Synthesis of Functionalized *N*-Methylpyrroles

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The preparation of some new *N*-methylpyrroles is shown. These heterocyclic compounds were used to synthesize polyenic substances with polysubstituted pyrrole rings.

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Introduction

A large number of synthetic retinoids appears in the literature. In some of them, the group 1,6,6-trimethyl-1-cyclohexenyl (present in Vitamin A) is replaced by a cyclopentane, thiopyran, cycloheptane, norbornane, benzene, thiophene or furan ring [1], but retinoids with a pyrrole hitherto have not been described [2].

We are developing a research program related to the synthesis of new retinoids with substituted heterocyclic rings. The additional study of the biological activity of these compounds will contribute to the knowledge of their chemical structure-pharmacological activity relationships. With this aim we projected the preparation of retinoids with 1,2,4-trimethylpyrrole ring bearing different substituents in C-3′ (Figure 1).

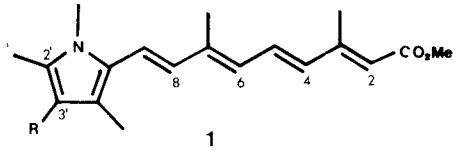

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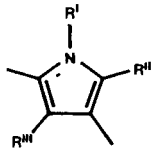
Figure 1

R: HC≡C- (**a**), $H_2C=CH$- (**b**), CH_3-CH_2- (**c**), H- (**d**)

To obtain the substances **1a-d**, we needed the heterocycles **2**, **3**, **4** and **5** whose formyl groups allow the introduction of the polyenic side chain of the retinoids, through Wittig reactions with the proper ylides.

This paper shows the synthesis of these and other related heterocycles (Figure 2).



	R'	R''	R'''
2	Me	CH=O	-C≡CH
3	Me	CH=O	-CH=CH_2
4	Me	CH=O	Et
5	Me	CH=O	H
6	Me	H	Ac
7	Me	CO_2Et	Ac
8	H	CO_2Et	Ac
9	Me	CO_2Et	-C(Cl)=CH_2
10	Me	CO_2H	Ac
11	Me	CH=O	-C(Cl)=CH_2
12	Me	CH=O	Ac
13	Me	H	Et
14	Me	H	H
15	Me	CO_2Et	H
16	Me	CH_2OH	H
17	H	CO_2Et	H
18	Me	CO_2Et	Me
19	H	CO_2Et	Me
20	Me	Me	H

Figure 2

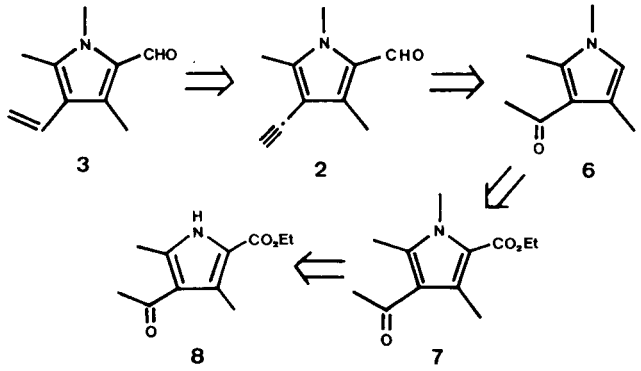


Figure 3

Results and Discussion

We followed the retrosynthetic analysis shown in Figure 3 for compounds **2** and **3**. The heterocycle **8** is easy to obtain through a Knorr synthesis [3], the key step in the scheme being the formation of **2** from **6**.

Mironov *et al.* reported the reaction between acetylpyrroles (no substituent on the nitrogen atom) and phosphorus oxychloride in dimethylformamide giving a chlorovinyl derivative that, with subsequent alkali treatment, leads to the corresponding acetylene [4,5,6] (Figure 4).

We tried this method with the *N*-methyl substituted pyrrole **7**. This compound was prepared by the reaction between methyl iodide and the sodium salt of **8**. Treatment of **7** with phosphorus oxychloride in DMF gave a 75%

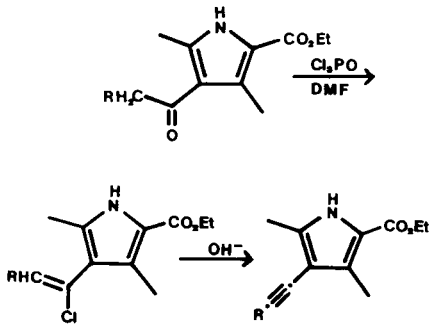


Figure 4

yield of 3-(1'-chlorovinyl)-5-ethoxycarbonyl-1,2,4-trimethylpyrrole (**9**). The structure of this new compound was established through its spectral and analytical data. In its mass spectrum M^+ does not appear but shows fragments at m/e (relative intensity) 206 (11) and 205 (100) corresponding to the loss of Cl and ClH respectively, that confirms the molecular weight and justifies the unusual ease for dehydrohalogenation of these chlorovinylpyrroles.

