

## The Reduction of 1-Methyl-3-methoxy-5-arylpyrrole-2- and -4-carboxylic Esters with Selected Reducing Agents (1)

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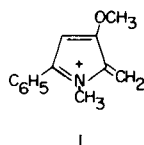
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Three new methoxypyrrole esters, ethyl 1-methyl-3-methoxy-5-phenylpyrrole-2-carboxylate, diethyl 1-methyl-3-methoxy-5-phenylpyrrole-2,4-dicarboxylate, and ethyl 1-methyl-2-phenyl-4-methoxypyrrole-3-carboxylate were reduced with diborane/tetrahydrofuran, lithium aluminum hydride, and some related reducing agents. In each case diborane reduced the ethoxycarbonyl group to a methyl group and lithium aluminum hydride reduced it to a hydroxymethyl group.

We were in possession of some new methoxypyrrole esters (3) and in light of the unusual reduction of some pyrrole esters reported by Sonnet (4) we subjected these pyrrole esters to various reducing agents.

The pyrrole esters which were used are indicated in Scheme I: ethyl 1-methyl-3-methoxy-5-phenylpyrrole-2-carboxylate (1), diethyl 1-methyl-3-methoxy-5-phenylpyrrole-2,4-dicarboxylate (2), and ethyl 1-methyl-2-phenyl-4-methoxypyrrole-3-carboxylate (3). We found that in each case the ethoxycarbonyl group was reduced to a methyl group in good yield by diborane in tetrahydrofuran, giving compounds 4, 5, and 6, 1,2-dimethyl-3-methoxy-5-phenylpyrrole, 1,2,4-trimethyl-3-methoxy-5-phenylpyrrole, and 1,3-dimethyl-4-methoxy-2-phenylpyrrole, respectively. Compound 6 proved to be unstable and was characterized as the *p*-nitrophenylazo derivative, 6a, as was done previously with another  $\alpha$ -unsubstituted methoxypyrrole (3). Compound 1 was also treated with aluminum hydride and with lithium aluminum hydride/aluminum chloride, giving in each case the 2-methyl compound 4.

Although Sonnet found variable yields in the reduction of pyrrole esters with diborane, depending upon the substituents on the pyrrole nucleus, our yields were in the range of 65-85%. Biswas (5) has suggested that the reduction of formyl pyrroles to methyl pyrroles with diborane depends upon the ability of an electron-rich pyrrole nucleus to stabilize an intermediate such as I. These methoxypyrroles were previously shown to be very reactive toward electrophilic reagents when not stabilized by two electron withdrawing groups (3). It is presumably this same reactivity that contributes to the facile reduction of these pyrrole esters with diborane.



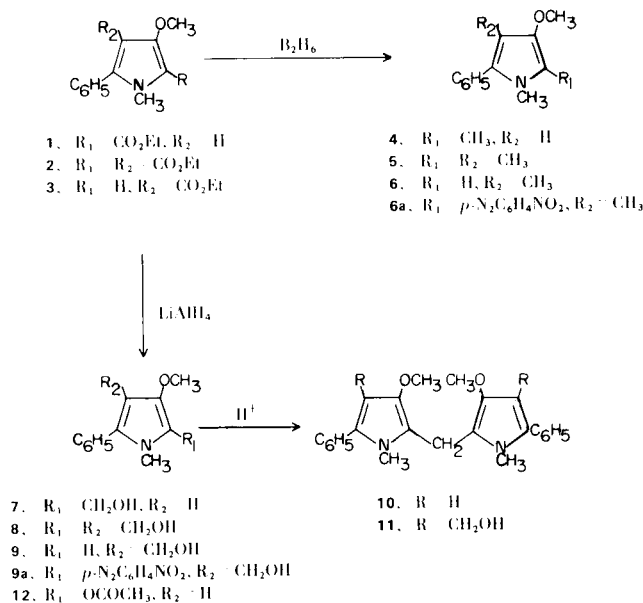
The reaction of pyrrole esters 1, 2, and 3 with lithium aluminum hydride in tetrahydrofuran gave, in each case, the hydroxymethyl derivatives, 7, 8, and 9, 1-methyl-3-methoxy-5-phenyl-2-hydroxymethylpyrrole, 1-methyl-3-methoxy-5-phenyl-2,4-bishydroxymethylpyrrole, and 1-methyl-4-methoxy-2-phenyl-3-hydroxymethylpyrrole respectively. Compound 7 was previously reported (3) and was unstable except in certain solutions. Compound 8 was isolated as a crystalline solid but was very unstable to traces of acid, and compound 9 decomposed over a period of hours in air and was characterized as the *p*-nitrophenylazo derivative. Compound 1 was treated with lithium tri-*t*-butoxyaluminum hydride but no reaction was observed.

