Syntheses of Some 1,2- and 1,4-Dihydropyridines and X-Ray Crystal Structures of 1-Dimethylamino-5-ethoxycarbonyl-1,4-dihydro-3-methoxycarbonyl-2-methyl-4-phenylpyridine, 3-Cyano-3,4-dihydro-5-methoxycarbonyl-6-methyl-4-phenylpyridin-2(1*H*)-one and 5-Ethoxycarbonyl-1,4-dihydro-3-methoxycarbonyl-1,2-dimethyl-4-phenylpyridine

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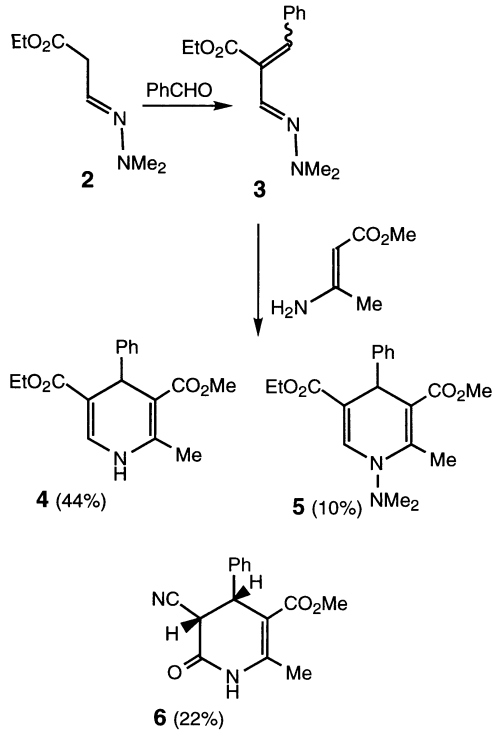
We describe a synthesis of an α-unsubstituted 1,4-dihydropyridine **10** and its 1,2-dihydro isomer, and crystal structures of **10** and some by-products **5** and **6** obtained during the ring synthesis.

Considerable interest in the synthesis of 1,4-dihydropyridines derives from their activity as calcium antagonists and thus for the development of drugs for the treatment of cardiovascular diseases.[4] 1,4-Dihydropyridines are also candidates for the treatment of multidrug resistance (MDR) during cancer chemotherapy,[6] as possible thromboxane synthetase inhibitors,[7] PAF-acether antagonists,[8] and antithrombotic-antihypertensive agents.[10] An alternative to the usual means for the synthesis of 1,4-dihydropyridines[2] is the partial reduction[11] of pyridinium salts.

The addition of 1,1-dimethylhydrazine to ethyl propiolate produced the imine **2**, condensation of which with benzaldehyde provided the hydrazone **3**.

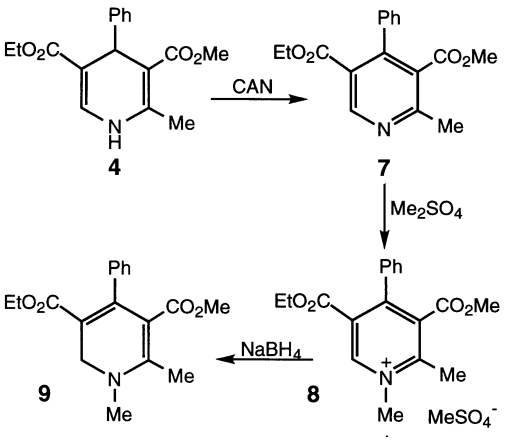
The heterocyclic ring was produced by the reaction of **3** with methyl 3-aminocrotonate in hot acetic acid giving the dihydropyridine **4** accompanied by two other compounds, the structures of which were established by X-ray determinations: **5** and **6**.

Oxidation of **4** with cerium(IV) ammonium nitrate[17] produced **7**, subsequent quaternisation giving the salt **8**.



Reduction of the salt **8** with sodium borohydride in the presence of sodium carbonate produced the 1,2-dihydropyridine **9**, whereas reduction with sodium dithionite gave a mixture of the 1,4-dihydropyridine **10** (62%) with **9** (20%).

X-ray Crystallography.—Data from crystals (**5**, approx. $0.30 \times 0.45 \times 0.56$ mm; **6**, $0.40 \times 0.42 \times 0.60$ mm; **10**, $0.25 \times 0.35 \times 0.50$ mm) were obtained using a Rigaku AFC5R diffractometer with graphite-monochromated CuKα radiation



and a 12 kW rotating anode generator. Structures were solved by direct methods.[19] All calculations were performed using the TEXSAN crystallographic software package.[21]

Data for **5**.—There were 2982 unique ($R_{int} = 0.049$) reflections in the 3134 collected. The final cycle of full-matrix least-squares refinement was based on 2450 observed reflections [$I > 3.00\sigma(I)$] and 227 variable parameters and converged (largest parameter shift was <0.01 times its esd) with unweighted and weighted agreement factors of $R = 0.064$ and $R_w = 0.086$. The standard deviation of an observation of unit weight was 3.50.

Crystal data for **5**. Colourless, prismatic, monoclinic, M, 344.41; $V = 1873.5(2)$ Å^3; $a = 12.404(1)$, $b = 9.5640(6)$, $c = 15.8180(0)$ Å; $\beta = 93.260(6)°$; space group $P2_1/n$ (No. 14); $Z = 4$; $D_{calc} = 1.221$ g cm^{-3}; $F(000) = 736$; h, 0 to 13, k, 0 to 10, l, −17 to 17.

