Studies on Fused Pyrimidine Derivatives. Part 12.[1] Reaction of 6-(Alk-2-enylamino)-5-formyl-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-diones with α-Amino Acid Derivatives

Tomonori Inazumi,[a] Kazuo Yamada,[a] Yoshiaki Kuroki,[a] Akikazu Kakehi*[,b] and Michihiko Noguchi*[,a]

[a] *Department of Applied Chemistry, Faculty of Engineering, Yamaguchi University, Tokiwadai, Ube 755, Japan*

[b] *Department of Chemistry and Material Engineering, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380, Japan*

The reactions of 6-(alk-2-enylamino)-5-formyl-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-diones **1** with α-amino acid derivatives are described. The reaction of compounds of **1** with *N*-substituted amino acid derivatives affords azomethine ylides through well known condensation processes. A similar reaction with *N*-unsubstituted amino acid derivatives gives pyrimido[4,5-*b*]azepine derivatives *via* an intramolecular ene reaction of the imines, obtained from diones **1** and *N*-unsubstituted amino acid derivatives. The reaction profiles depend upon the *N*-substituent patterns of the amino acid derivatives utilised.

The condensation of aldehyde and α-amino acid derivatives has been recognised as a versatile route of access to azomethine ylide intermediates. *N*-Substituted azomethine ylide intermediates are directly formed by the condensation with *N*-substituted amino acid esters[2] or by the decarboxylative condensation with *N*-substituted amino acids.[3] On the other hand, *N*-unsubstituted (or *N*-protonated) ylides are generated *via* a 1,2-hydrogen shift of imines,†[,4] which are formed initially from aldehydes and *N*-unsubstituted amino acids and amino acid esters.

In previous papers, we described the successful utilisation of intramolecular azomethine imine[6] and nitrile imine [3 + 2]-cycloaddition[7] in pyrimidine-2,4(1*H*,3*H*)-dione systems leading to pyrazolo[3',4':4,5]pyrido[2,3-*d*]pyrimidine derivatives. In order to extend the scope and utility of such cyclisations, we attempted to examine the reaction of 6-(alk-2-enylamino)-5-formyl-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-diones **1** with amino acid derivatives. The reaction profiles, interestingly, depended upon the substituent patterns on the nitrogen of the amino acid derivatives.

The reaction of diones **1** with *N*-substituted amino acid and amino acid esters gave azomethine ylide intermediates, which underwent an intramolecular [3 + 2] cycloaddition as expectedly. On the other hand, 1,3-dimethyl-5-(substituted amino)-6,9-(dihydro-5*H*-pyrimid[4,5-*b*]azepine-2,4(1*H*,3*H*)-diones and/or 3-substituted-6,8-dimethyl-1,2,3,4-tetrahydro-2,4-ethanopyrimido[4,5-*d*]pyrimidine-5,7(6*H*,8*H*)-diones were obtained in the reaction of compounds **1** with *N*-unsubstituted amino acid derivatives. The latter products, 2,4-ethanopyrimido[4,5-*d*]pyrimidines, were found to be products from the pyrimidoazepines. For the synthesis of the pyrimidoazepine framework, a similar pathway to the intramolecular ene reaction of 6-(alk-2-enylamino)-1,3-dimethyl-5-(substituted imino)methylpyrimidine-2,4(1*H*,3*H*)-diones is proposed, which were obtained initially from diones **1** and *N*-unsubstituted amino acid derivatives.

Results and Discussion

Reactions of Pyrimidine-2,4(1H,3H)-*diones* **1** *with* N-*Methylglycine and its Ethyl Ester*.—The reaction of 6-(*N*-allylbenzylamino)-5-formyl-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **1a** with *N*-methylglycine **2** in 1,4-dioxane under reflux for 5 days afforded the pyrrolo[2',3':4,5]pyrido[2,3-*d*]pyrimidine **3a** in 74% yield.

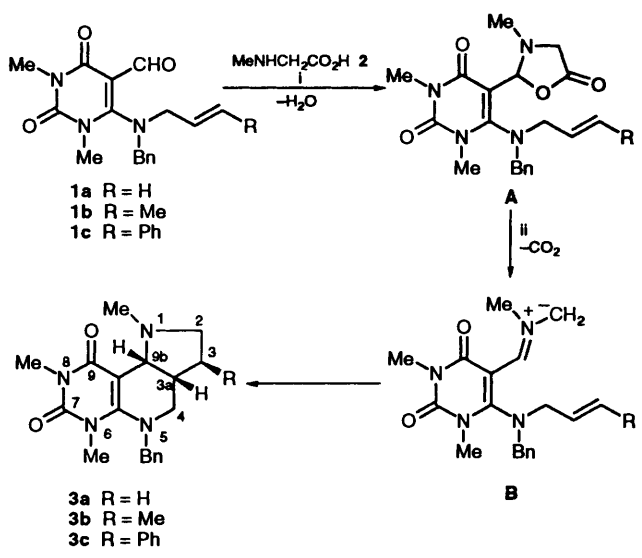
The structure of compound **3a** was assigned on the basis of its spectral data and elemental analysis. The configuration between the protons at the 3a- and 9b-position was deduced to be *cis* from their coupling constant (*J* 4.8 Hz). The reaction of 6-{*N*-benzyl-[(*E*)-but-2-enyl]amino}- **1b** and 6-{benzyl-[(*E*)-cinnamyl]amino}-5-formyl-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione **1c** with compound **2** afforded the same type of products, compounds **3b** and **3c** in 43 and 48% yield, respectively (Scheme 1). The configurations between the protons at positions 3 and 3a, and 3a and 9b, in compounds **3b** and **3c** were again assigned to be *trans* and *cis* from their coupling constants and the rules of stereochemistry of azomethine ylide cycloaddition by comparison with precedents.[8] These results mean that the decarboxylation of oxazolidinone intermediate **A**, prepared from substrates **1** and **2**, gives azomethine ylide **B**, which undergoes an intramolecular [3 + 2]cycloaddition in an *endo*-approaching manner to afford tricyclic products **3** with a 3a,9b-*cis* configuration.

Our next concern was directed toward the reaction of formyl diones **1** with *N*-substituted amino acid esters. The reaction of compound **1a** with *N*-benzylglycine ethyl ester **4** in toluene under reflux for 5 days gave pyrrolopyridopyrimidine **5a** in 74% yield. The structure of compound **5a** was confirmed by X-ray structure analysis and the configurations between the protons at positions 2 and 3a, and 3a and 9b, were found to be *trans* and *cis*, respectively. A similar reaction of compound **1a** with *N*-methylglycine ethyl ester **6** afforded the same type of product, compound **7a**.

However, slightly different results were found in the reaction of compounds **1b** and **1c** with the methylglycinate **6**; a mixture of two diastereoisomeric pyrrolopyridopyrimidines **7** and **8** was obtained (Scheme 2, Table 1). The assignments of the elaborate ^{1}H NMR spectra of products **7** and **8** showed that the configurations between the protons at positions 2 and 3, 3 and 3a, and 3a and 9b for products **7** were *cis*, *trans*, and *cis*. On the other hand, those for products **8** were *trans*, *trans*, and *cis* (see Experimental section).

