Monatshefte für Chemie 117, 631—652 (1986)

Monatshefte für Chemie
Chemical Monthly

Configurational and Conformational Aspects of some 5-Methylenedisubstituted-3-pyrrolin-2-ones

Ramon Mercè, Merce Pujol, Josep M. Ribó*, Francesc R. Trull, Genis Valera, and **Asunción Vallès**

Departament de Química Orgànica, Facultat de Química, Universitat de Barcelona, E-08028 Barcelona, Catalunya, Spain

(Received 24 July 1985. Accepted 4 September 1985)

The influence of the disubstitution at the exocyclic carbon atom of 5-methylene-3-pyrrolin-2-ones upon the configurational and conformational equilibria is studied. The results obtained confirm and extend the observations reported in the literature about the factors determining the configurational and conformational equilibria in monosubstituted systems, i.e.: 5-arylmethylene-3-pyrrolin-2-ones and 5(1*H*)-pyrromethenones.

(Keywords: Bile pigment models; NOE; Lanthanide induced shifts; IR spectra; UV/VIS spectra)

Zur Konfiguration und Konformation von einigen 5-Methylen-disubstituierten-3-pyrrolin-2-onen

Es wird der Einfluß der Disubstitution des exocyclischen C-Atoms von 5-Methylen-3-pyrrolin-2-onen auf das Konfigurations- und Konformationsgleichgewicht untersucht. Die erhaltenen Resultate stehen im Einklang mit der Literatur, die sich auf monosubstituierte Verbindungen [5-Arylmethylen-3-pyrrolin-2-one, 5(1*H*)-Pyrromethenone und strukturverwandte Gallenpigmente] beziehen, und vertiefen das Verständnis der Faktoren, die für diese Gleichgewichte maßgebend sind.

Introduction

The configurational and conformational study of 5-aryl-methylene-3-pyrrolin-2-ones and 5(1*H*)-pyrromethenones has helped to clarify many open questions in related bile pigments[1]. The preferred configuration is the *Z* one. This is mainly the result of the nonbonded interactions due to alkyl substitution at the pyrrolinone C-4 carbon atom[1a]. However, other factors must also be taken into account in order to explain this configurational equilibrium, e.g. the influence of permanent partial dipole moments on the conformational angle[1b], and the intermolecular association of 5(1*H*)-pyrromethenones in solution[1c].

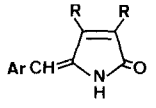
We have previously reported on the nucleophilic addition of HCN to, and the electrophilic substitution (nitration and bromination) on 5-ylidene-3-pyrrolin-2-ones[2,3]. These two types of reactions lead to replacement of the hydrogen atom at the exocyclic double bond by the cyano, nitro or bromo groups. In this paper we present our work on the configuration and conformation of the resulting disubstituted compounds. All methods used in this study had already been utilized by other authors in their work with the monosubstituted precursors.

Results and Discussion

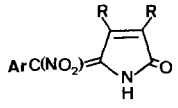
The 5-nitromethylene derivatives **II a**, **b**, **e**, **g**, and *N*-CH_3-**II a**, **b** and bromomethylene derivatives **III a**, **b**, **e**, and *N*-CH_3-**III a** were obtained by nitration and bromination[3] of the corresponding 3,4-dimethyl-5-methylene-3-pyrrolin-2-ones (**I**). The cyanomethylene derivatives (**IV**) were obtained by oxidation with dichlorodicyano-*p*-benzoquinone (*DDQ*) from the corresponding 5-cyanomethylene-pyrrolidin-2-ones (**V**); the latter compounds were obtained by nucleophilic attack of cyanide ion[2] to the 5-ylidene-3-pyrrolin-2-ones (**I**) (Scheme 1).

Scheme 1

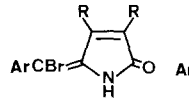
	R	Ar
a	CH_3	4-$CH_3\phi$
b	CH_3	2-$CH_3\phi$
c	CH_3	2,4,6-$(CH_3)_3\phi$
d	CH_3	2,6-$(CH_3)_2\phi$
e	CH_3	4-$CH_3O\phi$
f	C_2H_5	2-$CH_3\phi$
h	CH_3	2-*pyrrolyl*
i	CH_3	N-CH_3-2-*pyrrolyl*
j	CH_3	2-*pyridyl*



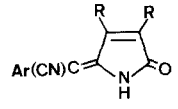
Ia-f



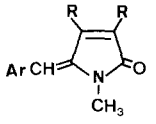
IIa, b, e



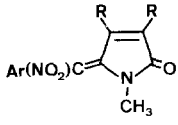
IIIa, b, e



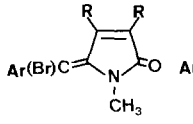
IVa-c



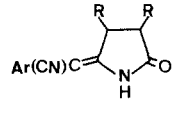
N-CH_3-Ia, b



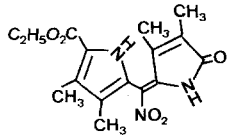
N-CH_3-IIa, b



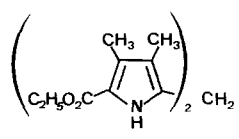
N-CH_3-IIIa



Va-c, f, h-j



(*z*)-IIg



VI

Starting from the compounds **I** containing a lactam hydrogen, we have obtained the nitro- and bromomethylene derivatives (**II** and **III**) always as a single configurational isomer. However, the N-methyl derivatives *N*-CH_3-**II a**, **b**, and *N*-CH_3-**III a** were obtained as mixtures of the *E* and *Z* isomers. The 5-cyanomethylene-3-pyrrolin-2-ones (**IV**) and the 5-cyanomethylene-pyrrolidin-2-ones (**V**) have always been obtained as a mixture of the two configurational isomers, with one of them clearly predominating.

Configuration at the Exocyclic Double Bond

Long range nuclear *Overhauser* experiments upon the nitro and bromo derivatives **II a**, **b**, and **III a**, indicate the existence of a nuclear *Overhauser* effect (NO*E*) between the aromatic protons and the methyl group whose signal appears at higher fields (CH_3-C4, see Table 1). In the mixtures of *E* and *Z* isomers of *N*-CH_3-**II a** and *N*-CH_3-**III a** two NO*E* effects are observed one: between the aromatic protons and the CH_3-C4 signal at higher field (corresponding to one isomer) and other between the aromatic protons and the CH_3—N signal at higher field (corresponding to the other isomer) (Scheme 2). Concerning the 5-cyanomethylene-3-pyrrolin-2-one (**IV a**), one of the two isomers (the minor), with CH_3—C signals at 1.91 and 1.55 ppm (δ), shows a NO*E* between the aromatic protons and the signal at 1.55 ppm; the other configurational isomer, on the contrary, shows no NO*E* effect. In all the above experiments no other NO*E*'s have been observed upon irradiation of the aromatic protons.

The conclusions are: the nitro and bromo derivatives (**II** and **III**) exist as the *Z* isomer (phenyl group *cis* to the CH_3-C4 group); for the N—CH_3 derivatives ^{1}H-NMR signals corresponding to each isomer can be assigned; for the 5—cyanomethylene derivatives (**IV** and **V**) the major component of the mixture has the *E* configuration (aryl group *cis* to the lactam nitrogen).

The above assignements are in agreement with the results of the calculation of the magnetic anisotropy effect of the cyano or nitro groups in these type of compounds. These calculations indicate that the large displacement of the CH_3-C4 signal to higher fields observed in the spectrum of the unique configurational isomer of type **II** and of the minor isolated configurational isomer of type **IV** can only be attributed to the anisotropic effect of an aromatic ring with a conformational angle close to 90° (see below). This indication is strengthened by the similar displacement shown by the bromo derivatives **III** in spite of the different magnetic anisotropic effect of the bromo or of the nitro and cyano substituents.