We prepared **6** in good yield by saponification of **7** and decarboxylation of the resulting acid **10**. Previously [7], the characterization and preparation of **6** from the potassium salt of 3-acetyl-2,4-dimethylpyrrole was incompletely reported. Elemental analysis and mass spectrum of **10** agreed with $C_{10}H_{13}O_3N$ and its ir spectrum showed absorption bands of a conjugated carboxylic acid between 3100 and 2900, and 1687 cm^{-1}. In its ^{13}C nmr spectrum, the signals corresponding to the carbonyl and carboxyl carbons appeared at 195.27 and 163.01 ppm respectively. This compound could have antiinflamatory and central nervous system depressant activities by analogy with other related carboxypyrroles [8,9].

Compound **6** showed M^+ at m/e 151 that in addition with its elemental analysis agreed with $C_9H_{13}NO$. In its pmr spectrum a broad singlet at 6.27 ppm appeared due to the aromatic proton on C-5. Treatment with the Vilsmeier reagent allowed both the formylation in C-5 and conversion of the acetyl group into the ethynyl group to obtain **2** (75%) together with **11** (10%) and **12** (10%). The overall yield in the major product **2** can be increased by dehydrohalogenation of **11** which, in sodium ethoxide/ethanol takes place quantitatively. The pmr spectrum of **2** showed signals at 9.54 ppm characteristic of an aldehyde proton and a singlet at 3.18 ppm due to an acetylene hydrogen. The triple bond presence was confirmed in the ir spectrum by the appearance of bands at 3249 and 2102 cm^{-1} and in the ^{13}C nmr spectrum by the two acetylene carbon atoms at 76.72 (CH) and 80.95 ppm (C), the carbonyl carbon atom resonating as a positive signal at 177.21 ppm.

The presence of a chlorine atom in **11** was suggested from its M^+ at 197 (50) and 199 (15). In its pmr spectrum appeared two geminal olefin protons (5.21 ppm, d, J = 1 Hz, and 5.66 ppm, d, J = 1 Hz), three methyl groups and an aldehyde proton. Finally the mass spectrum and the elemental analysis of **12** were in agreement with $C_{10}H_{13}NO_2$. Its pmr spectrum showed signals at 2.47 and 2.54 ppm (CH_3-C-2 and CH_3-C-4), 2.50 ppm (CH_3-CO-), 3.87 ppm (CH_3-N) and a singlet of the aldehyde hydrogen at 9.77 ppm. Its ^{13}C nmr spectrum confirmed the structure having two carbonyls at 178.05 (CHO) and 195.13 ppm (CH_3-CO-). Compound **11** when refluxed in DMF with an aqueous solution of potassium carbonate gave a mixture of **2** (75%) and **12** (25%) indicating that it is the precursor of both substances.

Partial hydrogenation of **2** in the presence of poisoned Lindlar catalyst afforded the ethylene derivative **3** (M^+ at m/e 163). In its pmr spectrum we also observed three olefin protons (with a coupling model typical of a monosubstituted double bond), three methyl singlets and an aldehyde hydrogen. Its ^{13}C nmr spectrum was in accord with the proposed structure.

The synthesis of **4** was achieved in two ways, either by catalytic hydrogenation of **2**, to give **4** quantitatively, or by formylation and methylation of kryptopyrrole (3-ethyl-2,4-dimethylpyrrole), with a total yield of 50% [10]. Trying to perform these procedures, we reduced **6** with lithium aluminium hydride at room temperature, yielding 3-ethyl-1,2,4-trimethylpyrrole (**13**) (95%) which structure was confirmed by ms (M^+ at m/e 137) and pmr (1.07 (t) and 2.38 ppm (q) due to ethyl group). Compound **13** could not be successfully purified by column chromatography (neutral alumina or silica gel) in which it polymerized. The low stability of this product is due to the high number of electron donor substituents, increasing its π-exceeding character. Treatment of **13** with the Vilsmeier reagent gave **4**, in poor yield (30%).

