Synthesis of 3-(2-Aminoethyl)pyrrole Derivatives [1]

Vassilis J. Demopoulos

Division of Pharmaceutical Chemistry, Department of Pharmacy, University of Thessaloniki, Thessaloniki, Greece 540 06

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3-(2-Di-*n*-propylaminoethyl)pyrrole (**1a**) was prepared in good yield by reduction of pyrrole-3-(*N*,*N*-di-*n*-propylglyoxamide) (**9**) with lithium aluminum hydride. 3-(2-Di-*n*-propylaminoethyl)-5-acetylpyrrole (**1b**) was prepared by first acetylation of 1-*p*-toluenesulfonyl-3-(2-di-*n*-propylaminoethyl)pyrrole (**6**) followed by hydrolysis of the *p*-toluenesulfonyl substituent. The starting material **6** was prepared by homologation of 1-(*p*-toluenesulfonyl)pyrrole-3-carboxaldehyde (**3**) to the corresponding acetaldehyde followed by reductive amination of the latter.

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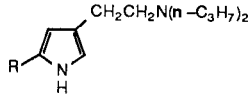
The 3-(2-aminoethyl)pyrrole moiety of ergolines has been suggested to be an important structural feature for manifestation of certain dopamine agonist activities [2,3]. The target compounds in the present study were the derivatives **1a-b** of this biologically active structure. The *n*-propyl substituents on the basic nitrogen of **1a-b** were chosen because they are usually necessary for maximum activity in diverse dopamine agonists [4]. Furthermore, the 5-acetyl substituent in **1b** will decrease the p*K*a of the pyrrole acidic hydrogen [5]. The p*K*a of this pyrrole acidic hydrogen therefore approaches closely the *m*-OH of dopamine which is important for agonist-receptor interactions [4].



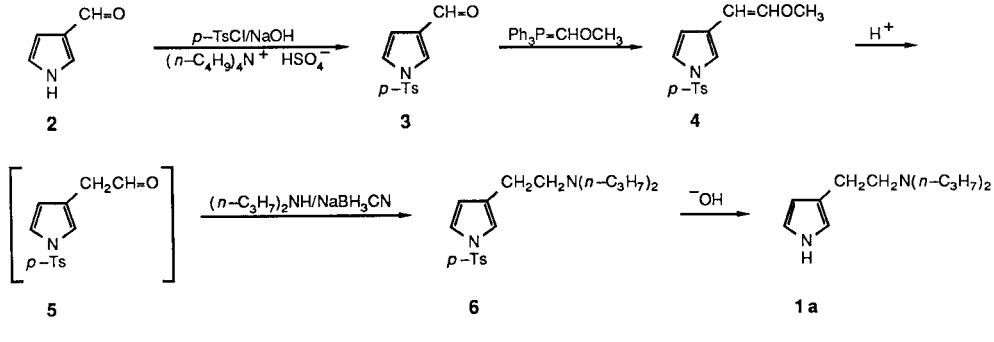
1a R = H
1b R = $COCH_3$

3-(2-Aminoethyl)pyrrole has been prepared previously from the diester of 4-(2-aminoethyl)pyrrole-2,3-dicarboxylic acid [6] and from 1-(phenylsulfonyl)pyrrole-3-carboxaldehyde [7]. Herein are described synthetic approaches which give access to derivatives bearing substituents on the basic nitrogen as well as on the pyrrole ring.

