STERICALLY CROWDED HETEROCYCLES. XII. ATROPISOMERISM OF (1-ARYL-3,5-DIPHENYL-1*H*-PYRROL-2-YL)(PHENYL)METHANONES

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Dedicated to Professor Otakar Červinka on the occasion of his 75th birthday.

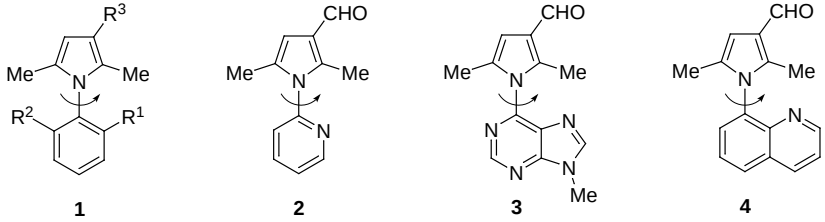
Some 1-(2-substituted phenyl)- and 1-(1-naphthyl)-2,4,6-triphenylpyridinium perchlorates were treated with potassium hexacyano ferrate(III)–potassium hydroxide reagent to give the title pyrroles. Restricted rotation around the C–N bond in the products is demonstrated by NMR experiments with homochiral shift reagents, by semiempirical PM3 calculations as well as using their atropodiastereoselective and enantioselective transformations. Racemisation barriers for the (*R*)-2-(*N*-methyl-*N*-phenylcarbamoyl) derivative were estimated from NMR and polarimetric measurements.

Key words: Pyrroles; Pyridinium salts; Atropisomerism; Axial chirality; Biaryls; Racemisation; Semiempirical calculations; X-Ray diffraction.

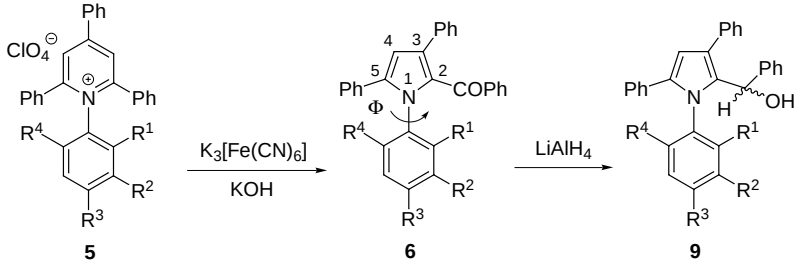
Almost twenty years ago an original pyrrole synthesis has been discovered[1] in our laboratory. This approach is based on the ferricyanide oxidation of 1-substituted 2,4,6-triarylpyridinium salts and has been later generalised[2] for preparation of various pyrrole derivatives. In this way, 1-aryl-2,3,5-trisubstituted pyrroles are easily accessible, which may exhibit atropisomerism on the C(sp^2)–N(sp^2) bond as reported in a recent preliminary communication[3].

Only limited examples of the C(sp^2)–N(sp^2) atropisomerism in five-membered heterocyclic molecules are known[4] for several 3-substituted 1-(het)aryl 2,6-dimethylpyrroles. Thus, the pyrrole **1** ($R^1 = R^3 = CO_2H$, $R^2 = H$)

was resolved into its enantiomers *via* diastereoisomeric brucine salts[4a]. Chiral NMR shift reagents were used[4b] to demonstrate atropisomerism of six *ortho*-substituted 1-phenylpyrroles **1** (R^1 = Cl, CN, Me, OMe, OEt, OCH_2Ph; R^2 = H; R^3 = CHO) as well as of one *ortho*,*ortho*-disubstituted 1-phenylpyrrole **1** (R^1 = Cl, R^2 = Me, R^3 = CHO). Chiral HPLC techniques were successful[4b,4c] in detection of enantiomeric 1-hetarylpyrroles **2** and **3** or even in separation of enantiomers of compounds possessing bulkier *ortho*-substituents, namely of 1-phenylpyrrole **1** (R^1 = OCH_2Ph, CH_2Ph; R^2 = H; R^3 = CHO) and 1-(quinolin-8-yl)pyrrole **4**. The corresponding barriers to rotation were estimated[4b,4c] to be in the range from 12.4 to 31.0 kcal/mol. Similar studies have been reported for atropisomeric *N*-(2-*tert*-butylphenyl)-2-methylmaleimide[5a] and 3-benzyl-1-(2-*tert*-butylphenyl)-5-methoxymethyl-2-pyrrolidone[5b].



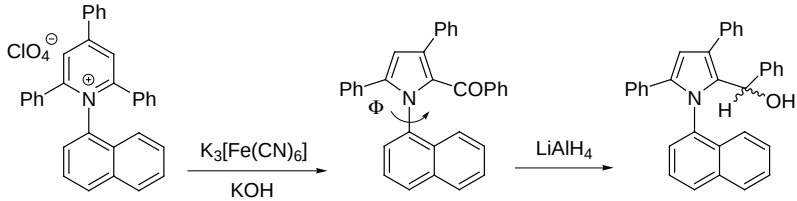
In the start of this paper the known procedure[2a] of the ferricyanide oxidation of **5a** to **6a** has been extended to other quaternary pyridinium salts **5b**–**5f** (Scheme 1) which gave the expected new pyrrole derivatives **6b**–**6f** in



5,6,9	R^1	R^2	R^3	R^4
a	H	H	H	H
b	Me	H	H	H
c	Me	Me	H	H
d	Me	H	Me	Me
e	MeO	H	H	H
f	CO_2H	H	H	H

SCHEME 1

satisfactory yields. Analogously, 1-(1-naphthyl) substituted pyridinium salt **7** afforded the corresponding pyrrole **8** (Scheme 2).



7 **8** **10**

SCHEME 2

The expected atropisomerism of ketones **6a**–**6e** and **8** has been investigated by ^{1}H NMR using the chiral shift reagent europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] [(+)-Eu(hfc)$_3$] in C_6D_6 solutions. As follows from Table I, only 2-substituted derivatives **6b**, **6c**, **6e** and 1-naphthyl derivative **8** exhibit typical 1 : 1 splitting of the proton singlet signals indicating the racemic nature of the compounds while the parent phenyl derivative **6a** and 2,4,6-trimethylphenyl derivative **6d** do not show the presence of enantiomers due to their molecular symmetry.

In addition to these findings, reductions of ketones **6a**–**6e** and **8** to corresponding secondary alcohols **9a**–**9e** and **10** have been attempted as a chemical axial chirality probe confirmed earlier for sterically crowded imidazo[1,2-*a*]heteroaromatic molecules[6]. In agreement with the above

TABLE I

Chemical shifts (δ, ppm) of selected singlet signals in ^{1}H NMR spectra (400 MHz, C_6D_6 solutions) of compounds **6a**–**6e** and **8** in the presence of (+)-Eu(hfc)$_3$

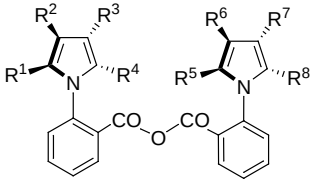
Compound	CH-4		CH_3[a]		CH_3[b]	
6a	6.81	–	–	–	–	–
6b	7.04	7.06	2.05	2.06	–	–
6c	6.87	6.88	2.13	2.17	1.83	1.86
6d	6.73	–	2.03	–	2.27	–
6e	6.87	6.88	3.31	3.33	–	–
8	6.90	6.92	–	–	–	–

[a] In the substituent R^1; [b] in the substituents R^2 or R^3.