Another of the pyrroles synthesized was **5** [11], obtained by reduction of **15** and oxidation of the resulting alcohol. Compound **15** could be prepared either by treatment of **17** the sodium salt [12] with methyl iodide (60%) (also giving **18** [13] (20%) and **19** [12] (5%)), or better yield by deacetylation of **7** with ethylene glycol and *p*-toluenesulphonic acid [14,15] (this deacetylation procedure, previously applied to **6**, yielded 88% of **14**). Reduction of **15** with lithium aluminum hydride was highly influenced by the experimental conditions because the instability of the resulting alcohol **16** [16]. At room temperature, **15** suffers hydrogenolysis to give 1,2,3,5-tetramethylpyrrole (**20**) whereas at -10° and carrying out the hydrolysis of the aluminum complex with 1*N* sulphuric acid, **21** was the recovered product. Nevertheless at the same low temperature and *p*H = 7, the alcohol **16** could be obtained in almost quantitative yield (Figure 5).

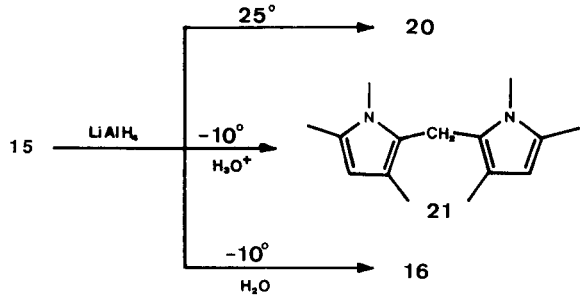


Figure 5

Compounds **16** and **21** were characterized by their spectroscopic properties. The ir spectrum of **16** does not present any band due to a carbonyl group, in contrast a band of the O-H group at 3227 cm^{-1} appears. The presence of the hydroxymethylene group was also confirmed in the ^{13}C nmr spectrum (53.62 ppm, CH_2). The mass spectrum showed M^+ at 139 and $[M-1]^+$, $[M-2]^+$, $[M-3]^+$, $[M-OH]^+$ and $[M-CH_2OH]^+$ typical of benzylic alcohols [17]. The product **21** was found to be very unstable with easy polymerization. It presents M^+ at 230 and in its pmr spectrum we could see a singlet which integrates for two protons assignable to a methylene between two pyrrole rings [18,19]. This was corroborated by ^{13}C nmr showing one methylene (DEPT) at 21.80 ppm. The formation of this substance can be explained on the basis of an electrophylic substitution on the carbon bearing the hydroxymethylene group, confirmed by the isolation of **21** when **16** was treated with a saturated solution of ammonium chloride (Figure 6).

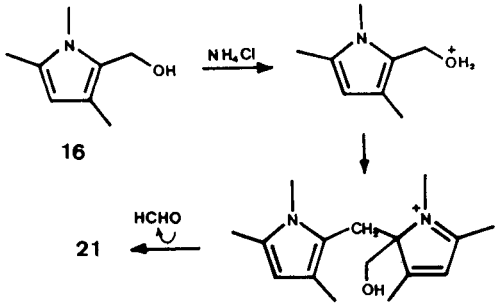


Figure 6

Finally, reaction between **16** and manganese dioxide gave the aldehyde compound **5** in 33% yield.

EXPERIMENTAL

3-Acetyl-5-ethoxycarbonyl-1,2,4-trimethylpyrrole (**7**).

To a stirred solution of 1 g (4.78 mmoles) of 3-acetyl-5-ethoxycarbonyl-2,4-dimethylpyrrole (**8**) [3] dissolved in 30 ml of absolute tetrahydrofuran, 0.156 g (5.2 mmoles) of sodium hydride (in 20% paraffin oil) was added under nitrogen atmosphere. Once the hydride was completely dissolved, 1.5 ml (24.1 mmoles) of methyl iodide in 5 ml of absolute tetrahydrofuran was incorporated. The stirring was maintained for one hour at room temperature and two hours under reflux. The solvent was evaporated and water (20 ml) and ethyl ether (30 ml) added. The ethereal layer was separated, washed, dried and the solvent was evaporated to yield 1.053 g (quantitative) of **7**, mp 64-65° (lit 66°) [7].

3-(1'Chlorovinyl)-5-ethoxycarbonyl-1,2,4-trimethylpyrrole (**9**).

