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NUCLEOPHILIC SUBSTITUTION IN THE SIDE CHAIN OF 5-MEMBERED HETEROCYCLES—I

REACTIONS OF FURFURYL, 2-THENYL AND BENZYL CHLORIDES WITH ANILINE IN ACETONITRILE AND IN BENZENE

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Abstract—The reaction kinetics of furfuryl, 2-thenyl and benzyl chlorides with aniline has been studied in acetonitrile and benzene solutions. The reactions are third order overall, first order with respect to the chloromethyl compound and second order with respect to aniline. In benzene solutions the kinetics at high aniline concentrations (≥ 0.8 M) deviate from the third order equation. The remarkable increase in k_3, not depending on the polarity of the reaction medium, is ascribed to the association of aniline in benzene. The reactions in acetonitrile are faster than in benzene; in both solvents furfuryl chloride reacts faster than 2-thenyl and benzyl chlorides, the latter being the less reactive. The large negative activation entropies, consistent with an ordered and highly polar transition state, determine the observed rate sequence. The rate constants were correlated with the polar constants for heterocycles.

In the past few years considerable interest in the nuclear reactivity of 5-membered heterocycles has included investigations on electrophilic[1] and nucleophilic substitutions.[2] Nevertheless non solvolytic nucleophilic substitutions in the side chain of these aromatic systems have not been widely investigated.[3]

Kinetic data for reactions of furoyl and thenoyl chlorides[4] and furan- and thiophene-sulphonyl chlorides[5] with substituted anilines were previously reported, and compared with those of the corresponding benzene derivatives.

We now report the reaction kinetics of furfuryl, 2-thenyl and benzyl chlorides with aniline. These reactions yield the secondary amines, according to eqn (1):

$$ArCH_2Cl + 2H_2NC_6H_5 \rightarrow ArCH_2NHC_6H_5 + C_6H_5\overset{+}{N}H_3\,Cl^- \quad (1)$$

Ar = 2-furyl, 2-thienyl, phenyl

The reactions were carried out in a dipolar aprotic solvent (acetonitrile) and in a non polar aprotic solvent (benzene). Protic solvents were not used in order to avoid solvolytic displacements of the heterocyclic derivatives.[6,7]

This work provides kinetic data which elucidate the reaction mechanism in the examined solvents and the relative reactivities for furfuryl, 2-thenyl and benzyl groups which were not determined previously under homogeneous conditions. The few available data in this respect concern the reaction of 2-thenyl and benzyl chlorides with sodium amoxide[8] and the halogen exchange reaction.[9] The reaction of benzyl chloride with aniline has been studied kinetically in ethanol[10] and in 80% nitrobenzene-ethanol[11] solutions.

RESULTS AND DISCUSSION

Kinetics in acetonitrile. The kinetics were followed by continuous titration of the acid produced (Experimental). All the reactions, carried out with a large excess of aniline, gave excellent pseudo first order kinetics to at least 70% completion.

The reaction is second order with respect to aniline, the plot of first order rate constant (k_{obs}) against square aniline concentration being linear (Fig. 1). The slopes gave overall third order rate constants (k_3), according to the rate law (2):

$$rate = k_3[ArCH_2Cl]\,[C_6H_5NH_2]^2. \quad (2)$$

The second order in aniline was confirmed by the initial rates (V_0) method.[12] In fact on keeping $ArCH_2Cl$ concentrations constant and varying aniline concentrations (A_0), the plot of log V_0 against log A_0 is linear and its slope is *two* (Fig. 2). The results for the reaction of 2-thenyl chloride in acetonitrile at 30° are reported in Table 1. The third order rate constants and the activation parameters are reported in Table 2.

Kinetic data show that the reaction of chloromethyl derivatives with aniline in acetonitrile is a third order nucleophilic substitution, first order with respect to the substrate and second order with respect to aniline. The rate determining contribution of the second aniline molecule implies a base catalysis due to the excess of

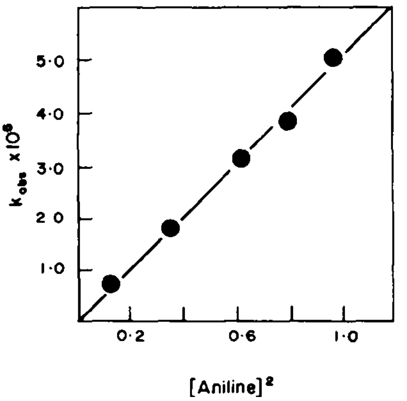


Fig. 1. Plot of k_{obs} vs square aniline concentration for the reaction of 2-thenyl chloride with aniline in acetonitrile at 30°.

