[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE RICE INSTITUTE]

The Mustard Oil of Rape Seed, Allylcarbinyl Isothiocyanate, and Synthetic Isomers

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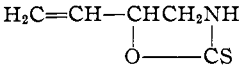
The mustard oil of rape seed was proved to be allylcarbinyl isothiocyanate, which was synthesized with *cis*- and *trans*-crotyl isothiocyanates.

The seed of rape (*Brassica napus* L.; in French, colza) furnishes on maceration a five-carbon unsaturated isothiocyanate,[1] liberated enzymatically, a higher homolog of the oil allyl isothiocyanate of black mustard (*Brassica nigra*). The precursor, named gluconapin,[2] has not been isolated in pure condition but presumably resembles sinigrin, the glucoside of allyl isothiocyanate. Interest in the mustard oil of rape originated from its supposed toxicity to cattle fed on seed cake and was spurred by recognition[3,4] of its probable close relation to the natural antithyroid factor *l*-5-vinyl-2-thioöxazolidone[3] (I), also combined in rape seed. Indeed, I differs in skeleton solely by the increment of the allylic oxygen atom from the mustard oil, which is allylcarbinyl isothiocyanate (II).



$$\begin{array}{l} H_2C{=}CH{-}\overset{}{C}HCH_2NH \\ \qquad\qquad\; | \qquad\quad | \\ \qquad\qquad\; O{-}{-}{-}CS \end{array}$$

I

$H_2C{=}CHCH_2CH_2NCS$

II

Sjollema[1] isolated from rape seed 0.2% of an unsaturated, optically inactive mustard oil, of formula C_5H_7NS, to which he fortuitously[5] assigned structure II. The substance was characterized through reaction with ammonia as the thiourea, which formed needles, m.p. 64°. The isolation was repeated by Schmalfuss[6] (n^{18}D 1.5252; thiourea, m.p. 67–68°) and by André and Delaveau.[7] Kjaer, *et al.*,[8] subjected the crude thioureas from rape seed cake to countercurrent distribution and obtained allylcarbinylthiourea, m.p. 65.5–66°, identified with a synthetic sample.

The species *Brassica napus*, with haploid chromosome number *n* of 19, originated according to general belief from amphiploid hybrids of *B. oleracea* ($n = 9$), the cabbages, and *B. campestris* ($n = 10$), the turnips, turnip-rapes (French, navette) and allies.[11,12] The ten-chromosome members of *Brassica* include the so-called colzas of India, sarson and toria,[13] and the so-called Chinese cabbages of the Far East, often segregated as *B. chinensis*.[11] The predominant mustard oil of *B. oleracea*, as present data[14] indicate, is allyl isothiocyanate. However, the mustard oil of *napus* rape does occur also in the *campestris* ancestor, European turnip-rape,[15] often in greater amount, and in other members of the ten-chromosome complex, Indian colza[16] and Chinese colza.[9,17]

Schimmel and Company[18] found the oil from an exceptional shipment of Indian mustard seed, *Brassica juncea*, to consist of approximately equal parts of allyl isothiocyanate and an optically inactive "crotonyl" mustard oil, n^{20}D 1.5240, giving a thiourea as needles, m.p. 69–70°, different from the synthetic crotylthiourea mentioned subsequently. Identification of the Schimmel five-carbon mustard oil with that of rape appears highly plausible from physical properties.[19] Since *B. juncea* ($n = 18$), comprising the Oriental and leaf mustards, is considered[11,20] to be a group of amphiploids of *B. nigra* ($n = 8$) and ten-chromosome Brassicas (*campestris, chinensis*), a member might[21] contain substantial amounts of both allyl and allylcarbinyl isothiocyanates, like the artificial hybrid *B. pseudojuncea*.[14,20] However, later investigators[14,22] of the volatile oil of natural *juncea* have identified only allyl isothiocyanate. The exceptional Schimmel seed parcel may have been mixed with Indian colza, and the identity of the derived mustard oil seems more certain than its botanical provenance.

The starting material in the present experiments

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(1) B. Sjollema, *Rec. trav. chim.*, **20**, 237 (1901).

(2) H. ter Meulen, *ibid.*, **24**, 444 (1905).

(3) E. B. Astwood, M. A. Greer and M. G. Ettlinger, *J. Biol. Chem.*, **181**, 121 (1949).

(4) D. Libermann, quoted by R. Pitt-Rivers, *Physiol. Revs.*, **30**, 194 (1950).

(5) The natural compound was designated commonly as "crotonyl" mustard oil and indexed in recent *C. A.* as 2-butenyl (crotyl) isothiocyanate.

(6) H. Schmalfuss, *Forschungsdienst, Sonderheft*, **1**, 37 (1936).

(7) E. André and P. Delaveau, *Compt. rend.*, **229**, 555 (1949); **231**, 872 (1950).

(8) A. Kjaer, J. Conti and K. A. Jensen, *Acta Chem. Scand.*, **7**, 1271 (1953). These authors ignored the discrepancy of melting points reported[9] for the phenylthiourea from the rape isothiocyanate (54°) and claimed[10] for synthetic N-allylcarbinyl-N′-phenylthiourea (123–127°).

(9) A. Viehoever, J. F. Clevenger and C. O. Ewing, *J. Agr. Research*, **20**, 117 (1920).

(10) A. Kjaer, K. Rubinstein and K. A. Jensen, *Acta Chem. Scand.*, **7**, 518 (1953).

(11) V. G. Sun, *Bull. Torrey Botan. Club*, **73**, 244, 370 (1946).

(12) K. J. Frandsen, *Dansk Bot. Arkiv*, **12**, No. 7 (1947). For a genealogical table of kinds of *B. napus* (rape, rutabaga, rape-kale), see M. B. Crane, *J. Roy. Hort. Soc.*, **68**, 172 (1943), reproduced in M. B. Crane and W. J. C. Lawrence, "The Genetics of Garden Plants," 3rd ed., The Macmillan Co., London, 1947, p. 243.

(13) Z. Alam, *Ann. Bot.*, **50**, 85 (1936); *cf.* H. W. Howard, *Current Sci.*, **9**, 494 (1940).

