# Alkyl Substituted 3-PPP Derivatives. Synthesis and Biological Investigation



Haile Tecle*, Stephen C. Bergmeier, Lawrence D. Wise,
Fred M. Hershenson, Linda L. Coughenour and Thomas G. Heffner

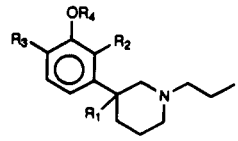
Parke-Davis Pharmaceutical Research Division,
Warner-Lambert Company,
Ann Arbor, MI 48105-2430

Received January 19, 1989

Synthesis of alkyl substituted derivatives of 3-(1-propyl)-3-piperidinyl)phenol (**3-PPP**), **2-8**, was carried out in an attempt to improve on the pharmacodynamic properties of **3-PPP**. No significant improvement was attained.

*J. Heterocyclic Chem.*, **26**, 1125 (1989).

3-(1-Propyl-3-piperidinyl)phenol, **3-PPP (1)**, has recently emerged as the prototype dopamine autoreceptor agonist [1], thus opening a new vista for the rational synthesis of novel psychotropic agents which may find use in treating disease states such as schizophrenia, Huntington's



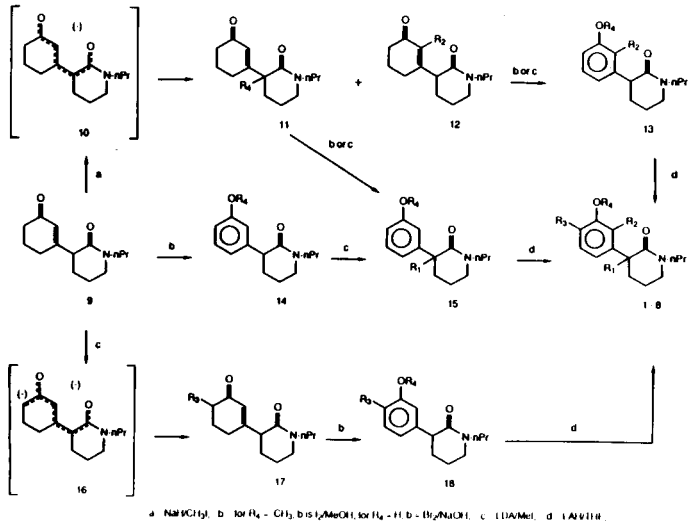
1. $R_1 = R_2 = R_3 = R_4 = H$ (3-PPP)
2. $R_1 = R_4 = CH_3$, $R_2 = R_3 = H$
3. $R_1 = CH_3$, $R_2 = R_3 = R_4 = H$
4. $R_1 = C_2H_5$, $R_4 = CH_3$, $R_2 = R_3 = H$
5. $R_1 = C_2H_5$, $R_2 = R_3 = R_4 = H$
6. $R_3 = CH_3$, $R_1 = R_2 = R_4 = H$
7. $R_2$ = Allyl, $R_1 = R_3 = R_4 = H$
8. $R_3$ = Allyl, $R_1 = R_2 = R_4 = H$

Chorea, Parkinsonism, and tardive dyskinesia [1]. However, **3-PPP** has poor oral activity and a short duration of action. In an attempt to study the effects of substituents on activity, the synthesis of alkylated derivaties **2-8** was carried out.

A general synthetic route was conceived [2] whereby compounds **2-8** could be synthesized from the common precursor **9** (Scheme I). To this end, anion **10** and dianion **16** were generated using sodium hydride and two equivalents of lithium diisopropylamide, respectively. These were quenched with methyl iodide to give enone amides **12** and **17** in good yield. Only enone amide **12** was obtained; none of **11** was observed. Attempted aromatization of **12** and **17** to the corresponding 3-aryllactams **13** and **18** was unsuccessful under various conditions (bromine/sodium hydroxide [2]; iodine/methanol [3]; sulfur/toluene [4]; 2,3-dichloro-5,6-dicyanoquinone/*p*-toluenesulfonic acid [5]; copper(II) bromide/lithium bromide/acetonitrile [6]). In each case, recovery of starting material and/or formation of multiple products was observed.