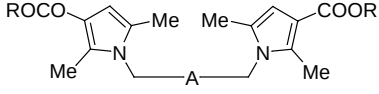
mentioned ^{1}H NMR data, $LiAlH_4$ reductions were found to proceed atroposelectively only with the racemic substrates **6a**–**6c**, **6e** and **8** leading to atropodiastereoisomeric mixtures of alcohols **9a**–**9c**, **9e** and **10** from which major stereoisomers could be isolated as individuals. Expectedly, the $LiAlH_4$ reductions of non-atropisomeric ketones **6a** and **6d** gave only individual alcohols **9a** and **9d**.

Atropisomerism of acid **6f** has been investigated by several chemical and physical procedures. Thus, its conversion with DCC to corresponding atropodiastereoisomeric anhydrides **11** and **12** demonstrates the axial chirality of the starting compound **6f**. Relative configurations of the products, of racemate **11** and mesoform **12** were assigned by ^{1}H NMR using the chiral chemical shift reagent. For **12**, a clearly separated doublet at δ 7.82 ppm present in the C_6D_6 solutions of the both stereoisomers is shifted only to δ 7.89 ppm after addition of (+)-Eu(hfc)$_3$ while it is splited into two signals at δ 7.75 and 7.98 ppm for the racemate **11** indicating the presence of the two enantiomers **11a** and **11b**.

It may be noted it is a new example related to the known[7] *ortho*-linked atropodiastereoisomeric dipyrrylarenes **13** in which the bridge A involves either a *meta*-attachment (A = 3,3-dimethylbiphenyl-1,3-phenylene, R = H)[7a] or *para*- and *para*,*para*-attachments (A = 2,5-dimethyl-1,4-phenylene, R = H (ref.[7a]) and A = 3,3′-dimethylbiphenyl-4,4′-diyl, R = Et (ref.[7b])). The authors[7] have assigned the racemic structure to the higher melting and less soluble *meta*-linked atropodiastereoisomer[7a] but the *meso* configuration to the *para*- and *para*,*para*-linked atropodiastereoisomers[7a,7b]. In our case more soluble (polar) but lower melting atropodiastereoisomer **11** is actually racemic.



11, 12

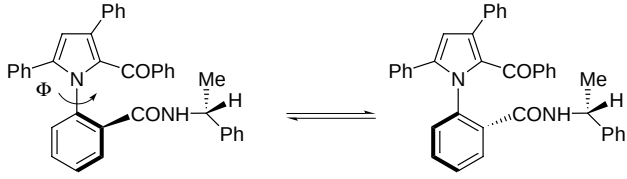


13

	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8
11a	Ph	H	H	PhCO	PhCO	Ph	H	Ph
11b	PhCO	Ph	H	Ph	Ph	H	Ph	PhCO
12	Ph	H	Ph	PhCO	Ph	H	Ph	PhCO

An additional proof of racemic nature of the acid **6f** is its conversion by DCC method with (*R*)-1-phenylethylamine to a *ca* 1 : 1 mixture of two atropodiastereoisomeric amides **14** and **15**. Absolute configurations of the both products were determined by the X-ray diffraction analysis of the higher melting stereoisomer to which formula **14** could be assigned (Fig. 1).

The opposite and strongly different optical rotations found for the atropodiastereoisomers **14** and **15** ($[\alpha]_D$ +54.5 and –124.9) suggest that the strongly different data, evidently influenced in by mutual configurations within the 1-phenyl-pyrrolic π-electronic systems, might be a useful characteristic in our future investigations of absolute stereochemistry of the **6**-like compounds.



14 **15**

Configurational stability of compounds **6a**–**6d**, **6f** and **8** has also been investigated by quantum chemical calculations of rotation barriers using the PM3 method[8a] and an earlier reported procedure[8b]. From Table II, where the symbols Φ_S, Φ_{ATS1} and Φ_{ATS2} denote torsion angles of (*S*)-enantiomers and in the pairs of approximate transition states[8c], it follows that non-atropisomeric 1-phenylpyrrole **6a** exhibits low barriers to rotation around various bonds (1.2–6.2 kcal/mol) and represents the case without

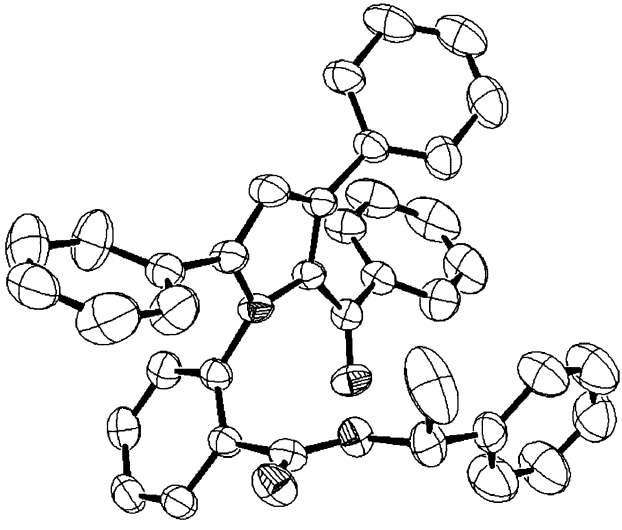


FIG. 1
The ORTEP drawing of amide **14**

any hope of detecting rotational isomers under usual conditions. The second non-atropisomeric 1-(2,4,6-trimethylphenyl)pyrrole **6d** contains the aryl group almost incapable to rotate (39.6–43.4 kcal/mol) but the corresponding torsion angle Φ = 90° excludes any axis chirality identical with the N–C(sp^2) bond. On the other hand, the PM3 models of all atropisomeric 1-arylpyrroles **6b**, **6c**, **6f** and **8**, exhibit the corresponding rotation barriers within the range from 19.3 to 27.1 kcal/mol, thus supporting the expected type of axial chirality.

An analogous approach to the PM3 calculations of the transformation barriers between atropodiastereoisomers **14** and **15** did not turn out to be unique because of the conformational flexibility of the side chains associated with small changes in molecular energy. Thus, the first energy minimum of the $\Delta H_f = f(\Phi)$ curve corresponds to the *anti*-conformer of **14** (with respect to mutual space orientation of both C=O bonds) but the atropodiastereoisomerisation *anti*-**14** → **15** represented by a stepwise increase in the torsion angle Φ results in *syn*-conformer of **15**. Similarly, after the transformation of *syn*-**15** to *anti*-**15** (by small Φ variations and subsequent energy optimisation), the reverse atropisomerisation procedure *anti*-**15** → **14** results in *syn*-conformer of **14**. These facts suggest that a deeper conformational changes may be expected in the mutual atropodiastereoisomerisations of **14** and **15**.

