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COMPETING DIMERISATION OF SOME N,O-HETEROCYCLICS

THERMODYNAMIC VERSUS KINETIC CONTROL OF ISOMERIC PRODUCTS†

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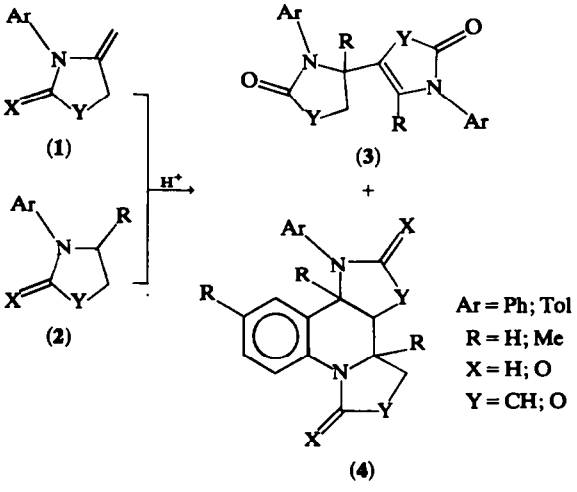
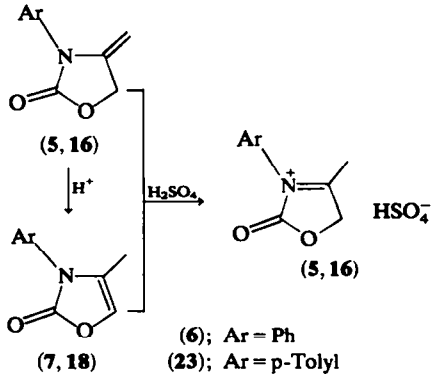
Abstract—The behaviour of substituted 1,3-oxazolidin-2-ones (**1**) and 1,3-oxazolin-2-ones (**2**) on treatment with acid is reported. Electrophylic addition of iminium cations to 1,3-oxazolin-2-onic monomers occurs, yielding the kinetically preferred dimers (**3**). The elimination pathway to **3** is in direct competition with the formation of the cyclodimerisation products resulting from a thermodynamically controlled process. The stereochemistry of the cyclodimers is discussed on the basis of X-ray analysis. Qualitative energetic considerations on the overall reaction and NMR characteristics are discussed using deuterium labelling experiments.

The conversion of isomeric systems of the type **1** and **2** into the dimers **3** and **4** was achieved with good yields under different reaction conditions and acid catalysis.[1-3] These dimeric products **3** and **4** were obtained from a characteristic group of polyfunctional derivatives, i.e. **1** and **2**, through previous electrophylic addition of the most stable cation onto the double bond of the most stable monomer, followed either by an elimination to an alkene **3** or by an aromatic substitution onto the activated aromatic necleus.[3] Although both dimerisation channels could be controlled according to reaction conditions, i.e. strong acidic media[3] favoured the production of the condensed dimer **4**, while the use of more dilute acids[1-3] enhanced the formation of the linear isomers **3**. Selected experiments provided information on the influence of substitution in the substrates **1** and **2**, when they were substituted-1,3-oxazolidin-2-ones and substituted-Δ^4-1,3-oxazolin-2-ones. Thus the entire system at equilibrium was governed by thermodynamic and kinetic factors.



Scheme 1

The use of strong acidic media for the isomerisation of substituted-4-methylen-1,3-oxazolidin-2-ones to substituted-4-Δ^4-1,3-oxazolin-2-ones has been widely investigated.[4] The reaction, using various methods, yielded mainly a catalysed migration of hydrogen cations;[4] but, the concentration of the acid catalyst had a marked effect on the reaction path and therefore on the mixture of products formed.[5] In fact, when 4-methylen-3-phenyl-1,3-oxazolidin-2-one (**5**) was dissolved in 96% sulphuric acid, the corresponding iminium salt (**6**), reported in Scheme 2, was stable. The ^{1}H NMR spectral analysis of **6**, which contained the characteristic singlets for the 4-methyl and 5-methylene



Scheme 2

†N,O-Heterocyclics, Part X: Part IX see ref. 13*b*

groups at δ3.0 and 5.9 respectively and a multiplet centred at 7.6 for the aromatic protons, confirmed the assignment of the structure in analogy with similar systems.[6] Likewise, 4-methyl-3-phenyl-Δ⁴-1,3-oxazolin-2-one (**7**) gave **6** (Scheme 2) when similarly treated. The common behaviour of the two isomers **5** and **7** agreed with the chemical nature of the compounds which were characterised by the enamine functional group.[7] When the method was modified,[4,8] and a solution of **5** poured after a few minutes onto a water-organic solvent with stirring, **7** was recovered in almost quantitative yield (**8** less than 1%) while the formation of **8** in 5% yield was obtained if the iminium salt was left for several hours. Complete isomerisation of **5** to **7**[9] was obtained by adding a catalytic amount of conc sulphuric acid to a dry ether solution of **5** and allowing the reaction to proceed for several hours.

