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A SYNTHESIS OF 3-ISOTHIAZOLONES

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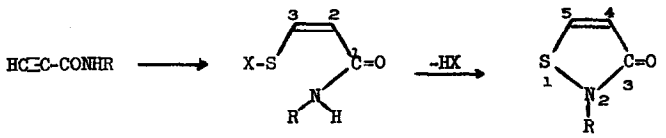
For aid in the identification of products resulting from the rearrangement of 1,4-thiazepine derivatives (1) we sought a general method for the synthesis of 3-isothiazolones (III). We were guided by the very recent developments in the chemistry of isothiazoles (2). A model (I→II→III) for ring closure was suggested by the nucleophilic displacement by amide nitrogen on a sulfenyl halide intermediate (1) and by the method of isothiazole synthesis of Wille, Capeller and Steiner (2g), in which the ring system was approached through an acetylenic carbonyl compound. The necessary N-sub-



I II III

stituted propiolamides were prepared by reaction of methyl propiolate with the appropriate amine at -30 to -60° and reaction times of 5-20 minutes, leading to propiolamide (93%), N-methylpropiolamide (76%, m.p. 90-91°) and N-ethylpropiolamide (72%, b.p. 76-77°/0.8 mm.) (3).

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The addition of thiosulfate was examined initially, but the Bunte salts (II, X = $SO_3^- M^+$, R=H) were not obtained crystalline, thus leading to problems in assessing the stereochemistry of addition and the subsequent course of cyclization. Treatment of the Bunte salt with iodine resulted in conversion to 3-isothiazolone, m.p. 74-75° (64%), and similar conversion could be effected by warming with 1N acid under a stream of nitrogen, with evolution of sulfur dioxide (50%). An improvement in the process was realized through the addition of thiocyanate to the propiolamides, since crystalline products could be isolated. In the case of propiolamide itself, acid-catalyzed addition led to a mixture (87% yield) of cis (II, X=CN, R=H) and trans isomers in a ratio of 4:1, separable by employing aqueous dimethyl sulfoxide as a solvent. In the cases of the N-methyl and N-ethylpropiolamides only the cis isomers were isolated; examination of the mother liquors showed the presence of isothiazolones and unreacted propiolamides but not the trans-3-thiocyanoacrylamides.

The structure of cis-3-thiocyanoacrylamide (II, X=CN, R=H), m.p. 153-154°, was established by analysis and spectral considerations, including infrared absorption indicative of cis hydrogens attached to a double bond (4) and a coupling constant of 9.0 c.p.s. (5) for the 2- and 3-hydrogens in the nuclear magnetic resonance spectrum. The n.m.r. τ-values (in DMSO) were assignable as 2.22 and 2.55 (NH_2), 2.79 (doublet) (3-H) and 3.59 p.p.m. (doublet) (2-H) based on exchange of the N-H protons by deuterium and synthesis of the 2-deuteriated isomer by addition of DSCN to propiolamide (leaves only a singlet at 2.69 for the 3-proton). The trans-3-thiocyanoacrylamide, m.p. 193-194°, showed infrared absorption indicative of trans hydrogens attached to a double bond (6) and, in the n.m.r. spectrum, a coupling constant of 14.5 c.p.s. (5) for these two hydrogens (τ values: 2.71 (3-H) and 3.51 (2-H), while the N-protons were observed at 2.25 and

2.75 p.p.m. The structures of cis-N-methyl-3-thiocyanoacrylamide, m.p. 129-130° (58% yield), and cis-N-ethyl-3-thiocyanoacrylamide, m.p. 144-145° (37% yield), could then be established by infrared and n.m.r. spectral comparison with cis-3-thiocyanoacrylamide.

The three cis isomers here described (II, X=CN, R=H, CH_3, C_2H_5), all of which had an odor of hydrogen cyanide, evolved this gas readily on boiling 1-5 min. in dilute acid and were converted cleanly to 3-isothiazolone, C_3H_3NSO, m.p. 74-75° (63% yield), 2-methyl-3-isothiazolone, C_4H_5NSO, m.p. 50-51° (80%), and 2-ethyl-3-isothiazolone, C_5H_7NSO, m.p. 61-62° (88%) (III, R=H, CH_3, C_2H_5, respectively). By contrast, trans-3-thiocyanoacrylamide was recovered unchanged from hot dilute acid; in fact, the trans isomer could be freed conveniently from the cis isomer by this method. The favored formation of cis products (II) from thiocyanate addition and the favored closure of the 3-isothiazolones (III) from the cis acrylamides indicate processes of stereochemical specificity and interest. The 3-isothiazolones were characterized by ultraviolet, infrared and n.m.r. spectra; the values obtained for 2-methyl-3-isothiazolone may be regarded as representative (cf. 2j): λ_{max} 272 mμ (ε 7250); $\nu_{max}^{CCl_4}$ 2920, 2860, 1660 (CO), 1629, 1512, 1320, 1280, 1120, 1082, 920, 710, 668, 655 cm.$^{-1}$; n.m.r. τ-values ($CDCl_3$): 6.63 (N-CH_3), 1.71 (doublet) (5-H), 3.72 p.p.m. (doublet) (4-H) (assignment checked by DSCN addition to propiolamide and conversion of the intermediate to 3-isothiazolone), $J_{4,5}$ = 6.5 c.p.s.

This facile synthesis of 3-isothiazolones from cis-3-thiocyanoacrylamides and the similarity in certain spectral properties of these two classes of compounds suggested to us that reversal of the ring closure might also be accomplished readily. We were gratified to find that the ring opening of 3-isothiazolone, for example, proceeded smoothly and instantaneously at room temperature when treated with cyanide to regenerate cis-3-thiocyano-

acrylamide (III→II). Investigation of ring opening of 3-isothiazolones with other nucleophiles is in progress, and many interconversions in the series II⇄III are now predictable.

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(3) Satisfactory C, H and N analyses were obtained on all compounds reported.

(4) Additional data for cis-3-thiocyanoacrylamide: $\nu_{max}^{CCl_4}$ 3387, 3155 (NH); 2163 (SCN); 1687 (CO); 1636, 778, 799 (C=C); 1596 (N-deuteriation does not shift this band); 1424; 1310 cm.$^{-1}$

(5) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p. 85.

(6) Additional data for trans-3-thiocyanoacrylamide: $\nu_{max}^{CCl_4}$ 3410, 3175 (NH); 2162 (SCN); 1712, 1677 (CO); 1630, 1645, 940 (C=C); 1598 cm.$^{-1}$ (N-deuteriation does not shift this band).