Stereochemistry of Ion-Pair Return. I. Resolution and Isomerization of (−)-4-Chlorobenzhydryl Thiocyanate[1a]

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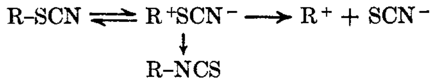
Received April 25, 1969

The synthesis of one enantiomer of 4-chlorobenzhydryl thiocyanate and its correlation of configuration with the corresponding isothiocyanate is described. It is demonstrated that the isomerization R–SCN → R–NCS occurs with net retention of configuration.

Recent kinetic work has established that the isomerization of thiocyanates of benzhydrylic structure proceeds by way of a rate-determining ionization,[2a] which, however, does not need reach the stage of separate carbonium and thiocyanate ions.[2b] The picture thus is that of an ionization mechanism largely proceeding up to the stage of intimate ion pairs,[3] only a minor fraction of which may dissociate before returning to the covalent state.



$$\begin{tikzcd} R\text{-}SCN \arrow[r, shift left] & R^+SCN^- \arrow[l, shift left] \arrow[r] \arrow[d] & R^+ + SCN^- \\ & R\text{-}NCS & \end{tikzcd} \quad (1)$$

For example, it was established by means of tracer experiments that for 4,4′-dimethylbenzhydryl thiocyanate in acetonitrile, the maximum fraction of intimate ion pairs which dissociate rather than undergo covalent return is only about 5%.[4] Clearly for substrates giving raise to carbonium ions less stable than 4,4′-dimethylbenzhydryl, or for solvents less polar than acetonitrile, still smaller fractions will prevail.

A further particularization of the ionization process one can hope to obtain by means of stereochemical experiments. These may provide information about the relative motion of the ionic fragments within the ion pair and may help to distinguish between structurally different ion-pair intermediates which may be formed in the ionization process.[5]

To do such studies an optically active benzhydryl thiocyanate had to be made available, having the asymmetric center at the carbon atom bound to the SCN group. In this first paper we describe the synthesis of one enantiomer of 4-chlorobenzhydryl thiocyanate and the correlation of its configuration with that of the isothiocyanate obtained by thermal isomerization.

A number of reasons have suggested the 4-chloro substrate as a suitable one to carry out the prospected stereochemical work. In the first place, several workers have already used substrates having the 4-chlorobenzhydryl moiety in investigations of covalent return phenomena (Winstein and his students have used the chloride,[6] Goering and Levy the 4-nitrobenzoate,[5,7] Smith the thiobenzoate[8]) so that the results aimed at were likely to allow useful and interesting comparisons with those obtained in similar systems. Secondly, 4-chlorobenzhydryl thiocyanate was known from previous studies[2b] to undergo isomerization at easily manageable rates but not too fast, so that it could be reasonably hoped that once prepared in optically active form, it would not appreciably loose activity during manipulation. Last but not least, the resolution has already been achieved of both the amine[9] and the alcohol[10] derived from this substrate, which obviously reduced the amount of labor involved in the prospected correlative work.

Results

Since no method affording direct resolution of organic thiocyanates is available, it was necessary to resort to the resolution of a precursor from which the thiocyanate could be obtained by way of reactions whose stereochemical course was known or could be inferred with reasonable certainty.

Three different routes have been considered. The first approach involved resolution of the thiol, for which general criteria of resolution exist, followed by reaction with cyanogen bromide to give the thiocyanate.[11] Although the stereochemistry of the Von Braun reaction[12] is not known, it could be reasonably assumed to occur with retention of configuration. However, this route was abandoned after preliminary experiments had shown the material yield to be very low in the Von Braun reaction. The second approach involved resolution of the chloride followed by reaction with ionic thiocyanate under conditions leading to predominant inversion of configuration. Although it could hardly be hoped to obtain a thiocyanate of high optical purity, this route recommended itself in view of the recent partial resolution of the chloride.[7,13] However, this route also had to be discarded for the rate of substitution by the ionic thiocyanate in acetone was found to be slow compared to the rate of racemization of the chloride. The third approach, which was finally pursued to the end, involved resolution of 4-chlorobenzhydrylthiosulfuric acid, from which thiocyanate could

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(1) (a) The financial support of Consiglio Nazionale delle Ricerche, Rome, is gratefully acknowledged; (b) to whom inquiries about this paper are to be addressed: Laboratoire de Chimie Organique Ecole de Chimie, Genève, Switzerland.

