# Chemistry of 1-Methoxypyrrole-2-carboxylic Acid

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1-Methoxypyrrole-2-carboxylic acid and its derivatives were prepared. Fridel-Crafts bromination occurs first at 4-position and then at 5-position. Acylation of 3-methyl derivative was also directed to 4-position.

## Introduction

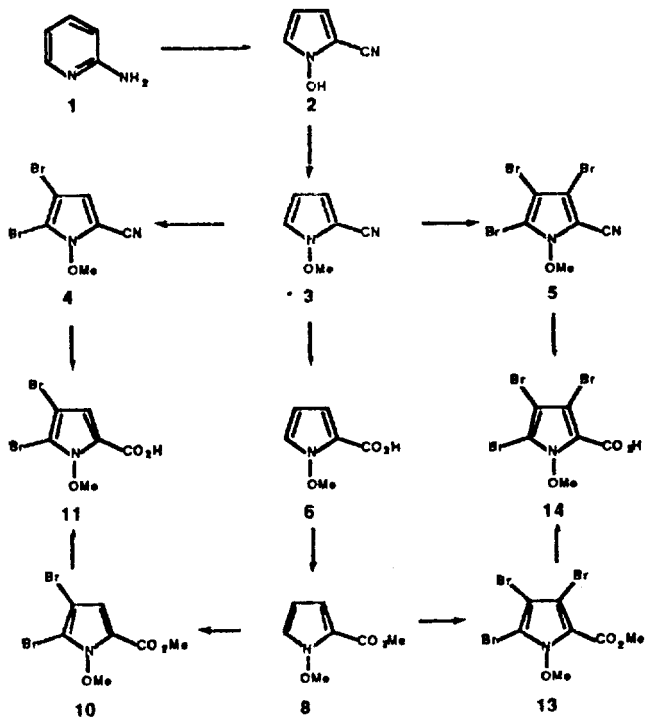
Although 1-hydroxypyrroles have interesting structure and are generally considered to be stable compounds, there is little known about them.[1] No general methods are available for the oxidation of a pyrrole to a 1-hydroxypyrrole. The first example was prepared by Knorr[2] who treated diethyl 2,3-diacetylsuccinate with hydroxylamine to obtain diethyl 2,5-dimethyl-1-hydroxypyrrole-3,4-dicarboxylate. This method still constitutes a general route to 1-hydroxypyrroles. Use of methoxyamine in place of hydroxylamine gave corresponding 1-methoxypyrrole.[3] 1-Methoxy derivative was also prepared by the reaction of diethyl 2-formyl-3-(diethoxymethyl)succinate and methoxyamine.[4] 1-Hydroxypyrroles with aryl substituents were prepared either by reaction of acetyl chloride or acetic anhydride with cyclic nitrones or reduction of 2-methoxy derivatives with sodium.[5,6] Similar derivatives were also prepared by reaction of the oximes of α-haloketones.[7-9] These derivatives could be oxidized with lead oxide to stable nitroxide radicals.[7,10-12]

Other methods include reaction of vinyltriphenylphonium bromide with the monooximes of α-diketones,[13] pyrolysis of 2-azidopyridine-1-oxides,[14] or dehydrogenation of dihydropyrroles with mecuric oxide.[5] Recently 2,5-dialkylthio derivatives were prepared by deprotonation of *N*-methoxydithiosuccinimide with LDA followed by alkylations.[3]

The reactions of the ring system were also first reported by Knorr. Diethyl 2,5-dimethyl-1-hydroxypyrrole-3,4-dicarboxylate was hydrolyzed and decarboxylated to 2,5-dimethyl-1-hydroxypyrrole.[15] Bromination of dimethyl 1-hydroxypyrrole-3,4-dicarboxylate with bromine in carbon tetrachloride in the presence of iron powder gave 2,5-dibromide. The only other reactions reported for the ring system are nitrosation with nitrous acid[16] and deoxygenation with zinc and acetic acid.[5,8,12,17-19] 1-Hydroxy and 1-acetoxy pyrroles react extremely readily with dienophiles to give the [$_\pi$2+$_\pi$4] cycloadducts.[20]

