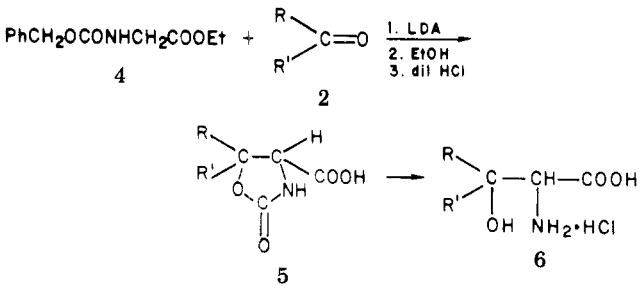
Scheme II



isomerization to the trans configuration upon treatment with base.[9] The latter ring systems may however easily be cleaved to the corresponding threo-α-amino-β-hydroxy acids[8] (Scheme II). Following this line of thought, *N*-carbobenzoxyglycine ethyl ester (**4**) was condensed under basic reaction conditions with a series of carbonyl compounds **2** to the corresponding oxazolidone derivatives **5**. NMR analysis of the crude reaction products revealed for all cases studied the exclusive formation of the transoid oxazolidones **5** (Table II). Subsequent hydrolytic cleavage with concentrated hydrochloric acid afforded the corresponding *threo*-α-amino-β-hydroxy acids **6** in quantitative yields.

The major advantages of the two procedures for the preparation of α-amino-β-hydroxy acids are their stereospecificity, ease of performance, and broad range of applicability, requiring only commonly available starting materials. The use of the synthesized amino acids for the preparation of stereochemically pure fluorinated derivatives is under current investigation.

Experimental Section

Preparation of *dl-allo*-Threonine (3a). Dry diisopropylamine (0.75 mL, 5.31 mmol) was added at 0 °C to a solution of 2 N *n*-butyllithium in hexane (1.92 mL, 3.84 mmol) in freshly distilled THF (25 mL). The colorless solution was then stirred for 30 min, at 0 °C, cooled to −78 °C, and treated dropwise with **1** (1.083 g, 3.75 mmol). The resulting light-brown reaction mixture was stirred for 1 h at the same temperature and subsequently treated with acetaldehyde (0.42 mL, 7.5 mmol). Stirring was continued for 1 h at −78 °C and for 0.5 h at 0 °C. Subsequent acidification of the solution with ethanolic hydrogen chloride and removal of the volatile components in vacuo provided the crude reaction products containing the salts of threonine, glycine, and diisopropylamine. Chromatography of the crude material on a column of AG 50W-X8, 200–400 mesh, H-form, and elution with aqueous ammonium hydroxide afforded *dl-allo*-threonine and glycine (in a 7:3 ratio by NMR) in 92% yield. Recrystallization from ethanol provided pure hydroxyamino acid **3a**. Amino acids **3b–d** were prepared by analogous reaction procedures, as summarized in Table I. The separation of the hydroxyamino acids from the glycine was achieved by fractionating crystallization from ethanol or by rechromatography on AG 50W-X8, 200–400 mesh, H-form, using 1 N HCl as eluent.

Preparation of *dl-trans*-5-Methyl-2-oxazolidone-4-carboxylic Acid (5a). To a cold solution of lithium diisopropylamide in THF, prepared from 5.5 mmol of *n*-butyllithium and 7.5 mmol of diisopropylamine as described above, was added 592 mg (2.5 mmol) of *N*-carbobenzoxyglycine ethyl ester (**4**). The resulting turbid solution was stirred for 1 h at −78 °C and subsequently treated with acetaldehyde (0.4 mL, 7.1 mmol). Stirring was continued for 1 h at the same temperature and for 1 h at 0 °C. Then 1 mL of ethanol was added and the reaction mixture allowed to warm up to room temperature. The reaction mixture was subsequently concentrated in vacuo and the residue was dissolved in water, washed with ether, and acidified at 0 °C with 4 N HCl. Extraction with ethyl acetate provided the crude reaction product (370 mg) containing oxazolidone **5a** and hydrolyzed starting material in a 5:1 ratio as established by NMR analysis. Recrystallization from ethyl acetate–*n*-hexane provided a pure sample of the oxazolidone **5a**.

Preparation of *dl*-Threonine (6a). A sample of *dl-trans*-5-methyl-2-oxazolidone-4-carboxylic acid (100 mg) was hydrolyzed with 2 mL of 6 N HCl in an evacuated sealed tube at 100 °C for 36 h. The reaction mixture was concentrated in vacuo and the residue chromatographed on a column of AG 50W-X8, 200–400 mesh, H-form. Elution with aqueous ammonium hydroxide gave pure *dl*-threonine, 80 mg.

