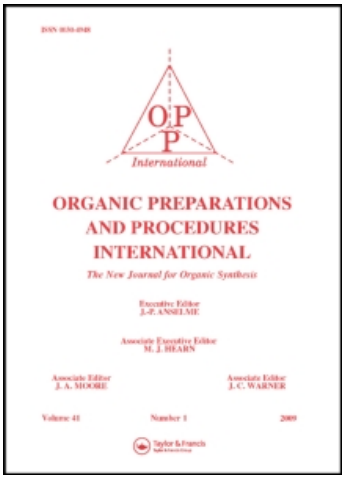

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SYNTHESIS OF 4-(NITROBENZYL- AND BENZOYL)PIPERIDINE DERIVATIVES BY NITRATION OF ARYLALKYLPIPERIDINES†

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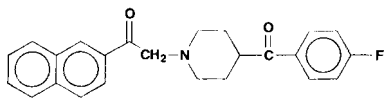
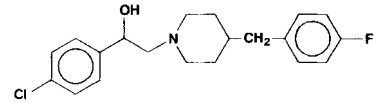
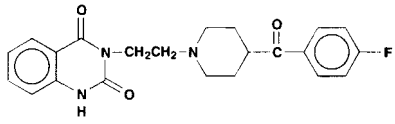
4-Benzoyl- and 4-benzylpiperidines are important intermediates which have been employed for the synthesis of a variety of biologically active molecules (**1-4**). [1-7] In general, they have been prepared (i) by the Friedel-Crafts reaction of an appropriate benzene derivative with an isonipecotic acid chloride in the presence of aluminum chloride[1,6] (ii) by the condensation of an appropriately



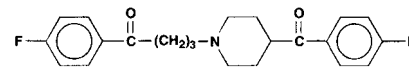
1 (*E 2001*)



2 (*SL 82.0715*)



3 (*Ketanserin*)

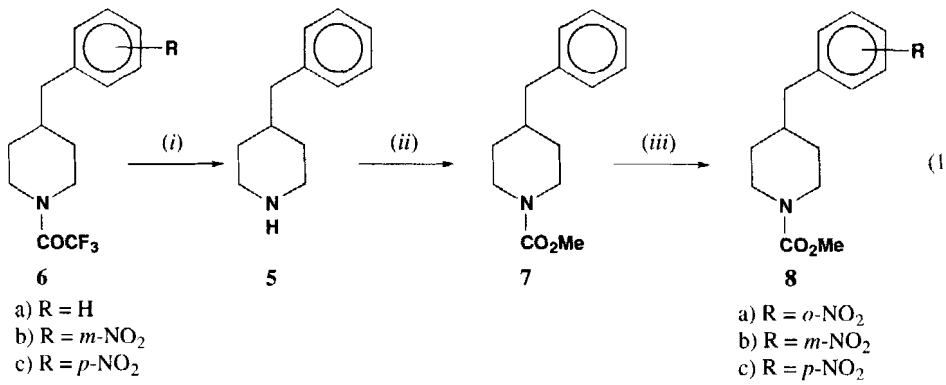


4 (*Lenperone*)

substituted 4-piperidone and arylmethyl cyanide, followed by hydrogenation and oxidation[3] (iii) by the Grignard reaction of 4-piperidinylmagnesium halide with aryl cyanide[3] and (iv) by the oxidative cleavage of the double bond of 3-(4-piperidinyl)indole derivatives and subsequent acidic hydrolysis.[3,4] These methods are encumbered with limitations that make many substitution patterns inaccessible; in addition many substituents such as $-NO_2$, C≡N, etc. do not tolerate the reaction conditions employed in procedures (i)-(iii). The 3-(4-piperidinyl)indole derivatives used as starting materials in method (iv) are not readily available. Furthermore, the nature of the substituents is subject to the usual restrictions of Friedel-Crafts reactions. Thus, it is evident that routes (i)-(iv) are not applicable for the preparation of proposed target compounds such as 4-*o,m,p*-nitrobenzoyl- and benzylpiperidine derivatives. In our efforts to develop efficient and new synthetic methodologies for positron emitting radio-

labeled pharmaceuticals of potential interest of positron tomographic studies, 4-*m,p*-nitrobenzoyl- and benzylpiperidine intermediates were required as precursors for the preparation of 4-*m* or *p*-^{18}F-benzoyl- and benzylpiperidines. The displacement of an activated nitro group can be easily achieved [8,9] by reaction of the [^{18}F]fluoride ion which is readily available for on-line synthesis in our laboratory. A literature search of these 4-*o,m,p*-nitrobenzoyl- and benzylpiperidines revealed that these compounds have not been reported previously. This account describes a simple synthesis of 4-(*o,m,p*-nitrobenzyl- and benzoyl)piperidines from commercially available 4-benzylpiperidine.

