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3-AMINOPYRROLE-2,5-DIONES 3*. SYNTHESIS OF BENZENEHEXA-CARBOXYLIC ACID TRIMETHYLIMIDE AND 1,1'-DIMETHYL-4-METHYLAMINO-[3,3']BIPYRROLYL-2,5,2',5'-TETRAONE BY THE REACTION OF 1-METHYL-3-METHYLAMINOPYRROLE-2,5-DIONE WITH HYDROGEN CHLORIDE

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In the presence of hydrogen chloride in aqueous methanol 1-methyl-3-methylaminopyrrole-2,5-dione forms benzenehexacarboxylic acid trimethylimide but gives 1,1'-dimethyl-4-methylamino[3,3']bi-pyrrolyl-2,5,2',5'-tetraone when absolute methanol is used.

Keywords: 3,3'-bipyrrolyl-2,5,2',5'-tetraone, pyrrole-2,5-dione, benzenehexacarboxylic acid trimethyl-imide.

We have previously shown [1, 2] that the reaction of 1-alkyl-3-alkylaminopyrrole-2,5-diones with the hydrochlorides or 4-tolylsulfonates of primary arylamines with a p*K*a value from 5.63 (4-aminophenol) to 1.00 (4-nitroaniline) [3] in methanol gives the corresponding 1-alkyl-3-arylaminopyrrole-2,5-diones.

Continuing the investigation we have discovered that reaction of 1-methyl-3-methylaminopyrrole-2,5-dione **1** with the weaker bases 2-nitroaniline, 2-bromo-4-nitroaniline, or 2,4-dinitroaniline (with p*K*a's of -0.25, -1.18 (calculated value), and -4.27 [3]) in the presence of hydrogen chloride (molar ratio of reagents 1:1.2:1 with refluxing over 5 min) did not give the expected 3-arylamino-1-methylpyrrole-2,5-diones. Reaction occurs only in about 50% yield to the benzenehexacarboxylic acid trimethylimide **2** which had been obtained previously in the reaction of N-methyl-5-methyloxazolium methosulfate with potassium oxalate in water [4, 5].

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* For Communication 2 see [1].

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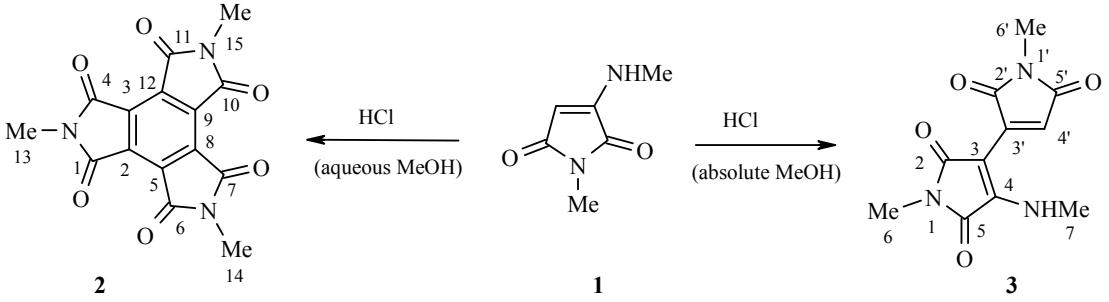
Maleimide **1** reacts under analogous conditions with 4-nitroaniline to give a mixture of 1-methyl-3-(4-nitrophenylamino)pyrrole-2,5-dione with the trimethylimide **2** in the ratio ~ 7:1 (according to the integrated intensities of the NMe group signals at 2.92 and 3.11 ppm in the 300 MHz ^{1}H NMR spectrum in DMSO-d_6 solvent). In the case of N,N-dimethylaniline only the trimethylimide **2** is produced in 52.4% yield and not the expected 3-(4-N,N-dimethylaminophenyl)-1-methylpyrrole-2,5-dione.

A repeated study of the reaction of compound **1** with aniline (p*K*a 4.60 [3]) in the presence of hydrochloric acid (molar ratio of reagents 1:1:1, refluxing in methanol for 1 h) showed that the main product of the reaction 1-methyl-3-phenylaminopyrrole-2,5-dione was formed together with the trimethylimide **2** in up to 5% yield. Use of 15-20% excess of aniline or carrying out the reaction in absolute methanol with aniline hydrochloride excludes the formation of the trimethylimide **2**.

On the other hand, reaction of the pyrrole-2,5-dione **1** with hydrochloric acid in aqueous methanol gives the trimethylimide **2** in high yield but the use of dry hydrogen chloride in absolute methanol gives 1,1'-dimethyl-4-methylamino[3,3']bipyrrolyl-2,5,2',5'-tetraone (**3**) which is also obtained in 38% yield using concentrated (10.75 N) HCl (molar ratio of reagents 1:1, refluxing in methanol for 5 min). The 4-amino-[3,3']bipyrrolyl-2,5,2',5'-tetraone derivatives had been prepared previously by alkylation of 3-amino derivatives of pyrrole-2,5-dione by 4-chloropyrrole-3-(4-methylphenyl)-1-phenyl-2,5-dione in THF in the presence of sodium hydride [6] and also by the action of strong acids (HCl, $HClO_4$) on N-(4-methylphenyl)-2-alkylamino-maleimides [7].

It should be noted that a similar dimerization type reaction with formation of 4-hydroxy-1,5,1',2'-tetrahydro[3,3']bipyrrolyl-2,5'-diones has been reported for pyrrolidine-2,4-diones when refluxed with or without acid in an aqueous medium [8-12].