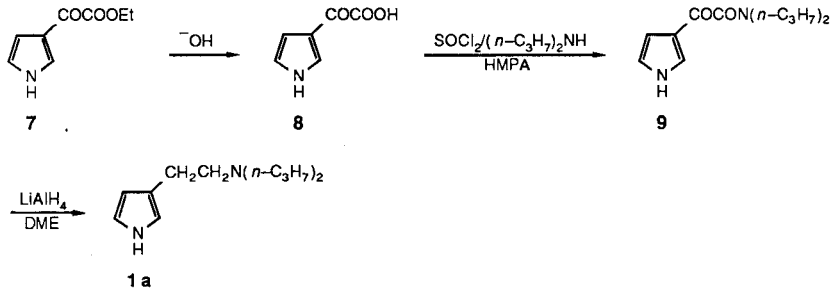
One of the syntheses (Scheme I) was based on the homologation of pyrrole-3-carboxaldehyde. It was found necessary to mask the pyrrole ring nitrogen in order to prevent formation of pyrrolyl phosphonium salts under the conditions of the Wittig reaction [8]. Thus, pyrrole-3-carboxaldehyde (**2**) [9] was first converted to 1-*p*-toluenesulfonyl derivative **3** under phase transfer catalysis [10] and then reacted with methoxymethylenetriphenylphosphorane [11] to give the vinyl ether **4** as a mixture of two isomers (*E*/*Z* approximate ratio of 55/45, based on nmr data) which was used in the next step without separation. The hydrolysis of **4** to the corresponding aldehyde **5** under a number of literature methods (perchloric acid in ether [12], mercuric acetate and potassium iodide [13], or chlorotrimethylsilane and sodium iodide [14]) was unsuccessful, as was its direct conversion to the corresponding di-*n*-propylenamine with di-*n*-propylamine and mercuric acetate [11]. However, aldehyde **5** was formed on refluxing **4** in a mixture of 2-propanol-water with a catalytic amount of *p*-toluensulfonic acid and a strict exclusion of oxygen. Aldehyde **5** decomposed to some extent on attempts to purify it by column chromatography, and therefore it was converted directly to amine **6** under conditions of a reductive amination [15]. The last step of the sequence was the basic hydrolysis [16] of the *p*-toluenesulfonyl substituent in **6**.

The shorter and higher overall yield route (Scheme II) parallels the known synthesis of tryptamines from the corresponding indole-3-glyoxamides [17]. Thus, ethylpyrrole-3-glyoxalate (**7**) [18] was hydrolyzed and the formed acid **8**

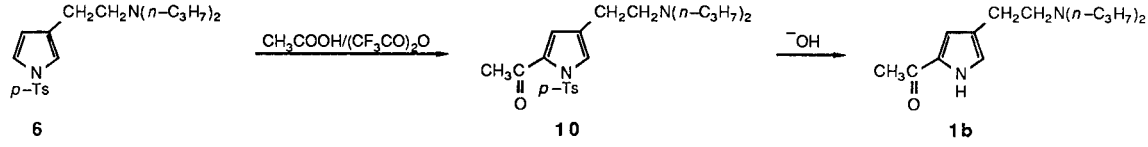
Scheme I



Scheme II



Scheme III



was converted to the corresponding amide **9** with thionyl chloride and di-*n*-propylamine in hexamethylphosphoramide [19]. An attempt to synthesize amide **9** directly from **7** (di-*n*-propylamine and sodium hydride [20] or *n*-butyllithium [21]) gave only a low yield of the desired product. Reduction of the amide function and hydrogenolysis to **1a** was effected in a single step by the action of an excess lithium aluminum hydride in refluxing dimethoxyethane. This reaction was surprisingly clean and gave a high yield of product (72%). The mechanism of the hydrogenolysis step probably involved an intermediate 1-azafulvenium species [16,22]. The overall yield of this latter route was 35% from **7**, or 22% from pyrrole itself, and represents an easy access to this type of substituted pyrrole.

The synthesis of **1b** is shown in Scheme III. Acylation of **6** with the mixed acetic-trifluoroacetic anhydride [23] gave **10** along with its 2-acetyl isomer in an approximate ratio of 80/20, based on nmr data [24]. From this mixture, amine **10** was isolated as the hydrochloride salt by recrystallization and its isomeric purity was ascertained from tlc and nmr analysis. This was then converted to the target amine **1b** by a basic hydrolysis of the *p*-toluenesulfonyl substituent.

Amines **1a** and **6** were characterized as the oxalate salts, amine **1b** was characterized as the hydrochloride salt and amine **10** was characterized as both the free base and the hydrochloride salt.

EXPERIMENTAL

Melting points are uncorrected and were determined in open glass capillaries using a Büchi 510 apparatus. Infrared spectra were recorded with a Perkin-Elmer 597 spectrophotometer, and nuclear magnetic resonance spectra were recorded with a Brücker AW-80 spectrometer with internal tetramethylsilane reference. Elemental analyses were performed on a Perkin-Elmer 240 automated analyzer (Department of Chemistry, University of Thessaloniki). Flash chromatography [25] was carried out using Merck 9385 silica gel. Petroleum ether refers to the fraction of bp 40-60°.

