A facile route to pyrroles, isoindoles and hetero fused analogues

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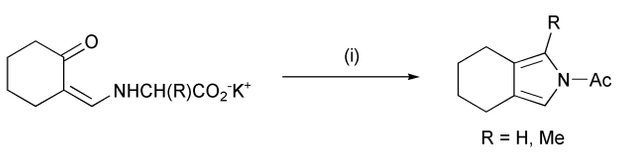
Enamino acids derived from 1,2-dimethylaminomethylene- or 1,2-hydroxymethylene-carbonyl compounds and amino acids undergo a decarboxylative cyclisation to pyrroles, isoindoles and other fused pyrroles. A two atom ring expansion occurs preferentially with enamino acids from cyclohexane-1,3-diones and α-alkyl-α-amino acids leading to oxocino[2,3-*c*]pyrroles.

Introduction

The pyrrole unit[1] occurs in a range of naturally occurring compounds, pharmaceutical products and polymers.[2] The synthesis of this ring system has been widely investigated and has featured in a number of reviews.[3,4] Nevertheless, ring syntheses of pyrroles unsubstituted at the 2- and 5-positions and routes which involve formation of the C-2–C-3 bond are uncommon.[4a] Probably the single most convenient entry to compounds of this type involves the condensation of α,β-unsaturated ketones, esters and nitriles and nitroalkenes with tosylmethyl isocyanide (TosMIC) and related compounds.[4b] Several routes to pyrroles involve the reaction of 1,3-dicarbonyl compounds and α-amino acids, but in all of these examples a carboxylate function is retained in the pyrrole.[5] Since its discovery in 1973 by Zav'yalov *et al.*[6] the efficient synthesis of pyrroles based on the acetic anhydride-promoted cyclisation of the salt of an enamino acid (Scheme 1) has



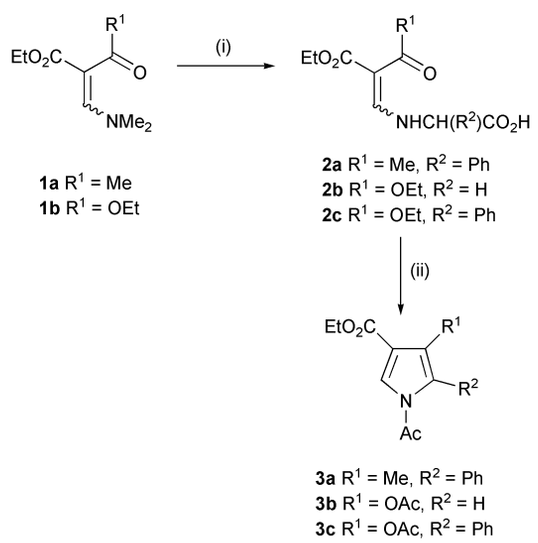
Scheme 1 *Reagents and conditions*: (i) Ac_2O, Δ.

been rarely used.[7] We now report the synthesis of some novel substituted pyrroles and fused analogues through the application of this methodology and describe a unique ring expansion reaction that affords the oxocino[2,3-*c*]pyrrole system.

Discussion

Dimethylaminomethylene carbonyl compounds **1a**[8] and **1b**[9] were obtained by standard protocols. Their addition–elimination reaction with DL-2-phenylglycine and glycine in aqueous ethanol containing sodium acetate gave the enamino acids **2a**–**c** in high yield (Scheme 2). The ^{1}H NMR spectrum of **2a** indicated that an unequal mixture (*ca.* 3 : 1) of *E*- and *Z*-isomers had been isolated. In the former, the NH proton is strongly H-bonded to the acetyl carbonyl resulting in a low field signal (δ 11.68). In the *Z*-isomer intramolecular H-bonding is weaker because of participation of the ester group as evidenced by the upfield shift of this signal to δ 10.06.

A deep red colour was instantaneously produced when the enamino acids **2a**–**c** were heated with acetic anhydride containing triethylamine and this was accompanied by the vigorous evolution of CO_2 (lime water bubbler) as the internal reaction temperature reached reflux. After *ca.* 30 minutes, the reaction mixture was cooled and subjected to an aqueous work-up. TLC examination of the crude reaction mixtures revealed the presence of a fast running major component contaminated with dark base line material rendering initial purification by flash chromatography easy.

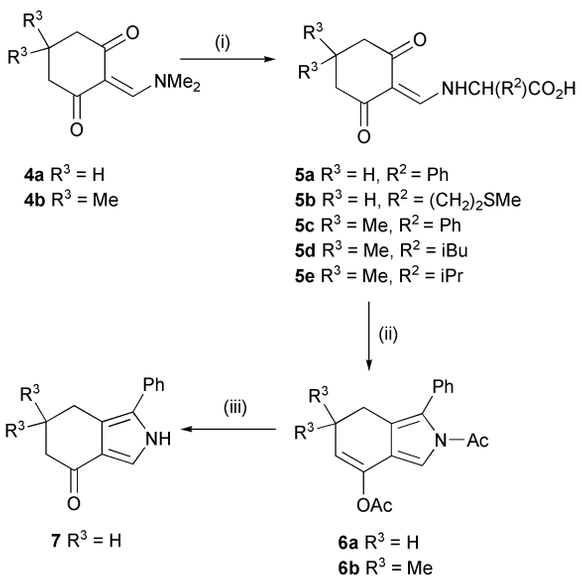


Scheme 2 *Reagents and conditions*: (i) 1.05 eq. α-amino acid, 1.05 eq. $NaOAc{\cdot}3H_2O$, aq. EtOH, Δ; (ii) Ac_2O, Et_3N, Δ.

The cyclisation of the isomeric enamino acids **2a** proceeded with the expected regioselectivity of cyclisation on to the more electrophilic ketonic carbonyl group rather than the ester function to afford a single pyrrole, **3a**, confirmed by the presence of signals in its ^{1}H NMR spectrum associated with the ethyl ester moiety. The pyrrole ring proton resonates significantly downfield at δ 7.93 as a consequence of the adjacent ester function; the 4-methyl group and the *N*-acetyl function are observed at δ 2.08 and δ 2.21, respectively.

Of particular note is the relatively efficient preparation (*ca.* 40% overall yield) of the 2,5-unsubstituted pyrrole **3b**. Existing routes to compounds of this type are often laborious and low yielding.[3c,f,h,4a] The ^{1}H NMR spectrum of this compound displayed the expected singlets at δ 7.25 and 7.78 for 5-H and 2-H respectively.

Cyclohexane-1,3-dione and dimedone were converted according to literature procedures into the respective enamino ketones **4a**[10] and **4b**,[11] which were reacted with a range of α-amino acids according to the above method to afford the enamino acids **5a**–**e** (Schemes 3 and 4). The facile addition



Scheme 3 *Reagents and conditions*: (i) 1.05 eq. α-amino acid, 1.05 eq. $NaOAc·3H_2O$, aq. EtOH, Δ; (ii) Ac_2O, Et_3N, Δ (iii) AcOH, c. HCl, Δ.

and elimination of amino acids to 5,5-dimethyl-2-(dimethylaminomethylene)cyclohexane-1,3-dione **4b** has been advocated as an amino protection–deprotection sequence useful in solid phase synthesis.[12] The cyclisation of **5a**–**e** was then investigated. Heating the enamino acids derived from DL-2-phenylglycine (**5a** and **5c**) with acetic anhydride containing Et_3N gave the expected dihydroisoindoles **6a** and **6b**, respectively. The ^{1}H NMR spectra of these compounds displayed a singlet at *ca.* δ 7.1 for the pyrrole ring proton. The remaining carbonyl function of the starting dione had been converted to the enol acetate as indicated by the presence of a signal at ~δ 5.4 for the alkenic proton and at ~δ 2.2 for the OAc group. Compound **6a** was efficiently de-acetylated on heating in aqueous acetic acid containing conc. HCl to afford **7** (92%). The presence of a broad singlet at δ 9.7 for the pyrrole NH and the absence of the signal for the alkenic proton associated with the enol acetate unit in the ^{1}H NMR spectrum of **7** indicated that both acetyl functions had been removed. The ^{13}C NMR of this compound displayed a low field signal at δ 196.9 for the carbonyl group carbon.

In marked contrast to our observation noted for the cyclisation of the enamino acids **2a**–**c** and **5a**,**c**, only slight evolution of CO_2 was observed when enamino acids **5b**,**d**, and **e** were heated in acetic anhydride containing Et_3N, suggesting that some other reaction sequence had occurred (Scheme 4), although the ^{1}H NMR spectrum of the product derived from **5b** appeared to be in agreement with structure **8a**. However, HRMS and elemental analysis data did not support this structure, instead suggesting that the molecule contained an additional CO_2. The presence of a third low field signal between δ 168–169 in the ^{13}C NMR spectrum confirmed these data; this chemical shift range is indicative of a carboxylate-type carbon. Attempts to obtain a crystal structure of this compound were unsuccessful since the compound decomposed during repeated recrystallisation.

We next turned our attention to the product obtained from the cyclisation of **5d**. The ^{1}H NMR spectrum of this compound recorded at ambient temperature (24 °C) was uninformative since many signals in the range δ 0.5–3.5 were poorly resolved (Fig. 1), but a signal at δ 7.7, a chemical shift that is comparable

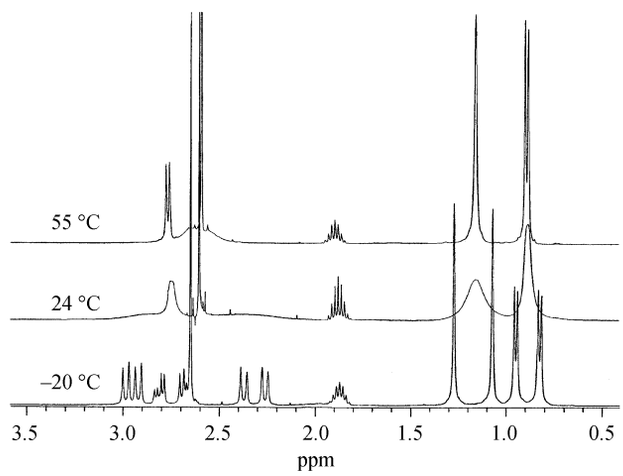
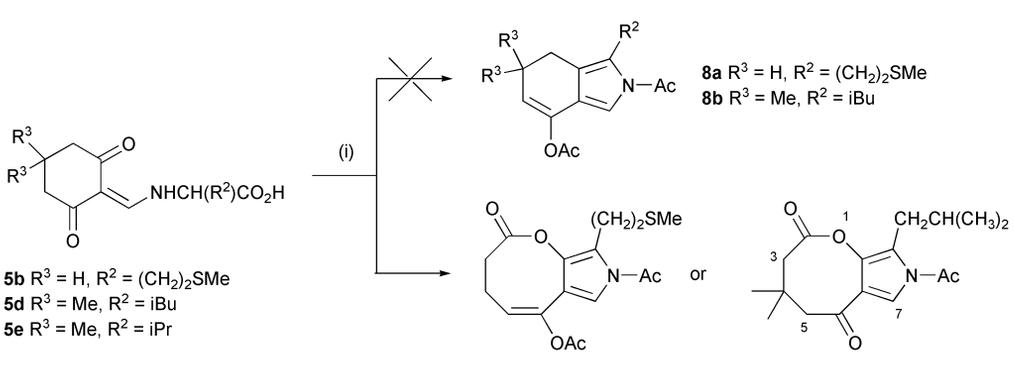


