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Dedicated to Professor John C. Sheehan on the occasion of his sixty-fifth birthday.

A method for the synthesis of  $\alpha$ -amido- $\beta$ -lactams without the intermediacy of an  $\alpha$ -amino- $\beta$ -lactam is described. The appropriate  $\beta$ -keto ester is used for preparing a vinylamino  $\beta$ -lactam *via* a "Dane salt" by a previously reported method. Oxidation with ruthenium tetroxide and periodic acid of this product leads directly to the desired "V", or "G" or analogous  $\alpha$ -amido side chain.

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The amide side chain in penicillins and cephalosporins is an important structural requirement for antibiotic activity. Of the several approaches available for generating this side chain during the total synthesis of  $\beta$ -lactam antibiotics, the one most commonly used involves the acylation of an  $\alpha$ -amino- $\beta$ -lactam (2). Recently we reported a non-hazardous synthesis of  $\alpha$ -amino- $\beta$ -lactams using a substituted vinylamino acetic acid as a key intermediate (3). We describe here an adaptation of this preparative method leading to the "V", the "G" and analogous  $\alpha$ -amido side chains without the intermediacy of an  $\alpha$ -amino- $\beta$ -lactam.

Methyl phenoxyacetylacetate (2, R = PhOCH<sub>2</sub>), the starting material for the synthesis of the "V" side chain, was prepared by a minor modification of a known method (4) (see Scheme 1) involving the acylation of Meldrum acid (5) (1). "Dane salt" (3) was obtained from the reaction of this  $\beta$ -keto ester (2), glycine, and potassium hydroxide following the method of Dane, *et al.* (6). The  $\beta$ -lactam (5) was synthesized from 3 and the azomethine (4) by the general method described previously by us (3).

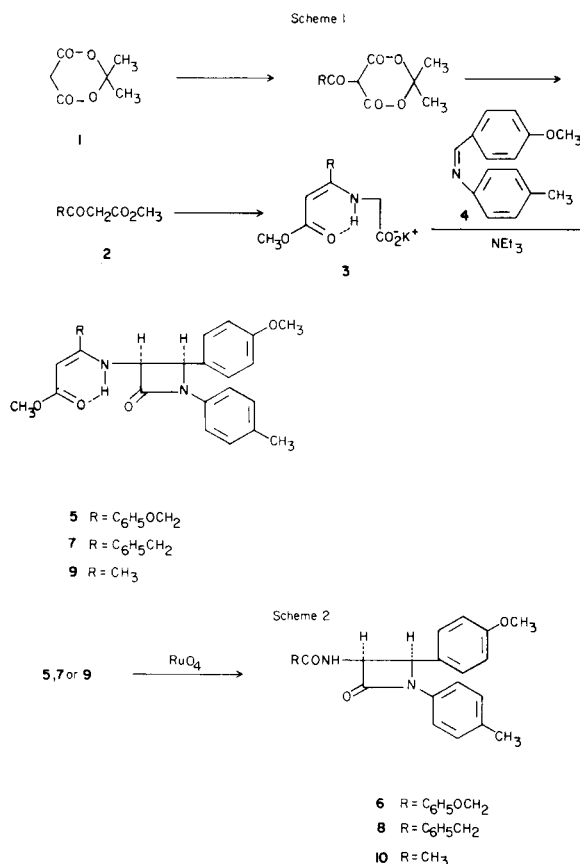
The  $\beta$ -lactam (5) was oxidized in acetone solution with ruthenium tetroxide (generated from ruthenium dioxide and sodium periodate in aqueous acetone). The only product isolated after the usual work up was the  $\alpha$ -amido- $\beta$ -lactam (6) with a "V" side chain (see Scheme 2).

Starting with methyl phenylacetylacetate (2, R = C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>), and methyl acetoacetate and following the reactions described above the amido  $\beta$ -lactams 8 and 10, respectively, were prepared. The amido  $\beta$ -lactam (10) has been prepared previously by the oxonolysis of (9) (7).

The above sequence of reactions was stereospecific, only the *cis*  $\beta$ -lactam was formed, thereby simplifying the work up as chromatographic separation became unnecessary.

