# The Ansamycins: Synthesis of the Naphthoquinonoid Nucleus of Rifamycin W; Crystal Structure Verification of a Key Naphthalenic Intermediate

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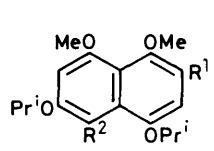
1,4-Benzoquinone has been converted into 8-acetyl-5,7-dihydroxy-6-methyl-3-propionylamino-1,4-naphthoquinone (**29**) in six steps in an overall yield of 20%. A key reaction involves the dimethylation of the intermediate 8-acetyl-3-acetylamino-1,4,5,7-tetramethoxynaphthalene (**9**); the structure has been confirmed by *X*-ray crystallography. Steric crowding prevents acetylation of 3-acetyl-1,4,5,7-tetramethoxy-6-methylnaphthalene (**18**) with premixed acetic acid and trifluoroacetic anhydride; 8-acetyl-1,4,5,7-tetramethoxy-6-methylnaphthalene (**22**) is converted by the same reagent into compound (**18**) by acetyl migration.

The ansamycins have attracted considerable attention recently, largely because of their range of biological activities. Rifampicin, a semi-synthetic derivative of rifamycin B, is widely used for the treatment of tuberculosis and other infections caused by gram-positive organisms.[1] Other derivatives of the rifamycin and streptovaricin sub-groups are employed as biological probes.[2] Maytansine and analogues are effective anti-tumour agents.[3] The laboratory synthesis of an ansamycin has in general involved the independent construction of the aromatic nucleus and the ansa chain, and their subsequent combination.[4] We report here a synthesis of a 1,4-naphthoquinoid nucleus (**29**) with the substitution pattern typical of a number of ansamycins,[5] including rifamycin W.[6]

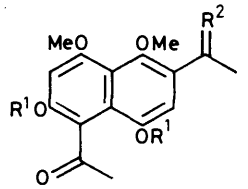
## Results and Discussion

We recently reported that acetylation of 1,7-bisisopropoxy-4,5-dimethoxynaphthalene† (**1**) with premixed acetic acid and trifluoroacetic anhydride afforded a mixture of two monoacetyl derivatives, the 3-acetyl† compound (**2**) and the 8-acetyl isomer (**3**), together with a small amount of the 3,8-diacetyl derivative (**4**).[7] This diacetylated product appeared to be a potential precursor of the nucleus of some naphthoquinonoid ansamycins, possessing as it does oxygenation at carbon atoms 1,4, 5, and 7, and acyl substituents at C-3 and C-8. Insertion of nitrogen between the naphthalene ring and the acetyl group at C-3 would afford the acylamino substituent common to this class of compound. Such a nitrogen insertion into compound (**4**) appeared feasible by a Beckmann rearrangement provided that a mono-oxime could be formed at the C-3 acetyl substituent and also provided that the hydroxy group of the derived oxime was *anti* to the naphthyl group. Both these provisos seemed reasonable on steric grounds; the first since the 8-acetyl, flanked by both an *ortho*- and *peri*-isopropoxy substituent would be considerably more crowded than the alternative acetyl which had only a methoxy group *ortho* to it, and the second since crowding between the methoxy and oxime functions would be minimised (little reason for hydrogen bonding between these two groups was apparent).

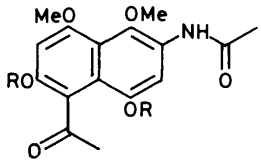
Experimental evidence for the first suggestion, that the C-8 acyl substituent was indeed more crowded than that at C-3 in compound (**4**), was provided by i.r. and $^1$H n.m.r. spectra. Two carbonyl stretching frequencies appeared at 1 660 and 1 707 cm$^{-1}$, assigned to the C-3 and C-8 acetyl groups respectively,




(**1**) $R^1 = R^2 = H$
(**2**) $R^1$ = COMe, $R^2$ = H
(**3**) $R^1$ = H, $R^2$ = COMe




(**4**) $R^1 = Pr^i$, $R^2$ = O
(**5**) $R^1 = Pr^i$, $R^2$ = *anti*-NOH
(**6**) $R^1$ = Me, $R^2$ = O
(**7**) $R^1$ = Me, $R^2$ = *anti*-NOH




(**8**) R = $Pr^i$
(**9**) R = Me

and the 3-acetyl and 8-acetyl protons gave rise to chemical shifts of δ 2.72 and 2.55, respectively. These differences were consistently observed as a pattern for all the C-3 and C-8 acetyl compounds described in this and the accompanying paper.[7] The figures pointed to the C-8 acetyl group being twisted out of the plane of the naphthalene ring; conclusive evidence for this was subsequently obtained from the crystal structure of compound (**8**) (see later); the acetyl C–C(O)–C plane was found to be at an angle of *ca.* 90° to the naphthalene plane. It was therefore decided to use compound (**4**) to investigate the foregoing predictions as a model for the synthesis of the target quinone (**29**).

Treatment of the naphthalene (**1**) with an excess of premixed acetic acid and trifluoroacetic anhydride smoothly afforded the 3,8-diacetyl derivative (**4**) in 72% yield. This compound was treated with hydroxylamine hydrochloride and 1 mol equiv. of potassium hydroxide to form a single mono-oxime (**5**). The crude oxime (**5**) was converted by phosphorus pentachloride into the amide (**8**) in an overall yield of 68% from the diacetyl derivative (**4**). The product showed *inter alia* two one-proton aromatic singlets in the $^1$H n.m.r. spectrum at δ 6.58 (6-H) and 8.00 (2-H), as well as two three-proton singlets at δ 2.52 and 2.21 due to the ketonic and amidic methyl groups, respectively. A crystal structure determination confirmed the assignment of structure (**8**) (Figure).

† As in the preceding papers, the numbering used throughout is based on the 1,4,5,7-tetraoxygenated naphthalene system, for clarity.

