Novel Resolution of Chiral Lactams

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A practical method of resolving chiral lactams, *e.g.* **1**, has been evolved, based on the hydroxymethylation of the lactam, followed by esterification of the product **2** with an optically active *N*-protected amino acid derivative, *e.g.* *N*-benzyloxycarbonylphenylalanine pentafluorophenyl ester **3**. Chromatographic separation of the unreacted hydroxymethylated lactam **2** and the ester **4** and subsequent dehydroxymethylation of the former and aminolysis of the latter afforded pure enantiomer, (*R*)-**1** and (*S*)-**1**.

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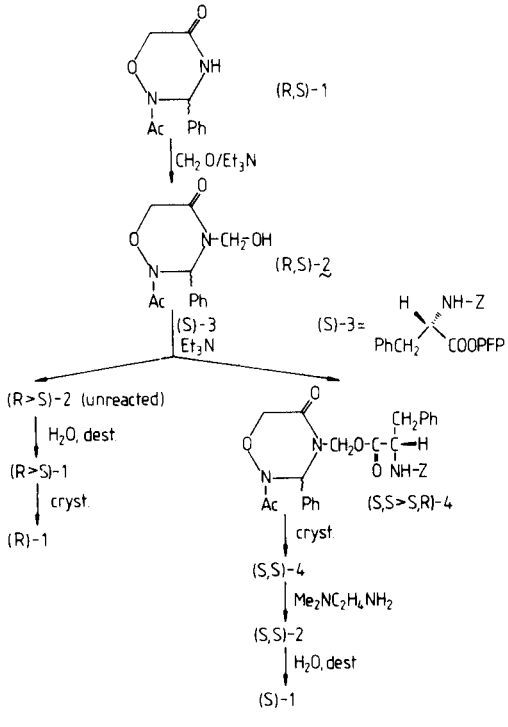
Recently we have published the synthesis, properties and chemical transformations of novel, biologically active 3,4-dihydro-2*H*-1,2,4-oxadiazin-5(6*H*)-ones [1]. The most effective member of the series, 2-acetyl-3,4-dihydro-3-phenyl-2*H*-1,2,4-oxadiazin-5-(6*H*)-one (**1**, RGH-4615) has an anticonvulsive effect similar to that of Phenytoin. It was of interest to prepare the enantiomers of this compound and to test their biological activities.

Optical resolutions are achieved even nowadays mainly *via* formation of diastereomeric derivatives. Common lactam reactions, however, do not lead to derivatives fulfilling the requirements of a useful optical resolution procedure, which are (a) a high yield, (b) stability during the separation procedure, (c) easy recovery of the starting compound without decomposition. Therefore, the usual procedure is to resolve the lactam precursor [2]; to our knowledge, there is only one early publication [3] dealing with the direct resolution of lactams.

Scheme 1



Results and Discussion.

We have found that hydroxymethylation of compound **1** followed by esterification of the hydroxymethylated derivative **2** with an appropriate optically active acid derivative complies with the requirements mentioned above, and proved to be a convenient way for the resolution of **1** (Scheme 1). This method may be a useful tool also for resolving other racemic lactams.

Table 1

Amino acid derivative	[a]	Coupling reagent	ee, %
Z-Ala	0.5	DCCI	6
Z-Phe	0.5	DCCI	6
Z-Phe	0.5	DCCI + PfpOH	27
Z-Phe-OPfp	0.65	Et_3N	41
Z-Pro-OPfp	0.65	Et_3N	12

Z = benzyloxycarbonyl
DCCI = dicyclohexylcarbodiimide
Pfp = pentafluorophenyl
[a] = mole of amino acid derivative/mole of **2**
ee = enantiomer excess in the unreacted fraction

Hydroxymethylation of **1** was accomplished in nearly quantitative yield wilth aqueous formaldehyde in the presence of triethylamine [4]. For the esterification of **2**, *N*-protected amino acids were used. The reaction proceeded with higher or lower stereoselectivity, depending on the acid derivative and the coupling method used (Table 1). The best results were obtained by esterification with *N*-benzyloxycarbonylphenylalanine pentafluorophenyl ester **3** [5]. Less than one equivalent of the acid derivative was used; the unreacted **2** and the resulting ester **4** were separated by chromatography on silica gel column.

The unreacted **2** was dehydroxymethylated by dissolving it in hot water and evaporating the solution twice or three times. Recrystallization gave one of the enantiomers of **1** in optically pure form.

The ester fraction **4** was recrystallized to yield diastereohomogeneous **4**. The ester bond was split by aminolysis with *N,N*-dimethylethylenediamine and subsequent dehydroxymethylation by the above method gave the opposite enantiomer of **1**. In this way, by combining kinetic and termodynamic resolutions, both enentiomers could be isolated in a single procedure, using only one resolving agent.

EXPERIMENTAL

Melting points were determined on a Büchi-Tottoli melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 257 spectrophotometer in potassium bromide pellets. The ^{1}H-nmr spectra were taken on a Varian EM-60 instrument using TMS as the internal standard. The reactions were followed and the purity of products checked by tlc on pre-coated Merck plates (Kieselgel 60 F_{254}, No 5714). Optical rotations were determined on a Perkin-Elmer 241 polarimeter.

2-Acetyl-3,4-dihydro-4-hydroxymethyl-3-phenyl-2*H*-1,2,4-oxadiazin-5(6*H*)-one (**2**).

