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Reaction of 3,4-Diformyl-2,5-dimethylpyrrole with 1,2(substituted)diphenyl-1,2-diaminoethanes*

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3,4-Diformyl-2,5-dimethylpyrrole (**1**) reacts with 1,2-diphenyl-1,2-diamine derivatives to form the potentially tautomeric 2:2 macrocyclic adduct (**6**)=(**7**). ^{1}H and ^{13}C n.m.r. spectral data along with acidity measurements indicate that the 2-azafulvene structure (**7**) is predominant for all adducts.

Introduction

The incorporation and specific metal complexation properties of macrocyclic molecules, such as porphyrins and polyamidic enzymes with their important role in the metabolism of living systems, has prompted the growth of intensive efforts in research to find systems with similar metal bonding properties, and the investigation of the physical and chemical properties of synthetic macrocyclic compounds capable of binding cations or anions has been given considerable attention, both practically and theoretically, during the past three decades[1–3].

It is well established that 3,4-diformyl-2,5-dimethylpyrrole (**1**) reacts with α,ω-diaminoalkanes, H_2N-$(CH_2)_nNH_2$ to form either potentially tautomeric 2:2 macrocyclic adducts (**2**)=(**3**), when n=2, or potentially tautomeric 1:1 bicyclic adducts (**4**)=(**5**), when n=4,5,6 or 12[4,5]. By the same analogy the formation of 2:2 macrocyclic adducts (**6**)=(**7**) is to be expected from the reaction of 1,2-di(p- or o-substituted)phenyl-1,2-diaminoethane with 3,4-diformyl-2,5-dimethylpyrrole (**1**).

Under the described conditions, 2 moles of 3,4-diformyl-2,5-dimethylpyrrole (**1**) was reacted with 2 moles of 1,2-diphenyl-1,2-diamino ethane (**I**), 1,2-di(m- or p-chloro)phenyl-1,2-diaminoethane (**II, III**) and 1,2-di(m- or p-nitro)phenyl-1,2-diaminoethane (**IV, V**).

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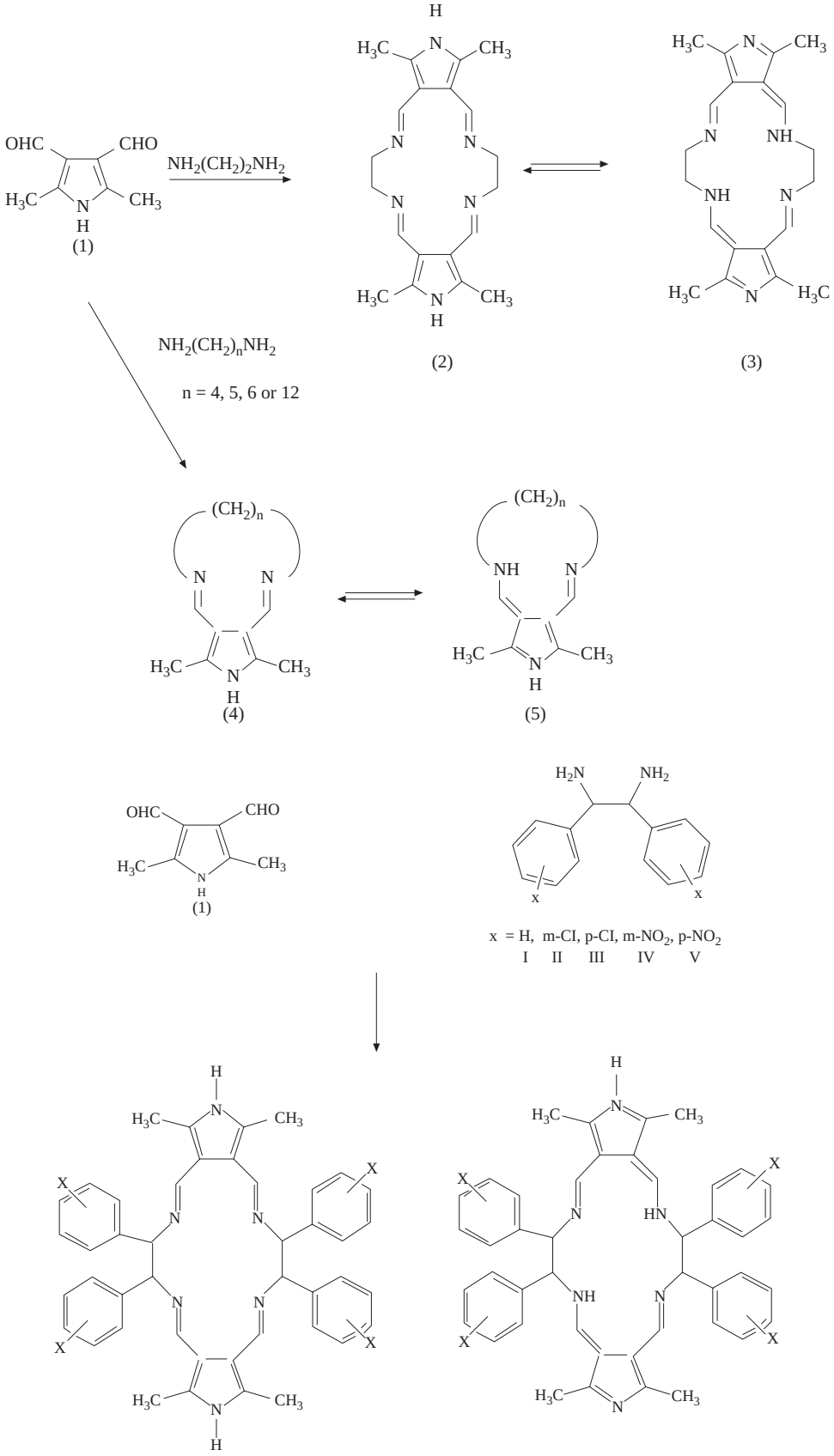