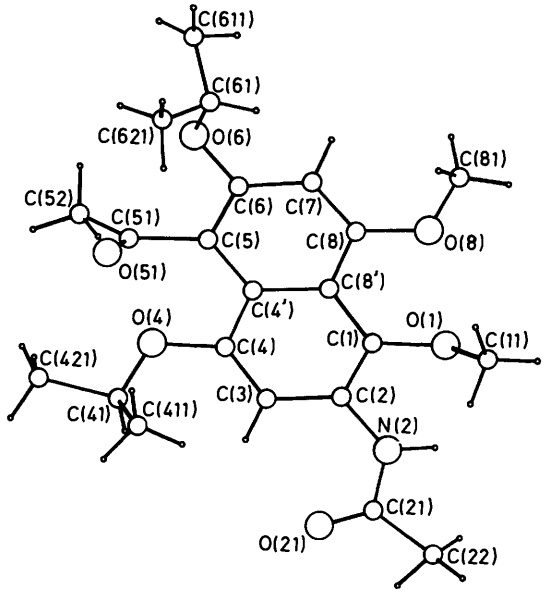
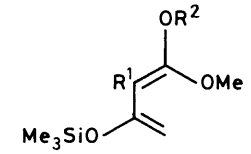
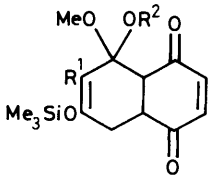


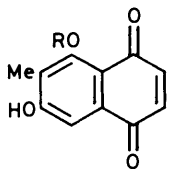

**Figure.** Crystal structure of the amide (**8**)



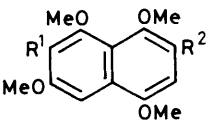
(**10**) $R^1$ = Me, $R^2$ = $SiMe_3$
(**11**) $R^1$ = H, $R^2$ = Me



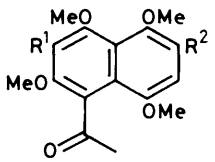
(**12**) $R^1$ = Me, $R^2$ = $SiMe_3$
(**13**) $R^1$ = H, $R^2$ = Me



(**14**) R = H
(**15**) R = Me



(**16**) $R^1$ = $R^2$ = H
(**17**) $R^1$ = Me, $R^2$ = H
(**18**) $R^1$ = Me, $R^2$ = COMe
(**19**) $R^1$ = Me, $R^2$ = NHCOMe
(**20**) $R^1$ = Me, $R^2$ = $NHCOCH_2Me$



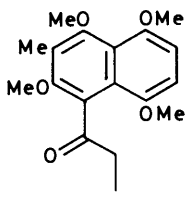
(**21**) $R^1$ = $R^2$ = H
(**22**) $R^1$ = Me, $R^2$ = H
(**23**) $R^1$ = Me, $R^2$ = COMe
(**24**) $R^1$ = Me, $R^2$ = NHCOMe
(**25**) $R^1$ = Me, $R^2$ = $NHCOCH_2Me$

Attention was then focussed on a similar synthesis of a C-6 methyl analogue (**24**) of compound (**8**) since naphthoquinonoid ansamycins commonly carry an aromatic methyl group at this position. In view of the fact that an additional substituent on the naphthalene nucleus might well introduce considerable crowding, it was decided that further efforts should be made with 1,4,5,7-tetramethoxynaphthalene (**16**) rather than the di-isopropoxy derivative (**1**). It was hoped that by reducing the size of the protecting groups on O-1 and O-7, these methoxy substituents would still be sufficiently large to discourage oxime formation at the 8-acetyl group, while more readily accommodating an additional methyl group at C-6.

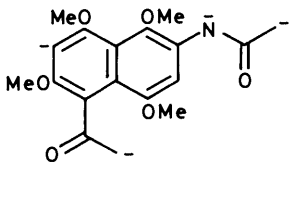
Initial efforts explored the formation of amide (**24**) from the Diels–Alder adduct (**12**) derived from the diene (**10**)[8] and 1,4-benzoquinone. It was possible to obtain a mixture of the naphthoquinones (**14**) and (**15**) directly, although this route was marred by low yields of the quinones and their inconvenient separation. The individual compounds were identified by $^1H$ n.m.r. and high resolution mass spectrometry, and were methylated as a mixture to give a 30% overall yield of 5,7-dimethoxy-6-methyl-1,4-naphthoquinone. The alternative diene (**11**)[9] was therefore used to afford the adduct (**13**) with benzoquinone, and this was exhaustively methylated with potassium carbonate and dimethyl sulphate in acetone to afford 1,4,5,7-tetramethoxynaphthalene (**16**).[10,11] This compound was cleanly and selectively methylated between the two *meta*-oriented methoxy substituents to afford the naphthalene (**17**) in a yield of 83%, with butyl-lithium followed by methyl iodide. On reaction of compound (**17**) with an excess of premixed acetic acid and trifluoroacetic anhydride, the monoacetyl derivative (**18**) was formed as the sole product in 79% yield. All attempts failed to acylate this further at C-8 to yield the diacetyl compound (**23**), no doubt on account of the steric crowding of the single unsubstituted aromatic position on the ring bearing the methyl group. The ketone (**18**) could also undergo a Beckmann rearrangement, giving the acetylaminonaphthalene (**19**). Attempts to acylate the new product (**19**) also failed to yield the 8-acetyl derivative (**24**).

The 8-acetylnaphthalene (**21**),[10] the major product of monoacetylation of 1,4,5,7-tetramethoxynaphthalene (**16**), was also considered as a starting point for the synthesis of the naphthoquinone (**29**). Its conversion into its 6-methyl derivative (**22**) with an excess of butyl-lithium was envisaged; this reagent would presumably abstract one of the more acidic acetyl protons first and then the C-6 aromatic proton. We hoped that the dianion so derived could be quenched with just sufficient methyl iodide to alkylate the more reactive aromatic anion. The dianion was red and the reaction was complete as soon as this colour had been discharged. Careful control of the conditions permitted the isolation of the required product (**22**) in 95% yield, none of the product (**26**) of dimethylation being observed under these optimised conditions. Acetylation of this naphthalene with premixed acetic acid and trifluoroacetic anhydride quantitatively afforded an isomeric monoacetyl derivative, which proved to be the naphthyl ketone (**18**) already described. It was clear that a deacylation–reacylation reaction was being initiated by protonation of (**22**) at C-8 (bearing the acetyl substituent) by the trifluoroacetic acid generated on formation of the mixed anhydride. The C-8 acylium ion was then lost from the derived σ-complex to form the mixed anhydride, which then reacetylated the intermediate (**17**) at C-3. Compound (**26**) could be prepared by treating the dianion obtained from the naphthalene (**21**) with an excess of methyl iodide.

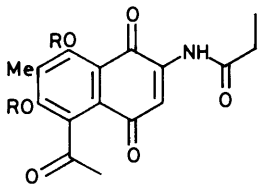
The diacetyl derivative (**6**) was obtained in 83% yield by acetylation of the tetramethoxynaphthalene (**16**) by the mixed anhydride method, as for its analogue (**1**). Compound (**6**) was treated with an excess of butyl-lithium followed by methyl iodide in an attempt to form the 6-methyl derivative. This reaction gave a complex mixture which was not further investigated. Conversion of the diacetylnaphthalene (**6**) *via* the monooxime (**7**) into the amide (**9**) was achieved as for the synthesis of the analogue (**8**). The amide (**9**) was treated with 5 mol equiv. of



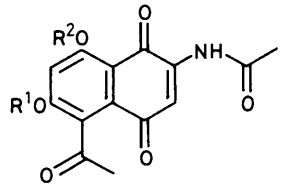
(26)



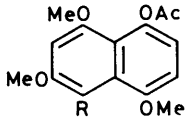
(27)



