Crystal Structures of Some N-substituted 2,5-Dimethylpyrrole Derivatives

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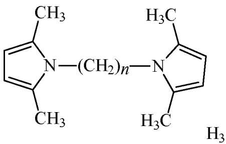
Z. Naturforsch. **2010**, *65b,* 611 – 616; received January 4, 2010

The crystal and molecular structures of five di-(2,5-dimethylpyrrole) and one tri-(2,5-dimethylpyrrole) derivatives have been determined. These compounds were synthesized from the respective diamino derivatives and hexane-2,5-dione in direct and simple reactions. The molecular packings are largely based on C–H$\cdots\pi$ interactions.

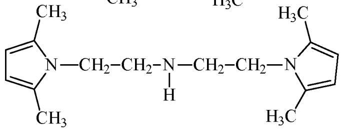
Key words: N-Pyrrole Derivatives, 2,5-Dimethylpyrrole, Solid-state Structure

Introduction

Hexane-2,5-dione has been found as a urinary metabolite of *n*-hexane. It was identified as a 2,5-dimethylpyrrole derivative obtained from the reaction of a urine sample hydrolyzed with hydrochloric acid and then neutralized [1]. Bis-(2,5-dimethylpyrrol-1-yl) compounds were synthesized from hexane-2,5-dione and amines in ethanol or benzene solutions [2] and examined by electron spin resonance spectroscopy in fluid solutions [3].



1 $n = 2$
2 $n = 3$
3 $n = 4$
4 $n = 5$



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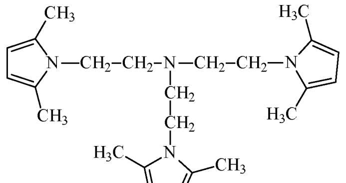

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In our experiments to synthesize bis-(2,5-dimethylpyrrol-1-yl) compounds we used a procedure without solvents as described in [4]. In the Paal-Knorr synthesis, hexane-2,5-dione is cyclocondensed with α,ω-diaminoalkanes producing N-substituted 2,5-dimethylpyrroles. Simple separation and crystallization procedures (details in Experimental Section) yielded crystals suitable for X-ray diffraction analysis.

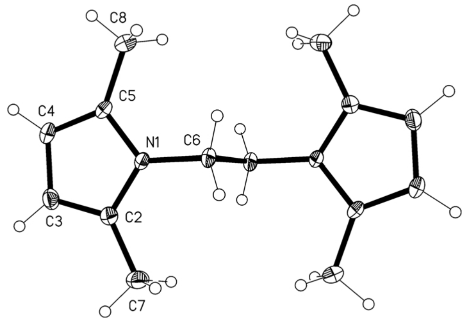


Fig. 1a. The molecule of compound **1** in the crystal. Only the asymmetric unit is numbered. Displacement ellipsoids correspond to 50 % probability levels. Selected bond lengths (Å) and angles (deg): N1–C2 1.382(1), N1–C5 1.385(1), N1–C6 1.454(1); C2–N1–C5 109.85(6), C2–N1–C6 124.91(6), C5–N1–C6 125.24(6).

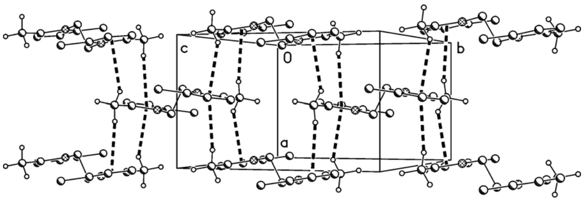
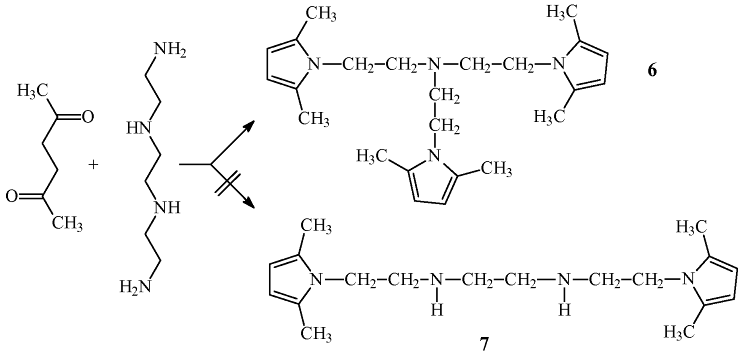


Fig. 1b. Packing diagram of compound **1** showing the $H_{Me}\cdots\pi$ interactions (thick dashed lines) in the region $z \approx 1$.

