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Reactions between pyrrole and orthoesters: preparation of tri-(pyrrol-2-yl)alkanes

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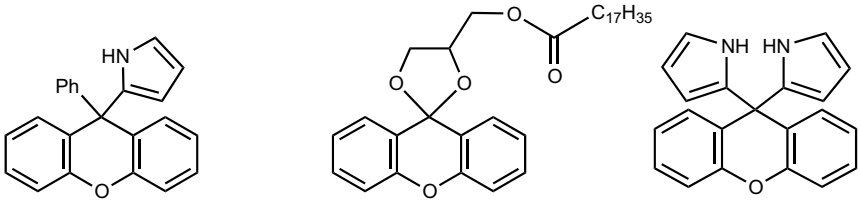
Abstract—Reactions between triethyl orthoformate, trimethyl orthoacetate and triethyl orthopropionate with pyrrole and chloroacetic acid lead to moderate yields of the corresponding tri-(pyrrol-2-yl)alkanes **5a**, **5b** and **5c**, respectively. Under the same conditions, trimethyl orthobenzoate reacts with pyrrole and dichloroacetic acid to give the dipyrrin **7** in a relatively good yield.

Some 15 years ago, we reported[1] that pyrrole facilitated the acid-catalyzed unblocking of 5′-*O*-(9-phenylxanthen-9-yl) ethers of nucleotide derivatives and that 2-(9-phenylxanthen-9-yl)pyrrole **1** was obtained as a by-product. We have recently shown[2] that when 1-*O*-stearoyl-2,3-*O*-(xanthen-9-ylidene)glycerol **2** was treated in the same way with pyrrole and dichloroacetic acid in dichloromethane solution at room temperature, the acetal protecting group was rapidly and quantitatively removed and 9,9-di-(pyrrol-2-yl)xanthene **3** was obtained as a by-product in high yield. It then occurred to us that the reaction between orthoesters **4** and pyrrole in the presence of acid should lead to the formation of unsubstituted tri-(pyrrol-2-yl)alkanes **5**, an interesting and to the best of our knowledge previously unreported group of compounds.

We now report that when triethyl orthoformate **4a**; $R^2 = Et$ (1 mol equiv.), pyrrole (9 mol equiv.) and chloroacetic acid (9 mol equiv.) were allowed to react together in dichloromethane solution at 0°C for 30 min, tri-(pyrrol-2-yl)methane **5a** was obtained and isolated from the products as a crystalline solid in 34% yield.[3] Moderate yields of compound **5a** were obtained when



a ; $R^1 = H$ **b** ; $R^1 = Me$ **c** ; $R^1 = Et$ **d** ; $R^1 = Ph$

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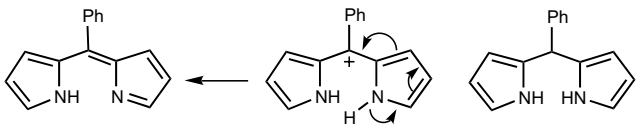
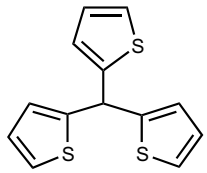
triethyl orthoformate **4a**; $R^2=Et$ was replaced by trimethyl orthoformate **4a**; $R^2=Me$ and also when chloroacetic acid (pK_a 2.85) was replaced by dichloroacetic acid (pK_a 1.25). Further experiments will be necessary if the yield of compound **5a** is to be optimized. Treatment of tri-(pyrrol-2-yl)methane **5a** with dimethyl sulfate and sodium hydride in THF at 0°C gave tri-(1-methylpyrrol-2-yl)methane **6**, which was isolated as a crystalline solid in 90% yield.[4] The latter compound **6** was obtained directly and in 22% isolated yield when 1-methylpyrrole, triethyl orthoformate **4a**; $R^2=Et$ and chloroacetic acid were allowed to react together under the same conditions as were used[3] in the above preparation of tri-(pyrrol-2-yl)methane **5a**. Tri-(1-methylpyrrol-2-yl)methane **6** had previously been reported[5] as one of the numerous products obtained, all in very low yield, when a mixture of 1-methylpyrrole and 1-methylpyrrole-2-carboxaldehyde was treated with a catalytic quantity of M-hydrochloric acid at room temperature.

