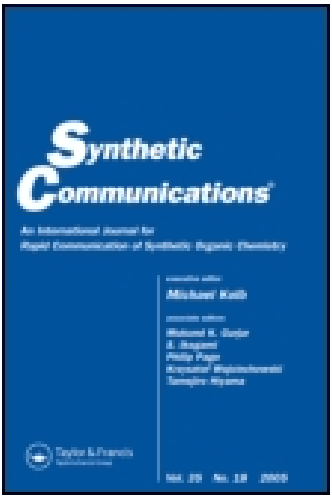

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A NEW SYNTHETIC APPROACH TO *N*,*N*′-DISUBSTITUTED 1,*n*-ALKANEDIAMINES

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ABSTRACT

A general procedure is described for the synthesis of unsymmetrically substituted *N*-aryl-*N*′-alkyl (or aryl) 1,*n*-alkanediamines **1** ($n = 2-5$) by reduction of ω-alkyl (or aryl) aminoalkanamides **2** with borane. Compounds **2** are easily obtained by aminolysis of the corresponding ω-haloalkanamides **3**.

INTRODUCTION

Naturally occurring polyamines are of biochemical interest as they are involved in cellular proliferation and differentiation processes,[1] while some synthetic analogues behave as potent antibiotics and antineoplastics.[2] Among polyamines, 1,*n*-diamines have been extensively studied as they are biosynthetic precursors of polyamines. Besides, suitably substituted

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derivatives share some pharmacological features of polyamines,[3] or act as modulators of enzymes involved in their metabolism.[4] In particular, *N*,*N*′-disubstituted 1,*n*-diamines display a variety of pharmacological activities, in addition to the antitumoral activity reported for some members.[3] Thus, suitably substituted 1,3-propanediamines have been employed as platelet antiagregants[5] and microbicidal agents,[6] while higher homologues (putrescine and cadaverine derivatives) display affinity for cholinergic[7] and NMDA[8] receptors.

The synthesis of symmetrically *N*,*N*′-disubstituted derivatives starting from 1,*n*-diamines is generally accomplished through direct alkylation or by reduction of the corresponding diamides or diimines. Such synthetic approaches, as well as other methods based on the aminolysis of α,ω-dihaloalkanes, cannot be successfully employed for the preparation of unsymmetrically substituted analogues, as both groups in the substrate have the same reactivity.[9] The synthesis of such derivatives was achieved in the case of di and trimethylene compounds through cyclic intermediates such as amidines or aminals,[10] but those methods lack general applicability and generally involve *N*-monosubstituted 1,*n*-diamines as starting materials, themselves accessible through multistep synthesis.[11]

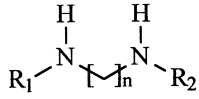
Within this context, in the course of our research on potentially bioactive 1,*n*-diamines, we developed a synthetic procedure for the preparation of *N*-alkyl (or aralkyl)-*N*′-aryl-1,*n*-diamines from *N*-(ω-haloalkyl)amides.[12] As one of the *N*-substituents is generated by reduction of an amide, such procedure was limited to the synthesis of derivatives with primary *N*-alkyl (or aralkyl) substituents and could not be employed for unsymmetrically substituted *N*-*N*′-diarylalkylenediamines. To circumvent such limitations, we present here an alternative sequence for the synthesis of unsymmetrically substituted *N*-aryl-*N*′-alkyl (or aryl)-1,*n*-diamines **1** (Table), which were not accessible by the above mentioned procedure.

RESULTS AND DISCUSSION

The sequence depicted in Scheme 1 involves acylation of aliphatic or aromatic amines with ω-haloalkanoyl chlorides, followed by aminolysis of the corresponding ω-haloamides **3**. The resulting aminoamides **2** are then reduced with borane/THF to yield the desired 1,*n*-diamines **1**.