Aromatization of **9** to **14** (bromine/sodium hydroxide for $R_4 = H$) went poorly. On the other hand, aromatization of **9** to **14** (iodine/methanol for $R_4 = CH_3$) went smoothly. Alkylation at the benzylic carbon (lithium diisopropyl-

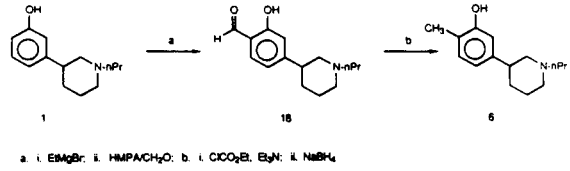
Scheme I



amide/alkyl iodide) proceeded in good yield to give the desired 3-aryl lactams **15** ($R_4 = CH_3$ and $CH_2CH_3$) which, upon reduction with lithium aluminum hydride/tetrahydrofuran, afforded compound **2** and **4**. Subsequent *O*-demethylation of ethers **2** and **4** gave phenols **3** and **5**.

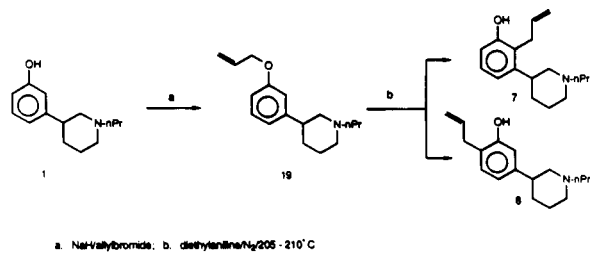
Synthesis of **6** was achieved *via* an alternative route (Scheme II). Magnesium phenoxides have been shown to react regioselectively with aldehydes [7]. Consequently, reaction of **3-PPP (1)** with ethylmagnesium bromide followed by addition of paraformaldehyde and hexamethylphosphoramide in toluene, gave only the 4'-formyl regioisomer **18**, with no detectable amount of the 2'-formyl isomer. Treatment of **18** with ethyl chloroformate and reduction of the ensuing carbonate with sodium borohydride [8] gave target molecule **6**.

Scheme II



The 2'- and 4'-allyl analogs of **3-PPP**, **7** and **8**, respectively, were prepared *via* Claisen rearrangement of allyl ether **19** (Scheme III). Heating **19** in diethylaniline under nitrogen gave regioisomers **7** and **8** in a 1:1 ratio.

Scheme III



a. NaH-allylbromide. b. diethylaniline/$N_2$/205 - 210° C

The title compounds were tested behaviorally for their ability to inhibit spontaneous locomotor activity in mice (MLA) [9], as reported in Table I. None of the analogs were found to be more potent than **3-PPP (1)**. Analogs **6** and **7** appear to have comparable but less potent activity than **3-PPP**. Analogues **3** and **8** are more toxic than **3-PPP**. The title compounds showed weak affinity for the dopamine receptor in an in an *in vitro* assay.

Table I

Pharmacological Data

| Compound | Dose, mg/kg ip | MLA % inh | deaths per no. tested |
|---|---|---|---|
| **1** | 10 | 60 | 0/9 |
| | 30 | 83 | 0/9 |
| | 100 | 91 | 1/9 |
| **3** | 10 | 44 | 0/9 |
| | 30 | 73 | 1/9 |
| | 100 | 95 | 9/9 |
| **5** | 10 | 9 | 0/9 |
| | 30 | 18 | 0/9 |
| **6** | 10 | 20 | 0/9 |
| | 30 | 74 | 0/9 |
| | 100 | 72 | 0/9 |
| **7** | 10 | 9 | 0/9 |
| | 30 | 27 | 0/9 |
| | 100 | 65 | 0/9 |
| **8** | 10 | 9 | 0/9 |
| | 30 | 27 | 0/9 |
| | 100 | 90 | 4/9 |

## EXPERIMENTAL

Melting points are uncorrected. Proton nuclear magnetic resonance ($^1$H-nmr) spectra were obtained on EM-390 (90 MHz) and Varian XL-200 (200 MHz) spectrometers. Chemical shifts are expressed in parts per million (ppm) on the $\delta$ scale with tetramethylsilane as internal standard. The ir spectra were measured on a Digilab Model FTP-14 spectrometer.

