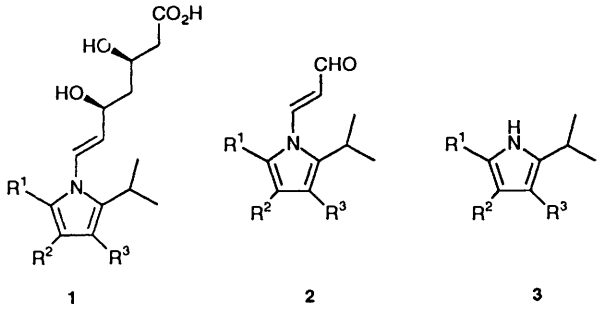
A Novel Oxidatitive Rearrangement of a Pentasubstituted Pyrrole to an Unsaturated Hydroxy γ-Lactam

Panayiotis A. Procopiou* and Rona M. Highcock
Glaxo Group Research, Greenford, Middlesex, UK UB6 0HE

Treatment of a pentasubstituted bromopyrrole with *N*-bromosuccinimide resulted in a novel oxidative rearrangement involving insertion of oxygen, debromination and migration of an isopropyl group to give 3-[2-(4-fluorophenyl)-1,5-dihydro-2-hydroxy-4-isopropyl-5-oxo-3-(4-pyridyl)-1*H*-pyrrol-1-yl]propionitrile, an X-ray crystallographic structural determination of which is described.

We have recently described[1] the synthesis and biological activity of a series of 7-(2,3-diaryl-5-isopropyl-1*H*-pyrrol-1-yl)-3,5-dihydroxyhept-6-enoates **1**, a novel class of potent inhibitors of the enzyme 3-hydroxy-3-methylglutaryl CoA-reductase. These compounds were prepared by addition of the dianion of methyl acetoacetate to the 3-(pyrrol-1-yl)acrylaldehyde **2**, followed by stereoselective reduction of the resulting δ-hydroxy β-keto ester. The aldehydes **2** were, in turn,



1 **2** **3**

prepared by reaction of the anion of the pyrrole **3** with ethyl propiolate, followed by a two-step reduction–oxidation process.

N-Alkylation of the trisubstituted pyrroles **3** proceeded cleanly in contrast to that of tetrasubstituted compounds which gave a predominance of *C*-alkylated products in a messy reaction. Furthermore, enhanced biological activity was observed with the heptenoates **1** bearing a 3-bromo substituent **1** (R^3 = Br). We envisaged preparing compound **2** (R^1 = 4-fluorophenyl, R^2 = 4-pyridyl) by introducing a double bond into the cyanoethyl side-chain of the pyrrole **4** and then converting the nitrile group into an aldehyde. Thus, treatment of the diketone[2] **5** with 3-aminopropionitrile in refluxing acetic acid gave **6** (39%). Treatment of compound **6** with lithium bis(trimethylsilyl)amide (1 equiv.), followed by D_2O quench provided cleanly the parent pyrrole **3** by elimination. Bromination[3] of compound **6** with *N*-bromosuccinimide (NBS; 1 equiv.) in *N*,*N*-dimethylformamide (DMF) at 20 °C gave the bromopyrrole **4** (72%). In an attempt to introduce bromine into the propionitrile side-chain to facilitate the formation of the olefinic bond, treatment of **4** with further (1 equiv.) NBS at 20 °C for 2 days provided no product. However, addition of a catalytic amount of the radical initiator AIBN resulted in the novel and highly substituted lactam **7** (42%) by an unprecedented oxidative rearrangement. The structure of **7** was confirmed by an X-ray crystallographic determination (Fig. 1). Although the mechanism of this reaction is not known, it is plausible that it proceeds by addition of molecular oxygen to form the 2,5-transannular peroxide **8** which then undergoes rearrangement to the epoxide