Table 1. Initial rates (V_0) and rate constants for the reaction of 2-thenyl chloride with aniline in acetonitrile at 30°C

Initial concn. (mol l^{-1}) $C_4H_3SCH_2Cl$	Initial concn. (mol l^{-1}) $C_6H_5NH_2$	$V_0 . 10^{7a}$ (mol l^{-1} sec^{-1})	$k_{obs} . 10^{5b}$ (sec^{-1})	$k_3 . 10^{5c}$ (l^2 mol^{-2} sec^{-1})
0·02	0·4	1·44	0·735	4·59
0·02	0·6	3·64	1·86	5·17
0·02	0·8	5·71	3·19	4·98
0·02	0·9	7·34	3·75	4·63
0·02	1·0	9·03	5·04	5·04

[a] Calculated from the slope of the plot *conversion* vs *time*, below 10% completion.
[b] Calculated from the slope of the plot $ln(a-x)$ vs *time*, until 70% completion.
[c] Calculated by dividing k_{obs} by square aniline concentration.

Table 2. Third order rate constants and activation parameters for the reactions of arylmethyl chlorides with aniline in acetonitrile

Aryl	T, °C	$k_3 . 10^5$ (l^2 mol^{-2} sec^{-1})	$\Delta H^{\neq}$ (kcal mol^{-1})	$\Delta S^{\neq}$ (cal mol^{-1} $°K^{-1}$)
2-Furyl	20	3·70		
	30	7·07		
	40	12·4	11·1 (0·4)	−41·0 (1·5)
	50	24·5		
2-Thienyl	30	4·92		
	40	9·89	10·3 (1·0)	−44·7 (3·2)
	50	17·9		
	60	24·6		
Phenyl	30	1·37		
	40	2·72	8·7 (1·0)	−52·0 (3·2)
	50	4·04		
	60	5·59		

Standard deviation in parentheses.

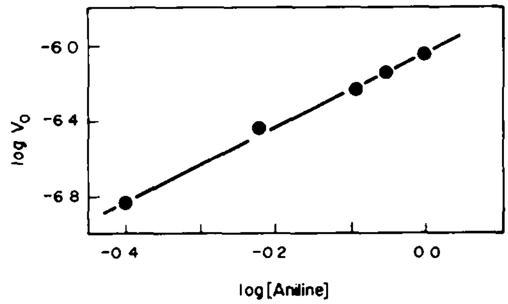


Fig. 2. Reaction order with respect to aniline, calculated by initial rates method, for the reaction of 2-thenyl chloride with aniline in acetonitrile at 30°.

amine, analogously to other nucleophilic reactions with amines,[13] which in some cases are so strongly dependent on the amine catalysis that they are essentially second order in amine.[14]

Moreover it seems likely that aniline acts as a bifunctional catalyst favouring both the N–H and C–Cl breaking (Scheme I), as suggested by Brewis, *et al.* for the reaction of 2-fluoro-3-cyano-5-nitrophyridine with aniline in ethyl acetate.[15]

The highly negative activation entropies, indicating an ordered and polar transition state structure, are the rate determining parameter.

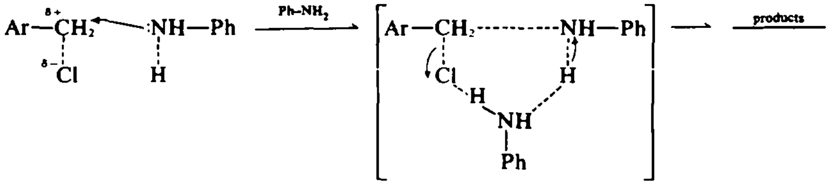
Kinetics in benzene. The reaction rate was measured by titration of the anilinium chloride, insoluble in benzene, after filtration and dissolution in water (Experimental). The kinetics, with a large excess of aniline, were first order with respect to the chloromethyl compound to at least 70% completion.

For aniline concentrations ≤0·6 M, the reaction is second order in aniline. The reaction is then third order overall and its mechanism seems to be analogous to that in acetonitrile.