1-(*p*-Toluenesulfonyl)pyrrole-3-carboxaldehyde (**3**).

To a well stirred and cooled (ice bath) mixture of 50% aqueous sodium hydroxide solution (60 ml) and dichloromethane (60 ml) was added tetrabutylammonium hydrogen sulfate (0.15 g, 1.5 mmoles) and pyrrole-3-carboxaldehyde (**2**) [9] (2.85 g, 30 mmoles). Then, a solution of *p*-toluenesulfonyl chloride (6.3 g, 33 moles) in dichloromethane (30 ml) was added dropwise over a period of 5 minutes and the mixture was stirred vigorously at the same temperature for 15 minutes. The reaction mixture was poured into a saturated aqueous sodium chloride solution (100 ml) and extracted with dichloromethane (3 x 100 ml). The combined organic extracts were filtered through celite, washed with saturated aqueous sodium chloride solution (1 x 100 ml), dried over anhydrous sodium sulfate and the solvents were evaporated under reduced pressure. The residue was flash chromatographed on silica gel with ether-petroleum ether (1:1) as the eluent to afford 6.6 g (88%) of product which crystallized on standing. An analytical sample was recrystallized from dichloromethane-petroleum ether, mp 61-62°; ir (nujol): 1600, 1680 cm^{-1}; nmr (deuteriochloroform): δ 2.41 (s, 3H, $ArCH_3$), 6.71 (m, 1H, H-4), 7.18 (m, 1H, H-5), 7.23-7.45 (m, 2H, phenyl H), 7.65-7.75 (m, 3H, H-2 and phenyl H), 9.82 (s, 1H, CHO).

Anal. Calcd. for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.89; H, 4.48; N, 5.58.

1-*p*-Toluenesulfonyl-3-(2-methoxyvinyl)pyrrole (**4**).

To a stirred and cooled (ice bath) mixture of anhydrous (distilled from Na) tetrahydrofuran (50 ml), (methoxymethyl)triphenylphosphonium chloride (11.2 g, 32.7 mmoles) and diisopropylamine (3.4 ml, 24 mmoles), under a nitrogen atmosphere, was added a solution of 2.5 *M* n-butyllitium in hexane (9.6 ml, 24 mmoles). The mixture was warmed to room temperature over 1 hour. Then, the reaction mixture was cooled (ice bath) and a solution of 3 (4 g, 16 mmoles) in anhydrous (distilled from Na) tetrahydrofuran (20 ml) was added. The reaction mixture was stirred at room temperature for 2 hours, then it was cooled (ice bath), treated with water (100 ml) and extracted with ether (3 x 100 ml). The combined

ethereal extracts were washed with a saturated aqueous sodium chloride solution (1 x 100 ml), dried over anhydrous sodium sulfate and the solvents were evaporated under reduced pressure. The residue was flash chromatographed on silica gel with ether-petroleum ether (1:4) as the eluent to afford 3.53 g (78%) of product which crystallized on standing. An analytical sample was recrystallized from ether-petroleum ether, mp 83-85°; ir (nujol): 1600, 1655 cm^{-1}; nmr (deuteriochloroform): δ 2.38 (s, 3H, CH_3), 3.58 (s, OCH_3, *E* isomer), 3.70 (s, OCH_3, *Z* isomer), 5.08 (d, C=CH, J = 6.5 Hz, *Z* isomer), 5.56 (d, C=CH, J = 13 Hz, *E* isomer), 6.03 (d, C=CH, J = 6.5 Hz, *Z* isomer), 6.15 (m, H-4, *E* isomer), 6.50 (m, H-4, *Z* isomer), 6.80 (d, C=CH, J = 13 Hz, *E* isomer), 6.93 (m, H-2, *E* isomer), 7.03 (m, H-5 of both isomers and H-2 of *Z* isomer), 7.13-7.40 (m, 2H, phenyl H), 7.59-7.88 (m, 2H, Phenyl H).

Anal. Calcd. for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.38; H, 5.38; N, 5.06.

1-*p*-Toluenesulfonyl-3-(2-di-*n*-propylaminoethyl)pyrrole Oxalate (**6**).

