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The Cyclisation of 1-Aryl-2-Benzamidoalkan-1-Ols to 4,5-Dihydro-Oxazoles or Isoquinolines

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ABSTRAK

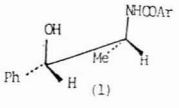
Pencakeraan terbitan N-*benzoil 2-amino-1-fenilpropan-1-o1 telah dilakukan dengan menggunakan kaedah Pictet-Gams yang mengubahsuaikan tindak balas Bischler-Napieralski. Pembentukan 4,5-dihidro-okzazola atau isokuinolina bergantung kepada jenis kumpulan penukar ganti pada kumpulan* N-*benzoil. Cara pembentukannya akan dijelaskan.*

ABSTRACT

The cyclisation of several N-*benzoyl derivatives of 2-amino-1-phenylpropan-1-o1 were carried out employing the Pictet-Gams modification of the BischlerNapieralski reaction. The formation of 4, 5-dihydro-oxazoles or isoquinolines depends on the substituents on the* N-*benzoyl group. The mode of formation of the products is discussed.*

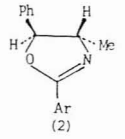
INTRODUCTION

The products from cyclisations of erythro1-aryl1-2-benzamidoalkan-1-ols e.g. (1) in the presence of phosphorus pentaoxide in inert solvents depend primarily on the reaction temperature (Fitton *et al.* 1973). At the temperature of refluxing toluene or xylene, the products are usually *trans/cis* mixtures of 5-phenyl-4,5-dihydro-oxazoles e.g. (2+3), but at higher temperatures. (e.g. that of refluxing decalin), the products are mainly isoquinolines (4), (sometimes rearranged), (Ardabilchi *et al.* 1977), and it is well-established that the pathway to the isoquinolines normally involves 4,5-dihydro-oxazole intermediacy (Fitton *et al.* 1974). On the other hand, the action of polyphosphoric acid (PPA) at 100^{0}C leads only to *trans/cis* 4,5-dihydro-oxazole mixtures, usually in high yield. We have now extended the work by cyclising under various conditions, several *N*-benzoyl derivatives of *erythro* 2-amino-1-phenylpropan-1-o1 (la-d) in which the electronic porperties of the benzoyl groups are altered by incorporation of either methoxy or nitro groups.



(1)

a) ; Ar = 4-$MeOC_6H_4$
b) ; Ar = 3,4-$(MeO)_2C_6H_3$
c) ; Ar = 4-$NO_2C_6H_4$
d) ; Ar = 3,5-$(NO_2)_2C_6H_3$



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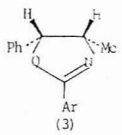

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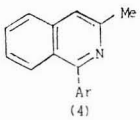

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MATERIAL AND METHODS

All melting points are uncorrected. Infrared spectra (IR) were measured either as nujol mulls or liquid films with a Perkin-Elmer model 257 recording spectrophotometer. ^{1}H NMR spectra were recorded with a Varian A90 spectrometer using tetramethylsilane as the internal standard. Mass spectra (MS) were obtained on an AEI MS12 spectrometer.

Preparation of erythro-2-benzamido-1-phenylpropan-1-ols (1, a -d)

Erythro-2-benzamido-1-phenylpropan-1-ols (1,a - d) (Table 1) were prepared by acylation of the corresponding amines as described by Fitton and Smalley (1968).

General Procedure for Cyclisation of erythro-2-benzamido-1-phenylpropan-1-ols (1,a -d);

To a suspension of the amide 1 (10 g) in the appropriate solvent (30ml) (Table 2) was added phosphorus pentaoxide (10 g) and the mixture was heated under reflux for 1 or 3 h. After cooling, crushed ice was added portionwise to destroy excess dehydrating agent and separate the organic layer. The aqueous layer was washed with ether (100 ml), then basified with 30% aqueous sodium hydroxide until pH 8. The basic layer was extracted with ether (4x100 ml) and the combined extract was washed with water and dried. Evaporation of the solvent gave the cyclised product (Table 2).

TABLE 1
2-Benzamido-1-phenylpropan-1-ols(1)

Compound	Formula	Yield (%)	M.p. (^{0}C)	Found (%) (Required) C	H	N	ν max (cm^{-1})	δ(p.p.m.)/$CDCl_3$
(1a)*	$C_{17}N_{19}NO_3$	63.5	122-123	71.3 (71.6	6.5 6.7	4.9 4.9)	3400, 3300, 1685	7.4(9H,m,ArH), 3.8 (3H,s, OMe), 4.9 (1H,s, OH), 4.0 (1H,m,CH), 5.15 (1H,d,J =6 Hz,CH), 1.0 (3H,d,J=6 Hz,Me)
(1b)	$C_{18}H_{21}NO_4$	68.1	49-150	54.5 (54.8	4.2 4.2	10.6 10.6)	3400, 3318, 1628	6.85 (8H,m,ArH), 7.85 (1H,s,NH), 4.15 (1H,m, CH), 4.85 (1H,d,J=6Hz, CH), 3.35(1H,s,OH), 3.85 (1H,s,2 x OMe), 1.0 (3H,d,J = 6Hz, Me).
(1c)	$C_{16}H_{16}N_2O_4$	186-188		63.8 (64.0	5.5 5.3	9.8 9.3)	3390, 3320, 1690	8.0(9H,m,ArH),4.8 (1H,s, OH), 4.3(1H,m,CH), 4.8 (1H,d,J=6Hz,CH), 1.1(3H,d,J=6Hz,Me).
(1d)	$C_{16}H_{15}N_3O_6$	61.4	156-157	55.5 (55.7	4.3 4.4	12.2 12.2)	3400, 3320, 1640	9.14-7.35(8H,m,ArH), 8.8 (1H,s,NH),4.4,(1H,m, CH)4.9(1H,d,J=6Hz, CH), 3.7 (1H,s,OH), 1.15 (3H,d,J=6Hz,Me).

