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SYNTHESIS OF 2-(2-OXOPYRROLIDIN-1-YL)-1,4-QUINONES AND A HYDROGEN-BONDED 2-ALKYLAMINO-1,4-NAPHTHOQUINONE

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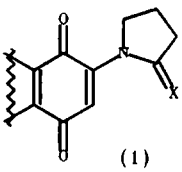
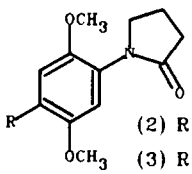
Abstract. Oxidation of four 1-(2,5-dimethoxyaryl)pyrrolidin-2-ones with silver(II) oxide in acidic medium gave the corresponding quinones in moderate to good yield. 1,4-Naphthoquinone and 2-methoxy-Δ^1-pyrroline reacted in methanol to give 2-(3-methoxycarbonylpropylamino)-1,4-naphthoquinone [**16**], the structure and hydrogen bonding characteristics of which were determined by *X*-ray crystallography

1,4-Benzoquinones and 1,4-naphthoquinones bearing 2-acylamino substituents are component structures of certain classes of natural products[1], notably the ansamycin antibiotics. Quinones fused to heterocyclic rings are also widespread in nature, the mitomycin antibiotics[2] providing examples of particular interest. For model studies relating to the synthesis of some of these compounds and their synthetic analogues, we required quinone-substituted pyrrolidinones and pyrrolidinethiones of general structure [**1**]. Perhaps half-a-dozen compounds of this sort have been reported in the literature[3-5], and their preparation has hitherto only been by oxidation or cyclisation of suitable aminoquinones. Having ready access to a number of 1-(2,5-dimethoxyaryl)pyrrolidin-2-ones for another project[6], we examined the feasibility of preparing the target quinones by oxidative demethylation of these substrates according to one of several methods currently available for the oxidative demethylation of *p*-dimethoxyarenes[7].

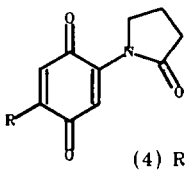
1-(2,5-Dimethoxyphenyl)pyrrolidin-2-one [**2**][6] was used in exploratory work. On treatment of [**2**] with the nitric acid - dichloromethane reagent developed by Rapoport and Luly[8], the only product isolated was 1-(2,5-dimethoxy-4-nitrophenyl)pyrrolidin-2-one [**3**] (94%). Another commonly used oxidant, ceric ammonium nitrate[9], also produced the nitrated product [**3**] in variable but low yield, the reaction providing an example of an unusual, but not unprecedented[10], aromatic nitration by a metal nitrate. Ceric ammonium nitrate used in conjunction with the *N*-oxide of pyridine-2,6-dicarboxylic acid[11], or preceded by demethylation of the substrate with boron tribromide[12], led to destruction of starting material; while the use of nitrous acid[13] or manganese dioxide - nitric acid[14] left the starting material largely untouched. Only with another Rapoport reagent, silver(II) oxide - nitric acid,[15] were we able to isolate the desired, but unstable, quinone [**4**] in moderate yield (26.6%). An alternative approach to quinone [**4**], involving treatment of the phenolic lactam [**5**][16] with Fremy's salt[17], also failed.



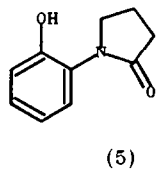
(1)



(2) R = H
(3) R = NO_2
(6) R = Br
(8) R = OCH_3



(4) R = H
(7) R = Br
(12) R = OCH_3



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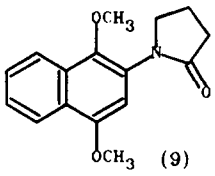

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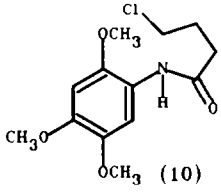

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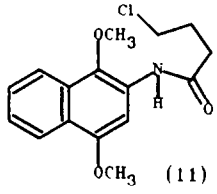

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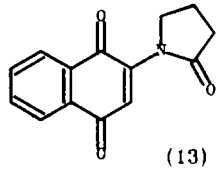
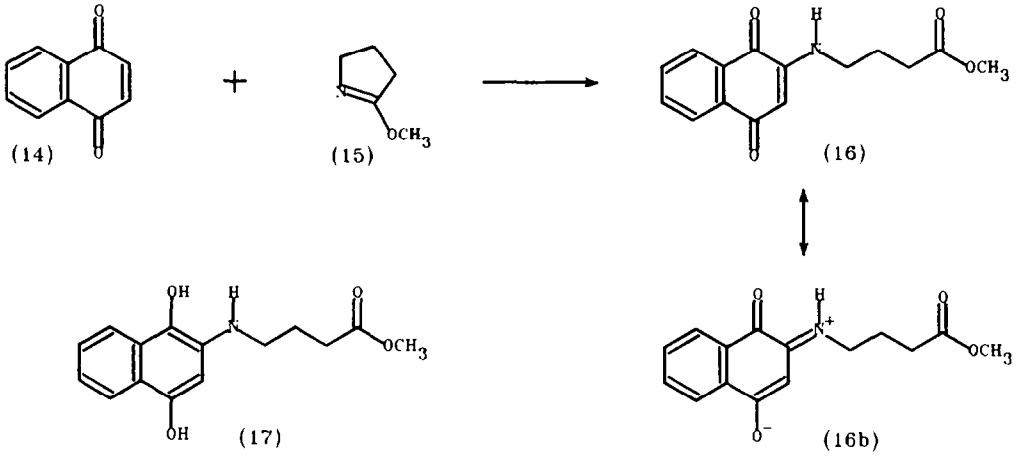


(13)

The problem in accomplishing the oxidation of lactam [**2**] must stem, at least in part, from the nucleophilicity of the 4-position of the aromatic ring. The obvious extension was thus to examine the effect of blocking groups at this position. The 4-bromo group was easily and quantitatively introduced by treating [**2**] with bromine in acetic acid. Oxidation of the brominated product [**6**] with silver(II) oxide and nitric acid was also easy, and reproducibly gave quantitative yields of quinone [**7**]. Thus encouraged, we prepared two further "blocked" lactams [**8**] and [**9**] by acylating the appropriate anilines with 4-chlorobutanoyl chloride and cyclising the amide products [**10**] and [**11**] with sodium ethoxide in ethanol. Oxidation of lactams [**8**] and [**9**] with the silver(II) oxide reagent gave quinones [**12**] and [**13**] in yields of 39% and 77% respectively. The substitution patterns in these two cases are reminiscent of those found in several quinonoid natural products. The four quinones prepared by this route were isolated by flash chromatography[18] and could be purified for spectroscopic characterisation up to a point by the same technique, but did not survive prolonged handling.