Third order rate constants (k_3) at 50° are reported in Table 3. At higher aniline concentrations (≥0·8 M), instead, third order coefficients increase unexpectedly, showing remarkable deviations from the reaction order.† Under these concentrations (up to 35–40% of aniline in benzene), in fact, medium effects can be superimposed on other effects. To understand this kinetic behaviour further experiments were carried out.

As the polarity of benzene, given by $E_T = 34·5$,[16] is lower than that of aniline ($E_T = 44·3$), the polarity of the reaction medium increases on increasing aniline concentration. The higher medium polarity, which favours nucleophilic substitutions, might determine the increase in k_3.

In order to verify this hypothesis, the rate constants (k_3) for the reaction of benzyl chloride with aniline (≤0·6 M) were measured in various solvents of different polarity (Table 4). In Fig. 4 are reported log k_3 values for the reactions at low aniline concentrations in various solvents and the log k_3 values in benzene at high aniline concentrations, against the polarity of the reaction medium (E_T).



Scheme 1.

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†This behaviour was not observed for the analogous reactions in acetonitrile, where k_3 values are constants also for aniline concentrations >1·0 M.

Table 3. Pseudo first order rate constants (k_{obs}) and third order rate constants (k_3) for the reactions of furfuryl, 2-thenyl and benzyl chlorides with aniline in benzene at 50°C

	Aniline		Furfuryl chloride		2-Thenyl chloride		Benzyl chloride	
M	X_A[a]	β[b]	$k_{obs} . 10^5$	$k_3 . 10^5$[c]	$k_{obs} . 10^6$	$k_3 . 10^6$[c]	$k_{obs} . 10^7$[c]	$k_3 . 10^7$[c]
0·40			0·224	1·40	0·615	3·84	0·463	2·89
0·45			—	—	—	—	0·564	2·79
0·50			0·423	1·69	0·988	3·95	0·701	2·80
0·55			—	—	—	—	0·772	2·55
0·60			0·562	1·56	1·31	3·64	1·02	2·83
0·80	0·071	0·85	1·58	2·47	4·04	6·31	2·30	3·59
1·0	0·089	0·82	—	—	—	—	5·87	5·87
1·25	0·11	0·78	—	—	—	—	10·6	6·78
1·50	0·13	0·75	—	—	—	—	17·4	7·75
2·0	0·18	0·68	20·8	5·20	66·5	16·6	—	—
2·5	0·22	0·63	—	—	—	—	97·2	15·6
3·0	0·27	0·57	—	—	247·0	27·4	—	—
4·0	0·36	0·49	212·0	13·3	935·0	58·4	548·0	34·2
5·0	0·45	0·43	—	—	—	—	1054	42·2

[a] Molar fraction of aniline in benzene; [b] Fraction of momomer aniline molecules; [c] Calculated by dividing k_{obs} by square aniline concentrations.

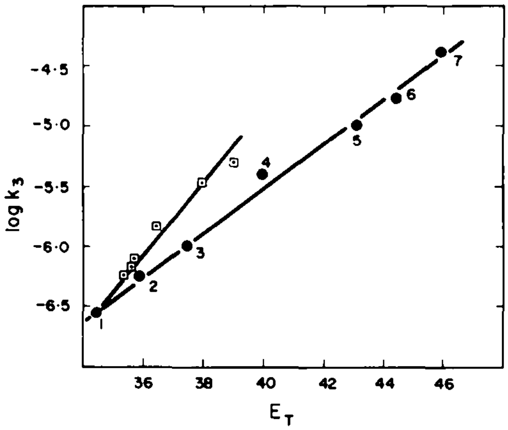


Fig. 3. Plot of log k_3 vs E_T values: ⊡, Reactions of benzyl chloride, in benzene at 50°C, with aniline 1·0–5·0 M. For E_T values of the mixtures benzene-aniline see Table 4, footnote (a). ●, Reactions of benzyl chloride with aniline 0·4–0·6 M at 50° in the same solvents (1–7) as in Table 4.

The values at high concentrations do not lie on the line obtained from the reaction in "inert" solvents. The above hypothesis is then not verified by the experimental data, which point out that the increase in k_3 cannot be ascribed only to the polarity of the reaction medium.