2-Hydroxymethylpyrroles are known to condense with the loss of formaldehyde to give symmetrical dipyrrolymethanes (6). When compounds 7 and 8 were treated with a trace of acetic acid in tetrahydrofuran the dipyrrolymethanes 10 and 11 were obtained in moderate yield. Hydroxymethylpyrrole 9, however, gave only a complex mixture of products which was not analyzed.

Finally, the reaction of compound 1 with sodium borohydride in refluxing isopropanol was very sluggish, giving some dipyrrolymethane, 10, after 16 hours along with much unreacted starting material. The hydroxymethylpyrrole 7 is probably formed slowly, and then condenses at the elevated temperature of the reaction. Possibly the condensation of 7 to give 10 is catalyzed by an alkoxyborohydride that ionizes to give the electrophilic species I. None of the 2-methylpyrrole 4 was found in this reaction so I must not be reduced by borohydride but, rather, condenses with an equivalent of 7 to give dipyrrolymethane 10 after elimination of formaldehyde.

In support of this hypothesis, it was found that treatment of the hydroxymethylpyrrole 7 with acetic anhydride in hot pyridine gave a good yield of 10. A similar result

SCHEME 1



was observed in a different system (7) and it was postulated that the initially formed acetoxy compound (12 in this case) ionizes to give an electrophile like I which attacks another molecule of the acetoxy compound to give a symmetrical dipyoxymethane after the elimination of a one carbon fragment (probably formaldehyde).

#### EXPERIMENTAL

Melting points were obtained on a Mel-Temp capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer model 137 infrared spectrometer. Nmr spectra were taken on a Varian Associates' HA-100 instrument operating in the frequency sweep mode and using tetramethylsilane as the standard. Mass spectra were determined on a Varian MAT CH-7 spectrometer or an Associated Electrical Industries' MS-9 spectrometer at 70 eV.

Thin layer chromatography was done on glass slides, coated with silica gel GF-254 (Brinkmann). The slides were eluted with 10% tetrahydrofuran in benzene except where otherwise indicated and visualization was by ultraviolet light. Analyses were obtained courtesy of Galbraith Laboratories, Knoxville, Tennessee.

#### 1,2-Dimethyl-3-methoxy-5-phenylpyrrole (4).

A.

The methoxyester **1** (3) (0.50 g., 1.93 mmoles) was dissolved in 5 ml. of dry THF and added to 12 ml. of 1M diborane in THF (12 mmoles) under a nitrogen atmosphere. The mixture was brought to reflux and monitored by tlc. After 24 hours all the starting material was consumed and was replaced by a new material. The excess diborane was hydrolyzed with 10 ml. of saturated sodium chloride solution and the organic layer was separated. The aqueous layer was extracted with 10 ml. of ether and the combined organic layers were dried (potassium carbonate) and concentrated under reduced pressure. Compound **4** solidified as white crystals, 0.25 g. (64%), after one recrystallization from petroleum ether (60-90°), m.p. 112-113°; nmr (carbon tetrachloride):  $\delta$  2.12 (s, 3H, 2-CH<sub>3</sub>),

3.41 (s, 3H, OCH<sub>3</sub>), 3.63 (s, 3H, NCH<sub>3</sub>), 5.74 (s, 1H, H-4), 7.20-7.28 (m, 5H, aryl H's).

*Anal.* Calcd. for C<sub>13</sub>H<sub>15</sub>NO: C, 77.58; H, 7.51; N, 6.96; M.W. 201. Found: C, 77.45; H, 7.49; N, 7.10; M<sup>+</sup> 201.

B.

Lithium aluminum hydride (0.04 g., 1.1 mmoles) and aluminum chloride (0.14 g., 1.0 mmole) were added to 3 ml. of anhydrous ether under a nitrogen atmosphere. To this suspension was added 0.2 g. (0.77 mmole) of the methoxyester **1**. Hydrogen evolution was immediate, giving a homogeneous, pale green solution. This solution was quenched after 30 minutes with 0.1 ml. of 20% sodium hydroxide, and then 0.3 ml. of water, then filtered and the salts boiled with THF and filtered again. Concentration of the combined, dried (potassium carbonate) organic phases gave gummy material which, after one recrystallization from petroleum ether gave white crystals that were identical by nmr, tlc, and mixture melting point with the 2-methyl compound isolated in A above.