An alternative approach to the synthesis of quinone [**13**] was also investigated. Addition of the anion of pyrrolidin-2-one to a 1,4-quinone followed by reoxidation of the phenolic product seemed a reasonable option for preparing compounds of general structure [**1**, X = O], since conjugate additions to quinones are well documented[19]. However, though examples of the addition of amines to quinones abound, the only amides that appear to have been investigated are urea[20] and a number of (3*H*)-quinazolin-4-ones[21]. When trial reactions between pyrrolidin-2-one and 1,4-naphthoquinone [**14**] failed to produce the desired adduct, we turned to the masked pyrrolidinone derivative 2-methoxy-Δ^1-pyrroline [**15**] as nucleophile, our reasoning being that the more nucleophilic imine should show a

greater tendency towards amine-like reactivity with quinones than the parent lactam would. In the event, while the reaction of 1,4-naphthoquinone and pyrroline [**15**] in methanol at 50 °C was not clean, one major new compound was isolated in moderate yield (25%) after column chromatography, together with unreacted naphthoquinone (23.5%) and 2-methoxy-1,4-naphthoquinone (18%). The new product, an intensely orange solid, was shown by elemental analysis and mass spectrometry to have the molecular formula $C_{15}H_{15}NO_4$. The open-chain structure [**16**], resulting from methanolysis of the heterocyclic ring of the expected structure [**13**], was indicated by the proton and carbon n.m.r. spectra. The sequence of events in the formation of [**16**] was not investigated, but mechanistic considerations suggest the intermediacy of a hydroquinone such as [**17**], which undergoes conversion to the observed product by redox exchange with quinone species present in the reaction mixture.



The nitrogen atom in [**16**], as part of a resonance-stabilised vinylogous amide system, should be planar. The n.m.r. spectrum shows distinct coupling between the N-H proton and the adjacent methylene group (J 5.6 Hz), implying that the conformation at N must be comparatively rigid. A strong nuclear Overhauser effect is also manifested between this methylene group and the vinylic hydrogen on the quinone ring. For this portion of the structure, the evidence supports an average conformation in solution as depicted in [**16**], with the N-H and C(1) = O bonds pointing roughly in the same direction. A small but noticeable concentration dependence of the N-H chemical shift suggests intermolecular hydrogen bonding in solution[22]. It is likely that hydrogen bonding and conformational effects are interdependent; if so, the orientations of the N-H bond and the proximal quinonoid carbonyl group are ideal for facilitating the intermolecular formation of hydrogen-bonded dimers or higher clusters. A single-crystal X-ray diffraction study was therefore undertaken to clarify conformational effects in the solid state, and to cast light on possible hydrogen bonding interactions.

The structure of [**16**] is shown in Figure 1. The C(2)-N-C(9) angle of 120.5° and the unequivocal planarity of the nitrogen atom both accord with a structure stabilised by a contribution from the canonical form [**16b**]. Further support for resonance stabilisation is provided by the N-C(2) bond length of 1.345 Å, which is close to the reported mean value of 1.339 Å for enamine systems[23]; the longer C(4)-O(2) bond relative to C(1)-O(1) (*cf.* Table 2); the noticeable shortness of C(3)-C(4) compared with C(1)-C(2); and the virtual coplanarity of the atoms of the quinone system and the side chain as far as C(9). The packing diagram given in Figure 2 shows the putative hydrogen bonding scheme. Within the unit cell, molecules at symmetry positions (x, $-y + 1.5$, $z - 0.5$) and ($1 - x$, $y + 0.5$, $-z + 1.5$) associate as dimers, while those at symmetry positions (x, y, z) and ($1 - x$, $1 - y$, $1 - z$) pair up similarly with molecules at ($1 - x$, $1 - y$, $2 - z$) and (x, y, $z - 1$) respectively in neighbouring unit cells on either side. Hydrogen atoms were placed in calculated positions during structural refinement, so one must regard the indicated locations of the H(N) atoms with circumspection. Even so, the O(1)...H-N intermolecular distance of 2.045 Å and the corresponding intramolecular distance of 2.288 Å are both short enough[24] to give credibility to the proposed arrangement of hydrogen bonds, which, as shown in the Figure, may well be bifurcated. It is of interest that the Cambridge Structural Database (Version 3.4, 1989) contains about 30 examples of acylamino- or aminoquinones, but only two of these (2-bromo-3-amino-1,4-naphthoquinone[25] and 3,6-dichloro-2,5-bis(methylamino)-1,4-benzoquinone[26]) seem to form the same type of dimeric aggregates that compound [**16**] does.

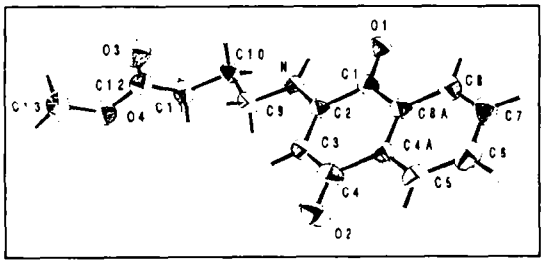


Figure 1. ORTEP-generated diagram of 2-(3-methoxycarbonylpropylamino)-1,4-naphthoquinone[**16**]showing the numbering scheme adopted for non-hydrogen atoms. Thermal ellipsoids are at 50% probability.