TABLE II
Calculated rotation barriers $\Delta E_{1,2}$, uncertainties in heats of formation $\delta\Delta H_f$ (kcal/mol) and torsion angles Φ (±5°)[a] calculated by the PM3 method

Molecule	Bond	ΔE_1	ΔE_2	$\delta\Delta H_f$	Φ_S	Φ_{ATS1}	Φ_{ATS2}
6a	N1–Ar	4.6	4.8	+0.1	70	0	180
	C2–CO	3.8	6.2	+0.2	70	0	180
	C3–Ph	1.4	1.4	0.0	60	0	180
	C5–Ph	1.2	1.3	+0.1	120	0	150
	OC–Ph[b]	2.0	–	–	130	60	–
6b	N1–Ar	24.0	19.3	+0.3	90	20	190
6c	N1–Ar	22.0	21.2	–0.4	110	20	190
6d	N1–Ar	43.4	39.6	–0.01	90	30	200
	C2–CO	4.6	6.0	+0.4	60	0	190
6f	N1–Ar	21.4	20.2	–0.9	70	20	200
8	N1–Ar	27.1	22.8	–0.1	90	35	200

[a] Φ changing from 0 to 360°; [b] the highest barrier only.

As shown in Table III, complete molecular geometry optimisations with respect to all degrees of freedom lead to *syn*- and *anti*-conformers of **14** and **15** possessing very similar heats of formation. In fact, a real number of all conformers of amides **14** and **15** might be hardly accessible by the simple procedure[8b]. Hence, only the energy barriers $\Delta E_{1,2}$ = 25.4–29.4 kcal/mol for the selected transformations *anti*-**14** → *syn*-**15** and *anti*-**15** → *syn*-**14** could be calculated and compared with experimental activation Gibbs energies $\Delta G^{\ddagger}$ obtained by ^{1}H NMR and polarimetric measurements of amides **14** and **15** mutually isomerised in solution at the temperatures 363 to 396 K.

The experimental barriers $\Delta G^{\ddagger}$ given in Table IV were obtained in two different ways. A more accurate approach was based on kinetic measurements

TABLE III
Heats of formation ΔH_f and selected isomerisation barriers $\Delta E_{1,2}$ calculated by the PM3 method (in kcal/mol)

Conformer	ΔH_f^a	Isomerisation	ΔE_1	ΔE_2
anti-**14**	87.5	*anti*-**14** → *syn*-**15**	29.4	28.8
syn-**14**	89.5			
anti-**15**	89.5	*anti*-**15** → *syn*-**14**	25.4	25.7
syn-**15**	86.2			

[a] Minimised with respect to all geometry degrees of freedom.

TABLE IV
Kinetic and thermodynamic data for the isomerisations **14** → **15** and **15** → **14**

T, K	k_1, $s^{-1} \cdot 10^{-5}$	k_2, $s^{-1} \cdot 10^{-5}$	ΔG^*, kcal mol^{-1}	K	ΔG^0, cal mol^{-1}
363[b]	4.22	5.25	28.6; 28.5	0.804	157.2
380[b]	17.44	20.77	29.0; 28.8	0.840	131.6
380[c]	6.25	6.25	29.7 ± 0.1	1[d]	–
396[c]	13.90	13.90	30.4 ± 0.1	1[d]	–

[a] For the meaning of the symbols, see Experimental; [b] by ^{1}H NMR in DMSO-d_6 solutions; [c] polarimetric determination for diglyme solutions; [d] approximation for roughly enantiomeric structures, see ref.[10b].

of the isomerisation **14** → **15** in DMSO-d_6. It started from atropodiastereoisomer **14** and proceeded to the equilibrium mixtures of **14** and **15** being monitored by integral intensities of methyl doublets in ^{1}H NMR spectra at δ 0.67 (**14**) and 1.37 (**15**) ppm. An alternative kinetic procedure considering both atropodiastereoisomers **14** and **15** to be roughly enantiomeric was based on polarimetric measurements during the opposite isomerisations **15** → **14** in diglyme. In all cases comparable $\Delta G^{\ddagger}$ values within the range from 28.5 to 30.4 kcal/mol were obtained (Table IV) being not so far from the above mentioned theoretical $\Delta E_{1,2}$ data given in Table III.

EXPERIMENTAL

The temperature data are uncorrected. Melting points were determined on a Boetius block. IR spectra (ν, cm^{-1}; $CHCl_3$ solutions) were measured on a FTIR spectrometer Nicolet 740. NMR spectra (δ, ppm; *J*, Hz) were measured on a Varian GEMINI 300HC and on a Bruker AM400 and DRX 500 Avance instruments at 297 K. HPLC analyses were performed using an LCP 4000 pump and an LCD 2082 UV/VIS detector and Nucleosil C-18 Macherey–Nagel column, mobile phase was CH_3OH–H_2O (8 : 2 or 7 : 3). Commercial Silufol plates (Kavalier, Sázava, Czech Republic) were used for TLC. Optical rotation was measured on an OPTON polarimeter using a 10 cm cuvette at 293 K, specific rotations are given in deg cm^3/g l. The X-ray analysis was performed on an Enraf CAD4 diffractometer. The samples for elemental analyses were dried in vacuum for 4–20 h, some at the toluene boiling point, and analysed on a Perkin–Elmer 240 C automatic analyser. Chlorine contents were determined potentiometrically on a mercury and calomel $Ba(NO_3)_2$ electrodes.

1-Aryl-2,4,6-triphenylpyridinium Perchlorates **5a**–**5f** and **7**

The known procedures[9] were used for preparation of the perchlorates **5a** (m.p. 271–273 °C), **5b** (m.p. 252–254 °C), **5e** (m.p. 244–246 °C), **5f** (263–265 °C) and **7** (m.p. 282–283 °C).

1-(2,3-Dimethylphenyl)-2,4,6-triphenylpyridinium perchlorate (**5c**). 2,3-Dimethylaniline (1.82 g, l5 mmol) was added to a refluxed solution of 2,4,6-triphenylpyrylium perchlorate[9c] (5 g, 12 mmol) in ethanol (100 ml). After cooling the precipitated salt **5c** was filtered off and recrystallised from ethanol. Yield 5.79 g (94%), m.p. 282–283 °C. ^{1}H NMR ($CDCl_3$): 1.80 s, 3 H (CH_3-2′); 2.01 s, 3 H (CH_3-3′); 6.90–7.90 m, 18 H; 8.05 s, 2 H (H-3 and H-5). ^{13}C NMR ($CDCl_3$): 15.74 CH_3; 20.46 CH_3; 126.76 2 CH (C-3 and C-5); 128.25 CH; 128.97 CH; 129.26 CH; 130.00 CH; 130.34 CH; 131.08 CH; 132.27 2 C; 132.36 CH; 133.25 C; 135.20 C; 138.70 C; 139.03 C; 157.34 2 C (C-2 and C-6); 158.60 C (C-4). For $C_{31}H_{26}ClNO_4$ (512.0) calculated: 72.72% C, 5.12% H, 6.92% Cl, 2.74% N; found: 72.82% C, 5.13% H, 7.09% Cl, 2.54% N.