For the synthesis of *N*-aryl-*N*′-alkyl derivatives, except for **1a**, the sequence that involves aminolysis of the ω-haloacyl chloride with alkyl amines followed by aminolysis of the product with the arylamine was the most suitable in order to avoid intramolecular dehydrohalogenation of precursors **3**. In all cases, aminolysis of ω-haloamides **3** lead to better yields

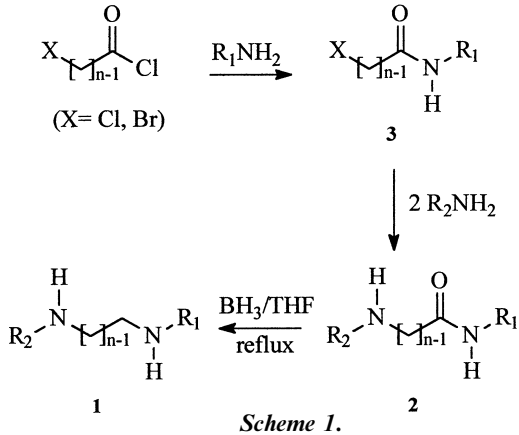
Table.



1

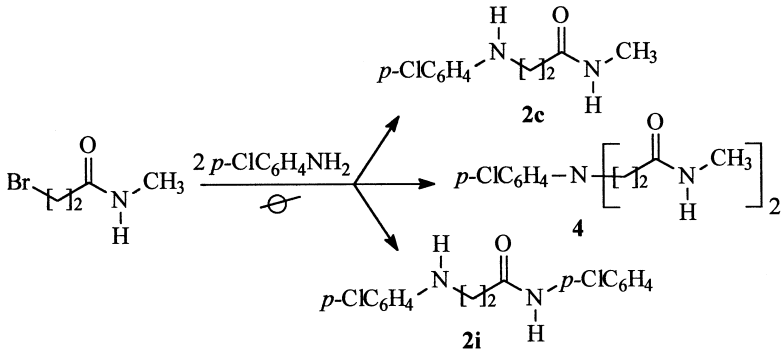
Compound 1	n	R_1	R_2
a	2	C_6H_5	CH_3
b	2	C_6H_5	*p*-ClC_6H_4
c	3	CH_3	*p*-ClC_6H_4
d	3	C_6H_5	*p*-ClC_6H_4
e	3	*iso*-C_3H_7	*p*-ClC_6H_4
f	4	C_6H_5	*p*-$CH_3C_6H_4$
g	4	*tert*-C_4H_9	*p*-ClC_6H_4
h	5	*p*-ClC_6H_4	C_6H_5

when carried out in the presence of a second equivalent of the amine as hydracid acceptor. Optimum conditions for those reactions were found to be different according to the nature of the reactants. Active α-chloroacetamides react with aliphatic amines at room temperature in aqueous solution,[13] while reaction with arylamines (less nucleophilic) was carried out by heating in the absence of solvent for 1 hour at 80°C. For higher homologues (n = 3–5), the best yields were accomplished by heating at 120°C in



Scheme 1.

solvent free conditions. By employing such reaction conditions it was possible to minimize some colateral products arising from alkylation and transamidation of aminoamides **2**. As an example, in the aminolysis of *N*-methyl-3-bromopropanamide with *p*-chloroaniline two by-products were isolated which were identified as *N*,*N*-bis[2-(methylaminocarbonyl)ethyl]-*p*-chloroaniline (**4**) and 3-(*p*-chlorophenylamino)-*N*-(*p*-chlorophenyl)propanamide **2i** (**2**, $R_1 = R_2 = p\text{-}ClC_6H_4$, $n = 3$), arising respectively from alkylation and thermal transamidation of the main product **2c** (Scheme 2).



Scheme 2.

CONCLUSIONS

The synthetic strategy presented in this work is applicable for the preparation of unsymmetrically substituted *N*-alkyl (or aryl)-*N*′-aryl di, tri, tetra and pentamethylenediamines, not accessible by reduction of the corresponding *N*-acyl-*N*′-aryl-α,ω-alkanediamines.[12] The procedure is methodologically simple, involves easily available starting materials and leads to high yields of the desired products. The method can in principle be extrapolated to *N*-tri and tetrasubstituted derivatives.