Data for **6**.—There were 2182 unique ($R_{int} = 0.049$) reflections in the 2341 collected. The final cycle of full-matrix least-squares refinement was based on 1589 observed reflections [$I > 3.00\sigma(I)$] and 182 variable parameters and converted (largest parameter shift was <0.01 times its esd) with unweighted and weighted agreement factors of $R = 0.086$ and $R_w = 0.130$. The standard deviation of an observation of unit weight was 5.57.

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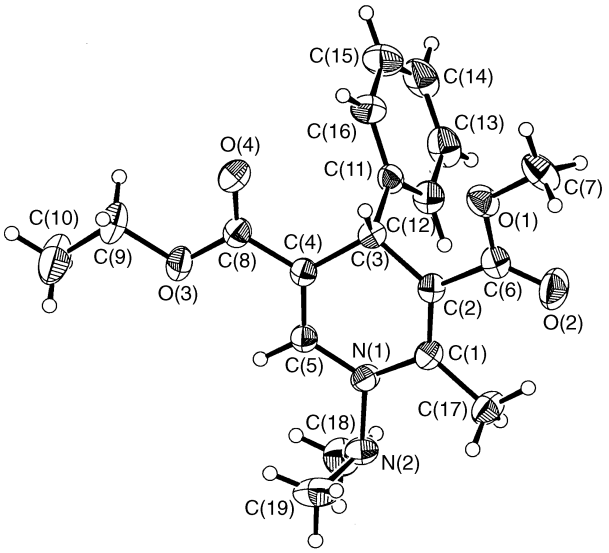

Fig. 1 ORTEP plot of **5**

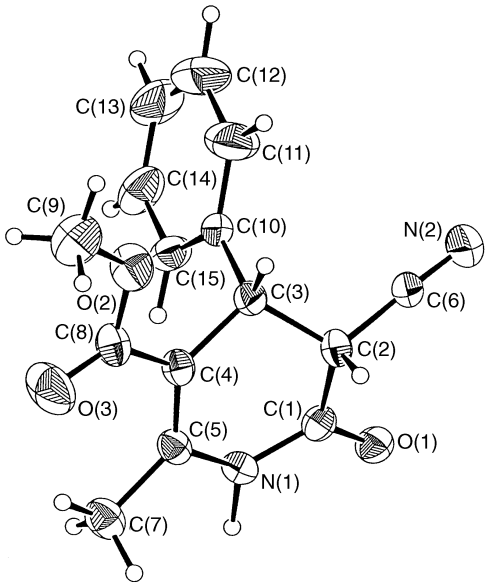

Fig. 2 ORTEP plot of **6**

Crystal data for **6**. Colourless prismatic, monoclinic, M, 270.29; $V = 1393.2(4)$ Å^3; $a = 13.581(2)$, $b = 11.6960(8)$, $c = 8.7717(6)$ Å; $\beta = 90.700(8)°$; space group $P2_1/c$ (No. 14); $Z = 4$; $D_{calc} = 1.288$ g cm^{-3}; $F(000) = 568$; h, -15 to 15, k, -13 to 9, l, -8 to 9.

Data for **10**.—There were 2462 unique ($R_{int} = 0.102$) reflections in the 2621 collected. The final cycle of full-matrix least-squares refinement was based on 2168 observed reflections [$I > 3.00\sigma(I)$] and 208 variable parameters and converged (largest parameter shift was < 0.01 times its esd) with unweighted and weighted agreement factors of $R = 0.071$ and $R_w = 0.103$. The standard deviation of an observation of unit weight was 4.39.

Crystal data for **10**. Colourless, prismatic, triclinic, M, 315.37; $V = 831.0(2)$ Å^3; $a = 10.279(1)$, $b = 13.837(2)$, $c = 5.921(1)$ Å; $\alpha = 95.28(1)$, $\beta = 93.260(6)$, $\gamma = 83.489(9)°$; space group $P\bar{1}$ (No. 2); $Z = 2$; $D_{calc} = 1.260$ g cm^{-3}; $F(000) = 336$; h, -8 to 11, k, -15 to 15, l, -6 to 6.

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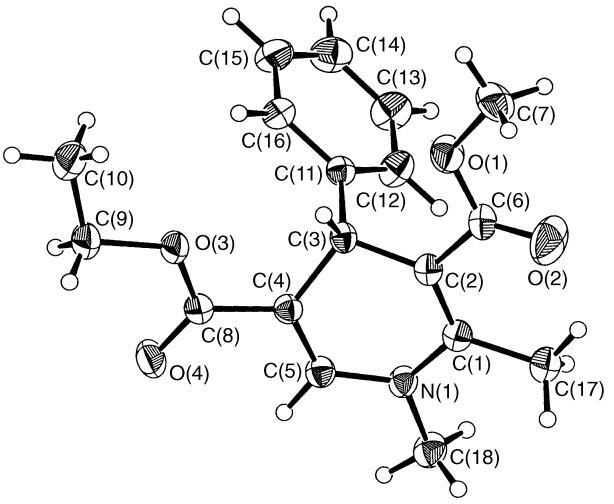

Fig. 3 ORTEP plot of **10**

Techniques used: IR, UV, ^{1}H NMR, mass spectrometry, X-ray crystallography

References: 22

Schemes: 1

Tables 1–9: Positional parameters and B(eq) values, intramolecular distances (non-hydrogen atoms) and intramolecular bond angles (non-hydrogen atoms) for **5**, **6** and **10**

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