100 °K are comparable to those of  $\alpha$ -MnSe and  $\alpha$ -MnS. The remarkably large Weiss constants obtained for  $\beta$ - and  $\gamma$ -MnS which one might have attributed to the effect of a tetrahedral environment as compared to an octahedral environment are not duplicated in  $\beta$ -MnSe.

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# The Synthesis of 1-Benzyl-2-carbomethoxy-3,3-dimethyl Aziridine and its Ring Opening with Excess Acids

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The synthesis of 1-benzyl-2-carbomethoxy-3,3-dimethyl aziridine and its ring opening with various excess acids such as hydrogen chloride, acetic, propionic, and thioacetic acids and benzyl mercaptan are herein described.

La synthèse du benzyl-1 méthoxycarbonyl-2 diméthyl-3,3 aziridine et de ses ouvertures, par différents acides en excès tels que: le chlorure d'hydrogène, les acides acétique, propionique, et thiolacétique, et par le benzyl mercaptan, est décrite.

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In our attempt to synthesize penicillamine via the aziridine route (1), the preparation and reactions of 1-benzyl-2-carbomethoxy-3,3-dimethylaziridine (2) were undertaken. Due to the failure, in our case, of the synthesis of such a highly substituted aziridine by the methods of Cromwell and Huisgen (2, 3), the use of triphenylphosphine dibromide (4) on methyl *N*-benzyl- $\beta$ -hydroxyvalinate (1) was attempted and permitted the formation of aziridine (2), b.p. 95–100°/0.05 mm, yield 76%.

Reaction of aziridine (2) with anhydrous hydrogen chloride in benzene at  $25 \,^{\circ}$ C gave a white solid identified as methyl 3-benzylamino-2-chloro-3-methylbutyrate hydrochloride (3).

m.p.  $174-175^{\circ}$ ; yield 87%. Structure 3 was differentiated, from its possible 2-benzylamino-3-chloro-isomer, by the fact that its mass spectrum showed a large fragment at m/e 148



When aziridine 2 was heated at reflux in benzene with acetic acid, the product obtained was methyl 2-(*N*-benzylacetamido)-3-methylcrotonate (4*a*); b.p. 133–136°/0.15 mm; yield 41%. The n.m.r. of product 4*a* showed a marked non-equivalence between the two methyls on the double bond which appeared as two singlets at  $\tau$  (CCl<sub>4</sub>) 8.60 and 7.90. To distinguish the



two methyl groups from the acetamido group at  $\tau$  (CCl<sub>4</sub>) 8.20, the methyl 2-(*N*-benzylpropionamido)-3-methylcrotonate (4b) was prepared. Product 4b showed an almost identical spectrum, except that the singlet of the acetamido group was replaced by a triplet and a quadruplet at  $\tau$  (CCl<sub>4</sub>) 8.97 and 8.00 (Scheme 1).

In the case of reaction of aziridine (2) with thioacetic acid in benzene at 25 °C, at least four products could be obtained depending upon the concentration of thioacetic acid used.

At low concentration of thioacetic acid, two products were obtained: (i) methyl 3-methyl-2thioacetoxycrotonate (5), b.p.  $65-70^{\circ}/0.05$  mm, yield (23%), and *(ii)* methyl 3-(*N*-benzylacetamido)-3-methyl-2-thiobutyrate (**6**), yield (54\%), whose mass spectrum showed a high peak at m/e 190



Product 6 which is unstable was further proved by acetylation with acetyl chloride to give a white solid identified as methyl 3-(N-benzylacetamido)-3-methyl-2-thioacetoxybutyrate (7), m.p. $<math>118-119^\circ$ , yield (56%).

Use of higher concentration of thioacetic





NOTES

SCHEME 2

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acid with aziridine 2 gave, beside product 5 and 7, an orange solid suspected to be 3-benzyl-5-methoxycarbonyl-4,4-dimethyl-2-(2'-thioxopropylidene)thiazolidine (8), m.p. 175–176°, yield (12%).

