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The Intramolecular 1,3-Dipolar Cyclisation of Mesoionic Species Generated by the Thermolysis of the Mixed Anhydrides of Acetic and N-Alkynoyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic Acids

*Malcolm Sainsbury[a], Rosalind H. Strange[a],
Peter R. Woodward,[b] and Paul A. Barsanti[a]
[a]School of Chemistry, University of Bath, BA2 7AY;[b] Medicinal Chemistry II, Glaxo Group Research Ltd., Greenford, Middlesex UB6 0HE.

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Abstract: The intramolecular cyclisations of mesoionic intermediates formed by heating *N*-alkynoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids [alkynoyl side chains: $RC{\equiv}C\text{-}(CH_2)_nCO$, where n = 3 or 4] with acetic anhydride, have been investigated. The final products are octahydro-pentaleno[2,3-*a*]isoquinolines and hexahydroindeno[2,3-*a*]isoquinolines respectively, formed by the expulsion of carbon dioxide from the initial adducts. The behaviour of alkenes and alkynes as dienophiles in intermolecular versions of the cycloaddition reactions have also been studied. Alkynes bearing electron withdrawing groups afford pyrrolo[1,2-*b*]isoquinolines, but unless alkenes, such as benzylidenemalonodinitrile are used (where the first formed adduct can eliminate HCN, prior to loss of CO_2), the reactions fail.

The pentacycle (1) (mitoquidone) has cytotoxic activity and derivatives have been considered for clinical evaluation as anticancer drugs[1]. Electron density mapping[2] indicate a relationship between (1) and the alkaloid camptothecin (2)[3], and it is interesting that both molecules act as inhibitors of topoisomerase-1[4]. Modelling experiments also show that the structures of other compounds bear a close resemblance to camptothecin and have similar charge density patterns. One such example is 1,2,3,4,5,10-hexahydroind-eno[2,3-*a*]isoquinoline (3), derivatives of which we have targeted as potential topoisomerase-1 inhibitors.

The pentacycle (1) was first synthesised at Bath in 1981[5,6], by heating the isoquinoline (4, R = R′ = H) with 1,4-naphthoquinone in acetic anhydride. It is surmised that a mesoionic intermediate (a münchnone[7])(5) is formed which then enters into a 1,3-dipolar addition reaction[8] with 1,4-naphthoquinone to afford the adduct (6). This undergoes oxidation to the dehydro adduct (7), prior to loss of carbon dioxide.

We have circumstantial evidence for the second step of this mechanism since when 1,4-naphthoquinone was replaced by alkenes, such as methyl acrylate, dimethyl fumarate, or dimethyl maleate, reactions with the putative münchnone (5) seemed to occur, but failed to yield the expected pyrroloisoquinolines (9), giving rise instead to complex products. However, unlike the adduct (6), the initial addition products (8) from these alkenes would be less prone to oxidation and thus do not provide an opportunity for the concerted loss of carbon dioxide. In line with this conclusion we have shown that when benzylidenemalonodinitrile was used as the dipolarophile 2-cyano-4,9-dihydro-3-methyl-1-phenylpyrrolo[1,2-*b*]isoquinoline (9, R = CN; R′ = Ph)

was obtained in 77% yield. Here the initial adduct [8, R = $(CN)_2$; R′ = Ph] can eliminate hydrogen cyanide, thereby increasing its oxidation state to allow the release of carbon dioxide and the formation of the pyrroloisoquinoline. Similarly, if the oxidation state of the dipolarophile was increased and dimethyl acetylenedicarboxylate was employed then the adduct (10, R = Me)[5] was formed in 63% yield. Interestingly, there appears to be little regioselectivity in the cycloaddition between the münchnone (5) and methyl propiolate which afforded a mixture of the two adducts (9, R = CO_2Me; R′ = H) and (9, R = H; R′= CO_2Me) in approximately equal amounts (overall yield 74%). In other cases, however, we were only able to isolate one isomer in the pure state even though TLC analyses indicated that the alternative adduct may have been present in the reaction mixture. Thus the only products obtained from reactions of the münchnone with ethyl phenylpropiolate and with 3-butyn-2-one were the pyrroloisoquinolines (9, R = Ph; R′= CO_2Et) (56%) and (9; R = COMe, R′= H) (71%), respectively.

The assignment of the structures of these adducts rests on ^1H N.M.R. data: thus in the spectrum of compound (9, R = CO_2Me; R′= H) the protons of the C-3 methyl group resonate as a doublet (J = 0.9Hz) at δ 2.29, coupled to H-2, the signal of which appears as a quartet at δ 6.31 (J = 0.9Hz). In the spectrum of the isomer (9, R = H; R′= CO_2Me) the C-3 methyl protons resonate as a singlet at δ 2.61, and the methine proton as a triplet (J = 1.0Hz) at δ 6.33 - coupled to the signal of the methylene hydrogen atoms at C-9. The resonance of the C-9 protons for isomer (9, R = CO_2Me; R′= H) appears at δ 4.39 due to the deshielding influence of the adjacent methoxycarbonyl group, whereas in the alternative isomer this resonance is found at δ 3.99.

