Preparation and Benzoylation of 3-Hydroxy-2,3,5,5-tetramethyl-1-pyrroline 1-Oxide (3-Hydroxy-2,3,5,5-tetramethyl-4,5-dihydro-3*H*-pyrrole 1-Oxide)†,[1]

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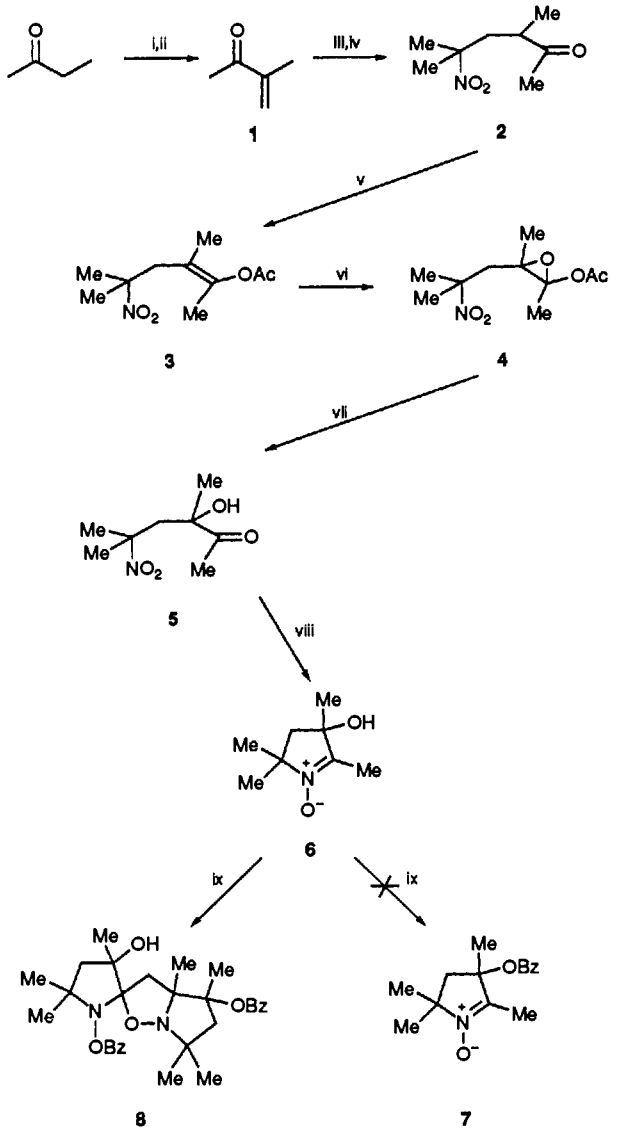
Treatment of 2,3,5,5-tetramethyl-3-hydroxy-1-pyrroline 1-oxide **6**, prepared from butanone in six steps, with benzoyl chloride under Schotten–Baumann conditions leads to an unprecedented dimerisation to give a spiro, tricyclic *N*-benzoyloxypyrrolidine in good yield.

The acylation of nitrones has been widely studied.[2-5] Nitrones lacking a proton β to the nitronyl carbon usually undergo *O*-acylation followed by a 1,2 migration of the acyloxy group to give an α-acyloxy imine which undergoes acidolysis resulting in the formation of an amide.[2] In the case of nitrones with a β proton, *O* acylation is usually followed by the 1,3 hetero-Cope migration of the acyloxy group to give β-acyloxy imines.[3-5] Aldo 1-pyrroline 1-oxides give 3-acyloxy 1-pyrrolines when treated with acid anhydrides,[3] acid chlorides[4] and chloroformates.[5] During our studies[1] of the preparation of 1-pyrroline 1-oxides bearing an electrophilic substituent at C-3, suitable to act as spin traps for the superoxide radical anion, we prepared the 3-hydroxy-1-pyrroline 1-oxide **6** which was treated with benzoyl chloride and pyridine in order to effect esterification. The desired putative ester, 3-benzoyloxy-2,3,5,5-tetramethyl-1-pyrroline 1-oxide **7** was not expected to be a useful spin trap for superoxide since it lacks a proton α to the nitronyl carbon and all spin adducts would give ESR spectra which were simple triplets as is observed for TMPO **16**.[6] However, it was intended to establish the principle that a 1-pyrroline 1-oxide with an electrophilic group at C-3 such as **7** could spin trap superoxide and subsequently 'cap' the hydroperoxy functionality of the resulting adduct *via* an intramolecular transesterification.

