ACTA CHEMICA SCANDINAVICA 8 (1954) 1335—1340

*iso*Thiocyanates X. Synthesis and Characterization of *cis*-Crotyl *iso*Thiocyanate

ANDERS KJÆR and KURT RUBINSTEIN

Chemical Laboratory, University of Copenhagen, Denmark

In the first paper of this series [1] the synthesis and characterization of 3-butenyl, α-methallyl, β-methallyl and *trans*-crotyl *iso*thiocyanate were reported. The preparation of the heretofore unknown *cis*-isomer of the latter (I), which was desired in current investigations, has now been effected and an account of the results are given in the present communication.

Nearly all methods used in the preparation of *iso*thiocyanates require the corresponding primary amines as starting materials. *cis*-Crotylamine (II), which is needed in the present case, appears to be a hitherto unknown substance, although the *trans*-isomer is mentioned repeatedly in the literature.

$$\begin{array}{ccc} \mathrm{H-C-CH_3} & \mathrm{H-C-CH_3} & \mathrm{H-C-CH_3} \\ \| & \| & \| \\ \mathrm{H-C-CH_2-NCS} & \mathrm{H-C-CH_2-NH_2} & \mathrm{H-C-CN} \\ \mathrm{I} & \mathrm{II} & \mathrm{III} \end{array}$$

In view of our previously described successful reduction of allyl cyanide to 3-butenylamine with lithium aluminium hydride [1], it was a logical extension to apply the same reagent to *cis*-crotonitrile (III). The latter has become easily accessible as a result of the extensive studies of Bruylants and his coworkers [2-4] on the isomerization of allyl cyanide. Quite unexpectedly, the reduction of *cis*-crotonitrile (III) did not take the desired course. Numerous experiments, conducted under widely varied and carefully controlled conditions, yielded *n*-butylamine as the only seizable reaction product, indicating simultaneous reduction of the nitrile-group and the conjugated double bond. Although reduction of a conjugated carbon-carbon double bond with lithium aluminium hydride has been noticed occassionally (*cf*. Ref.[5]) its occurrence in the present type of compounds seems rather unprecedented. Hatch and Nesbitt [6] reduced *iso*crotonic acid to *cis*-crotyl alcohol without saturation of the double bond, a fact which renders the present observation even more surprising.

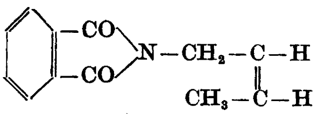
Consequently, a different approach to the synthesis of *cis*-crotylamine was sought. We formerly obtained the *trans*-isomer from *trans*-crotyl bromide by Gabriel-synthesis and subsequent hydrazinolysis [1]. A similar sequence of reactions has been effected now with *cis*-crotyl chloride as the starting material.

Table 1.

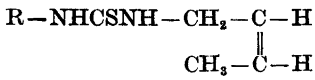
Amine	Formula	Composition	M. p., °C.	Analyses Nitrogen Calcd.	Nitrogen Found	Sulphur Calcd.	Sulphur Found
Ammonia	Va	$C_5H_{10}N_2S$ [a]	88.5	21.53	21.54	24.63	24.51
Aniline	Vb	$C_{11}H_{14}N_2S$ [b]	87	13.58	13.36	15.54	15.63
p-Toluidine	Vc	$C_{12}H_{16}N_2S$ [b]	61	12.73	12.50	14.55	14.76
α-Naphthylamine	Vd	$C_{15}H_{16}N_2S$ [b]	120.5	10.93	10.98	12.50	12.46

[a] Recrystallized from water. [b] Recrystallized from aqueous ethanol.