OHC
CHO
H3C
CH3
N
H
(1)
NH2(CH2)2NH2
(2)
(3)
NH2(CH2)nNH2
n = 4, 5, 6 or 12
(CH2)n
(4)
(5)
H2N
NH2
x = H, m-CI, p-CI, m-NO2, p-NO2
I II III IV V

Experimental

The melting points were determined with a Buchi melting point apparatus in open capillaries and were uncorrected. The compounds were routinely checked for homogeneity by T.L.C. using Kieselgel GF_{254} 60 as adsorbent. The IR spectra wer recorded on a Hitachi Spectrophotometer model 270-30 as KBr pellets. ^{1}H-NMR and ^{13}C-NMR spectra were recorded with Brucker AC or Brucker AC 200 instrument using TMS as internal reference. Elemental analysis was carried out with Carlo Erba 1106 of Hewlett-Packart model 185. A Kratos MS25 mass spectrometer produced the mass spectral data.

All the solvents and reagents were from Merck, Aldrich or BDH. None of these was further purified.

General Procedure

The diformylpyrrole (1) (1.51g, 0.01 mol) and the appropriate diaminoalkane (0.01 mol) in methanol (15ml) were stirred at 25°C for 12 h in the presence of a 4A molecular sieve. The temperature was increased to 50°C and stirred for 10 h. The precipitated product was collected, separated from the molecular sieve, washed with ice-cold methanol (2 × 25ml) and recrystallised from the appropriate solvent.

2,5-Dimethylpyrrole

This compound was synthesized by a method described in the literature[6] (86 %), b.p. 78-80°C/25mm Hg.ν_{max} 3350, 2950, 750 cm^{-1}; δ(90MHz) 2.65(s, 6H), 6.33(s, 2H), 7.75(broad, 1H).

1,4-Diformyl-2,5-dimethypyrrole (1)

This compound was synthesized by a method described in the literature[7] (73 %), m.p.207°C (Lit.[7] m.p.207°C). (Found: C,63.5; H,5.8; N,9.3, $C_8H_9NO_2$ requires C,63.5; H,6.0; N,9.3). ν_{max}(KBr) 3180, 1620 cm^{-1}; δ(90MHz, $CDCl_3$) 2.81(s, 6H), 9.48(s, 1H).

