A Novel Synthesis of 2,4-Thiophenediamines and Their Behavior as Stable Reactive Enamines (1)

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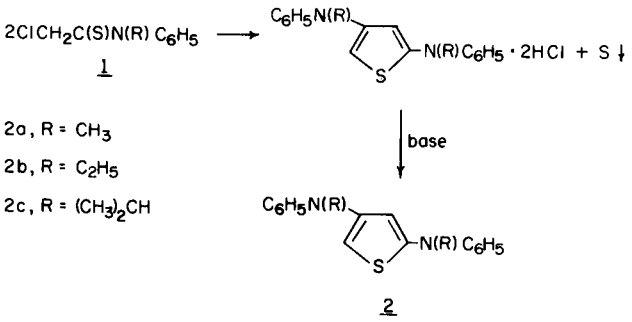
Reaction of α-chlorothioacetanilides (**1**) in refluxing methanol provides a new route to stable, reactive 2,4-thiophenediamines (**2**). These materials display interesting chemical and physical properties, based in large part on the interaction of the anilino groups with nuclear substituents *alpha* to the thiophene sulfur. Thus **2** is easily protonated, with rapid exchange of the 5-proton, while α-carbon-nitrogen cleavage has been observed for the first time during Raney nickel degradation. The susceptibility of the thiophenediamines to electrophilic attack is further demonstrated by facile formation of 3,5-diamino-2-thiophene carboxanilides (**3**) and 3,5-diamino-2-thienylphenyl ketones (**4**) from respective reaction of isocyanates, isothiocyanates, and acid chlorides with **2**. Certain interesting and unusual spectral characteristics of these compounds, resembling enamines and enaminoketones, are presented and discussed.

The preparation of thiophenamine derivatives are usually attended by difficulties from arduous multistep syntheses and instability of finished product. Thus a classical synthesis (2) of 2,4-thiophenediamine from the parent heterocycle *via* nitration and reduction involves five steps, with the diamine preserved by benzoylation in an additional sixth step. More recently several novel syntheses have become available for the preparation of thiophenamines utilizing direct cyclization reactions to arrive at the desired heterocycle. Ring closure of *cis* 4-benzylthiocrotonitrile proceeds in a hydrogen chloride-ether system to give 2-thiophenamine hydrochloride (3). Preparation of thioiminium salts from phenacyl bromides and 3° thioamides of phenylacetic acids, followed by subsequent cyclization affords stable 2-amino-3,4-diarylthiophenes (4). Unsymmetrical amino- and 2,4-diaminothiophenes, encumbered however with acid moieties in the remaining nuclear positions have been reported, derived from cyclization of carbon disulfide or aryl isothiocyanate adducts to active methylene reagents (5).

With the present availability of α-chlorothioacetanilides (6), their chemistry has been subject to investigation. It was found that by merely refluxing these reagents in methanol, hydrochloride salts of the corresponding 2,4-thiophenediamines could be obtained, and these converted quite simply to their stable free bases (Scheme 1). In actual practice the hydrochloride salt recovered contains about one and one-half moles of hydrogen chloride per mole of thiophenediamine. The reaction appears to proceed only in protic solvents, as **1** was recovered after refluxing in ethyl acetate, acetonitrile, or benzene. The thiophenediamines are listed in Table I.

SCHEME I



The nmr spectra of the materials are in accord with their structural assignment. For example **2c** reveals a ratio Ar*H*:thiophene *H*:C*H*$(CH_3)_2$:CH$(CH_3)_2$ of 10:2:2:12. Although the structure of **2c** would presuppose finding two doublets for the two dissimilar isopropyl groups, only one is evident. The two methine protons however easily show different heptets. The dissimilarity of the anilino groups are further seen in the spectra of **2a** where N–CH_3 appears as two finely separated singlets at δ 3.2.