Over 758 mg (10.4 mmoles) of dimethylformamide, 170 mg (1.1 mmoles) of phosphorus oxychloride and 223 mg (1 mmole) of 3-acetyl-5-ethoxycarbonyl-1,2,4-trimethylpyrrole (**7**) were added at -10°. Then the temperature was kept at 35° for 1 hour. Ice (350 mg) and 440 mg (11 mmoles) of sodium hydroxide in 0.8 ml of water were added. The resulting suspension was heated until the boiling point, cooled to room temperature and extracted with ethyl ether. The ethereal layer was separated, dried and the solvent was evaporated *in vacuo* obtaining 180 mg (75%) of **9**; ir (film): ν 1689 (C=O), 1544, 1481, 1408, 1210 and 857 cm^{-1}; pmr (deuteriochloroform): δ 1.37 (t, J = 7, 3H, -O-CH_2CH_3), 2.25 (s, 3H, CH_3-C-2), 2.32 (s, 3H, CH_3-C-4), 3.78 (s, 3H, CH_3-N), 4.32 (q, J = 7, 2H, -O-CH_2CH_3), 5.19 (d, J = 1, 1H, CH_2=C(Cl)-), 5.65 (d, J = 1, 1H, CH_2=C(Cl)-); ^{13}C nmr (deuteriochloroform): δ 10.72 (CH_3, CH_3-C-4), 11.92 (CH_3, CH_3-C-2), 14.32 (CH_3, -O-CH_2CH_3), 32.84 (CH_3, CH_3-N), 59.41 (CH_2, -O-CH_2CH_3), 117.49 (CH_2, CH_2=C(Cl)-), 118.94 (C, C-4), 121.09 (C, CH_2=C(Cl)-), 127.16 (C, C-5), 134.08 (2C, C-2 and C-3), 161.98 (CH, CHO); ms: m/z (relative intensity) 206 (11) $[M-Cl]^+$, 205 (100) $[M-HCl]^+$, 176 (65) $[M-HCl-Et]^+$, 133 (58) $[M-Cl-COOEt]^+$, 132 (52) $[M-HCl-COOEt]^+$.

Anal. Calcd. for $C_{12}H_{16}ClNO_2$: C, 59.61; H, 6.62; N, 5.79. Found: C, 59.43; H, 6.46; N, 5.78.

3-Acetyl-1,2,4-trimethylpyrrole (**6**).

3-Acetyl-5-ethoxycarbonyl-1,2,4-trimethylpyrrole (**7**) (33.25 g, 0.149 mole) was dissolved in 450 ml of 2*N* alcoholic potassium hydroxide and 50 ml of water. The solution was refluxed for 15 minutes, the ethanol evaporated and the base neutralized with 381 ml of 2*N* hydrochloric acid. The solid residue was filtered, washed with water and dried *in vacuo* affording 25.05 g (86%) of 3-acetyl-5-carboxy-1,2,4-trimethylpyrrole (**10**), mp 140-145° dec; ir (potassium bromide): ν 3100-2900 (broad signal, O-H), 1687 (C=O), 1529, 1480 and 1418 cm^{-1}; pmr (deuteriochloroform): δ 2.45 (s, 6H, CH_3-CO and CH_3-C-2), 2.59 (s, 3H, CH_3-C-4), 3.81 (s, 3H, CH_3-N), 10.50 (broad singlet, 1H, COOH); ^{13}C nmr (DMSO-d_6): δ 12.06 (CH_3, CH_3-C-4), 13.05 (CH_3, CH_3-C-2), 31.64 (CH_3, CH_3-CO-), 32.71 (CH_3, CH_3-N), 120.65 (C, C-5), 122.39 (C, C-3), 128.16 (C, C-4), 139.93 (C, C-2), 163.01 (C, COOH), 195.27 (C, CH_3-CO-); ms: CI m/z (relative intensity) 196 (100) $[M+1]^+$, 152 (19) $[M+1-CO_2]^+$.

Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.54; H, 6.67; N, 7.18. Found: C, 61.68; H, 6.68; N, 7.50.

Ethanolamine (15 g, 0.229 mole) and 25.05 g (0.128 mole) of **10** were refluxed for 1 hour and then 70 ml of cold water was added. The formed precipitate was filtered and was crystallized from hexane as pale yellow needles, 12.6 g (65%) of **6**, mp 77-79°; ir (potassium bromide): ν 1631 (C=O), 1503, 1477, 1411 cm^{-1}; pmr (deuteriochloroform): δ 2.24 (d, J = 1, 3H, CH_3-C-4), 2.41 (s, 3H, CH_3-C-2), 2.47 (s, 3H, CH_3-CO-), 3.47 (s, 3H, CH_3-N), 6.27 (br s, 1H, H-C-5); ^{13}C nmr (deuteriochloroform): δ 11.86 (CH_3, CH_3-C-4), 13.38 (CH_3, CH_3-C-2), 30.80 (CH_3, CH_3-CO-), 33.01 (CH_3, CH_3-N), 118.65 (C, C-3), 120.28 (CH, C-5), 121.27 (C, C-4), 135.89 (C, C-2), 195.09 (C, C=O); ms: m/z (relative intensity) 151 (35) $[M]^+$, 136 (100) $[M-CH_3]^+$, 43 (19) $[CH_3CO]^+$, 42 (28) $[C_2H_4N]^+$, 41 (11) $[C_2H_3N]^+$ and 39 (10) $[C_3H_3]^+$.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.52; H, 8.61; N, 9.27. Found: C, 71.67; H, 8.68; N, 9.24.

