Ozonolysis of 3,4-Dehydroproline

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Ozonolysis of protected 3,4-dehydro-DL-proline (**2**) in methanol gives as the initially isolable product, a seven-membered ring cyclic peroxide (**5**). Compound **5** undergoes rearrangement thermally to give methyl *N*-tosylglycinate (**8**) and a stereochemical mixture of oxazolidine aldehyde esters (**7**). Structural evidence for **7** came from detailed ^{13}C nmr studies of **7** and its reduction product (**9**).

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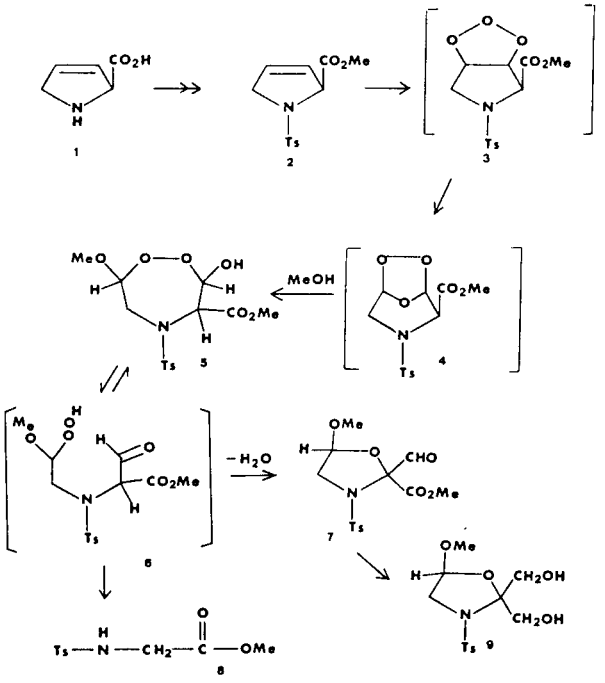
3,4-Dehydroproline is a synthetic imino acid (1) with interesting biological properties. It is a proline antagonist and inhibits the growth of a number of microorganisms (2-5). It is readily incorporated in both plant and bacterial protein replacing an equimolar amount of proline (6). 3,4-Dehydroproline is a substrate for snake venom amino acid oxidases (7,8). Our interest in the oxidation products (9,10,11) of 3,4-dehydroproline prompted examination of the reaction of ozone with this compound (12,13).

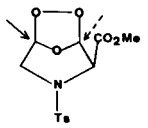
We discovered that at -60° appropriately protected 3,4-dehydro-DL-proline (**2**) in methanol reacts slowly with ozone to give as the initially isolable but unstable product, a seven-membered ring cyclic peroxide (**5**) (14). The structure proposed for this compound is consistent with its ir spectrum, its ^1H nmr, and its decomposition products. At room temperature (and much more rapidly at higher temperatures), the cyclic peroxide undergoes a rearrangement and dehydration to give a colorless oil with molecular formula $C_{14}H_{17}NSO_7$. Its ^1H nmr showed resonances for the tosyl group protons, two sets of methyl groups, an ABX multiplet, and a single absorption peak at δ 9.72 indicative of an aldehyde. Its ^{13}C nmr spectrum correlated well with the proton spectrum but for one difference. Whereas the ^1H spectrum appeared to be that of a single compound the ^{13}C spectrum showed all the features of being that of a mixture, very likely a stereochemical one. When this compound was reduced with sodium borohydride the ^{13}C nmr spectrum of the product was considerably simpler than that of its precursor and consistent with introduction of symmetry into the structure. A striking clue to the structure of the latter product came from the off-resonance decoupled ^{13}C nmr spectrum (see Experimental Section). On the basis of this, the reduction product was assigned the oxazolidine structure (**9**). Further substantiation of this came from elemental analysis, and mass spectral and ^1H nmr data. The product from rearrangement and dehydration of the cyclic peroxide (**5**) must therefore be the oxazolidine (**7**).