When **2** is isolated and purified by recrystallization from pentane, the nmr spectral absorptions in carbon tetrachloride for the 3- and 5- thiophene hydrogens appear at δ 6.2-6.5, one as a sharp singlet, with the other proton displaying a broad absorption (Fig. 1A). The usual coupling constant for 2,4-thiophene protons is *ca.* 1.5. Hence the appearance of a sharp singlet uncoupled with a broader absorption must be due to a rapidly exchanging 5-proton. It would be expected that the 5-position would be more susceptible to electrophile attack (*i.e.* H^+) than the 3-

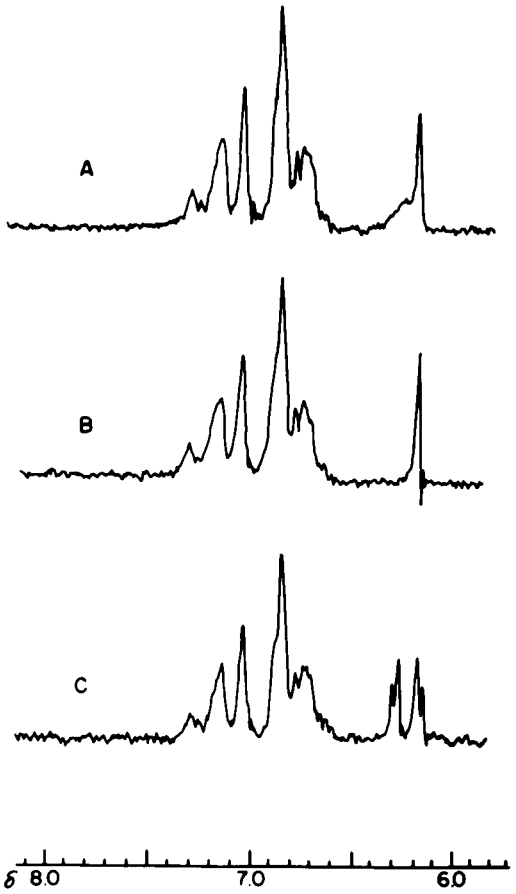


Fig. 1. NMR spectrum of N,N'-Diisopropyl-N,N'-diphenyl-2,4-thiophenediamine, 2c: A. In carbon tetrachloride B. In carbon tetrachloride, previously washed with D_2O. C. In carbon tetrachloride, previously slurried with 85% KOH

position because 1) it is *alpha* to the sulfur, the usual position for electrophilic attack (7,8) and 2) both amino groups, through resonance, can reinforce the electron enrichment of the 5-position.

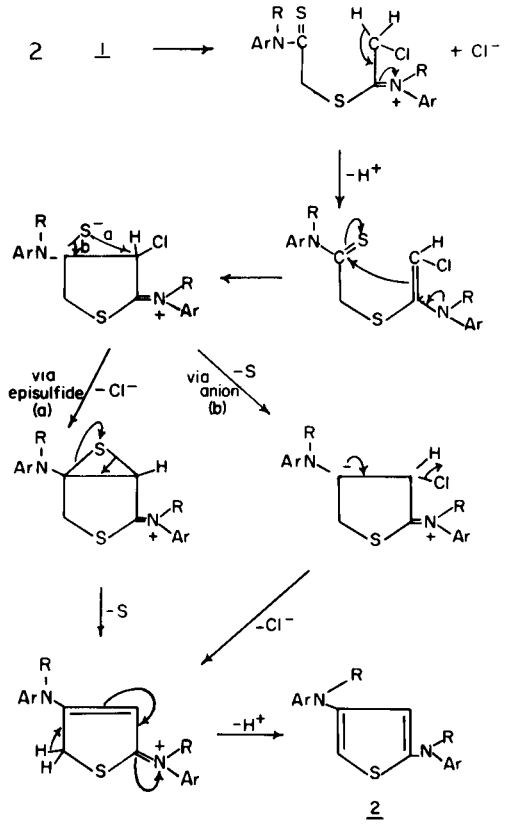
The acid catalyzed exchange reaction is substantiated by the fact that when a sample of **2c** is dissolved in carbon tetrachloride that has been previously slurried with alkali, a typical AB resonance pattern (J=1.5 Hz) is displayed by the thiophene protons (Fig. 1C). The absence of acid bodies thus slows the exchange rate sufficiently to cause a typical coupling to occur. Rapid exchange is also verified by the ready disappearance of the 5-proton resonance, and emergence of a singlet in place of the 3-proton doublet when the carbon tetrachloride solution is simply shaken with deuterium oxide (Fig. 1B).

Mechanistically, the reaction of **1** to give an unsymmetrically disubstituted thiophene appears reasonable only for the formation of the 2,4-derivative. Scheme 2 details a mechanism, with alternative loss of sulfur through the (a) episulfide, or (b) anion. The route involves initial alkylation of sulfur, followed by reaction of a carbanion with the positive pole of the remaining thiocarbonyl group. Sulfur is split out rather than the more commonly found hydrogen sulfide or water (4), (5).