Fig. 1 Variable temperature ^{1}H NMR spectra (δ 0.5–3.5) for oxocinopyrrole **9b**.

to that of 2-H in **3a**–**c**, was clear. However, dramatic improvements in resolution were achieved by recording the spectrum at either elevated (55 °C) or reduced (−20 °C) temperature (Fig. 1) indicating that the molecule is undergoing conformational interconversion. Once again the ^{1}H NMR spectrum of this product appeared to suggest that isoindole **8b** had been isolated, though this data was again incompatible with other spectroscopic evidence. The ^{13}C NMR spectrum displayed a signal for an additional carbon atom at *ca.* δ 169. Infrared spectroscopy was inconclusive with only two bands present in the C=O stretching region. However, X-ray crystallography of this compound indicated the oxocino[2,3-*c*]pyrrole structure **9b**.[13] With the structure of **9b** to hand, it is evident that the product from the cyclisation of **5b** is the related acetoxy oxocinopyrrole **9a**. It is noteworthy that the ^{1}H NMR spectrum of **9a** is well resolved at ambient temperature as a consequence of the rigidity imparted into the oxocine ring by the enol acetate function. The absence of this structural feature in **9b** allows



Scheme 4 *Reagents and conditions*: (i) Ac_2O, Et_3N, Δ.

broadening of the signals in its ^{1}H NMR spectrum as a consequence of the oxocine ring existing in equilibrium between several conformers.[14]

The low temperature ^{1}H NMR spectrum of **9b** merits some further comment. The four methylene protons (3-C and 5-C) are non-equivalent and each gives rise to a doublet with J 12.3 Hz. In order to confirm this coupling a ^{1}H–^{1}H COSY experiment at −40 °C was recorded (Fig. 2). This revealed that the

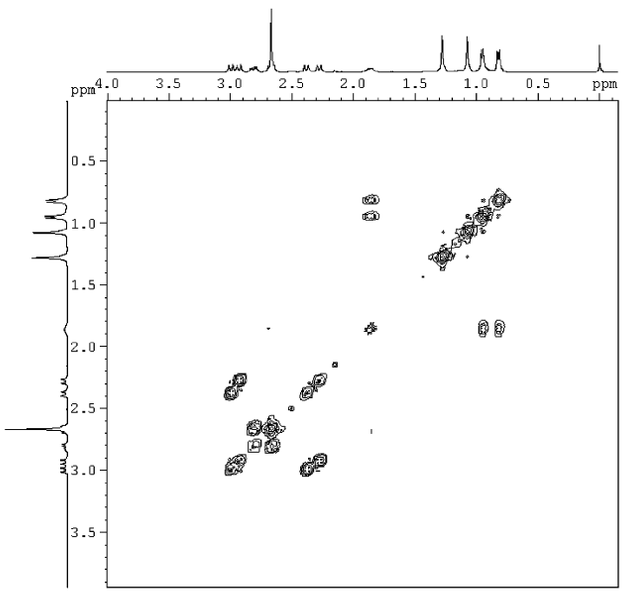


Fig. 2 Low temperature (−40 °C) ^{1}H–^{1}H COSY spectrum for oxocinopyrrole **9b**.

12.3 Hz coupling was not due to a geminal interaction but was instead a consequence of one of the 3-H protons coupling to one of the 5-H protons, *i.e.* 4-bond coupling. The magnitude of this coupling in **9b** is quite unusual since ^4J is typically 1–2 Hz.[15a] However, substantially larger ^4J coupling constants have been reported for rigid bicyclic systems where more than one coupling pathway may operate.[15b]

In order to confirm this unexpected long-range relationship between 3- and 5-H we selectively decoupled the doublet at δ 2.28 (3-H). Whilst some loss of resolution of the doublet at δ 2.38 was observed due to the decoupling pulse employed, more significantly the signal at δ 2.93 resolved into a singlet confirming the coupling arrangement (Fig. 3).

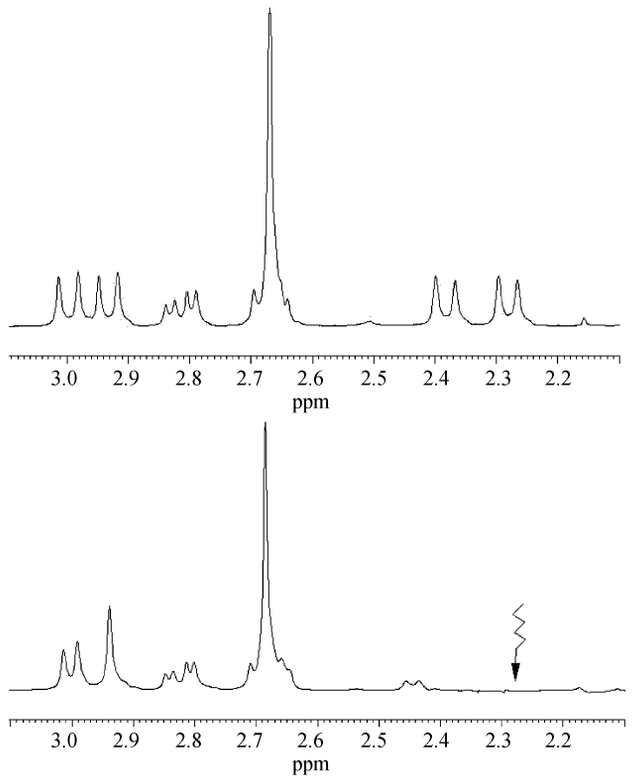
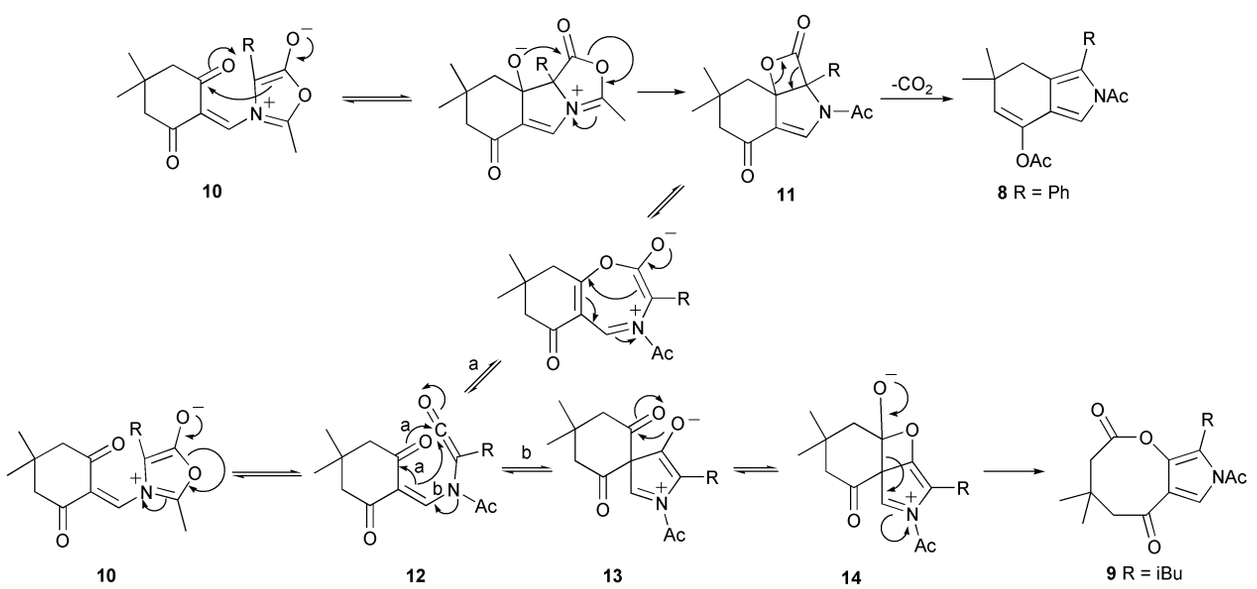


Fig. 3 Low temperature (−40 °C) ^{1}H NMR homo decoupling of the doublet at δ 2.28 in oxocinopyrrole **9b**.

Unfortunately the product derived from heating enamino acid **5e**, derived from **4b** under the standard conditions, decomposed on storage at room temperature.

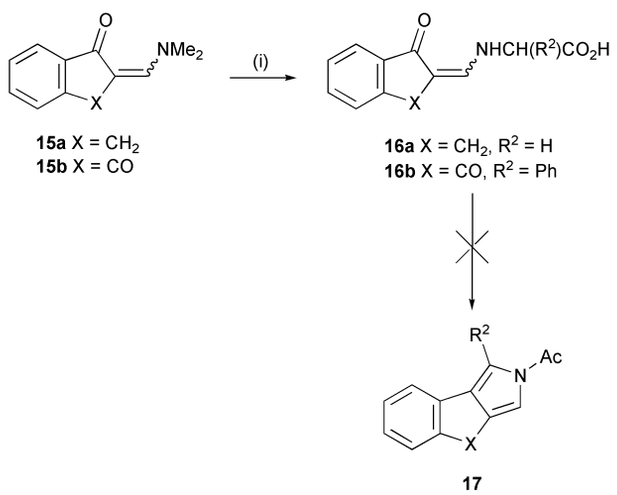
A possible mechanism for the formation of the isoindoles **8** and oxocinopyrroles **9** is outlined in Scheme 5. We favour pathways involving the intermediacy of a ketene since their formation *via* elimination from mixed anhydrides is especially facile under basic conditions, many examples of this for *N*- and *O*- linked alkanoic acids have been documented.[16a] The acylation of *N*-substituted amino acids proceeds with cyclodehydration to provide mesoionic 1,3-oxazolium-5-olates (münchnones)[16b] and evidence has accrued that these are tautomeric with *N*-acyl ketenes.[16c] The mesoionic heterocycle **10** may react by two distinct pathways to afford **8**. We propose that, when R = phenyl, the extended conjugation imparts



Scheme 5

stability to the münchnone tautomer which then attacks the proximal C=O group. The alkoxide species thus generated forms the lactone **11** with concomitant oxazole ring cleavage. Alternatively, cyclisation of the valence tautomer **12** (path a) provides an oxazepine intermediate which contracts to **11**. It is pertinent to note that a similar dipolar species, a dioxepine, has been invoked in the Ac_2O-mediated cyclisation of *o*-acylphenoxyalkanoic acids to benzofurans.[16d] Cycloreversion of CO_2 from **11** and subsequent *O*-acylation completes the route to the dihydroisoindoles **8**. Conversely, when R = alkyl, the münchnone **10** undergoes ring–chain tautomerism to the *N*-acyl ketene **12**. Intramolecular acylation of the enamine function affords the spirocycle **13** (path b). Oxetane ring formation and subsequent ring cleavage of **14** effects the ring expansion to the oxocinopyrrole system **9**.

