Enantiomers and Barriers to Racemization of Sterically Hindered *N*-Aryl- and *N*-Heteroarylpyrroles

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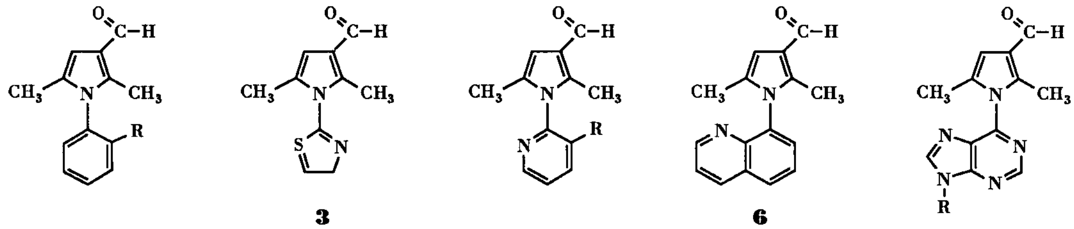
Received December 19, 1990

The *N*-aryl- and *N*-heteroaryl-2,5-dimethylpyrrole-3-carbaldehydes **2-8** have been synthesized by condensation of hexane-2,5-dione with the appropriate amine and subsequent Vilsmeier-Haack formylation of the pyrrole ring. Diastereomeric association complexes of the racemic pyrrole **8** were studied by pmr chemical shifts and the splittings induced by (+)-1-(9-anthryl)-2,2,2-trifluoroethanol. Enrichment of the enantiomers **M** and **P** of **2** and **6** was achieved by liquid chromatography on triacethylcellulose. The barrier to partial rotation about the C-N bond in **6** was determined by thermal racemization and its lower limits in **2** and **8** were estimated.

J. Heterocyclic Chem., **29**, 327 (1992).

The preparation of enantiomers is of increasing interest in the field of chemical, pharmaceutical and particularly biochemical reasearch and productions [1]. One of the reasons for such an interest undoubtedly is pure scientific curiosity [2]. However, the main reason is an applied one, the necessity of being able to produce physiologically active compounds in enantiomerically pure forms. The strict requirements for comparative evaluations of the activities, toxicities and pharmacokinetics of the two enantiomers of racemic drugs results in systematic demands for enantiomerically homogeneous drugs [3]. There are two operationally different approaches leading to enantiomerically pure compounds:enantioselective or asymmetric synthesis [4] which is based on fascinating stereospecificity of chemical reactions and physical separation of racemic mixtures. The second approach requires formation of diastereomeric derivatives and their separation, usually by crystallization or chromatography. However, a prerequisite for the application of that method is the presence of special functional groups (*e.g.* COOH) in the molecule. Additionally, that method is associated with a number of disadvantages, *e.g.* a considerable loss of the second enantiomer [2]. Contrary to this, the main advantage of the chromatographic separation of enantiomers on an optically active stationary phase is that both enantiomers can be obtained if the chromatographic peaks are fully resolved [2]. It has been shown that liquid chromatography on triacetylcellulose has been successfully applied to the separation of enantiomers of different classes of organic compounds [1] including compounds of pharmaceutical interest, *e.g.* anaesthetic ketamine [1] and methaqualone [5]. In connection with our previous studies on some *N*-arylpyrroles [6], *N*-aryl-2(1*H*)-quinolones [7], *N*-aryl-(5*H*)-phenanthridinones [7], and *N*-aryl-4-pyridones [8] we have studied *N*-aryl- and *N*-heteroaryl-2,5-dimethylpyrrole-3-carbaldehydes **1-2** and **3-8**, respectively. The ground state of com-

Scheme



3

6

R

F 1
CH₂Ph 2

R

H 4
CH₃ 5

R

H 7
CH₃ 8

pounds **1-8** could be nonplanar, *i.e.*, chiral due to restricted rotation about the C-N bond between the aryl and pyrrole rings.

If the barrier to partial rotation about the C-N bond is sufficiently high (approximately 100 kJ mol^{-1} at room temperature [9], separation of enantiomeric rotational isomers would be possible. The fact that pyrrole aldehydes have found according to patent literature [10] "use in treating brain disorders" stimulated additionally our interest for this class of compounds. The initial aim of this study was to separate enantiomers **M** and **P** [11] of the pyrroles **1-8** by liquid chromatography and to determine the barriers to partial rotation about the C-N bond.

Results and Discussion.

Synthetic Work.

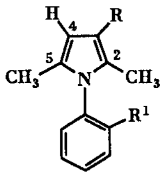
The desired *N*-aryl and *N*-heteroaryl-2,5-dimethylpyrrole-3-carbaldehydes **2-8** were obtained by Knorr-Paal condensation of hexane-2,5-dione with the appropriate amine and subsequent Vilsmeier-Haack formylation [6] of the pyrrole ring. Compound **1**, needed for this study, which has been described previously [12], was also prepared by the method mentioned above.