EXPERIMENTAL

Melting points were determined with a Büchi capillary apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker MSL 300 MHz spectrometer, using deuteriochloroform as the solvent. Chemical shifts are reported in ppm (δ) relative to TMS as an internal standard. D_2O was employed to confirm exchangeable protons (ex.). Splitting multiplicities

are reported as singlet (s), broad signal (bs), doublet (d), double doublet (dd), triplet (t), double triplet (dt), quartet (q), pentet (p) and multiplet (m). Mass spectra (EI) were recorded with a GC-MS Shimadzu QP-1000 spectrometer operating at 20 eV. TLC analyses were carried out an aluminium sheets Silica Gel 60 F_{254} using chloroform-methanol (9:1), ethyl acetate-methanol (20:1) or diethyl either-isopropylamine (10:1) as the solvent. Flash column chromatographies were performed on Silica Gel 60 (0.040–0.063 mm). Reagents, solvents and starting materials were purchased from standard sources and purified according to literature procedures.

N-Alkyl (or aryl)-ω-haloalkanamides **3** were synthesized by acylation of the corresponding amines with ω-haloalkanoyl chlorides following literature procedures.

Compound **2a** was described in the literature.[13]

ω-Aryl (or alkyl)aminoalkanamides 2b–h. General Procedure

A mixture of the corresponding ω-haloamide **3** (5 mmol) and the arylamine (10 mmol) was heated for 1 hour at 80°C (for compound **2b**) or 120°C (for compounds **2c–h**). The reaction mixture was treated with boiling water (20 ml), the mixture was allowed to cool and the aqueous layer was eliminated. The crude products were purified by flash column chromatography.

2-(*p*-Chlorophenylamino)-*N*-phenylacetamide (**2b**)

The product had mp 118°C (92%).

MS: m/z = 260 ($M^{+\bullet}$).

^{1}H NMR: δ = 8.49 (1H, bs, ex., NHCO), 7.50 (2H, d, C_6H_5 2 *ortho* H), 7.31 (2H, t, C_6H_5 2 *meta* H), 7.17 (2H, d, *p*-ClC_6H_4 2 *meta* H), 7.11 (1H, t, C_6H_5 *para* H), 6.59 (2H, d, *p*-ClC_6H_4 2 *ortho* H), 4.46 (1H, bs, ex., N*H*CH_2), 3.86 (2H, s, CH_2).

Anal. calcd. for $C_{14}H_{13}ClN_2O$: C 64.50, H 5.03, N 10.74; found: C 64.35, H 5.15, N 10.82.

3-(*p*-Chlorophenylamino)-*N*-methylpropanamide (**2c**)

The product had mp 99°C (67%).

MS: m/z = 212 ($M^{+\bullet}$).

^{1}H NMR: δ 7.12 (2H, dd, *p*-ClC_6H_4, 2 *meta* H), 6.55 (2H, dd, *p*-ClC_6H_4, 2 *ortho* H), 5.67 (1H, bs, ex., NHCO), 4.39 (1H, bs, ex., NHAr), 3.42 (2H, t, ArNHCH_2), 2.80 (3H, s, CH_3), 2.45 (2H, t, CH_2CO).

Anal. calcd. for $C_{10}H_{13}ClN_2O$: C 56.47, H 6.16, N 13.17; found: C 56.60, H 6.20, N 13.25.

Two other compounds were isolated from the crude product, which were purified by column chromatography and identified as 3-(*p*-chlorophenylamino)-*N*-(*p*-chlorophenyl)propanamide **2i** and *N*,*N*-bis-[2-(methylaminocarbonyl)ethyl]-*p*-chloroaniline **4**.

3-(*p*-Chlorophenylamino)-*N*-(*p*-chlorophenyl)propanamide (**2i**)

This compound was obtained as an oil.

MS: m/z = 308 ($M^{+\bullet}$).

^{1}H NMR: $\delta = 7.65$ (1H, bs, ex., NHCO), 7.40 (2H, dd, *p*-ClC_6H_4NHCO, 2 *meta* H), 7.24 (2H, dd, *p*-ClC_6H_4NHCO, 2 *ortho* H), 7.12 (2H, dd, *p*-$ClC_6H_4NHCH_2$, 2 *meta* H), 6.60 (2H, dd, *p*-$ClC_6H_4NHCH_2$, 2 *ortho* H), 3.50 (2H, t, CH_2CH_2CO), 2.62 (2H, t, CH_2CH_2CO).

Anal. calcd. for $C_{15}H_{14}Cl_2N_2O$: C 58.27, H 4.56, N 9.06; found: C 58.48, H 4.48, N 9.20.