By subtracting from k_3 (Table 3) the values predicted by the medium effect ($k_{3\,calcd}$) Δk_3 were obtained (Table 5). These differences are poorly correlated with aniline concentrations, but an excellent correlation is obtained with square aniline concentrations ($r = 0·996$). Thus

$$\Delta k_3 = k_3 - k_{3calcd} = k_5[A]^2. \qquad (3)$$

This suggests that *four* aniline molecules are involved in the reactions at high nucleophile concentrations.

Consequently an alternative model, which takes into account aniline association, was proposed to interpret the kinetic data. Aniline, which in non polar solvents is strongly associated by hydrogen bonding,[17,18] was assumed to react and to catalyse in the associated form, mainly as dimer, which ought to be a stronger nucleophile, owing to the greater electron density on one N atom (4):

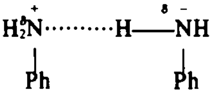
Table 4. Third order rate constants for the reaction of benzyl chloride with aniline at 50° in various solvents of different polarity (E_T)

Solvent	E_T[a]	$k_3 . 10^6$
(1) Benzene	34·5	0·266[b]
(2) Benzene-Chlorobenzene (0·53)[c]	35·9	0·602
(3) Chlorobenzene	37·5	1·02
(4) Benzene-Acetonitrile (0·50)[c]	40·3	4·08
(5) Benzene-Acetonitrile (0·25)[c]	43·1	9·55
(6) Benzene-Acetonitrile (0·13)[c]	44·5	15·0
(7) Acetonitrile	46·0	40·4

[a] C. Reichardt, *Angew. Chem. Internat. Ed.* 4, 29 (1965). The E_T values for the solvent mixtures were calculated by the following equation: $E_{T_{mixt}} = E_{T_{s_1}} . X_{s_1} + E_{T_{s_2}} . X_{s_2}$, where $E_{T_{s_1}}$ and $E_{T_{s_2}}$ are the E_T values for the pure solvents (s_1 and s_2) and X_{s_1} and X_{s_2} are the respective molar fractions in the mixtures.

[b] Obtained by least-squares treatment of k_{obs} vs. [Aniline]^2, (Table 3).

[c] Molar fraction of benzene.



$$H_2^{\delta}\overset{+}{N}(Ph)\cdots\cdots H—\overset{\delta\,-}{N}H(Ph) \qquad (4)$$

Literature data about the association of aniline in benzene[18] provide the β parameter, which is the fraction of monomer aniline at a given concentration of aniline (A) in benzene; the concentration of the associated aniline is then $(1-\beta)A$.

The plot of k_{obs} against square associated aniline concentration is linear (intercept ≃ *zero*), indicating that the reaction of chloromethyl derivatives with aniline ≥0·8 M in benzene follows the rate law (5):

$$k_{obs} = k_3'[(1-\beta)A]^2 \qquad (5)$$

where k_3' is the rate constant determined by the associated nucleophile. The plot relative to the reactions of benzyl chloride with aniline at 50° is reported in Fig. 4.

The linear relationship between k_{obs}, which vary about 500 times, and $[(1-\beta)A]^2$ provides good experimental evidence for the proposed hypothesis.

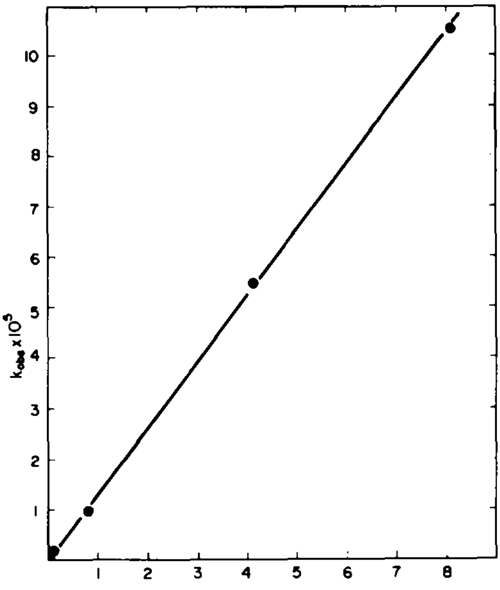


Fig. 4. Plot of k_{obs} vs $[(1-\beta)A]^2$ for the reaction of benzyl chloride with aniline (1·0–5·0 M) in benzene at 50°.