^{1}H and ^{13}C NMR Shifts.

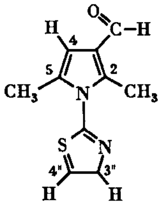
In order to prove the structures of the pyrroles **2-8** and **10-16** their ^{1}H and ^{13}C nmr spectra were examined in detail. The spectral assignments are given in Tables 1 and

Table 1

Values of δ_H (ppm) and J/Hz. Solvent is d_6 -DMSO-for **7** and deuteriochloroform for all other Pyrroles



2,10



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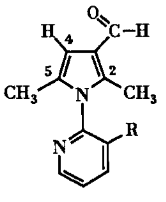
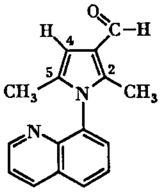
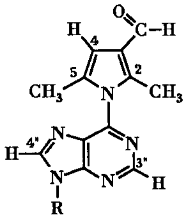


4,5,12,13



6,14

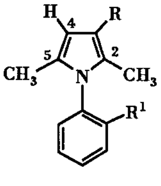


7,8,15,16

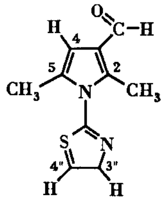
	R	R^1	2-CH$_3$ and 5-CH$_3$		4-H	3''-H	4''-H	Others
2	CHO 9.8 (s)	CH$_2$Ph 3.6 (s)	1.9 (s)	1.8 (s)	6.4 (s)	–	–	6.8-7.4 (m)
3	CHO 9.9 (s)	–	2.4 (s)	2.2 (s)	6.4 (d) $^4J = 0.9$	7.5(d) $^3J = 3.5$	7.8 (d) $^3J = 3.5$	
4	CHO 9.9 (s)	H	2.4 (s)	2.1 (s)	6.4 (d) $^4J = 0.9$	–	–	7.2-8.7 (m)
5	CHO 9.9 (s)	CH$_3$ 1.9 (s)	2.2 (s)	2.1 (s)	6.4 (s)	–	–	7.4-8.5 (m)
6	CHO 9.9 (s)	–	2.2 (s)	1.9 (s)	6.5 (s)	–	–	7.4-8.9 (m)
7	CHO 9.9 (s)	H	2.4 (s)	2.1 (s)	6.4 (s)	9.0 (s)	8.7 (s)	–
8	CHO 9.9 (s)	CH$_3$ 4.0 (s)	2.4 (s)	2.2 (s)	6.5 (s)	9.0 (s)	8.2 (s)	–
10	H 5.9 (s)	CH$_2$Ph 3.6 (s)	1.8 (s)	1.8 (s)	5.9 (s)	–	–	6.9-7.3 (m)
11	H 5.9 (s)	–	2.2 (s)	2.2 (s)	5.9 (s)	7.4 (d) $^3J = 3.6$	7.7 (d) $^3J = 3.6$	–
12	H 6.1 (s)	H	2.2 (s)	2.2 (s)	6.1 (s)	–	–	7.4-8.9 (m)
13	H 5.9 (s)	CH$_3$ 2.0 (s)	1.9 (s)	1.9 (s)	5.9 (s)	–	–	6.5-8.5 (m)
14	H 6.0 (s)	–	1.9 (s)	1.9 (s)	6.0 (s)	–	–	7.2-8.9 (m)
15	H 6.0 (s)	H	2.2 (s)	2.2 (s)	6.0 (s)	9.0 (s)	8.2 (s)	–
16	H 5.9 (s)	CH$_3$ 4.0 (s)	2.2 (s)	2.2 (s)	5.9 (s)	8.9 (s)	8.1 (s)	–

Table 2

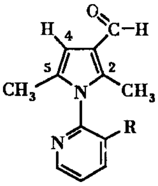
^{13}C NMR Chemical Shift Values (ppm) [a]



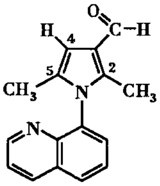
2,10



3,11



4,5,12,13



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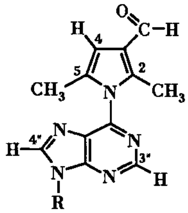