Reaction Between 3-Acetyl-1,2,4-trimethylpyrrole (**6**), Dimethylformamide and Phosphorus Oxychloride.

The reaction was carried out in the same manner as for compound **9** and the residue was fractionated on a silica gel column. Elution with hexane:ether mixtures gave **11**, **2** and **12** (10, 75 and 10% yields, respectively).

3-(1'-Chlorovinyl)-1,2,4-trimethylpyrrole-5-carboxaldehyde (**11**).

This compound was obtained as a white solid, mp 96-97°; ir (potassium bromide): ν 1641 (C=O), 1484, 1398 and 822 cm^{-1}; pmr (deuteriochloroform): δ 2.26 (s, 3H, CH_3-C-2), 2.33 (s, 3H, CH_3-C-4), 3.84 (s, 3H, CH_3-N), 5.21 (d, J = 1, 1H, CH_2=C(Cl)-), 5.66 (d, J = 1, 1H, CH_2=C(Cl)-), 9.66 (s, 1H, CHO); ^{13}C nmr (deuteriochloroform): δ 9.20 (CH_3, *C*H_3-C-4), 10.52 (CH_3, *C*H_3-C-2), 32.56 (CH_3, CH_3-N), 117.98 (CH_2, *C*H_2=C(Cl)-), 121.80 (C, CH_2=*C*(Cl)-), 127.13 (C, C-4), 132.63 (C, C-3), 133.09 (C, C-5), 137.83 (C, C-2), 177.51 (CH, CHO); ms: m/z (relative intensity) 199 (15) $[M+2]^+$, 197 (50) $[M]^+$, 162 (100) $[M-Cl]^+$, 161 (16) $[M-HCl]^+$, 56 (26) $[CH_3CNCH_3]^+$, 42 (27) $[C_2H_4N]^+$, 41 (8) $[C_2H_3N]^+$, 39 (21) $[C_3H_3]^+$.

Anal. Calcd. for $C_{10}H_{12}ClNO$: C, 60.76; H, 6.12; N, 7.09. Found: C, 60.87; H, 6.10; N, 7.06.

3-Ethynyl-1,2,4-trimethylpyrrole-5-carboxaldehyde (**2**).

This compound was obtained as a white solid, mp 109°; ir (potassium bromide): ν 3249 (≡C-H), 2102 (C≡C), 1637 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 2.29 (s, 3H, CH_3-C-2), 2.35 (s, 3H, CH_3-C-4), 3.18 (s, 1H, HC≡C-), 3.82 (s, 3H, CH_3-N), 9.59 (s, 1H, CHO); ^{13}C nmr (deuteriochloroform): δ 9.66 (CH_3, *C*H_3-C-4), 10.87 (CH_3, *C*H_3-C-2), 32.84 (CH_3, CH_3-N), 76.72 (CH, H*C*≡C-), 80.95 (C, HC≡*C*-), 105.09 (C, C-3), 127.46 (C, C-4), 137.00 (C, C-5), 142.82 (C, C-2), 177.21 (CH, CHO); ms: m/z (relative intensity) 161 (100) $[M]^+$, 160 (56) $[M-1]^+$, 146 (27) $[M-CH_3]^+$, 132 (27) $[M-CHO]^+$, 117 (14) $[M-CHO-CH_3]^+$, 42 (16) $[C_2H_4N]^+$, 39 (16) $[C_3H_3]^+$.

Anal. Calcd. for $C_{10}H_{11}NO$: C, 74.53; H, 6.83; N, 8.69. Found: C, 74.61; H, 6.67; N, 8.69.

3-Acetyl-1,2,4-trimethylpyrrole-5-carboxaldehyde (**12**).

This compound was obtained as a white solid, mp 72°; ir (potassium bromide): ν 1650 (C=O), 1632 (C=O) cm^{-1}; pmr (deuteriochloroform): δ 2.47 (s, 3H, CH_3-C-2), 2.50 (s, 3H, CH_3-CO-), 2.54 (s, 3H, CH_3-C-4), 3.87 (s, 3H, CH_3-N), 9.77 (s, 1H, CHO); ^{13}C nmr (deuteriochloroform): δ 11.09 (CH_3, *C*H_3-C-4), 11.81 (CH_3, *C*H_3-C-2), 31.55 (CH_3, *C*H_3-CO-), 32.14 (CH_3, CH_3-N), 122.99 (C, C-3), 127.46 (C, C-4), 134.51 (C, C-5), 143.33 (C, C-2), 178.05 (CH, CHO), 195.13 (C, CH_3-*C*O-); ms: m/z (relative intensity) 179 (49) $[M]^+$, 164 (100) $[M-CH_3]^+$, 42 (24) $[C_2H_4N]^+$, 41 (11) $[C_2H_3N]^+$, 39 (19) $[C_3H_3]^+$.