C.

Treatment of the methoxyester **1** (0.1 g., 0.39 mmole) with amine stabilized aluminum hydride (Lithcoa) as described under B above for lithium aluminum hydride and aluminum chloride again gave material that was shown to be identical with the compound isolated under A.

#### 1,2,4-Trimethyl-3-methoxy-5-phenylpyrrole (5).

The methoxydiester, **2** (3), (0.5 g., 1.51 mmoles) was treated with 20 ml. of 1M diborane in THF (20 mmoles) as described for compound **4** under A. Workup gave 0.28 g. (86%) of **5** as an oil which distilled at 1 mm in an oil bath kept at 100°; nmr (carbon tetrachloride):  $\delta$  1.92 (s, 3H, 4-CH<sub>3</sub>), 2.12 (s, 3H, 2-CH<sub>3</sub>), 3.25 (s, 3H, OCH<sub>3</sub>), 3.63 (s, 3H, NCH<sub>3</sub>), 7.10-7.24 (m, 5H, aryl H's). This material darkened rapidly and a satisfactory analysis could not be obtained. M.W., Calcd. for C<sub>14</sub>H<sub>17</sub>NO: 215.1311. Found: M<sup>+</sup> 215.1315.

#### 1,3-Dimethyl-4-methoxy-2-phenylpyrrole (6).

The methoxyester **3** (3), (0.5 g., 1.93 mmoles) was treated as for compounds **1** and **2** with 12 ml. of 1M diborane (12 mmoles) in THF. Workup gave material that darkened rapidly and did not give satisfactory spectra for **6**. If, however, the initially obtained material was treated with *p*-nitrobenzenediazonium acetate as previously described for the 3-ester, **3** (3), red brown crystals (0.5 g., 74%) of the 2-azo derivative **6a** were obtained; m.p. 159-160° (ethanol/water); nmr (deuteriochloroform):  $\delta$  1.92 (s, 3H, 3-CH<sub>3</sub>), 3.66 (s, 3H, NCH<sub>3</sub>), 4.10 (s, 3H, OCH<sub>3</sub>), 7.10-7.40 (m, 5H, 5-phenyl), 7.68 (d, 2H, J<sub>ortho</sub> = 9 Hz, *p*-nitrophenyl), 8.19 (d, 2H, J<sub>ortho</sub> = 9 Hz).

*Anal.* Calcd. for C<sub>19</sub>H<sub>18</sub>N<sub>4</sub>O<sub>3</sub>: C, 65.13; H, 5.18; N, 15.99. Found: C, 65.30; H, 5.21; N, 15.85.

#### 1-Methyl-3-methoxy-5-phenyl-2,4-bis-hydroxymethylpyrrole (8).

The methoxydiester, **2** (3), (2.9 g., 6.0 mmoles) was treated with lithium aluminum hydride in dry THF as previously described (3) for the 2-ester, **1**. Workup gave 1.0 g. (67%) of **8** as white crystals that were very sensitive to acidic impurities in solvents. Recrystallization was best effected from ethyl acetate containing a trace of pyridine; m.p. 150-152°; ir (potassium bromide): 3.10  $\mu$  (-OH); nmr (pyridine-d<sub>5</sub>):  $\delta$  3.50 (s, 3H, NCH<sub>3</sub>), 3.98 (s, 3H, OCH<sub>3</sub>), 4.72 (s, 2H, 4-CH<sub>2</sub>-), 4.90 (s, 2H, 2-CH<sub>2</sub>-), 5.70-6.40 (broad, 2H, -OH), 7.20-7.58 (m, 5H, aryl H's).

#### 1-Methyl-4-methoxy-2-phenyl-3-hydroxymethylpyrrole (9).

The methoxy ester, **3**, (0.3 g., 1.16 mmoles) was treated as described for compound **1** with lithium aluminum hydride in dry THF to give, upon workup, 0.20 g. (80%) of **9** as an oil; ir (sodium chloride, neat):  $3.10 \mu$  (-OH), nmr (deuteriochloroform):  $\delta$  3.34 (s, 3H, OCH<sub>3</sub>), 3.64 (s, 3H, NCH<sub>3</sub>), 4.34 (s, 2H, 3-CH<sub>2</sub>-), 6.06 (s, 1H, H-5), 7.24 (s, 5H, aryl H's).