It was of interest to explore the versatility of this route for the formation of other fused pyrrole containing systems. Thus indan-1-one and indane-1,3-dione were readily converted into the dimethylaminomethylene ketones **15a**,[17] **b**[10] respectively. Treatment with an ethanolic solution of an α-amino acid containing sodium acetate gave the respective enamino acids **16a**,**b** in high yield (Scheme 6). Unfortunately attempts to

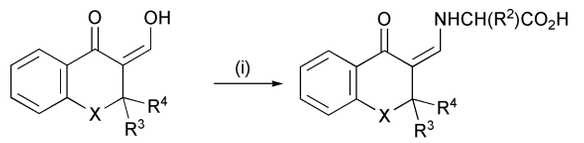


Scheme 6 *Reagents and conditions*: (i) 1.05 eq. α-amino acid, 1.05 eq. $NaOAc·3H_2O$, aq. EtOH, Δ.

cyclise these compounds in the usual manner gave only tarry multicomponent reaction mixtures from which no indeno[*c*]-fused pyrroles **17** could be isolated. It is possible that the postulated intermediate in the formation of **17**, a tricyclic 5–5–4 system (*cf.* **11**), is too strained to form thus preventing the cycloreversion of the lactone ring that ultimately affords the product.

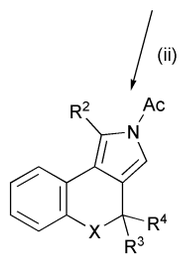
2-Hydroxymethylene-1-tetralone **18a** is readily available by the formylation of 1-tetralone.[18] Treatment of this β-dicarbonyl compound with glycine according to the above procedure gave enamino acid **19a** as bright yellow microcrystals in 74% yield. Enamino acids **19b**–**e** were similarly obtained from the appropriate amino acids (Scheme 7). With the exception of **19a** from which only a small amount of 1-tetralone could be isolated from the tarry residue, the cyclisation of these enamino acids proceeded smoothly to give the benzo[*e*]isoindoles **20b**–**e**.

The cyclisation of **19d**, derived from DL-methionine sulfoxide, yielded two products that were separated by elution from silica. The less polar component was characterised as acetoxymethylene-1-tetralone **21**.[19] The nitrogen containing product was not the expected benzo[*e*]isoindole containing the $(CH_2)_2S(O)CH_3$ group but was instead **20d**, arising from a regiospecific Pummerer rearrangement[20] of the $(CH_2)_2S(O)CH_3$ function under the reaction conditions to provide the $(CH_2)_2SCH_2OAc$ side-chain. The ^1H NMR spectrum of this compound displayed singlets at δ 2.09 and 2.55 for the *O*- and



18a X = CH_2, R^3 = R^4 = H
18b X = $(CH_2)_2$, R^3 = R^4 = H
18c X = O, R^3 = R^4 = Me
18d X = O, R^3, R^4 = $(CH_2)_5$
18e X = S, R^3 = H, R^4 = Me
18f X = S, R^3 = R^4 = Me

19a X = CH_2, R^2 = R^3 = R^4 = H
19b X = CH_2, R^2 = Ph, R^3 = R^4 = H
19c X = CH_2, R^2 = $(CH_2)_2SMe$, R^3 = R^4 = H
19d X = CH_2, R^2 = $(CH_2)_2S(O)Me$, R^3 = R^4 = H
19e X = CH_2, R^2 = $(CH_2)_2CO_2Me$, R^3 = R^4 = H
19f X = $(CH_2)_2$, R^2 = R^3 = R^4 = H
19g X = $(CH_2)_2$, R^2 = $(CH_2)_2SMe$, R^3 = R^4 = H
19h X = O, R^2 = H, R^3 = R^4 = Me
19i X = O, R^2 = H, R^3, R^4 = $(CH_2)_5$
19j X = S, R^2 = R^3 = H, R^4 = Me
19k X = S, R^2 = Ph, R^3 = H, R^4 = Me
19l X = S, R^2 = H, R^3 = R^4 = Me
19m X = S, R^2 = Ph, R^3 = R^4 = Me
19n X = S, R^2 = R^3 = R^4 = Me



20a X = CH_2, R^2 = R^3 = R^4 = H
20b X = CH_2, R^2 = Ph, R^3 = R^4 = H
20c X = CH_2, R^2 = $(CH_2)_2SMe$, R^3 = R^4 = H
20d X = CH_2, R^2 = $(CH_2)_2SCH_2OAc$, R^3 = R^4 = H
20e X = CH_2, R^2 = $(CH_2)_2CO_2Me$, R^3 = R^4 = H
20f X = $(CH_2)_2$, R^2 = R^3 = R^4 = H
20g X = $(CH_2)_2$, R^2 = $(CH_2)_2SMe$, R^3 = R^4 = H
20h X = O, R^2 = H, R^3 = R^4 = Me
20i X = O, R^2 = H, R^3, R^4 = $(CH_2)_5$
20j X = S, R^2 = Ph, R^3 = H, R^4 = Me
20k X = S, R^2 = H, R^3 = R^4 = Me
20l X = S, R^2 = Ph, R^3 = R^4 = Me

Scheme 7 *Reagents and conditions*: (i) 1.05 eq. α-amino acid, 1.05 eq. $NaOAc·3H_2O$, aq. EtOH, Δ; (ii) Ac_2O, Et_3N, Δ.

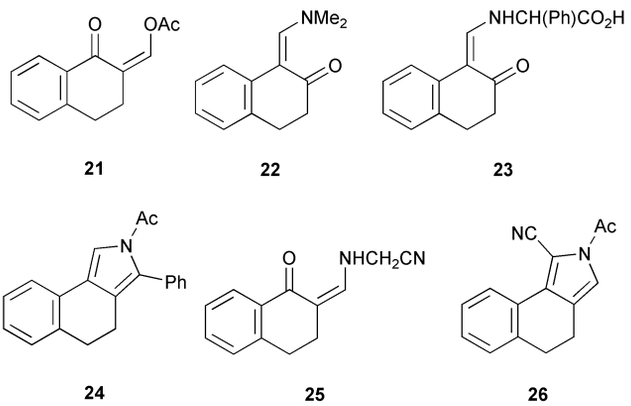
N-acetyl groups and a further singlet at δ 5.29 was assigned to the methylene function of the *O*,*S*-acetal.

We next explored the application of enamino acids **19f**,**g** derived from the tetralone homologue, 2-hydroxymethylene-1-benzosuberone **18b**,[21] for the formation of further fused pyrrroles (Scheme 7). Both **19f** and **19g** cyclised smoothly to afford the expected pyrroles **20f**,**g** in good yield.

From our research projects on chromanones and thiochromanones we had access to a range of 3-hydroxymethylene-(thio)chromanones **18c**–**f**.[22,23] The enamino acids, **19h** and **19i**, derived from glycine and the 3-hydroxymethylenebenzopyrans **18c** and **18d** respectively, cyclised to give the benzopyrano[3,4-*c*]pyrroles **20h** and **i**. The benzopyrano[3,4-*c*]pyrrole ring system has recently been accessed by the photogeneration of radicals from α-stannyl ethers and their conjugate addition to enones,[24] through the displacement of the iron residue in 4-[η^5-cyclopentadienyl(dicarbonyl)iron]-2*H*-chromene-3-carbaldehyde with primary amines[25] and by the Fischer-Fink reaction of 4-chloro-3-formylcoumarins with amino acid esters.[26] The benzopyrano[3,4-*c*]pyrrole unit has found application in photocrosslinkable polymers[27] and as the structural unit in some methine dyes.[28] The enamino acids **19j**–**n**, derived from hydroxymethylenethiochromanones **18e** and **f**, gave mixed results on heating in Ac_2O–Et_3N. Compounds **19l** and **m** obtained from the 2,2-dimethyl-3-hydroxymethylenethiochromanone **18f** gave the expected benzothiopyrano[3,4-*c*]pyrroles **20k** and **l** in *ca.* 50% yield and constitutes the first synthesis of this ring system.

However, we were unable to obtain any benzothiopyrano[3,4-*c*]-pyrrole from the attempted cyclisation of enamino acid **19n** which was derived from DL-alanine and **18f**. The enamino acid **19j** derived from glycine and the 3-hydroxymethylene-2-methylthiochromanone **18e** also failed to afford any isolable pyrrole, although, that derived from **18e** and DL-2-phenylglycine (**19k**) gave the pyrrole **20j** in a respectable 64% yield.

1-Dimethylaminomethylene-2-tetralone **22** was prepared by heating 2-tetralone in *N*,*N*-dimethylformamide dimethyl acetal.[29] Subsequent reaction with DL-2-phenylglycine in aqueous ethanol containing $NaOAc{\cdot}3H_2O$ gave the enamino acid **23** in 53% yield. Cyclisation of **23** using the standard protocol gave the isomeric 3-phenylbenzo[*e*]isoindole **24** after elution from silica in 56% yield.

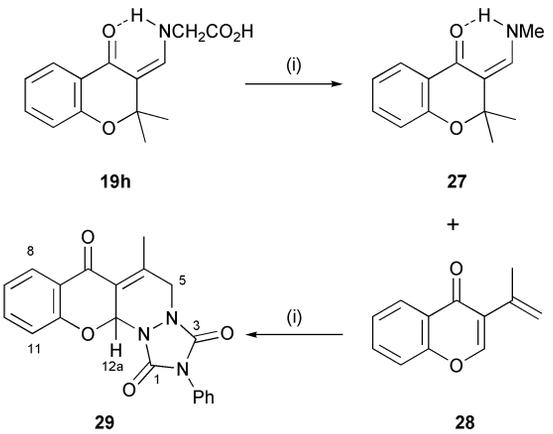


The ^{1}H NMR spectra of the fused pyrroles and isoindoles **20** merit some comment. For the 1-alkyl substituted compounds **20c**,**d**,**e** and **g** the pyrrole ring proton (3-H) resonates at *ca*. δ 6.9. This signal is shifted downfield by *ca*. 0.3 ppm on replacement of the alkyl group by a phenyl ring *e.g*. **20b**,**j** and **l**. The pyrrole ring proton (1-H) of the isomeric 3-phenyl substituted isoindole **24** appears further downfield at δ 7.64. Noticeably 9-H resonates at δ 7.54 in **24** but is shifted significantly upfield to δ 6.69 in **20b**. It would appear that 9-H lies in the shielding zone of the 1-phenyl substituent, suggesting that the disposition of the phenyl ring must approach perpendicularity with respect to the major plane of the molecule. A similar situation has been previously noted for some related benzothiopyranopyrazoles.[23] In the ^{1}H NMR spectra of **20d** and **20j** 3-H appeared as a doublet with J = 1.0 Hz as a result of allylic coupling to 4-H. In the case of 1,3-unsubstituted fused pyrroles, (**20a**, **20f**, **20h**, **20i**, **20k**) the signals from 1-H and 3-H overlap with the aromatic signals.