## Results and Discussion

The requisite 1-methoxypyrrole-2-carboxylic acid **6** was easily prepared from 2-aminopyridine **1** in high yield following the literature procedure.[21] For ease of handling, *O*-methylation was performed with methyl iodide and potassium carbonate in acetone before hydrolysis to acid.[22] Nitrile **3** was hydrolyzed with sodium hydroxide. Phosphoric acid was more effective for acidification compared to strong acids, such as hydrochloric, or sulfuric acid. Thus the synthesis was accomplished in higher than 50% overall yield in five steps. The acid **6** was converted to methyl ester **8** also with methyl iodide and potassium carbonate in acetone.



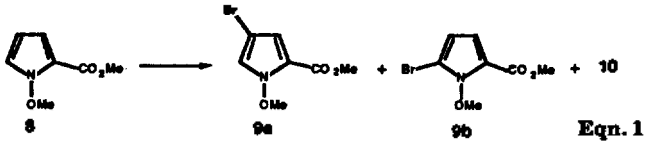
**Scheme 1**

Then monobromination was attempted only to obtain a mixture of mono- and dibrominated compounds, **9a**, **9b** and **10** in a 65:8:20 ratio determined by GC. The position of the bromination for the major isomer **9a** was assigned to 4 on the basis of NMR coupling constants and chemical shifts. Although it was not clear with 60 MHz NMR spectra, it became clearer with 300 MHz NMR spectra (Table 1). The ring protons of **9a** appeared at $\delta$6.73 and $\delta$7.00 with $J$ = 2.30 Hz. For unsubstituted compounds **8**, **7b** and **7d**, the ring protons showed coupling constants of 4.30-4.53 Hz for $J_{3,4}$, 1.98-2.14 Hz for $J_{3,5}$, and 2.86-2.96 Hz for $J_{4,5}$. According to a study for 1-oxypyrrole-2-carbonitrile§, the following coupling constants were observed: $J_{3,4}$ = 3.5-5.5 Hz; $J_{3,5}$ = 1.5-2.0 Hz; $J_{4,5}$ = 2.5-4.0 Hz.[14] In another study for 1-oxy-3-phenylpyrroles, $J_{4,5}$ were in a range of 2.8-3.3 Hz.[13] For methyl 1-methoxy-3-methylpyrrole-2-carboxylate (*vide infra*) **22**, the ring protons showed chemical shifts of $\delta$5.84 and $\delta$ 6.87 with coupling constant of 2.88 Hz.[23] Also chemical shifts of $H_4$ range from $\delta$ 5.51 to $\delta$ 6.43 for widely ranging mono- to tri-substituted 1-oxypyrroles including this

**Table 1.** NMR Data of Selected Compounds for Ring protons[a]

| Compound | $H_3$ | $H_4$ | $H_5$ | $J_{3,4}$ | $J_{3,5}$ | $J_{4,5}$ |
|---|---|---|---|---|---|---|
| **8** | 6.75 | 6.00 | 6.98 | 4.53 | 2.14 | 2.87 |
| **7b** | 6.77 | 6.04 | 6.93 | 4.49 | 2.12 | 2.94 |
| **7d** | 6.12 | 5.96 | 6.83 | 4.30 | 1.98 | 2.96 |
| **9a** | 6.73 | — | 7.00 | — | 2.30 | — |
| **9b** | 6.75 | 6.07 | — | 4.74 | — | — |
| **22** | — | 5.84 | 6.87 | — | — | 2.88 |
| **10** | 6.84 | — | — | — | — | — |

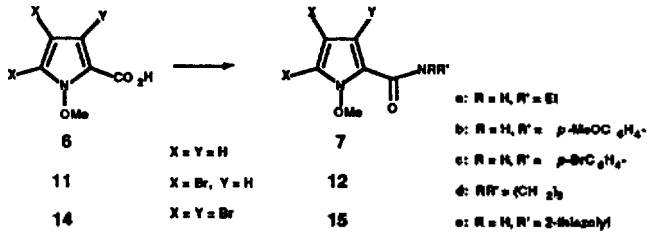
[a]Spectra was taken with Bruker AM-300 NMR spectrometer at 300.133 MHz with computer digital resolution of 0.164–0.188 Hz.