The formation of products **7** and **8** could be interpreted in terms of the *endo* approach of S-shaped azomethine ylide **C**

† The thermal imine–azomethine ylide tautomerisation *via* a 1,2-hydrogen shift has also been reviewed.[5]



Scheme 1 *Reagents and conditions:* i, **2**, 1,4-dioxane, reflux

and W-shaped rotamer **D**, respectively (Fig. 1). However, W-shaped azomethine ylide **D** is expected to be unfavourable due to considerable steric repulsion between the *N*-substituent and the ester moiety.[8] The conversion of compound **7c** into its stereoisomer **8c** under basic conditions suggests that isomers **8** would be formed by epimerisation at the 2-position of compounds **7** (Scheme 2). As mentioned above, the reaction of formyl diones **1** with *N*-substituted amino acid and amino acid esters afforded azomethine ylide intermediates through well known condensation processes.

Reactions of Pyrimidine-2,4(1H,3H)-*diones* **1** *with α-Phenylglycine and* N-*Unsubstituted Amino Acid Esters.*—The reaction of compound **1a** with α-phenylglycine **9** in 1,4-dioxane under reflux for 2 days gave not the expected azomethine ylide adduct, a pyrrolopyridopyrimidine derivative, but a mixture of two products **10a** and **11a** in 55% total yield. The formulae of products **10a** and **11a** correspond to that of a product from substrates **1a** and **9** after dehydration and decarboxylation. The IR spectrum of compound **10a** showed a characteristic NH absorption at 3310 cm^{-1}. Its ^{13}C NMR spectrum exhibited six sp^3- and 14 sp^2-carbon signals, of which the signals at δ_C 128.5 and 107.9 were assignable to those of the enamine moiety. In its ^1H NMR spectrum, the array of methine (δ 4.47), methylene (δ 2.3–2.4), olefin (δ 4.77), and olefin protons (δ 5.89) was elucidated by 2D nuclear Overhauser effect spectroscopy (NOESY) techniques. The structure of compound **10a** was deduced to be 9-benzyl-5-benzylamino-1,3-dimethyl-5,6-dihydro-5*H*-pyrimido[4,5-*b*]azepine-2,4(1*H*,3*H*)-dione. On the other hand, the IR spectrum of compound **11a** showed no absorption bands due to NH stretching. In the ^{13}C NMR spectrum of compound **11a** eight sp^3- and twelve sp^2-carbon signals were observed. Therein, the carbon signals at δ_C 56.8 and 77.1 were assigned to be methine signals by DEPT measurements. Its ^1H NMR spectrum showed the array of methine (δ 4.09), methylene (δ 2.0), methylene (δ 2.2), and methine protons (δ 4.20). The ratio of products **10a** and **11a** depended upon the reaction conditions; in particular, compound **11a** was obtained as the major product in 52% yield together with compound **10a** (trace) on utilising toluene-*p*-sulfonic acid (PTSA) as a dehydration catalyst. Treatment of compound **10a** with PTSA also gave the isomer **11a** (Scheme 3). Therefore, the structure of compound **11a** was assigned to be 1,3-dibenzyl-6,8-dimethyl-1,2,3,4-tetrahydro-2,4-ethanopyrimido[4,5-*d*]pyrimidine-5,7(6*H*,8*H*)-dione. The structures

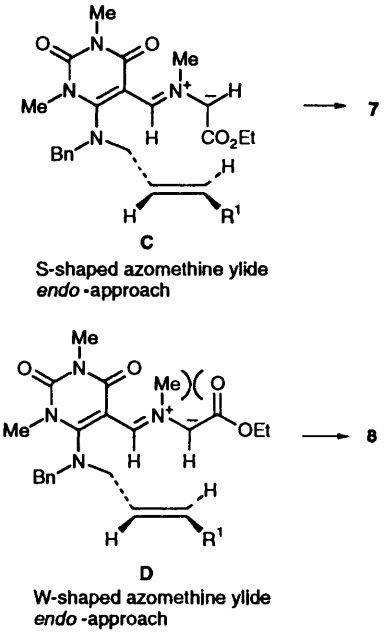


Fig. 1 Transition states for cyclisation of azomethine ylides leading to adducts **7** and **8**

Table 1 Preparation of pyrrolo[2′,3′:4,5]pyrido[2,3-*d*]pyrimidines **5a**, **7** and **8**

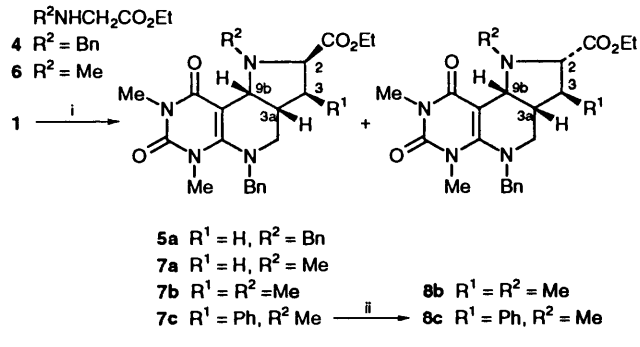
Run	R^1	R^2	Time (*t*/h)	Products	(Yield[a]/%)
1	H	Bn	120	**5a** (74)	
2	H	Me	48	**7a** (78)	
3	Me	Me	30	**7c** (54)	**8c** (10)
4	Ph	Me	30	**7d** (51)	**8d** (22)

[a] Isolated yield.

10a and **11a** were also confirmed by X-ray crystal-structure analyses (see Experimental section).

The reaction of compound **1b** with α-phenylglycine **9** in refluxing toluene gave **10b** (44%) and **11b** (10%) as mixtures of two inseparable diastereoisomers. In the same way, possible four products (**10c** and **11c**) were formed as an intractable mixture in the identical reaction of compounds **1c** and **9**.

In order to obtain a better understanding of this interesting cyclisation, the reactions of formyl dione **1a** with *N*-unsubstituted amino acid esters were examined. Pyrimidazepine **13a** and ethanopyrimidopyrimidine **14a** were formed in excellent total yield by the reaction with glycine ethyl ester **12a**. A similar reaction with L-tyrosine methyl ester **12b** gave ethano-

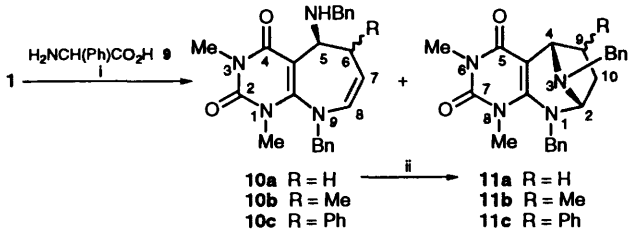


Scheme 2 *Reagents and conditions:* i, **4** (or **6**), toluene, reflux; ii, EtONa (cat.), toluene, reflux

Table 2 Reaction of compound **1a** with *N*-unsubstituted amino acid esters **12**

Run	R	R′	Time (*t*/h)	Products	Yield[a] (%)
1	H	Et	5	**13a** (61)	**14a** (34)
2	$CH_2C_6H_4$-OH(*p*)	Me	4		**14b**[b] (80)
3	Pr^i	Me	8		**14c**[c] (85)
4	Me	Me	5		**14d**[c] (84)

[a] Isolated yield. [b] Single isomer. [c] Mixture of two diastereoisomers.