Most of the limitations of the reported routes described earlier may be avoided by using 4-benzylpiperidine (**5**). The nitration of **5** with ammonium nitrate[10] in trifluoroacetic anhydride at room temperature gave a mixture of the three products in the ratios of 1:2:4 (GC). This crude mixture was separated by chromatography on silica gel using hexane-ethyl acetate mixture as eluent. The separated products were characterized by ^{1}H NMR and IR as N-trifluoroacetyl-4-benzylpiperidine (**6a**), N-trifluoroacetyl-4-(*o*-nitrobenzyl)piperidine (**6b**), and N-trifluoroacetyl-4-(*p*-nitrobenzyl)piperidine (**6c**), respectively. These results suggest that the amine is first acylated to **6a** which is subsequently nitrated to **6b** and **6c**. In order to circumvent this problem, **5** was converted into N-carbomethoxy 4-benzylpiperidine (**7**) by reaction of 4-benzylpiperidine with methyl chloroformate (Eq. 1). Nitration of

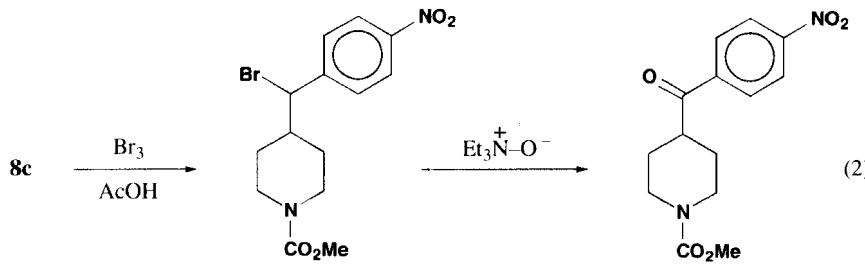


(1)

i) NH_4NO_3, $(CF_3CO)_2O$; *ii*) $ClCO_2Me$, K_2CO_3; *iii*) Ac_2O, Δ; *iv*) HNO_3, Ac_2O, 0°

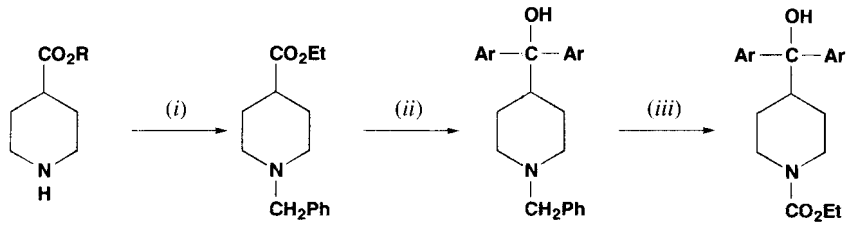
7 with fuming nitric acid in acetic anhydride resulted a mixture of the nitrobenzylpiperidines **8a-c** in a ratios of 3:5:1 (GC) which were separated by silica gel chromatography using CH_2Cl_2-CH_3OH mixture as eluent. The compounds were assigned to be N-carbomethoxy 4-(*m*-nitrobenzyl)piperidine (**8b**), N-carbomethoxy 4-(*o*-nitrobenzyl)piperidine (**8a**), and N-carbomethoxy 4-(*p*-nitrobenzyl)piperidine (**8c**), respectively. Attempts to oxidize, N-carbomethoxy 4-(*p*-nitrobenzyl)piperidine (**8c**) to the corresponding 4-(*p*-nitrobenzoyl)piperidine derivative **10** under a variety of conditions such as CrO_3-CH_3COOH, SeO_2-diglyme afforded untractable complex mixtures. In an alternate route, compound **8c** was brominated with bromine in acetic acid to afford N-carbomethoxy 4-(α-bromo, α-*p*-nitrophenyl)methylpiperidine (**9**). However, reaction of **9** with trimethylamine N-oxide[11] provided only a

trace amount of N-carbomethoxy 4-(*p*-nitrobenzoyl)piperidine (**10**) (Eq. 2).



