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PREPARATIVE AND CONFORMATIONAL STUDIES ON [8](2,5)HETEROCYCLOPHANES

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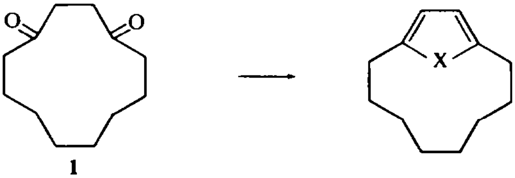
Abstract—[8](2,5)Heterocyclophanes **2a–c** have been obtained by means of Paal-Knorr synthesis applied to 1,4-cyclododecanedione (**1**). N-Substituted pyrrolophanes (**2d, e** and **3a–d**) also have been prepared from **1** and primary amines. In addition, a novel type of ansa compounds **5a–c** were obtained from **1** and *p*-phenylenediamine derivatives. Conformations of these compounds are discussed on the basis of UV and NMR spectra.

CYCLOPHANE chemistry[1] has now been extended to include furan, pyrrole, and thiophene derivatives bridged by an octamethylene chain across the 2,5-positions.* The key starting material was 1,4-cyclododecanedione (**1**) which had previously been prepared by Camerino.[3]

Paal–Knorr syntheses of the heterocyclophanes.† Dehydration of **1** with phosphorus pentoxide in ethanol[5] (80°, 1 hr) yields **2a** in an 83% yield. Treatment of **1** with ammonium carbonate (100–120°, 2 hr) affords **2b** in an 83% yield. Heating of **1** with phosphorus pentasulphide (80°, 1 hr) produces **2c** in a 51% yield. The pyrrolophane **2b** is a colourless solid, m.p. 154–154·5°, whereas **2a** and **2c** are liquids. The furanophane **2a** is the first compound of this class and the thiophenophane **2c** has the shortest polymethylene chain reported.



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2a: X = O
b: NH
c: S

An entropy effect would account for the unusually facile formation of these strained heterocyclophanes in the Paal–Knorr reaction which has previously been applied only to open chain 1,4-dicarbonyl compounds.

Structure of [8](2,5)*heterocyclophanes.* Inspection of Dreiding models of **2a–c** reveals the presence of considerable strain which should possibly result in distortion of heteroaromatic rings. This is evidenced by the red shift of UV absorptions as summarized in Table 1.[6, 7]

The consequence should be the inhibition of free inversion of polymethylene chains, which has been investigated by means of NMR spectra of **2a–c** shown in Fig. 1. At

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* Some previous workers have recorded this kind of [n](2,5)heterocyclophanes such as [4](2,5)pyrrolophane (ref. 2a) and [9](2,5)thiophenophane (ref. 2b).

† Communicated in a preliminary form (Ref. 4).

TABLE 1. UV MAXIMA OF **2a–c** AS COMPARED WITH THOSE OF 2,5-DIMETHYL ANALOGUES (IN *n*-HEXANE)

	nm	($\log \varepsilon_{max}$)		nm	($\log \varepsilon_{max}$)
2a	225	(3·91)	2,5-dimethylfuran	218·5	(3·88)
2b	223	(3·86)	2,5-dimethylpyrrole	216	(3·76)
2c	199	(3·90)	2,5-dimethylthiophene	194	(3·92)
	250	(3·79)		196	(3·93)
				237	(3·86)

150° (the first row) the three heterocyclophanes show analogous patterns of aliphatic proton signals which on cooling to room temperature, remain practically unchanged for **2a** and **2b**. The triplets in the lower field are ascribed to α-methylene protons and the equivalency of these is explained by assuming free inversion of polymethylene chains. The pattern of **2c** at room temperature and that of **2a** at −97° are alike in that the lower field triplets are very distorted. The strongly shielded protons shift to higher field and the signal area shows the strength of two protons instead of four protons at higher temperature. At −97° **2c** exhibits an abnormally shielded one proton.

