

Synthesis of 2-chloro-3-(4-X-phenyl)propyl isothiocyanates

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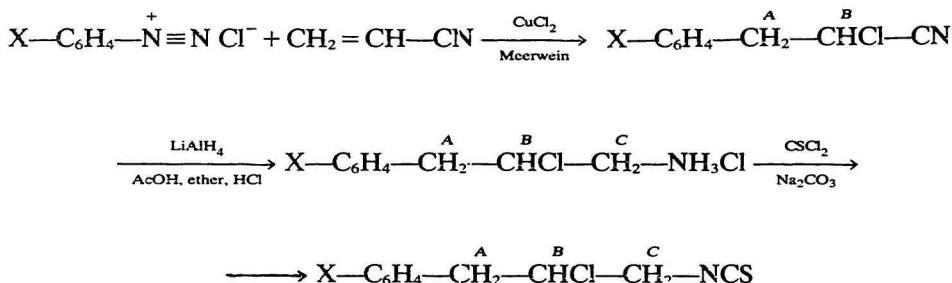
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2-Chloro-3-(4-X-phenyl)propyl isothiocyanates ($X = H, CH_3, OCH_3, Br, NO_2$) have been synthesized and their structure has been confirmed by i.r. and 1H -n.m.r. spectroscopy. The temperature dependence of the 1H -n.m.r. features resulting from the conformational change of the studied substances is also discussed.

В работе описывается синтез 2-хлор-3-(4- X -фенил)пропил изотиоцианатов ($X = H, CH_3, OCH_3, Br, NO_2$), определение их структуры при помощи ИК спектров и спектров 1H -ЯМР и изменений последних с температурой измерения.

p-Substituted 2-chloro-3-phenylpropyl isothiocyanates have been prepared in order to obtain compounds suitable as the starting materials in the synthesis of new heterocyclic derivatives.

In the formation of heterocycles from isothiocyanates the aliphatic residue of the latter normally does not take part in the reaction and remains, as a substituent at a certain position of the product, unchanged [1]. Isothiocyanates having, in addition to the $-NCS$ group, another reactive site in the molecule — a prerequisite for addition-cyclization reactions — have only been described in a limited number of works [2—5]. Since isothiocyanates show, depending upon the nature of the aliphatic residue, pronounced biological activity their properties, from this point of view, may be affected by the presence of a halogen located close to the $-NCS$ group. The title substances have been synthesized according to the following scheme



The *p*-substituted 2-chloro-3-phenylpropionitriles were obtained *via* copper dichloride-catalyzed Meerwein reaction [6—8] of diazonium salts with acrylonitrile. The products were reduced with lithium aluminium hydride in dry ether in the presence of acetic acid to give *p*-substituted 2-chloro-3-phenylpropyl amines, isolated as the corresponding chlorides which were subsequently reacted with thiophosgene [9] to afford the wanted isothiocyanates.

The structure of the intermediate propionitriles followed unambiguously from their ^1H -n.m.r. spectra (Table 1) containing, in addition to the signals of the aromatic and substituent protons, a doublet of the $\text{CH}_{2(\text{A})}$ and a triplet of the $\text{CH}_{(\text{B})}$ group. The observed chemical shifts ($\text{CH}_{2(\text{A})}$: 3.12—3.30 p.p.m., $\text{CH}_{(\text{B})}$: 4.37—4.75 p.p.m.) were in agreement with the more pronounced electron-withdrawing power of the substituents at the benzene ring. The i.r. spectra, measured in chloroform solution at the substrate concentration of 1 M, did not show the absorption band characteristic of the $-\text{CN}$ group, the intensity of which was reduced as a result of the presence of the halogen at the carbon atom next to the nitrile group.

