## Synthesis and Reactions of Some Acetal Derivatives of Formylpyrroles

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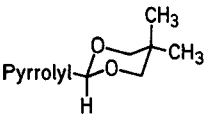
Formylpyrroles are of great utility as intermediates in synthetic approaches to the pyrrole pigments[1]. Owing to the diversity of reaction conditions employed, formyl groups must be protected against premature reaction by masking or else be inserted at a late stage in the synthetic sequence; this latter alternative can be troublesome. The traditional formyl-protected group in pyrrole chemistry is the dicyanovinyl function[2], but this suffers from its vulnerability towards hydrogenation, its cleavage only under strongly alkaline conditions, and its strongly electron-withdrawing characteristics which tend to decrease the nucleophilicity of the protected pyrrole[3]. In this communication, we report the results of an investigation into the use of the acetal from neopentanediol (2,2-dimethylpropan-1,3-diol) for formyl protection.

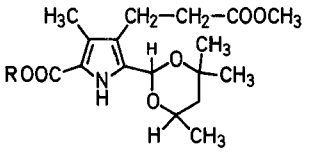
The acetals commonly used in organic chemistry, namely those from methanol or ethyleneglycol, are unsuitable in the pyrrole series[3,4] mainly because of their lability. We have therefore concentrated on the acetals **2** from neopentanediol, which should be more stable than those from ethyleneglycol owing to formation of the six-membered 1,3-dioxane ring[5]. Clezy et al.[4] chose the acetal from 2-methylpentan-2,4-diol; we discarded this alternative because use of an unsymmetrical diol introduces a chiral centre which may give rise to unnecessary difficulties.

The formylpyrrole **1a** and neopentanediol were refluxed under a Dean-Stark head in benzene containing a catalytic amount of toluene-*p*-sulphonic acid during 2 hours. After work-up and chromatography, a 68% yield of the required acetal **2a** was obtained; recycling of the recovered starting material **1a** gave an overall yield of 96% of highly crystalline material.

The $^1$H-N.M.R. spectrum of **2a** was consistent with the proposed structure, the geminal dimethyl appearing as two high-field singlets at $\delta = 0.76$ and 1.23 ppm which could not be equilibrated at high temperature ($\leq 100°$). This pattern is predicted if the 1,3-dioxane ring is in the chair conformation **3** with the bulky pyrrole substituent acting as a conformational lock to prevent ring flipping, and on this basis the high-field resonance is assigned to the axial methyl[6]. The dioxane methylene groups appear as an AB quartet with $J_{AB} = 11$ Hz.



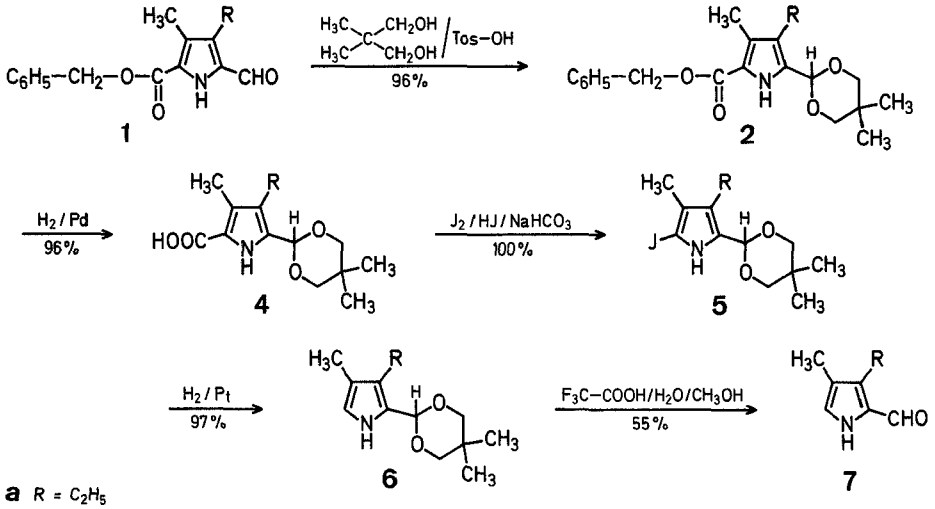

**3**




**8** R = $C_6H_5$–$CH_2$–
**9** R = H

The versatility of the protected pyrrole is demonstrated by the sequence of reactions shown in the Scheme, wherein the 2-unsubstituted 5-formylpyrrole **7a** is prepared. Pyrrole **7a**, an important building block in syntheses of some pyrrole pigments, was originally prepared by Fischer[8], but the best recent synthesis of **7a** involves[8] Vilsmeier formylation of 3-ethyl-4-methylpyrrole followed by separation through frac-