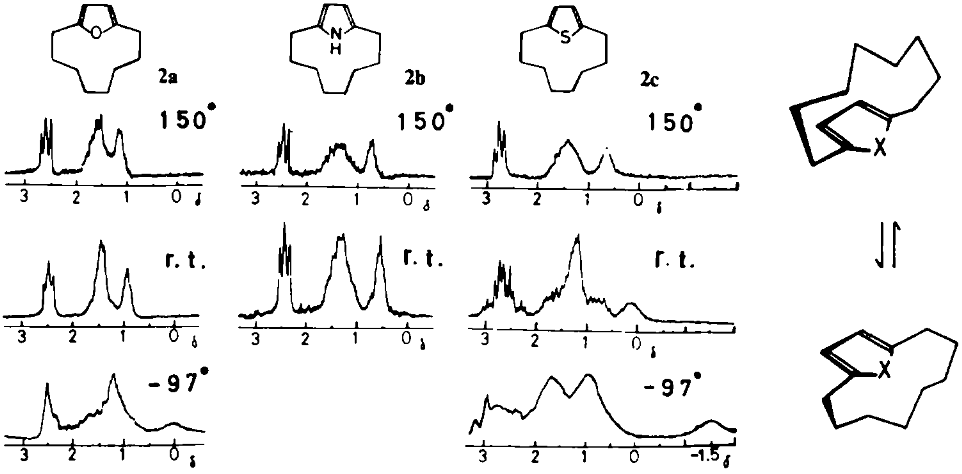

FIG. 1 Aliphatic parts of NMR spectra of **2a–c**. Temperature dependence*†

The shielding effect observed in all cases of **2a–c** must be ascribed to the magnetic anisotropy of heteroaromatic rings and/or to the anisotropy of hetero atoms. The difference of atomic and van der Waals radii of hetero atoms would account for the observed variety of the temperature dependence.

10-*Substituted*[8](2,5)*pyrrolophanes*. The proton attached to the nitrogen of **2b** was found to be inert to deuterium exchange even after treatment with sodium hydride or with potassium t-butoxide in DMSO. This is ascribed to a new mode of steric hindrance which is characteristic of a functional group completely surround by a polymethylene chain. The N-substituted derivatives have, however, been prepared quite

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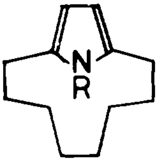
[*] Spectra at −97° were obtained in carbon disulphide solutions and others in *o*-dichlorobenzene solutions. Negligible solvent effect was observed.

[†] At −97° **2b** solution deposited crystals and the spectrum could not be obtained.

easily by the reaction of the diketone **1** with various primary amines in the presence of a trace of hydrochloric acid.

10-Methyl- and 10-allyl[8](2,5)pyrrolophane (**2d**, **2e**) have been prepared in this way. The NMR spectra of **2d** and **2e** in Fig. 2 show at room temperature, patterns of polymethylene protons similar to those of **2a** at −97° and **2c** at room temperature. This may be taken as evidence supporting the above postulation, since flipping of polymethylene bridge must be suppressed by the N-substituents in **2d** and **2e**.



2d: R = Me

2e: R = $-CH_2CH=CH_2$

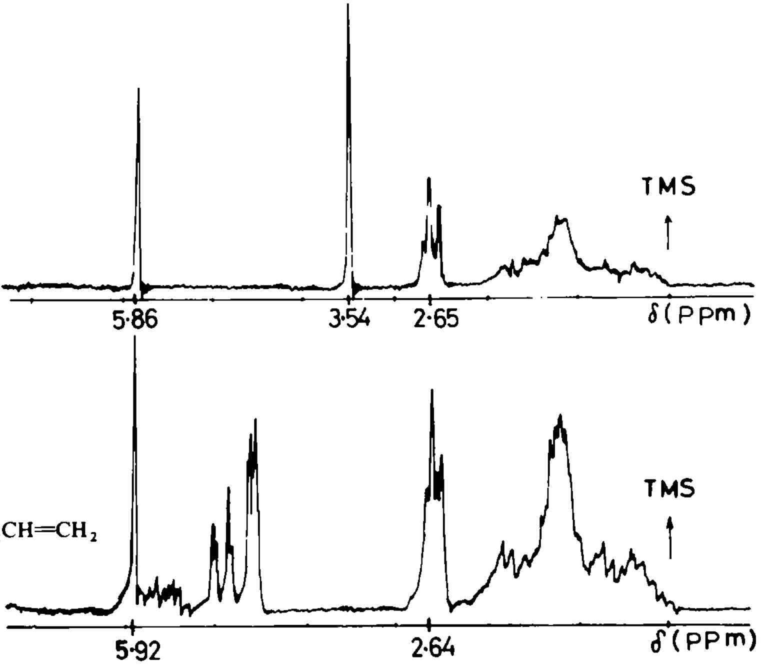
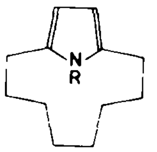
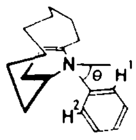


FIG. 2 NMR spectra of **2d** and **2e** (in $CDCl_3$).