Anal. Calcd. for $C_{10}H_{13}O_2N$: C, 67.04; H, 7.26; N, 7.82. Found: C, 67.24; H, 7.32; N, 7.85.

3-Ethynyl-1,2,4-trimethylpyrrole-5-carboxaldehyde (**2**) by Dehydrohalogenation of **11**.

The halogenated derivative 3-(1'-chlorovinyl)-1,2,4-trimethylpyrrole-5-carboxaldehyde (**11**) (500 mg, 2.54 mmoles) was treated for 10 minutes with 517 mg (7.61 mmoles) of sodium ethoxide in 8 ml of ethanol. The solvent was removed and the residue was extracted with ether. The ethereal extract was washed and dried. The solvent was removed and 408 mg of **2** were obtained.

2-Carboxaldehyde-4-vinyl-1,3,5-trimethylpyrrole (**3**).

3-Ethynyl-1,2,4-trimethylpyrrole-5-carboxaldehyde (**2**) (100 mg, 0.62 mmole) dissolved in 4 ml of absolute methanol, and 10 mg of Lindlar catalyst poisoned with 1 mg of 2,2'-(ethylenedithio)diethanol were placed at 1 atmosphere hydrogen pressure and the mixture was stirred for 12 hours. The solid products were removed by filtration, the filtrate was evaporated *in vacuo* and the residue was separated by column chromatography (silica gel, hexane:ether 85/15), obtaining a 65% of **3**; ir (film): ν 1644 (C=O), 1484, 1440, 1415, 993 and 913 cm^{-1}; pmr (deuteriochloroform): δ 2.25 (s, 3H, CH_3-C-2), 2.33 (s, 3H, CH_3-C-4), 3.83 (s, 3H, CH_3-N), 5.22 (dd, J = 2, J = 11, 1H, *H*$_2$C=CH-), 5.28 (dd, J = 2, J = 18, 1H, *H*$_2$C=CH-), 6.58 (dd, J = 11, J = 18, 1H, H_2C=C*H*-), 9.64 (s, 1H, CHO); ^{13}C nmr (deuteriochloroform): δ 9.73 (CH_3, *C*H_3-C-4), 10.44 (CH_3, *C*H_3-C-2), 32.28 (CH_3, CH_3-N), 114.26 (CH_2, *C*H_2=CH-), 120.06 (C, C-4), 127.38 (C, C-3), 128.37 (CH, CH_2=*C*H-), 132.34 (C, C-5), 137.74 (C, C-2), 177.17 (CH, CHO); ms: m/z (relative intensity) 163 (100) $[M]^+$, 162 (51) $[M-1]^+$, 148 (21) $[M-CH_3]^+$, 134 (42) $[M-CHO]^+$, 56 (34) $[CH_3CNCH_3]^+$, 42 (31) $[C_2H_4N]^+$, 41 (13) $[C_2H_3N]^+$, 39 (29) $[C_3H_3]^+$.

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.62; H, 7.97; N, 8.59. Found: C, 72.98; H, 7.95; N, 8.56.

3-Ethyl-1,2,4-trimethylpyrrole-5-carboxaldehyde (**4**).

This compound was obtained by two different procedures.

Procedure A.

By hydrogenation of **2** in the same way as seen for compound **3**, using palladium catalyst, **4** was obtained [10] in quantitative yield.

Procedure B.

Through formylation of **13**, as for **2**, **9**, **11** and **12**, 27% of **4**, after silicagel column chromatography with hexane:ethyl ether 4:1, was obtained.

3-Ethyl-1,2,4-trimethylpyrrole (**13**).

To a suspension of 10 g (0.263 mole) of lithium aluminium hydride in 200 ml of ether 8 g (0.053 mmole) of 3-acetyl-1,2,4-trimethylpyrrole (**6**) was added. The mixture was stirred at room temperature for 12 hours, poured into water and extracted with ether. The solvent was evaporated giving 7.2 g (95%) of **13**; pmr (deuteriochloroform): δ 1.07 (t, J = 7, 3H, C*H*$_3$-CH$_2$), 2.01 (d, J = 1.2, 3H, CH_3-C-4), 2.12 (s, 3H, CH_3-C-2), 2.38 (q, J = 7, 2H, CH_3-C*H*$_2$-), 3.46 (s, 3H, CH_3-N), 6.28 (broad singlet, 1H, H-5); ms: m/z (relative intensity) 137 (31) $[M]^+$, 122 (100) $[M-CH_3]^+$, 42 (10) $[C_2H_4N]^+$, 41 (6) $[C_2H_3N]^+$, 39 (6) $[C_3H_3]^+$.