(28) R = Me
(29) R = H



(30) $R^1 = Pr^i$, $R^2$ = Me
(31) $R^1 = R^2$ = H



(32) R = H
(33) R = $CO[CH_2]_4CH_3$
(34) R = COCH=CHMe-(*E*)
(35) R = COCMe=CHMe-(*E*)
(36) R = $COCF_3$

butyl-lithium and 10 equiv. of tetramethylethylenediamine in tetrahydrofuran, followed by just sufficient methyl iodide to discharge the orange colour. This procedure yielded largely a single product, as shown by t.l.c. Purification afforded a single compound in 60% yield, the mass spectrum of which showed a highest mass signal at *m/z* 375, indicating that two methyl groups had been added. The $^1$H n.m.r. spectrum showed only one aromatic singlet at low field (δ 8.10) corresponding to 2-H, *ortho* to an acylamino function [*cf.* the value for 2-H (δ 8.05) and 6-H (δ 6.66) for the naphthalene (**9**)]. In addition to the four methoxy signals, two *C*-methyl singlets occurred at δ 2.36 and 2.51, and a quartet at δ 2.49 and a triplet at δ 1.29 indicated that either the *C*- or the *N*-acetyl group had been converted into propionyl. In qualitative consideration of the relative ease of removal of four protons from the amide (**9**) with butyl-lithium, the proton on nitrogen would be the most labile, followed by one from the C-8 acetyl, then that from C-6, and a further proton from the acetamido function, giving rise to the tetra-anion (**27**). Methylation of this would occur in the reverse sense, on the amide and aromatic carbon atoms initially. The expected product of dimethylation would therefore be (**25**), and this assignment was supported by the chemical shift of the crowded C-8 acetyl methyl group (δ 2.51), consistent with the values for this substituent discussed earlier. This was borne out in practice: treatment of the product of methylation with trifluoroacetic acid afforded the 3-propionylaminonaphthalene (**20**) slowly but quantitatively. Deacetylation at C-8 had once again occurred as for the conversion of compound (**22**) to give (**18**). The $^1$H n.m.r. spectra of compounds (**20**) and (**19**) were identical except for the differences of the acylamino groups. The fact that methylation of naphthalene (**9**) had occurred not only at C-6 but also on the acetylamino substituent was useful since naturally occurring ansamycins invariably carry methyl on the α-carbon atom of the acylamino substituent.

The naphthalene (**25**) was oxidised in high yield to the quinone (**28**) by Rapoport's method,[12] and this quinone was converted into the target dihydroxynaphthoquinone (**29**) in high yield with anhydrous aluminium chloride in methylene dichloride. Similar oxidation of the naphthalene (**8**) with silver(II) oxide gave the quinone (**30**), which could be deprotected with the same Lewis acid to yield the quinone (**31**). The six-step conversion of benzoquinone into the naphthoquinone (**29**) was effected in an overall yield of 20%.

In spite of the greater crowding at C-8 in comparison with C-3 in the naphthalenes (**1**) and (**16**), exclusive substitution at the former site could be effected by a number of acyl groups of varying steric requirement on compound (**32**), obtained by replacing the 4-methoxy group in compound (**16**) with an acetoxy substituent. The reaction of this acetate[10] with trifluoroacetic anhydride premixed with hexanoic, (*E*)-but-2-enoic, or (*E*)-2-methylbut-2-enoic acid gave good yields of the corresponding 8-acyl derivatives (**33**)—(**35**), respectively, together with a minor amount of the 8-trifluoroacetyl analogue (**36**) in the latter two cases.

It is expected that the synthesis described here may be varied by changing the nature of the acylating groups, *via* analogues of the naphthalene (**6**) in which the two acyl substituents are the same or different. A propionyl substituent at C-8 in the quinone (**29**; $CH_3CH_2CO$ in place of $CH_3CO$) has previously been shown[13] to be capable of conversion, *via* oxidation to pyruvoyl, into the hydroxydihydrofuranone ring present in rifamycin B, rifamycin S, rifaldehyde, and rifampicin.[2]

The crystal structure determination on compound (**8**) confirmed both sites of acetylation in the diacetyl derivative (**4**) as well as which of the two acetyl substituents had participated in the Beckmann rearrangement. This study corroborated the assignment made on spectroscopic grounds (Figure). All bond lengths and angles were of the expected order of magnitude. The two rings are approximately planar; the maximum deviation of any ring atom from the least-squares plane for the ring atoms (equation of plane: $7.58x - 12.06y + 3.42z = -3.85$) is 0.05 Å. The N(2)–C(21)–O(21)–C(22) group is also approximately planar, as evidenced by torsion angles C(2)–N(2)–C(21)–O(21) −4° and C(2)–N(2)–C(21)–C(22) 176°. The torsion angle C(3)–C(2)–N(2)–C(21) (−24°) reveals that this group and the two rings are not coplanar. Furthermore, the carbonyl group C(51)–O(51) is nearly normal to the two-ring plane [C(6)–C(5)–C(51)–O(51) −86°].

## Experimental

All $^1$H n.m.r. spectra were measured for solutions in [$^2$H]chloroform with tetramethylsilane as internal reference; i.r. spectra were measured for Nujol mulls, unless otherwise stated. Preparative layer chromatography (p.l.c.) was performed on glass plates coated with Merck Kieselgel 60 $F_{254}$; column chromatography refers to dry-packed columns of the same gel (70—230 mesh). Light petroleum refers to the fraction of b.p. 60—80 °C and 'ether' to diethyl ether. The phrase 'residue obtained upon work-up' refers to the material remaining when the organic layer was separated, dried ($MgSO_4$), and evaporated under reduced pressure.

3,8-*Diacetyl*-4,5-*dimethoxy*-1,7-*bisisopropoxynaphthalene* (**4**).—A premixed solution of trifluoroacetic anhydride (3.1 g, 9 equiv.) and acetic acid (0.9 g, 9 equiv.) was added to 1,7-bis-isopropoxy-4,5-dimethoxynaphthalene (**1**) (500 mg, 1.6 mmol) in dry methylene dichloride (20 ml). The mixture was stirred for 66 h at room temperature and then quenched by successive additions of an excess of methanol and saturated aqueous sodium hydrogen carbonate. The organic material was extracted into methylene dichloride and the residue obtained upon work-up was chromatographed (eluant 10—20% ethyl acetate–light petroleum) to afford the *diacetylnaphthalene* (**4**)

(433 mg, 72%) as white plates, m.p. 137—138 °C (from methanol) (Found: C, 67.8; H, 7.2. $C_{22}H_{28}O_6$ requires C, 68.05; H, 7.2%); $\nu_{max.}$ 1 707 (8-C=O) and 1 660 $cm^{-1}$ (3-C=O); δ 1.26—1.48 [12 H, m, $CH(CH_3)_2$], 2.55 (3 H, s, 8-$COCH_3$), and 2.72 (3 H, s, 3-$COCH_3$), 3.76 and 4.01 (each 3 H, s, $OCH_3$), 4.68 [2 H, sept., *J* 6 Hz, $CH(CH_3)_2$], 6.64 (1 H, s, 6-H), and 7.03 (1 H, s, 2-H); *m/z* 388 ($M^+$, 86%), 346 (54), 304 (85), 289 (84), 269 (21), 244 (11), and 72 (100).