1-(2,4,6-Trimethylphenyl)-2,4,6-triphenylpyridinium perchlorate (**5d**). 2,4,6-Trimethylaniline (2.5 g, 18 mmol) was added to a suspension of 2,4,6-triphenylpyrylium perchlorate[9c] (5 g, 12 mmol) in ethanol (100 ml) and the mixture was heated for 1 h. After cooling, the slightly brownish crystals were precipitated and recrystallisation from ethanol afforded 5.6 g (87%) perchlorate **5d**, m.p. 258–261 °C. ^{1}H NMR ($CDCl_3$): 1.96 s, 6 H (2′-CH_3 and 6′-CH_3); 2.13 s, 3 H (4′-CH_3); 6.69 s, 2 H (H-3′and H-5′); 7.23–8.00 m, 15 H; 8.14 s, 2 H (H-3 and H-5). ^{13}C NMR ($CDCl_3$): 19.24 (CH_3-2′ and CH_3-6′); 21.66 (CH_3-4′); 127.74 2 CH (C-3 and C-5); 129.31 4 CH; 129.50 CH; 129.82 CH; 130.43 CH; 130.54 CH; 131.77 CH; 132.55 2 C;

133.24 CH; 134.40 C; 134.59 C; 135.36 C; 141.86 2 C (C-2′and C-6′); 157.17 2 C (C-2 and C-6); 158.86 C (C-4). For $C_{32}H_{28}ClNO_4$ (526.0) calculated: 73.07% C, 5.37% H, 6.74% Cl, 2.66% N; found: 72.78% C, 5.57% H, 7.01% Cl, 2.61% N.

Ferricyanide Oxidation of Perchlorates **5a**–**5f** and **7**. General Procedure

Suspension of a given perchlorate (1 mmol) in ethanol (50 ml) was stirred under heating and then a solution of potassium ferricyanide (4 mmol) and potassium hydroxide (8 mmol) in water (25 ml) was added dropwise. After 1 h, the reaction mixture was cooled and poured onto crashed ice and extracted with dichloromethane. The collected extracts were dried with magnesium sulfate, HPLC-analysed, evaporated and the residue was recrystallised from ethanol. The earlier described[1b] pyrroles **6a** (m.p. 177–178 °C) and **6d** (m.p. 170–172 °C) were obtained by the procedure from perchlorates **5a** and **5d** in the yields of 84 and 88%, respectively.

[1-(2-Methylphenyl)-3,5-diphenyl-1H-pyrrol-2-yl](phenyl)methanone (**6b**). The oxidation of perchlorate **5b** (3 g, 20 mmol) gave white crystals of ketone **6b** (2.0 g, 83%), m.p. 162–163 °C. For IR, ^{1}H NMR and ^{13}C NMR spectra, see ref.[3]. For $C_{30}H_{23}NO$ (413.2) calculated: 87.14% C, 5.61% H, 3.39% N; found: 87.24% C, 6.12% H, 3.42% N.

[1-(2,3-Dimethylphenyl)-3,5-diphenyl-1H-pyrrol-2-yl](phenyl)methanone (**6c**). The oxidation of perchlorate **5c** (2 g, 3.9 mmol) gave yellowish crystals of ketone **6c** (1.4 g, 84%), m.p. 166–168 °C. IR: 1 628 (C=O). ^{1}H NMR ($CDCl_3$): 1.84 s, 3 H (CH_3-2′); 2.19 s, 3 H (CH_3-3′); 6.64 s, 1 H (H-4); 7.00–7.26 m, 16 H; 7.60 m, 2 H (H-*ortho* in COPh). ^{13}C NMR ($CDCl_3$): 14.79 CH_3; 20.76 CH_3; 111.29 CH (C-4); 125.98 CH; 127.05 CH; 127.87 CH; 128.16 CH; 128.24 2 CH; 128.50 2 CH; 128.80 2 CH; 129.05 2 CH; 129.96 2 CH; 130.60 CH; 130.64 2 CH; 130.94 C; 132.52 CH; 132.58 C; 133.59 C; 135.61 C; 136.01 C; 138.25 C; 138.85 C; 139.29 C; 140.39 C; 180.57 C (CO). For $C_{31}H_{25}NO$ (427.6) calculated: 87.00% C, 5.89% H, 3.28% N; found: 86.75% C, 6.20% H, 3.18% N.

[1-(2-Methoxyphenyl)-3,5-diphenyl-1H-pyrrol-2-yl](phenyl)methanone (**6e**). The oxidation of perchlorate **5e** (1.2 g, 2.4 mmol) gave white crystals of ketone **6e** (0.73 g, 71%), m.p. 211–213 °C. IR: 1 628 (C=O). ^{1}H NMR ($CDCl_3$): 3.49 s, 3 H (CH_3O-2′); 6.63 s, 1 H (H-4); 6.82–7.30 m, 17 H; 7.66 m, 2 H (H-*ortho* in COPh). ^{13}C NMR ($CDCl_3$): 55.91 CH_3O; 111.38 CH (C-4); 112.35 CH; 121.35 CH; 121.26 CH; 127.03 CH; 127.16 CH; 128.08 CH; 128.23 2 CH; 128.52 2 CH; 128.68 C; 128.73 2 CH; 129.38 2 CH; 129.94 CH; 130.02 2 CH; 130.54 CH; 130.79 2 CH; 132.48 CH; 132.83 C; 132.99 C; 136.07 2 C; 139.26 C; 139.65 C; 155.39 C; 188.95 C (CO). For $C_{30}H_{23}NO_2$ (429.5) calculated: 83.89% C, 5.40% H, 3.26% N; found: 84.14% C, 5.59% H, 3.12% N.

2-(2-Benzoyl-3,5-diphenyl-1H-pyrrol-1-yl)benzoic acid (**6f**). In the oxidation of perchlorate **5f** (3.3 g, 6.3 mmol) the reaction mixture was heated for 3 h and after pouring into crushed ice acidified with 1 M HCl to pH 5. The crude product was purified by column chromatography (200 g silica gel, dichloromethane–ethanol 98 : 2) and crystallisation from heptane–ethanol 3 : 1. Yield 1.56 g (56%) of carboxylic acid **6f**, yellow crystals, m.p. 204–205 °C. IR: 1 625 (C=O, ketone); 1 701 and 1 795 (C=O, carboxylic). ^{1}H NMR ($CDCl_3$): 6.62 s, 1 H (H-4); 6.96–7.43 m, 16 H; 7.65 d, 2 H, J = 7.1; 7.79 dd, 1 H, J = 1.6 and 7.7. ^{13}C NMR ($CDCl_3$): 113.31 CH (C-4); 127.75 CH; 128.58 2 CH; 128.70 2 CH; 129.13 3 CH; 129.78 2 CH; 130.02 CH; 130.22 3 CH; 130.60 CH; 131.48 2 CH; 132.30 C; 132.52 CH; 133.76 CH; 134.65 C; 135.19 C; 137.57 C; 137.93 C; 138.03 C; 145.20 C; 169.55 C (CO_2H-2′); 190.22 C (COPh).

