resulting precipitate was removed by filtration and dried: yield 638 g (95%); mp 84–89 °C. One recrystallization from cyclohexane/petroleum ether gave 605 g (90%) of **12**: mp 89–91 °C; IR (KBr) 3200 (NH, OH), 1623 cm^{-1} (C=N); NMR (CCl_4) δ 1.74 (m, 8 H), 7.35 (m, 4 H). Anal. Calcd for $C_{12}H_{14}ClNO$: C, 64.43; H, 6.31; N, 6.26. Found: C, 64.57; H, 6.54; N, 6.14.

2-Amino-2-(2-chlorophenyl)cyclohexanone (13). A solution of 655 g (2.93 mol) of **12** in 750 mL of *i*-PrOH was saturated with anhydrous HCl and then diluted to 1.5 L with anhydrous Et_2O. The crystals that formed were removed by filtration and dried to give 758 g (100%) of **12** as the hydrochloride salt. To 3 L of Dowtherm-A at 200 °C was added 379 g (1.46 mol) of **12** (hydrochloride salt) which caused the temperature to fall to 180 °C, where it was maintained for 7 min. The reaction mixture was cooled to 10 °C, and the solid was removed by filtration and dissolved in H_2O. The filtrate was diluted to 3 L with Et_2O and extracted with H_2O. The combined aqueous fractions were washed with Et_2O, made basic with 50% aqueous NaOH, and extracted with Et_2O. The ether layer was washed with water, dried, decolorized with charcoal, filtered through Celite, and concentrated. The residue was distilled to give 288 g (88%) of **13**: bp 123–125 °C (0.1 mm); IR (film, free base) 3310, 3385 (NH_2), 1718 cm^{-1} (C=O); NMR (CCl_4) δ 1.33–2.97 (m, 10 H), 7.48 (m, 4 H). A small sample was converted to the hydrochloride salt by using 2-propanolic hydrogen chloride and recrystallized from *i*-PrOH/Et_2O to afford the analytical sample, mp 236–237 °C. Anal. Calcd for $C_{12}H_{14}ClNO{\cdot}HCl$: C, 55.40; H, 5.81; N, 5.38. Found: C, 55.20; H, 5.83; N, 5.29.

2-Bromo-6-amino-6-(2-chlorophenyl)cyclohexanone Hydrobromide (14). A solution of 298 g (1.33 mol) of **13** in 1.2 L of 48% aqueous HBr was heated to 70 °C, and 216 g (1.35 mol) of bromine was added dropwise. The mixture was stirred for 10 min after the addition was complete and cooled to 5 °C. The crystals were removed by filtration, washed copiously with acetone, and dried to give 408 g of **13**, mp 142–145 °C. A second crop (30 g, mp 142–145 °C) was obtained by decolorizing and concentrating the acetone washes. An NMR was run in D_2O and showed the presence of excess protons in the HOD peak. The entire yield of 441 g was azeotroped in 500 mL of xylene, with the recovery being 420 g (82%; mp 209–210 °C) and the water collected in a Dean–Stark trap corresponding to a monohydrate. A small sample was converted to the free base for spectral analysis: mp 146–148 °C; IR (KBr) 3358 (NH_2), 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.48–3.14 (m, 6 H), 2.20 (s, 2 H), 4.72 (m, 1 H), 7.63 (m, 4 H). The two-hydrogen singlet at δ 2.20 could be exchanged with D_2O. Anal. Calcd for $C_{12}H_{13}BrClNO$: C, 47.63; H, 4.33; N, 4.63. Found: C, 47.90; H, 4.23; N, 4.42.