Table 1

Relevant ^1H -n.m.r. spectral data for 2-chloro-3-(4-X-phenyl)propionitriles

| X | δ , p.p.m. | | | |
|-----------------------|-------------------|---------------------------|--------------------------|------------------------|
| | CH_3 | $\text{CH}_{2(\text{A})}$ | $\text{CH}_{(\text{B})}$ | C_6H_4 |
| H | — | 3.21 | 4.42 | 7.25 |
| CH_3 | 2.35 | 3.17 | 4.40 | 7.08 |
| CH_3O | 3.70 | 3.12 | 4.37 | 6.91 |
| Br | — | 3.21 | 4.47 | 7.27 |
| NO_2 | — | 3.30 | 4.75 | 7.75 |

A method suitable for the reduction of the nitriles to *p*-substituted 2-chloro-3-phenylpropyl amines, isolated as chlorides, has been developed during this work. It has been found that the yields of the products of the reduction increased when the reaction was conducted at low temperature (0°C) in the presence of a small amount of glacial acetic acid, to slow down the reaction rate.

The structure of the amines, isolated as chlorides, was confirmed by i.r. and ^1H -n.m.r. spectroscopy (Table 2). The i.r. spectra (measured by the KBr technique) showed a broad band at $\sim 3000\text{ cm}^{-1}$ of the overlapping NH_3^+ and $\text{C}-\text{H}$ (aromatic and aliphatic) vibrations. The doublet at 3.22—3.42 p.p.m. present in the ^1H -n.m.r. spectra was assigned to the methylene group next to the aromatic ring on the basis of the similarity of the observed chemical shift to that of $\text{CH}_{2(\text{A})}$.

Table 2

Characterization of 2-chloro-3-(4-X-phenyl)propyl ammonium chlorides

| X | Formula | M | Calculated/found | | | Yield % | M.p. °C | ¹ H-n.m.r. δ, p.p.m. | | | |
|-------------------|--|--------|------------------|--------------|----------------|---------|---------|---------------------------------|--------------------|--|-------------------------------|
| | | | % C | % H | % N | | | X | CH _{2(A)} | CH _{2(C)} , CH _(B) | C ₆ H ₄ |
| H | C ₉ H ₁₃ Cl ₂ | 206.12 | 54.44 54.04 | 6.35 6.15 | 6.79 6.59 | 72.5 | 175—177 | — | 3.3 d | 3.87—4.37 m | 7.6 s |
| CH ₃ | C ₁₀ H ₁₅ Cl ₂ | 220.1 | 54.55 54.25 | 6.86 7.01 | 6.36 6.26 | 83.7 | 152—154 | 2.55 s | 3.25 d | 3.87—4.25 m | 7.47 s |
| CH ₃ O | C ₁₀ H ₁₅ NOCl ₂ | 236.15 | 50.80 51.10 | 6.40 6.62 | 5.92 5.68 | 76.0 | 215—217 | 4.02 s | 3.22 d | 3.87—4.25 m | 7.35 m |
| Br | C ₉ H ₁₃ NBrCl ₂ | 285.0 | 37.90 38.01 | 4.24 4.31 | 4.91 4.83 | 68.4 | 220 | — | 3.27 d | 3.87—4.37 m | 7.62 m |
| NO ₂ | C ₉ H ₁₂ N ₂ O ₂ Cl ₂ | 251.1 | 43.05 43.22 | 4.81 5.01 | 11.15 10.89 | 56.3 | 182—184 | — | 3.42 d | 3.87—4.50 m | 8.05 m |

s — singlet, d — doublet, m — multiplet.

(3.12—3.3 p.p.m.) of the nitriles. The multiplet at 4.02—4.07 p.p.m. (integrated intensity ratio 3 : 2 with respect to the $\text{CH}_{2(\text{A})}$ doublet) was assigned to the overlapping signals of $\text{CH}_{2(\text{C})}$ and $\text{CH}_{(\text{B})}$, the overlapping being caused by the downfield shift of the signal of the protons at the carbon atom next to the NH_3^+ group.