The anisotropic effects were calculated using standard internal coordinates and the values described in the literature for the magnetic anisotropy of the cyano,

Scheme 2

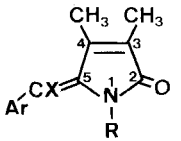


Table 1. *Selected* ^{1}*H-NMR chemical shifts and UV spectral data of several representative compounds of types* **I**, **II**, **III**, *and* **IV**

Structure	Isomer	^{1}H-NMR chemical shifts ($CDCl_3$, δ, ppm)					UV (ethanol), λ_{max} nm (ε)
		CH_3-3	CH_3-4	CH=	H—N[f]	CH_3—N	
(X = H)							
Ia	Z[a, b]	1.94	2.11	6.12	7.9	—	336 (25 000)
	E[a, b]	1.92	1.78	6.62	8.5	—	313 (11 700)
Ib	Z[b]	1.93	2.12	6.16	7.5	—	317 (16 500)
	E[b]	1.90	1.62	6.51	8.8	—	281 (15 000)
Ic	Z[b]	1.90	2.12	6.04	6.7	—	297 (14 400)
	E[b]	1.82	1.43	6.31	8.7	—	266 (14 600)
Id	Z[b]	1.90	2.14	6.05	6.6	—	290 (16 000)
	E[b]	1.90	1.46	6.37	8.7	—	270 (17 700)
N-CH_3-**Ia**	Z[c]	1.93	2.10	6.28	—	2.89	313 (14 100)
	E[d]	1.89	1.69	6.40	—	3.30	307 (10 000)
(X = NO_2)							
IIa	Z[e]	1.88	1.29	—	9.7	—	332 (12 000)

II b	Z^e	1.91	1.24	—	9.8	—	332 (12 000)
N-CH_3-**II a**	E^e	1.95	2.02	—	—	2.58	265 (12 000), 273 (12 600), sh 378 (1 300)[g]
	Z^e	1.88	1.38	—	—	3.09	
N-CH_3-**II b**	E^e	1.97	2.06	—	—	2.45	
	Z^e	1.88	1.29	—	—	3.11	
II g	Z^e	1.89	1.41	—	9.7	—	sh 250, sh 270, 280 (18 000), sh 320 (12 500)
(X = Br)							
III a	Z^e	1.80	1.44	—	7.5	—	302 (17 600)
III b	Z^b	1.78	1.31	—	7.4	—	297 (18 700)
N-CH_3-**III a**	E^e	1.91	2.36	—	—	2.51	
	Z^e	1.80	1.31	—	—	3.52	
(X = CN)							
IV a	E^b	1.97	2.45	—	7.4	—	333 (12 100)
	Z^b	1.91	1.55	—	7.7	—	302 (14 300)
IV b	E^b	1.97	2.47	—	6.9	—	293 (14 800)
	Z^b	1.89	1.38	—	7.6	—	289 (12 500)
IV c	E^b	1.96	2.47	—	6.7	—	282 (14 000)
	Z^b	1.89	1.34	—	7.6	—	285 (15 500)

[a] Ref. [1a, e].
[b] This work.
[c] Ref. [27].
[d] Ref. [1e].
[e] Ref. [12] and Ref. [3].
[f] Chemical shifts depending on concentration.
[g] UV spectra of a mixture of E and Z isomers ($\cong$ 1/1).

nitro, phenyl, and pyrrolyl group[4–7]. The results obtained were in accord with the experimental ones; e.g. in the case of **IV a** no effect is expected on the CH_3-C3 groups in any of the two configurations and for any conformation; on the contrary, when the cyano group is *cis* to the CH_3-C4 group, then an estimated shift of this signal to lower fields of about 0.5 ppm should result [compare the chemical shift of 2.45 ppm for (*E*)-**IV a** to the value of 2.1 ppm for (*Z*)-**I a**].

The quantitative analysis of the lanthanide induced shifts (LIS) also supports the suggestion that in all compounds of the series **I**–**V** the large displacement to higher fields of either the CH_3-C4 or the *R*-N signals must be attributed to the aromatic residue. When a quantitative LIS analysis is performed[8–10] on the bromo derivative **III a** (see experimental part), it gives *R*(%) values—for the structure of the *Z* isomer (Br *cis* to lactam N)—of 1.6, 1.4, 2.8, and 2.7, corresponding to conformational angles of 0°, 30°, 60°, and 90° respectively. For the same conformational angles of the *E* isomer, the *R*(%) values found are 18.8, 21.0, 12.4, and 12.5. Application of the *Hamilton* test to these *R* values permits the exclusion of the *E* isomer to a significance level higher than 95%.

Conformational Aspects

Nitro Group

The results obtained show that the CH_3—N nitro derivatives *N*-CH_3-**II a**, and **b** have different conformation of the nitro group than the respective N—H derivatives **II a**, **b**, **e**, and **g**. The electronic spectra of compounds **II a** and *N*-CH_3-**II a** are so distinct from each other (see Table 1), that the difference cannot be explained only by the mixture of *E* and *Z* isomers in *N*-CH_3-**II a**; rather, very different chromophoric systems must be involved in the two compounds. On the other hand, even simple magnetic anisotropy considerations about the nitro group[5] indicate that, only when the nitro group in *N*-CH_3-**II a** or **b** is orthogonal to the plane of the 5-methylene-3-pyrrolin—2-one fragment, it can produce the observed slight diamagnetic effect ($\cong$ 0.1 ppm) upon the CH_3-C4 or CH_3—N signals [compare in Table 1 the chemical shifts of the pairs (*E*)-*N*-CH_3-**I a**—(*Z*)-*N*-CH_3-**II a**, and (*Z*)-*N*-CH_3-**I a**—(*E*)-*N*-CH_3-**II a**]; contrarily, a nitro group coplanar to the methylene-pyrrolinone fragment must produce a paramagnetic shift upon CH_3-C4 or CH_3—N.

For the N—H nitro derivatives **II**, only the *Z* isomer (nitro group *cis* to the lactam hydrogen) can be isolated. This makes it difficult to extract any information about the nitro group conformation from the ^{1}H-NMR data. Nevertheless, the higher chemical shift (9.5–9.7 ppm) of the N—H signal found for the compounds of type **II** compared to their precursors **I** (7.5–7.8 ppm) seems to confirm a conformation where the nitro group is coplanar to the 5-methylene-3-pyrrolin-2-one fragment, thus exerting a

paramagnetic shift upon the NH and/or binding the lactam hydrogen through an internal hydrogen bond. Indeed, the IR spectrum analysis of the NH stretching bands confirms this nitro group conformation: **I a** in CCl_4 shows a free stretching band at 3 466 cm^{-1}, and an associated one at 3 238 cm^{-1}. The last band is even detected at concentrations as low as $8 \cdot 10^{-4}$ mol dm^{-3}, in agreement with the reported association constant (close to 1) for the equilibrium between monomeric and dimeric lactam[1c]. In turn, **II a** in CCl_4 (at all concentrations between $1 \cdot 10^{-4}$ and $1 \cdot 10^{-2}$ mol dm^{-3}) shows a unique band at 3 430 cm^{-1}. In CCl_4 : Dioxane (4 : 1), **I a** displays the associated broad band at 3 320 cm^{-1}, but **II a** does not show such a band, and the absorption at 3 430 cm^{-1} has not shifted. These results—position and behaviour of the NH stretching band—indicate the formation of an intramolecular hydrogen bond in **II a** between the nitro group and the NH, which is only possible in a conformation where the nitro group stays coplanar to the methylene pyrrolinone fragment.

Aryl Group

As shown above, the high field resonances of the CH_3-C4 protons of (*Z*)-5-nitro-, (*Z*)-5-bromo-, and (*Z*)-5-cyano-, -methylene-3,4-dimethyl-3-pyrrolin-2-ones, (*Z*)-**II**, (*Z*)-**III** and (*Z*)-**IV** respectively, are characteristic of these series of compounds. It is known that in the (*E*)-arylmethylene-3,4-dimethyl-3-pyrrolin-2-one **I** (aromatic ring *cis* to CH_3-C4), the magnetic anisotropy of the aromatic residue—its conformational angle taken into account—determines the diamagnetic shift of the CH_3-C4 group with respect to the value in the corresponding *Z* isomer[1d]. This anisotropic effect of the aromatic ring, although not easily related to the conformational angle, is also noticed upon the hydrogen of the exocyclic double bond (see Table 1). In the (*Z*)-5-methylene disubstituted 3-pyrrolin-2-ones **II**, **III**, and **IV**, the anisotropy of the phenyl upon CH_3-C4 is even larger [compare in Table 1 (*E*)-**I a** with (*Z*)-**II a**, (*Z*)-**III a**, and (*Z*)-**IV a**]. Although electronic effects of the second substituent at the exocyclic double bond cannot be excluded, they probably are not too important, as proved by the similar chemical shifts of CH_3-C3 in (*E*)-**I a**, (*Z*)-**II a**, (*Z*)-**III a** and (*Z*)-**IV a**, even though the electronic effects of the cyano and nitro groups are quite different from these of the bromine. In order to demonstrate that the mentioned high diamagnetic shift is principally produced by the aromatic ring being at a conformational angle close to 90°, we carried out the ^{1}H-NMR conformational analysis of the *E* and *Z* isomers of **I b**, **c**, and **d** (see formula scheme). The results of Table 1 show how the *ortho* methyl substitution at the phenyl ring (compounds of type I) determines a diamagnetic shift of the CH_3-C4 signal in the *E* isomer

(phenyl group *cis* to the CH_3-C4) which increases with the number of *ortho*-methyl groups present. Furthermore, for the 2′,6′-dimethylphenyl substituted compounds (*E*)-**I c**, and **d**, the shift is of the same order of magnitude as for the *Z* isomers of the nitro-, bromo-, and cyano-substituted series (in all cases, phenyl *cis* to CH_3-C4), suggesting a similar conformational angle in all these compounds. On the other hand, the quantitative LIS analysis (see experimental part) on the *E* and *Z* isomers of compounds **I c**, and **d**, also shows this increase of the conformational angle, and thus, for the *Z* isomers of those compounds, the *Hamilton*'s test gives an 80% significance level at 45°–75°, and 45°–70° respectively [30°–40° for (*Z*)-**I a**[1d]]. Quantitative LIS analysis does not work for **I b**, because of the existence of an equilibrium between the two diastereomeric *syn* and *anti* conformers. Concerning the *E* isomers, it is well known that—as a consequence of the structure of the lanthanide-substrate complex—they do not give good significance tests compared to the corresponding *Z* isomers[1d, 10]. Even so, this procedure gives for (*E*)-**I b**, **c**, and **d** conformational angles closer to 90° than for the respective *Z* isomers. In agreement with that, the electronic spectra (see examples of Table 1) show (within each pair of configurational isomers of the series **I**) a bathochromic shift of the *Z* with respect to the *E* isomer. This shift can be related to a higher conformational angle (about 10° to 20°) in the *E* configuration[1d]. In summary, the *ortho*-substitution produces an increase of the conformational angle which, in turn, results into a diamagnetic shift of the CH_3-C4 group in the *E* isomers of **I** (phenyl *cis* to CH_3-C4). When the conformational angle is close to 90° the shift is of the same order of magnitude than the observed one for the *Z* isomers of the nitro, bromo, and cyano substituted derivatives [**II**, **III**, and **IV**(phenyl *cis* to CH_3-C4)], an additional indication of the aryl group conformational angle in this type of compounds.