The latter was obtained from 3-chloro-2-buten-1-ol (kindly furnished by Dr. L. F. Hatch); the carbinol was dehydrochlorinated and catalytically reduced to *cis*-crotyl alcohol. This was finally converted into *cis*-crotyl chloride, all steps being conducted as described by Hatch and Nesbitt [6]. *cis*-Crotyl chloride reacted smoothly with potassium phthalimide in dimethylformamide solution to N-*cis*-crotylphthalimide (IV), the reaction proceeding without stereomutation as evident from the nature of the further reaction products as well as from the sharp melting point.



IV



V

a. R = H
b. R = C_6H_5
c. R = *p*-$CH_3C_6H_4$
d. R = α-$C_{10}H_7$

A preliminary attempt to utilize the mild hydrazinolysis procedure of Schumann and Boissonnas [7] with phenylhydrazine proved fruitless, the starting material being recovered in good yield. The desired cleavage of (IV) was then effected by the ordinary Ing and Manske procedure [8], after it had been demonstrated that (IV) did not stereomutate under the influence of the acid employed in the reaction. The crude *cis*-crotylamine hydrochloride was in turn submitted to reaction with thiocarbonyl chloride and alkali according to the modified Dyson procedure [9] which we previously had found useful for the synthesis of numerous *iso*thiocyanates. This method is more satisfactory and convenient than the Andreasch-Kaluza procedure formerly used for the synthesis of *trans*-crotyl *iso*thiocyanate [1]. The new *cis*-*iso*thiocyanate was obtained as a distillable, colourless liquid with a strong mustard smell. Owing to its supposed instability the main part of the product was immediately submitted to reactions with ammonia, aniline, *p*-toluidine and α-naphthylamine to give the highly crystalline thiourea-derivatives (V, a—d), for which data are presented in Table 1. From this it will be seen that three of the four derivatives have melting points below those of the corresponding *trans*-thioureas [1], as would be expected, whereas *cis*-crotylthiourea (Va) melts 28° higher than the *trans*-isomeride.

The allocation of *cis*-configuration to the higher-melting crotylthiourea was further strengthened by studies of the infra-red spectra. In Fig. 1 are schematically presented the spectra of various *cis*- and *trans*-crotylthioureas. Apart from the intensive band at *ca.* 6.50 μ, attributable to the C = S-stretching

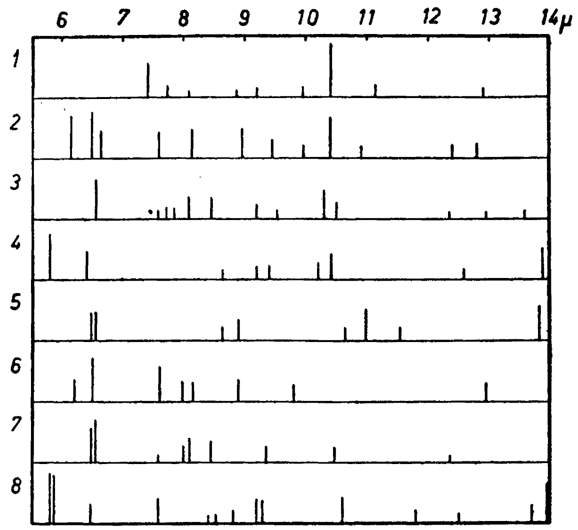


Fig. 1. Schematic presentation of infra-red absorption spectra. 1. trans-*Crotyl* iso*thiocyanate (in addition to the lines presented above, this substance exhibited a very strong absorption band at 4.60 μ, attributable to the N = C = S-group); 2.* trans-*Crotylthiourea; 3.* trans-*Crotylphenylthiourea; 4. N*-trans-*Crotylphthalimide; 5.* cis-*Crotylamine hydrochloride; 6.* cis-*Crotylthiourea; 7.* cis-*Crotylphenylthiourea; 8. N*-cis-*Crotylphthalimide.*

vibration, the most striking feature of the spectra is the characteristic line at about 10.3—10.4 μ in the *trans*-derivatives, which can be assigned to the out-of-plane deformation vibrations of the two hydrogen atoms attached to the *trans*-double bond, as has been frequently noticed in various structurally related compounds (*cf. e.g.* Ref.[10]). Throughout the present work this *trans*-absorption line proved of much diagnostic value because its absence, in lack of a correspondingly characteristic *cis*-absorption band, indicated *cis*-configuration of the compound under investigation. Thus the spectroscopic results are considered to be a proof of the correct assignment of structure, despite the anomalous melting point data. Another representative can therefore be added to the very limited group of crystalline, authentic *cis*-compounds melting higher than their corresponding *trans*-isomerides.

