# Pyrrole Studies. Part 35.[1] Aerial Oxidation of 4-Substituted 3-Amino-2,5-dimethylpyrroles. An *X*-Ray Crystallographic and Spectroscopic Study of the Oxidation Products

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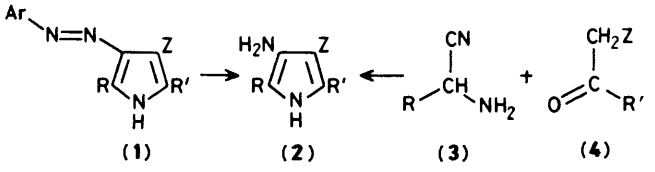
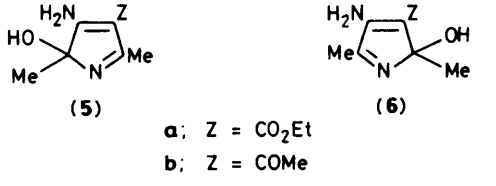
The attempted preparation of ethyl 3-amino-2,5-dimethylpyrrole-4-carboxylate and 4-acetyl-3-amino-2,5-dimethylpyrrole by standard ring synthesis procedures resulted in the exclusive isolation of 2-hydroxy-2*H*-pyrroles, as indicated by $^1$H and $^{13}$C n.m.r. spectral data. The structure of ethyl 3-amino-2-hydroxy-2,5-dimethyl-2*H*-pyrrole-4-carboxylate (**5a**) has been confirmed by single crystal *X*-ray crystallographic analysis and circumstantial evidence that the 2-hydroxy-2*H*-pyrroles (**5a, b**) arise from the initially formed 1*H*-pyrroles (**2**; R = R′ = Me, Z = $CO_2Et$ or COMe) is provided by the observation that ethyl 3-amino-5-methyl-2-phenylpyrrole-4-carboxylate (**7**) undergoes aerial oxidation to give ethyl 3-amino-2-hydroxy-5-methyl-2-phenyl-2*H*-pyrrole-4-carboxylate (**8**).

As part of a wider study of the chemical reactivity of β-amino-pyrroles,[2] we required a series of 4-substituted 3-amino-2,5-dimethylpyrroles (**2**; R = R′ = Me). β-Aminopyrroles (**2**) are generally obtained by reduction of the corresponding nitroso, nitro, or arylazo derivatives (**1**) or by ring synthesis from the appropriately substituted 2-aminoacetonitrile (**3**) and an activated methylene ketone (**4**).[3]




Although there are reports of the ring synthesis of 4-substituted 3-amino-2-aryl-5-methylpyrroles in moderate yield,[4] our studies have shown that the method is not entirely satisfactory and the procedure fails completely for the synthesis of the 2,5-dimethyl derivatives (**2**; R = R′ = Me, Z = $CO_2Et$ or COMe). The products of the reaction of 2-aminopropionitrile (**3**; R = Me) with ethyl 3-oxobutanoate (**4**; R′ = Me, Z = $CO_2Et$) and with pentane-2,4-dione (**4**; R′ = Me, Z = COMe) were closely similar in structure, as shown by their $^{13}$C n.m.r. spectral data (Table 1), but their chemical and physical properties were totally at variance with those of other 3-substituted 2,5-dimethylpyrrol-4-yl esters and ketones.[5] Elemental analysis clearly indicated the formation of simple oxidation products and the $^1$H and $^{13}$C n.m.r. and i.r. spectral data, in particular the $^1$H and $^{13}$C n.m.r. signals at *ca.* 1.2 and 2.2 p.p.m., and between 15 and 20 p.p.m. and at *ca.* 25 p.p.m. attributable to the two α-methyl groups and the $^{13}$C n.m.r. signal near 94 p.p.m. characteristic of the C(2) atom, were indicative of a 2-hydroxy-2*H*-pyrrole system.[6] Although these data did not distinguish unequivocally between the two isomers (**5**) and (**6**), the 3-amino-2-hydroxy-2*H*-pyrrole structure (**5a**) was established by a single crystal *X*-ray analysis (Figure) of the oxidised derivative of (**2**; R = R′ = Me, Z = $CO_2Et$).