This effect of *ortho* substitution found in series **I** is also observed—through the ^{1}H-NMR chemical shifts (see Table 1)—in the series **III** and **IV**: i.e. (*Z*)-**III b** and (*Z*)-**IV b** (one *ortho* methyl group) seem to have diedral angles larger than (*Z*)-**III a** and (*Z*)-**IV a** respectively (no *ortho* substitution); however, (*Z*)-**IV c** (two *ortho* methyl groups) is not different from (*Z*)-**IV b** (one *ortho* methyl group), an indication that both compounds have similar conformational angles near 90° as a result of the non bonding interactions due to the bulky *ortho* substituents. The electronic spectra also agree with this hypothesis (see Table 1).

The nitro series deserves a special comment: the CH_3-C4 chemical shift in (*Z*)-**II a** and (*Z*)-**II b** is similar and particularly low (see Table 1), the electronic spectra of these two compounds are also alike (see below), both observations indicate similar phenyl group conformational angles close to 90° in the two compounds. This can be explained by the spatial

requirements of the nitro group coplanar to the methylene-pyrrolinone fragment. On the contrary, an *ortho*-substitution effect is observed between (*Z*)-*N*-CH_3-**II a** and (*Z*)-*N*-CH_3-**II b**, indicating that the spatial requirements of a nitro group orthogonal to the methylene-pyrrolinone fragment are much smaller than those of a coplanar nitro group. As already stated, another proof of the phenyl-to-methylenepyrrolinone orthogonality within the N-unsubstituted (*Z*)-**II** series comes from the electronic spectra. (*Z*)-**II a**, **b**, and **e** show indistinguishable electronic spectra above 290 nm: all three compounds display a broad band at 332 nm ($\varepsilon = 12\,000$). The nitromethylene pyrromethenone (*Z*)-**II g** in turn shows a spectrum which can be exactly reproduced (above 290 nm) by superimposing the spectrum of (*Z*)-**II a** [chromophore: (*Z*)-5-nitromethylene-3-pyrrolin-2-one] and one "half" of the spectrum of the dipyrrylmethane **VI** (chromophore: substituted pyrrole). This result suggests that (*Z*)-**II g** has the pyrrole ring orthogonal to a planar nitromethylene-3-pyrrolin-2-one fragment. Such a behaviour has also been observed in the 5-nitroverdins[11, 12, 13], which have the same *Z* configuration at the nitromethylene bridge like the compounds of type **II** and also a conformational angle of 90°: consequently, the 5-nitroverdins have a violin-like electronic spectrum[11], with the exception of the UV band [($\cong$ 320 nm) of intensity $\varepsilon = 40\,000$] higher than the one displayed by the "pure" tripyrrinone system[14] ($\varepsilon = 20\,000$); on the basis of the above, we explain this higher intensity by the addition of the absorption of the 5-nitromethylene-3-pyrrolin-2-one system to that of the tripyrrinone itself.

Interconversion between E and Z Isomers

The thermal interconversion between the *E* and *Z* isomers of the compounds belonging to the monosubstituted series **I** has already been described[1a, e, f]. In this series one of the isomers, (*E*), is much less stable than the other, (*Z*), so that only this isomer is obtained almost exclusively. However, photoisomerization from the most stable configuration permits the isolation and subsequent study of the two isomers[10]. Unfortunately, we have been unable to prepare photochemically the less stable isomer of the series **II**, **III**, and **IV**, because reactions other than photoisomerisation take place during the irradiation. In the cases of compounds **IV** and **V**, the less stable isomer is formed although in little amounts during their synthesis, therefore chromatographic separation of the two isomers following synthesis permits to study their thermal interconversion. Within the series **II** only the interconversion of the N—CH_3 compounds can be studied; this is because for *N*-CH_3-**II a** random crystallization of either one or the other isomer takes place[12]. A (*E*)-*N*-CH_3-**II a** solution in $CDCl_3$

at 37° (monitored by ^{1}H-NMR; see experimental part) reaches the equilibrium with an observed rate constant of $(8.01 \pm 0.1) \cdot 10^{-4} s^{-1}$, and the corresponding *Z* isomer with one of $(6.6 \pm 0.3) \cdot 10^{-4} s^{-1}$. The small discrepancy between these two values must be attributed to the difficulty in reproducing the experimental conditions, as a result of the high sensitivity of such isomerizations to acid and base catalysis. These results indicate that thermal interconversion is faster within the nitro series (**II**) than between their unsubstituted precursors **I**[1a].

Interconversion experiments with **III b** and *N*-CH_3-**III a** do not allow to change the isomer ratio obtained in their synthesis.

The compounds **IV** and **V** isomerize more slowly than the respective unsubstituted precursors **I** and the *ortho*-substitution results in an even smaller isomerisation rates. For the cyano derivatives **IV** and **V** the isomerisation rates, even at high temperature (422 °K), are experimentally measurable only when acid or base catalysis is used (see experimental part). In the cyano unsaturated series (**IV**), under acid catalysis, each of the two isomers of the 4-methylphenyl derivative **IV a** yield 90% of the concentration values corresponding to the equilibrium mixture in a period of 20 days [80 mmol dm^{-3} solutions in *o*-dichlorobenzene (*DCB*) at 422 ± 1 °K]. Under very similar experimental conditions (see experimental part) **IV b** reaches the same composition after 90 days and **IV c** needs over 250 days. With base catalysis—more effective in this case than acid catalysis—and under analogous experimental conditions, the cyano 3,4-dihydro series (**V**) shows similar isomerisation rates: 4 to 6 days to achieve 90% of the equilibrium concentration values starting with either pure isomer of **V a**, **b**, **f**, and **i**, but for the bulkier **V c** a much slower rate ($\cong$ 50 days) is found.

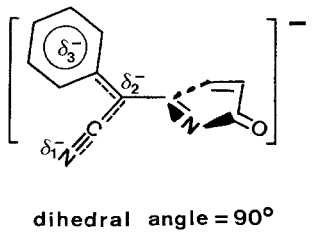
An interesting result is found for the 2′,6′-dimethylphenylsubstituted compounds **I c** and **I d**: starting from the photochemical accessible *E* isomers we have been unable to achieve thermal equilibration to the respective *Z* forms under the conditions described in the literature for this type of compounds (435 °K). Only under base catalysis the interconversion to equilibrium took place within a reasonable period of time. This effect of *ortho*substitution upon the $E \rightleftharpoons Z$ isomerisation rate may also be important in bile pigments, depending on the nature of the pyrrole substituents α to the bridge single bond (C_7, C_{13}, N_{22}, and N_{23}, in tetrapyrrolic bile pigments).

Because of the already mentioned difficulty to obtain reproducible experimental conditions and the unaccuracy of the experimental methods used, the results reported here can only be discussed from a qualitative or semi-quantitative point of view. Nevertheless, the effect of the *ortho*-substitution suggests that the thermal isomerisation proceeds via a reaction pathway which requires coplanarity of the aromatic residue with a sp^2 hybridised exocyclic carbon atom. Such an intermediate or activated

complex for the base catalyzed pathway of a compound of type IV is indicated in Scheme 3.