(14) K. A. Jensen, J. Conti and A. Kjaer, *Acta Chem. Scand.*, **7**, 1267 (1953).

(15) E. André and M. Kogane-Charles, *Ann. agron.*, n. s., **18**, 547 (1948).

(16) E. H. Stein, quoted in ref. 8, 9 and 15.

(17) The plant was named[9] *B. campestris chinoleifera* and was seemingly identical with Sun's[11] *B. chinensis pandurata*.

(18) *Semi-Ann. Rept. Schimmel and Co.*, p. 81 (Oct. 1910).

(19) The Schimmel chemists apparently disclaimed identity of their natural thiourea with Sjollema's solely because of the 5° difference in m. ps. *dl*-α-Methylallylthiourea and β-methylallylthiourea melt over 20° higher.[10] The Schimmel mustard oil was also characterized as a bornylthiourethane (not analyzed) but such a derivative could not be obtained in present work.

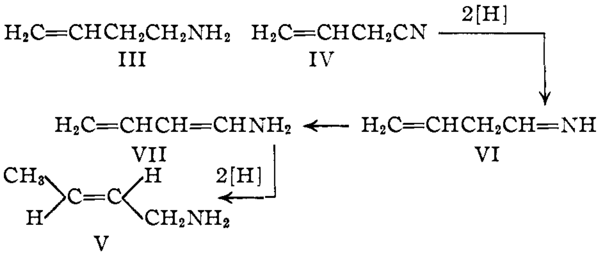
(20) S. Ramanujam and D. Scrinivasachar, *Indian J. Genetics and Pl. Breed.*, **3**, 73 (1943); K. J. Frandsen, *Dansk Bot. Arkiv*, **11**, No. 4 (1943).

(21) E. André and M. Maille, *Ann. inst. natl. recherche agron.*, **Ser. A**, *Ann. agron.*, **2**, 442 (1951).

(22) A. Viehoever, C. O. Ewing and J. F. Clevenger, *Science*, **46**, 545 (1917); M. C. Albrech, quoted by L. H. Bailey, *Gentes Herbarum*, **2**, 211 (1930); H. Schmalfuss and H. P. Mueller, *Forschungsdienst*, **17**, 205 (1944); [*Chem. Zentr.*, **115**, II, 776 (1944)].

was whole seed of the commercial Dwarf Essex[23] winter rape (*Brassica napus biennis*), containing 0.2% of mustard oil and 0.7% of thioöxazolidone. The mustard oil was isolated in yield of 0.07% of seed by maceration and steam distillation. The pure isothiocyanate of formula C_5H_7NS, characterized as the thiourea, m.p. 66.5–67°, and the N'-phenylthiourea, m.p. 56–57°, was optically inactive and according to the infrared spectrum contained a vinyl and no methyl group. The absence of a C-methyl group was confirmed by the determination with chromic acid. These facts sufficed to prove that the rape seed mustard oil was II.

The first recorded attempt[24] to prepare allylcarbinylamine (III) proceeded by the slow reduction of allyl cyanide (IV) with coppered zinc in acetic acid. Judged by the high[25] boiling point and refractive index of the amine, formed in slight yield, and the melting point of the derived phenylthiourea, the product was largely *trans*-crotylamine (V). The carbon–carbon double bond of IV or the intermediate aldimine VI might have shifted into conjugation, or VI might have tautomerized to 1-amino-1,3-butadiene (VII), which underwent 1,4-reduction. The reduction[10] of IV by the strongly



basic lithium aluminum hydride, a step in the previous synthesis of allylcarbinylthiourea, also seems a dubious mode of preparation of known pure III. In the present work, III was obtained by the Gabriel reaction according to Roberts and Mazur[25] and was identified with the product of the remarkable reaction[26] of formaldehyde and α-allylbenzylamine. The isothiocyanate II was prepared from III by a modification of Kaluza's method,[27] with base-catalyzed[28] decomposition of the carboethoxy alkenyldithiocarbamate, and converted to allylcarbinylthiourea, m.p. 67–67.5°. N-Allylcarbinyl-N'-phenylthiourea, m.p. 56.5–57°, was obtained from III. Synthetic II was identical with the natural product.

The three previous synthetic preparations of N-allylcarbinyl-N'-phenylthiourea have been reported to melt at 91°,[24] 44.5–45°,[25] and 123–127°.[10] The first material was probably impure N-*trans*-crotyl-N'-phenylthiourea (m.p. 106°[24]). The second preparation, kindly provided by Dr. John D. Roberts, may have existed as a low-melting polymorph but was found now to melt at 56°. The last thiourea, melting over a wide range though giving a correct analysis, was obtained after high-vacuum "sublimation" of the crude substance, which apparently had been washed with acid to remove excess aniline and hence may have contained aniline hydrochloride. Pyrolytic disproportionation,[29-31] perhaps acid catalyzed, exchange of amine[31,32] or cyclization[33] might have occurred. In the present experiments, pure N-allylcarbinyl-N'-phenylthiourea was unaltered on distillation at 0.02 mm. and gave oil at higher pressures, whereas a mixture with aniline hydrochloride furnished a sublimate, m.p. 119–128°, better matching previous description. The solid was inhomogeneous, containing N,N'-diphenylthiourea (thiocarbanilide).

In an experiment to prepare the unknown N-*t*-butyl-N'-phenylthiourea, *t*-butyl isothiocyanate was heated with aniline in benzene to give as the sole isolable pure product thiocarbanilide. N-*t*-Butyl-N'-phenylthiourea was obtained at room temperature from *t*-butyl isothiocyanate and aniline or *t*-butylamine and phenyl isothiocyanate and was found to exchange with aniline in boiling benzene to form thiocarbanilide and *t*-butylamine. Under the same conditions, aniline did not react with phenylthiourea or N-ethyl-N'-phenylthiourea, though facile exchanges of diarylthioureas with ammonia[34] or arylamines[30,35] were known. The displacement of *t*-butylamine appears unusually rapid for the aliphatic series and may proceed by sterically favored dissociation of the phenylthiourea to phenyl isothiocyanate and the amine.