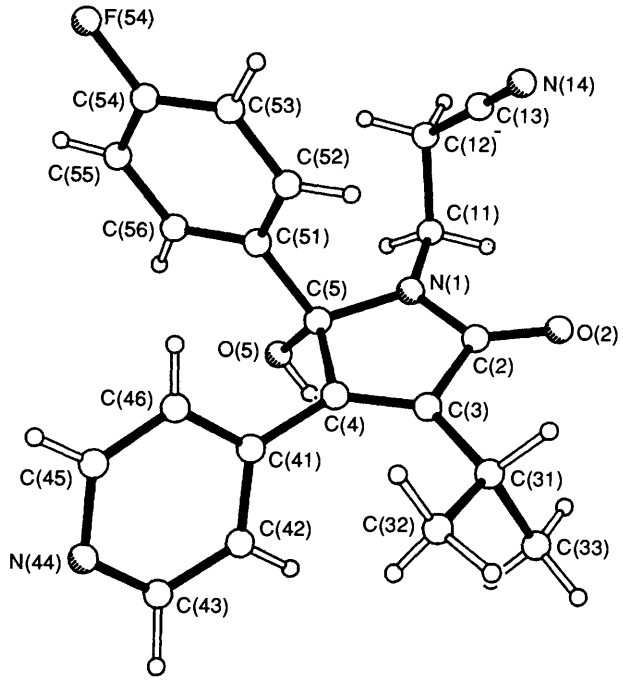
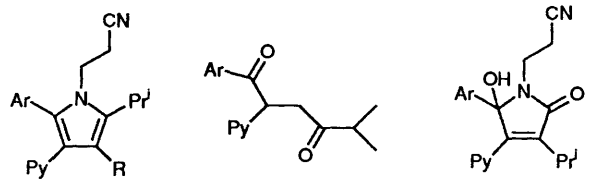


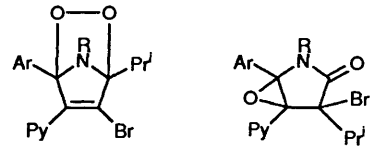
Fig. 1

9; elimination of bromine from this provides the allylic alcohol **7**. Intermediates analogous to the 2,5-endoperoxide **8** and epoxide **9** in substituted furans have been isolated[4,5] and reported to rearrange to 5-hydroxyfuran-2(5*H*)-ones **10**. Similarly, photooxygenation of the trisubstituted pyrrole **11** is



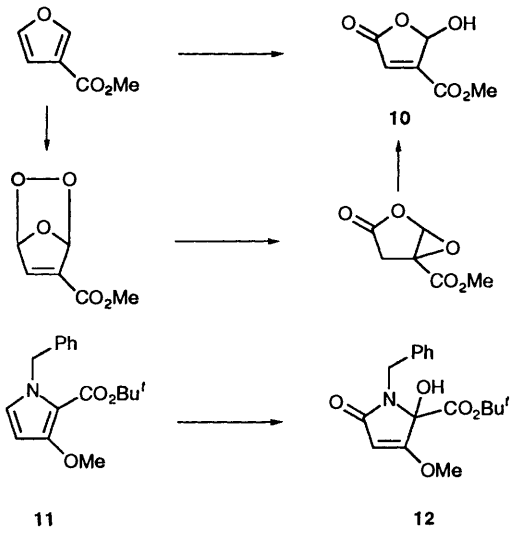
4 R = Br
6 R = H

5 **7**



8 **9**

Ar = *p*-FC_6H_4, Py = 4-pyridyl



reported[6] to give the hydroxy lactam **12** (45%). The oxidative rearrangement of **4**, however, is unusually facile in that it proceeded in the absence of any sensitiser or photolysis equipment.

Experimental

Organic solutions were dried over $MgSO_4$, and column chromatography was performed on silica gel 60 (Merck, Art. No. 7734). IR spectra were recorded on a Nicolet 5SXC FTIR spectrometer, NMR spectra were recorded on a Bruker AM250, and UV spectra were recorded on a Hewlett-Packard 8452A spectrophotometer. Mass spectrometry was performed on a Finnigan MAT TSQ70B spectrometer, and elemental microanalyses were determined with a Perkin-Elmer 240C or a Carlo-Erba 1106 elemental analyser. *J* Values are recorded in Hz.

Synthesis of 3-[2-(4-*Fluorophenyl*)-5-*isopropyl*-3-(4-*pyridyl*)-1*H*-*pyrrol*-1-*yl*]*propionitrile* **6**.—A solution of 1-(4-fluorophenyl)-5-methyl-2-(4-pyridyl)hexane-1,4-dione **5** (2.44 g, 8 mmol) and 3-aminopropionitrile (1.75 g, 25 mmol) in glacial acetic acid (8 cm^3) was heated to reflux for 3 h. The mixture was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate and aqueous sodium hydrogen carbonate. The organic phase was washed with brine, dried and evaporated to dryness. The residue was recrystallised from methanol (30 cm^3) to give the title compound **6** as needles (1.04 g, 39%) (Found: C, 75.35; H, 6.1; F, 5.6; N, 12.5. $C_{21}H_{20}FN_3$ requires C, 75.65; H, 6.05; F, 5.7; N, 12.6%); $\nu_{max}(CHBr_3)/cm^{-1}$ 1599, 1510 and 845; λ_{max}(EtOH)/nm 258 (ε 15 500) and 300 (10 000); δ_H(250 MHz; $CDCl_3$) 1.36 [6H, d, *J* 7.5, $CH(CH_3)_2$], 2.37 (2 H, t, *J* 8, CH_2CN), 2.97 [1 H, sept, *J* 7.5, $CH(CH_3)_2$], 4.12 (2 H, t, *J* 8, NCH_2), 6.30 (1 H, s, pyrrole 4 H), 6.94 (2 H, d, *J* 6, pyridine 3- and 5-H), 7.18 (2 H, t, *J* 9, phenyl 3- and 5-H), 7.31 (2 H, dd, *J* 9 and 6, phenyl 2- and 6-H) and 8.33 (2 H, d, *J* 6, pyridine 2- and 6-H).