So far the kinetic aspects of the $E \rightleftharpoons Z$ interconversion were considered. About thermodynamic considerations of this isomerisation—even though in an approximate manner—the assumption of a set of

Scheme 3



dihedral angle = 90°

simplifications permits us to draw some conclusions about the effect of substituents at the exocyclic methylene carbon atom upon the energy differences between the *E* and *Z* isomers. Briefly, the approximations made are: (1) In the case of the nitro derivatives **II**, on the basis of the easy (*E*)-*N*-CH_3-**II a** $\rightleftharpoons$ (*Z*)-*N*-CH_3-**II a** interconversion (see above), we have taken the composition of solutions of nitro derivatives **II** (determined by ^{1}H-NMR at 37°) to be the same as that of the equilibrium mixture; (2) We have assumed the equilibrium composition to be solvent independent and unaffected by acid or base catalysis; (3) We have neglected the vibrational entropy contribution and the rotational entropy contribution*, therefore presuming $\Delta G^\circ = \Delta H^\circ$. This allows us to calculate for the four series (**I**–**IV**) the equilibrium mixture at a given temperature, as shown in Table 2; 4). Experience shows that for this type of compounds the composition of the mixture of isomers obtained by synthetic methods is not much different from the equilibrium mixture; specifically, we have confirmed this for the bromo derivative *N*-CH_3-**III a** and for the cyano series **IV** and **V**. This will give an indication about the energy differences between the *E* and *Z* isomers in those cases where it is not possible to undertake an $E \rightleftharpoons Z$ interconversion experiment.

On the basis of these approximations we have noticed some general trends concerning the effect of methylene substitution upon the composition of the equilibrium mixture:

---

* Entropy calculations from the rotational inertia moments give rotational entropy differences between the two isomers lower than 0.03 s.e.u.; e.g., for **III a** the difference is 0.02 s.e.u.

Effect of Ortho Substitution at the Aryl Group

In the series I (see Table 2), the introduction of an *ortho* methyl group at the phenyl ring produces a slight increase of *E* isomer (phenyl *cis* to CH_3-C4) in the equilibrium mixture. This might be attributed to an increase of the conformational angle determined by *ortho* substitution (see above). This increase is of the same order in the two isomers; however, since in the *E* configuration the dihedral angle is closer to 90°, the loss of π-conjugation energy due to this variation is larger in the *Z* isomer than in the *E* isomer.

The same effect of *ortho* substitution at the phenyl ring is observed in the cyano series **IV** (see Table 2): there is a difference in the equilibrium composition of **IV a** and **IV b**, but not between **IV b** and **IV c**. The latter indicates a nonbonded interaction between the cyano group and the methyl substituent which modifies the *syn-anti* conformational equilibrium to the same extent if only one or two *ortho*-methyl groups exist. In contrary to the series **IV**, the effect of *ortho* substitution at the benzene ring cannot be detected in the series **V** (within the limits of our experimental error).

Effect of the Second Substituent

It is well documented that in the series I (monosubstituted at the exocyclic carbon atom), the energy difference between the *E*, and *Z* diastereoisomers is principally the result of the relative spatial requirements of the substituents at the position 4 and at the lactam nitrogen[1]. Consequently, a very important change in the position of the $E \rightleftharpoons Z$ equilibrium is found in the methylene disubstituted derivatives with respect to the values in the monosubstituted series. The results of Table 2 indicate that the spatial requirements imposed by the CH_3-C4 group are more severe for bromine than for the cyano group. In the nitro derivatives **II**, the *Z* isomer (nitro *cis* to lactam N) is further stabilized by the formation of an internal hydrogen bond (see above). In this relation, it is important to compare in the Table 2 the *E*/*Z* values for **V j** and the rest of the series **V**: the higher proportion of *E* isomer found for **V j** can only be explained by the internal hydrogen bonding between the lactam hydrogen and the pyridyl nitrogen[15]. If the results of the N—CH_3 compounds are compared, it is shown that the spatial requirements of the bromine are larger than those of an orthogonal nitro group (compare in Table 2 the results for *N*-CH_3-**II a**, and **b**, with those for *N*-CH_3-**III a**): Indeed, the spatial requirements of the nitro group in the N—CH_3 derivatives are not the same as those in the corresponding N—H compounds. This is due to the different conformation of the nitro group in the two series of compounds (NO_2 is coplanar to the lactam ring in the N—H series, but

Table 2. *Concentration ratio between the two configurational isomers (Z/E for compounds of type* **I**, *and E/Z for compounds of types* **II**, **III**, **IV**, *and* **V**) *at the equilibrium, extrapolated to room temperature (293 K; see the text)*

	Z/E	*E/Z*				*Z/E*	*E/Z*	
Structure	**I** ($X = H$)	**II**[b] ($X = NO_2$)	**III**[b] ($X = Br$)	**IV**[c] ($X = CN$)	**V**[c] (3,4-dihydro) ($X = CN$)	*N*-CH_3-**I** ($X = H$)	*N*-CH_3-**II**[b] ($X = NO_2$)	*N*-CH_3-**III**[b] ($X = Br$)
4′-$CH_3C_6H_4$	**a** $\geqslant 110$[a]	$\leqslant 0.01$	$\leqslant 0.01$	10.7 ± 2.2	5.9 ± 2.3	2.4[a]	1.05 ± 0.01	0.5 ± 0.1
2′-$CH_3C_6H_4$	**b** 60 ± 20[c]	$\leqslant 0.07$[d, f]	$\leqslant 0.01$	5.4 ± 0.9	5.8 ± 2.1		1.05 ± 0.01	
2′,4′,6′-$(CH_3)_3C_6H_2$	**c** 30 ± 5[c]			4.3 ± 1.0	8.2 ± 2.9			
2′,6′-$(CH_3)_2C_6H_3$	**d** 30 ± 5[c]							
4′-$CH_3OC_6H_4$	**e** $\geqslant 90$[c]	$\leqslant 0.01$						
3,4-diethyl-2′-$CH_3C_6H_4$	**f** $\cong 70$[c, d]				12.6 ± 2.9			
N′-Methyl-2′-pyrrolyl	**i** $\cong 70$[d, e]				7.9 ± 2.3			
2′-pyridyl	**j** $\geqslant 80$[d, e]				$\geqslant 30$[d]			

[a] Determined at 435 K in mesitylene (**I a**[1c], *N*-CH_3-**I a**[1a]).
[b] Determined at 310 K in $CDCl_3$ (see experimental part).
[c] Determined at 422 K in *DCB* (see experimental part).
[d] The experimental method (monitoring by ^{1}H-NMR; see experimental part) does not allow a more accurate quantitative analysis.
[e] Estimated from the reaction mixture of the synthesis.
[f] Estimated data of Ref.[12] are erroneous.

orthogonal in the N—CH_3 derivatives; see above); furthermore, the results for the compounds *N*-CH_3-**II a** and *N*-CH_3-**II b** indicate that the spatial requirements of an orthogonal phenyl group are very similar to those of an orthogonal nitro group; on the contrary, *N*-CH_3-**III a** demonstrates the spatial requirements of bromine to be larger than those of a perpendicular phenyl; this must be so, because in the predominating *Z* isomer, bromine stays *cis* to the lactam nitrogen, which has the ability to increase the *p* character of its hybridisation much better than the C4, thus reducing more efficiently those steric interactions.

The results reported in the literature for the 3,4-dihydro-5(1*H*)-pyrromethenones indicate differences of energies between the *E* and *Z* isomers smaller than within the unsaturated series. This tendency is consistens with the results of Table 2 with respect to the 3,4-dihydro-5-cyano series (**IV a** *vs.* **V a**).

The relatively higher amount of *E*-isomer in 5-methylenepyrrolidin-2-ones or 3,4-dihydro-5(1*H*)-pyrromethenones (aryl ring *cis* to C4) than in 5-methylene-3-pyrrolin-2-ones has already been reported in the literature, both from equilibration experiments[16] and from results of their synthesis[17]: e.g. we have reported[18] that 5-(2-pyrrolyl)methylene-pyrrolidin-2-one, 5-(N-methyl-2-pyrrolyl)-methylene-pyrrolidin-2-one and 5-phenylmethylene-pyrrolidin-2-one are always obtained in a *E*/*Z* ratio of approximately 2.5, and a similar ratio has also been reported for C4 unsubstituted 3,4-dihydro-5(1*H*)-pyrromethenones[17]. These *E*/*Z* ratios are larger than those reported for the unsaturated structures not substituted at C4; e.g. 0.1–0.3 for 5-[(4-methylphenyl)methylene]-3-methyl-3-pyrrolin-2-one[1a].

To explain these experimental differences between the saturated and unsaturated series, it might be also interesting to consider the dipole-dipole interactions between permanent partial dipole moments of the molecule. When this model[1c, 19] is applied using standard geometries and partial dipole moments, either from the literature[20] or from MINDO/3 calculations[21], a slightly favourable dipole interaction is found for the *E* isomer compared to the *Z* isomer in the unsaturated series. Nevertheless, in the 3,4-dihydro series the dipole-dipole interaction favours clearly the *E* isomer; the slight change in the relative orientation of the partial dipole moment and the change of position of the positive charge center in the 5-methylene-pyrrolidin-2-one structure determines in the 3,4-dihydro series—compared to the 5-methylene-3-pyrrolin-2-one of the unsaturated series—a smaller distance between the two partial dipole moments. In consequence, the reported smaller energy differences between the *E* and *Z* isomers of the 3,4-dihydro series could also be partially attributed to the dipole-dipole interaction between permanent partial dipole moments.