A second product from the thermal breakdown of the cyclic peroxide (**5**) was a white crystalline compound, m.p. 81-83°. Its 70 eV mass spectrum and elemental analysis established its molecular formula as $C_{10}H_{13}NSO_4$. Its infrared spectrum (Nujol) showed diagnostic absorption peaks at 3275 and 1725 cm^{-1} and its ^1H nmr spectrum (in deuteriochloroform) exhibited peaks at 2.41 (s, 3H),



3.60 (s, 3H), 3.77 (d, 2H), 5.45 (t, br, 1H, exchanges with deuterium oxide), and 7.15-7.89 (m, 4H). Collectively, the data are consistent with the compound being methyl *N*-tosylglycinate (**8**). An independent synthesis of **8** confirmed its structure (17). Acid hydrolysis of **5** also gave the glycine derivative (**8**).

A plausible reaction pathway for the ozonolysis of 3,4-dehydroproline in the presence of a participating solvent, methanol, is *via* capture of the secondary ozonide (**4**) by methanol. Nucleophilic attack of methanol on the ozonide (**4**) can occur on either of the two ozonide carbons. However, attack at one of the carbons (shown by dashed arrow) is subject to considerable steric hindrance so that the ring expansion of the ozonide (**4**) brought about by methanol must give the cyclic peroxide (**5**) as the predominant product. The two products from the thermal breakdown of **5** can be rationalized as occurring through the intermediacy of **6**, a reactive hydroperoxide. Dehydrative cyclization of the hydroperoxide then would produce the stereochemical mixture of oxazolidine aldehyde esters (**7**). Although the detailed pathway for the formation of **8** from **5** is not known, it is suggested that **8** might arise from **6** by C-N bond fission.



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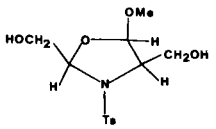

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Carbon magnetic resonance data provided excellent indirect support for the structure of **5**. Its rearrangement, dehydration, and subsequent reduction would produce **9**. The isomer of **5** with the methoxyl and hydroxyl groups interchanged would give **11**. Both the broad-band ^1H noise decoupled ^{13}C nmr spectrum and the splitting pattern observed for the off-resonance decoupled spectrum are inconsistent with **11** but totally consistent with **9**. The mass spectrum also supports structure **9**.

EXPERIMENTAL

3,4-Dehydro-DL-proline (**1**) and *N*-Tosyl-3,4-dehydro-DL-proline Methyl Ester (**2**).

These two compounds were prepared as described previously (15,16). The protected dehydroproline (**2**) showed the following carbon-13 resonances; ^{13}C nmr δ TMS (deuteriochloroform): 21.58, 52.64, 55.18, 68.11, 124.72, 127.58, 128.68, 129.85, 135.18, 143.89, 170.27.

Ozonolysis of *N*-Tosyl-3,4-dehydro-DL-proline Methyl Ester (**2**).

Into a solution of 1.124 g. (4 mmoles) of *N*-tosyl-3,4-dehydroproline methyl ester (**2**) in 100 ml. of methanol was bubbled ozone from a Walsbach ozone generator for 30 minutes at -60°. The dry ice-acetone bath was then removed and the light blue solution was purged with nitrogen and allowed to attain room temperature. The solvent was then removed *in vacuo* at 25° and the residual material was chromatographed on preparative layer silica gel PF_{254} plates using 50% dichloromethane-ether as the developing solvent. The cyclic peroxide (**5**) was obtained as a colorless oil (0.795 g., 55%); ir ν max (neat): 3400, 1730 cm^{-1}; ^1H nmr δ TMS (deuteriochloroform): 2.39 (s, 3H), 3.36-4.05 (m, 9H), 5.00 (m, 2H), 6.31 (br, s, 1H, exchanged with deuterium oxide), 7.18-8.10 (m, 4H).

Anal. Calcd. for $C_{14}H_{19}NSO_8$: C, 46.53; H, 5.30; N, 3.88. Found: C, 46.92; H, 5.51; N, 3.50.

Thermolytic Rearrangement of **5**.