The generality of this pyrrole ring synthesis was investigated further by reacting hydroxymethylene **18c** with 2-amino-acetonitrile which under routine conditions gave the enamino nitrile **25** in high yield. However, attempts to cyclise this nitrile to the pyrrolecarbonitrile **26** failed.

It is noteworthy that the formation of the pyrroles **3**, isoindoles **6** and the fused analogues **9**, **20** and **24** is chemo-selective, and in no instances did we observe the presence of any α-amino ketones resulting from a Dakin–West reaction.[30] Furthermore the formation of the oxocinopyrroles **9** only occurs with the combination of an α-alkyl-α-amino acid and a cyclohexane-1,3-dione; replacement of either one of these components results in the formation of the pyrrole or isoindole.

We next explored the possibility of a thermal cyclisation of enamino acid **19h**. Heating **19h** in bromobenzene effected the gradual evolution of CO_2 and resulted in the formation of two products that were resolved by flash chromatography (Scheme 8). The less polar fraction was characterised as the 3-(methyl-aminomethylene)chromanone **27** formed through decarboxylation of the glycine residue. In the ^{1}H NMR spectrum of this compound the NH proton resonated at δ 10.23 as a consequence of intramolecular H-bonding to the carbonyl



Scheme 8 *Reagents and conditions*: (i) PhBr, Δ (ii) PTAD, CH_2Cl_2, rt.

function and the alkenyl proton appeared at δ 6.83, typical for such aminomethylene compounds.[31] The more polar fraction was characterised as 3-isopropenylchromone **28** and had physical and spectroscopic properties comparable with authentic material.[22] The formation of 3-alkenyl- chromones[22] and thiochromones[23] by the rearrangement of 3-hydroxy-methylene(thio)chromanones has been reported by us previously though in both instances the presence of acid was used to effect the rearrangement. The alkenylchromone **28** was subsequently reacted with 4-phenyl-1,2,4-triazoline-3,5-dione[32] (PTAD) in dichloromethane at room temperature to afford the novel fused tetracycle **29** in 92% yield. The ^{1}H NMR spectrum of **29** displayed an AB system for 5-H with J = 17.7 Hz. The methine proton, 12a-H, appeared as a singlet at δ 6.83, a feature that confirmed that the double bond had not migrated into the pyran ring, a process that has been observed with cyclo-additions to 2-styrylchromones.[33] 8-H resonates furthest downfield of the aromatic signals due to its proximity to the anisotropic carbonyl group at C-7.

In conclusion, this route to the pyrrole system is highly versatile, since it offers potential for the formation of novel 2,5-unsubstituted pyrroles when glycine is employed as the α-amino acid, is compatible with a range of α-amino acids and α-hydroxy- and α-amino-methylene carbonyl compounds, is applicable to the synthesis of 3-hydroxypyrrole derivatives, isoindoles and fused pyrrole derivatives, and provides facile access to the novel oxocino[2,3-*c*]pyrrole ring system by a two atom ring expansion process.

Experimental

Melting points were determined in capillary tubes and are uncorrected. Distillations were performed using a Kugelrohr (Buchi GKR-50 Glass Tube Oven) and all boiling points quoted relate to the oven temperature at which the distillation commenced. Fourier transform infrared spectra were recorded on a Mattson Polaris spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker WM 250 or Avance 400 MHz or a JEOL λ series 400 MHz instrument for solutions in $CDCl_3$ unless stated otherwise; coupling constants J are given in Hz. Flash chromatographic separations were performed on chromatography silica as supplied by Fluorochem Ltd. (MPD 40–63μ) according to the published procedure.[34]

General method for the preparation of carboxymethylamino-methylene derivatives

The dimethylamino- and hydroxy-methylene compound (15 mmol) was dissolved in ethanol (35 cm^3) and a solution of the amino acid (18 mmol) and sodium acetate trihydrate (18 mmol) in the minimum volume of aqueous ethanol to effect complete dissolution was added in a single portion. The resulting

solution was refluxed for 4 h. and then reduced in volume to *ca*. 25 cm^3. The product was precipitated by the addition of ice–water (40 cm^3) and the pH of the solution adjusted to ~6 with dilute hydrochloric acid (2 M, aq.). The precipitate was collected by vacuum filtration, washed thoroughly with cold water and air-dried. The following compounds were obtained by this protocol.

1 DL-(*E*)- and DL-(*Z*)-Ethyl 2-(1-carboxy-1-phenylmethylaminomethylene)-3-oxobutanoate 2a. From **1a** and DL-2-phenylglycine as a pale yellow solid (yield 73%), mp 128–130 °C; ν_{max}(KBr) 3440, 2983, 2517, 1729, 1691 cm^{-1}; δ_H (major *E*-isomer) 1.22 (3H, t, *J* 7.1, CH_2CH_3), 2.45 (3H, s, Me), 4.12 (2H, q, *J* 7.1, CH_2CH_3), 5.14 (1H, d, *J* 6.9, NC*H*CO_2H), 7.36–7.38 (5H, m, Ar–H), 7.94 (1H, d, *J* 13.9, alkenyl-H), 11.19 (1H, br s, CO_2H), 11.68 (1H, m, NH); δ_H (minor *Z*-isomer) 1.32 (3H, t, *J* 7.2, CH_2CH_3), 2.39 (3H, s, Me), 4.24 (2H, q, *J* 7.2, CH_2CH_3), 5.18 (1H, d, *J* 6.9, NC*H*CO_2H), 7.34–7.36 (5H, m, Ar–H), 8.19 (1H, d, *J* 13.8, alkenyl-H), 10.06 (1H, m, NH), 11.19 (1H, br s, CO_2H) (Found: C, 61.7; H, 5.9; N, 4.7. $C_{15}H_{17}NO_5$ requires C, 61.8; H, 5.9; N, 4.8%).

2 Diethyl 2-(1-carboxymethylaminomethylene)propane-1,3-dicarboxylate 2b. From **1b** and glycine as a fluffy off-white solid (yield 69%), mp 138–140 °C; ν_{max}(KBr) 3313, 2990, 1715, 1680, 1626 cm^{-1}; δ_H 1.65 (6H, m, 2 × CH_2CH_3), 4.04 (6H, m, 2 × CH_2CH_3, NCH_2CO_2H), 7.80 (1H, d, *J* 14.2, alkenyl-H), 9.15 (1H, m, NH), 9.60 (1H, br s, CO_2H) (Found: C, 49.1; H, 6.1; N, 5.7. $C_{10}H_{15}NO_6$ requires C, 49.0; H, 6.2; N, 5.7%).

3 DL-Diethyl 2-(1-carboxy-1-phenylmethylaminomethylene)-propane-1,3-dicarboxylate 2c. From **1b** and DL-2-phenylglycine as an off-white solid (yield 53%†); δ_H 1.25 (6H, m, 2 × CH_2CH_3), 4.12 (4H, m, 2 × CH_2CH_3), 5.06 (1H, d, *J* 6.7, NC*H*CO_2H), 7.29–7.33 (5H, m, Ar–H), 7.90 (1H, d, *J* 9.1, alkenyl-H), 8.52 (1H, br s, CO_2H), 9.90 (1H, m, NH).

4 DL-2-(1-Carboxy-1-phenylmethylaminomethylene)cyclohexane-1,3-dione 5a. From **4a** and DL-2-phenylglycine as a cream solid (yield 83%), mp 164–166 °C; ν_{max}(KBr) 3446, 2551, 1730, 1665, 1580, 1557 cm^{-1}; δ_H 1.92 (2H, m, 5-CH_2), 2.47 (4H, m, 2 × CH_2), 5.22 (1H, d, *J* 6.8, NC*H*CO_2H), 6.36 (1H, br s, CO_2H), 7.34–7.38 (5H, m, Ar–H), 8.18 (1H, d, *J* 14.2, alkenyl-H), 11.95 (1H, m, NH) (Found: C, 65.9; H, 5.4; N, 5.0. $C_{15}H_{15}NO_4$ requires C, 65.9; H, 5.5; N, 5.1%).

5 DL-2-(1-Carboxy-3-methylthiopropylaminomethylene)-cyclohexane-1,3-dione 5b. From **4a** and DL-methionine as a cream solid (yield 85%), mp 166–167 °C; ν_{max}(KBr) 3424, 3212, 2571, 1724, 1657, 1608, 1581, 1544 cm^{-1}; δ_H 1.95–2.65 (10H, m, 4,5,6-CH_2, MeS(CH_2)$_2$), 2.13 (3H, s, SMe), 4.36 (1H, m, NC*H*CO_2H), 5.07 (1H, br s, CO_2H), 8.22 (1H, d, *J* 14.1, alkenyl-H), 11.31 (1H, m, NH) (Found: C, 53.0; H, 6.3; N, 5.1. $C_{12}H_{17}NO_4S$ requires C, 53.1; H, 6.3; N, 5.2%).

6 DL-5,5-Dimethyl-2-(1-carboxy-1-phenylmethylamino-methylene)cyclohexane-1,3-dione 5c. From **4b** and DL-phenylglycine as a pale yellow solid (yield 81%), mp 177–178 °C; ν_{max}(KBr) 3423, 2546, 1724, 1654, 1587, 1550 cm^{-1}; δ_H 0.83 (6H, s, 5-Me), 2.09 (2H, s, CH_2), 2.17 (2H, s, CH_2), 4.97 (1H, d, *J* 6.9, NC*H*CO_2H), 7.13–7.18 (5H, m, Ar–H), 7.83 (1H, d, *J* 14.1, alkenyl-H), 9.54 (1H, br s, CO_2H), 11.62 (1H, m, NH) (Found: C, 67.5; H, 6.3; N, 4.6. $C_{17}H_{19}NO_4$ requires C, 67.8; H, 6.4; N, 4.7%).

7 L-5,5-Dimethyl-2-(1-carboxy-3-methylbutylamino-methylene)cyclohexane-1,3-dione 5d. From **4b** and L-leucine as a pale yellow solid (yield 94%), mp 168–170 °C; ν_{max}(KBr) 3444, 2512, 1732, 1657, 1582, 1551 cm^{-1}; δ_H 0.78–0.82 (6H, m, CH(CH_3)$_2$), 1.00 (6H, s, 5-Me), 1.48–1.67 (3H, m, CH_2CH(CH_3)$_2$), 2.18 (2H, s, CH_2), 2.22 (2H, s, CH_2), 3.90 (1H, m, NC*H*CO_2H), 6.82 (1H, vbr s, CO_2H), 7.90 (1H, d, *J* 14.1, alkenyl-H), 11.03 (1H, m, NH) (Found: C, 64.0; H, 8.1; N, 4.8. $C_{15}H_{23}NO_4$ requires C, 64.0; H, 8.3; N, 5.0%).