Results and Discussion

3-Hydroxy-2,3,5,5-tetramethyl-1-pyrroline 1-oxide was prepared from butanone according to Scheme 1. Butanone was treated with aqueous, basic paraformaldehyde to give the hydroxymethyl aldol adduct which, although not isolated, was then dehydrated with polyphosphoric acid and copper to give 3-methylbut-3-en-2-one **1** according to the method of Cook and Waring.[7] The α,β-unsaturated ketone **1** underwent the Michael addition of 2-nitropropane to give the γ-nitro ketone **2**. When **2** was treated with concentrated perchloric acid and acetic anhydride the enol acetate **3** was formed slowly. The extent of reaction was readily monitored by observing the diminution of the absorbance of the carbonyl stretch of the ketone at 1720 cm^{-1} with the simultaneous increase in the carbonyl stretch of the enol acetate at 1750 cm^{-1}. The enol acetate **3** was treated with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane to afford the acetoxy epoxide **4**, treatment of which with mineral acid in refluxing ethanol afforded the 3-hydroxyhexan-2-one **5**. Reduction of the γ-nitro ketone with zinc dust and aqueous ammonium chloride afforded the 3-hydroxy-1-pyrroline 1-oxide **6** in good yield.



Scheme 1 i, $(CH_2O)_n$, $NaOH_{aq}$; ii, H_2PO_4, Cu, reflux; iii, Me_2CHNO_2, Triton B©, THF; iv, HCl_g; v, Ac_2O, CCl_4, $HClO_4$(conc.); vi, *m*-CPBA; vii, 2 mol dm^{-3} HCl, EtOH, reflux; viii, Zn, NH_4Cl, THF, H_2O; ix, py, PhCOCl (1 equiv.).

The IR spectrum of the hydroxy nitrone **6** shows strong absorptions at 3129 (hydroxy) and 1617 cm^{-1} (C=N). The ^1H NMR spectrum shows four methyl groups including one with a chemical shift of 1.97 ppm which is consistent with a 2-methyl-

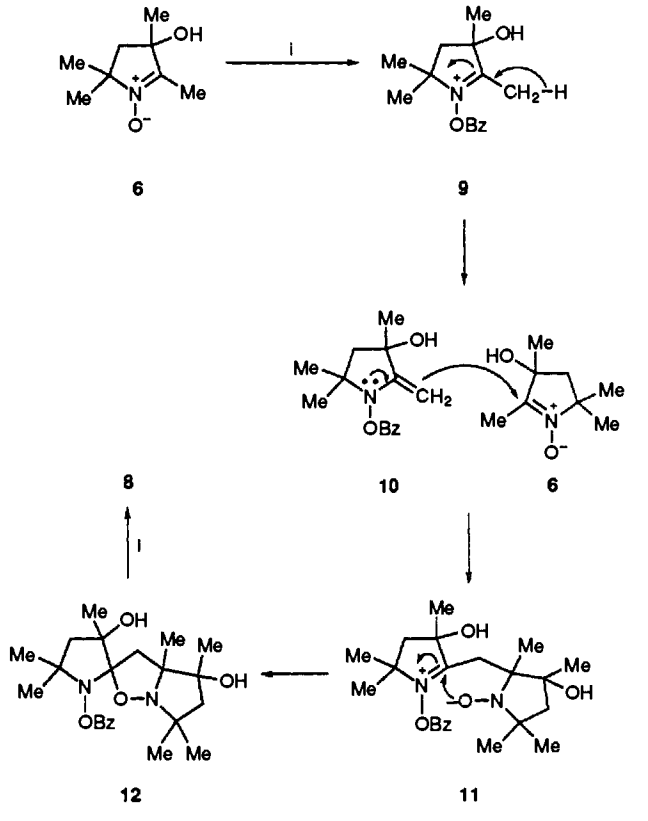
† Although in the earlier sections of this paper the compounds are, for convenience, described as 1-pyrrolines, the IUPAC-approved names are given in the Experimental section.

