Dihydroimidazoles in Synthesis: C-Acylation of Lithiodihydroimidazoles

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1-Benzyl-2-methyl-4,5-dihydroimidazole has been lithiated and C-acylated by reaction with esters and a nitrile. The products do not exist as 2-(2-oxoalkyl)dihydroimidazoles but as the alternative tautomers, as indicated by spectroscopic and crystallographic data.

We have recently reported that 2-alkyl-1-benzyl-4,5-dihydroimidazoles (**1**) can be metallated at the α-position by treatment with butyl-lithium, and that the resulting lithiodihydroimidazoles (**2**) can be alkylated.[1] The α-substituted dihydroimidazoles (**3**) so produced may be cleaved hydrolytically to give carboxylic acids in a homologation sequence;[1] alternatively they may be quaternised with methyl iodide and then converted into ketones by addition of Grignard reagents and subsequent hydrolysis (Scheme).[2] This use of 4,5-dihydroimidazoles in the transfer of functionalised carbon parallels the reactions of tetrahydrofolate coenzymes in nature.[3] The varied biological activities shown by many dihydroimidazoles,[4] and the possible uses of lithiodihydroimidazoles in carbon–carbon bond forming processes (*cf.* the dihydro-oxazole and -thiazole counterparts[5]) have led us to explore further reactions of the anions (**2**). We describe here the results of some C-acylation experiments performed on compound (**2**; R^1 = H).

Results and Discussion

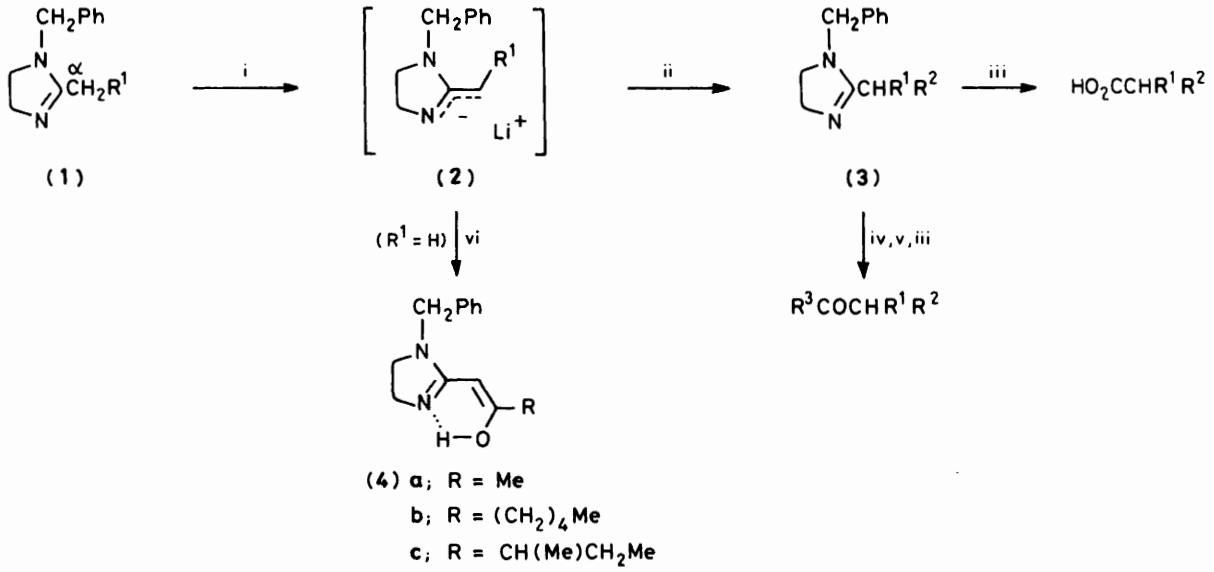
1-Benzyl-2-methyl-4,5-dihydroimidazole (**1**; R^1 = H) was lithiated in the usual way[1] and a solution of this anion (yellow-orange) in tetrahydrofuran (THF) was added to a solution of an ester (RCO_2Et) in THF at −78 °C. The mixture was maintained at this temperature for 1 h before being allowed to warm to 20 °C. It was found necessary to leave the reaction mixture at 20 °C overnight as after shorter times the reaction had not reached completion (t.l.c.). Aqueous work-up gave good recoveries (*ca.* 80%) of waxy solids that proved to be the C-acylation products, containing traces of the starting dihydroimidazole (**1**; R^1 = H). These materials were recrystallised to afford moderate yields of the pure C-acylation products.† Another acylation experiment was carried out in the same way, but using hexanenitrile in place of the ester; acidic hydrolysis on work-up and purification by recrystallisation afforded the same C-acylated material as had been obtained from ethyl hexanoate, and in a somewhat better yield.

