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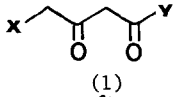
FURTHER INFORMATION ON THE STERIC COURSE OF THE BAKER'S YEAST REDUCTION OF 4-SUBSTITUTED-3-OXOBUTANOATES

Claudio Fuganti, Piero Grasselli, P.Fausto Seneci and Paolo Casati

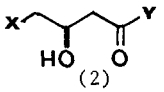
(Dipartimento di Chimica del Politecnico, Centro del CNR per la Chimica delle Sostanze Organiche Naturali, 20133 Milano, Italy, and Sclavo, Divisione Biochimica DE.BI., 20060 Cassina de'Pecchi, Italy)

Yeast reduction of (6), (7), (8), (12) and (13) affords (3R)(9) and (3R)(10) of high optical purity, racemic (11), and (3S)(14) and (3S)(15).

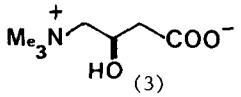
There is a current interest in defining rules for the structural limits of acceptability of non conventional substrates by synthetically useful enzymes.[1] This is particularly the case of 4-heterosubstituted-3-oxobutanoate derivatives (1) reducible by oxidoreductases to carbinols (2), intermediates in the synthesis of the practically important aminoacid (R) carnitin (3). Baker's yeast, the most suited system to perform the reduction of the carbonyl compounds (1) due to its availability, has been shown to contain enzymes acting on the same substrate with opposite stereochemistry and the results obtained up to now point to the presence of a long, hydrophobic alkyl ester moiety (Y= $O(CH_2)_nCH_3$, with n> 7) as the structural requirement for the conversion of (1) with X= Cl, Br into (2) of high optical purity,[2] whereas when X= N_3 products of type (2) are obtained irrespectively of the nature and the length of the ester moiety.[3] Products (1), bearing X= Cl, Br and a short n-alkyl ester, afford preferencially reduction materials enantiomers of (2), optically inactive n-pentyl 4-chloro-3-hydroxybutyrate (5) being obtained in the yeast treatment of (4).[2]



(1)



(2)

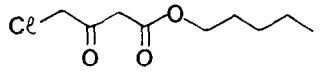


(3)

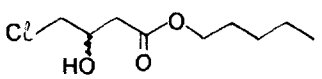
We now report on the steric course of the yeast reduction of a series of substrates of type (2), bearing X and Y substituents of quite different nature, showing the empiricism still informing this area of the applied enzymology.

Thus, yeast reduction of the 4-chloro- and 4-azido amides (6) and (7), containing a five atoms framework as carboxyl group substituent, as (4), affords in 70-80% yield reduction materials shown to contain ca. 90 and 100%, respectively, of the (3R) enantiomers (9) and (10). Indeed, product (7), $[\alpha]_D^{20}$ +19° (c 1, $CHCl_3$), on acid methanolysis, Me_3N treatment and acid

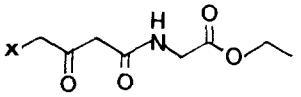
hydrolysis afforded (R) carnitin (3), $[\alpha]_D^{20}$ -25° (c 2, H_2O). The (+) MTPA derivative of (9) was shown by glc to be a 88:12 mixture of enantiomers. Similarly, (10) on hydrolysis and hydrogenation (PtO_2) yields (3R) 4-amino-3-hydroxybutyric acid (GABOB), $[\alpha]_D^{20}$ -21.2° (c 2, H_2O).[3] The tolerance of the yeast enzyme(s) towards (6) and (9) is relevant, up to 140 g of (6) being reduced with 1 kg of yeast. However, product (8) gives rise with yeast in 20% yield to (11), $[\alpha]_D^{20}$ +1° (c 1, EtOH). This material is nearly racemic because product (11) prepared (H_2/PtO_2/ Ac_2O/AcOH) from optically pure (10) showed $[\alpha]_D^{20}$ +12° (c 1, EtOH). However, the N-acetyl and N-trifluoroacetyl esters (12) and (13), at 40 and 80 g/kg yeast, afforded reduction products containing, irrespectively of the lenght of the ester moiety, 90-95% excess of the (3S) enantiomers (14) and (15), in 60-80% yield. The stereochemical correlations were made by comparing the optical properties of (14) and (15) with those of the enantiomeric materials prepared from the corresponding (3R) 4-azido materials[3] and on the basis of ^1H NMR studies onto the O-acetyl derivatives of (14) and (15) in the presence of tris[3-(heptafluoropropyl-hydroxymethylene)-d-camphorato]europium (III).



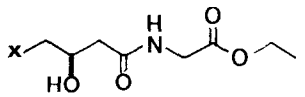
(4)



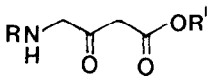
(5)



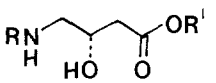
(6) X= Cl
(7) X= N_3
(8) X= $NHCOCH_3$



(9) X= Cl
(10) X= N_3
(11) X= $NHCOCH_3$



(12) R= $COCH_3$; R^1= C_2H_5; n-octyl
(13) R= $COCF_3$; R^1= C_2H_5; n-octyl



(14) R= $COCH_3$; R^1= C_2H_5; n-octyl
(15) R= $COCF_3$; R^1= C_2H_5; n-octyl

These results, seen together, thus indicate that the 'peptide-like' $NHCH_2COOCH_2CH_3$, Y group substituent in (1) is a better 'S-type' enzyme orienting group that the 'fatty-like' long alkyl ester chain,[4] and confirm the ability of a polar 4-substituent (X group in (1)) to shift towards 'R-type' enzymes.

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