For $C_{30}H_{21}NO_3$ (443.5) calculated: 81.24% C, 4.77% H, 3.16% N; found: 81.22% C, 5.20% H, 3.06% N.

[1-(1-Naphthyl)-3,5-diphenyl-1H-pyrrol-2-yl](phenyl)methanone (**8**). The oxidation of perchlorate **7** (3 g, 5.6 mmol) was performed by the general procedure but the crude product was purified by column chromatography (100 g silica gel, petroleum ether–dichloromethane 1 : 1) prior the recrystallisation from ethanol. Yield 2.35 g (93%) of ketone **8**, slightly yellowish crystals, m.p. 156–158 °C. For IR, ^{1}H NMR and ^{13}C NMR spectra, see ref.[3]. For $C_{33}H_{23}NO$ (449.6) calculated: 87.77% C, 5.58% H, 3.10% N; found: 87.69% C, 5.49% H, 2.99% N.

Reduction of Ketones **6a**–**6e** and **8**. General Procedure

A solution of a ketone (1 mmol) in dry diethyl ether (12 ml) was stirred and cooled to –30 °C under argon atmosphere. Then $LiAlH_4$ (2 mmol) in dry diethyl ether (8 ml) was added dropwise at the temperature not exceeding –25 °C and the stirring was continued at –25 to –30 °C for 1 h. After the starting ketone was fully converted to products (TLC, petroleum ether–dichloromethane 1 : 1) the reaction mixture was decomposed with aqueous 4% NaOH (4 ml per 1 g $LiAlH_4$), heated to the room temperature, diluted with benzene (15 ml) and filtered. Evaporation of the filtrates gave considerably pure products which were, after HPLC and ^{1}H NMR analyses, separated by chromatography and/or crystallisation.

(1,3,5-Triphenyl-1H-pyrrol-2-yl)(phenyl)methanol (**9a**). The reduction of ketone **6a** (3 g, 7.5 mmol) gave a white solid the individuality of which (t_R = 6.1 min) followed from HPLC (methanol–water 9 : 1) analysis. Crystallisation from benzene–methanol 1 : 1 afforded white crystals (2.8 g, 92%) of hydroxy derivative **9a**, m.p. 159–162 °C. IR (KBr): 3 549 (OH). ^{1}H NMR (DMSO-d_6): 5.88 d, 1 H, J = 3.8 (CCHO); 6.08 d, 1 H, J = 3.8 (OH); 6.60 s, 1 H (H-4); 6.81–7.65 m, 20 H. ^{13}C NMR (DMSO-d_6): 65.71 CH (C-OH); 109.83 CH (C-4); 124.65 C; 125.15 CH; 125.66 CH; 125.93 CH; 126.33 CH; 127.18 CH; 127.65 CH; 128.16 CH; 128.31 CH; 128.67 CH; 132.75 C; 134.03 C; 134.35 C; 136.12 C; 138.64 C; 143.05 C. For $C_{29}H_{23}NO$ (401.5) calculated: 86.75% C, 5.77% H, 3.49% N; found: 86.67% C, 6.16% H, 3.39% N.

Atropodiastereoisomeric [1-(2-methylphenyl)-3,5-diphenyl-1H-pyrrol-2-yl](phenyl)methanol (**9b**). The reduction of ketone **6b** (0.35 g, 0.85 mmol) gave a white-yellowish solid (m.p. 129–133 °C, yield 89%) containing two isomers (t_R = 111.6 and 121.5 min) in the ratio 7 : 3 (HPLC, methanol–water 7 : 3). For IR and NMR data, see ref.[3]. For $C_{30}H_{25}NO$ (415.5) calculated: 86.71% C, 6.06% H, 3.37% N; found: 86.36% C, 6.31% H, 3.39% N. A sample (200 mg) was subjected to preparative TLC (15 g of Aldrich high-purity silica gel with gypsum binder and fluorescent indicator at 254 nm, 20 × 20 cm plates) which after elution (10 times) with petroleum ether–dichloromethane (5 : 1) gave almost pure (>99%) major atropodiastereoisomer of **9b** (lower R_F), white crystals, m.p. 130–134 °C. NMR data are given in ref.[3].

Atropodiastereoisomeric [1-(2,3-dimethylphenyl)-3,5-diphenyl-1H-pyrrol-2-yl](phenyl)methanol (**9c**). The reduction of ketone **6c** (0.5 g, 1.17 mmol) gave a white solid (m.p. 126–132 °C, yield 94%) as a mixture of two isomers (HPLC, methanol–water 4 : 1, two partly overlapped peaks at 30.9 and 34.7 min) in the ratio 2 : 1. IR (KBr): 3 542. A part of ^{1}H NMR (DMSO-d_6): 0.92 s, 3 H; 1.67 s, 3 H; 1.81 s, 3 H; 2.14 s, 3 H; 6.55 s, 1 H; 6.64 s, 1 H. For $C_{31}H_{27}NO$ (429.6) calculated: 86.68% C, 6.34% H, 3.26% N; found: 86.35% C, 6.72% H, 3.18% N. The preparative TLC performed as above afforded almost pure (>99%) major atropodiastereoisomer of **9c** (lower R_F), white crystals, m.p. 130–134 °C. ^{1}H NMR (DMSO-d_6): 0.92 s, 3 H (Me); 1.81 s, 3 H (Me); 5.90 m, 2 H (OH and H-6); 6.58 s, 1 H (H-4); 6.70–7.76 m, 19 H.

^{13}C NMR (DMSO-d_6): 13.53 CH_3; 19.43 CH_3; 65.85 CH (C-6); 108.77 CH (C-4); 124.40 C; 124.78 CH; 125.08 2 CH; 125.41 CH; 126.00 CH; 126.36 CH; 126.80 2 CH; 127.27 2 CH; 128.12 2 CH; 128.12 2 CH; 128.43 2 CH; 128.78 2 CH; 128.94 CH; 129.66 CH; 132.88 C; 133.55 C; 134.67 C; 135.32 C; 136.40 C; 136.52 C; 137.47 C; 142.73 C.