1,2,4-Trimethylpyrrole (**14**).

A mixture of 15.1 g (0.1 mole) of 3-acetyl-1,2,4-trimethylpyrrole (**6**), 200 ml of absolute benzene, 6.2 g (0.1 mole) of ethylene glycol and 1.9 g (0.01 mole) of monohydrated *p*-toluenesulphonic acid was refluxed under a Dean-Stark trap for two hours. After solvent evaporation, 100 ml of water was added and extracted with ethyl ether. The organic layer was dried (sodium sulphate) and evaporated to yield 9.6 g (88%) of **14** [20,21].

Reaction Between the Sodium Salt of 2-Ethoxycarbonyl-3,5-dimethylpyrrole (**17**) and Methyl Iodide.

To a stirred suspension of 5.52 g (0.175 mole) of sodium hydride (in 20% paraffin oil) in 500 ml of absolute tetrahydrofuran, under a nitrogen atmosphere 10 g (59.88 mmoles) of 2-ethoxycarbonyl-3,5-dimethylpyrrole (**17**) dissolved in 50 ml of absolute THF was added. After one hour 33.97 g (0.239 mole) of methyl iodide was added and the mixture was stirred for 15 minutes at room temperature and one more hour at reflux. The solvent was removed *in vacuo*, water (25 ml) added and then extracted with ethyl ether. The ethereal extract was washed, dried and the solvent evaporated *in vacuo* to give 9.8 g of an oily residue that was separated on a silicagel column. The first fraction (6.05 g, eluted with hexane:ethyl ether 9:1) was analyzed by gc-ms (nitrogen as carrier gas, working between 100 and 240° at 5°/minute in a Carbowax 20 M capillary column, 70 eV) identifying **15** and **18** in 80 and 20%, respectively.

2-Ethoxycarbonyl-1,3,5-trimethylpyrrole (**15**) [13].

Compound **15** had a retention time of 0.05 minutes; ms: m/z (relative intensity) 181 (100) $[M]^+$, 152 (75) $[M-Et]^+$, 136 (84) $[M-EtO]^+$, 122 (8) [M-COOEt]$^+$, 108 (69) $[M-COOEt-CH_3]^+$.

2-Ethoxycarbonyl-1,3,4,5-tetramethylpyrrole (**18**) [22].

This compound had a retention time of 1.63 minutes; ms: m/z (relative intensity) 195 (100) $[M]^+$, 189 (39) $[M-CH_3]^+$, 166 (97) $[M-Et]^+$, 152 (50) $[M-CH_3-Et]^+$, 150 (65) $[M-EtO]^+$, 149 (37) $[M-EtOH]^+$, 136 (41) [M-COOEt]$^+$, 122 (75) $[M-COOEt-CH_3]^+$, 108 (44) $[M-COOEt-2CH_3]^+$.

In the second fraction (1.03 g, eluted with hexane:ethyl ether 7:1) **17** and **19** were obtained in 75 and 25% respectively, and were identified by gc-ms (under the same conditions as seen for **15** and **18**).

2-Ethoxycarbonyl-3,5-dimethylpyrrole (**17**) [12,14,23].

This compound had a retention time of 5.72 minutes; ms: m/z (relative intensity) 167 (83) $[M]^+$, 138 (29) $[M-Et]^+$, 122 (82) $[M-EtO]^+$, 121 (100) $[M-EtOH]^+$, 93 (32) $[M-COOEt-CH_3]^+$.

2-Ethoxycarbonyl-3,4,5-trimethylpyrrole (**19**) [12].

This compound had a retention time of 7.28 minutes; ms: m/z (relative intensity) 181 (94) $[M]^+$, 152 (23) $[M-Et]^+$, 136 (77) $[M-EtO]^+$, 135 (100) $[M-EtOH]^+$, 120 (12) $[M-EtOH-CH_3]^+$, 107 (34) $[M-COOEt-CH_3]^+$.

2-Ethoxycarbonyl-1,3,5-trimethylpyrrole (**15**).