Treatment of Compound **6** with *Base*.—A solution of the nitrile **6** (102 mg, 0.3 mmol) in THF (3 cm^3) was added at −70 °C to a THF solution of sodium bis(trimethylsilyl)amide (1 mol dm^{-3}; 0.5 cm^3) to give, immediately, a dark brown solution. The mixture was stirred at −70 °C for 10 min after which D_2O (1 cm^3) was added to it and the whole allowed to warm to room temperature. The mixture was acidified with 2 mol dm^{-3} hydrochloric acid and extracted with ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and brine, dried, evaporated to dryness, filtered to remove a polymeric material (presumably polyacrylonitrile) and purified by preparative TLC (ethyl acetate–cyclohexane, 1:1) to give the pyrrole **3** (R^1 = 4-fluorophenyl, R^2 = 4-pyridyl, R^3 = H) (70 mg, 83%) (Found: C, 76.9; H, 6.2; N, 9.8. $C_{18}H_{17}FN_2$ requires C, 77.1; H, 6.1; N, 10.0%); δ_H(250 MHz; [$^2H_6$]DMSO) 1.25 [6 H, d, *J* 7, $CH(CH_3)_2$], 2.90 [1 H, sept, *J* 7, $CH(CH_3)_2$], 6.13 (1 H, d, *J* 2, pyrrole 4-H), 7.15 (2 H, d, *J* 7, pyridine 3- and 5-H), 7.22 (2 H, t, *J* 9, phenyl 3- and 5-H), 7.37 (2 H, dd, *J* 9 and 5, phenyl 2- and 6-H), 8.34 (2 H, d, *J* 5, pyridine 2- and 6-H) and 11.08 (1 H, br s, NH).

Synthesis of 3-[3-*Bromo*-5-(4-*fluorophenyl*)-2-*isopropyl*-4-(4-*pyridyl*)-1H-*pyrrol*-1-*yl*]*propionitrile* **4**.—A solution of compound **6** (106 mg, 0.32 mmol) in DMF (2 cm^3) was treated with NBS (60 mg, 0.34 mmol) in one portion and the solution was stirred at 20 °C for 5 h. The mixture was then diluted with ethyl acetate and poured into water. The organic phase was washed with aqueous sodium bisulphite, aqueous sodium hydrogen carbonate and brine, dried and evaporated to dryness. The residue was chromatographed on silica gel eluting with ether–cyclohexane (1:1) to give **4** as a white solid (94 mg, 72%) (Found: C, 61.2; H, 4.7; N, 9.9. $C_{21}H_{19}BrFN_3$ requires C, 61.2; H, 4.6; N, 10.2%); ν_{max}(Nujol)/cm^{-1} 2250w, 1601, 1513 and 846; λ_{max}(EtOH)/nm 260 (ε 12 700); δ_H(250 MHz; $CDCl_3$) 1.53 [6 H, d, *J* 7, $CH(CH_3)_2$], 2.44 (2 H, t, *J* 8, CH_2CN), 3.20 [1 H, sept, *J* 7, $CH(CH_3)_2$], 4.17 (2 H, t, *J* 8, NCH_2), 7.00–7.22 (6 H, m, ArH) and 8.42 (2 H, d, *J* 5.5, pyridine 2- and 6-H); *m/z* (thermospray) 412 and 414 [$(M + H)^+$, 100%].