tional crystallisation of the two isomeric formylpyrroles. Since this final separation was unlikely to be general, we tested the generality of the acetal approach using the pyrrole **1b**; the 2-unsubstituted 5-formylpyrrole **7b** was obtained via **2b**,**4b**,**5b**, and **6b** in yields similar to those in the Scheme. Attempts to decarboxylate pyrrole **4** thermally to give **6** were unsuccessful and the indirect method through **5** was employed.



**a** R = $C_2H_5$
**b** R = $-CH_2-CH_2-COOCH_3$

Clezy et al.[4] have described a method using pyrrole acetals from 2-methylpentan-2,4-diol for preparation of 2-unsubstituted 5-formylpyrroles, but no yields were reported. This acetal was cleaved using an ingenious two-phase acid/ether partition method. When subjected to the same conditions, the acetal **2a** remained intact in our hands. In order to ascertain whether the acetal from neopentanediol is more stable than that from 2-methylpentan-2,4-diol or whether the pyrroles used in our study are less labile due to our use of more heavily substituted pyrroles, the acetal **8** was prepared. It was obtained as an oil which could not be crystallised but it did afford a crystalline carboxylic acid (**9**) after hydrogenolysis. The acetal **8** is stable towards treatment in ether with aqueous 1–5% hydrochloric acid.

**Benzyl 2-(5,5-Dimethyl-1,3-dioxan-2-yl)-3-ethyl-4-methylpyrrole-5-carboxylate (2a):**

Compound **1a**[9] (6 g), neopentanediol (32.6 g, 14 equiv), and toluene-*p*-sulphonic acid hydrate (500 mg) are refluxed in benzene (400 ml) during 2 h under a Dean-Stark head. The cooled mixture is poured into aqueous sodium hydrogen carbonate and the organic layer is washed with water, dried ($Na_2SO_4$), and evaporated to give a brown oil. This oil is chromatographed on alumina (Brockmann Grade III, neutral) using light petroleum (b.p. 60–80°)/toluene. Evaporation of the appropriate eluates (T.L.C. monitoring) gives an oil which readily crystallises (5.4 g; 69%). Elution of the column with ethyl acetate/toluene gives starting material **1a** as an oil; this is treated as before with neopentanediol (10.9 g) and toluene-*p*-sulphonic acid hydrate (200 mg) in benzene (200 ml) and gives a further 2.2 g; total yield: 7.6 g (96%); colorless plates from light petroleum, m.p. 106–107°.

| | | | | |
|---|---|---|---|---|
| $C_{21}H_{27}NO_4$ | calc. | C 70.56 | H 7.61 | N 3.92 |
| (357.4) | found | 70.37 | 7.56 | 4.19 |

M.S.: $m/e$ = 357 (40%), 271 (55), 180 (27), 162 (15), 91 (100).

I.R. (KBr): $\nu_{max}$ = 1785 (C=O), 3280 (NH) $cm^{-1}$.

$^1$H-N.M.R. ($CDCl_3$): $\delta$ = 0.76, 1.23 (each s, 3H, acetal $CH_3$), 1.06 (t, 3H, $-CH_2-C\underline{H}_3$), 2.23 (s, 3H, $CH_3$), 2.32 (q, 2H, $-C\underline{H}_2-CH_3$), 3.61 (q, 4H, acetal $CH_2$, $J_{AB}$ = 11 Hz, $\delta_{A,B}$ = 3.58, 3.69), 5.25 (s, 2H, $C_6H_5-C\underline{H}_2$), 5.41 (s, 1H, OC$\underline{H}$O), 7.34 (m, 5H, $C_6H_5$), 8.97 ppm (br s, 1H, NH).

**Benzyl 2-(5,5-Dimethyl-1,3-dioxan-2-yl)-3-(2-methoxycarbonylethyl)-4-methylpyrrole-5-carboxylate (2b):**

This compound is similarly prepared from **1b**[10] (8 g), neopentanediol (40.8 g), and toluene-*p*-sulphonic acid hydrate (500 mg) in benzene (500 ml); yield: 8.6 g (85%); m.p. 79–81°, from ether/hexane.

| | | | | |
|---|---|---|---|---|
| $C_{23}H_{29}NO_6$ | calc. | C 66.49 | H 7.04 | N 3.37 |
| (415.5) | found | 66.43 | 6.96 | 3.46 |

M.S.: $m/e$ = 415 (53%), 328 (100), 300 (46), 220 (63), 91 (100).