7,15

Compound	**2**	**3**	**4**	**5**	**6**	**7**	**10**	**11**	**12**	**13**	**14**	**15**
R	CHO 184.9 (d)	CHO 185.3 (d)	CHO 185.0 (d)	CHO 185.3 (d)	CHO 185.3 (d)	CHO 185.6 (d)	H	H	H	H	H	H
R^1	CH_2Ph 37.6 (t)	–	H	CH_3 16.6 (q)	–	H	CH_2Ph 37.0 (t)	–	H	CH_3 16.0 (q)	–	H
C-2	135.7 (s)	139.8 (s)	138.6 (s)	138.1 (s)	140.2 (s)	140.0 (s)	130.3 (s)	129.8 (s)	128.5 (s)	127.0 (s)	129.2 (s)	129.8 (s)
C-3	121.9 (s)	122.9 (s)	122.2 (s)	122.1 (s)	121.4 (s)	122.8 (s)	105.5 (d)	107.9 (d)	106.9 (d)	105.5 (d)	105.6 (d)	109.8 (d)
C-4	105.9 (d)	106.9 (d)	106.1 (d)	106.0 (d)	105.7 (d)	106.2 (d)	105.5 (d)	107.9 (d)	106.9 (d)	105.5 (d)	105.6 (d)	109.8 (d)
C-5	130.1 (s)	131.8 (s)	130.6 (s)	130.0 (s)	132.0 (s)	131.5 (s)	130.3 (s)	129.8 (s)	128.5 (s)	127.0 (s)	129.2 (s)	129.8 (s)
2'-CH_3	10.6 (q)	11.1 (q)	11.0 (q)	10.6 (q)	11.1 (q)	11.0 (q)	12.4 (q)	13.1 (q)	13.1 (q)	11.7 (q)	12.8 (q)	13.4 (q)
5'-CH_3	12.1 (q)	12.6 (q)	12.6 (q)	12.0 (q)	12.4 (q)	12.7 (q)	12.4 (q)	13.1 (q)	13.1 (q)	11.7 (q)	12.8 (q)	13.4 (q)
C-1"	139.4 (s) [b]	156.8 (s)	150.0 (s)	149.2 (s)	134.6 (s)	145.9 (s)	140.0 (s) [b]	159.2 (s)	151.1 (s)	150.7 (s)	136.8 (s)	148.4 (s)
C-2"	138.8 (s) [b]	–	123.9 (d)	131.8 (s)	129.7 (d)	–	139.2 (s) [b]	–	122.2 (d)	131.5 (s)	129.7 (s)	–
C-3"	128.8 (d) [b]	141.3 (d)	138.8 (d)	140.2 (d)	126.1 (d)	151.9 (d)	128.0 (d) [b]	140.5 (d)	137.9 (d)	138.9 (d)	126.0 (d)	152.4 (d)
C-4"	131.2 (d) [b]	121.4 (d)	122.4 (d)	124.8 (d)	129.6 (d)	–	128.3 (d) [b]	119.6 (d)	122.0 (d)	123.1 (d)	128.5 (d)	–
C-5"	127.8 (d) [b]	–	149.7 (d)	147.6 (d)	136.3 (d)	–	126.9 (d) [b]	–	149.3 (d)	146.6 (d)	136.0 (d)	–
C-6"	126.4 (d) [b]	–	–	–	122.1 (d)	147.6 (s)	125.9 (d) [b]	–	–	–	121.6 (d)	146.6 (d)
C-7"	–	–	–	–	151.8 (d)	–	–	–	–	–	151.3 (d)	–
C-8"	–	–	–	–	144.6 (s)	127.2 (s)	–	–	–	–	145.4 (s)	127.2 (s)
C-9"	–	–	–	–	129.4 (s)	156.8 (s)	–	–	–	–	–	156.5 (s)

[a] Solvents d_6DMSO for **7** and **15**, and deuteriochloroform for all other pyrroles. Peak multiplicities in off resonance decoupled spectra are represented by (s) singlet, (d) doublet, (t) triplet and (q) quartet. [b] Tentative assignment. Overlapped with benzyl aromatic signals.

2. The ^{1}H nmr spectra showed close similarity of all comparable signals through the series. The 4-H signal occurs at lower field in **2-8** (δ = 6.4-6.5) than in **10-16** (δ = 5.9-6.1) (Table 2) due to the proximity of 4-H to the carbonyl group in the compounds **2-8**. The assignments in the thiazolyl ring of **3** and **11** and the purinyl ring of **7**, **8**, **15** and **16** is in good agreement with related heterocyclic molecules such as thiazole [13] and purine [14]. The assignment of *C*-2 to *C*-5, 2-CH_3, 5'-CH_3 and *C*HO carbon atoms of the pyrrole ring in ^{13}C nmr spectra of **2-7** and **10-15** (Table 2) is consistent with the corresponding one of the structurally related *N*-arylpyrroles whose ^{13}C nmr analysis has been given in our previous paper [12]. The assignment of carbon atoms in heteroaryl derivatives **3-7** and **11-15** is in accord with the literature data for the related heterocyclic molecules such as 2-aminopyridine [13], 1,3-thiazole [13], quinoline [13] and purine [14]. In conclusion, spectroscopic and analytical data were consistent with the structures **2-8** and **10-16**.

