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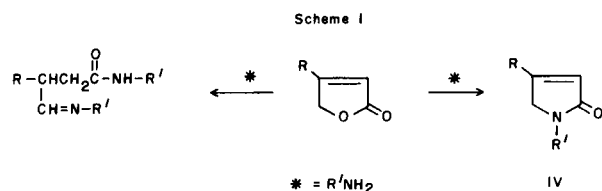
A series of substituted 4-aminobut-2-enolide derivatives have been synthesized by reaction of a variety of substituted amines with methyl tetronate. The  $^1\text{H}$  and  $^{13}\text{C}$  nmr spectral analysis of all compounds synthesized are given.

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Several synthetic methods for the preparation of nitrogenous naturally occurring butenolids have been described in the literature [1-6]. However, few of these methods have practical value for the production of substituted 4-aminobut-2-enolides III as a precursor in the synthesis of these natural compounds.

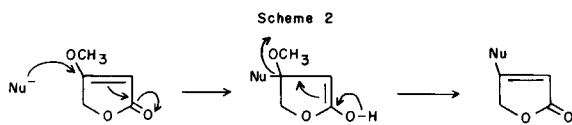
In the present work we report a simple one step synthesis of compounds III from the reaction of methyl tetronate moiety I with some substituted aliphatic and aromatic amines. This moiety was prepared in good yield, through our synthesis to the naturally occurring butenolide-piperolide, from commercially available ethyl acetoacetate [7].

The reaction of primary amines with some butenolides has been reported to give  $\Delta^3$ -pyrrolinones IV the end products [8] (Scheme 1).

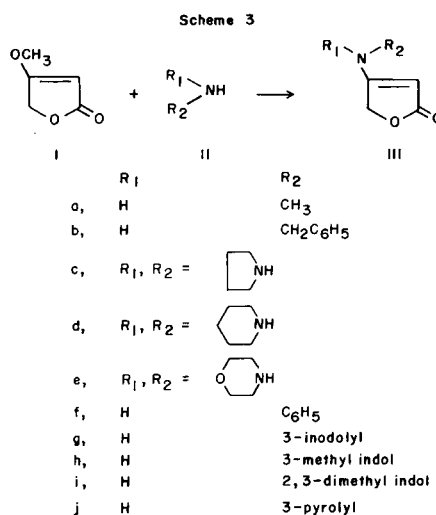


Jones and coworkers [9] summarized three types of reactions of amines on butenolides are possible: Michael addition of the base to the double bond in the lactone ring, attack by the base on the carbonyl carbon to give an amide derivative, and attack on the  $\gamma$ -position on the lactone to give carboxylic acid derivative.

From the reaction of methyl tetronate with substituted amine, it was found that Michael addition was favoured to give III. This agrees with the mechanism indicated in Scheme 2 in which the nucleophile substitutes the methoxy group at position four. Owing to this addition the elimination step is easy.



The initial experiment was conducted using methyl tetronate and an excess solution of methyl amine in ethanol at reflux temperature to give IIIa (Scheme 3).



This product could be easily separated by concentration of the sole reaction product *in vacuo* and was identified by analytical and nmr ( $^1\text{H}$  and  $^{13}\text{C}$ ) criteria. The pmr of this compound (Table 1) showed a singlet at  $\delta$  4.40 which was integrated for one proton, this was assigned to  $\text{H}_3$ . A singlet at  $\delta$  4.52, integrated for two protons, was assigned to  $\text{H}_5$ . A signal at  $\delta$  7.41 was assigned to the NH proton of

Table 1

Physical and Analytical Data of Compounds III

Compound No.	Yield	Mp $^\circ\text{C}$ Solvent	Formula	Analysis Calcd./Found %		
				C	H	N
a	85	180-182 Ethanol	$\text{C}_5\text{H}_7\text{O}_2\text{N}$	53.9	6.19	12.38
				53.13	6.12	12.42
b	60	137-139 Benzene	$\text{C}_{11}\text{H}_{11}\text{O}_2\text{N}$	69.84	5.82	7.40
				69.89	5.73	7.29
c	72	83-85 Benzene	$\text{C}_8\text{H}_{11}\text{O}_2\text{N}$	62.74	7.18	9.15
				62.88	7.01	9.07
d	65	85-88 Benzene	$\text{C}_9\text{H}_{13}\text{O}_2\text{N}$	64.67	7.78	8.38
				64.66	7.89	8.36
e	74	62-66 Benzene	$\text{C}_8\text{H}_{11}\text{O}_3\text{N}$	56.80	6.50	8.28
				56.71	6.52	8.18

Table 2  
Spectral Data of Compounds III

Compound No.	IR bands $\nu$ cm <sup>-1</sup> [b]	<sup>1</sup> H-NMR [a] $\delta$		<sup>13</sup> C-NMR ppm [a]			
		H-3 [c]	H-5 [d]	C-2	C-3	C-4	C-5
a [e]	1730	4.40	4.52	170.41	78.18	175.92	67.07
b [f]	1740	4.64	4.71	168.58	81.23	176.38	67.78
c [g]	1730	4.46	4.60	166.37	80.45	175.79	67.07
d [h]	1735	4.62	4.73	166.51	80.52	175.83	67.13
e [i]	1735	4.63	4.63	168.45	82.66	175.14	66.81