**8** **9a** **9b** **Eqn. 1**

study.[13,14] Thus the coupling constant of 2.30 Hz was attributable to $J_{3,5}$ and chemical shifts for the isomer **9a** were attributable to $H_3$ and $H_5$, respectively. So it is definitive that the substitution position is 4 for the major isomer **9a**. Other evidence came from the minor isomer **9b** which showed chemical shifts of $\delta$ 6.07 and $\delta$ 6.75 with coupling constant of 4.74 Hz which was attributable to $J_{3,4}$. Also a minute amount of methyl 3,4-dibromo-1-methoxypyrrole-2-carboxylate was detected by 300 MHz NMR.

Thus the 1-methoxy group does not seem to play a significant role in directing substitution pattern of preferring 4-position for pyrroles with electron-withdrawing substitutents at 2-position, or 1-sulfonyl derivatives.[24] Since it seemed impractical to control the reaction at monobromination stage, attempt of selective monobromination was not pursued any further.




**6** **7**
**11** **12**
**14** **15**

**Scheme 2**

Dibromination of either nitrile **3** or ester **8** with two equivalents of bromine in acetic gave good yields of 4,5-dibromo derivatives **4** and **10**, respectively. These were easily hydrolyzed to dibromocarboxylic acid **11**. Tribromination was also accomplished easily with three equivalents of bromine to give tribromo derivatives **5** and **13**, respectively. Tribromocarboxylic acid **14** was analogously obtained by hydrolysis of **5** or **13**. The reaction between tribromide **5** and thiourea to introduce sulfur functionality did not proceed.

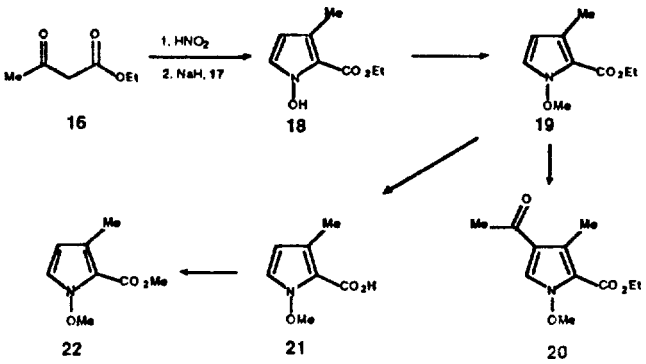
Some derivatives of 4,5-dihalopyrrole-2-carboxamides are known to possess moderate antibacterial activity.[25] Thus the acids **6**, **11**, and **14** were converted to representative amides **7**, **12**, and **14**, respectively (Table 2). Two methods were used for the conversion, *i.e.* through acid chloride or mixed anhydride with ethyl chloroformate. Unfortunately no noticeable activity was observed when their biological activities were tested against microorganisms.

3-Methyl derivatives were synthesized by modification of Schweizer's method using ethyl acetoacetate **6**.[13] Thus ethyl acetoacetate **16** was nitrosated at the methylene followed by cyclization using vinyltriphenylphosphonium bromide **17** and sodium hydride to obtain ethyl ester **19** in 22% overall yield. Methyl ester **22** was prepared in a straightforward manner from ethyl 3-methyl-1-methoxypyrrolecarboxylate **19** by hydrolysis and esterification with methyl iodide and potassium carbonate. Acetylation by Friedel-Crafts reaction using