A mixture of 4 (0.6 g, 2.2 mmoles), *p*-toluenesulfonic acid (monohydrate) (0.03 g, 0.16 mmole), 2-propanol (10 ml) and water (10 ml) was flushed with nitrogen and then refluxed under a nitrogen atmosphere for 12 hours. The reaction mixture was cooled to room temperature, poured into a saturated aqueous sodium chloride solution (100 ml) and extracted with ether (3 x 50 ml). The combined organic extracts were washed with saturated aqueous sodium chloride solution (1 x 50 ml) and dried over anhydrous potassium carbonate. Evaporation of the solvents under reduced pressure afforded crude aldehyde **5** as an oil which was used in the next step without purification; ir (film): 1600, 1730 cm^{-1}; nmr (deuteriochloroform): δ 2.40 (s, CH_3), 3.46 (s, CH_2), 6.18 (m, H-4), 7.06 (m, H-2, H-5), 7.20-7.35 (m, phenyl H), 7.60-7.83 (m, phenyl H), 9.62 (s, CHO).

A mixture of crude aldehyde **5**, di-*n*-propylamine hydrochloride (0.94 g, 6.8 mmoles) and methanol (20 ml) was stirred at room temperature for 3 hours in the presence of 3 Å molecular sieves and with adjustment of the *p*H to 6-7 by the addition of glacial acetic acid. To this was then added sodium cyanoborohydride (0.2 g, 3.2 mmoles), the *p*H of the reaction mixture was adjusted again to 6-7 by the addition of glacial acetic acid and the stirring was continued for 12 hours at room temperature. The reaction mixture was poured into a 5% aqueous sodium hydroxide solution (50 ml) and extracted with ether (3 x 30 ml). The combined ethereal extracts were filtered through celite, washed with saturated aqueous sodium chloride solution (1 x 50 ml), cooled by the addition of ice and then extracted with dilute aqueous hydrogen chloride solution (4 x 20 ml). The combined aqueous extracts were cooled (ice bath), made strongly alkaline with the addition of solid sodium hydroxide and extracted with ether (3 x 50 ml). The combined ethereal extracts were washed with saturated aqueous sodium chloride solution (1 x 50 ml), dried over anhydrous potassium carbonate and the volatiles evaporated under reduced pressure. The residue (0.386 g) was dissolved in acetone and was treated with a solution of anhydrous oxalic acid (0.1 g) in acetone. The solvents were evaporated under reduced pressure and the solid residue was recrystallized from 2-propanol-acetone-ether to afford 0.433 g (46%) of product, mp 150-152° (evolution of gases); nmr (deuteriochloroform): (free base) δ 0.65-0.96 (m, 6H, aliphatic H), 1.10-1.64 (m, 4H, aliphatic H), 2.19-2.67 (m, 11H, aliphatic H), 6.14 (m, 1H, H-4), 6.94 (m, 1H, H-2), 7.05 (m, 1H, H-5), 7.15-7.37 (m, 2H, phenyl H), 7.62-7.83 (m, 2H, phenyl H).

Anal. Calcd. for $C_{21}H_{30}N_2O_6S$: C, 57.51; H, 6.90; N, 6.39. Found: C, 57.21; H, 7.08; N, 6.33.

Pyrrole-3-glyoxalic acid (**8**).

A mixture of ethyl pyrrole-3-glyoxalate (**7**) [18] (2 g, 12 mmoles) and 5% aqueous sodium hydroxide solution (30 ml) was stirred overnight at room temperature. The reaction mixture was cooled (ice bath) and acidified by the dropwise addition of concentrated aqueous hydrochloric acid solution. The precipitate was collected by filtration. The filtrate was saturated with sodium chloride and extracted with ethyl acetate (3 x 20 ml). The organic layer was washed with a saturated aqueous sodium chloride solution (1 x 50 ml), dried over anhydrous sodium sulfate and the solvents evaporated under reduced pressure to give a solid residue which was combined with the precipitate and dried under high vacuum to afford 1.52 g (91%) of a yellowish solid which was used in the next step without purification.

An analytical sample was recrystallized from isopropanol-ether-petroleum ether, mp 154-156° dec; ir (nujol): 1600, 1725, 3250 cm^{-1}; nmr (dimethylsulfoxide, d_6): δ 6.57 (m, 1H, H-4), 6.90 (m, 1H, H-5), 7.70 (m, 1H, H-2), 11.70 (br s, 1H, NH).