10-Aryl[8](2,5)pyrrolophanes (**3a–d**) have been obtained by application of the Paal–Knorr synthesis to aniline and its C-methylated derivatives. The UV spectra of **3a–d** are similar to those of N-aryl-2,5-dimethylpyrroles previously discussed by Kofod[8] and Davoll[9]. The absence of 253 nm absorption indicates that the N-aryl group and pyrrole system are orthogonal in **3a–d** as is the case with N-aryl-2,5-dimethyl-pyrroles. Kofod[8] has established that the N atom in N-aryl-2,5-dimethylpyrroles has a pyramidal-like structure. The postulated conformation given in Fig. 3 has been examined by means of aryl proton signals.

All aromatic signals form singlets at room temperature, but show characteristic splitting at lower temperature. Compound **3a** exhibits 1:3:1 peaks and compound **3b** 1:2:1 peaks. Compound **3c** shows splitting into 1:1 two peaks and compound **3d** remains unchanged. Comparison of chemical shifts of these signals shows remarkable correlation and we are therefore safe to consider that H^1 in the deshielding zone of the pyrrole ring has its signal in the 7·4–7·8 ppm region, whereas H^2 in the shielding zone is in the 6·2–6·6 ppm region. The protons at *m*- and *p*-positions exhibit the signals in





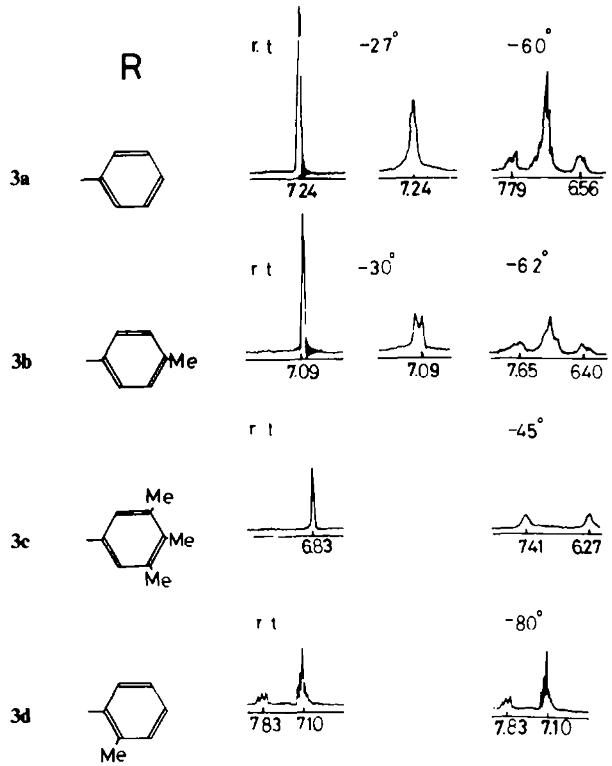


FIG. 3 Aromatic parts of NMR spectra of **3a–d** (in CS_2). Temperature dependence

the middle region. Rotation around the N-aryl bond of **3a–c** occurs rapidly at room temperature, but is frozen at lower temperature. The rotation of **3d** is inhibited at room temperature and the preferred conformation must be the one, in which H^2 is replaced by a Me group. The spectrum of **3d** remains unchanged even at 150°, indicating the rigid conformation induced by the *o*-Me group. The rotational barrier of **3c** at $-32°$ is calculated by Gutowsky's equation to be 6·9 kcal/mole.

Comparison of NMR spectrum of **3d** with that of N-*o*-tolyl-2,5-dimethyl-pyrrole (**4**) indicates that the *o*-Me protons of **3d** are more shielded (0·33 ppm) than those of **4** and that the H^1-proton of **3d** is less shielded (0·70 ppm) than that of **4**. These facts are interpreted by the following assumption. Repulsion between the polymethylene chain and the H^1-proton increases the angle θ as compared with that of **4** and places the *o*-Me group in the shielding zone of the pyrrole ring and the H^1-proton in the deshielding zone.

