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ENAMIDE OXIDATIONS: PREPARATION AND PROPERTIES OF 4-(1-HYDROXYETHYL)-4-METHOXYPERHYDRO-1,3-OXAZIN-2-ONE and 5,5-DIMETHOXY-4-METHYLPERHYDRO-1,3-OXAZEPIN-2-ONE[1]

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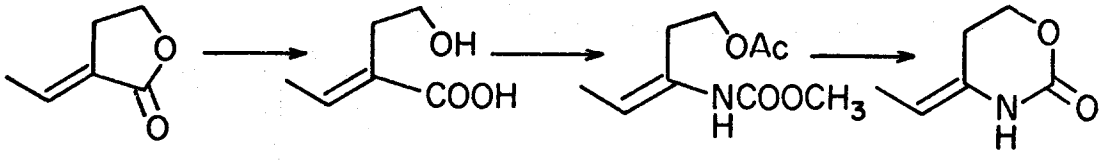
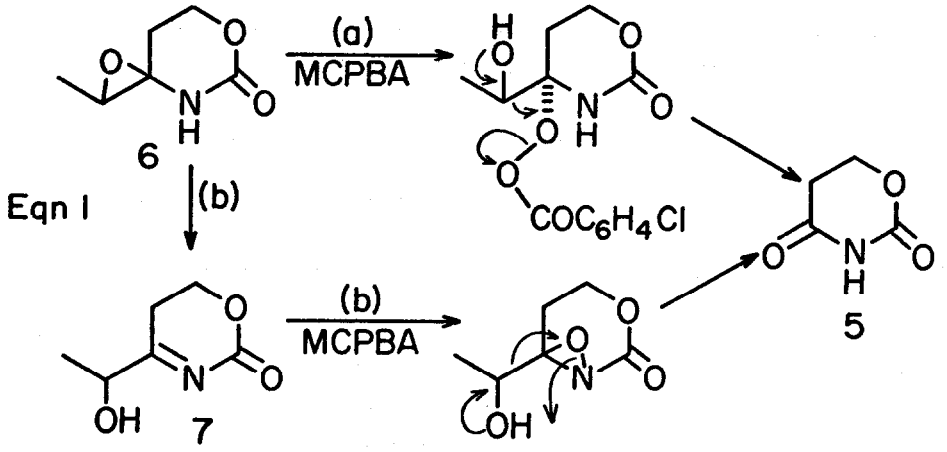
In the course of recent studies directed toward the synthesis of multifunctional cyclic carbamates[2] we prepared the enamide E-4-ethylideneperhydro-1,3-oxazin-2-one (1) and investigated its oxidation with m-chloroperbenzoic acid and with Tl (III) salts. Compound 1 was obtained as follows: Hydrolysis of the known[3] E-2-ethylidene-γ-butyrolactone (2) furnished the hydroxy acid 3, m.p. 104°, in 90% yield[4]. Consecutive treatment of 3 with acetic anhydride-pyridine, ethyl chloroformate-triethylamine and sodium azide gave the corresponding acyl azide (92%). Curtius rearrangement of the azide followed by addition of methanol to the resulting isocyanate gave the carbamate 4 (94%). Deacetylation of 4 using aqueous potassium carbonate, followed by cyclization with sodium hydride gave 1 (73%†), m.p. 121.5°, ^{1}H nmr signals at δ 9.17 (1H, s), 4.97 (1H, q, J = 7 Hz), 4.34 (2H, t, J = 6 Hz), 2.63 (2H, t, J = 6 Hz) and 1.62 (3H, d, J = 7 Hz).