Except for these two reaction procedures, different products were obtained when precursors **5** and **7** were treated with variable amounts of acid.[3-5] Treatment of **5** in the presence of 85% sulphuric acid at room temperature and for 2 hr gave **8** in 90% yield (Scheme 1, where Ar = Ph, R = H, X = O, and Y = O; structure determined by spectroscopic methods), (Table I). Similarly **7** gave **8** under the same reaction conditions and with comparable reaction time. On the other hand, starting from **5** or from **7** using a dilute acid solution (60%) at room temperature for 1.5 hr yielded **9** as the only product isolated (and less than 1% of **8** by NMR). The structure of **9** was assigned on the basis of analytical (Table I) and spectral data (Table III).[3] However, using 65% sulphuric acid solution, **5** yielded a mixture of **9** and **8** at different reaction times. Therefore, NMR monitoring at intervals during the reaction of **5** in 65% acid solution was undertaken in order to follow the reaction process. The ^{1}H NMR spectral analysis of the isomeric **9** and **8** at 100 MHz showed high-field Me absorptions at δ 1.57 (4-Me_3) and 1.46 (13-Me_3) as singlets which increased their area with the time. The dimer **9** was the major product at the inital stage of the reaction of **5** under the conditions described. But when the reaction time was extended (Table II), the condensed dimer **8** was present in increasing amounts together with **9**, until the initial reagent had been completely converted. After prolonged treatment of **5** under these conditions for 20 hr, only the condensed dimer **8** could be isolated as crystalline solid. Similar results were obtained when the precursor **7** was used, as is shown in Table II. The conversion of **9** to **8** (Scheme 1), was further substantiated when **9** was dissolved in 96% or 65% H_2SO_4. In both cases, the linear dimer **9** reacted to yield quantitatively the condensed **8** the reaction was complete.

Total deuteration of **7** at the methyl and the methylene groups yielding **10** was obtained either from **5** or **7**. Similarly, **9** could be obtained in both methyl and the methylene groups yielding **11** or 4′-methyl and 5′-methylene (**12**) could be selectively marked with D, and also 4-Me (**13**) could be selectively deuterated. In the presence of 96% D_2SO_4 at r.t. for 4 hr compound **13** cyclised to the crystalline deuterated dimer analogous to **8** having 13-CD_3 and 4-CD, while **12** gave **15** (5-CD_3 and 6-CD_2) when similarly treated but using H_2SO_4. Dimerisation and subsequent cyclisation of the monomers **16** (Ar = *p*-CH_3-C_6H_4, Scheme 1), in the manner described, but much a lower acid concentration, the precursor being more reactive at 65–50%, resulting in the formation of **20** (Ar = *p*-$CH_3C_6H_4$, Scheme 1) and **17** (Ar = *p*-CH_3-C_6H_4; R = CH_3, Scheme 1), as shown in Table II. Similar results were obtained when **18** was used. Therefore, the synthesis of the linear dimer **20** could be performed in 50% H_2SO_4 solution after 2 hr obtaining a unique product, while, in contrast to the chemical behaviour of the phenyl substituted derivatives **9** and **8**, **17** could be prepared as the exclusive product, after a longer reaction time. Apparently, the lower concentration of the catalyst, i.e. 50% H_2SO_4, induced the initial formation of the hydration product[4] (**19**) due to the addition of water on to the double bond either of **16** or **18**, as confirmed by the NMR spectra[4] taken within 15 min; the alcohol initially formed disappeared