Unexpectedly, the NMR spectrum of **3d** at −80° indicates that two pyrrole ring protons are no longer equivalent to exhibit an AB-quartet ($J = 3$ c/s), whereas this is not observed in **3a–c**. The nonequivalency may be explained by assuming that the conformational interchange shown in Fig. 4 is probably frozen at very low temperature. The preference of the skewed, nonorthogonal conformation should be ascribed to the repulsion between the *o*-Me group and the pyrrole ring π-electron cloud in conjunction with the repulsion between the H^1-proton and the polymethylene chain.

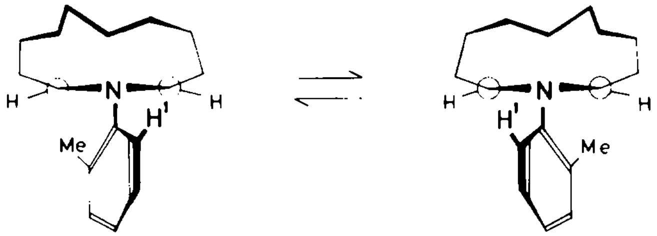


Fig. 4 Possible explanation for nonequivalent pyrrole protons of **3d**.

N,N′-p-*Phenylenedi*[8](2,5)*pyrrolophanes* (**5a–c**). The Paal–Knorr synthesis was extended to *p*-phenylenediamine and its C-methylated derivatives to afford **5a–c**. All of these amorphous solids decompose before melting. The NMR spectra given in Fig. 5 merit some discussions. The orthogonality of the pyrrole and benzene rings in **5a** should give rise to a chemical shift difference of benzene ring protons, which appear as a singlet at room temperature and as 2 : 1 : 2 three broad peaks at −65°. The splitting can not be explained on the basis of any single conformation of **5a** and is open to research in the future.

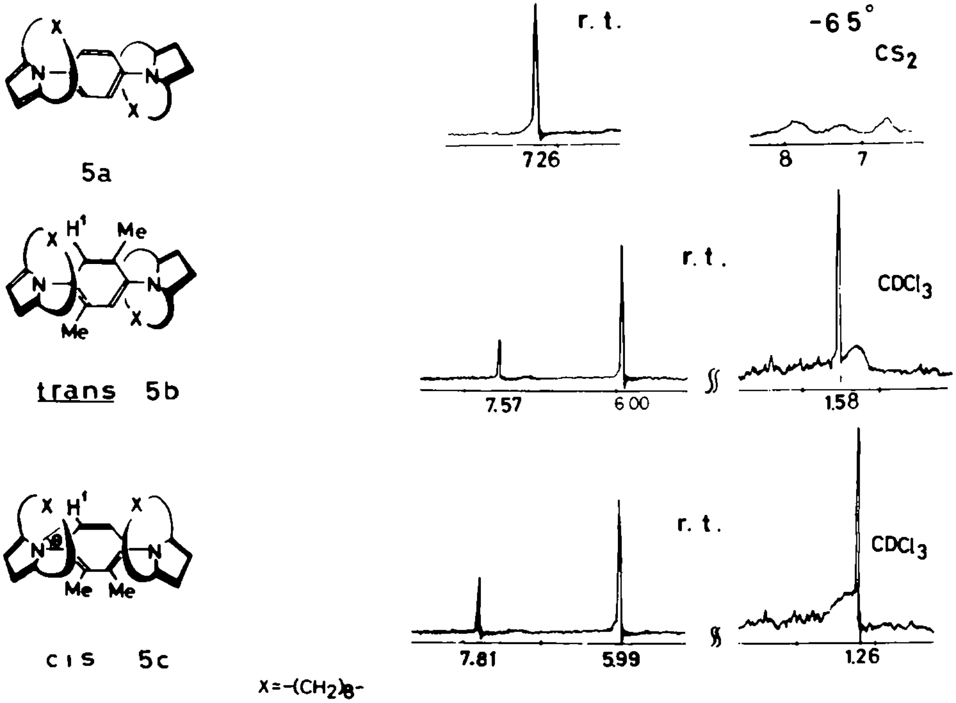


Fig. 5 Conformations and NMR spectra of **5a–c**.