Separation of Enantiomers and Barriers to Rotation.

Chromatographic parameters for separation of enantiomers are summarized in Table 3. **MP-1** showed at +20° only marginal resolution of enantiomers by liquid chromatography (lc) on triacetylcellulose (TAC). However, for

Table 3

Results of Liquid Chromatography of Enantioners. k: Mean capacity factors [1.15]

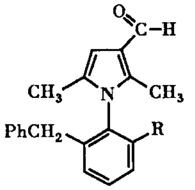
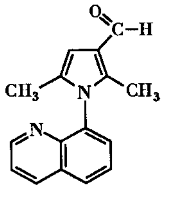
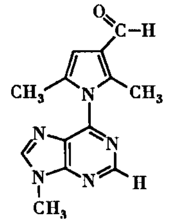
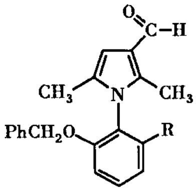
	R^1	k	Polarimetric detection [a]
2	CH_2Ph	1.1 [b]	(+), (-)
3	–	0.8 [b]	none
4	H	0.7 [c]	(-), (+)
5	CH_3	0.6 [b]	none
6	–	0.6 [b,d]	(+), (-)
7	H	0.6 [b]	none
8	CH_3	1.3 [b]	none

[a] Signs of rotation at 365 nm. [b] Triacetylcellulose [1] as a sorbent and ethanol:water (96:4 v/v) as an eluent. [c] (+)-Poly(tritylmethacrylate)/silica gel [16] as a sorbent and methanol as an eluent at -25°. [d] See Figure.

MP-2 possessing two phenyl groups a semipreparative enrichment of enantiomers was obtained by lc on TAC. This is consistent with the earlier observation [6] that separation of enantiomers in atropisomeric *N*-arylpyrroles is improved by the presence of an additional phenyl group which increases the retention differences of enantiomers. Contrary to this fact, **MP-5** showed no separation on TAC at 20°. High-performance liquid chromatography (hplc) on silica coated with (+)-poly(tritylmethacrylate) [16] (PTMA) as well as hplc on tribenzoylcellulose [17,18] (TBC) yielded also no separation of enantiomers of **MP-5**. Though racemization of preparatively enriched (−)-**2** was not observed in diglyme even at +150°, this highest temperature of the experiment permitted to calculate a lower limit of 128 kJ mol^{-1} for the free anthalpy of activation, $\Delta G^{\neq}$ (Table 4).

Table 4

Barriers to Partial Rotation About the C-N Bond

	TS [a]	Medium T/°C	$\Delta G^{\neq}$ [b]/kJ mol^{-1}
MP-2		Diglyme 150 [c]	>128 [d]
MP-6		Diglyme 134 [e]	130 ± 2 [f]
MP-8		CD_2Cl_2 -29 [g]	52 [h]
MP-9		Diglyme 108	125 ± 0.2 [6]

[a] Probable transition state for enantiomerizations **P** ⇌ **M**. [b] Free enhalpies of activation obtained by thermal racemization of enriched enantiomers. [c] Highest temperature of measurement by polarimetry. [d] Lower limit for the barrier obtained after preparative enrichement of (-)- **2**. [e] A slight change of colour indicating a possible decomposition of **6** was observed. [f] Obtained from two polarimetric measurements of preparatively enriched (-)- **6** at 436 nm and at 546 nm. [g] Lower limit for the coalescence temperature. [h] Lower limit for the barrier estimated by variable temperature pmr spectroscopy.

The experiments with **MP-3** at +20° and **MP-4** at +20° yielded no separation of enantiomers by lc on TAC. However, **MP-4** showed a week separation of enantiomers at −25° by hplc on PTMA. Attempts to measure racemizations without preparative enrichment of enantiomers using the solution of an enriched enantiomer in the polarimetric cell [8,19,20] were not successful for **4** which is possibly due to the low specific rotations of the enantiomers. An enrichment of enantiomers was achieved for **MP-6** by lc on TAC at +20° (Figure). A probable explanation for the deviation of **3** and **4** from the chromatographic behaviour of **2** and **6** could be their lower barriers to rotation. No racemization of enriched (−)-**6** contained in a polarimetric cell [8,19,20] was observed up to +82°. This was the highest temperature which could be used in the experiment without danger for the cell. Therefore, the barrier to partial rotation about the C-N bond in **6** was determined by thermal racemization of preparatively enriched (−)-**6**. First-order kinetics were followed by polarimetry during 2 half-lives. The free enthalpy of activation for interconversion of the enantiomeric rotational isomers of **6**

