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CYCLOADDITION REACTIONS OF N-ALKOXYCARBONYL-4-QUINOLONES

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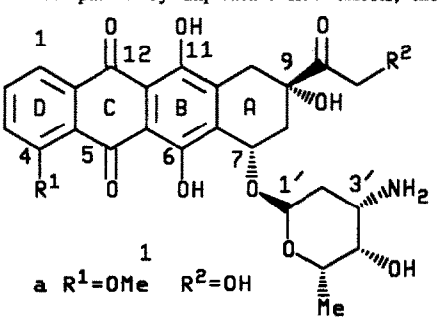
Abstract. 3-Ethoxycarbonyl-4-1(H)-quinolone (2) and 3-nitro-4-1(H)-quinlone (3) reacted with a variety of chloroformates to give the N-acyl-3-ethoxycarbonyl-4-1(H)-quinolones (4a-d) and N-acyl-3-nitro-4-1(H)-quinolones (5a,b) respectively. Reaction of (4a,b,d) with 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (6) gave the respective[4+2]cycloadduct,5,10a-diethoxycarbonyl-3,10-dioxo-1-methoxy-octahydroacridine(7a)and the analogues (7b,d). Treatment of (5a,b) with the above diene gave rise to two cycloadducts 3,10-dioxo-5-ethoxycarbonyl-1-methoxy-10a-nitro-octahydroacridines which had arisen from addition from the exo and endo transistion states. The quinolones (4a,b) on reaction with Gesson's diene (12) and the ketene acetals (15) and (16), afforded Michael adducts 2-[1,3-biscarboethoxy-1,2-dihydroquinolin-2-yl-4-hydroxy]-methyl-1-carboethoxy-4-methoxycyclohexa-1,3-diene (14a), and (14b),(17),(18) respectively. Base treatment of (14a,b) gave the aminoketone 7-(2'-aminobenzoyl)-8-hydroxy-3-methoxy-1,2-dihydronaphthalene (19) which was acetylated to afford (20). The latter could be selectively O-deacetylated to give 7-(2'-acetamidobenzoyl)-8-hydroxy-3-methoxy-1,2-dihydronaphthalene (21).

The anthracycline antibiotics[1] (1) are currently used in the treatment of various carcinomas. Adriamycin (1a) plays a significant role in the treatment of acute leukemia, breast cancer, Hodgkins disease, lymphomas and sarcomas, and is currently the leading anticancer drug capturing *ca* 20% of the market.[2] However, as with all cancer-chemotherapeutic agents, its use is accompanied by unpleasant side effects, the most serious of which is dose-related cardiotoxicity.[3]



1

a R^1=OMe R^2=OH

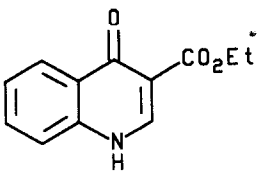
There is, thus, a need for a design of analogues of anthracyclines which retain the cytoxicity but possess negligible cardiotoxicity.

There is good evidence that the onset of cardiotoxicity depends on the property of the quinone moiety to undergo microsomal reductions followed by reactions with molecular oxygen to generate reactive oxygen species.[4] Thus, structures modified in ring C to give non-reducible analogues of anthracyclines become attractive targets. Recently Lown *et al.*[5] reported the synthesis of xanthone based analogues and others have reported studies directed towards the same aim,[6] and other structural variants.[7]

We were attracted to the synthesis of acridone-based systems and we considered that these could possibly be approached by Diels-Alder reactions using quinolones as CD ring precursors.

Our studies herein described confirm that quinolones bearing electron withdrawing groups at N-1 and C-3 can be used as dienophiles with certain electron rich dienes, whereas with other electron rich dienes Michael addition products arise. A somewhat similar study on Diels-Alder reactions of chromones has recently been reported.[8]

Prior to utilising the quinolones (2)[9] and (3)[10] for cycloaddition reactions the nitrogen was N-acylated with various chloroformates to afford (4a-d) and (5a,b).



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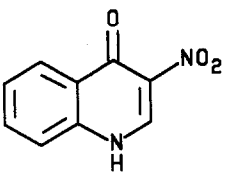

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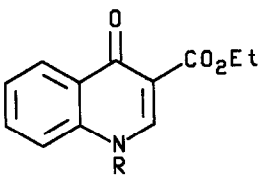

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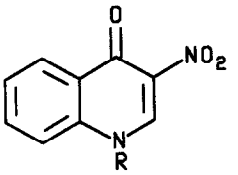


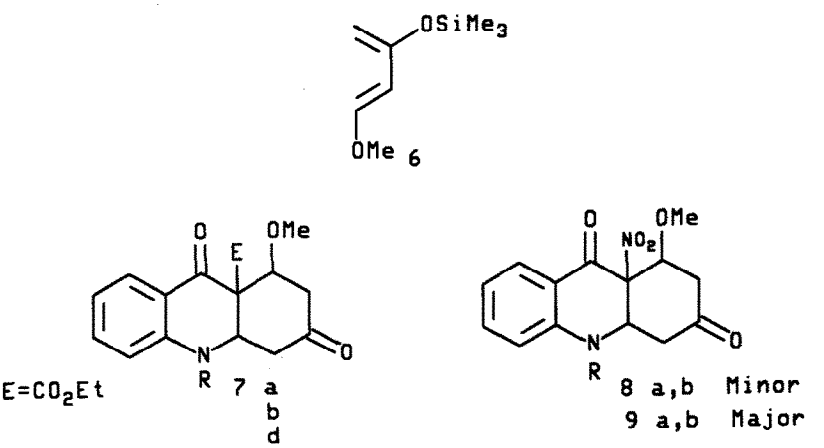
5

a R=CO_2Et
b R=$PhCH_2OCO$
c R=FMOC
d R=$(pNO_2\text{-}C_6H_4)_2CHCH_2OCO$

N-Acylation of the quinolones (2) and (3) was accomplished in refluxing chloroform using the appropriate chloroformate and N,N-di-isopropylamine or sodium carbonate as base. The latter gave the products without resort to a chromatographic purification and without any decrease in yield.

That acylation had occurred on nitrogen and not oxygen was strongly supported by the observation that in the ^{1}H NMR the H-2 signals occurred at *ca.* ∂9 in the case of compounds (4) and at ∂9.55 for (5), in good agreement with data published for comparable systems.[11]

With the substituted quinolones in hand we undertook a study of their chemistry with a variety of dienes. When the quinolones (4a,b,d) were treated with 1.2 equivalents of 1-methoxy-3-(trimethylsilyloxy)-1, 3-butadiene (Danishefsky's diene),(6), in refluxing toluene or benzene, the [4+2] cycloadducts (7a,b,d) were isolated in high yield after chromatography.



a,b,c,d are as for 4&5 and apply to all the formulae 4 -9 and to 13, 14.

Surprisingly (4c) did not afford a cycloadduct on treatment with the diene (6), the parent quinolone (2) being the sole product isolated. This result tends to indicate that the Fmoc group is too labile for some synthetic operations whilst the recently developed BNPOC protecting group[12] is more robust.

In the NMR spectrum of the diketone (7a) the H-1 proton at 4.20ppm shows a coupling of 8.2 Hz to the axial H-2 proton at 2.84ppm, whilst H-4a at 5.30ppm has a coupling constant of 13.2 Hz to the axialH-4 at 2.68ppm. This suggests that the hydrogens H-1 and H-4a both occupy axial positions as indicated in (7a'). Since the NMR spectra for (7b) and (7d) were very similar to that of (7a), a similar stereochemistry is presumed.

The general structural features of the cycloadduct (7a) were confirmed by an X-ray crystallographic study. Although (7a) is a single isomer, the crystal structure, depicted in Figure 1 together with the numbering

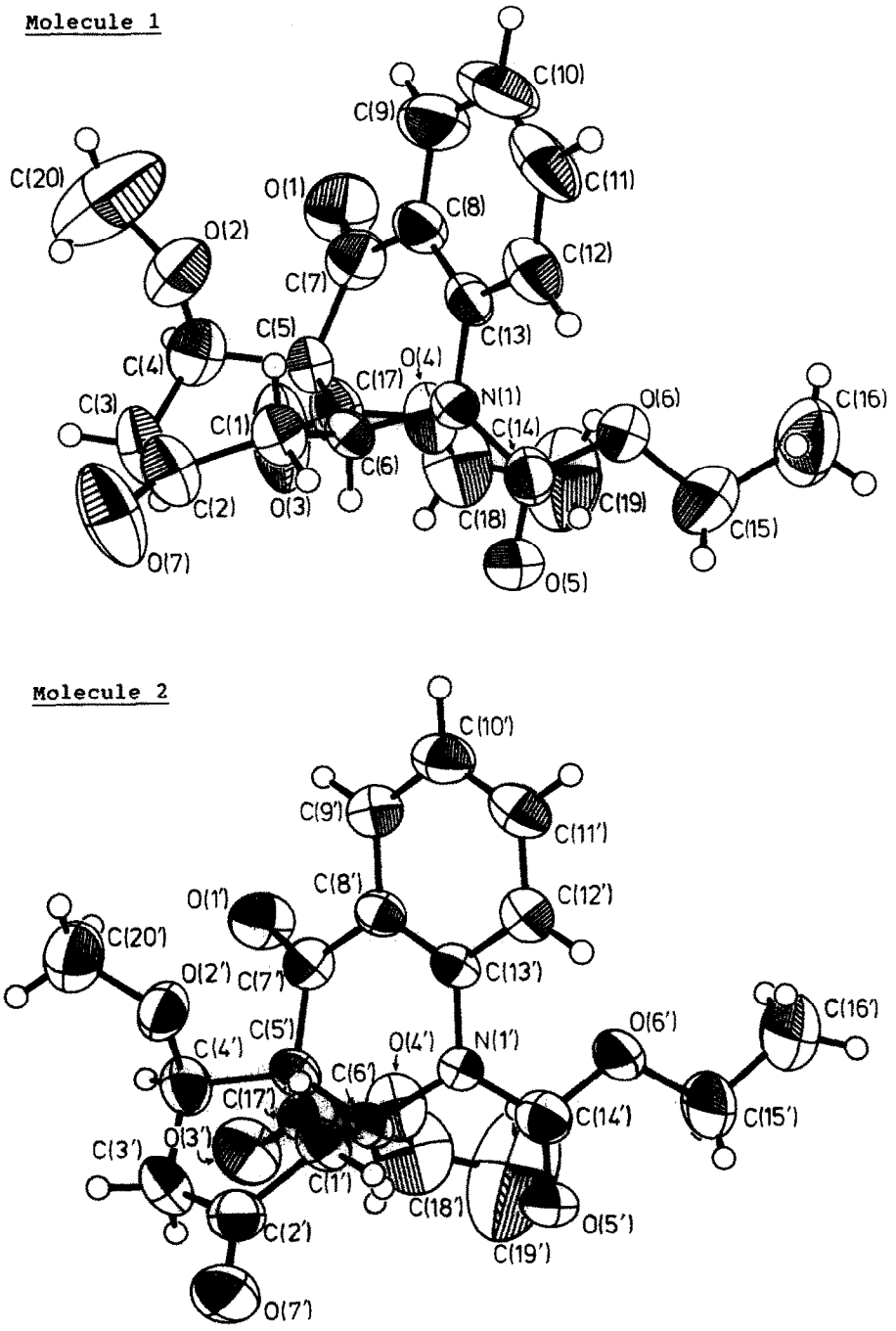
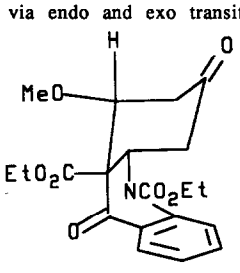


Figure 1. X-ray crystal structure of cycloadduct (7a) (ORTEP, 50% probability ellipsoids, ref. 17). The hydrogen atom labels have been omitted for clarity.