The NMR spectra of **5b** at −60 ~ 150° are alike and the benzene protons exhibit a singlet. This is explained by the rigid "*trans*" conformation given in Fig. 5. The NMR spectrum of **5c** also is unchanged at −60 ~ 150° and is consistent with the rigid "*cis*" conformation as indicated. The chemical shifts of peaks of **5c** were compared with those of 1,4-di(2,5-dimethylpyrryl)2,3-dimethylbenzene (**6**) and of **5b**. The *o*-Me protons of **5c** appear 0·59 ppm higher field than those of **6** and 0·32 ppm higher field than those of **5b**, whereas the H^1-protons of **5c** are 0·69 ppm lower than those of **6** and 0·24 ppm lower than those of **5b**. This is probably due to the steric repulsion between the two polymethylene chains increasing the angle θ. It is remarkable that the interaction of two polymethylene chains is not as large as the repulsion between the polymethylene chain and *o*-Me group.

EXPERIMENTAL

All m.ps are corrected. NMR spectra were obtained on JOEL C-60-H spectrometer with TMS as an internal reference. Chemical shifts are given in ppm from this reference together with the multiplicity of signals indicated in an abbreviated form. All spectra refer to those at room temp unless otherwise stated.

[8](2,5)*Furanophane* (**2a**). A soln of **1**[3] (2·0 g, 10·2 mmoles) in dry ether (20 ml) was added dropwise to a well stirred mixture of P_2O_5 (18·0 g) and EtOH (13·5 g)[5] at 80° for 30 min. The resulting mixture was kept at 80° for an additional 30 min under N_2 atm. After cooling, the reaction mixture was extracted with ether. The ethereal extracts were combined and washed with sat $NaHCO_3$ aq (20 ml) and then twice with water. The organic layer was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was chromatographed on Silica-gel. Elution with n-hexane, followed by distillation *in vacuo*, gave **2a** as a colourless oil (1·5 g, 83%), b.p. 104–106°/11 mm; IR (neat): 3095 (=CH—), 1570 (C=C), 1020 (COC), 780 cm^{-1} (2,5-disubstituted furan); NMR ($CDCl_3$): δ5·60 *s* (2 H, =CH—), 2·50 *t* (4 H, α-CH_2), 1·80–1·10 *m* (8 H, CH_2), 1·10–0·70 *m* (4 H, CH_2). (Found: C, 80·9; H, 10·3. $C_{12}H_{18}O$ requires: C, 80·9; H, 10·2%).

[8](2,5) *Pyrrolophane* (**2b**). An intimate mixture of **1** (2·0 g, 10·2 mmoles) and $(NH_4)_2CO_3$ (5·0 g, 52 mmoles) was heated at 100–120° for 2 hr under N_2, and then cooled and extracted with ether several times. The ethereal extracts were combined, washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to give a pale yellow solid. The solid was sublimed and recrystallized twice from n-hexane to give white crystals (**2b**; 1·5 g, 83%), m.p. 154– 154·5° (sealed tube); IR (KBr): 3375 (NH), 3120 (=CH—), 1585, 1505 (C=C), 760 cm^{-1} (2,5-disubstituted pyrrole); NMR ($CDCl_3$): δ7·85 *m* (1 H, NH), 5·80 *d* (2H, =CH—), 2·50 t (4H, α-CH_2), 1·90–1·00 *m* (8H, CH_2), 0·90–0·40 *m* (4H, CH_2). (Found: C, 81·1; H, 11·0; N, 8·1. $C_{12}H_{19}N$ requires: C, 81·3; H, 10·8; N, 7·9%).

[8](2,5)*Thiophenophane* (**2c**). A mixture of **1** (2·0 g, 10·2 mmoles) and P_2S_5 (1·5 g, 6·8 mmoles) was heated at 80° for 1 hr under N_2, cooled and extracted with ether several times. The ethereal extracts were combined, washed with water, and dried (Na_2SO_4). Concentration followed by distillation *in vacuo* over Na metal gave **2c** as a colourless oil (1·0 g, 51%), b.p. 80–81°/1·5 mm; IR (neat): 3075 (=CH—), 790 cm^{-1} (2,5-disubstituted thiophene); NMR ($CDCl_3$): δ 6·65 s (2H, =CH—), 3·20–2·30 m (4H, α-CH_2), 2·00–0·50 m (10H, CH_2), 0·40 ~ −0·40 m (2H, CH_2). (Found: C, 73·9; H, 9·1; S, 16·6. $C_{12}H_{18}S$ requires: C, 74·2; H, 9·3; S, 16·5%).