Finally, when aziridine 2 was heated at reflux in toluene with benzylmercaptan, a breakdown of aziridine 2 occurred and the only product which could be isolated was methyl *N*-benzylglycinate (9) which was characterized as its hydrochloride (10), m.p. 127–128° (lit. 128° (5)), yield 17% (Scheme 2).

#### Experimental

All solvents used were thoroughly dried by the conventional methods. All melting and boiling points are uncorrected.

The i.r. spectra were recorded on a Beckman IR-8 double beam spectrometer. The n.m.r. spectra were recorded on a Varian A-60 spectrometer. High resolution mass-spectra were done on an A.E.I. MS902 coupled with a PDP-8

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computer. Elemental analyses were performed by Midwest Microlab. Inc., Indianapolis, Indiana.

## Methyl N-Benzyl- $\beta$ -hydroxyvalinate (1)

To a solution of N-benzyl- $\beta$ -hydroxyvaline (6) (4.005 g, 0.0179 mol) in methanol (50 ml) an ethereal solution of diazomethane was added. The solution was evaporated *in vacuo* and chromatographed on silica gel and eluted with ether-hexane (50:50 v/v) to give product 1; yield 3.715 g (87%), b.p. 104–106°/0.05 mm Hg. I.r. bands (CCl<sub>4</sub>) at 3540, 3360 and 1735 cm<sup>-1</sup>;  $\tau$  (CCl<sub>4</sub>): 8.96 and 8.80 (6H, singlet), 7.35 (2H, hump), 7.00 (1H, singlet), 6.36 (5H, singlet and AB system for --CH<sub>2</sub>-- of benzyl, J = -10 Hz), 2.76 (5H, singlet).

Anal. Calcd. for  $C_{13}H_{19}NO_3$ : C, 65.80; H, 8.08. Found. C, 65.88; H, 8.35.

## 1-Benzyl-2-carbomethoxy-3,3-dimethylaziridine (2)

To a 0 °C cooled solution of triphenylphosphine (7.62 g, 0.0282 mol) in acetonitrile (50 ml) a solution of bromine (4.45 g, 0.0282 mol) in acetonitrile (30 ml) was added dropwise under stirring. The addition finished, product 1 (6.61 g, 0.0279 mol) in acetonitrile (40 ml) was added dropwise during 1/2 h. To the solution obtained, triethylamine (5.69 g, 0.0564 mol) in acetonitrile (40 ml) was added during 1/2 h. The solution was stirred at 0 °C for 2 h and an additional 2 h at 20 °C.

Triethylamine hydrobromide was filtered off. The solution was concentrated *in vacuo* and ether (100 ml) was added. Triphenylphosphine oxide was filtered off, and the ethereal solution evaporated *in vacuo*. The oily residue was chromatographed on silica gel and eluted with ether 20%/hexane to give pure aziridine 2; yield 4.63 g (76%); b.p. 95–100°/ 0.05 mm Hg; i.r. bands (CCl<sub>4</sub>) at 3090, 3050, 2980, 1750, 1725, 1600 cm<sup>-1</sup>;  $\tau$  (CCl<sub>4</sub>): 8.75 (6H, singlet), 8.04 (1H, singlet), 6.43 (3H, singlet), 6.34 (2H, singlet (broad)), 2.76 (5H, multiplet).

Anal. Calcd. for  $C_{13}H_{17}NO_2$ : C, 71.20; H, 7.81. Found: C, 70.99; H, 7.89.

#### Methyl 3-Benzylamino-2-chloro-3-methylbutyrate Hydrochloride (3)

Product 2 (0.330 g, 0.00151 mol) in anhydrous benzene (5 ml) was bubbled at 20 °C with anhydrous hydrogen chloride for 5 min. The solution was stirred for 2 h. The white solid was filtered and recrystallized in a dichloromethane/ether mixture.

Product 3, 0.384 g (87%); m.p.  $174-175^{\circ}$ ; i.r. bands (Nujol) at 2740, 2360, 1755, 1740, and 1565 cm<sup>-1</sup>;  $\tau$  (D<sub>2</sub>O): 8.40 and 8.32 (6H, singlet), 6.07 (3H, singlet), 5.65 (2H, singlet), 5.20 (2H, DHO singlet), 4.82 (1H, singlet), 2.47 (5H, singlet).

