cold EtOAc (300 mL), and acidified to pH 2.0 with phosphoric acid (20 %). The aqueous layer was extracted again with EtOAc (200 mL). The combined organic layer was washed quickly with water (2 × 100 mL, 0 °C), dried briefly ($Na_2SO_4$), and filtered. Addition of 3 mL of 1 M potassium 2-ethylhexanoate solution in EtOAc and of anhydrous $Me_2CO$ (50 mL) afforded crystals of **1b** (potassium salt), which were collected and washed with anhydrous $Me_2CO$ (20 mL) to yield 0.687 g (62%) of product: $R_f$ ($Me_2CO$–HOAc, 19:1) 0.66, ($C_6H_6$–$Me_2CO$–HOAc, 75:20:5) 0.63; IR (KBr) $\nu_{max}$ 3360, 1670, 1485 (amide), 1780, 1760 (sh, β-lactam) 1615, 1400 (carboxylate), 700 (phenyl) $cm^{-1}$; $^1H$ NMR ($D_2O$, DSSA) δ 1.55 (s, $CH_3$), 1.58 (s, $CH_3$), 3.55 (s, $CH_2CO$), 4.33 (s, 3-H), 4.70 (s, HOD), 5.48 (s, 5-H), 7.25 (s, $C_6H_5$). Iodometric titration indicated that only 1.7% penicilloic acid was present. Loss on drying (60 °C in vacuo over $P_2O_5$) was 1.1%.

**Epimerization and Deuteration of (Phenoxymethyl)penicillin (*S*)-*S*-Oxide Benzyl Ester (7a) and of Its 6-Epimer (8a).** The progress of the epimerization of **7a** and **8a** and the percentage decomposition of these penicillin *S*-oxides were followed by high-pressure LC using a 250 × 4.6 mm LiChrosorb RP-18 (10 μm) column with $CH_3OH$–$H_2O$ (70:30) as the mobile phase at a flow rate of 2.5 mL/min and UV detection at 254 nm. Molar ratios of **7a** (or **8a**), $D_2O$, and $Et_3N$ were identical with those described for the isomerization of **4a**. The penicillin *S*-oxide esters **7a** or **8a** (228 mg, 0.5 mmol) were dissolved in a stock solution (2.3 mL), consisting of $CH_3CN$ (50 mL), $D_2O$ (5.63 mL), $Et_3N$ (1.75 mL), and naphthalene (500 mg) as internal standard. The solution was kept at room temperature and at regular intervals 10-μL samples were taken, diluted with MeOH (1 mL), and analyzed by high-pressure LC. The percentage of epimerization was calculated from the **7**/**8** ratio, which was obtained from the peak areas of **7** ($k'$ = 4.8) and **8** ($k'$ = 2.9). A ratio of 40:60 was considered as a 100% epimerization. The percentage degradation of **7** and **8** was calculated from their peak areas and from that of the internal standard ($k'$ = 11). For the determination of the percentage deuteration as a function of the reaction time, 1-mmol samples of **7a** and **8a** were epimerized under the conditions mentioned for **4a**. For reaction times up to 24 h the epimerization mixture was worked up as described for **4a** and both isomers were separated by crystallization from MeOH and $C_6H_6$. Crystalline **7** and **8** were analyzed for deuterium at C-6 by $^1H$ NMR spectroscopy. In the case of reaction times exceeding 24 h, chromatography on a silica gel column with $C_6H_6$–$Me_2CO$ (90:10) was used for separation of **7** and **8**. The percentages of epimerization and degradation were calculated from the amounts of both isomers, isolated after column chromatography.

**Acknowledgment.** We are indebted to Professor M. Szwarc, University of Southern California, and to one of the referees for their helpful comments with regard to the mechanism of deuteration. We also thank Dr. G. Janssen for mass spectral determinations and I. Quintens and L. Kerremans for technical assistance. Financial support of this research by the Belgian Fonds voor Wetenschappelijk Geneeskundig Onderzoek is gratefully acknowledged. P. Herdewijn is Aspirant of the Belgian Nationaal Fonds voor Wetenschappelijk Onderzoek.

**Registry No. 1b**, 76757-86-3; **2a**, 24652-72-0; **2a** *N*-*d* derivative, 76773-02-9; **3a**, 41536-91-8; **4a**, 54275-92-2; **4b**, 76757-87-4; **5a**, 73036-92-7; **5b**, 76757-88-5; **6b**, 76757-89-6; **7a**, 42879-04-9; **8a**, 42879-05-0.

# Syntheses of Amine Derivatives of Phencyclidine

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3-Aminophencyclidine (**5**) was synthesized by reduction of 3-nitrophencyclidine (**3**) using either $H_2$ with Pd/C or $Na_2S$ in refluxing methanol. Attempts to isolate 4-aminophencyclidine (**2**), which we hoped to synthesize by hydrolysis of carbamate **15** which was isolated after reaction of amide **10** under Hofmann conditions employing bromine in $CH_3O^-/CH_3OH$ at −40 °C, were unsuccessful. 4-Aminomethylphencyclidine (**18**) was synthesized by LAH reduction of nitrile **13** as well as by reductive amination of aldehyde **20**. Nitrile **13** and aldehyde **20** were synthesized from 4-bromophencyclidine (**11**) as was alcohol **26** which served as a precursor to 4-(2-aminoethyl)phencyclidine (**19**). Amine **19** was also synthesized by $NaBH_4$ reduction of β-nitrostyrene **29** which was generated from aldehyde **20** by condensation with nitromethane using 1,5-diazabicycloundecene as the base catalyst followed by LAH reduction of the resulting 4-(2-nitroethyl)phencyclidine (**30**). Mass spectra and $^{13}C$ NMR spectra have been obtained on most of the phencyclidine derivatives.

As part of a fluorescence immunoassay for phencyclidine (1-(1-phenylcyclohexyl)piperidine (**1**), we required derivatives of **1** which would be sufficiently nucleophilic that they could be covalently coupled to appropriate fluorescent dyes and proteins. Although many phencyclidine analogues have been synthesized,[1] the general procedure used to make most of them precludes incorporation of functional groups, such as primary amines, which contain acidic protons. Recently however 1-[1-(4-aminophenyl)cyclohexyl]piperidine (**4**) was reported[2] to have been prepared by reduction of a nitro phencyclidine, thought to be **2**, which was obtained after nitration of **1** (eq 1). We[3] have repeated this work and find the major product resulting from nitration of **1**, under a variety of conditions, is 3-nitrophencyclidine (**3**) as would be expected from the nitration of a benzylamine.[4] Isomer **2** could be isolated by preparative high-performance LC as a minor product

(1) (a) A. Kalir, H. Edery, Z. Pelah, D. Bolderman, and G. Porath, *J. Med. Chem.*, **12**, 473 (1969), and references cited therein. (b) V. H. Maddox, E. F. Godefroi, and R. F. Parcell, *J. Med. Chem.*, *8*, 230 (1965). For more recent approaches to phencyclidine-type systems see A. Gabrielevitz et al., *Life Sci.*, **26**, 89 (1980).

(2) A. Kalir, S. Maayani, M. Rehavi, R. Elkavets, I. Pri-Bar, O. Buchman, and M. Sokolovsky, *Eur. J. Med. Chem.*, **13**, 17 (1978).

(3) While our work was being completed another group also isolated and characterized **2** and **3**. See P. Geneste, J-M. Kamenka, and A. Mas, *Bull. Soc. Chem. Fr.*, 609 (1978).