10-*Methyl*[8](2,5)*pyrrolophane* (**2d**). A drop of conc HCl was added to a mixture of **1** (1·00 g, 5·1 mmoles) and 30% ethanolic $MeNH_2$ (2·0 g, 20 mmoles). The mixture was heated to reflux for 1 hr under N_2 and then extracted with benzene. The extracts were combined, washed with dil HCl and then with water. The organic layer was dried (Na_2SO_4) and evaporated. Distillation *in vacuo* gave **2d** as a colourless oil (0·78 g, 79%), b.p. 95–97°/3 mm; IR (neat): 3100 (=CH—), 1510 (C=C), 750 cm^{-1} (2,5-disubstituted pyrrole). (Found: C, 81·6; H, 11·2; N, 7·1. $C_{13}H_{21}N$ requires: C, 81·6; H, 11·1; N, 7·3%).

10-*Allyl*[8](2,5)*pyrrolophane* (**2e**). Similar treatment of a mixture of **1** (1·00 g, 5·1 mmoles) and allylamine (0·40 g, 7·0 mmoles) gave **2e** as a colourless oil (0·77 g, 70%), b.p. 75–78°/0·095 mm; IR (neat): 3095, 3015 (=CH—), 1650 (C=C), 762, 752 cm^{-1} (pyrrole). (Found: C, 83·0; H, 10·9; N, 6·2. $C_{15}H_{23}N$ requires: C, 82·9; H, 10·7; N, 6·5%).

10-*Phenyl*[8](2,5)*pyrrolophane* (**3a**). A drop of conc HCl was added to a mixture of **1** (1·00 g, 5·1 mmoles) and aniline (1·0 g, 10·7 mmoles). The resulting mixture was heated at 130–140° for 4 hr under N_2. The hexane extracts were combined, washed with water, dried (Na_2SO_4), and concentrated *in vacuo* to give a pale yellow oil. Chromatography on alumina with n-hexane as an eluant gave a white solid, which was recrystallized twice from MeOH to afford **3a** (0·83 g, 63%), m.p. 54–45·5°; IR (Nujol): 3061, 3027, 770, 702 (=CH—), 1595, 1495 cm^{-1} (C=C); UV (*n*-hexane). 240·5 nm (log ε_{max} 3·08). NMR ($CDCl_3$): δ7·35 *s* (5H, benzene ring), 6·05 *s* (2H, pyrrole ring), 2·73–2·25 *m* (4H, α-CH_2), 2·25–0·00 *m* (12H, CH_2). (Found: C, 85·1; H, 9·2; N, 5·5. $C_{18}H_{23}N$ requires: C, 85·3; H, 9·2; N, 5·5%).

10-*p-Tolyl*[8](2,5)*pyrrolophane* (**3b**). The use of *p*-toluidine instead of aniline in the above preparation of **3a** gave **3b** (69% yield), m.p. 94–94·5° (from EtOH); IR (Nujol): 3045, 822, 768 (=CH—), 1512 cm^{-1} (C=C); UV (*n*-hexane): 240·5 nm (log ε_{max} 4·16). NMR ($CDCl_3$): δ7·20 *s* (4H, benzene ring), 6·04 *s* (2H, pyrrole ring), 2·97–2·27 *m* (4H, α-CH_2), 2·36 *s* (3H, CH_3), 2·17–0·10 *m* (12H, CH_2). (Found: C, 85·4; H, 9·6; N, 5·2. $C_{19}H_{25}N$ requires: C, 85·3; H, 9·4; N, 5·2%).

10-(3,4,5-*Trimethylphenyl*([8](2,5)*pyrrolophane* (**3c**). A mixture of **1** (1·00 g, 5·1 mmoles), 3,4,5-trimethylaniline[10] (0·95 g, 7·0 mmoles) and a drop of conc HCl was heated at 110–120° for 28 hr. Work up gave **3c** (0·87 g, 58%), m.p. 95–95·5° (from EtOH); IR (Nujol): 3090, 878, 768 (=CH—), 1605 cm^{-1} (C=C); UV (*n*-hexane): 240·5 nm (log ε_{max} 4·12). NMR ($CDCl_3$): δ6·99 *s* (2H, benzene ring), 6·02 *s* (2H, pyrrole ring), 2·85–0·06 *m* (16H, CH_2), 2·30 *s* (6H, *meta*-CH_3), 2·17 *s* (3H, *para*-CH_3). (Found: C, 85·3; H, 9·8; N, 4·8. $C_{21}H_{29}N$ requires: C, 85·4; H, 9·9; N, 4·7%).