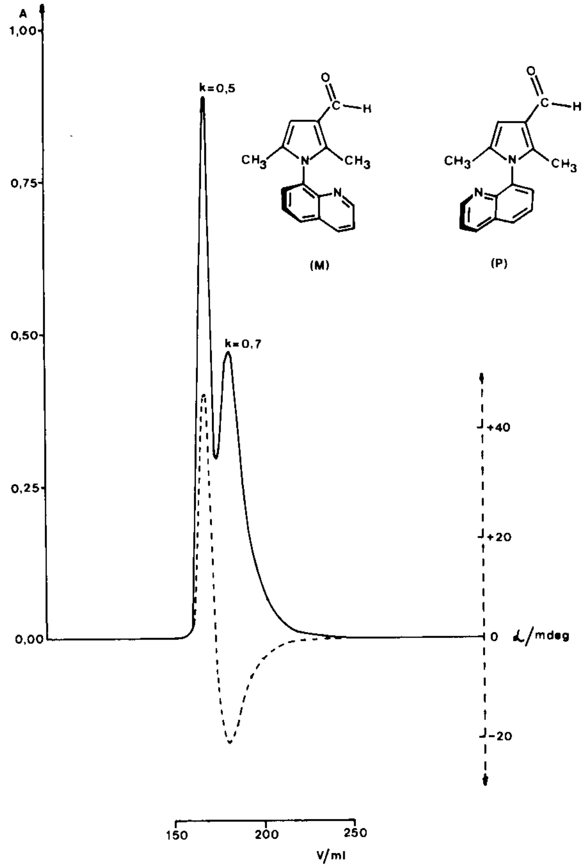


Figure. Chromatography of **MP-6** in ethanol:water (96:4) on triacetylcellulose (particle size 0.02-0.03 mm) at 20°. (———) Rotation angle (α) at 365 nm: (———) absorbance (A) at 278 nm; V, volume of eluate; k, capacity factor.

was found to be 130 ± 2 kJ mol^{-1} (Table 4). The presence of an *ortho*-substituent on the six-membered ring in **2** and **9** as well as two fused six-membered rings in **6** (*cf.* Scheme) gives rise to such high barriers (equal to 125.2 kJ mol^{-1} in **9** and larger than 125 kJ mol^{-1} in **2** and **6**, Table 4) that there was no chance for the coalescence of ^{1}H nmr signals in the presence of optically active auxiliaries. It has been observed that a methyl group exerts a similar steric effect as a benzyl group in restricting internal rotation about the aryl-CO bond in benzamides [21]. Furthermore in terms of steric requirements one may considered the lone pair of the pyridine nitrogen atom in **5** as similar [22] to the aromatic hydrogen atom in the *ortho*-position of the *N*-aryl group in **2** (Scheme). The rotational barrier in **5**, containing an aza nitrogen atom in the *ortho*-position of the pyridine ring, should also be similar to the corresponding one obtained for **2** ($>$128 kJ mol^{-1}, Table 4) which contains a methine group instead of the nitrogen atom in the proximity of the exocyclic C-N bond (*cf.* Scheme). Therefore, the barrier to rotation in **2** cannot be determined by the coalescence of ^{1}H nmr signals.

Surprisingly, the *N*-(6-purinyl) derivative of pyrrole **7** showed no separation of enantiomers. The reason for this behaviour could be the presence of the acidic proton (N-H) in this molecule. This assumption was based on our earlier observation that separation of enantiomers on TAC could not be achieved in molecules containing acidic O-H protons such as *N*-aryl-3-hydroxy-2-methyl-4-pyridones and *N*-aryl-4-hydroxy-3-methyl-2(1*H*)-quinolones [23]. Contrary to this finding the corresponding *O*-methyl substituted derivatives of *N*-aryl-4-pyridones [8] and *N*-aryl-2(1*H*)-quinolones [7] were suitable for chromatographic resolution of enantiomers. Therefore, we have prepared the corresponding *N*-methyl-substituted compound **8**. However, this compound showed also no separation of enantiomers on TAC and TBC at 20°. It seems that the barrier to rotation around the C-N bond in **8** containing fused six- and five-membered puring rings (*cf.* Scheme) is still not sufficiently high to give rise to stable enantiomers which can then be separated by liquid chromatography on an optically active stationary phase. For this reason we have applied another method for determination of rotational barriers, variable temperature ^{1}H nmr spectroscopy in the presence of optically active solvating agents [24,25]. Externally enantiotopic groups in **8** become diastereotopic by association with the auxiliary compound (+)-1-(9-anthryl)-2,2,2-trifluoroethanol (ATFE) and may be anisochronous [25], *i.e.*, they could display unequal pmr shifts. The splitting of pmr signals was effected by lowering the temperature and the best shift differences were achieved in the presence of 5.25 equivalents of (+)-ATFE at −70°.