* Zakaria and Fitton 1973.

TABLE 2
Cyclisation of 2-benzamido-1-phenylpropan-1-ols (1)

Starting amide	Cyclisation conditions	Product (s)	Yield (%)
(1a)	A	(2a) + (3a) (86:14)	66
(1a)	B	(2a) + (3a) (82:18)	43
(1a)	C	(2a) + (3a) (90:10)	93
(1a)	D	(2a) + (3a)	Trace
(1a)	E	Tar	–
(1b)	A	(2b) + (3b) (86:14)	65
(1b)	B	(2b) + (3b) (82:18)	50
(1b)	C	(2b) + (3b) (87:13)	90
(1b)	D	(2b) + (3b)	Trace
(1b)	E	Tar	–
(1c)	A	(1c) recovered	–
(1c)	B	(4c)	17
(1c)	C	(1c) recovered	–
(1c)	E	(4c)	28
(1d)	A	(1d) recovered	–
(1d)	B	(4b)	17
(1d)	C	(1d) recovered	–
(1d)	E	(4d)	36

A Phosphorus pentaoxide in refluxing toluene for 3h.
B Phosphorus pentaoxide in refluxing xylene for 3h.
C Polyphosphoric acid at 100°C for 3h.
D Phosphorus pentaoxide in refluxing decalin for 1h.
E Phosphorus pentaoxide in refluxing decalin for 3h.

Typical Procedure Using Conditions C
To the amides (1 g) in an apparatus described by Fitton and Smalley (1968) was added polyphosphoric acid (20 g) and the mixture was stirred at 100° for 3 h. Excess dehydrating agent was destroyed by addition of ice-water. The aqueous layer was basified with 30% aqueous sodium hydroxide until pH 8 and the basic layer was extracted with ether (4x100 ml). The combined extract was washed with water and dried. Evaporation of the ether gave the mixture of *trans*- and *cis*-4,5-dihydro-oxazole (2 and 3) (Table 2).

1-(p-Nitrophenyl)-3-methylisoquinoline (4c). (See Table 3).

1-(3,5-Dinitrophenyl)-3-methylisoquinoline (4d). (See Table 3).

Trans-cis-2-(p-methoxyphenyl)-5-phenyl-4-methyl-4,5-dihydro-oxazole (2d and 3d). (Ardabilchi *et al.* 1979).

Trans-cis-2-(3,4-Dimethoxyphenyl)-5-phenyl-4-methyl-4,5-dihydro-oxazole (2e and 3e). (Ardabilchi *et al.* 1979).

RESULTS AND DISCUSSION

The benzamides (1a-d) (Table 1) were synthesised by benzoylation in aqueous sodium hydroxide and ethers of *erythro* 2-amino-1-phenylpropan-1-ol, itself prepared by the method of Fitton and Smalley (1968). The benzamide cyclisations were carried out under various conditions, and the results are given in Table 2.

In the presence of phosphorus pentaoxide in refluxing toluene or xylene for 3 h, the

TABLE 3
1-Aryl-3-methylisoquinoline

Compound	Formula	M.p. (°C)	Found (%) (Required)			ν max (cm^{-1})	δ (p.p.m.)/$CDCl_3$
			C	H	N		
(4a)	–	161-162 (Lit.* 158-159)	–	–	–	1640,1600	7.6-8.4(9H,m,ArH), 2.8(3H,s,Me).
(4b)	$C_{22}H_{14}N_6O_7$	208-210 (picrate)	61.7 (62.1	3.5 3.6	13.1 13.6)	1625,1590	7.6-9.1(8H,m,ArH), 2.8(3H,s,Me).

*Zakaria and Fitton 1973.

methoxybenzamides (1a) and (1b) both gave reasonable yields of *trans/cis* mixtures of the 2-(methoxyphenyl)-4,5-dihydro-oxazoles (2a + 3a) and (2b + 3b), respectively. When these cyclisations were repeated in refluxing decalin only tars resulted, although low yields of the corresponding 4,5-dihydro-oxazoles were isolable when the heating period was reduced to 1 h. Increased yields of the 4,5-dihydro-oxazoles were obtained in both cases when the cyclisations were carried out in PPA at 100° for 3 h.