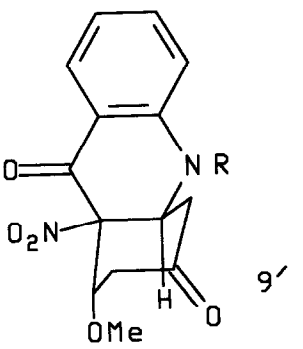
system used in this study, consists of two independent molecules per asymmetric unit which show no significant differences between corresponding geometrical parameters. There are, however, some variations in the spatial arrangements adopted by the ester substituents in each molecule. The molecules of (7a) are well-separated with the only significant intermolecular contacts [H-6...0(5') 2.41(1) Å and H(6')...0(5) 2.50(1) Å] occurring between the two independent molecules. Moreover, the geometrical parameters around each molecule are well within the expected ranges.[18] A selection of bond distances and angles is given in Table 1.

The region around the aromatic ring exhibits a high degree of planarity; deviations from the least-squares planes through N(1), C(7), C(8), C(9), C(10), C(11), C(12) and C(13) and the corresponding atoms in the second molecule were within ± 0.021 and ± 0.008 Å respectively. The central heterocyclic ring adopts a flattened boat conformation with the nitrogen atom N(1) having a planar, trigonal geometry. Consistent with the suprafacial-suprafacial mode of cycloaddition, the ring junction at C(5) and C(6) is *cis*. In contrast, however, to the solution phase structure of (7a) deduced from ^{1}H nmr data, the ring formed in the cycloaddition reaction preferentially adopts a distorted boat conformation with the methoxyl group at C(4) in an axial position. Although this might intuitively be regarded as a less favourable conformation, there is no structural evidence of either abnormal geometrical distortion around the ring or severe intramolecular steric interactions. The non-bonded distances [0(2)...H(1A) 2.46(1) Å] and [0(2')...H(1A') 2.40(1) Å] suggest that the 1,4-syn-axial interaction is of a comparatively minor nature. Inspection of molecular models indicates that there are several possible conformations for (7a). In conformation (7a'), there is a destabilising gauche-type interaction between the methoxyl group and the adjacent ester group which is absent in the solid state structure. Moreover, since the solid state structure appears to be conformationally more flexible then that of (7a'), it may give rise to a more efficient packing arrangement in the crystal. On the other hand, the additional effects of solvation must favour the conformer (7a') in solution.

When the nitro compounds (5a) and (5b) were allowed to reacted with Danishefsky's diene (6), under the same reaction conditions, two isomeric products were produced, in a ratio of *ca.* 3:2 in each case. On the basis of ^{1}H NMR and NOE data we assign structure (8a) and (8b) to the minor isomers, which correspond stereochemically to compounds (7). The major isomers (9a) and (9b) each showed in their ^{1}H NMR spectra a narrow triplet for H-1 at 4.9 ppm with a coupling of 3 Hz, and a doublet of doublets for H-4a at 6.05 ppm with coupling constants of 12.75 and 6.23 Hz. We assign the structures (9a,b) with an axial methoxy group as indicated in (9') on the basis of the ^{1}H nmr data, and this structure has been confirmed in the case of (9a) by X-ray crystallography (K.J. McCullough, unpublished data). These structures can be regarded as arising from [4+2] cycloaddition of (5a,b) with E-(6) via endo and exo transition states respectively.

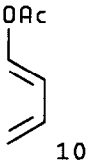


7a'



9'

Having been successful with Danishefsky's diene we found that the quinolone (4b) failed to react with 1-acetoxy-1,3-butadiene (10) and 2,3-dimethoxy-1,3-butadiene (11) in toluene. Lewis acid catalysis gave no improvement.



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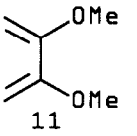

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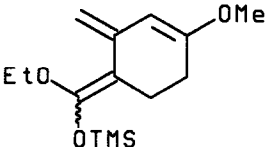

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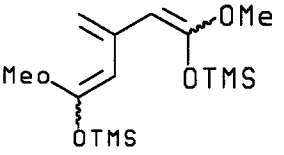

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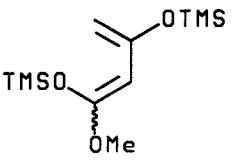


15

It, therefore seemed that 1,3-diactivated dienes were required for reaction. Armed with this information we turned to electron rich ketene acetals, and in particular we studied the reaction of Gesson's diene, (12),[13] since [4+2] cycloaddition would be expected to lead to a tetracycle.

Treatment of (4a) or (4b) with (12) in refluxing toluene, afforded in each case, after chromatographic desilylation and purification, a crystalline product in good yield. That the products were not the expected cycloadducts (13a,b), was evident from mass spectrometry and ^{1}H NMR, which indicated that the adducts contained the elements of ethanol additional to formulae (13 a,b). The ^{13}C NMR indicated no ketonic carbonyl signals and the ^{1}H NMR showed a lowfield (12.15 ppm) exchangeable singlet. The same adducts also resulted when the reaction was performed in acetonitrile as a solvent using $ZnCl_2$ as a Lewis acid catalyst, in a comparable yield, but much shorter reaction times.

This data is consistent with the formulation (14a,b), and the structure of (14b) was subsequently established by X-ray crystallography. Thus, the product from the reaction of the quinolone (4b) and Gesson's diene (12) was shown to be the Michael adduct (14b), in good agreement with the spectroscopic data mentioned above. The molecular structure is depicted in Figure 2 together with the numbering system adopted for the X-ray study. No significantly short intermolecular contacts were observed. The bond lengths and angles around the molecule are generally unexceptional.[18] In the solid state, molecule (14b) also exists in the enolic form with the tautomeric hydrogen atom (H1') intramolecularly bonded to the oxygen atom O(2) [O(1)-H(1') 0.94(5) Å, H(1')...O(2)1.79(5) Å]. The latter intramolecular hydrogen bonding distance is intermediate between that observed in dimethyl 2,6-dichloro- 2,5-dihydroxyterephthalate [2.04 Å][19] and 2-acetyltetralone [1.37 Å].[20] A selection of the more important derived geometrical parameters are listed in Table 2.

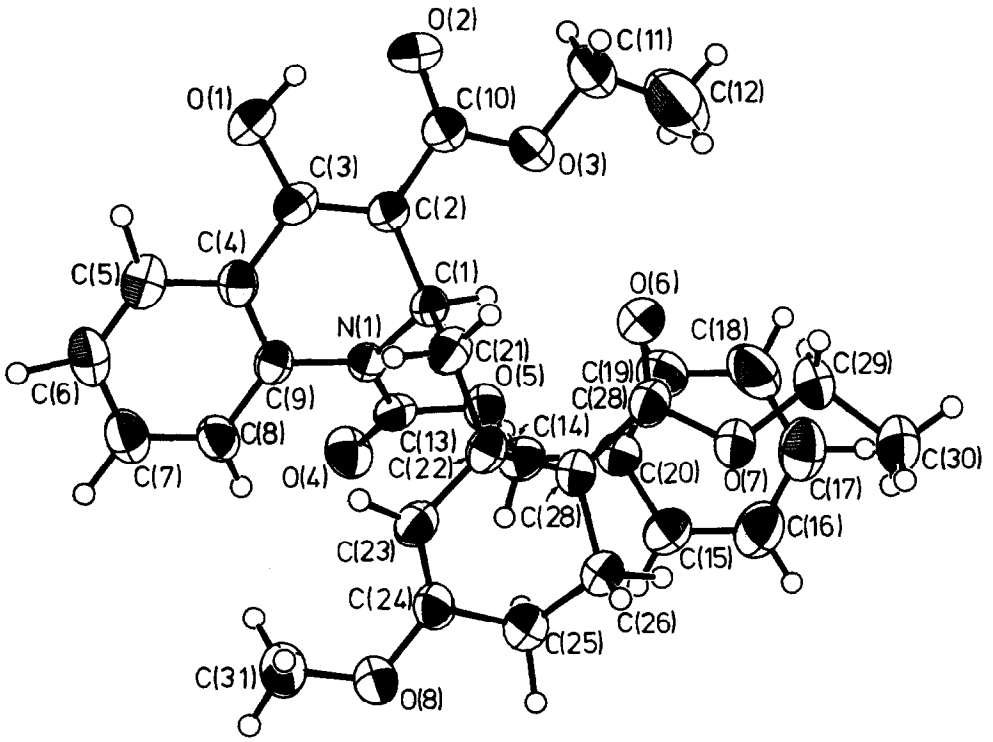
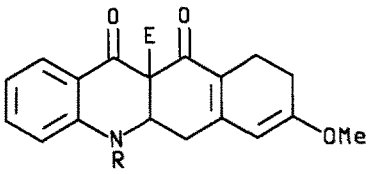
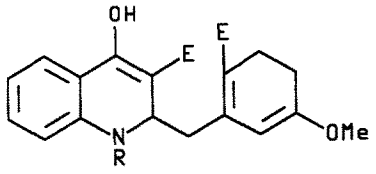


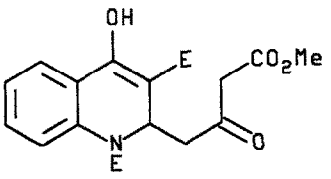
Figure 2. X-ray crystal structure of adduct (14b) (ORTEP, 50% probability ellipsoids, ref. 17). The hydrogen atom labels have been omitted for clarity.



13 a,b

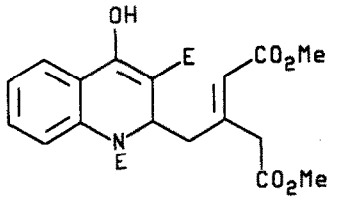


14 a,b



17

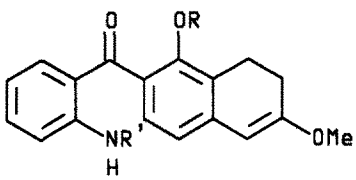
E= CO_2Et



18

The formation of (14a,b) seems to imply that with a triply activated diene an ionic mechanism dominates, presumably due to the stability of the presumed carbocation intermediate. This is borne out with other triply activated dienes (15)[14] and (16)[15], which resulted in the adducts (17) and (18) respectively when allowed to react with (5a) under the same conditions as previously.