(2) (a) A. Iliceto, A. Fava, and U. Mazzuccato, *Tetrahedron Lett.*, **No. 11**, 27 (1960); (b) A. Iliceto, A. Fava, U. Mazzuccato, and O. Rossetto, *J. Amer. Chem. Soc.* **83**, 2729 (1961).

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(5) H. L. Goering and J. F. Levy, *ibid.*, **86**, 120 (1964), and subsequent papers by Goering and coworkers.

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(7) (a) H. L. Goering and J. F. Levy, *Tetrahedron Lett.*, 644 (1961); (b) *J. Amer. Chem. Soc.*, **84**, 3853 (1962); (c) H. L. Goering, R. G. Briody, and J F. Levy, *ibid.*, **85**, 3059 (1963).

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(9) G. R. Clemo, C. Gardner, and R. Raper, *J. Chem. Soc.*, 1959 (1939).

(10) G. H. Green and J. Kenyon, *ibid.*, 751 (1950).

(11) See Houben-Weyl, "Die Methoden der organischen Chemie," Vol. 9, Georg Thieme, Stuttgart, 1955, p 865, and references therein.

(12) J. Von Braun, *Ber.*, **33**, 1438 (1900).

(13) The authors wish to express their appreciation to Professor Winstein for making available the experimental details of the resolution prior to publication.

be obtained by reaction with ionic cyanide. The procedure is summarized in eq 2.

$$\mathrm{RBr} \xrightarrow{\mathrm{Na_2S_2O_3}} \mathrm{RS_2O_3^-Na} \xrightarrow{\mathrm{QHCl}} \mathrm{RS_2O_3^-Q^+H} \xrightarrow{\mathrm{LiOH}} \mathrm{RS_2O_3^-Li^+} \xrightarrow{\mathrm{LiCN}} \mathrm{RSCN} \qquad (2)$$

R = 4-chlorobenzhydryl
Q = quinine

Separation of one diastereomer of the quinine salt of 4-chlorobenzhydrylthiosulfuric acid was achieved through repeated crystallization from acetone–water solvent mixture.

Great care had to be exercised in the subsequent reactions involving alkaline media for, under these conditions, the organic thiosulfate was found to undergo a base-catalyzed elimination (eq 3), the occurrence of

$$\mathrm{Ar_1Ar_2CHSSO_3^-} + \mathrm{OH^-} \longrightarrow \mathrm{H_2O} + \mathrm{SO_3^{-2}} + \mathrm{Ar_1Ar_2C{=}S} \qquad (3)$$

which was evidenced by the appearance of the intense blue color of the thio ketone.[14] Since the reaction by the ionic cyanide is a bimolecular displacement at the divalent sulfur atom, a compromise had to be reached between the requirement of having a high concentration of $\mathrm{CN^-}$, in order to obtain a rapid conversion of thiosulfate to thiocyanate, and that of keeping the pH low, to minimize the elimination. Optimum conditions were realized with a $\mathrm{CN^-}$–HCN buffer having a pH of about 9.2. Under these conditions, while displacement (4) proceeded at convenient speed, elimination (3) was practically suppressed.

$$\mathrm{RSSO_3^-} + \mathrm{CN^-} \longrightarrow \mathrm{RSCN} + \mathrm{SO_3^{-2}} \qquad (4)$$

Reaction sequence 2 led to levorotatory thiocyanate,[17] which was purified by crystallization from ether–petroleum ether (bp 30–50°). It is important to remark that such crystallization may provide a method for the resolution of partially resolved thiocyanate. It was observed, in fact, that, in this particular medium, the racemic mixture is more soluble than the pure enantiomer. The specific rotatory power of the thiocyanate thus obtained and purified was $[\alpha]^{25}\mathrm{D}$ − 21.3° ($\mathrm{CCl_4}$, l 1, c 4.21). This limiting value was confirmed in a number of different preparations.