[1-(2,4,6-Trimethylphenyl)-3,5-diphenyl-1H-pyrrol-2-yl](phenyl)methanol (**9d**). The reduction of ketone **6d** (0.5 g, 1.2 mmol) resulted in 0.47 g (92%) of crude compound **9d** (HPLC, methanol–water 7 : 3, one peak at 204.8 min) giving by recrystallisation from methanol white-yellowish crystals, m.p. 129–132 °C. IR (KBr): 3 559 (OH). ^{1}H NMR (DMSO-d_6): 1.60 s, 3 H (Me); 2.00 s, 3 H (Me); 2.26 s, 3 H (Me); 5.88 d, 1 H, J = 4.6 (CCHO); 5.86 d, 1 H, J = 4.7 (OH); 6.68 s, 1 H (H-4); 6.68–7.72 m, 18 H. ^{13}C NMR (DMSO-d_6): 17.34 CH_3; 18.03 CH_3; 20.58 CH_3; 66.20 CH (C-O); 109.76 CH (C-4); 124.49 C; 125.61 CH; 125.87 2 CH; 125.98 CH; 126.41 CH; 126.63 2 CH; 127.16 2 CH; 127.85 2 CH; 128.35 2 CH; 128.62 CH; 128.70 CH; 128.89 2 CH; 132.32 C; 132.95 C; 133.06 C; 134.42 C; 136.34 C; 137.00 C; 137.20 C; 137.73 C; 143.13 C. For $C_{32}H_{29}NO$ (443.6) calculated: 86.65% C, 6.59% H, 3.16% N; found: 86.36% C, 6.65% H, 3.16% N.

Atropodiastereoisomeric [1-(2-methoxyphenyl)-3,5-diphenyl-1H-pyrrol-2-yl](phenyl)methanol (**9e**). The reduction of ketone **6e** (0.3 g, 0.7 mmol) afforded 0.28 g (88%) of a white-yellowish mixture (m.p. 122–152 °C) of two isomers (HPLC, methanol–water 4 : 1, two peaks at 15.2 and 19.3 min) in the ratio 3 : 2. IR (KBr): 3 541 (OH). A part of ^{1}H NMR (DMSO-d_6): 3.06 s, 3 H; 3.60 s, 3 H; 6.50 s, 1 H; 6.58 s 1 H. For $C_{30}H_{25}NO_2$ (431.5) calculated 83.50% C, 5.84% H, 3.25% N; found: 83.08% C, 6.02% H, 3.22% N. A white sample enriched by the major atropodiastereoisomer (>95%), m.p. 149–155 °C, was obtained by crystallisation from methanol and diethyl ether–heptane. ^{1}H NMR (DMSO-d_6): 3.06 s, 3 H (MeO); 5.88 m, 2 H (CHOH); 6.44 d, 1 H, J = 8.2; 6.58 s, 1 H (H-4); 6.74–7.70 m, 18 H. ^{13}C NMR (DMSO-d_6): 54.51 CH_3; 65.70 CH (C-O); 108.59 CH (C-4); 111.08 CH; 119.28 CH; 124.56 C; 125.11 2 CH; 125.22 CH; 125.92 CH; 126.27 CH; 126.75 2 CH; 127.15 C; 127.22 2 CH; 127.93 2 CH; 128.45 2 CH; 128.61 2 CH; 129.67 CH; 131.91 CH; 133.14 C; 133.24 C; 135.18 C; 136.53 C; 142.44 C; 154.81 C.

Atropodiastereoisomeric [1-(1-naphthyl)-3,5-diphenyl-1H-pyrrol-2-yl](phenyl)methanol (**10**). The reduction of ketone **8** (0.5 g, 1.2 mmol) gave a white-yellowish product, m.p. 165–171 °C (0.48 g, 94%) exhibiting only one broad HPLC peak (methanol–water 4 : 1 and 7 : 3, 26.3 and 160.1 min, respectively) but a couple of the (H-4) signals (6.69 s, 1 H and 6.74 s, 1 H) in ^{1}H NMR (DMSO-d_6) indicated the presence of two isomers of **10**. IR (KBr): 3 545 (OH). For $C_{33}H_{25}NO$ (451.6) calculated: 87.77% C, 5.58% H, 3.10% N; found: 87.44% C, 6.15% H, 3.18% N. Recrystallisations from methanol and diethyl ether–heptane afforded a sample enriched by one of the atropodiastereoisomers (>90%), m.p. 169–174 °C. ^{1}H NMR (DMSO-d_6): 5.86 d, 1 H, J = 3.8 (CHO); 5.93 d, 1 H, J = 3.8 (OH); 6.69 s, 1 H (H-4); 6.44–7.96 m, 22 H. ^{13}C NMR (DMSO-d_6): 65.88 CH (C-O); 109.39 CH (C-4); 123.18 CH; 124.70 CH; 124.77 CH; 124.96 CH; 125.75 CH; 126.12 CH; 126.19 CH; 126.44 CH; 126.54 CH; 127.17 CH; 127.44 CH; 128.03 CH; 128.44 CH; 128.86 CH; 129.05 CH; 130.78 C; 132.97 C; 133.13 C; 134.92 C; 135.23 C; 135.63 C; 136.32 C; 142.17 C.

Atropodiastereoisomeric Bis[2-(2-benzoyl-3,5-diphenyl-1*H*-pyrrol-1-yl)]benzoic Anhydrides **11** and **12**

A mixture of compound **6f** (1.0 g, 2.26 mmol) and DCC (460 mg, 2.26 mmol) in dichloromethane (25 ml) was stirred at room temperature and HPLC-monitored (methanol–

water 4 : 1, 0.8 ml/min). After 30 min the precipitated dicyclohexylurea was filtered off and the filtrate containing anhydrides **11** and **12** in the ratio 1 : 3.8 was evaporated in vacuum. The residue was column-chromatographed on silica gel (120 g, toluene with 0 to 5% gradient of ethyl acetate).

Minor less polar *meso*-atropodiastereoisomer **12** (70 mg) was recrystallised from acetone giving yellow crystals, m.p. 207–212 °C. For $C_{60}H_{40}N_2O_5$ calculated: 868.9858 (M); HR MS found: 868.2952. IR ($CHCl_3$): 995 and 1 017 (COC); 1 626 (C=O); 1 734 and 1 797 (anhydride). ^{1}H NMR ($CDCl_3$): 6.96–7.05 m, 10 H; 7.10–7.22 m, 20 H; 7.36 dd, 2 H, J = 1.6 and 8.2; 7.41–7.52 m, 4 H; 7.56 d, 4 H, J = 7.1. ^{13}C NMR ($CDCl_3$) : 111.79 2 CH; 126.35 2 CH; 127.48 4 CH; 127.61 4 CH; 127.66 2 CH; 128.14 4 CH; 128.22 2 CH; 129.11 4 CH; 129.43 4 CH; 130.10 2 CH; 131.25 2 CH; 131.70 2 CH; 133.23 2 CH; 134.20 2 C; 135.11 2 C; 138.47 2 C; 140.01 2 C; 140.01 2 C; 140.04 2 C; 159.47 2 C (CO, anhydride); 187.76 2 C (CO, ketone).