In both these compounds the enolic OH was clearly evident in the ^1H NMR, whilst (17) displayed only one ketonic carbonyl in its ^{13}C spectrum and (18) had no signals below 170.5 ppm. In the case of (17) the presence of some of the bisenol form was evident by NMR. The triester (18) was obtained as one geometrical isomer, to which we assign the Z-stereochemistry, on nmr evidence; in particular, the CH_2 part of the CH_2CO_2Me appears as a widely-split AB system (∂3.6 and 4.3) implying restricted rotation and deshielding by the *cis*-carbonyl function.



19 R= R'= H
20 R= R'= Ac
21 R= H R'= Ac

With the ready availability of the Michael adduct (14a) we investigated whether it was possible to cyclise it to a tetracyclic system. We have been unsuccessful in this but among our findings is the observation that when (14a) is treated with 3 equivalents of aqueous KOH in ethanol the ketone (19) is formed in 60% yield. A possible mechanism for the formation of (19) is outlined in the scheme.

Acetylation using acetic anhydride and pyridine gave the diacetate (20) in greater than 95% yield. The structure of (20) and consequently of (19) was established by analysis of its ^1H NMR spectrum, which showed an AB for the system in the aromatic region. The keto diacetate (20) could be selectively deacetylated on oxygen using sodium methoxide and methanol, which gives the phenol (21) in 95% yield. We have recently isolated the phenol (22) by treatment of the Michael adduct (14a) with one equivalent of aqueous KOH; this points towards the proposed mechanism in the scheme as being probable.

From a synthetic view point the results with Danishefsky's diene (6) are significant since the resulting adducts (7) and (8) may allow regiospecific synthesis of acridones.

EXPERIMENTAL

IR spectra were recorded on a J J Lloyd FT 600 spectrometer; UV spectra were obtained on a Pye-Unicam SP8100 spectrophotometer. Mass spectrometry was performed with VG micromass 16 F and AEI MS 902 spectrometers using an ionisation energy of 70 eV. NMR spectra were recorded on Perkin-Elmer R12, Bruker WP80, Bruker WP200 and WH360 spectrometers using deuteriochloroform as solvent. Melting points were determined using a Reichert apparatus in open capillaries and are uncorrected. Absorption chromatography was carried out using Kieselgel 7734 (Merck). All air sensitive reactions were performed in flame-dried apparatus under a nitrogen atmosphere. Petrol refers to light petroleum with a boiling range of 40-60° unless otherwise stated.

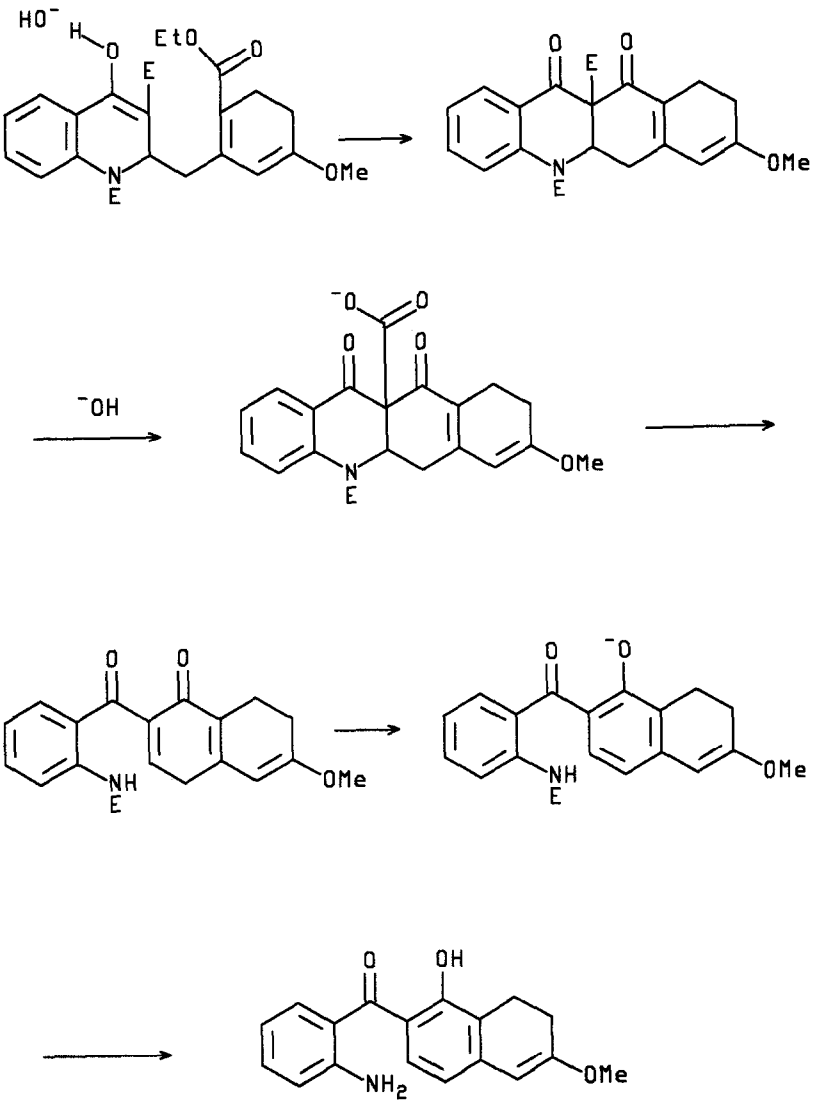
3-Ethoxycarbonyl-4-(1H)-quinolone(2)

Aniline (13.95g, 150 mMol) and diethyl ethoxymethylenemalonic ester (32.40g, 150 mMol) were heated at 130° for 2 hours. The mixture was then allowed to cool to room temperature (RT). Crystallisation was effected by cooling to -78° (CO_2/methanol). Recrystallisation from ether (40ml) at -78° afforded **diethylanilinomethylenemalonic ester** as white needles (37.8g, 96%), m.p. 49-51° (lit[16] 50°).ν_{max},($CHCl_3$), 1720, 1695, 1650, 1625 cm^{-1};∂ (60 MHz), 1.2-1.5 (6H, m, 2xOCH_2CH_3), 4.05-4.45,(m, 2xOCH_2CH_3), 6.85-7.45 (5H, m, ArH), 7.4 (2H, d, J 12Hz), 10.9(1H, d, J 12Hz,NH).

To Dowtherm A (50 ml) at 255° was added the malonic ester, prepared above, (10.00g, 38 mMol); heating was continued at 255° for 30 minutes. The mixture was cooled to RT and allowed to stand for 0.5h. The resultant crystals were collected under suction and washed with a copious amount of petrol, (60-80°), dried. Recrystallisation from glacial acetic acid gave the product(2) as white crystals, (6.0g, 73%), m.p. 272° (lit[9] 264-274°). ν_{max},(KBr), 1710, 1700, 1625, 1295, 1095 cm^{-1}; ∂(60MHz, TFA, $CDCl_3$\ TMS internal standards), 1.55 (3H,t,OCH_2CH_3), 4.65 (2H, q, OCH_2CH_3), 7.08 (3H, m), 7.60 (1H, m), 9.25 (1H, br.s, **alkene**); m/z 217(M^+,37%), 171(100), 144(11), 117(13).

3-Nitro-4-(1H)-quinolone (3)

To a mechanically stirred solution of sodium hydroxide (134g, 3.35 Mol) in water (268 ml), cooled to 0°-5°, nitromethane (67g, 1.1 Mol) was added dropwise so as to maintain an internal temperature of 25°-30°. After the addition was complete, the cooling bath was removed, causing a spontaneous rise in temperature to 70°, and a red colouration to develop. The mixture was then cooled to 25°-30° and a further portion of nitromethane (67g, 1.1 Mol) was added, maintaining the temperature at 25°-30°. The resulting orange red solution was **carefully** poured onto ice (300 ml) and HCl (conc, 300 ml); this afforded methazonic acid. A previously filtered solution of anthranilic acid (137g, 1Mol), and HCl (Conc; 92 ml) in water (21), was added to the solution of methazonic acid. The solution was allowed to stand at RT for 18 hours. The crystals were collected under suction, washed with copious amounts of water and dried at 110°. Grinding and sieving afforded *2-[2-nitroethylideneamino]benzoic acid* as a microcrystalline solid (140g, 67%), m.p. 197° (lit[10] 196-7°). ∂(60 MHz, DMSO-d_6), 6.70 (2H, d, J 6Hz,CH_2), 6.90-7.30 (2H, brm, ArH), 8.42 (1H, t, J 7.3Hz,alkene), 12.85 (1H, brs, CO_2H). A mechanically stirred suspension of the benzoic acid above (52g, 0.25 Mol) in acetic anhydride


HO⁻
H
O
E
EtO
O
OMe
N
E
O
E
O
OMe
N
E
⁻OH
⁻O
O
O
O
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OMe
N
E
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O
NH
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NH
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NH₂
OMe

(250 ml) was heated at 100-150° until dissolution was accomplished. The reaction mixture was then cooled to 40° and anhydrous potassium carbonate (25g, 0.255 Mol) was added with vigorous stirring. The mixture was refluxed for 15 minutes at 140° and then cooled to RT. The resulting solid was collected under suction and washed extensively with glacial acetic acid until the washings were colourless. The solid was then washed with water and dried at 100°. This gave tan-coloured crystals of *3-nitro-4-(1H)-quinolone (3)* (20g, 42%), m.p. 343-5°. ν_{max} (KBr), 1630, 1500, 1345, 770 cm^{-1}; m/z, 190 (M^+,83%), 173(10), 157(30), 143(42), 129(52), 115(100), 102(75), 89(70), 76(45).

General procedure for the N-protection of 4-(1H) quinolones (2) and (3)

Method A

To a stirred suspension of the 4-(1H)-quinolone in dry $CHCl_3$ (30 ml/g) was added N,N-diisopropylethylamine (1.1 eq) followed by the requisite chloroformate (leq); the mixture was then heated at reflux for 20 hours. Concentration *in vacuo* followed by chromatography on silica ($CHCl_3$) afforded the products.

Method B

To a stirred suspension of the 4-(1H)-quinolone and anhydrous sodium carbonate (1.1 eq) in dry $CHCl_3$ (30 ml/g) was added the respective chloroformate. The mixture was heated at reflux for 18 hours. Filtration of the hot mixture followed by evaporation of the solvent gave the crude product, which could be recrystallised from a suitable solvent.