Thermal isomerization of levorotatory thiocyanate in a variety of solvents (acetonitrile, acetone, dioxane, and benzene) yielded dextrorotatory isothiocyanate.

$$(-)\text{-R-SCN} \longrightarrow (+)\text{-R-NCS}$$

Correlation of configuration between the two isomers was achieved through the sequences shown in eq 5.

$$\begin{tikzcd}
(-)\text{-RSCN} \arrow[r, "\mathrm{Et_4N^+N_3^-}"] \arrow[d] & (-)\text{-RN}_3 \arrow[r, "\mathrm{LiAlH_4}"] & (-)\text{-RNH}_2 \arrow[d, "\mathrm{R'NCS}"] \\
(+)\text{-RNCS} \arrow[d, "\mathrm{R'NH_2}"] & & (-)\text{-RNH}\underset{\underset{\mathrm{S}}{\|}}{\mathrm{C}}\text{NHR}' \\
(+)\text{-RNH}\underset{\underset{\mathrm{S}}{\|}}{\mathrm{C}}\text{NHR}' & &
\end{tikzcd} \qquad (5)$$

R = 4-chlorobenzhydryl
R′ = phenyl

Beside isomerization, only one reaction in the sequence of eq 5, the azide ion displacement, involved the asymmetric center. This displacement was carried out in acetone, where it bears all the earmarks of an $\mathrm{S_N2}$ displacement. It takes place very smoothly at 25° while reactions of 4-chlorobenzhydryl thiocyanate, which proceed by way of a rate-determining ionization, such as isomerization, for instance, proceed at comparable rates in a temperature range 50° higher. It follows a second-order rate law; and the substitution is highly stereospecific, for the whole correlative sequence from 4-chlorobenzhydryl thiocyanate to (−)-N-(4-chlorobenzhydryl)-N′-phenylthiourea had an overall optical yield of 86%.[18] That the azide ion displacement is an $\mathrm{S_N2}$ substitution is highly likely also in view of the circumstance that the analogous displacement by thiocyanate ion (isotopic exchange), a much weaker nucleophile, has been identified as a direct displacement[19] and shown to occur with inversion of configuration.[20]

From what precedes it may be safely assumed that displacement by azide involves net inversion of configuration. On this basis, the opposite sign of the N-(4-chlorobenzyhydryl)-N′-phenylthiourea, obtained at the end of the two branches of sequence 5 demonstrates that *isomerization occurs with net retention of configuration.*

The optical purity of the isothiocyanate obtained in isomerization can be evaluated by comparing the rotation of (+)-N-(4-chlorobenzhydryl)-N′-phenylthiourea obtained from aniline and (+)-4-chlorobenzhydryl isothiocyanate, with the rotation of the thiourea obtained from (+)- or (−)-4-chlorobenzhydrylamine of known optical purity and phenyl isothiocyanate. For example, the isothiocyanate obtained after essentially complete isomerization of the thiocyanate in acetonitrile (~six half-lives) was found to have an optical purity of 23% relative to that of the parent thiocyanate.

The finding that isomerization occurs with net retention is consistent with the mechanistic picture which emerged from the kinetic and tracer experiments. If an internal ion pair is the main intermediate and isomerization arises as a result of collapse of the ion pair to covalent material (with the N-tooth), it is natural that such collapse more likely occurs from the same side of the plane, defined by the carbonium ion, from which the leaving group departed, than from the other side.

The really interesting question, however, is that of the chance that the two ionic fragments have to rotate one relative to the other before collapse to the covalent state occurs (to give racemic isothiocyanate), *i.e.*, the question of the stereospecificity of the isomerization. This information cannot be obtained simply from the optical purity of the isothiocyanate product (although this establishes the lower limit of stereospecificity), for other factors beside stereospecificity may concur to determine the optical purity of the isothiocyanate. This question has been briefly discussed in a recent

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[14] The product had the same absorption spectrum in the visible region ($\lambda_{\max}$ 600 mμ)[15] as that of an authentic sample of 4-chlorobenzhydryl thioketone prepared from the oxygen analog.[15,16]

[15] A. Ceccon, U. Miotti, and U. Tonellato, *Chem. Commun.*, 586 (1966).