(4) H. M. Gilow et al., *J. Org. Chem.*, **36**, 1745 (1971).

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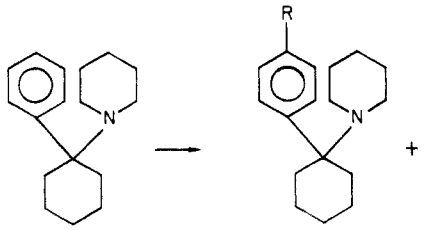
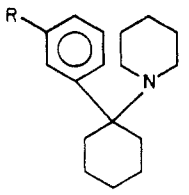


1

2, R = $NO_2$
4, R = $NH_2$
8, R = N=N (diazo)
15, R = $NHCO_2Me$
16, R = $N(CH_3)_2$



(1)

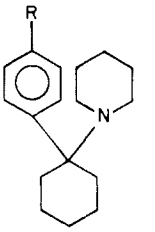
3, R = $NO_2$
5, R = $NH_2$
9, R = N=N (diazo)
17, R = NHCSNHPh

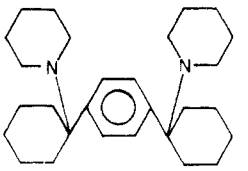
from the crude reaction mixture which was shown by high-performance LC to contain an 8/2 ratio of **3** and **2**.

3-Nitrophencyclidine was readily reduced to 3-aminophencyclidine (**5**) in 70–80% yield by either hydrogenation over 5% Pd/C catalyst or by refluxing it with 1.2 equiv of $Na_2S·9H_2O$ in methanol. Attempts to reduce **2** to **4** employing similar procedures resulted in either reductive or eliminative loss of piperidine to give (4-aminophenyl)-cyclohexane (**6**)[5] or 1-(4-aminophenyl)cyclohexene (**7**).[5] Reduction with LAH converted **2** and **3** into their respective azo compounds **8** and **9** in good yields.[6] Our inability to reduce **2** to **4** prompted us to consider alternate routes to **4** such as Hofmann rearrangement of amide **10**. Toward this goal 4-bromophencyclidine (**11**) was synthesized in 79% yield along with varying amounts (5–15%) of the previously unreported diadduct **12**. Reaction of **11** with 5 equiv of CuCN in DMF at 110 °C for 3 days gave 4-cyanophencyclidine (**13**) in 71% yield.[7] Higher reaction temperatures resulted in significant elimination of piperidine to give 1-(4-cyanophenyl)cyclohexene (**14**).[8] Hydrolysis of **13** in 30% hydrogen peroxide–aqueous $K_2CO_3$/acetone[9] for 3 h at −40 °C allowed isolation of the desired 4-carbamylphencyclidine (**10**). Treatment of **10** under Hofmann reaction conditions,[10] MeONa/MeOH followed by addition of $Br_2$ at −40 °C, gave carbamate **15**, which, while unstable to silicic acid, could be purified by column chromatography on neutral alumina, using ether/ethanol as the eluant. Reaction of **15** in aqueous $K_2CO_3$/MeOH at 25 °C for 6 h led to recovery of **15** while hydrolysis at 60 °C in aqueous KOH/MeOH for 4–6 h resulted in the isolation of **7** most likely via initial hydrolysis to give **4** followed by rapid elimination of piperidine. Interestingly 4-(dimethylamino)phencyclidine (**16**), which we synthesized as part of this series, proved to be a stable solid which showed little inclination to eliminate piperidine at moderate temperatures (<100 °C).

While 3-aminophencyclidine reacted at 40 °C with 1 equiv of phenyl isothiocyanate in $Me_2SO$ containing a catalytic amount of triethylamine to give mixed thiourea **17**,[11] it was found not to be sufficiently nucleophilic to react with activated carboxyl groups on the protein bovine serum album under conditions reported to couple alkyl primary amines.[12]

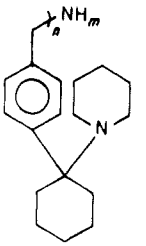
In search of more nucleophilic amine derivatives of phencyclidine, we have synthesized primary amines 4-(aminomethyl)- (**18**) and 4-(2-aminoethyl)phencyclidine (**19**), each by several routes which would be amenable to specific tritium incorporation. Reduction of nitrile **13** by addition of **13** to LAH in refluxing ether gave benzylamine **18** in 83% yield. Because of the reported difficulties in handling $LA^3H$,[13] a procedure which would allow the use of $NaBH_4$ or $NaCNBH_3$ (or their $^3H$ derivatives) was also sought. Metalation of **11** with BuLi in THF at −78 °C followed by reaction of the anion generated with dry DMF gave 4-formylphencyclidine (**20**) in 78% yield. Reductive amination of **20** using $NaBH_4$ in MeOH with $NH_4OAc$ at 25 °C for 2 days gave the amine **18** in moderate yield along with varying amounts of secondary amine **21**, tertiary amine **22**, and benzyl alcohol **23**. Reaction of **20** for 4 days with $NH_4OAc$ and $NaCNBH_3$ in MeOH at 25 °C gave, however, good yields, 78%, of **18** as a low-melting solid. Reduction of oxime **24**, prepared from aldehyde **20**, by either Zn/AcOH or hydrogenation over 10% Pd/C resulted in competitive hydrogenolysis of the benzylic piperidine. Reaction of **24** with LAH in refluxing THF gave mixtures of **18**, **21**, and **22**.





12

10, R = $CONH_2$
11, R = Br
13, R = CN
18, R = $CH_2NH_2$
20, R = CH=O
23, R = $CH_2OH$
24, R = CH=NOH
25, R = $CH_2CH$=O
33, R = $CH_2NHCSNHPh$
35, R = $CH_3$
36, R = $CH_2Br$

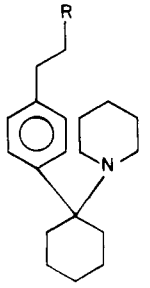


21, $n$ = 2, $m$ = 1
22, $n$ = 3, $m$ = 0

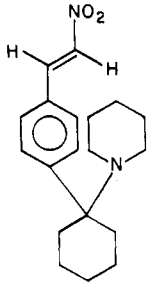
Phenethylamine **19** was to be prepared by reductive amination of phenylacetaldehyde **25**. However, oxidation of phenethyl alcohol **26**, prepared by reaction of the Grignard reagent derived from bromide **11** with ethylene oxide, by procedures which had been reported to be good for this type of conversion,[14] resulted mainly in formation

(5) P. G. Ferini et al., German Patent 2421, 121 (1975); *Chem. Abstr.*, **82**, 156126 (1975).
(6) For other examples of this reductive coupling reaction see A. Puszynski and Z. Rykowski, *Rocz. Chem.*, **51**, 2451 (1977). While further reduction of **8** represents an approach to **2**, we have not pursued it.
(7) A modification of the procedure of H. O. House and W. F. Fischer, *J. Org. Chem.*, **34**, 3626 (1969). We have subsequently found that this reaction is over in 1 day without concomitant formation of **14** when 4-iodophencyclidine is employed as the starting material.
(8) R. C. Hahn, T. F. Corbi, and H. Shechter, *J. Am. Chem. Soc.*, **90**, 3404 (1968).
(9) K. B. Wiberg, *J. Am. Chem. Soc.*, **77**, 2519 (1955).
(10) P. Radlick and L. R. Brown, *Synthesis*, 290 (1974).
(11) For modification of a procedure used to couple fluorescent dye isothiocyanates to aromatic amines, see T. L. Deits, G. R. Gapski, and J. M. Whiteley, *J. Pharm. Sci.*, **66**, 434 (1977).
(12) For aqueous conditions using the water-soluble carboxyl-activating reagent 1-cyclohexyl-3-(2-morpholin-1-ylethyl)carbodiimide metho-*p*-toluenesulfonate, see T. L. Goodfriend, L. Levine, and G. D. Fasman, *Science*, **144**, 1344 (1964).
(13) Manufacturer's (New England Nuclear) technical sheet recommends use within 7 days.