1,3-Dicarboethoxy-1,4-dihydroquinolin-4-one (4a)

Yield 93%, m.p. 112-3° (Et_2O/Petrol), ν_{max} ($CHCl_3$); 1765, 1730, 1700, 1645, 1615 cm^{-1}; ∂(200MHz), 1.45 (6H,2t,2xOCH_2CH_3), 4.60 (4H, 2q, 2xOCH_2CH_3) 7.47 (1H, ddd, J 1.04, 7.14, 8.07 Hz, H-7), 7.69 (1H, ddd, J 1.82, 7.13, 8.87 Hz, H-6), 8.45 (1H, ddd, J 0.48, 1.81, 7.98 Hz, H-8), 8.55 (1H, ddd, J 0.49, 1.02, 8.80Hz, H-5), 9.19 (1H, s, H-2); ∂_C(50MHz), 14.1, 14.3, 61.4, 65.9, 114.1, 119.8, 126.3, 127.4, 128.0, 133.1, 137.5, 144.5, 150.9, (NCO_2Et), 164.6, 174.8; m/z 289 (M^+,70%), 243(62), 171(100). (Found C, 62.3; H, 5.2; N, 4.7; $C_{15}H_{15}NO_5$ requires C,62.3; H,5.2; N,4.8%).

1-Benzyloxycarbonyl-3-carboethoxy,1, 4-dihydroquinolin-4-one (4b)

Yield 95%,m.p. 108-9° (EtOAc); ν_{max} ($CHCl_3$), 1770, 1740, 1705, 1650, 1620 cm^{-1},∂(200MHz), 1.37(3H,t,OCH_2CH_3),4.4(2H,q,OCH_2CH_3),5.5(2H,s,OCH_2Ph),7.56(7H,m,ArH),8.50(2H,m,ArH),9.1(1H,s,H2);m/z 351(M^+,3%),307(12),262(5%),217(68),171(25), 91(100); (Found C,68.6; H,4.8;N,3.9; $C_{20}H_{17}NO_5$ requires C,68.4; H,4.8;N,4.0%).

3-Carboethoxy-1-fluourenylmethoxycarbonyl-1,4-dihydroquinoilin-4-one (4c)

Yield 95%, m.p. 156-7° ($CHCl_3$ /60-80 Petrol); ν_{max}($CHCl_3$) 3020, 1760, 1735, 1700, 1645, 1615,1470cm^{-1}; ∂(200 MHz), 1.40 (3H, t, OCH_2CH_3), 4.4 (3H, m, OCH_2CH_3, H-9), 4.87 (2H, d, J 3Hz, OCH_2CHAr), 7.40 (6H, m, ArH), 7.60 (2H,d,ArH), 7.80 (2H,d,ArH) 8.1 (1H, dd, ArH), 8.45 (1H,dd, ArH), 9.05 (1H, s, H-2); m/z, 439 (M^+,1%), 419(2), 395(10), 257(5), 239(3), 217 (80),91(100),(probe at 115°). (Found C, 73.5; H, 4.8; N, 3.3; $C_{27}H_{21}NO_5$ requires C, 73.8; H, 4.8; N, 3.2%).

3-Carboethoxy-1-[2',2',-bis-(4-nitrophenyl)ethoxycarbonyl]-1,4-dihydroquinolin-4-one (4d)

Yield 82%, m.p. 94-7° (dec) ($CHCl_3$/Petrol 60-80);ν_{max} ($CHCl_3$), 3005, 1760, 1720, 1700, 1635, 1600, 1510 cm^{-1}, ∂(200 MHz, acetone-d_6), 1.25 (3H, t, OCH_2CH_3), 2.9 (2H, brs; H_2O), 4.2 (2H, q, OCH_2CH_3), 5.15-5.40 (3H, m, CH_2-CH-Ar_2), 7.45 (1H, t, ArH), 7.65 (1H, td, ArH), 7.87 (4H, m, ArH), 8.33 (6H, m, ArH), 8.85 (1H, s, H-2); m/z 373(1%), 271(26), 259(3), 255(8), 241(10), 217(41), 171(100). (Found C, 59.2; H, 3.9; N, 7.4; $C_{27}H_{21}N_3O_9.H_2O$) requires C, 59.0; H, 4.2, N, 7.6%).

1-Ethoxycarbonyl-3-nitro-1,4-dihydroquinolin-4-one (5a)

Yield 81%, m.p. 129-131° ($CHCl_3$/Petrol 60-80); ν_{max} ($CHCl_3$), 1775, 1665, 1620, 1530, 1475, 1215 cm^{-1}. ∂(80 MHz), 1.55 (3H, t, OCH_2CH_3), 4.65 (2H, q, OCH_2CH_3), 7.45-7.90 (2H, m, H-6, H-7), 8.56 (2H, m, H-5, H-8), 9.55 (1H, s, H-2); m/z 262 (M^+,85%), 216(6), 188(100). (Found C, 54.9; H, 3.8; N, 10.6; $C_{12}H_{10}N_2O_5$ requires C, 55.0; H, 3.8, N, 10.7%).

1-Benzyloxycarbonyl-3-nitro-1,4-dihydroquinolin-4-one (5b)

Yield 66%, m.p. (120-2° (Et_2O/Petrol); ν_{max} ($CHCl_3$), 1785, 1680, 1630, 1535, 1485, 1350, 1325, 1290 cm^{-1}; ∂(200 MHz), 5.55 (2H, s,-CH_2Ph), 7.53 (6H, m, ArH), 7.78 (1H, ddd, ArH), 8.50 (1H, dd, ArH), 8.62 (1H, d, ArH), 9.55 (1H, s, H-2); m/z 324 (M^+,1%), 278(6), 91(100). (Found C, 62.7; H, 3.8; N, 8.6; $C_{17}H_{12}NO_5$ requires C, 63.0; H, 3.7; N, 8.6%).

(1R,4aS*,10aS*)-5,10a-Diethoxycarbonyl-1-methoxy-3,10-dioxo- octahydroacridine (7a)*
1,3-Dicthoxycarbonyl-4-(1H)-quinolone (4a), (2.0g, 6.92 mMol), in toluene (20 ml) was treated with Danishefsky's diene (6) (1.43g, 8.3 mMol, 1.2 eq) and the mixture heated at reflux for 18 hours. The solvent was removed *in vacuo* and the residue partitioned between ethylacetate (50ml) and 2M HCl (20ml). The organic layer was dried (Na_2SO_4) and evaporated *in vacuo* to afford a yellow oil. Chromatography [toluene/acetonitrile (19:1)] afforded the title compound, (2.3g 85%), m.p. 99-100° (Et_2O/Petrol, 50:50). ν_{max} ($CHCl_3$), 3020, 1740, 1730, 1710, 1690 cm^{-1}; ∂(360 MHz) 1.1 (3H, t, OCH_2CH_3), 1.32 (3H, t, OCH_2CH_3), 2.55 (1H, ddd, J 16.18, 5.12, 0.75 Hz, H-4_{ax}), 2.68 (1H, dd, J 13.25, 16.15 Hz, H-4_{ax}), 2.77 (1H, ddd, J 16.22, 3.53, 0.75 Hz, H-2_{eq}), 2.84 (1H, dd, J 8.24, 16.1Hz, H-2_{ax}), 3.29 (3H, s, OCH_3), 4.07-4.37 (5H, m, 2xOCH_2CH_3, H-1), 5.30 (1H, dd, J 13.23, 5.10 Hz, H-4a), 7.2 (1H, ddd, H-8), 7.54 (1, ddd, H-7), 7.68 (1H, d, H-6), 7.96 (1H, dd, H-9); ∂_C(50 MHz), 13.39, 14.06, 41.32, 53.69 (C4a), 57.93, 61.50, 61.97, 62.60, 78.80 (C1), 124.19, 124.55, 125.51, 126.92 134.19, 139.14 (C10a), 153.22, 169.12, 189.14 (C10) 204.11 (C3); m/z 389 (M^+,35%), 374(8), 316(14), 284(100), 212(59); λ_{max} (EtOH),232(*em 21,200*), 260(6,219), 323(1,922) nm. (Found C, 61.5; H, 6.0; N, 3.5; $C_{20}H_{23}NO_7$ requires C, 61.7; H, 6.0; N, 3.6%). (Found M^+ 389.147; $C_{20}H_{23}NO_7$ requires 389.147).

(1R,4aS*,10aS*)-5-Benzyloxycarbonyl-10a-ethoxycarbonyl-1-methoxy-3,10-dioxo-octahydroacridine(7b)*
Yield 94%, m.p. 122-4° (Et_2O/Petrol);ν_{max} ($CHCl_3$), 3010, 1740, 1720, 1700, 1685, 1600 cm^{-1}; ∂(200 MHz), 0.97 (3H, t, OCH_2CH_3), 2.65 (4H, m, 2xH4, 2xH2), 3.3 (3H, s, OCH_3), 4.05 (2H, m, OCH_2CH_3), 4.20 (1H dd, H-1), 5.25-5.40 (3H, m, OCH_2Ph, H-4a), 7.2-8.05 (9H, m, ArH); m/z 451 (M^+,6%), 407(1), 321(2), 316(2), 308(13), 302(10), 91(100);λ_{max} (EtOH),228(em 8,880),254(20,600),280(6,677),340(1,890)nm. (Found C, 66.3; H, 5.5; N, 3.0; $C_{25}H_{25}NO_7$ requires C, 66.5; H, 5.5; N, 3.1%).

(1R,4aS*,10aS*),-5-[2'2'-Di(4-nitrophenyl)ethoxycarbonyl]-10a-ethoxycarbonyl-1-methoxy-3,10-dioxo-octahydroacridine (7d).*
Yield 83%, m.p. 90° (Et_2O/Petrol): ν_{max} ($CHCl_3$), 1745, 1725, 1710, 1690, 1610, 1520, 1485, 1465, 1350,1240 cm^{-1}; ∂(200MHz) 1.07(3H, t, OCH_2CH_3), 2.50 (4H, m, H-2, H-4), 3.30 (3H, s, OCH_3), 4.12 (2H, m, OCH_2CH_3), 4.45 (1H, m, H-1), 4.75 (3H, m, -CH_2CH Ar_2), 5.11 (1H, m, H-4a); 7.20 (1H, m, ArH), 7.42 (5H, m, ArH), 7.95 (1H, m, ArH), 8.24 (5H, m, ArH); m/z 315(10%); (Found C, 60.5, H, 4.6, N, 6.7%;$C_{32}H_{29}N_3O_{11}$requires C,60.8;H,4.6;N,6.7%).