[16] A. Schönberg in ref 11, p 710.

[17] In early experiments the brucine salt of 4-chlorobenzhydryl thiosulfuric acid had been partially resolved. Subject to cyanuration as in sequence 2, it yielded dextrorotatory thiocyanate.

[18] This value sets a lower limit of the optical purity of levorotatory 4-chlorobenzhydryl thiocyanate.

[19] A. Ceccon, I. Papa, and A. Fava, *J. Amer. Chem. Soc.*, **88**, 4643 (1966).

[20] U. Tonellato and A. Ceccon, *Gazz. Chim. Ital.*, **96**, 71 (1966).

communication[21] and will be dealt with in detail in forthcoming papers.

Experimental Section

Sodium 4-Chlorobenzhydryl Thiosulfate.—A dioxane solution of 4-chlorobenzhydryl bromide[2b] (100 g in 450 ml) was added slowly, at room temperature, under stirring, to an aqueous solution of sodium thiosulfate (265 g in 720 ml) containing some sodium bicarbonate (30 g). Stirring was continued for 3 hr. Upon addition of ethyl ether (500 ml) three layers separated out; the middle one consisted of a water–dioxane solution of the organic thiosulfate. After evaporation, the residue was crystalized from ethanol (47.5 g, 40% yield).

Anal. Calcd for $C_{13}H_{10}O_3S_2ClNa$: Cl, 10.50. Found: Cl, 10.42.

Quinine 4-Chlorobenzhydryl Thiosulfate.—A saturated aqueous solution of quinine hydrochloride (27.35 g in 510 ml) was added dropwise to an aqueous solution of sodium 4-chlorobenzhydryl thiosulfate (25.55 g in 2200 ml). A white crystalline solid precipitated out; when filtered, washed with water, and dried *in vacuo* over P_2O_5 it weighed 42.5 g: mp 202–204°, $[\alpha]^{25}{}_D$ $-77°$ ($CHCl_3$, *l* 2, *c* 1).

Anal. Calcd for $C_{33}H_{25}O_5N_2S_2Cl$: Cl, 5.56; N, 4.38; S, 10.01. Found: Cl, 5.47; N, 4.25; S, 10.05.

After many attempts with several solvents, resolution was achieved by crystallization from acetone–water (1:2.7 v/v). The crystalline solid was dissolved in acetone at room temperature (1.8 g in 100 ml); after addition of the required volume of water, the solution was kept at about 4° for several hours (usually overnight). The yield at each crystallization varied from 61 to 75%. After the fourth crystallization (eight crystallizations were carried out) both the melting point and the specific rotatory power remained constant: mp 223–224°; $[\alpha]^{25}{}_D$ $-91°$ ($CHCl_3$, *l* 2, *c* 1).

Anal. Calcd for $C_{33}H_{25}O_3N_2S_2Cl$: Cl, 5.56; N, 4.38; S, 10.01. Found: Cl, 5.62; N, 4.25; S, 10.04.

Recrystallization from another solvent pair (dioxane–petroleum ether, 1:2.3 v/v) did not affect these physical properties.

(−)-4-Chlorobenzhydryl Thiocyanate.—The diastereomer of quinine 4-chlorobenzhydryl thiosulfate, isolated as described in the preceding section, was dissolved in chloroform (30.5 g in 240 ml) and treated dropwise with 200 ml of 0.2 *N* LiOH under vigorous stirring. The aqueous layer, containing the lithium salt of 4-chlorobenzhydryl thiosulfate, after washing with chloroform several times to remove traces of quinine, was treated with 220 ml of a buffer solution formed by mixing 110 ml each of 2 *M* LiCN and 1 *N* HCl. The resulting solution had a pH value of about 9.2. By means of rough kinetic experiments, the displacement by cyanide (eq 3) was established to go to completion under these conditions in about 18 hr at 20°.[22] The reacting solution was constantly stirred in the presence of 100 ml of CCl_4 which extracted the thiocyanate as it was formed. The organic layer was washed with water, dehydrated over Na_2SO_4, and evaporated to dryness.