Scheme 3 *Reagents and conditions:* i, **9**, 1,4-dioxane, reflux; ii, PTSA (cat.), toluene, reflux

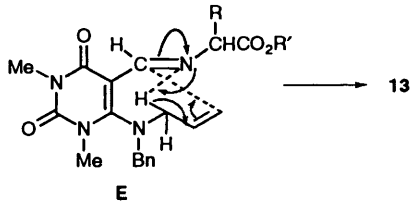
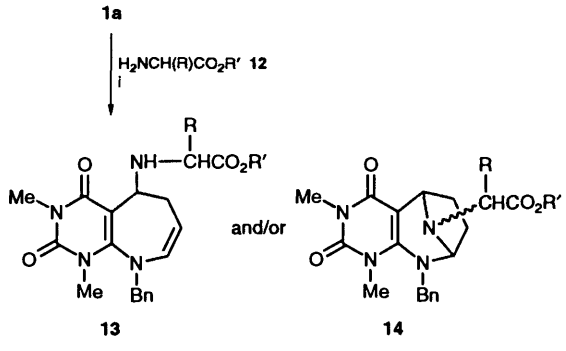


Fig. 2 Intramolecular ene reaction of species **E** leading to pyrimidazepines **13**

pyrimidopyrimidine **14b** as a single isomer (Scheme 4). The reaction of **1a** with L-leucine methyl ester **12c** and L-alanine methyl ester **12d** gave ethanopyrimidopyrimidines **14c** and **14d**, respectively. Products **14c** and **14d** thus obtained were found to be mixtures of two diastereoisomers. Both isomers of compound **14c** and one of compound **14d** were isolated pure, but their configurations could not be determined. These results are summarised in Table 2. The reactions of formyl diones **1b** and **1c** with amino acid esters **12a** and **12c** were also performed, to yield intractable mixtures of pyrimidazepines and ethanopyrimidopyrimidines.



Scheme 4 *Reagents and conditions:* i, **12**, toluene, reflux

Therefore, the condensation reaction of formyl diones **1** with *N*-unsubstituted amino acid and amino acid esters afforded pyrimidazepine derivatives **10** and **13** probably through formation of 6-(alk-2-enylamino)-1,3-dimethyl-5-[(substituted imino)methyl]pyrimidine-2,4(1*H*,3*H*)-diones **E**. The bond formation between the outer olefin carbon atom and the imine carbon atom in species **E** provides azepines fused by pyrimidine nuclei.

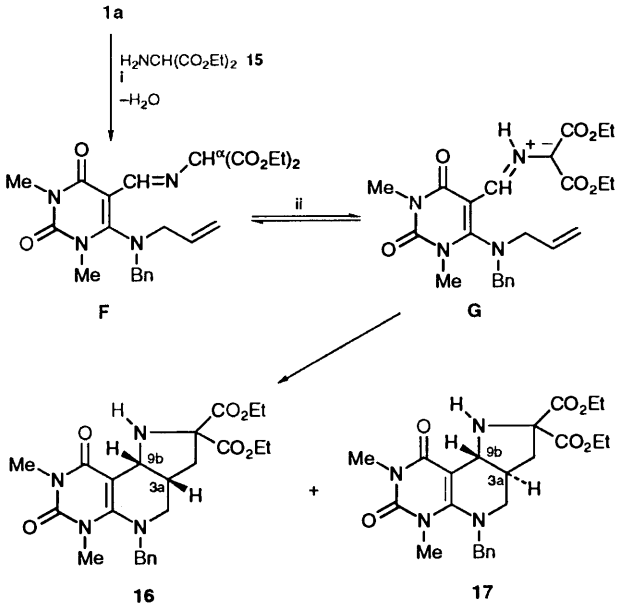
From the facts obtained so far and the results of the reaction of compounds **1** with primary amines,[9] an ene reaction process is proposed for this azepine ring construction (Fig. 2). This means that, in the imine system **E**, ene reaction occurs in preference to a 1,2-hydrogen shift leading to an *N*-protonated (*N*-unsubstituted) azomethine ylide.

No products arising from azomethine ylide intermediates were formed in the above condensations of formyl diones **1** with *N*-unsubstituted amino acid and amino acid esters. However, an exception was observed in the reaction of compound **1a** with diethyl aminomalonate **15**. Two pyrrolopyridopyrimidines, **16** and **17**, were formed in 30 and 54% yield, respectively. These were characterised as isomers by the configuration between protons at the 3a- and 9b-position from their coupling constants; *cis* for **16** (*J* 6.8 Hz) and *trans* for **17** (*J* 10.3 Hz), respectively (Scheme 5). This means that the imine **F**, resulting from condensation of compounds **1** and **15**, quickly tautomerised into *N*-protonated azomethine ylide **G**. The ylide **G** underwent an intramolecular cycloaddition in the *endo*- and *exo*-approaching manner, respectively, to give products **16** and **17**. The highly acidic α-hydrogen in **F** facilitates the tautomerisation into the ylide **G**, which could be stabilised by two ethoxycarbonyl groups at the α-position.[10]

In summary, we have shown here that the reaction profiles of formyl diones **1** with α-amino acids and esters depend upon the substituent patterns of the amino nitrogen; the condensation reaction of compounds **1** with *N*-substituted amino acid derivatives gave azomethine ylides. On the other hand, the imines formed by the condensation of compounds **1** with *N*-unsubstituted amino acid derivatives underwent an intramolecular ene reaction leading to pyrimidazepine derivatives.

Experimental

M.p.s were measured on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were measured on a JASCO IR-Report-100 spectrophotometer from samples as KBr pellets. ^1H NMR and ^{13}C NMR spectra of deuteriochloroform solution were measured on JEOL GSX-400 and/or 270 spectrometers. $SiMe_4$ was used as internal standard and *J*-values are given in Hz. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal; and ov, overlapping with each other. Mass spectra were determined on a JEOL JMS-021G-2 or JMS-D spectrometer. Elemental analyses were performed on a Hitachi 026 CHN analyser. All non-aqueous reactions were run under a positive pressure of argon. All solvents were dried by standard methods before use. The progress of reactions was monitored by TLC (Silica Gel 60F-254, Merck). Chromatographic purification was performed with Wakogel C-200 (Wako Pure Chemical Industries) and/or Silica Gel 60 (230–400 mesh, Merck). Amino acid derivatives therein are commercially available and esters **6**,



Scheme 5 *Reagent and conditions:* i, **15**, 1,4-dioxane, reflux; ii, 1,2-hydrogen shift

12a, **12c**, **12d** and **15** were obtained by treatment of the corresponding hydrochlorides with diisopropylethylamine *in situ*.

Reaction of 6-(N-*allylbenzylamino*)-5-*formyl*-1,3-*dimethylpyrimidine*-2,4(1H,3H)-*dione* **1a** *with* N-*Methylglycine* **2**; *Typical Procedure*.—A solution of compound **1a** (0.313g, 1 mmol) and *N*-methylglycine **2** (0.089 g, 1 mmol) in dry 1,4-dioxane (5 cm^3) was heated under reflux for 5 days. The mixture was concentrated to dryness. The residue was subjected to column chromatography on silica gel with hexane–ethyl acetate (1 : 5) to give the pyrrolopyridopyrimidine **3a** (0.246 g, 74%).