3,10-DIoxo-5-ethoxycarbonyl-1-methoxy-10a-nitro-octahydroacridine (8a), (9a).
1-Ethoxycarbonyl-3-nitro-1,4-dihydroquinolin-4-one (5a) (1.05g, 4 mMol) and Danishefsky's diene (6) (0.83g, 4.8 mMol), were refluxed in dry toluene (10 ml) for 18h. The solvent was removed in *in vacuo* and the residue chromatographed on silica (toluene/acetonitrile, 49:1), affording the title compounds as crystalline isomers (1.2g, 83%). **Major (9a)**, (0.68g, 57% of total), m.p. 129-131°, (Et_2O/Petrol); Rf 0.55(MeCN/Toluene,20:80); ν_{max} ($CHCl_3$), 1735, 1720, 1690, 1600, 1555, 1480, 1460, 1320, 1220 cm^{-1}; ∂(360 MHz), 1.43 (3H, t, OCH_2CH_3), 2.6 (2H, m), 2.86 (2H, m), 3.35 (3H, s, OCH_2CH_3), 4.42 (2H, m, OCH_2CH_3), 4.90 (1H, t, J 3.0 Hz, H-1), 6.05 (1H, dd, J 12.75, 6.23 Hz, H-4a), 7.20 (1H, td, H-8), 7.65 (1H, td, H-7), 7.90, (1H, d, H-6), 8.07 (1H, dd, H-9); ∂_C(50MHz), 14.12 (OCH_2CH_3), 40.82 (2C, C-2, C-4), 53.45 (C-4a), 57.54, 63.25, 78.55 (C-1), 91.00 (C-10a), 119.53, 123.51, 124.08, 128.38, 136.84, 140.00, 153.19, (NCO_2Et), 180.69 (C-10), 201.87 (C-3); m/z, 361 (M^+,70%), 316(7), 285(25), 258(30),212(30), 186(74),158(100),λ_{max} (EtOH), 237(em 19,310), 274(9,560), 356(2,422) nm. (Found C, 56.35; H, 5.0; N, 7.7; $C_{17}H_{18}N_2O_7$ requires C, 56.35, H, 5.0; N, 7.7%).
Minoradduct(8a),(0.52g,43%oftotal),m.p.147-9°/Petrol),Rf0.4(MeCN/toluene,20:80),ν_{max}($CHCl_3$), 1730,1720,1695,1600,1555,1480,1460,1395,1370,1320,1230cm^{-1}.
∂(360MHz)1.33(3H,t,OCH_2CH_3),2.68(2H,m,2xH4,),2.89(2H,m,2xH2),3.32(3H,s,OCH_3),4.30(2H,m,OCH_2CH_3),4.48(1H,t,J5.5Hz,H1),5.60(1H,m,J8.83,9.97Hz,H4a),7.28(1H,td,ArH),7.6(2H,m,ArH),8.07(1H,dd,ArH),∂_C(50MHz),14.11,41.03,41.22,54.98(C-4a), 58.57,63.46,78.23(C-1), 91.83(C-10a), 124.67, 124.91, 125.52, 127.82, 135.51,

139.21, 153.11 (NCO_2Et), 183.00 (C-10), 202.26 (C-3); m/z 361 (M^+,65%), 316(7), 285(26),258(28), 212(30), 186(75), 158(100),λ_{max} (EtOH), 233(ϵm 18,100), 274(9,560), 334(2,150) nm. (Found C, 56.30; H, 5.0; N, 7.5; $C_{17}H_{18}N_2O_7$ requires C, 56.35, H, 5.0; N, 7.7%).

5-Benzyloxycarbonyl-3,10-dioxo-1-methoxy-10a-nitro-octahydroacridine (9b, 8b)
Yield (0.72g), 86%.
Major cycloadduct 9b
(0.42g, 58% of total yield), m.p. 142-144°C;ν_{max} ($CHCl_3$) 1735, 1700, 1685, 1600, 1560, 1215 cm^{-1}; ∂ (360 MHz) 2.57 (2H, m, J 16.3, 2.76 Hz, methylenes), 2.85 (2H, m, J 13.02, 6.37 Hz, methylenes), 3.38 (3H, s, OCH_3), 4.89 (1H, t, J 3.0 Hz,H-1), 5.39 (2H,S,CO_2CH_2Ph), 6.12 (1H, dd, J 12.77, 6.09 Hz,H-4a), 7.20 (1H, ddd, H-7), 7.40 (5H, m, ArH), 7.60 (1H, ddd, H-8), 7.90 (1H, d, H-6), 8.05 (1H, m, H-9); m/z 424 (M^+,5%), 382(1), 91(100) (Found : C 62.0;H,4.7; N,6.4 $C_{22}H_{20}N_2O_7$ requires C, 62.3; H, 4.7; N, 6.6%).
Minor cycloadduct 8b
(0.3g, 42% of total yield), m.p. 64-65°C;ν_{max} ($CHCl_3$) 1730, 1715, 1695, 1600, 1550, 1215 cm^{-1}; ∂ (360 MHz) 2.70 (2H, m), 2.87 (2H, m), 3.32 (3H, s, OCH_3), 4.48 (1H, dd, J 6.22, 4.53 Hz, H-1), 5.26 (2H, dd, CO_2CH_2Ph), 5.62 (1H, dd, J 10.88, 7.92 Hz, H-4a) 7.28 (1H, ddd, H-7), 7.37 (6H, m, H-9+ArH), 7.62(1H,m,H-8), 8.0(1H,m,H-6); m/z 424 (M^+5%), 382(1), 91(100);λ_{max} (EtOH) 214(ϵm 11,600), 233(22,020), 267(9,685), 334(2,714) nm. (Found : C, 62.2; H, 4.9; N, 6.3; $C_{22}H_{20}N_2O_7$ requires C, 62.3; H, 4.7; N, 6.6%).

1-Carboethoxy-2-[1,3-biscarboethoxy-4-hydroxy-1,2-dihydroquinolin-2-yl]methyl-4-methoxycyclohexa-1,3-diene (14a)
To the quinolone (4a) (1.8g, 6.23 mMol), was added Gesson's diene (12) (2.0g, 7.46 mMol) in toluene (20 ml). The mixture was heated at reflux for 18 h, filtered and the solvent removed *in vacuo*. Chromatography on silica (toluene/acetonitrile; 49:1) afforded the title compound, (2.75g, 91%). mp 67-8° (Et_2O/Petrol);ν_{max} ($CHCl_3$) 1740, 1720, 1700, 1685, 1650, 1555, 1405, 1380 cm^{-1}; δ(360 MHz), 1.10-1.45 (9H, m, 3 x OCH_2CH_3), 2.10 (2H, m), 2.45 (2H, m), 2.85 (2H, J 12.7, 8.10, 5.64Hz, AB of ABX), 3.61 (3H, S, OCH_3), 3.97 (6H, m, 3 x OCH_2CH_3), 4.87 (1H, s, alkene), 5.77 (1H, dd, J 8.10, 5.65 Hz,H-2), 7.1 - 7.85 (4H, m, ArH), 12.13 (1H, s, OH); ∂_C (50MHz), 13.94, 13.99, 14.11, 25.01, 26.93, 37.14, 50.61, 54.64 (OCH_3), 59.30, 60.65, 61.96, 98.97 (alkene CH), 99.16, 116.43, 122.57, 123.63,123.98, 124.51, 130.60, 137.81, 143.99, 153.46 (NCO_2Et), 162.24, 1263.24, 167.27, 170.08; m/z, 485 (M^+,1%), 440(1), 413(1), 290(100);.(Found C, 64.2; H, 6.6; N, 3.1; $C_{26}H_{31}NO_8$ requires C, 64.3; H, 6.4; N, 2.9%).

1-Carboethoxy-2-[1-carbobenzyloxy-3-carboethoxy-4-hydroxy-1,2-dihydroquinolin-2-yl]methyl-4-methoxycyclohexa-1,3-diene (14b)
Yield 65%, m.p. 96-8° (Et_2O/Petrol); ν_{max} ($CHCl_3$), 3020, 1720, 1700, 1690, 1655 cm^{-1}; ∂(200 MHz), 1.10 (3H, t, OCH_2CH_3), 1.37 (3H, t, OCH_2CH_3), 2.02 (2H, m), 2.35 (2H, m), 2.75-3.0 (2H, AB of ABX), 3.50 (3H, s, OCH_3), 3.95 (2H, m, OCH_2 CH_3), 4.25 (2H, m, OCH_2 CH_3), 4.80 (1H, s, alkene), 5.20 (2H, dd, CO_2CH_2Ph), 5.80 (1H, dd, X of ABX), 7.15-7.85 (9H, m, ArH), 12.15 (1H, s, OH); ∂_C(50 MHz), 14.09, 14.17, 25.15, 27.08, 37.31, 51.00, 54.78 (OCH_3), 59.50, 60.84, (2 xOCH_2CH_3), 67.81, 98.98, 99.35, 116.70, 122.89, 124.06, 124.07, 124.26, 124.74, 127.82, 128.06, 128.45, 130.86,136.07, 137.83, 144.08, 153.53 (NCO_2CH_2Ph), 162.43, 163.48, 167.49, 170.25; m/z, 547 (M^+,4%), 502(1), 428(2), 352(100), 308(66), 262(45), 218(12), 91(75); (Found, C, 67.7; H, 6.0; N, 2.5; $C_{31}H_{33}NO_8$ requires C, 68.0; H, 6.0; N, 2.6%).

1,3-Bisethoxycarbonyl-4-hydroxy-2-[2-oxo-3-carbomethoxy]propyl-1,2-dihydroquinoline (17)
The quinolone (4a) (1.63g, 5.64 mMol) and 1,3-bis(trimethylsilyloxy)-1-methoxybuta-1,3-diene[14] (15), (1.76g, 6.77 mMol) were refluxed in toluene (15ml) for 18h. The mixture was filtered and the solvent removed *in vacuo*. Chromatography, silica (toluene/acetonitrile, 19:1) gave the title compound, (2.20g, 96%) as a viscous yellow oil.ν_{max} ($CHCl_3$), 1740, 1715, 1705, 1650, 1625 cm^{-1}; ∂(200 MHz), 1.32 (6H, m, 2 x OCH_2CH_3), 2.23 (0.5 H, AB of ABX, 25% enol), 2.63 (1.5H, AB of ABX), 3.54 (2H, dd,$COCH_2CO$), 3.66 (3H, 2s), 4.30 (4H, m, $CO_2CH_2CH_3$), 4.85 (0.25H, enol OH), 5.80 (0,25H, dd, enol H-2), 5.93 (0.75H, dd, J 6.0, 2.5 Hz,H-2), 7.20 (1H, m, ArH), 7.46 (1H, dt, ArH), 7.58 (1H, d, ArH), 7.78 (1H, d, J5 Hz ArH), 11.85 (0.25 H, enol OH), 12.10 (0.75 H, enol OH); ∂_C(50 MHz), 13.64, 14.03, 38.80, 45.86, 47.86, 48.54 (enol), 50.78 (enol), 51.88, 60.80 (enol), 60.94, 62.12 (enol), 62.45, 76.35, (enol), 90.47 (enol), 98.86, 99.10 (enol), 122.42, 124.16, 124.40, 124.76, 125.08, 127.94, (enol), 128.75 (enol), 131.23, 131.57, 136.90 (enol), 153.27, 162.55, 166.97, 169.28, 169.63 (enol),

172.41 (enol), 174.15 (enol), 199.06; m/z, 405 (M^+,1%), 372(1), 358(1), 331(3), 326(1), 289(100), 243(12), 171(13). (Found, C, 59.0; H, 5.7; N, 3.6; $C_{20}H_{23}NO_8$ requires C, 59.3; H, 5.7; N, 3.5%).