The cyclic peroxide (**5**) (200 mg.) in 10 ml. of toluene was heated under reflux for 6 hours. After evaporation of solvent the residue was chromatographed on preparative layer plates (silica gel PF 254) using 35% ether-pentane as the developing solvent. The top band (Rf 0.7) gave 30 mg. (22%) of methyl *N*-tosylglycinate (**8**) as white plates, m.p. 81-83° (Lit. (17) m.p. 89-91°); ir ν max (Nujol): 3275, 1725, 1590 cm^{-1}; ^1H nmr δ TMS (deuteriochloroform): 2.41 (s, 3H), 3.60 (s, 3H), 3.77 (d, 2H), 5.45 (t, br, 1H), 7.15-7.89 (m, 4H); mass spectrum: (direct inlet) m/e 243 (M^+), 184 (M^+-CO_2CH_3), 155 (Ts).

Anal. Calcd. for $C_{10}H_{13}NSO_4$: C, 49.50; H, 5.35; N, 5.76. Found: C, 49.50; H, 5.14; N, 5.43.

The middle band (Rf 0.4) gave 106 mg. (56%) of the oxazolidine (**7**) as a colorless oil; ir ν max (Nujol): 1735, 1580, 1435, 1320, 1145 cm^{-1}; ^1H nmr δ TMS (deuteriochloroform): 2.42 (s, 3H), 3.39 (s, 3H), 3.42-3.75 (m, 2H), 3.80 (s, 3H), 5.32 (q, 1H), 7.23-7.86 (m, 4H), 9.72 (s, 1H); ^{13}C nmr δ TMS (deuteriochloroform): 21.58, 52.45, 52.77, 52.90, 56.28, 56.61, 95.02, 96.06, 102.81, 104.50, 127.25, 127.71, 129.66, 129.79, 135.69, 144.60, 166.89, 190.88; mass spectrum: m/e 314 (M^+-HCO), 283, 243, 184, 155, 139, 91.

Anal. Calcd. for $C_{14}H_{17}NSO_7$: C, 48.97; H, 4.99; N, 4.08. Found: C, 49.50; H, 5.51; N, 3.01.

Reduction of Oxazolidine (**7**) with Sodium Borohydride.

A solution of 343 mg. (1 mmole) of **7** in 20 ml. of methanol was treated with 380 mg. (10 mmoles) of sodium borohydride in 10 ml. of methanol at 0°. The reaction mixture was stirred for 30 minutes at 0° and then allowed to stir at room temperature for 4 hours. It was subsequently acidified with 1*M* hydrochloric acid and concentrated. The residual aqueous solution was extracted with dichloromethane and the combined extracts were dried (sodium sulfate). Removal of solvent gave the reduced oxazolidine (**9**) as white crystals (210 mg., 66%), m.p. 115-117°; ir ν max (Nujol): 3360, 1590, 1180, 1075, 1035 cm^{-1}; ^1H nmr δ TMS (deuteriochloroform): 2.40 (s, 3H), 2.67 (s, br, 2H), 3.28-3.95 (m, 6H), 3.39 (s, 3H), 5.16 (q, 1H), 7.20-7.85 (m, 4H); ^{13}C nmr δ TMS (deuteriochloroform): 21.58 (q, CH_3), 54.14 (q, OCH_3), 55.76 (t, 5-CH_2), 64.41 (t, CH_2OH), 101.45 (s, 2-C), 101.90 (d, 4-CH), 127.64 (d), 129.79 (d), 136.22 (s), 144.28 (s) (aromatic carbons); mass spectrum: (direct inlet) m/e 227 (M^+-$HOCH_2$-$COCH_2OH$), 171 (NH_2-Ts), 155 (Ts), 91.

Anal. Calcd. for $C_{13}H_{19}NSO_6$: C, 49.20; H, 6.03; N, 4.41. Found: C, 49.27; H, 5.85; N, 4.20.

Acid-Catalyzed Hydrolysis of Cyclic Peroxide (**5**).

To a solution of 340 mg. of **5** in 10 ml. of methanol was added 10 ml. of 2*M* hydrochloric acid and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was neutralized with aqueous sodium bicarbonate and extracted with dichloromethane. The combined extracts were dried (sodium

sulfate), concentrated, and then chromatographed on preparative plates (silica gel PF 254) using 10% dichloromethane-ether as the developing solvent. The top band (Rf 0.85) gave, after extraction, methyl *N*-tosylglycinate (**8**) as white plates (93 mg., 41%), m.p. 81-83°.

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