Table I. Physical data for some monomers and dimers of schemes 2 and 3

Compd	Solvent	Ar	R	Mp, °C	Molecular formula		Anal., % C	H	N
16	MeOH	p-CH_3-C_6H_6	-	109-111	$C_{11}H_{11}NO_2$	calcd	69.82	5.86	7.40
						found	70.06	5.81	7.19
18	acetone/ pet. ether	p-$CH_3C_6H_4$	-	91.5-92.5	$C_{11}H_{11}NO_2$	calcd	69.82	5.86	7.40
						found	70.37	6.02	7.43
9	MeOH	C_6H_5	-	137-138	$C_{20}H_{18}N_2O_4$	calcd	68.56	5.18	8.00
						found	68.56	5.17	8.09
20	MeOH	p-CH_3-C_6H_4	-	138-140	$C_{22}H_{22}N_2O_4$	calcd	69.82	5.86	7.40
						found	68.85	5.71	7.25
8	DMSO	C_6H_5	H	290-291	$C_{20}H_{18}N_2O_4$	calcd	68.56	5.18	8.00
						found	68.28	5.26	7.89
17	MeOH	p-CH_3-C_6H_4	CH_3	198-200	$C_{22}H_{22}N_2O_4$	calcd	69.82	5.86	7.40
						found	70.08	5.78	7.54

Table II. Product ratios of linear (**9** and **20**) and condensed (**8** and **17**) dimers formed from different precursors in H_2SO_4

Precursor	Composition of product mixture (%)[a]				Reaction time, h
	9[b]	20[b]	8[b]	17[b]	
5	98		1		1.5[c]
5	40		60		3.5
5	15		85		8.0
5	-		100		20.0
7	96		3		1.5[c]
7	38		62		3.5
7	13		87		8.0
7	-		100		20.0
16		100		-	2.0
16		81		19	43.0
16		14		86	74.0
16		-		100	130.0
18		100		-	2.0
18		78		22	43.0
18		12		88	74.0
18		-		100	130.0

a Ratios are determined by NMR measured methyl protons for each product. Values are ± 2%.

b 9 and 8 are formed in 65% H_2SO_4, 20 and 17 in 50% H_2SO_4.

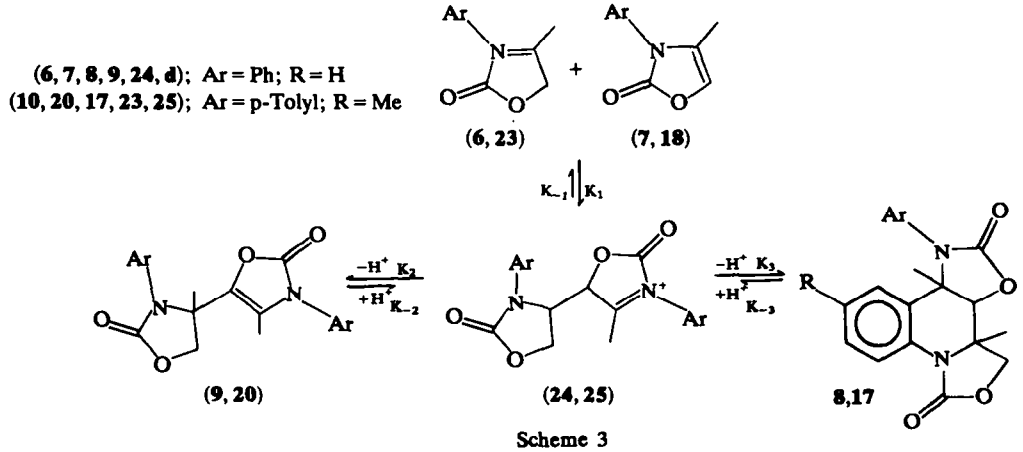
c The iminium salt 5 is still present (1% ca.).

rapidly to give the linear dimer **20**. The formation of **20** from **19** was experimentally checked by an independent procedure. **20** was also partially converted to **17** and the product ratio at different times was in agreement with expectation. The best reaction condition for the synthesis of **17** required 65% of H_2SO_4 and 38 hr.

Under the latter conditions, the precursors **16** and **18** were not completely converted to the corresponding dimers, since their iminium salts were still present in trace amounts during the NMR experiment and **18** was isolated after 48 hr.

Simple structural changes had marked effects on the reactivity of the isomeric dimers. Oxidation of **9** yielded 4-methyl-3-phenyl-1,3-oxazolidin-2-on-4-oic acid (**21**). Bromine substitution gave compound **22** with a bromine in place of an allylic hydrogen, i.e. that on the Me in position 4. Repeated experiments aimed at degrading compound **8** were unsuccessful, since they yielded either tary material or unreacted product because of the very low solubility of **8** to all organic solvents. The solubility of **17** permitted reaction.[10]

The results reported together with earlier experimental findings,[1-5] imply that the condensed dimers **8** and **17** are the thermodynamically more stable