Further confirmation of the stereochemical relationship was incidentally obtained when a small sample of the original *cis*-crotyl *iso*thiocyanate, which had been kept for two weeks at 0°, was found to yield essentially pure *trans*-crotylthiourea upon reaction with ammonia in the usual way. Infra-red inspection of the specimen clearly demonstrated it to be the *trans*-isomer (*cf.* Fig. 1), formed by spontanous rearrangement at 0° of the original product, which had consequently consisted of the labile *cis*-*iso*thiocyanate. No further studies were made of the rate with which the stereomutation takes place.

Paper chromatography of *cis*- and *trans*-crotylthiourea, performed according to our standard method [11], gave undiscernible spots, a fact of no serious consequence however for the systematic search for naturally occurring *iso*thiocyanates, because neither of the crotyl derivatives have so far been encountered in nature.

With all the standard thioureas derived from unsaturated five-carbon *iso*thiocyanates on hand *, a few comments can be made regarding some similar products of dubious structure listed in the literature. Luchmann [12] treated γ-chlorobutylamine with potassium hydroxide at elevated temperature and obtained an unsaturated amine, forming a phenylthiourea with m.p. 94—7° upon treatment with phenyl *iso*thiocyanate. Tentatively, the structure (VI) was suggested for the product, but Galand [13] later assumed Luchmann's product to be an impure *trans*-crotylthiourea (VII). The first possibility can now be definitely excluded, because authentic 3-butenylphenylthiourea has the m.p. 124—126° [1]. Inspection of the melting points in Table 1 seems to support Galand's interpretation. The same author [13] further reported the reduction of allyl cyanide to an unsaturated amine, characterized by its phenylthiourea-derivative of m.p. 88—91°. The latter was claimed to be authentic (VI), an assignment which has now proved clearly untenable.

$CH_2{=}CH{-}CH_2{-}CH_2{-}NHCSNH{-}C_6H_5$

VI

$C_6H_5{-}NHCSNH{-}CH_2{-}C{-}H$
$\qquad\qquad\qquad\qquad\qquad\quad \|$
$\qquad\qquad\qquad\qquad\qquad H{-}C{-}CH_3$

VII

The formation of *cis*-crotylamine by the reduction of allyl cyanide, as performed by Galand, seems to be a very remote possibility. Hence, the reported m.p. of the phenylthiourea-derivative is not reconcilable with any of the authentic samples, a fact which lends support to the belief that Galand's derivative represents an impure preparation. In 1907 Stein [14] reported the isolation from Indian rape seeds of an unsaturated five-carbon *iso*thiocyanate, which was characterized by its phenylthiourea-derivative with m.p. 53°. No derivative with nearly as low a m.p. has been encountered during our studies of the isomeric *iso*thiocyanates; no explanation can be offered for the observation of Stein. Again, an unsaturated five-carbon *iso*thiocyanate, isolated by Schimmel & Co.[15] from *Brassica juncea* Hook et Thoms, was characterized as its thiourea-derivative with m.p. 69—70°, depressed on admixture with authentic *trans*-crotylthiourea. From the series of authentic derivatives prepared in this laboratory we conclude that the essential oil above does not represent any pure unsaturated five-carbon *iso*thiocyanate. Finally, comparison with the authentic samples on hand indicates that the alleged synthetic crotyl *iso*thiocyanate of Searle [16], for which a thiourea-derivative with m.p. 91.8—92.5° is reported, hardly represents any unsaturated five-carbon *iso*thiocyanate.