A yield of 61%, 7.4 g, of raw product was obtained. It was crystallized from ethyl ether–petroleum ether (1:2) at 20°. From the infrared spectrum this product appeared to contain no appreciable amount of isothiocyanate, as indicated by the absence of the –NCS asymmetric stretching absorption band in the region 2050–2100 cm^{-1}. In contrast to the racemic material, which melts at 38–39°,[3a] the optically active thiocyanate melted at 42–43°. Polarimetric data: $[\alpha]^{25}{}_D$ $-21.3°$ (CCl_4, *l* 1, *c* 4.21); $[\alpha]^{25}{}_D$ $-22.1°$; $[\alpha]^{25}_{578}$ $-23.3°$; $[\alpha]^{25}_{546}$ $-26.9°$; $[\alpha]^{25}_{436}$ $-51.7°$; $[\alpha]^{25}_{365}$ $-100.2°$ (CCl_4, *l* 1, *c* 2.13).

Anal. Calcd for $C_{14}H_{10}NSCl$: Cl, 13.58; N, 5.40; S, 12.32. Found: Cl, 13.53; N, 5.47; S, 12.28.

(+)-4-Chlorobenzyhydryl Isothiocyanate.—Isomerization of (−)-4-chlorobenzhydryl thiocyanate, $[\alpha]^{25}{}_D$ 20.7° (CCl_4; *l* 2; *c* 4.21), was effected by heating in acetonitrile at 70° for 48 hr (corresponding to six half-lives of isomerization). The isothiocyanate was purified by column chromatography on alumina[23] using light petroleum as eluent: $[\alpha]^{25}{}_D$ + 3.36° (CH_3CN, *l* 1, *c* 3.59); $[\alpha]^{25}{}_D$ +5.17° ($CHCl_3$, *l* 1, *c* 1.36).

Anal. Calcd for $C_{14}H_{10}NSCl$: Cl, 13.58; N, 5.40; S, 12.32. Found: Cl, 13.47; N, 5.42; S, 12.31.

(+)-N-(4-Chlorobenzhydryl)-N′-phenylthiourea. A. From (+)-4-Chlorobenzhydryl Isothiocyanate.—The isothiocyanate, 0.260 g, $[\alpha]^{25}{}_D$ +3.36° (CH_3CN; *l* 1, *c* 3.59), was treated with aniline (0.110 g) in cyclohexane. The product (0.320 g) was filtered and washed with cyclohexane: mp 167.5–168° (lit.[3a] 168–168.5°); $[\alpha]^{25}{}_D$ +7.76° (acetone, *l* 1, *c* 0.98).

B. From (+)-4-Chlorobenzhydrylamine.[24]—The amine, 0.315 g, $[\alpha]^{25}{}_D$ +9.87° (ethanol, *l* 2, *c* 2.19), optical purity 91.3%,[9] was treated with phenyl isothiocyanate (0.205 g). The product (0.442 g) was filtered and washed with cyclohexane: mp 168–169°, $[\alpha]^{25}{}_D$ +30.7 (acetone, *l* 1, *c* 1.09).

(−)-N-(4-Chlorobenzhydryl)-N′-phenylthiourea. A. From (−)-4-Chlorobenzhydrylamine.—The amine, $[\alpha]^{25}{}_D$ $-10.58°$ (ethanol, *l* 2, *c* 4.98), optical purity 97%,[9] was treated with phenyl isothiocyanate as described for the other enantiomer: mp 167.5–169°; $[\alpha]^{25}{}_D$ $-32.0°$ (acetone, *l* 1, *c* 1.3).