1,2-Diphenyl-1,2-diaminoethane(I)

This compound was synthesized by a method described in the literature[8] (3 %), m.p.121°C (Lit[8] m.p.120.5-121.5°C).ν_{max}(KBr) 3365, 1640, 1520, 600-800 cm^{-1}; δ(90MHz, $DMSOD_6$) 7.2-7.6(m, 10H), 5.1(t, 2H), 1.6 (broad, 4H).

1,2-Di(m-chlorophenyl)-1,2-diaminoethane (II)

m-Chlorobenzaldehyde (30g, 199mmol) was refluxed with dry ammonium acetate (60g, 779mmol) for 3 h, and washed with ethanol (2 × 25ml) after filtration. N-(m-chlorobenzoil)-N-(m-chlorobenzylidene)mezzo–1,2-bis(m-chlorophenyl)-1,2-diaminoethane was obtained (6g, 20%). This product (5g) was refluxed with conc.sulphuric acid (60 ml) for 20 min. The mixture was then poured onto ice. The product suspension was extracted with ether. The aqueous phase was made alkaline with 2N NaOH. The precipitated crude product was dissolved in methanol (50 ml) and passed through an alimuna column (20 × 2.5cm) and pure crystals were obtained (0.9g, 2.8%), m.p.148°C, (Found: C,60.0; H,4.8; N,9.8, $C_{14}H_{14}N_2$ requires C,60.0; H,5.0; N,10.0 %). ν_{max}(KBr) 3300, 3080, 1640, 1540, 1090 cm^{-1}; δ(90MHz, $DMSOD_6$) 7.4(m, 8H), 5.4(t, 2H), 1.6(s, 4H).

1,2-Di(p-chlorophenyl)-1,2-diaminoethane (III)

The same procedure used with compound II was applied to react p-chlorobenzaldehyde with ammonium acetate to obtain compound III (0.79g, 2.5%), m.p.137°C (Lit.[8] m.p.137-138°C).ν_{max}(KBr) 3365, 1640, 1090 cm^{-1}; δ(90MHz, $CDCl_3$) 7.4(q, 8H), 5.47(q, 2H), 1.56(broad, 4H).

1,2-Di(m-nitrophenyl)-1,2-diaminoethane (IV)

The same procedure used with compound II was applied to react m-nitrobenzaldehyde with ammonium acetate to obtain compound IV (1.8g, 30%), m.p.190°C(Lit[8]. m.p.189-190°C).ν_{max}(KBr) 3365, 1530, 1350,

650-820 cm^{-1}; δ(90MHz, $DMSOD_6$) 7.33,8.51(m, 8H), 6.16(t, 2H), 4.8(broad, 4H).

1,2-Di(p-nitrophenyl)-1,2-diaminoethane (V)

The same procedure used with compound II was applied to react p-nitrobenzaldehyde with ammonium acetate to obtain compound V (0.85g, 2.8%), m.p.238°C (Found: C,53.6; H,4.6; N,18.7 $C_{14}H_{14}N_4O_4$ requires C,55.6; H,4.6; N,18.2 %), ν_{max}(KBr) 3350, 3050, 1520, 1320, 850-650 cm^{-1}.

5,6,7,14,15,16-Hexahydro-6,7,15,16-tetraphenyl-1,3,10,12-tatremethyldipyrrolo[3,4-f][3',4'-n][1,4,9,12]tetraazacyclohexadecine (VI)

Applying the general procedure described before, the precipitate was obtained and the crude product was recrystallized from aqueous ethanol (0.5g, 70%), m.p.¿300°C (Found: C,78.48; H,5.80; N,12.40 $C_{44}H_{42}N_6$ H_2O requires C,78.57; H,6.25; N,12.50 %), ν_{max}(KBr) 3600-2800, 1636-1528 cm^{-1}; δ(200MHz, $CDCl_3$) 7.73(d, 2H), 7.42(d, 4H), 7.0-7.37(m, 20H), 5.53(m, 4H), 2.52(s, 12H).