(2)

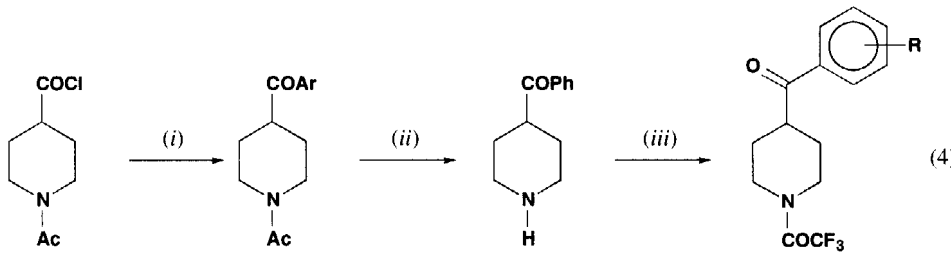
The 4-(*m*-nitrobenzoyl)piperidine requires 4-benzoylpiperidine (**17**) as an intermediate which can be prepared easily by either literature procedure[6] or *via* a Grignard reaction[12] of phenylmagnesium bromide with ethyl N-benzylisonipecotate (**12**) readily obtainable by benzylation of ethyl isonipecotate (**11**) with benzyl bromide. However, the Grignard reaction of phenyl- and *p*-fluorophenylmagnesium bromide with **12** afforded the N-benzyl 4-(diarylhydroxymethyl)piperidines (**13a-b**) as sole products (Eq. 3). Compound **13a**, on reaction with ethyl chloroformate in toluene at



(3)

i) $C_6H_5CH_2Br$, K_2CO_3, THF; *ii*) XC_6H_4MgBr, THF; *iii*) $ClCO_2Et$, toluene

reflux temperature, afforded N-carbethoxy 4-(diphenylhydroxymethyl)piperidine (**14**). This route did not work well in our hands under a variety of reaction conditions such as reverse addition of the Grignard reagent, different molar ratio etc. In order to circumvent this problem, N-acetyl-4-benzoyl piperidines (**16a** and **b**) were prepared by a reaction of N-acetylisonipecotic acid chloride (**15**) with an appropriate benzene derivative using the literature procedure.[6] The nitration of N-acetyl-4-benzoylpiperidine (**16a**) was studied with two different nitrating reagents. The reaction of HNO_3-Ac_2O with compound **16a** at 0°, followed by stirring the resulting reaction mixture at room temperature resulted a deacetylated product 4-benzoylpiperidine (**17**) which was characterized by ^1H NMR, IR and GC/MS. Nitration of the compound **17** with ammonium nitrate in trifluoroacetic anhydride at 10-20° yielded a mixture which on separation on silica gel gave major N-trifluoroacetyl-4-(*m*-nitrobenzoyl)piperidine (**18a**) as the major product with a trace amount of the N-trifluoroacetyl-4-(*p*-nitrobenzoyl)piperidine (**18b,** Eq. 4).



(4)

i) $AlCl_3$, C_6H_5X; *ii*) HNO_3, Ac_2O; *iii*) NH_4NO_3, $(CF_3CO)_2O$

The separated products were characterized by ^1H NMR and GC/MS. The reaction of ammonium nitrate with N-acetyl-4-benzoylpiperidine (**16a**) under similar reaction conditions afforded **18a** as a major product along with a trace amounts of **18b**. These observations suggest that transamidation takes place in the reaction conditions reported here.

In addition, we have also investigated the nitration of N-acetyl-4-benzoylpiperidine with other nitrating agents such as HNO_3-H_2SO_4, $AgNO_3$-AcCl, and nitronium tetrafluoroborate. However, these agents were less than satisfactory in our hands, and resulted a intractable mixture. The results from this study suggest that ammonium nitrate-trifluoroacetic anhydride and HNO_3-Ac_2O are ideal for nitration of 4-benzoyl- and benzylpiperidines. The methods described here for the preparation of 4-(*o,m,p*-nitrobenzyl- and benzoyl) piperidines will provide an efficient and rapid route for the preparation of a variety of bioactive compounds labeled with the positron-emitting radionuclide fluorine-18.