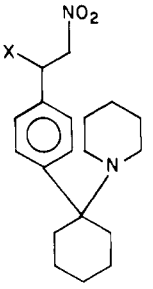
of aldehyde **20**, with only small amounts of **25** being isolatable, or in no reaction. Alcohol **26** could be converted to amine **19** by classical routes not particularly suited to radiolable incorportion by converting it to mesylate **27** followed by reaction with potassium phthalimide in DMF and subsequent deprotection of pthalimide derivative **28** with hydrazine in ethanol. An alternate route to **19** involves in situ reduction of β-nitrostyrene **29** with $NaBH_4$ in $Me_2SO$.[15] Specifically, reaction of aldehyde **20** with 5 equiv of nitromethane in $Me_2SO$ at 25 °C containing a catalytic amount of 1,5-diazabicycloundecene resulted in rapid (ca. 5 min), quantitative formation of nitro alcohol **30**. This reaction had to be quenched carefully with acetic acid and worked up so as not to reverse the addition reaction. Traditional procedures[16] involving $NH_4OAc$ in EtOH or NaOH resulted in 60/40 mixtures of **20** and **30** after 1 to 2 days. Attempts to eliminate $H_2O$ from **30** to give styrene **29**[17] resulted in concomitant loss of piperidine.



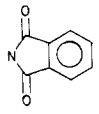
**19**, R = $NH_2$
**26**, R = OH
**27**, R = $OSO_2CH_3$



**29**



**30**, X = OH
**31**, X = OAc



**28**, R =

**32**, R = $NO_2$
**34**, R = NHCSNHPh

Alcohol **30** could be converted to its acetate **31** by reacting it with 1 equiv of acetic anhydride in acetic acid containing 1.1 equiv of $H_2SO_4$. Acetate **31** was reduced, without isolation, with $NaBH_4/Me_2SO$ to give 4-(2-nitroethyl)phencyclidine (**32**) in 63% yield. The nitro compound was subsequently converted to phenethylamine **19** by reduction with LAH in ether. As anticipated, amines **18** and **19** reacted rapidly with phenyl isothiocyanate, using standard conditions, to give mixed thioureas **33** and **34**, respectively.

Finally, our inability to brominate 4-methylphencyclidine (**35**), using either $Br_2$ or NBS in refluxing $CCl_4$ with light and/or benzoyl peroxide, without concomitant loss of the piperidine group prevented use of 4-(bromomethyl)phencyclidine (**36**) as a reaction intermediate in the synthesis of **18** or **19**. Syntheses of other classes of nucleophilic derivatives of phencyclidines are in progress.

## Experimental Section

**General Procedures.** Melting points were taken on a Thomas-Hoover Unimelt and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer. The $^1H$ NMR spectra were taken on a Varian T-60 or CFT-80 spectrometer and are reported in parts per million downfield from $Me_4Si$. The $^{13}C$ NMR spectra were taken on a Varian CFT-20 spectrometer and are reported in parts per million downfield from $Me_4Si$. The abbreviations s (singlet), d (doublet), t (triplet), and q (quartet) refer to the multiplicity of the absorption in an off-resonance decoupled spectrum. Mass spectra were determined on a Varian MAT-7 spectrometer using the direct inlet system. Gas chromatography was carried out by using programmed temperature control on a Varian 1740 instrument equipped with a flame-ionization detector and a 2- or 4-ft glass column packed with SE-30, SE-52, or Carbowax 20M on Chromosorb P. High-performance LC separations were performed on a Waters 500 Prep Instrument, using Prep PAK columns. Microanalyses were performed by Micro-Tech Laboratories, Skokie, IL. All reactions were executed under dry nitrogen.

**1-(1-Phenylcyclohexyl)piperidine (1).** Phencyclidine was prepared as described[1] in 80–85% yield: mp 45–46 °C (EtOH); $^1H$ NMR ($CDCl_3$) δ 1.0–1.7 (m, 12), 1.9–2.1 (m, 4), 2.1–2.4 (m, 4), 7.32 (br s, 5); $^{13}C$ NMR[18] ($CDCl_3$) δ 140.3 (s), 127.5 (d), 127.3 (d), 126.0 (d), 61.0 (s), 46.6 (t), 33.7 (t), 27.2 (t), 26.5 (t), 25.1 (t), 22.5 (t).

**1-[1-(3-Nitrophenyl)cyclohexyl]piperidine (3) and 1-[1-(4-Nitrophenyl)cyclohexyl]piperidine (2).** To 12.2 g (0.05 mol) of 1 dissolved in 25 mL of concentrated $H_2SO_4$ at 0 °C was added dropwise 3.9 g (0.06 mol) of chilled $HNO_3$ (1.5 d). After the exothermic reaction mixture was allowed to stir for 1 h at 25 °C, it was diluted with 100 mL of $H_2O$, made basic with concentrated $NH_4OH$, and extracted with $CHCl_3$ to give, after removal of solvent, 13 g of a pale yellow solid. High-performance LC analysis showed the solid to be an 8/2 mixture of two components. The major component was isolated in 70% yield by crystallization from $CH_3OH$ and identified by its spectra as 3-nitrophencyclidine: mp 84–85 °C (lit.[3] mp 83–84 °C); IR ($CHCl_3$) 2930, 2850, 2795, 1524, 1350, 1205 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.0–1.6 (m, 12), 1.8–2.0 (m, 4), 2.0–2.2 (m, 4), 7.35–7.7 (m, 2), 7.9–8.15 (m, 2); $^{13}C$ NMR ($CDCl_3$) δ 148.1 (s), 143.4 (s), 133.4 (d), 128.4 (d), 121.9 (d), 121.2 (d), 61.1 (s), 47.6 (t), 34.6 (t), 27.1 (t), 26.3 (t), 24.9 (t), 22.2 (t); mass spectrum, *m/e* (70 eV, relative intensity) 288 ($M^+$, 25), 287 (14), 246 (21), 245 (100), 231 (18), 199 (8), 166 (25), 84 (35) with a metastable ion at *m/e* 208.4 ($245^2/288$).

The minor component which was isolated by preparative high-performance LC, using silicic acid Prep Pak columns with hexane–acetone eluant, was crystallized from EtOH and identified as 4-nitrophencyclidine: mp 89–90 °C (lit.[4] mp 90–91 °C); $^1H$ NMR ($CDCl_3$) δ 1.0–1.6 (m, 12), 1.8–2.0 (m, 4), 2.1–2.3 (m, 4), 7.42 (d, 2, *J* = 9 Hz), 8.18 (d, 2, *J* = 9 Hz).