5,6,7,14,15,16-Hexahydro-6,7,15,16-tetrice(m-chlorophenyl)-1,3,10,12-tetramethyldiprrolo[3,4-f][3',4'-n][1,4,9,12]tetraazacyclohexadecine (VII)

Applying the previously described general procedure, the precipitate was obtained and the crude product was recrystallized from N,N-dimethylformamide (0.3g, 60%), m.p.¿300°C (Found: C,64.70; H,4.60; N,9.80 $C_{44}H_{38}N_6Cl_4$ $2H_2O$ requires C,63.77; H,4.59; N,10.14 %), ν_{max}(KBr) 3450, 2780, 1540, 1090, 700-800 cm^{-1}; δ(200MHz, CF_3COOH) 8.62(s, 2H), 8.34(s, 4H), 6.9-7.6(m, 16H), 5.5(m, 4H), 3.27(d, 12H).

5,6,7,14,15,16-Hexahydro-6,7,15,16-tetrice(m-nitrophenyl)-1,3,10,12-tetramethyldiprrolo[3,4-f][3',4'-n][1,4,9,12]tetraazacyclohexadecine (VIII)

Applying the previously described general procedure, the precipitate was obtained and the crude product was recrystallized from N,N-dimethylformamide (0.6g, 60%) m.p.¿300°C (Found: C,62.80; H,4.00; N,16.19 $C_{44}H_{38}N_{10}O_8$ H_2O requires C,61.20; H,4.46; N,16.43 %), ν_{max}(KBr) 3000-3600, 1660, 1520, 1340, 700-900 cm^{-1}; δ(^{13}C-NMR, 200MHz $DMSOD_6$) 120-132 (CH_2), 137(CH_3); M^+834 a.m.u.

5,6,7,14,15,16-Hexahydro-6,7,15,16-tetrice(m-nitrophenyl)-1,3,10,12-tetramethyldiprrolo[3,4-f][3',4'-n][1,4,9,12]tetraazacyclohexadecine (IX)

Applying the previously described general procedure, the precipitate was obtained and the crude product was recrystallized from N,N-dimethylformamide (0.25g, 60%) m.p.¿300°C (Found: C,60.68; H,4.07; N,14.84 $C_{44}H_{38}N_{10}O_8$ $2H_2O$ requires C,60.69; H,4.37; N,16.09 %), υ_{max}(KBr) 2700-3600, 1658, 1594, 1510, 1332, 700-900 cm^{-1}; δ(200MHz, CF_3COOH) 9.85(s, 2H), 9.0(s, 4H), 8.29(s, 8H), 7.6-7.8(m, 4H).

Results and Discussion

The compounds II, V, VI, VII, VIII and IX were synthesized for the first time. Spectral and microanalysis data are given in Table 1. As seen in Table 1, the yields for compounds II and V were extremely low. It is reported in the literature[8] that yields go down at the hydrolysis stage in H_2SO_4. Thus we had to repeat those reactions several times to obtain a reasonable amount of starting material to react with 2,5-dimethyl-3,4-diformylpyrrole (**1**). Since our ultimate aim was to synthesize the macrocyclic compounds VI-IX, the starting materials had to be very pure. After several attempts to recrystallize the amino derivatives I-V from different solvents, we found the best method of purification to be passing them through neutral alumina columns. This purification technique was another reason for the low yield.

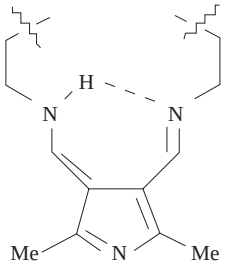
Following purification of the diamine derivatives, the reaction between those products and 2,5-dimethyl-3,4-diformylpyrrole (1) was productive and the yields of 2:2 macrocyclic adducts VI-IX were quantitative (Table 1), with the exception of compound IX, which was unisolable.