The first preparation of pure *trans*-crotyl isothiocyanate[10,18] (VIII) was accomplished in the present work by the modified Kaluza synthesis from V, obtained by the Gabriel reaction[25,36] from *trans*-crotyl chloride. The melting point and crystal form (leaflets) of the earliest reported[18] crotylthiourea were confirmed,[37] but the mustard oil whence it derived was evidently inhomogeneous (n^{15}_{D} 1.5172; *cf.* pure VIII, n^{26}_{D} 1.5236; *n*-butyl isothiocyanate,[38] n^{20}_{D} 1.5010), having been obtained from a probable mixture of V and *n*-butylamine,

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[23] A. F. Musil, *U. S. Dept. Agr., Misc. Pub.*, No. 643 (1948).

[24] E. Galand, *Bull. soc. chim. Belg.*, **39**, 529 (1930).

[25] J. D. Roberts and R. H. Mazur, THIS JOURNAL, **73**, 2509 (1951).

[26] R. M. Horowitz and T. A. Geissman, *ibid.*, **72**, 1518 (1950).

[27] L. Kaluza, *Monatsh.*, **33**, 363 (1912).

[28] J. E. Hodgkins, forthcoming publication; *cf.* O. E. Schultz and E. Barthold, *Arch. Pharm.*, **285**, 267 (1952).

[29] W. Weith, *Ber.*, **8**, 1523 (1875); E. Lellmann, *Ann.*, **221**, 1 (1883); E. Lellmann and E. Wuerthner, *ibid.*, **228**, 199 (1885); A. Hugershoff, *Ber.*, **36**, 1138 (1903).

[30] C. Kjellin, *ibid.*, **36**, 194 (1903).

[31] T. L. Davis and H. W. Underwood, Jr., THIS JOURNAL, **44**, 2595 (1922).

[32] The dissociation of N-allylcarbinyl-N'-phenylthiourea to phenyl isothiocyanate and allylcarbinylamine in the presence of aniline hydrochloride would lead to formation of allylcarbinylamine hydrochloride and N,N'-diphenylthiourea. Similarly, the decomposition of diarylthioureas to isothiocyanates and amines becomes nearly complete if the amine is combined as a salt in hot, strong acid (A. W. Hofmann, *Ber.*, **15**, 985 (1882)).

[33] B. Prager, *ibid.*, **22**, 2991 (1889).

[34] W. Gebhardt, *ibid.*, **17**, 3033, 3043 (1884).

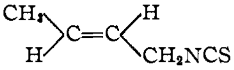
[35] R. v. Walther, *J. prakt. Chem.*, [2] **74**, 222 (1906); F. Zetzsche and A. Fredrich, *Ber.*, **73**, 1420 (1940).

[36] D. Y. Curtin and S. M. Gerber, THIS JOURNAL, **74**, 4052 (1952).

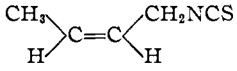
[37] A recent preparation (N. E. Searle, U. S. Pat. 2,462,433) of methallylthiourea (β-methylallylthiourea) from the corresponding methallyl chloride was erroneously depicted in the abstract (*C. A.*, **43**, 3843 (1949)) to concern the crotyl compounds (*cf.* ref. 10). The "crotonic-benzylthiourea" reported as a derivative of VIII (L. E. Weller, C. D. Ball and H. M. Sell, THIS JOURNAL, **74**, 1104 (1952)) probably was the α-methylallyl isomer (*cf.* O. Mumm and H. Richter, *Ber.*, **73**, 843 (1940)).

[38] E. Schmidt, *et al.*, *Ann.*, **585**, 230 (1954).

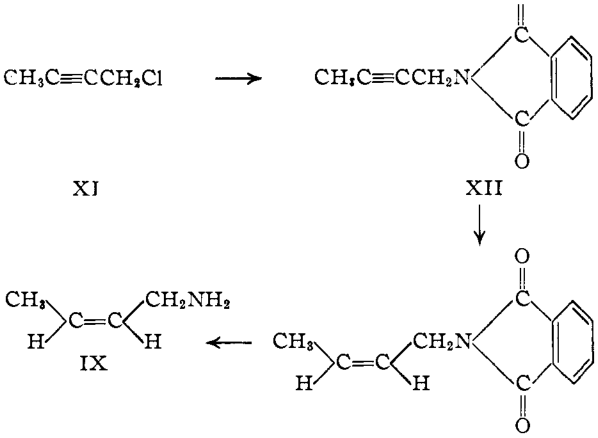
formed by sodium amalgam reduction of crotonaldoxime.[39]



VIII



X



XI

XII

IX

XIII

The previously unknown *cis*-crotylamine (IX) and *cis*-crotyl isothiocyanate (X) were synthesized from 2-butynol, which was converted by an improved method to 2-butynyl chloride[40,41] (XI) and thence to N-2-butynylphthalimide (XII), melting nearly as high as phthalanil. Hydrogenation of XII on a lead-poisoned palladium catalyst[42] furnished in almost quantitative yield N-*cis*-crotylphthalimide (XIII), which could be reduced further over platinum to N-*n*-butylphthalimide. The isomerization of XIII to the *trans*-compound could not be effected by fusion with iodine and illumination, but was accomplished under catalysis by nitrogen dioxide.[43] Hydrazinolysis of XIII gave IX, which was shown to be free from the *trans*-isomer V by infrared analysis. The infrared spectrum of the isothiocyanate X prepared from IX did not exclude partial steric inversion, but from reaction with ammonia spectroscopically pure *cis*-crotylthiourea could be isolated.

The investigation was supported by a research grant (A-238) from the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, Public Health Service. Dr. Reed C. Rollins, Director of the Gray Herbarium, Harvard University, courteously provided an introduction to the botanical literature.