Anal. Calcd. for $C_6H_5NO_3$: C, 51.80; H, 3.62; N, 10.07. Found: C, 52.08; H, 3.72; N, 10.18.

Pyrrole-3-(*N*,*N*-di-*n*-propylglyoxamide) (**9**).

A mixture of **8** (0.87 g, 6.25 mmoles) and hexamethylphosphoramide (10 ml) was stirred until the solid was dissolved. Then, it was cooled (ice bath) and treated first with thionyl chloride (0.5 ml, 6.85 mmoles) and then with di-*n*-propylamine (1 ml, 13.87 mmoles). The reaction mixture was stirred at room temperature overnight. Then, it was poured into water (100 ml) and extracted with ether (3 x 50 ml). The combined ethereal extracts were washed with dilute aqueous hydrogen chloride solution (3 x 50 ml), saturated aqueous sodium chloride solution (1 x 50 ml), dried over anhydrous sodium sulfate and the solvents evaporated under reduced pressure. The residue crystallized slowly on standing and recrystallized from chloroform-petroleum ether to afford 0.74 g (53%) of product, mp 83-85°; ir (nujol): 1615, 1650, 3150 cm^{-1}; nmr (deuteriochloroform): δ 0.53-1.10 (m, 6H, CH_3), 1.34-1.92 (m, 4H, CH_2), 2.95-3.62 (m, 4H, NCH_2), 6.62 (m, 2H, H-4 and H-5), 7.27 (m, 1H, H-2), 10.30 (br s, 1H, NH).

Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 65.18; H, 8.53; N, 12.83.

3-(2-Di-*n*-Propylaminoethyl)pyrrole Oxalate (**1a**).

I.

A mixture of **6** (free base) (0.18 g, 0.5 mmole), methanol (5 ml) and a 5% aqueous sodium hydroxide solution (3 ml) was refluxed for 12 hours. The reaction mixture was cooled to room temperature, poured into saturated aqueous sodium chloride solution (20 ml) and extracted with ether (3 x 20 ml). The combined ethereal extracts were washed with saturated aqueous sodium chloride solution, dried over anhydrous potassium carbonate and the solvents evaporated under reduced pressure. The residue (0.09 g) was dissolved in acetone and this was treated with a solution of anhydrous oxalic acid (0.04 g) in acetone. The solvents were evaporated under reduced pressure (bath temperature <30°) and the solid residue was recrystallized from 2-propanol-ether to afford 0.1 g (67%) of product, mp 107-108°; nmr (deuteriochloroform): (free base) δ 0.66-1.00 (m, 6H, aliphatic H), 1.20-1.70 (m, 4H, aliphatic H), 2.27-2.75 (m, 8H, aliphatic H), 6.07 (m, 1H, H-4), 6.52 (m, 1H, H-2), 6.62 (m, 1H, H-5), 8.50 (br s, 1H, NH).

Anal. Calcd. for $C_{14}H_{24}N_2O_4$: C, 59.13; H, 8.51; N, 9.85. Found: C, 59.13; H, 8.51; N, 9.69.

II.

A mixture of **9** (0.6 g, 2.7 mmoles) and lithium aluminum hydride (0.6 g, 15.8 mmoles) in dimethoxyethane (30 mmoles) was refluxed under a nitrogen atmosphere for 8 hours. After cooling to room temperature, saturated aqueous sodium sulfate was added dropwise until a white suspension was formed. This mixture was filtered through celite, the precipitate was washed on the filter with several portions of ether and the combined filtrate and washings were evaporated under reduced pressure. The residue (0.517 g) was dissolved in acetone and was treated with a solution of anhydrous oxalic acid (0.23 g) in acetone. The volatiles were evaporated under reduced pressure (bath temperature <30°) and the solid residue was recrystallized from 2-propanol-ether to afford 0.55 g (72%) of a product which was identical in all respects with the product as prepared from procedure I.

1-*p*-Toluenesulfonyl-3-(2-di-*n*-propylaminoethyl)-5-acetylpyrrole Hydrochloride (**10**).