1-pyrroline 1-oxide.[8] The 4-CH_2 protons give an AB quartet (J 12 Hz) and there is a broad, exchangeable signal arising from the hydroxy proton. The ^{13}C NMR spectrum shows only seven signals due to equivalence of two of the methyl groups. C-2 has a chemical shift of 147.4 ppm which is characteristic of a 2-methyl-1-pyrroline 1-oxide[8] while C-3 has a chemical shift of 72.34 ppm which is consistent with a quaternary carbon bonded to a hydroxy group.

Treatment of the 3-hydroxy-1-pyrroline 1-oxide **6** with benzoyl chloride (1 equiv.) and pyridine in dichloromethane failed to induce simple esterification of the hydroxy functionality to give the ester **7**, but, instead, the spiro tricyclic *N*-benzoyloxyamine **8** was isolated in good yield. The latter shows strong absorption in the IR region at 3397 (hydroxy) and 1746 and 1738 cm^{-1} (C=O). Apart from a weak band at 1601 cm^{-1} arising from the 'ring breathing' stretch of the phenyl C=C bonds there is no absorbance in the range 1500–1700 cm^{-1} which demonstrates the absence of C=N bonds.

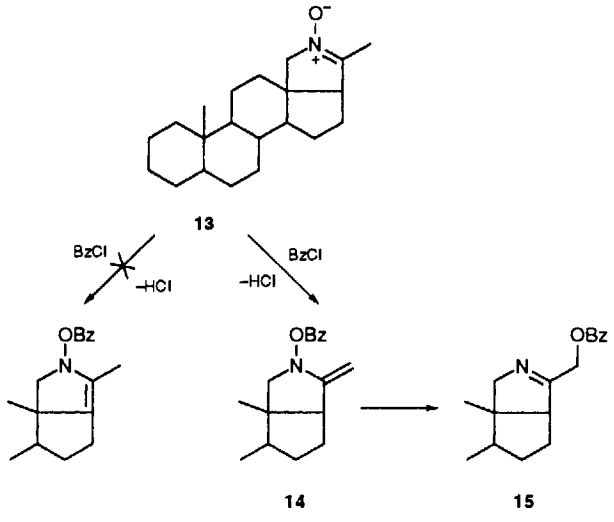
The ^1H NMR spectrum of **8** shows seven methyl resonances, signals from six other aliphatic protons comprising three AB spin systems and also signals arising from ten aromatic protons. There is a broad signal which integrates for one proton which is assigned to an OH group. The ^{13}C and 3/4 π NMR spectra reveal the following: (a) There are 26 non-equivalent carbons including 7 methyls, 3 methylenes, 6 aliphatic quaternaries, 8 aromatics and 2 carbonyls. (b) There are no signals which may be assigned to a 1-pyrrolinyl carbon (160–175)[8,9] or to a keto 1-pyrroline 1-oxide (140–150 ppm).[8] (c) Of the 6 aliphatic quaternary carbons, one has a chemical shift of 106.1 ppm and therefore must be bonded to two electronegative atoms. There is only one singlet arising from a carbon bonded to a benzoyloxy group (87.72 ppm) and, consequently, only one of the hydroxy groups is esterified and the remaining benzoyl group must be present as an acyloxyamine. The unesterified tertiary alcohol gives rise to a signal at 75.48 ppm.

A suggested mechanism for the formation of **8** is shown in Scheme 2. It has been shown that the nitronyl oxygen of 1-pyrroline 1-oxides is a good electrophile[1] and it would be expected that treating the nitrone **6** with benzoyl chloride would lead initially to the formation of the *N*-benzoyloxyiminium cation **9**. It is proposed that the cation **9** undergoes deprotonation at the 2-methyl group to give the *N*-benzoyloxy-2,2′-*exo*-methylenepyrrolidine **10** which does not undergo the expected hetero-Cope rearrangement to 2-benzoyloxymethyl-3,5,5-trimethyl-3-hydroxy-1-pyrroline but adds nucleophilically to a molecule of unchanged nitrone **6** with the tandem ring closure of the intermediate bridged *N*-benzoyloxyiminium-*N*′-hydroxonium species **11** to give the spiro tricyclic dialcohol **12**. This dialcohol undergoes selective benzoylation of one of the hydroxy groups. It was not possible to determine the site of benzoylation spectrometrically. Molecular modelling of the dialcohol **12** suggests that the hydroxy groups are in practically identical environments since the fused bicyclic rings attached at the pyrrolidinyl 2′-position do not give rise to increased steric crowding of the 3′-OH. In structure **8** the 6-OH has been arbitrarily indicated as the site of benzoylation in preference to 3′-OH, however this is conjectural.