To a solution of 2-acetyl-3,4-dihydro-3-phenyl-2*H*-1,2,4-oxadiazin-5(6*H*)-one (**1**) (1.1 g, 5 mmoles) in (10 ml) of tetrahydrofuran were added 1 ml of triethylamine and 0.4 ml of commercial formaldehyde solution. After standing overnight, the solvent was removed *in vacuo*. Rubbing the residue with ether gave **2** (1.16 g, 93%), mp 123-126°; ir (potassium bromide): 3330, 1053 (OH), 1675 (C=O), 1648 (C=O), 753, 710 cm^{-1} (Ar); nmr (dimethylsulfoxide-d_6 + deuteriochloroform): δ 2.0 (s, CH_3), 4.7 (AB quadr, CH_2-C=O), 4.8 (AB quadr, N-CH_2-OH), 6.0 (t, OH), 7.0 (s, CH), 7.5 ppm (s, 5H, Ar).

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.49; H, 6.03; N, 10.99.

Acylation of **2** with (*S*)-Benzyloxycarbonylphenylalanine Pentafluorophenyl Ester (**3**).

To a solution of **2** (30 g, 120 mmoles) in dry dioxane (600 ml) were added compound **3** (36 g, 78 mmoles) and dry triethylamine (25.2 ml). After stirring the solution at room temperature for 2.5 hours, the solvent was removed *in vacuo*. The residue was dissolved in 500 ml of ethyl acetate, and extracted successively with 150 ml of 10% citric acid solution 2 x 150 ml water, 150 ml saturated sodium hydrogen carbonate solution and 150 ml water. The organic layer was dried over sodium sulfate and the solvent removed *in vacuo*.

The residue was separated on a silica gel column containing 900 g of silica gel (Merck Kieselgel 60, 0.063-0.2 mm) with a mixture of benzene and acetone (1:1, v/v). The fractions, containing the ester **4** [R_f = 0.65 in benzene-acetone (1:1) on Merck silica gel plates] and the fractions containing unreacted **2** (R_f = 0.4) were separately collected and evaporated to give fraction I (24 g) and fraction II (8.0 g), respectively.

(+)-2-Acetyl-3,4-dihydro-3-phenyl-2*H*-1,2,4-oxadiazin-5(6*H*)-one [(+)-**1**].

Fraction II was dissolved inl boiling water (100 ml) and evaporated to dryness at 80 mm-Hg pressure and 80° bath temperature on a rotavapor apparatus. This procedure was repeated three times. Finally 2 x 50 ml of ethanol was added and evaporated to remove traces of water. Dissolving the residue in 35 ml of hot ethanol, decolorizing with charcoal, seeding at room temperature with racemic **1**, and crystallization at 7° for 3 hours gave almost racemic **1** [3.18 g, $[\alpha]_D$ +20.6° (c = 1, chloroform)]. Evaporation of the mother liquor, and recrystallization of the residue from 35 ml of water gave optically pure (+)-**1** monohydrate (2.6 g, 18%, Calcd. for the theoretical 14.2 g), mp 115°, $[\alpha]_D$ = +264° (c = 1, chloroform); nmr (dimethylsulfoxide-d_6 + deuteriochloroform): 2.13 (s, CH_3), 3.2 (s, H_2O), 4.56 (AB quadr, CH_2), 6.70 (broad, CH), 7.45 (s, 5H, Ar), 9.2 ppm (broad, NH).

Anal. Calcd. for $C_{11}H_{12}N_2O_3$ + H_2O: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.48; H, 6.07; N, 11.70.

(−)-2-Acetyl-3,4-dihydro-3-phenyl-2*H*-1,2,4-oxadiazin-5(6*H*)-one [(−)-**1**].

(*a*) (S)-Benzyloxycarbonylphenylalanine Ester of (−)-**2** (**4**).

Fraction I was recrystallized from 70 ml of ethanol to give diastereopure **4** (20.0 g, 63%), mp 128°, $[\alpha]_D$ = −130° (c = 1, chloroform); nmr (deuteriochloroform): 2.06 (s, CH_3), 3.06 (d, CH_2), 4.53 (t, CH), 4.63 (s, CH_3), 5.01 (s, CH_2), 5.38 (AB quadr, CH_2), 5.41 (d, NH_2), 6.86 (s, CH), 7-7.7 (m), 7.36 (s), 7.43 ppm (s, 15H, Ar).

Anal. Calcd. for $C_{28}H_{27}N_3O_6$: C, 63.03; H, 5.10; N, 7.87. Found: C, 63.11; H, 5.27; N, 7.87.

(*b*) Aminolysis of Ester **4** and Subsequent Dehyroxymethylation to (−)-**1**.

The optically pure ester **4** (10 g, 18 mmoles) was dissolved in 100 ml of chloroform *N,N*-Dimethylethylenediamine (8.5 ml, 78 mmoles) was added. After standing at room temperature for 72 hours, the solution was extracted with 100 and 50 ml of *N* hydrochloric acid, and 2 x 50 ml of water, dried over sodium sulfate and evaporated. The residue was dehydroxymethylated as given above for the isolation of (+)-1, to give (−)-1 monohydrate (3.5 g, 78%, $[\alpha]_D$ = −264° (c = 1, chloroform). Other data are the same as those of the (+)-isomer.

Anal. Found: C, 55.37; H, 6.10; N, 11.82.

REFERENCES AND NOTES

† Deceased.

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