

SYNTHESIS AND REACTION OF OPTICALLY ACTIVE
2-ARYL-cis- AND trans-HEXAHYDRO-3,1,4-BENZOXAZONES

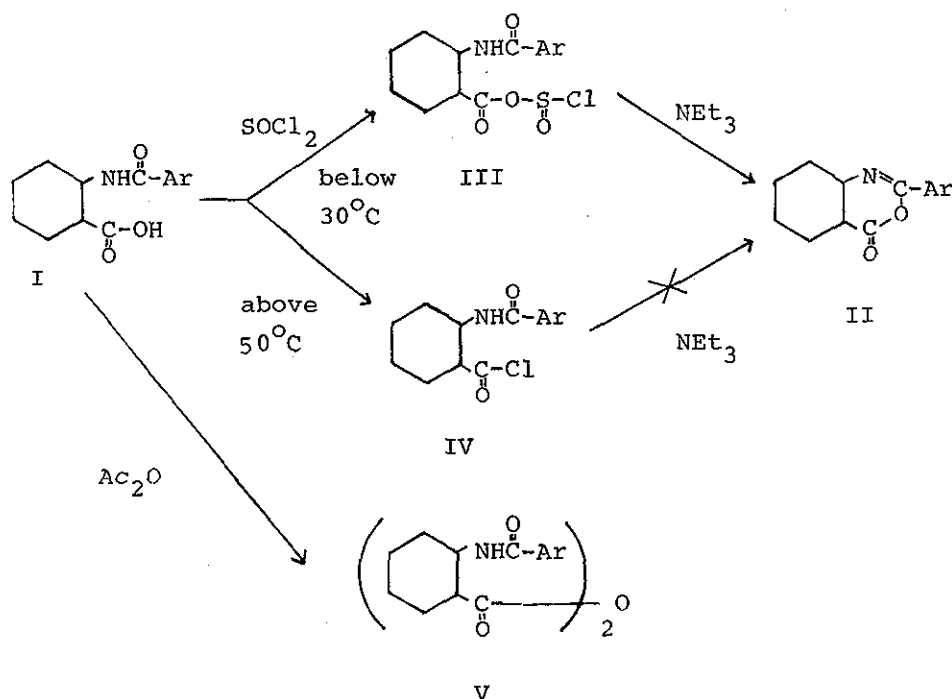
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The titled compounds (II) were prepared from the corresponding optically active N-aryl-cis- and trans-2-aminocyclohexanecarboxylic acids (I) by the action of thionyl chloride and successive treatment with triethylamine. The oxazones readily reacted with alcohols and amines to give the corresponding esters (VI) and amides (VII), providing a convenient method for the resolution of racemic alcohols.

In the course of studies on the synthesis of diastereomeric esters of racemic alcohols and optically active N-phenyl-trans-2-aminocyclohexanecarboxylic acid (trans-I, Ar=Ph), crystals occasionally separated from the reaction mixture. The results of elemental analysis, ir and mass spectra suggested that the crystals have a 3,1,4-oxazone ring structure, that is, 2-phenyl-trans-5a,5,6,7,8,8a-hexahydro-3,1,4-benzoxazone (trans-II, Ar=Ph).

By closer examination for the condition yielding the oxazone, it turned out that the oxazone was derived from the mixed anhydride (III) by the action of triethylamine and that the mixed anhydride was derived from I by the action of thionyl chloride at a temperature below 30°C.



It has been known that 2-aryl-3,1,4-benzoxazones can be prepared by the action of acetic anhydride on N-arylanthranilic acids.¹ The action of acetic anhydride on I, however, failed to give II, and resulted in giving the corresponding anhydride (V) as a viscous oil, Ar=Ph; ir(neat): 3300(NH), 1780(C=O, anhydride), 1715(C=O, anhydride), 1660(C=O, amide), 700(Ph) cm^{-1} ; nmr(CCl_4): δ 1.1-2.3 (m, 18H), 2.4-2.7 (m, 2H), 3.5-3.7 (m, 2H), 7.2-7.4 (m, 6H),

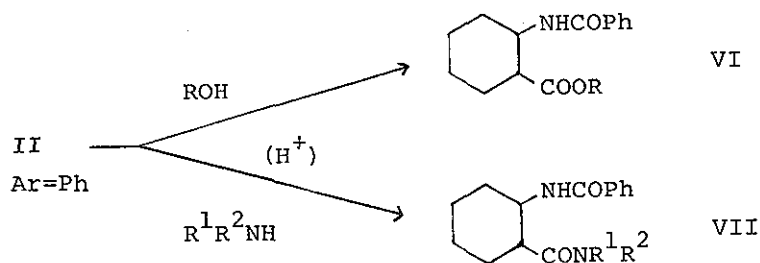
7.5-7.9 (m, 4H). The action of triethylamine on the acid chloride (IV), which was prepared by the reaction of I with thionyl chloride at a temperature above 50°C, also failed to give II. In this case, the product was a very labile liquid, the structure of which was not confirmed so far. A typical procedure for preparation of II now established is as follows. Two grams (8.1×10^{-3} moles) of ($\pm$)-trans-I, Ar=Ph, was treated with 11.7 ml of thionyl chloride for 30 min at room temperature. Then, thionyl chloride was evaporated under reduced pressure. The residual liquid was flash-evaporated with dry ether to remove thionyl chloride completely. This treatment gave the mixed anhydride (III) as a hygroscopic solid, Ar=Ph; ir(KBr): 3380(NH), 1805(C=O, anhydride), 1650(C=O, amide), 1195(C-O), 1130(S=O); Found: N, 4.04%, Calcd. for $C_{14}H_{16}ClNO_4S$: N, 4.25%. Then, III was treated with 2.4 ml of triethylamine in 25 ml of dry benzene for 20 hr at room temperature. After removal of triethylamine hydrochloride by filtration, benzene was evaporated under reduced pressure to give 1.79 g (96.7%) of crude II. Recrystallization from ether gave 1.52 g (82.2%) of pure ($\pm$)-trans-II, Ar=Ph; mp 97°C; ir(KBr): 2920(CH), 1775(C=O), 1660(C=N), 690(Ph) cm^{-1} ; mass: m/e 229 (M^+), 105 (PhCO), 77 (Ph); Found: N, 6.27%, Calcd. for $C_{14}H_{15}NO_2$: N, 6.11%.

