

## The Reaction of Tetrahydro-2H-1,3-oxazine-2-thione and Methyl Iodide

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The alkylation of tetrahydro-2H-1,3-oxazine-2-thione (I) has been reported by McKay and Kreling (1), and the product was formulated as the hydroiodide of 2-methylthio-5,6-dihydro-4H-1,3-oxazine (II). However, these workers were unable to use this product satisfactorily as an intermediate in reactions with benzylamine and other amines; the reactivity of this methylthiodihydrooxazine in such processes was considered to be low.

We wished to prepare a quantity of 2-methylthio-5,6-dihydro-4H-1,3-oxazine (II) as an intermediate, and since we had found previously (2,3) that 2-oxazolidinethiones could be alkylated effectively with alkyl halides in the presence of sodium ethylate, we employed these conditions for the methylation of tetrahydro-2H-1,3-oxazine-2-thione (I). When I was refluxed with methyl iodide and an equivalent of sodium ethylate, the spectroscopic properties of the base obtained confirmed its identity as the desired methylthiodihydrooxazine II. This compound reacted smoothly with benzylamine to afford 2-benzylamino-5,6-dihydro-4H-1,3-oxazine (III).

The reaction of tetrahydro-2H-1,3-oxazine-2-thione and methyl iodide without sodium ethylate gave, after purification, a product (m.p. 62.5-64°) with properties similar to those reported by McKay and Kreling for the compound considered to be the hydroiodide of II. However, this compound, which was insoluble in water (4), failed to give a picrate, and its infrared spectrum did not show the strong C-O-C absorption. The cleavage of 2-oxazolidinethione (V) to methyl N-(2-iodoethyl)thiocarbamate (VI) on extended refluxing with methyl iodide has been reported by Mukaiyama, *et al.* (5), and the properties of the com-

pound obtained here from thione I indicate that an analogous cleavage has taken place. The compound with melting point 62.5-64° was indeed obtained on treatment of I with methyl iodide under the conditions of Mukaiyama, *et al.* Its n.m.r. spectrum confirmed its identity as methyl N-(3-iodopropyl)thiocarbamate (IV).

Thus whereas tetrahydro-2H-1,3-oxazine-2-thione can be alkylated satisfactorily with methyl iodide when sodium ethylate is present, ring opening occurs when the hydrogen iodide formed is not neutralized. It seems likely that the unsatisfactory behavior of the intermediate of McKay and Kreling was due to the presence, at least to a considerable extent, of the cleavage product IV, which is a formula isomer of the hydroiodide of II. It appears that 2-methylthio-5,6-dihydro-4H-1,3-oxazine (II), similarly to the corresponding methylthiodihydrothiazine (6,7) and other methylthio heterocycles, will react readily with amines.

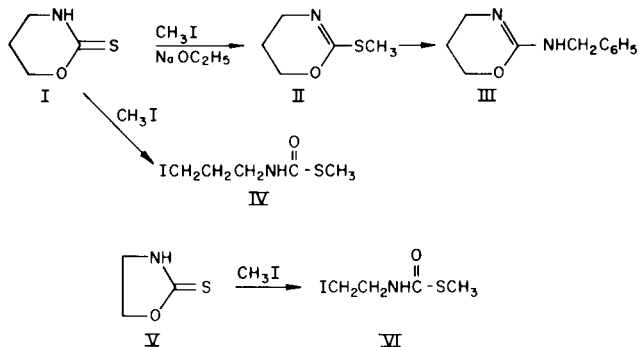
It is interesting to note that methylation of 4,4-dimethyl-2-oxazolidinethione by methyl iodide without sodium ethylate has given an intermediate that reacted satisfactorily with benzylamine (8). Though the conditions used in the methylation in this case were somewhat milder, this may reflect stabilization by 4,4-dimethyl substitution. The stabilizing effect of 4,4-dimethyl substituents on the oxazolidine ring has recently been observed (9), and it has been found that the 4,4-dimethyl derivative of 2-(2-mercaptoethylamino)-2-oxazoline did not undergo a rearrangement involving ring opening that was encountered in other instances (3,10).

## EXPERIMENTAL

Melting points were taken in capillary tubes in a Hershberg apparatus. The n.m.r. spectra were determined in deuteriochloroform solution at 60 Mc with a Varian A-60 spectrometer; chemical shifts are reported in p.p.m. relative to tetramethylsilane as an internal standard. Plates of silica gel G were used for thin layer chromatography, and the spots were visualized with iodine vapor.

## 2-Methylthio-5,6-dihydro-4H-1,3-oxazine (II).

To a solution prepared from 1.02 g. (0.0445 g.-atom) of sodium and 175 ml. of absolute ethanol was added 5.23 g. (0.0445 mole) of tetrahydro-2H-1,3-oxazine-2-thione (1,11) and a solution of 6.5 g. (0.046 mole) of methyl iodide in 35 ml. of absolute



ethanol. After the solution had been allowed to stand at room temperature for 45 minutes, it was refluxed for 50 minutes. The solvent was removed under reduced pressure, and the concentrate was extracted several times with ether. After removal of the ether from the filtered extracts, distillation yielded 4.15 g. (71%) of colorless liquid, b.p. 76-77° (8 mm);  $\lambda$  max (chloroform) 6.05 (N=C-S), 8.8  $\mu$  (C-O-C). The n.m.r. spectrum showed a triplet at  $\delta$  4.25 (CH<sub>2</sub>N), a triplet at 3.45 (CH<sub>2</sub>S), a quintuplet at 1.95 (C-CH<sub>2</sub>-C), and a singlet at 2.25 (SCH<sub>3</sub>).