**1-[1-(3-Aminophenyl)cyclohexyl]piperidine (5). A.** A solution of 2.88 g (0.01 mol) of 3 in 100 mL of EtOH containing 5 mL of 10% aqueous $K_2CO_3$ was hydrogenated in a Parr apparatus at 20–50 psi and 25 °C for 1–2 h, using 0.5 g of 5% Pd/C as the catalyst. Removal of the Pd/C by filtration and solvents under reduced pressure gave a solid which was crystallized from EtOH–$H_2O$ to give 2.28 g (88%) of amine 5: mp 123–125 °C; IR ($CHCl_3$) 3440, 2950, 1625, 1365, 1230 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.0–1.6 (m, 12), 1.8–2.0 (m, 4), 2.1–2.4 (m, 4), 3.4 (br s, 2, absent in $D_2O$), 6.5–7.3 (m, 4); $^{13}C$ ($CDCl_3$) δ 145.6 (s), 141.6 (s), 128.1 (d), 118.1 (d), 114.4 (d), 112.9 (d), 60.9 (s), 46.6 (t), 33.8 (t), 27.2 (t), 26.5 (t), 25.1 (t), 22.5 (t); mass spectrum, *m/e* (70 eV, relative intensity) 258 ($M^+$, 32), 257 (27), 216 (18), 215 (100), 201 (20), 175 (30), 174 (20), 173 (28), 166 (25), 165 (60), and 84 (90), with a metastable ion at *m/e* 179.1 ($215^2/258$).

**B.** A solution of 2.88 g (0.01 mol) of 3 was refluxed with 2.9 g (0.012 mol) of $Na_2S·9H_2O$ in 100 mL of $CH_3OH$ for 1 h. The solvent was removed under reduced pressure at 25 °C and the residue extracted with $H_2O/CHCl_3$. The organic layer was dried with $MgSO_4$ and solvent evaporated to give 70–85% yields of 5.

**LAH Reduction of Nitrophencyclidines 2 and 3.** Reaction of 3 and 2 with excess LAH in refluxing ether gave, in good yields, the respective azo compounds 9 and 8 as orange solids. For 3,3′-bis[1-(1-piperidyl)cyclohexyl]azobenzene (9): mp 213–215 °C (hexane); $^1H$ NMR ($CDCl_3$) 1.1–1.7 (m, 24), 1.9–2.1 (m, 8), 2.1–2.4 (m, 8), 7.3–8.0 (m, 8); mass spectrum, *m/e* (70 eV, relative

(14) (a) R. Filler and Y. S. Rao, *J. Org. Chem.*, *39*, 3304 (1974); (b) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
(15) G. B. Bachman and R. J. Maleski, *J. Org. Chem.*, **37**, 2810 (1972).
(16) A. I. Meyers and J. C. Sircar, *J. Org. Chem.*, **32**, 4134 (1967).
(17) In our case, the electron-withdrawing para substituent inhibits acid-catalyzed elimination processes. See R. T. Borchandt and D. R. Thakker, *J. Med. Chem.*, **18**, 152 (1975).
(18) The $^{13}C$ NMR spectra of a number of unrelated phencyclidine hydrochloride salts have recently been reported. See G. A. Brine, E. E. Williams, K. G. Boldt, and F. I. Carroll, *J. Heterocycl. Chem.*, **16**, 1425 (1979).

intensity) 512 ($M^+$, 40), 511 (100), 470 (30), 469 (75), 384 (20), 166 (50), with a metastable ion at $m/e$ 429.8 ($469^2/512$).

Anal. Calcd for $C_{34}H_{48}N_4$: C, 79.64; H, 9.44; N, 10.93. Found: C, 79.90; H, 9.11; N, 10.75.

For 4,4′-bis[1-(1-piperidyl)cyclohexyl]azobenzene (**8**): mp 225–227 °C (hexane); $^1H$ NMR ($CDCl_3$) $\delta$ 1.1–1.8 (m, 24), 1.9–2.1 (m, 8), 2.2–2.4 (m, 8) 7.75 (d, 4, $J$ = 9 Hz), 7.95 (d, 4, $J$ = 9 Hz).

Anal. Calcd for $C_{34}H_{48}N_4$: C, 79.64; H, 9.44; N, 10.93. Found: C, 79.45; H, 9.56; N, 10.77.

**1-[1-[4-(Dimethylamino)phenyl]cyclohexyl]piperidine (16).** *p*-(Dimethylamino)phencyclidine was synthesized by following a general procedure[1] in 71% yield from 10 g (0.09 mol) of 4-bromo-*N*,*N*-dimethylaniline. For **16**: mp 107–109 °C (EtOH); IR ($CHCl_3$) 2920, 2840, 2780, 1605, 1510 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.0–1.6 (m, 12), 1.8–2.1 (m, 4), 2.1–2.3 (m, 4), 2.90 (s, 6), 6.75 (2, d, $J$ = 9 Hz), 7.15 (2, d, $J$ = 9 Hz); $^{13}C$ ($CDCl_3$) $\delta$ 148.2 (s), 128.3 (d), 119.2 (s), 111.5 (d), 60.6 (s), 46.5 (q), 40.5 (t), 33.8 (t), 27.1 (t), 26.5 (t), 25.0 (t), 22.5 (t); mass spectrum, $m/e$ (70 eV, relative intensity) 286 ($M^+$, 5), 285 (4), 243 (4), 202 (100), 201 (87), 200 (25), 173 (4), 172 (25), 134 (25), 84 (20), with a large doubly charged ion at $m/e$ 121.5.

Anal. Calcd for $C_{19}H_{30}N_2$: C, 79.66; H, 10.56; N, 9.78. Found: C, 79.34; H, 10.42; N, 9.98.

**Reaction of 5 with Phenyl Isothiocyanate.** A solution of 0.36 g of **5** and 0.15 g (1.3 equiv) of phenyl isothiocyanate in 1 mL of $Me_2SO$ containing 5 drops of triethylamine was warmed at 40 °C for 2 h. Ethanol (2 mL) was added and the mixture cooled to give thiourea **17** in good yield: mp 140–142 °C (EtOH); IR ($CHCl_3$) 1650 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.0–1.7 (m, 12), 1.8–2.1 (m, 4), 2.1–2.3 (m, 4), 6.9–7.8 (m, 10), 8.2 (br s, 2, absent in $D_2O$).

Anal. Calcd for $C_{24}H_{31}N_3S$: C, 73.24; H, 7.94; N, 10.67. Found: C, 73.21; H, 7.83; N, 10.91.

**1-[1-(4-Bromophenyl)cyclohexyl]piperidine (11).** 4-Bromophencyclidine was synthesized by using a modification of a general procedure.[1] *p*-Dibromobenzene, 60.9 g (0.25 mol), in 300 mL of dry benzene was added all at once to a Morton flask containing 4.5 g (0.18 mol) of Mg turnings in 200 mL of ether. After a mildly exothermic reaction in which all the Mg reacted, the mixture was brought to reflux and 32 g (0.16 mol) of 1-piperidyl-1-cyanocyclohexane in 200 mL of ether was added dropwise over 1 h. The mixture was allowed to stir for an additional 4 h at reflux, cooled in ice, quenched with aqueous $K_2CO_3$ until basic, and extracted with $CHCl_3$. The $CHCl_3$ layer was back extracted with 20% HCl which was washed well with $CHCl_3$ to remove 4,4′-dibromobiphenyl, cooled, and made basic with $K_2CO_3$. The aqueous basic layer was extracted with $CHCl_3$ which was distilled to give 41.1 g (79%) of **11**: bp 175–180 °C (0.2 mm); mp 44–47 °C [lit.[1] bp 130–135 °C (0.5 mm); mp 46–48 °C]; IR ($CHCl_3$) 2920, 2840, 2785, 1050 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.0–1.8 (m, 12), 1.9–2.0 (m, 4), 2.1–2.3 (m, 4), 7.20 (d, 2, $J$ = 8 Hz), 7.48 (d, 2, $J$ = 8 Hz); $^{13}C$ ($CDCl_3$) $\delta$ 139.4 (s), 130.5 (d), 129.0 (d), 120.0 (s), 60.7 (s), 46.4 (t), 33.5 (t), 27.1 (t), 26.4 (t), 24.9 (t), 22.3 (t); mass spectrum, $m/e$ (70 eV, relative intensity) 321 ($M^+$, 35, Br), 320 (30, Br), 278 (100, Br), 264 (20, Br), 169 (35, Br), 166 (35), 84 (80).