5-*Benzyl*-1,6,8-*trimethyl*-2,3,r-3a,4,5,c-9b-*hexahydro*-1H-*pyrrolo*[2′,3′ : 4,5]*pyrido*[2,3-d]*pyrimidine*-7,9(6H,8H)-*dione* **3a** was obtained as needles from benzene–hexane; m.p. 178–179 °C (Found: C, 67.35; H, 7.15; N, 16.5. $C_{19}H_{24}N_4O_2$ requires C, 67.03; H, 7.11; N, 16.46%); ν_{max}/cm^{-1} 1690 and 1630 (CO); δ_H(270 MHz) 1.25 (1 H, m, 3-H), 1.85 (1 H, m, 3a-H), 2.02 (1 H, m, 3-H), 2.32 (1 H, dd, *J* 9.4 and 19.0, 2-H), 2.45 (3 H, s, 1-Me), 2.90 (1 H, dd, *J* 4.4 and 13.7, 4-H), 3.05 (1 H, m, 2-H), 3.20 (1 H, d, *J* 4.8, 9b-H), 3.30 (1 H, m, 4-H), 3.35 and 3.37 (each 3 H, each s, 6- and 8-Me), 4.14 and 4.24 (each 1 H, each d, *J* 16.6, C*H*$_2$Ph) and 7.3–7.4 (5 H, Ph); δ_C(67 MHz) 26.0 (6-Me), 28.0 (C-3), 29.4 (C-3a), 34.6 (8-Me), 41.2 (1-Me), 50.8 (*C*H$_2$Ph), 54.6 and 56.6 (C-4 and -9b), 59.1 (C-2), 95.9 (C-9a), 126.6, 127.8, 129.0 and 135.9 (Ph C), 152.6 (C-5a), 156.2 (C-7) and 163.1 (C-9); *m*/*z* 340 (M^+).

5-*Benzyl*-1,3,6,8-*tetramethyl*-2,t-3,r-3a,4,5,c-9b-*hexahydro*-1H-*pyrrolo*[2′,3′ : 4,5]*pyrido*[2,3-d]*pyrimidine*-7,9(6H,8H)-*dione* **3b** was obtained as prisms from benzene–hexane; m.p. 110–112 °C (Found: C, 68.1; H, 7.55; N, 15.8. $C_{20}H_{26}N_4O_2$ requires C, 67.77; H, 7.39; N, 15.81%); ν_{max}/cm^{-1} 1685 and 1630 (CO); δ_H(270 MHz) 1.01 (3 H, d, *J* 6.8, 3-Me), 1.35 (1 H, m, 3-H), 1.67 (1 H, m, 3a-H), 1.94 (1 H, dd, *J* 7.3 and 9.8, 2-H), 2.42 (3 H, s, 1-Me), 2.95 (1 H, dd, *J* 4.0 and 13.7, 4-H), 3.1–3.2 (total 2 H, ov, 2- and 4-H), 3.29 (1 H, d, *J* 5.4, 9b-H), 3.34 and 3.37 (each 3 H, each s, 6- and 8-Me), 4.14 and 4.24 (each 1 H, each d, *J* 17.1, C*H*$_2$Ph) and 7.3–7.4 (5 H, Ph); δ_C(67 MHz) 14.2 (3-Me), 26.9 (6-Me), 33.0 (C-3), 33.4 (8-Me), 37.1 (C-3a), 40.2 (1-Me), 49.1 (*C*H$_2$Ph), 55.5 and 56.7 (C-4 and -9b), 62.9 (C-2), 94.6 (C-9a), 125.6, 127.6, 127.9 and 134.8 (Ph C), 151.5 (C-5a), 155.2 (C-7) and 162.0 (C-9); *m*/*z* 354 (M^+).

1-*Benzyl*-1,6,8-*trimethyl*-3-*phenyl*-2,t-3,r-3a,4,5,c-9b-*hexahydro*-1H-*pyrrolo*[2′,3′ : 4,5]*pyrido*[2,3-d]*pyrimidine*-7,9-(6H,8H)-*dione* **3c** was obtained as plates from hexane–ethyl acetate, m.p. 168–171 °C (Found: C, 72.0; H, 6.7; N, 13.5. $C_{25}H_{28}N_4O_2$ requires C, 72.09; H, 6.78; N, 13.45%); ν_{max}/cm^{-1} 1690 and 1630 (CO); δ_H(270 MHz) 1.90 (1 H, m, 3a-H), 2.44 (1 H, t, *J* 8.4, 2-H), 2.50 (3 H, s, 1-Me), 2.72 (1 H, dd, *J* 6.2 and 8.4, 2-H), 3.07 (1 H, dd, *J* 4.5 and 12.9, 4-H), 3.3–3.4 (total 2 H, ov, 3- and 4-H), 3.35 and 3.39 (each 3 H, each s, 6- and 8-Me), 3.60 (1 H, d, *J* 5.5, 9b-H), 4.14 and 4.25 (each 1 H, each d, *J* 16.9, C*H*$_2$Ph) and 7.1–7.4 (10 H, Ph); δ_C(67 MHz) 28.1 (6-Me), 34.4 (8-Me), 38.9 and 41.0 (C-3 and -3a), 46.1 (1-Me), 50.6 (*C*H$_2$Ph), 56.3 and 59.6 (C-4 and -9b), 65.1 (C-2), 95.6 (C-9a), 126.5 (× 2), 127.6, 127.7, 128.6, 129.0, 135.6 and 144.3 (Ph C), 152.5 (C-5a), 156.3 (C-7) and 163.1 (C-9); *m*/*z* 416 (M^+).

Reaction of Compound **1a** *with* N-*Methylglycine Ethyl Ester* **6**. *Typical Procedure*.—A suspension of compound **1a** (1 mmol), ethyl *N*-methylglycinate hydrochloride (1 mmol) and diisopropylethylamine (1.3 mmol) in toluene (5 cm^3) was heated under reflux for 2 days. The resultant precipitates were filtered off and the filtrate was concentrated to dryness. The residue was subjected to column chromatography on silica gel with hexane–ethyl acetate (1 : 1) to afford compound **7a** (0.323 g, 78%).