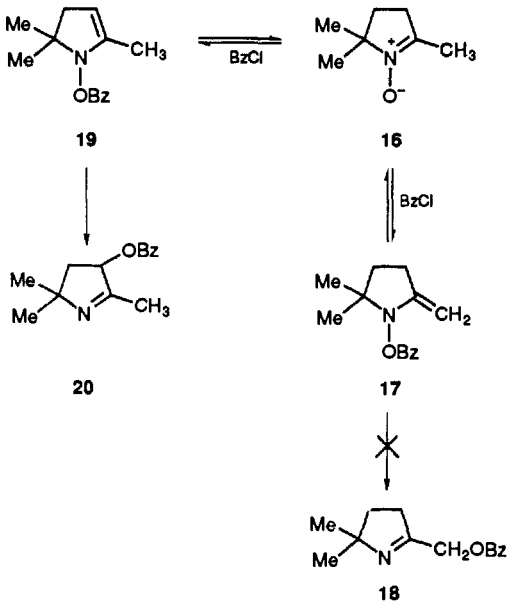
Scheme 2 i, PhCOCl (0.5 equiv.)

When Alazard and co-workers[10] treated the fused pentacyclic 2-methyl-1-pyrroline 1-oxide **13** with benzoyl chloride, *O*-benzoylation was followed by deprotonation of the 2-methyl group to give the exocyclic 2,2′-*exo*-methylene-*N*-benzoyloxypyrrolidine **14** which underwent a hetero-Cope rearrangement to give the 2-benzoyloxymethylpyrrolidine **15**. There is no report of the nucleophilic attack of the intermediate **14** upon unchanged 1-pyrroline 1-oxide, probably due to the large steric bulk of these steroid-based nitrones. Also no β-deprotonation at C-3 was observed since this would necessitate forming a bridgehead double bond at the junction of two fused five-membered rings which would not be favoured.



Scheme 3

When Black and Strauch[11] treated 2,5,5-trimethyl-1-pyrroline 1-oxide **16** with benzoyl chloride in pyridine, of the two possible β-benzoyloxy-1-pyrrolines only the 3-benzoyloxy adduct **20** was formed. Initial benzoylation is followed by β deprotonation to give an α,β unsaturated *N*-benzoyloxypyrrolidine prior to the Hetero–Cope rearrangement to the product β-benzoyloxy-1-pyrroline. It is unclear whether the non-formation of the 2-benzoyloxymethyl-1-pyrroline **18** is due to the relative rate of β-deprotonation at C-3 being greater than at 2-Me so that the formation of the 2,2′-*exo*-methylene-*N*-benzoyloxypyrrolidine **17** is disfavoured or whether both the α,β unsaturated *N*-benzoyloxypyrrolidines **17** and **19** exist in equilibrium but the latter undergoes rearrangement to the β-



Scheme 4

benzoyloxy-1-pyrroline at a much faster rate than does the former.

The benzoylation of the 3,3-disubstituted-1-pyrroline 1-oxide **6** presents an intermediate case. As with the fused bicyclic nitrone **13**, *O*-benzoylation can only be followed by β-deprotonation of the 2-methyl group to give the *N*-benzoyloxy-2-*exo*-methylenepyrrolidine **10**. In this case nucleophilic attack by **10** on unchanged nitrone is more rapid than rearrangement to the corresponding 2-benzoyloxymethyl-1-pyrroline. This observation suggests that such rearrangements are slow and are probably only feasible when, for structural reasons, both β-deprotonation at C-3 is prevented and when nucleophilic reactions of the intermediate *N*-benzoyloxy-2-*exo*-methylenepyrrolidine are sterically hindered.