Better separation of proton signals of the individual groups was observed in the spectra of *p*-substituted 2-chloro-3-phenylpropyl isothiocyanates (Table 3). Here again, in addition to the signals of the aromatic and substituent protons, a doublet at 2.98—3.15 p.p.m. was present which was assigned to $\text{CH}_{2(\text{A})}$ on the basis of the above-discussed interpretation. The signal of $\text{CH}_{2(\text{C})}$ appeared at 3.52—3.7 p.p.m. as a quartet the splitting of which was temperature-dependent. This phenomenon was studied at -80 to $+60^\circ\text{C}$. (in chloroform-*d*). For the bromo derivative even at 0°C a slight splitting of the $\text{CH}_{2(\text{C})}$ doublet was noticeable. At -20°C the doublet clearly splitted to a quartet (Fig. 1) and by gradually raising the temperature to $+60^\circ\text{C}$ it again degenerated to a doublet (J 5 Hz; Fig. 2). The observed coupling constant of the $\text{CH}_{2(\text{A})}$ doublet (J 7 Hz) was temperature-independent. Similar splitting variations were observed also for other derivatives under investigation, except for the nitro derivative for which even at $+60^\circ\text{C}$ the $\text{CH}_{2(\text{C})}$ quartet remained unchanged. Its presence indicates a magnetical unequivalency of the $\text{CH}_{2(\text{C})}$ protons due to the presence of conformers, present even at ambient temperature, resulting from free rotation around the $\text{C}_1\text{—C}_2$ bond (Fig. 3).

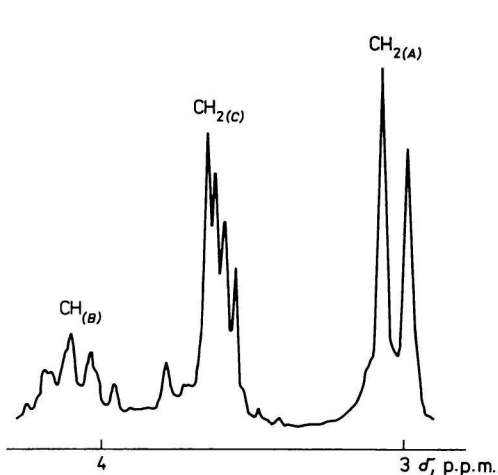


Fig. 1. ^1H -N.m.r. spectrum of 2-chloro-3-(4-bromophenyl)propyl isothiocyanate measured in CDCl_3 at -20°C and a sweep width of 250 Hz.

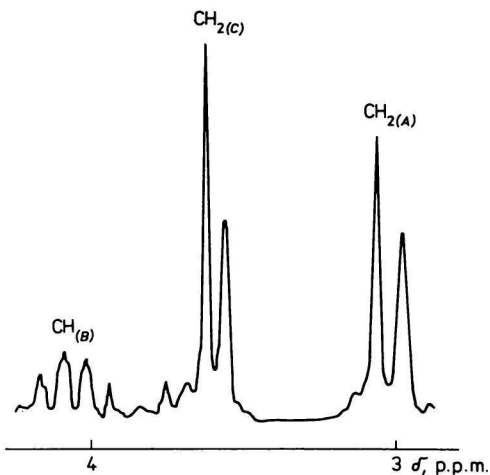


Fig. 2. ^1H -N.m.r. spectrum of 2-chloro-3-(4-bromophenyl)propyl isothiocyanate measured in CDCl_3 at 60°C and a sweep width of 250 Hz.