This compound was obtained in a 75% yield by deacetylation of **7** in a similar manner as for **14** [14,15], mp 37-38°; ir (film): ν 1687 (C=O), 1482, 1434 and 1418 cm^{-1}; pmr (deuteriochloroform): δ 1.34 (t, J = 7, 3H, -O-CH_2-CH_3), 2.19 (s, 3H, CH_3-C-5), 2.28 (s, 3H, CH_3-C-3), 3.74 (s, 3H, CH_3-N), 4.28 (q, J = 7, 2H, -O-CH_2-CH_3), 5.75 (s, 1H, H-4); ^{13}C nmr (deuteriochloroform): δ 12.05 (CH_3, CH_3-C-5), 14.02 (CH_3, CH_3-C-3), 14.25 (CH_3, CH_3-CH_2-O-), 32.39 (CH_3, CH_3-N), 58.88 (CH_2, CH_3-CH_2-O-), 110.24 (CH, C-4), 118.00 (C, C-3), 129.01 (C, C-2), 135.09 (C, C-5), 161.93 (C, CO_2Et).

Reactions Between 2-Ethoxycarbonyl-1,3,5-trimethylpyrrole (**15**) and Lithium Aluminium Hydride.

To a solution of 580 mg (3.2 mmoles) of **15** in 7 ml of absolute ethyl ether a suspension of 98 mg (2.57 mmoles) of lithium aluminum hydride in 4 ml of the same solvent was added. The mixture was stirred for 3 hours at room temperature. To the suspension two drops of water were added and the organic product was extracted with ether. The solvent was removed giving an oily residue that was purified on a silica gel column to yield 40 mg (10%) of 1,2,3,5-tetramethylpyrrole (**20**) [21].

In a second experiment performed at -10° and the ethereal layer washed with 5% sulfuric acid, 3% potassium hydroxide and water, 50 mg (20%) of bis-(1,3,5-trimethyl-2-pyrryl)methane (**21**) was obtained; pmr (deuteriochloroform): δ 1.92 (s, 6H, CH_3-C-5), 2.14 (s, 6H, CH_3-C-3), 3.21 (s, 6H, CH_3-N), 3.80 (s, 2H, -CH_2-), 5.65 (broad singlet, 2H, H-4); ^{13}C nmr (deuteriochloroform): δ 11.30 (CH_3, CH_3-C-3), 12.33 (CH_3, CH_3-C-5), 21.80 (CH_2, -CH_2-), 30.14 (CH_3, CH_3-N), 108.95 (CH, C-4), 114.98 (C, C-3), 124.36 (C, C-2), 127.65 (C, C-5).

A third experiment achieved at the same temperature with the second one, washing the ethereal layer only with water gave 620 mg (95%) of 2-hydroxymethyl-1,3,5-trimethylpyrrole (**16**), mp 59-60°; ir (film): ν 3214 (O-H), 1516, 1468, 1396 and 999 cm^{-1}; pmr (deuteriochloroform): δ 2.09 (s, 3H, CH_3-C-3), 2.20 (s, 3H, CH_3-C-5), 3.52 (s, 3H, CH_3-N), 4.58 (s, 2H, CH_2-OH), 5.68 (s, 1H, H-4); ^{13}C nmr (deuteriochloroform): δ 10.59 (CH_3, CH_3-C-3), 11.80 (CH_3, CH_3-C-5), 29.86 (CH_3, CH_3-N), 53.62 (CH_2, CH_2OH), 106.98 (CH, C-4), 116.14 (C, C-3), 127.01 (C, C-2), 128.75 (C, C-5); ms: m/z (relative intensity) 139 (23) $[M]^+$, 138 (15) $[M-1]^+$, 137 (5) $[M-2]^+$, 136 (12) $[M-3]^+$, 122 (100) $[M-OH]^+$, 121 (16) $[M-H_2O]^+$, 108 (26) $[M-CH_2-OH]^+$.

Anal. Calcd. for $C_8H_{13}NO$: C, 69.06; H, 9.35; N, 10.07. Found: C, 68.86; H, 9.29; N, 10.04.

Conversion of **16** into **21**.

A mixture of 100 mg (0.76 mmole) of 2-hydroxymethyl-1,3,5-trimethylpyrrole (**16**) 4 ml of ethanol and 2 ml of a saturated solution of ammonium chloride was stirred at room temperature for 3 hours. The methanol was evaporated *in vacuo* and the residue extracted with ethyl ether to afford 60 mg (60%) of **21**.

1,3,5-Trimethylpyrrole-2-carboxaldehyde (**5**).

To a stirred solution of 26 mg (0.187 mmole) of 2-hydroxymethyl-1,3,5-trimethylpyrrole (**16**) dissolved in 4 ml of dry hexane was added 0.24 g (2.80 mmoles) of manganese dioxide [24], maintaining the stirring for 24 hours at room temperature. The organic phase gave after evaporation an oily residue formed by 1,3,5-trimethylpyrrole-2-carboxaldehyde (**5**) [11] 33%.

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