A minor product, 1,4-bis[1-(1-piperidyl)cyclohexyl]benzene (**12**), was isolated in varying yields from the dibromobenzene Grignard reaction. For **12**: mp 172–173.5 °C (hexane–EtOH); IR ($CHCl_3$) 3080, 2920, 2840, 2785, 1450, 960 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.0–1.7 (m, 24), 1.8–2.0 (m, 8), 2.1–2.3 (m, 8), 7.2 (s, 4); $^{13}C$ ($CDCl_3$) $\delta$ 137.7 (s), 126.4 (d), 60.6 (s), 46.6 (t), 33.6 (t), 27.1 (t), 26.6 (t), 25.1 (t), 22.4 (t); mass spectrum (70 eV, relative intensity), $m/e$ 408 ($M^+$, 100), 407 (15), 366 (20), 365 (80), 325 (37), 324 (55), 240 (15), 166 (20).

Anal. Calcd for $C_{28}H_{44}N_2$: C, 82.29; H, 10.86; N, 6.86. Found: C, 82.12; H, 10.59; N, 7.21.

**1-[1-(4-Formylphenyl)cyclohexyl]piperidine (20).** To 80 mL of dry THF was added 12.5 g (0.039 mol) of **11**. The solution was cooled to −78 °C and 30 mL of 1.5 M butyllithium in hexane was added via syringe. After the mixture was allowed to stir for 30 min at −78 °C, 2.6 g of freshly distilled DMF in 10 mL of THF was added slowly. The mixture was allowed to warm to 25 °C over 2 h, quenched with 10% $NH_4Cl$, and extracted with $CHCl_3$ to give, after evaporation of solvent, 8.2 g (78%) of a yellow oil which was further purified by standard bisulfite extraction followed by short path distillation: bp 140–145 °C (0.02 mm); mp 83–84.5 °C (EtOH); IR ($CHCl_3$) 2920, 2840, 2780, 2720, 1695, 1605 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.0–1.8 (m, 12), 1.8–2.1 (m, 4), 2.1–2.3 (m, 4), 7.45 (d, 2, $J$ = 9 Hz), 7.85 (d, 2, $J$ = 9 Hz), 9.90 (s, 1); $^{13}C$ ($CDCl_3$) $\delta$ 191.9 (d), 148.2 (s), 134.5 (s), 129.0 (d), 127.8 (d), 61.3 (s), 46.6 (t), 33.6 (t), 27.2 (t), 26.4 (t), 25.0 (t), 22.4 (t); mass spectrum, $m/e$ (70 eV, relative intensity) 271 ($M^+$, 37), 270 (15), 229 (20), 228 (100), 224 (15), 166 (25), 91 (25), 84 (45), with a metastable ion at $m/e$ 191.2 ($228^2/271$).

Anal. Calcd for $C_{18}H_{25}NO$: C, 79.66; H, 9.29; N, 5.16. Found: C, 79.91; H, 9.18; N, 5.32.

**1-[1-(4-Oximinophenyl)cyclohexyl]piperidine (24).** A mixture of 2.71 g (0.01 mol) of aldehyde **20**, 0.8 g (0.16 mol) of hydroxylamine hydrochloride, and 1 g of $K_2CO_3$ in 5 mL of $H_2O$ was added to 50 mL of methanol and the mixture refluxed for 10 h. The methanol was removed in vacuo to give a solid which was crystallized to give 2.49 g (86%) of oxime **24**: mp 198–199 °C (EtOH); IR ($CHCl_3$) 3580, 3020, 2940, 2860, 1620 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.0–1.6 (m, 12), 2.0–2.4 (m, 8), 7.3 (br s, 1, absent in $D_2O$), 7.35 (d, 2, $J$ = 9 Hz), 7.65 (d, 2, $J$ = 9 Hz), 8.25 (s, 1); mass spectrum, $m/e$ (70 eV, relative intensity) 286 ($M^+$, 45) 285 (30), 244 (20), 243 (100), 229 (15), 166 (15), 134 (25), 84 (20), with a metastable ion at $m/e$ 206.6 ($243^2/286$).

Anal. Calcd for $C_{18}H_{26}N_2O$: C, 75.48; H, 9.15; N, 9.78. Found: C, 75.63; H, 9.23; N, 9.51.

**1-[1-[4-(Hydroxymethyl)phenyl]cyclohexyl]piperidine (23).** A mixture of 2.7 g (0.01 mol) of aldehyde **20** and 0.39 g (0.01 mol) of $NaBH_4$ were stirred in 50 mL of EtOH for 10 h. Aqueous $NH_4Cl$ was added to the solution and it was extracted extensively with $CHCl_3$ which was evaporated to give a near quantitative yield of **23**: mp 148–148.5 °C (EtOH–hexane); IR ($CHCl_3$) 3580, 3005, 2940, 2860, 2800, 1450, 1210 $cm^{-1}$; $^1H$ ($CDCl_3$) $\delta$ 1.0–1.6 (m, 12), 1.8–2.4 (m, 8), 2.6 (s, 1, absent in $D_2O$), 4.61 (s, 2), 7.15 (br s, 4); $^{13}C$ ($CDCl_3$) $\delta$ 139.3 (s), 138.6 (s), 127.7 (d), 127.3 (d), 65.1 (t), 61.1 (s), 46.5 (t), 33.7 (t), 27.0 (t), 26.4 (t), 24.9 (t), 22.5 (t); mass spectrum, $m/e$ (70 eV, relative intensity) 273 ($M^+$, 35), 272 (35), 231 (20), 230 (100), 216 (15), 166 (15), 121 (20), 84 (25), with a metastable ion at $m/e$ 194.2 ($230^2/272$).

Anal. Calcd for $C_{18}H_{27}NO$: C, 79.07; H, 9.95: N, 5.12. Found: C, 79.11; H, 9.82; N, 5.41.

**1-[1-(4-Cyanophenyl)cyclohexyl]piperidine (13).** A mixture of 3.2 g (0.01 mol) of 4-bromophencyclidine (**11**)[7] and 5 equiv of CuCN in 50 mL of dry DMF was heated at 120 °C for 3 days. After the mixture was cooled to 0 °C, 100 mL of $H_2O$ containing 5 g of KCN was added to the mixture which was then extracted with $CHCl_3$. Evaporation of $CHCl_3$ gave 1.9 g (71%) of **13**: mp 104–105 °C (MeOH); IR ($CHCl_3$) 2860, 2780, 2740, 2180 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.1–1.6 (m, 12), 1.8–2.0 (m, 4), 2.0–2.3 (m, 4), 7.31 (d, 2, $J$ = 8 Hz), 7.55 (d, 2, $J$ = 8 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 146.5 (s), 131.3 (d), 127.9 (d), 119.1 (s), 109.8 (s), 61.2 (s), 46.5 (t), 33.3 (t), 27.1 (t), 26.2 (t), 24.9 (t), 22.2 (t); mass spectrum, $m/e$ (70 eV, relative intensity) 268 ($M^+$, 30), 267 (28), 225 (100), 221 (55), 166 (58), with a metastable ion at $m/e$ 189 ($225^2/268$).