8 DL-5,5-Dimethyl-2-(1-carboxy-2-methylpropylamino-methylene)cyclohexane-1,3-dione 5e. From **4b** and DL-valine as off-white microcrystals from hexane and ethanol (yield 88%), mp 184.0–188.0 °C (lit.[12] mp 200–201 °C); ν_{max}(KBr) 3438, 2508, 1730, 1656, 1591 cm^{-1}; δ_H 1.05 (12H, m, 5-*Me*, CH(CH_3)$_2$), 2.32 (1*H*, m, CH(CH_3)$_2$), 2.37 (2H, s, CH_2), 2.40 (2H, s, CH_2), 3.93 (1H, m, NC*H*CO_2H), 8.12 (1H, d, *J* 14.2, alkenyl-H), 10.91 (1H, br s, CO_2H), 11.37 (1H, m, NH) (Found: C, 62.8; H, 7.7; N, 5.0. $C_{14}H_{21}NO_4$ requires C, 62.9; H, 7.9; N, 5.2%).

9 2-(1-Carboxymethylaminomethylene)indanone 16a. From **15a** and glycine, from hexane and ethanol as pale brown cubes (yield 73%), mp 187.0–193.0 °C (decomp.); ν_{max}(KBr) 3245, 1731, 1651, 1608 cm^{-1}; δ_H (DMSO-d_6) 3.52 (2H, s, 3-CH_2), 4.09 (2H, d, *J* 6.1, NCH_2CO_2H), 7.19 (1H, d, *J* 12.8, alkenyl-H), 7.36 (1H, m, Ar–H), 7.49 (3H, m, Ar–H), 9.31 (1H, m, NH), 12.9 (1H, br s, OH) (Found: C, 66.3; H, 5.1; N, 6.4. $C_{12}H_{11}NO_3$ requires C, 66.4; H, 5.1; N, 6.5%).

10 DL-2-(1-Carboxy-1-phenylmethylaminomethylene)-indane-1,3-dione 16b. From **15b** and DL-2-phenylglycine, from ethanol as a fluffy yellow solid (yield 85%), mp 210.5–215.0 °C (decomp.); ν_{max}(KBr) 3273, 3068, 3032, 1727, 1702, 1651, 1605 cm^{-1}; δ_H (DMSO-d_6) 5.45 (1H, d, *J* 6.1, NC*H*CO_2H), 7.19 (5H, m, Ar–H), 7.45 (4H, m, Ar–H), 7.63 (1H, d, *J* 14.3, alkenyl-H), 9.77 (1H, dd, *J* 14.3, 7.2, NH), 13.2 (1H, br s, OH) (Found: C, 70.3; H, 4.1; N, 4.3. $C_{18}H_{13}NO_4$ requires C, 70.4; H, 4.3; N, 4.6%).

11 2-(1-Carboxymethylaminomethylene)-1,2,3,4-tetrahydronaphthalen-1-one 19a. From **18a** and glycine as yellow microcrystals from hexane and ethanol (yield 74%), mp 192.0–196.0 °C (decomp.); ν_{max}(KBr) 3406, 2523, 1733, 1641, 1604, 1580 cm^{-1}; δ_H (DMSO-d_6) 2.50 (2H, m, CH_2), 2.79 (2H, m, CH_2), 4.02 (2H, d, *J* 7.7, NCH_2CO_2H), 7.02 (1H, d, *J* 12.6, alkenyl-H), 7.18–7.56 (3H, m, Ar–H), 7.81 (1H, d, *J* 7.6, 8-H), 9.92 (1H, br m, NH), 12.9 (1H, br s, OH) (Found: C, 67.3; H, 5.6; N, 6.0. $C_{13}H_{13}NO_3$ requires C, 67.5; H, 5.7; N, 6.1%).

12 DL-2-(1-Carboxy-1-phenylmethylaminomethylene)-1,2,3,4-tetrahydronaphthalen-1-one 19b. From **18a** and DL-2-phenylglycine as a pale yellow solid (yield 74%), mp 104.0–107.0 °C; ν_{max}(KBr) 3417, 2661, 1728, 1636, 1601 cm^{-1}; δ_H (DMSO-d_6) 2.48 (2H, m, CH_2), 2.78 (2H, m, CH_2), 5.29 (1H, d, *J* 7.8, NCH_2CO_2H), 7.04 (1H, d, *J* 12.5, alkenyl-H), 7.23–7.42 (8H, m, Ar–H), 7.82 (1H, d, *J* 7.8, 8-H), 10.64 (1H, m, NH) (Found: C, 74.0; H, 5.3; N, 4.6. $C_{19}H_{17}NO_3$ requires C, 74.2; H, 5.6; N, 4.6%).

13 DL-2-(1-Carboxy-3-methylthiopropylaminomethylene)-1,2,3,4-tetrahydronaphthalen-1-one 19c. From **18a** and DL-methionine as a bright yellow solid (yield 74%), mp 163.0–165.0 °C; ν_{max}(KBr) 3417, 2494, 1712, 1632, 1601, 1577, 1499 cm^{-1}; δ_H (DMSO-d_6) 1.99 (2H, m, CH_2), 2.06 (3H, s, SMe), 2.53 (4H, m, 2 × CH_2), 2.79 (2H, m, CH_2), 4.14 (1H, m, NC*H*CO_2H), 7.04 (1H, d, *J* 13.1, alkenyl-H), 7.20–7.36 (3H, m, Ar–H), 7.81 (1H, d, *J* 7.8, 8-H), 10.13 (1H, m, NH) (Found: C, 62.8; H, 6.3; N, 4.4. $C_{16}H_{19}NO_3S$ requires C, 62.9; H, 6.3; N, 4.6%).

14 DL-2-(1-Carboxy-3-methylsulfinylpropylamino-methylene)-1,2,3,4-tetrahydronaphthalen-1-one 19d. From **18a** and DL-methionine sulfoxide as a dull yellow solid (yield 67%), mp 117.5–121.0 °C; ν_{max}(KBr) 3423, 2479, 1712, 1631, 1600,

† Yield of crude material that was cyclised directly to **3c**.

1576, 1475, 1379 cm^{-1}; δ_H (DMSO-d_6) 2.30–3.00 (8H, br m, 4 × CH_2), 2.69 (3H, s, S(O)Me), 4.18 (1H, m, NC*H*CO_2H), 7.17–7.50 (4H, m, Ar–H and alkenyl-H), 7.96 (1H, dd, *J* 8.0, 1.6, 8-H), 10.30 (1H, m, NH) (Found: C, 59.5; H, 5.9; N, 4.3. $C_{16}H_{19}NO_4S$ requires C, 59.8; H, 6.0; N, 4.4%).

15 L-2-[1-Carboxy-3-(methoxycarbonyl)propylamino-methylene]-1,2,3,4-tetrahydronaphthalen-1-one 19e. From **18a** and L-glutamic acid 5-methyl ester as a yellow solid (yield 78%), mp 153.0–155.0 °C; ν_{max}(KBr) 3418, 2949, 2841, 1733, 1642, 1602 cm^{-1}; δ_H 2.21 (2H, m, CH_2), 2.52 (4H, m, 2 × CH_2), 2.85 (2H, m, CH_2), 3.67 (3H, s, CO_2Me), 3.98 (1H, m, NC*H*CO_2H), 6.81 (1H, d, *J* 9.1, alkenyl-H), 7.18 (1H, d, *J* 7.4, 5-H), 7.33 (2H, m, Ar–H), 7.86 (1H, br s, CO_2H), 7.97 (1H, dd, *J* 7.8, 1.4, 8-H), 10.29 (1H, m, NH) (Found: C, 64.3; H, 6.0; N, 4.4. $C_{17}H_{19}NO_5$ requires C, 64.3; H, 6.1; N, 4.4%).

16 DL-1-(1-Carboxy-1-phenylmethylaminomethylene)-1,2,3,4-tetrahydronaphthalen-2-one 23. From **22** and DL-2-phenylglycine as a bright yellow solid (yield 53%), mp 73.0–76.0 °C; ν_{max}(KBr) 3422, 1728, 1639, 1599, 1565 cm^{-1}; δ_H 2.54 (2H, m, CH_2), 2.85 (2H, m, CH_2), 5.18 (1H, d, *J* 6.1, NCH_2-CO_2H), 6.99–7.46 (10H, m, (9-Ar–H), (alkenyl-H)), 8.04 (1H, br s, CO_2H), 11.19 (1H, m, NH) (Found: C, 74.1; H, 5.5; N, 4.4. $C_{19}H_{17}NO_3$ requires C, 74.2; H, 5.6; N, 4.6%).

17 2-(1-Carboxymethylaminomethylene)-4,5-dihydro-3*H*-benzocycloheptan-1(2*H*)-one 19f. From **18b** and glycine as a bright yellow solid (yield 58%), mp 181.0–184.0 °C (decomp.); ν_{max}(KBr) 3427, 2932, 1740, 1636, 1600 cm^{-1}; δ_H 1.69 (2H, m, CH_2), 1.83 (2H, m, CH_2), 2.47 (2H, m, CH_2), 3.80 (2H, d, *J* 6.7, NCH_2CO_2H), 6.49 (1H, d, *J* 13.9, alkenyl-H), 6.92 (1H, m, Ar–H), 7.08 (2H, m, Ar–H), 7.34 (1H, dd, *J*, 7.8, 1.5, 9-H), 8.51 (1H, vbr s, CO_2H), 9.93 (1H, m, NH) (Found: C, 68.2; H, 6.0; N, 5.6. $C_{14}H_{15}NO_3$ requires C, 68.5; H, 6.2; N, 5.7%).

18 DL-2-(1-Carboxy-3-methylthiopropylaminomethylene)-4,5-dihydro-3*H*-benzocycloheptan-1(2*H*)-one 19g. From **18b** and DL-methionine as a bright yellow solid (yield 69%), mp 108.0–111.0 °C; ν_{max}(KBr) 3417, 2533, 1717, 1635, 1601 cm^{-1}; δ_H 1.88–2.10 (6H, m, 3 × CH_2), 2.06 (3H, s, SMe), 2.65 (4H, m, 2 × CH_2), 4.15 (1H, m, NC*H*CO_2H), 6.79 (1H, d, *J* 13.8, alkenyl-H), 7.14 (1H, m, Ar–H), 7.24–7.25 (2H, m, Ar–H), 7.57 (1H, d, *J* 8.2, 9-H), 8.46 (1H, br s, CO_2H), 10.35 (1H, m, NH) (Found: C, 63.9; H, 6.5; N, 4.2. $C_{17}H_{21}NO_3S$ requires C, 63.9; H, 6.6; N, 4.4%).