Experimental

Preliminary Assays.—The starting material, Dwarf Essex rape seed, was analyzed for *l*-5-vinyl-2-thioöxazolidone by the known method.[3] For determination of isothiocyanate, 50 g. of seed was milled to 40 mesh and stirred 30 minutes at room temperature with 200 cc. of petroleum ether, which removed some 4 g. of fatty oil. The dry residue was digested with 250 cc. of water during an hour at 60–70°, without added myrosin, and the mixture was steam distilled until approximately 300 cc. was collected. The distillate was treated with 35 cc. of concentrated ammonia, let stand overnight, and partly evaporated to remove excess ammonia. The ultraviolet absorption spectrum was measured in water at known dilution and the original content of isothiocyanate calculated. Pure allylcarbinylthiourea in aqueous solution absorbed maximally at 237 mμ (ϵ 13100), with respective extinctions at 220, 240 and 260 mμ of 7200, 12300 and 1130. The spectra observed in assays could be corrected for assumed linear extraneous absorption,[3,44] but the distillates were sufficiently pure that the uncorrected maximum optical densities were generally not more than 10% higher than computed values.

In the assay for mustard oil, omission of either the wash with petroleum ether or the digestion period with water halved the yield. Maceration resulted as well at 80° as at 60°, whereas use of a temperature of 40° for one to four hours diminished the yield by 30–40%. When the ground seed was extracted continuously with petroleum ether during 15 hours, approximately 40% was removed as oil. The residue contained 5 g./kg. of vinylthioöxazolidone and 1 g./kg. of mustard oil based on original weight.

Isolation.—A 2-kg. portion of ground rape seed was stirred with 2.7 kg. of petroleum ether during two hours and filtered, and the dried residue was macerated with 4 l. of water for an hour at 65° and steam distilled with a little silicone antifoam compound until 2.5–3 l. was collected. A fourth l. contained less than 30 mg. of mustard oil. The distillate was saturated with salt and extracted continuously with ether during 20 to 40 hours. The ethereal extract (700 cc.) from a total of 10 kg. of rape seed was dried over sodium sulfate and concentrated under a Vigreux column, and the residue was fractionated at 26 mm. through a center rod column. The fore-run, 2.2 g., b.p. 51–75°, n^{26}D 1.4104–1.4751, was followed by the fractions of mustard oil: 1.28 g., b.p. 75–77°, n^{26}D 1.4978; 8.13 g., b.p. 77–82°, n^{26}D 1.5162; and 2.4 g., b.p. 83–94° (bath 130–153°), n^{26}D 1.5119; the residue weighed 3 g. Redistillation of the combined mustard oil furnished 0.6 g. of fore-run, b.p. 73–77°, n^{26}D 1.4849–1.5013; a main fraction of 6.46 g., b.p. 78.5° at 26 mm. (lit.[6,7] 57.5–58.5° at 11.5 mm., 74.5–75° at 19 mm.), n^{26}D 1.5177, $[\alpha]$D −0.02° (pure liquid), followed by 0.6 g., b.p. 81–83°, n^{26}D 1.5186; 0.67 g., b.p. 86–91° (bath 120–135°), n^{26}D 1.5162; and 1.35 g. of residue. The main portion, **allylcarbinyl isothiocyanate**, was analyzed.

Anal. Calcd. for C_5H_7NS: C, 53.06; H, 6.23. Found: C, 53.59; H, 6.21; CH_3-C, nil.

The infrared absorption spectrum of the pure liquid showed aliphatic C–H stretching and bending bands at 3.4, 6.9 and 6.95 μ, peaks at 3.25, 5.42 (weak), 6.1, 10.08 and 10.83 μ attributed to a vinyl group,[45] a very strong, broad band centered at 4.75 μ caused by the isothiocyanate group, and a strong, sharp band at 7.43 μ.[46] There was no maximum attributable to deformation of a methyl group, exhibited by the crotyl isothiocyanates and crotylamines and α-methylallylamine at 7.27–7.33 μ.

Allylcarbinylthiourea, prepared from the isothiocyanate and aqueous ammonia at room temperature (advantageously with addition of ethanol), crystallized from benzene as long needles, m.p. 66.5–67°.

Anal. Calcd. for $C_5H_{10}N_2S$: C, 46.12; H, 7.74. Found: C, 46.38; H, 7.50.

N-Allylcarbinyl-N′-phenylthiourea, prepared from the natural isothiocyanate and aniline at 100° or in boiling ben-

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[39] The reduction product of crotonaldoxime by lithium aluminum hydride[36] also seems a mixture of amines (n^{20}D 1.4113; *cf.* pure V,[36] n^{26}D 1.4290; *n*-butylamine, n^{20}D 1.4009 (A. I. Vogel, *J. Chem. Soc.*, 1825 (1948))).

[40] L. F. Hatch and V. Chiola, THIS JOURNAL, **73**, 360 (1951).

[41] L. Crombie, S. H. Harper, R. E. Stedman and D. Thompson, *J. Chem. Soc.*, 2445 (1951); M. S. Schechter and F. B. LaForge, U. S. Pat. 2,574,500 [*C. A.*, **46**, 5078 (1952)].

[42] H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

[43] Suggested by Dr. J. F. Brown, Jr. ADDED IN PROOF.—A. Kjaer and K. Rubinstein (*Acta Chem. Scand.*, **8**, 1335 (1954)) have described XIII and thioureas of X and a spontaneous rearrangement of X to VIII.

[44] A. Kjaer, J. Conti and I. Larsen, *Acta Chem. Scand.*, **7**, 1276 (1953).

[45] R. S. Rasmussen and R. R. Brattain, *J. Chem. Phys.*, **15**, 120 (1947); R. S. Rasmussen, R. R. Brattain and P. S. Zucco, *ibid.*, **15**, 135 (1947).

[46] All isothiocyanates investigated in this work possessed strong absorption maxima at 7.4–7.6 μ, of unknown origin. The isothiocyanate "symmetric" stretch, largely a carbon-sulfur vibration, can contribute to fundamental absorption only beyond 9 μ (J. Goubeau and O. Gott, *Ber.*, **73**, 127 (1940); C. Reid, *J. Chem. Phys.*, **18**, 1512 (1950); W. J. O. Thomas, *J. Chem. Soc.*, 2383 (1952)).

zene, crystallized from aqueous ethanol when seeded with a sample (m.p. 55.5–56.5°) obtained from Dr. J. D. Roberts and melted at 56–57°.