3-(3-Oxo-1-cyclohexen-1-yl)-1-propyl-2-piperidinone (**9**).

Step 1: Preparation of 1-Propyl-2-piperidone.

To a suspension of powdered potassium hydroxide (89.14 g, 1588.62 mmoles) in dimethylsulfoxide (800 ml), 2-piperidinone (39.37 g, 397.16 mmoles) followed by 1-bromopropane (72.16 ml, 794.31 mmoles) was added. This was stirred at room temperature for two hours. The reaction mixture was poured into 3 l of water, and extracted with chloroform. The organic layer was washed with water, dried (magnesium sulphate) and concentrated to an oil. The oil was distilled to give 47.8 g (85% yield) of 1-propyl-2-pyridinone, bp 80-82° (1 mm Hg); $^1$H-nmr (deuteriochloroform): $\delta$ 3.27 (m, 4H), 2.33 (m, 2H), 1.77 (m, 6H), 1.55 (y, 2H), 0.9 (t, 3H).

Step 2: Alkylation of 1-Propyl-2-piperidinone.

Lithium diisopropylamide was prepared from diisopropylamine (3.50 ml, 25 mmoles) and *n*-butyl lithium (11.90 ml of 2.1 *M* solution in hexane, 25 mmoles) in tetrahydrofuran (10 ml) under nitrogen at −10 to 0°. To this, 1-propyl-2-piperidinone (3.53 g, 25 mmoles) in tetrahydrofuran (10 ml) was added. Stirring at −10 to 0° was continued for 30 minutes, after which 3-(1-methylpropoxy)-2-cyclohexen-1-one (3.70 g, 22 mmoles) in tetrahydrofuran (10 ml) was added. The reaction mixture was allowed to warm to room temperature. After further stirring at room temperature for two hours, the reaction was shown to be complete by gc. The reaction mixture was acidified with 10% hydrochloric acid, stirred for 0.5 hour, and extracted with dichloromethan. The organic layer was dried (magnesium sulfate) and the oil obtained after evaporation of the solvent was chromatographed, silica-ethyl acetate, to give 4.97 g (86%) of **9** as a solid, mp 43-45°; $^1$H-nmr (deuteriochloroform): 5.88 (s, 1H), 3.91-3.16 (m, 5H), 2.34 (m, 4H), 2.05-1.51 (m, 8H), 0.88 (t, 3H).

*Anal.* Calcd. for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.36; H, 9.07; N, 5.94.

3-(3-Hydroxyphenyl)-1-propyl-2-piperidinone (**14**, $R_4$ = H).

To a solution of **9** (2.36 g, 10 mmoles) in dichloromethane (4 ml), bromine (0.48 ml, 9.5 mmoles) was added, while keeping the temperature below 30°. After stirring at room temperature for one hour, sodium hydroxide (1.2 g, 30 mmoles) in water (8.5 ml) was added and stirred for 15 minutes, still keeping the temperature below 30°. The reaction mixture was extracted with dichloromethane and the aqueous layer treated with concentrated hydrochloric acid (2.4 ml) and methanol (2 ml), keeping the temperature below 30°. After further stirring for one hour, the reaction mixture extracted with dichloromethane, dried (magnesium sulfate) and concentrated to give only a few milligrams of **12** ($R_4$ = H) as an oil; $^1$H-nmr (deuteriochloroform): $\delta$ 7.9 (bs, 1H), 6.99 (m, 1H), 6.50 (m, 3H), 3.46 (m, 4H), 2.05 (m, 1H), 1.74 (m, 6H), 0.94 (t, 3H).

3-(3-Methoxyphenyl)-1-propyl-2-piperidinone (**14**, $R_4$ = $CH_3$).