To provide a stable derivative for analysis, this oil was reacted with *p*-nitrobenzenediazonium acetate as described for **6** to give red-brown crystals of the azo derivative **9a**, m.p. 188-189° (ethanol/water); nmr (deuteriochloroform):  $\delta$  1.98 (broad, 1H, -OH), 3.72 (s, 3H, NCH<sub>3</sub>), 4.20 (s, 3H, OCH<sub>3</sub>), 4.40 (s, 2H, 4-CH<sub>2</sub>-), 7.40 (s, 5H, 5-phenyl), 7.68 (d, 2H, J<sub>ortho</sub> = 9 Hz, *p*-nitrophenyl), 8.20 (d, 2H, J<sub>ortho</sub> = 9 Hz).

*Anal.* Calcd. for C<sub>19</sub>H<sub>18</sub>N<sub>4</sub>O<sub>4</sub>: C, 62.29; H, 4.95; N, 15.29; M.W. 366. Found: C, 62.22; H, 4.95; N, 15.18; M<sup>+</sup> 366.

1,1'-Dimethyl-3,3'-dimethoxy-5,5'-diphenyl-2,2'-dipyrrylmethane (**10**).

A solution of **7** in THF which resulted from the reduction of **1** (0.5 g., 1.93 mmoles) with lithium aluminum hydride was treated with three drops of glacial acetic acid. After 30 minutes the solution was washed with a saturated solution of sodium bicarbonate, dried (potassium carbonate), and concentrated under reduced pressure to give a dark oil which, after one recrystallization from ethanol/water, gave **10** as white crystals, (0.16 g., 43%) m.p. 144-145°; nmr (deuteriochloroform):  $\delta$  3.46 (s, 6H, NCH<sub>3</sub>), 3.72 (s, 6H, OCH<sub>3</sub>), 3.96 (s, 2H, *meso*-CH<sub>2</sub>-), 5.92 (s, 2H, H-4), 7.16-7.32 (m, 10H, aryl H's).

*Anal.* Calcd. for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>: C, 77.69; H, 6.78; N, 7.25; M.W. 386. Found: C, 77.64; H, 6.69; N, 7.12; M<sup>+</sup> 386.

1,1'-Dimethyl-3,3'-dimethoxy-4,4'-bis-hydroxymethyl-5,5'-diphenyl-2,2'-dipyrrylmethane (**11**).

The bis-hydroxymethylpyrrole **8**, (0.20 g., 0.81 mmole) was treated in THF with glacial acetic acid as above. Workup gave a gummy solid which after one recrystallization from benzene/hexane amounted to 0.09 g., (50%) and had m.p. 167-170°; ir (potassium bromide):  $3.10 \mu$  (-OH); nmr (pyridine-d<sub>5</sub>):  $\delta$  3.40 (s, 6H, NCH<sub>3</sub>), 4.00 (s, 6H, OCH<sub>3</sub>), 4.06 (s, 2H, *meso*-CH<sub>2</sub>-), 4.72 (s, 4H, 4-CH<sub>2</sub>-), 4.80 (s, broad, 2H, -OH), 7.10-7.50 (m, 10H, aryl H's).

After passing this material over a short column of neutral

alumina (benzene) to remove a little colored material and recrystallizing it once more it failed to give a satisfactory analysis, even though TLC showed it to be pure. M.W. Calcd. for C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub>: 446.2207. Found: M<sup>+</sup> 446.2195.

The Reduction of **1** with Sodium Borohydride.

The methoxyester **1** (0.10 g., 0.39 mmole) was refluxed overnight in 10 ml. of 2-propanol with 0.03 g. (0.78 mmole) sodium borohydride. Examination by TLC in three solvent systems (10% THF/benzene, chloroform, benzene) showed that the starting material was mostly unchanged, with the dipyrromethane **10** present in a small amount.

The Reaction of **7** with Acetic Anhydride.

To a THF solution of **7** which resulted from the reduction of **1** (0.5 g., 1.93 mmoles) with lithium aluminum hydride was added 10 ml. of pyridine. The THF was evaporated under reduced pressure at less than 50° and excess acetic anhydride was added. This mixture was heated for 10 minutes on a steam bath and then water was added, causing a gummy solid to precipitate. Recrystallization from ethanol/water gave 0.23 g. (63%) of material that was identical to **10** by tlc, ir and mixture melting point.

## REFERENCES

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