Anal. Calcd for $C_{18}H_{24}N_2$: C, 80.55; H, 9.01; H, 10.88. Found: C, 80.44; H, 9.20, N, 10.79.

**1-[1-[4-(Aminomethyl)phenyl]cyclohexyl]piperidine (18). A.** To a flask containing 0.40 g (10 mmol) of LAH in refluxing THF was added, slowly over 10 min as a solid, 0.67 g (2.5 mmol) of nitrile **13**. After the mixture was allowed to reflux an additional 3 h, the mixture was cooled, quenches with aqueous $NH_4Cl$, and extracted with $CHCl_3$ which was evaporated to give an oil which was distilled by short path to give 0.62 g (89%) of pure **18** as a low-melting solid: bp 140–150 °C (0.25 mm); mp 45–47 °C; IR ($CHCl_3$) 3200–3100 ($NH_2$) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.0–1.7 (m, 12), 1.6 (br s, 2, absent in $D_2O$), 1.8–2.0 (m, 4), 2.1–2.3 (m, 4), 3.65 (s, 2), 7.00 (s, 4); $^{13}C$ ($CDCl_3$) $\delta$ 140.7 (s), 138.7 (s), 127.6 (d), 126.2 (d), 60.9 (s), 46.6 (t), 46.2 (t), 33.8 (t), 27.2 (t), 26.5 (t), 25.1 (t), 22.5 (t); mass spectrum, $m/e$ (70 eV, relative intensity) 272 ($M^+$, 55), 271 (40), 230 (20), 229 (100), 215 (15), 188 (10), 166 (15), with a metastable ion at $m/e$ 192.8 ($229^2/272$).

**B.** Reduction of oxime **24** by LAH under conditions described above gave monoamine **18** in 62% along with variable amounts of related secondary, **21**, and tertiary, **22**, amines. For **21**: mp 44–47 °C; IR ($CHCl_3$) 3300 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.0–1.8 (m, 24), 1.8–2.3 (m, 16), 3.65 (s, 4), 7.05 (s); mass spectrum, $m/e$ (70 eV, relative intensity) 527 ($M^+$, 10), 444 (100), 442 (60).

For **22**: mp 156–158 °C (EtOH); $^1H$ NMR ($CDCl_3$) $\delta$ 1.0–1.7 (m, 36), 1.8–2.4 (m, 24), 3.58 (br s, 8), 7.35 (AB, 12); $^{13}C$ NMR

($CDCl_3$) δ 138.7 (s), 137.4 (s), 127.8 (d), 127.1 (d), 60.8 (s), 57.9 (t), 46.5 (t), 33.8 (t), 27.1 (t), 26.5 (t), 24.9 (t), 22.4 (t); mass spectrum, *m/e* (70 eV, relative intensity) 782 ($M^+$, trace), 699 (50), 614 (100), with a metastable ion at *m/e* 541 ($614^2/699$).

Anal. Calcd for $C_{54}H_{78}N_4$: C, 82.81; H, 10.02; N, 7.15. Found: C, 82.73; H, 10.29; N, 7.31.

**Reaction of 18 with Phenyl Isothiocyanate.** Amine **18**, 100 mg, was reacted neat with 1 equiv of phenyl isothiocyanate. After a mild exothermic reaction the reaction mixture went solid. After recrystallization in EtOH, pure, mixed thiourea **33** was obtained in high yield: mp 178–179 °C (EtOH); IR ($CHCl_3$) 3400, 3370, 2950, 1590, 1520 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.0–1.6 (m, 12), 1.8–2.4 (m, 8), 4.8 (d, 2, *J* = 6 Hz), 7.2 (m, 9), 7.6 (br s, 1, NH), 8.1 (br s, 1, NH); $^{13}C$ NMR ($CDCl_3$) δ 180.9 (s, C=S), 49.16 (t, $PhCH_2N$); mass spectrum, *m/e* (70 eV, relative intensity) 407 ($M^+$, 58), 364 (30), 322 (52), 271 (22), 171 (100).

Anal. Calcd for $C_{25}H_{33}N_3S$: C, 73.66; H, 8.16; N, 10.32. Found: C, 73.45; H, 8.01; N, 9.93.

**1-[1-(4-Carbamylphenyl)cyclohexyl]piperidine (10).** To a flask containing 3 mL of 30% $H_2O_2$, 3 mL of $H_2O$, 20 mL of acetone, and 3 mL of 10% $K_2CO_3$ was added 0.8 g (3 mmol) of nitrile **13**. The mixture exothermed to 40 °C and was maintained at that temperature for 3 h at which time it was diluted with $H_2O$ and extracted with $CHCl_3$ to give, after removal of solvent, 0.65 g (76%) of amide **10**: mp 94.5–96.5 °C ($CH_2Cl_2$/hexane); IR ($CHCl_3$) 3400, 3340, 3170, 1670, 1380 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.0–1.8 (m, 12), 1.8–2.1 (m, 4), 2.1–2.4 (m, 4), 6.55 (br s, 1, absent in $D_2O$), 7.40 (d, 2, *J* = 9 Hz), 7.85 (d, 2, *J* = 9 Hz); $^{13}C$ NMR ($CDCl_3$) 169.7 (s), 145.0 (s), 131.1 (s), 127.5 (d), 126.7 (d), 61.1 (s), 46.6 (t), 33.6 (t), 27.1 (t), 26.6 (t), 25.0 (t), 22.4 (t); mass spectrum, *m/e* (70 eV, relative intensity) 286 ($M^+$, 5), 243 (12), 166 (25), 84 (100).

Anal. Calcd for $C_{18}H_{26}N_2O \cdot H_2O$: C, 71.01; H, 9.22; N, 9.20. Found: C, 71.11; H, 8.87; N, 9.17.

When higher reaction temperatures were employed, 1-(4-carbamylphenyl)cyclohexene[8] was also isolated in variable yield.

**Hofmann Rearrangement of Amide 10.** To a dry flask containing 3 mL of $CH_3OH$ at −45 °C was added 0.14 g (6 mmol) of sodium. After reaction, 0.38 g (2.1 mmol) of bromine was added and the mixture was allowed to stir until all color was discharged. To this mixture was added, dropwise, 0.5 g (1.7 mmol) of amide **10** dissolved in a 1/1 mixture of dioxane/$CH_3OH$. The reaction was allowed to slowly warm to 40 °C and then stirred an additional 30 min. The mixture was cooled, neutralized with aqueous acetic acid, and extracted with $CHCl_3$. After removal of solvent, the organic residue was chromatographed on neutral alumina, using ether and ether–$CH_3OH$ eluant, to give 0.6 g (66%) of pure carbamate **15**.

For **15**: IR ($CHCl_3$) 3420 (NH), 2930, 1722, 1515, 905 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.0–1.8 (m, 12), 1.8–2.1 (m, 4), 2.1–2.4 (m, 4), 3.75 (s, 3), 71, (br s, 1, absent in $D_2O$), 7.2–7.5 (ABCD, 4, goes to singlet at ca. 80 °C); $^{13}C$ NMR ($CDCl_3$) 168.9 (s), 154.2 (s), 135.9 (s), 128.2 (d), 117.9 (d), 61.1 (s), 52.3 (q), 46.5 (t), 33.6 (t), 26.9 (t), 26.4 (t), 24.9 (t), 22.4 (t); mass spectrum, *m/e* (70 eV, relative intensity) 316 ($M^+$, 65), 315 (40), 273 (80), 259 (10), 243 (20), 233 (22), 232 (100), 231 (30), 225 (20), 166 (25), 164 (52), 84 (30), with a metastable ion at *m/e* 205.8 ($273^2/316$).