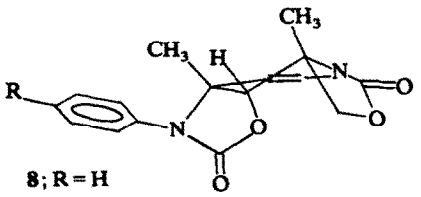
Scheme 3

products and the linear **9** and **20** are initially formed kinetic products which then isomerise to **8** and **17** under acid catalysis. The first step of the reaction from monomers **5**, **16** or **7**, **18** involves electrophylic addition of the iminium cation **6** and **23** onto the double bond of **7**, or **18** thus yielding the intermediate **24** or **25** shown in Scheme 3. The common intermediate **24** or **25** for the production of **9** or **20** and **8** or **17** collapses very rapidly since it is not observed during the time scale of the NMR experiments. This cation gives rise to different reaction products, i.e. **9** and **8**, *via* deprotonation which follows two distinct reaction channels. The competing processes could be selected according to the duration of the acid treatment. In fact, if the reaction under study was stopped before the reverse reaction of **9** to **24** and then to **8** became crucial, the unique or the major isolation product from the reaction mixture was **9** since it was formed more rapidly and then k_2 must be greater than k_3. On the other hand, when the process was continued until the entire system reached the equilibrium, the product isolated was **8** since it was the more stable and thus $k_2 > k_3$. The kinetic and thermodynamic preference observed in the dimerisation process of **5**, **16** and **7**, **18** can be rationalised in terms of different mechanisms involved. The subsequent competing reactions of the cationic intermediate **24** or **25**, i.e., the proton elimination to yield compound **9** or **20** and the electrophylic aromatic substitution which provided the cyclic moiety **8** and **17**, differ in entropy and enthalpy of activation. The product that predominated initially requires a less cogent entropy term since less energy must be expended in the reaction to orginate the looser molecule **9**. On the contrary, the tight transition state to create the most ordered molecule **8**, associated with stringent conformational strain energy (see below), affects the kinetics of the formation of **8**, while the difference in bond energies among reactants and products ($\Delta\Delta H_f^\circ \simeq 29.57$ Kcal/mol, calculated for model systems,[11] as reported in the Appendix) determines the resulting equilibrium-controlled reaction. Thus, by prolonged incubation under strong acid catalysis the most stable product ultimately predominates, even at different reaction time as in the case of **8** and **17**. The higher nucleophylic character of Ar in **25**, i.e. *p*-tolyl, is reflected in the reversibility of the cyclisation process thus yielding an equilibrium which, according to the principle of microscopic reversibility, favours a marked presence of less stable product, as shown in Table II, for a longer period of reaction time.

Additional qualitative considerations, because of the lack of kinetic data related to such or similar systems, on the kinetics and energetics of the overall process, i.e. the isomerisation of **5** and **7**, the dimerisation and the cyclisation, can be inferred from the experiments of H/D exchange, from the comparable reaction rates for each step and from the distinctive fragmentation aptitude of **9** and **8** when ionised in the gas phase under electron impact.[12] All the treatment leading to deuterium incorporation or selective labelling, i.e. the synthesis of compounds **13**, **14** and **12**, **15** respectively, clearly demonstrated that the dimerisation step from **5** or **7** to **9** was not reversible to any measurable extent. In fact, D atoms were completely retained in their original positions without exchange. In addition to the inferences discussed above, the labelling experiments permitted a clear assignment of the NMR absorption signals to the proper group of protons in the case of **9** and **8**, which in turn permitted a similar operation to the **20** and **17** homologous systems by analogy with resonance absorption of the same groups of **9** and **8**. Treatment of **9** with D_2SO_4 provided compound **13** having the 4-Me fully deuterated. The NMR spectrum of **13** shows a singlet at σ 1.77 which is assigned to the 4-Me, This is also confirmed by the disappearance of the signal at δ 1.72 while the deuterium exchange procedure improves the isotopic incorporation. It is worthwhile to note that the allylic protons of 4-Me are observed at lower field than those of 4'-Me in $CDCl_3$ solution probably because of conformational through space interaction and that this interaction changes drastically in sulphuric acid solution since the 4-Me signal shifts to much higher field than that of 4'-Me. In a similar manner, the formation of **14** from **13**, both specifically labelled at 13-Me and 4-Me gave the possibility of demonstrating that the 13-Me signal of **8** occurs at σ 1.55, while that at 2.03 relates to the 5-Me, because of the appearance of the singlet at 2.03 only in the spectrum of **14**. By analogy with **8**, the NMR spectrum of **17** can be interpreted as far as 5- and 13-Me's are concerned, while the tolyl-Me and the 11-Me can be assigned comparing the values obtained for the corresponding monomer. The close position of both tolyl-Me does not allow, however, any rational interpretation without additional information.