Results

The surprising aspect of the synthetic work is compound **6**, which was obtained from triethylenete-



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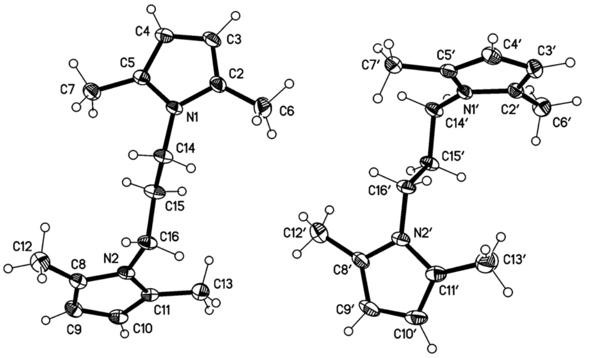

Fig. 2a. The two independent molecules of compound **2** in the crystal. Displacement ellipsoids correspond to 50 % probability levels. Selected bond lengths (Å), angles and torsion angles (deg) (values for both molecules are given): N1–C2 1.384, 1.382(1), N1–C5 1.387, 1.386(1), N1–C14 1.459, 1.460(1), N2–N8 1.381, 1.382(1), N2–C11 1.383, 1.383(1), N2–C16 1.455, 1.460(1); C2–N1–C5 109.41(8), 109.48(7), C2–N1–C14 125.31(8), 124.41(8), C5–N1–C14 125.00(8), 126.04(8), C8–N2–C11 109.72(7), 109.66(8), C8–N2–C16 124.59(8), 125.19(8), C11–N2–C16 125.67(8), 125.15(8); N1–C14–C15–C16 175.3(1), 60.8(1), C14–C15–C16–N2 162.8(1), 178.1(1).

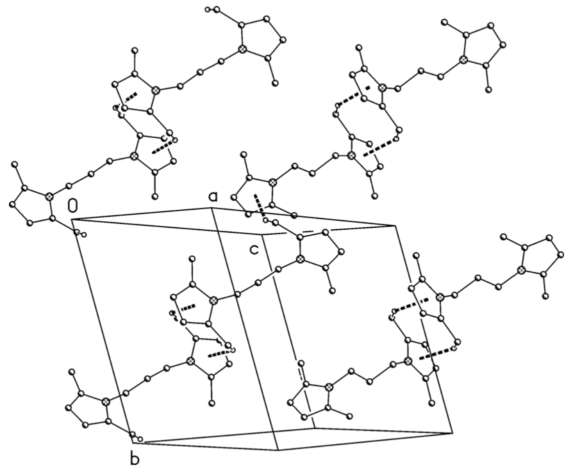

Fig. 2b. Packing diagram of compound **2** showing the $H_{Me}\cdots\pi$ interactions (thick dashed lines). View direction perpendicular to (10$\bar{2}$). Left: pairs of molecule 1; right: pairs of molecule 2; center: connection between molecule 1 and 2.

tramine [2,2′-ethylene-di-imino-bis(ethylamine)]. The ^{1}H NMR and ^{13}C NMR spectra for **6** are simple. The ^{1}H NMR spectrum shows the pyrrole 3- and 4-protons at 5.78 ppm, two singlets for the two CH_2 group protons at 3.75 and 2.76 ppm, and a singlet at 2.26 ppm for the CH_3 protons. The ^{13}C NMR spectrum displays signals for two pyrrole carbons at 127.3 and 105.7 ppm and only three signals for aliphatic carbons at 55.9, 42.5 and 12.7 ppm. The mass spectrum shows a peak at m/z = 381 $[M+H]^+$. The above results confirmed that the expected compound **7** had not formed, and that the product is symmetrical. Single crystals of the compound were grown from methanol solution, and the crystal structure analysis of compound **6** confirmed the proposed structure.