B. From (−)-4-Chlorobenzhydryl Azide.—The azide, 0.59 g, $[\alpha]^{25}{}_D$ $-22.5°$ (CCl_4, *l* 1, *c* 3.48), was reduced with $LiAlH_4$ in ether for 1 hr at 0° and then for 2 hr at 25°. After addition of water and 6 *N* HCl, the solution was made alkaline with 10% NaOH and extracted with ether. The ether extract was dehydrated over Na_2SO_4 and Drierite, the solvent removed under reduced pressure, and the residue treated with phenyl isothiocyanate in cyclohexane. The thiourea precipitated out was filtered and washed with cyclohexane (0.546 g): mp 167–168.5°; $[\alpha]^{25}{}_D$ $-26.2°$ (acetone, *l* 1, *c* 1.15). The optical purity of this sample was 79.5%. Relative to the thiocyanate employed in the azide displacement, the optical purity was 86%.

(−)-4-Chlorobenzhydryl Azide from (−)-4-Chlorobenzhydryl Thiocyanate.—(−)-4-Chlorobenzhydryl thiocyanate (0.92 g) was dissolved in 27 ml of a 0.137 *M* solution of tetraethylammonium azide in dry acetone. After standing 16 hr at room temperature, the solution was extracted with 50 ml each of cyclohexane and water. The organic layer, after washing and drying with Na_2SO_4 and Drierite, was treated with 3-diethylamino-1-propylamine (0.15 g) and left standing for 30 min before extracting with aqueous perchloric acid. (This procedure had the purpose of removing any isothiocyanate, which might have formed during the displacement, by transforming it into N-(4-chlorobenzhydryl)-N′-(3-diethylamino-1-propyl)thiourea which can be quantitatively removed by acid extraction.) After drying the solution with Na_2SO_4 and Drierite, the organic solvent was removed under reduced pressure. The residue (0.69 g) was an oily liquid which appeared to essentially consist of 4-chlorobenzhydryl azide. It displayed a strong infrared absorption band at 2110 cm^{-1}, typical of organic azides. The liquid was not subjected to further purification: $[\alpha]^{25}{}_D$ $-22.5°$ (CCl_4, *l* 1, *c* 3.48).

Anal. Calcd for $C_{13}H_{10}N_3Cl$: N, 17.27; Cl, 14.57. Found: N, 17.21; Cl, 14.51.

Kinetics of Reaction of $Et_4N^+N^-{}_3$ with 4-Chlorobenzhydryl Thiocyanate.—Kinetics were determined by following the appearance of SCN^-. Solutions of tetraethylammonium azide in acetone were mixed at the desired temperature with solutions of 4-chlorobenzhydryl thiocyanate. Aliquots were withdrawn at appropriate time intervals and extracted with water–carbon tetrachloride. The aqueous layer, after washing with carbon tetrachloride, was treated with nitrous acid to destroy excess ionic azide and titrated with standard $AgNO_3$. The rate of appearance of SCN^- followed a second-order law. The initial concentration of ionic azide was varied by a factor of about 4, in the range $2.2–0.5 \times 10^{-2}$ *M* (keeping the concentration of organic thiocyanate constant at about 1.1×10^{-2} *M*) without changing appreciably the second-order rate coefficient. The second-order specific rates ($1\ mol^{-1}\ sec^{-1} \times 10^3$) were as follows: at 25°, 5.1; 35°, 13.7; 45°, 30.4. From these data an energy of activation is calculated of about 17 kcal/mol.

Registry No.—Quinine 4-chlorobenzhydryl thiosulfate, 21333-47-1; (−)-4-chlorobenzhydryl thiocyanate, 10203-73-3; (+)-4-chlorobenzhydryl isothiocyanate, 21333-49-3; (−)-N-(4-chlorobenzhydryl-N′-phenylthiourea, 21333-50-6; (−)-4-chlorobenzhydryl azide, 21333-51-7.

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[21] A. Fava, U. Tonellato, and L. Congiu, *Tetrahedron Lett.*, 1657 (1965).

[22] The kinetics were followed by the growth of ionic sulfite with time.

[23] Control experiments have shown that adsorption on alumina does not affect the optical activity of the iosthiocyanate.

[24] Both (+)- and (−)-4-chlorobenzhydrylamine have been obtained by the method of Clemo and coworkers.[9]