2 **1** **3**

The ^{13}C NMR spectrum of trimethylimide **2** shows signals for the carbon atoms in the benzene ring (132.57) and carbonyl group (162.84 ppm) and the IR spectrum shows carbonyl group absorption bands at 1785 and 1735 cm^{-1} in agreement with data for benzenehexacarboxylic acid trialkylimides [13]. The ^{1}H NMR spectrum of compound **3** shows a vinyl proton singlet at 7.11 and broad NH group singlet at 10.15 ppm and the IR spectrum shows stretching bands for the NH group at 3350-2900, C=C at 1645, and for the asymmetric (1745) and symmetric (1705 cm^{-1}) stretching bands of the carbonyl groups in agreement with data given by the authors of [7].

EXPERIMENTAL

^{1}H NMR Spectra were taken on a Varian VXR-300 spectrometer (300 MHz) and ^{1}H and ^{13}C NMR spectra on a Varian Gemini-2000 spectrometer (400 and 100 MHz respectively) with TMS as internal standard. Assignments of the signals in the ^{13}C NMR spectra were made using the ACD/CNMR DB program [3]. IR spectra were recorded on an Agilent 1100/DAD/MSD VL G1965a spectrometer and mass spectra on a Varian

1200L instrument. Monitoring of the reaction course and the purity of the materials was carried out chromatographically on Silufol UV-254 plates with chloroform–methanol (10:1) and revealed using UV light and/or iodine vapor.

1-Methyl-3-methylaminopyrrole-2,5-dione **1** was prepared according to method [14]. Absolute methanol was distilled from CaH_2.

1-Methyl-3-methylaminopyrrole-2,5-dione (1). IR spectrum, ν, cm^{-1}: 3365 (NH), 3125, 3040, 2960, 1745 $(C=O)_{as}$, 1705 $(C=O)_s$, 1645 (C=C), 1520, 1455, 1430, 1395, 1255, 1165, 1140, 1100, 995, 810, 765.

Benzenehexacarboxylic acid trimethylimide (2). HCl (5.95 N, 2.4 ml) was added to a solution of the pyrrole-2,5-dione **1** (2.01 g, 14.3 mmol) in aqueous methanol (80%, 24 ml), refluxed for 5 min, and cooled. The precipitate was filtered off, washed with methanol, and dried to give the trimethylimide **2** (1.22 g, 78.3%). Crystallization from acetic acid gave 0.67 g (43%) [mixture of acetonitrile and benzene = 0.49 g (31.4%)] of compound **2** with mp > 350ºC (sublimes at ~ 400ºC [4]). IR spectrum, ν, cm^{-1}: 1785, 1735 (C=O), 1655 (C=C), 1445, 1380, 1275, 1135, 1045, 960, 775, 735, 620 (1745, 1709, 1681, 1653, 1567 [5]). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 3.13 (9H, s, $3CH_3$). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 24.55 (C-13,14,15); 32.57 (C-2,3,5,8,9,12); 162.84 (C-1,4,6,7,10,11). HPLC-mass spectrum, *m/z* (I_{rel}, %), peak area, %: 327.2 $[M]^-$ (19) 100. Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 327 $[M]^+$ (100), 328 $[M+1]^+$ (12.1), 270 (99.6), 187 (19.3), 185 (16.2), 101 (26.4), 100 (29.0), 71 (13.6). Found, %: C 54.94; H 2.63; N 12.90. $C_{15}H_9N_3O_6$. Calculated, %: C 55.05; H 2.77; N 12.84.

1,1'-Dimethyl-4-methylamino[3,3']bipyrrolyl-2,5,2',5'-tetraone (3). Dry HCl (4.78 N solution in absolute methanol, 3.7 ml) was added to a solution of maleimide **1** (2.50 g, 17.9 mmol) in absolute MeOH (38 ml) and left for 18 h at 20ºC. The precipitate formed was filtered off, washed with absolute MeOH, and dried to give compound **3** (2.1 g, 94.8%) with mp 166-168ºC (portion A). The filtrate was evaporated to dryness *in vacuo* and the residue was triturated with a small amount of methanol. The precipitate formed was washed with methanol and dried to give additional amount of compound **3** (40 mg, 1.8%) with mp 170-174ºC (portion B). Portions A and B were combined and recrystallized twice from 2-propanol, to give compound **3** (1.45 g, 65.3%) with mp 172-173ºC. IR spectrum (3% solution in chloroform, cuvet diameter 0.24 mm), ν, cm^{-1}: 3350-2900 (broad band, NH), 2960, 1745 $(C=O)_{as}$, 1705 $(C=O)_s$, 1695, 1645 (C=C), 1570, 1450, 1410, 1395, 1330, 1300, 1270, 1210, 1180, 1125, 1085, 1020, 1005, 855, 810. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 3.04 (3H, s, NCH_3); 3.05 (3H, s, NCH_3); 3.51 (3H, d, ^3J = 5.6, $NHC\underline{H}_3$); 7.11 (1H, s, CH); 10.15 (1H, br. s, NH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 23.59 (C-6'); 23.61 (C-6); 31.89 (C-7); 116.56 (C-3); 138.05 (C-3',4'); 146.68 (C-4); 164.71 (C-2'); 169.18 (C-5); 170.82 (C-5'); 173.62 (C-2). HPLC mass spectrum, *m/z* (I_{rel}, %), peak area, %: 248.1 $[M-H]^+$ (80), 234.2 $[M-Me]^+$ (50) (100). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 249 $[M]^+$ (100), 250 $[M+1]^+$ (12.9), 164 (37.7), 163 (19.8), 162 (34.1), 106 (19.1), 79 (58.0), 78 (16.2), 64 (15.5). Found, %: C 52.85; H 4.37; N 16.92 $C_{11}H_{11}N_3O_4$. Calculated, %: C 53.01; H 4.45; N 16.86.

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