1,3-Biscarboethoxy-4-hydroxy-2[2-methoxycarbonylmethyl-3-methoxycarbonylprop-2-enyl]methyl-1,2-dihydroquinoline (18)

The quinolone (5a) (1.15, 3.95 mMol) and the triene (16),[15](1.5g, 4.7 mMol) in toluene (10ml) were treated at 65° for 18h. The solvent was removed *in vacuo* and the residue chromatographed on silica, (toluene/acetonitrile, 49:1) to give the title compound (1.2g 66%); m.p. 79°; ν_{max} ($CHCl_3$) 3020, 1740, 1720,1710,1660,1650,1630 cm^{-1},∂(200MHz), 1.33(6H,2t,OCH_2CH_3), 2.30(2H,ABofABX), 3.60(1H,d,J15Hz,CH_2CO_2Me), 3.70(6H,s,$2CO_2Me$), 4.3(5H,m,$CO_2CH_2CH_3$,CH_2CO_2Me), 5.60(2H,s+m,alkene+H2), 7.21(1H,d,J8Hz,ArH), 7.45(1H,t,J,7Hz,ArH), 7.61(1H,bd,ArH), 7.82(1H,dd,J8,2,Hz,ArH), 12.06(1H,s,OH);∂_C(50MHz), 14.15, 14.31, 36.39, 42.34, 49.35(C2), 51.08(OMe), 51.83(OMe), 61.10, 62.52, 99.47, 121.03(alkene), 122.84, 124.50, 124.57, 125.03, 131.49, 136.94, 149.98, 153.70(NCO_2Et), 162.66, 166.14, 169.76, 170.50; m/z 461 (M^+1%), 388(2), 290(100), 218(14), 200(36), 172(42). (Found C, 59.9; H, 6.0; N, 3.0; $C_{23}H_{27}NO_9$ requires C, 59.9; H, 5.9; N, 3.0%).

Crystal data for compound (7a): $C_{20}H_{23}NO_7$, M = 389.4, monoclinic, space group $P2_1/n$ (non-stand. No. 14), a = 19.118 (12), b=13.972 (3), c = 14.968 (6) Å, ß= 95.99 (4)°, U = 3976.4 $Å^3$, Z = 8, D_c = 1.301 g cm^{-3}, μ(Mo-K_α) = 0.93 cm^{-1}, crystal dimensions *ca.* 0.4 x 0.4 x 0.2 mm.

Data Collection.. The intensity data were collected on a CAD4 diffractometer in the ω-2Θ mode using Mo-K_α X-radiation (λ = 0.710693 Å). A total of 5527 data were measured over the quadrant (+h, +k, ±l; 1<Θ<23°). After correction for polarisation and Lorentz effects, 2826 intensities were found to have I>3σ(I) and were used in subsequent structure solution and refinement.

Structure Solution and Refinement The positions of the non-hydrogen atoms of each of the independent molecules were readily located by application of Direct Methods techniques (SHELXS86[17]). Subsequent blocked-matrix least-squares refinement(SHELX76[17]) with anisotropic temperature factors for the non-hydrogen atoms and fixed isotopic temperature factors for the hydrogen atoms (U_{iso}= 0.10 $Å^2$) gave discrepancy indices R and R_w of 0.065 and 0.077 respectively at convergence. The weighting scheme ω=[σ^2(F) +0.00014(F^2)]$^{-1}$,where σ(F) is derived from counting statistics, gives satisfactory analyses of variance. As a consequence of disorder, the refinement of the positions of the ethoxy group carbon atoms was poor; the C-C distances were constrained to an idealised value of 1.52 Å. The final difference Fourier map contained a residual maximum of +0.44 e $^-$ $Å^{-3}$ of no chemical significance, with a general noise level of *ca.* ± 15 e $^-$ $Å^{-3}$.

Crystal data for compound (14b): $C_{31}H_{33}NO_8$, M = 547.6, monoclinic, space group $P2_1/a$ (non-stand. No. 14), a = 21.390 (3), b = 8.774 (2), c = 15.559 (2) Å, ß= 105.64 (1)°, U = 2811.9 $Å^3$ Z= 4, D_c = 1.293 g cm^{-3}, μ(Mo-K_α) = 0.87 cm^{-1}, crystal dimensions *ca.* 0.37 x 0.37 x 0.25 mm.

Data Collection 4945 unique data in the quadrant (±h, +k, +l; 1.5 < Á<25°) were collected on a CAD4 diffractometer using graphite monochromated Mo-K_α X-radiation. After Lorentz and polarisation correction, 2316 data had I>3σ(I) and were used in the structure and refinement.

Structure Solution and Refinement. The structure was solved by direct methods (SHELXS86 [17]) and refined (SHELX76 [17]) by full-matrix least squares methods with anisotropic temperature factors for the non-hydrogen atoms. The phenyl group and the methyl group at C(31) were treated as idealised rigid groups. With the exception of the enolic hydrogen H1' whose positional parameters were refined, the hydrogen atoms were inculded in the refinement calculations at idealised postions with either group or fixed (U_{iso}=0.10 $Å^2$) temperature factors. At convergence, the conventional and weighted R- factors R and R_w were 0.050 and 0.052 respectively.The weighting scheme ω = [σ^2(F) + 0.00017 $(F)^2$]$^{-1}$ gave satisfactory analyses of variance. The final difference Fourier map contained no features greater than ± 0.23 e $^-$$Å^{-3}$ with a general noise level around ±0.12 e $^-$$Å^{-3}$.

The atomic coordinates for structures (7a) and (14b) are listed in Tables 3 and 4 respectively. The program CALC [17] was used for all incidental calculations and in the preparation of the tables. Additional data, including tables of anisotropic temperature factors, hydrogen atom coordinates, and observed and calculated structure factors have been deposited as supplementary material.

7-(2'-Aminobenzoyl)-8-hydroxy-3-methoxy-1,2-dihydronaphthalene (19)

To the Michael adduct (14a), (0.8g, 1.65 mMol) in ethanol (12ml) was added 1M aqueous KOH (5ml). The solution was heated at reflux for 72 h. The mixture was then neutralised with Zeolite H^+ ion-exchange resin, filtered and concentrated *in vacuo*. Chromatography on silica, (toluene/ acetonitrile, 49:1), yielded the title compound (0.30 g, 62%), m.p. 116-8° (EtOAc/Petrol). ν_{max}($CHCl_3$) 3400-3000, 1640, 1605, 1575, 1550 cm^{-1}; ∂(200 MHz) 2.47 (2H, t), 2.97 (2H, t), 3.75 (3H, s), 5.0 (2H, brs, NH_2), 5.50 (1H, s), 6.45 (1H, d, ArH), 6.75 (2H, m, ArH), 7.3 (3H, m, ArH), 12.35 (1H, s, OH); m/z, 295 (M^+,100%), 279(13), 201(25), λ_{max} (EtOH), 205(ϵm 13,130), 224(19,200), 353(16,780) nm. (Found, C, 72.9; H, 5.8; N, 4.5; $C_{18}H_{17}NO_3$ requires C, 73.2; H, 5.8; N, 4.7%).

7-(2'-Acetamidobenzoyl)-8-acetoxy-3-methoxy-1,2-dihydronaphthalene (20)

The Dihydronaphthalene (19) (200mg, 0.6 mMol) in dry pyridine (2 ml), was added to acetic anhydride (4.5 ml). The solution was allowed to stand at RT for 72h, after which time it was concentrated *in vacuo*. The residue was partioned between EtOAc (50 ml) and H_2O (10 ml). The aqueous layer was further extracted with EtOAc (2 x 50 ml). The combined organics were dried (Na_2SO_4), filtered and concentrated. Chromatography on silica; (toluene/acetonitrile, 49:1 then 20:1) gave the title compound (245 mg, 95%), m.p. 140-1° (C_6H_6/Et_2O). ν_{max} ($CHCl_3$), 3350, 1760, 1700, 1685, 1650, 1630, 1610 cm^{-1}; ∂(200 MHz), 2.10 (3H,s), 2.15 (3H, S), 2.43 (2H, t), 2.80 (2H, t), 3.75 (3H, s), 5.60 (1H, s alkene), 6.88 (1H, d, J 7.84 Hz, ArH), 7.05 (1H, m, ArH), 7.16 (1H, d, J 7.87 Hz. ArH), 7.53 (2H, m, ArH), 8.54 (1H, dd, J 8.8, 1.1 Hz, ArH), 10.6 (1H, S, NH); ∂_C (50MHz), 20.32, 21.80, 24.99, 26.39, 55.00, 95.92, 121.26, 121.58, 122.25, 124.44, 124.71, 128.06, 129.29, 133.13, 133.94, 139.91, 141.53, 145.87, 163.01, 169.06, (2 x $COCH_3$), 197.50; m/z 379 (M^+,35%), 337(17), 319(4), 294(17), 162(100); λ_{max} (EtOH), 212(ϵm 23,720), 232 (Sh)(22,690),266(11,990), 336(16,240) nm. (Found, C, 69.8; H, 5.6; N, 3.4; $C_{22}H_{21}NO_5$ requires C, 69.7; H, 5.5; N, 3.7%).

7-(2'-Acetamidobenzoyl)-8-hydroxy-3-methoxy-1,2-dihydronaphthalene (21)

To the diacetate (20), (100mg, 0.26 mmol), in methanol (5ml) was added sodium methoxide (14mg, 0.26 mmol), and the solution allowed to stand, at RT, for 1.5h. The mixture was neutralised with 1M citric acid and concentrated *in vacuo*. The residue was partitioned between ethylacetate (50 ml) and water (10ml). The organics were dried, filtered and concentrated *in vacuo* to yield a bright yellow oil. Chromatography on silica, [toluene/acetonitrile (49:1, then 20:1)], yielded the title compound, (80 mg, 91%), m.p. 155-7° (CH_2Cl_2). ν_{max} ($CHCl_3$), 3380, 2950, 1690, 1615, 1590 cm^{-1}; ∂(200MHz), 2.15 (3H, s, $COCH_3$), 2.50 (2H, t), 2.95 (2H, t), 3.75 (3H, S, OCH_3), 5.55 (1H, s alkene), 6.50 (1H, d, ArH), 7.10 (1H, t, ArH), 7.25 (1H, d, ArH), 7.50 (2H, m, ArH), 8.35 (1H, d, ArH), 9.25 (1H, s, NH), 12.25 (1H, S, OH); m/z 337 (M^+,100%), 319(19), 294(37), 275(19), 162(42); λ_{max} (EtOH), 209(ϵm 22,120), 222(26,200), 356(25,180) nm. (Found C, 71.1; H, 6.0; N, 4.0; $C_{20}H_{19}NO_4$ requires C, 71.2; H, 5.7; N, 4.15%).