Ethyl 5-*benzyl*-1,6,8-*trimethyl*-7,9-*dioxo*-t-2,3,r-3a,4,5,6,7,8,9,c-9b-*decahydro*-1H-*pyrrolo*[2′,3′ : 4,5]*pyrido*[2,3-d]*pyrimidine*-2-*carboxylate* **7a** was obtained as prisms from ethanol; m.p. 149–151 °C (Found: C, 64.3; H, 6.9; N, 13.6. $C_{22}H_{28}N_4O_4$ requires C, 64.06; H, 6.84; N, 13.58%); ν_{max}/cm^{-1} 1720, 1695 and 1635 (CO); δ_H(270 MHz) 1.31 (3 H, t, *J* 7.3, CH$_2$*Me*), 1.59 (1 H, ddd, *J* 1.1, 9.2, and 13.6, 3-H), 1.93 (1 H, m, 3a-H), 2.21 (1 H, ddd, *J* 3.7, 8.4, and 13.6, 3-H), 2.47 (3 H, s, 1-Me), 2.92 (1 H, dd, *J* 4.4 and 13.2, 4-H), 3.15 (1 H, dd, *J* 12.8 and 13.2, 4-H), 3.37 (6 H, ov, 6- and 8-Me), 3.69 (1 H, dd, *J* 3.7 and 9.2, 2-H), 4.14 and 4.27 (each 1 H, each d, *J* 16.9, C*H*$_2$Ph), 4.16 (1 H, d, *J* 4.8, 9b-H), 4.20 (2 H, q, *J* 7.3, C*H*$_2$Me) and 7.2–7.4 (5 H, Ph); δ_C(67 MHz) 14.5 (CH$_2$*Me*), 28.0, 29.3 and 30.7 (C-3, -3a, and 6-Me), 34.4 and 35.8 (1- and 8-Me), 50.6 (*C*H$_2$Ph), 55.1 (C-4), 56.4 (C-9b), 60.3 (C-2), 63.8 (O*C*H$_2$Me), 95.8 (C-9a), 126.7, 127.9, 129.1 and 135.8 (Ph C), 152.6 (C-5a), 156.2 (C-9), 163.0 (C-7) and 174.0 (CO$_2$); *m*/*z* 412 (M^+).

Ethyl 1,5-*dibenzyl*-6,8-*dimethyl*-7,9-*dioxo*-t-2,3,r-3a,4,5,6,7,8,9,c-9b-*decahydro*-1H-*pyrrolo*[2′,3′ : 4,5]pyrido[2,3-d]*pyrimidine*-2-*carboxylate* **5a** was obtained as prisms from hexane–ethyl acetate; m.p. 148–150 °C (Found: C, 68.9; H, 6.6; N, 11.3. $C_{28}H_{32}N_4O_4$ requires C, 68.83; H, 6.60; N, 11.47%); ν_{max}/cm^{-1} 1730, 1695 and 1630 (CO); δ_H(400 MHz) 1.27 (3 H, t, *J* 7.3, CH$_2$*Me*), 1.60 (1 H, ddd, *J* 1.1, 9.5 and 13.6, 3-H), 1.90 (1 H, m, 3a-H), 2.14 (1 H, ddd, *J* 3.7, 8.4 and 13.6, 3-H), 2.94 (1 H, dd, *J* 4.0 and 13.2, 4-H), 3.3 (1 H, ov, 4-H), 3.31 and 3.37 (each 3 H, each s, 6- and 8-Me), 3.35 (1 H, dd, *J* 3.7 and 9.5, 2-H), 3.8–4.3 (total 6 H, ov, C*H*$_2$Ph and OC*H*$_2$Me), 4.43 (1 H, d, *J* 4.8, 9b-H) and 7.1–7.4 (10 H, Ph); δ_C(100 MHz) 14.4 (CH$_2$*Me*), 28.0, 29.1 and 30.7 (C-3, -3a and 6-Me), 34.4 (8-Me), 50.8 and 51.6 (*C*H$_2$Ph), 54.4 (C-4), 56.4 (C-9b), 59.4 (O*C*H$_2$Me), 60.2 (C-2), 95.9 (C-9a), 126.5, 126.7, 127.8, 127.9, 128.2 (× 2), 129.1, 135.8 and 140.4 (Ph C), 152.5 (C-5a), 156.2 (C-9), 163.1 (C-7) and 174.1 (CO$_2$); *m*/*z* 488 (M^+).

The structue of compound **5a** was confirmed by X-ray crystal-structure analysis and the crystal data are summarised in Table 3.

Ethyl 5-*benzyl*-1,3,6,8-*tetramethyl*-7,9-*dioxo*-t-2,t-3,r-3a,4,5,6,7,8,9,c-9b-*decahydro*-1H-*pyrrolo*[2′,3′ : 4,5]*pyrido*[2,3-d]-*pyrimidine*-2-*carboxylate* **7b** was obtained as prisms from ethanol; m.p. 169–171 °C (Found: C, 64.85; H, 7.1; N, 12.9. $C_{23}H_{30}N_4O_4$ requires C, 64.77; H, 7.09; N, 13.14%); ν_{max}/cm^{-1} 1725, 1685 and 1635 (CO); δ_H(270 MHz) 0.98 (3 H, d, *J* 7.3,

Table 3 Crystal data for compounds **5a**, **10a** and **11a**

	5a	**10a**	**11a**
Molecular formula	$C_{28}H_{32}N_4O_4$	$C_{24}H_{26}N_4O_2$	$C_{24}H_{26}N_4O_2$
Relative molecular mass	488.59	402.49	402.49
Crystal system	Triclinic	Monoclinic	Triclinic
Space group	$P\bar{1}$(#2)	$P2_1/a$(#14)	$P\bar{1}$(#2)
Cell constants			
a(Å)	11.042(2)	13.004(3)	14.982(2)
b(Å)	12.798(2)	14.565(4)	16.610(3)
c(Å)	10.412(2)	12.710(2)	9.507(1)
α(°)	95.62(1)		102.83(1)
β(°)	116.00(1)	119.31(1)	96.30(1)
γ(°)	101.49(1)		111.720(1)
Volume (Å^3)	1267.0(4)	2099.0(9)	2094.3(5)
Z	2	4	4
D_c (g cm^{-3})	1.281	1.273	1.276

3-Me), 1.31 (3 H, t, *J* 7.3, CH_2Me), 1.65 (1 H, m, 3a-H), 2.14 (1 H, m, 3-H), 2.50 (3 H, s, 1-Me), 3.01 (1 H, dd, *J* 4.9 and 13.7, 4-H), 3.10 (1 H, dd, *J* 10.3 and 13.7, 4-H), 3.36 and 3.37 (each 3 H, each s, 6- and 8-Me), 3.80 (1 H, d, *J* 8.8, 2-H), 4.1–4.3 (total 3 H, ov, OCH_2Me and CHHPh), 4.32 (1 H, d, *J* 16.6, CHHPh), 4.50 (1 H, d, *J* 6.4, 9b-H) and 7.3–7.4 (5 H, Ph); δ_C(67 MHz) 14.5 (CH_2Me), 15.6 (3-Me), 28.0 (6-Me), 33.9 (8-Me), 36.3 (C-3a), 37.7 (C-3), 39.9 (1-Me), 49.7 (CH_2Ph), 54.4 (C-4), 56.2 (C-9b), 59.9 (C-2), 70.1 (OCH_2Me), 96.9 (C-9a), 126.7, 127.8, 129.0 and 135.8 (Ph C), 152.5 (C-5a), 155.8 (C-9), 163.1 (C-7) and 171.9 (CO_2); *m*/*z* 426 (M^+).