Experimental

For instrumentation details see previous paper in series.[1]

3-*Methylbut*-3-*enone* **1**.—The ketone **1** was prepared from butanone according to the method of Cook and Waring;[7] b.p. 98–100 °C (lit.,[7] 98–100 °C), m.p. of 2,4-dinitrophenylhydrazone 186–187 °C (lit.,[7] 189.5–191.5 °C).

3,5-*Dimethyl*-5-*nitrohexan*-2-*one* **2**.—3-Methylbut-3-enone (11.47 g, 0.136 mol) in dried tetrahydrofuran (THF) (30 cm^3) was added over 2 h to a solution of freshly distilled 2-nitropropane (18.25 g, 0.205 mol) and Triton B* (1 cm^3) in dried THF (20 cm^3) at 5 °C with vigorous stirring. The reaction mixture was quenched by acidification with hydrogen chloride gas and concentrated to afford an oil which was distilled to give the title nitro ketone (19.3 g, 82%) as an oil, b.p. 80–85 °C at 0.1 mmHg (lit.,[3b] 118–120 °C at 2 mmHg); ν_{max}/cm^{-1} 1718 and 1537.

3-*Hydroxy*-3,5-*dimethyl*-5-*nitrohexan*-2-*one* **5**.—A solution of the hexanone **2** (3.92 g, 0.022 mol) in carbon tetrachloride (20 cm^3) was treated with acetic anhydride (8.13 g, 0.080 mol) and perchloric acid (70%; 0.5 cm^3) with stirring. After 24 h the FTIR spectrum of the solution revealed that the carbonyl stretch of the ketone at 1718 cm^{-1} was absent and had been replaced by a band at 1750 cm^{-1} arising from the enol acetate **3**. Water (50 cm^3) and ether (70 cm^3) were added to the dark brown solution followed by potassium hydrogen carbonate, added in portions until all effervescence ceased. The aqueous phase was separated and extracted with ether (50 cm^3) and the combined ether fractions were washed with water (30 cm^3), dried ($CaCl_2$) and concentrated to afford an oil. This was taken up in dichloromethane (DCM) (20 cm^3) and *m*-CPBA (50% active peracid; 7.80 g, 0.022 mol) was added slowly to the solution with stirring. After 48 h the precipitated *m*-chlorobenzoic acid was collected and the filtrate was concentrated under reduced pressure to 15 cm^3. After 2 h a further crop of *m*-chlorobenzoic acid was collected and the filtrate was reduced to a colourless solid. This was taken up in ethanol (100 cm^3) and treated with hydrochloric acid (2 mol dm^{-3}; 20 cm^3) for 2 h under reflux. The cooled solution was concentrated to 30 cm^3 and extracted with chloroform (2 × 40 cm^3). The combined extracts were washed successively with sat. aqueous sodium hydrogen carbonate (2 × 30 cm^3) and water (2 × 30 cm^3) and then dried ($MgSO_4$) and evaporated to give the title hydroxy ketone (1.77 g, 45% based on ketone **2**) which was recrystallised from DCM to give large off-white prisms, m.p. 72–73 °C (Found: C, 51.2; H, 8.1; N, 7.3. $C_8H_{15}NO_6$ requires C, 50.8; H, 8.0; N, 7.4%); ν_{max}/cm^{-1} 3451, 1700, 1541, 1455, 1406, 1352, 1192, 1169 and 1151; δ_H 1.31 (3 H, s, 3-CH_3), 1.50, 1.55 (both 3 H, s, *gem*-CH_3), 2.26 (3 H, s, $COCH_3$), 2.48 (1 H, d, *J* 15.5, 4-H), 2.67 (1 H, d, *J* 15.5, 4′-H) and 3.56 (1 H, br s, OH); δ_C 23.52, 25.26, 27.76, 28.32 (4 × CH_3), 46.51 (C-4), 77.69 (C-3), 86.07 (C-5) and 211.6 (C=O).