7-(2'-Ethoxycarbonylaminobenzoyl)-8-hydroxy-3-methoxy-1,2-dihydronaphthalene (22)

To the Michael adduct (14a) (0.25g, 0.52 mMol) in ethanol (5ml), was added 0.1M aqueous sodium hydroxide (5.2 ml), and the mixture heated at reflux for 72h. The solution was then concentrated *in vacuo*. Chromatography on silica (toluene/ acetonitrile 200 : 1), gave the title compound (0.15g, 79%), m.p. 123-5°. ν_{max} ($CHCl_3$), 3480, 3000, 1730, 1645 cm^{-1}; ∂ (200MHz), 1.28 (3H, t, CO_2CH_3), 2.46 (2H, m), 2.98 (2H, m), 3.74 (3H,s,-OCH_3), 4.18 (2H,q,$CO_2CH_2CH_3$), 5.52 (1H, s, alkene),6.48 (1H, d, ArH), 7.08 (1H, ddd, ArH), 7.25 (1H, d, ArH), 7.38 (1H, dd, ArH), 7.45 (1H, ddd, ArH), 8.22 (1H, d, ArH), 8.58 (1H, s, NH),9.80 (1H, s,OH); m/z, 367(M^+,100%), 294(17),279(35),236(6); λ_{max} (EtOH),205(ϵm 18,230),227(25,760),355(21,880) nm. (Found M^+ 367.142 $C_{21}H_{21}NO_5$ requires 367.142).

Table 1. Derived Geometrical Parameters for (7a)

(a) Bond Lengths (Å) with standard deviations for (7a)

N(1) - C(6)	1.472(8)	N(1') -C(6')	1.462(7)
N(1) -C(13)	1.430(8)	N(1') -C(13')	1.414(8)
N(1) -C(14)	1.369(9)	N(1') -C(14')	1.372(9)
C(1) - C(2)	1.504(10)	C(1') -C(2')	1.490(9)
C(1) - C(6)	1.525(8)	C(1') -C(6')	1.528(8)
C(2) - O(7)	1.181(10)	C(2') -O(7')	1.210(9)
C(2) - C(3)	1.502(11)	C(2') -C(3')	1.502(10)
C(3) - C(4)	1.535(10)	C(3') -C(4')	1.501(10)
C(4) - C(5)	1.541(10)	C(4') -C(5')	1.554(9)
C(4) - O(2)	1.416(9)	C(4') -O(2')	1.438(8)
C(5) - C(6)	1.547(8)	C(5') -C(6')	1.570(8)
C(5) - C(7)	1.546(9)	C(5') -C(7')	1.526(9)
C(5) -C(17)	1.524(10)	C(5') -C(17')	1.517(10)
C(7) - C(8)	1.469(10)	C(7') -C(8')	1.471(9)
C(7) - O(1)	1.205(9)	C(7') -O(1')	1.217(8)
C(8) - C(9)	1.400(11)	C(8') -C(9')	1.388(9)
C(8) -C(13)	1.370(9)	C(8') -C(13')	1.373(8)
C(9) -C(10)	1.383(13)	C(9') -C(10')	1.376(10)
C(10) -C(11)	1.367(14)	C(10')-C(11')	1.367(10)
C(11) -C(12)	1.372(12)	C(11')-C(12')	1.384(9)
C(12) -C(13)	1.387(9)	C(12')-C(13')	1.388(9)
C(14) - O(5)	1.189(9)	C(14')-O(5')	1.199(9)
C(14) - O(6)	1.343(9)	C(14')-O(6')	1.345(8)
O(6) -C(15)	1.413(10)	O(6') -C(15')	1.441(9)
C(15) -C(16)	1.520(13)	C(15')-C(16')	1.511(13)
C(17) - O(3)	1.180(10)	C(17')-O(3')	1.198(9)
C(17) - O(4)	1.319(9)	C(17')-O(4')	1.332(9)
O(4) -C(18)	1.432(10)	O(4') -C(18')	1.441(10)
C(18) -C(19)	1.515(14)	C(18')-C(19')	1.505(16)
O(2) -C(20)	1.400(14)	O(2') -C(20')	1.403(9)

(b) Angles (°) with standard deviations

C(6) - N(1) -C(13)	115.5(5)	C(6') -N(1') -C(13')	118.1(5)
C(6) - N(1) -C(14)	117.7(5)	C(6') -N(1') -C(14')	116.8(5)
C(13) - N(1) -C(14)	126.6(5)	C(13')-N(1') -C(14')	124.4(5)
C(2) - C(1) - C(6)	112.2(5)	C(2') -C(1') -C(6')	107.5(5)
C(1) - C(2) - O(7)	122.7(7)	C(1') -C(2') -O(7')	122.9(6)
C(1) - C(2) - C(3)	114.7(6)	C(1') -C(2') -C(3')	115.6(6)
O(7) - C(2) - C(3)	122.6(7)	O(7') -C(2') -C(3')	121.5(6)
C(2) - C(3) - C(4)	110.4(6)	C(2') -C(3') -C(4')	113.8(6)
C(3) - C(4) - C(5)	112.2(6)	C(3') -C(4') -C(5')	112.4(5)
C(3) - C(4) - O(2)	108.2(6)	C(3') -C(4') -O(2')	108.7(5)
C(5) - C(4) - O(2)	105.6(5)	C(5') -C(4') -O(2')	106.7(5)
C(4) - C(5) - C(6)	110.9(5)	C(4') -C(5') -C(6')	111.6(5)
C(4) - C(5) - C(7)	106.4(5)	C(4') -C(5') -C(7')	105.3(5)
C(4) - C(5) -C(17)	109.3(5)	C(4') -C(5') -C(17')	108.6(5)
C(6) - C(5) - C(7)	114.2(5)	C(6') -C(5') -C(7')	114.8(5)
C(6) - C(5) -C(17)	108.3(5)	C(6') -C(5') -C(17')	108.3(5)
C(7) - C(5) -C(17)	107.6(5)	C(7') -C(5') -C(17')	108.0(5)
N(1) - C(6) - C(1)	110.1(5)	N(1') -C(6') -C(1')	112.2(5)
N(1) - C(6) - C(5)	110.7(5)	N(1') -C(6') -C(5')	110.4(5)
C(1) - C(6) - C(5)	112.6(5)	C(1') -C(6') -C(5')	111.7(5)
C(5) - C(7) - C(8)	117.4(6)	C(5') -C(7') -C(8')	118.1(5)
C(5) - C(7) - O(1)	119.6(6)	C(5') -C(7') -O(1')	119.0(6)
C(8) - C(7) - O(1)	122.9(7)	C(8') -C(7') -O(1')	123.0(6)
C(7) - C(8) - C(9)	119.1(6)	C(7') -C(8') -C(9')	119.3(6)
C(7) - C(8) -C(13)	120.6(6)	C(7') -C(8') -C(13')	120.3(5)
C(9) - C(8) -C(13)	120.4(7)	C(9') -C(8') -C(13')	120.3(6)
C(8) - C(9) -C(10)	118.2(8)	C(8') -C(9') -C(10')	120.7(6)
C(9) -C(10) -C(11)	120.3(9)	C(9') -C(10')-C(11')	118.6(6)
C(10) -C(11) -C(12)	122.2(9)	C(10')-C(11')-C(12')	121.7(6)
C(11) -C(12) -C(13)	117.7(7)	C(11')-C(12')-C(13')	119.4(6)
N(1) -C(13) - C(8)	118.1(6)	N(1') -C(13')-C(8')	118.8(5)
N(1) -C(13) -C(12)	120.7(6)	N(1') -C(13')-C(12')	122.0(5)
C(8) -C(13) -C(12)	121.2(6)	C(8') -C(13')-C(12')	119.3(6)
N(1) -C(14) - O(5)	125.2(7)	N(1') -C(14')-O(5')	124.5(6)
N(1) -C(14) - O(6)	109.4(6)	N(1') -C(14')-O(6')	111.6(6)
O(5) -C(14) - O(6)	125.4(7)	O(5') -C(14')-O(6')	123.9(6)
C(14) - O(6) -C(15)	114.5(6)	C(14')-O(6') -C(15')	113.0(5)
O(6) -C(15) -C(16)	108.4(7)	O(6') -C(15')-C(16')	106.7(7)
C(5) -C(17) - O(3)	124.6(7)	C(5') -C(17')-O(3')	125.7(7)
C(5) -C(17) - O(4)	110.9(6)	C(5') -C(17')-O(4')	109.2(6)
O(3) -C(17) - O(4)	124.5(7)	O(3') -C(17')-O(4')	125.1(7)
C(17) - O(4) -C(18)	114.7(6)	C(17')-O(4') -C(18')	113.7(6)
O(4) -C(18) -C(19)	109.0(7)	O(4') -C(18')-C(19')	110.0(8)
C(4) - O(2) -C(20)	114.7(7)	C(4') -O(2') -C(20')	114.4(5)

Table 2. Derived Geometrical Parameters for (14b)

(a) Bond Lengths(Å) with standard deviations

N(1) - C(1)	1.475(5)	C(11) -C(12)	1.404(8)
N(1) - C(9)	1.428(5)	O(4) -C(13)	1.203(5)
N(1) -C(13)	1.368(5)	C(13) - O(5)	1.348(5)
C(1) - C(2)	1.521(5)	O(5) -C(14)	1.460(5)
C(1) -C(21)	1.535(5)	C(14) -C(20)	1.503(5)
C(2) - C(3)	1.354(5)	C(21) -C(22)	1.521(5)
C(2) -C(10)	1.438(6)	C(22) -C(23)	1.469(5)
C(3) - C(4)	1.452(5)	C(22) -C(27)	1.352(5)
C(3) - O(1)	1.342(5)	C(23) -C(24)	1.335(6)
C(4) - C(5)	1.414(6)	C(24) -C(25)	1.502(6)
C(4) - C(9)	1.398(5)	C(24) - O(8)	1.359(5)
C(5) - C(6)	1.372(6)	C(25) -C(26)	1.518(6)
C(6) - C(7)	1.390(6)	C(26) -C(27)	1.524(5)
C(7) - C(8)	1.388(6)	C(27) -C(28)	1.474(6)
C(8) - C(9)	1.386(5)	C(28) - O(6)	1.202(5)
H(1') - O(1)	0.94 (5)	C(28) - O(7)	1.358(5)
C(10) - O(2)	1.221(5)	O(7) -C(29)	1.445(5)
C(10) - O(3)	1.332(5)	C(29) -C(30)	1.494(6)
O(3) -C(11)	1.462(6)	O(8) -C(31)	1.438(6)