3,8-*Diacetyl*-1,4,5,7-*tetramethoxynaphthalene* (**6**).—A premixed solution of trifluoroacetic anhydride (7.62 g, 9 equiv.) and acetic acid (2.18 g, 9 equiv.) was added to 1,4,5,7-tetramethoxynaphthalene (**16**) (1.00 g, 4.03 mmol) in dry methylene dichloride (20 ml). The mixture was stirred at room temperature for 44 h. Quenching of this as before yielded, after chromatography (eluant 20—30% ethyl acetate–light petroleum), the *product* (**6**) as white needles (1.02 g, 83%), m.p. 132—133 °C (from methanol) (Found: C, 65.1; H, 5.95. $C_{18}H_{20}O_6$ requires C, 65.1; H, 6.0%); $\nu_{max.}$ 1 703 (8-C=O) and 1 663 $cm^{-1}$ (3-C=O); δ 2.50 (3 H, s, 8-$COCH_3$), 2.73 (3 H, s, 3-$COCH_3$), 3.77, 3.82, 3.91, and 4.03 (each 3 H, s, $OCH_3$), 6.70 (1 H, s, 6-H), and 7.06 (1 H, s, 2-H); *m/z* 332 ($M^+$, 100%), 317 (91), 301 (44), 287 (17), and 151 (11).

8-*Acetyl*-3-*acetylamino*-1,7-*bisisopropoxy*-4,5-*dimethoxynaphthalene* (**8**).—The naphthalene (**4**) (650 mg, 1.7 mmol) dissolved in ethanol (40 ml) was treated with hydroxylamine hydrochloride (350 mg, 5 mmol) and a solution of potassium hydroxide (90 mg, 1.7 mmol) in water (10 ml). The solution was boiled for 2 h. The mixture was diluted with water (100 ml) and acidified with 5M hydrochloric acid. The derived oxime (**5**) was extracted into ether, and the residue obtained upon work-up was dissolved in dry ether (150 ml). After treatment of the solution with phosphorus pentachloride (410 mg, 1.2 equiv.) at 0 °C for 2 h, water was added to quench the reaction. The residue obtained upon work-up was chromatographed (eluant 40% ethyl acetate–light petroleum) to give the *amide* (**8**) as white needles (459 mg, 68%), m.p. 149—150 °C (from methylene dichloride–light petroleum) (Found: C, 65.35; H, 7.1; N, 3.5. $C_{22}H_{29}NO_6$ requires C, 65.5; H, 7.2; N, 3.5%); $\nu_{max.}$ 3 316 (NH), 1 703 (8-C=O), and 1 658 $cm^{-1}$ (amide C=O); δ 1.32 and 1.34 [each 6 H, d, *J* 7 Hz, $CH(CH_3)_2$], 2.21 (3 H, s, $CH_3CONH$), 2.53 (3 H, s, 8-$COCH_3$), 3.75 and 3.96 (each 3 H, s, $OCH_3$), 4.57 and 4.73 [each 1 H, sept., *J* 7 Hz, $CH(CH_3)_2$], 6.60 (1 H, s, 6-H), 7.93br (1 H, s, NH), and 8.02 (1 H, s, 2-H); *m/z* 403 ($M^+$, 100%), 346 (53), 304 (71), 260 (91), 246 (29), 220 (18), 43 (80), and 20 (77).

8-*Acetyl*-3-*acetylamino*-1,4,5,7-*tetramethoxynaphthalene* (**9**).—The naphthalene (**6**) (883 mg, 2.6 mmol) dissolved in ethanol (50 ml) was treated with hydroxylamine hydrochloride (0.35 g, 5 mmol) in a solution of potassium hydroxide (0.14 g, 2.6 mmol) in water (20 ml). The solution was boiled for 2.5 h. The mixture was diluted with water (150 ml) and acidified with 5M-hydrochloric acid. The derived oxime (**7**) was extracted into methylene dichloride and the residue obtained upon work-up was dissolved in dry tetrahydrofuran (150 ml). After treatment of the solution with phosphorus pentachloride (0.65 g, 1.2 equiv.) at 0 °C for 3 h, an excess of water was added to quench the reaction. The residue obtained upon work-up was chromatographed (eluant ethyl acetate) yielding light brown crystals of the *amide* (**9**) (683 mg, 70%), m.p. 192—193 °C (from propan-2-ol) (Found: C, 62.05; H, 6.1; N, 4.0. $C_{18}H_{21}NO_6$ requires C, 62.25; H, 6.05; N, 4.0%); $\nu_{max.}$ 3 310 (NH), 1 710 (8-C=O), and 1 655 (amide C=O); δ 2.23 (3 H, s, $NHCOCH_3$), 2.51 (3 H, s, 8-$COCH_3$), 3.75, 3.84, 3.88, and 4.00 (each 3 H, s, $OCH_3$), 6.66 (1 H, s, 6-H), 7.98br (1 H, s, NH), and 8.05 (1 H, s, 2-H); *m/z* 347 ($M^+$, 76%), 332 (25), 290 (100), 260 (13), and 93 (22).

5,7-*Dihydroxy*-6-*methyl*-1,4-*naphthoquinone* (**14**) *and* 7-*Hydroxy*-5-*methoxy*-6-*methyl*-1,4-*naphthoquinone* (**15**).—1,4-Benzoquinone (1.0 g, 9.25 mmol) was dissolved in dry toluene (120 ml) under nitrogen at −78 °C. The diene (**10**)[8] (2.53 g, 9.25 mmol) and pyridine (1.46 ml, 18.5 mmol) were added. The solution was stirred for 5 min at −78 °C and then warmed to room temperature. The toluene was evaporated off. The organic residue was extracted into methylene dichloride and washed with dilute hydrochloric acid. The residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate–light petroleum) to afford the *quinone* (**14**) (Found: $M^+$, 204.042. $C_{11}H_8O_4$ requires *M*, 204.042); δ 2.12 (3 H, s, $CCH_3$), 3.11br (1 H, s, 7-OH), 6.90 (2 H, s, 2- and 3-H), and 7.11 (1 H, s, 8-H), and 12.91 (1 H, s, 5-OH); followed by the *quinone* (**15**) (Found: $M^+$, 218.057. $C_{12}H_{10}O_4$ requires *M*, 218.058); δ 2.20 (3 H, s, $CCH_3$), 2.95br (1 H, s, OH), 3.80 (3 H, s, $OCH_3$), 6.83 (2 H, s, 2- and 3-H); and 7.36 (1 H, s, 8-H).