In the spectrum of the adduct formed between the münchnone and ethyl phenylpropiolate the resonance of the C-3 methyl protons occurs at δ 2.66 [0.37 ppm down-field relative to the corresponding resonance in the compound (9, R = CO_2Me; R′= H), but almost identical to that exhibited in the spectrum of its isomer (9, R = H; R′= CO_2Me)]. The C-9H_2 protons resonate at the relatively high-field position of δ 3.93. These facts indicate that for the ethyl phenylpropiolate adduct the ethoxycarbonyl group is at C-2, rather that at C-1. Additionally, the proton signals of the ethoxycarbonyl group are complicated because of restricted rotation enforced in the structure (9, R = Ph; R′= CO_2Et) where the ethoxycarbonyl function is sandwiched by the 'large' phenyl substituent at C-1 and the methyl group at C-3. Non-bonded interactions of this type would be even more acute in the alternative formulation (9, R = CO_2Et; R′= Ph) and this disfavours the formation of this isomer.

In the spectrum of the adduct (9, R = Ph; R′= CO_2Et) the C-4 methylene protons resonate at 5.01 ppm, this is virtually the same chemical shift as noted for the C-4 methylene protons of the product formed when the münchnone is reacted with benzylidenemalonodinitrile. However, the chemical shifts for the C-9 methylene proton signals in the two compounds are different: δ 3.93 and δ 4.23, respectively, suggesting that in the latter compound the phenyl substituent is located at C-2 not at C-1, i.e. the structure of this adduct is (9, R = CN; R′ = Ph). Support for this conclusion is provided by a n.O.e experiment which shows that irradiation at the resonance position of the C-3 methyl protons strongly enhances the aromatic proton signals of the phenyl substituent. Presumably in this adduct the cylindrical symmetry of the cyanide group reduces non-bonded interactions sufficiently to allow the phenyl group to occupy C-2.

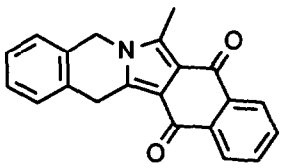
Finally, in the adduct formed between (5) and 3-butyn-2-one the signal due to the methylene protons at C-9 is relatively deshielded (δ 4.44), showing that the acetyl group is bonded to C-1 and thus exerts a deshielding influence upon the chemical shift of the C-9 methylene signal. The methine resonance at δ 6.32 is spin-spin coupled (^4J = 0.9Hz) to the signal of the C-3 methyl protons at δ 2.39. Thus this compound must have structure (9, R = Ac; R′ = H) and this is confirmed by n.O.e. studies which demonstrate that irradiation at 6.32 ppm causes an enhancement of *both* the C-Me and COMe proton signals.

We observed that the *N*-formyltetrahydroisoquinoline (4, R = H; R′= CHO) reacted with acetic anhydride and dimethyl acetylenedicarboxylate to give the indenoisoquinoline (10, R = H) in 54% yield. An *N*-acetyl group is therefore not a prerequisite for reaction, however, it is necessary to have a free carboxyl group at C-3. The isoquinoline (4, R = Et; R′= H) fails to yield a 1,3-dipolar intermediate when reacted with acetic anhydride. Presumably the carboxylic acids are converted into mixed anhydrides (11) during treatment with acetic anhydride, the anhydride function thus provides a suitable leaving group for intramolecular displacement by the oxygen atom of the amide unit.

With these results in hand we considered that an intramolecular version of the reaction might be used to synthesise analogues [e.g. (14, n = 2)] of the indenoisoquinoline (3) *via* the corresponding mesoionic derivatives (12, n = 2). For this purpose we reacted the isoquinoline (4, R = Et; R′= H) with 7-methoxycarbonylhept-6-ynoic acid, pre-treated with cyanuric acid. This gave the amide (13, R = Et, R′ = Me; n = 2), which when hydrolysed and heated with acetic anhydride at 60-70°C afforded the tetracycle (14, R = Ac; n = 2) in 45% yield. A similar three step procedure using 6-methoxycarbonylhex-5-ynoic acid gave first the amide (13, R = Et; R′ = Me; n = 1) and then the tetracycle (14; R = Ac, n = 1) in 37% yield. These anhydrides readily hydrolyse to the corresponding acids if stored in contact with air.

The yields in these reactions were rather disappointing and we note that the amides (13) exist as mixtures of *E*- and *Z*-isomers[9] in approximately the ratio 1:1. This may be significant since from N.M.R. temperature dependence studies of similar substrates[10] free rotation about the amide bond occurs in the range 60-120°C. For the intermolecular cycloadditions reaction temperatures between 70-130°C were used, however, at temperatures above 80°C the reaction mixtures containing the amides (13) became very dark. In future work we intend to investigate the effect of ultrasonication as a means of ensuring mobility within the amide group thus facilitating access to the necessary geometry for intramolecular cyclisation to the corresponding münchnones.

Despite these problems it is now clear that an intramolecular version of the original 1,3-dipolar cyclisation reaction opens the way for the construction of more complex derivatives of the 1,2,3,4,5,10-hexahydroindeno-[2,3-*a*]isoquinoline system (3), especially those which bear further ring fusions and groupings related to the lactone assembly of the camptothecin prototype. However, we have some evidence that the alkynoyl side chain should be terminated by an electronegative group since all attempts to cyclise the amide (15, R = H) *via* the corresponding münchnone (16) failed, as indeed did intermolecular reactions between the münchnone (5) and non-functionalised alkynes[5].