#### EXPERIMENTAL

Melting points were determined in open capillary tubes using a "Mel-Temp" apparatus and are uncorrected. Infrared spectra were obtained with a Perkin Elmer Infracord and Perkin Elmer 247 grating spectro-

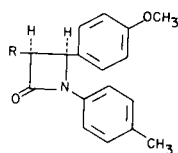


meter. Pmr spectra were recorded on a Varian EM 390 spectrometer in deuteriochloroform solution containing tetramethylsilane as an internal standard. Mass spectra were obtained with a CIMS-Biospect (Scientific Research Instrument) mass spectrometer. Elemental analyses were performed by Guelph Chemical Laboratories, Ontario, Canada.

#### Methyl Phenoxyacetoacetate (2).

To a stirred suspension of 28.8 g. (0.2 mole) of Meldrum's acid (5) (prepared from malonic acid, acetone and acetic anhydride) in 200 ml. of methylene chloride containing 32 g. (0.4 mole) of pyridine, were added at 0° and under nitrogen atmosphere a solution of 37.5 g. (0.22 mole) of phenoxy acetyl chloride in 100 ml. of methylene chloride. Stirring was continued for 1 hour at 0° and for an additional 1 hour at room temperature. Evaporation of the solvent under reduced pressure gave the crude acylated product as a solid. This solid was refluxed in 200 ml. of

Table 1



Compound No.	R	M.p. °C	Yield %	Molecular Formula	Analytical Data (a)			Spectral Data
					C	H	N	
5	PhOCH <sub>2</sub> C(=CHCO <sub>2</sub> CH <sub>3</sub> )NH	185	20	C <sub>26</sub> H <sub>26</sub> N <sub>2</sub> O <sub>5</sub>	Analytically pure sample could not be prepared			ir (Nujol): 3230, 1745 cm <sup>-1</sup> ; nmr (deuteriochloroform): δ 8.3 (d, 1H), 7.43-6.82 (m, 13H), 5.28 (m, 2H), 4.64 (s, 1H), 4.5 (dd, 2H), 3.76 (s, 3H), 3.45 (s, 3H), 2.23 (s, 3H); ms: M <sup>+</sup> at m/e 472
6	PhOCH <sub>2</sub> CONH-	165	52	C <sub>25</sub> H <sub>24</sub> N <sub>2</sub> O <sub>4</sub>	72.60 (72.10)	5.98 (5.81)	6.73 (6.73)	ir (Nujol): 3370, 1765 cm <sup>-1</sup> ; nmr (deuteriochloroform): δ 7.3-6.6 (m, 14H), 5.7 (dd, 1H), 4.35 (m, 3H), 3.78 (s, 3H), 233 (s, 3H); ms: M <sup>+</sup> at m/e 416
7	PhCH <sub>2</sub> C(=CHCO <sub>2</sub> CH <sub>3</sub> )NH	202	45	C <sub>28</sub> H <sub>28</sub> N <sub>2</sub> O <sub>4</sub>	74.38 (b) (73.66)	6.40 (6.18)	5.93 (6.14)	ir (Nujol): 3226, 1730, 1615 cm <sup>-1</sup> ; nmr (deuteriochloroform): δ 8.97 (d, 1H), 7.5-6.9 (m, 13H), 5.1 (dd, 1H), 4.9 (d, 1H), 4.4 (s, 1H), 3.7 (s, 3H), 3.45 (s, 5H), 2.15 (s, 3H); ms: M <sup>+</sup> at m/e 456
8	PhCH <sub>2</sub> CONH-	218	40	C <sub>25</sub> H <sub>24</sub> N <sub>2</sub> O <sub>3</sub>	74.64 (74.98)	5.81 (6.04)	7.09 (6.99)	ir (Nujol): 3280, 1750 cm <sup>-1</sup> ; nmr (deuteriochloroform): δ 7.3-6.7 (m, 14H), 5.7 (d, 1H), 5.27 (d, 1H), 3.83 (s, 3H), 3.36 (s, 2H), 2.27 (s, 3H); ms: M <sup>+</sup> at m/e 400
9	CH <sub>3</sub> C(=CHCO <sub>2</sub> CH <sub>3</sub> )NH	175	61	C <sub>22</sub> H <sub>24</sub> N <sub>2</sub> O <sub>4</sub>	69.32 (69.46)	6.10 (6.36)	7.42 (7.36)	ir (Nujol): 1730, 1640 cm <sup>-1</sup> ; nmr (deuteriochloroform): δ 8.62 (d, 1H), 7.4-6.9 (m, 8H), 5.35-5.06 (m, 2H), 4.36 (s, 1H), 3.8 (s, 3H), 3.5 (s, 3H), 2.3 (s, 3H), 1.9 (s, 3H); ms: M <sup>+</sup> at m/e 380
10	CH <sub>3</sub> CONH-	165	40	C <sub>19</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub>	71.19 (70.35)	6.36 (6.21)	8.58 (8.64)	ir (Nujol): 3280, 1750 cm <sup>-1</sup> ; nmr (deuteriochloroform): δ 7.3-6.7 (m, 8H), 6.25 (d, 1H), 5.6 (dd, 1H), 5.3 (d, 1H), 3.8 (s, 3H), 2.3 (s, 3H), 1.73 (s, 3H); ms: M <sup>+</sup> at m/e 324