In summary, the values of Table 2 can be explained principally by the relative spatial requirements of the substituents at the exocyclic methylene

imposed by the substituents at C4 and at the lactam nitrogen. Less important is the effect of an *ortho* substituent at the aryl residue. This modifies the conformational angle in such a way that, probably, a decrease of the π-delocalisation energy results, which is larger in one configurational isomer than in the other. A second substituent at the exocyclic carbon atom determines an increase of the conformational angle of the aryl residue attached at this carbon atom. Finally, other effects such as internal hydrogen bonding must be considered in specific cases: i.e. in the nitro derivatives **II** or in componds related to **V j**.

Acknowledgements

We are grateful to Dr. *M. Feliz* for NMR measurements. We thank Prof. *R. Bonnett* (Queen Mary College, London University) for the access to the 400 MHz NMR instrument. This work received a grant (0345/81) of the CAICYT.

The majority of this work corresponds to the dissertation of A. V.

Experimental

Melting points were determined on a *Kofler*-Reichert microhot stage apparatus. Preparative thin layer chromatography (PTLC) was carried out on 20×20 cm plates using 60 HF_{254} silica (1 mm thickness). All products separated by PTLC were subsequently purified by chromatography on a small column of Merck 60 (230–400 mesh) silica. High pressure liquid chromatography was carried out on RadialPak silica columns with a double pump (Waters) using a variable wavelength detector 5 FA 339. Preparative HPLC (PHPLC) at the semimicro scale was carried out by repetitive injection using the same system and conditions as for HPLC. UV/VIS spectra were recorded on a Perkin-Elmer Lambda 5 instrument. IR spectra were recorded on a Perkin-Elmer 681 spectrometer. Mass spectra (MS) were determined on a Hewlett-Packard 5700-A instrument. ^{1}H-NMR spectra were recorded on a Varian XL 200 (200 MHz) instrument or on a Perkin-Elmer R 12 A (60 MHz) instrument, some spectra were also recorded in a 400 MHz instrument (Bruker): CCl_3D was always freshly percolated over basic alumina (Merck; activity I).

Hydrogen bond association was studied by IR spectroscopy (**I a** and **II a**) using substrate concentrations of $1.6 \cdot 10^{-4}$, $8 \cdot 10^{-4}$, $1.6 \cdot 10^{-3}$, $8.0 \cdot 10^{-3}$, $3.7 \cdot 10^{-2}$, $1.6 \cdot 10^{-2}$, and $3.7 \cdot 10^{-2}$ mol dm^{-3} in CCl_4 and in CCl_4 : dioxane (4 : 1).

Long range NO*E* experiments were performed using $CDCl_3$ solutions freshly purged with argon, in the 200 MHz instrument and through obtention of the difference spectra (program DELTA for automatic difference spectrum; Varian library). *Eu(dpm)*$_3$ was used as lanthanide shift reagent (LSR). The LIS measurements were performed at a fixed substrate concentration: LIS were linear along the experimental ratio of concentrations LSR/Substrate (0–0.5) used. For the quantitative LIS analysis, the program PDGIM[8] was used and the *Hamilton*'s significance testing[9] was applied. For more experimental details about the quantitative LIS analysis see[22, 23].

Rotational entropy differences between the *E* and *Z* isomers were obtained from the rotational inertia moments, which were calculated using standard internal coordinates and with the aid of the program THERMO[24].

The synthesis and properties of the following compounds are described in the literature: **Ia**[10], **Ib**[12], **Ic**[25], **Id**[25], **Ie**[12], **If**[26], *N*-CH_3-**Ia**[27], *N*-CH_3-**Ib**[12], **IIa**[12], **IIb**[12], **IIe**[12], **IIg**[12], *N*-CH_3-**IIa**[12], *N*-CH_3-**IIb**[12], **IIIa**[3], **IIIe**[3], *N*-CH_3-**IIIa**[3], **Va**[2], **Vh**[2].

(Z)-3,4-Dimethyl-5-[(2-methylphenyl)bromomethylen]-3-pyrrolin-2-one (**IIIb**, $C_{14}H_{14}BrNO$)

Prepared from **Ib** following the general procedure described in the literature[3] with Br_2 in CH_2Cl_2, and isolated by PTLC in 45% yield (the reaction crude contains only **IIIb** and starting material **Ib**); m.p. 200–204°.

^{1}H-NMR (60 MHz, δ, $CDCl_3$): 7.4 (broad s, NH), 7.15 (broad s, aromatic H), 2.30 (s, aromatic CH_3), 1.78 (s, CH_3-3), 1.31 (s, CH_3-4).

IR (cm^{-1}, KBr): 1705 (C=O), 1645 (C=C), 1160, 735.

UV/VIS [λ_{max} nm (ε); $CHCl_3$]: 297 (18700).

MS (*m*/e, 70 eV): 293/291 (M^+, 61%), 212 (100), 198 (54), 184 (74).

General Procedure for the Synthesis of 5-[(Aryl)cyanomethylene]-3-pyrrolin-2-one (**IV**) *from 5-[(Aryl)cyanomethylene]pyrrolidin-2-one* (**V**)

1.0 mmol of **V**, 2 mmol of anhydrous *p*-toluenesulfonic acid and 1.2 mmol of dichlorodicyano-*p*-benzoquinone (*DDQ*) were heated at 110° during 15 h under argon atmosphere in 4 ml of anhydrous dioxane. After filtration, neutralization with $KHCO_3$, washing with water and evaporation, a residue was obtained, which contains principally starting **V** and the *E* and *Z* isomers of **IV**. The *E* isomer shows by TLC[$CHCl_3$: CH_3CN (10 : 1)] a higher *Rf* value than the *Z* isomer. In the reaction mixture also 5-carbamoylmethylen derivatives were identified by ^{1}H-NMR, MS, and IR spectroscopy. PTLC and in some cases, subsequent purification by PHPLC give pure (*E*)-**IV** and (*Z*)-**IV**.

3,4-Dimethyl-5-[(4-methylphenyl)cyanomethylene]-3-pyrrolin-2-one (**IVa**, $C_{15}H_{14}N_2O$)

Obtained from (*E*)-**Va** following the general procedure, as a mixture of the *E* and *Z* isomers. By PTLC using $CHCl_3$: CH_3CN (10 : 1) followed by purification by PHPLC [*n*-hexane($CHCl_3$: CH_3OH, 10 : 1) 9 : 1] gives (*E*)-**IVa** and (*Z*)-**IVa** in 25% and 10% yield respectively. (*E*)-**IVa**: m.p. 204–212°.

^{1}H-NMR (200 MHz, δ, $CDCl_3$): 7.41 (broad s, NH), 7.32 (m, aromatic H), 2.45 (q, J = 1.2 Hz, CH_3-4), 2.40 (s, aromatic CH_3), 1.97 (q, J = 1.2 Hz, CH_3-3). NO*E* was not observed by irradiation between 7.36 and 7.28 ppm.

IR (cm^{-1}, KBr): 3230 NH), 2210 (C≡N), 1715 (C=O), 1613, 1602, 1161, 819, 756.

UV/VIS [λ_{max} nm (ε)] (CH_3OH): 333 (12100); ($CHCl_3$): 334 (12900).

MS (*m*/e, 70 eV): 239 (M^+ + 1, 20%), 238 (M^+, 100), 223 (37), 209 (42), 195 (71).

(*Z*)-**IVa**:

^{1}H-NMR (200 MHz, δ, $CDCl_3$): 7.71 (broad s, NH), 7.24 (broad s, aromatic H), 2.40 (s, aromatic CH_3), 1.91 (q, J = 1.2 Hz, CH_3-3), 1.55 (q, J = 1.2 Hz, CH_3-4). NO*E* effect was observed on the signal at 1.55 by irradiation at 7.24 ppm.

IR (cm^{-1}, KBr): 3230 (NH), 2208 (C≡N), 1715 (C=O), 1603, 818, 755.

UV/VIS [λ_{max} (ε)] (CH_3OH): 302 (14300); ($CHCl_3$): 305 (13900).

MS (*m*/e, 70 eV): Fragmentation does not allow to distinguish it from the *E* isomer.

3,4-Dimethyl-5-[(2-methylphenyl)cyanomethylene]-3-pyrrolin-2-one (**IV b**, $C_{15}H_{14}N_2O$)

Obtained from **V b** following the general procedure, as a mixture of the *E* and *Z* isomers. PTLC and PHPLC (see **IV a**) give pure (*E*)-**IV b** and (*Z*)-**IV b** in 10% and 7% yields respectively.

(*E*)-**IV b**: m.p. 127–132°.

^{1}H-NMR (200 MHz, δ, $CDCl_3$): 7.30 (m, aromatic H), 6.88 (broad s, NH), 2.47 (q, $J = 1.2$ Hz, CH_3-4), 2.36 (s, aromatic CH_3), 1.97 (q, $J = 1.2$ Hz, CH_3-3).

IR (cm^{-1}, film): 3200 (NH), 2210 (C≡N), 1710 (C=O), 762.