6-Amino-6-(2-chlorophenyl)-2-cyclohexen-1-one (15). A solution of 35 g (0.28 mol) of 1,5-diazabicyclo[4.3.0]non-5-ene, 200 mL of acetonitrile, and 74 g (0.25 mol) of **14** (free base) was refluxed for 20 h. The solvent was evaporated and the residue

diluted with ether and 5% aqueous NaOH. The layers were separated, and the organic layer was extracted with 5% aqueous HCl. The combined acid-water layers were decolorized with charcoal, filtered through Celite, and made basic with 50% aqueous NaOH. The crystalline precipitate was removed by filtration, washed with water, and dried to give 31 g (57%) of **15**, mp 120-123 °C. Two recrystallizations from benzene/petroleum ether and one from ethanol/water afforded the analytical sample: mp 128-130 °C; IR (KBr) 1656 (C=O), 3380 and 3310 cm^{-1} (NH_2); NMR ($CDCl_3$) δ 1.97 (s, 2 H), 2.42 (m, 4 H), 6.22 (d, 1 H), 6.97 (m, 1 H), 7.36 (m, 4 H). The signal at δ 1.97 (s, 2 H) could be exchanged with D_2O. Anal. Calcd for $C_{12}H_{12}ClNO$: C, 65.01; H, 5.46; N, 6.32. Found: C, 64.71; H, 5.42; N, 6.21.

5-(2-Chlorophenyl)-6-(chlorosulfonyl)-6-azabicyclo-[3.2.0]heptan-7-one (16). To a solution of 14.2 g (0.1 mol) of chlorosulfonyl isocyanate (CSI) in 20 mL of CH_2Cl_2 was added all at once 17.9 g (0.1 mol) of 1-(2-chlorophenyl)cyclopentene (**7**).[12] After a 5-min induction period the reaction reached a gentle reflux which continued for ~0.5 h. The solvent was evaporated in vacuo, and the residue was diluted with ice and H_2O. After the mixture was neutralized to pH 7.0 with 10% NaOH, the precipitate was removed by filtration, washed with H_2O, and dried in vacuo to give 26.0 g (81%) of **16**: mp 108-109 °C; IR (KBr) 1811 (C=O), 1405 and 1180 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 1.92-2.59 (m, 5 H), 2.73-3.02 (m, 1 H), 4.03-4.16 (m, 1 H), 7.19-7.46 (m, 3 H), 7.50-7.68 (m, 1 H). Anal. Calcd for $C_{12}H_{11}Cl_2NSO_3$: C, 45.01; H, 3.46; N, 4.38. Found: C, 45.18; H, 3.64; N, 4.62.

5-(2-Chlorophenyl)-6-azabicyclo[3.2.0]heptan-7-one (17). A solution of 4.7 g (14.7 mmol) of **16** in 60 mL of 50% aqueous EtOH was treated with 1.0 g of KI and neutralized to pH 7.0 by the dropwise addition of 10% aqueous KOH. When the pH was constant at 7.0, the EtOH was removed at reduced pressure, and the aqueous phase and precipitate were extracted with Et_2O. The Et_2O layer was washed with H_2O, dried ($MgSO_4$), filtered, and evaporated in vacuo to give 2.7 g (84%) of **17**, mp 122-125 °C. One recrystallization from $EtOH/H_2O$ and two recrystallizations from cyclohexane afforded the analytical sample: mp 123-125 °C; IR ($CHCl_3$) 3170 (NH), 1758 and 1770 cm^{-1} (doublet, C=O); NMR ($CDCl_3$) δ 1.77-2.28 (m, 6 H), 3.60-3.75 (m, 1 H), 6.67-6.96 (m, 1 H), 7.07-7.39 (m, 4 H). Anal. Calcd for $C_{12}H_{12}ClNO$: C, 65.01; H, 5.46; N, 6.32. Found: C, 65.00; H, 5.36; N, 6.34.

5-(2-Chlorophenyl)-6-methyl-6-azabicyclo[3.2.0]heptan-7-one (3). A solution of 1.1 g (5.0 mmol) of **17** in 10 mL of THF was added dropwise to a suspension of 0.48 g (10.0 mmol) of 50% NaH in mineral oil in 20 mL of THF. The reaction was stirred until gas evolution ceased (~0.5 h) and 1 h thereafter. The flocculent suspension was treated dropwise with 1.42 g (10 mmol) of CH_3I in 5 mL of THF and then stirred at room temperature overnight. The solvent was removed in vacuo and the residue diluted with Et_2O and H_2O. The organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated in vacuo to give 1.0 g (85%) of **3** (mp 64-66 °C) which had IR and NMR spectra identical with those of the material produced by the action of sodium amide in liquid ammonia on **2a**.