Anal. Calcd. for  $C_{13}H_{19}NO_2Cl_2$ : C, 53.43; H, 6.55. Found: C, 53.14; H, 6.84.

#### Methyl 2-(N-Benzylacetamido)-3-methylcrotonate (4a)

Product 2 (0.324 g, 0.00148 mol) and acetic acid (2.00 g, 0.033 mol) in benzene (10 ml) were heated at reflux for 14 h. Benzene was evaporated *in vacuo* and ether (50 ml) added. The solution was washed with 5% sodium carbonate dried on magnesium sulfate and chromatographed on silica gel and eluted with ether 40%/hexane.

Product 4a, 0.156 g (45%); b.p. 133-135°/0.15 mm Hg;

i.r. bands (CCl<sub>4</sub>) 2960, 1720, 1665, 1640;  $\tau$  (CCl<sub>4</sub>): 8.60 (3H, singlet), 8.20 (3H, singlet), 7.90 (3H, singlet), 6.45 (3H, singlet), 5.11 and 5.97 (2H, doublet,  $J_{gem} = -14$  Hz), 2.78 (5H, singlet).

Anal. Calcd. for  $C_{15}H_{19}NO_3$  (mol. wt. 261.1364): C, 69.32; H, 7.34. Found (261.1361 (mass spectrum)): C, 69.75; H, 7.30.

## Methyl 2-(N-Benzylpropionamido)-3-methylcrotonate (4b)

Prepared as 4a. Reaction of product 2 (0.333 g, 0.00152 mol) with propionic acid (2.79 g, 0.0377 mol) was followed by chromatography on silica gel and pure product 4b 0.152 g (37%) was obtained. I.r. bands (CCl<sub>4</sub>) at 3000, 2960, 1720, 1665 and 1635 cm<sup>-1</sup> (shoulder);  $\tau$  (CCl<sub>4</sub>): 8.97 (3H, triplet, J = 7.5 Hz), 8.65 (3H, singlet), 8.00 (2H, quadruplet, J = 7.5 Hz), 7.91 (3H, singlet), 6.47 (3H, singlet), 5.09 and 5.99 (2H, AB system,  $J_{gem} = -14$  Hz) 2.80 (5H, singlet).

Anal. Calcd. for  $C_{16}H_{21}NO_3$ : C, 69.79; H, 7.68. Found: C, 69.50; H, 7.62.

## Methyl 3-Methyl-2-thioacetoxycrotonate (5) and Methyl 3-(N-Benzylacetamido)-2-mercapto-3-

methylbutyrate (6)

To a solution of aziridine 2 (0.345 g, 0.00158 mol) in benzene (3 ml) a solution of thioacetic acid (0.360 g, 0.0047 mol) in benzene (3 ml) was added dropwise. The solution was stirred at 20 °C for 2 h and then evaporated *in vacuo*. The yellow oil was chromatographed on silica gel and eluted first with ether 20%/hexane to give 5 and then with ether 50%/hexane to give 6 which gave a positive test for the mercapto group.

Product 5, 0.070 g(23%); b.p.  $65-70^{\circ}/0.05$  mm; i.r. bands (CCl<sub>4</sub>) at 2970, 1720, and 1700 cm<sup>-1</sup> (shoulder);  $\tau$  (CCl<sub>4</sub>): 7.97 (3H, singlet), 7.75 (3H, singlet), 7.68 (3H, singlet), 6.31 (3H, singlet).

Anal. Calcd. for  $C_8H_{12}O_3S$ : C, 51.04; H, 6.42. Found: C, 50.72; H, 6.41.

Product 6, 0.250 g (54%); i.r. bands (CCl<sub>4</sub>) at 2970, 2350, 1730, and 1650 cm<sup>-1</sup>;  $\tau$  (CCl<sub>4</sub>): 8.50 (6H, singlet), 8.02 (3H, singlet), 7.7 (1H, broad), 6.30 (3H, singlet), 5.42 (2H, singlet), 5.02 (1H, doublet (broad)), 2.75 (5H, multiplet). Mass spectrum: fragments at m/e 277, 190, and 148.