Registry No. **1**, 5630-82-0; **3a**, 71264-40-9; **3b**, 71264-41-0; **3c**, 71264-42-1; **3d**, 71264-43-2; **4**, 1145-81-9; **5a**, 37791-36-9; **5b**, 50706-25-7; **5c**, 50706-23-5; **5d**, 71264-44-3; **6a**, 60143-52-4; acetaldehyde, 75-07-0; glycine, 56-40-6; isobutanal, 78-84-2; benzaldehyde, 100-52-7; acetone, 67-64-1.

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Selective Reduction of Aldehydes in the Presence of Ketones

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In synthetic organic chemistry, it is often necessary to reduce selectively an aldehyde in the presence of a ketone. The usual reagents such as $LiAlH_4$ or $LiBH_4$ show little selectivity so that if such a reduction is carried out in homogeneous solution, both aldehyde and ketone are reduced to a similar extent. Posner[1] has shown that isopropyl alcohol adsorbed on alumina can selectively reduce aldehydes in the presence of ketones, and a variety of other reducing agents derived from borohydrides or aluminum hydrides have been investigated by Brown.[2-4] We here report the selective reduction of aldehyde by $LiBH_4$ adsorbed on molecular sieve zeolites of types A and X.

The stereochemistry of aldehyde and ketone groups is different, and simple geometric calculations show that an aldehyde can penetrate the pore opening of the 5A zeolite, whereas, because of its greater critical diameter, a ketone (even acetone) will be excluded. We therefore decided to investigate the possibility of achieving a selective reduction of aldehyde by using as the reducing agent a 5A sieve containing preadsorbed $LiBH_4$. It proved possible to prepare such a reducing agent by contacting the dehydrated zeolite crystals with a dilute solution of $LiBH_4$ in tetrahydrofuran (THF); when contacted with representative aldehyde–ketone mixtures, this reagent showed the expected selectivity. The results of the competitive reduction experiments are summarized in Table I, and details of both the reagent preparation and the procedure in the reduction experiments are given below. In all experiments, the main product of reaction was the primary alcohol which was obtained in 70–80% yield with no trace of secondary alcohols. The remaining 20–30% of the

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Table I. Summary of Results of Competitive Reduction Experiments

no.	aldehyde	ketone	zeolite	A^a	B^b
1	3-phenylpropionaldehyde	6-methoxy-1-indanone	3A, 5A, 13X	70	90
2	3-phenylpropionaldehyde	cyclohexanone	3A, 5A	75	
3	3-phenylpropionaldehyde	acetophenone	3A, 5A	78	
4	cyclohexanecarboxaldehyde	6-methoxy-1-indanone	3A, 5A, 13X	70	90
5	cyclohexanecarboxaldehyde	cyclohexanone	3A, 5A	75	
6	cyclohexanecarboxaldehyde	acetophenone	3A, 5A	70	

[a] A = percent of conversion to primary alcohol. [b] B = percent of ketone recovered.

reaction product consisted of polymeric compounds formed from the reactants by side reactions. The reactions carried out with 6-methoxy-1-indanone (numbers 1 and 4 in Table I) were carried out quantitatively, and the products of reaction were found to contain no unreacted aldehyde, whereas 90% of the ketone originally present was recovered.

Measurements of the adsorption of $LiBH_4$ on 5A sieve from dilute solution in THF (details are given below) show that at equilibrium the zeolite contains only about 0.5% wt of $LiBH_4$. This low equilibrium capacity suggests that the $LiBH_4$ does not penetrate the zeolite cage structure and is adsorbed only on the external surface of the zeolite crystals. This was confirmed by experiments with 3A sieve (smaller effective pore size through which $LiBH_4$ would certainly not penetrate), which showed about the same equilibrium capacity for $LiBH_4$. The aldehyde/ketone reduction experiments were therefore repeated, using similar reducing agents prepared from the 3A zeolite and from the 13X zeolite. The pore opening of the 13X sieve is large enough to freely admit both aldehyde and ketone molecules, as well as those of $LiBH_4$. As indicated in Table I, the reagents prepared from 3A and 13X zeolites showed almost the same selectivity in the reduction of aldehyde as did the original reagent prepared from the 5A zeolite. Clearly therefore the selectivity of the reducing agent does not arise, as originally postulated, from a simple molecular sieve effect since the evidence suggests that, at least with the 5A and 3A sieves, the reaction takes place on the external surface of the crystals, rather than in the interior, and the external surface is equally accessible to both aldehyde and ketone. Thus, although the potential usefulness of this type of reagent has been demonstrated, elucidation of the reaction mechanism will require a more detailed investigation.