Ethyl 5-benzyl-1,3,6,8-tetramethyl-7,9-dioxo-c-2,t-3,r-3a,4,5,6,7,8,9,c-9b-decahydro-1H-pyrrolo[2′,3′:4,5]*pyrido*[2,3-d]*-pyrimidine-2-carboxylate* **8b** was obtained as crystals; m.p. 159–160 °C (Found: C, 65.0; H, 7.2; N, 13.1%); ν_{max}/cm^{-1} 1740, 1690 and 1625 (CO); δ_H(270 MHz) 1.17 (3 H, d, *J* 7.3, 3-Me), 1.26 (3 H, t, *J* 7.3, CH_2Me), 1.36 (1 H, m, 3a-H), 1.73 (1 H, m, 3-H), 2.44 (3 H, s, 1-Me), 2.74 (1 H, d, *J* 6.4, 2-H), 2.93 (1 H, dd, *J* 4.4 and 13.2, 4-H), 3.34 and 3.36 (each 3 H, each s, 6- and 8-Me), 3.47 (1 H, dd, *J* 12.2 and 13.2, 4-H), 3.62 (1 H, d, *J* 5.4, 9b-H), 4.15 and 4.26 (each 1 H, each d, *J* 16.1, CH_2Ph), 4.1–4.2 (total 2 H, ov, OCH_2Me) and 7.3–7.5 (5 H, Ph); δ_C(67 MHz) 14.2 (CH_2Me), 20.6 (3-Me), 28.6 (6-Me), 34.5 (8-Me), 36.9 (C-3a), 40.0 and 40.3 (C-3 and 1-Me), 49.6 (CH_2Ph), 56.6 and 57.2 (C-4 and -9b), 60.7 (C-2), 75.2 (OCH_2Me), 95.2 (C-9a), 126.6, 127.8, 129.0 and 135.6 (Ph C), 152.5 (C-5a), 156.3 (C-9), 163.0 (C-7) and 173.3 (CO_2).

Ethyl 5-benzyl-1,6,8-trimethyl-7,9-dioxo-3-phenyl-t-2,t-3,r-3a,4,5,6,7,8,9,c-9b-decahydro-1H-pyrrolo[2′,3′:4,5]*pyrido*[2,3-d]*-pyrimidine-2-carboxylate* **7c** was obtained as pale yellow prisms from benzene; m.p. 107–109 °C (Found: C, 68.8; H, 6.8; N, 11.4. $C_{28}H_{32}N_4O_4$ requires C, 68.83; H, 6.60; N, 11.47%); ν_{max}/cm^{-1} 1730, 1715, 1695 and 1630 (CO); δ_H(270 MHz) 0.86 (3 H, dd, *J* 6.8 and 7.3, CH_2Me), 2.35 (1 H, m, 3a-H), 2.57 (3 H, s, 1-Me), 3.11 (1 H, dd, *J* 4.9 and 13.1, 4-H), 3.22 (1 H, dd, *J* 3.9 and 9.3, 3-H), 3.30 (1 H, dd, *J* 9.8 and 13.1, 4-H), 3.36 and 3.40 (each 3 H, each s, 6- and 8-Me), 3.69 (1 H, dq, *J* 6.8 and 10.7, OCH*H*Me), 3.69 (1 H, dq, *J* 7.3 and 10.7, OCH*H*Me), 4.07 (1 H, d, *J* 9.3, 2-H), 4.16 and 4.32 (each 1 H, each d, *J* 17.1, CH_2Ph), 4.81 (1 H, d, *J* 6.3, 9b-H) and 7.1–7.4 (10 H, Ph); δ_C(67 MHz) 13.8 (CH_2Me), 28.0 (6-Me), 34.0 (8-Me), 36.4 (C-3a), 38.0 (1-Me), 49.8 (C-3), 50.3 (CH_2Ph), 55.6 (C-4), 56.2 (C-9b), 59.7 (C-2), 71.5 (OCH_2Me), 96.7 (C-9a), 126.6, 127.0, 127.7, 128.1, 128.7, 129.0, 135.1 and 139.9 (Ph C), 152.5 (C-5a), 155.8 (C-9), 163.1 (C-7) and 170.9 (CO_2); *m*/*z* 488 (M^+).

Ethyl 5-benzyl-1,6,8-trimethyl-7,9-dioxo-3-phenyl-c-2,t-3,r-3a,4,5,6,7,8,9,c-9b-decahydro-1H-pyrrolo[2′,3′ : 4,5]*pyrido*[2,3-d]*-pyrimidine-2-carboxylate* **8c** was obtained as prisms from benzene–hexane; m.p. 180–182 °C (Found: C, 68.7; H, 6.65; N, 11.6%); ν_{max}/cm^{-1} 1740, 1695 and 1640 (CO); δ_H(270 MHz) 1.22 (3 H, t, *J* 7.3, CH_2Me), 1.92 (1 H, m, 3a-H), 2.53 (3 H, s, 1-Me), 2.83 (1 H, d, *J* 6.8, 3-H), 3.08 (1 H, dd, *J* 4.4 and 13.2, 4-H), 3.24 (1 H, d, *J* 6.8, 2-H), 3.35 and 3.39 (each 3 H, each s, 6- and 8-Me), 3.60 (1 H, dd, *J* 12.2 and 13.2, 4-H), 3.98 (1 H, d, *J* 5.4, 9b-H), 4.10 and 4.29 (each 1 H, each d, *J* 16.6, CH_2Ph), 4.1–4.2 (2 H, ov, OCH_2Me) and 7.1–7.4 (10 H, Ph); δ_C(67 MHz) 14.2 (CH_2Me), 28.1 (6-Me), 34.5 (8-Me), 37.8 (1-Me), 39.8 (C-3a), 50.0 (CH_2Ph), 51.6 (C-3), 56.5 (C-4), 59.4 (C-9b), 60.9 (C-2), 76.0 (OCH_2Me), 95.3 (C-9a), 126.4, 127.0, 127.5, 127.8, 128.7, 129.0, 135.5 and 143.0 (Ph C), 152.4 (C-5a), 156.4 (C-9), 163.0 (C-7) and 174.8 (CO_2); *m*/*z* 488 (M^+).

The stereochemical relationship between the protons at positions 2 and 3 for compounds **7** and **8** were assigned on the basis of the coupling constants (lager one is *cis*) according to precedent.[8] While the ethyl protons in the ethoxy group of ester **7c** are apparently shielded magnetically, the proton at the 2-position of stereoisomer **8c** was observed at higher field (Δδ 0.83 ppm) than that of compound **7c**, due to the phenyl group at the 3-position.

Conversion of β-Ester **7c** *into α-Ester* **8c** *under Basic Conditions.*—A solution of compound **7c** (0.06 g, 0.14 mmol) and a catalytic amount of sodium ethoxide in toluene (1 cm^3) was heated under reflux for 8 h. The reaction mixture was passed through a Florisil pad and the pad was washed with toluene (3 × 3 cm^3). The toluene filtrate was evaporated to dryness to give a 36 : 64 mixture of stereoisomers **7c** and **8c** (0.055 g, 92%).

Reaction of Compound **1a** *with Phenylglycine* **9**; *Typical Procedure.*—A solution of reagents **1a** (1.0 mmol) and **9** (1.0 mmol) in 1,4-dioxane (5 cm^3) was heated under reflux for 52 h. The reaction mixture was concentrated to dryness, which was subjected to column chromatography on silica gel with hexane–ethyl acetate (2:1) to give isomeric products **11a** (trace) and **10a** (0.206 g, 54%).