Major racemic atropodiastereoisomer **11** (372 mg). For $C_{60}H_{40}N_2O_5$ calculated: 868.9858; HR MS found: 868.2975) was then crystallised from methyl *tert*-butyl ether–acetone forming, in agreement with HPLC analysis, a stable solvate, m.p. 154–158 °C. For $C_{60}H_{40}N_2O_5 \cdot 0.5\ C_5H_{12}O \cdot 0.5\ H_2O$ calculated: 81.41% C, 5.14% H, 3.04% N; found: 81.33% C, 5.27% H, 3.06% N. IR ($CHCl_3$): 995 and 1 016 (COC); 1 625 (C=O); 1 732 and 1 797 (anhydride). ^{1}H NMR ($CDCl_3$): 1.20 s, 9 H (Me_3C-solvent); 3.22 s, 3 H (MeO-solvent); 6.97–7.08 m, 20 H; 7.08–7.21 m, 40 H; 7.32 d, 4 H, J = 7.7; 7.43 d, 4 H, J = 7.7; 7.50 d, 4 H, J = 8.2; 7.55 d, 8 H, J = 7.7. ^{13}C NMR ($CDCl_3$): 26.94 3 CH_3 (solvent); 49.41 CH_3 (solvent); 111.73 2 CH; 126.34 2 CH; 127.45 4 CH; 127.60 4 CH; 127.66 2 CH; 128.08 4 CH; 128.23 2 CH; 129.09 4 CH; 129.46 4 CH; 130.10 4 CH; 131.27 2 CH; 131.40 2 CH; 131.60 2 CH; 133.36 2 CH; 134.26 2 C; 135.16 2 C; 138.50 2 C; 140.18 2 C; 140.26 2 C; 159.63 2 C (CO, anhydride), 187.64 2 C (CO, ketone).

Atropodiastereoisomeric (*R*)- and (*S*)-2-(2-Benzoyl-3,5-diphenyl-1*H*-pyrrol-1-yl)-*N*-[(*R*)-1-phenylethyl]benzamides (**14**) and (**15**)

DCC (116 mg, 0.564 mmol) and (*R*)-1-phenylethylamine (73 µl, 0.564 mmol) were added to compound **6f** (250 mg, 0.564 mmol) in dichloromethane (8 ml) and the reaction mixture was stirred at room temperature for 24 h. The main fraction of the precipitated dicyclohexylurea was filtered off and the filtrate was evaporated in vacuum. The residue was dissolved in a minimum of dichloromethane and impurities were removed by a preparative TLC (toluene–ethyl acetate 9 : 1, six times developed). The resulting mixture (*ca* 1 : 1) of amides **14** and **15** (261 mg, yield 85%, HPLC detection) was further submitted to TLC (toluene–ethyl acetate 91 : 9) by repeated separation of yellowish zones. The fraction containing less polar (*S*,*R*)-amide **14** was crystallised from acetone–heptane (1 : 6) affording yellowish crystals (85 mg), m.p. 170–174 °C and $[\alpha]_D$ +54.5 ($CHCl_3$), which were X-ray analysed. ^{1}H NMR ($CDCl_3$): 1.16 d, 3 H, J = 6.6 (Me); 5.08 qd, 1 H, J = 6.6 and 7.7 (NCH); 6.65 s, 1 H (H-4); 7.03–7.44 m, 21 H; 7.60–7.72 m, 2 H; 8.09 d, 1 H, J = 7.7 (NH). ^{13}C NMR ($CDCl_3$): 22.49 CH_3 (Me); 48.95 CH (HCN); 111.41 CH; 126.15 2 CH; 126.77 CH; 127.08 CH; 127.88 2 CH; 127.96 2 CH; 128.16 CH; 128.25 2 CH; 128.31 CH; 128.52 2 CH; 128.82 2 CH; 129.11 CH; 129.24 2 CH; 129.39 CH; 130.13 2 CH; 132.82 CH; 134.20 C; 134.67 C; 135.98 C; 137.12 C; 137.65 C; 141.86 C; 143.26 C; 165.69 C (NCO); 189.21 C (PhCO). For $C_{38}H_{30}N_2O_2$ (546.6) calculated: 83.49% C, 5.53% H, 5.13% N; found: 83.87% C, 5.89% H, 5.15% N.

The fraction containing more polar (*R*,*R*)-amide **15** was again TLC separated and after crystallisation from benzene–hexane yielded a yellow product (60 mg), m.p. 137–138 °C and $[\alpha]_D$ –124.9 ($CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.51 d, 3 H, *J* = 7.1 (Me); 5.15 qd, 1 H, *J* = 7.1 and 7.7 (NCH); 6.48 s, 1 H (H-4); 6.91–7.42 m, 21 H; 7.64–7.74 m, 2 H; 8.56 d, 1 H; *J* = 7.7 (NH). ^{13}C NMR ($CDCl_3$): 22.44 CH_3 (Me); 49.10 CH (HCN); 111.71 CH; 125.87 2 CH; 126.67 CH; 126.71 CH; 127.81 2 CH; 128.00 2 CH; 128.12 CH; 128.31 2 CH; 128.98 2 CH; 129.06 CH; 129.28 2 CH; 129.54 CH; 130.11 CH; 130.31 2 CH; 132.72 CH; 134.54 C; 135.01 C; 135.73 C; 137.39 C; 137.62 C; 165.90 C (NCO); 189.21 C (PhCO). For $C_{38}H_{30}N_2O_2$ (546.6) calculated: 83.49% C, 5.53% H, 5.13% N; found: 83.58% C, 5.72% H, 5.09% N.

TABLE V
Data collection and structure refinement parameters

Crystal dimenions, mm	0.18 × 0.25 × 0.56
Difractometer and radiation used, Å	Enraf–Nonius CAD4, λ(CuKα) = 1.54184
Scan technique	ω/1θ
Temperature, K	293
No. and θ range of reflections for lattice parameter refinement, °	20; 38–40
Range of *h*, *k* and *l*	0→9, –20→–20, –13→13
Standard reflections monitored in the interval; intensity fluctuation, min; %	60; 2.08
Total number of reflections measured; 2θ range, °	5 959; 4–140
No. of observed reflections	2 804
Criterion for observed reflections	$I \geq 1.96\sigma(I)$
Function minimised	$w(\lvert F_o\rvert - \lvert F_c\rvert)^2$
Weightening scheme	Chebychev polynomial (ref.[11])
Parameters refined	379
Value of *R*, *wR* and *S*	0.0868, 0.0588, 0.8479
Ratio of max. least squares shift to e.s.d. in the last cycle	0.001
Max. and min. heights in final Δρ map, e Å^{-3}	0.38, –0.71
Program used	CRYSTALS (ref.[12a]), SIR92 (ref.[12b]), ORTEP (ref.[12c])

Kinetic Measurements

More accurate activation barriers $\Delta G^{\ddagger}$ were obtained by monitoring the changes in the integral intensities of methyl doublet signals at δ 0.67 (**14**) and 1.37 (**15**) ppm in the ^{1}H NMR spectrum of the solutions of amide **14** in DMSO-d_6 at 90 and 107 °C using the first-order rate equation[10a] $-d[\mathbf{14}]/dt = (k_1 + k_2)[\mathbf{14}] - K[\mathbf{14}]_0$, where $[\mathbf{14}]_0$ and [**14**] are starting and actual concentrations of the substrate, k_1 and k_2 are the rate constants for the processes **14** → **15** and **15** → **14**, and K is the corresponding equilibrium constant. For calculation of alternative pseudoracemisation barrier $\Delta G^{\ddagger}$ of amides **14** and **15** ($k_1 \div k_2$), changes in the $[\alpha]_D$ values of the diglyme solutions of starting amide **15** at 107 and l23 °C were polarimetrically monitored. The rate expression[10b] $t^{-1} \ln ([\mathbf{15}]_0/[\mathbf{15}]_0 - 2\,[\mathbf{15}]) = 2k$ for reversible first-order isomerisation, where $[\mathbf{15}]_0$ is the starting concentration and [**15**] concentration at time t. All obtained data are summarised in Table IV.