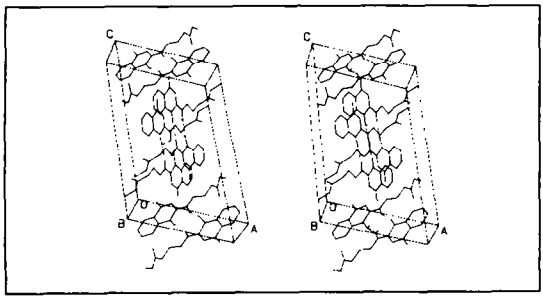


Figure 2. Stereoscopic packing diagram of [**16**]. Hydrogen atoms not involved in hydrogen bonding have been omitted for clarity.

EXPERIMENTAL

Routine measurements were on Kofler micro hot-stage (m.p), Pye-Unicam SP3-300 or PU 9512 (i.r.), Cary 2300 (u.v), AEI MS-9 and Varian MAT 212 (m.s), and Varian EM-360A and Bruker AC200 (n.m.r.) spectrometers CH-correlated and DEPT spectra were used for the complete assignment of n.m r signals. Unless otherwise stated, ^1H spectra were recorded at 200.13 MHz, and ^{13}C spectra at 50 32 MHz T.l.c was on pre-coated silica gel plates (Merck F254), and column chromatography was on Merck silica gel (particle size 0.063 - 0.200 mm) or Merck silica gel (particle size 0 040 - 0 063 mm) for flash chromatography[18].

1-(2,5-Dimethoxy-4-nitrophenyl)pyrrolidin-2-one [3].-
A solution of nitric acid in CH_2Cl_2 (21.5 mℓ), prepared as described by Rapoport and Luly[8], was added to a stirred solution of 1-(2,5-dimethoxyphenyl)pyrrolidin-2-one[6] **[2]** (445 mg, 2.01 mmol) in CH_2Cl_2 (21.5 mℓ) at room temperature. The reaction was quenched after 10 min with aqueous $NaHCO_3$ solution (10%, 80 mℓ). CH_2Cl_2 (40 mℓ) was added, and the layers were separated The organic layer was washed with water (80 mℓ), dried ($MgSO_4$) and evaporated *in vacuo* to give *1-(2,5-dimethoxy-4-nitrophenyl)pyrrolidin-2-one* **[3]** as a chromatographically homogeneous yellow solid (505 mg, 94%). Recrystallisation of a portion from ethyl acetate - hexane gave yellow needles, m p 144-145 °C (Found. C, 53.98, H, 5.16; N, 10.43 $C_{12}H_{14}N_2O_5$ requires C, 54.13; H, 5.30, N, 10 52%). R_F 0.27 (ethyl acetate). ν_{max} ($CHCl_3$) 3005, 2950, 2845, 1690, 1585, 1510, 1348, 1298 and 1038 cm^{-1}, δ_H ($CDCl_3$) 7 53 (1H, s, arom 3-H), 7 21 (1H, s, arom 6-H), 3.92, 3.87 and 3 87 (8H, s, s, and t, *J* 7 0 Hz, 2 × OCH_3 and CH_2N), 2 57 (2H, td, *J* 8 0 and 0.7 Hz, $CH_2C{=}O$), 2.21 (2H, quintet with further fine coupling, *J* 7 5 Hz, $CH_2\underline{CH_2}CH_2$), δ_C ($CDCl_3$) 175.0 (C = O), 147 4 and 147 2 (arom C-2, C-5), 136.5 (arom C-1), 133 0 (arom C-4), 113.7 and 109 2 (arom C-3. C-6), 56.8 and 56.1 (2 × $O\underline{C}H_3$), 49 4 ($\underline{C}H_2N$), 31 0 ($\underline{C}H_2C{=}O$), 18 8 ($CH_2\underline{C}H_2CH_2$)

1-(4-Bromo-2,5-dimethoxyphenyl)pyrrolidine-2-one [6].-
Bromine (0.29 mℓ, 5 6 mmol) was added to a solution of 1-(2,5-dimethoxyphenyl)pyrrolidin-2-one **[2]** (1 241 g, 5.61 mmol) in acetic acid (25 mℓ) at room temperature After 15 min, aqueous $NaHCO_3$ (100 mℓ) was added, and the solution was extracted with CH_2Cl_2 (3 × 100 mℓ) The organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give *1-(4-bromo-2,5-dimethoxyphenyl)pyrrolidine-2-one* **[6]** (1.682 g, 100%) as a chromatographically homogeneous fawn-coloured powder A sample recrystallised from ethyl acetate - hexane gave colourless needles, m p 128-128.5 °C (Found C, 47 62, H, 4.67, N, 4.50 $C_{12}H_{14}BrNO_3$ requires C, 48.02, H, 4 70; N, 4 67%), R_F 0 39 (ethyl acetate). ν_{max} ($CHCl_3$) 1685 (C = O) and 1495 cm^{-1}, δ_H ($CDCl_3$) 7 15 (1H, s, arom 3-H), 6.89 (1H, s, arom 6-H), 3 83 (s, OCH_3), 3 78 and 3 76 (5H, s and t, *J* 7 0 Hz, OCH_3 and CH_2N), 2.55 (2H, t, *J* 8.0 Hz, $CH_2C{=}O$), 2 18 (2H, quintet with further fine coupling, *J* 7 6 Hz, $CH_2\underline{CH_2}CH_2$), δ_C ($CDCl_3$) 175.0 (C – O), 149.7 and 148 8 (arom C-2, C-5), 126 6 (arom C-1), 117 1 (arom C-6), 112.4 (arom C-3), 110 0 (arom C-4), 56 6 and 56.2 (2 × $O\underline{C}H_3$), 49.5 ($\underline{C}H_2N$), 30 9 ($\underline{C}H_2C{=}O$), 18 7 ($CH_2\underline{C}H_2CH_2$)