EXPERIMENTAL SECTION

All chemicals were of research grade and were used as obtained from the commercial suppliers. The ammonium nitrate, isonipecotic acid, and 4-benzylpiperidine were purchased from Aldrich Chemical Company. Gas chromatography analysis was performed on a Varian 3400 series Gas Chromatograph equipped with a thermal conductivity detector using a 5% methyl silicone oil, OV-101 column, 50cm X 1/8" and helium as a carrier gas. ^1H NMR spectra were obtained on General Electric GN-300 and GN-500 MH_z spectrometer. Chemical shift values (δ) are reported in parts per million downfield from the tetramethylsilane as internal standard. Mass spectra were recorded on a VG-70s (VG-analytical). Infrared spectra were obtained on Perkin Elmer Model 1620 and BOMEM, MB-100. Elemental analyses were performed by Onieda Research Laboratories, Whitesboro, NY.

N-Trifluoroacetyl-4-(*o,p*-nitrobenzyl)piperidines (6b-c).- To a cold stirred mixture of 4-benzylpiperidine **5** (4.66 g, 20 mmol) and ammonium nitrate (1.68 g, 21 mmol), trifluoroacetic anhydride (20 mL) was added dropwise at 15°. During addition of the trifluoroacetic anhydride, a thick brown mass precipitated out and dissolved slowly to give yellowish brown solution. The resulting reaction

mixture was stirred for 3 hrs at 15°. Then solvent was evaporated under vacuum at room temperature. The resulting viscous oil was diluted with water (50 mL), and compound was extracted with CH_2Cl_2 (75 mL x 2) and the combined organic layer was washed with H_2O, dil. $NaHCO_3$ solution and H_2O, respectively. The organic layer was dried over Na_2SO_4 and on evaporation under reduced pressure gave 4.8 g of a crude viscous oil which consists of three products in the ratios of 1:2:4 analyzed by gas chromatography [5% methyl silicone oil, OV-101, column size 50cm x 1/8", temperature programmed 200° (2 min hold) to 275° with a rate of 15°/min, flow rate of helium gas 31 mL/min]. The crude mixture was subjected to silica gel chromatography [column size 2.54 x 60 cm, silica gel 60 g]. The elution of column with hexane-ethyl acetate mixture (100-80:0-20) afforded 0.5 g of N-trifluoroacetyl-4-benzylpiperidine (**6a**) as a brown viscous oil. ^1H NMR ($CDCl_3$): δ 1.25-2.0 (m, 2H, C-CH_2), 1.60-1.8 (m, 3H, C-CH_2, C-CH), 2.40-2.63 (m, 2H, N-CH_2) 2.70 (t, 1H, N-CH), 3.05 (t, 1H, N-CH), 3.98 (bd, 1H, C_6-CH), 4.5 (bd, 1H, C_6-CH) and 7.0-7.70 (m, 5H, Ar-H). The R_f value of product **6a** was 0.7143 [silica gel/ethyl acetate- hexane (1:3)]. Further elution of column with hexane- ethyl acetate mixture (3:1) gave 1.0 g of N-trifluoroacetyl-4-(*o*-nitrobenzyl)piperidine (**6b**) as a viscous brown oil. The R_f value of compound **6b** under similar conditions as described above was 0.443. IR (KBr, cm^{-1}): 2920 (-CH_2CH_2-), 1691 (NCOCF_3), 1527 (-NO_2), 1350 (-NO_2), 745 (-C_6H_4-). ^1H NMR ($CDCl_3$): δ 1.05-1.43 (m, 2H, C-CH_2), 1.66-2.07 (m, 3H, CH-CH_2), 2.70 (t, 1H, N-CH), 2.75-2.80 (m, 2H, N-CH_2), 3.06 (m, 1H, N-CH), 4.0 (bd, 1H, C_6-CH), 4.52 (bd, 1H, C_6CH), 7.7 (d, 1H, Ar-H), 7.39 (t, 1H, Ar-H) 7.52 (t, 1H, Ar-H), 7.95 (d, 1H, Ar-H); MS (m/e^+): 317, MH^+, and 1.75 g of N-trifluoroacetyl-4-(*p*-nitrobenzyl)piperidine (**6c**) as a thick brown oil, R_f value of compound **6c** was 0.343; IR (KBr, cm^{-1}): 2912 (-CH_2-CH_2-), 1691 (N-COCF_3), 1519 (-NO_2), 1346 (-NO_2), 751 (-C_6H_4-). ^1H NMR ($CDCl_3$): δ 1.17-1.47 (m, 2H, C-CH_2), 1.65-2.02 (m, 3H, -CH-CH_2), 2.50-2.90 (m, 3H, HC-N-CH_2), 3.05 (t, 1H, -N-CH), 4.01 (bd, 1H, C_6-CH), 4.55 (bd, 1H, C_6-CH). 7.30 (d, 2H, Ar-H), 8.15 (d, 2H, Ar-H); MS (m/e^+): 317, MH^+.