19 3-(Carboxymethylaminomethylene)-2,3-dihydro-2,2-dimethyl-4*H*-1-benzopyran-4-one 19h. From **18c** and glycine, from methanol as lemon coloured cubes (yield 80%), mp 166–168 °C (decomp.); ν_{max}(Nujol) 3600–2400 (br), 1718, 1635, 1605 cm^{-1}; δ_H (DMSO-d_6) 1.51 (6H, s, 2-Me), 4.13 (2H, d, *J* 7.0, NCH_2CO_2H), 6.80–7.84 (5H, Ar–H and alkenyl-H), 10.25 (1H, m, NH), 12.62 (1H, br s, CO_2H) (Found: C, 64.3; H, 6.0; N, 5.4. $C_{14}H_{15}NO_4$ requires C, 64.3; H, 5.8; N, 5.4%).

20 3-(Carboxymethylaminomethylene)-3,4-dihydrospiro-[1-benzopyran-2,1′-cyclohexan]-4-one 19i. From **18d** and glycine, from methanol as a bright yellow solid (yield 73%), mp 186–187 °C (decomp.); ν_{max}(Nujol) 3600–2400 (br), 1720, 1635, 1600 cm^{-1}; δ_H (DMSO-d_6) 1.55–2.08 (10H, m, -$(CH_2)_5$-), 4.13 (2H, d, *J* 6.0, NCH_2CO_2H), 6.86 (1H, d, *J* 7.7, 8-H), 7.00 (1H, m, 6-H), 7.19 (1H, d, *J* 12.6, alkenyl-H), 7.39 (1H, m, 7-H), 7.73 (1H, dd, *J* 7.7, 1.7, 5-H), 10.31 (1H, m, NH), 12.80 (1H, br s, CO_2H) (Found: C, 67.7; H, 6.4; N, 4.7. $C_{17}H_{19}NO_4$ requires C, 67.8; H, 6.4; N, 4.7%).

21 3-(1-Carboxymethylaminomethylene)-2,3-dihydro-2-methyl-4*H*-1-benzothiopyran-4-one 19j. From **18e** and glycine as a bright yellow solid from ethyl acetate and methanol (yield 76%), mp 157.0–160.0 °C (decomp.); ν_{max}(KBr) 3471, 3219, 3055, 2960, 1717, 1635, 1590 cm^{-1}; δ_H 1.39 (3H, d, *J* 6.7, 2-Me), 3.94 (1H, q, *J* 6.7, 2-H), 4.06 (2H, d, *J* 5.7, NCH_2CO_2H), 7.16–7.51 (4H, m, Ar–H and alkenyl-H), 7.70 (1H, br s, CO_2H), 7.91 (1H, dd, *J* 8.0, 1.7, 5-H), 10.15 (1H, m, NH) (Found: C, 59.2; H, 4.9; N, 5.6; S, 12.0. $C_{13}H_{13}NO_3S$ requires C, 59.3; H, 5.0; N, 5.3; S, 12.2%).

22 DL-3-(1-Carboxy-1-phenylmethylaminomethylene)-2,3-dihydro-2-methyl-4*H*-1-benzothiopyran-4-one 19k. From **18e** and DL-phenylglycine (yield 83%‡); δ_H (DMSO-d_6) 1.36 (3H, d, *J* 7.0, 2-Me), 3.93 (1H, q, *J* 7.0, 2-H), 4.05 (2H, d, *J* 5.9, NCH_2CO_2H), 7.31 (5H, m, Ar–H, alkenyl-H and CO_2H), 7.89 (1H, dd, *J* 8.4, 1.7, 5-H), 10.15 (1H, m, NH).

23 3-(Carboxymethylaminomethylene)-2,3-dihydro-2,2-dimethyl-4*H*-1-benzothiopyran-4-one 19l. From **18f** and glycine, from ethyl acetate and methanol as bright yellow microcrytals (yield 86%), mp 245.0–247.0 °C; ν_{max}(KBr) 3400, 1720, 1635, 1590 cm^{-1}; δ_H (DMSO-d_6) 1.52 (6H, s, 2-Me), 3.73 (2H, d, *J* 5.1, NCH_2CO_2H), 7.30 (4H, m, Ar–H and alkenyl-H), 7.91 (1H, dd, *J* 8.7, 1.8, 5-H), 10.62 (1H, br m, NH) (Found: C, 60.3; H, 5.2; N, 5.0. $C_{14}H_{15}NO_3S$ requires C, 60.6; H, 5.5; N, 5.1%).

24 DL-3-(1-Carboxy-1-phenylmethylaminomethylene)-2,3-dihydro-2,2-dimethyl-4*H*-1-benzothiopyran-4-one 19m. From **18f** and DL-2-phenylglycine, from ethyl acetate as a bright yellow solid (yield 73%), mp 120.0–121.5 °C; ν_{max}(KBr) 3427, 1729, 1629, 1588, 1567 cm^{-1}; δ_H (DMSO-d_6) 1.07 (3H, s, 2-Me), 1.10 (3H, s, 2-Me), 4.61 (1H, d, *J* 7.0, NC*H*CO_2H), 6.58 (1H, d, *J* 12.6, alkenyl-H), 6.77–7.02 (8H, m, Ar–H), 7.61 (1H, d, *J* 8.5, 5-H), 10.86 (1H, br m, NH) (Found: C, 67.8; H, 5.1; N, 3.9. $C_{20}H_{19}NO_3S$ requires C, 68.0; H, 5.4; N, 4.0%).

25 DL-3-(1-Carboxyethylaminomethylene)-2,3-dihydro-2,2-dimethyl-4*H*-1-benzothiopyran-4-one 19n. From **18f** and DL-alanine as bright yellow microcrystals from ethyl acetate and hexane (yield 62%), mp 170.0–172.0 °C; ν_{max}(KBr) 3423, 2561, 1718, 1635, 1589, 1566 cm^{-1}; δ_H 1.58 (6H, s, 2-Me), 1.62 (3H, d, *J* 7.9, NCHCH_3), 4.06 (1H, q, *J* 7.9, NC*H*CH_3), 7.00 (1H, d, *J* 12.2, alkenyl-H), 7.19–7.35 (3H, m, Ar–H), 8.05 (1H, d, *J* 8.0, 5-H), 8.16 (1H, br s, CO_2H), 10.78 (1H, br m, NH) (Found: C, 61.9; H, 5.9; N, 4.8; S, 10.8. $C_{15}H_{17}NO_3S$ requires C, 61.8; H, 5.9; N, 4.8; S, 11.0%).

26 3-(1-Cyanomethylaminomethylene)-2,3-dihydro-2,2-dimethyl-4*H*-1-benzopyran-4-one 25. From **18f** and 2-amino-acetonitrile as pale yellow cubes from ethyl acetate and hexane (yield 79%), mp 140.0–141.0 °C; ν_{max}(Nujol) 3280, 2220, 1648, 1605 cm^{-1}; δ_H (DMSO-d_6) 1.58 (6H, s, 2-Me), 4.16 (2H, d, *J* 5.9, NCH_2CN), 6.77 (1H, d, *J* 12.0, alkenyl-H), 6.88 (1H, d, *J* 7.9, 8-H), 6.99 (1H, m, 6-H), 7.39 (1H, m, 7-H), 7.85 (1H, dd, *J* 7.0, 1.4, 5-H), 10.20 (1H, m, NH) (Found: C, 69.5; H, 5.9; N, 11.6. $C_{14}H_{14}N_2O_2$ requires C, 69.4; H, 5.8; N, 11.6%).

General method for the cyclisation of the carboxymethylamino-methylene derivatives

The carboxymethylaminomethylene derivatives (10 mmol) and triethylamine (10 cm^3) were refluxed in acetic anhydride (30 cm^3) until the vigorous evolution of CO_2 (limewater bubbler) ceased, after approximately 30 min, and then allowed to cool to RT. The resulting dark red solution was poured into water (400 cm^3) and stirred for 1 h and extracted with CH_2Cl_2 (4 × 50 cm^3). The combined organic extracts were washed with water (2 × 100 cm^3), saturated $NaHCO_3$ solution (5 × 50 cm^3) and finally with water (100 cm^3). Removal of the dried (Na_2SO_4) solvent afforded a red–brown oil which either crystallised on standing or was eluted from silica. The following compounds were isolated by this protocol.

‡ Yield of crude material that was cyclised directly to **20j**.

1 Ethyl 1-acetyl-4-methyl-5-phenylpyrrole-3-carboxylate 3a. From **2a** as a pale yellow solid after elution from silica with 30% EtOAc in hexane (yield 48%), bp 120 °C at 7×10^{-2} mmHg, mp 76.5–78.0 °C; ν_{max}(KBr) 1714, 1701 cm^{-1}; δ_H 1.36 (3H, t, *J*, 7.2, CH_2CH_3), 2.08 (3H, s, 4-Me), 2.21 (3H, s, N–Ac), 4.29 (2H, q, *J* 7.2, CH_2CH_3), 7.23–7.25 (2H, m, Ar–H), 7.36–7.41 (3H, m, Ar–H), 7.93 (1H, s, 2-H); δ_C 10.6, 14.3, 24.7, 59.9, 118.0, 123.2, 125.7, 128.1, 128.2 (2 × C), 130.4 (2 × C), 131.6, 132.6, 164.4, 166.5 (Found: C, 70.8; H, 6.4; N, 5.1. $C_{16}H_{17}NO_3$ requires C, 70.8; H, 6.3; N, 5.2%).

2 Ethyl 4-acetoxy-1-acetylpyrrole-3-carboxylate 3b. From **2b** as a colourless oil after elution from silica with 20% EtOAc in hexane (yield 57%), bp 220 °C at 1×10^{-1} mmHg; ν_{max}(KBr) 1745, 1710 cm^{-1}; δ_H 1.32 (3H, t, *J* 7.3, CH_2CH_3), 2.30 (3H, s, O–Ac), 2.54 (3H, s, N–Ac), 4.26 (2H, q, *J* 7.3, CH_2CH_3), 7.25 (1H, d, *J* 2.1, 5-H), 7.78 (1H, d, *J* 2.1, 2-H); δ_C 14.2, 20.5, 21.5, 60.3, 110.2, 113.3, 122.5, 138.2, 162.0, 166.8, 168.6 (Found: C, 54.9; H, 5.5; N, 5.7. $C_{11}H_{13}NO_3$ requires C, 55.2; H, 5.5; N, 5.9%).