**1-[1-[4-(2-Hydroxyethyl)phenyl]cyclohexyl]piperidine (26).** To a flask containing 0.6 g (0.026 mol) of Mg in 100 mL of a 2/1 mixture of ether/THF was added dropwise 6.42 g (0.02 mol) of 4-bromophencyclidine in 25 mL of THF. After reaction of the bromide, ethylene oxide was slowly bubbled into the flask until no more reagent remained (as judged by aliquots). Cold aqueous $NH_4Cl$ was added to the mixture and it was extracted with ether. The ether was dried with $MgSO_4$, filtered, and evaporated to give 4.8 g (86%) of very pure alcohol as a viscous oil: bp 145–150 °C (0.02 mm); IR ($CHCl_3$) 3600, 3400, 2970, 1440, 1040 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.0–1.8 (m, 12), 1.8–2.4 (m, 8), 2.8 (2, t), 3.4 (br s, 1, absent in $D_2O$), 3.8 (2, t), 7.15 (s, 4); $^{13}C$ NMR ($CDCl_3$) 137.6 (s), 136.3 (s), 128.1 (d), 127.6 (d), 63.3 (t), 61.0 (s), 46.5 (t), 38.8 (t), 33.6 (t), 26.9 (t), 26.5 (t), 24.9 (t), 22.5 (t); mass spectrum, *m/e* (70 eV, relative intensity) 287 ($M^+$, 20), 286 (35), 256 (10), 244 (100), 166 (35).

**1-[1-[4-(2-Phthalimidoethyl)phenyl]cyclohexyl]piperidine (28).** A mixture of 1.4 g (4.8 mmol) of alcohol **26**, 0.5 g (5.7 mmol) of triethylamine, and 0.6 g (5.3 mmol) of freshly distilled methanesulfonyl chloride in 20 mL of $CH_2Cl_2$ was stirred at 0 °C for 3 h at which time the mixture was extracted with cold $CHCl_3$/aqueous $K_2CO_3$ mixture. The organic layer was washed with $H_2O$ and dried over $K_2CO_3$ to give, after removal of solvent, 1.7 g (96% yield) of mesylate **27** [$^1H$ NMR ($CDCl_3$) δ 2.8 (3, s, $SO_2CH_3$), 3.1 (2, t, $CH_2CH_2O$), 4.5 (2, t, $CH_2CH_2O$)] which was reacted without further purification with 1.9 g (1.1 equiv) of potassium phthalimide in 20 mL of dry DMF containing 0.1 g of KI. After being allowed to stir for 10 h at room temperature the mixture was extracted with $CHCl_3/H_2O$ and the organic layer washed with $H_2O$ until the DMF was gone. Removal of solvent gave 1.8 g (93%) of **28**: mp ($CH_3OH$) 109–111 °C; IR ($CHCl_3$) 2940, 1770, 1710, 1395, 1360 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.0–1.7 (m, 12), 1.8–2.3 (m, 8), 2.95 (t, 2, *J* = 8 Hz), 3.90 (t, 2, *J* = 8 Hz), 7.1 (s, 4), 7.65 (AB, 4).

Anal. Calcd for $C_{27}H_{32}O_2N_2$: C, 77.85; H, 7.74; N, 6.72. Found: C, 77.62; H. 7.61; N, 6.81.

**1-[1-[4-(2-Aminoethyl)phenyl]cyclohexyl]piperidine (19).** A mixture of 0.16 g (0.38 mmol) of **28** and 0.05 g of 85% hydrazine hydrate in 5 mL of methanol was heated at reflux for 5 h and cooled. Water was added to the mixture and it was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with 20% HCl which was made basic with $K_2CO_3$ and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and evaporated to 0.1 g (91%) of amine **19** as a viscous oil: bp 150–160 °C (0.4 mm); IR ($CHCl_3$) 3390, 2940, 1442, 910 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.0–1.8 (m, 12), 1.9–2.2 (m, 4), 2.2–2.5 (m, 4), 2.6–3.1 (m, 4), 7.2 (s, 4); $^{13}C$ NMR ($CDCl_3$) δ 137.3 (s), 137.2 (s), 128.0 (d), 127.7 (d), 61.2 (s), 46.6 (d), 43.5 (d), 39.7 (d), 33.5 (d), 26.9 (d), 26.4 (d), 24.9 (d), 22.5 (d); mass spectrum, *m/e* (70 eV, relative intensity) 286 ($M^+$, 60), 285 (30), 256 (10), 243 (100), 229 (10), 173 (20), 172 (20), 166 (20), 105 (65), 84 (25), with a metastable ion at *m/e* 206.6 ($243^2/286$).

**Reaction of Amine 19 with Phenyl Isothiocyanate–Thiourea, 34.** Amine **19** was converted to mixed thiourea **34** in 68% yield by reacting it neat with phenyl isothiocyanate at 25 °C.

For **34**: mp 141.5–143.5 ($CHCl_3/C_6H_{14}$); IR ($CHCl_3$) 3400, 2940, 1600, 1525, 1495 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 1.1–1.7 (m, 12), 1.8–2.1 (m, 4), 2.2–2.4 (m, 4), 2.9 (t, 2), 3.9 (q, 2, t in $D_2O$), 6.1 (br s, 1, absent in $D_2O$), 7.0–7.6 (m, 9), 8.1 (br s, 1, absent in $D_2O$); mass spectrum, *m/e* (70 eV, relative intensity) 421 ($M^+$, 3), 420 (5), 386 (8), 377 (5), 343 (10), 286 (60), 285 (45), 243 (100), 173 (25), 172 (25), 166 (25), 135 (95), 105 (40), 84 (40), with a metastable ion at *m/e* 206.5 ($243^2/286$).

Anal. Calcd for $C_{26}H_{35}N_3S$: C, 74.07; H, 8.37; N, 9.96. Found: C, 73.87; H, 8.19; N, 9.78.

**Synthesis of 1-[1-[4-[2-Nitro-1-hydroxyethyl]phenyl]-cyclohexyl]piperidine (30) and 1-[1-[4-(2-Nitroethyl)-phenyl]cyclohexyl]piperidine (32).** To a flask containing 25 mL of $Me_2SO$, 2.7 g (0.01 mol) of aldehyde **20** and 5 equiv of nitromethane was added 3 drops of 1,5-diazabicycloundecene. After 5 min the mixture was cooled and sufficient, cold acetic acid was added to neutralize the mixture which was then extracted with cold $H_2O/CHCl_3$. The organic layer was washed with cold $H_2O$ till no $Me_2SO$ remained, dried over $MgSO_4$, and evaporated to give **30**. The yield of this reaction (60–90%) was a function of workup: mp 94–95 °C ($CH_2Cl_2$); IR ($CHCl_3$) 3600, 3400, 2950, 1550, 1380 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 1.0–1.7 (m, 12), 1.9–2.4 (m, 8), 3.1 (br s, 1, absent in $D_2O$), 4.6 (AB of ABX, 2), 5.5 (X of ABX, 1), 7.4 (s, 4); mass spectrum, *m/e* (70 eV, relative intensity) 332 ($M^+$, 5), 289 (25), 271 (30), 228 (100), 166 (38).