These shift differences $\Delta\delta$ decrease with increasing temperature and were extrapolated to −29°. Although complete coalescence of the 4-H signals (*cf.* Table 1, δ = 6.1, $\Delta\delta$ = 0.08) was not observed at −29°, a calculation [26] of a lower limit for the free enthalpy of activation, $\Delta G^{\neq}$, for the interconversion of the enantiomers of **8** was possible, giving a value greater than 52 kJ mol^{-1} (Table 4).

EXPERIMENTAL

Melting points were determined on Kofler Mikroheiztisch (Reichert, Wien) instrument and are not corrected. The ir spectra were recorded on a Perkin-Elmer 297 Infracord and uv spectra on a Hitachi Perkin-Elmer 124 spectrometer. The pmr spectra of **2-4,6,7** and **10-15** were recorded on JEOL FX-90Q (PFT mode, 8K data points, 90 MHz). The pmr spectra of **5**, **8** and **16** were taken on Bruker WH 250 (PFT mode 32K data points, 250 MHz) and Bruker AW-80 spectrometers respectively. The ^{13}C nmr spectra of **2-7** and **10-15** were recorded on JEOL FX-90Q spectrometer operating at 22.55 MHz for ^{13}C resonance. The measurement conditions were: spectral width 5200 Hz, addresses 8K, pulse width 5 sec and pulse repetition 1-2.5 s. In the latter case, the techniques used were: broadband proton decoupling and off-resonance decoupling. The eims (electron impact mass spectra) of **2-4**, **6**, **7**, **11**, **12** and **15** were recorded on a Varian MAT CH7 instrument with ionizing energy 70 eV and emission current 0.1 mA. The eims of **16** was recorded on gas chromatograph Varian 3400 using a 15 m x 0.32 mm DB-1 column at 170°, equipped with mass spectrometer Finigan MAT ion trap detector 800. The eims of **8** was recorded on a Varian MAT 711 double focusing mass spectrometer with ionizing energy 80 eV and emission current 0.8 mA. The exact measurement of **8** was performed by using the same instrument at resolution 10,000 (10% relative value definition). Low resolution mass spectrum of **13** was recorded on Varian MAT 90 spectrometer with ionizing energy 70 eV. High resolution mass spectra of **13** and **16** were recorded on the same instrument. Elemental analyses were performed by the Central Analytical Service, Institut "Rudjer Bošković", Zagreb.

Chromatography.

Low-pressure liquid chromatography (column 300-25 mm) at flow rate 3.3-4.3 cm^3 min^{-1}, Δp = 1.9-2.1 bar [27] on TAC as a stationary phase with particle diameter of 0.02-0.03 mm and ethanol:water, 96:4 (v/v), as the eluent at 22-25° was used for separations of enantiomers. Injected quantities of racemates were 1.3-5.0 mg in 1 cm^3 of ethanol. Sample injection and detector systems along with other details of the chromatographic equipment have been described previously [1]. High performance liquid chromatography at flow rate 0.5 cm^3 min^{-1}, Δp = 48-100 bar [27], on PTMA [16] as a stationary phase and methanol as the eluent at +15 and −25° was used for separation of enantiomers of **4**. Injected quantities of racemates were 0.04-0.5 mg. Low-pressure liquid chromatography at flow rate 4 cm^3 min^{-1}, Δp = 1.6-2.0 bar [27] on TBC as a stationary phase with methanol as the eluent at 22-25° was used for some separations. Preparative thin layer chromatography was carried out on preparative Kieselgel 60 F$_{254}$ plates (1 mm) (E. Merck, Darmstadt, Germany).

N-Aryl- and *N*-Heteroaryl-2,5-dimethylpyrroles **10-14**.

These were prepared by Knorr-Paal condensation of hexane-2,5-dione with a suitable amine (dissolved in benzene) and phosphoryl chloride by analogy to the procedure in the literature [28]. The following compounds were obtained in this way.

N-(2-Benzylphenyl)-2,5-dimethylpyrrole (**10**).

This compound was obtained by recrystallization of the crude product from methyl alcohol as colorless crystals mp 69-71°; uv (absolute ethanol): λ max 224 nm (log ε 4.01).

Anal. Calcd. for $C_{19}H_{19}N$: C, 87.31; H, 7.33; N, 5.36. Found: C, 87.38; H, 7.11; N, 5.39.

N-(2-Thiazolyl)-2,5-dimethylpyrrole (**11**) [29].