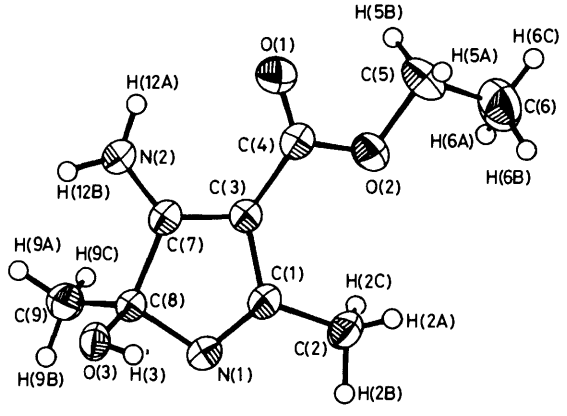



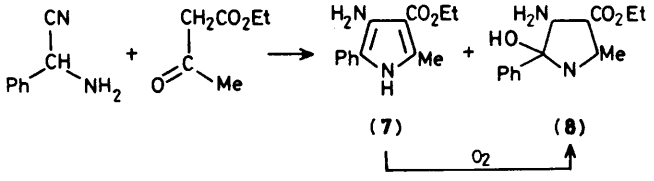

**Figure.** The molecular structure of (**5a**). The orientation of the planar $NH_2$ group (Σ angles = 359.9°) and the H(12a)···O(1) and H(12b)···O(3) distances of 2.35 and 2.77 Å, respectively, strongly suggest H-bonding interactions

It is of interest that the formation of this oxidation product is analogous to the aerial oxidation of 3-hydroxypyrroles, which has been reported to yield 2-hydroxy-2*H*-pyrrol-3-ones.[7] It is reasonable to postulate that the 3-amino-2-hydroxy-2*H*-pyrroles (**5a, b**) are produced *via* the oxidation of the initially formed 3-aminopyrroles. Some evidence for this conclusion comes from our observation that the ring synthesis of ethyl 3-amino-5-methyl-2-phenylpyrrole-4-carboxylate (**7**), utilising a procedure based upon that described in the literature,[4] and *via* the reductive cleavage of ethyl 5-methyl-3-(4-nitro-

**Table 1.** $^{13}C$ N.m.r. chemical shifts of 3-substituted 2,5-dimethylpyrrole-4-carboxylic esters and ketones [5] and the related 2-hydroxy-2*H*-pyrroles (**5a, b**)

| Compound | C-2 | C-3 | C-4 | C-5 |
|---|---|---|---|---|
| 3-Substituted 2,5-dimethylpyrrole-4-carboxylic esters | 122—136 | 63—122 | 107—110 | 133—137 |
| (**5a**) | 93.3 | 180.5 | 95.7 | 169.0 |
| 3-Substituted 4-acetyl-2,5-dimethylpyrroles | 122—134 | 62—122 | 117—122 | 131—135 |
| (**5b**) | 94.6 | 182.0 | 105.5 | 168.9 |

phenylazo)-2-phenylpyrrole-4-carboxylate (**1**; R = Ph, R′ = Me, Ar = 4-$NO_2C_6H_4$, Z = $CO_2Et$),[8] produced both (**7**) and the 2-hydroxy-2*H*-pyrrole (**8**). In addition, it was noted that a solid pure sample of (**7**) became contaminated with the oxidised compound (**8**), as shown by t.l.c. analysis, after exposure to air for *ca.* 1 year and, when stirred in an open flask at room temperature, a dilute ethanolic solution of (**7**) was completely converted into (**8**) within 5 days.




## Experimental

I.r. spectra were measured for Nujol mulls or for solutions in $CHBr_3$ using a Perkin-Elmer 297 i.r. spectrometer. $^1H$ and $^{13}C$ N.m.r. spectra were measured at 100 and 25 MHz, respectively, for *ca.* 40% solutions in $(CD_3)_2SO$ using a JEOL JMN-100FT n.m.r. spectrometer. All chemical shifts are recorded downfield of the internal standard ($Me_4Si$).