**Table 2.** Synthesis of 1-Methoxypyrrole-2-carboxamides

| Compound | Method[a] | Yield | mp. (°C) | NMR[b] | Mass[c] |
|---|---|---|---|---|---|
| **7a** | B | 63 | - | 1.17(t, 3H), 3.37(2q, 2H), 3.98(s, 3H), 5.85(dd, 1H), 6.53(dd, 1H), 6.73(b, 2H) | 168(30) |
| **7b** | A | 39 | - | 3.64(s, 3H), 3.97(s, 3H), 5.87(dd, 1H), 6.83(m, 4H), 7.35(d, 2H), 8.39(b, 1H) | 246(57) |
| **12a** | A | 62 | - | 1.20(t, 3H), 3.38(2q, 2H), 4.02(s, 3H), 6.63(s, 1H), 8.48(b, 1H) | 328(6), 326(11), 324(6) |
| **12b** | A | 84 | 118–120 | 3.70(s, 3H), 4.05(s, 3H), 6.68(s, 1H), 6.70(d, 2H), 7.32(d, 2H), 8.23(b, 1H) | *d* |
| **12c** | A | 88 | 129–131 | 4.06(s, 3H), 6.73(s, 1H), 7.35(m, 4H), 8.37(b, 1H) | 456(17), 454(50), 452(52), 450(19) |
| **12d** | A | 70 | 70–72 | 1.61(m, 6H), 3.50(m, 4H), 4.05(s, 3H), 6.15(s, 1H) | 368(5), 366(10), 364(5) |
| **12e** | A | 77 | - | 3.50(b, 2H), 4.09(s, 3H), 7.03(d, 1H), 7.30(s, 1H), 7.40(d, 1H) | 352(56), 350(93), 348(42)[e] |
| **15a** | B | 79 | 124–126 | 1.23(t, 3H), 3.43(2q, 2H), 4.08(s, 3H), 6.47(b, 1H) | 406(10), 404(9) |
| **15b** | A | 78 | 162–164 | 3.69(s, 3H), 4.05(s, 3H), 6.72(d, 1H), 7.54(d, 1H), 9.83(b, 1H) | 486(17), 484(50), 482(45), 480(15) |
| **15c** | A | 85 | 172–174 | 4.06(s, 3H), 7.30(d, 2H), 7.55(d, 2H), 10.5(b, 1H) | 534(33), 532(69), 530(41) |
| **15d** | B | 52 | - | 1.62(b, 6H), 3.44(m, 4H), 4.03(s, 3H) | 448(4), 446(13), 444(11), 442(5) |

[a]See Experimental section for **7c** and **7d**. [b]Coupling constants are not shown. [c]Only prominent molecular masses are shown. [d]Mass spectrum was not taken for this compound. [e]Only masses for ($M^+$ - MeO) were observed.



Scheme 3

acetic anhydride was also directed to 4-position in a 50% yield. Side chain bromination using *N*-bromosuccinimide was met with failure while 2,5-dimethylpyrrole-3,4-dicarboxylate was successfully converted to dibromomethyl derivative.[3]

In summary, 1-methoxypyrrole-2-carboxylic acid derivatives was prepared. Fridel-Crafts bromination occurs first at 4-position and then at 5-position. The structural assignment was based on high-field NMR study. Acylation on 3-methyl derivative was also directed to 4-position. Since deoxygenation of 1-hydroxypyrroles is known to be facile, this work might provide a mean to synthesize substituted pyrroles.[6-9,12,17-19]

## Experimental

IR spectra were obtained using Shimadzu IR-435. NMR spectra were collected using Varian T-60A and Bruker AM-300 with tetramethylsilane as internal standard. Mass spectra were obtained using GSMS GP-1000 (Shimadzu) and melting point measurements were done with Electrothermal digital melting point apparatus. TLC and column chromatography was performed using Merck products. Most of the reagents were commercially available and used as received. Solvents were purified by well-established methods when deemed necessary. For interpretation of NMR data s, d, t, q, m, and b represents singlet, doublet, triplet, quartet, multiplet, and broad singlet, respectively, and chemical shifts are expressed in $\delta$. $M^+$ represents molecular ion in the interpretation of mass spectra.

**1-Methoxypyrrole-2-carbonitrile (3).** A mixture of 1.00 g (9.26 mmol) of 1-hydroxypyrrole-2-carbonitrile[14] **2**, 1.41 g (10.2 mmol) of $K_2CO_3$ and 2.63 g (18.5 mmol) of methyl iodide in 40 m*l* of acetone was heated under reflux for 6 h. The solid residue was filtered off and the filtrate was concentrated *in vacuo*. The residue was extracted with 100 m*l* of ether and the ethereal solution was concentrated *in vacuo* to give 1.13 g (98%) of methoxypyrrole **3** as a yellowish brown oil: IR 2205 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 4.05 (s, 3H), 5.94 (dd, 1H, $J$ = 2.5, 3.7 Hz), 6.53 (dd, 1H, $J$ = 1.2, 3.7 Hz), 6.85 (dd, 1H, $J$ = 1.2, 2.5 Hz); mass spectrum *m/e* (relative intensity) 122 ($M^+$, 100), 107 (21), 91 (20), 80 (42)