## Methyl 3-(N-Benzylacetamido)-3-methyl-2-

thioacetoxybutyrate (7)

To a solution of product 6 (0.050 g, 0.00017 mol), and acetyl chloride (0.014 g, 0.00017 mol) in benzene (0.5 ml), a solution of triethylamine (0.018 g, 0.00017 mol) in benzene (0.5 ml) was added dropwise. The solution was stirred at 25 °C for 24 h. The triethylamine hydrochloride was filtered off and the solution evaporated and the residue was crystallized in an ether-hexane mixture.

Product 7, 0.032 g (56%), m.p.  $117-118^{\circ}$ ; i.r. bands (CHCl<sub>3</sub>) at 2970, 1730, 1700, and 1645 cm<sup>-1</sup>;  $\tau$  (CDCl<sub>3</sub>): 8.54 (6H, singlet), 8.01 (3H, singlet), 7.68 (3H, singlet), 6.32 (3H, singlet), 5.45 (2H, singlet), 4.42 (1H, singlet), 2.74 (5H, singlet).

Anal. Calcd. for C<sub>17</sub>H<sub>23</sub>NO<sub>4</sub>S: C, 60.51; H, 6.87. Found: C, 60.45; H, 6.66.

#### 3-Benzyl-5-methoxycarbonyl-4,4-dimethyl-2-

(2'-thioxopropylidene)thiazolidine (8)

To a stirred solution of aziridine 2 (0.844 g, 0.00386 mol)

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thioacetic acid (3.00 g, 0.040 mol) was added dropwise during 10 min. The solution was stirred 1/2 h and excess thioacetic acid was evaporated *in vacuo*. The red oil obtained was chromatographed on silica gel and eluted with ether 10%/hexane, ether 20%/hexane, and ether 30%/hexane to give product 5, 0.319 g (43%), 8, 0.161 g (12%), and 7, 0.144 g (11%), respectively.

Products 5 and 7 were identified by comparison of their spectra, t.l.c., b.p., and m.p., which proved identical in every way to those obtained earlier.

Product 8 had the following characteristics: m.p.  $175-177^{\circ}$ ; i.r. bands (CHCl<sub>3</sub>) at 2960, 1735, 1500 cm<sup>-1</sup>;  $\tau$  (CDCl<sub>3</sub>): 8.58 and 8.48 (6H, singlet), 7.48 (3H, singlet), 6.20 (3H, singlet), 6.01 (1H, singlet), 5.40 (2H, singlet), 3.58 (1H, singlet), 2.60 (5H, singlet). Mass spectrum: m/e 335 (two sulfurs, P + 2/P = 12%); u.v. (EtOH 95%):  $\lambda$  235 ( $\epsilon$  25 000);  $\lambda$  288 ( $\epsilon$  5200).

Anal. Calcd. for  $C_{17}H_{21}NO_2S_2$ : C, 60.86; H, 6.33. Found: C, 60.61; H, 6.35.

#### Methyl N-Benzylglycinate Hydrochloride (10)

Product 2 (0.266 g, 0.00192 mol), benzylmercaptan (1.80 g, 0.0121 mol), and toluene (2 ml) were heated at reflux for 20 h. The solution was then chromatographed on silica gel and eluted first with hexane to get rid of the unreacted

mercaptan and then with ether-hexane (50-50 v/v). The fraction was evaporated and ether (25 ml) added. The ethereal solution was saturated with hydrogen chloride and the precipitate crystallized in a dichloromethane-ether mixture.

Product **10**, 0.045 g (17%), m.p. 127–128 °C (lit. (5) 128°), fused m.p. with an authentical sample, 127–128 °C; i.r. bands (CH<sub>2</sub>Cl<sub>2</sub>) at 3100–2200 (broad), 1750 and 1560 cm<sup>-1</sup>;  $\tau$  (D<sub>2</sub>O): 6.22 (3H, singlet), 6.00 (2H, singlet), 5.70 (2H, singlet), 5.20 (2.7H, singlet DHO), 2.50 (5H, singlet).

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