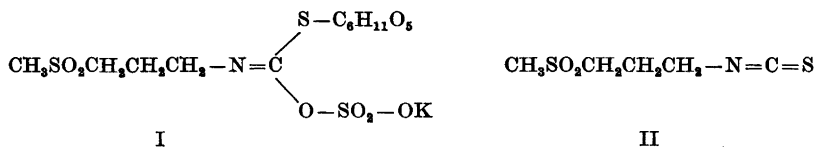


**isoThiocyanates VI. A Synthesis of Cheiroline  
( $\gamma$ -Methylsulphonylpropyl isoThiocyanate)**

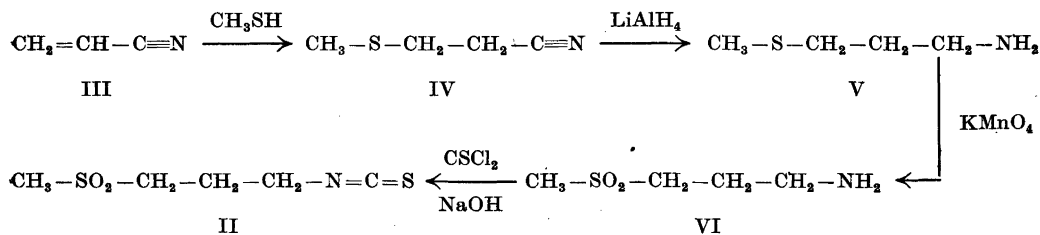
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From seeds of the wall-flower (*Cheiranthus cheiri* L.) Schneider and Schütz<sup>1</sup> isolated a crystalline isothiocyanate glucoside (I), named glucocheiroline. The aglucone, cheiroline, had been shown in an earlier communication by Schneider<sup>2</sup> to possess the remarkable structure (II) which was proved by degradation and confirmed by synthesis. The latter proceeded through several steps, many of which gave rather poor yields and involved a great number of troublesome and time-consuming operations.



In the course of our studies of naturally occurring isothiocyanates a need arose for a supply of cheiroline (II). Here we wish to report our preparative route to cheiroline which we believe represents an improvement over Schneider's synthesis. Contrary to the latter the present synthesis proceeds from readily accessible starting materials in few steps, all of which give satisfactory yields. The reactions involved are outlined in the following scheme.



Following the directions by Hurd and Gershbein<sup>3</sup>, methanethiol was added to acrylonitrile (III) to give  $\beta$ -methylthiopropionitrile (IV) in 90 % yield. The latter was smoothly reduced with lithium aluminium hydride in ethereal solution to  $\gamma$ -methylthiopropylamine (V) in ca. 70 % yield. To our knowledge, this reaction represents the first example of reduction with lithium aluminium hydride of a nitrile containing a sulphide-grouping. It is of interest to note that no concomitant fission of the carbon-sulphur linkage was observed, indicating the inertness of the reagent towards the sulphide-grouping, which is known to be easily hydrogenolysed by other reducing reagents, such as Raney nickel. Furthermore, it appeared that satisfactory yields were obtained only when at least one molecular proportion of the hydride was applied. Although this requirement is not easily reconcilable with the stoichiometric equation, the present finding is in accord with the results of Amundsen and Nelson<sup>4</sup>. They showed that only half the hydrogen of lithium aluminium hydride is available for the reduction of nitriles to primary amines. The oxidation of (V) to the sulphoneamine (VI) was performed in 76 % yield, essentially as described by Schneider<sup>2</sup>. For the conversion of the amine (VI) into cheiroline (II) the traditional methods of isothiocyanate syntheses were at disposal. By far the best and most convenient approach, however, proved to be a modification of the method of Dyson *et al.*<sup>5,6</sup>. Whereas their standard procedure involved the simple reaction between thiocarbonyl chloride and the amine, we found it advantageous to add slightly less than two equivalents of sodium hydroxide to the mixture, resulting in a fast reaction as inferred from the disappearance of the red colour of the thiophosgene. Cheiroline (II) was obtained in 73 % yield as a crystalline product, melting only about one degree below a specimen for analysis, prepared by a further recrystallisation from ethyl ether. The pure cheiroline appeared as colourless crystals, m.p. 46–47°, with physical and chemical properties in accord with the statements in Schneider's paper<sup>2</sup>.

Cheiroline was transformed into its thiourea (VII), m.p. 116–117°, upon reaction with ethanolic ammonia. Again, the derivative possessed properties agreeing well with those reported by Schneider for his N- $\gamma$ -methylsulphonylpropylthiourea. For further characterisation, cheiroline was brought into reaction with aniline, *p*-toluidine and  $\alpha$ -naphthylamine, respectively, to give the corresponding substituted thioureas, (VIII)–(X), (*cf.* Table 1).

Table 1.