5,7-*Dimethoxy*-6-*methyl*-1,4-*naphthoquinone*.—Benzoquinone (1.0 g, 9.25 mmol) was dissolved in dry toluene (120 ml) under nitrogen at −78 °C. The diene (**10**) (2.53 g, 9.25 mmol) and dry pyridine (1.46 ml, 18.5 mmol) were added, and the mixture was stirred at −78 °C for 5 min, warmed to room temperature, stirred for a further 10 min, poured into dilute hydrochloric acid (150 ml), and extracted exhaustively with methylene dichloride. The residue obtained upon work-up was dissolved in dry chloroform (200 ml). Methyl iodide (60 ml) and silver(I) oxide (4 g) were then added and the solution was stirred at room temperature for 96 h. The solid material was filtered off and the solution evaporated. The residue was chromatographed (eluant 30% ethyl acetate–light petroleum) to afford the *quinone* (644 mg, 30%) as yellow needles, m.p. 126—127 °C (from methylene dichloride–light petroleum) (Found: $M^+$, 232.074. $C_{13}H_{12}O_4$ requires *M*, 232.074); $\nu_{max.}$ 1 672 and 1 654 (C=O), and 1 582 $cm^{-1}$ (C=C); δ 2.21 (3 H, s, $ArCH_3$), 3.80 and 3.97 (each 3 H, s, $OCH_3$), 6.78 (2 H, s, 2- and 3-H), and 7.36 (1 H, s, 8-H); *m/z* 232 ($M^+$, 100%), 217 (28), 202 (20), 187 (24), 161 (13), and 148 (13).

1,4,5,7-*Tetramethoxy*-6-*methylnaphthalene* (**17**).—1,4,5,7-Tetramethoxynaphthalene (**16**) (140 mg, 0.56 mmol) was dissolved in dry tetrahydrofuran (10 ml) at −78 °C and the reaction vessel was flushed with nitrogen. Butyl-lithium (1.4 mol equiv.) was added over 2 min. The solution was stirred at −78 °C for 30 min, warmed to 0 °C, and stirred for a further 30 min. Methyl iodide (10 mol equiv.) was added and the solution stirred at room temperature for 15 min, added to water, and extracted exhaustively with ether. The residue obtained upon work-up was chromatographed (eluant 10% ethyl acetate–light petroleum) to afford the *product* (**17**) as a colourless oil (120 mg, 82%) (Found: C, 68.45; H, 7.1. $C_{15}H_{18}O_4$ requires C, 68.7; H, 6.9%); $\nu_{max.}$(film) 1 605 $cm^{-1}$ (C=C); δ 2.30 (3 H, s, $ArCH_3$), 3.77 (3 H, s, $OCH_3$), 3.90 (9 H, s, 3 × $OCH_3$), 6.61 (2 H, s, 2- and 3-H), and 7.34 (1 H, s, 8-H); *m/z* 262 ($M^+$, 100%), 247 (88), and 131 (15).

3-*Acetyl*-1,4,5,7-*tetramethoxy*-6-*methylnaphthalene* (**18**).—(*a*) Compound (**17**) (107 mg, 0.41 mmol) was dissolved in dry methylene dichloride (5 ml). A premixed solution of trifluoroacetic anhydride (770 mg, 3.7 mmol) and glacial acetic acid (220 mg, 3.7 mmol) was added. This solution was stirred at room temperature for 20 h. The reaction was quenched with methanol and saturated aqueous sodium hydrogen carbonate. The organic material was extracted into methylene dichloride and the residue obtained upon work-up was chromatographed (eluant 10% ethyl acetate–light petroleum) to give the *product* (**18**) (98 mg, 79%) as a yellow oil (Found: C, 67.25; H, 6.65. $C_{17}H_{20}O_5$ requires C, 67.1; H, 6.6%); $\nu_{max.}$(film) 1 662 (3-C=O) and 1 603 $cm^{-1}$ (C=C); δ 2.30 (3 H, s, $ArCH_3$), 2.74 (3 H, s,

$COCH_3$), 3.79, 3.81, 3.94, and 3.96 (each 3 H, s, $OCH_3$), 7.25 (1 H, s, 2-H), and 7.34 (1 H, s, 8-H); *m/z* 304 ($M^+$, 100%), 289 (30), 246 (12), and 231 (12).

(*b*) Compound (**22**), treated as described in (*a*), gave compound (**18**) in quantitative yield; t.l.c. behaviour and i.r., $^1H$ n.m.r., and mass spectra were identical with those of the material described in (*a*).

3-*Acetylamino*-1,4,5,7-*tetramethoxy*-6-*methylnaphthalene* (**19**).—The naphthalene (**18**) (300 mg, 0.98 mmol) dissolved in absolute ethanol (20 ml) was treated with hydroxylamine hydrochloride (200 mg, 2.49 mmol) and a solution of potassium hydroxide (40 mg, 0.98 mmol) in water (10 ml). The solution was boiled for 1 h, and the crude oxime, obtained as described for compound (**8**), was converted directly into the corresponding crude amide (**19**). This was chromatographed (eluant 30% ethyl acetate–light petroleum) to give the *amide* (**19**) (203 mg, 65%) as white needles, m.p. 131—132 °C (from light petroleum–methylene dichloride) (Found: C, 63.95; H, 6.75; N, 4.15. $C_{17}H_{21}NO_5$ requires C, 63.95; H, 6.6; N, 4.4%); $\nu_{max.}$ 3 230 (NH), 1 653 (C=O), and 1 604 (C=C) $cm^{-1}$; δ 2.24 (3 H, s, $NHCOCH_3$), 2.29 (3 H, s, $ArCH_3$), 3.75, 3.80, 3.92, and 3.98 (each 3 H, s, $OCH_3$), 7.32 (1 H, s, 8-H), and 8.20br (2 H, s, NH and 2-H); *m/z* 319 ($M^+$, 65%), 304 (25), 262 (100), and 245 (16).

8-*Acetyl*-1,4,5,7-*tetramethoxy*-6-*methylnaphthalene* (**22**).—Compound (**21**) (173 mg, 0.60 mmol) was dissolved in dry tetrahydrofuran (5 ml) and the reaction vessel was flushed with dry nitrogen. Butyl-lithium (3.0 mmol, 5 mol equiv.) was added to the solution at −78 °C. The red mixture was then taken to 0 °C and stirred for 15 min. Methyl iodide was added dropwise until the red colour was just dispersed, and the clear solution was stirred for 1 min before quenching with water. The mixture was extracted with methylene dichloride. The residue obtained upon work-up was chromatographed (eluant 10% ethyl acetate-light petroleum) to give the product (**22**) (170 mg, 95%) as white needles, m.p. 107—108 °C (from propan-2-ol) (Found: C, 67.15; H, 6.45. $C_{17}H_{20}O_5$ requires C, 67.1; H, 6.6%); $\nu_{max.}$ 1 704 (8-C=O) and 1 578 $cm^{-1}$ (C=C); δ 2.35 (3 H, s, $ArCH_3$), 2.56 (3 H, s, $COCH_3$), 3.75, 3.78, 3.80, and 3.93 (each 3 H, s, $OCH_3$), and 6.74 (2 H, s, 2- and 3-H); *m/z* 304 ($M^+$, 100%), 289 (77), 273 (35), and 259 (13).