N,*N*-Bis[2-(methylaminocarbonyl)ethyl]-*p*-chloroaniline (**4**)

This compound was obtained as an oil.

MS: m/z = 297 ($M^{+\bullet}$).

^{1}H NMR: $\delta = 7.16$ (2H, dd, *p*-ClC_6H_4, 2 *meta* H), 6.70 (2H, dd, *p*-ClC_6H_4, 2 *ortho* H), 5.93 (2H, bs, ex., NHCO), 3.55 (4H, t, CH_2CH_2CO), 2.79 (6H, s, CH_3), 2.40 (4H, t, CH_2CO).

Anal. calcd. for $C_{14}H_{20}ClN_3O_2$: C 56.47, H 6.77, N 14.11; found: C 56.39, H 6.84, N 14.21.

3-(*p*-Chlorophenylamino)-*N*-phenylpropanamide (**2d**)

The product had mp 107°C (63%).

MS: m/z = 274 ($M^{+\bullet}$).

^{1}H NMR: $\delta = 7.54$ (1H, bs, ex., NHCO), 7.46 (2H, d, C_6H_5 2 *ortho* H), 7.26–7.34 (3H, m, C_6H_5 2 *meta* and *para* H), 7.13 (2H, dd, *p*-ClC_6H_4 2 *meta* H), 6.58 (2H, dd, *p*-ClC_6H_4 2 *ortho* H), 4.20 (1H, bs, ex., NHAr), 3.51 (2H, t, CH_2CH_2CO), 2.63 (2H, t, CH_2CH_2CO).

Anal. calcd. for $C_{15}H_{15}ClN_2O$: C 65.57, H 5.50, N 10.20; found: C 65.72, H 5.59, N 10.09.

3-(*p*-Chlorophenylamino)-*N*-isopropylpropanamide (**2e**)

The product had mp 99°C (60%).

MS: m/z = 240 ($M^{+\bullet}$).

^{1}H NMR: $\Delta = 7.11$ (2H, dd, *p*-ClC_6H_4 2 *meta* H), 6.53 (2H, dd, *p*-ClC_6H_4, 2 *ortho* H), 5.38 (1H, bs, ex., NHCO), 4.20 (1H, bs, ex., NHAr), 4.05 (1H, m, C*H*$(CH_3)_2$), 3.41 (2H, t, ArNHC*H*$_2$), 2.40 (2H, t, C*H*$_2$CO), 1.13 (6H, d, CH(C*H*$_3$)$_2$).

Anal. calcd. for $C_{12}H_{17}ClN_2O$: C 59.87, H 7.12, N 11.64; found: C 59.95, H 7.20, N 11.53.

4-(*p*-Methylphenylamino)-*N*-phenylbutanamide (**2f**)

The product had mp 73°C (65%).

MS: m/z = 268 ($M^{+\bullet}$).

^{1}H NMR: $\delta = 7.60$ (1H, bs, ex., NHCO), 7.45 (2H, d, C_6H_5, 2 *ortho* H), 7.10-7.35 (3H, m, C_6H_5 2 *ortho* and *para* H), 6.98 (2H, d, *p*-$CH_3C_6H_4$ 2 *meta* H), 6.60 (2H, d, *p*-$CH_3C_6H_4$ 2 *meta* H), 4.30 (1H, bs, ex., NHAr), 3.83 (2H, t, C*H*$_2$NH), 2.60 (2H, t, CH_2CO), 2.35 (3H, s, CH_3), 2.15 (2H, m, CH_2C*H*$_2$$CH_2$).

Anal. calcd. for $C_{17}H_{20}N_2O$: C 76.09, H 7.51, N 10.44; found: C 76.00, H 7.60, N 10.34.

4-(*p*-Chlorophenylamino)-*N*-*tert*-butylbutanamide (**2g**)

This compound was obtained as an oil (68%).

MS: m/z = 268 ($M^{+\bullet}$).

^{1}H NMR: $\delta = 7.03$ (2H, d, *p*-ClC_6H_4, 2 *meta* H), 7.00 (2H, d, *p*-ClC_6H_4, 2 *ortho* H), 5.50 (1H, bs, ex., NHCO), 4.00 (1H, bs, ex., NHAr), 3.05 (2H, t, C*H*$_2$NH), 2.15 (2H, t, C*H*$_2$CO), 1.85 (2H, m, CH_2C*H*$_2$$CH_2$), 1.30 (9H, s, CH_3).