When trimethyl orthoacetate **4b**; $R^2=Me$ and triethyl orthopropionate **4c**; $R^2=Et$ were allowed to react with an excess each of pyrrole and chloroacetic acid, under the same conditions as were used[3] in the preparation of tri-(pyrrol-2-yl)methane **5a** and with the same stoichiometry, 1,1,1-[tri-(pyrrol-2-yl)]ethane **5b**[6] and 1,1,1-[tri-(pyrrol-2-yl)]propane **5c**,[7] respectively, were obtained and isolated in yields of 35.5 and 38%. It is interesting to note that the highest abundance peak in the EI mass spectra of both compounds **5b** and **5c** is at m/z 210.1, corresponding to the tri-(pyrrol-2-yl)methyl ion.



7 **8** **9**

The acid-catalyzed reaction between trimethyl orthobenzoate **4d**; $R^2=Me$ and pyrrole was then examined. When trimethyl orthobenzoate, pyrrole and dichloroacetic acid were allowed to react together under essentially the same conditions as were used[3] in the preparation of tri-(pyrrol-2-yl)methane **5a**, no tri-(pyrrol-2-yl) derivative **5d** was detected in the products. However, the *meso*-substituted dipyrrin **7** was obtained and isolated from the products as a brown oil in 51% yield.[8] The latter compound **7** can result from the loss of a proton from its putative cationic precursor **8**. For steric reasons, this is presumably a more favorable process than the alkylation of a third pyrrole molecule to give the tri-(pyrrol-2-yl) derivative **5d**. The yield of the dipyrrin **7** was much lower when dichloroacetic was replaced by chloroacetic acid. The dipyrrin **7** had previously been prepared[9] by oxidation of the corresponding dipyrrylmethane **9** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The present orthoester approach may well prove to be of general application in the synthesis of dipyrrins and hence, of porphyrins with *meso*-aryl substituents.



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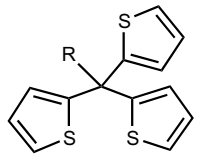

11 **a** ; R = Me
b ; R = $(CH_2)_5Me$

In conclusion, we believe that the tri-(pyrrol-2-yl)alkanes **5** constitute a potentially useful new group of compounds. Tri-(thiophen-2-yl)methane **10** has long been known[10,11] and recently trialdehydes derived from **11a** and **11b** have been converted[12] into interesting cage compounds. Clearly, the corresponding derivatives of tri-(pyrrol-2-yl)alkanes **5** and their *N*-alkyl derivatives (e.g. **6**) could be expected to undergo similar transformations. Tri-(pyrrol-2-yl)alkanes **5** are also potentially useful starting materials for the preparation of dendrimers.

References

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3. A solution of triethyl orthoformate **4a**; $R^2=Et$ (0.83 ml, 5.0 mmol) in dichloromethane (10 ml) was added dropwise over a period of 10 min to a stirred solution of pyrrole (3.12 ml, 45 mmol) and chloroacetic acid (4.25 g, 45 mmol) in dichloromethane (40 ml) at 0°C (ice–water bath). After a further period of 20 min, the products were poured into saturated aqueous sodium hydrogen carbonate (30 ml). The organic layer was separated, washed with saturated aqueous sodium hydrogen carbonate (2×20 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was fractionated by short column chromatography on silica gel: the appropriate fractions, which were eluted with dichloromethane, were combined and concentrated under reduced pressure to give *tri-(pyrrol-2-yl)methane* **5a** (0.360 g, 34%) (found in material recrystallized from aqueous ethanol: C, 73.6; H, 6.2; N, 19.6. $C_{13}H_{13}N_3$ requires: C, 73.91; H, 6.20; N, 19.89%. HRMS Found $M^+=211.1101$. $^{12}C_{13}{}^{1}H_{13}{}^{14}N_3$ requires: 211.1109) as a greenish yellow solid, mp 128°C dec; δ_H [$(CD_3)_2SO$] 5.32 (1H, s), 5.70 (3H, m), 5.88 (3H, dd, *J* 2.7 and 5.5), 6.58 (3H, dd, *J* 2.5 and 4.2), 10.44 (3H, br); δ_C [$(CD_3)_2SO$] 37.37, 105.75, 107.02, 116.86, 133.21.
4. Sodium hydride (0.80 g, 60% dispersion in mineral oil, 20.0 mmol) was washed with petroleum spirit (bp 40–60°C, 3×10 ml) and the remaining solvent was evaporated under reduced pressure. The residual solid was suspended in dry THF (20 ml). A solution of tri-(pyrrol-2-yl)methane **5a** (0.422 g, 2.0 mmol) in THF (10 ml) was added to the cooled (ice–water bath), stirred suspension. After the effervescence had ceased, the mixture was allowed to warm up to room temperature and a solution of dimethyl sulfate (1.40 ml, 14.8 mmol) in dry THF (10