Anal. Calcd for $C_{14}H_{15}N_2F_3O_3$: C, 53.17; H, 4.75; N, 8.86. Found: C, 53.14; H,4.86; N, 8.79

N-Carbomethoxy-4-(*o,m,p*-nitrobenzyl)piperidines (8a-c).- A 90% aqueous solution of nitric acid (1.2 mL) was added dropwise to a stirred solution of N-carbomethoxy 4-benzyl piperidine (4.0 g, 17.15 mmol) in acetic anhydride (20 mL) at 0°. The resulting reaction mixture was allowed to warm up with stirring to room temperature. The progress of reaction was monitored by GC [5% methyl silicone oil, OV-101, 50 cm x 1/8", temperature programmed 150° (1.0 min hold) to 275° (5.0 min hold) with a rate of 25°/min, helium gas flow 30 mL/min] and TLC [silica gel/ CH_2Cl_2-MeOH (99:1)]. After 16 hrs, the reaction mixture was cooled to 0°, and an additional 90% solution of HNO_3 (2.0 mL) was added, and stirring was continued for additional 4 hrs. Then reaction mixture was poured into an ice-water mixture, and the resulting suspension was stirred overnight at room temperature. A gummy yellow solid was extracted with ether (200 mL x 2). The combined ethereal layer was evaporated under vacuum to give 5.0 g of a crude material as a yellow oil which on GC analysis under above reaction conditions showed three peaks at 6.14 min, 6.78 min and 8.19 min in a ratio of 3:5:1, respectively. TLC analysis also showed presence of three products which R_f values 0.805, 0.732, and 0.366,

respectively. This mixture was separated by silica gel column chromatography [size 5 cm x 60 cm, silica gel 200-425 mesh, 150 g] using CH_2Cl_2 as an eluent with increasing concentration of CH_3OH (0.5%, 1%, 1.5%, 2%, 3%, 5%, and 10%). The spectroscopic data (^1H NMR and IR) the compounds of lower R_f value (0.366) and middle R_f value (0.732) products were identical to the compounds **6b** and **6c**, respectively except an ester peak at 3.70 (s, 3H, CO_2CH_3) in ^1H NMR and 1709 cm^{-1} (CO_2CH_3) in IR spectrum instead of trifluoroacetyl group. On the basis of spectroscopic and chromatographic data lower and middle R_f values products were assigned as N-carbomethoxy 4-(*p*-nitrobenzyl)piperidine **8c** and N-carbomethoxy 4-(*o*-nitrobenzyl) piperidine **8a**, respectively. The minor product which possesses highest R_f value (0.805) was assigned as N-carbomethoxy 4-(*m*-nitrobenzyl) piperidine **8b**. HR/MS (m/e$^+$) calcd for $C_{14}H_{18}N_2O_4$ 278.336, found 278.1262.