Synthesis of Allylcarbinyl Isothiocyanate.—Allylcarbinol, the starting material, was satisfactorily prepared from allylmagnesium chloride[47] and monomeric[48] formaldehyde. Birch and McAllan[49] had obtained only a 10% yield of allylcarbinol from the reaction of allyl chloride, trioxane and magnesium. The Grignard reagent, more dilute than originally specified, was prepared by the slow addition of 172 g. of allyl chloride in 600 cc. of anhydrous ether to 50 g. of magnesium in 2 l. of ether stirred with a glass paddle at 0° and was treated with the gaseous depolymerizate of 100 g. of paraformaldehyde. After an hour at room temperature, the mixture was poured into excess saturated aqueous ammonium chloride (600 cc.), treated with 20 cc. of concentrated ammonia to bind excess formaldehyde completely as hexamethylenetetramine and prevent acetal formation, and let stand overnight. The ether was decanted, dried and distilled and the residue fractionated to furnish 75.3 g. (51%) of allylcarbinol, b.p. 113.5°, $n^{27}\text{D}$ 1.4188.

The reaction of allylcarbinol and thionyl chloride according to Roberts and Mazur[25] furnished in 79% yield allylcarbinyl chloride, b.p. 73–75°, $n^{27}\text{D}$ 1.4195, which was converted[25] with potassium phthalimide and iodide and dimethylformamide in 72% yield to N-allylcarbinylphthalimide. A sample of the phthalimide twice crystallized from ethanol melted at 51.5–52.5° (lit.[25] 51–51.5°). Hydrazinolysis[25] afforded in 45% yield allylcarbinylamine, b.p. 76–77°, $n^{26}\text{D}$ 1.4184. Filtration of the phthalhydrazide could be greatly facilitated by digestion of the acidified reaction mixture two hours at 70°. The amine picrate, crystallized from chloroform–methanol, melted at 139.5–140.5° (lit.[26] 136.8–137.4°) and did not depress the melting point of a sample kindly provided by Dr. T. A. Geissman.

N-Allylcarbinyl-N′-phenylthiourea, prepared from the amine and phenyl isothiocyanate and crystallized from aqueous ethanol, melted at 56.5–57° and did not depress the melting point of a sample derived from rape seed.

Anal. Calcd. for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58; S, 15.54. Found: C, 63.89; H, 6.96; N, 13.31; S, 15.65.

A mixture of 10 cc. of water and 5 cc. of carbon disulfide in a sealable pressure bottle was cooled in ice–salt, and 5 g. of allylcarbinylamine was added slowly down the side of the vessel to avoid contact with the carbon disulfide. The closed bottle was shaken and chilled, and a solution of 4.75 g. of potassium hydroxide pellets in 5 cc. of water was added. After the carbon disulfide had again reacted, the dithiocarbamate solution was heated to 95° for 15 minutes, chilled, treated dropwise with 6.85 cc. of ethyl chlorocarbonate, and let stand an hour at room temperature. To decompose the carboethoxy allylcarbinyldithiocarbamate, which had separated as a heavy oil, the mixture was treated with a solution of 4 g. of potassium hydroxide in 5 cc. of water and agitated ten minutes, with care that the temperature did not rise above 50°. The carboethoxy compound dissolved as the salt and the isothiocyanate appeared as the upper layer, which was extracted by ether, dried and fractionated to furnish 5.96 g. (75%) of allylcarbinyl isothiocyanate, b.p. 77.5° at 28 mm., $n^{26.5}\text{D}$ 1.5182. The infrared spectra of the synthetic and natural products were identical.

Allylcarbinylthiourea prepared from the synthetic isothiocyanate melted at 67–67.5° and did not lower the melting point of a sample derived from nature.

Distillation of N-Allylcarbinyl-N′-phenylthiourea.—N-Allylcarbinyl-N′-phenylthiourea distilled unchanged (m.p. of condensate 57–58°) at 70° and 0.02 mm. At 1–5 mm. and 100–140° the product was an uncrystallizable oil with only a trace of solid. When a mixture of 40 mg. of N-allylcarbinyl-N′-phenylthiourea and 20 mg. of aniline hydrochloride was fused an hour at 100° and distilled at 135° and 4.5 mm., the condensate melted at 119–128° after two crystallizations from dilute ethanol. After three more crystallizations, the substance melted at 153–153.5° and did not depress the melting point of authentic N,N′-diphenylthiourea. Distillation of mixed thiourea and anilinium salt at 120° and 1 mm. gave the same result: the product after three recrystallizations melted at 127–132° and as estimated from the ultraviolet absorption spectrum ($\lambda_{\text{max.}}$ 269 mμ) contained 60% of thiocarbanilide. The ultraviolet absorption maximum of thiocarbanilide in ethanol lay at 272 mμ (log ε 4.32).

Thiourethane Formation.—O-Ethyl allylthiocarbamate[50] was prepared from allyl isothiocyanate and alcoholic sodium ethoxide and characterized by the ultraviolet absorption maximum in ethanol at 244 mμ (log ε 4.09). However, attempts to obtain O-bornyl allylthiocarbamate[51] from allyl isothiocyanate and sodium bornyloxide prepared with sodium in ethanol–xylene (the original method) or xylene or with sodamide did not succeed, nor did reactions of allyl isothiocyanate and borneol with potassium *t*-butoxide, or triethylamine in boiling chloroform, or of the mustard oil and borneol in a sealed tube at 100–150° afford the desired product. No solid save borneol was isolated and in the absence of ethanol no thiocarbamate was spectroscopically detected in yield of more than 10%.

Alkylphenylthioureas.—N-Ethyl-N′-phenylthiourea was found to melt at 102–103.5° (lit. 101–102°,[52] 107°[53]). **N-Isopropyl-N′-phenylthiourea** melted at 102–103° (lit.[53] 102°; no analysis).

Anal. Calcd. for $C_{10}H_{14}N_2S$: C, 61.81; H, 7.26. Found: C, 62.12; H, 7.21.