4-Chloro-N-(2,4,5-trimethoxyphenyl)butanamide [10].-
4-Chlorobutanoyl chloride (1 0 mℓ, *ca.* 1 26 g, *ca* 8 6 mmol) was added at room temperature to a stirred solution of 2,4,5-trimethoxyaniline[27] (1 310 g, 7 19 mmol) in chloroform (200 mℓ) containing a suspension of anhydrous Na_2HPO_4 (2 52 g, 17 8 mmol) After 72 h, inorganic solids were removed by filtration, and the filtrate was washed with NaOH solution (1M, 2 × 50 mℓ) and water (50 mℓ) The organic layer was dried ($MgSO_4$) and evaporated *in vacuo*, and the crude product was purified by chromatography on silica gel with hexane - ethyl acetate mixtures to give *4-chloro-N-(2,4,5-trimethoxyphenyl)butanamide* **[10]** (1 361 g, 66%) as needles, m p 75-75 5 °C (from diisopropyl ether) (Found C, 54 22, H, 6 27, N, 4 89 $C_{13}H_{18}ClNO_4$ requires C. 54 27, H, 6 30, N, 4 87%), R_F 0.46 (hexane - ethyl acetate 1 1). ν_{max} ($CHCl_3$) 3426 (N-H), 1682 (C – O), 1531, 1466, 1408, 1203 and 1038 cm^{-1}, δ_H ($CDCl_3$) 8 10 (1H, s, arom 6-H), 7 71 (1H, s, NH), 6.54 (1H, s, arom 3-H), 3.86, 3.86 and 3 85 (9H, 3 × s, 3 × OCH_3), 3 66 (2H, t, *J* 6 2 Hz, CH_2Cl), 2 58 (2H, t, *J* 7 0 Hz, $CH_2C{=}O$), 2 19 (2H, quintet, *J* 6 6 Hz, $CH_2\underline{CH_2}CH_2$), δ_C ($CDCl_3$) 169 4 (C – O), 144 7, 142 5 and 141 7 (arom C-2, C-4, C-5), 120 3 (arom C-1), 105 1 (arom C-6), 97 2 (arom C-3), 56 3, 56 3 and 56 2 (3 × $O\underline{C}H_3$), 44 3 ($\underline{C}H_2Cl$), 34 1 ($\underline{C}H_2C{=}O$), 27 8 ($CH_2\underline{C}H_2CH_2$)

1-(2,4,5-Trimethoxyphenyl)pyrrolidin-2-one [8].-
4-Chloro-N-(2,4,5-trimethoxyphenyl)butanamide **[10]** (1 180 g, 4 10 mmol) was stirred for 15 h at room temperature with a solution of sodium ethoxide (made from 200 mg Na, 8 7 mmol) in absolute ethanol (45 mℓ) The solution was neutralised with hydrochloric acid (11M) and evaporated *in vacuo* Water (30 mℓ) was added to the residue, and the solution was extracted with CH_2Cl_2 (3 × 30 mℓ) The combined extracts were dried (MgSO4) and evaporated *in vacuo*, and the crude product was purified by column chromatography with hexane - ethyl acetate mixtures to give *1-(2,4,5-trimethoxyphenyl)pyrrolidin-2-one* **[8]** (797 mg, 77%) as needles, m p 114 5-115 °C (from diisopropyl ether) (Found C, 61 85, H, 6 77, N, 5 68 $C_{13}H_{17}NO_4$ requires C. 62 14, H, 6 82, N, 5 57%). R_F 0 05 (hexane - ethyl acetate 1 1). ν_{max} (CH_3Cl) 1684 (C O), 1522, 1460 and 1038 cm^{-1}, δ_H ($CDCl_3$) 6 79 (1H, s, arom 6-H), 6 58 (1H, s, arom 3-H), 3 88, 3 83 and 3 81 (9H, 3 × s, 3 x OCH_3), 3 72 (2H, t, *J* 7 0 Hz, CH_2N), 2 54 (2H, t, *J* 7 4 Hz, $CH_2C{=}O$), 2 17 (2H, quintet, *J* 7 6 Hz, $CH_2\underline{CH_2}CH_2$), δ_C ($CDCl_3$) 175 1 (C – O), 149 0, 148 6 and 142 8 (arom C-2,

C-4, C-5), 119.0 (arom C-1), 112.0 (arom C-6), 98 4 (arom C-3), 56.4, 56.3 and 56 1 (3 × O$\underline{C}H_3$), 49 9 ($\underline{C}H_2N$), 30.9 ($\underline{C}H_2C=O$), 18.6 ($CH_2\underline{C}H_2CH_2$)