Experimental Section

1. Preparation of Reagent. Molecular sieve crystals (70 g) (diameter ~ 1 μm) were dehydrated at 450 °C in a stream of He for 2 days and then suspended in 200 mL of dry THF. A solution of 1% $LiBH_4$ in THF (5 mL) was added, and the suspension was stirred in a dry atmosphere at 50 °C. Progress of the adsorption of $LiBH_4$ was followed by removing at intervals a drop of supernatant solution and testing it with wet pH paper. After about 8 h, a neutral reaction was obtained, indicating that all $LiBH_4$ had been adsorbed.

2. Adsorption Experiments. The adsorption experiments were carried out essentially as in (1) above, except that the quantities of reagents were modified. Experiments were carried out using various quantities of zeolite and $LiBH_4$ in order to establish the saturation concentration. The quantity of $LiBH_4$ remaining in the solution was estimated by titration. A small sample of the supernatant solution was removed and hydrolyzed by boiling it with water for 10 min in an Erlenmeyer flask. The solution was then titrated against standard HCl. The original $LiBH_4$ solution (1 mL) was also titrated, after hydrolysis, with the standard HCl solution, and the quantity of $LiBH_4$ adsorbed by the zeolite was then found by difference. The same procedure was repeated several times, using different quantities of the 1% $LiBH_4$ solution in THF, and it was found that on average 10 g of zeolite adsorbed about 0.05 g of $LiBH_4$.

One experiment was carried out with a large excess of zeolite (30 g Davison 3A sieve with 150 mL of THF and 3 mL of the 1% solution of $LiBH_4$ in THF). After 10 h, a sample of the zeolite was removed, filtered, and washed with THF and dried in vacuo. Both this sample of sieve and a sample of the supernatant solution were analyzed for Li by atomic absorption spectrophotometry. No detectable amount (<0.1 ppm) of Li was found in the THF solution, whereas the sieve sample contained 199 ppm of Li. This experiment confirms that in the presence of an excess of zeolite virtually all the $LiBH_4$ is adsorbed.

3. Reduction of 3-Phenylpropionaldehydes in the Presence of 6-Methoxy-1-indanone. Reagent (70 g) was prepared as in (1) above. To the suspension of the reagent in THF were added 0.15 g of 6-methoxy-1-indanone and 0.125 g of 3-phenylpropionaldehyde. The mixture was stirred for 6 h in a dry atmosphere at room temperature. Distilled water (100 mL) was added and the mixture stirred for a further period of 1 h. The suspension was then filtered and washed with THF (2 × 100 mL) and then diethyl ether (100 mL). The solvents were removed under reduced pressure, and the residual liquid was extracted with ether. The extract was dried over $MgSO_4$ (anhydrous) and then evaporated to dryness under reduced pressure. The residual products were separated by chromatography on silica gel to afford 0.135 g (90%) of unreacted 6-methoxy-1-indanone and 0.09 of g 3-phenylpropanol in 70% yield: IR (CCl_4) 3440 cm^{-1} (OH); NMR (CCl_4) δ 7.1 (s, 3), 3.5 (t, 2), 2.63 (m, 2), 1.8 (m, 2); mass spectrum parent (70 eV) m/e 136. IR, NMR, and MS were identical with those of 3-phenylpropanol obtained directly from reduction of 3-phenylpropionaldehyde by direct reduction with $LiBH_4$ in THF solution.

The procedure for the reactions with cyclohexanone and acetophenone was essentially the same except that in the workup the solvents were carefully distilled, using a 4 in. fractionating column. Here also 3-phenylpropanol was obtained in 70–80% yield with no trace of the corresponding secondary alcohol.

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Registry No. 3-Phenylpropionaldehyde, 104-53-0; cyclohexanecarboxaldehyde, 2043-61-0; 3-phenylpropanol, 122-97-4; cyclohexanemethanol, 100-49-2.

Methylene Dioxime Formation Using Phase-Transfer Catalysis

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The use of phase-transfer catalysis has been an important tool in the construction of compounds in organic preparations.[1] Dichloromethane has been commonly employed as the solvent in these reactions; however, dichloromethane has also been used as the electrophile in phase-transfer catalysis to form bis(aryloxy)methanes,[2]

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