N-Trifluoroacetyl-4-(*m*-nitrobenzoyl)piperidine (18a) and N-Trifluoroacetyl-4-(*p*-nitrobenzoyl)-piperidine (18b).- A mixture of 4-benzoylpiperidine (0.89 g, 4.73 mmol) and ammonium nitrate (0.55 g, 6.88 mmol) in trifluoroacetic anhydride (6 mL) was stirred at 10-15° for 1 hr. The progress of reaction was monitored by TLC [silica gel/ethyl acetate- hexane (2:3)]. The solvent was then evaporated under reduced pressure at room temperature, and the resulting residue was diluted with H_2O and basified with dil. $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (100 mL x 2), and the combined organic layer was dried over Na_2SO_4 and on evaporation under reduced pressure gave 0.98 g of a crude mixture which possesses two products of R_f values 0.55 and 0.42, respectively. This mixture was purified by chromatography [column size 2.54 cm x 60 cm, silica gel 230-425 mesh, 50 g] using hexane as a eluent with increasing concentration of ethyl acetate (0%, 5%, 10%, 15%, 20%, 30%, 40%). Appropriate fractions on evaporation gave compound **18b** as a light yellow solid, mp 183.5-185°; ^1H NMR (DMSO-d_6): δ 1.43-1.67 (m, 2H, C-CH_2), 1.68-1.85 (m, 2H, C-CH_2-), 3.07-3.40 (m, 3H, CH-CO, N-CH_2), 4.12-4.38 (m, 2H, N-CH_2), 7.82 (d, 2H, Ar-H), 8.02 (d, 2H, Ar-H), and 18% yield of product **18a** as a light yellow solid, mp 98-101°; IR (KBr, cm^{-1}): 2942-2874 (-CH_2-CH_2-), 1684 (N-$COCF_3$), 1535 (-NO_2), 1349 (-NO_2), 713 and 693 (C_6H_4-); ^1H NMR ($CDCl_3$): δ 1.66 (m, 4H, CH_2-C-CH_2), 3.0-4.0 (m, 3H, N-CH_2, CH-CO), 4.70-5.0 (m, 2H, N-CH), 7.72 (t, 1H, Ar-H), 8.30 (d, 1H, Ar-H), 8.45 (d, 1H, Ar-H), 8.75 (s, 1H, Ar-H): HR/MS (m/e$^+$) calcd for $C_{14}H_{13}N_2F_3O_4$ 330.262, found 331.0904, MH^+. Since products **18a** and **18b** possess very close R_f values, hence, the remaining fractions on evaporation afforded 52% yield of a mixture which contains **18a** as the major product.

Ethyl N-Benzylisonipecotate (12).- To a stirred mixture of ethyl isonipecotate (3.14 g, 20 mmol) and K_2CO_3 (1.67 g, 12 mmol) in absolute ethanol (30 mL), benzyl bromide (3.5 g, 22 mmol) was added. The resulting reaction mixture was stirred at reflux temperature for 18 hrs. The reaction progress was monitored by TLC [silica gel/$CHCl_3$-MeOH (9:1), the R_f values for product and starting material were 0.48 and 0.19, respectively]. After completion of the reaction, the solvent was evaporated under vacuum and the resulting residue was acidified with 2N HCl. The nonbasic impurities were removed by extraction with ether (75 mL x 2), and aqueous layer was basified with 7% NaOH solution. The compound was extracted with ether (100 mL x 3), and combined ethereal layer was dried over

Na_2SO_4. The ethereal layer on evaporation afforded 2,56 g (52%) of product **12** as a viscous oil; IR (KBr, cm^{-1}): 2945 ($-CH_2-CH_2$), 1730 ($-CO_2C_2H_5$), 737 and 698 (C_6H_5); ^1H NMR ($CDCl_3$): δ 1.20 (t, 3H, $C-CH_3$), 1.65-1.73 (m, 2H, $C-CH_2$), 1.75-1.87 (m, 2H, $C-CH_2$), 1.90-2.03 (m, 2H, $N-CH_2$), 2.23 (m, 1H, CH-CO), 2.80 (bd, 2H, $N-CH_2$), 3.45 (5, 2H, $N-CH_2-C_6$), 4.10 (q, 2H, $-CO_2CH_2-$), 7.13-7.30 (m, 5H, Ar-H).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.03; H, 8.53; N, 5.68

