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YEAST-CATALYZED ASYMMETRIC REDUCTION OF BENZIL AND BENZOIN TO HYDROBENZOIN

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Abstract: The double reduction of benzil by different yeast strains is carried out with varying enantio- and diastereoselectivity. With selected strains, it is possible to obtain in reasonable yields nearly optically pure (R,R) or (S,S) hydrobenzoin.

The use of microbial reduction of various diketones to obtain one of the optically active **threo** diols has been occasionnally described [1-3] . The reduction of benzil (and substituted unsymmetrical benzil derivatives) has been particularly examined, using Curvularia falcata [1] or Cryptococcus macerans [2] strains; either (R,R) or (S,S)-hydrobenzoin were obtained, together with variable amounts of optically active benzoin and (R,S)-diol. Recently, the reduction of benzil by a bacterium, Xanthomonas oryzae [4] was claimed to afford exclusively (R)-benzoin. In order to clarify some of these conflicting data and to obtain a simple and preparative access to both **threo** hydrobenzoin enantiomers, we have studied the reduction of benzil and benzoin by some currently used yeast strains. Such compounds may represent valuable asymmetric synthons in the preparation of chiral cyclic phosphine ligands used as rhodium complex catalysts.

$$C_6H_5\text{-}CO\text{-}CO\text{-}C_6H_5 \longrightarrow C_6H_5\text{-}CH(OH)\text{-}CO\text{-}C_6H_5 \longrightarrow C_6H_5\text{-}CH(OH)\text{-}CH(OH)\text{-}C_6H_5$$

All cultures were grown [5] at 37°C with moderate shaking during 48 h, then solid benzil or rac-benzoin (50 mg / 50 ml) was added to the suspension, together with glucose (2.5 g), and the cultivation was continued until all the keto-substrate disappeared (usually 3-5 days). The products were extracted with ethyl acetate and analyzed by GPC to determine the extent of reduction to benzoin and hydrobenzoin. The stereochemistry of the reduction products was determined by GPC of the acetylated mixture on a chiral capillary column [6] . The results of typical experiments are reported in table I. From a comparison of the stereochemistry of the reduction products obtained from benzil or from rac-benzoin in similar conditions, it is possible to deduce easily the stereochemical course of each successive reduction. Nearly all cases are represented in the few strains described: interestingly, two of them (S. uvarum, S. montanus) afforded, from benzil, 90-95% optically pure (S,S)-hydrobenzoin, besides an equal amount of the **erythro** diol, through different stereochemical pathways; one strain (R. mucilaginosa) afforded in high yield a 97% optically pure (R,R)-hydrobenzoin. Except for the case of R.glutinis where both reduction steps are of opposite enantioselectivities, the predominance of the same enantioselectivity in both steps, or the higher enantioselectivity in one step, contributes to the formation of high amounts of the **threo** diol isomers, compared to the exclusive formation of the **erythro** diol in the reduction of the same substrates by sodium borohydride. The surprisingly high amounts of (R,R) hydrobenzoin

obtained in the reduction of rac-benzoin by R. mucilaginosa may be attributed to some interconversion of the products and substrate in the culture medium [7].

Table 1: Stereochemistry of the reduction of benzil and (RS)-benzoin to hydrobenzoin isomers by various yeast strains, compared to sodium borohydride.

	Hydrobenzoin obtained from						Enantioselectivity of the	
	benzil reduction			rac-benzoin reduction			1rst reduction	2nd reduction
	%RS	%RR	%SS	%RS	%RR	%SS		
Saccharomyces uvarum	46	2	52	42	35	24	S>>R	S<R
S. montanus	49	2	49	47	17	36	S=R	S>R
Rhodotorula glutinis	82	5	3	46[+]	24[+]	2[+]	S>>R	R>>S
R. mucilaginosa	18	81	1	40	58	2	R>>S	R>>S
NaBH4	100	-	-	100	-	-		

[+] with 28% remaining (S)-benzoin (18% ee).

A preparative experiment using the S.montanus reduction of benzil on a 1g scale yielded after chromatographic separation [8] 0.4 g of (S,S)-hydrobenzoin, mp 145-6 °C, $[\alpha]_D^{20} = -87°$ (c 1.06,EtOH) (94% ee [6]). A similar experiment using R.mucilaginosa yielded 0.55 g of the (R,R) isomer, mp 146-7 °C, $[\alpha]_D^{20} = +87°$ (c 0.97,EtOH) (96% ee [6]). Both isomers could be brought to >98% optical purity by one crystallization.

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5- One litre of liquid medium contained: pancreatic peptones, 5 g; yeast extract, 5 g; malt extract, 5 g; glucose, 20 g.
6- The crude acetylation product (Ac_2O, pyridine) was extracted in ether, washed with diluted HCl and water, and directly injected on a fused silica column (50m x 0.25 mm) coated with XE-60 (S)-valine (S)α-phenylethylamide (Chrompack) to separate the (R,S), (S,S) and (R,R) hydrobenzoins with respective retention times of 40.5 min., 46.5 min. and 48 min. (He pressure: 1.5 bar; 175°C).
7- The interconversion of the reduction products, probably through multiple equilibrated oxido-reductions, was demonstrated by the slow formation of optically pure (S,S)-product from (R,S)-hydrobenzoin, in a 3 weeks incubation with S. uvarum.
8- Medium-pressure chromatography on silicagel H60 (Merck), solvent: CH_2Cl_2-EtOAc (8:2).

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