(a) Values in parentheses refer to calculated values. (b) Best analytical values obtainable for compound 7.

methanol for 2 hours. Evaporation of methanol under vacuum followed by distillation gave 23 g. of the title compound, b.p. 128-130°/0.7 mm, and was used as such.

Potassium (2'-carbomethoxy-1'-phenoxy methyl)vinylamino acetate (3) was prepared from glycine, methyl phenoxyacetate and alcoholic potassium hydroxide by the method described by Dane and co-workers (6).

#### General Method for the Synthesis of β-Lactams.

*cis* 1-*p*-Tolyl-3-(2'-carbomethoxy-1'-phenoxy methyl)vinylamino-4-*p*-anisyl-azetidin-2-one (5).

To a stirred suspension containing **3** (4 g., 0.015 mole) in 50 ml. of dry tetrahydrofuran and 2.1 ml. (0.015 mole) of triethylamine at -25° under a nitrogen atmosphere, were added 1.1 g. (0.015 mole) of ethyl chloroformate. After ½ hour, 2.1 ml. (0.02 mole) of triethylamine were added and the stirring continued for additional ½ hour. A solution of 2.25 g. (0.01 mole) of *p*-anisylidene-*p*-toluidine (**4**) in 50 ml. tetrahydrofuran was

added dropwise over a period of ½ hour and the stirring continued an additional 1 hour. The solvent was then evaporated from the reaction mixture under reduced pressure. The resulting semi solid mass was dissolved in methylene chloride. This solution was washed with water and dried (magnesium sulfate). Evaporation of the solvent afforded 1.2 g. (20% yield of the title compound), m.p. 185° (dichloromethane).

Using essentially the same reaction conditions and appropriate "Dane Salt", the β-lactams **7** and **9** were also prepared. Physical characteristics of all these β-lactams are given in Table 1.

#### Ruthenium Tetroxide Oxidation of Vinylamino β-Lactams.

*cis*-1-*p*-Tolyl-3-phenoxyacetamido-4-*p*-anisylazetidine 2-one (6).

To a cooled (0°) solution of 1 g. of sodium periodate in 20 ml. of acetone and 10 ml. of water were added 20 mg. of ruthenium dioxide and the contents were stirred for 1 hour. This solution was added dropwise to a cooled (0°) solution of 0.5 g. of **5** in 25 ml. of acetone. A solution of 1 g. of sodium periodate in 20 ml. of water was then added over a period of 15

minutes. Stirring was continued for an additional  $\frac{1}{2}$  hour. The course of the reaction was monitored by thin layer chromatography. The reaction mixture was filtered and acetone evaporated under reduced pressure. Residual aqueous solution was extracted with ethyl acetate. The organic layer was dried (sodium sulfate) and evaporated. The solid residue after crystallization from methylene chloride-petroleum ether afforded 270 mg. of **6**.

The oxidation of **7** and **9** with ruthenium tetroxide under similar conditions gave the amido  $\beta$ -lactams **8** and **10**, respectively.

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(7) Previously we have used ozonation for preparing  $\alpha$ -amido side-chains but large scale ozonation is not free of hazards (see reference 3b).