Although 1,4-dithienes have been shown to form thiophenes on thermal cracking (9), its involvement here appears remote, because no dithiene is isolated, while the temperature of refluxing methanol is much lower than that commonly employed for dithiene degradation. Moreover attempts to prepare the dithiene or **2c** by reaction of α-mercapto-*N*-isopropylacetanilide or its thioanalogue failed. This method, with α-mercapto ketones, is commonly employed for 1,4-dithiene preparation (10).

Degradation by simultaneous Raney nickel desulfurization and hydrogenation has been the usual method of choice in providing structure proofs for thiophene derivatives (11), (12), (13). Material **2c** was refluxed 15 minutes in ethanol with excess Raney nickel (14). Both *N*-isopropylaniline and *N*-isopropyl-*N*-*sec*-butylaniline (the latter contaminated with the former) were isolated. The structure of both anilines was verified by their nmr and mass

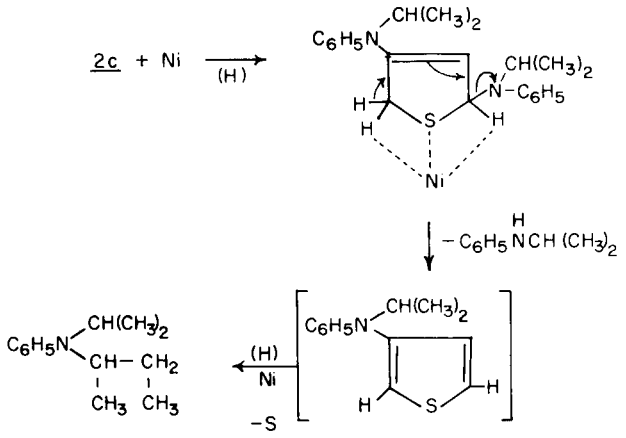
SCHEME 2



spectra, which were respectively identical, as was the retention time from VPC, to authentic samples. Consequently there appears to be ready cleavage of the 2-anilino group in the degradation, which as illustrated in Scheme 3, could arise from initial 2,5-hydrogen addition, followed by loss of *N*-isopropylaniline with subsequent further hydrogenation and sulfur cleavage.

The cleavage of nitrogen from a thiophene ring during Raney nickel treatment has not been previously reported (11), (12). Actually 2-amido groups can survive the degradation (12). Carbon-nitrogen bond fission has however been observed during Raney nickel desulfurization of certain thioamides (15). The absence of this observation in thiophenes until now is probably more due to the scarcity of stable thiophenamines than to intrinsic resistance to C–N cleavage. That the 2- rather than 4-anilino group is cleaved reflects the closer proximity of the 2,5 rather than 2,3 or 4,5 position to the hydrogen rich catalyst surface arising from the mutual attraction of sulfur and nickel.

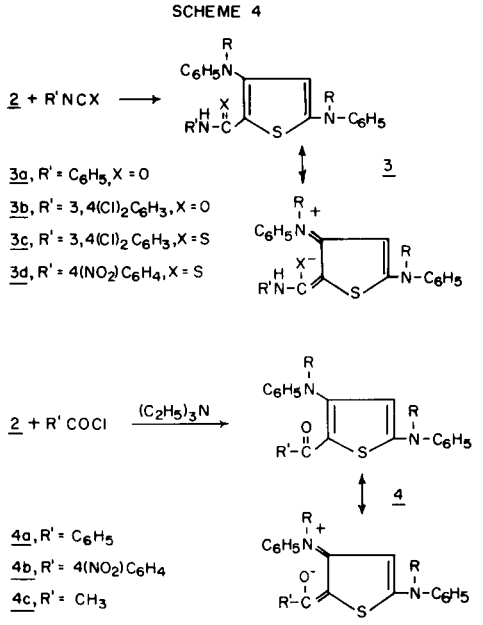
SCHEME 3



The aforementioned acid catalyzed proton exchange suggests the susceptibility of the electron-rich 5-position to electrophilic substitution. At room temperature, electrophiles such as isocyanates, isothiocyanates and acyl chlorides do indeed readily react to give stable products (Scheme 4 and Table I). It is noteworthy however that these materials do not react further at the 3-position. Compound **4b** was recovered when it was refluxed in toluene with more 3,4-dichlorophenyl isocyanate.