3 Ethyl 4-acetoxy-1-acetyl-5-phenylpyrrole-3-carboxylate 3c. From **2c** as colourless needles from hexane and EtOAc after elution from silica with 30% EtOAc in hexane (yield 51%), mp 122.0–124.0 °C; ν_{max}(KBr) 1750, 1715, 1699 cm^{-1}; δ_H 1.32 (3H, t, *J* 7.1, CH_2CH_3), 2.17 (3H, s, Ac), 2.27 (3H, s, Ac), 4.28 (2H, q, *J* 7.1, CH_2CH_3), 7.25–7.30 (2H, m, Ar–H), 7.37–7.41 (3H, m, Ar–H), 7.90 (1H, s, 2-H) (Found: C, 64.6; H, 5.4; N, 4.3. $C_{17}H_{17}NO_5$ requires C, 64.7; H, 5.4; N, 4.4%).

4 4-Acetoxy-2-acetyl-6,7-dihydro-1-phenylisoindole 6a. From **5a** as pale yellow needles from light petroleum (bp 40–60 °C) and diethyl ether after elution from silica with 30% EtOAc in hexane (yield 69%), mp 74.5–76.0 °C; ν_{max}(KBr) 1751, 1713 cm^{-1}; δ_H 2.17 (3H, s, Ac), 2.27 (3H, s, Ac), 2.46 (4H, m, 6,7-CH_2), 5.55 (1H, t, *J* 4.4, 5-H), 7.12 (1H, s, 3-H),7.25–7.42 (5H, m, Ar–H) (Found: C, 66.9; H, 6.3; N, 5.9. $C_{18}H_{17}NO_3$ requires C, 66.9; H, 6.5; N, 6.0%).

A solution of the aforegoing isoindole **6a** (4.0 mmol) in 80% aqueous acetic acid (25 cm^3) and conc. HCl (2 cm^3) was maintained at 100 °C for 15 min. The cooled solution was poured into water (200 cm^3) and extracted with ethyl acetate (3 × 50 cm^3). The combined extracts were washed with water (2 × 100 cm^3), aqueous saturated $NaHCO_3$ (4 × 50 cm^3) and water (100 cm^3). Removal of the dried (Na_2SO_4) ethyl acetate and elution of the dark brown solid from silica with 40% EtOAc in hexane gave *4-oxo-1-phenyl-4,5,6,7-tetrahydroisoindole* **7** (92%), mp 167.0–173.5 °C (decomp.) as grey microcrystals from hexane and ethyl acetate; δ_H 2.07 (2H, m, 6-CH_2), 2.52 (2H, t, *J* 6.1, 7-CH_2), 2.88 (2H, t, *J* 6.2, 5-CH_2), 7.25–7.47 (6H, m, Ar–H, 3-H), 9.70 (1H, br s, NH); δ_C 22.6, 25.0, 39.1, 120.2, 123.1, 125.7 (2 × C), 126.5 (2 × C), 127.3, 128.8 (2 × C), 132.2, 196.9 (Found: M^+, 211.0997; C, 79.4; H, 6.2; N, 6.5. $C_{14}H_{13}NO$ requires M^+, 211.0997(14); C, 79.6; H, 6.2; N, 6.6%).

5 4-Acetoxy-2-acetyl-6,7-dihydro-6,6-dimethyl-1-phenyl isoindole 6b. From **5c** as colourless needles from hexane, light petroleum (bp 40–60 °C) and ether (yield 72%), mp 89.5–92.0 °C; ν_{max}(KBr) 1755, 1717 cm^{-1}; δ_H 1.09 (6H, s, 6-Me), 2.18 (3H, s, Ac), 2.25 (3H, s, Ac), 2.34 (2H, s, 7-CH_2), 5.36 (1H, s, 5-H), 7.11 (1H, s, 3-H), 7.28–7.40 (5H, m, Ar–H); δ_C 20.9, 24.9, 28.8 (2 × C), 34.3, 34.6, 113.0, 118.0, 124.1, 125.3 (2 × C), 127.8, 128.2 (2 × C), 129.2 (2 × C), 132.9, 141.1, 168.5, 168.9 (Found: C, 74.1; H, 6.5; N, 4.3. $C_{20}H_{21}NO_3$ requires C, 74.3; H, 6.6; N, 4.3%).

6 2-Acetyl-4,5-dihydro-1-phenyl-2*H*-benzo[*e*]isoindole 20b. From **19b** from hexane and ethyl acetate after elution from silica with 30% EtOAc in hexane (yield 69%), mp 102.0–104.0 °C; ν_{max}(KBr) 1718 cm^{-1}; δ_H 2.17 (3H, s, N–Ac), 2.74 (2H, m, CH_2), 2.92 (2H, m, CH_2), 6.69 (1H, d, *J* 8.2, 9-H), 6.88 (1H, m, Ar–H), 7.05 (1H, m, Ar–H), 7.19 (1H, d, *J* 8.1, Ar–H), 7.22 (1H, s, 3-H), 7.46 (5H, m, Ar–H) (Found: C, 83.6; H, 5.9; N, 4.8. $C_{20}H_{17}NO$ requires C, 83.6; H, 6.0; N, 4.9%).

7 2-Acetyl-4,5-dihydro-3-phenyl-2*H*-benzo[*e*]isoindole 24. From **23** from light petroleum (bp 40–60 °C) after elution from silica with 30% EtOAc in hexane (yield 56%), mp 61.5–63.5 °C; ν_{max}(KBr) 1728 cm^{-1}; δ_H 2.27 (3H, s, N–Ac), 2.59 (2H, m, CH_2), 2.86 (2H, m, CH_2), 7.27 (3H, m, Ar–H), 7.31 (5H, m, Ar–H), 7.54 (1H, d, *J* 8.2, 9-H), 7.64 (1H, s, 1-H) (Found: C, 83.7; H, 6.0; N, 4.9. $C_{20}H_{17}NO$ requires C, 83.6; H, 6.0; N, 4.9%).

8 2-Acetyl-1-[2-(methylthio)ethyl]-4,5-dihydro-2*H*-benzo[*e*]-isoindole 20c. From **19c** from ethyl acetate and hexane after elution from silica with 20% EtOAc in hexane (yield 46%), mp 113.0–114.0 °C; ν_{max}(KBr) 1702 cm^{-1}; δ_H 2.26 (3H, s, SMe), 2.56 (3H, s, N–Ac), 2.63 (2H, m, CH_2), 3.89 (4H, m, 2 × CH_2), 3.48 (2H, m, CH_2), 6.87 (1H, s, 3-H), 7.24 (3H, m, Ar–H), 7.55 (1H, dd, *J*, 8.4, 1.9, 9-H) (Found: M^+, 285.1187; C, 71.9; H, 6.8; N, 5.0; S, 11.3. $C_{17}H_{19}NOS$ requires M^+, 285.1187(38); C, 71.5; H, 6.7; N, 4.9; S, 11.2%).

9 2-Acetoxymethylene-1,2,3,4-tetrahydronaphthalen-1-one 21. From **19d** from hexane as colourless needles (yield 24%), mp 129.5–131.5 °C; δ_H 2.26 (3H, s, O–Ac), 2.87–2.95 (4H, m, 2 × CH_2), 7.23 (1H, d, *J* 7.8, 5-H), 7.35 (1H, m, Ar–H), 7.45 (1H, m, Ar–H), 8.07 (1H, dd, *J* 7.6, 1.1, 8-H), 8.38 (1H, t, *J* 1.7, alkenyl-H) and *1-[2-(acetoxymethylthio)ethyl]-2-acetyl-4,5-dihydro-2H-benzo[e]isoindole* **20d** as colourless microcrystals from ethyl acetate and hexane after elution from silica with 20% EtOAc in hexane (yield 51%), mp 97.0–98.5 °C; ν_{max}(KBr) 1741, 1704, 1696 cm^{-1}; δ_H 2.09 (3H, s, Ac), 2.55 (3H, s, Ac), 2.63 (2H, m, CH_2), 2.81 (2H, m, CH_2), 3.06 (2H, m, CH_2), 3.51 (2H, m, CH_2), 5.29 (2H, s, $AcOCH_2S$), 6.87 (1H, d, *J* 1.0, 3-H), 7.23 (3H, m, Ar–H), 7.52 (1H, dd, *J* 8.1, 1.6, 9-H) (Found: C, 66.4; H, 6.2; N, 4.1; S, 9.4. $C_{19}H_{21}NO_3S$ requires C, 66.4; H, 6.2; N, 4.1; S, 9.3%).

10 2-Acetyl-4,5-dihydro-1-[2-(methoxycarbonyl)ethyl]-2*H*-benzo[*e*]isoindole 20e. From **19e** as very pale brown needles from ethyl acetate, hexane and light petroleum (bp 40–60 °C) (yield 64%), mp 112.5–114.0 °C; ν_{max}(KBr) 1734, 1702 cm^{-1}; δ_H 2.53 (3H, s, N–Ac), 2.62 (2H, m, CH_2), 2.81 (4H, m, 2 × CH_2), 3.52 (2H, m, CH_2), 3.68 (3H, s, CO_2Me), 6.85 (1H, s, 3-H), 7.17 (1H, m, Ar–H), 7.25 (2H, m, Ar–H), 7.52 (1H, d, *J* 8.2, 9-H); δ_C 21.0, 23.5, 24.6, 30.9, 33.5, 51.6, 114.9, 122.9, 124.7, 124.9, 126.4, 126.9, 128.7, 129.5, 130.8, 137.6, 169.2, 173.4 (Found: C, 72.6: H, 6.6; N, 4.5. $C_{18}H_{19}NO_3$ requires C, 72.7; H, 6.5; N, 4.5%).

11 2-Acetyl-2,4,5,6-tetrahydrobenzo[3,4]cyclohepta[1,2-*c*]-pyrrole 20f. From **19f** as a pale yellow oil (yield 57%), bp 180 °C at 1×10^{-1} mmHg; ν_{max}(Nujol) 1707 cm^{-1}; δ_H 2.08 (2H, m, 5-CH_2), 2.49 (2H, m, CH_2), 2.55 (3H, s, N–Ac), 2.68 (2H, m, CH_2), 7.23–7.37 (6H, m, Ar–H, 1-H, 3-H) (Found: C, 79.8; H, 6.7; N, 6.4. $C_{15}H_{15}NO$ requires C, 80.0; H, 6.7; N, 6.2%).

12 2-Acetyl-2,4,5,6-tetrahydro-1-[2-(methylthio)ethyl]-benzo[3,4]cyclohepta[1,2-*c*]pyrrole 20g. From **19g** as colourless crystals from light petroleum (bp 40–60 °C) and ethyl acetate after elution from silica with 30% EtOAc in hexane (yield 64%), mp 92.5–94.0 °C; ν_{max}(KBr) 1707 cm^{-1}; δ_H 2.00 (2H, m, 5-CH_2), 2.03 (3H, s, SMe), 2.36 (2H, m, CH_2), 2.56 (3H, s, N–Ac), 2.61 (2H, m, CH_2), 2.78 (2H, m, CH_2), 3.30 (2H, m, CH_2), 6.87 (1H, s, 3-H), 7.23–7.29 (4H, m, Ar–H); δ_C 14.9, 21.9, 24.4, 27.0, 29.0, 32.1, 33.8, 115.8, 126.3, 126.6, 127.1, 128.2, 128.7, 129.3, 130.1, 134.2, 140.4, 168.8 (Found: M^+, 299.1344; C, 72.2; H, 7.1; N, 4.6; S, 10.8. $C_{18}H_{21}NOS$ requires M^+, 299.1343(88); C, 72.2; H, 7.1; N, 4.7; S, 10.7%).