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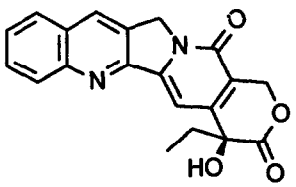

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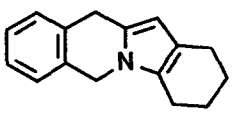

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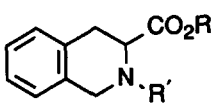

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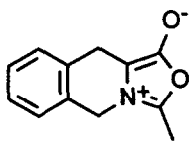

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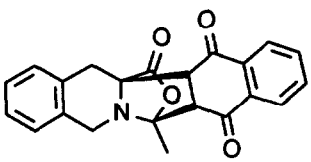

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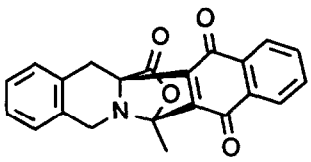

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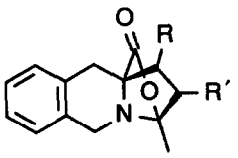

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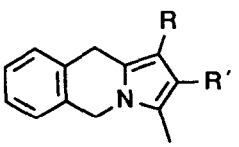

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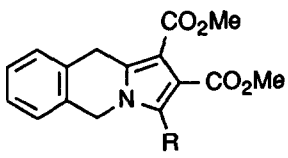

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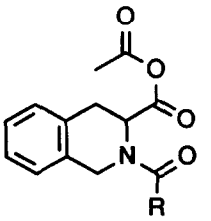

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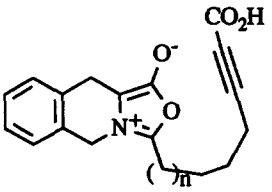

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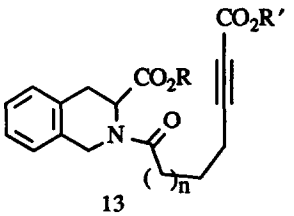

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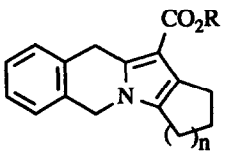

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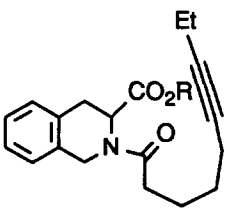

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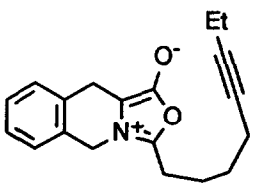

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Experimental

All solvents were dried and distilled before use. Petrol refers to petroleum ether boiling in the range 60-80°C. Medium pressure flash column chromatography was routinely employed using Amicon Matrex or Merck 9385 silica gel.

Infrared spectra were recorded in the range 4000-600 cm^{-1} using a Perkin-Elmer 1310 spectrophotometer. Samples were prepared as liquid films, Nujol mulls or chloroform solutions, as indicated. ^1H N.M.R. spectra were recorded on either JEOL GX FT 270 (270 MHz) or JEOL GX FT 400 (400 MHz) instruments. $CDCl_3$ was used as the solvent and chemical shifts (δ) are expressed in ppm downfield from internal tetramethylsilane. Mass spectra were recorded using a VG Analytical 7070E spectrometer with a VG 2000 data system. Chemical ionisation (C.I.) methods used isobutane or ammonia as the reagent gas.

1-Cyano-4,9-dihydro-3-methyl-2-phenylpyrrolo[1,2-*b*]isoquinoline (9, R = CN; R′ = Ph)
The isoquinoline (4, R = R′ = H) (88 mg, 0.50 mmol) and benzylidenemalonodinitrile (185 mg, 1.20 mmol) in acetic anhydride (25 cm^3) were heated at reflux for 2h under an atmosphere of nitrogen, excess reagents were removed and the residual oil chromatographed, eluting with ethyl acetate : petrol (1:4). This afforded the title compound as yellow prisms (109 mg, 77%), m.p. 171-171.5°C (ethanol); $\nu_{max}cm^{-1}$ 2214 (CN); δ_H 7.45-7.27 (9H, m, aromatic protons), 5.02 (2H, brs, 4-H_2), 4.23 (2H, brs, 9-H_2), 2.37 (3H, s, 3-Me); *m/z* 284 (100%), 269 (74%) [Found: *m/z* 284.1314; $C_{20}H_{16}N_2$ requires: 284.1313]

2-Ethoxycarbonyl-4,9-dihydro-3-methyl-1-phenylpyrrolo[1,2-*b*]isoquinoline (9, R = Ph; R′= CO_2Et)
The isoquinoline (4; R = R′= H) (159 mg, 0.9 mmol) was added to acetic anhydride (10 cm^3) and ethyl phenylpropiolate (37 cm^3, 2.25 mmol) and the mixture was heated at 80°C for 8h. The solvent was removed and the remaining yellow oil was chromatographed, eluting with ethyl acetate : petrol (1:9 - 1:4), to give the title compound as a yellow oil (166 mg, 56%); $\nu_{max}cm^{-1}$ 1680 (CO); δ_H 7.42-7.21 (9H, m, aromatic protons), 5.01 (2H, brs, 4-H_2), 4.08 (2H, q*, *J* = 7 Hz, OCH_2Me), 3.93 (2H, brs, 9-H_2), 2.66 (3H, , 3-Me), 1.05 (3H, t*, *J* = 7 Hz, OCH_2Me); *m/z* 331(10%), 105(96%), 77(100%) [Found: *m/z* 331.1571; $C_{22}H_{21}NO_2$ requires: 331.1572]
*Although these signals clearly show the multiplicities indicated, they are complicated by satellite peaks arising from restricted rotation of the ethyl group, the spectrum is simplified by heating the sample to *ca* 70°C.