The substitution products **3**, and **4** possess certain unusual spectral characteristics. Compound **3** has normal N–H stretching and carbonyl frequencies at 3.1 μ and *ca.* 6.0 μ respectively, while the former moiety is clearly observable by nmr between δ 8-11. However the resonance of the remaining thiophene proton in both **3** and **4** has been dramatically shifted upfield from *ca.* δ 6.2 to δ 5.4-5.6. Apparently at this high field the thiophene hydrogen has lost much of its deshielding due to diminished aromatic

SCHEME 4



ring currents, arising from important resonance forms, several of which are shown in Scheme 4. Similarly, non-thiophene resonance causes **4** (but not **3**) to display carbonyl absorption at longer wavelength (*i.e.* greater than 6.3 μ) rather than in the normal 6.0 μ region (Fig. 2A,B).

Support for this thesis is the appearance of a medium intense carbonyl absorption in the infrared spectrum at 6.0 δ of the hydrochloride salt of **4a** (Fig. 2C). Protonation of base centers in **4** would be expected to diminish the importance of the non-thiophene resonance forms and restore a greater order of normal carbonyl frequency to the ketone grouping.

The thiophenediamines (**2**) presented here thus bear a marked resemblance in their physical and chemical properties to enamines, while the spectral properties of **4** appear analogous to those found for α,β enaminoketones. A shift of the carbonyl absorption to longer wavelengths in 3° enamino ketones (16) and thienylenaminoketones (17) is well known. Similarly, the upfield shift of an olefinic proton in enaminoketones over those found in normal olefins have also been documented (18,19,20). Resonance forms in Scheme 4 are also supported by the bathochromic shift observed from the uv absorption spectra of **2c** (λ max 322) *vs.* **4a** (λ max 355). Similar shifts have been noted between enamines and enaminoketones (20).

EXPERIMENTAL (17)

The following specific procedures are suitable as general preparations for the materials contained in Table I. The nmr, and ir absorptions specifically listed below for **2a**, **3a**, **4a**, **4c** are similar in magnitude to the respective absorptions recorded for the other materials of the same type.

TABLE I

Thiophene Diamines and Derivatives

Material	Yield	M.p. °C	Molecular Formula	MW	Analysis Calcd. C	H	N	MW (a)	Found C	H	N
2a	---	oil	$C_{18}H_{18}N_2S$	294	73.4	6.16	9.52	294	73.8	6.31	9.36
2b	14	27.5-29	$C_{20}H_{22}N_2S$	322	74.5	6.88	8.69	322	74.4	6.90	8.58
2c	35-49	74	$C_{22}H_{26}N_2S$	350	75.4	7.44	8.00	350	75.0	7.94	8.01
3a	83	143	$C_{29}H_{31}N_3OS$		74.2	6.65	8.95		74.3	6.45	8.56
3b	36	112-113	$C_{29}H_{29}Cl_2N_3OS$		64.7	5.43	7.80		64.6	5.48	7.64
3c	82	155-156	$C_{29}H_{29}Cl_2N_3S_2$		62.8	5.27	7.58		62.9	5.26	7.40
3d	79	175-176	$C_{29}H_{30}N_4O_2S_2$		65.6	5.70	10.6		65.6	5.51	10.3
4a	69	98-100	$C_{29}H_{30}N_2OS$		76.6	6.65	6.16		77.0	6.44	5.98
4b	70	147-149	$C_{29}H_{29}N_3O_3S$		69.7	5.85	8.41		69.8	5.93	8.22
4c	23	148-150	$C_{24}H_{28}N_2OS$		73.4	7.19	7.14		73.9	7.33	6.98

(a) By MS (parent peak).

N,N'-Diisopropyl-*N,N'*-diphenyl-2,5-thiophenediamine (**2c**).

α-Chloro-*N*-isopropylthioacetanilide (**1c**), m.p. 67-68° (13.1 g., 0.058 mole) prepared by Smith's method (6), was placed in 100 ml. methanol and the mixture refluxed for twelve hours. After cooling, crystalline sulfur was removed by filtration and the methanol solution vacuum treated to remove solvent. The residue (12,8 g.) was triturated with ether. Only small portions of the residue when so treated readily formed solid salt (see below for analysis of this salt); the bulk did so only slowly. The whole was extracted with water and the aqueous solution in turn extracted with ether (2x 50 ml.). The aqueous phase was neutralized with sodium bicarbonate, and the resulting oil extracted with ether. After drying over magnesium sulfate, and subsequent ether removal, the remaining oil, **2c** (4.9 g., 48% yield) completely solidified and possessed a clean nmr spectrum. Analytical purification was carried out by one recrystallization (charcoal) from cold pentane. The neutral fraction (6.4 g.) recovered from the ether extracts prior to neutralization displayed complex spectra. Moreover, upon heating this material an additional 12 hours in methanol, only traces of **2c** were isolated. Spectral results for **2c** are as follows: uv λ max (ethanol) 254 (ϵ=15,000), 322 (ϵ=15,000); nmr (carbon tetrachloride), δ 1.20 [d, 12, J=7Hz, $CH(CH_3)_2$], 3.9-4.5 [2 m, 2, J=7Hz, $CH(CH_3)_2$], remaining thiophene and phenyl protons see Fig. 1.