However, attempted cyclisations in PPA of the nitrobenzamides (1c) and (1d) led only to recovery of the starting materials. Similarly, no reactions occurred when the cyclisations were carried out using phosphorus pentaoxide in refluxing toluene for 3 h. However, in refluxing xylene, both amides (1c) and (1d) gave respectively isoquinolines (4c) and (4d) in yields of 17% and 16% which were increased to 28% and 35% respectively when refluxing xylene was replaced by refluxing decalin for a similar 3 h heating period.

Attempted transformations of the 4,5-dihydro-oxazole mixtures (2a + 3a) and (2b + 3b) into the corresponding isoquinolines, by heating with phosphorus pentaoxide in refluxing decalin were unsuccessful with only intractable tars being obtained.

The products were identified from their ^1H n.m.r. spectra. The *trans/cis*-4,5-dihydro-oxazole isomer mixture were not separated, but the isomer ratios were established from the integration of the 4,5-dihydro-oxazole 5-methyl proton signals (doublets), those of the *cis*-isomers appearing upfield ($\delta \sim 0.9$ p.p.m.) compared with those of the corresponding protons of the *trans* isomers which appear at $\delta \sim 1.5$ p.p.m.

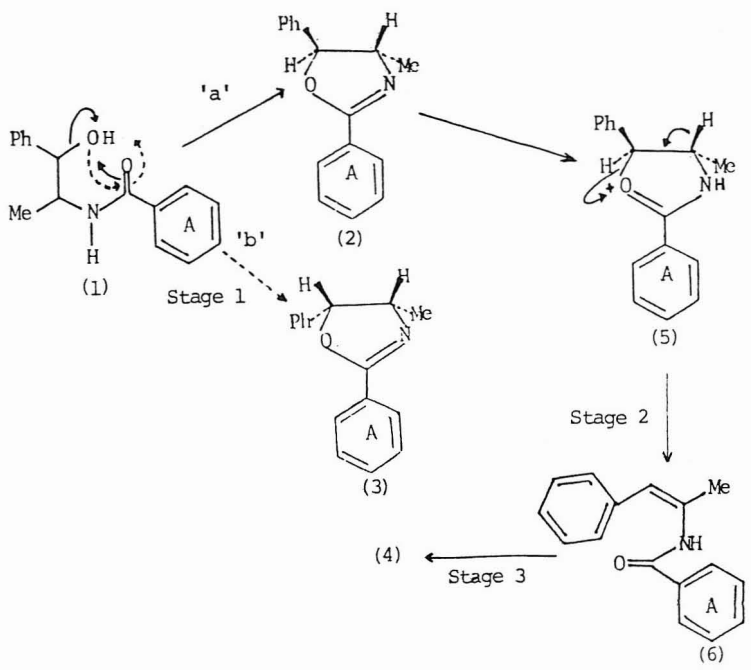
Mechanistic Implications

Since the products from the various cyclisations were exclusively 5-phenyl-4,5-dihydro-oxazole mixtures from methoxybenzamides (1a) and (1b) or isoquinolines from nitrobenzamides (1c) and (1d), the course of the reaction clearly depends on whether the aryl ring A (see Scheme) is overall electron-donationg or electron-attracting. On the basis of 4,5-dihydro-oxazole intermediacy, the formation of isoquinolines from 1-aryl-2-benzamidoalkan-1-ols involves three distinct stages and the opposing effects of the methoxy and nitro groups on ring A are likely to be important in each stage.

5-Phenyl-4,5-dihydro-oxazole formation. - Two mechanisms ('a' and 'b' in Scheme) have been proposed (Welsh 1949) to explain the formation of *trans* and *cis*-4,5-dihydro-oxazoles from *erythro* amides, and the general predominance of the *trans* isomer in the products from these reactions, indicates that mechanism 'a' operates overwhelmingly. If A is electron-donating, this mechanism would clearly be favoured and *trans*-4,5-dihydro-oxazole formation would be promoted. The opposite would be true when A is electron-withdrawing.

5-Phenyl-4,5-dihydro-oxazole ring-opening - This process leads to a vinylamide (e.g. 5) and will clearly be favoured when A is electron withdrawing. Conversely, ring-opening will be hindered when A is electron-donating.

Scheme



Isoquinoline formation - Cyclisation of the vinylamide (6) resulting from stage 2, to an isoquinoline will be favoured when A is electron-withdrawing, but hindered when it is electron-donating.

The results can thus be rationalised on the above basis. Cyclisations involving *erythro* amides (1a) and (1b) lead one to 5-phenyl-4,5-dihydro-oxazoles (mainly *trans*) since the reactions proceed via mechanism 'a'. Ring-opening of the resulting 4,5-dihydro-oxazoles and eventual cyclisation of the vinylamides are both disfavoured.

On the other hand, the alternative but less-common pathway ('b') to the 4,5-dihydro-oxazole will be favoured for *erythro* amides (1c) and (1d) but the resulting (presumably *cis*) 4,5-dihydro-oxazoles are not observed since they are likely to undergo rapid ring-opening, with subsequent cyclisation of the resulting vinylamides to isoquinolines also being favoured.

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