EXPERIMENTAL **

cis-*Crotylphthalimide* (IV). A suspension of 23.2 g of potassium phthalimide in 95 ml of dimethylformamide was placed in a three-necked flask, provided with thermometer, dropping funnel, reflux condenser and a mercury-sealed stirrer. 10.7 g of *cis*-crotyl chloride [6] were added dropwise under vigorous stirring and the suspension kept for 3 hours

* That is, excepting isomers containing an α,β-double bond. No attempts have been made to synthetize such compounds which would most likely be very unstable as derivatives of vinylamine.

** All melting points recorded are determined with a calibrated thermometer in capillary tubes in an oil bath.

at 80°. After stirring for another 3 hours at room temperature 475 ml of water were added and the mixture extracted with one 140-ml and two 50-ml portions of chloroform. After drying the chloroform layer, the solvent was removed *in vacuo* and the residual oil brought to crystallization on cooling and scratching. After one recrystallization from aqueous ethanol, 19.0 g (80 %) of essentially pure *cis*-crotylphthalimide remained. Two additional recrystallizations from dilute ethanol furnished a specimen for analysis. M. p. 65°. (Found: C 71.86; H 5.46; N 6.92. Calc. for $C_{12}H_{11}O_2N$ (201.2): C 71.62; H 5.51, N 6.96).

The corresponding *trans*-derivative was previously found [1] to melt at 75—76°. Infra-red data for both isomers are presented in Fig. 1.

cis-*Crotylamine hydrochloride.* After a preliminary experiment had shown that *cis*-crotylphthalimide could be recovered unchanged from the acid treatment employed in Ing and Manske's hydrazinolysis procedure, the above imide was deacylated as formerly described for the *trans*-derivative [1]. From 14 g of *cis*-crotylphthalimide there was obtained 7.1 g (95 %) of crude *cis*-crotylamine hydrochloride, which was used in the following step without further purification. A sample for analysis was recrystallized twice from 2-butanone and once from anhydrous ethanol and ether. The hydrochloride separated in flat prisms with m. p. 138°. Its infra-red spectrum is reproduced in Fig. 1. (Found: N 13.09; Cl 32.93. Calc. for $C_4H_{10}NCl$ (107.6): N 13.02; Cl 32.95).

cis-*Crotyl* iso*thiocyanate* (I). A solution of 5.82 g (54 mmoles) of *cis*-crotylamine hydrochloride in 54 ml of 1 *N* NaOH was slowly added to a cooled solution of 6.23 g (54 mmoles) of thiocarbonyl chloride in 70 ml of chloroform. After addition of 92 ml of 1 *N* NaOH the solution was shaken for one hour at room temperature. A copious brown precipitate was removed by filtration through a sintered glass plate and thoroughly washed with chloroform. The filtrate was separated and the aqueous layer extracted with three 10-ml portions of fresh chloroform. The organic phase was dried over magnesium sulphate and the solvent removed by distillation through a small column. The residue was distilled *in vacuo* and the *iso*thiocyanate (2.47 g) was collected as a vesicant colourless liquid, b. p. 71—73° at 11 mm. Owing to the rather small amount of substance on hand, no attempts were made to purify the sample further for analysis; it was immediately transformed into its thiourea-derivatives for characterization.

The new *iso*thiocyanate should be used shortly after its preparation. Otherwise stereomutation may occur as noticed from the infra-red spectrum (*cf.* Fig. 1) of a small specimen which had been kept for two weeks at 0°. During this period it was quantitatively converted into the stereoisomeric *trans*-crotyl *iso*thiocyanate.

cis-*Crotyl-thioureas* (V, a—d). On reaction with ammonia, aniline, *p*-toluidine and *a*-naphthylamine in the usual way, the freshly prepared *cis*-crotyl *iso*thiocyanate above was rapidly transformed into the respective thioureas (V, a—d) for which analyses and melting points are presented in Table 1. The infra-red spectra of the four derivatives were determined; some of the results, supplemented with the spectra of the corresponding *trans*-isomers are recorded in Fig. 1.