8-*Acetyl*-1,4,5,7-*tetramethoxy*-6-*methyl*-3-*propionylamino*-*naphthalene* (**25**).—Tetramethylethylenediamine (0.35 ml, 2.3 mmol 10 mol equiv.) was dissolved in dry tetrahydrofuran (5 ml) and the reaction vessel was flushed with nitrogen. Butyl-lithium (1.15 mmol, 5 mol equiv.) was added to this solution at 0 °C. The amide (**9**) (80 mg, 0.23 mmol) dissolved in dry tetrahydrofuran (10 ml) was added to this mixture at −78 °C over 5 min. The solution was then stirred at 0 °C for 15 min. Methyl iodide (0.05 ml) was added and the mixture stirred at room temperature for 15 min. The reaction was then quenched with water. The organic material was extracted into ether and the residue obtained upon work-up was flash chromatographed (eluant 30% ethyl acetate–light petroleum) to give the *product* (**25**) (52 mg, 60%) as white needles, m.p. 154—155 °C (from methylene dichloride–light petroleum) (Found: C, 63.95; H, 6.5; N, 3.75. $C_{20}H_{25}NO_6$ requires C, 64.0; H, 6.7; N, 3.7%); $\nu_{max.}$ 3 337 (NH), 1 695 (8-C=O), and 1 618 $cm^{-1}$ (C=C); δ 1.29 (3 H, t, *J* 8 Hz, $CH_2CH_3$), 2.36 (3 H, s, $ArCH_3$), 2.49 (2 H, q, *J* 8 Hz, $CH_2CH_3$), 2.51 (3 H, s, $COCH_3$), 3.72 (6 H, s, $OCH_3$), 3.79 and 3.88 (each 3 H, s, $OCH_3$), and 8.10br (2 H, s, 2-H and NH); *m/z* 375 ($M^+$, 89%), 360 (18), and 304 (100).

1,4,5,7-*Tetramethoxy*-6-*methyl*-3-*propionylaminonaphthalene* (**20**).—The amide (**25**) (30 mg, 0.08 mmol) was dissolved in dry methylene dichloride (3 ml). A catalytic amount of trifluoroacetic acid was added and the mixture was boiled for 48 h, then quenched with water. The organic material was extracted with ether and washed with aqueous sodium hydrogen carbonate. The residue obtained upon work-up was chromatographed (eluant 30% ethyl acetate–light petroleum) to afford the *product* (**20**) (28 mg, 100%) as off-white needles, m.p. 110—111 °C (from methylene dichloride–light petroleum) (Found: C, 64.5; H, 6.8; N, 4.1. $C_{18}H_{23}NO_5$ requires C, 64.9; H, 6.9; N, 4.2%); $\nu_{max.}$ 3 251 (NH), 1 660 (C=O), and 1 607 $cm^{-1}$ (C=C); δ 1.30 (3 H, t, *J* 8 Hz, $CH_2CH_3$), 2.30 (3 H, s, $ArCH_3$), 2.50 (2 H, q, *J* 8 Hz, $CH_2CH_3$), 3.76, and 3.80, 3.92, and 4.00 (each 3 H, s, $OCH_3$), 7.34 (1 H, s, 8-H), and 8.10br (2 H, s, NH and 2-H); *m/z* 333 ($M^+$, 75%), 318 (15), and 262 (100).

8-*Acetyl*-5,7-*dimethoxy*-6-*methyl*-3-*propionylamino*-1,4-*naphthoquinone* (**28**).—The naphthalene (**25**) (36 mg, 0.096 mmol), silver(II) oxide (48 mg, 0.385 mmol, 4 mol equiv.), and dioxane (8 ml) were stirred together at room temperature and the reaction was initiated by addition of nitric acid (6M; 4 mol equiv.). After 5 min the reaction was stopped by addition of methylene dichloride–water (8:2; 20 ml), and the organic layer was washed with aqueous sodium hydrogen carbonate and then water. The residue obtained upon work-up was chromatographed (eluant 20% ethyl acetate–light petroleum) to yield the *quinone* (**28**) (32 mg, 97%) as yellow needles, m.p. 183—184 °C (from methanol) (Found: C, 62.55; H, 5.45; N, 4.05. $C_{18}H_{19}NO_6$ requires C, 62.6; H, 5.5; N, 4.1%); $\nu_{max.}$ 3 180 (NH), 1 696 (8-C=O), 1 675 and 1 636 (C=O), and 1 620 $cm^{-1}$ (C=C); δ 1.24 (3 H, t, *J* 8 Hz, $CH_2CH_3$), 2.31 (3 H, s, $ArCH_3$), 2.50 (3 H, s, 8-$COCH_3$), 2.51 (2 H, q, *J* 8 Hz, $CH_2CH_3$), 3.78 and 3.87 (each 3 H, s, $OCH_3$), 7.74 (1 H, s, 2-H), and 8.46br (1 H, s, NH); *m/z* 345 ($M^+$, 15%), 330 (23), and 274 (100).

8-*Acetyl*-5,7-*dihydroxy*-6-*methyl*-3-*propionylamino*-1,4-*naphthoquinone* (**29**).—The quinone (**28**) (70 mg, 0.20 mmol) was dissolved in dry methylene dichloride (10 ml). Aluminium trichloride (521 mg, 4 mmol) was added and the solution stirred at room temperature for 52 h. The reaction was then quenched with water, and the organic layer extracted into ethyl acetate. The residue obtained upon work-up was chromatographed (eluant 70% ethyl acetate–light petroleum) to yield the *quinone* (**29**) (55 mg, 85%) as orange needles, m.p. 183—184 °C (from methanol) (Found: C, 60.15; H, 4.5; N, 4.3%; $M^+$, 317.0878. $C_{16}H_{15}NO_6$ requires C, 60.55; H, 4.75; N, 4.4%; *M*, 317.0899); $\nu_{max.}$ 3 325 (NH), 1 704 (8-C=O), 1 639 (C=O), and 1 617 $cm^{-1}$ (C=C); δ 1.26 (3 H, t, *J* 8 Hz, $CH_2CH_3$), 2.18 (3 H, s, $COCH_3$), 2.37 (3 H, s, $ArCH_3$), 2.54 (2 H, q, *J* 8 Hz, $CH_2CH_3$), 7.76 (1 H, s, 2-H), 8.38br (1 H, s, NH), 9.20br (1 H, s, 7-OH), and 12.12 (1 H, s, 5-OH); *m/z* 317 ($M^+$, 57%), 261 (20), 246 (100), and 233 (20).