*General Procedure for the Synthesis of 2-Hydroxy-2H-pyrroles* (**5**).—2-Aminopropiononitrile (1.40 g, 0.02 mol), obtained in the Strecker reaction of acetaldehyde with ammonium chloride and potassium cyanide, and the appropriate 1,3-dicarbonyl compound (0.02 mol) in dry benzene (100 ml) were heated under reflux in the presence of toluene-*p*-sulphonic acid (0.05 g) for 6 h with azeotropic removal of water. Solvent was distilled off under reduced pressure and the residual oil, dissolved in ethanol (50 ml), was added dropwise with stirring to ethanolic sodium ethoxide [prepared from sodium (5.0 g, 0.217 mol) in ethanol (100 ml)] at 0 °C. The mixture was allowed to come to room temperature after which it was stirred for 6 h and then poured onto crushed ice (500 g). The crude 2*H*-pyrroles were either filtered off or extracted from the aqueous mixture with dichloromethane (6 × 200 ml).

*Ethyl 3-amino-2-hydroxy-2,5-dimethyl-2H-pyrrole-4-carboxylate* (**5a**) (1.98 g, 50%), m.p. 187 °C (Found: C, 54.5; H, 7.1; N, 14.05. $C_9H_{14}N_2O_3$ requires C, 54.5; H, 7.1; N, 14.1%); $\nu_{max.}(CHBr_3)$ 3 370, 3 230, 1 720, 1 705, and 1 593 $cm^{-1}$; $\delta_H$ 1.22 (t, 3 H), 1.26 (s, 3 H), 2.12 (s, 3 H), 4.12 (q, 2 H), 5.93 (s, 1 H), 7.48 (s, 1 H), and 8.22 (br s, 1 H); $\delta_C$ 14.4 (q), 19.7 (q), 25.2 (q), 58.1 (t), 93.5 (s), 95.7 (s), 164.2 (s), 169.0 (s), and 180.5 (s).

*4-Acetyl-3-amino-2-hydroxy-2,5-dimethyl-2H-pyrrole* (**5b**) (1.68 g, 50%), m.p. 165 °C (Found: C, 57.4; H, 7.1; N, 16.5. $C_8H_{12}N_2O_2$ requires C, 57.1; H, 7.2; N, 16.7%); $\nu_{max.}(CHBr_3)$ 3 480, 3 335, 1 690, 1 600(infl.), and 1 530 $cm^{-1}$; $\delta_H$ 1.27 (s, 3 H), 2.23 (s, 6 H), 5.95 (br s, 1 H), and 8.74 (br s, 2 H); $\delta_C$ 20.8 (q), 25.2 (q), 29.2 (q), 94.6 (s), 105.5 (s), 168.9 (s), 182.0 (s), and 191.6 (s).

**Table 2.** Fractional atomic co-ordinates ( × $10^4$)

| Atom | *x/a* | *y/b* | *z/c* |
|---|---|---|---|
| N(1) | −157(1) | −366(0.5) | 1 440(1) |
| C(1) | −358(1) | −1 686(2) | 1 307(1) |
| C(2) | −1 400(1) | −2 177(2) | 921(1) |
| C(3) | 515(1) | −2 587(2) | 1 578(1) |
| C(4) | 591(1) | −4 094(2) | 1 573(1) |
| O(1) | 1 361(1) | −4 724(1) | 1 894(1) |
| O(2) | −267(1) | −4 735(1) | 1 163(1) |
| C(5) | −239(2) | −6 250(2) | 1 066(3) |
| C(6) | −1 251(2) | −6 727(3) | 582(3) |
| C(7) | 1 314(1) | −1 705(2) | 1 909(1) |
| N(2) | 2 270(1) | −1 983(2) | 2 256(1) |
| C(8) | 924(1) | −204(2) | 1 761(1) |
| C(9) | 1 261(2) | 452(2) | 1 038(1) |
| O(3) | 1 259(1) | 664(1) | 2 516(1) |