A mixture of **6** (free base) (0.15 g, 0.43 mmole), glacial acetic acid (0.16 g, 2.7 mmoles), trifluoroacetic anhydride (1.5 ml) and dichloromethane

(1.5 ml) was refluxed for 24 hours. The mixture was cooled to room temperature, to this was added glacial acetic acid (0.16 g, 2.7 mmoles) and the refluxing was continued for 24 hours. The volatiles were evaporated under reduced pressure, the residue was taken up in ethyl acetate, basified with the addition of triethylamine, washed with water (1 x 20 ml) and saturated aqueous sodium chloride solution (1 x 20 ml), dried over anhydrous potassium carbonate and the solvents evaporated under reduced pressure. The residue was dissolved in ether and acidified by the addition of anhydrous ethereal hydrochloric acid. The volatiles were evaporated under reduced pressure and the residue was recrystallized from 2-propanol-ether to afford 0.1 g (54%) of product, mp 195-196°; ir (nujol): 1600, 1680 cm^{-1}; nmr (deuteriochloroform): (free base) δ 0.60-1.10 (m, 6H, aliphatic H), 1.20-1.80 (m, 4H, aliphatic H), 2.14-2.75 (m, 14H, aliphatic H), 6.95 (d, 1H, J = 2 Hz, H-4), 7.20-7.45 (m, 2H, phenyl H), 7.64 (d, 1H, J = 2 Hz, H-2), 7.75-8.00 (m, 2H, phenyl H).

Thin layer chromatography of the free base (silica gel, ethyl acetate) R_f 0.22.

Anal. Calcd. for $C_{21}H_{31}N_2O_3SCl$: C, 59.07; H, 7.32; N, 6.56. Found: 58.86; H, 7.26; N, 6.81.

The mother liquors from the recrystallization of **10** were concentrated and the residue partitioned between ether and a 5% aqueous sodium hydroxide solution. The organic layer was evaporated under reduced pressure and the residue was flash chromatographed on silica gel with ethyl acetate-petroleum ether (3:2) containing 0.3% triethylamine as the eluent to afford 0.017 g of an oil which was assigned the structure of the 2-acetyl isomer; ir (film): 1600, 1670 cm^{-1}; nmr (deuteriochloroform): 0.60-1.00 (m, 6H, aliphatic H), 1.10-1.60 (m, 4H, aliphatic H), 2.20-2.60 (m, 14H, aliphatic H), 6.15 (d, 1H, J = 3 Hz, H-4), 7.20-7.45 (m, 3H, H-5 and pheny H), 7.50-7.75 (m, 2H, phenyl H). Thin layer chromatography (silica gel, ethyl acetate) R_f 0.31.

The free base of **10** crystallized on refrigerating and recrystallized from ether-petroleum ether to give an analytical sample, mp 72-73°.

Anal. Calcd. for $C_{21}H_{30}N_2O_3S$: C, 64.58; H, 7.74; N, 7.17. Found: C, 64.51; H, 7.91; N, 7.32.

3-(2-Di-*n*-Propylaminoethyl)-5-acetylpyrrole Hydrochloride (**1b**).

A mixture of **10** (0.2 g, 0.47 mmole), methanol (30 ml) and a 5% aqueous sodium hydroxide solution (10 ml) was stirred at room temperature for 48 hours. The reaction mixture was poured into saturated aqueous sodium chloride solution (50 ml) and extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were washed with saturated aqueous sodium chloride solution, dried over anhydrous potassium carbonate and the solvents evaporated under reduced pressure. The residue was dissolved in ether and acidified by the addition of anhydrous ethereal hydrochloric acid. The volatiles were evaporated under reduced pressure and the semisolid residue was recrystallized from 2-propanol-ether to afford 0.094 g (73%) of product, mp 201-203°; ir (nujol): 1650, 3300 cm^{-1}; nmr (deuteriochloroform): (free base) δ 0.60-1.10 (m, 6H, aliphatic H), 1.20-1.80 (m, 4H, aliphatic H), 2.20-2.80 (m, 11H, aliphatic H), 6.75 (m, 1H, H-4), 6.85 (m, 1H, H-2), 9.35 (br s, 1H, NH).

Anal. Calcd. for $C_{14}H_{25}N_2OCl$: C, 61.64; H, 9.24; N, 10.27. Found: C, 61.38; H, 9.12; N, 10.29.

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