4-Chloro-N-(1,4-dimethoxy-2-naphthyl)butanamide [11].-
4-Chlorobutanoyl chloride (0.54 mℓ, *ca* 680 mg, 4 8 mmol) was added at room temperature to a stirred solution of 1,4-dimethoxy-2-naphthylamine (prepared by heating the corresponding nitro compound with finely granulated tin and hydrochloric acid, rather than by catalytic hydrogenatlon as described in the literature[28]; 816 mg, 4 01 mmol) in dry chloroform (50 mℓ) containing a suspension of anhydrous Na_2HPO_4 (1.43 g, 10 0 mmol) After 4.5 h, inorganic solids were removed by filtration, and the filtrate was washed with NaOH solution (1M, 250 mℓ). The aqueous phase was extracted with $CH_2C\ell_2$ (3 × 50 mℓ) The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo*, and the crude product was purified by chromatography on silica gel with hexane - ethyl acetate mixtures to give *4-chloro-N-(1,4,-dimethoxy-2-naphthyl)butanamide* **[11]** (901 mg, 73%) as needles, m.p 98-98 5 °C (from acetone - diisopropyl ether) (Found. C, 62.38; H, 5 87; N, 4 64. $C_{16}H_{18}C\ell NO_3$ requires C, 62 44; H, 5.89; N, 4.55%); R_F 0.42 (hexane - ethyl acetate 4.1), ν_{max} ($CHC\ell_3$) 3418 (N-H), 1688 (C=O), 1630, 1605, 1520, 1497, 1460, 1379, 1203 and 1096 cm^{-1}, δ_H ($CDC\ell_3$) 8.20 (1H, ddd, *J* 8 3, 1.5 and 0 7 Hz, arom 5-H or 8-H), 7.98 and 7 93 (3H, br s and ddd, *J* 8.3, 1 3 and 0.75 Hz, NH, arom 3-H, and arom 5-H or 8-H), 7.51 (1H, ddd, *J* 8 3, 6.8 and 1 5 Hz, arom 6-H or 7-H; on irradiation at δ 8.20, simplifies to dd, *J* 8.3 and 6 8 Hz), 7.39 (1H, ddd, *J* 8 3, 6.9 and 1.4 Hz, arom 6-H or 7-H), 3 99 (3H, s, OCH_3), 3 87 (3H, s, OCH_3), 3.68 (2H, t, *J* 6.1 Hz, $CH_2C\ell$), 2.65 (2H, t, *J* 7 0 Hz, $CH_2C=O$), 2 22 (2H, quintet, *J* 6 5 Hz, $CH_2\underline{C}H_2CH_2$); δ_C ($CDC\ell_3$) 170.1 (amide C=O), 152.1 and 136.3 (arom C-1, C-4), 127 6, 127 3 and 123 0 (arom C-2, C-4a, C-8a), 126.9 (arom C-6 or C-7; correlates with δ_H 7.51), 124.2 (arom C-6 or C-7, correlates with δ_H 7.39), 122.5 (arom C-5 or C-8; correlates with δ_H 8.20), 120.8 (arom C-5 or C-8; correlates with δ_H 7 93), 98.4 (arom C-3), 61.5 and 55.7 (2 × O$\underline{C}H_3$), 44.3 ($\underline{C}H_2C\ell$), 34 3 ($\underline{C}H_2C=O$), 27 8 ($CH_2\underline{C}H_2CH_2$)

1-(1,4-Dimethoxy-2-naphthyl)pyrrolidin-2-one [9].-
4-Chloro-N-(1,4-dimethoxy-2-naphthyl)butanamide **[11]** (649 mg, 2 11 mmol) was stirred overnight at room temperature with a solution of sodium ethoxide (made from 71 mg Na; 3 2 mmol) in absolute ethanol (25 mℓ). The solution was neutralised with hydrochloric acid (11M) and evaporated *in vacuo*. Water (30 mℓ) was added to the residue, and the solution was extracted with $CH_2C\ell_2$ (3 × 30 mℓ) The combined extracts were dried (MgSO4) and evaporated *in vacuo*, and the crude product was purified by column chromatography with hexane - ethyl acetate mixtures to give *1-(1,4-dimethoxy-2-naphthyl)pyrrolidin-2-one* **[9]** (493 mg, 86%) as needles, m p 108-108 5 °C (from di-isopropyl ether) (Found C, 70.86; H, 6 31; N, 5.26 $C_{16}H_{17}NO_3$ requires C, 70 83, H, 6.32; N, 5 16%); R_F 0.30 (hexane - ethyl acetate 1:1), ν_{max} ($CHC\ell_3$) 3024, 1684 (C=O), 1450, 1419 and 1375 cm^{-1}; δ_H ($CDC\ell_3$) 8.22 (1H, 7 lines, arom 5-H), 8.07 (1H, 7 lines, arom 8-H), 7.54 (1H, 7 lines, *J ca.* 8 3, 6 8 and 1 7 Hz, arom 6-H or 7-H), 7 48 (1H, 7 lines, *J ca* 8 3, 6 8 and 1.6 Hz, arom 6-H or 7-H), 6 75 (1H, s, arom 3-H), 3 98 (3H, s, OCH_3 on C-4), 3.92 (2H, t, *J* 7.0 Hz, CH_2N), 3 86 (3H, s, OCH_3 on C-1), 2 64 (2H, t, *J* 8 2 Hz, $CH_2C=O$), 2 27 (2H, quintet, *J* 7 5 Hz, $CH_2\underline{C}H_2CH_2$), δ_C ($CDC\ell_3$) 175 4 (C=O), 152 1 and 144 7 (arom C-1, C-4), 128 9 (arom C-4a, C-8a) 126 8 (arom C-6 or C-7; correlates with δ_H 7 54), 125 7 (arom C-6 or C-7, correlates with δ_H 7 48), 122 3 (arom C-5), 121.6 (arom C-8), 103.3 (arom C-3), 94.8 (spurious?), 49 9 ($\underline{C}H_2N$), 31 3 ($\underline{C}H_2C=O$), 19 3 ($CH_2\underline{C}H_2CH_2$)

General procedure for oxidations with silver(II) oxide.-
Nitric acid (6M, 5 - 8 eq) was added dropwise to a stirred solution of the appropriate 1-arylpyrrolidin-2-one (1 eq) in dioxan (*ca.* 15 mℓ for 1 mmol) containing suspended silver (II) oxide[29] (4 eq). After 20 min at room temperature, water (5 mℓ) and $CH_2C\ell_2$ (20-30 mℓ) were added The organic phase was separated, dried (MgSO4) and evaporated *in vacuo* The crude product was purified rapidly by flash chromatography on silica gel with hexane - ethyl acetate mixtures as eluant. Attempts at further purification by recrystallisation resulted in decomposition