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

Registry No. **1**, 6740-88-1; **1**·HCl, 1867-66-9; **2a**, 79548-68-8; **2a**·HBr, 79548-69-9; **2a**·HCl, 79548-70-2; **2e**, 79548-71-3; **3**, 79517-34-3; **4**, 79499-53-9; **5**, 79517-35-4; **6**, 79517-36-5; **7**, 38793-82-7; **8**, 79517-37-6; **9**, 79499-54-0; **10**, 79499-55-1; **11**, 79499-56-2; **12**, 79499-57-3; **12**·HCl, 79499-58-4; **13**, 35211-10-0; **13**·HCl, 79499-59-5; **14**, 79499-60-8; **14** (free base), 79499-61-9; **15**, 57683-62-2; **16**, 79499-62-0; **17**, 79499-63-1; (1-bromocyclopentyl)(2-chlorophenyl)methanone, 6740-86-9.

Tandem Alkylation-Reduction of 2-Acylpyrroles. Convenient One-Pot Syntheses of 2-Benzylpyrroles[1]

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Received July 14, 1981

Tandem alkylation-reduction of 2-acylpyrroles is described for the convenient one-pot syntheses of 2-benzylpyrroles. By this convenient procedure 2-(*p*-methoxybenzyl)pyrrole (**2**), 2-benzylpyrrole (**3**), 2-(*p*-methylbenzyl)pyrrole (**4**), 2-(*o*-methoxybenzyl)pyrrole (**5**), and 2-(*m*-methoxybenzyl)pyrrole (**6**) were prepared from *p*-methoxyphenyllithium, phenyllithium, *p*-tolyllithium, *o*-methoxyphenyllithium, and *m*-methoxyphenyllithium, respectively. Arylation-reduction of 2-acetylpyrrole (**7**) and 2-benzoylpyrrole (**11**) were the only entries that did not result in a direct one-pot synthesis of the corresponding α-methyl- and α-phenyl-2-benzylpyrrole. In contrast to the organolithium reagents, employment of Grignard reagents in this alkylation-reduction sequence requires N-protection of the pyrrole ring, otherwise low yields of the 2-benzylpyrroles are observed. Examples of useful synthetic procedures include the alkylation-reduction of *N*-methylpyrrole-2-carboxaldehyde (**14**), *N*-benzylpyrrole-2-carboxaldehyde (**16**), and *N*-[(β-methoxyethoxy)methyl]pyrrole-2-carboxaldehyde (**17**) with *p*-methoxyphenylmagnesium bromide to prepare *N*-methyl-2-(*p*-methoxybenzyl)pyrrole (**15**), 2-(*p*-methoxybenzyl)pyrrole (**2**), and *N*-[(β-methoxyethoxy)methyl]-2-(*p*-methoxybenzyl)pyrrole (**18**), respectively; *N*-[(β-methoxyethoxy)methyl]-2-(*p*-methylbenzyl)pyrrole (**19**) was prepared from **17** and *p*-tolylmagnesium bromide.

In our studies[1] extending the usefulness of tandem alkylation-reductions of carbonyl compounds, we have not investigated to any extent the applicability of this synthetically useful procedure to acyl heterocycles.[3] Recently, the need arose in this research group for an efficient synthesis of 2-benzylpyrroles, and 2-(*p*-methoxybenzyl)pyrrole (**2**) in particular. We envisioned the application of our tandem alkylation-reduction procedure as outlined below.

(1) Part 13 in the series "Alkylation-Reduction of Carbonyl Systems". For part 12 see: Ryan Zilenovski, J. S.; Hall, S. S. *J. Org. Chem.* **1981**, *46*, 4139-4142.

(2) Taken in part from the Ph.D Thesis of D.P.S. that was submitted to the Graduate School, Rutgers University, Newark, NJ, May 1981. H. Martin Friedman Thesis Award (Rutgers University), May 1981.

(3) Furan-2-carboxaldehyde was effectively phenylated-reduced in a survey project, while 2-acetylthiophene led to a mixture of products. See: Hall, S. S.; McEnroe, F. J. *J. Org. Chem.* **1975**, *40*, 271-275.

0022-3263/81/1946-5060$01.25/0