*Ethyl 3-Amino-5-methyl-2-phenylpyrrole-4-carboxylate* (**7**) *and Ethyl 3-Amino-2-hydroxy-5-methyl-2-phenyl-2H-pyrrole-4-carboxylate* (**8**).—*Method A.* Using a procedure analogous to that described in the literature [4] for the synthesis of 3-amino-2-aryl-5-methylpyrrole-4-carboxylic esters, 2-amino-2-phenylacetonitrile (2.64 g, 0.02 mol) and ethyl 3-oxobutanoate (2.60 g, 0.02 mol) were heated under azeotropic conditions. After treatment of the intermediate enamino ester with base, the reaction mixture was worked up by extraction with dichloromethane. The organic extracts were evaporated and *ethyl 3-amino-2-hydroxy-5-methyl-2-phenyl-2H-pyrrole-4-carboxylate* (0.78 g, 15%), m.p. 173 °C (Found: C, 64.5; H, 6.15; N, 10.8 $C_{14}H_{16}N_2O_3$ requires C, 64.6; H, 6.15; N, 10.8%); $\nu_{max.}$(Nujol) 3 410, 3 310, 3 250, 1 670, 1 635, and 1 575 $cm^{-1}$; $\delta_H$ 1.16 (t, 3 H), 2.24 (s, 3 H), 4.08 (q, 2 H), 6.77 (br s, 1 H), 7.31 (s, 5 H), 7.51 (br s, 1 H), and 7.97 (br s, 1 H); $\delta_C$ 14.4 (q), 19.8 (q), 58.4 (t), 94.4 (s), 98.0 (s), 125.4 (d), 127.6 (d), 127.9 (d), 141.0 (s), 164.4 (s), 172.1 (s), and 181.0 (s), crystallised from the residual oil. Purification of the residual oil by column chromatography from Merck silica gel, using dichloromethane as the eluant, gave *ethyl 3-amino-5-methyl-2-phenylpyrrole-4-carboxylate* (2.0 g, 41%), m.p. 105 °C (Found: C, 68.9; H, 6.65; N, 11.4. $C_{14}H_{16}N_2O_2$ requires C, 68.8; H, 6.6; N, 11.4%); $\nu_{max.}$(Nujol) 3 450, 3 350, 3 290, and 1 640 $cm^{-1}$; $\delta_H$ 1.28 (t, 3 H), 2.41 (s, 3 H), 4.19 (q, 2 H), 4.83 (br s, 2 H), 6.95—7.60 (m, 5 H), and 10.91 (br s, 1 H); $\delta_C$ 13.8 (q), 14.4 (q), 58.4 (t), 101.8 (s), 110.8 (s), 123.0 (d), 123.4 (d), 128.5 (d), 132.8 (s), 133.0 (s), 133.5 (s) and 165.8 (s). Further elution with ethyl acetate–methanol (9:1) gave an additional yield of the 2-hydroxy-2*H*-pyrrole (0.25 g, 10%).

*Method B.* Aqueous sodium nitrite (30% w/v; 3.7 ml) was added dropwise with stirring at 0 °C to 4-nitroaniline (1.38 g, 0.01 mol) in hydrochloric acid (6M; 6.5 ml), followed by ethyl 2-methyl-5-phenylpyrrole-3-carboxylate [9] (2.29 g, 0.01 mol) and sodium acetate (2.5 g) in acetic acid (50 ml). The mixture was stirred at 0 °C for 1 h and then poured onto crushed ice (400 g). The crude product was collected, washed with aqueous ethanol (10% v/v, 20 ml), and recrystallised from ethanol to give *ethyl 5-methyl-3-(4-nitrophenylazo)-2-phenylpyrrole-4-carboxylate* (3.78 g, 100%), m.p. 203 °C (Found: C, 63.7; H, 4.8; N, 14.75. $C_{20}H_{18}N_4O_4$ requires C, 63.5; H, 4.8; N, 14.8%); $\nu_{max.}$(Nujol) 3 340 and 1 730 $cm^{-1}$; $\delta_H(CDCl_3)$ 1.31 (s, 3 H), 2.45 (s, 3 H), 4.33 (q, 2 H), 7.26—8.33 (m, 9 H), and 8.99 (br s, 1 H). The nitrophenylazopyrrole (3.78 g, 0.01 mol) was added slowly with stirring in small portions to $SnCl_2 \cdot 2H_2O$ (20 g) in acetic acid (20 ml) at 80 °C. The mixture was stirred until it became colourless and it was then cooled to room temperature and poured

**Table 3.** Bond lengths (Å) (standard deviations in parentheses)

| | | | |
|---|---|---|---|
| C(1)–N(1) | 1.294(3) | C(8)–N(1) | 1.467(3) |
| C(2)–C(1) | 1.487(3) | C(3)–C(1) | 1.459(3) |
| C(4)–C(3) | 1.442(4) | C(7)–C(3) | 1.377(3) |
| O(1)–C(4) | 1.210(3) | O(2)–C(4) | 1.333(3) |
| C(5)–O(2) | 1.456(3) | C(6)–C(5) | 1.469(5) |
| N(2)–C(7) | 1.321(3) | C(8)–C(7) | 1.526(4) |
| C(9)–C(8) | 1.519(5) | O(3)–C(8) | 1.406(3) |