1-Acetyl-4,9-dihydro-3-methylpyrrolo[1,2-*b*]isoquinoline (9, R = Ac; R′ = H)
The isoquinoline (4; R = R′= H) (159 mg, 0.9 mmol) was added to acetic anhydride (10 cm^3) and 3-butyn-2-one (1.8 cm^3, 2.25 mmol) and the solution was heated at 130°C for 1.5h. Excess reagents were removed and the residue was purified by preparative plate chromatography eluting with ethyl acetate : petrol (1:3). This gave the title compound as yellow prisms (144 mg, 71%), m.p. 167-169°C; $\nu_{max}cm^{-1}$ 1660 (CO); δ_H 7.32 - 7.24 (4H, m, aromatic protons), 6.32 (1H, q, ^4J = 0.9Hz, 2-H), 4.95 (2H, brs, 4-H_2), 4.44 (2H, brs, 9-H_2), 2.39 (3H, d, ^4J = 0.9 Hz, 3-Me), 2.32 (3H, s, COMe); *m/z* 225 (100%) [Found: *m/z* 225.1152 $C_{15}H_{15}NO$ requires: 225.1158]

Methyl 4,9-dihydro-3-methylpyrrolo[1,2-*b*]isoquinoline-1-carboxylate and methyl 4,9-dihydro-3-methylpyrrolo[1,2-*b*]isoquinoline-2-carboxylate (9, R = CO_2Me; R′ = H) and (9, R = H; R′ = CO_2Me)
The isoquinoline (4; R = R′= H) (159 mg, 0.9 mmol) was added to acetic anhydride (10 cm^3) and ethyl propiolate (37 cm^3, 2.25 mmol) and the mixture heated at 80°C for 8h. The solvent was removed under reduced pressure and the remaining yellow oil was purified by column chromatography eluting with ethyl acetate : petrol (1:9 - 1:3). This yielded the mixed regioisomers (9, R = CO_2Me; R′ = H) and (9, R = H; R′ = CO_2Me), in the molar ratio ~ 1:1, as a pale yellow oil (89 mg, 74%); υ_{max} (liquid film) cm^{-1} 1670 (C=O); δ_H 7.25 (8H, m, aromatic protons), 6.33 (1H, t, ^4J = 1.0 Hz, 1-H), 6.31 (1H, q, ^4J = 0.9 Hz, 2-H), 4.93 (2H, brs, 4-H_2), 4.92 (2H, brs, 4-H_2), 4.39 (2H, brs, 9-H_2), 3.99 (2H, d, ^4J = 1.0 Hz, 9-H_2), 3.81 (3H, s, CH_3O), 3.79

(3H, s, CH_3O), 2.61 (3H, s, 3-Me), 2.29 (3H, d, ^4J = 0.9Hz, 3-Me). All attempts to separate these two compounds failed.

Dimethyl 4,9-dihydropyrrolo[1,2-*b*]isoquinoline-2,3-dicarboxylate (10, R = H)

A solution of the amide (4, R = H; R′ = CHO) (26 mg, 0.13 mmol) and dimethylacetylene dicarboxylate (21 mg, 0.15 mmol) in acetic anhydride (5 cm^3) was heated at 70°C for 1h under an atmosphere of nitrogen. Excess reagents were removed and the remaining oil purified by preparative plate chromatography eluting with ethyl acetate : petrol, (1:3) to give the title compound as a pale yellow low m.p. solid (19 mg, 54%); υ_{max} ($CHBr_3$) cm^{-1} 1718 (C=O), 1064 (C-O); δ_H 7.25 (4H, m, aromatic protons), 6.39 (1H, s, 3-H), 5.06 (2H, brs, 4-H_2), 4.30 (2H, brs, 9-H_2), 3.88, 3.82 (2 x 3H, 2 x s, 2 x CH_3-O); *m/z* (C.I.) 286 (100%, MH^+), 254 (100%).

Dimethyl 4,9-dihydro-3-methylpyrrolo[1,2-*b*]isoquinoline-2,3-dicarboxylate (10, R = Me)

Method A

The isoquinoline (4; R = R′= H) (88 mg, 0.5 mmol) was added to acetic anhydride (10 cm^3) containing dimethyl acetylenedicarboxylate (170mg, 1.2 mmol). The mixture was stirred and heated at 80°C for 12h, then the solvent was removed under reduced pressure to yield a tan coloured solid. This was crystallised from ethanol to give colourless prisms (95 mg, 63%), m.p. 126-128°C (lit.,[5] 128-129°C); υ_{max} ($CHCl_3$) cm^{-1} 1670 (C=O); δ_H 7.28 (4H, m, aromatic protons), 4.95 (2H, brs, 4-H_2), 4.30 (2H, brs, 9-H_2), 3.85 (6H, s, 2 x CH_3-O), 2.46 (3H, s, 3-Me); *m/z* 299 (50%, M^+), 268 (100%) [Found: C, 68.1; H, 5.8; N, 4.6 Calc. for $C_{17}H_{17}NO_4$: C, 68.2; H, 5.7; N, 4.7%]