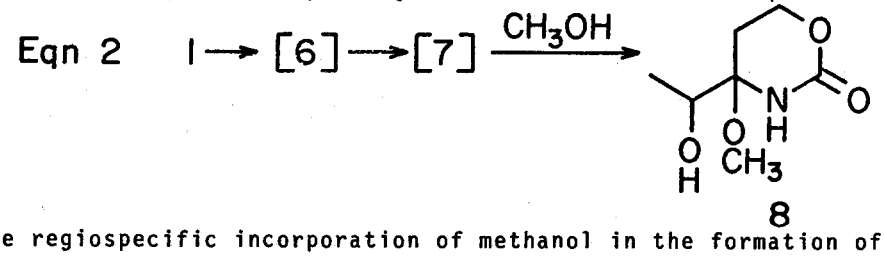
2 3 4 1

When enamide 1 reacted with one equivalent of m-chloroperbenzoic acid (MCPBA) in methylene chloride, half of the starting material remained unchanged and the major product[4] was the imide 5, m.p. 109° (lit.[5] m.p. 112°). When two moles of MCPBA were used per mole of 1, the imide was formed in 86% yield.

Clearly, either the intermediate epoxide 6 or the derived hydroxyimine 7 was much more reactive to MCPBA than 1. This oxidative cleavage is in full accord with the recent observations of Mahajan and co-workers[6]. Two possible mechanisms are shown in Eqns. 1a and 1b.



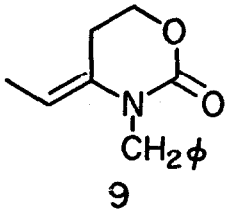
In contrast, however, the desired product 4-(1-hydroxyethyl)-4-methoxyperhydro-1,3-oxazin-2-one (8) was formed in nearly quantitative yield[7] when the epoxidation was carried out by slow addition of MCPBA in methylene chloride to an equimolar amount of 1 in methanol (Eqn. 2). Compound 8 was a 2:1 mixture of diastereoisomers as evidenced by its ^1H nmr spectrum. Repeated recrystallization from chloroform-hexane gave the major isomer[4], m.p. 126°, ^1H nmr signals at δ 7.20 (1H, s), 4.44 (2H, m), 3.92 (1H, m), 3.42 (3H, s)[8], 2.75 (1H, d, J = 5 Hz), 1.97 (2H, m) and 1.27 (3H, d, J = 6 Hz). The ratio of the isomers was not significantly changed when the reaction was performed at -80°.



The regiospecific incorporation of methanol in the formation of 8 was demonstrated by facile exchange of the methoxyl group in the mixture of isomers in ethanol containing a trace of p-toluenesulfonic acid or by the action of trideuteriomethoxide ion in methanol-d_4. In the latter case, the nondeuterated starting material was regenerated with the original isomer ratio by methoxide ion in methanol. The N-acylimine 7 is a probable intermediate in these exchanges.

Enamide 1 was N-benzylated with excess benzyl chloride and sodium hydride in DMF at 100° for 3 h, providing derivative 9 in 81% yield[4], with ^1H nmr

signals at δ 7.30 (5H, s), 5.05-4.60 (3H, m superimposed on s at 4.97), 4.34 (2H, t, J = 6 Hz), 2.73 (2H, t, J = 6 Hz) and 1.57 (3H, d, J = 7 Hz). The latter compound was oxidized with MCPBA in methanol in the same manner as 1, affording derivative 10 in 73% yield[4], m.p. 140°, ^{1}H nmr signals at δ 7.37 (5H, s), 5.05-3.90 (5H, m), 3.20 (3H, s), 2.55-2.20 (3H, m) and 0.88 (3H, d, J = 7 Hz). This appeared to be a single isomer (tlc, nmr). O-Methylation of 10 in neat methyl iodide and excess sodium hydride provided the dimethoxy derivative 11 in 87% yield[4]. It distilled over a short path at 140°, 0.1 mm; ^{1}H nmr signals at δ 7.35 (5H, s), 5.00-3.88 (3H total, d 4.85, J = 16 Hz; q 4.63, J = 7 Hz; d 4.02, J = 16 Hz), 3.52-3.09 (8H, m superimposed on s at 3.25 and 3.20), 2.08-1.70 (2H, m) and 1.45 (3H, d, J = 7 Hz). The latter compound was stable to (i) refluxing sodium methoxide in methanol, (ii) lithium azide in DMF at 140° and (iii) hydrogenation (1 atm, room temperature) over Pd-charcoal in 1% acetic acid-methanol.