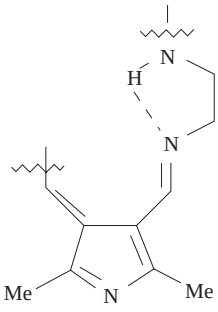
Table 1. The spectral and microanalysis data for the newly synthesized compounds

Compounds	Yield (%)	^{1}H-NMR (ppm)	IR(cm^{-1}	Microanalysis(%)		
II	2.8	7.40(Ar-H), 5.40(CH), 1.6(NH)	3300,1640 (NH)	60.00	5.00	10.00 calculated
			3080 (CH)	60.00	4.80	9.80 found
			1540 (1^o amine)			
			1090 (Ar-Cl)			
V	2.8		3350 (NH)	55.60	4.60	18.20 calculated
			3050 (CH)	53.60	4.60	18.70 found
			1520,1320 (Ar-NO_2)			
			650-850 (NO_2,CH)			
VI	70	7.73 (NH), 7.42 (N=CH), 7.0-7.73 (Ar-H)	2800-3600 (NH, CH)	78.57	6.25	12.50 calculated
		5.53 (CH), 2.52 (CH_3)	1528-1636 (Ar C=C,C=N)	78.48	5.80	12.40 found
VII	60	8.62 (NH), 8.34 (N=CH), 6.90-7.60 (Ar-H)	3450, 1540 (NH)	63.77	4.59	10.14 calculated
		5.50 (CH), 3.27 (CH_3)	2780 (CH), 1090 (Ar-Cl)	64.70	4.60	9.80 found
VIII	60	^{13}C-NMR 120-132 (CH), 137 (CH_3)	3000-3600 (NH, CH)	61.20	4.46	16.43 calculated
		m/z 834,819,687,560,175,157,119 a.m.u				
X	60	9.85 (NH), 9.00 (N=CH), 8.29 (Ar-H),	2700-3600 (NH,CH)	60.90	4.37	16.09 calculated
		7.60-7.80 (CH), 3.32 (CH_3)	1658 (NH)	60.80	4.07	14.04 found
			1594,1510,1332 (Ar-NO_2)			
			700-900 (NO_2, CH)			

The spectral and microanalysis data of 2:2 macrocyclic adducts conformed to the predicted structure. A detailed analysis of compound VIII by mass spectra revealed that the predicted structure was correct.

^{1}H- and ^{13}C-NMR studies on synthesized molecules did not provide any clues the predominance of any tautomeric form (i.e. pyrrole(**6**) or 2-azafulvene(**7**) to) due to insolubility of these macrocycles in organic solvents. The NMR measurements had to be made in CF_3COOH, and it was not possible to decide where protonation took place. However, previous ^{13}C-NMR studies on similar molecules indicated that the presence of two signals at 158.6 at 114.5 ppm due to pyrrolyl ring carbons is not characteristic for 1H-pyyrole, and the molecule exists in azafulvene form[9]. The stability of 2-azafulvene can be accounted for by the formation of hydrogen bonding in these macrocyclic systems, as shown below:





Preliminary acidity measurement in macrocycle VI indicated that the proton-loss pK_a value is 11.87. This value is on the order of the proton-loss pK_a of similar macrocycles which do exist in the 2-azafulvene structure[10]. The proton-gain pK_a values of macrocycle VI were found to be -4.17 and -7.32 for the first and second protonations, respectively. The small energy difference of 4.32 kcal mol^{-1} (ΔpK_a = pK_{a1} - pK_{a2} = -4.17-(-7.32) = 3.15, since one pK_a unit is equal to 1.37 kcal mol^{-1}, then 3.15 $\times$ 1.37 = 4.32 kcal) between the first and second protonation is another indication that these two proton-uptakes take place in nitrogen atoms which are located far away from each other and occur on pyrrole rings. Therefore, it is possible to predict that the molecule exists predominantly in 2-azafulvene form.

Detailed Molecular Orbital calculations are currently being carried out by this research group, both at *abinitio* and *semiempirical* levels, in order to clarify the tautomeric forms of the synthesized macrocycles.

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