Method B

Acetyl chloride (12.5 mg, 0.16 mmol) was added to the amide (4, R = H; R′= Ac) (35 mg, 0.16 mmol), triethylamine (19 mg, 0.16 mmol), and dimethyl acetylenedicarboxylate (34 mg, 0.24 mmol) in diethyl ether (20 cm^3) protected by an atmosphere of nitrogen. This reaction mixture was heated to about 70°C allowing the diethyl ether to evaporate. After 1h, it was cooled and ethyl acetate (30 cm^3) was added and the solution was washed successively with dilute hydrochloric acid (3 x 20 cm^3), saturated aqueous sodium hydrogen carbonate (2 x 20cm^3), water (2 x 20 cm^3) and brine (2 x 20 cm^3). The organic phase was separated and evaporated affording an oil which was dissolved in hot ethanol. On cooling, the title compound was obtained as a microcrystalline solid (34 mg, 71%).

6-Methoxycarbonylhex-5-ynoic acid

To methyl 7-hydroxyhept-2-ynoate (100 mg, 0.6 mmol) in acetone (5 cm^3), was added chromium(VI) oxide (100 mg) in water (30 cm^3) containing conc. sulphuric acid (2 cm^3). The reaction mixture was stirred at room temperature for 1h. Water (20 cm^3) was then added and the solution extracted with ethyl acetate (4 x 20 cm^3). The organic extracts were combined and re-extracted with 50% sodium carbonate solution (4 x 20 cm^3). These extracts were acidified with dilute hydrochloric acid and extracted with ethyl acetate (3 x 20 cm^3). The combined organic extracts were washed with water (2 x 2 cm^3) and brine (2 x 20 cm^3), dried, and evaporated to yield the title compound as a colourless oil (55 mg, 54%); υ_{max} (liquid film) cm^{-1} 3100 (O-H), 2239 (C≡C),

1712 (br, ester/acid); δ_H 9.51 (1H, br, O-H), 3.76 (3H, s, CH_3-O), 2.51 (4H, m, CH_2-C=O, CH_2C≡C), 1.60 (2H, m, C*H*$_2$-CH_2-C=O); *m/z* (C.I.) 171 (5%, M+1), 138 (46%), 111 (47%), 97 (70%), 79 (100%).

7-(Methoxycarbonyl)hept-6-ynoic acid

To a solution of methyl 8-hydroxyoct-2-ynoate (60 mg, 0.35 mmol) in acetone (1 cm^3), was added chromium(VI) oxide (2 g) in water (3 cm^3) and concentrated sulphuric acid (1.7 cm^3) until the orange colour of the oxidant persisted. The solution was stirred for 1h at room temperature. Water (10 cm^3) was then added and the mixture extracted with diethyl ether (3 x 10 cm^3). The combined extracts were re-extracted with 50% sodium carbonate solution (3 x 10 cm^3) and the combined aqueous phases were then acidified with 2M hydrochloric acid and extracted with diethyl ether (3 x 10 cm^3). The organic extracts were washed with water (2 x 10 cm^3), brine (2 x 10 cm^3), dried and evaporated. The residue was chromatographed eluting with ethyl acetate : petrol (1:3 - 3:1) to yield the title compound as a colourless oil (37 mg, 57%); υ_{max} ($CHBr_3$) cm^{-1} 2237 (C≡C), 1710 (br, ester/acid); δ_H 5.5 (1H, br, O-H), 3.69 (3H, s, CH_3-O), 2.32 (4H, m, CH_2-C=O, CH_2-C≡C), 1.64 (4H, m, C*H*$_2$-C*H*$_2$-CH_2-C=O); *m/z* (C.I.) 202 (100%, MHN_4^+), 185 (87%, MH^+).

Ethyl 2-(6-methoxycarbonylhex-5-yn-1-oyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13, R = Et; R′ = Me; n = 1)

Triethylamine (45.7 mg, 0.45 mmol) was added to a solution of 6-methoxycarbonylhex-5-ynoic acid (76.6 mg, 0.45 mmol) and cyanuric chloride (61.7 mg, 0.33 mmol) in dry acetone (5 cm^3) under an atmosphere of nitrogen. The solution was stirred at room temperature for 1.5h, then sodium carbonate (47.7 mg, 0.45 mmol) and the isoquinoline (4, R = R′ = H) (100 mg, 0.54 mmol) were added and the mixture was stirred at room temperature for 15h. After filtration, the solvent was removed from the filtrate and the red oil which remained was re-dissolved in ethyl acetate (50 cm^3) and washed in turn with 2M hydrochloric acid (2 x 20 cm^3), 2M sodium carbonate (2 x 20 cm^3) and brine (2 x 20 cm^3). The solvent was removed and the residue purified by chromatography, eluting with ethyl acetate : petrol (1:19). This yielded the title compound as a sweet-smelling yellow oil (94 mg, 63%)(a mixture of *E*- and *Z*-isomers in the ratio ~ 1:1); υ_{max} ($CHBr_3$) cm^{-1} 1706 (ester), 1640 (amide), 1079 (C-O, ester); δ_H 7.22 (8H, m, aromatic protons), 5.38 (1H, dd, ^3J = 6.0 Hz, ^3J = 3.7 Hz , 3-H), 4.82 (1H, d, ^2J = 17.4 Hz, 1-H), 4.78 (1H, m, 3-H), 4.64 (2H, m, 1-H_2), 4.50 (1H, d, ^2J = 17.4 Hz, 1-H), 3.99 (4H, m, 2 x CH_2-O), 3.69 (3H, s, CH_3-O), 3.68 (3H, s, CH_3-O), 3.17 (4H, m, 2 x 4-H_2), 2.58 (2H, t, ^3J = 7.1 Hz, CH_2-C=O), 2.56 (2H, t, ^3J = 6.9 Hz, CH_2-C=O), 2.43 (4H, m, 2 x CH_2-C≡C), 1.93 (4H, m, 2 x CH_2-CH_2-C=O), 1.05 (3H, t, ^3J = 7.1 Hz, CH_3-CH_2), 1.01 (3H, t, ^3J = 7.1 Hz, CH_3-CH_2); *m/z* (C.I.) 358 (36%, MH+), 204 (100%), 132 (97%), 71 (57%).