3,5-Bis(*N*-isopropylanilino)-2-thiophenecarboxanilide (**3a**).

Thiophenediamine **2c** (1.5 g., 0.43 mole) was placed in 30 ml. of benzene and an equimolar amount of phenyl isocyanate (0.55 g.) was added. The homogeneous solution was permitted to stand four hours, after which time the solution showed no further ir absorption at 4.4 μ for isocyanate. Solvent was removed under vacuum and the residue recrystallized from a mixture of methylcyclohexane and heptane, to give 1.5 g. (83% yield). Spectral results are as follows: ir (chloroform) see Fig. 2A; nmr (carbon tetrachloride), δ 1.21 [d, 12, J=7Hz, $CH(CH_3)_2$], 3.9-4.5 [2 m, 2, J=7Hz, $CH(CH_3)_2$], 5.48 [s, 1, thiophene *H*], 6.7-7.5 [m, 10, phenyl *H*, 9.66 [s (broad), 1, N*H*].

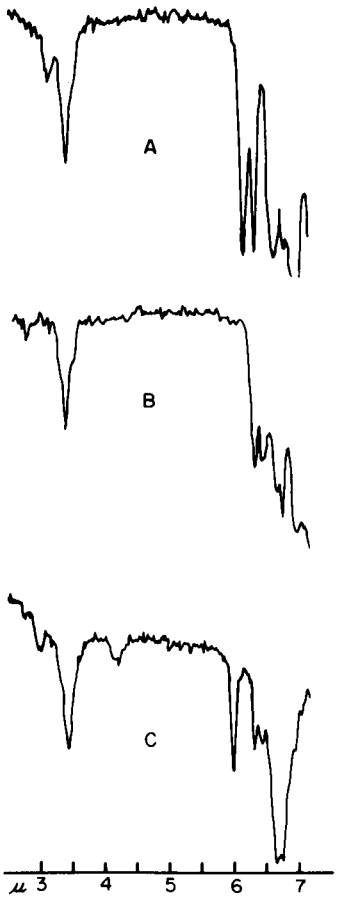


Fig. 2. IR spectrum in Chloroform: A. 3,5-Bis(N-isopropylanilino)-2-thiophenecarboxanilide, 3a. B. 3,5-Bis(N-isopropylanilino)-2-thienyl phenyl ketone, 4a. C. Hydrochloride salt of 4a.

3,5-Bis(*N*-isopropylanilino)-2-thienyl Phenyl Ketone (**4a**).

Thiophenediamine **2c** (1 g., 0.0028 mole) was placed in ether solution with an equimolar amount of triethylamine. To the mixture was added benzoyl chloride (0.00286 mole). After standing four hours, the mixture was filtered to remove triethylamine hydrochloride. The ether was removed from the filtrate, and the residue crystallized from aqueous methanol to give 0.9 g. **4a**. Spectral results are as follows: uv λ max (ethanol) 251 (ϵ=18,000), 355 (ϵ=18,000); nmr (carbon tetrachloride), δ 1.03 [d, 6, J=7 Hz, $CH(CH_3)_2$], 1.22 [d, 6, J=7 Hz, $CH(CH_3)_2$], 3.7-4.5 [2 m, 2, J=7 Hz, $CH(CH_3)_2$], 5.55 [s, 1, thiophene *H*], 6.6-7.6 [m, 10, phenyl *H*]; ir (chloroform) see Fig. 2; ir (carbon tetrachloride), no carbonyl absorption below 6.3 μ.

3,5-Bis(*N*-isopropylanilino)-2-thienyl Methyl Ketone (**4c**).