**4,5-Dibromo-1-methoxypyrrole-2-carbonitrile (4).** To 500 mg (4.10 mmol) of methoxypyrrole **3** in 20 m*l* of acetic acid was added 1.32 g (8.22 mmol) of bromine at room temperature and the resulting mixture was heated to 60-70 °C for 1 h. The reaction mixture was evaporated *in vacuo* to driness and the residue was washed with 30 m*l* of ether-*n*-hexane (1:5) to give 880 mg (77%) of dibromopyrrole **4** as light yellow crystals: mp. 84-86 °C; IR 2220, 1420 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 4.07 (s, 3H), 6.57 (s, 1H); mass spectrum *m/e* (relative intensity) 282 ($M^+$, 35), 280 ($M^+$, 64), 278 ($M^+$, 33), 251 (28), 249 (54), 247 (27), 201 (18), 200 (16), 199 (20), 198 (17), 174 (26), 173 (26), 172 (29), 171 (28), 144 (91), 142 (71), 141 (40), 67 (68), 63 (100).

**3,4,5-Tribromo-1-methoxypyrrole-2-carbonitrile 5.** was similarly prepared with three equivalents of bromine in 56% yield as light yellow crystals: mp 66-68 °C; IR 2220, 1500, 1420 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 4.09 (s, 3H).

**1-Methoxypyrrole-2-carboxylic Acid (6).** A solution of 1.15 g (9.43 mmol) of methoxypyrrole **3** in 13 m*l* of 40% NaOH and 20 m*l* of ethanol was heated overnight under reflux and concentrated *in vacuo*. The residue was dissolved in 10 m*l* of water and pH of the resulting solution was adjusted to 3 by addition of 50% phosphoric acid, and concentrated in vacuo. The residue was extrated with two 100-mL portions of chloroform and the combined organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 1.10 g (83%) of acid **6** as brown solid: mp. 82-84 °C; IR 2600, 1690 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 4.11 (s, 3H), 6.04 (dd, 1H, $J$ = 3.5, 4.5 Hz), 6.91 (dd, 1H, $J$ = 2.0, 4.5 Hz), 7.02 (dd, 1H, $J$ = 2.0, 3.5 Hz).

**Methyl 1-Methoxypyrrole-2-carboxylate (8).** A mixture of 1.00 g (7.09 mmol) of acid **6**, 2.94 g (21.3 mmol) of $K_2CO_3$ and 4.03 g (28.4 mmol) of methyl iodide in 40 m*l* of acetone was heated overnight under reflux. Acetone was removed *in vacuo* and the residue was extracted with two 100-m*l* portions of ether. The combined ethereal layer was condensed *in vacuo* to give 1.08 g (98%) of ester **8**: mp. 42-43 °C; IR 1710 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 3.77 (s, 3H), 4.02 (s, 3H) 5.89 (dd, 1H, $J$ = 2.8, 4.2 Hz), 6.65 (dd, 1H, $J$ = 2.2, 4.2 Hz), 6.77 (dd, 1H, $J$ = 2.2, 2.8 Hz); mass spectrum *m/e* (relative intensity) 155 ($M^+$, 51), 124 (56), 96 (29), 94 (100).

**Monobromination of Methyl Ester 8 (9a, 9b).** To 1.00 g (6.45 mmol) of ester **8** in 30 m*l* of acetic acid was added dropwise 1.14 g (7.10 mmol) of bromine at room temperature and the resulting solution was stirred at 50-60 °C for 1 h. The solvent was removed under reduced pressure and the residue was analyzed by gas chromatography so that **9a**:**9b**:**10** = 65:8:20, and chromatographed over silica gel to give pure sample of methyl ester **9a**: IR 1705 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 3.82 (s, 3H), 4.07 (s, 3H), 6.75 (d, 1H, $J$ = 2.5 Hz), 6.99 (d, 1H, $J$ = 2.5 Hz); mass spectrum *m/e* (relative intensity) 235 ($M^+$, 34), 233 ($M^+$, 37), 204 (14), 202 (12), 174 (23), 173 (34), 172 (30), 171 (37), 170 (28), 162 (23), 149 (24), 134 (27), 132 (23), 103 (17), 42 (100).