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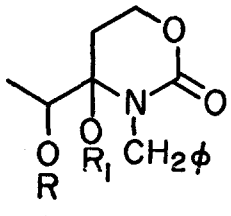
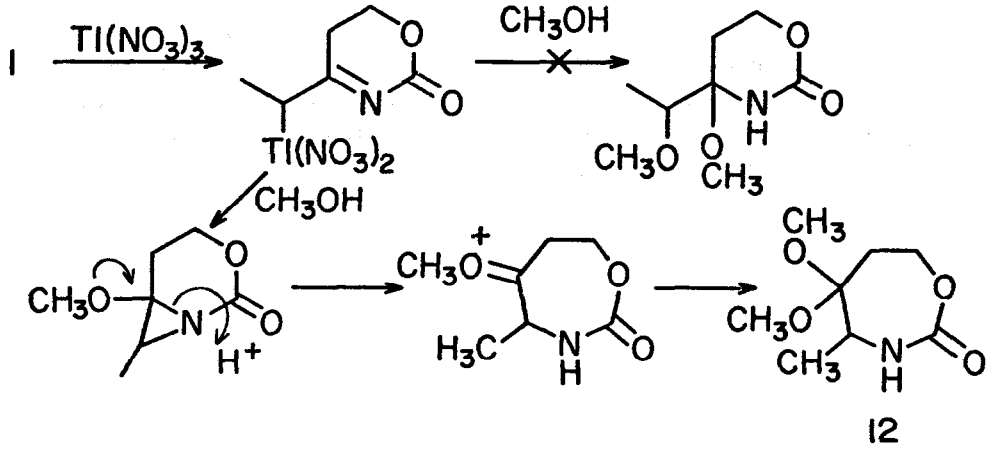


10 R=H R_1=CH_3

11 R=R_1=CH_3

The action of thallium (III) acetate on enamines gave, after aqueous workup, α-acetoxy ketones[9]. However, the action of this salt on 1 was complex. Thallium (III) nitrate reacted with 1 to give as major product (44%) 5,5-



12

SCHEME 1

dimethoxy-4-methylperhydro-1,3-oxazepin-2-one (12)[4]. It distilled over a short path at 130°, 0.1 mm and gave ^{1}H nmr signals[10] at δ 6.62 (1H, d, J = 7 Hz), 4.40-4.07 (2H, m), 3.60-3.15 (7H, m superimposed on s at 3.27 and 3.25), 2.31-1.95 (2H, m) and 1.37 (3H, d, J = 7 Hz). A possible mechanism for its formation is illustrated in scheme 1. Thus, although the desired simple oxidation was not achieved, a new entry into the pharmacologically interesting oxazepines was accomplished.

References and Footnotes

(1) Issued as NRCC No.

(2) a) W.A. Court, O.E. Edwards, C. Grieco, W. Rank and T. Sano, *Can. J. Chem.*, *53*, 463, (1975).
b) O.E. Edwards and P.T. Ho, *Can. J. Chem.*, *55*, 371, (1977).

(3) G.A. Howie, P.E. Manni and J.M. Cassady, *J. Med. Chem.*, *17*, 840, (1974).

(4) A satisfactory elemental analysis was obtained for this compound.

(5) S. Ozaki and T. Kato, *J. Polym. Sci.*, Part C, 695, (1966).

(6) J.R. Mahajan, G.A.L. Ferreira, H.C. Araujo and B.J. Nunes, *Synthesis*, 112, (1976).

(7) Removal of m-chlorobenzoic acid was conveniently effected by filtration of an acetone solution of the products through a short column of alumina.

(8) The methoxyl signal of the minor stereoisomer was at δ 3.30.

(9) M.E. Kuehne and T.J. Giacobbe, *J. Org. Chem.*, *33*, 3359, (1968).

(10) Decoupling experiments confirmed the structure of 12. The methine proton (δ ca. 3.4) was coupled to both the amide proton (δ 6.62) and the methyl group (δ 1.37). The two sets of methylene protons (δ ca. 4.2 and 2.1) were coupled only to each other.