This compound was obtained by distillation of the crude product bp 122-123°/12 Torr; uv (absolute ethanol): λ max 258 nm (log ε 3.72); λ max 227 (log ε 3.6); ms: m/z 178 (M$^{+\cdot}$, 100%), 177 (43), 163 (48), 94 (37) and 58 (13).

Anal. Calcd. for $C_9H_{10}N_2S$: C, 60.54; H, 5.65; N, 15.72. Found: C, 60.58; H, 5.86; N, 15.94.

N-(2-Pyridyl)-2,5-dimethylpyrrole (**12**) [30].

This compound was isolated from the crude product by distillation, bp 159-162°/44 Torr. The oily product crystallized from light petroleum (40-70°) in the refrigerator, mp 26-28°; uv (absolute ethanol): λ max 288 nm (log ε 3.56); λ max 236 (log ε 7.01); ms: m/z 172 (M$^{+\cdot}$, 100%), 171 (69), 157 (36), 145 (25) and 94 (33).

Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.70; H, 6.99; N, 16.23.

N-(6-Methyl-2-pyridyl)-2,5-dimethylpyrrole (**13**) [30].

This compound was obtained by recrystallization of the crude product from methyl alcohol as colorless crystals, mp 58°; uv (absolute ethanol): λ max 261 nm (log ε 3.66); λ max 218 nm (log ε 4.02); ms: m/z 186.1165 (M$^{+\cdot}$, 100%), 185 (50), 171 (71), 94 (25) and 92 (14).

Anal. Calcd. for $C_{12}H_{14}N_2$: C, 77.39; H, 7.58; N, 15.04. Found: C, 77.41; H, 7.49; N, 15.10.

N-(8-Quinolyl)-2,5-dimethylpyrrole (**14**) [30,31].

This compound was obtained by recrystallization of the crude product as colorless crystals, mp 143°; uv (absolute ethanol): λ max 285 nm (log ε 3.60); λ max 283 nm (log ε 3.05).

Anal. Cacd. for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.08, H, 6.55; N, 12.41.

N-(6-Purinyl)-2,5-dimethylpyrrole (**15**).

A stirred mixture containing 4.05 g (0.03 mole) of adenine and 7 ml (6.84 g, 0.06 mole) of hexane-2,5-dione was heated at 160° for 48 hours. An excess of the hexane-2,5-dione was removed by extraction with light petroleum (bp 40-70°). An oily residue was then extracted twice with 50 ml of hot benzene and the insoluble adenine was filtered off. When the benzene solution was concentrated by partial evaporation, yellowish crystals were obtained mp 100-102°; uv: λ max 280 nm (log ε 3.97), λ max 223 nm (log ε 3.86); ms: m/z 213 (M$^{+\cdot}$, 100%), 212 (63), 198 (50), 119 (23) and 94 (50).

Anal. Calcd. for $C_{11}H_{11}N_5$: C, 61.96; H, 5.20; N, 32.84. Found: C, 61.92; H, 5.48; N, 32.62.

N-(9-Methyl-6-purinyl)-2,5-dimethylpyrrole (**16**).

This compound was obtained by monomethylation of **15** at position 9 by the procedure using potassium carbonate and methyl iodide and following the one given for *N*-substituted derivatives of acyclovir [32]. The crude product was purified by double column chromatography on silica (0.063-0.2 mm) with methanol:-chloroform, 1:6 (v/v), as the eluent. The solidified product was obtained after standing in the refrigerator overnight. Recrystallization from ethanol gave yellow crystals, mp 100-102°; uv: (absolute ethanol): λ max 279 nm (log ε 4.12); λ max 212 nm (log ε 3.80): ms: m/z 227.11664 (M$^{+\cdot}$, 100%), 226 (88) and 212 (50).

N-Aryl- and *N*-Heteroaryl-2,5-dimethylpyrrole-3-carbaldehydes **2-8**.

These were prepared by Vilsmeier-Haack formylation of the corresponding *N*-aryl- and *N*-heteroaryl-2,5-dimethylpyrroles **10-16** according to the procedure given in the literature [6]. Yield varied from 17-35% [33]. Compounds **3-5** were purified by column chromatography on silica gel (0.063-0.2 mm) and methanol:-chloroform, 1:6 (v/v), as the eluent. The oily products obtained in this way solidified after trituration with acetone.

N-(2-Benzylphenyl)-2,5-dimethylpyrrole-3-carbaldehyde (**2**).

This compound was obtained by recrystallization of the crude solidified product from methyl alcohol, mp 85-87°; ir (potassium bromide): ν C=O 1660 cm^{-1}; uv (absolute ethanol): λ max 289 nm (log ε 3.82); λ max 250 nm (log ε 4.01); λ max 222 nm (log ε 3.88); ms: m/z 280 (M$^{+\cdot}$, 100%), 275 (31), 261 (46) and 247 (42).