The molecular structures of compounds **1**–**6** are presented in Figs. 1a–6, with corresponding packing diagrams (excluding **6**, see below) in Figs. 1b–5b. Compounds **1** and **3** crystallize with imposed inversion symmetry, as did the related compound 2,2′,5,5′-tetramethyl-1,1′-(hexane-1,6-diyl)-di-*1H*-pyrrole [5], which has a $(CH_2)_6$ bridge between the dimethylpyrrole units; the other compounds display no crystallographic symmetry. The central bridging chains show an extended conformation, and the rings are perpendicular to the bridges (interplanar angles 85° and 89°, respectively). Of the two independent molecules of compound **2**, one molecule (unprimed atoms) has approximate twofold symmetry (r. m. s. deviation 0.27 Å) with antiperiplanar (*ap*) conformations about the bridge bonds, whereas the other has an *ap* geometry about C15′–C16′ but +*sc* about C14′–C15′. Compound **4** has twofold symmetry to a good approxi-

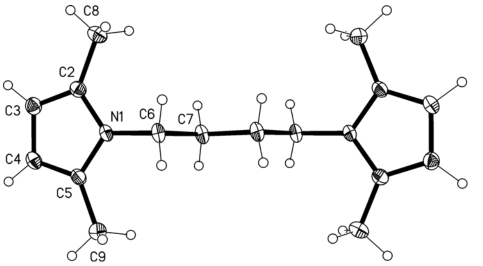

Fig. 3a. The molecule of compound **3** in the crystal. Only the asymmetric unit is numbered. Displacement ellipsoids correspond to 50 % probability levels. Selected bond lengths (Å), angles and torsion angles (deg): N1–C2 1.382(1), N1–C5 1.382(1), N1–C6 1.461(1); C2–N1–C5 109.34(7), C2–N1–C6 125.38(7), C5–N1–C6 125.26(7); N1–C6–C7–C7#1 177.5(1).

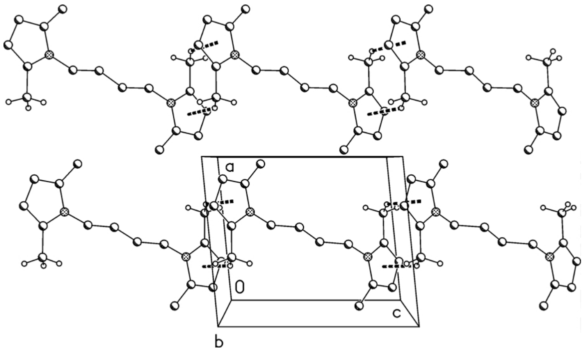

Fig. 3b. Packing diagram of compound **3** showing the $H_{Me}\cdots\pi$ interactions (thick dashed lines) in the region $y \approx 1/2$.

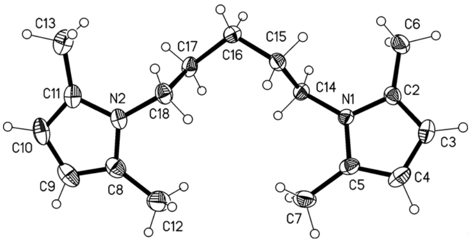

Fig. 4a. The molecule of compound **4** in the crystal. Displacement ellipsoids correspond to 50 % probability levels. Selected bond lengths (Å), angles and torsion angles (deg): N1–C2 1.377(1), N1–C5 1.378(1), N1–C14 1.453(1), N2–C8 1.377(1), N2–C11 1.379(1), N2–C18 1.456(1); C2–N1–C5 109.5(1), C2–N1–C14 124.7(1), C5–N1–C14 125.7(1), C8–N2–C11 109.7(1), C8–N2–C18 126.0(1), C11–N2–C18 124.3(1); N1–C14–C15–C16 177.5(1), C14–C15–C16–C17 68.3(1), C15–C16–C17–C18 65.8(1), C16–C17–C18–N2 171.5(1).

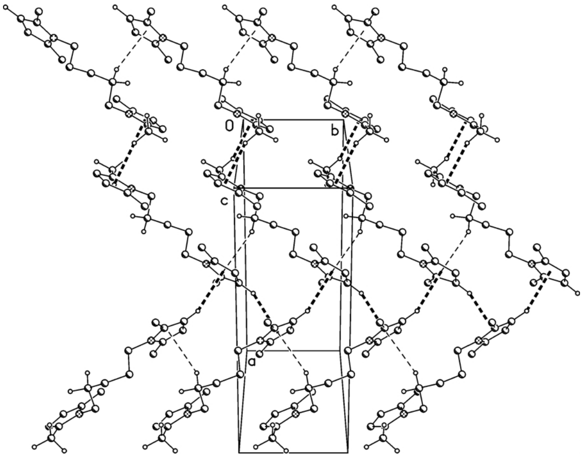

Fig. 4b. Packing diagram of compound **4** (layer structure) showing the $H\cdots\pi$ interactions in the region $x \approx 1/4$, $z \approx 3/4$. View direction perpendicular to $(\bar{1}\,02)$. The slightly longer $H_{bridge}\cdots\pi$ interactions are shown as thin, other $H\cdots\pi$ interactions as thick dashed lines. Note the pairs of $H_{Me}\cdots\pi$ interactions around inversion centers (same horizontal level as the axis labels O, *b*, *c*).