Amine	Formula	Composition	M.p., °C	Analyses			
				Nitrogen		Sulphur	
				Calcd.	Found	Calcd.	Found
Ammonia	VII	C <sub>5</sub> H <sub>12</sub> O <sub>2</sub> N <sub>2</sub> S <sub>2</sub>	116–117 <sup>a</sup>	14.28	14.31	32.66	32.44
Aniline	VIII	C <sub>11</sub> H <sub>16</sub> O <sub>2</sub> N <sub>2</sub> S <sub>2</sub>	138 <sup>b</sup>	10.29	10.37	23.54	23.38
<i>p</i> -Toluidine	IX	C <sub>12</sub> H <sub>18</sub> O <sub>2</sub> N <sub>2</sub> S <sub>2</sub>	150	9.78	9.81	22.39	22.20
1-Naphthylamine	X	C <sub>15</sub> H <sub>18</sub> O <sub>2</sub> N <sub>2</sub> S <sub>2</sub>	182–183	8.69	8.69	19.89	19.85

<sup>a</sup> Ref.<sup>2</sup> reports 116°. <sup>b</sup> Ref.<sup>2</sup> reports 136°.

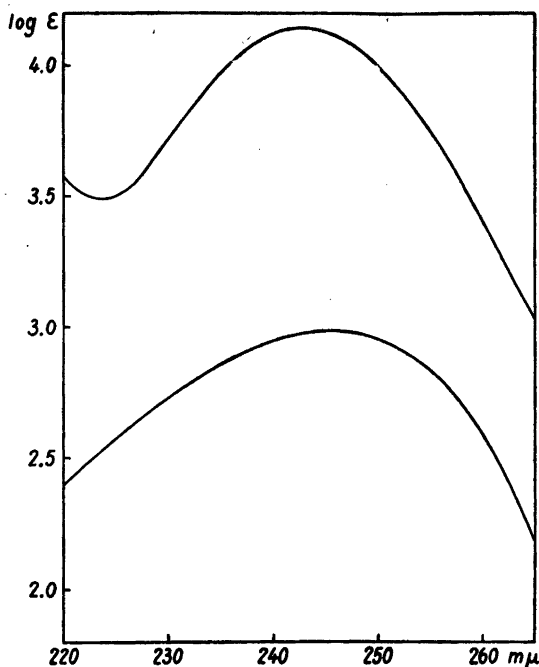
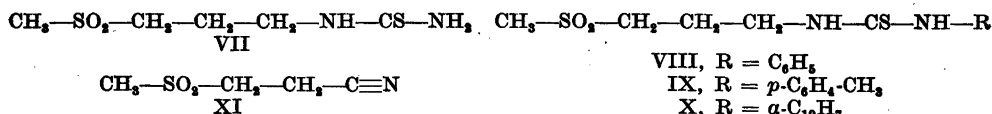


Fig. 1. Ultra-violet absorption spectra, determined in ethanol solutions. Lower curve: cheiroline (II). Upper curve: *N*-( $\gamma$ -methylsulphonylpropyl)-thiourea (VII).



In the preliminary phases of the present work  $\beta$ -methylthiopropionitrile (IV) was oxidised in glacial acetic acid with hydrogen peroxide to the heretofore unknown  $\beta$ -methylsulphonylpropionitrile (XI). Attempts to reduce the nitrile-grouping of (XI) with lithium aluminium hydride failed, presumably because of its slight solubility in ether and tetrahydrofuran. In experiments, conducted in a Soxhlet-apparatus over an extended period of time, the formation of methanethiol was definitely established, indicating the occurrence of hydrogenolysis of the carbon-sulphur linkage during the long exposure to the reagent.

The ultra-violet absorption spectra in ethanol of cheiroline and its thiourea-derivative (VII) are presented in Fig. 1. The broad maximum of rather low extinction in the spectrum of cheiroline is characteristic of the  $\text{N}=\text{C}=\text{S}$ -grouping. The thiourea absorption data are equally typical when compared with the curves for analogous mono-substituted derivatives (*cf.* Ref. 7). Both spectra clearly indicate the sulphonyl-grouping as a spectroscopically non-interfering part of the molecules.

EXPERIMENTAL\*

*β*-Methylthiopropionitrile (IV). This substance was prepared from methanethiol and acrylonitrile in benzene solution, essentially as previously described<sup>2</sup>. It proved advantageous to increase the amount of catalytically acting sodium methoxide to 1 g per 27.5 g of methanethiol. A 90 % yield of the colourless nitrile was obtained, b.p. 96° at 14 mm.

*γ*-Methylthiopropylamine (V). In a three-necked flask, equipped with a mercury-sealed stirrer, separatory funnel, reflux condenser and an inlet for dry nitrogen, was placed a solution of 16.0 g (0.42 mole) of lithium aluminium hydride in 350 ml of dry ether. The flask was swept with nitrogen and a solution of 30.3 g (0.30 mole) of *β*-methylthiopropionitrile in 60 ml of anhydrous ether added from the separatory funnel under vigorous stirring in the course of half an hour. The reaction mixture was then refluxed for one hour in order to complete the reaction and thereafter cooled in an ice-bath. From the funnel were carefully added 20 ml of water, 20 ml of 15 % sodium hydroxide and 70 ml of water, successively. The precipitate was removed by filtration with gentle suction and thoroughly washed with several portions of ether. The ethereal phase was dried over potassium hydroxide, the ether removed over a small column and the residue distilled *in vacuo*. 21.5 g (68 %) of *γ*-methylthiopropylamine distilled as a colourless liquid of unpleasant smell, b.p. 66–67° at 14 mm.