Table 5. Separation of the medium effect, k_3 *calculated*, from k_3 values at high aniline concentrations

Aniline, M	E_T	$10^7\,k_{3calcd}$^{a}	$10^7\Delta k_3$
1·0	35·4	4·37	1·50
1·25	35·6	4·74	2·04
1·50	35·8	5·15	2·60
2·50	36·7	7·46	8·14
4·0	38·0	12·8	21·4

^{a}Calculated by the following equation (Fig. 3): $\log k_{3calcd} = 0{\cdot}179\,E_T - 12{\cdot}695$.

Further support is obtained by measuring the rate constants at high aniline concentrations for the reactions in carbon tetrachloride, β values for this solvent being available.[18] In Table 6 are reported k_{obs} and β values in CCl_4. The linear plot of k_{obs} against $[(1-\beta)A]^2$ confirms the validity of eqn (5). k_3' values in benzene at various temperatures are reported in Table 7 together with the activation parameters.

Relative reactivities. The results show that, at low aniline concentrations, the reactivity in acetonitrile is greater than in benzene, probably because a more polar solvent stabilizes the transition state better.

Table 6. Pseudo first order rate constant (k_{obs}) for the reaction of benzyl chloride with aniline in carbon tetrachloride at 50°

Aniline mol l^{-1}	 Mol. Fract.	β	$[(1-\beta)A]^2$ (mol^2 l^{-2})	$k_{obs}\cdot10^{6a}$ (sec^{-1})
1·5	0·144	0·54	0·476	4·87
2·0	0·191	0·45	1·21	13·5
2·5	0·238	0·38	2·40	27·4

^{a}k_3' value ($1{\cdot}17\times10^5$, l^2 mol^{-2} sec^{-1}) was obtained by least-square treatment of k_{obs} vs $[(1-\beta)A]^2$, $r = 0{\cdot}9999$.

Table 7. Rate constants (k_3) and activation parameters for the reaction of arylmethyl chlorides with aniline in benzern^a

Aryl	T°, C	$k_3'\cdot10^5$ (l^2 mol^{-2} sec^{-1})	$\Delta H^{\neq}$ (kcal mol^{-1})	$-\Delta S^{\neq}$ (cal mol^{-1} °K^{-1})
2-Furyl	20	5·45		
	30	13·4		
	40	22·4	12·9 (0·9)	33·9 (2·9)
	50	50·6		
2-Thienyl	20	2·88		
	30	6·12		
	40	13·3	12·4 (0·6)	37·1 (2·0)
	50	22·1		
Phenyl	30	0·325		
	40	0·681	12·5 (0·4)	42·5 (1·1)
	50	1·32		
	60	2·29		

^{a}Aniline concentration = 1·0–5·0 M.
Standard deviation in parentheses.

Table 8. Relative reactivities for the reactions of arylmethyl chlorides with aniline in acetonitrile and in benzene at 50°C

		$\frac{k_{ArCH_2Cl}}{k_{PhCH_2Cl}}$	
Aryl	$\frac{k_{Acetonitrile}}{k_{Benzene}}$	Acetonitrile	Benzene
2-Furyl	15·6	6·1	59·0
2-Thienyl	49·7	4·4	15·5
Phenyl	151·9	1·0	1·0

In both solvents the reactivity order is: *furfuryl chloride* > *2-thenyl chloride* > *benzyl chloride*. In Table 8 are reported the relative reactivities calculated from k_3 at 50°. This sequence is agreement with the polar effect sequence for the aromatic rings, given by σ^*.[19]

In Fig. 5 is reported the Hammett plot: the rate dependence on the substrate structural effects in benzene is greater than in acetonitrile, $\rho^*_B > \rho^*_A$, in agreement with the general observation that ρ values increase when the solvent dielectric constant decreases.[20]

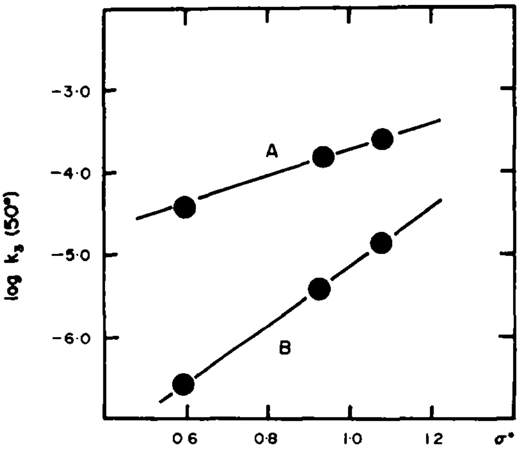


Fig. 5. Hammett plots: A, Acetonitrile, $\rho^*_A = 1{\cdot}68$, $r = 0{\cdot}990$, B, Benzene, $\rho^*_B = 3{\cdot}67$, $r = 0{\cdot}999$.