The C-acylation products are formally 2-(2-oxoalkyl)-4,5-dihydroimidazoles, but are probably best represented by the tautomeric structures (**4a—c**), as evidenced by their spectral properties. All three displayed in their i.r. spectra (KBr discs) bands corresponding to a hydrogen-bonded OH (*ca.* 3 300 cm^{-1}), no carbonyl stretching bands in the 1 650—1 750 cm^{-1} region, but absorption in the 1 600 cm^{-1} region with a broader band at 1 530—1 540 cm^{-1} [2-alkyl-1-benzyl-4,5-dihydroimidazoles (**1**) generally show bands at 1 600—1 610 cm^{-1} and 1 490—1 500 cm^{-1}]. The u.v. spectra revealed a long wavelength absorption (*ca.* 290 nm) with high extinction (2.7—2.8 × 10^4), and the ^1H n.m.r. spectra exhibited a one-proton vinyl resonance and a broad one-proton signal (OH), both exchangeable with D_2O. Such tautomeric behaviour is not unexpected.[6] A single crystal *X*-ray diffraction study was performed on the 2-(2-hydroxyprop-1-enyl) compound (**4a**), which crystallised from ethyl acetate–light petroleum (b.p. 40—60 °C) as monoclinic needles, space group $P2_1/c$, a = 10.766(2) Å, b = 5.575(3) Å, c = 19.740(5) Å, β = 93.56(2)°, with four molecules per unit cell. The structure, which was determined (see Experimental section) from only 513 observed reflections and refined to R 6.84%, reveals (Figure) the planar nature of the N(3)–C(2)–C(6)–C(7)–O system [torsion angles: N(3)–C(2)–C(6)–C(7), −3.4°, and C(2)–C(6)–C(7)–O(9), 0.5°]; the bond lengths C(2)–C(6) and C(6)–C(7) are both 1.39(1) Å (see Table 2 for the molecular dimensions), intermediate between a double and single bond. It would appear that there is a contribution to the crystal structure of compound (**4a**) from the enamino-ketone tautomer, although no hydrogen atom bonded to N(3) or O(9) could be located. Interestingly the 1-benzyl aromatic ring occupies a plane very nearly perpendicular to the dihydroimidazole ring.

When diethyl carbonate was used as the acylating agent, the corresponding C-acylation product was isolated in lower yield after recrystallisation. This material was identical with a sample prepared in good yield from *N*-benzyl-1,2-diaminoethane and the imidate derived from treatment of ethyl cyanoacetate with ethanol and hydrogen chloride. It showed bands in the i.r. spectrum at 3 350 cm^{-1} (NH), 1 640 cm^{-1} (C=O stretch of hydrogen bonded ester) and 1 580 cm^{-1}, with an absorption band in the u.v. spectrum at 272 nm (ε 3.2 × 10^4) and relevant signals in the ^1H n.m.r. spectrum at δ 7.7 (1 H, br s, NH, disappears with D_2O) and 4.02—4.26 (3 H, s and q, simplifying to 2 H, q, OCH_2CH_3 on deuteriation), *i.e.* one vinyl proton at δ 4.26. These data indicate that this compound should be represented as the tautomer (**5a**). Similar observations have been reported for the 1-phenyl analogue (**5b**).[7]

As an extension of our use of dihydroimidazoles as precursors to carboxylic acids,[1] compound (**5a**) may be envisaged as a synthetic equivalent of unsymmetrically esterified malonic acid,[8] and indeed we have shown in preliminary experiments that treatment of compound (**5a**) with butyl-lithium in THF at −30 °C followed by addition of either methyl iodide or benzaldehyde afforded products of C-methylation or addition, respectively. It should, of course, be possible to deprotonate compound (**5a**) under less strongly basic conditions, and we are investigating this.