To a solution of enone **9** (15 g, 63.7 mmoles) in methanol (290 ml), iodine (32.36 g, 127.4 mmoles) was added in portions. After completion of addition of iodine, the reaction mixture was refluxed for three hours. The solvent was removed and the residue partitioned between toluene and sodium hydrogen carbonate solution. The organic layer was washed with 10% aqueous solution of sodium hydrosulfite (sodium dithionite, $Na_2S_2O_4$), 2% aqueous solution of sodium hydroxide and water, respectively. After drying (magnesium sulfate), the solvent was removed to give 8.06 g (51%) of **14** ($R_4$ = $CH_3$) as an oil; $^1$H-nmr (deuteriochloroform): $\delta$ 7.21 (m, 1H), 6.74 (m, 3H), 3.77 (s, 3H), 3.39 (m, 4H), 1.68 (m, 7H), 0.92 (t, 3H).

*Anal.* Calcd. for $C_{15}H_{21}NO_2 \cdot \frac{1}{4}H_2O$: C, 71.53; H, 8.61; N, 5.56.

Found: C, 71.40; H, 8.64; N, 5.40.

3-(3-Methoxyphenyl)-3-methyl-1-propyl-2-piperidinone (**15**, $R_1$ = $R_4$ = $CH_3$).

To a solution of lithium diisopropylamide in tetrahydrofuran (20 ml) prepared from diisopropylamine (3.08 ml, 22 mmoles) and *n*-butyllithium (10.5 ml of 2.1 *M* solution in hexane, 22 mmoles), at −30°, a solution of **14** ($R_4$ = $CH_3$) (5.0 g, 20.22 mmoles) in tetrahydrofuran (20 ml) was added. After stirring for 30 minutes at −10° to 0°, methyl iodide (1.49 ml, 24 mmoles) was added and the reaction mixture allowed to warm to room temperature and stirred for two hours. This was poured into ethyl ether, the organic layer washed with water, 10% hydrochloric acid, brine and dried (magnesium sulfate). The solvent was removed and the resulting oil chromatographed, silca-hexane/ethyl acetate (2:1), to give 4.6 g (87%) of **15** ($R_1$ = $R_4$ = $CH_3$) as an oil; $^1$H-nmr (deuteriochloroform): δ 7.20 (m, 1H), 6.85 (m, 1H), 3.70 (s, 3H), 3.5-3.0 (4H), 2.1-1.5 (m, 6H), 1.0 (m, 6H).

Similarly, 3-(3-methoxyphenyl)-3-ethyl-1-propyl-2-piperidinone (**15**, $R_1$ = $C_2H_5$, $R_4$ = $CH_3$), was obtained as an oil in 93% yield by replacing methyl iodide with ethyl iodide; $^1$H-nmr (deuteriochloroform): δ 7.15 (m, 1H), 6.8 (m, 3H), 3.68 (s, 3H), 3.4-3.1 (m, 4H), 2.1-1.4 (m, 8H), 0.90 (m, 6H).

3-(3-Methoxyphenyl)-3-methyl-1-propylpiperidine (**2**).

To a suspension lithium aluminum hydride (1.33 g, 17.6 mmoles) in tetrahydrofuran (50 ml), a solution of **15** ($R_1$ = $R_4$ = $CH_3$) (4.6 g, 17.6 mmoles) in tetrahydrofuran (20 ml) was added. The reaction mixture was refluxed for four hours, diluted with ethyl ether, and excess lithium aluminum hydride destroyed by adding 1.3 ml of water, followed by 1.3 ml 15% sodium hydroxide and 3.9 ml water. The resulting precipitate was filtered off and the filtrate concentrated to give 3.84 g (88%) of **2** as an oil; $^1$H-nmr (deuteriochloroform): δ 7.13 (m, 1H), 6.90 (m, 2H), 6.60 (m, 1H), 3.70 (s, 3H), 2.23 (m, 6H), 1.53 (m, 6H), 1.23 (s, 3H), 0.87 (t, 3H).