10-*o-Tolyl*[8](2,5)*pyrrolophane* (**3d**). A mixture of **1** (1·00 g, 5·1 mmoles), *o*-toluidine (0·75 g, 7·0 mmoles) and a drop of conc HCl was heated at 130° for 48 hr. Work up gave **3d** as a colourless oil (0·27 g, 20%), b.p. 140–150°/0·02 mm; IR (neat): 3110, 3061, 3027, 763, 729 (=CH—), 1605, 1488 cm^{-1} (C=C); UV (*n*-hexane): 237 nm (log ε_{max} 4·07). NMR ($CDCl_3$): δ8·09–7·86 *m* (1H, *ortho*-H of benzene ring), 7·35–7·06 m (3H, *meta*- and *para*-H of benzene ring), 6·05 *s* (2H, pyrrole ring), 2·80–0·16 *m* (16H, CH_2), 1·57 *s* (3H, CH_3). (Found: C, 85·1; H, 9·3; N, 5·2. $C_{19}H_{25}N$ requires: C, 85·3; H, 9·4; N, 5·2%).

N,N′-p-*Phenylenedi*[8](2,5)*pyrrolophane* (**5a**). Heating a mixture of **1** (1·00 g, 5·1 mmoles), *p*-phenylenediamine (0·28 g, 2·6 mmoles) and a drop of conc HCl gave an oily mass, which was chromatographed on alumina. Evaporation of the fraction eluted with n-hexane-benzene (1:1) gave a white solid. Recrystallization from AcOEt afforded **5a** as an amorphous solid (0·43 g, 20%), which had no m.p. and coloured black at 180° (sealed tube); IR (Nujol): 3090, 839, 765, 705 (=CH—), 1510 cm^{-1} (C=C); UV (*n*-hexane): 248 nm (log ε_{max} 4·34). NMR ($CDCl_3$): δ7·38 *s* (4H, benzene ring), 6·11 *s* (4H, pyrrole ring), 3·09–0·10 *m* (32H, CH_2). (Found: C, 84·1; H, 9·5; N, 6·3. $C_{30}H_{40}N_2$ requires: C, 84·1; H, 9·4; N, 6·5%).

N,N′-(2,5-*Dimethyl*-p-*phenylene*)*di*[8](2,5)*pyrrolophane* (**5b**). Similar treatment of **1** and 2,5-dimethyl-*p*-phenylenediamine[11] gave **5b** as an amorphous solid (2·8% yield), which had no m.p. and coloured black at 250° (sealed tube); IR (Nujol): 3100, 879, 760, 720, 700 cm^{-1} (=CH—); UV (*n*-hexane): 238 nm (log ε_{max} 4·22). (Found: C, 83·9; H, 10·0; N, 6·1. $C_{32}H_{44}N_2$ requires: C, 84·2; H, 9·7; N, 6·1%).

N,N′-(2,3-*Dimethyl*-p-*phenylene*)di[8](2,5)*pyrrolophane* (**5c**). Similar treatment of **1** and 2,3-dimethyl-*p*-phenylenediamine[12] gave **5c** as an amorphous solid (17% yield), which also had no m.p. and coloured black at 250° (sealed tube); IR (Nujol): 3100, 820, 763 (=CH—), 1482 cm^{-1} (C=C); UV (*n*-hexane): 238·5 nm (log ε_{max} 4·32). (Found: C, 84·0; H, 9·9; N, 6·1. $C_{32}H_{44}N_2$ requires: C, 84·2; H, 9·7; N, 6·1%).

1,4-*Di*(2,5-*dimethylpyrryl*)-2,3-*dimethylbenzene* (**6**). Condensation of acetonylacetone with 2,3-dimethyl-*p*-phenylenediamine gave **6** (56% yield) as an amorphous solid (from AcOEt), which decomposed at 200–230°; IR (Nujol): 3100, 750, 720 cm^{-1} (=CH—); NMR ($CDCl_3$): δ7·12 *s* (2H, benzene ring), 5·95 *s* (4H, pyrrole ring), 1·95 *s* (12H, methyl groups attached to pyrrole rings), 1·85 *s* (6H, Me groups attached to benzene ring). (Found: C, 82·0; H, 8·2; N, 9·6. $C_{14}H_{24}N_2$ requires: C, 82·1; H, 8·3; N, 9·6%).

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