In a procedure similar to the preparation of **4a**, **4c** (0.9 g.) was isolated in 23% yield from reaction of an equimolar amount of acetyl chloride, triethylamine and **2c**. Spectral results are as follows: ir (chloroform), no absorption for C=O at shorter wavelengths than 6.3 μ; ir (carbon tetrachloride), 6.2 μ (C=O); nmr (carbon tetrachloride), δ 1.18 [d, 6, J=7 Hz, $CH(CH_3)_2$], 1.21 [d, 6, J=7 Hz, $CH(CH_3)_2$], 2.19 [s, 3, CH_3CO], 3.9-4.5 [2 m, 2, J=7 Hz, $CH(CH_3)_2$], 5.45 [s, 1, thiophene *H*], 6.5-7.5 [m, 10, phenyl *H*].

Hydrochloride Salts of Thiophenediamine Derivatives.

To demonstrate the basicity of the thiophenediamines, 0.1 g. of **2c** was dissolved in 50 ml. ether. Dry hydrogen chloride was added slowly and sparging stopped when it appeared that a maximum amount of white solid had precipitated. The solid was separated by filtration. Compound **2c** was obtained on neutralization of this salt with sodium bicarbonate.

Anal. Calcd. for $C_{22}H_{26}N_2S$·HCl: Cl, 9.20; N, 7.24. Found: total Cl, 10.0; ionic Cl, 9.94; N, 7.10.

The solid hydrochloride salt of **2c** as derived from reaction of **1c** in methanol (see above) could be transformed to **2c** by neutralization with sodium bicarbonate. Analysis of the salt showed it was a mixture of the monochloride (above) and dihydrochloride salt (below).

Anal. Calcd. for $C_{22}H_{26}N_2S$·1.4HCl; Cl, 12.4. Found: Cl, 12.5.

The hydrochloride salt of **4a** was prepared by dissolving 0.5 g. of **4a** in 50 ml. ether and adding gaseous dry hydrogen chloride. After filtration 0.5 g. solid remained. The solid obtained after neutralization of this salt displayed no absorption in the carbonyl region, while recrystallization from aqueous methanol again gave pure **4a**. The salt appears to be mostly but not entirely the dihydrochloride, the ir of which is given in Fig. 2C.

Anal. Calcd. for $C_{29}H_{30}N_2OS$·2HCl: Cl, 13.4; N, 5.31. Found: Cl, 12.5; N, 5.14.

Raney Nickel Degradation of **2c**;

Compound **2c** (2 g.) was refluxed 15 minutes in ethanol with 10 g. Raney nickel. The cooled mixture was cautiously filtered, and the filtrate, after solvent removal, distilled through a six inch vigreux column to give *N*-isopropylaniline, b.p. 50° (0.5-1.0 mm.) and *N*-*sec*-butyl-*N*-isopropylaniline, b.p. 70-80° (0.5 mm.). The structures of the two anilines were verified by respective comparison with authentic samples (see below) of their ir, nmr, and mass spectrum, the latter obtained on a mass spectrograph in tandem with a VPC column.

N-*sec*-Butyl-*N*-isopropylaniline.

This new aniline was prepared by refluxing for one week, *sec*-butyl bromide (69 g., 0.45 mole) with *N*-isopropylaniline (61 g., 0.45 mole) in 100 ml. of acetonitrile. During this time, as analyzed by VPC (6 ft. 5% GE-SE-30 on Chromosorb W at 150°, flow rate 75 ml./min.), a constant ratio of *N*-isopropylaniline and *N*-*sec*-butyl-*N*-isopropylaniline (64:36) developed. The mixture was vacuum treated to remove solvent, washed with caustic, and the dried solution acetylated with acetic anhydride. The residue was distilled, and *N*-*sec*-butyl-*N*-isopropylaniline collected at 70-72° (0.5 mm.), n_D^{26} 1.5187. Spectral results are as follows: nmr (carbon tetrachloride), δ 0.85 [t, 3, J=7 Hz, CH_3CH_2], 1.12 [d, 6, J=7 Hz, $CH(CH_3)_2$], 1.13 [d, 3, J=7 Hz, $CHCH_3$], 1.23-1.8 [m, 2, CH_3CH_2CH], 3.1-4.9 [m, 2, J=7 Hz, $NCH(CH_3)CH_2-$], 6.45-7.25 [m, 5, phenyl *H*].

Anal. Calcd. for $C_{13}H_{21}N$: C, 81.6; H, 11.1; N, 7.32. Found: C, 81.4; H, 11.0; N, 7.54.

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