I.R. (KBr): $\nu_{max}$ = 1665, 1735 (C=O), 3300 (NH) $cm^{-1}$.

$^1$H-N.M.R. ($CDCl_3$): $\delta$ = 0.58, 1.08 (each s, 3H, acetal $CH_3$), 2.16 (s, 3H, $CH_3$), 2.35 (m, 2H, $CH_2-C\underline{H}_2-CO$), 2.69 (m, 2H, $C\underline{H}_2-CH_2-CO$), 3.43 (q, 4H, acetal $CH_2$, $J_{AB}$ = 11 Hz, $\delta_{A,B}$ = 3.40, 3.51), 3.46 (s, 3H, $COOCH_3$), 5.12 (s, 2H, $C_6H_5C\underline{H}_2$), 5.33 (s, 1H, OC$\underline{H}$O), 7.18 (m, 5H, $C_6H_5$), 9.21 ppm (br s, 1H, NH).

**2-(5,5-Dimethyl-1,3-dioxan-2-yl)-3-ethyl-4-methylpyrrole-5-carboxylic Acid (4a):**

Pyrrole **2a** (6.2 g) in tetrahydrofuran (120 ml) and triethylamine (2 drops) is hydrogenated at room temperature and atmospheric pressure over 10% palladised charcoal (700 mg) until uptake of hydrogen ceases (1 h, calc. uptake: 439 ml, observed: 510 ml). The catalyst is filtered off on Celite and the filtrate is concentrated to ~25 ml. Light petroleum (b.p. 60–80°; ~30 ml) is added, the solvent mixture evaporated to low volume, and product **4a** isolated by filtration; yield: 4.3 g (96%); m.p. 153–154° (dec), from tetrahydrofuran.

| | | | | |
|---|---|---|---|---|
| $C_{14}H_{21}NO_4$ | calc. | C 62.90 | H 7.92 | N 5.24 |
| (267.3) | found | 63.17 | 7.88 | 5.09 |

I.R. (KBr): $\nu_{max}$ = 1650, 1720 (C=O) $cm^{-1}$.

$^1$H-N.M.R. ($CDCl_3$): $\delta$ = 0.08, 1.17 (each s, 3H, acetal $CH_3$), 1.01 (t, 3H, $-CH_2-C\underline{H}_3$), 2.18 (s, 3H, $CH_3$), 2.34 (q, 2H, $-C\underline{H}_2-CH_3$), 3.66 (q, 4H, acetal $CH_2$, $J_{AB}$ = 11 Hz, $\delta_{A,B}$ = 3.61, 3.72), 5.34 (s, 1H, OC$\underline{H}$O), 9.00, 10.01 ppm (each br s, 1H, NH, COOH).

**2-(5,5-Dimethyl-1,3-dioxan-2-yl)-3-(2-methoxycarbonylethyl)-4-methylpyrrole-5-carboxylic Acid (4b):**

This compound is similarly prepared from **2b**; yield: ~100%; fibrous needles from tetrahydrofuran/heptane, m.p. 105–107°.

| | | | | |
|---|---|---|---|---|
| $C_{16}H_{23}NO_6$ | calc. | C 59.06 | H 7.13 | N 4.31 |
| (325.4) | found | 59.32 | 7.23 | 4.24 |

I.R. (KBr): $\nu_{max}$ = 1665, 1645 (C=O) $cm^{-1}$.

$^1$H-N.M.R. ($CDCl_3$): $\delta$ = 0.77, 1.23 (each s, 3H, acetal $CH_3$), 2.37 (s, 3H, $CH_3$), 2.60 (m, 2H, $CH_2-C\underline{H}_2-CO$), 2.93 (m, 2H, $C\underline{H}_2-CH_2-CO$), 3.62 (s, 3H, $COOCH_3$), 3.75 (q, 4H, acetal $CH_2$, $J_{AB}$ = 11 Hz, $\delta_{A,B}$ = 3.60, 3.71), 5.47 (s, 1H, OC$\underline{H}$O), 9.17, 10.86 ppm (each br s, 1H, NH, COOH).