Upon paper chromatography in chloroform solution as previously described [11], *cis*-crotylthiourea (Va) gave a spot with an R_{Ph}-value of 0.76, while the spot of the corresponding *trans*-derivative had an R_{Ph}-value of 0.77.

Infra-red absorption spectra. The infra-red absorption spectra were determined in Nujol mulls with one exception, *viz.* that of *trans*-crotyl *iso*thiocyanate. This substance was applied directly to the rock salt plates as a thin film. The measurements were conducted on a Beckman IR-2 instrument.

SUMMARY

A synthesis of *cis*-crotyl *iso*thiocyanate, proceeding from *cis*-crotyl chloride *via cis*-crotylphthalimide and *cis*-crotylamine, is described. The stereochemical authenticity of the new *iso*thiocyanate has been secured through studies of the infra-red absorption spectra. Spontaneous stereomutation of the *cis-iso*thiocyanate has been observed, even at 0°.

The *iso*thiocyanate has been characterized by its transformation into thioureas upon reaction with aniline, *p*-toluidine, *α*-naphthylamine and ammonia. The derivative with the latter represents a new member of the rather limited group of authentic *cis*-compounds, melting higher than their corresponding *trans*-isomers.

The chemical nature of various *iso*thiocyanates and derivatives, reported in the literature and of questionable structures, are discussed in the light of our own results.

We are much indebted to Dr. L. F. Hatch, the University of Texas, Austin, U.S.A., for his generous gift of a sample of 3-chloro-2-buten-1-ol, which facilitated the preparation of *cis*-crotyl chloride considerably.

Microanalyses were performed in this laboratory by Mr. W. Egger. One of us (K. R.) wishes to acknowledge a scholarship from *Det teknisk-videnskabelige Forskningsråd.* The present work is part of investigations supported by *Carlsbergfondet (The Carlsberg Foundation).*

REFERENCES

1. Kjær, A., Rubinstein, K. and Jensen, K. A. *Acta Chem. Scand.* **7** (1953) 518.
2. Bruylants, P. *Bull. soc. chim. Belges* **31** (1922) 175, 225.
3. Bruylants, P. *Bull. soc. chim. Belges* **32** (1923) 256.
4. Bruylants, P. *Bull. soc. chim. Belges* **33** (1924) 331.
5. Solms, U. *Chimia (Switz.)* **5** (1951) 25.
6. Hatch, L. F. and Nesbitt, S. S. *J. Am. Chem. Soc.* **72** (1950) 727.
7. Schumann, I. and Boissonnas, R. A. *Helv. Chim. Acta* **35** (1952) 2235.
8. Ing, H. R. and Manske, R. H. F. *J. Chem. Soc.* **1926** 2348.
9. Kjær, A., Marcus, F. and Conti, J. *Acta Chem. Scand.* **7** (1953) 1370.
10. Crombie, L. *Quart. Revs. (London)* **6** (1952) 101.
11. Kjær, A. and Rubinstein, K. *Acta Chem. Scand.* **7** (1953) 528.
12. Luchmann, A. *Ber.* **29** (1896) 1420.
13. Galand, E. *Bull. soc. chim. Belges* **39** (1930) 529.
14. Stein, E. H. „*Über die chemische Natur und die Giftigkeit des aus Raps und verwandten Kruziferen entwickelten Senföles*". Dissertation, Berlin 1907.
15. *Ber. Schimmel & Co. Akt.-Ges.* **1910** 112.
16. Searle, N. E. *U. S. 2462433; cf. Chem. Abstracts* **43** (1949) 3843.

Received May 13, 1954.