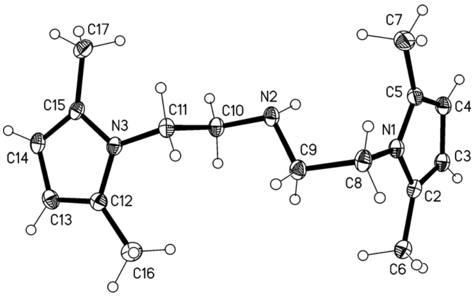

Fig. 5a. The molecule of compound **5** in the crystal. Displacement ellipsoids correspond to 30 % probability levels. Selected bond lengths (Å), angles and torsion angles (deg): N1–C2 1.388(2), N1–C5 1.380(2), N1–C8 1.462(2), N2–C9 1.463(2), N2–C10 1.461(2), N3–C11 1.458(2), N3–C12 1.379(2), N3–C15 1.386(2); C2–N1–C5 109.3(1), C2–N1–C8 124.4(2), C5–N1–C8 126.2(1), C9–N2–C10 112.5(1), C12–N3–C15 109.8(1), C11–N3–C12 124.7(1), C11–N3–C15 125.4(1); N1–C8–C9–N2 −66.9(2), C8–C9–N2–C10 169.9(1), C9–N2–C10–C11 82.7(2), N2–C10–C11–N3 −172.2(1).

mation (r. m. s. deviation 0.09 Å); in the central bridge, the conformation is *ap* about C14–C15 and C17–C18 but +*sc* about C15–C16 and C16–C17. Compound **5** has a conformationally asymmetric bridge, with *ap* geometry about C9–N2 and C10–C11 but −*ac*, +*sc* geometries about C8–C9 and N2–C10, respectively. Compound **6** has formal threefold symmetry according to the chemical formula, but the $(CH_2)_2$ bridges show different conformations; *ap* about C11–C12 and C21–22 and −*ac* about C1–C2. Bond lengths and angles may be regarded as normal. Selected molecular dimensions are given explicitly in the Figure captions.

Table 1. Details of X–H···π interactions (X = C, N)[a].

Compound	Interaction X–H···π	X–H (Å)	H···π (Å)	X–H···π (deg)	Symmetry operator
1	C8–H8B···Cg	1.08	2.74	129	$-\frac{1}{2}+x,\ 1\frac{1}{2}-y,\ -z$
	C8–H8C···Cg	1.08	2.69	153	$\frac{1}{2}+x,\ 1\frac{1}{2}-y,\ -z$
2	C13–H13B···Cg2	1.08	2.76	137	$2-x,\ 1-y,\ 1-z$
	C7′–H7′3···Cg1′	1.08	2.75	150	$-x,\ 1-y,\ -z$
	C7–H7B···Cg2′	1.08	2.61	152	$x,\ 1+y,\ z$
3	C8–H8A···Cg	1.08	2.57	145	$1-x,\ 1-y,\ -z$
4	C6–H6C···Cg1	1.08	2.58	149	$-x,\ -y,\ 1-z$
	C10–H10···Cg2	1.08	2.72	147	$1-x,\ \frac{1}{2}+y,\ 1\frac{1}{2}-z$
	C15–H15B···Cg2	1.08	2.89	142	$x,\ -1+y,\ z$
5	C6–H6C···Cg1	1.08	2.79	146	$1-x,\ 1-y,\ 2-z$
	C14–H14···Cg1	1.08	2.45	157	$1-x,\ 1-y,\ 1-z$
	C10–H10B···Cg3	1.08	2.85	116	$1-x,\ 1-y,\ 1-z$
	N2–H2···Cg3	0.92	3.12	127	$1-x,\ 1-y,\ 1-z$
6	C8–H8A···Cg3	1.08	2.72	127	$-x,\ -\frac{1}{2}+y,\ \frac{1}{2}-z$
	C22–H22B···Cg3	1.08	2.70	108	$x,\ 1\frac{1}{2}-y,\ \frac{1}{2}+z$
	C7–H7A···Cg4	1.08	2.74	155	$1-x,\ 1-y,\ 1-z$
	C12–H12A···Cg4	1.08	2.88	122	$x,\ 1\frac{1}{2}-y,\ -\frac{1}{2}+z$

[a] Cg = center of gravity; Cg*n* refers to the ring with nitrogen N*n*.