Anal. calcd. for $C_{14}H_{21}ClN_2O$: C 62.56, H 7.87, N 10.42; found: C 62.75, H 7.95, N 10.37.

5-(Phenylamino)-*N*-(*p*-chlorophenyl)valeramide (**2h**)

This compound was obtained as an oil (60%).

MS: m/z = 302 ($M^{+\bullet}$).

^{1}H NMR: $\delta = 7.50$ (1H, bs, ex. NHCO), 7.45 (2H, d, *p*-ClC_6H_4 2 *ortho* H), 7.28 (2H, d, *p*-ClC_6H_4, 2 *meta* H), 7.18 (2H, t, C_6H_5 2 *meta* H), 6.71 (1H, t, C_6H_5 *para* H), 6.61 (2H, d, C_6H_5 2 *ortho* H) 3.16 (2H, t, CH_2NHAr), 2.40 (2H, t, CH_2CONH), 1.85 (2H, p, CH_2CH_2NHAr), 1.80-1.68 (2H, m, CH_2CH_2CONH).

Anal. calcd. for $C_{17}H_{19}ClN_2O$: C 67.43, H 6.32, N 9.25; found: C 67.55, H 6.40, N 9.13.

N-Alkyl (or aryl)-*N*′-aryl-1,*n*-alkanediamines. General Procedure

Compounds **2** (5 mmol) were treated with borane in dry tetrahydrofurane (20 ml saturated solution) and heated under reflux in a nitrogen atmosphere for 4 hours. The solvent was evaporated *in vacuo* and the residue boiled with 20% hydrochloric acid (20 ml) for 2 hours. The acid solution was diluted with water (5 ml) and made alkaline (pH = 12) with sodium hydroxide pellets. The mixture was extracted with chloroform (3×20 ml) and the organic layer was washed with water and dried with anhydrous sodium sulphate. The solution was concentrated *in vacuo* and the crude products were purified by column chromatography on Silica Gel.

Compound **1a** was described in the literature.[14]

N-(*p*-Chlorophenyl)-*N*′-phenylethylenediamine (**1b**)

This compound had mp 121°C (87%).

MS: m/z = 246 ($M^{+\bullet}$).

^{1}H NMR: $\delta = 7.35$–7.59 (5H, m, C_6H_5), 7.10 (2H, dd, *p*-ClC_6H_4 2 *meta* H), 6.71 (2H, dd, *p*-ClC_6H_4 2 *ortho* H), 5.00 (2H, bs, ex., NH), 3.52 (4H, s, CH_2CH_2).

Anal. calcd. for $C_{14}H_{15}ClN_2$: C 68.15, H 6.13, N 11.35; found: C 68.32, H 6.07, N 11.43.

N-(*p*-Chlorophenyl)-*N*′-methyl-1,3-propanediamine (**1c**)

This compound was obtained as an oil (81%).

MS: m/z = 198 ($M^{+\bullet}$).

^{1}H NMR: $\delta = 7.10$ (2H, dd, 2 *meta* H), 6.51 (2H, dd, 2 *ortho* H), 3.45 (1H, bs, ex., N*H*Ar), 3.15 (2H, t, CH_2NHAr), 2.71 (2H, t, CH_2NHCH_3), 2.42 (3H, s, *N*-CH_3), 1.81 (2H, p, CH_2CH_2CH_2), 1.29 (1H, bs, ex., N*H*CH_3).

Anal. calcd. for $C_{10}H_{15}ClN_2$: C 60.45, H 7.61, N 14.10; found: C 60.72, H 7.70, N 14.01.

N-(*p*-Chlorophenyl)-*N'*-methyl-1,3-propanediamine (**1d**)

This compound was obtained as an oil (85%).

MS: m/z = 260 ($M^{+\bullet}$).

^{1}H NMR: $\delta = 7.19$ (2H, dt, C_6H_5 2 *meta* H), 7.13 (2H, dd, *p*-ClC_6H_4 2 *meta* H), 6.73 (1H, dt, C_6H_5 *para* H), 6.62 (2H, dd, C_6H_5 2 *ortho* H), 6.53 (2H, dd, *p*-ClC_6H_4 2 *ortho* H), 3.68–3.74 (2H, bs, ex., N*H*Ar), 3.21–3.39 (4H, m, $CH_2CH_2CH_2$), 1.93 (2H, p, $CH_2CH_2CH_2$).