8-*Acetyl*-3-*acetylamino*-5-*methoxy*-7-*isopropoxy*-1,4-*naphthoquinone* (**30**).—The amide (**8**) (66 mg, 0.16 mmol), silver(II) oxide (80 mg, 0.64 mmol), and dioxane (10 ml) were stirred together at room temperature. Nitric acid (6M; 0.8 ml) was added and the mixture stirred for 4 min. A mixture of methylene dichloride (20 ml) and water (5 ml) was added and the organic layer was separated and washed with more water. The residue obtained upon work-up was chromatographed (eluant 70% ethyl acetate–light petroleum) affording the *quinone* (**30**) as pale yellow flakes (43 mg, 77%), m.p. 221 °C (from propan-2-ol) (Found: C, 62.7; H, 5.5; N, 4.1. $C_{18}H_{19}NO_6$ requires C, 62.6; H, 5.5; N, 4.1%); $\nu_{max.}$ 3 299 (NH), 1 707 (8-C=O), and 1 653 $cm^{-1}$ (C=O); δ 1.38 [6 H, d, *J* 7 Hz, $CH(CH_3)_2$], 2.24 (3 H, s, $NHCOCH_3$), 2.47 (3 H, s, $CCOCH_3$), 4.00 (3 H, s, $OCH_3$), 4.68 [1 H, sept., *J* 7 Hz, $CH(CH_3)_2$], 6.64 (1 H, s, 6-H), 7.64 (1 H, s, 2-H), and 8.54br (1 H, s, NH); *m/z* 345 ($M^+$, 11%), 330 (22), 266 (21), and 245 (100).

8-*Acetyl*-3-*acetylamino*-5,7-*dihydroxy*-1,4-*naphthoquinone* (**31**).—The quinone (**30**) (16 mg, 0.046 mmol) in dry methylene dichloride (5 ml) containing anhydrous aluminium trichloride (122 mg, 20 mol equiv.) was stirred at room temperature for 15 min. Water was added and the aqueous layer washed with ethyl acetate. The residue obtained upon work-up was chromatographed (eluant ethyl acetate) to afford the *product* (**31**) (12 mg, 83%) as yellow needles, m.p. 222—226 °C (decomp.) (from methanol) (Found: $M^+$, 289.058. $C_{14}H_{11}NO_6$ requires $M$, 289.058); $\nu_{max.}$ 3 315 (NH), 1 690 (8-C=O), and 1 645 $cm^{-1}$ (C=O); δ[$(CD_3)_2SO$] 2.21 (3 H, s, $NHCOCH_3$), 2.29 (3 H, s, $CCOCH_3$), 6.56 (1 H, s, 6-H), 7.48 (1 H, s, 2-H), 9.86br (1 H, s, NH), and 11.87br (1 H, s, OH); *m/z* 289 ($M^+$, 35%), 232 (100), and 43 (49).

4-*Acetoxy*-8-*hexanoyl*-1,5,7-*trimethoxynaphthalene* (**33**).—Hexanoic acid (50 mg, 0.43 mmol) premixed with trifluoroacetic anhydride (120 mg, 0.54 mmol) was rapidly added to the naphthalene (**32**) (100 mg, 0.36 mmol) dissolved in dry methylene dichloride (3 ml). The mixture was stirred at room temperature for 38 h with addition of further portions of the mixed anhydride at 2, 12, and 20 h. The reaction was quenched by successive additions of an excess of methanol and saturated aqueous sodium hydrogen carbonate. The organic material was extracted into methylene dichloride and the residue obtained upon work-up was chromatographed (eluant 25% ethyl acetate–light petroleum) affording the *product* (**33**) (86 mg, 64%) as white needles, m.p. 124.5—125 °C (from ethanol–acetone) (Found: C, 67.15; H, 7.05. $C_{21}H_{26}O_6$ requires C, 67.35; H, 6.95%); $\nu_{max.}$ 1 751 (OAc) and 1 689 $cm^{-1}$ (8-C=O); δ 1.08—2.02 [9 H, m, $(CH_2)_3CH_3$], 2.37 (3 H, s, $OCOCH_3$), 2.58—3.00 (2 H, m, $COCH_2$), 3.87, 3.92, and 3.97 (each 3 H, s, $OCH_3$), 6.77 (1 H, s, 6-H), and 6.83 and 7.00 (each 1 H, d, *J* 9 Hz, 2- and 3-H); *m/z* 374 ($M^+$, 38%), 332 (41), 303 (42), 261 (100), and 246 (26).

4-*Acetoxy*-1,5,7-*trimethoxy*-8-*trifluoroacetylnaphthalene* (**36**) *and* 4-*Acetoxy*-8-[(E)-*but*-2-*enoyl*]-1,5,7-*trimethoxynaphthalene* (**34**).—The naphthalene (**32**) (100 mg, 0.36 mmol) in dry methylene dichloride (5 ml) was treated at room temperature with two portions of a mixture of (*E*)-but-2-enoic acid (31 mg, 0.43 mmol) and trifluoroacetic anhydride (100 mg, 0.43 mmol) over 26 h. The residue obtained upon work-up (as just described) was chromatographed (eluant 5—20% ethyl acetate–light petroleum) to afford first the *trifluoroacetylnaphthalene* (**36**) (34 mg, 26%) as white needles, m.p. 160—162 °C (from methanol) (Found: C, 55.05; H, 4.2. $C_{17}H_{15}F_3O_6$ requires C, 54.85; H, 4.05%); $\nu_{max.}$ 1 762 and 1 744 (C=O) and 1 619 $cm^{-1}$ (C=C); δ 2.30 (3 H, s, $COCH_3$), 3.78, 3.85, and 3.90 (each 3 H, s, $OCH_3$), 6.57 (1 H, s, 6-H), and 6.67 and 6.85 (each 1 H, d, *J* 8 Hz, 2- and 3-H); *m/z* 372 ($M^+$, 26%), 330 (58), 261 (100), 246 (39), and 231 (15). This was followed by the *naphthalene* (**34**) (92 mg, 73%) as pale yellow cubes, m.p. 184—185.5 °C (from methanol) (Found: C, 66.1; H, 6.05. $C_{19}H_{20}O_6$ requires C, 66.3; H, 5.8%); $\nu_{max.}$ 1 751 and 1 654 (C=O) and 1 620 $cm^{-1}$ (C=C); δ 1.80 (3 H, dd, *J* 2 and 6 Hz, $C{=}CCH_3$), 2.30 (3 H, s, $OCOCH_3$), 3.68, 3.78, and 3.88 (each 3 H, s, $OCH_3$), 6.27—6.40 (2 H, m, vinyl-CH), 6.63 (1 H, s, 6-H), and 6.70 and 6.87 (each 1 H, d, *J* 8 Hz, 2- and 3-H); *m/z* 344 ($M^+$, 73%), 302 (100), 271 (98), 261 (29), and 231 (23).