A mixture of the N-ethyl- and N-isopropyl-N′-phenylthioureas melted at 80–90°.

A solution of 0.4 g. of *t*-butyl isothiocyanate[54] and 0.4 g. of aniline in 10 cc. of petroleum ether was let stand three weeks at room temperature. The product, crystallized from aqueous ethanol and benzene–petroleum ether, was **N-*t*-butyl-N′-phenylthiourea**, m.p. 118.5–119.5°.

Anal. Calcd. for $C_{11}H_{16}N_2S$: C, 63.42; H, 7.74. Found: C, 63.52; H, 7.80.

A mixture of 1 g. of *t*-butylamine hydrochloride,[55] 1.4 cc. of triethylamine, 1.25 g. of phenyl isothiocyanate and 20 cc. of ethanol let stand two days at room temperature also furnished N-*t*-butyl-N′-phenylthiourea, m.p. 116–117.5°.

When *t*-butyl isothiocyanate and an equivalent of aniline in benzene solution were boiled under reflux during 24 hours, the product, crystallized from ethanol, was thiocarbanilide, m.p. 151–151.5°, undepressed on mixture with an authentic sample. When 0.1 g. of N-*t*-butyl-N′-phenylthiourea and 0.2 g. of aniline in 10 cc. of benzene were boiled six hours, 0.05 g. of thiocarbanilide, m.p. 151.5–152.5°, identified as before, was obtained. During another, 24 hour, reaction of N-*t*-butyl-N′-phenylthiourea and aniline in boiling benzene, the apparatus was swept with nitrogen and the effluent gas passed through a trap containing dilute hydrochloric acid. *t*-Butylamine was recovered from the acid by treatment with base and distillation with benzene and identified as N-*t*-butyl-N′-phenylthiourea, m.p. 118–119°.

When phenylthiourea (m.p. 155°, in mixture with thiocarbanilide 135–152°) or N-ethyl-N′-phenylthiourea were treated six hours with aniline in boiling benzene, the starting thiourea was recovered.

***trans*-Crotyl Isothiocyanate.**—*trans*-Crotyl alcohol[56] (b.p. 121°, $n^{27}\text{D}$ 1.4231) was converted by concentrated hydrochloric acid in 70% yield to a mixture of crotyl and α-methylallyl chlorides. The predominant crotyl chloride (b.p. 84–85°, $n^{30}\text{D}$ 1.4288) could be separated by fractionation in a center rod column, or isomerized to the more volatile α-methylallyl chloride (b.p. 63.5–64°, $n^{27}\text{D}$ 1.4104) by slow distillation through the column from a trace of cuprous chloride.[57] Use of ferric chloride[36,58] to catalyze the allylic equilibrium caused extensive polymerization. Reaction[25]

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of α-methylallyl chloride and potassium phthalimide furnished N-α-methylallylphthalimide, m.p. 86–86.5°, cleaved[25] to α-methylallylamine, b.p. 60–60.5°, n^{26}D 1.4093. The pure liquid had infrared absorption bands at 2.95, 3.00 and 6.28 μ of the amino group, 3.35 and 3.45 μ of C–H bonds, 3.22, 5.37, 6.12, 7.07, 10.12 and 10.98 μ of the vinyl group, 6.9 and 7.33 μ of the methyl group, and others at 7.63, 8.67, 9.1 and 11–12.5 μ.

N-*trans*-Crotylphthalimide,[10] prepared[25] from crotyl chloride and potassium phthalimide in 77% yield, melted at 78.5–79.5° after crystallization from dilute ethanol and in an oil mull had characteristic infrared absorption maxima beyond 10 μ at 10.23, 11.53, 11.03, 11.85, 12.6, 13.97 and 14.18 μ. A mixture with N-α-methylallylphthalimide melted at 53–55.5°. The crotylphthalimide was cleaved[25] in 55% yield to *trans*-crotylamine, b.p. 83–84°, n^{26}D 1.4263, which as the pure liquid had infrared absorption bands at 2.95, 3.00 and 6.30 μ of the amino group, 3.39 and 6.92 μ of C–H bonds and methylene groups, 7.27 μ of the methyl group, 10.38 μ of the *trans*-1,2-disubstituted double bond, and others at 8.97, 9.25, 9.65 and 11.3–12.2 μ. The double bond stretching absorption was not detectable, perhaps because the low polarity of the amino group renders the substance effectively centro-symmetric like *trans*-2-butene.[45] N-*trans*-Crotyl-N′-phenylthiourea crystallized from dilute ethanol as platelets, m.p. 109.5–110.5° (lit. 106°,[24] 106–107°,[36] 105.5°[10]), and in an oil mull had absorption maxima at 10.35 and at 9.25, 9.6, 10.57, 11.0, 11.3, 11.95, 12.42, 13.0, 13.65 and 14.53 μ.

trans-**Crotyl isothiocyanate**, b.p. 79.5° at 26 mm., n^{26}D 1.5236, was prepared from crotylamine (3.7 g.) in 59% yield by the method used for synthesis of allylcarbinyl isothiocyanate.

Anal. Calcd. for C_5H_7NS: C, 53.06; H, 6.23; N, 12.38. Found: C, 53.33; H, 6.35; N, 12.17.

The infrared absorption spectrum of the liquid had maxima at 3.43 and 7.0 μ of carbon–hydrogen, 4.85 μ of the isothiocyanate group, 6.0 and 10.45 μ of the double bond, 7.3 μ of the methyl group, and others at 7.52, 7.80, 8.93, 9.28, 11.27 and 12.95 μ.

trans-**Crotylthiourea**, prepared from the isothiocyanate and ammonia in aqueous ethanol at 0° during five days and crystallized from chloroform–petroleum ether, melted at 66–66.5° (lit. 65–66°,[18] 58–60°[10]).

Anal. Calcd. for $C_5H_{10}N_2S$: C, 46.12; H, 7.74. Found: C, 46.30; H, 7.68.