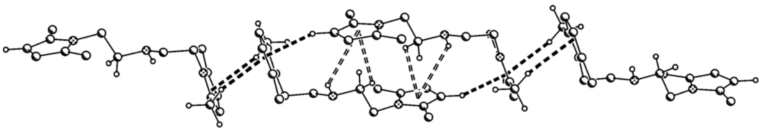

Fig. 5b. Packing diagram of compound **5** showing the H···π interactions (dashed lines) in one chain of dimers parallel to the *z* axis. One complete dimer is shown in the center of the Figure. The bifurcated interactions (see text) are indicated by open dashed bonds. View direction approximately parallel to the *y* axis.

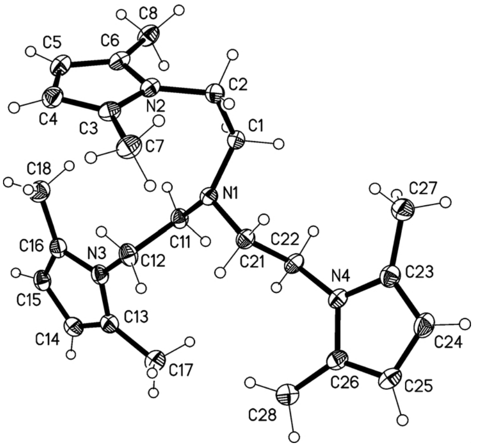

Fig. 6. The molecule of compound **6** in the crystal. Displacement ellipsoids correspond to 50 % probability levels. Selected bond lengths (Å), angles and torsion angles (deg): N1–C11 1.457(1), N1–C21 1.458(1), N1–C1 1.463(1), N2–C6 1.384(1), N2–C3 1.384(1), N2–C2 1.457(1), N3–C13 1.381(1), N3–C16 1.384(1), N3–C12 1.459(1), N4–C23 1.382(1), N4–C26 1.382(1), N4–C22 1.456(1); C11–N1–C21 115.6(3), C11–N1–C1 115.4(1), C21–N1–C1 113.8(1), C6–N2–C3 109.3(1), C6–N2–C2 125.2(1), C3–N2–C2 125.5(1), C13–N3–C16 109.5(1), C13–N3–C12 125.2(1), C16–N3–C12 125.2(1), C23–N4–C26 109.8(1), C23–N4–C22 124.9(1), C26–N4–C22 125.3(1); N1–C1–C2–N2 −55.1(1), N1–C11–C12–N3 178.6(1), N1–C21–C22–N4 169.4(1).

The molecular packing may, at least for compounds **1**–**5**, be analyzed in terms of C–H···π interactions, leading to simple structural motifs. Details of these are given in Table 1 (C–H normalized to 1.08 Å). Perhaps surprisingly, there are no C–H···N or (for **5**) N–H···N interactions. Compound **1** forms thick layers of molecules parallel to the *xy* plane at $z \approx 0$, 1, *etc.*, *via* two $H_{Me}\cdots\pi$ interactions involving the same methyl group (C8). Compound **2** forms layers parallel to $(10\bar{2})$ *via* three $H_{Me}\cdots\pi$ interactions; two of these link pairs of molecules around inversion centers, whereas the third links the two independent molecules by translation. For **3**, the packing is even simpler; one $H_{Me}\cdots\pi$ interaction links the molecules pairwise across inversion centers to form chains parallel to the *z* axis. Compound **4** forms a layer structure parallel to $(\bar{1}02)$ *via*

Table 2. Crystallographic data for compounds **1** – **6**.