N-Benzyl-4-[(*bis*-*p*-fluorophenyl)hydroxymethyl]piperidine (13b).- A solution of ethyl N-benzylisonipecotate (2.56 g, 10.4 mmol) in dry ether (30 mL) was added dropwise to a stirred solution of 4-fluorophenylmagnesium bromide (1.99 g, 10 mmol) in ether (50 mL). The resulting reaction mixture was stirred at reflux temperature for 16 hrs. The progress of reaction was monitored by TLC [silica gel/$CHCl_3$-MeOH (9:1)]. After 16 hrs, additional dry THF (15 mL) was added to the above reaction mixture, and stirring was continued for 10-12 hrs at 70°. Then reaction mixture was poured into a saturated solution of NH_4Cl, and product was extracted with ether (100 mL x 2). The organic phase on evaporation afforded 3.12 g of **13b.** An analytically pure sample was obtained by silica gel column chromatography using $CHCl_3$ as eluent. The R_f values for compound **13b** and starting material were 0.462 and 0.654, respectively. Yield 0.85 g (21%); ^1H NMR ($CDCl_3$): δ 1.38-1.55 (m, 4H, $-CH_2-C-CH_2-$), 1.9-2.1 (m, 2H, $N-CH_2$), 2.33 (m, 1H, -CH- C-OH), 2.93 (d, 2H, $N-CH_2$), 3.50 (5, 2H, $N-CH_2-C_6$), 6.90-7.07 (m, 4H, Ar-H), 7.16-7.24 (m, 9H, Ar-H).

Anal. Calcd for $C_{25}H_{25}F_2NO$: C, 76.31; H, 6.44; N, 3.56. Found: C, 76.00; H, 6.51; N, 3.51.

N-Benzyl-4-(diphenylhydroxymethyl)piperidine (13a).- It was prepared in similar manner as described for the preparation of the compound **13b**, yield (48.5%); mp 86.8-90.2°; IR ($CHCl_3$, cm^{-1}): 3017-2944 (CH_2-CH_2), 755 (C_6H_5). ^1H NMR ($CDCl_3$): δ 1.34-1.57 (m, 4H, $-CH_2-C-CH_2-$), 1.90-2.07 (m, 2H, $N-CH_2$), 2.40 (m, 1H, CH-C-OH), 2.90 (d, 2H, $N-CH_2$), 7.02-7.74 (m, 15H, Ar-H).

Anal. Calcd for $C_{25}H_{27}NO$. 0.25 H_2O: C, 82.99; H, 7.66; N, 3.89. Found: C, 82.73; H, 7.89; N, 3.93

N-Carbethoxy-4-(diphenylhydroxymethyl)piperidine (14).- To a stirred solution of compound **13a** (1.67 g, 6 mmol) in dry toluene (15 mL) was added ethyl chloroformate (0.95 mL). The resulting reaction mixture was stirred at reflux temperature for 2 hrs. The progress of reaction was monitored by TLC [silica gel/ CH_2Cl_2-MeOH (95:5)]. After completion of reaction, the solvent was removed under reduced pressure, and resulting residue was chromatographed over a silica gel column [size 2.54 x 50 cm, silica gel 200-425 mesh, 25 g], and eluted with CH_2Cl_2-CH_3OH (100 : 0 to 95 : 5). Appropriate fractions were mixed, and evaporated to give 1.35 g (85%) of **14.** An analytical pure sample was prepared by crystallization from ethanol. Mp 161.8-162.8°; IR (KBr, cm^{-1}): 3441 (-OH), 2950 ($-CH_2CH_2$), 1679 ($N-CO_2C_2H_5$), 751 and 701 (C_6H_5); ^1H NMR ($CDCl_3$): δ 1.20 (t, 3H, $C-CH_3$), 1.24-1.39 (m, 2H, $-C-CH_2$), 1.40-1.59 (m, 2H, $C-CH_2$), 2.53 (m, 1H, -CH-C-), 2.75 (t, 2H, $N-CH_2$), 4.08 (q, 2H, OCH_2), 4.05-4.35 (m, 2H, $N-CH_2$), 7.07-7.53 (m, 10H, Ar-H).

Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.32; H, 7.57; N, 4.18

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† Dedicated to Professor Leroy B. Townsend on the occasion of his 60th birthday.

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