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REARRANGEMENT OF A 1,4-THIAZEPINE RING AND FORMATION OF 3-ISOTHIAZOLONES

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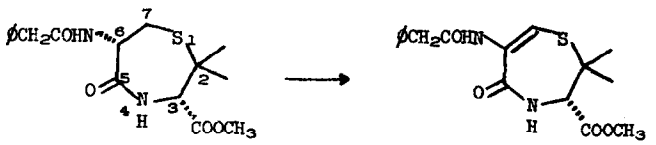
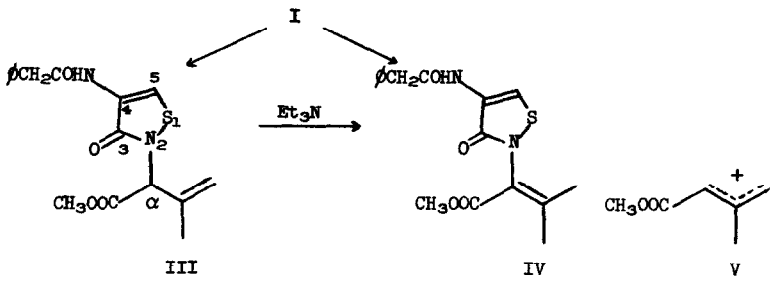
In the normal case, chlorination of an alkyl sulfide leads to the formation of an α-chlorosulfide or the related vinyl sulfide (1). We have reported in the preceeding Communication (2) an example of an oxidative transformation of the perhydro-1,4-thiazepine I to the tetrahydrothiazepine II via chlorination-dehydrochlorination. We are also able to describe an



I II

unexpected rearrangement of the thiazepine ring to the 3-isothiazolone system under these chlorination conditions, constituting an example of a new general oxidative synthesis of 3-isothiazolones (3).

Chlorination of 3D-carbomethoxy-2,2-dimethyl-5-oxo-6D-phenylacetamido-perhydro-1,4-thiazepine (I) at -60°, followed by heating to 60°, afforded by chromatographic separation, in addition to II, the isomeric 3-isothiazolones III and IV, the former optically active, the latter optically inactive. The interrelation of III and IV was established chemically, for III was isomerized to IV by the action of triethylamine. A prominent peak



III IV V

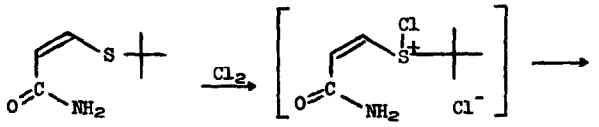
(52% of the base peak) at m/e 113 in the mass spectrum of III was accounted for as the ion V derived by cleavage of the allylic C-N bond. The peak at this mass in the spectrum of IV was at the level of the background.

In addition to the fragmentations observed in the mass spectrum, the infrared, ultraviolet and n.m.r. spectral characteristics were consistent with assigned structure III, methyl α-isopropenyl-4-phenylacetamido-3-isothiazolone-2-acetate(4), m.p. 150-152°, $[\alpha]_D^{25}$ -40.6° (9% in $CHCl_3$): ν_{max}^{KBr} 3365 (amide NH), 1739 (ester C=O), 1680, 1625, 1580, 1520 and 1490 $cm.^{-1}$; λ_{max}^{EtOH} 296.5 (ε 10,800), 222.5 mμ (sh) (ε 10,200). Anal. Calcd. for $C_{17}H_{18}N_2O_4S$: C, 58.94; H, 5.24; N, 8.09; mol. wt., 346.40. Found: C, 59.03; H, 5.38; N, 8.11; mol. wt., 346 (mass spectrum, molecular ion). The n.m.r. spectrum showed a singlet peak for methyl at τ-value 8.22, broadened by the vinylic protons (6), which occurred at 4.77 and 4.95 p.p.m. The tertiary proton of the side chain appeared at 4.40. The remaining assignments were as follows: 1.40 (isothiazolone ring proton, 6.34 (CH_3OOC-), 6.27 ($C_6H_5CH_2$-), and 2.67 ($C_6H_5CH_2$-).