† Since the preparation of this manuscript we have discovered that the C-acylation products are readily purified by column chromatography on silica gel using chloroform–methanol (9:1 v/v), being the first eluted materials. This high R_F value compared with those of the dihydroimidazoles (**1**) presumably reflects the intramolecularly hydrogen-bonded structure of the C-acylation products (see text).



Scheme. *Reagents:* i, Bu^{n}Li, −78 °C; ii, R^2X (X=Br,I); iii, H_3O^+; iv, MeI; v, R^3MgBr; vi, RCO_2Et

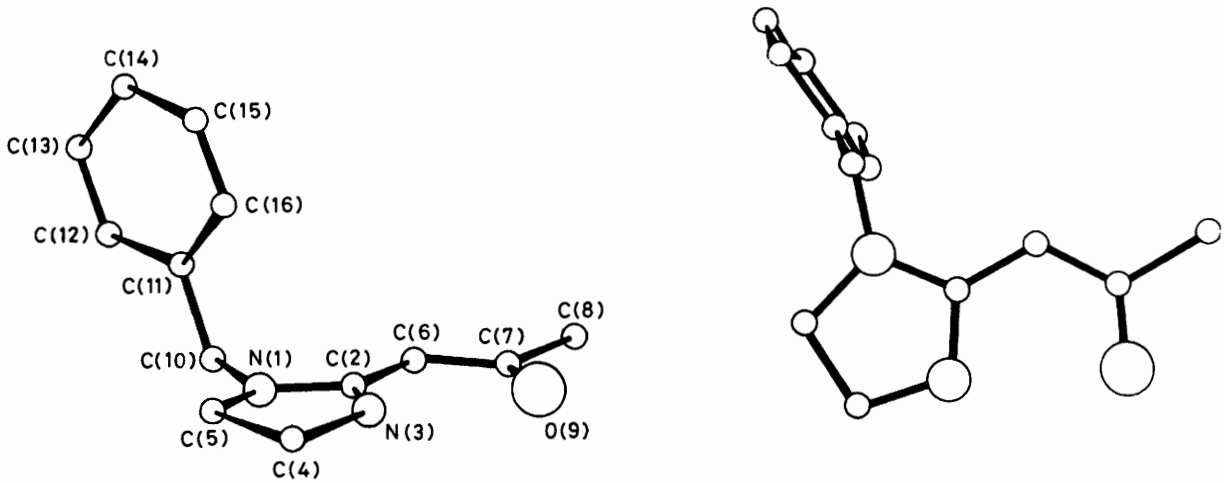
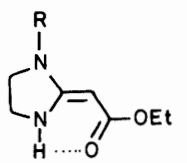


Figure. Crystal structure of compound (**4a**) (two views) and atomic numbering scheme



(**5**) a; R = CH_2Ph
b; R = Ph

Experimental

M.p.s were measured on a capillary apparatus and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 710B spectrometer as KBr discs unless otherwise stated; u.v. spectra were recorded for solutions in 95% ethanol using a Unicam SP 800 spectrometer. N.m.r. spectra were determined in deuteriochloroform solution (tetramethylsilane as internal standard) at 100 or 90 MHz using JEOL MH-100 or Perkin-Elmer R32 spectrometers, respectively. Mass spectra were obtained using an A.E.I. MS902 spectrometer. THF was distilled from $LiAlH_4$ immediately prior to use, and butyl-lithium solutions were standardised by the diphenylacetic acid method.[9] Ether refers to diethyl ether.