Anal. Calcd. for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.09; H, 6.71; N, 4.56.

N-(2-Thiazolyl)-2,5-dimethylpyrrole-3-carbaldehyde (**3**).

This compound was obtained as colorless crystals (acetone), mp 72-74°; ir: (potassium bromide): ν C=O 1660 cm^{-1}; uv (absolute ethanol): λ max 252 nm (log ε 4.02); λ max 223 nm, shoulder (log ε 3.14); ms: m/z (206 M$^{+\cdot}$, 100%), 205 (28), 191 (21), 177 (45) and 122 (17).

Anal. Calcd. for $C_{10}H_{10}N_2SO$: C, 58.23; H, 4.89; N, 13.58. Found: C, 58.40; H, 5.08; N, 13.32.

N-(2-Pyridyl)-2,5-dimethylpyrrole-3-carbaldehyde (**4**) [30].

This compound was obtained as colorless crystals (acetone), mp 65-67°; ir (potassium bromide): ν C=O, 1650 cm^{-1}; uv (absolute ethanol): λ max 298 nm, shoulder (log ε 3.17); λ max 250 nm (log ε 4.0); λ max 220 nm (log ε 3.69; ms: m/z 200 (M$^{+\cdot}$, 83%), 199 (38), 185 (17), 171 (100) and 78 (42).

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.90; H, 6.24; N, 13.71.

N-(6-Methyl-2-pyridyl)-2,5-dimethylpyrrole-3-carbaldehyde (**5**) [30].

This compound was obtained as colorless crystals (acetone), mp 131-133°; ir (potassium bromide): ν C=O 1660 cm^{-1}; uv (absolute ethanol): λ max 285 nm, shoulder (log ε 3.26); λ max 249 nm (log ε 3.50); λ max 210 nm (log ε 3.52).

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.86; H, 6.59; N, 13.08. Found: C, 72.83; H, 6.54; N, 13.12.

N-(8-Quinolyl)-2,5-dimethylpyrrole-3-carbaldehyde (**6**) [30].

This compound was obtained by recrystallization of the crude product from methyl alcohol mp 144-145°; ir (potassium bromide): ν C=O 1640 cm^{-1}, uv (absolute ethanol): λ max 276 nm (log ε 4.09); λ max 245 nm (log ε 4.06); λ max 220 nm (log ε 4.1).

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.49; H, 5.75; N, 11.0.

N-(6-Purinyl)-2,5-dimethylpyrrole-3-carbaldehyde (**7**).

This compound was obtained by recrystallization of the crude product from methyl alcohol as colorless crystals, mp 198-200°; uv (absolute ethanol): λ max 278 nm (log ε 4.22); λ max 257 nm, shoulder (log ε 4.10); λ max 213 nm (log ε 4.14); ms: m/z 241 ($M^{+\cdot}$, 100%), 240 (28), 226 (30) and 212 (60).

Anal. Calcd. for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.91; H, 4.46; N, 28.97.

N-(9-Methyl-6-purinyl)-2,5-dimethylpyrrole-3-carbaldehyde (**8**).

This compound could not be isolated from the reaction mixture by column chromatography on silica gel with methanol:chloroform, 1:6 (v/v), but partial purification of the crude product was achieved. Final purification was effected by preparative thin layer chromatography on silica gel with methanol:chloroform, 1:6, and recrystallization of the oily product from ethanol. Colorless crystals were obtained in this way, mp 161-164°; ir (potassium bromide): ν C=O 1670 cm^{-1}; uv (absolute ethanol): λ max 275 nm (log ε 4.08); λ max 214 nm (log ε 4.04), ms: m/z 255.112118 ($M^{+\cdot}$, 100%), 254 (29), 240 (25), 227 (18) and 226 (68).

Anal. Calcd. for $C_{13}H_{13}N_5O$: C, 61.17; H, 5.13; N, 27.43. Found: C, 61.32; H, 4.95; N, 27.35.

Acknowledgement.

This study was performed on the basis of a bilateral German-Croatian scientific co-operation program and supported by grants from Internationales Büro, Kernforschungsanlage Jülich, Working Community for International Scientific Co-operation "Alps-Adria", Republic Administration for Technical Cooperation of Croatia, Fonds der Chemischen Industrie (Federal Republic of Germany) and the Ministry for Scientific Work of Republic Croatia to whom we are grateful. We would like to thank Dr. Th. Burgemeister and Mrs. N. Pustet (Regensburg) for variable temperature pmr spectra in the presence of an optically active auxiliary, Mr. Željko Marinić (Zagreb) for ^{13}C nmr spectra and Dr. Gerhard Holzmann (Berlin) for high resolution mass spectra.

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