Ethyl 2-(7-methoxycarbonylhept-6-yn-1-oyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (13, R = Et; R′ = Me; n = 2)

A solution of 7-methoxycarbonylhept-6-ynoic acid (100 mg, 0.54 mmol) and cyanuric chloride (75.2 mg, 0.40 mmol) in dry acetone (5 cm^3) was stirred at room temperature. Triethylamine (54.8 mg, 0.54 mmol) was then added and the solution stored at room temperature for 1h. The isoquinoline (4, R = Et; R′ = H) (137 mg, 0.54 mmol) and sodium carbonate (57 mg, 0.54 mmol) were added and the mixture was stirred for 14h. The

triazine which had precipitated was then removed and the filtrate evaporated. The remaining yellow oil was taken up in diethyl ether (10 cm^3) and dichloromethane (1 cm^3) and washed with dilute hydrochloric acid (2 x 5 cm^3), sodium carbonate (2 x 5 cm^3), water (2 x 5 cm^3) and brine (2 x 5 cm^3). The solvent was removed and the residue chromatographed eluting with ethyl acetate : petrol (1:9 - 1:1) to afford the title compound as a sweet-smelling yellow oil (116 mg, 58%) (a mixture of *E*- and *Z*-isomers, ratio ~ 1:1); υ_{max} ($CHBr_3$) cm^{-1} 1707 (ester), 1641 (amide); δ_H 7.15 (8H, m, aromatic protons), 5.43 (1H, dd, ^3J = 3.8 Hz, ^3J = 5.7 Hz, 3-H), 4.88 (1H, d, ^2J = 17.1 Hz, 1-H), 4.80 (1H, dd, ^3J = 3.8 Hz, ^3J = 5.7 , 3-H), 4.67 (2H, m, 1-H_2), 4.52 (1H, d, ^2J = 17.1 Hz, 1-H), 4.08 (4H, m, 2 x CH_2-O), 3.73 (6H, s, 2 x CH_3-O), 3.20 (4H, m, 2 x 4-H_2), 2.51 (4H, m, 2 x CH_2-CO), 2.38 (4H, m, 2 x CH_2-C≡C), 1.75 (8H, m, 2 x CH_2-CH_2), 1.24, 1.10 (2 x 3H, 2 x t, ^3J = 7.1 Hz, 2 x CH_3-CH_2); *m/z* (C.I.) 372 (28%, MH+), 204 (70%), 132 (56%), 71 (100%).

2-(6-Carboxyhex-5-yn-1-oyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (13, R = R′ = H; n = 1)
Sodium hydroxide (11 mg, 0.27 mmol) was added to a solution of the isoquinoline (13, R = Et; R′ = Me; n = 1) (40 mg, 0.11 mmol) in tetrahydrofuran (5 cm^3) and water (5 cm^3). The solution was stirred at room temperature for 2h, before the organic co-solvent was removed. The residual aqueous solution was acidified with 2M hydrochloric acid and extracted with ethyl acetate (3 x 10 cm^3). The extracts were combined and re-extracted with saturated sodium carbonate solution (3 x 10 cm^3). The combined aqueous extracts were acidified with 2M hydrochloric acid and extracted again with ethyl acetate (3 x 10 cm^3). The ethyl acetate extracts were combined, washed with water (2 x 10 cm^3), and brine (2 x 10 cm^3) and evaporated to yield the title compound as a pale yellow oil (28.4 mg, 82%) (a mixture of *E*- and *Z*-isomers, ratio ~ 1:1); υ_{max} (liquid film) cm^{-1} 3000 (br, O-H), 1710 (acid), 1645 (amide); δ_H 7.25 (4H, br, 4 x O-H), 7.10 (8H, m, aromatic protons), 5.34 (1H, dd, ^3J = 6.0 Hz, ^3J = 3.6Hz , 3-H), 4.81 (1H, d, ^2J = 17.4 Hz, 1-H), 4.80 (1H, m, 3-H), 4.64 (2H, s, 1-H_2), 4.50 (1H, d, ^2J = 17.4 Hz, 1-H), 3.15 (4H, m, 2 x 4-H_2), 2.55 (4H, m, 2 x CH_2-C=O), 2.40 (4H, m, 2 x CH_2-C≡C), 1.87 (4H, m, 2 x CH_2); *m/z* (C.I.) 316 (MH+, 3%), 253 (52%), 176 (100%), 132 (86%).