Anal. calcd. for $C_{15}H_{17}ClN_2$: C 69.09, H 6.57, N 10.74; found: C 69.21, H 6.63, N 10.61.

N-(*p*-Chlorophenyl)-*N'*-isopropyl-1,3-propanediamine (**1e**)

This compound was obtained as an oil (81%).

MS: m/z = 226 ($M^{+\bullet}$).

^{1}H NMR: $\delta = 7.10$ (2H, dd, 2 *meta* H), 6.50 (2H, dd, 2 *ortho* H), 4.30 (1H, bs, ex., N*H*Ar), 3.15 (2H, t, CH_2NHAr), 2.78 (1H, m, $CH(CH_3)_2$), 2.73 (2H, t, $CH_2NHC_3H_7$), 2.20 (1H, bs, ex., NHC_3H_7), 1.78 (2H, p, $CH_2CH_2CH_2$), 1.06 (6H, d, $CH(CH_3)_2$).

Anal. calcd. for $C_{12}H_{19}ClN_2$: C 63.56, H 8.45, N 12.35; found: C 63.50, H 8.55, N 12.24.

N-Phenyl-*N'*-(*p*-tolyl)-1,4-butanediamine (**1f**)

This compound was obtained as an oil (76%).

MS: m/z = 254 ($M^{+\bullet}$).

^{1}H NMR: $\delta = 7.10$ (2H, t, C_6H_5, 2 *meta* H), 7.00 (2H, d, *p*-$CH_3C_6H_4$ 2 *meta* H), 6.60–6.40 (3H, t, C_6H_5, 2 *ortho* and *para* H), 6.50 (2H, d, *p*-$CH_3C_6H_4$ 2 *ortho* H), 4.25 (2H, bs, ex., NH), 3.23 (4H, t, CH_2N), 2.20 (3H, s, CH_3), 1.98 (4H, m, $CH_2CH_2CH_2CH_2$).

Anal. calcd. for $C_{17}H_{22}N_2$: C 80.27, H 8.72, N 11.01; found: C 80.20, H 8.76, N 11.13.

N-*tert*-Butyl-*N'*-(*p*-chlorophenyl)-1,4-butanediamine (**1g**)

This compound was obtained as an oil (74%).

MS: m/z = 254 ($M^{+\bullet}$).

^{1}H NMR: $\delta = 7.05$ (2H, dd, 2 *meta* H), 6.50 (2H, dd, 2 *ortho* H), 4.30 (2H, bs, ex., N*H*Ar), 3.05 (2H, t, CH_2NHAr), 2.15 (2H, t, CH_2NHC$_4$H$_9$), 1.65–1.45 (4H, m, CH$_2$CH_2CH_2CH$_2$), 1.10 (9H, s, CH$_3$).

Anal. calcd. for $C_{14}H_{23}ClN_2$: C 65.99, H 9.10, N 10.99; found: C 66.13, H 9.17, N 10.87.

N-(*p*-Chlorophenyl)-*N*′-phenyl-1,5-pentanediamine (**1h**)

This compound was obtained as an oil (74%).

MS: m/z = 288 ($M^{+\bullet}$).

^{1}H NMR: $\delta = 7.18$ (2H, t, C$_6$H$_5$, 2 *meta* H), 7.11 (2H, d, *p*-ClC$_6$H$_4$ 2 *meta* H), 6.71 (1H, t, C$_6$H$_5$ *para* H), 6.61 (2H, dd, C$_6$H$_5$ 2 *ortho* H), 6.52 (2H, d, *p*-ClC$_6$H$_4$ 2 *ortho* H), 3.53 (2H, bs, ex., NH) 3.16-3.07 (4H, m, NHCH_2), 1.70–1.62 (4H, m, CH_2CH$_2$NH), 1.56-1.48 (2H, m, CH$_2$CH$_2$CH_2CH$_2$CH$_2$).

Anal. calcd. for $C_{17}H_{21}ClN_2$: C 70.70, H 7.33, N 9.70; found: C 70.85, H 7.40, N 9.58.

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