13 2-Acetyl-4,4-dimethyl-2*H*,4*H*-1-benzopyrano[3,4-*c*]-pyrrole 20h. From **19h** as a pale yellow solid from ethyl acetate and hexane (yield 78%), mp 124.5–125.5 °C; δ_H 1.59 (6H, s, 4-Me), 2.55 (3H, s, N–Ac), 6.95 (2H, m, Ar–H), 7.12 (2H, m, Ar–H), 7.43 (2H, m, Ar–H) (Found: C, 74.6; H, 6.2; N, 5.7. $C_{15}H_{15}NO_2$ requires C, 74.7; H, 6.2; N, 5.8%).

14 2-Acetyl-2*H*-spiro[1-benzopyrano[3,4-*c*]pyrrole-4,1′-cyclohexane] 20i. From **19i** as pale brown crystals from ethyl acetate and hexane (yield 62%), mp 145.5–147.0 °C; δ_H 1.28–1.40 (10H, m, -$(CH_2)_5$-), 2.60 (3H, s, N–Ac), 6.80–7.60 (6H, m, Ar–H) (Found: C, 76.8; H, 6.7; N, 4.8. $C_{18}H_{19}NO_2$ requires C, 76.9; H, 6.7; N, 5.0%).

15 2-Acetyl-4-methyl-1-phenyl-2*H*,4*H*-1-benzothio-pyrano[3,4-*c*]pyrrole 20j. From **19k** from ethyl acetate and hexane as pale brown microneedles (yield 64%), mp 182.0–183.5 °C; ν_{max}(Nujol) 1728 cm^{-1}; δ_H 1.63 (3H, d, *J* 6.8, 4-Me), 2.12 (3H, s, N–Ac), 4.16 (1H, dq, *J* 1.0, 6.8, 4-H), 6.75 (2H, m, Ar–H), 7.00 (1H, m, Ar–H), 7.24 (1H, d, *J* 1.0, 3-H), 7.39 (6H, m, Ar–H) (Found: C, 75.1; H, 5.3; N, 4.4; S, 10.4. $C_{20}H_{17}NOS$ requires C, 75.2; H, 5.4; N, 4.4; S, 10.0%).

16 2-Acetyl-4,4-dimethyl-2*H*,4*H*-1-benzothiopyrano[3,4-*c*]-pyrrole 20k. From **19l** from ethyl acetate and hexane as pale brown needles (yield 47%), mp 137.5–138.5 °C; ν_{max}(Nujol) 1731 cm^{-1}; δ_H 1.63 (6H, s, 4-Me), 2.57 (3H, s, N–Ac), 7.16 (4H, m, Ar–H, 1-H, 3-H), 7.35 (1H, m, Ar–H), 7.57 (1H, m, Ar–H) (Found: C, 70.1; H, 5.9; N, 5.4; S, 12.2. $C_{15}H_{15}NOS$ requires C, 70.0; H, 5.9; N, 5.4; S, 12.5%).

17 2-Acetyl-4,4-dimethyl-1-phenyl-2*H*,4*H*-1-benzothio-pyrano[3,4-*c*]pyrrole 20l. From **19m** from ethyl acetate and hexane as colourless needles (yield 53%), mp 194.5–195.5 °C; ν_{max}(Nujol) 1729 cm^{-1}; δ_H 1.65 (6H, s, 4-Me), 2.12 (3H, s, N–Ac), 6.72–6.80 (2H, m, Ar–H), 7.01 (1H, m, Ar–H), 7.32 (1H, s, 3-H), 7.39–7.48 (6H, m, Ar–H) (Found: C, 75.5; H, 5.6; N, 4.1; S, 9.3. $C_{21}H_{19}NOS$ requires C, 75.6; H, 5.8; N, 4.2; S, 9.6%).

18 6-Acetoxy-8-acetyl-2,3,4,8-tetrahydro-9-(2-methylthio-ethyl)-2-oxooxocino[2,3-*c*]pyrrole 9a. From **5b** after elution from silica with 30% ethyl acetate in hexane, as colourless cubes from ethyl acetate and hexane (yield 45.4%), mp 151.5–152.5 °C, ν_{max}(Nujol) 1759, 1717 cm^{-1}, δ_H 2.15 (3H, s, SMe), 2.35 (3H, s, N–Ac), 2.47 (2H, m, S–CH_2), 2.54 (3H, s, OAc), 2.68 (4H, m, 2 × CH_2), 3.01 (2H, m, CH_2), 5.50 (1H, t, *J* 4.6, alkenic-H), 7.23 (1H, s, 7-H); δ_C 15.2, 19.2, 20.6, 23.5, 25.4, 28.3, 32.3, 100.8, 113.8, 116.1, 125.8, 134.6, 144.5, 168.2, 168.8, 168.9 (Found: C, 57.15; H, 5.85; N, 4.2; S, 9.8 %; MH^+, 338.1060. $C_{16}H_{19}NO_5S$ requires C, 56.9; H, 5.7; N, 4.15; S, 9.5 %; MH^+, 338.1062).

19 8-Acetyl-4,4-dimethyl-2,6-dioxo-9-(2-methylpropyl)-2,3,4,5,6,8-hexahydrooxocino[2,3-*c*]pyrrole 9b. From **5d** after elution from silica with 40% ethyl acetate in hexane, as colourless cubes from ethyl acetate and hexane (yield 49.5%), mp 152.5–153.5 °C; ν_{max}(KBr) 2962, 1766, 1742, 1670, 1594, 1524, 1274, 1189 cm^{-1}; δ_H (253 K) 0.82 (3H, d, *J* 6.6, CHCH_3), 0.94 (3H, d, *J* 6.6, CHCH_3), 1.07 (3H, s, 4-CH_3), 1.27 (3H, s, 4-CH_3), 1.87 (1H, m, *J* 6.6, C*H*$(CH_3)_2$), 2.25 (1H, d, *J* 12.3, 3-CH_2), 2.37 (1H, d, *J* 12.3, 3-CH_2), 2.68 (1H, dd, *J* 13.9, 8.3, CH_2CH$(CH_3)_2$), 2.65 (3H, s, NAc), 2.81 (1H, dd, *J* 13.9, 8.3, CH_2CH$(CH_3)_2$), 2.92 (1H, d, *J* 12.3, 5-CH_2), 2.99 (1H, d, *J* 12.3, 5-CH_2), 7.70 (1H, s, 7-H); δ_C (299K) 22.1, 23.5, 28.2, 29.4, 33.2, 34.6, 42.5, 53.4, 120.0, 122.3, 126.5, 137.4, 169.0, 169.4, 192.8 (Found: C, 66.85; H, 7.60; N, 4.55 %; M^+ 305.1627. $C_{17}H_{23}NO_4$ requires C, 66.85; H, 7.60; N, 4.60 %; M^+ 305.1627).

Thermolysis of 3-(1-carboxymethylaminomethylene)-2,3-dihydro-2,2-dimethyl-4*H*-1-benzopyran-4-one 19h

A solution of **19h** (5 mmol) in bromobenzene (25 cm^3) was refluxed until evolution of CO_2 (limewater bubbler) ceased and no starting material remained (TLC, 2.5 h). The bromobenzene was removed under reduced pressure and the viscous brown residue eluted with 40% EtOAc in hexane to afford two fractions. **Fraction 1**. *2,3-Dihydro-2,2-dimethyl-3-(methylamino-methylene)-4H-1-benzopyran-4-one* **27**, mp 128.5–129.0 °C, from hexane (yield 32 %); ν_{max}(Nujol) 3219, 1649 cm^{-1}; δ_H 1.53 (6H, s, 2-Me), 3.03 (3H, d, *J* 5.2, N–Me), 6.79 (1H, d, *J* 8.1, 8-H), 6.83 (1H, s, alkenyl-H), 6.98 (1H, m, 6-H), 7.29 (1H, m, 7-H), 7.87 (1H, dd, *J* 8.3, 1.7, 5-H), 10.23 (1H, br s, NH); δ_C 28.7 (2 × C), 35.4, 79.4, 107.0, 117.5, 120.6, 123.2, 126.1, 133.4, 150.4, 157.8, 181.4 (Found: C, 71.8; H, 7.0; N, 6.3. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 7.0; N, 6.5%). **Fraction 2**. *3-Isopropenyl-4H-1-benzopyran-4-one* **28** from light petroleum (bp 40–60 °C) (yield 36%), mp 57.5–59.0 °C [lit.[22] mp 57.0–59.0 °C]; ν_{max}(Nujol) 1639 cm^{-1}; δ_H 2.10 (3H, s, Me), 5.16 (1H, m, isopropenyl-H), 5.45 (1H, m, isopropenyl-H), 7.37 (2H, m, Ar–H), 7.60 (1H, m, Ar–H), 7.88 (1H, s, 2-H), 8.22 (1H, dd, *J* 8.3, 1.9, 5-H).

A solution of the aforegoing 3-isopropenyl-4*H*-1-benzopyran-4-one **28** (10 mmol) was dissolved in dichloromethane (25 cm^3). PTAD [prepared according to the procedure described by Moriarty *et al.*[35]] (10 mmol) in dichloromethane (30 cm^3) was added dropwise with stirring. The red colour of the PTAD was instantly discharged and after stirring for 5 h the precipitated cycloadduct was collected by vacuum filtration and washed thoroughly with ether to afford analytically pure *6-methyl-2-phenyl-2,3,5,12a-tetrahydro-1H,7H-[1]benzopyrano-[2,3-c][1,2,4]triazolo[1,2-a]pyridazine-1,3,7-trione* **29** as colourless microcrystals (yield 92%), mp 189.0–205.0 °C (decomp.); ν_{max}(Nujol) 1770, 1715, 1675, 1635 cm^{-1}; δ_H (DMSO-d_6) 2.35 (3H, s, 6-Me), 4.41 (1H, d, *J* 17.7, 5-H), 4.62 (1H, d, *J* 17.7, 5-H), 6.83 (1H, s, 12a-H), 7.21 (1H, d, *J* 8.3, 11-H), 7.30 (1H, m, 9-H), 7.61 (5H, m, Ar–H), 7.70 (1H, m, 10-H), 7.96 (1H, dd, *J* 8.1, 1.3, 8-H) (Found: C, 66.3; H, 4.1; N, 11.5. $C_{20}H_{15}N_3O_4$ requires C, 66.5; H, 4.2; N, 11.6%).

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