UV/VIS [λ_{max} nm (ε)] (CH_3OH): 293 (14800); ($CHCl_3$): 299 (14700).

MS (*m*/e, 70 eV): 238 (M^+, 20%), 128 (76), 127 (38), 115 (50), 103 (54), 102 (100), 101 (66).

(*Z*)-**IV b**: m.p. 195–205°.

^{1}H-NMR (200 MHz, δ, $CDCl_3$): 7.64 (broad s, NH), 7.28 (m, aromatic H), 2.36 (s, aromatic CH_3), 1.89 (q, $J = 1.2$ Hz, CH_3-3), 1.38 (q, $J = 1.2$ Hz, CH_3-4).

IR (cm^{-1}, film): 3270 (NH), 2210 (C≡N), 1725 (C=O), 1610, 760.

UV/VIS [λ_{max} nm (ε)] (CH_3OH): 289 (12500); ($CHCl_3$): 291 (12200).

MS (*m*/e, 70 eV): Fragmentation does not distinguish it from the *E* isomer.

3,4-Dimethyl-5-[(2,4,6-trimethylphenyl)cyanomethylene]-3-pyrrolin-2-one (**IV c**, $C_{17}H_{18}N_2O$)

Obtained from **V c** following the general procedure, as a mixture of the *E* and *Z* isomers. Repetitive PTLC using $CHCl_3$: CH_3CN (10 : 1) gives pure (*E*)-**IV c** and (*Z*)-**IV c** in 6% and 4% yield respectively. (*E*)-**IV c**: m.p. 197–206°.

^{1}H-NMR (200 MHz, δ, $CDCl_3$): 6.95 (broad s, aromatic H), 6.67 (broad s, NH), 2.47 (q, $J = 1.2$ Hz, CH_3-4), 2.31 (s, one aromatic CH_3), 2.23 (s, two aromatic CH_3), 1.96 (q, $J = 1.2$ Hz, CH_3-3).

IR (cm^{-1}, film): 3200 (NH), 2205 (C≡N), 1715 (C=O), 1622 (C=C).

UV/VIS [λ_{max} nm (ε)] (CH_3OH): 282 (13900); ($CHCl_3$): 285 (14200).

MS (*m*/e, 70 eV): 267 ($M^+ + 1$, 22%), 266 (M^+, 100), 251 (48), 115 (43).

(*Z*)-**IV c**: m.p. 156–165°.

^{1}H-NMR (200 MHz, δ, $CDCl_3$): 7.60 (broad s, NH), 6.94 (broad s, aromatic H), 2.31 (s, one aromatic CH_3), 2.23 (s, two aromatic CH_3), 1.89 (q, $J = 1.2$ Hz, CH_3-3), 1.34 (q, $J = 1.2$ Hz, CH_3-4).

IR (cm^{-1}, film): 3210 (NH), 2208 (C≡N), 1710 (C=O), 1620.

UV/VIS [λ_{max} nm (ε)] (CH_3OH): 285 (15500); ($CHCl_3$): 285 (15000).

MS (*m*/e, 70 eV): 267 ($M^+ + 1$, 22%), 266 (80), 251 (42), 223 (40), 128 (43), 115 (80), 111 (100).

3,4-Dimethyl-5-[(2-methylphenyl)cyanomethylene]pyrrolidin-2-one (**V b**, $C_{15}H_{16}N_2O$)

Obtained from **I b** following the procedure described in the literature[2], as a mixture of the *E* and *Z* isomers, in 92% yield. PTLC [$CHCl_3$: CH_3CN (10 : 1)] gives pure (*E*)-**V b** and (*Z*)-**V b** in 40% and 20% yield respectively.

(*E*)-**V b**: m.p. 105–110°.

^{1}H-NMR (200 MHz, δ, $CDCl_3$)[28]: 7.4 (broad s, NH), 7.23 (m, aromatic H), 3.57 (m, $J_{ac} = 8.4$ Hz, $J_{af} = 7.3$ Hz, H-4 *cis*; a), 3.07 (m, $J_{bd} = 3.4$ Hz, $J_{be} = 7.2$ Hz, H-4 *trans*; b), 2.93 (m, $J_{ca} = 8.4$ Hz, $J_{ch} = 7.4$ Hz, H-3 *cis*; c), 2.37 (m, J_{db}

= 3.4 Hz, J_{dg} = 7.5 Hz, H-3 *trans*; d), 2.33 (s, aromatic CH_3), 1.59 (d, J_{eb} = 7.2 Hz, CH_3-4 *trans*; e), 1.40 (d, J_{fa} = 7.3 Hz, CH_3-4 *cis*; f), 1.33 (d, J_{gd} = 7.5 Hz, CH_3-3 *trans*; g), 1.22 (d, J_{hc} = 7.4 Hz, CH_3-3 *cis*; h).

IR (cm^{-1}, KBr): 3210 (NH), 2205 (C≡N), 1742 (C=O), 1636 (C=C).

UV/VIS [λ_{max} nm (ε)] (CH_3OH): 261 (22700); ($CHCl_3$): 260 (24000).

MS (*m*/e, 70 eV): 241 (M^+ + 1, 19%), 240 (M^+, 100), 225 (34), 197 (33).

(*Z*)-**V b**:

^{1}H-NMR (200 MHz, δ, $CDCl_3$)[28]: 7.93 (broad s, NH), 7.26 (m, aromatic H), 3.20 (m, J_{ab} = 8.5 Hz, J_{ah} = 7.3 Hz, H-4 *cis*; a), 2.88 (m, J_{ba} = 8.5 Hz, J_{bf} = 7.4 Hz, H-3 *cis*; b), 2.76 (m, J_{cd} = 4.1 Hz, J_{cg} = 7.1 Hz, H-4 *trans*; c), 2.37 (s, aromatic CH_3), 2.30 (m, J_{dc} = 4.1 Hz, J_{de} = 7.4 Hz, H-3 *trans*; d), 1.30 (d, J_{ed} = 7.4 Hz, CH_3-3 *trans*; e), 1.15 (d, J_{fb} = 7.4 Hz, CH_3-3 *cis*; f), 0.83 (d, J_{gc} = 7.1 Hz, CH_3-4 *trans*; g), 0.78 (d, J_{ha} = 7.3 Hz, CH_3-4 *cis*; h).

IR (cm^{-1}, KBr): 3220 (NH), 2205 (C≡N), 1750 (C=O), 1634 (C=C).

UV/VIS [λ_{max} nm (ε)] (*Et*OH): 262 (18000); ($CHCl_3$): 262 (20000).

MS (*m*/e, 70 eV): 240 (M^+, 93%), 115 (42), 111 (100), 110 (58).

3,4-Dimethyl-5-[(2,4,6-trimethylphenyl)cyanomethylene]pyrrolidin-2-one
(**V c**, $C_{17}H_{20}N_2O$)

Obtained from **I c** following the procedure described in the literature[2], as a mixture of the *E* and *Z* isomers, in 92% yield. PTLC (see **V b**) gives pure (*E*)-**V c** and (*Z*)-**V c** in 60% and 20% yields respectively.

(*E*)-**V c**:

^{1}H-NMR (200 MHz, δ, $CDCl_3$)[28]: 7.0 (broad s, NH), 6.97 (s, aromatic H), 3.60 (m, J_{ac} = 8.5 Hz, J_{af} = 7.7 Hz, H-4 *cis*; a), 3.10 (m, J_{bd} = 3.2 Hz, J_{be} = 7.7 Hz, H-4 *trans*; b), 2.94 (m, J_{ca} = 8.5 Hz, J_{ch} = 7.7 Hz, H-3 *cis*; c), 2.33 (m, J_{db} = 3.2 Hz, J_{dg} = 7.8 Hz, H-3 *trans*; d), 2.30 (s, one aromatic CH_3), 2.24 (s, two aromatic CH_3), 1.60 (d, J_{eb} = 7.7 Hz, CH_3-4 *trans*; e), 1.42 (d, J_{fa} = 7.7 Hz, CH_3-4 *cis*; f), 1.34 (d, J_{gd} = 7.8 Hz, CH_3-3 *trans*; g), 1.23 (d, J_{hc} = 7.7 Hz, CH_3-3 *cis*; h). NO*E* was not observed by irradiation at 2.24 ppm.

IR (cm^{-1}, KBr): 3150 (NH), 2195 (C≡N), 1730 (C=O), 1630 (C=C).

UV/VIS [λ_{max} nm (ε), *Et*OH]: 258 (25600).

MS (*m*/e, 70 eV): 269 (M^+ + 1, 23%), 268 (M^+, 95), 253 (36), 115 (38), 111 (100), 110 (41).