1-*Benzyl*-2-*methyl*-4,5-*dihydroimidazole*.—A solution of *N*-benzyl-1,2-diaminoethane[10] (41 g, 0.275 mol) and ethyl acetimidate hydrochloride[11] (34 g, 0.275 mol) in dry ethanol (250 ml) was heated under reflux for 3 h under nitrogen. Evaporation of the ethanol under reduced pressure and trituration of the resulting oil with ether gave the dihydroimidazole hydrochloride, m.p. 167—169 °C (from ethanol–ether). The crude hydrochloride was taken up in the minimum of water, treated with excess of sodium hydroxide solution (30% w/v), and the mixture extracted with chloroform (2 × 100 mol). The organic solution was dried ($MgSO_4$), the solvent removed under reduced pressure, and the residue fractionally distilled under reduced pressure to afford 1-*benzyl*-2-*methyl*-4,5-*dihydroimidazole* (35 g, 73%), b.p. 102—106 °C at 1 mmHg (Found: C, 76.2; H, 8.2; N, 16.3%; M^+, 174.117. $C_{11}H_{14}N_2$ requires C, 75.8; H, 8.1; N, 16.1%; *M*, 174.116); $\nu_{max.}$

Table 1. Final atomic co-ordinates of compound (**4a**) (e.s.d.s in parenthesis)

Atom	*x/a*	*y/b*	*z/c*
N(1)	0.270 2(8)	0.063(2)	0.401 8(5)
C(2)	0.188 9(10)	0.250(3)	0.409 3(6)
N(3)	0.145 6(8)	0.241(2)	0.472 7(4)
C(4)	0.193 1(10)	0.027(2)	0.508 5(5)
C(5)	0.293 1(10)	−0.068(2)	0.465 1(6)
C(6)	0.150 5(10)	0.417(2)	0.360 1(5)
C(7)	0.058 6(10)	0.586(2)	0.369 4(6)
C(8)	0.017 3(9)	0.763(2)	0.314 4(5)
O(9)	0.002 8(7)	0.604(1)	0.422 8(4)
C(10)	0.345 9(10)	0.034(2)	0.344 6(5)
C(11)	0.472 4(12)	0.158(2)	0.351 2(6)
C(12)	0.571 2(14)	0.074(2)	0.316 7(5)
C(13)	0.683 7(15)	0.189(4)	0.323 2(8)
C(14)	0.702 1(16)	0.388(4)	0.365 0(10)
C(15)	0.603 6(16)	0.467(3)	0.399 5(8)
C(16)	0.491 9(11)	0.352(2)	0.394 0(6)

(liquid film) 1 610, 1 490 cm^{-1}; δ 2.0 (3 H, s, CH_3), 3.1—3.9 (4 H, 2t, NCH_2CH_2N), 4.3 (2 H, s, benzyl-CH_2), and 7.3 (5 H, s, Ph); *m/z* 174 (M^+), 92, 91 (100%), 83, and 65.

1-*Benzyl*-2-(2-*hydroxyprop*-1-*enyl*)-4,5-*dihydroimidazole* (**4a**).—n-Butyl-lithium (6.9 ml of a 1.6M-solution in hexane, 11 mmol) was added to a stirred solution of 1-benzyl-2-methyl-4,5-dihydroimidazole (1.61 g, 9.25 mmol) in THF (25 ml) under nitrogen at −78 °C, and the mixture stirred for 1 h. This solution was added *via* a syringe to a stirred solution of ethyl acetate (0.9 g, 10 mmol) in THF (25 ml) under nitrogen at −78 °C. The mixture was stirred for 1 h at this temperature, allowed to warm to 20 °C during 1 h, and then stirred for a further 16 h. The solution was then concentrated under reduced pressure, the residue partitioned between chloroform (50 ml) and ice–water (50 ml), and the organic extract dried ($MgSO_4$) and concentrated under reduced pressure to leave the crude product (1.87 g, 94%). Recrystallisation from ethyl acetate-light petroleum (b.p. 40—60 °C) afforded 1-*benzyl*-2-(2-*hydroxyprop*-1-*enyl*)-4,5-*dihydroimidazole* (**4a**) as white needles (1.44 g, 72%), m.p. 111—113 °C (Found: C, 72.45; H, 7.75; N, 12.7%; M^+, 216.129. $C_{13}H_{16}N_2O$ requires C, 72.2; H, 7.45; N, 12.95%; *M*, 216.126); $\nu_{max.}$ 3 280, 1 605, and 1 530br cm^{-1}; $\lambda_{max.}$ 289 nm (ε 2.71 × 10^4); δ 2.0 (3 H, s, CH_3), 3.2—3.7 (4 H, m, NCH_2CH_2N), 4.3 (2 H, s, benzyl-CH_2), 4.85 (1 H, s, vinyl-CH, exchanges with D_2O), 7.4 (5 H, s, Ph), and 9.5 (1 H, br s, OH, exchanges with D_2O); *m/z* 216 (M^+), 200, 172, 131, and 91 (100%).