Furthermore, the formation of the condensed dimer **8** is fast and is controlled by the rate of the previous dimerisation step which depends on the acid strength of the catalysts used. This is evidenced by the slow reaction from **7** leading to **8** when concentrated H_2SO_4 is employed, despite the fast process from **9** to **8** under the same reaction conditions. The degree of fragmentation in the mass spectra of **9** and **8** parallels their molecular stability;[12] thus **8** shows a molecular ion at m/z 350 which is the base peak of the mass spectrum, while **9**, ionised by electron impact, denounces an increased trend towards unimolecular degradation, $M^{+\cdot}$ being 45% of the base peak.[12]

Moreover, in order to gather additional information on the structural effect in relation to the different chemical behaviour towards most reagents and to evaluate the stereochemistry of both cyclic dimers, the data from the structural analysis by X-ray studies[13] should be discussed. The stereochemistry of the molecules **8** and **17** are very similar, being both characterised by *cis*-fused rings onto the tetrahydroquinoline moiety (Scheme 4). This part of the molecule is rather planar in both homologous compounds, C5 deviating by 0.693 Å (**8**) and 0.745 Å (**17**) from the plane, while C4 is almost in the plane. The aryl ring at position 1 is bent at an angle of 59.7° and 54.2° to the plane of the lactone-lactame functional group for **8** and **17** respectively. Therefore, the less rigid part of the



8; R = H
17; R = Me

Scheme 4

tetrahydroquinoline group in both heterocyclic molecules **8** and **17** adopts a half-chair conformation, reported in Scheme 4, which is distorted from that of a normal conformation of this type because of the steric hinderance of the 1-aryl group and the 5- and 13-Me's of structures **8** and **17**. Furthermore, the largest substituents on the part of the molecule shown in Scheme 4, i.e. that at position 4 and 13, occupy the *pseudo*-axial-*pseudo*-equatorial position respectively relative to the aromatic group of the tetrahydroquinoline, since this axial-equatorial orientation becomes partially relieved of the hindrance due to the 1-aryl group and the adjacent eclipse equatorial position of the condensed aromatic group. In conclusion, the X-ray data[13] show that the chemical differences experimentally observed (*vide supra*) between the two homologous compounds **8** and **17** apparently cannot be justified by stereochemical effects, which in turn, determine the unimolecular fragmentation under electron impact defined by a strongly directing Me expulsion from the molecular ions.[14] The different behaviour of **8** and **17** must be interpreted in terms of electronic effects in respect to their equilibrium ratios in the dimerisation reaction and can probably be related to the two ordered crystal structures which may have a dissimilar clustering tendency of the molecules, thus essentially assigned to their solubility in the solvents used.

EXPERIMENTAL

Mps were obtained with a Kofler hot-stage apparatus and are uncorrected. Elemental analyses were carried out in a Perkin-Elmer 240 Elemental Analyser. Ir spectra were recorded for Nujol mulls on a Perkin-Elmer 225 instrument. ^{1}H NMR spectra were obtained by means of a Varian EM360 spectrometer and of a XL-100 Varian spectrometer for 10% solns in ^{2}H chloroform, $^2H_6$ acetone, trifluoroacetic acid, or $^2H_2SO_4$ with TMS as internal or external standard. Peak positions are reported in terms of σ (ppm) downfield from TMS. Mass spectra