[a] Deuteriochloroform was used as a solvent. [b] only the lactone absorption bands were reported. [c] s, 1H. [d] s, 2H. [e] 2.70, d, 3H, CH<sub>3</sub>; 7.4, s, 1H, NH; 30.67, CH<sub>3</sub>. [f] 4.43, d, 2H, CH<sub>2</sub>; 7.48, s, 5H, C<sub>6</sub>H<sub>5</sub>; 7.96, s, 1H, NH; 49.00, CH<sub>2</sub>; (126.6, 126.99, 129.13, 136.6) Ar. [g] 2.0, m, 4H, 2CH<sub>2</sub>; 3.22, t, 4H, 2CH<sub>2</sub>N; 24.95, 25.54, 2CH<sub>2</sub>, 47.37, 49.19, 2CH<sub>2</sub>N. [h] 1.55, b, 6H, 3CH<sub>2</sub>; 3.14, b, 4H, 2CH<sub>2</sub>N; 24.75, 24.61, 25.21, 3CH<sub>2</sub>; 47.41, 47.54, 2CH<sub>2</sub>N. [i] 3.15, t, 4H, J = 1.2 Hz, 2CH<sub>2</sub>N; 3.67, t, 4H, J = 1.2 Hz, 2CH<sub>2</sub>O; 47.96, 2CH<sub>2</sub>N; 65.90, 2CH<sub>2</sub>O.

the amino group. The most interesting feature in this spectrum is the doublet at  $\delta$  2.71, which integrated for three protons. This was assigned to the methyl group attached to the secondary amine.

In order to obtain some additional information about the compound IIIa we investigated the <sup>13</sup>C spectrum data. These data indicated in Table 2, which confirmed the proposed structure of IIIa. Single-frequency off-resonance (sfor) as well as the known chemical shift rules [10] were used to confirm the assignments of the carbon atoms.

The signal, due to the C-2, C-3, C-4 and C-5 could be assigned unambiguously on the basis of their multiplicity and chemical shifts. The signal due to C-2 and C-4 could be assigned as shown previously [12] by using gated decoupled spectrum. Similarly the chemical shift for C-3 and C-5 are that to be expected of methyl crotonate and is almost the same as that in methyl tetronate (I).

Similarly, compounds IIIa-e were easily prepared by refluxing of methyl tetronate with the corresponding amine in good yields. This reaction failed with aromatic amines IIf-j under these conditions.

#### EXPERIMENTAL

All melting points are uncorrected. Infrared (ir) spectra for Nujol mulls were obtained with a Beckmann Acculab T-M Spectrophotometer

and the uv spectra were recorded in methanol on a Pye Unicam SP8-200 spectrophotometer. The nmr spectra were taken on a Bruker WH 90 Ds spectrometer equipped with ASPECT 2000, 32 K Computer, operating at 22.63 MHz. Elemental analysis were performed by Alfred Bernhardt Laboratories, Ruhr, Germany.

#### Preparation of Methyl Tetronate I [7 and 11].

Ethyl  $\gamma$ -bromo- $\beta$ -methoxycrotonate (100 g), anhydrous zinc bromide (0.5 g), and dry *p*-xylene (100 ml) were added to a 500 ml round-bottom flask equipped with a reflux condenser and drying tube. The mixture was heated under reflux for six hours, and the solvent removed at the pump. Addition of 300 ml of a mixture of chloroform:diethyl ether (2:8) caused the zinc bromide to come out as a gum. The solution was decanted and set aside for 18 hours at 0° when a solid (30 g), mp 64-65°, crystallized out and was filtered off. The filtrate was evaporated under vacuum and the same solvent mixture (ca. 75 ml) added to the residue. From this, a further crop (6 g) was collected. Repeating the same procedure gave a further 2 g of the same product. The total yield of methyl tetronate was 38 g (75%).

#### General Procedure for Preparing Substituted 4-Aminobut-2-enolides III.

A mixture of (0.01 mole) of methyl tetronate, 30 ml of ethanol and (0.05 mole) of amine was stirred at reflux for x hours (x = 2 for compound a, x = 5.30 for compound b, x = 6.30 for compound c, x = 5.0 for compound d, x = 3.30 for compound e). The solution was cooled, and the reaction mixture was evaporated to dryness *in vacuo*. Crystallization of the residue from the appropriate solvent yielded the corresponding product (Table 1).

#### REFERENCES AND NOTES

- [1] R. R. Schmidt and J. Talbiersky, *Angew. Chem.*, **89**, 891 (1977).
- [2] R. R. Schmidt and J. Talbiersky, *Angew. Chem., Int. Ed. Engl.*, **17**, 204 (1978).
- [3] R. R. Schmidt and J. Talbiersky, *Synthesis*, 869 (1977).
- [4] K. J. Boosen, *Chimia*, **27**, 541 (1973).
- [5] J. V. Greenhill, M. Ramli and T. Tomassini, *J. Chem. Soc., Perkin Trans. I*, 588 (1975).
- [6] E. R. H. Jones and M. C. Whiting, *J. Chem. Soc.*, 1423 (1949).
- [7] A. Pelter, M. T. Ayoub, J. Schulz, R. Hansel and D. Reinhardt, *Tetrahedron Letters*, 1627 (1979).
- [8] T. H. Bemby, R. C. Elderfield, and G. L. Krueger, *J. Org. Chem.*, **25**, 1175 (1960); M. Semonski, A. Cerny, R. Kotva, V. Zikan, and B. Kavak, *Collect. Czech. Chem. Commun.*, **33**, 2698 (1968).
- [9] J. B. Jones and J. M. Young, *Can. J. Chem.*, **44**, 1059 (1966).
- [10] J. B. Sothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, 1972.
- [11] M. T. Ayoub, Ph.D. Thesis, University College of Swansea, U.K.
- [12] A. Pelter and M. T. Ayoub, *J. Chem. Soc.*, 1173 (1981).