Table 3

Characterization of 2-chloro-3-(4-X-phenyl)propyl isothiocyanates

| X | Formula | M | Calculated/found | | | | Yield % | B.p. °C/kPa | $\bar{\nu}$ (NCS) cm ⁻¹ | ¹ H-n.m.r. δ , p.p.m. | | | | |
|-------------------|--|--------|------------------|------|-------|-------|------------|----------------|---------------------------------------|---|------|------|------|--|
| | | | % C | % H | % N | % S | | | | X | A | B | C | C ₆ H ₄ ^a |
| H | C ₁₀ H ₁₀ NSCl | 211.72 | 56.70 | 4.76 | 6.16 | 15.10 | 89 | 118 | 2080 | — | 3.03 | 4.08 | 3.56 | 7.28 |
| | | | 56.51 | 4.62 | 6.02 | 15.01 | | 0.02 | | | | | | |
| CH ₃ | C ₁₁ H ₁₂ NSCl | 225.74 | 58.53 | 5.36 | 6.20 | 14.20 | 86 | 118 | 2085 | 3.77 | 2.98 | 4.02 | 3.52 | 7.20 |
| | | | 58.42 | 5.32 | 6.01 | 14.32 | | 0.02 | | | | | | |
| CH ₃ O | C ₁₁ H ₁₂ NOSCl | 241.74 | 54.65 | 5.00 | 5.80 | 13.30 | 78.5 | 137 | 2090 | 3.78 | 2.97 | 4.03 | 3.55 | 7.00 |
| | | | 54.78 | 5.01 | 5.72 | 13.52 | | 0.02 | | | | | | |
| Br | C ₁₀ H ₉ NSBrCl | 290.62 | 41.33 | 3.12 | 4.80 | 11.00 | 80.4 | 134 | 2080 | — | 3.00 | 4.06 | 3.56 | 7.27 |
| | | | 41.21 | 3.08 | 4.85 | 11.09 | | 0.02 | | | | | | |
| NO ₂ | C ₁₀ H ₉ N ₂ O ₂ SCl | 256.70 | 46.78 | 3.53 | 10.90 | 12.50 | 67.2 | 160—163 | 2080 | — | 3.15 | 4.17 | 3.70 | 7.80 |
| | | | 46.54 | 3.51 | 10.79 | 12.71 | | 0.001 | | | | | | |

a) Centres of A₂B₂ quartets of the aromatic protons.

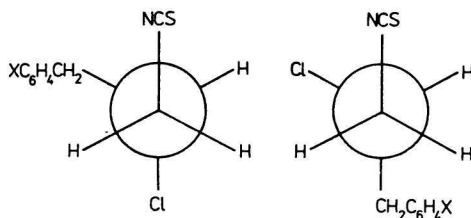


Fig. 3. Conformational isomers of 2-chloro-3-(4-X-phenyl)propyl isothiocyanates.

Experimental

The i.r. spectra for chloroform solutions were measured at $800\text{--}3600\text{ cm}^{-1}$ with a double-beam UR-20 (Zeiss, Jena) spectrophotometer. The instrument was calibrated against a polystyrene foil. The ^1H -n.m.r. spectra were obtained at 80 MHz with a Tesla BS 487 instrument using hexamethyldisiloxane as the internal standard. Melting points were determined on a Kofler hot-stage.

2-Chloro-3-(4-X-phenyl)propyl amines and their chlorides

Powdered lithium aluminium hydride (2.83 g; 0.075 mol) was added portionwise at 0°C to a stirred mixture of *p*-substituted 2-chloro-3-phenylpropiononitrile (10 g; 0.04–0.06 mol) and acetic acid (1 ml) in dry ether (150 ml), and the mixture was allowed to react for 12 h. After addition of water (~ 25 ml), the supernatant solution was decanted, the precipitate washed with ether and the combined ethereal solutions were concentrated. The oily residue was dissolved in chloroform (100 ml), the solution was dried with anhydrous calcium chloride, filtered and concentrated. Dry hydrogen chloride was passed through the solution of the crude amine in benzene (150 ml, in the case of the nitro derivative benzene–ether 1 : 1) whereupon the ammonium chloride separated as a solid or an oil. The organic solvent was evaporated *in vacuo* and the residue was dissolved in water ($\sim 150\text{--}200$ ml). Some undissolved oil was removed and the boiling aqueous solution was treated with charcoal. After cooling and addition of ether (150 ml) the free base was liberated with 70–80% sodium hydroxide. Owing to the instability of the amines the analyses and spectral measurements were run with the chlorides.

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