(*Z*)-**V c**:

^{1}H-NMR (200 MHz, δ, $CDCl_3$)[28]: 8.19 (broad s, NH), 6.93 (broad s, aromatic H), 2.86 (m, H-3 *cis* and H-4 *cis*), 2.44 (m, J_{ab} = 4.0 Hz, J_{ac} = 7.1 Hz, H-4 *trans*; a), 2.30 (s, two aromatic CH_3), 2.25 (m, H-3 *trans*; b), 2.24 (s, one aromatic CH_3), 1.28 (d, J = 7.4 Hz, CH_3-3 *trans*), 1.14 (d, J = 7.0 Hz, CH_3 *cis*), 0.85 (d, J = 7.1 Hz, CH_3-4 *trans*; c), 0.79 (d, J = 6.5 Hz, CH_3-4 *cis*). NO*E* was observed on the signal at 0.85 by irradiation at 2.30 ppm.

IR (cm^{-1}, KBr): 3150 (NH), 2200 (C≡N), 1730 (C=O), 1637, 1230.

UV/VIS [λ_{max} nm (ε), *Et*OH]: 263 (23000).

MS (*m*/e, 70 eV): Fragmentation does not distinguish it from the *E* isomer.

3,4-Diethyl-5-[(2-methylphenyl)cyanomethylene]pyrrolidin-2-one
(**V f**, $C_{15}H_{16}N_2O$)

Obtained from **I f** following the procedure described in the literature[2], as a mixture of the *E* and *Z* isomers in 91% yield. PTLC (see **V b**) gives pure (*E*)-**V f** and (*Z*)-**V f** in 60% and 20% yields respectively.

(*E*)-*trans* **V f**: m.p. 105–111°.

^{1}H-NMR (400 MHz, δ, $CDCl_3$)[28]: 7.28 (m, NH and three aromatic H), 7.15 (m, one aromatic H), 3.10 (m, $J_{ab} = 2.0$ Hz, $J_{ac} = 3.8$ Hz, $J_{ad} = 8.8$ Hz, H-4; a), 2.39 (m, $J_{ba} = 2.0$ Hz, $J_{be} = 5.2$ Hz, $J_{bf} = 7.6$ Hz, H-3; b), 2.33 (s, aromatic CH_3), 2.07 (m, $J_{ca} = 3.8$ Hz, $J_{cd} = 13.8$ Hz, $J_{c,CH_3} = 7.5$ Hz, one H of CH_3—CH_2-4; c), 1.91 (m, $J_{da} = 8.8$ Hz, $J_{dc} = 13.8$ Hz, $J_{d,CH_3} = 7.5$ Hz, one H of CH_3—CH_2-4; d), 1.82 (m, $J_{eb} = 5.2$ Hz, $J_{ef} = 13.6$ Hz, $J_{e,CH_3} = 7.5$ Hz, one H of CH_3—CH_2-3; e), 1.67 (m, $J_{fb} = 7.6$ Hz, $J_{fe} = 13.6$ Hz, $J_{f,CH_3} = 7.5$ Hz, one H of CH_3—CH_2-3; f), 1.08 (t, $J = 7.5$ Hz, CH_3—CH_2-3 or CH_3—CH_2-4), 1.05 (t, $J = 7.5$ Hz, CH_3—CH_2-4 or CH_3—CH_2-3).

IR (cm^{-1}): 3210 NH), 2205 (C≡N), 1735 (C=O), 1630 (C=C).

UV/VIS [λ_{max} nm (ε); $CHCl_3$]: 261 (19200).

MS (*m*/e, 70 eV): 268 (M^+, 81%), 240 (56), 239 (69), 225 (41), 211 (100), 128 (49).

(*Z*)-*trans* **V f**: m.p. 125–132°.

^{1}H-NMR (400 MHz, δ, $CDCl_3$)[28]: 8.14 (broad s, NH), 7.23 (m, aromatic H), 2.81 (m, $J_{ab} = 2.5$ Hz, $J = 3.1$ Hz, $J = 8.2$ Hz, H-4 *trans*; a), 2.38 (s, aromatic CH_3), 2.33 (m, $J_{ab} = 2.5$ Hz, $J = 5.2$ Hz, $J = 7.7$ Hz, H-3 *trans*; b), 1.79 (m, J_{cb} and J_{cd} undetermined, $J_{c,CH_3} = 7.5$ Hz, one H of CH_3—CH_2-3; c), 1.68 (m, J_{db} and J_{dc} undetermined, $J_{d,CH_3} = 7.5$ Hz, one H of CH_3—CH_2-3; d), 1.25 (m, J_{ea} and J_{ef} undetermined, $J_{e,CH_3} = 7.5$ Hz, one H of CH_3—CH_2-4; e), 1.18 (m, J_{fa} and J_{fe} undetermined, $J_{f,CH_3} = 7.5$ Hz, one H of CH_3—CH_2-4, f), 1.03 (t, $J = 7.5$ Hz, CH_3—CH_2-3), 0.74 (t, $J = 7.5$ Hz, CH_3—CH_2-4).

IR (cm^{-1}, KBr): 3205 (NH), 2205 (C≡N), 1730 (C=O), 1635 (C=C).

UV/VIS [λ_{max} nm (ε); $CHCl_3$]: 263 (19200).

MS (*m*/e, 70 eV): Fragmentation does not distinguish it from the *E* isomer.

3,4-Dimethyl-5-[(1-methylpyrrol-2-yl)cyanomethylene]pyrrolidin-2-one
(**V i**, $C_{13}H_{15}N_3O$)

Obtained from 3,4-dimethyl-5-[(1-methylpyrrol-2-yl)methylene]-3-pyrrolin-2-one[29] following the procedure described in the literature[2], as a mixture of the *E* and *Z* isomers. PTLC (see **V b**) gives **V h** as a mixture of the *E* and *Z* isomers (7 : 3) in 35% yield.

^{1}H-NMR (60 MHz, δ, $CDCl_3$)[28]: 7.95 (broad s, NH), 6.68 (m, H-5′), 6.12 (m, H-3′ and H-4′), 3.62 (s, CH_3—N, *E*), 3.59 (s, CH_3—N, *Z*), 3.5–2.3 (m, two H), 1.57 (d, $J = 7.2$ Hz, CH_3-4, *E-trans*), 1.39 (d, $J = 7.3$ Hz, CH_3-4, *E-cis*), 1.31 (d, $J = 7.3$ Hz, CH_3-3, *E-trans*), 1.28 (d, $J = 6.9$ Hz, CH_3-3, *Z-trans*), 1.21 (d, $J = 7$ Hz, CH_3-3, *E-cis*), 0.90 (d, $J = 6.9$ Hz, CH_3-4, *Z-trans*), 0.76 (d, $J = 7.3$ Hz, CH_3-4, *Z-cis*).

IR (cm^{-1}, film): 3250 (NH), 2210 (C≡N), 1755–1730 (C=O), 1635 (C=C).

MS (*m*/e, 70 eV): 230 (M^+, 21%), 229 (M^+, 89), 214 (40), 186 (100).

(E)-3,4-Dimethyl-5-[(2-pyridyl)cyanomethylen]pyrrolidin-2-one
(**V j**, $C_{13}H_{13}N_3O$)

Obtained from (*Z*)-3,4-dimethyl-5-[(2-pyridyl)methylene)-3-pyrrolin-2-one[15] following the procedure described in the literature[2]. PTLC in CH_2Cl_2 : CH_3OH (30 : 1) gives (*E*)-**V j** in 40% yield as a mixture of the *trans* and *cis* isomers (8 : 3).

^{1}H-NMR (200 MHz, δ, $CDCl_3$)[28]: 8.50, 7.77, 7.60, and 7.16 (m, aromatic H), 3.58 (m, $J_{ac} = 8.2$ Hz, $J_{af} = 7.3$ Hz, H-4 *cis*; a), 3.10 (m, $J_{bd} = 2.7$ Hz, $J_{be} = 7.2$ Hz, H-4 *trans*; b), 2.89 (m, $J_{ca} = 8.2$ Hz, $J_{ch} = 7.5$ Hz, H-3 *cis*; c), 2.34 (m, $J_{db} = 2.7$ Hz, $J_{dg} = 7.5$ Hz, H-3 *trans*; d), 1.56 (d, $J_{eb} = 7.2$ Hz, CH_3-4 *trans*; e),

1.38 (d, J_{fa} = 7.3 Hz, CH_3-4 *cis*; f), 1.35 (d, J_{gd} = 7.5 Hz, CH_3-3 *trans*; g), 1.27 (d, J_{hc} = 7.5 Hz, CH_3-3 *cis*; h).

IR (cm^{-1}, film): 3 200 (NH), 2 225 (C≡N), 1 755 (C=O), 1 620 (C=C), 1 598.

UV/VIS [λ_{max} nm (ε)] (CH_3OH): 314 (18 800), 265 (14 600); ($CHCl_3$): 317 (19 400), 267 (15 400).

MS (*m*/e, 70 eV): 227 (M^+, 51%), 212 (100), 184 (70).