Table III. Spectral data for some precursors and the dimerisation products

Compd	IR spectra, cm^{-1}	^{1}H NMR spectral assignments, chemical shifts, δ[1]	Mass spectra (m/e, rel. intensity)
16	1764(CO),1645,1511,1414, 1348,1250,1208,1087, 1017,822,727.	7.28(s,4H,ArH),5.08(t,$J_{long-range}$ = 2.0Hz, 2H,5-CH_2),4.17 and 4.08(six lines,$J_{long-range}$ = =J_{gem}=2.0Hz,2H,4-CH_2) and 2.37(s,3H, tol-CH_3)[a].	189(M^+,100),145(25),144(50), 117(45),116(23),91(25).
18	1739(CO),1513,1397,1274, 1076,828.	7.5-7.0(m,4H,ArH),6.67(dd,$J_{long-range}$=1.0Hz, 1H, 5-CH), 2,38(s, 3H,tol-CH_3) and 1.89(d, $J_{long-range}$ = 1.0Hz, 3H, 4-CH_3)[b]	189(M^+,75), 133(11), 132(100), 91(24), 65(13).
9	1760(2 -CO), 1735(2-CO),1500, 1490, 1405, 1350, 1115, 700.	7.6-7.0(m,10H,ArH), 4.71 and 4.27 (dd AB gem, J = 9.0Hz, 2H, 5'-CH_2), 1.77(s,3H,4'-CH_3) and 1.72 (s,3H,4-CH_3)[b].	350(M^+,45),231 (100),214(42), 118(55),77(88).
20	1754(2'-CO), 1739(2-CO), 1513, 1395, 1351, 1105, 756.	7.4-6.9(m, 8H, ArH), 4.70 and 4.25 (dd AB gem, J = 9.0Hz, 2H, 5'-CH_2), 2.38(s, 3H, 3-tol-CH_3), 2.35(s,3H,3'-tol-CH_3), 1.75(s,3H,4'-CH_3), 1.68 (s, 3H, 4-CH_3)[b].	378(M^+, 50), 246(100), 229(56) 133(65), 91(40), 83(46).
8	1761(CO), 1739(CO), 1490, 1412, 1350, 1062, 756.	8.1-6.6(m, 9H, ArH), 5.07(s, 1H, 4-CH), 5.01 and 4.49 (dd AB gem, J = 9.0Hz, 2H, 6-CH_2), 2.03 (s, 3H, 5-CH_3) and 1.55(s, 3H, 13-CH_3)[c].	350(M^+, 100), 335(30), 291(4), 247(4), 231(10), 216(64), 202 (14), 187(10), 172(22), 158 (16), 156(9), 144(24), 143(11), 130(8), 119(11), 91(8), 77(14).
17	1761(CO),1748(CO), 1511, 1502, 1404, 1359, 1340, 1230, 1221, 1139, 1079, 1066, 1021, 824, 820, 760, 754.	7.86(d,J_{9-10} = 8.0Hz, 1H, 9-CH), 7.17(broad d, J_{9-10} = 8.0Hz, J_{10-12}= not appreciable, 1H,10-,CH), 7.13 and 6.67 (dd A_2B_2, J_{orto} = 8.5Hz, 4H, 1-ArH), 6.25(broad s, J_{10-12}=not appreciable, 1H, 12-CH), 4.78 and 4.15 (dd AB gem, J_{gem}=8.5 Hz, 2H, 6-CH_2), 4.63(s,1H,4-CH), 2.37(s,3H,1-tol-CH_3), 2.07 (s, 3H, 11-CH_3), 1.80(s,3H, 5-CH_3) and 1.38(s,3H,13-CH_3).[b]	378(M^+,100), 363(26),246(13), 230(82), 216(18), 214(6), 201 (9), 186(17), 184(8), 172(12), 170(13), 158(19), 157(9), 133 (16), 132(17), 91(16), 85(20), 83(32).

1 Spectra obtained in (a, acetone-d_6, (b) $CDCl_3$, (c) CF_3COOH,

were determined on a Varian MAT CH-5DF mass spectrometer, equipped with a Spectro System SS-100 computer, operating at 70 eV and 3 KV. Samples were introduced *via* the direct inlet system, the sample probe temperature being in the region of the mps of the products.

Starting materials. Compounds **5** and **16** were prepared as described.[4] The isomerised **7** and **18** were obtained according to the lit.[9] Analytical and spectroscopic data are given in Tables I and III.

4-[$^2H_3$]-*Methyl*-3-*phenyl*-Δ^4-1,3-*oxazolin*-2-*one* (**10**). A soln of **7** (0.35 g, 0.002 mol) in dry ether (50 ml) was exchanged with D_2SO_4 (96%, 2 ml) in a SVL Sovirel glass tube at r.t. overnight. The soln was washed with dil Na_2CO_3 aq and water until neutral. The operation was repeated twice. The product was isolated after drying (Na_2SO_4) and evaporation of the solvent as an oil which crystallized from n-esane to yield **10** (0.28 g, 80%, [$^2H_4$], 81%; [$^2H_3$], 13%; [$^2H_2$], 4% [$^2H_1$], 2%.