Similarly, 3-ethyl-3-(3-methoxyphenyl)-1-propylpiperidine (**4**) was obtained as an oil in 88% yeild; $^1$H-nmr (deuteriochloroform): δ 7.3 (t, 1H, J = 9 Hz), 6.0 (m, 2H), 6.8 (d, 1H, J = 9 Hz), 3.8 (s, 3H), 2.82 (d, 1H), 2.45-2.15 (m, 4H), 1.9-1.4 (m, 9H), 0.9 (t, 3H, J = 6 Hz), 0.56 (t, 3H, J = 6 Hz).

3-(3-Hydroxyphenyl)-3-methyl-1-propylpiperidine (**3**).

A solution of compound **2** in 48% hydrobromic acid (20 ml) was refluxed for two hours. After evaporation of the solvent, the residue was dried under high vacuum to give 4.4 g (90%) **3**·HBr as a tan solid, mp 90-94°; $^1$H-nmr (DMSO-$d_6$): δ 9.39 (s, 1H), 9.15 (m, 1H), 6.82 (m, 2H), 6.64 (t, 3H), 3.32-2.88 (m, 5H), 2.48 (m, 2H), 1.84-1.58 (m, 5H), 1.37 (s, 3H), 0.86 (t, 3H).

*Anal.* Calcd. for $C_{15}H_{23}NO$·HBr: C, 57.33; H, 7.70; N, 4.46. Found: C, 57.26; H, 7.70; N, 4.39.

Similarly, 3-ethyl-3-(3-hydroxyphenyl)-1-propylpiperidine (**5**) was obtained as the hydrobromide salt in 79% yield, mp 171-173°; $^1$H-nmr (deuteriochloroform): δ 7.2 (m, 1H), 6.75 (m, 3H), 3.0 (m, 6H), 2.5 (m, 1H), 2.1-1.3 (m, 7H), 0.9 (t, 3H), 0.55 (t, 3H).

*Anal.* Calcd. for $C_{16}H_{25}NO$·HBr: C, 58.54; N, 7.98; 4.27. Found: C, 58.31; H, 8.03; N, 4.23.

3-(2-Methyl-3-oxo-1-cyclohexen-1-yl)-1-propyl-2-piperidinone (**12**).

To a suspension of sodium hydride (0.64 g, 60% in oil, 16 mmoles) in tetrahydrofuran (15 ml) a solution of **9** (3.54 g, 15 mmoles) in tetrahydrofuran (15 ml) was added and the reaction mixture refluxed for one hour. This was cooled to room temperature, methyl iodide (1.0 ml, 10 mmoles) added and refluxing resumed for three hours. The cooled reaction mixture was poured into 10% hydrochloric acid and extracted with ethyl ether. The ether layer was dried (magnesium sulfate) and passed through a silica gel column. Evaporation of the eluent gave 3.0 g (80%) of **12** as a yellow oil; $^1$H-nmr (deuteriochloroform): δ 3.32 (m, 4H), 2.30 (m, 3H), 1.82 (m, 8H), 1.77 (s, 3H), 1.53 (q, 2H), 0.90 (t, 3H).

3-(4-Methyl-3-oxo-1-cyclohexen-1-yl)-1-propyl-2-piperidinone (**17**).

To a solution of lithium diisopropylamide in tetrahydrofuran (30 ml) prepared from diisopropylamine (4.48 ml, 32 mmoles) and *n*-butyllithium (15.2 ml of 2.1 *M* in hexane, 32 mmoles) at −40° under nitrogen, a solution of **9** (3.53 g, 15 mmoles) in tetrahydrofuran (30 ml) was added gradually. After stirring at −40° for one hour, the reaction mixture was allowed to warm to room temperature; methyl iodide (1.00 ml, 10 mmoles) was added, and stirring at room temperature continued for three hours. The reaction mixture was poured into 10% hydrochloric acid and extracted with ethyl ether. The ethyl ether layer, after drying (magnesium sulfate), was passed through a silica gel column. Evaporation of the eluent gave 2.33 g (62%) of **17** as an oil; $^1$H-nmr (deuteriochloroform): δ 5.83 (bs, 1H), 3.30 (m, 4H), 2.33 (m, 2H), 1.96 (m, 8H), 1.57 (q, 2H), 1.22 (d, 3H), 6.90 (t, 3H).