2-(2-Oxo-1-pyrrolidinyl)-1,4-benzoquinone [4].-
This was prepared according to the general procedure from nitric acid (6M, 1.2 mℓ), 1-(2,5-dimethoxyphenyl)pyrrolidin-2-one **[2]** (261 mg, 1 18 mmol) and silver(II) oxide (600 mg, 4 8 mmol) The title compound **[4]** (60 mg, 26 6%) was obtained as an orange - red powder that melted over a wide range, R_F 0 47 (hexane - ethyl acetate 1 1), ν_{max} ($CH_2C\ell_2$) 1725 and 1661 (C=O), 1584, 1265 and 909 cm^{-1}, λ_{max} (ϵ_{max}, EtOH) 302 (3566) nm; δ_H ($CDC\ell_3$) 7 16 (1H, d, *J* 1 2 Hz, arom 3-H), 6 72 (2H, d, *J* 1 2 Hz, arom 5-H, 6-H), 4 00 (2H, t, *J* 7 0 Hz, CH_2N), 2 56 (2H, t with further fine coupling, *J ca.* 8.0 and 0 5 Hz, $CH_2C=O$), 2 14 (2H, quintet with further fine coupling, *J ca* 7 5 and 0.5 Hz, $CH_2\underline{C}H_2CH_2$), *m/z* 191 (M^+, 100%), 162 (20), 138 (22), 136 (68), 135 (23), 134 (27), 108 (43), 107 (21), 106 (32), 83 (40), 81 (34) (Found M^+, 191 0580 $C_{10}H_9NO_3$ requires 191.0582)

2-Bromo-5-(2-oxo-1-pyrrolidinyl)-1,4-benzoquinone [7].-
This was prepared according to the general procedure from nitric acid (6M, 0.51 mℓ), 1-(4-bromo-2,5-dimethoxyphenyl)pyrrolidin-2-one **[6]** (152 mg, 0 51 mmol) and silver(II) oxide (252 mg, 2 0 mmol) The title compound **[7]** (137 mg, *ca.* 100%) was obtained as a reddish powder, melting range 111-122 °C (from $CH_2C\ell_2$), R_F 0 74 (ethyl acetate), ν_{max} ($CHC\ell_3$) 1725 and 1670 (C=O) cm^{-1}, λ_{max} (ϵ_{max}, EtOH) 303 (8720) nm. δ_H ($CDC\ell_3$) 7 42 (1H, s, quinone

3-H), 7.23 (1H, s, quinone 6-H), 4.03 (2H, t, *J* 7.0 Hz, CH_2N), 2.55 (2H, t, *J* 8.0 Hz, $CH_2C{=}O$), 2.15 (2H, quintet, *J* 7.5 Hz, $CH_2CH_2CH_2$), δ_C ($CDCl_3$) 180.9 and 176.1 (C=O), 141.6 (quinone C-5), 137.0 (quinone C-2), 136.6 (quinone C-3), 122.6 (quinone C-6), 49.5 (CH_2N), 31.4 ($CH_2C{=}O$), 18.9 ($CH_2CH_2CH_2$), *m/z* 273 (29%), 271 ([^{81}Br]-M^+, 100), 269 ([^{79}Br]-M^+, 79), 218 (32), 216 (68), 214 (38), 134 (38), 85 (68), 83 (97) (Found [^{79}Br]-M^+, 268.9671 $C_{10}H_8BrNO_3$ requires 268.9680)

2-Methoxy-5-(2-oxo-1-pyrrolidinyl)-1,4-benzoquinone [12].-
This was prepared according to the general procedure from nitric acid (6M, 0.9 mℓ), 1-(2,4,5-trimethoxyphenyl)-pyrrolidin-2-one **[8]** (244 mg, 0.97 mmol) and silver(II) oxide (500 mg, 4.0 mmol). The title compound **[12]** (83 mg, 39%) was obtained as orange crystals, melting range 102-121 °C; R_F 0.36 (hexane - ethyl acetate 1:1); ν_{max} ($CHCl_3$) 1721 and 1659 (C=O), 1584 and 1390 cm^{-1}; λ_{max} (ϵ_{max}, EtOH) 296 (12400) nm, δ_H ($CDCl_3$) 7.20 (1H, s, arom 3-H), 5.87 (1H, s, arom 6-H), 4.05 (2H, t, *J* 7.0 Hz, CH_2N), 3.84 (3H, s, OCH_3), 2.55 (2H, t, *J* 7.8 Hz, $CH_2C{=}O$), 2.19 (2H, quintet, *J* 7.5 Hz, $CH_2CH_2CH_2$); δ_C ($CDCl_3$) 183.9 and 181.9 (quinone C=O), 176.4 (lactam C=O), 158.3 (arom C-4), 141.9 (arom C-2), 122.2 (arom C-3), 106.5 (arom C-6), 56.4 (OCH_3), 50.1 (CH_2N), 31.7 ($CH_2C{=}O$), 19.3 ($CH_2CH_2CH_2$) *m/z* 221 (M^+, 63%), 193 (30), 176 (28), 166 (30), 165 (32), 164 (21), 150 (20), 137 (32), 108 (34), 84 (20), 69 (100) (Found M^+, 221.0689 $C_{11}H_{11}NO_4$ requires 221.0688).