Dimerisation of substituted 1,3-*oxazolidin*-2-*ones*, Δ^4-1,3-*oxazolin*-2-*ones and linear dimers* **3**

General procedure. The appropriate compound (0.002 mol) was added to a flask equipped with rubber septum, containing 20 ml H_2SO_4 at chosen concentration and a magnetic stirring bar. The reaction vessel was maintained at room temp and the mixture was stirred for the period indicated above and in Table II. The homogeneous soln was then poured into water (50 ml) and a ppt formed. The product was filtered off, washed until neutral and recrystallisation of the crude material from the solvent reported in Table I produced the crystalline isomeric compounds. In all reactions a nearly quantitative recovery of material was observed. To obtain the data given in Table II and the other ratios of isomeric products at various reaction times and conditions the NMR spectrum of each mixture was determined by withdrawing the required amount of soln from the reaction vessel. Analytical data are reported in Table I and IR, ^1H NMR and mass spectrometric data are given in Table II.

Deuterium exchange of 4-*methyl*-3-*phenyl*-5-[4'-*methyl*-3'-*phenyl*-*oxazolidin*-2'-*on*-4'-*il*]-Δ^4-*oxazolin*-2-*one* (**9**)

A general procedure was devised in order to obtain the labelled products from the corresponding precursors. This procedure will be illustrated with the preparation of **13**. A dry dimethyoxyethane (5 ml) and D_2SO_4/D_2O (4.8 ml, 50%) soln of the starting linear dimer **9** (0.001 mole) was stirred overnight, at r.t. The soln was then rapidly treated with CH_2Cl_2 (20 ml) and H_2O (20 ml) in a separatory funnel. The organic layer was washed with dil Na_2CO_3 aq, and then with conc NaCl aq. The solvent was removed *in vacuo* and the residual solid was extracted with acetone. Evaporation of the acetone left a product which contained more than 70% deuterium incorporation. The compound thus labelled was again treated in the same manner to yield the product **13** (70%, [$^2H_3$] 89%; [$^2H_2$] 8%; [$^2H_1$] 2%; [$^2H_0$] 1%. The labelled compound **11** was obtained from 9 under dimerisation conditions described using D_2SO_4/D_2O (50%, 2 hr), while the labelled linear dimer **12** was prepared by back exchange employing the method reported above for **13** with the modification of the use of H_2SO_4/H_2O.

Synthesis of labelled 4*H*-5,13-*dimethyl*-1-*phenyl*-1-*aza*-3,7-*dioxa*-*dicyclopenta*-[a,c]-*quinolin*-2,8-*dione* (**14** and **15**). The general dimerisation procedure was followed using 0.003 mol of the linear dimers **13** with D_2SO_4 (96%, 5 ml) for 2 hr to yield (80%, [$^2H_1$] 92%, [$^2H_3$] 5%, [$^2H_2$] 2%, [$^2H_1$] 1%). Identical method starting from **12** with H_2SO_4 (96%, 5 ml) for 2 hr gave 15 (85%, [$^2H_5$] 83%; [$^2H_4$] 9%, [$^2H_3$] 5%, [$^2H_2$] 2%; [$^2H_1$] 1%.

Permanganate oxidation of **9**. The dimer **9** (0.5 g, 0.0014 mol) was added to $KMnO_4$ (2 g) and NaOH (1 ml, 5%) in water (100 ml) and refluxed for 2 hr. The mixture was worked up to give a yellow solid (65% yield) which was recrystallised from aceton-petroleum to the colourless crystalline **21** m.p. 174–175°. (Found: C, 59.94; H, 5.01; N, 6.51: calcd for $C_{11}H_{11}NO_4$; C, 59.73; H, 5.01; N, 6.33%) IR: 2632, 2584, and 2525 (OH), 1736 (CO-OH), 1681 (2-CO) cm^{-1}. ^1H NMR (acetone d_6) σ 7.5–7.2 (m, 5H, ArH), 5.50 (broad s, 1H, OH), 4.68 and 4.29 (dd AB gem, J = 9.0 Hz, 2H, 5-CH_2) and 1.58 (s, 3H, 4-CH_3). Mass spectrum *m/z* (rel. intensity) 221 ($M^{+\cdot}$, 13), 177 (15), 176 (100), 175 (15), 132 (20), 119 (24), 118 (32), 117 (18), 93 (22), 91 (19), 77 (37).