Bis[3,4-dimethyl-5-ethoxycarbonyl-2(1H)-pyrrolyl]methane (**VI**, $C_{19}H_{26}N_2O_4$)

Obtained as a byproduct in the synthesis of ethyl 3,4-dimethyl-5-formyl-(1*H*)-pyrrole-2-carboxylate from ethyl 3,4,5-trimethyl-(1*H*)-pyrrole-2-carboxylate by oxidation with $Pb(AcO)_4$[30]. It shows the same physical data as the ones described in the literature[31]; m.p. 198–203°.

^{1}H-NMR (60 MHz, δ, $CDCl_3$): 9.3 (broad s, NH), 4.25 (q, J = 7.5 Hz, —COO—CH_2—CH_3), 3.83 [s, (aromatic)$_2CH_2$], 2.22 [s, aromatic CH_3-4(4′)], 1.93 [s, aromatic CH_3-3(3′)], 1.30 (t, J = 7.5 Hz, —COO—CH_2—CH_3).

IR (cm^{-1}, KBr): 3 360, 1 690, 1 650.

UV/VIS [λ_{max} nm (ε), *Et*OH]: 250 (8000), 275 (14 800), 290 (17 200).

MS (*m*/e, 70 eV): 346 (M^+, 100%).

Table 3. *Some of the experimental conditions used in the thermal equilibration of several compounds of Table 2 at 422 K in DCB*

No.	Initial concentration ($1 \cdot 10^{-3}$ mol dm^{-3})		Base catalyst	Acid catalyst	^{1}H-NMR (MHz)
	(*Z*)	(*E*)			
Ib	40 ± 1	20 ± 1	+	−	60
Ic	53 ± 1	25 ± 1	+	−	60
Id	62 ± 1	18 ± 1	+	−	60
Ie	55 ± 1	20 ± 1	+	−	60
If	65 ± 1	15 ± 1	+	−	200
N-CH_3-**IIIa**[a]	40 ± 1	20 ± 1	−	−	60
IVa	80 ± 1		−	+	60
IVa		80 ± 1	−	+	60
IVb	25 ± 1	3 ± 1	−	+	200
IVb		20 ± 1	−	+	200
IVc	15 ± 1		−	+	200
IVc	1 ± 1	10 ± 1	−	+	200
Va	70 ± 5	10 ± 5	+	−	60
Vb	83 ± 1		+	−	60
Vb		86 ± 1	+	−	60
Vc	72 ± 1		+	−	60
Vc		74 ± 1	+	−	60
Vf	75 ± 1		+	−	200
Vf		71 ± 1	+	−	200
Vi	84 ± 4	27 ± 4	+	−	60, 200

[a] In $CDCl_3$ at 310 K.

Kinetic Measurements for the E—Z Isomerization of N-CH_3-II a

A 0.2 mol dm^{-3} solution of *N*-CH_3-**II a**—either pure *Z* or *E* isomer—in $CDCl_3$ was monitered by ^{1}H-NMR spectroscopy (37°) until the equilibrium was reached (aproximately 45 min). Plotting of $\ln [E]/[E]^{\infty} - [E]$ (for the isomerization of *E*) or $\ln [Z]/[Z]^{\infty} - [Z]$ (for the isomerization of *Z*) against time gave a straight line (correlation coefficient better than 0.99) with a slope ($k = k_1 + k_{-1}$) of $(8.01 \pm 0.1) \cdot 10^{-4}\,s^{-1}$ (for *E*) and $(6.55 \pm 0.30) \cdot 10^{-4}\,s^{-1}$ (for *Z*).

Thermal Equilibration Experiments

o-Dichlorobenzene solutions (see Table 3) in ^{1}H-NMR tubes were maintained, in the absence of light, at fixed temperature and their ^{1}H-NMR spectra were periodically recorded. Base or acid catalyst was added. Base catalyst was a solution 3 mol dm^{-3} of CD_3ONa in CD_3OD, which was added to obtain $3 \cdot 10^{-3}$ mol dm^{-3} solutions in CD_3ONa. Acid catalyst was *p*-toluenesulfonic acid, which was added to obtain $2 \cdot 10^{-3}$ mol dm^{-3} concentrations. Initial concentrations and other experimental conditions are indicated in the Table 3. By comparison of the concentration changes with time, an arrangement of some compounds of each series according to their isomerization rates was possible due to the great differences found between related compounds.

References

[1] See *inter alia*: a) *Falk H., Grubmayr K., Hofer O., Neufingerl F., Ribo J.*, Monatsh. Chem. **107**, 831 (1976). b) *Falk H., Ribo J.*, Monatsh. Chem. **107**, 307 (1976). c) *Falk H., Grubmayr K., Höllbacher G., Hofer O., Leodolter A., Neufingerl F., Ribo J.*, Monatsh. Chem. **108**, 1113 (1977). d) *Falk H., Grubmayr K., Hofer O., Neufingerl F.*, Monatsh. Chem. **106**, 991 (1975). e) *Falk H., Grubmayr K., Schlederer T.*, Monatsh. Chem. **109**, 1191 (1978). f) *Falk H., Höllbacher G., Hofer O., Müller N.*, Monatsh. Chem. **112**, 391 (1981).

[2] *Ribo J. M., Trull F.*, Monatsh. Chem. **110**, 201 (1979).

[3] *Daroca A., Merce R., Ribo J. M., Trull F., Valles A.*, Monatsh. Chem. **115**, 357 (1984).

[4] *Giralt E., Lopez F., Alvarez M.*, Org. Magn. Res. **7**, 585 (1975).

[5] *Yamaguchi I.*, Molecular Phys. **1963 b**, 105.

[6] *Johnson C. E., Bovey T. A.*, J. Chem. Phys. **29**, 1012 (1958).

[7] *Falk H., Hofer O., Leodolter A.*, Monatsh. Chem. **106**, 57 (1975).

[8] a) *Willcott M. R.* III, *Lenkinski R. E., Davis R. E.*, J. Am. Chem. Soc. **94**, 1472 (1972). b) *Davis R. E., Willcott M. R.* III, *ibid.* **94**, 1744 (1972).

[9] *Hamilton W. C.*, Acta Crystallogr. **18**, 502 (1965).

[10] *Falk H., Grubmayr K., Hofer O.*, Monatsh. Chem. **106**, 301 (1975).

[11] *Bonfiglio J. V., Bonnett R., Hursthouse M. B., Malik K. M. A., Naithiani S. C.*, J. C. S. Chem. Comm. **1977**, 829.

[12] *Ribo J. M., Trull F.*, Liebigs Ann. Chem. **1983**, 1.

[13] *Bonfiglio J. V., Bonnett R., Buckley D. G., Hanzetash D., Hursthouse M. B., Malik K. M. A., Naithani S. C., Trotter J.*, J. C. S. Perkin I **1982**, 1291.

[14] *Falk H., Gergely S., Grubmayr K., Hofer O.*, Z. Naturforsch. **32 b**, 299 (1977).

[15] *Falk H., Grubmayr K.*, Monatsh. Chem. **108**, 625 (1977).

[16] *Falk H., Grubmayr K., Kapl G., Zrunek U.*, Monatsh. Chem. **113**, 1329 (1982).

[17] *Gossauer A., Blacha M., Sheldrick W. S.*, J. C. S., Chem. Comm. **1976**, 764.

[18] *Ribo J. M., Serra X.*, Monatsh. Chem., in press.

[19] *Lehn J.-L., Ourisson G.*, Bull. Soc. Chim. France **1963**, 1113.
[20] *McClellan A. L.*, Tables of Experimental Dipole Moments. San Francisco: W. H. Freeman and Co. 1963.
[21] *Ribo J. M., Valles A.*, J. Chem. Res. (S) **1983**, 284.
[22] *Hofer O.*, Topics in Stereochem. **9**, 111 (1976).
[23] *Ribo J. M., Serra X.*, Org. Magn. Res. **12**, 467 (1977).
[24] Program THERMO. Facultat de Quimica. Universitat de Barcelona.
[25] *Ribo J. M., Trull F.*, Monatsh. Chem. **114**, 1987 (1983).
[26] *Lightner D. A., Park Y.-T.*, J. Heterocyclic Chem. **14**, 415 (1977).
[27] *Falk H., Gergely S., Grubmayr K., Hofer O.*, Liebigs Ann. Chem. **1977**, 565.
[28] Besides some typographic errors in Ref.[2], some ^{1}H-NMR assignments are mistaken.
[29] *Falk H., Grubmayr K., Herzig U., Hofer O.*, Tetrahedron Lett. **1975**, 559.
[30] *Paine J. B.* III, *Woodward R. B., Dolphin D.*, J. Org. Chem. **41**, 2826 (1976).
[31] a) *Fischer H., Nenitzescu C.*, Liebigs Ann. Chem. **433**, 124 (1925); *Fischer H., Orth H.*, in: Die Chemie des Pyrrols, Vol. 1, p. 341, Leipzig 1934. New York: Johnson Reprint Co. 1968. b) *Melentleva T. A., Pekel N. D., Berezovski V. M.*, Zh. Obsch. Khim. **40**, 165 (1970); C. A. 72, 121502k. c) *Beveridge S., Huppatz J. L.*, Australian J. Chem. **25**, 1341 (1972).