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PROSTAGLANDIN SYNTHESIS. II. A NOVEL RESOLUTION OF ALDEHYDE AND KETONE INTERMEDIATES

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In a separate communication, we described an efficient synthesis leading to PGE_2, $PGF_2\alpha$, PGE_1 and $PGF_1\alpha$ (1). This synthesis proceeds via intermediates whose only handles for resolution are aldehyde and ketone functionalities. In order that the efficiency of the synthesis might be maintained in the preparation of the natural prostaglandins, a resolution which would utilize these carbonyl functionalities directly was sought. Since the known methodology in this area is quite limited, (2-5) we initiated a search for alternatives. A new method of resolving aldehydes and ketones has been developed and is described below.

In this method the aldehyde or ketone is reacted with an amino alcohol to produce an oxazolidine (6-7). In the cases presented here, we have used ephedrine as the amino alcohol component because it is commercially available in both optical forms, it has generally produced crystalline oxazolidines and it has tended to produce diastereomerically simple mixtures.

The nature of the diastereomeric mixture is of importance because in the formation of an oxazolidine a new chiral center is created. Thus, the reaction of an optically active amino alcohol with a racemic carbonyl compound could possibly produce a mixture consisting of essentially equal parts of four diastereomers. It seems unlikely that such a mixture would be readily separable by crystallization. However, it is clear from molecular models that some of the diastereomers, in cases we have studied, are sterically less favored than others. Just how effective this steric factor can be in reducing the complexity of mixtures has already been shown for the oxazolidines produced from achiral benzaldehydes and ephedrine. In those cases only one diastereomer was detected (7). In the examples presented here, we do not have sufficient evidence to exclude the presence of more than two diastereomers, but the fact that we were able to obtain crystals and achieve a resolution (in very high yield in one case) suggests to us that a predominance of two diastereomers is formed.

Treatment of bicyclic aldehyde 1 with one equivalent of '-ephedrine in methylene chloride at room temperature produced a nearly quantitative yield of an oxazolidine mixture 2 showing two sets of peaks for some hydrogens in the nmr spectrum [nmr($CDCl_3$) δ2.20(s, 1.5, N-C<u>H</u>$_3$), 2.29(s, 1.5, N-C<u>H</u>$_3$), 3.42(d, 0.5, J=8.5 Hz, C_6H_5C<u>H</u>OCH), 3.47(d, 0.5, J=8.5 Hz, C_6H_5C<u>H</u>OCH), 5.4-5.75(m, 1.5,=C<u>H</u>), 5.75-6.0 ppm(m, 0.5, =C<u>H</u>)]. Several crystallizations of this material from isopropyl ether or methanol-water gave a 15% yield (30% of theory for a resolution) of crystals, mp 98-102°, now appearing homogeneous by nmr [nmr($CDCl_3$) δ2.30(s, 3, N-C<u>H</u>$_3$), 3.47(d, 1, J=8.5Hz, C_6H_5C<u>H</u>OCH), 5.4-5.75 (m, 1, =C<u>H</u>), 5.75-6.0 ppm(m, 1, =C<u>H</u>)]. These data suggest that only two diastereomers were formed and that they were separated by crystallization. That the desired separation had occurred was readily shown by acid hydrolysis of the oxazolidine to the optically active aldehyde (CD) hexane, λ(nm), [θ], 350 [0], 322.5[-4,854], 312[-5,683], 302.5[-4,854], 269[0], 250[2,368], 240[0], 210[-34,600]. Moreover, treatment of the optically active aldehyde with *l*-ephedrine produced an oxazolidine with an nmr spectrum identical to that of the oxazolidine purified by several recrystallizations. Thus, the fact that a resolution had occurred and the completeness of that resolution could be determined by nmr spectroscopy!

Similarly, treatment of lactone aldehyde 3 with d-ephedrine in methylene chloride produced oxazolidines 4. This time, however, we were unable to distinguish between diastereomers in the nmr spectrum [nmr($CDCl_3$) δ0.67(d, 3, J=6Hz, CHC<u>H</u>$_3$), 2.32(s, 3, N-C<u>H</u>$_3$), 3.26(d, 1, J=8.5Hz, C_6H_5C<u>H</u>OCH), 4.97 ppm(d, 1, J=8Hz, -C<u>H</u>OH)]. Recrystallization from methanol-isopropyl ether gave crystals, mp 133.5-134.5, in 20% of theory for a resolution. Hydrolysis afforded optically active lactone aldehyde (8), mp 61-64° [$(\alpha)_D$ -30°, (C 0.5, CH_3OH)].

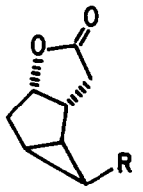
In the third example, treatment of cyclobutanone 5 with *l*-ephedrine and p-toluenesulfonic acid in refluxing benzene produced oxazolidines 6 which again show two sets of peaks for some of the hydrogens in the nmr spectrum [nmr $CDCl_3$) δ3.97(d, 0.5, J=8Hz, C_6H_5C<u>H</u>OCH), 4.00(d, 0.5, J=8Hz, C_6H_5C<u>H</u>OCH), 4.94(d, 0.5, J=8Hz, CH-C<u>H</u>$(OR)_2$), 5.02 ppm(d, 0.5, J=8Hz, CHC<u>H</u>$(OR)_2$]. One recrystallization from methanol gave, in 75% theoretical yield for a resolution, crystals, mp 159-166°, now homogeneous bv nmr [nmr($CDCl_3$) δ3.97 (d, 1), 4.94 ppm(d, 1)]. Hydrolysis (H_2O-THF-HOAC) afforded the optically active ketone 5, mp 43-47° [$(\alpha)_D$ = 84° (C, 0.7, $CHCl_3$)].

Of further interest, chromatography of the oxazolidines on silica gel or alumina resulted in hydrolysis back to the carbonyl compound and ephedrine. This provides a very mild method for hydrolysis of sensitive compounds as might be found for example in compounds with a site subject tc

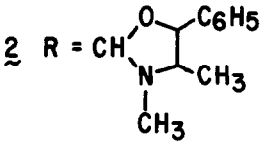
racemization adjacent to the carbonyl functionality.

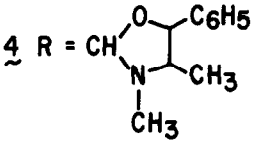
The relative stereochemistries of compounds 1, 3 and 5 were determined by chemical transformation of each to later intermediates on the synthetic pathway to prostaglandins. In this way, it was found that *l*-ephedrine gives the antipodes with the same relative stereochemistry for aldehyde 1 and ketone 5, but of the opposite stereochemistry for aldehyde 3. Further, the absolute stereochemistries of these intermediates were determined by x-ray crystallographic analysis on the optically active dichlorocyclobutanone 7 and by conversion of the intermediates to prostaglandins of the natural configuration (1,8). Thus, it was found that isomers of the natural configuration are obtained by resolving aldehyde 1 and ketone 5 with *l*-ephedrine.

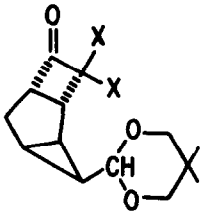
1 R = CHO



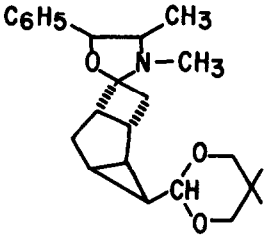
3 R = CHO







5 X = H
7 X = Cl



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8. The x-ray analysis was kindly carried out by Dr. D. Duchamp and C. Chidester, The Upjohn Company.