2-(7-Carboxyhept-6-yn-1-oyl)-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (13, R = R′ = H; n =2)
The isoquinoline (13, R = Et; R′ = Me; n = 2) (0.1 g, 0.27 mmol) and sodium hydroxide (25.9 mg, 0.65 mmol) in tetrahydrofuran (5 cm^3) and water (5 cm^3) were stored at room temperature for 1h. The solvent was removed under reduced pressure and the aqueous solution was acidified with 2M hydrochloric acid. The suspension was extracted with diethyl ether (2 x 10 cm^3), and the combined extracts re-extracted with sodium carbonate solution (3 x 10 cm^3). These aqueous extracts were acidified with dilute hydrochloric acid and again extracted with diethyl ether (3 x 10 cm^3). The combined phases were then washed with water (2 x 5 cm^3) and brine (2 x 5 cm^3) and then evaporated to afford an oil which was distilled (bulb to bulb under reduced pressure) to yield the title compound as a yellow oil (a mixture of *E*- and *Z*-isomers, ratio ~ 1:1) (81 mg, 91%); υ_{max} ($CHBr_3$) cm^{-1} 2900 (br, OH), 1713 (acid), 1640 (amide); δ_H 7.10 (8H, m, aromatic protons), 7.01 (4H, br, 4 x O-H), 5.33 (1H, dd, ^3J = 6.2 Hz, ^3J = 4.2 Hz, 3-H), 4.87 (1H, d, ^2J = 17.6 Hz, 1-H), 4.82 (1H, m, 3-H), 4.63 (2H, s, 1-H_2), 4.48 (1H, d, ^2J = 17.6 Hz, 1-H), 3.15 (4H, m, 2 x 4-H_2), 2.52 (4H, m, 2 x CH_2-CO), 2.35 (4H, m, 2 x CH_2-C≡C), 1.70 (8H, m, 2 x CH_2-CH_2); *m/z* (F.A.B.) 330 (100%, MH+), 176

(32%).

10-Acetoxycarbonyl-1,2,3,4,9-pentahydropentaleno[2,3-*a*]isoquinoline (14, R = Ac; n = 1)
The isoquinoline (13, R = R′ = H; n = 1) (31.5 mg, 0.1 mmol) in acetic anhydride (5 cm^3) was heated at *ca* 70°C for 3h. The solvent was removed and the remaining oil purified by preparative plate chromatography eluting with ethyl acetate : petrol (1:1) to yield the title compound as a yellow oil (10.9 mg, 37%); υ_{max} (liquid film) cm^{-1} 1790 (C=O), 1720 (C=O); δ_H 7.30 (4H, m, aromatic protons), 4.97 (2H, t, ^4J = 2.2 Hz, 4-H_2), 4.40 (2H, s, 9-H_2), 2.75 (4H, m, 1-H_2, 3-H_2), 2.46 (2H, m, 4-H_2), 2.27 (3H, s, CH_3); *m/z* (E.I.) 295 (23%, M+), 253 (64%), 236 (45%), 208 (100%) [Found: *m/z* 295.1214 $C_{18}H_{17}NO_3$ requires: 295.1208].

11-Acetoxycarbonyl-1,2,3,4,5,10-hexahydroindeno[2,3-*a*]isoquinoline (14, R = Ac, n = 2)
The isoquinoline (13, R = R′ = H; n = 2) (70 mg, 0.2 mmol) in acetic anhydride (10 cm^3) was heated at 60-70°C for 2h. The solvent was removed under reduced pressure and the residue purified by column chromatography eluting with ethyl acetate : petrol (1:9 - 1:1) to yield the title compound as a yellow oil (26.5 mg, 43%); υ_{max} (liquid film) cm^{-1} 1780 (C=O), 1705 (C=O); δ_H 7.25 (4H, m, aromatic proton), 4.91 (2H, s, 5-H_2), 4.40 (2H, s, 10-H_2), 2.70 (2H, t, ^3J = 7Hz, 1-H_2), 2.61 (2H, t, ^3J = 7Hz, 4-H_2), 2.31 (3H, s, CH_3), 1.80 (4H, m, 2-H_2, 3-H_2); *m/z* (E.I.) 309 (47%, M), *267 (95%), 250 (33%), 222 (100%).
*There was a delay of about two weeks before this sample was analysed and we note that this mass corresponds to that required by the molecular ion of the corresponding tetracyclic acid. After the elapse of a further week, the mol. ion peak of the anhydride was not detected in the mass spectrum of the sample, instead the mol. ion of the acid was now the peak of highest mass [Found: *m/z* 267.1280 $C_{17}H_{17}NO_2$ requires: 267.1259]. The infrared spectrum of the crude sample (liquid film) showed the absence of the anhydride bands exhibited by the parent compound, but exhibited a broad hydroxy absorption at υ_{max} 3100 cm^{-1} and a broad carbonyl band at 1710-1700 cm^{-1}.