**Methyl 4,5-Dibromo-1-methoxypyrrole-2-carboxylate (10).** To 4.00 g (26.0 mmol) of ester **8** in 30 m*l* of acetic acid was added dropwise 8.30 g (52.0 mmol) of bromine at room temperature and the resulting solution was stirred at 70-80 °C for 1 h. The solvent was removed under reduced pressure and the residue was washed with 50 m*l* of *n*-hexane to give 6.90 g (85%) of ester **10** as dark brown syrup: IR 1720 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 3.79 (s, 3H), 4.06 (s, 3H), 6.77 (s, 1H); mass spectrum *m/e* (relative intensity) 315 ($M^+$, 41), 313 ($M^+$, 93), 311 ($M^+$, 45), 253 (18), 251 (32), 249 (17), 226 (25), 212 (30), 206 (55), 204 (50), 144 (37), 66 (100).

**Methyl 3,4,5-Tribromo-1-methoxypyrrole-2-carboxylate (11).** was similarly prepared with three equiva-

lents of bromine in 89% yield as light yellow crystals: mp. 110–111 °C; IR 1710, 1467, 1430 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 3.87 (s, 3H), 4.12 (s, 3H); mass spectrum *m/e* (relative intensity) 393 ($M^+$, 12), 391 ($M^+$, 12), 315 (22), 313 (44), 311 (16), 293 (13), 291 (10), 286 (16), 284 (20), 282 (13), 253 (20), 251 (37), 249 (22), 206 (29), 204 (33), 59 (100).

**4,5-Dibromo-1-methoxypyrrole-2-carboxylic Acid (13).** To 4.00 g (12.8 mmol) of ester **10** and 2.15 g (51.2 mmol) of sodium hydroxide in 50 m*l* of 95% ethanol was stirred overnight at room temperature, and concentrated *in vacuo*. The residue was triturated with ether and dissolved in 60 m*l* of water and 200 m*l* of chloroform. The pH of the mixture was adjusted to 3 with dilute hydrochloric acid and the organic layer was separated. The aqueous layer was extracted with 100 m*l* of chloroform and the combined organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give 2.95 g (77%) of the acid **13** as pale yellow solid: mp. 170–171 °C; IR 2900, 1660 $cm^{-1}$; NMR (DMSO-$d_6$) $\delta$ 3.97 (s, 3H), 6.78 (s, 1H,) 7.72 (b, 1H); mass spectrum *m/e* (relative intensity) 301 ($M^+$, 46), 299 ($M^+$, 100), 297 ($M^+$, 51), 253 (25), 251 (43), 249 (21), 221 (12), 213 (17), 212 (34), 211 (24), 192 (23), 160 (59), 159 (58), 158 (54), 157 (55).

**1-Methoxy-3,4,5-tribromo-2-carboxylic acid (14).** was similarly prepared in 77% yield as straw colored solid: mp 212–214 °C (dec.); IR 2900, 1660, 1497, 1425 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 4.07 (s, 3H), 6.57 (s, 1H); mass spectrum *m/e* (relative intensity) 381 ($M^+$, 33), 379 ($M^+$, 93), 377 ($M^+$, 100), 375 ($M^+$, 39), 240 (43), 239 (36), 238 (91), 237 (75), 236 (47), 235 (38).