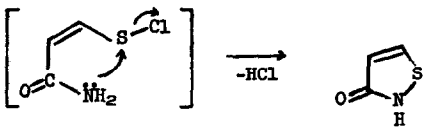
The isomeric product IV, methyl α-isopropylidene-4-phenylacetamido-3-isothiazolone-2-acetate, m.p. 232-233°, $[\alpha]_D^{25}$ < 2°, not measurable on the Bendix Spectropolarimeter, had distinctive spectral characteristics: ν_{max}^{KBr} 3270 (amide NH), 1710 (conj. ester C=O), 1680, 1619, 1572, 1525 and

1489 cm.$^{-1}$; λ_{max}^{EtOH} 295.5 (ε 10,000), 307 mμ (sh) (ε 7,900). Anal. Found: C, 58.90; H, 5.31; N, 8.23; mol. wt., 346 (mass spectrum, molecular ion). The n.m.r. spectrum consisted entirely of uncoupled, sharp singlets: τ-values 6.24 (CH_3OOC-), 7.82 and 8.19 ((CH_3)$_2$C=), 1.30 (isothiazolone ring proton), 6.37 ($C_6H_5CH_2$-), 2.68 ($C_6H_5CH_2$-), and 1.02 p.p.m. (amide proton, exchangeable with D_2O).

A probable intermediate in the reaction sequence I → III and IV is a vinylsulfenyl chloride derived from II. In substantiation of this hypothesis, treatment of II with chlorine afforded III in greater than 90% yield as determined by n.m.r. and in 45% yield as isolated, crystalline compound. In this case, the acidic character of the reaction mixture and the work-up procedure suppressed the isomerization to IV. In order to test the reaction sequence with a simple model which would also serve as a probe for the generality of the synthesis of 3-isothiazolones, cis-(2-t-butylthio)-acrylamide (VI), m.p. 159-160.5° (7), was converted by chlorine to 3-iso-



VI



VII

thiazolone (VII), m.p. 73-74° (8), which was identical with a sample prepared by Crow and Leonard (3b). The conversions described above follow a common pathway illustrated by VI → VII. The fragmentation of chlorosul-

fonium chlorides is known (9), but our synthesis represents a special case in which the sulfenyl chloride undergoes ready internal nucleophilic attack, with ring closure to 3-isothiazolones.

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(3) The 3-isothiazolone system has been formed under oxidative conditions (a) J. Goerdler and W. Mittler, Chem. Ber., 96, 944 (1963), and by a non-oxidative route (b) W.D. Crow and N.J. Leonard, Tetrahedron Letters, 23, 1477 (1964).

(4) The reaction of I, probably racemic, with N-chlorosuccinimide has been reported to yield II (rac.) (5). In our hands the published procedure provided III from the 3D-6D precursor and proved to be the easiest method for its preparation.

(5) I. L. Knunyants, O.V. Kil'disheva, M.P. Krasuskaya, M.G. Lin'kova, V. V. Shokina, Z.V. Benevolenskaya and L.P. Rasteikene, Bull. Acad. Sci., U.S.S.R., Div. Chem. Sci., 1702 (1959).

(6) Broadening of methyl peaks in similar structures is usually attributable to the cis proton, e.g., see Varian Spectra Catalog, vol. 1 and vol. 2.

(7) Additional data: $\nu_{max}^{CHCl_3}$ 3500, 3465, 3390, 3315, 3150, 1664, 1570 cm.$^{-1}$; λ_{max}^{EtOH} 215 (ϵ 2060), 282 mμ (13,000); n.m.r. signals at τ-values 2.92 (doublet) and 4.10 (doublet, J = 10.5 c.p.s.), and 8.61 p.p.m. Anal. Calcd. for $C_7H_{13}NOS$: C, 52.79; H, 8.23; N, 8.80. Found: C, 52.84; H, 8.26; N, 8.86.

(8) Additional data: $\nu_{max}^{CCl_4}$ 3090, 3030, 2980, 2800, 2690, 2630, 2540, 1659, 1639, 1573 and 1546 cm.$^{-1}$; λ_{max}^{EtOH} 257 (ϵ 6400), 280 mμ (sh) (ϵ 1360); n.m.r. signals at τ-values -1.90, 1.56 (doublet) and 3.42 p.p.m. (doublet, J= 5.0 c.p.s.).

(9) For lead references, see (a) D.S. Tarbell and D.P. Harnish, Chem. Revs., 49, 1 (1951); (b) K.C. Schreiber and V.P. Fernandez, J. Org. Chem., 26, 2478 (1961).