Ethyl 2-(dec-7-yn-1-oyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (15, R = Et)
To a solution of 7-decynoic acid (0.50 g, 3 mmol) and cyanuric chloride (0.28 g, 1.5 mmol) in dry acetone (10 cm^3) was added triethylamine (0.4 cm^3, 3 mmol). The solution was warmed at 40°C for 2h, ethyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate (0.62 g, 3 mmol) and sodium carbonate (0.31 g, 3 mmol) were then added and the reaction mixture was stored for 3h at about 40°C. After filtration, the acetone was removed from the filtrate and the remaining oil was re-dissolved in a mixture of diethyl ether (45 cm^3) and dichloromethane (5 cm^3). The solution was washed with dilute hydrochloric acid (2 x 25 cm^3), 2M sodium hydroxide (2 x 15 cm^3), and water (2 x 15 cm^3). The solvent was removed and the residue was purified by column chromatography eluting with ethyl acetate: petrol (1:9-1:2) to yield the title compound as a clear yellow oil (0.85 g, 75%); υ_{max} (liquid film) cm^{-1} 1720 (C=O, ester), 1625 (amide); δ_H (mixture of isomers, ratio ~ 1:1) 7.20 (8H, m, aromatic protons), 5.47 (1H, dd, ^{3}J = 3.6 Hz, ^3J = 6.0 Hz, 3-H), 4.92 (1H, d, ^2J = 17.4 Hz, 1-H), 4.83 (1H, dd, ^3J = 3.1 Hz, ^3J = 5.5 Hz , 3-H), 4.70 (2H, s, 1-H_2), 4.53 (1H, d, ^2J = 17.4 Hz, 1-H), 4.06 (4H, m, 2 x CH_2-CH_3), 3.22 (4H, m, 2 x 4-H_2), 2.52 (2H, t, ^3J = 7.8 Hz, CH_2-CO), 2.51 (2H, t, ^3J =

7.7 Hz, CH_2-CO), 2.22 (4H, m, 2 x CH_2-C≡C), 2.11 (4H, m, 2 x CH_2-C≡C), 1.81 (4H, m, 2 x CH_2CO), 1.53 (8H, m, 4 x CH_2), 1.13 (3H, t, ^3J = 7.1 Hz, CH_3), 1.07 (3H, t, ^3J = 7.1 Hz, CH_3), 0.96 (3H, t, ^3J = 7.3 Hz, CH_3), 0.95 (3H, t, ^3J = 7.3 Hz, CH_3); *m/z* (C.I.) 356 (100%, MH+), 204 (82%), 132 (66%), 130 (29%).

2-(Dec-7-yn-1-oyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (15, R = H)

Method A

Ethyl 2-(dec-7-yn-1-oyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (15, R = Et) (99 mg, 0.28 mmol), 1,4,7,10,13,16-hexaoxacyclooctadecane (22 mg, 0.084 mmol) and potassium superoxide (60 mg, 0.84 mmol) were added to dry benzene (5 cm^3). The solution was maintained at room temperature overnight and then water (5 cm^3) and 2M hydrochloric acid were added until the solution was acidic. The organic layer which separated was collected, and the aqueous solution was extracted with diethyl ether (2 x 20 cm^3). The extracts and the organic layer were combined and re-extracted with 2M sodium bicarbonate solution (3 x 20 cm^3). These extracts were combined and acidified with 2M hydrochloric acid, then re-extracted with diethyl ether (3 x 20 cm^3). The combined extracts were washed with water (2 x 10 cm^3) and brine (2 x 10 cm^3), and then finally dried, before the solvent was removed to leave an oil. This was distilled under reduced pressure to yield the title compound as a pale yellow oil (70 mg, 77%); υ_{max} (liquid film) cm^{-1} 1720 (acid), 1630 (amide); δ_H (a mixture of *E*- and *Z*-isomers, ratio ~ 1:1) 7.22 (8H, m, aromatic protons), 5.40 (1H, dd, ^3J = 6.4 Hz, ^3J = 4.4 , 3-H), 5.80 (2H, brs, 2 x O-H), 4.94 (1H, d, ^2J = 17.6 Hz, 1-H), 4.86 (1H, dd, ^3J = 5.1 Hz, ^3J = 2.6 Hz, 3-H), 4.68 (1H, d, ^2J = 16.4 Hz, 1-H), 4.64 (1H, d, ^2J = 16.4 Hz, 1-H), 4.49 (1H, d, ^2J = 17.6 Hz, 1-H), 3.25 (4H, m, 2 x 4-H_2), 2.51 (2H, t, ^3J = 7.6 Hz, CH_2-CO), 2.50 (2H, t, ^3J = 7.5 Hz, CH_2-CO), 2.21 (4H, m, 2 x CH_2-C≡C), 2.11 (4H, m, 2 x CH_2-C≡C), 1.80 (4H, m, 2 x CH_2CO), 1.50 (8H, m, 4 x CH_2), 0.95 (6H, t, ^3J = 7.3 Hz, 2 x CH_3); *m/z* (C.I.) 328 (46%, MH+), 176 (45%), 151 (42%), 132 (60%), 109 (100%).

Method B

Ethyl 2-(dec-7-yn-1-oyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (99 mg) and sodium hydroxide (13 mg) were dissolved in tetrahydrofuran (5 cm^3) and water (5 cm^3). The solution was stored at room temperature for 12h and then acidified with 2M hydrochloric acid. The organic layer was separated and the remaining aqueous phase was extracted with diethyl ether (2 x 20 cm^3). The extracts were combined and re-extracted with 2M sodium bicarbonate solution (3 x 20 cm^3). After acidification with 2M hydrochloric acid, the sodium bicarbonate extracts were re-extracted with diethyl ether (3 x 20 cm^3). The combined diethyl ether extracts were washed with water (2 x 10 cm^3) and with brine (2 x 10 cm^3). Removal of the solvent from the dry organic phase gave an oil which was distilled (bulb to bulb) under reduced pressure to yield the title compound as a light yellow oil (72 mg, 79%).

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