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OXIDATION OF BENZYLOXYCARBONYL THREONINE AND SERINE METHYL ESTERS TO AN OXAMATE DERIVATIVE

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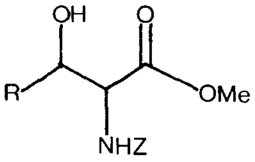
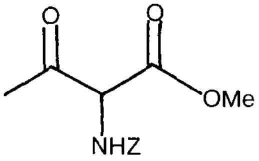
Summary

Both benzyloxycarbonyl threonine and serine methyl esters, when subjected to oxidation with reagents based on chromium (VI) oxide, gave rise to the same N-protected methyl oxamate, whose structure was confirmed by an independent preparation.

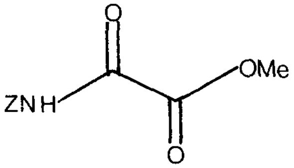
The amino-acid literature contains remarkably little information on the oxidation of serine and threonine side-chains to the ketonic level[1]. A novel course has been observed for such an oxidation, giving the same product from either amino-acid.



(1) R = Me
(2) R = H



(3)



(4)

Z = Benzyloxycarbonyl

In connection with other work in progress in these laboratories, Z-D-Thr-OMe (1) was prepared and subjected to oxidation under a variety of conditions. Z-D-Thr-OH (m.p. 102.5 - 103.5°), $[\alpha]^{20}_{D}$ + 6.7° (c 2, AcOH); (lit. m.p. [2] 101-2°, $[\alpha]^{20}_{D}$ - 5.8°(c 2, AcOH), for L-enantiomer), was prepared according to a standard procedure[3]. Esterification ($MeOH-CH_3C_6H_4$-p-SO_3H) afforded Z-D-Thr-OMe [4] (1) as colourless needles, m.p. 91.5 - 92°, $[\alpha]^{20}_{D}$+ 18.7° (c 1.1, MeOH); ^1H n.m.r. δ ($CDCl_3$) 3.73 (3H, s). None of the oxidation conditions tried gave a synthetically useful yield of the desired ketone (3). When oxidations based on the use of chromium (VI) oxide and related species were employed, an unexpected by-product was obtained. In the case of pyridinium chlorochromate [5], the ketone (3) could be separated in low yield (15%) by chromatography, still not wholly pure. (^1H n.m.r. $\delta[CDCl_3]$ 2.35 [3H, s, ketonic $-CH_3$]). Even with large excesses of the reagent (5 - 10 equiv.) there was considerable unreacted (1). Oxidation with DMSO-based reagents, e.g. DMSO-DCCI-acetic anhydride [6] or DMSO-trifluoroacetic anhydride[7] gave mixtures containing small amounts of (3) (n.m.r.)

On the other hand, oxidation with CrO_3-pyridine in methylene chloride[8], again using about 10 equivs. of reagent, gave complete consumption of (1). A product essentially homogeneous by t.l.c. was obtained (50% yield), m.p. 88.5 - 89.5°, empirical formula $C_{11}H_{11}NO_5$, m/e 237 (M^+), i.r. (Nujol) ν_{max} 3280 (N-H), 1765, 1745 and 1710 cm^{-1} (C = O), $[\alpha]^{20}_{D}$ 0 in $CHCl_3$, MeOH or DMF, ^1H n.m.r. $\delta(CDCl_3)$ 3.95 (3H, s), 5.30 (2H, s), 7.45 (5H, s) and 9.0 p.p.m. (1H, br s, D_2O exch.), ^{13}C n.m.r. $\delta(CDCl_3)$[9] 54.1 (s), 68.6 (s), 128.6-128.9 (m, aryl C), 134.7 (s), 149.9 (s), 154.3 (s), 159.9 (s). The spectral data were most simply accommodated by structure (4) in which the whole threonine side chain had been oxidatively cleaved. A very similar outcome was observed when CrO_3-AcOH (5 eqs) was employed, but the product was less clean (t.l.c., n.m.r.).

The result suggested that the same by-product (4) should result from the corresponding serine derivative, and this was examined next. Z-Ser-OMe[10] (2) under Collins oxidation conditions did not go to completion even with a large excess of reagent, but the CrO_3/AcOH procedure gave, after chromatography, about 40% of reasonably pure (4) with superimposable i.r. and ^{13}C n.m.r. spectra to that obtained from (1). The nature of the by-product was further confirmed by an independent preparation of (4) from benzyl carbamate and methyl oxalyl chloride (Aldrich). Benzyl carbamate was removed by chromatography on silica gel, giving (4) which was indistinguishable (m.p., t.l.c., i.r., ^{13}C n.m.r.) from the oxidation products.

The mechanism of the reaction is open to investigation[11]. It is of interest, however, that the presence of a side chain is necessary. Z-Gly-OMe[12] was found not to be affected by Cr-based oxidants under the above conditions, nor by SeO_2 in aqueous dioxan at reflux.

The author is grateful to Prof. R. Ramage (UMIST) and Dr.G.T.Young (Oxford) for valuable discussions.

References and Notes.

(1) Oxidation of Z-Ser-OMe would presumably yield the enol tautomer, $ZNHC(=CH.OH)CO_2Me$.
(2) E.Wünsch and J.Jentsch, Chem.Ber., 1964, 97, 2490. (3) J.P.Greenstein and M.Winitz in 'Chemistry of the Amino-Acids', vol.2, p.895. (4) This compound and (4) both gave satisfactory microanalytical data. (5) E.J. Corey and J.W.Suggs, Tetrahedron Lett., 1975, 2647. (6) K.Pfitzner and J.Moffatt, J. Amer. Chem. Soc., 1965, 87, 5661, 5670.
(7) Dr.R.Southgate (Brockham Park), personal communication. (8) J.C.Collins, W.W. Hess and F.J.Frank, Tetrahedron Lett., 1968, 3363. (9) Fully proton decoupled spectrum, chemical shifts in p.p.m. downfield from Me_4Si, deuterium locked. (10) C.H.Hassall and J.O.Thomas, J.Chem. Soc. C., 1968, 1495. (11) Dehydration may occur, followed by oxidation of the double bond resulting. Alternatively, as suggested by Professor R.Ramage, an intermediate chromate ester may first be formed which could break down with loss of the side chain. These possibilities are being investigated. (12) Obtained in crystalline form for the first time, m.p. 25-6° (lit.[13] b.p. 170°/0.3mm). (13) F.Weygand, W.Steglich and W.Oettmeier, Chem Ber., 1970, 103, 1655.

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