1-*Benzyl*-2-(2-*hydroxyhept*-1-*enyl*)-4,5-*dihydroimidazole* (**4b**). This was prepared as above from 1-benzyl-2-methyl-4,5-dihydroimidazole (1.28 g, 7.35 mmol), n-butyl-lithium (6.2 ml of a 1.3M-solution in hexane, 8.1 mmol), and ethyl hexanoate (1.16 g, 8.0 mmol) to give a crude product (1.54 g, 77%); recrystallisation from light petroleum (b.p. 60—80 °C) gave the 2-(2-*hydroxyhept*-1-*enyl*)-4,5-*dihydroimidazole* (**4b**) as white needles (1.08 g, 54%), m.p. 70—71 °C (Found: C, 74.75; H, 9.1; N, 10.25%; M^+, 272.188. $C_{17}H_{24}N_2O$ requires C, 74.95; H, 8.9; N, 10.3%; *M*, 272.189); $\nu_{max.}$ 3 290, 1 595, 1 540br cm^{-1}; $\lambda_{max.}$ 291 nm (ε 2.72 × 10^4); δ 0.9 (3 H, t, CH_3), 1.3 (4 H, m, 2 × CH_2), 1.6 (2 H, m, CH_2), 2.3 (2 H, t, CH_2), 3.2—3.7 (4 H, m, NCH_2CH_2N), 4.25 (2 H, s, benzyl-CH_2), 4.7 (1 H, s, vinyl CH, exchanges with D_2O), 7.2 (5 H, s, Ph), and 9.3 (1 H, br s, OH, exchanges with D_2O); *m/z* 272(M^+), 216, 201, 174, 173, 120, and 91 (100%).

The dihydroimidazole (**4b**) was also prepared (with M. A. Gugan and G. D. James) from 1-benzyl-2-methyl-4,5-dihydroimidazole (2.57 g, 14.8 mmol), n-butyl-lithium, and hexanenitrile by the same procedure. After the reaction had taken place the solvents were removed under reduced pressure and the residue treated with 3M-hydrochloric acid. The acid solution was washed with ether, basified with solid sodium hydroxide, and extracted with chloroform. The chloroform solution was dried ($MgSO_4$) and evaporated under reduced pressure to leave a residue (3.5 g, 87%) that was crystallised from light petroleum (b.p. 60—80 °C) to afford compound (**4b**) (2.61 g, 65%), identical with the material prepared above from ethyl hexanoate.

1-*Benzyl*-2-(2-*hydroxy*-3-*methylpent*-1-*enyl*)-4,5-*dihydroimidazole* (**4c**). This was prepared as above from 1-benzyl-2-methyl-4,5-dihydroimidazole (1.34 g, 7.7 mmol), n-butyl-lithium (5.75 ml of a 1.48M-solution in hexane, 8.5 mmol), and ethyl 3-methylbutyrate (1.1 g, 8.46 mmol) to give the crude product (1.69 g, 85%); recrystallisation from light petroleum (b.p. 60—80 °C) gave 2-(2-*hydroxy*-3-*methylpent*-1-*enyl*)-4,5-*dihydroimidazole* (**4c**) as white needles (1.02 g, 51%), m.p. 75—77 °C (Found: C, 74.15; H, 8.75; N, 10.85%; M^+, 258.170. $C_{16}H_{22}N_2O$ requires C, 74.4; H, 8.6; N, 10.85%; *M*, 258.173); $\nu_{max.}$ 3 310, 1 600, and 1 540br cm^{-1}; $\lambda_{max.}$ 291 nm (ε 2.8 × 10^4); δ 0.9 (3 H, t, CH_3), 1.1 (3 H, d, CH_3), 1.5 (2 H, m, CH_2), 2.1 (1 H, m, CH), 3.1—3.7 (4 H, m, NCH_2CH_2N), 4.3 (2 H, s, benzyl-CH_2), 4.75 (1 H, s, vinyl CH, exchanges with D_2O), 7.2 (5 H, s,