**4′-Bromo-1-methoxypyrrole-2-carboxanilide (7c, Method A).** To the acid chloride [prepared from 1.00 g (6.27 mmol) of acid **6** and thionyl chloride] in 20 m*l* of pyridine was added 1.13 g (6.58 mmol) of 4-bromoaniline and the resulting solution was stirred for 4 h at room temperature. Excess pyridine was removed under reduced pressure and the residue was dissolved in 50 m*l* of chloroform. The solution was washed with 30 m*l* of 3 *N* hydrochloric acid, 20 m*l* of saturated sodium bicarbonate, and 100 m*l* of water, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed over silica gel to give 1.30 g (66%) of the anilide **7c** as a syrup: IR 1750, 1487 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 3.98 (s, 3H), 5.88 (dd, $J$ = 3, 4.5 Hz, 1H), 6.63 (dd, $J$ = 2, 4.5 Hz, 1H), 6.82 (dd, $J$ = 2, 3 Hz, 1H), 7.30 (m, 4H), 8.48 (b, 1H); mass spectrum *m/e* (relative intensity) 296 ($M^+$, 11), 294 ($M^+$, 12), 124 (100), 119 (31), 117 (31), 94 (11).

**1-Methoxy-*N*-piperidylpyrrole-2-carboxamide (7d, Method B).** To a mixture of 1.50 g (10.6 mmol) of acid **6** and 1.13 g (11.2 mmol) of triethylamine in 30 m*l* of chloroform was added 1.22 g (11.2 mmol) of ethyl chloroformate at −4 °C and the resulting mixture was stirred for 1 h with cooling in an ice bath followed by addition of 1.09 g (12.8 mmol) of piperidine. The mixture was stirred for 30 min at 0 °C and then for 1 h at room temperature. Solvent was removed under reduced pressure and the residue was dissolved in 100 m*l* of ethyl acetate–ether (1:1). The solution was washed with 30 m*l* of 3*N* hydrochloric acid, 50 m*l* of saturated sodium bicarbonate, and 100 m*l* of water, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was chromatographed over silica gel to give 0.85 g (39%) of the amide **7d** as a syrup: IR 1620, 1525, 1430 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.62 (m, 6H), 3.53 (m, 4H), 4.03 (s, 3H), 5.93 (m, 2H), 6.70 (b, 1H); mass spectrum *m/e* (relative intensity) 208 ($M^+$, 15), 177 (16), 124 (35), 94 (22), 84 (100). (Fair amount of piperidinyl carbamate was also formed).

**Ethyl 1-Hydroxy-3-methyl-2-pyrrolecarboxylate (18).** To a mixture of 1.60 g (10.0 mmol) of ethyl $\alpha$-isonitrosoacetoacetate[13] and 0.48 g (55%, 11.0 mmol) of sodium hydride in 30 m*l* of DMF was added portion wise 3.72 g (10.0 mmol) of vinyltriphenylphosphonium bromide **17** over a 5-min period. The resulting mixture was stirred for 1 h at room temperature, poured into 50 m*l* of water and extracted with two 200-m*l* portions of ether. The combined organic layer was washed with water, concentrated *in vacuo* and the residue was chromatographed over silica gel to give 0.57 g (34%) of hydroxypyrrole **18** as yellowish oil: IR 3250, 1660, 1550, 1420 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.33 (t, 3H, $J$ = 7.0 Hz), 2.20 (s, 3H), 4.28 (q, 2H, $J$ = 7.0 Hz), 5.70 (d, 1H, $J$ = 2.0 Hz), 6.78 (d, 1H, $J$ = 2.0 Hz), 11.60 (s, 1H).

**Ethyl 1-Methoxy-3-methyl-2-pyrrolecarboxylate (19).** To 500 mg (3.13 mmol) of hydroxypyrrole **18** and 0.48 g (3.46 mmol) of potassium carbonate in 30 m*l* of acetone was added 1.79 g (12.6 mmol) of methyl iodide at room temperature and the resulting mixture was stirred overnight at reflux. The solvent was removed *in vacuo* and the residue was extracted with 50 m*l* of ether. The extract was concentrated *in vacuo* to give 0.56 g (95%) of ester **19** as a light yellow oil: NMR ($CDCl_3$) $\delta$ 1.33 (t, 3H, $J$ = 7.0 Hz), 2.27 (s, 3H), 3.96 (s, 3H), 4.24 (q, 2H, $J$ = 7.0 Hz), 5.72 (d, 1H, $J$ = 3.0 Hz), 6.75 (d, 1H, $J$ = 3.0 Hz).