ml) was added with continued stirring. After 2 h, water (10 ml) was added with care, followed by diethyl ether (25 ml). The layers were separated and the aqueous layer was extracted with diethyl ether (10 ml). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (2×15 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was fractionated by short column chromatography on silica gel: the appropriate fractions, which were eluted with petroleum spirit (bp 40–60°C)-ethyl acetate (95:5 v/v), were combined and evaporated under reduced pressure to give *tri-(1-methylpyrrol-2-yl)methane* **6** (found in material recrystallized from aqueous ethanol: C, 75.9; H, 7.6; N, 16.6. $C_{16}H_{19}N_3$ requires: C, 75.85; H, 7.56; N, 16.59%) as a colorless solid (0.455 g, 90%), mp 98–99°C; δ_H [$CDCl_3$] 3.41 (9H, s), 5.23 (1H, s), 5.55 (3H, m), 6.01 (3H, dd, *J* 2.9 and 3.4), 6.57 (3H, t, *J* 2.3); δ_C [$CDCl_3$] 34.27, 34.91, 106.87, 109.00, 122.35, 132.24.

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6. Pyrrole (3.12 ml, 45 mmol), trimethyl orthoacetate **4b**; R^2 = Me (0.636 ml, 5.0 mmol) and chloroacetic acid (4.25 g, 45 mmol) were allowed to react together in dichloromethane solution at 0°C, under precisely the same conditions as those described above[3] to give 1,1,1-[*tri-(pyrrol-2-yl)*]*ethane* **5b** (0.400 g, 35.5%) as colorless crystals, mp 162–163°C (found, in material recrystallized from aqueous ethanol: C, 74.4; H, 6.8; N, 18.6. $C_{14}H_{15}N_3$ requires: C, 74.64, H, 6.71; N, 18.65%; HRMS Found: M^+ = 225.1265. $^{12}C_{14}{}^{1}H_{15}{}^{14}N_3$ requires: 225.1266); δ_H [$(CD_3)_2SO$] 1.92 (3H, s), 5.49 (3H, m), 5.85 (3H, dd, *J* 2.6 and 5.6), 6.59 (3H, dd, *J* 2.6 and 4.3), 10.29 (3H, br); δ_C [$CDCl_3$] 29.52, 41.12, 106.10, 108.88, 117.27, 136.82.
7. Pyrrole (3.12 ml, 45 mmol), triethyl orthopropionate (1.006 ml, 5.0 mmol) and chloroacetic acid (4.25 g, 45 mmol) were allowed to react together in dichloromethane solution at 0°C, under precisely the same conditions as those described above,[3] to give 1,1,1-[*tri-(pyrrol-1-yl)*]-*propane* **5c** (0.460 g, 38%) as an off-white powder, mp 173–174°C (found in material crystallized from aqueous ethanol: C, 73.1; H, 7.2; N, 16.95. $C_{15}H_{17}N_3 \cdot 0.4\ H_2O$ requires: C, 73.08; H, 7.28; N, 17.04%. HRMS Found: M^+, 2391428. $^{12}C_{15}{}^{1}H_{17}{}^{14}N_3$ requires: 239.1422); δ_H [$(CD_3)_2SO$] 0.69 (3H, t, *J* 7.3), 2.35 (2H, quart, *J* 7.3), 5.74 (3H, m), 5.88 (3H, dd, *J* 2.6 and 5.6), 6.58 (3H, dd, *J* 2.6 and 4.2), 10.10 (3H, br); δ_C [$(CD_3)_2SO$] 9.78, 31.53, 44.62, 105.44, 106.04, 116.66, 135.73.
8. Pyrrole (2.50 ml, 36 mmol), trimethyl orthobenzoate (0.687 ml, 4.0 mmol) and dichloroacetic acid (3.16 ml, 38 mmol) were allowed to react together in dichloromethane solution at 0°C, under the same conditions as those described above,[3] to give 5-*phenyl-4,6-dipyrrin* **7** (0.45 g, 51%) as a dark brown oil [HRMS found: M^+, 220.0998. $^{12}C_{15}{}^{1}H_{12}{}^{14}N_2$ requires 220.10005] λ_{max} [CH_2Cl_2–MeOH (99.5:0.5 v/v) containing a trace of aqueous NH_3] 309, 433 nm (lit.[9] 310, 434 nm); δ_H [$(CD_3)_2SO$] 6.43 (2H, dd, *J* 1.4 and 4.2), 6.47 (2H, dd, *J* 1.0 and 4.2), 7.50 (5H, m), 7.76 (2H, d, *J* 1.1), 12.68 (1H, br); δ_C [$(CD_3)_2SO$] 118.17, 128.15, 128.77, 129.46, 130.76, 137.17, 140.18, 141.81, 144.89.
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