Upon treatment of the amine with ethereal hydrogen chloride, the crystalline hydrochloride was obtained, m.p. 132°. It served to establish the identity of the amine (Schneider<sup>2</sup> reports the m.p. 136° for the amine hydrochloride).

*γ*-Methylsulphonylpropylamine (VI). A solution of 15.7 g of *γ*-methylthiopropylamine in 36 ml of 4.13 *N* hydrochloric acid and 500 ml of water was oxidised with a solution of 31.6 g of potassium permanganate in 1 000 ml of water containing 48.5 ml of 4.13 *N* HCl, as described by Schneider<sup>2</sup>. 19.7 g (76 %) of the sulphoneamine hydrochloride were obtained, m.p. 147.5–148.5° (Schneider<sup>2</sup> reports the m.p. 146°).

An additional amount of material (2.1 g) could be gained from the mother liquor.

*Cheiroline* (II). The following procedure was found to give the most satisfactory results. To an ice-cooled solution of 4.54 g of thiocarbonyl chloride in chloroform (50 ml) was added slowly and under constant shaking a solution of 6.86 g of *γ*-methylsulphonylpropylamine hydrochloride in 40 ml of 1 *N* sodium hydroxide. Then an additional amount of 68 ml of 1 *N* NaOH was added in small portions to the two-layer mixture and the latter vigorously shaken for about one hour. The red colour of the thiocarbonyl chloride rapidly faded to a yellow one. The chloroform layer was removed and the aqueous phase extracted with a small portion of fresh chloroform. The solvent was removed in a stream of air whereupon the cheiroline spontaneously crystallised. The crystals were dissolved in chloroform (17 ml), treated with Darco-60 and the suspension filtered through a thin layer of Celite. To the filtrate were added 50 ml of petroleum ether (b.p. 60–100°), whereupon an oil separated which immediately crystallised on seeding to give 5.15 g (73 %) of cheiroline, m.p. 44–46°. An additional recrystallization from ethyl ether gave analytically pure cheiroline as beautiful, colourless crystals. M.p. 46–47° (Schneider<sup>2</sup> reports the m.p. 46–48°).

$C_8H_{10}O_2NS_2$ (179.3)	Calc.	N 7.81	S 35.76
	Found	» 7.84	» 35.68

*Reactions between cheiroline and amines* (VII)–(X). As a standard method for the preparation of cheiroline-thioureas the following procedure was adopted. Cheiroline and a slight excess of the appropriate amine were dissolved in ethanol. The mixtures were gently heated on the water-bath, cooled and the products collected by filtration. The derivatives were recrystallized from ethanol before analysis. The results are summarized in Table 1.

*β*-Methylsulphonylpropionitrile (XI). To a cooled solution of 17.0 g of *β*-methylthiopropionitrile in 200 ml of glacial acetic acid were slowly added 75 ml of 30 % hydrogen peroxide. After standing at 0° for about two hours the reaction mixture was heated on the steam-bath for another two hours. Next day, the solution was concentrated to a small

\* All melting points are uncorrected and determined in capillary tubes in an electrically heated block.

volume *in vacuo* and placed in the ice-box. On prolonged keeping here, the solution deposited a crop of large, colourless prisms (8.0 g). Further concentration of the mother liquor and chilling gave an additional crop of crystals (9.0 g) of slightly lower purity. The sulphonylnitrile was soluble in water, insoluble in ether and could be recrystallised from ethanol. An analytical specimen melted at 71–72°.

$C_8H_7O_2NS$ (133.2)	Calc.	C 36.07	H 5.30	S 24.07
	Found	» 36.20	» 5.36	» 24.12

Due to its slight solubility in ether a reduction of the nitrile with lithium aluminium hydride in a Soxhlet-apparatus was attempted. Only after refluxing for more than 200 hours the substance had been completely removed from the thimble. Upon working up the mixture in the usual way no well-defined products could be obtained. A considerable formation of methanethiol was easily recognisable, indicating the occurrence of secondary reactions.

*Absorption spectra.* The ultra-violet absorption spectra reproduced in Fig. 1 were determined on a Beckman model DU quartz spectrophotometer in 1 cm cells.

#### SUMMARY

An improved synthesis of cheiroline, the aglucone of the isothiocyanate glucoside of wall-flower seeds, has been developed. It implies fewer steps than the original synthesis and proceeds from readily accessible starting materials in a good over-all yield.

Two new reaction products of cheiroline and aromatic amines are described.

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