2-Hydroxy-4-(1-propyl-3-piperidinyl)benzaldehyde (**18**).

To a solution of **3-PPP** (**1**) (6.4 g, 29.2 mmoles) in dry toluene (150 ml) cooled in an ice bath, ethyl magnesium bromide (14.6 ml of 2.0 *M* in tetrahydrofuran, 29.2 mmoles) was added. The ice bath was removed and the reaction mixture allowed warm to room temperature. Hexamethylphosphoramide (5.08 ml, 29.2 mmoles) and paraformaldehyde (6.66 g, 74 mmoles) were added successively. After refluxing for four hours, the reaction mixture was partitioned between ammonium chloride solution and ethyl acetate. The ethyl acetate layer was washed with water, brine, dried (magnesium sulfate) and concentrated. The resulting oil was chromatographed, silica-ethyl acetate. Evaporation of the eluent gave 6.0 g (83%) of aldehyde **18** as a yellow oil; $^1$H-nmr (deuteriochloroform): δ 9.73 (s, 1H), 7.23 (m, 1H), 6.80 (m, 2H), 2.77 (m, 6H), 2.23 (m, 3H), 1.67 (m, 4H), 0.83 (t, 3H).

2-Methyl-5-(1-propyl-3-piperidinyl)phenol (**6**).

To a solution of aldehyde **18** (1.24 g, 5 mmoles) in tetrahydrofuran (50 ml) at 0°, triethylamine (0.84 ml, 6 mmoles) and ethyl chloroformate (0.57 ml, 6 mmoles) were added. After stirring for 30 minutes at 0° the precipitated solid (triethylammonium chloride) was separated by filtration and discarded. The filtrate was added to sodium borohydride (1.13 g, 20 mmoles) in water (7.5 ml) at 0°. After stirring at room temperature for three hours, the reaction mixture was acidified with 10% hydrochloric acid and washed with ethyl ether. The aqueous layer was neutralized with sodium hydrogen carbonate and extracted with ethyl acetate, dried (magnesium sulphate) and concentrated to give 0.84 g (72%) of **6** as a yellow oil. This was dissolved in ethyl ether and treated with dry hydrogen chloride gas giving **6**·HCl acid as a white powder, mp 75-79°; $^1$H-nmr (DMSO-$d_6$): δ 9.32 (s, 1H), 6.99 (d, 1H), 6.63 (s, 1H), 6.4 (d, 1H), 2.96 (m, 4H), 2.47 (m, 3H), 2.04 (s, 3H), 1.89-1.68 (m, 6H), 0.85 (t, 3H).

*Anal.* Calcd. for $C_{15}H_{23}NO \cdot HCl \cdot H_2O$: C, 62.59; H, 8.40; N, 4.87. Found: C, 62.76; H, 8.79; N, 4.98.

3-[3-(2-Propenyloxy)phenyl]-1-propylpiperidine (**19**).

A solution of **3-PPP** (**1**) (3.41 g, 15.6 mmoles) in tetrahydrofuran (25 ml) was added to a suspension of sodium hydride (0.64 g of 60% in oil, 20 mmoles) in tetrahydrofuran (20 ml). After stirring for three hours at room temperature, allyl bromide (1.38 ml, 20 mmoles) was added and stirring at room temperature continued for an additional three hours. The reaction mixture was poured into water, and extracted with ethyl ether. The ethyl ether layer was washed with 10% sodium hydroxide, dried (magnesium sulfate) and concentrated to an oil. This was chromatographed, silica-ethyl acetate, yielding 3.01 g (75%) of allyl ether **19** as an oil; $^1$H-nmr (deuteriochloroform): $\delta$ 7.10 (m, 1H), 6.70 (m, 3H), 5.97 (m, 1H), 5.27 (n, 2H), 4.45 (dd, 2H), 2.87 (m, 4H), 2.27 (m, 3H), 1.67 (m, 6H), 0.87 (t, 3H).