**Table 4.** Bond angles (°) (standard deviations in parentheses)

| | | | |
|---|---|---|---|
| C(8)–N(1)–C(1) | 108.1(2) | C(2)–C(1)–N(1) | 120.8(2) |
| C(3)–C(1)–N(1) | 113.8(2) | C(3)–C(1)–C(2) | 125.3(3) |
| C(4)–C(3)–C(1) | 130.2(1) | C(7)–C(3)–C(1) | 105.9(2) |
| C(7)–C(3)–C(4) | 123.9(2) | O(1)–C(4)–C(3) | 123.6(3) |
| O(2)–C(4)–C(3) | 113.7(2) | O(2)–C(4)–O(1) | 122.7(3) |
| C(5)–O(2)–C(4) | 117.1(3) | C(6)–C(5)–O(2) | 107.9(3) |
| N(2)–C(7)–C(3) | 130.6(2) | C(8)–C(7)–C(3) | 107.5(2) |
| C(8)–C(7)–N(2) | 121.9(2) | C(7)–C(8)–N(1) | 104.2(2) |
| C(9)–C(8)–N(1) | 110.0(2) | C(9)–C(8)–C(7) | 108.2(2) |
| O(3)–C(8)–N(1) | 112.4(2) | O(3)–C(8)–C(7) | 114.6(2) |
| O(3)–C(8)–C(9) | 107.3(2) | | |

into aqueous potassium hydroxide (20% w/v, 200 ml) with stirring. After 30 min the aqueous mixture was extracted with dichloromethane (5 × 50 ml). The organic extracts were dried ($Na_2SO_4$) and evaporated under reduced pressure. Chromatographic separation of the crude product gave ethyl 3-amino-5-methyl-2-phenylpyrrole-4-carboxylate (2.05 g, 84%), m.p. 105 °C and ethyl 3-amino-2-hydroxy-5-methyl-2-phenyl-2*H*-pyrrole-4-carboxylate (0.26 g, 10%), m.p. 173 °C.

*X-Ray Structure Determination.*—Crystals of (**5a**) were obtained from dichloromethane. All *X*-ray measurements were made using a Nonius CAD4 diffractometer and Ni-filtered Cu-$K_\alpha$ radiation ($\lambda$ = 1.5418 Å) followed previously described procedures.[10] The structure was solved *via* direct methods (SHELXS84)[11] developed by difference syntheses (including all H atoms) and refined by full-matrix least squares (SHELX-76).[12]

*Crystal data.* $C_9H_{14}N_2O_3$, $M$ = 198.22, monoclinic, $a$ = 14.294(3), $b$ = 9.544(2), $c$ = 15.884(6) Å, $\beta$ = 109.23(2)°, $U$ = 2 046.00 Å$^3$, space group $C2/c$, $Z$ = 8, $D_c$ = 1.29 g cm$^{-3}$, $\mu$(Cu-$K_\alpha$) = 7.73 cm$^{-1}$, $F$(000) = 848.

*Data collection.* $\omega/2\theta$ scan, $\omega = 0.8 + 0.35\tan\theta$, $2 \leqslant \theta \leqslant 70°$, $\omega$ scan speed 1.44—6.70° min$^{-1}$, $\sigma(I)/I$ required 0.03 but $t_{max.}$ = 60 s. 1 827 Reflections measured, 1 558 unique, 1 377 observed [$I > 1.5\sigma(I)$].

*Structure refinement.* C, O, and N atoms anisotropic, H atoms isotropic, 182 parameters, $R$ = 0.0394, $R_w$ = 0.0534, weights = $[\sigma^2(F_o) + 0.0002F_o^2]^{-1}$. Final atomic positional parameters are given in Table 2; bond lengths and angles in Tables 3 and 4. Thermal parameters, tables of bond lengths and angles for the H atoms, and non-bonded distances are available on request from the Cambridge Crystallographic Data Centre.*

* For details see Instructions for Authors (1987), *J. Chem. Soc., Perkin Trans. 1*, 1987, Issue 1.

## Acknowledgements

We than the S.E.R.C. for provision of the *X*-ray systems and for financial support.

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*Received 25th July* 1986; *Paper* 6/1514