BIOREDUCTION WITH BAKERS' YEAST OF π - DEFICIENT HETEROCYCLIC ALDEHYDES

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Abstract: The reduction of a few π-deficient heterocyclic aldehydes by bakers' yeast *(Saccharomyces cerevisiae)* is presented. The structure of alcohols such obtained have been supported by spectral and elemental analysis.

Introduction

Biocatalytic reductions are achieved by the first class of enzymes, e.g. the oxidoreductases which catalyze reactions of reduction and oxidation, specifically removal or addition of hydrogen. The common bakers' yeast (*Saccharomyces cerevisiae*), a microorganism that can be used for such purpose is more available than purified reductases that have the disadvantage to need expensive cofactors like NADH or NADPH.

Literature data [1-3] show that this reagent was seldom used for reduction of aliphatic [4,5], aromatic [6], organometallic[7,8] or heterocyclic [9] aldehydes.

Due to the fact that heterocyclic alcohols show potential drug activity [10] we tried to obtain these compounds by reduction of the corresponding aldehydes using bakers' yeast.

Results and discussion

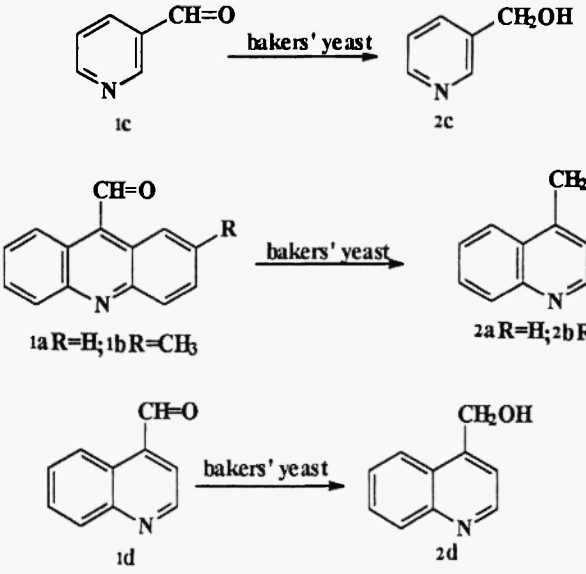
Using bakers' yeast reduction, we succeeded in obtaining a few known hydroxymethyl derivatives of acridine, pyridine, quinoline and three news compounds **2b**, **2e** and **2f** (see Scheme).

Experimental results are collected in Table. The heterocyclic hydroxymethanols were prepared by classical reduction procedures of corresponding carboxylic acids, aldehydes , nitriles, esters, using metal complex hydrides[15-20] or microbiological methods[21]. N-hydroxyalkylation of heterocycles with $R'CH_2OH$ (R'= H, or alkyl) in the presence of oxidizing agent is a rather general method for preparing this type of compounds.[22]

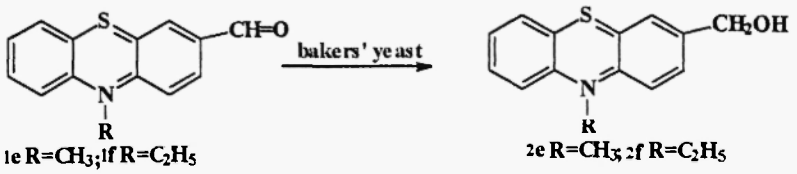
Table. π-Deficient heterocyclic alcohols prepared by reduction of corresponding aldehydes with bakers'yeast.

Com-pound	Reaction time (h)	Yield [yield in classical method] (%)	m.p./ b.p. [lit. m.p./ b.p.] (^{0}C)	Mass spectra m/z	^{1}H NMR (δ ,ppm)	IR ν_{C-OH} cm^{-1}
2a	24	82 [41(1)]	m.p. 164-165 [164 desc.(11)]		3.80,s (CH_2OH)	1050
2b	24	80	m.p.159-160 [159 (12)]		3.95,s (CH_2OH)	1040
2c	48	60 [41-50.4 (14, 15)]	b.p.152-154/28mm [154/28mm (13)]		4.70,s (CH_2OH)	1030
2d	48	50 [23-72(18,17)]	m.p. 98-99 [99-100 (16)]		4.00,s (CH_2OH)	1030
2e	28	74	m.p. 132-134	243 M^+, 228 (M^+-15), 212 (M^+ - 31), 198.	4.60, s (CH_2OH) 1.60, s ($N-CH_3$)	1060
2f	48	83	m.p.91-93	257 M^+, 228 (M^+-29), 225 (M^+- 31), 198	1.45, t (CH_3CH_2N) 3.90, q (CH_3CH_2N) 4.60, s (CH_2OH)	1020

Thus, the bioreduction was carried out according to the following reaction schemes:



Carbohydrates (saccharose, glucose) were used as feeding substrates in the presence of various amount of yeast. The drawback of these carbohydrates is that they are metabolized rapidly



by yeast before the reduction, causing important release of CO_2 with rapid acidification of the medium. But, in the range of molar ratio in which reaction was carried out, the quantity of CO_2 released did not modify the optimum pH range (4.0 - 7.0)[23].

Comparatively with the classical methods, which are in general material consuming (expenssive reagents, dry solvents) bakers' yeast allows to carry out reduction a quite simple installation, at room temperature, with an easy work-up of products and good yields.

Experimental

9-Formil-acridine and formil-phenothiazine derivatives were prepared according to the literature data.[24,25] Chinolin-4-carboxaldehyde and pyridin-3-aldehyde were obtained from Aldrich.

M.p. are given uncorrected. IR spectra were recorded in KBr pellets on a CARL ZEISS JENA UR 20 spectrophotometer. The mass spectra were recorded on a double focusing VARIAN MATT 311 spectrometer, with an electron impact source of 70 eV and 300 mA. The ^{1}H-NMR spectra were recorded with a VARIAN GEMINI-300 MHz instrument using DMSO-d_6 as solvent and TMS as internal standard. TLC analyses were run on plates covered with silica gel, eluted with benzene:ether (8:2, v/v), excepting for phenothiazine compounds, with which a mixture of toluene : acetone (9:1, v/v), was used, and visualized with iodine. Elemental analyses for C,N and H were within ± 0,4% of the theoretical values for the new compounds.

General procedure for reduction

Fresh bakers' yeast (100 g) and saccharose or glucose (4 g) was put into water (200 ml), and the suspension was stirred for 30 minutes. The heterocyclic aldehyde (2 mmol) was separately dissolved into ethanol (50 ml) and ethanolic solution poured into bakers' yeast suspension. The resulting mixture was filled in with water until 1 litre and magnetically stirred for a period of time (specified in the Table).

After that, benzene (100 ml) and ethylacetate (200 ml) were added for extraction of the reaction product; the stirring was continued for two hours. Subsequently, organic and aqueous layers were separated. The organic layer was filtered, dried on Na_2SO_4 sicc., and rotavaporated. The residue was work-up in a specific manner for each compound. Thus, 9-hydroxymethyl-acridine was purified by maceration with petroleum ether when a yellow-green precipitated was obtained. 9-Hydroxymethyl-2-methyl-acridine was obtained pure after evaporation of the organic

solvent; 3-hydroxymethyl-10-methyl phenothiazine was obtained as an oil, which was solidified by maceration with petroleum ether; 3-hydroxymethyl-10-ethyl phenothiazine was also separated as oil which solidified after purified by distillation *in vacuo*; 4-hydroxymethyl - quinoline was crystallized by maceration with hexane. Compounds were recrystallized from ethanol or obtained by vacuum distillation.

IV References

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