2-(2-Oxo-1-pyrrolidinyl)-1,4-naphthoquinone [13].-
This was prepared according to the general procedure from nitric acid (6M, 0.5 mℓ), 1-(1,4-dimethoxy-2-naphthyl)-pyrrolidin-2-one **[9]** (116 mg, 0.43 mmol) and silver (II) oxide (210 mg, 1.7 mmol). The title compound **[13]** (80 mg, 77%) was obtained as a yellow powder, melting range 110-122 °C; R_F 0.63 (hexane - ethyl acetate 1:1), ν_{max} ($CHCl_3$) 1719 and 1678 (C=O), 1390 and 1265 cm^{-1}; λ_{max} (ϵ_{max}, EtOH) 339 (4265), 333 (4217), 295 (6505) nm; δ_H ($CDCl_3$) 8.08-8.00 (2H, m, arom 5-H, 8-H), 7.78-7.68 (2H, m, arom 6-H, 7-H), 7.32 (1H, s, arom 3-H), 4.09 (2H, t, *J* 7.0 Hz, CH_2N), 2.59 (2H, t, *J* 8.1 Hz, $CH_2C{=}O$), 2.18 (2H, quintet, *J* 7.5 Hz, $CH_2CH_2CH_2$), δ_C ($CDCl_3$) 184.7 and 181.6 (quinone C=O), 175.9 (lactam C=O), 143.6 (arom C-2), 134.0, 133.5, 127.5, 126.7 and 125.8 (arom C-3, C-5, C-6, C-7, C-8), 131.6 and 131.4 (arom C-4a, C-8a), 49.8 (CH_2N), 31.6 ($CH_2C{=}O$), 19.2 ($CH_2CH_2CH_2$); *m/z* 241 (M^+, 100%), 212 (20), 186 (34), 185 (20), 104 (20), 76 (30) (Found: M^+, 241.0735 $C_{14}H_{11}NO_3$ requires 241.0739)

2-(3-Methoxycarbonylpropylamino)-1,4-naphthoquinone [16].-
A solution of 2-methoxy-Δ^1-pyrroline[30] (106 mg, 1.07 mmol) and 1,4-naphthoquinone (119 mg, 0.75 mmol) in methanol (5 mℓ) was heated at 50 °C for 8.3 h. The brownish mixture was kept at room temperature for 65 h, after which the solvent was removed *in vacuo*. The brown residue (181 mg) was purified by flash chromatography with hexane - ethyl acetate (2:1) as eluant, giving 1,4-naphthoquinone (28 mg, 23.5%), 2-methoxy-1,4-naphthoquinone (identified by n.m.r.: δ_H ($CDCl_3$) 6.18 (=CH), 3.91 (OMe), 26 mg, 18%), and *2-(3-methoxycarbonylpropylamino)-1,4-naphthoquinone* **[16]** (52 mg, 25%) as orange needles, m.p. 128 °C (from acetone - hexane) (Found: C, 66.10; H, 5.41; N, 4.97 $C_{15}H_{15}NO_4$ requires C, 65.93; H, 5.53; N, 5.13%), R_F 0.62 (ether), ν_{max} ($CHCl_3$) 3390 (N-H), 1730 (C=O), 1678, 1610, 1573, 1513, 1357, 1310 and 1257 cm^{-1}, λ_{max} (ϵ_{max}, EtOH) 451 (3380), 329 (shoulder, 2190), 270 (25190), 240 (shoulder, 13220), 232 (15310), and 223 (shoulder, 15540) nm, δ_H ($CDCl_3$) 8.07 (1H, ddd, *J ca* 7.5, 1.4 and 0.5 Hz, quinone 5-H or 8-H), 8.01 (1H, ddd, *J ca* 7.4, 1.5 and 0.5 Hz, quinone 5-H or 8-H), 7.72 (1H, td, *J* 7.5 and 1.5 Hz, quinone 6-H or 7-H), 7.61 (1H, td, *J* 7.5 and 1.5 Hz, quinone 6-H or 7-H), *ca* 6.20 (1H, br t, *J ca* 5.6 Hz, N-H, exchanges slowly with D_2O), 5.74 (1H, s, C=CH), 3.71 (3H, s, CO_2CH_3), 3.27 (2H, q, *J* 6.7 Hz, CH_2N, collapses to t, *J* 6.9 Hz, on addition of D_2O), 2.47 (2H, t, *J* 7.0 Hz, $CH_2C{=}O$), 2.04 (2H, quintet, *J* 7.0 Hz, $CH_2CH_2CH_2$), δ_C ($CDCl_3$) 182.8 and 181.7 (quinone C=O), 173.1 (ester C=O), 147.8 (N-C=CH), 134.6 and 131.8 (quinone C-6, C-7), 133.4 and 130.3 (quinone C-4a, C-8a), 126.1 and 126.0 (quinone C-5, C-8), 100.8 (C=CH), 51.8 (CO_2CH_3), 41.8 (CH_2N), 31.2 ($CH_2C{=}O$), 23.1 ($CH_2CH_2CH_2$)

Structure determination of 2-(3-methoxycarbonylpropylamino)-1,4-naphthoquinone [16].-
Crystals of compound **[16]** were grown by slow diffusion of hexane vapour into a solution of the compound in acetone. An orange needle of dimensions 0.55 × 0.25 × 0.13 mm was used for the study. The space group $P2_1/c$ (number 14) and preliminary lattice constants were determined from oscillation and Weissenberg photographs. Diffraction data were collected on a Enraf-Nonius CAD-4 automatic diffractometer with graphite-monochromated Mo-K_α radiation (λ 0.7107 Å, μ 0.62 cm^{-1}), scan mode $\omega/2\theta$, scan width (0.6 + 0.35 $\tan\theta$), variable scan speed 0.9 - 5.5 °min^{-1}. Cell dimensions were obtained by least squares refinement of 25 accurately measured high θ angle values ($6° \le \theta \le 19°$). The maximum time allowed per reflection was 60 sec. To ensure crystal stability, three standard reflections were monitored, and showed a 0.4% variation over the data collection. The data were corrected for Lorentz, polarisation and empirical absorption[31] effects. Compound **[16]**, $C_{15}H_{15}NO_4$, M_r 273.29, monoclinic, a = 12.514(2), b = 4.960(2), c = 21.520(4) Å, β = 104.38(2)°, V = 1293.98 Å^3, Z = 4, D_m (flotation) = 1.38, D_c = 1.40 g cm^{-3}, $F(000)$ = 576. Data collection: 4235 reflections measured, 2795 unique reflections ($2° \le \theta < 30°$, $-17 \le h \le 17$, $0 \le k \le 6$, $0 \le \ell \le 30$), 1470 with $F(\text{obs}) > 3\sigma(F)$, R_{int} 0.0265, number of parameters 182, maximum p/σ 0.005