*Anal.* Calcd. for C<sub>5</sub>H<sub>9</sub>NOS: C, 45.77; H, 6.92; N, 10.68. Found: C, 45.75; H, 6.93; N, 10.62.

The picrate, prepared in ethanol, crystallized from ethyl acetate as yellow prisms, m.p. 108-110°.

*Anal.* Calcd. for C<sub>11</sub>H<sub>12</sub>N<sub>4</sub>O<sub>8</sub>S: C, 36.67; H, 3.36; N, 15.55. Found: C, 36.61; H, 3.39; N, 15.58.

#### 2-Benzylamino-5,6-dihydro-4H-1,3-oxazine (III).

A solution of 0.59 g. (4.5 mmoles) of II and 0.49 g. (4.6 mmoles) of benzylamine in 20 ml. of methanol was refluxed for 7.5 hours. Thin layer chromatography (ethanol-29% ammonium hydroxide, 25:1) indicated that little starting material remained. The solvent was removed under reduced pressure, and the concentrate was treated with excess picric acid in ethanol. Filtration afforded 1.30 g. (69%) of picrate, m.p. 164-168°. Crystallization from ethanol gave 1.07 g. (57%) of yellow needles, m.p. 175-177°, and the analytical sample melted at 176-177.5°.

*Anal.* Calcd. for C<sub>17</sub>H<sub>17</sub>N<sub>5</sub>O<sub>8</sub>: C, 48.69; H, 4.09; N, 16.70. Found: C, 48.56; H, 3.94; N, 16.85.

The picrate (1.07 g.) was shaken in a separatory funnel with chloroform and 1N sodium hydroxide. The chloroform layer was shaken with several additional portions of 1N sodium hydroxide until it was colorless, and it was then washed with water, dried over anhydrous sodium sulfate, and concentrated to a crystalline solid; 0.461 g. (95% yield from picrate), m.p. 60-63°. On recrystallization from hexane 0.415 g. of colorless plates, m.p. 61.5-63.5°, was obtained. The analytical sample melted at 62.5-64.5°.

*Anal.* Calcd. for C<sub>11</sub>H<sub>14</sub>N<sub>2</sub>O: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.47; H, 7.33; N, 14.70.

The melting points reported for this base, prepared by the cyclization of 1-benzyl-3-(3-chloropropyl)urea, and its picrate are 64° and 178° respectively (12).

#### Methyl N-(3-Iodopropyl)thiolcarbamate (IV).

A solution of 0.300 g. (2.56 mmoles) of tetrahydro-2H-1,3-oxazine-2-thione (I) and 0.73 g. (5.1 mmoles) of methyl iodide in 10 ml. of tetrahydrofuran was refluxed for 20 hours. The solvent was removed, and the concentrate was extracted with three portions (15, 10, 10 ml.) of boiling hexane. The crystalline precipitate from the extracts amounted to 0.525 g. (79%), m.p. 59-62°. Recrystallization from hexane afforded 0.441 g. of glistening colorless plates, m.p. 62.5-64°;  $\lambda$  max (chloroform) 5.95  $\mu$  (COSCH<sub>3</sub>). The n.m.r. spectrum showed a broad band at  $\delta$  5.5-5.9 (NH), a quartet at 3.40 (CH<sub>2</sub>N), a triplet at 3.20 (CH<sub>2</sub>I) (13), a quintuplet at 2.05 (C-CH<sub>2</sub>-C), and a singlet at 2.33 (SCH<sub>3</sub>).

*Anal.* Calcd. for C<sub>5</sub>H<sub>10</sub>INOS: C, 23.17; H, 3.89; N, 5.41; I, 48.98. Found: C, 22.94; H, 3.79; N, 5.18; I, 48.45.

#### Reaction of Tetrahydro-2H-1,3-oxazine-2-thione (I) and Methyl Iodide without Sodium Ethylate.

To a mixture of 0.640 g. (5.46 mmoles) of I and 25 ml. of absolute ethanol was added 1.0 g. (7.0 mmoles) of methyl iodide. After 50 minutes of refluxing, the solvent was removed from the solution. The concentrate dissolved almost completely in 10 ml. of methanol, and 30 ml. of water was added to the filtered methanolic solution. The colorless solid (0.958 g.) that precipitated melted largely from 58 to 64°. It was extracted with three 25-ml. portions of hexane, and concentration of the extracts yielded 0.690 g. (49%) of crystalline solid, m.p. 61-63°, which gave a single spot on thin layer chromatography (chloroform). Recrystallization from hexane gave 0.573 g. of colorless glistening plates, m.p. 62.5-64°. This product was identical to the N-(3-iodopropyl)thiolcarbamate obtained above. The infrared spectrum in mineral oil showed the bands reported by McKay and Kreling (1); these are readily accommodated by the NH and COSCH<sub>3</sub> groups of the thiolcarbamate.

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