**Ethyl 4-Acetyl-1-methoxy-3-methyl-2-pyrrolecarboxylate (20).** To 540 mg (3.12 mmol) of ester **19** and 956 mg (9.36 mmol) of acetic anhydride in 20 m*l* of 1,2-dichloroethane was added 2.50 g (18.7 mmol) of aluminium chloride over a 20-min period and the mixture was stirred at room temperature for 1 h. To the resulting mixture was added ice-water and the organic layer was separated. The aqueous layer was extracted with 100 m*l* of ether and the combined organic layer was washed with saturated sodium bicarbonate and water, dried, filtered and concentrated *in vacuo*. The residue was chromatographed over silica gel to give 0.34 g (50%) of the acetylpyrrole **20** as yellow crystals: mp. 67–69 °C; IR 1720, 1430, 1403 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.40 (t, 3H, $J$ = 7.0 Hz), 2.31 (s, 3H), 2.52 (s, 3H), 4.01 (s, 3H), 4.25 (q, 2H, $J$ = 7.0 Hz), 7.27 (s, 1H).

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# Electric Field Gradients at Copper Sites in the High $T_c$ Superconductor $YBa_2Cu_3O_{7-x}$

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Quadrupole coupling constants of $^{63}Cu$ in the high $T_c$ superconductor $YBa_2Cu_3O_{7-x}$, as determined by NQR or NMR studies, are compared with the values for representative Cu(II) complexes determined by analyzing the forbidden lines in their EPR spectra. It is shown that the two NQR lines at 22 and 31 MHz correpsond to the quadrupole coupling constants of a square planar Cu(II) complex and a square pyramidal Cu(II) complex, respectively. This result is in agreement with the assignment of these lines to Cu(1) and Cu(2) sites in YBCO based on the NMR spectra of oriented single crystals.

## Introduction

Various experimental techniques have been used to study the high $T_c$ superconductor $YBa_2Cu_3O_{7-x}$(YBCO) first prepared by Wu *et al.*[1] The nuclear quadrupole resonance(NQR) and nuclear magnetic resonance(NMR), which can give information on the electric field gradient(efg) at the nucleus, might be useful in clarifying the electronic structure at the copper sites of YBCO.

The NQR spectra of $^{63}Cu$ and $^{65}Cu$ in YBCO have been reported by several authors.[2-4] $^{63}Cu$ shows two distinct NQR lines at frequencies of approximately 22 and 31 MHz. These lines may be attributed to the two inequivalent copper sites, namely the Cu(1) site in one-dimensional CuO chains running along the *b* axis and the Cu(2) site in two-dimensional CuO sheets in the *a-b* plane; see Figure 1.[5] Earlier papers assigned the 22 and 31 MHz lines to the Cu(2) and Cu(1) sites, respectively.[3,4] However, recently Pennington *et al.* assigned the 22 MHz line to the Cu(1) site and the 31 MHz line to the Cu(2) site on the basis of their NMR studies on the oriented single crystals of YBCO.[6] An independent NMR study of Shimizu *et al.* on a highly oriented powder sample gave the same result.[7]

Twenty years ago we determined the quadrupole coupl-

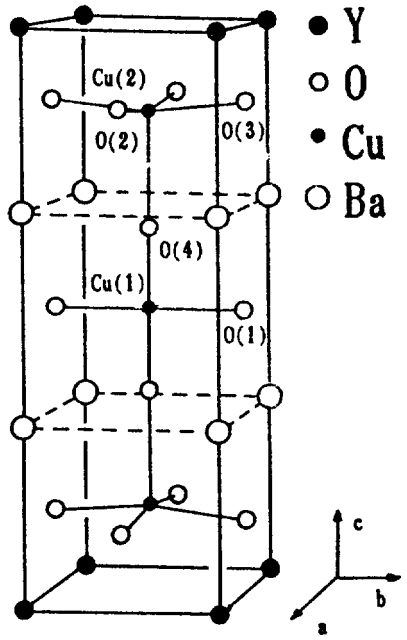


**Figure 1.** Unit cell of the $YBa_2Cu_3O_7$ crystal structure from Ref. 5.