	1	**2**	**3**	**4**	**5**	**6**
Formula	$C_{14}H_{20}N_2$	$C_{15}H_{22}N_2$	$C_{16}H_{24}N_2$	$C_{17}H_{26}N_2$	$C_{16}H_{25}N_3$	$C_{24}H_{36}N_4$
M_r	244.37	230.35	216.32	258.40	259.39	380.57
Temperature, K	100(2)	100(2)	103(2)	100(2)	103(2)	100(2)
Crystal size, mm^3	0.35×0.35×0.20	0.40×0.40×0.15	0.25×0.20×0.20	0.40×0.15×0.10	0.25×0.15×0.04	0.12×0.10×0.08
Crystal habit	colorless tablet	pale amber tablet	colorless, irregular	colorless prism	colorless tablet	colorless block
Radiation; λ, Å	MoK_α, 0.71073	MoK_α, 0.71073	MoK_α, 0.71073	MoK_α, 0.71073	CuK_α, 1.54184	CuK_α, 1.54184
Crystal system	orthorhombic	triclinic	monoclinic	monoclinic	monoclinic	monoclinic
Space group	*Pbca*	$P\bar{1}$	$P2_1/n$	$P2_1/c$	$P2_1/n$	$P2_1/c$
a, Å	7.1105(3)	8.9056(3)	7.5885(3)	16.716(3)	14.6518(6)	15.3186(3)
b, Å	11.1252(4)	11.2538(3)	10.6339(4)	6.3370(8)	7.5930(4)	11.2875(2)
c, Å	15.5341(5)	14.1242(5)	8.9323(3)	14.687(2)	14.9042(8)	13.7255(3)
α, deg	90	76.970(3)	90	90	90	90
β, deg	90	87.353(3)	95.547(4)	95.691(14)	114.941(6)	113.464(3)
γ, deg	90	80.910(3)	90	90	90	90
Volume, Å^3	1228.84(8)	1361.70(8)	717.42(6)	1548.1(4)	1503.47(13)	2177.01(7)
Z	4	4	2	4	4	4
$D_{\text{calc.}}$, g cm^{-3}	1.17	1.12	1.13	1.11	1.15	1.16
$F(000)$, e	472	504	268	568	568	832
2 $\theta_{\max}$, deg	60	60	60	57.4	142	141
Refl. coll. / indep.	24661 / 1774	69679 / 7856	27585 / 2099	14990 / 3932	12802 / 2759	35946 / 4095
R_{int}	0.024	0.034	0.031	0.047	0.033	0.019
Completeness, %	98.6	98.6	100.0	98.1	97.8 to 135°	99.7 to 135°
Ref. parameters	75	315	84	176	180	259
$R1$ [$I \geq 2\,\sigma(I)$]	0.036	0.0387	0.037	0.040	0.045	0.034
$wR2$ (all refl.)	0.113	0.0998	0.105	0.078	0.115	0.086
Goodness-of-fit on F^2	1.11	0.93	1.09	0.81	1.08	1.03
$\Delta\rho$ (max / min), e Å^{-3}	0.36 / −0.24	0.28 / −0.22	0.30 / −0.21	0.16 / −0.17	0.17 / −0.18	0.22 / −0.26

three H$\cdots\pi$ interactions involving one methyl, one pyrrole and one bridge hydrogen atom. The central feature of compound **5** is the formation of inversion-symmetric dimers. An initial inspection showed only an $H_{\text{pyrrole}}\cdots\pi$ interaction linking both molecules of the dimer, but a closer analysis has revealed a bifurcated interaction from the central NH and one bridge H to the centroid of the opposite molecule; the individual interactions are necessarily longer and have narrower angles than single H$\cdots\pi$ contacts. The dimers are linked by $H_{\text{Me}}\cdots\pi$ interactions across further inversion centers leading to chains of molecules parallel to the z axis. Neighboring chains lie in planes parallel to the yz plane at $x \approx 1/2$. For compound **6**, four interactions may be tentatively identified, but three have narrow angles. The combined packing is three-dimensional and less clearly defined than that of the other structures.

Experimental Section

Commercial samples of amines were used without further purification. The purity of the amines was monitored by ^{1}H and ^{13}C NMR spectroscopy. NMR spectra were obtained with a 400 MHz Bruker spectrometer in $CDCl_3$, and chemical shifts are reported in ppm downfield from TMS. ESI mass spectra were recorded on a Varian MS 500 instrument using a flow injection system.

*General procedure for the synthesis of 2,5-dimethylpyrrole derivatives **1** – **6***

The amine (0.1 mole) and hexane-2,5-dione (0.2 mole) were heated under reflux for 1 – 2 h. The reaction mixture was then cooled to room temperature and poured into a cooled mixture of water (50 mL) and concentrated hydrochloric acid (5 mL). The precipitate was collected by suction filtration, washed with cold water, and recrystallized from methanol. The products were obtained as colorless crystals but darkened to pale yellowish-brown after a few days in air. Colorless single crystals of **1** and **4** – **6** from methanol, **2** and **3** from ethanol solutions were obtained by slow evaporation.