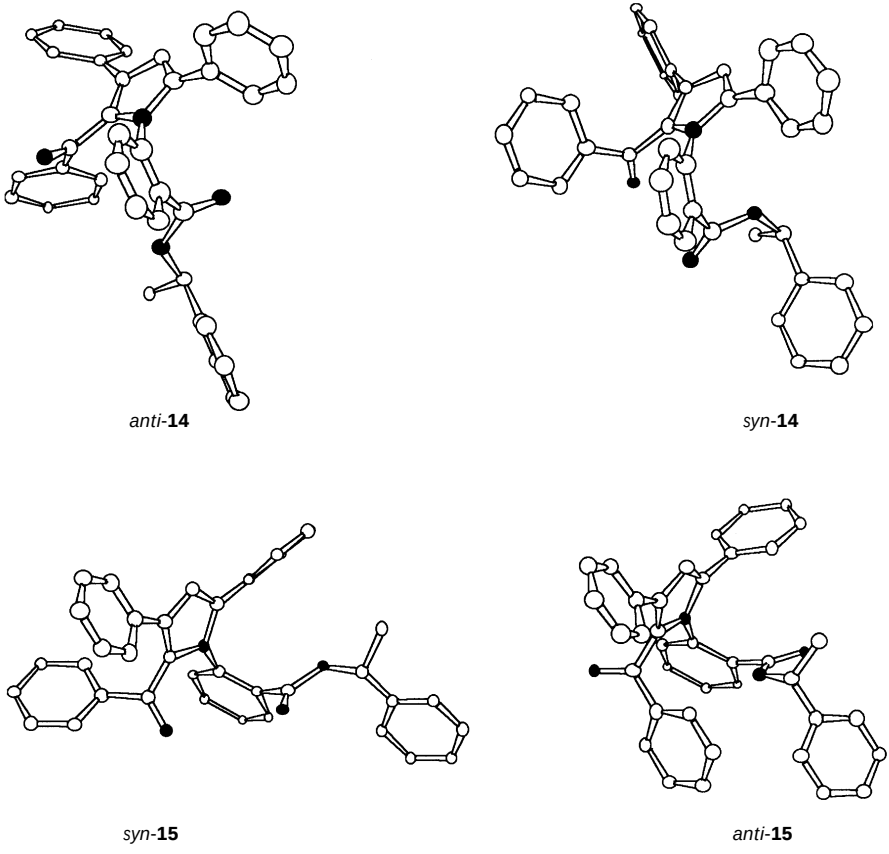


FIG. 2
Conformers of amides **14** and **15** optimised by the PM3 method (see text)

X-Ray Diffraction Analysis of Amide **14**

$C_{38}H_{30}N_2O_2$, M_f = 546.67, monoclinic system, space group $P2_1$ (No. 4), a = 8.0820(6) Å, b = 16.5282(8) Å, c = 11.4254(3) Å, β = 103.423(4)°, V = 1 484.5(1) Å^3, Z = 2, D_{calc} = 1.22 g/cm^3, μ(CuKα) = 0.59 mm^{-1}, F(000) = 576. The structure **14** was solved by direct methods. All of non-H atoms were refined anisotropically by full matrix least-squares method based on F values. The hydrogen atoms were placed respecting the ideal geometry and fixed in distance of 1.0 Å to the attached atom. The Friedel pairs were merged. Structure refinement parameters are listed in Table V. Crystallographic data for the structure of amide **14** reported in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-139914. Copies of the data can be obtained free of charge on application to CCDC, e-mail: deposit@ccdc.cam.ac.uk.

Calculations

All heats of formation ΔH_f were calculated by the semiempirical PM3 method[8a] and the approximate procedure[8c] was used to calculate barriers to intramolecular rotations ΔE_1 and ΔE_2. In addition to the energy data, the torsion angles for (*S*)-enantiomers Φ_S, as well as for pairs of approximate transition states Φ_{ATS1} and Φ_{ATS2} are given in Table II. The PM3 models of conformers *anti*-**14**, *syn*-**14**, *syn*-**15** and *anti*-**15** (Fig. 2) corresponding to minima on the $\Delta H_f = f(\Phi)$ curves were additionally optimised with respect to all geometrical degrees of freedom and used for the calculation of the $\Delta E_{1,2}$ isomerisation barriers shown in Table III. The conformer *anti*-**14** shows to be in good accordance with the structure obtained by the X-ray diffraction (Fig. 3).

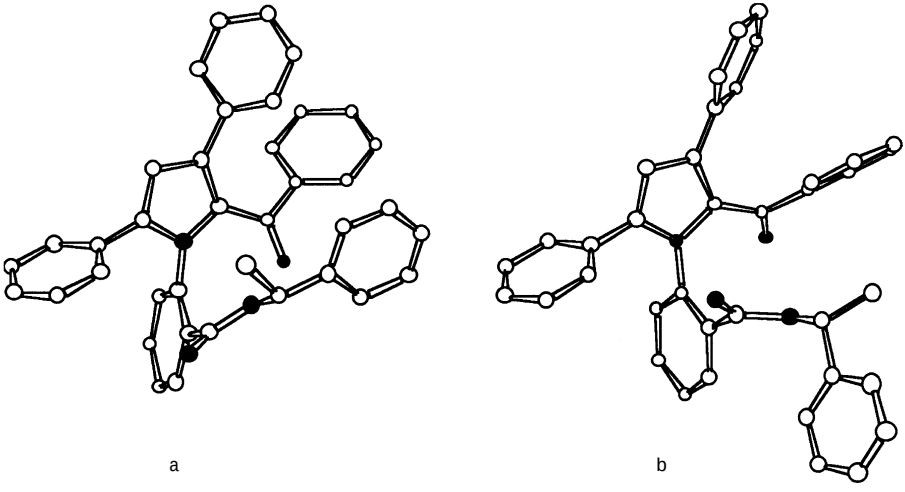


FIG. 3
Comparison of the X-ray molecular skeleton of amide **14** (a) with that obtained for *anti*-conformer of the compound calculated by the PM3 method (b)

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