The infrared absorption spectrum of an oil mull had characteristic bands at 10.42 and 7.67, 8.15, 9.0, 9.47, 12.43 and 12.85 μ. A mixture of *trans*-crotylthiourea and allylcarbinylthiourea melted at 43–52°.

cis-**Crotylamine and Derivatives.**—1,3-Dichloro-2-butene,[59] b.p. 127.2–128°, n^{25}D 1.4689, purified by distillation, was hydrolyzed[40,41,49] by boiling 5% sodium carbonate in 75% yield to 3-chloro-2-buten-1-ol, n^{28}D 1.4613. Dehydrochlorination[40,41,49] of the alcohol with excess boiling 20% alcoholic potassium hydroxide during seven hours furnished in 80% yield 2-butynol, b.p. 140–143°, n^{27}D 1.4492. The 3,5-dinitrobenzoate of 2-butynol (lit.[40] m.p. 71, 103°; no analyses) could not be crystallized.

2-Butynyl *p*-nitrobenzoate, obtained from 2-butynol and *p*-nitrobenzoyl chloride in pyridine at room temperature and crystallized from 80% ethanol, melted at 81–81.5°.

Anal. Calcd. for $C_{11}H_9O_4N$: C, 60.27; H, 4.14. Found: C, 59.97; H, 4.18.

2-Butynyl phenylcarbamate, obtained from 2-butynol and phenyl isocyanate at 100° and crystallized from petroleum ether, melted at 69–69.5°.

Anal. Calcd. for $C_{11}H_{11}O_2N$: C, 69.82; H, 5.86. Found: C, 69.88; H, 6.06.

The preparation of 2-butynyl chloride from 2-butynol with phosphorus trichloride and pyridine[40,41] gave variable yields of at most 54%. The reactions of 2-butynol with concentrated hydrochloric acid or with triphenyl phosphite[60] and benzyl chloride, ethyl chloroacetate, hydrogen chloride or ethyl bromoacetate afforded only traces of the desired halides. The use of thionyl chloride in ether[61] proved superior. Ten grams of 2-butynol was added dropwise during an hour to a solution of 18 g. of thionyl chloride and ten drops of pyridine in 50 cc. of boiling ether. The mixture was heated under reflux five hours and distilled to furnish 10.3 g. (81%) of 2-butynyl chloride, b.p. 102–104°. 2-Butynol and 2-butynyl chloride had acetylenic infrared absorption maxima at 4.50 and 4.47 μ, respectively, and no detectable anomalous bands such as have been reported[62] for primary propargylic alcohols and bromides at 5.75–5.9 μ.

A mixture of 10 g. of 2-butynyl chloride, 23 g. of potassium phthalimide, a crystal of potassium iodide and 40 cc. of dimethylformamide was heated to the beginning of a gently exothermic reaction at approximately 115–120° and thereafter boiled under reflux 1.5 hours and poured on 100 g. of ice. The precipitated solid was dissolved in chloroform (some 200 cc.) and the solution was washed with 1 *N* potassium hydroxide, 0.5 *N* hydrochloric acid and water and evaporated to leave 18.8 g. (83%) of product. **N-2-Butynylphthalimide**, recrystallized from acetone, formed large, glistening needles, m.p. 217–218°.

Anal. Calcd. for $C_{12}H_9O_2N$: C, 72.35; H, 4.55; N, 7.03; mol. wt., 199.2. Found: C, 72.55; H, 4.72; N, 6.62; mol. wt. (Rast), 201, 175.

The infrared spectrum of an oil mull had a weak acetylenic band at 4.48 μ.

A suspension of 20 g. of N-2-butynylphthalimide (precipitated in finely divided form from benzene solution by rapid dilution with petroleum ether) in 1100 cc. of ethyl acetate was hydrogenated at atmospheric pressure in the presence of 1 g. of Lindlar[42] palladium–lead catalyst and 1 cc. of quinoline until the consumption of hydrogen ceased after 3.5 hours at 1.03 molar equivalents. The solution was filtered with Celite and evaporated *in vacuo*, and the residue was crystallized from 50% ethanol to furnish 19.3 g. (96%) of fine needles of **N-*cis*-crotylphthalimide**, m.p. 66–66.5°.

Anal. Calcd. for $C_{12}H_{11}O_2N$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.82; H, 5.48; N, 7.13.

The infrared absorption spectrum of an oil mull had characteristic maxima beyond 10 μ at 10.65, 11.9, 12.57, 13.77, 14.08 and 14.42 μ. Mixtures of the *cis*- and *trans*-crotylphthalimides and of the *cis*-crotyl and allylcarbinyl compounds melted at 47–73° and 41–49°, respectively.

When N-*cis*-crotylphthalimide was hydrogenated in methanol over Adams platinum, the product after crystallization from aqueous ethanol was N-*n*-butylphthalimide, m.p. 32–33° (lit.[63] 34°, 36.5°), identified with an authentic sample.

When N-*cis*-crotylphthalimide was fused at 150–200° with a trace of iodine under an ultraviolet lamp during two hours or an ethanol solution of N-*trans*-crotylphthalimide was exposed three days to sunlight in a Pyrex flask, the respective starting materials were recovered without interconversion. However, when 0.1 g. of N-*cis*-crotylphthalimide was treated with a few cc. of gaseous nitrogen dioxide and fused two hours at 150°, the product after crystallization from aqueous ethanol melted at 70–75°, mixed with N-*trans*-crotylphthalimide at 76–77.5°, and as evidenced by the infrared spectrum between 10 and 15 μ was entirely the *trans*-isomer.

Hydrazinolysis of N-*cis*-crotylphthalimide furnished in 67% yield ***cis*-crotylamine**, b.p. 85–87°, n^{28}D 1.4295, d^{29} 0.793 g./cc.

Anal. Calcd. for C_4H_9N: C, 67.55; H, 12.76; N, 19.70. Found: C, 67.33; H, 12.71; N, 19.72.