Table 2. Molecular dimensions of compound (**4a**). Bond lengths (Å) and bond angles (°) (e.s.d.s in parentheses)

Bond lengths	
N(1)–C(2)	1.37(1)
N(1)–C(5)	1.46(1)
N(1)–C(10)	1.44(1)
C(2)–N(3)	1.36(1)
C(2)–C(6)	1.39(1)
N(3)–C(4)	1.46(1)
C(4)–C(5)	1.51(1)
C(6)–C(7)	1.39(1)
C(7)–C(8)	1.52(1)
C(7)–O(9)	1.25(1)
C(10)–C(11)	1.53(1)
C(11)–C(12)	1.38(1)
C(11)–C(16)	1.38(1)
C(12)–C(13)	1.37(2)
C(13)–C(14)	1.39(2)
C(14)–C(15)	1.37(2)
C(15)–C(16)	1.36(2)
Bond angles	
C(2)–N(1)–C(5)	111(1)
C(2)–N(1)–C(10)	125(1)
C(5)–N(1)–C(10)	123(1)
N(1)–C(2)–N(3)	109(1)
N(1)–C(2)–C(6)	127(1)
N(3)–C(2)–C(6)	124(1)
C(2)–N(3)–C(4)	110(1)
N(3)–C(4)–C(5)	105(1)
N(1)–C(5)–C(4)	103(1)
C(2)–C(6)–C(7)	123(1)
C(6)–C(7)–C(8)	122(1)
C(6)–C(7)–O(9)	124(1)
C(8)–C(7)–O(9)	115(1)
N(1)–C(10)–C(11)	115(1)
C(10)–C(11)–C(12)	121(1)
C(10)–C(11)–C(16)	121(1)
C(12)–C(11)–C(16)	118(1)
C(11)–C(12)–C(13)	120(1)
C(12)–C(13)–C(14)	122(2)
C(13)–C(14)–C(15)	118(2)
C(14)–C(15)–C(16)	121(2)
C(11)–C(16)–C(15)	121(1)

Ph), and 9.3 (1 H, br s, OH, exchanges with D_2O); *m/z* 258 (M^+), 230, 202, 201, 174, 173, 132, 92, and 91 (100%).

1-*Benzyl-2-ethoxycarbonylmethyleneimidazolidine* (**5a**). This was prepared as above from 1-benzyl-2-methyl-4,5-dihydroimidazole (1.41 g, 8.1 mmol), n-butyl-lithium (6.0 ml of a 1.48M-solution in hexane, 8.9 mmol), and diethyl carbonate (1.05 g, 8.9 mmol) to give the crude product (1.78 g, 89%); recrystallisation from aqueous ethanol gave the *2-ethoxycarbonylmethyleneimidazolidine* (**5a**) as white needles (0.72 g, 36%), m.p. 105—107 °C (Found: C, 68.6; H, 7.65; N, 11.45%; M^+, 246.139. $C_{14}H_{18}N_2O_2$ requires C, 68.25; H, 7.35; N, 11.35%; *M*, 246.137); $\nu_{max.}$ 3 350, 1 640, and 1 580 cm^{-1}; $\lambda_{max.}$ 272 nm (ε 3.2 × 10^4); δ 1.22 (3 H, t, OCH_2CH_3), 3.2—3.6 (4 H, m, NCH_2CH_2N), 4.14 (2 H, q, OCH_2CH_3), 4.26 (1 H, s, vinyl CH, exchanges with D_2O), 4.34 (2 H, s, benzyl-CH_2), 7.4 (5 H, s, Ph), and 7.7 (1 H, br s, NH, exchanges with D_2O); *m/z* 246 (M^+), 201, 174, 173, 104, and 91 (100%).