Bromination of **9**. 20 ml of a soln of Br_2 in $CHCl_3$ (1%) was added dropwise with stirring to a soln of **9** (0.004 mol) in $CHCl_3$ (75 ml) at 5°. After the usual workup a yellow oil was recovered and recrystallised from MeOH to afford **22**, m.p. 203–205°. (Found: C, 56.24; H, 4.23; N, 6.60; calcd for $C_{20}H_{17}N_2O_4Br$: C, 55.94; H, 3.96; N, 6.52%) IR: 1752 (CO), 1744 (CO) and 645 (CBr) cm^{-1}. ^1H NMR ($CDCL_3$) δ 7.6–7.1 (m, 1OH, ArH), 4.80 and 4.32 (dd AB gem, J = 9.0 Hz, 2H, 5'-CH_2), 4.00 and 3.85 (dd AB gem, J = 12.5 Hz, 2H, 4-CH_2Br) and 1.82 (s, 3H, 4-CH_3). Mass spectrum *m/z* (rel. intensity) 430 ($M^{+\cdot}$, 6) 428 ($M^{+\cdot}$, 6), 349 (17), 348 (62), 261 (6), 231 (7), 230 (18), 214 (6), 202 (7), 188 (7), 186 (18), 176 (19), 158 (8), 157 (6), 144 (10), 143 (6), 142 (9), 132 (18), 130 (10), 120 (7), 119 (20), 118 (63), 117 (42), 111 (35), 105 (6), 104 (12), 91 (19), 78 (8), 77 (100).

Appendix. The approximate standard heat of formation (ΔH_f°) for the comparison of the linear and condensed dimers are calculated for model system, i.e. 4-anilino-*trans*-2-pentene (**26**) and 2,4-di-methyl-1,2,3,4-tetrahydroquinoline (**27**) respectively, assuming the effect of both lactone-lactame rings identical. Laidler's method is followed, using appropriate Ladler's parameters for the ΔH_f° of different bonds.[11] In the case of compound **27**, the conventional ring strain energy (CRSE) of 1.3 Kcal mol^{-1} due to the cyclohexane ring, is ascribed to the ring strain of the hexatomic heterocyclic moiety. This does not cause a significant error since the CRSE's of cyclohexane and piperidine are almost the same (Δ CRSE = 0.02 Kcal mol^{-1}), owing to the similar C—C and C—N bond lengths. Steric interaction between 4-CH_3 and *ortho*-H has been neglected.[16] The contribution to the estimated heat of formation for **26** (29.57 Kcal mol^{-1}) and for **27** (4.07 Kcal mol^{-1})[11] from the additional ring strain of the pentacyclic moiety in both dimers can reduce the actual value of ΔH_f, particularly for the condensed isomer where steric interaction between the N-phenyl and the "vicinal" methyl group, as shown by X-ray analysis, provides similar effect.

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REFERENCES

[1]G. A. Swan and J. D. Wilcock, *J. Chem. Soc.* Perkin Trans. **1**, 885 (1974).
[2]J. B. P. A. Wijnberg, W. N. Speckamp and J. J. J. de Boer, *Tetrahedron Letters* 4077 (1974).
[3]G. Cum and N. Uccella, *Ibid*, 1343 (1975).
[4]G. Cum, N. Uccella, M. C. Aversa and M. Gattuso, *Atti Soc. Peloritana Sci. Fis. Mat. Nat.* **14**, 425 (1968) and refs therein.
[5]G. Sindona and N. Uccella, 10*th National Conference on Organic Chemistry*, c.p. 16. Ferrara, 3–7 oct (1977).
[6]H. D. Bartfeld and W. Flitsch, *Chem. Ber.* **106**, 1423 (1973).
[7]H. Bohne and M. Haake, *Advances in Organic Chemistry* Vol 9, p 112. Wiley-Interscience, New York (1976).

[8]P. J. Stoffel and W. D. Dixon, *J. Org. Chem.* **29**, 978 (1964).
[9]M. C. Aversa, G. Cum, P. D. Giannetto, G. Romeo and N. Uccella, *J. Chem. Soc.* Perkin Trans. **1**, 209 (1974).
[10]Results from our laboratory.
[11]J. D. Cox and G. Pilcher, *Thermochemistry of Organic and Organo-metallic Compounds*. Academic Press, London (1970).
[12]G. Sindona and N. Uccella, *4th National Conference on Mass Spectrometry*. 12–14 Sept. 1977, Catania (Italy): in preparation.
[13]G. Sindona, N. Uccella, G. Cum, S. Hauser and L. Riva di San Severino, *Cryst. Struct. Comm.* **6**, 809 (1977); G. Sindona, N. Uccella, S. Hauser and L. Riva di San Severino, *Ibid.* **7**, 413 (1978).
[14]G. Sindona and N. Uccella, *2nd Sandbjerg Symposium on Organic Mass Spectrometry*, Sonderborg (DK), 3–7 May (1978) submitted for publication.
[15]K. L. Laidler, *Can. J. Chem.* **34**, 626 (1956).
[16]H. A. Skinner, *J. Chem. Soc.* 4396 (1962).