**2-(5,5-Dimethyl-1,3-dioxan-2-yl)-3-ethyl-5-iodo-4-methylpyrrole (5a):**

Pyrrole **4a** (2 g) is dissolved in methanol (60 ml) and sodium hydrogen carbonate (1.57 g; 2.5 equiv.) in water (16 ml) is added over a 2 min period. Iodine (2 g, 1.05 equiv) and potassium iodide (2.5 g, 2 equiv) in methanol (14 ml) and water (7 ml) are added to the stirred solution during 75 min and stirring is then continued for a further 15 min. Then, 1 *M* aqueous sodium thiosulphate solution is dripped into the mixture until excess iodine has been decomposed. The pale pink solution is poured into water and dichloromethane. The organic layer is washed with water, dried ($Na_2SO_4$), and evaporated to give a pale pink oil which crystallises when placed under high vacuum; yield: 2.6 g (100%).

For micro-analysis, a sample was chromatographed on a short alumina column, eluting with ether. After evaporation, the residue was crystallised from light petroleum (b.p. 40–60°) and then from ether/hexane to give colorless crystals; m.p. 68.5–70.5°.

| | | | | |
|---|---|---|---|---|
| $C_{13}H_{20}JNO_2$ | calc. | C 44.71 | H 5.77 | N 4.01 |
| (349.2) | found | 44.52 | 5.77 | 4.16 |

$^1$H-N.M.R. ($CDCl_3$): $\delta = 0.28$, 1.21 (each s, 3H, acetal $CH_3$), 1.03 (t, 3H, $-CH_2-CH_3$), 1.89 (s, 3H, $CH_3$), 2.43 (q, 2H, $-C\underline{H}_2-CH_3$), 3.61 (q, 4H, acetal $CH_2$, $J_{AB} = 11$ Hz, $\delta_{A,B} = 3.56$, 3.67), 5.37 (s, 1H, OC$\underline{H}$O), 8.14 ppm (br s, 1H, NH).

**2-(5,5-Dimethyl-1,3-dioxan-2-yl)-5-iodo-3-(2-methoxycarbonylethyl)-4-methylpyrrole (5b):**

This compound is similarly prepared from **4b**; it is obtained as an oil which cannot be induced to crystallise; yield: 98%.

$^1$H-N.M.R. ($CDCl_3$): $\delta = 0.72$, 1.08 (each s, 3H, acetal $CH_3$), 1.92 (s, 3H, $CH_3$), 2.54 (m, 2H, $CH_2-C\underline{H}_2-CO$), 2.80 (m, 2H, $C\underline{H}_2-CH_2-CO$), 3.62 (m, 7H, acetal $CH_2$ and $COOCH_3$), 5.42 (s, 1H, OC$\underline{H}$O), 8.52 ppm (br s, 1H, NH).

**3-Ethyl-5-formyl-4-methylpyrrole (7a):**

*2-(5,5-Dimethyl-1,3-dioxan-2-yl)-3-ethyl-4-methylpyrrole* (**6a**): Adams platinum oxide catalyst (75 mg) is suspended in methanol (60 ml) and the suspension shaken in a hydrogen atmosphere during 4 h, after which time the catalyst is reduced. Pyrrole **5a** (2.6 g) in methanol (60 ml) and triethylamine (1 ml) is added to the platinum suspension and the mixture is shaken under an atmosphere of hydrogen for 18 h before removal of the catalyst by filtration through Celite. The filtrate is concentrated to ~50 ml and then poured into dichloromethane and water. The organic layer is washed with water, dried ($Na_2SO_4$), and evaporated to give **6a** as an oil which becomes red on prolonged standing; yield: 1.63 g (97%).

$^1$H-N.M.R. ($CDCl_3$): $\delta = 0.28$, 1.24 (each s, 3H, acetal $CH_3$), 1.10 (t, 3H, $-CH_2-C\underline{H}_3$), 1.99 (s, 3H, $CH_3$), 2.46 (q, 2H, $-C\underline{H}_2-CH_3$), 3.44 (q, 4H, acetal $CH_2$, $J_{AB} = 11$ Hz, $\delta_{A,B} = 3.38$, 3.49), 5.43 (s, 1H, OC$\underline{H}$O), 6.34 (d, $J = 3$ Hz, 1H, pyrrole 2-H), 8.15 ppm (br s, 1H, NH).