9-Benzyl-5-benzylamino-1,3-dimethyl-6,9-dihydro-5H-pyrimid[4,5-b]*azepine-2,4(1H,3H)-dione* **10a** was obtained as prisms from hexane–ethyl acetate; m.p. 145–146 °C (Found: C, 71.8; H, 6.6; H, 13.7. $C_{24}H_{26}N_4O_2$ requires C, 71.62; H, 6.51; N, 13.92%); ν_{max}/cm^{-1} 3310 (NH), 1690 and 1630 (CO); δ_H(400 MHz) 1.63 (1 H, m, NH), 2.36 (total 2 H, ov, 6-H_2), 3.30 and 3.41 (each 1 H, each d, *J* 13.6, NHCH_2Ph), 3.38 and 3.47 (each 3 H, each s, 1- and 3-Me), 4.24 and 4.32 (each 1 H, each d, *J* 13.9, 9-CH_2Ph), 4.47 (1 H, br, 5-H) 4.77 (1 H, m, 7-H), 5.89 (1 H, ddd, *J* 1.5, 1.8, and 9.6, 8-H) and 7.1–7.3 (10 H, Ph); δ_C(100 MHz) 28.6 (3-Me), 32.8 (C-6), 35.3 (1-Me), 49.5 and 51.4 (CH_2Ph), 58.2 (C-5), 107.9 (C-7), 108.2 (C-4a), 126.6,

128.0, 128.1, 128.5, 128.6, 128.8, 128.9, 135.1 and 140.4 (C-8 and Ph C), 151.4 (C-9a), 153.2 (C-2) and 162.8 (C-4); *m/z* 402 (M^+).

1,3-*Dibenzyl*-6,8-*dimethyl*-1,2,3,4-*tetrahydro*-2,4-*ethano*-*pyrimido*[4,5-d]*pyrimidine*-5,7(6H,8H)-*dione* **11a** was obtained as needles from hexane–ethyl acetate; m.p. 150–152 °C (Found: C, 71.5; H, 6.5; N, 14.0%); ν_{max}/cm^{-1} 1690 and 1640 (CO); δ_H(400 MHz) 1.95–2.33 (total 4 H, ov, 9- and 10-H), 3.29 and 3.40 (each 3 H, each s, 6- and 8-Me), 3.51 and 3.75 (each 1 H, each d, *J* 13.5, 3-CH_2Ph), 4.09 (1 H, d, *J* 5.4, 4-H), 4.2 (total 3 H, ov, 2-H and 1-CH_2Ph) and 7.0–7.4 (10 H, Ph); δ_C(100 MHz) 27.9 (6-Me), 30.3 and 33.8 (C-9 and -10), 34.3 (8-Me), 53.4 and 55.5 (2 × CH_2Ph), 56.8 (C-4), 77.1 (C-2), 99.2 (C-4a), 126.7, 127.4, 127.6, 128.5, 128.8, 128.9, 136.4 and 138.4 (Ph C), 152.6 and 152.9 (C-7 and -8a) and 161.3 (C-5); *m/z* 402 (M^+).

The structures of compounds **10a** and **11a** were confirmed by X-ray structure analyses and the crystal data are summarised in Table 3.

9-*Benzyl*-5-*benzylamino*-1,3,6-*trimethyl*-6,9-*dihydro*-5H-*pyrimid*[4,5-b]*azepine*-2,4(1H,3H)-*dione* **10b** was obtained as prisms from hexane–ethyl acetate; m.p. 148–149 °C (Found: C, 72.3; H, 6.75; N, 13.3. $C_{25}H_{28}N_4O_2$ requires C, 72.09; H, 6.78; N, 13.45%); ν_{max}/cm^{-1} 3340 (NH), 1695 and 1660 (CO); *m/z* 416 (M^+), 325 ($M^+ - CH_2Ph$) and 310 $M^+ - NHCH_2Ph$).

This product **10b** was obtained as an 89:11 mixture of two diastereoisomers. Isomer **10b** (major): δ_H(270 MHz) 1.05 (3 H, d, *J* 6.0, 6 Me), 1.3–1.7 (1 H, br, NH), 2.54 (1 H, m, 6-H), 3.28 (1 H, d, *J* 13.9, NHC*H*HPh), 3.4 (1 H, ov, NHCH*H*Ph), 3.39 and 3.48 (each 3 H, each s, 1- and 3-Me), 4.2 (1 H, ov, 5-H), 4.23 and 4.35 (each 1 H, each d, *J* 14.3, CH_2Ph), 4.46 (1 H, dt, *J* 1.8 and 9.9, 7-H), 5.77 (1 H, dd, *J* 2.6 and 9.9, 8-H) and 7.0–7.3 (10 H, Ph); δ_C(67 MHz) 21.0 (6-Me), 28.6 (3-Me), 35.5 (1-Me), 37.0 (C-6), 51.2 and 55.1 (2 × CH_2Ph), 58.3 (C-5), 109.0 (C-4a), 113.8 (3-7), 128.5 (C-8), 126.4, 126.5, 127.9, 128.0, 128.6, 129.1, 135.1 and 141.1 (Ph C), 150.9 (C-9a), 153.3 (C-2) and 163.0 (C-4).

Isomer **10b** (minor): δ_H(270 MHz) (assigned signals) 0.92 (d, *J* 6.9, 6-Me), 3.39 and 3.44 (each s, 1- and 3-Me) and 4.86 (dd, *J* 5.9 and 9.2, 7-H); δ_C(67 MHz) (assigned signals) 16.1 (6-Me), 28.3 (3-Me), 34.3 (1-Me), 39.3 (C-6), 53.0 and 57.1 (2 × CH_2Ph), 59.5 (C-5), 103.4 and 104.6 (C-4a and -7), 119.3, 126.7, 128.2, 128.4, 129.0 and 137.1 (C-8 and Ph C), 153.3 (C-2) and 163.5 (C-4).

1,3-*Dibenzyl*-6,8,9-*trimethyl*-1,2,3,4-*tetrahydro*-2,4-*ethano*-*pyrimido*[4,5-d]*pyrimidine*-5,7(6H,8H)-*dione* **11b** was obtained as a solid; m.p. 155–157 °C (Found: C, 71.85; H, 6.50; N, 13.23%); ν_{max}/cm^{-1} 1710 and 1640 (CO); *m/z* 416 (M^+), 325 ($M^+ - CH_2Ph$) and 310 ($M^+ - NHCH_2Ph$). This product was obtained as 56:44 mixture of two diastereoisomers.

11b (major): δ_H(270 MHz) 1.02 (3 H, d, *J* 6.8, 9-Me), 1.49 (1 H, dd, *J* 7.6 and 13.6, 10-H), 2.67 (1 H, m, 9-H), 3.26 and 3.34 (each 3 H, each s, 6- and 8-Me), 3.69 and 3.80 (each 1 H, each d, *J* 13.6, CH_2Ph), 4.10 (1 H, d, *J* 6.8, 4-H), 4.43 (2 H, s, CH_2Ph), 4.62 (1 H, d, *J* 6.0, 2-H) and 7.1–7.4 (Ph).

11b (minor): δ_H(270 MHz) 1.16 (3 H, d, *J* 6.4, 9-Me), 1.81 (1 H, dd, *J* 6.0 and 10.8, 10-H), 2.36 (total 2 H, ov, 9- and 10-H), 3.18 and 3.35 (each 3 H, each s, 6- and 8-Me), 3.83 and 3.90 (each 1 H, each d, *J* 13.7, CH_2Ph), 4.05 (1 H, d, *J* 4.8, 2-H), 4.28 (2 H, s, CH_2Ph), 4.30 (1 H, d, *J* 6.4, 4-H) and 7.1–7.4 (Ph).