Synthesis of 3-[2-(4-*Fluorophenyl*)-1,5-*dihydro*-2-*hydroxy*-4-*isopropyl*-5-*oxo*-3-(4-*pyridyl*)-1H-*pyrrol*-1-*yl*]*propionitrile* **7**.—A solution of compound **4** (88 mg, 0.21 mmol) in DMF (2 cm^3) was treated with NBS (48 mg, 0.27 mmol) and the mixture was stirred at 20 °C for 2 days. TLC showed no change. AIBN (3 mg) was added to the solution which was then stirred for a further 2 days at 20 °C. The mixture was diluted with ethyl acetate and poured into water. The organic phase was washed with water, aqueous sodium bisulphite, aqueous sodium hydrogen carbonate and brine, dried and evaporated to dryness. The residue was chromatographed on silica gel eluting with ethyl acetate–cyclohexane (1:1) and crystallised from methanol to give **7** (32 mg, 42%) (Found: C, 68.25; H, 5.45; N, 11.3. $C_{21}H_{20}FN_3O_2 \cdot 0.33CH_3OH$ requires C, 68.1; H, 5.7; N, 11.2%); $\nu_{max}(CHBr_3)/cm^{-1}$ 3551, 1697, 1602 and 1508; λ_{max}(EtOH)/nm 225 (ε 9600), 252infl (5200) and 267infl (4100); δ_H(250 MHz; $CDCl_3$) 1.24 and 1.28 [3 H each, d, *J* 7, $CH(CH_3)_2$], 2.56 (1 H, dt, *J* 17 and 7, CH_2CN), 2.82 [1 H, m, $CH(CH_3)_2$], 2.86 (1 H, dt, *J* 17 and 7, CH_2CN), 3.13 and 3.72 (1 H, each, dt, *J* 14 and 7 Hz, NCH_2), 4.36 (s, OH), 6.87 (2 H, d, *J* 5, pyridine 3- and 5-H), 7.04 (2 H, t, *J* 8, phenyl 3- and 5-H), 7.28 (2 H, dd, *J* 8 and 5, phenyl 2- and 6-H) and 8.46 (2 H, d, *J* 5, pyridine 2- and 6-H); $\delta_c(CD_3OD)$ 14.6 (t), 17.7 (q), 18.0 (q), 24.1 (d), 33.0 (t), 89.5 (s), 113.5 (dd, *J* 24), 115.9 (s), 122.1 (d), 126.4 (dd, *J* 10), 130.6 (s) 137.4 (s), 139.6 (s), 146.6 (d), 149.1 (s), 161.2 (d, *J* 250) and 167.9 (s); *m/z* (CI/CH_4) 394 [$(M + C_2H_5)^+$, 28%], 366 [$(M + H)^+$, 100%], 348 [$(MH - H_2O)^+$, 85%] and 322 [$(MH - H_2O - CN)^+$, 30%].

Crystal Structure Analysis of the Lactam **7**.—*Crystal data*. $C_{21}H_{20}FN_3O_2$, *M* = 365.41, Monoclinic, *a* = 8.491(2), *b* = 19.593(5), *c* = 11.926(2) Å, β = 107.77(1)°; *V* = 1889(1) Å^3 (by least-squares refinement on diffractometer angles for 18 automatically centred reflections, λ = 1.541 84Å). Space group $P2_1/n$ (alt. $P2_1/c$, No. 14), *Z* = 4, D_c = 1.28 g cm^{-3}, *F*(000) = 768, μ(Cu-Kα) = 0.71 mm^{-1}. Data crystal had approximate dimensions 0.41 × 0.30 × 0.25 mm.

Data collection and processing. Three-dimensional, room temperature (295 K) X-ray data collected on a Siemens R3m/V diffractometer with monochromatised Cu-Kα X-radiation. $2\theta/\omega$ mode with scan range (ω) 1.2 degrees plus Kα separation and a variable scan speed (1.95–14.65 deg min^{-1}). 2874 Reflections were measured ($0 < 2\theta < 115°$, min. *hkl* 0 0 −13, max. *hkl* 9 21 12) of which 2569 were unique [*R*(sigma) = 0.014, Friedel opposites merged] and 2289 had $I > 3.0\ \sigma(I)$. 3 Control data monitored every 97 reflections showed no appreciable decay during 41.2 h of exposure of the crystal to X-rays.

Structure Analysis and Refinement.—Direct methods resulted in the location of all the non-hydrogen atoms. Full matrix least-squares refinement with anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were refined isotropically. Individual weights were applied according to the scheme $w = [\sigma^2(F_o) + 0.0023\ |F_o|^2]^{-1}$, refinement converged at *R* 0.047, R_w 0.062, goodness-of-fit = 1.67. Maximum and mean shift/error in final cycle of refinement was 0.228 and 0.025 respectively. The final electron density difference synthesis showed no peaks >0.31 or holes< −0.27 e Å^{-3}. All computations were carried out using the SHELXTL PLUS [7] (μ-VAX II) system of programs.

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