3-*Hydroxy*-2,3,5,5-*tetramethyl*-4,5-*dihydro*-3H-*pyrrole* 1-*Oxide* **6**.—A mixture of the hexanone **5** (0.918 g, 4.85 mmol), THF (30 cm^3), water (30 cm^3) and ammonium chloride (1.35 g, 25.2 mmol) was cooled to 0–5 °C. Zinc dust (3.12 g, 47.7 mmol) was added slowly to the mixture over 2 h with vigorous stirring after which stirring was continued for a further 2 h. The zinc salts were then collected and washed with THF (2 × 20 cm^3) and the combined filtrate and washings were reduced to 20 cm^3 and extracted with chloroform (2 × 30 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure and the residue was recrystallised from ether–acetone (1:1) to give the title nitrone **6** (0.549 g, 72%) as large plates, m.p. 109–110 °C (Found: M^+, 157.1103. $C_8H_{15}NO_2$ requires M^+, 157.1103); ν_{max}/cm^{-1} 3219, 1617, 1474, 1458, 1437, 1375, 1319, 1310, 1242, 1227 and 1184; δ_H 1.6 (3 H, s, 3-CH_3), 1.44, 1.45 (both 3 H, s, *gem*-CH_3), 1.97 (3 H, s, 2-CH_3), 2.11 (1 H, d, *J* 12.0, 4-H), 2.22 (1 H, d, *J* 12.0, 4′-H) and 4.66 (1 H, br s, OH); δ_C 9.05, 26.48, 26.90 (4 × CH_3), 49.32 (C-4), 72.34 (C-3), 75.64 (C-5) and 147.4 (C-2); *m*/*z* (EI) 157 (M^+, 5%), 142 (10) and 43 (100); *m*/*z* (NH_3 chemical ionisation) 158 (M^+ + 1, 100%), 142 (10) and 140 (21).

1,6-*Dibenzoyloxy*-3′,5′,5′,5,6,8,8-*heptamethyl*-3′-*hydroxy*-*spiro*[2-*oxa*-1-*azabicyclo*[3.3.0]*octane*-3,2′-*pyrrolidine*] **8**.—A stirred solution of the 1-pyrroline 1-oxide **6** (98 mg, 0.62 mmol) and pyridine (49 mg, 0.62 mmol) in DCM (5 cm^3) was treated with benzoyl chloride (87 mg, 0.62 mmol) over 16 h. It was then diluted with DCM (20 cm^3), and washed with sat. aqueous potassium hydrogen carbonate (2 × 10 cm^3), dried ($MgSO_4$) and evaporated to provide a foam, m.p. 69–70 °C (Found: M^+ + 1, 523.2808. $C_{30}H_{39}N_2O_6$ requires *M* + 1, 523.2808); ν_{max}/cm^{-1} 3397, 1746, 1738, 1601, 1453, 1408, 1381, 1314 and 1246; δ_H 1.11, 1.19, 1.20, 1.21, 1.30, 1.37, 1.55 (each 3 H, s, 7 × CH_3), 1.60 (1 H, d, *J* 15.1), 1.81 (1 H, d, *J* 12.0), 1.85 (1 H, d, *J* 13.8), 2.21 (1 H, d, *J* 12.0), 2.45 (1 H, d, *J* 13.8), 2.48 (1 H, d, *J* 15.1), 5.14 (1 H, br s, OH) and 7.38–8.04 (10 H, m, 2 × ArH); δ_C 17.30q, 25.45q, 25.55q, 26.80q, 29.10q, 29.24q, 29.55q (7 × CH_3), 41.60t (C-4), 50.36t (C-4′), 51.16t (C-2), 62.22s (C-8), 65.16s (C-

* Triton B: Benzyltrimethylammonium hydroxide, 40% wt. solution in methanol, Aldrich Chemical Company Ltd.

5'), 74.00s (C-5), 75.48s (C-3'), 87.27s (C-6), 106.1 (C-3), 128.5d, 128.6d, 129.1d, 129.3d, 129.6d, 129.7d, 133.2d, 133.6d (2 × ArH), 166.3s and 166.9s (2 × C=O); *m/z* (EI) 523 (M^+ + 1, 2%), 401 (71), 343 (10), 302 (12), 281 (35), 279 (34), 262 (38), 244 (18), 221 (26), 264 (23), 140 (18), 124 (25), 122 (32), 105 (100), 77 (36) and 43 (33); *m/z* (NH_3 chemical ionisation) 523 (M^+ + 1, 10%), 401 (45), 281 (100), 279 (50), 262 (45) and 105 (18).

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