4-*Acetoxy*-1,5,7-*trimethoxy*-8-[(E)-2-*methylbut*-2-*enoyl*]-*naphthalene* (**35**).—The naphthalene (**32**) (100 mg, 0.36 mmol) was treated with three successive batches of a mixture of tiglic acid (36 mg, 0.43 mmol) and trifluoroacetic anhydride (120 mg, 0.54 mmol) over 23 h. The residue obtained upon work-up (as just described) was chromatographed (eluant 5—20% ethyl acetate–light petroleum) to yield the product (**36**) (28 mg, 21%) followed by the *naphthalene* (**35**) (98 mg, 72%) as yellow needles, m.p. 213—214 °C (from methanol) (Found: C, 66.9; H, 7.2. $C_{20}H_{22}O_6$ requires C, 67.05; H, 6.15%); $\nu_{max.}$ 1 753 (OAc) and 1 647 $cm^{-1}$ (C=O); δ 1.73br (3 H, d, *J* 7 Hz, $CH_3CH$), 1.97br (3 H, s, $CH_3CCO$), 2.33 (3 H, s, $OCOCH_3$), 3.67, 3.80, and 3.92 (each 3 H, s, $OCH_3$), 6.63 (1 H, s, 6-H), and 6.67 and 6.85 (each 1 H, d, *J* 9 Hz, 2- and 3-H); *m/z* 358 ($M^+$, 71%), 316 (100), 285 (48), 261 (50), 245 (24), and 43 (78).

**Table.** Fractional atomic co-ordinates ($\times 10^4$) for the non-hydrogen atoms of compound (**8**) (e.s.d.s in parentheses)

| Atom | *x/a* | *y/b* | *z/c* |
|---|---|---|---|
| C(1) | 747(4) | 3 791(3) | 418(5) |
| C(2) | 340(4) | 3 305(3) | −498(5) |
| C(3) | 856(4) | 3 216(3) | −1 797(5) |
| C(4) | 1 740(5) | 3 633(3) | −2 170(5) |
| C(4′) | 2 185(4) | 4 174(3) | −1 313(5) |
| C(5) | 3 060(4) | 4 644(3) | −1 782(5) |
| C(6) | 3 457(4) | 5 142(3) | −881(6) |
| C(7) | 3 013(5) | 5 196(3) | 450(5) |
| C(8) | 2 136(5) | 4 777(3) | 897(5) |
| C(8′) | 1 675(4) | 4 237(3) | 37(5) |
| O(1) | 242(3) | 3 779(2) | 1 701(3) |
| C(11) | −601(5) | 4 335(3) | 1 958(6) |
| N(2) | −583(4) | 2 871(2) | −44(4) |
| C(21) | −1 309(4) | 2 534(3) | −831(6) |
| O(21) | −1 259(3) | 2 615(2) | −2 031(3) |
| C(22) | −2 162(5) | 2 069(3) | −34(6) |
| O(4) | 2 332(3) | 3 559(2) | −3 402(3) |
| C(41) | 1 797(5) | 3 301(4) | −4 528(5) |
| C(411) | 895(6) | 3 829(4) | −4 793(7) |
| C(421) | 2 672(5) | 3 267(4) | −5 696(6) |
| C(51) | 3 596(5) | 4 668(3) | −3 208(6) |
| O(51) | 3 235(3) | 5 094(2) | −4 009(4) |
| C(52) | 4 598(5) | 4 210(4) | −3 544(6) |
| O(6) | 4 377(3) | 5 538(2) | −1 307(3) |
| C(61) | 4 347(5) | 6 363(3) | −1 094(6) |
| C(611) | 5 406(8) | 6 590(4) | −745(11) |
| C(621) | 4 136(8) | 6 743(5) | −2 374(8) |
| O(8) | 1 654(3) | 4 828(2) | 2 168(3) |
| C(81) | 1 997(6) | 5 429(3) | 2 992(6) |

X-*Ray Crystallographic Analysis of Compound* (**8**).—A single crystal (0.20 × 0.30 × 0.40 mm) of compound (**8**) was obtained by recrystallisation from methylene dichloride–light petroleum.

*Crystal data.* $C_{22}H_{29}NO_6$, $M$ = 403.48. Monoclinic, $a$ = 12.408(3), $b$ = 17.667(5), $c$ = 9.996(4) Å, β = 95.33(3)°, $V$ = 2 182 $Å^3$, by least-squares refinement on diffractometer angles for 25 automatically centred reflections ($16 \leqslant \theta \leqslant 17°$), λ = 0.710 69 Å. Space group $P2_1/c$, $Z$ = 4, $D_c$ = 1.23 Mg $m^{-3}$; μ(Mo-$K_\alpha$) = 0.053 $mm^{-1}$, $F(000)$ = 864.

*Data collection and processing.* CAD4 Diffractometer, ω/2θ mode with ω scan width 0.44 + 0.35 tan θ, aperture width 1.57 + 1.05 tan θ mm, graphite-monochromated Mo-$K_\alpha$ radiation; 2 622 unique reflections measured ($1 \leqslant \theta \leqslant 25°$), giving 1 648 with $I_{rel} > \sigma I_{rel}$. Variation in $F_{obs}$ for standard reflections < 2%.

*Structure analysis and refinement.* Direct methods using preliminary version of SHELX-S 84[14] (all non-hydrogen atoms), followed by normal Fourier analyses using SHELX-76.[15] Full-matrix least-squares refinement (in two blocks for final cycles); number of variables 292; all non-hydrogen atoms anisotropic; naphthyl and methine hydrogens in calculated positions with single isotropic temperature factors $U_{iso}$ = 0.073(12) and 0.100(15) $Å^2$ respectively; methyls as rigid groups, their hydrogens having a single isotropic temperature factor $U_{iso}$ = 0.153(9) $Å^2$; the amide hydrogen constrained to ride at 1.00(1) Å from its parent N, and refined isotropically, $U_{iso}$ = 0.100(16) $Å^2$. The weighting scheme $w = (\sigma^2 F)^{-1}$ gave

satisfactory agreement analyses. Final $R$ and $R_w$ values, 0.065 and 0.059, respectively. PARST[16] Used for derived molecular parameters, PLUTO[17] for drawings. Computer details and sources of scattering factor data given in ref. 18. Final atomic co-ordinates reported in the Table.*

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* Bond lengths and angles, hydrogen co-ordinates, and temperature factors have been deposited at the Cambridge Crystallographic Data Centre (see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, Issue 1, 1988).

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