The ethereal fore-run afforded the amine as the phenylthiourea equivalent to an additional 14% yield. The liquid amine had infrared absorption maxima at 2.95, 3.02, and 6.28 μ of the amino group, 3.43 and 6.9 μ of carbon–hydrogen, 6.15 μ of the double bond, 7.28 μ of the methyl group, and others at 7.45, 7.6, 8.98, 9.48, 10.15, 11.3–12.3 and 14.3 (broad) μ.

cis-**Crotylamine picrate**, crystallized from 85% ethanol, melted at 131.5–132.5°.

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(59) Generously donated by courtesy of the Organic Chemicals Department, E. I. du Pont de Nemours and Co., through Mr. J. C. Weyrich, Development Superintendent, Louisville, Ky.

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Anal. Calcd. for $C_{10}H_{12}O_7N_4$: C, 40.00; H, 4.03; N, 18.66. Found: C, 40.17; H, 4.05; N, 18.62.

N-*cis*-Crotyl-N'-phenylurea, prepared from the amine and phenyl isocyanate and crystallized from 40% ethanol, melted at 112–112.5°.

Anal. Calcd. for $C_{11}H_{14}ON_2$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.54; H, 7.69; N, 14.91.

N-*cis*-Crotyl-N'-phenylthiourea, prepared from the pure amine and crystallized as silky plates from 70% ethanol, melted at 85.5–86°.

Anal. Calcd. for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58. Found: C, 63.81; H, 6.80; N, 13.60.

The absorption spectrum of an oil mull had characteristic bands at 9.4, 10.53, 11.3, 11.93, 12.43, 13.45, 14.18 and 14.58 μ.

***cis*-Crotyl isothiocyanate**, b.p. 83° at 30 mm., $n^{27.5}_{D}$ 1.5265, was obtained from the amine (5 g.) in 70% yield.

Anal. Calcd. for C_4H_7NS: C, 53.06; H, 6.23; N, 12.38. Found: C, 53.49; H, 6.36; N, 12.58.

The infrared absorption spectrum of the liquid had maxima at 3.43 and 7.0 μ of carbon–hydrogen, 4.75 μ of the isothiocyanate group, 6.05 μ of the double bond, 7.3 μ of the methyl group, and others at 7.58, 7.97, 8.97, 9.3, 10.47, 11.25 and 13.4 (broad) μ.

cis-Crotyl isothiocyanate was allowed to react with aqueous-alcoholic ammonia at 0° during three days. The crude product, m.p. 71.5–75°, was crystallized repeatedly from benzene to give *cis*-**crotylthiourea**, m.p. 88–89°.

Anal. Calcd. for $C_5H_{10}N_2S$: C, 46.12; H, 7.74; N, 21.52; S, 24.63. Found: C, 46.13; H, 7.70; N, 20.95; S, 24.84.

In an oil mull the substance absorbed at 7.65, 8.03, 8.15, 8.92, 9.85 and 13.0 μ. On chromatography on paper in water-saturated chloroform,[64] *cis*-crotylthiourea migrated at a rate 0.94 of that of the *trans*-isomer, corresponding to a R_{Ph} of 0.73.

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HOUSTON, TEXAS

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY OF MICHIGAN STATE COLLEGE]

Carbonyl Derivatives of Thiophene. I. The Reformatsky Reaction with α-Bromoesters

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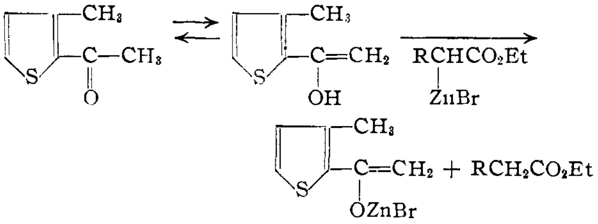
The Reformatsky reaction between 2- and 3-thienyl aldehydes, and the 2- and 3-thienyl alkyl ketones with α-bromoesters was carried out in an effort to correlate yields with steric factors, reaction solvents and inductive effects.

The Reformatsky reaction[2] involves the interaction of a carbonyl compound with an active organic halogen compound in the presence of zinc under anhydrous conditions, followed by hydrolysis with dilute acid to yield a hydroxy compound. Previous studies of the Reformatsky reaction with carbonyl derivatives of thiophene[3–5] have been restricted to the two substituted isomers. Moreover, only the aldehyde and methyl ketone were investigated. It was the purpose of the work described here to investigate more fully the Reformatsky reaction of 2-thienyl aldehyde, the 2-thienyl methyl, ethyl and *n*-propyl ketones as well as 3-thenal and 3-acetylthiophene with the ethyl esters of bromoacetic, α-bromopropionic and α-bromoisobutyric acids in an effort to determine possible correlations between yields, steric factors, solvent effects and inductive effects.

The reactions were carried out using the reactants in equimolar quantities under anhydrous conditions. The solvent employed was benzene since no reaction was found to have occurred in ethyl ether and excessive decomposition took place in toluene. The use of a benzene–toluene mixture gave no improvement in yields. With ethyl bromoacetate and ethyl α-bromopropionate yields ranging from 54–68% were obtained except in the instances where 2-acetyl-3-methylthiophene served as the carbonyl component. The low yields, 20–25%, with this reagent presumably are due to the blocking effect of the 3-methyl group which is analogous to the observation made by Newman[6] for acetylmesitylene. Approximately half of the 2-acetyl-3-methylthiophene was recovered from the reaction mixture and its recovery may be ascribed to enolization of the ketone by the organometallic intermediate.



On hydrolysis of the reaction mixture the ketone is regenerated. The amount of enolization has been found to be a function of the type of solvent, the halogen derivative employed and the steric blocking, of groups, in the ketone.[7,8] Usually the enolization reaction proceeds at a slower rate than the normal reaction except in those cases where steric factors hinder the formation of the normal product. As a measure of the amount of enolization, the percentages of recovered ketones are listed in Tables I and II. The interaction of 2-thenal and 3-thenal with the highly branched ethyl α-bromoisobutyrate resulted in yields of 64 and 63%, respectively, of the expected products. However, the use of the same bromoester with 2- and 3-acetylthiophene gave yields of only 15 and

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[1] Abstracted, in part, from the thesis submitted by Wm. H. Houff in partial fulfillment of the requirements for the degree Doctor of Philosophy at Michigan State College.

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