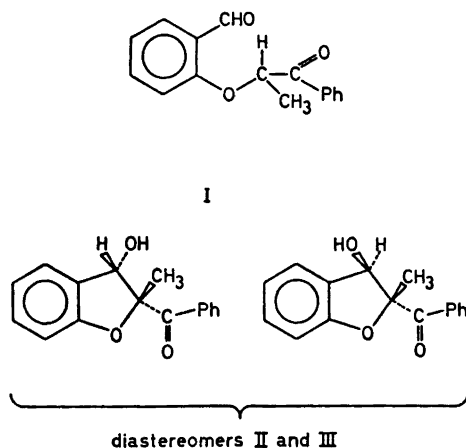


On an Asymmetric Aldol-Type Reaction

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In this paper we will briefly report a successful partial kinetic resolution of the keto-aldehyde I and the formation of optically active diastereomeric ketols II and III in the quinine catalyzed aldol-type condensation of I. Although a large number of asymmetric aldol-type reactions have been studied in detail,¹ this seems to be the first example of the use of a chiral catalytic reagent in a simple clearcut aldol reaction.



The factors determining the diastereomeric product ratio in aldolization reactions have been the subject of many investigations. Dubois and co-workers,² in their extensive studies of the dynamic stereochemistry of aldolization, have elegantly proved the fundamental stereochemical role of the cation in alkoxide catalyzed aldol reactions. Our studies³ of the tertiary amine catalyzed condensations of I, and of the corresponding non-methylated compound, show that the catalyzing amine molecule is of importance not only in the proton abstraction from the α -carbon atom, but also in the product

determining transition states. The formation of optically active ketols (II and III) when quinine was used as a catalyst is a nice probe for the product determining role of the catalyst. This reaction, if it is not run to completion is also a convenient way to obtain I in optically active form, which was necessary to have for our detailed mechanistic studies of the aldolization. These studies will be described fully in a later paper.

The aldol-type condensation of I to II and III goes practically to completion, and any equilibration between II and III is very slow compared to the condensation. The extent of the reaction as a function of time could be followed by PMR, and spectroscopic data indicate that the ketol numbered II in the experimental part below has the methyl- and hydroxyl group in the *cis*-position. The formulae shown do not indicate the absolute configuration of the preferentially formed products. Fig. 1 gives the results of a typical experiment where 60% of the originally racemic I had reacted in dimethyl sulphoxide as solvent. The reaction mixture, after work up, was separated on a Sephadex LH-20 chromatographic column. The eluate was independently analyzed by PMR, optical rotation and also by UV. The peaks in Fig. 1, which gives the optical rotation as a function of the elution volume, could therefore be identified with the substances I, II, and III. The degree of kinetic resolution of I and the stereoselectivity in the formation of the ketols II and III have not yet been determined.

Experimental. The PMR-spectra were recorded with a Varian A60-D spectrometer at 43°C (solvent: carbon tetrachloride, concentration 2.0 g/100 ml). Optical rotations were measured with a Perkin-Elmer 141 M apparatus at 546 nm. Spectra and other analytical data are in agreement with the structures proposed. These data as well as a detailed description of the synthesis of racemic I will be published in detail in a full paper.

Racemic 2-(o-formylphenoxy)-propiophenone (I) was prepared in 79% yield from equivalent amounts of carefully dried sodium salt of salicylaldehyde⁴ and 2-bromopropiophenone⁵ in DMSO as a solvent. When the reaction was complete, the mixture was diluted with excess water and extracted with ether. The product was purified by distillation (b.p. 151–153°C/0.08 mmHg) and repeated re-

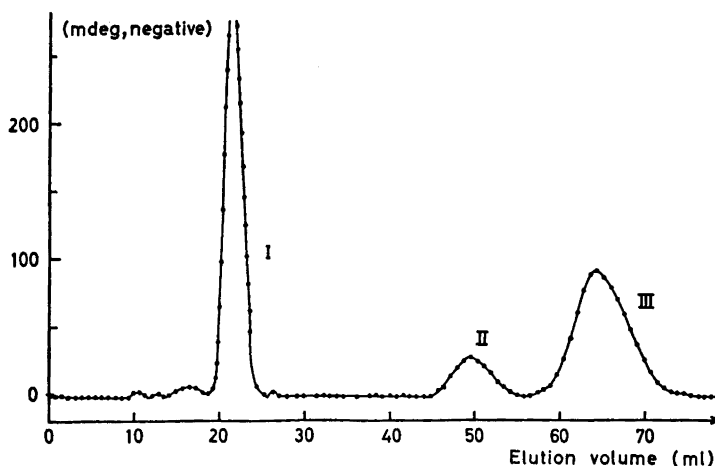


Fig. 1. Chromatographic separation showing the optical activity of the compounds I, II, and III (cf. the experimental section).

crystallization from anhydrous ether, m.p. 58.9–59.7° (uncorrected).

Kinetic resolution of I. To 0.659 g (2.59 mmol) of I was added 1.906 g (5.88 mmol) of quinine, and the mixture was dissolved in DMSO. The solution was made up to 10 ml in total and was then kept at $33 \pm 1^\circ\text{C}$ for 67 h. After that time the reaction had proceeded to 60 % as determined by PMR. The reaction mixture was diluted with 30 ml of carbon tetrachloride, chilled to 0°C , and 7 ml of 2 M hydrochloric acid was added slowly. After shaking and separation, the organic phase was extracted once more in the same way. Washing with water, drying with magnesium sulphate, and evaporation of the carbon tetrachloride gave an oil which contained 40 % of the keto-aldehyde I, 42 % of the ketol III and 18 % of the ketol II as determined by the relative areas of the methyl group absorption bands in PMR. A part of the oil (49 mg) was applied to a column (length 47 cm, diameter 1 cm) containing Sephadex LH-20 swollen in a solvent mixed of 80 vol. % 1,2-dichloroethane and 20 vol. % cyclohexane. Elution was made with the same solvent at a rate of 0.157 ± 0.008 ml/min. The eluting solvent was passed through a polarimetric cell and an ultraviolet detector in series. The optical rotation and the ultraviolet transmittance (254 nm) of the eluent could thus be monitored simultaneously

at all times. The optical rotation as a function of the elution volume is given in Fig. 1. In a separate experiment the keto-aldehyde I was resolved and separated in a similar way (extent of reaction 52 %), and its specific rotation in dioxane was determined to $[\alpha]_{546}^{25} = -29^\circ$ (c, 1.32 g/100 ml).

PMR chemical shifts (δ , ppm rel. TMS)
 I: 1.70 (d) methyl, 5.39 (q) methine, 6.6–8.8 (c) aromatic, 10.40 (s) formyl; II: 1.59 (s) methyl, 5.11 (s) methine, 6.6–8.1 (c) aromatic; III: 1.70 (s) methyl, 5.62 (s) methine, 6.6–8.1 (c) aromatic.

Acknowledgement. This work is part of a research project financially supported by the Swedish Natural Science Research Council.

- Morrison, J. D. and Mosher, H. S. *Asymmetric Organic Reactions*, Prentice-Hall, Englewood Cliffs, N. J. 1971, p. 142.
- Dubois, J.-E. and Fort, J.-F. *Tetrahedron* **28** (1972) 1665, and earlier papers.
- Obenius, U. *To be published*.
- Cajar, H. *Ber.* **31** (1898) 2804.
- Higginbotham, L., Lapworth, A. and Simpson, C. *J. Chem. Soc.* **125** (1924) 2343.

Received June 20, 1972.