The structure was solved by direct methods on a CDC Cyber 750 computer with the aid of the SHELX-76 routine[32] for centrosymmetric structures. The E-map was calculated using all reflections with E > 1 2. All non-hydrogen atoms were located from the electron density maps. The coordinates were refined by full-matrix least-squares methods. Non-hydrogen atoms were refined anisotropically, after which the hydrogen atoms were placed in calculated positions (C-H 1.08 Å) and refined with a common isotropic temperature factor (U 0 069(5) Å^2). Unit weights were used throughout. A final R of 0.066 was obtained, and the residual density was 0.34 eÅ^{-3}. Fractional atomic coordinates and equivalent isotropic temperature factors for non-hydrogen atoms and the hydrogen-bonded H are given in Table 1, and selected bond lengths and angles in Tables 2 and 3. Tables of anisotropic thermal parameters for non-hydrogen atoms, fractional atomic coordinates for hydrogen atoms and structure factors have been deposited as supplementary material.

Table 1. Fractional coordinates (x10^4) and equivalent isotropic temperature factors (Å^2, x10^3) for non-hydrogen atoms and the hydrogen-bonded H atom of 2-(3-methoxycarbonylpropylamino)-1,4-naphthoquinone **[16]**

	x/a	*y/b*	*z/c*	U_{eq}
O(1)	5903(3)	2431(8)	10089(2)	6(1)
O(2)	6483(3)	-3277(8)	8092(2)	55(1)
O(3)	1167(3)	3511(8)	7773(2)	55(1)
O(4)	1121(3)	5410(9)	6822(2)	54(1)
N	4632(3)	3614(9)	8929(2)	35(1)
C(1)	6069(4)	1141(10)	9644(2)	34(1)
C(2)	5398(4)	1672(11)	8973(2)	34(1)
C(3)	5567(4)	225(11)	8465(2)	36(1)
C(4)	6361(4)	-1892(11)	8546(2)	40(1)
C(4a)	7067(4)	-2466(10)	9203(2)	34(1)
C(5)	7854(4)	-4489(11)	9292(3)	42(1)
C(6)	8509(4)	-5003(13)	9901(3)	50(1)
C(7)	8377(4)	-3521(12)	10421(3)	50(1)
C(8)	7575(4)	-1523(12)	10344(2)	42(1)
C(8a)	6922(4)	-995(10)	9727(2)	34(1)
C(9)	3908(4)	4327(10)	8308(2)	37(1)
C(10)	3097(4)	6527(11)	8378(2)	37(1)
C(11)	2364(4)	7252(10)	7719(2)	38(1)
C(12)	1510(4)	5167(11)	7458(2)	39(1)
C(13)	246(5)	3591(15)	6532(3)	72(2)
H(N)	4553(3)	4654(9)	9356(2)	69(5)

Table 2. Bond lengths (Å) of 2-(3-methoxycarbonylpropylamino)-1,4-naphthoquinone **[16]**

O(1)-C(1)	1 211(5)	O(2)-C(4)	1.235(6)
O(3)-C(12)	1.209(6)	O(4)-C(12)	1 339(6)
O(4)-C(13)	1.437(7)	N-C(2)	1 345(6)
N-C(9)	1 460(5)	C(1)-C(2)	1 502(6)
C(1)-C(8a)	1.483(7)	C(2)-C(3)	1 367(6)
C(3)-C(4)	1.426(7)	C(4)-C(4a)	1.496(7)
C(4a)-C(5)	1 386(7)	C(4a)-C(8a)	1 393(6)
C(5)-C(6)	1 387(7)	C(6)-C(7)	1 382(8)
C(7)-C(8)	1 390(8)	C(8)-C(8a)	1 400(6)
C(9)-C(10)	1.522(7)	C(10)-C(11)	1 529(6)
C(11)-C(12)	1 493(7)		

Table 3. Bond angles (°) of
2-(3-methoxycarbonylpropylamino)-1,4-naphthoquinone **[16]**

C(12)-O(4)-C(13)	115.6(5)	C(2)-N-C(9)	120 5(4)
O(1)-C(1)-C(2)	120 2(5)	O(1)-C(1)-C(8a)	122.7(4)
C(2)-C(1)-C(8a)	117 1(4)	N-C(2)-C(1)	114.3(4)
N-C(2)-C(3)	124 7(4)	C(1)-C(2)-C(3)	121 0(5)
C(2)-C(3)-C(4)	122 0(5)	O(2)-C(4)-C(3)	122 1(5)
O(2)-C(4)-C(4a)	118 8(5)	C(3)-C(4)-C(4a)	119.0(4)
C(4)-C(4a)-C(5)	120 0(5)	C(4)-C(4a)-C(8a)	120 0(5)
C(5)-C(4a)-C(8a)	120 0(5)	C(4a)-C(5)-C(6)	119 7(5)
C(5)-C(6)-C(7)	120 4(5)	C(6)-C(7)-C(8)	120 7(5)
C(7)-C(8)-C(8a)	118 8(5)	C(1)-C(8a)-C(4a)	120 7(4)
C(1)-C(8a)-C(8)	118 9(5)	C(4a)-C(8a)-C(8)	120.4(5)
N-C(9)-C(10)	111 1(4)	C(9)-C(10)-C(11)	109.7(4)
C(10)-C(11)-C(12)	113 2(4)	O(3)-C(12)-O(4)	123.0(5)
O(3)-C(12)-C(11)	125 5(5)	O(4)-C(12)-C(11)	111 4(5)

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