*3-Ethyl-5-formyl-4-methylpyrrole* (**7a**): Compound **6a** (1.4 g) is stirred in methanol (30 ml) at 0° under a nitrogen atmosphere for 15 min; then, a mixture of trifluoroacetic acid (7.5 ml) and water (2.5 ml) is added, the red solution stirred for 10 min, and then poured into dichloromethane. Solid sodium hydrogen carbonate is added cautiously until the acid has been neutralised. The organic phase is washed with water, dried ($Na_2SO_4$), and evaporated to give a brown oil which is chromatographed (Brockmann Grade III, neutral alumina), eluting with toluene/light petroleum initially, and then with 20% ethyl acetate in toluene. Product **7a** is obtained from the latter eluates and the residue is sublimed at 100°/0.1 torr; yield: 475 mg (55%); m.p. 75–76° (Ref.[8], m.p. 79–80°).

$C_8H_{11}NO$ (137.2)

M.S.: *m/e* = 137 (100%), 122 (98), 108 (36), 94 (24), 67 (26).

I.R. (KBr): $\nu_{max} = 1645$ (CHO), 3260 (NH) cm$^{-1}$.

$^1$H-N.M.R. ($CDCl_3$): $\delta = 1.15$ (t, 3H, $-CH_2-C\underline{H}_3$), 1.98 (s, 3H, $CH_3$), 2.66 (q, 2H, $-C\underline{H}_2-CH_3$), 6.68 (d, $J = 3$ Hz, 1H, pyrrole 2-H), 9.56 ppm (s, 1H, CHO).

**2-Formyl-3-(2-methoxycarbonylethyl)-4-methylpyrrole (7b):**

*2-(5,5-Dimethyl-1,3-dioxan-2-yl)-3-(2-methoxycarbonylethyl)-4-methylpyrrole* (**6b**): This compound is similarly prepared from **5b**; yield: 94%.

$^1$H-N.M.R. ($CDCl_3$): $\delta = 0.71$, 1.19 (each s, 3H, acetal $CH_3$), 1.98 (s, 3H, $CH_3$), 2.45 (m, 2H, $CH_2-C\underline{H}_2-CO$), 2.82 (m, 2H, $C\underline{H}_2-CH_2-CO$), 3.61 (m, 7H, acetal $CH_2$ and $COOCH_3$), 5.53 (s, 1H, OC$\underline{H}$O), 6.39 (br s, 1H, pyrrole 2-H), 8.20 ppm (br s, 1H, NH).

*2-Formyl-3-(2-methoxycarbonylethyl)-4-methylpyrrole* (**7b**): This compound is similarly prepared from **6b**; yield: 57%; m.p. 92–93°, from light petroleum (b.p. 60–80°) (sublimation unnecessary).

| | | | | |
|---|---|---|---|---|
| $C_{10}H_{13}NO_3$ | calc. | C 61.52 | H 6.71 | N 7.18 |
| (195.2) | found | 61.75 | 6.86 | 7.27 |

M.S.: *m/e* = 195 (94%), 167 (53), 166 (30), 136 (74), 122 (100), 108 (41), 107 (46), 94 (61).

I.R. (KBr): $\nu_{max} = 1645$ (CHO), 1728 (C=O), 3250 (NH) cm$^{-1}$.

$^1$H-N.M.R. ($CDCl_3$): $\delta = 2.04$ (s, 3H, $CH_3$), 2.56 (m, 2H, $CH_2-C\underline{H}_2-CO$), 3.04 (m, 2H, $C\underline{H}_2-CH_2-CO$), 3.63 (s, 3H, $COOCH_3$), 6.84 (d, $J = 3$ Hz, 1H, pyrrole 2-H), 9.63 (s, 1H, CHO), 9.94 ppm (br s, 1H, NH).

**Benzyl 3-(2-Methoxycarbonylethyl)-4-methyl-2-(4,4,6-trimethyl-1,3-dioxan-2-yl)-pyrrole-5-carboxylate (8):**

Compound **1b**[10] (3.0 g), 2-methylpentan-2,4-diol (16.5 g), and toluene-*p*-sulphonic acid hydrate (50 mg) are refluxed in benzene (100 ml) under a Dean-Stark head during 18 h. The cooled mixture is poured into aqueous sodium hydrogen carbonate and the organic layer is washed with water, dried ($Na_2SO_4$), and evaporated to give an oil which is chromatographed on alumina (Brockmann Grade III, neutral) eluting with light petroleum/toluene. Evaporation of the eluates gives a yellow oil which cannot be induced to crystallise; yield 3.2 g (82%).