Compound (**5a**) was also prepared (with S. A. Cooke and S. J. King) by treating *N*-benzyl-1,2-diaminoethane[10] (12.2 g, 81 mmol) with ethyl cyanoacetimidate hydrochloride[12] (15.9 g, 81 mmol) in dry ethanol (100 ml) heated under reflux for 3 h under nitrogen. Evaporation of the ethanol under reduced pressure and trituration of the residue with ether gave the imidazolidine hydrochloride salt which was dissolved in the minimum of water, treated with an excess of aqueous sodium hydroxide (30% w/v; 20 ml), and extracted with chloroform (2 × 100 ml). The extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a solid that was recrystallised from aqueous ethanol to afford the imidazolidine (**5a**) (17 g, 85%), m.p. 105—107 °C, identical with the material prepared above.

Structure Determination of Compound (**4a**).—Crystals of compound (**4a**) were obtained as detailed above. Preliminary cell parameters and space group were initially determined photographically. For intensity measurements the crystal was mounted on an Ehraf-Nonius CAD4 diffractometer. Accurate lattice parameters were obtained by least squares refinement of the positions of 25 reflections measured on the diffractometer with θ *ca.* 20—25°. Intensity data were collected with Cu-K_α radiation using an ω scan of width 2° for reflections in the range $1° \leqslant \theta \leqslant 66°$. A total of 2 069 independent reflections was measured of which only 513 had $I \geqslant 3\sigma(I)$ and were considered observed and used in the subsequent refinement. The data were corrected for Lorentz and polarisation factors, but no absorption corrections were applied. Data reduction and subsequent crystallographic calculations were performed using the CRYSTALS system of programs.

Crystal data. $C_{13}H_{16}N_2O$, M = 216.3. Monoclinic, a = 10.766(2), b = 5.575(3), c = 19.740(5) Å, β = 93.56(1)°, U = 1 182.5 Å^3, Z = 4, D_c = 1.21 g cm^{-3}, $F(000)$ = 464. Space group $P2_1/c$ from systematic absences. Cu-K_α radiation, λ = 1.541 78 Å, μ(Cu-K_α) = 6.29 cm^{-1}.

Structure solution and refinement. The structure was solved by direct methods using the MULTAN program. 116 Reflections with $E > 1.4$ were used and the E map based on the best set of phases revealed the positions of all 16 non-hydrogen atoms in the molecule among the largest peaks in the map. Full-matrix isotropic least-squares refinement of these positions gave a value for R of 11.8%. Refinement was continued with anisotropic thermal parameters for all non-hydrogen atoms. A difference map next revealed the approximate positions of many of the hydrogen atoms. Geometric considerations were then used to calculate the accurate positions of all the hydrogen atoms whose location could be fixed in this way. The positions of the 8-methyl hydrogen atoms were taken directly from peaks in the difference map. No peak could be found for the crucial hydrogen atom bonded to a heteroatom [N(3) or O(9)]. The other 15 hydrogen atoms were then included in the calculations but without refinement. Analysis of the agreement between F_o and F_c suggested the adoption of a weighting scheme based on a Chebyshev polynomial. Refinement finally converged with the largest parameter shifts 0.1σ after 14 cycles of least squares refinement. The final values of the residuals at convergence were R 0.0684 and R_w 0.0647. A final difference map was calculated which showed no peaks or depressions > 0.2 e Å^{-3}, with no peak at any potential site for the missing hydrogen atom. Final atomic co-ordinates are listed in Table 1, and molecular dimensions in Table 2 and temperature factors and atomic co-ordinates are available as a Supplementary Publication (SUP No. 56066, 3 pp.).* Observed and calculated structure factors are available from the editorial office on request.

* For details of the Supplementary Publications Scheme see instructions for Authors (1984) in *J. Chem. Soc., Perkin Trans. 1*, 1984, Issue 1.

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