Analogous treatment of isomeric I including optically active I gave the corresponding oxazones in good yields. The results are summarized in Table 1. In this experiment, the optically active I was prepared by means of preferential crystallization.²⁻⁴

Table 1. Yields and Physical Properties of the Oxazones

Material I		Product II		
	Ar	Yield (%)	mp ($^{\circ}\text{C}$)	$[\alpha]_{589}^{25}$
(+)-trans,	Ph	96.7	96-97	+22.0 $^{\circ}$ (c 1.00, benzene)
(-)-trans,	Ph	87.6	96-97	-22.0 $^{\circ}$ (c 1.00, benzene)
(+)-trans,	p-Cl-Ph	95.8	109-111	+17.6 $^{\circ}$ (c 0.60, ether)
(+)-trans,	p-NO ₂ -Ph	66.0	124-125	
($\pm$)-cis,	Ph	94.0	75-76	
(+)-cis,	Ph	98.2	45-47	+44.9 $^{\circ}$ (c 0.93, benzene)
(-)-cis,	Ph	89.5	45-47	-45.5 $^{\circ}$ (c 0.93, benzene)

In the presence of a catalytic amount of a strong acid such as p-toluenesulfonic acid, these oxazones reacted easily with alcohols or amines to give the corresponding esters (VI) or amides (VII).



The reaction was smoothly carried out in an aprotic solvent such as benzene, ether or dioxane at a temperature of 30-60 $^{\circ}\text{C}$. Yields and properties of VI and VII are summarized in Table 2 and 3.

Table 2. Reaction of Oxazones with Alcohols

Materials		Product VI		
II, Ar=Ph	ROH	Yield (%)	mp (°C)	$[\alpha]_{589}^{25}$ in EtOH
(±)-trans	EtOH	99.4	127-128	
(-)-trans	EtOH	70.8	147-148	-40.8° (c 0.99)
(+)-cis	EtOH	99.0	95-96	+34.6° (c 1.00)
(±)-trans	n-BuOH	77.9	95-97	
(+)-trans	Ph(CH ₂) ₃ OH	94.4	122-123	+39.8° (c 1.00)
(-)-cis	Ph(CH ₂) ₃ OH	97.8	107-108	-25.6° (c 1.00)
(+)-trans	(-)-MnOH	93.2	129-130	-9.4° (c 1.00)
(-)-trans	(-)-MnOH	87.3	144-145	-72.5° (c 1.00)
(+)-cis	(-)-MnOH	87.3	144-146	-10.4° (c 0.50)
(-)-cis	(-)-MnOH	94.0	108-109	-79.4° (c 0.50)

Each product showed ir absorptions at 3330-3360(NH) 1720-1727(ester linkage), 1635-1640(amide linkage) cm⁻¹.

MnOH: Menthol

Table 3. Reaction of Oxazones with Amines

Materials		Product VII		
II, Ar=Ph	R ¹ R ² NH	Yield (%)	mp (°C)	$[\alpha]_{589}^{25}$ in EtOH
(-)-trans	NH ₃	90.3	297-299	-25.5° (c 0.28)
(+)-cis	NH ₃	83.7	134-136	-15.7° (c 0.64)
(-)-trans	PhNH ₂	81.9	301-303	-69.9° (c 0.35)
(+)-cis	PhNH ₂	98.0	123-124	+36.2° (c 0.43)
(+)-trans	PhCH ₂ NH ₂	99.5	287-289	+4.0° (c 0.10) ^{a)}
(-)-cis	PhCH ₂ NH ₂	99.0	142-143	+11.6° (c 0.45)
(+)-trans	n-Bu ₂ NH	52.0	95-96	+20.0° (c 0.30)
(-)-cis	n-Bu ₂ NH	73.3	oil ^{b)}	+7.4° (c 0.28)

a) in THF, b) bp_{3.2} 240°C (bath temp.)

Each product showed characteristic ir absorptions of amide linkages at 3270-3390 and 1620-1655 cm⁻¹.

As shown in Table 2, each alcohol reacted with the oxazones to give crystalline derivatives. Thus, (-)-menthol reacted with each pair of optically active oxazones to give the corresponding pair of crystalline, diastereomeric esters. This suggests that when an optically active oxazone is reacted with a racemic alcohol, the resulting product is a mixture of diastereomeric esters, which can be resolved by fractional crystallization. The resolution of ($\pm$)-menthol via the diastereomeric esters (VI) has been reported previously³, however, it has become clear that the optically active oxazones (II) can be used more conveniently than the acid chlorides (IV) as resolving agents for racemic alcohols. Further development along this line is now in progress.

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