(b) Angles(°) with standard deviations

C(1) - N(1) - C(9)	116.0(3)	C(10) - O(3) -C(11)	117.1(4)
C(1) - N(1) -C(13)	122.8(3)	O(3) -C(11) -C(12)	109.3(4)
C(9) - N(1) -C(13)	121.1(3)	N(1) -C(13) - O(4)	126.1(4)
N(1) - C(1) - C(2)	108.4(3)	N(1) -C(13) - O(5)	110.2(3)
N(1) - C(1) -C(21)	111.4(3)	O(4) -C(13) - O(5)	123.7(3)
C(2) - C(1) -C(21)	112.3(3)	C(13) - O(5) -C(14)	116.4(3)
C(1) - C(2) - C(3)	118.4(3)	O(5) -C(14) -C(20)	105.9(3)
C(1) - C(2) -C(10)	122.2(3)	C(1) -C(21) -C(22)	112.5(3)
C(3) - C(2) -C(10)	119.4(4)	C(21) -C(22) -C(23)	115.4(3)
C(2) - C(3) - C(4)	120.1(3)	C(21) -C(22) -C(27)	125.0(3)
C(2) - C(3) - O(1)	124.2(3)	C(23) -C(22) -C(27)	119.6(3)
C(4) - C(3) - O(1)	115.7(3)	C(22) -C(23) -C(24)	120.4(4)
C(3) - C(4) - C(5)	121.7(3)	C(23) -C(24) -C(25)	121.3(4)
C(3) - C(4) - C(9)	119.4(3)	C(23) -C(24) - O(8)	127.3(4)
C(5) - C(4) - C(9)	118.8(3)	C(25) -C(24) - O(8)	111.3(3)
C(4) - C(5) - C(6)	120.6(4)	C(24) -C(25) -C(26)	110.3(3)
C(5) - C(6) - C(7)	119.8(4)	C(25) -C(26) -C(27)	111.9(3)
C(6) - C(7) - C(8)	120.6(4)	C(22) -C(27) -C(26)	119.3(3)
C(7) - C(8) - C(9)	120.0(4)	C(22) -C(27) -C(28)	122.1(3)
N(1) - C(9) - C(4)	117.3(3)	C(26) -C(27) -C(28)	118.5(3)
N(1) - C(9) - C(8)	122.5(3)	C(27) -C(28) - O(6)	127.8(4)
C(4) - C(9) - C(8)	120.2(3)	C(27) -C(28) - O(7)	110.6(3)
C(3) - O(1) -H(1')	108.8(29)	O(6) -C(28) - O(7)	121.6(4)
C(2) -C(10) - O(2)	124.6(4)	C(28) - O(7) -C(29)	116.1(3)
C(2) -C(10) - O(3)	113.3(4)	O(7) -C(29) -C(30)	106.2(3)
O(2) -C(10) - O(3)	122.1(4)	C(24) - O(8) -C(31)	116.5(3)

Table 3. Fractional Coordinates of Atoms with Standard Deviations for (7a)

	x	y	z	Ueq
N(1)	0.3201(3)	0.2324(3)	0.3886(3)	0.044(3)
C(1)	0.3216(3)	0.1172(4)	0.5127(4)	0.058(5)
C(2)	0.3303(4)	0.1029(6)	0.6129(5)	0.075(6)
O(7)	0.2998(4)	0.0431(5)	0.6489(4)	0.124(5)
C(3)	0.3814(4)	0.1703(6)	0.6634(4)	0.084(6)
C(4)	0.4385(4)	0.2008(5)	0.6044(5)	0.068(5)
C(5)	0.4080(3)	0.2574(4)	0.5209(4)	0.050(4)
C(6)	0.3336(3)	0.2210(4)	0.4866(4)	0.045(4)
C(7)	0.4622(4)	0.2489(5)	0.4515(5)	0.066(5)
C(8)	0.4403(4)	0.1976(5)	0.3676(4)	0.056(5)
C(9)	0.4918(4)	0.1581(6)	0.3188(6)	0.088(6)
C(10)	0.4701(6)	0.1088(7)	0.2406(7)	0.104(8)
C(11)	0.4001(6)	0.0972(6)	0.2140(5)	0.091(7)
C(12)	0.3489(4)	0.1369(5)	0.2602(4)	0.065(5)
C(13)	0.3705(4)	0.1885(4)	0.3374(4)	0.048(4)
O(1)	0.5187(3)	0.2871(4)	0.4663(3)	0.094(4)
C(14)	0.2648(4)	0.2892(5)	0.3561(5)	0.058(5)
O(5)	0.2209(3)	0.3194(4)	0.3992(3)	0.081(4)
O(6)	0.26820(24)	0.3056(3)	0.2683(3)	0.072(4)
C(15)	0.2148(4)	0.3663(7)	0.2279(5)	0.113(8)
C(16)	0.2220(5)	0.3717(8)	0.1278(5)	0.136(9)
C(17)	0.4026(4)	0.3627(5)	0.5454(5)	0.073(6)
O(3)	0.4165(4)	0.3942(4)	0.6183(3)	0.128(5)
O(4)	0.3810(3)	0.4143(3)	0.4740(3)	0.073(4)
C(18)	0.3717(5)	0.5140(5)	0.4915(5)	0.115(8)
C(19)	0.3355(7)	0.5610(7)	0.4079(6)	0.159(11)
O(2)	0.4683(3)	0.1171(4)	0.5709(3)	0.083(4)
C(20)	0.5357(5)	0.0947(10)	0.6113(10)	0.196(14)
N(1′)	0.1128(3)	0.1950(3)	0.6164(3)	0.046(3)
C(1′)	0.1155(3)	0.0966(4)	0.4788(4)	0.051(4)
C(2′)	0.1223(4)	0.1081(5)	0.3811(5)	0.061(5)
O(7′)	0.1687(3)	0.0707(4)	0.3443(3)	0.085(4)
C(3′)	0.0699(4)	0.1740(5)	0.3312(4)	0.069(5)
C(4′)	0.0121(4)	0.2057(5)	0.3851(4)	0.060(5)
C(5′)	0.0408(3)	0.2491(4)	0.4773(4)	0.047(4)
C(6′)	0.1093(3)	0.1966(4)	0.5184(4)	0.046(4)
C(7′)	-0.0205(3)	0.2448(5)	0.5347(4)	0.050(4)
C(8′)	-0.0126(3)	0.1854(4)	0.6162(4)	0.045(4)
C(9′)	-0.0721(3)	0.1561(5)	0.6544(4)	0.056(5)
C(10′)	-0.0663(4)	0.1019(5)	0.7316(5)	0.066(5)
C(11′)	-0.0007(4)	0.0770(5)	0.7696(4)	0.062(5)
C(12′)	0.0594(3)	0.1056(4)	0.7328(4)	0.054(4)
C(13′)	0.0532(3)	0.1618(4)	0.6559(4)	0.042(4)
O(1′)	-0.07357(24)	0.2904(3)	0.5114(3)	0.072(3)
C(14′)	0.1699(4)	0.2381(5)	0.6628(5)	0.060(5)
O(5′)	0.22245(24)	0.2604(4)	0.6306(3)	0.075(3)
O(6′)	0.16063(23)	0.2502(3)	0.7500(3)	0.075(3)
C(15′)	0.2219(4)	0.2884(7)	0.8023(4)	0.113(7)
C(16′)	0.2101(5)	0.2762(10)	0.8998(5)	0.157(10)
C(17′)	0.0585(4)	0.3536(5)	0.4636(6)	0.062(5)
O(3′)	0.0503(3)	0.3960(3)	0.3938(3)	0.087(4)
O(4′)	0.0851(3)	0.3910(3)	0.5417(3)	0.074(4)
C(18′)	0.1102(5)	0.4876(6)	0.5346(6)	0.118(8)
C(19′)	0.1660(8)	0.5085(8)	0.6106(8)	0.241(17)
O(2′)	-0.02918(23)	0.1235(3)	0.4041(3)	0.062(3)
C(20′)	-0.0957(4)	0.1198(6)	0.3550(5)	0.091(6)

Table 4. Fractional Coordinates of Atoms with Standard Deviations for (14b)

	x	y	z	Ueq
N(1)	0.48989(12)	0.0846(3)	0.25390(18)	0.0369(19)
C(1)	0.43200(15)	0.1171(4)	0.17975(22)	0.0393(23)
C(2)	0.45360(16)	0.2014(5)	0.10724(23)	0.0409(24)
C(3)	0.51033(17)	0.1604(5)	0.09097(24)	0.0446(25)
C(4)	0.55154(16)	0.0467(5)	0.14660(25)	0.0435(25)
C(5)	0.60247(18)	-0.0255(5)	0.1201(3)	0.056(3)
C(6)	0.64190(18)	-0.1295(5)	0.1749(3)	0.058(3)
C(7)	0.63220(18)	-0.1631(5)	0.2576(3)	0.056(3)
C(8)	0.58310(17)	-0.0920(5)	0.28552(25)	0.047(3)
C(9)	0.54260(16)	0.0119(4)	0.23014(24)	0.0378(23)
O(1)	0.53362(13)	0.2223(4)	0.02698(18)	0.0644(21)
C(10)	0.41669(19)	0.3251(5)	0.0576(3)	0.055(3)
O(2)	0.43041(14)	0.3918(4)	-0.00376(19)	0.0756(23)
O(3)	0.36453(13)	0.3612(4)	0.08464(18)	0.0743(23)
C(11)	0.32425(23)	0.4866(7)	0.0384(3)	0.115(5)
C(12)	0.2766(3)	0.5210(7)	0.0823(4)	0.130(6)
O(4)	0.53949(12)	0.1001(3)	0.40397(16)	0.0576(19)
C(13)	0.49269(18)	0.1149(4)	0.34112(24)	0.0399(25)
O(5)	0.43506(11)	0.1686(3)	0.34751(15)	0.0470(17)
C(14)	0.43011(17)	0.2017(5)	0.43738(22)	0.052(3)
C(15)	0.32709(14)	0.1553(3)	0.47964(16)	0.064(3)
C(16)	0.26224(14)	0.1881(3)	0.47367(16)	0.084(4)
C(17)	0.23001(14)	0.3017(3)	0.41574(16)	0.078(4)
C(18)	0.26263(14)	0.3825(3)	0.36380(16)	0.077(4)
C(19)	0.32747(14)	0.3496(3)	0.36978(16)	0.067(3)
C(20)	0.35970(14)	0.2360(3)	0.42770(16)	0.0456(25)
C(21)	0.39431(16)	-0.0291(5)	0.14489(23)	0.047(3)
C(22)	0.37555(16)	-0.1179(4)	0.21820(23)	0.0407(24)
C(23)	0.42084(17)	-0.2392(5)	0.2602(3)	0.051(3)
C(24)	0.41965(17)	-0.2960(5)	0.3393(3)	0.049(3)
C(25)	0.37233(17)	-0.2384(5)	0.38763(25)	0.056(3)
C(26)	0.30968(17)	-0.1889(5)	0.32129(25)	0.051(3)
C(27)	0.32226(16)	-0.0909(5)	0.24685(24)	0.0439(25)
C(28)	0.27408(17)	0.0262(5)	0.2057(3)	0.048(3)
O(6)	0.28007(13)	0.1285(4)	0.15720(20)	0.0707(23)
O(7)	0.21780(11)	0.0039(3)	0.22858(17)	0.0577(19)
C(29)	0.16741(17)	0.1159(5)	0.1960(3)	0.062(3)
C(30)	0.11391(19)	0.0770(6)	0.2373(3)	0.084(4)
O(8)	0.46007(12)	-0.4025(3)	0.38828(19)	0.0645(20)
C(31)	0.50778(21)	-0.4664(6)	0.3490(4)	0.085(4)

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