EXPERIMENTAL

Materials. Furfuryl chloride was prepared by adding thionyl chloride to furfuryl alcohol in anhyd ether and pyridine at −10°. The product (b.p. 37°/15 mm; 50% yield) must be stored at low temp to avoid decomposition.[21]

The NMR peaks (δ) occur at 4·48 ppm (2H, s, CH_2), 6·25 ppm (2H, d, H_3 and H_4) and 7·30 ppm (1H, t, H_5).

2-Thenyl chloride was obtained by chloromethylation of thiophene using 40% formaldehyde and gaseous hydrogen chloride, b.p. 38–40°/0·5 mm, 40% yield.[22]

The NMR peaks (δ) occur at 4·69 ppm (2H, s, CH$_2$), 6·77 ppm (2H, m, H$_3$ and H$_4$) and 7·20 ppm (1H, q, H$_5$).[23]

Benzyl chloride and aniline, commercially available samples, were distilled before use. The solvents used were purified by known procedures.

Kinetic measurements

In acetonitrile. Rate measurements were done by continuous titration of the acid produced (eqn 1) with 0·1 M NaOH, following the procedure already described.[5]

In benzene. Standard solns of chloromethyl derivative and aniline were mixed in stoppered vessels at constant temp. At intervals, the anilinium chloride ppt was filtered off. The ppt was washed several times with benzene, dissolved in water and titrated with 0·1 M NaOH using phenolphthalein as indicator. The concentration range was 0·02–0·2 M for the chloromethyl derivative and 0·40–5·0 M for the aniline.

This procedure was used also for the reaction kinetics in chlorobenzene, benzene-chlorobenzene mixture, benzene-acetonitrile mixtures and carbon tetrachloride.

The first order rate constants (k_{obs}) were obtained from the slope of conventional plots of ln(a-x) vs time, using the least-squares method. The activation energies were calculated from the Arrhenius equation by least-squares method. The activation entropies were computed for 40° using the suitable equation.[24]

Product analysis. Solns of chloromethyl compound (0·05 mol) and aniline (0·25 mol) were allowed to react in acetonitrile and in benzene (100 ml) until completion. The conversion was followed by GLC analysis. The anilinium chloride was filtered off and the soln was distilled under reduced pressure. The product distilled after elimination of the solvent and of the excess of aniline: *ca* 85% yield.

N-*Furfuryl aniline*, b.p. 118–120°/6 mm.[25] The IR NH stretching (liquid film) occurs at 3405 cm^{-1}. The NMR peaks (δ) occur at 4·20 ppm (2H, s, CH$_2$), 5·45 ppm (1H, s, NH), 6·17 ppm (2H, d, H$_3$ and H$_4$), 6·51–7·07 ppm (5H, m, phenyl) and 7·20 ppm (1H, t, H$_5$).

N-2-*Thenyl aniline*, b.p. 155–158°/6 mm; m.p. 37–38° from light petroleum.[26] The IR NH stretching (CCl$_4$) occurs at 3405 cm^{-1}. The NMR peaks (δ) occurs at 3·74 ppm (1H, broad s, NH), 4·36 ppm (2H, s, CH$_2$) and 6·41–7·17 ppm (8H, m, H$_3$, H$_4$, H$_5$ and phenyl).

N-*Benzyl aniline*, b.p. 178–180°/12 mm; m.p. 36–37° from light petroleum.[27] The IR NH stretching (CCl$_4$) occurs at 3420 cm^{-1}. The NMR peaks (δ) occur at 3·47 ppm (1H, s, NH), 3·96 ppm (2H, s, CH$_2$), 6·28–7·02 ppm (5H, m, phenyl-N) and 7·08 ppm (5H, s, phenyl-C).

IR spectra were recorded on a Perkin Elmer mod. 237 spectrometer. NMR spectra were recorded in CCl$_4$ soln on a Varian A60D spectrometer, using TMS as internal standard.

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