$C_{24}H_{31}NO_6$ (429.3)

M.S.: *m/e* = 429 (14), 342 (30), 329 (11), 300 (24), 299 (18), 284 (20), 228 (13), 148 (20), 91 (100).

$^1$H-N.M.R. ($CDCl_3$): $\delta = 0.9$ (m, 11H, acetal $CH_3$ and $CH_2$), 1.80 (s, 3H, $CH_3$), 2.02 (m, 2H, $CH_2-C\underline{H}_2-CO$), 2.39 (m, 2H, $C\underline{H}_2-CH_2-CO$), 3.12 (s, 3H, $COOCH_3$), 3.51 (m, 1H, $C\underline{H}-CH_3$), 4.58 (s, 2H, $C_6H_5-C\underline{H}_2$), 5.36 (s, 1H, OC$\underline{H}$O), 6.76 (m, 5H, $C_6H_5$), 8.82 ppm (br s, 1H, NH).

**3-(2-Methoxycarbonylethyl)-4-methyl-2-(4,4,6-trimethyl-1,3-dioxan-2-yl)-pyrrole-5-carboxylic Acid (9):**

Compound **8** (3 g) in tetrahydrofuran (60 ml) and triethylamine (2 drops) is hydrogenated at room temperature and atmospheric pressure over 10% palladised charcoal (300 mg) until uptake of hydrogen ceases (45 min, calc. uptake: 168 ml, observed uptake: 186 ml). The catalyst is filtered off on Celite, the filtrate is concentrated to ~20 ml, and an equal volume of light petroleum (b.p. 60–80°) is added. Evaporation under reduced pressure gives a colourless oil which crystallises under petroleum containing a little ether; yield: 2.0 g (90%); m.p. 131–132°.

| | | | | |
|---|---|---|---|---|
| $C_{17}H_{25}NO_6$ | calc. | C 60.16 | H 7.43 | N 4.13 |
| (339.4) | found | 60.01 | 7.51 | 4.20 |

I.R. (KBr): $\nu_{max} = 1650$, 1720 (C=O) cm$^{-1}$.

$^1$H-N.M.R. ($CDCl_3$): $\delta = 1.4$ (m, 11H, acetal $CH_3$ and $CH_2$), 2.29 (s, 3H, $CH_3$), 2.49 (m, 2H, $CH_2-C\underline{H}_2-CO$), 2.80 (m, 2H, $C\underline{H}_2-CH_2-CO$), 3.66 (s, 3H, $COOCH_3$), 4.06 (m, 1H, $C\underline{H}-CH_3$), 5.85 (s, 1H, OC$\underline{H}$O), 9.21, 9.68 ppm (each br s, 1H, NH, COOH).

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[1] For reviews see:
A. H. Jackson, K. M. Smith, in: *Total Synthesis of Natural Products*, Ed. J. W. ApSimon, Vol. 1, John Wiley & Sons, New York, 1973, p. 143.
K. M. Smith, in: *Porphyrins and Metalloporphyrins*, Ed. K. M. Smith, Elsevier Publishing Co., Amsterdam, 1975, p. 29.

[2a] H. Fischer, H. Orth, *Die Chemie des Pyrrols*, Vol. I, Akademische Verlagsgesellschaft, Leipzig, 1934, p. 225.

[2b] A. Gossauer, *Die Chemie der Pyrrole*, Springer Verlag, Berlin, 1974, p. 302.

[3] G. S. Sach, *Ph. D. Thesis*, University of Liverpool, 1964.

[4] P. S. Clezy et al., *Aust. J. Chem.* **27,** 357 (1974).

[5] The use of neopentanediol for protection of formyl substituents in the porphyrin series has already been reported: A. H. Jackson, G. W. Kenner, J. Wass, *J. Chem. Soc., Perkin Trans. 1* **1974,** 480.

[6] J. N. Shoolery, M. T. Rogers, *J. Am. Chem. Soc.* **80,** 6098 (1958).

[7] Ref. 2a, p. 156.

[8] A. W. Johnson, R. L. N. Harris, I. T. Kay, *J. Chem. Soc.* [C] **1966,** 22.

[9] Prepared by dichlorination of benzyl 3-ethyl-2,4-dimethylpyrrole-5-carboxylate using sulphuryl chloride, followed by hydrolysis; cf. Ref.[10].

[10] A. H. Jackson, G. W. Kenner, G. S. Sach, *J. Chem. Soc.* [C] **1967,** 2045.