Anal. Calcd for $C_{19}H_{28}O_3N_2$: C, 68.64; H, 8.49; N, 8.43. Found: C, 68.51; H, 8.32; N, 8.48.

Alcohol **30**, 0.55 g (1.6 mmol), was dissolved in a mixture of 1.2 equiv of acetic anhydride and 1.2 equiv of sulfuric acid carefully over several minutes during which time the mixture warmed to ca. 40 °C. After 10 min, 20 mL of a $Me_2SO$ solution containing 0.64 g (1.6 mmol) of $NaBH_4$ was added to the mixture. The mixture was allowed to stir for 1 h and then was poured into 50 mL of ice/$H_2O$ which was extracted with $CHCl_3$. The organic layer was washed with $H_2O$ until the $Me_2SO$ was gone, dried over $MgSO_4$, and evaporated to give 0.33 g (63%) of **32** which was further purified by column chromatography on silic acid, using ether eluate: IR ($CHCl_3$) 2960, 1550, 1440, 1380 $cm^{-1}$; $^1H$ ($CDCl_3$) 1.0–1.7 (m, 12), 1.9–2.1 (m, 4), 2.1–2.4 (m, 4), 3.3 (t, 2), 4.6 (t, 2), 7.2 (s, 4).

**Reaction of 32 with LAH.** 4-(2-Nitroethyl)phencyclidine was converted, without further characterization, to 4-(2-amino-

ethyl)phencyclidine (19) in 90% by adding it to LAH in refluxing ether.

**1-[1-(4-Methylphenyl)cyclohexyl]piperidine (35).** 4-Methylphencyclidine was synthesized as described:[1] bp 120–130 °C (0.1 mm); mp 65–67 °C [lit.[1] mp 66–67 °C]; $^1$H NMR ($CDCl_3$) δ 1.1–1.7 (m, 8), 1.8–2.1 (m, 4), 2.1–2.4 (m, 4), 2.22 (s, 3), 7.30 (s, 4); $^{13}$C NMR ($CDCl_3$) δ 137.1 (s), 135.3 (s), 128.1 (d), 127.2 (d), 60.7 (s), 46.5 (t), 33.8 (t), 27.2 (t), 26.5 (t), 22.5 (t), 20.9 (q).

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# Chlorination of 2-Methyl- and 2-Phenylindole with NaOCl. Formation of Intermediates and Their Reactions with Alkaline Methanol[1]

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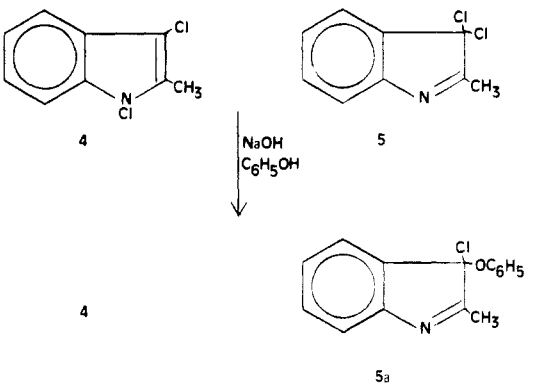
Chlorination of 2-methylindole (1) in carbon tetrachloride with excess sodium hypochlorite gave a 2:1 mixture of *N*,3-dichloro-2-methylindole (4) and 3,3-dichloro-2-methyl-3*H*-indole (5) in a total yield of 76–92%. *N*-Chloro-2-methylindole (2) was detected when the chlorination was carried out with an indole to NaOCl ratio of 10:1. Sodium hypochlorite was found to promote the rearrangement of *N*-chloroindoles 2 and 4. The chlorination of 2-phenylindole (6) gave a mixture of *N*,3-dichloro-2-phenylindole (8) and 3,3-dichloro-2-phenyl-3*H*-indole (9) in a total yield of 81–92%. The rearrangement of 8 to 9 was detected by IR and UV. This occurred in the presence or absence of NaOCl. Reactions of the dichloro intermediates with alkaline methanol gave a number of products. It is proposed that the *N*,3-dichloroindoles rearranged to their respective 3*H*-indoles in alkaline methanol and the products were formed by nucleophilic attack on either carbon (C-3) or chlorine of the 3*H*-indole.

Recently we reported the formation of *N*-chloroindole and its subsequent rearrangement in alcohols to 3-chloroindole.[3] The intermediacy of 3-chloro-3*H*-indole was also shown. Studies on the chlorination[4] of 2,3-disubstituted indoles have detected only the formation of 3-chloro-3*H*-indoles.[5-15] The chlorination of 2-methyl- and 3-methylindole with a number of chlorinating agents has been studied and the products depended on the chlorination medium.[16] It was of interest to determine the effect of substitutents on the nature and stability of the initially formed chlorination products. To this end the chlorination of 2-methyl- and 2-phenylindole with sodium hypochlorite was studied, and the reaction of the final intermediates with alkaline methanol was examined.

Scheme I

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(2) From the Tesis Especial de Grado of L. Carbognani, Universidad Simón Bolívar, 1977.
(3) (a) M. De Rosa and J. L. Triana Alonso, *J. Org. Chem.*, **43**, 2639 (1978); (b) M. De Rosa, *J. Chem. Soc., Chem. Commun.*, 482 (1975).
(4) For a review on the chlorination of indoles and its derivatives see: J. C. Powers in "Indoles", Part II, W. J. Houlihan, Ed., Wiley-Interscience, New York, 1972, pp 137–39 and 155–59.
(5) For reviews on the reactions of 3-halo-3*H*-indoles see: M. Ikeda and Y. Tamura, *J. Synth. Org. Chem. Jpn.*, **37**, 568 (1979); M. Ikeda and Y. Tamura, *Heterocycles*, **14**, 867 (1980).
(6) P. G. Gassman, G. A. Campbell, and G. Mehta, *Tetrahedron*, **28**, 2749 (1972).
(7) (a) R. J. Owellen, *J. Org. Chem.*, **39**, 69 (1974); (b) R. J. Owellen and C. A. Hartke, *ibid.*, **41**, 102 (1976).
(8) A. Walser, J. F. Blount, and R. I. Fryer, *J. Org. Chem.*, **38**, 3077 (1973).
(9) Y. Tamura, M. W. Chun, H. Nishida, and M. Ikeda, *Heterocycles*, **8**, 313 (1977).
(10) T. Hino, M. Endo, M. Tonozuka, Y. Hashimoto, and M. Nakagawa, *Chem. Pharm. Bull.*, **25**, 2350 (1977).
(11) F. M. Hershenson, K. A. Prodan, R. L. Kochman, J. L. Bloss, and C. R. Mackerer, *J. Med. Chem.*, **20**, 1448 (1977).
(12) M. E. Kuehne and R. Hafter, *J. Org. Chem.*, **43**, 3702 (1978).
(13) (a) Y. Tamura, M. W. Chun, H. Nishida, S. Kwon, and M. Ikeda, *Chem. Pharm. Bull.*, **26**, 2866 (1978); (b) Y. Tamura, M. W. Chun, K. Ohno, S. Kwon, and M. Ikeda, *ibid.*, **26**, 2874 (1978).
(14) G. I. Dmitrienko, E. A. Gross, and S. F. Vice, *Can. J. Chem.*, **58**, 808 (1980).
(15) For references to 3-chloro-3*H*-indole derivatives of indole alkaloids see ref 5 and 25.
(16) J. C. Powers, *J. Org. Chem.*, **31**, 2627 (1966).

0022-3263/81/1946-2054$01.25/0 