*2,2′,5,5′-Tetramethyl-1,1′-ethylene-di-1H-pyrrole (**1**):* M. p. 144 – 146 °C. – ^{1}H NMR ($CDCl_3$): δ = 5.77 (bs, 4H), 4.00 (s, 4H), 2.03 (s, 12H). – ^{13}C NMR ($CDCl_3$): δ = 127.7, 105.9, 44.0, 12.0. – MS ((+)-ESI): m/z = 217 [M+H]$^+$.

*2,2′,5,5′-Tetramethyl-1,1′-(propane-1,3-diyl)di-1H-pyrrole (**2**):* M. p. 80 – 81 °C. – ^{1}H NMR ($CDCl_3$): δ = 5.79 (s, 4H), 3.77 (t, 4H), 2.19 (s, 12H), 1.96 (q, 2H). – ^{13}C NMR ($CDCl_3$): δ = 127.2, 105.6, 40.7, 32.2, 12.4. – MS ((+)-ESI): m/z = 461 [2M+H]$^+$.

*2,2′,5,5′-Tetramethyl-1,1′-(butane-1,4-diyl)di-1H-pyrrole (**3**):* M. p. 160 – 162 °C. – ^{1}H NMR (CDCl$_3$): δ = 5.77 (s, 4H), 3.73 (t, 4H), 2.21 (s, 12H), 1.66 (q, 4H). – ^{13}C NMR (CDCl$_3$): δ = 127.3, 105.3, 43.3, 28.4, 12.6. – MS ((+)-ESI): *m/z* = 489 [2M+H]$^+$.

*2,2′,5,5′-Tetramethyl-1,1′-(pentane-1,5-diyl)di-1H-pyrrole (**4**):* M. p. 60 – 62 °C. – ^{1}H NMR (CDCl$_3$): δ = 5.80 (s, 4H), 3.75 (t, 4H), 2.24 (s, 12H), 1.68 (q, 4H), 1.43 (q, 2H). – ^{13}C NMR (CDCl$_3$): δ = 127.4, 105.2, 43.5, 30.9, 24.5, 12.6. – MS ((+)-ESI): *m/z* = 259 [M+H]$^+$.

*2,2′,5,5′-Tetramethyl-1,1′-(3-aza-pentane-1,5-diyl)di-1H-pyrrole (**5**):* M. p. 84 – 85 °C. – ^{1}H NMR (CDCl$_3$): δ = 5.79 (s, 4H), 3.87 (t, 4H), 2.81 (t, 4H), 2.26 (s, 12H). – ^{13}C NMR (CDCl$_3$): δ = 127.7, 105.5, 50.1, 43.9, 12.7. – MS ((+)-ESI): *m/z* = 260 [M+H]$^+$, 519 [2M+H]$^+$.

*Tris{2[1-(2,5-dimethyl-1H-pyrrolyl)]ethyl}amine (**6**):* M. p. 114 – 116 °C. – ^{1}H NMR (CDCl$_3$): δ = 5.78 (s, 6H), 3.75 (bs, 6H), 2.76 (bs, 6H), 2.24 (s, 18H). – ^{13}C NMR (CDCl$_3$): δ = 127.3, 105.7, 55.9, 42.5, 12.7. – MS ((+)-ESI): *m/z* = 381 [M+H]$^+$.

X-Ray structure determinations

Numerical details are presented in Table 2. Crystals were mounted in inert oil and transferred to the cold gas stream of the diffractometer (various Oxford Diffraction area detectors). Absorption corrections were performed for CuK_α data only, using the multi-scan method. Structures were refined anisotropically on F^2 using the program SHELXL-97 [6]. Hydrogen atoms of NH groups (compound **4**) were refined freely; other hydrogens were included using a riding model or idealized rigid methyl groups. All methyl hydrogens were clearly visible in difference syntheses, an important precondition for the discussion of weak hydrogen bonds involving these atoms.

CCDC 759296 (**1**), 766996 (**2**), 759297 (**3**), 759298 (**4**), 759299 (**5**), 759300 (**6**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center *via* www.ccdc.cam.ac.uk/data_request/cif.

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