2-(2-Propenyl)-3-(1-propyl-3-piperidinyl)phenol (**7**) and 2-(2-propenyl)-5-(1-propyl-3-piperidinyl)phenol (**8**).

Allyl ether **19** (3.02 g, 11.60 mmoles) and diethylaniline (1.85 g, 11.60 mmoles) were mixed and the reaction flask evacuated and refilled with nitrogen. The reaction mixture was heated at 205-210° for 24 hours, and then cooled and diluted with hexane. Analytically pure 2-allyl **3-PPP** (**7**) precipitated as white solid, yielding 1.0 g (33%); $^1$H-nmr (deuteriochloroform): $\delta$ 7.06 (d, 1H), 6.71 (s, 1H), 6.64 (d, 1H), 6.09-5.96 (m, 1H), 5.16-5.03 (m, 2H), 3.37 (d, 2H), 3.13 (m, 2H), 2.89 (m, 1H), 2.39-2.25 (m, 2H), 2.00-1.46 (m, 8H), 0.82 (t, 3H).

*Anal.* Calcd. for $C_{17}H_{25}NO$: C, 78.72; H, 9.71; N, 5.40. Found: C, 78.66; H, 9.46; N, 5.30.

The filtrate from above was concentrated and the resulting oil chromatographed, silica-ethyl acetate, to remove diethylaniline. The effluent was concentrated to an oil. The oil was dissolved in ethyl ether and treated with ether-hydrogen chloride, giving 1.14 g (33%) of **8**·HCl as white solid, mp 185-190°; $^1$H-nmr (DMSO-$d_6$): $\delta$ 9.44 (s, 1H), 6.99 (d, 1H, J = 7.8 Hz), 6.71 (m, 2H), 5.93-5.79 (m, 1H), 5.10 (dd, 1H, J = 1.9 Hz, J = 17.2 Hz), 4.89 (dd, 1H, J = 1.8 Hz, J = 10.0 Hz), 3.48-3.14 (m, 4H), 2.98-2.80 (m, 4H), 2.47 (m, 1H), 1.7 (m, 6H), 0.85 (t, 3H).

*Anal.* Calcd. for $C_{17}H_{25}NO \cdot HCl$: C, 69.02; H, 8.86; N, 4.73. Found: C, 68.85; H, 8.61; N, 4.60.

## REFERENCES AND NOTES

[1] H. Wikström, D. Sanchez, P. Lindberg, U. Hacksell, L. Arvidsson, A. Johnsson, S. Thorberg, J. Lars, G. Milsson, K. Svensson, S. Hjorth, D. Clark, and A. Carlsson, *J. Med. Chem.*, **27**, 1030 (1984), and references therein.

[2] For closely related reaction sequences see: G. Bradley, J. F. Cavalla, T. Edington, R. B. Shepherd, A. C. White, B. J. Bushell, J. R. Johnson and G. O. Westen, *Eur. J. Med. Chem.-Chim. Ther.*, **15**, 375 (1980).

[3] Y. Tamura and Y. Yoshimoto, *Chem. Ind.*, 889 (1980).

[4] D. E. Butler, P. Bass, I. C. Nordin, F. P. Hanck, and Y. J. L'Italien, *J. Med. Chem.*, **14**, 575 (1975).

[5] K. L. Cook and A. L. Waring, *J. Chem. Soc., Perkin Trans. I*, 529 (1973).

[6] D. Dondon, Y. Pietrasanta and B. Pucci, *Tetrahedron Letters*, 821 (1977).

[7] G. Casiraghi, G. Casnsti, M. Curnia, A. Pochini, G. Puglia, G. Sartori, and R. Ungao, *J. Chem. Soc., Perkin Trans. I*, 318 (1978).

[8] N. Minami and S. Kijima, *Chem. Pharm. Bull.*, **27**, 1490 (1979).

[9] L. L. Coughenour, J. R. McLean, and R. B. Parker, *Pharmacol. Biochem. Behav.*, **6**, 351 (1977).

[10] D. R. Burt, L. Creese, S. H. Snyder, *Mol. Pharmacol.*, **12**, 300 (1976).