N-(9-*Benzyl*-1,3-*dimethyl*-2,4-*dioxo*-2,3,4,5,6,9-*hexahydro*-1H-*pyrimid*[4,5-b]*azepin*-5-*yl*)*glycine ethyl ester* **13a** was obtained as prisms from ethanol; m.p. 152–153 °C (Found: C, 63.6; H, 6.6; N, 13.9. $C_{21}H_{26}N_4O_4$ requires C, 63.30; H, 6.58; N, 14.06%); ν_{max}/cm^{-1} 3320 (NH), 1715, 1690 and 1630 (CO); δ_H(400 MHz) 1.25 (3 H, t, *J* 7.3, CH_2Me), 1.25 (1 H, br, NH), 2.40 (total 2 H, ov, 6-H_2), 2.80 and 3.02 (each 1 H, each d, *J* 17.3, NHCH_2CO_2), 3.35 and 3.49 (each 3 H, each s, 1- and 3-Me), 4.12 (2 H, q, *J* 7.3, OCH_2Me), 4.27 and 4.36 (each 1 H, each d, *J* 14.2, CH_2Ph), 4.46 (1 H, br, 5-H), 4.77 (1 H, m, 7-H), 5.91 (1 H, br d, *J* 9.8, 8-H) and 7.2–7.4 (5 H, Ph); δ_C(100 MHz) 14.2 (CH_2Me), 28.5 (3-Me), 33.0 (C-6), 35.2 (1-Me), 48.8 (NH*C*H_2CO_2), 50.3 (C-5), 58.2 (*C*H_2Ph), 60.5 (O*C*H_2Me), 107.3 and 107.6 (C-4a and -7), 128.7, 128.8, 129.1 and 135.2 (Ph C and C-8), 151.6 (C-9a), 153.0 (C-2), 162.8 (C-4) and 171.9 (CO_2); *m/z* 398 (M^+).

Ethyl (1-*benzyl*-6,8-*dimethyl*-5,7-*dioxo*-1,2,3,4,5,6,7,8-*octa*-*hydro*-2,4-*ethanopyrimido*[4,5-d]*pyrimidin*-3-*yl*)*acetate* **14a** was obtained as prisms from hexane–ethyl acetate; m.p. 132–134 °C (Found: C, 63.1; H, 6.5; N, 14.0%); ν_{max}/cm^{-1} 1740, 1690 and 1630 (CO); δ_H(270 MHz) 1.25 (3 H, t *J* 7.3, CH_2Me), 2.0–2.3 (total 4 H, ov, 9- and 10-H), 3.24 (1 H, d, *J* 16.9, NCH_2CO_2), 3.24 and 3.32 (each 3 H, each s, 6- and 8-Me), 3.41 (1 H, d, *J* 16.9, NCH*H*CO_2), 4.17 (2 H, q, *J* 7.3, OC*HH*Me), 4.22 (1 H, br d, *J* 4.4, 4-H), 4.31 (1 H, d, *J* 17.3, CH*H*Ph), 4.37 (1 H, d, *J* 6.8, 2-H), 4.65 (1 H, d, *J* 17.3, CH_2Ph) and 7.3–7.4 (5 H, Ph); δ_C(67 MHz) 14.2 (CH_2Me), 27.9 (6-Me), 30.4 and 34.5 (C-9 and -10), 34.1 (8-Me), 50.6 (*C*H_2Ph), 55.5 and 57.7 (C-4 and N*C*H_2CO_2), 61.0 (O*C*H_2Me), 78.2 (C-2), 97.8 (C-4a), 126.2, 127.7, 129.1 and 136.5 (Ph C), 152.4 (C-8a), 152.8 (C-7), 161.1 (C-5) and 172.2 (CO_2); *m/z* 398 (M^+).

Methyl α-(1-*benzyl*-6,8-*dimethyl*-5,7-*dioxo*-1,2,3,4,5,6,7,8-*octahydro*-2,4-*ethanopyrimido*[4,5-d]*pyrimidin*-3-*yl*)-β-(p-*hydroxyphenyl*)*propionate* **14b** was obtained as prisms from ethanol; m.p. 202–203 °C (Found: C, 65.8; H, 6.1; N, 11.4. $C_{27}H_{30}N_4O_5$ requires C, 66.10; H, 6.16; N, 11.42%); ν_{max}/cm^{-1} 3280 (OH), 1740, 1695 and 1620 (CO); δ_H(270 MHz) 1.9–2.2 (total 4 H, ov, 9- and 10-H), 2.86 (1 H, t, *J* 11.7, NC*H*CH_2Ar), 3.30 (total 8 H, ov, 6- and 8-Me, and CHCH_2Ar), 3.34 (3 H, s, OMe), 4.16 (1 H, d, *J* 5.9, 4-H), 4.25 and 4.50 (each 1 H, each d, *J* 17.2, CH_2PH), 4.40 (1 H, d, *J* 4.8, 2-H), 6.71 and 6.92 (each 2 H, each br d, *J* 7.7, ArH), 7.3–7.4 (5 H, Ph) and 8.83 (1 H, s, OH); δ_C(67 MHz) 27.7 (6-Me), 29.5 and 33.8 (C-9 and -10), 33.1 (8-Me), 36.8 (CH*C*H_2Ar), 51.5 (OMe), 54.7 and 55.0 (*C*H_2Ph and C-4), 63.6 (NCH), 76.9 (C-2), 100.2 (C-4a), 115.4, 126.4, 126.6, 127.6, 128.9, 129.8, 136.0 and 156.1 (Ph C), 152.4 and 152.5 (C-7 and -9a), 160.7 (C-5) and 172.7 (CO_2); *m/z* 490 (M^+) and 383 ($M^+ - CH_2C_6H_4OH$).

Methyl α-(1-*benzyl*-6,8-*dimethyl*-5,7-*dioxo*-1,2,3,4,5,6,7,8-*octahydro*-2,4-*ethanopyrimido*[4,5-b]*pyrimidin*-3-*yl*)-β-*methyl butyrate* **14c** was obtained as prisms from hexane–ethyl acetate; m.p. 162–165 °C (Found: C, 64.8; H, 7.1; N, 13.3. $C_{23}H_{30}N_4O_4$ requires C, 64.77; H, 7.09; N, 13.14%); ν_{max}/cm^{-1} 1720, 1690 and 1640 (CO); *m/z* 426 (M^+) and 335 ($M^+ - CH_2Ph$).

This product was obtained as an 83:17 mixture of two diastereoisomers. *Isomer* **14c** (*major*) was isolated in an almost pure form and was obtained as prisms from hexane–benzene; m.p. 166–167 °C (Found: C, 64.8: H, 7.1; N, 13.2%); δ_H(270 MHz) 0.94 and 0.99 (each 3 H, each d, *J* 6.8, CHMe_2), 1.9–2.2 (total 5 H, ov, 9- and 10-H_2 and C*H*Me_2), 3.01 (1 H, d, *J* 6.9, NCH, 3.27 and 3.33 (each 3 H, each s, 6- and 8-Me), 3.50 (3 H, s, OMe), 4.16 (1 H, d, *J* 5.9, 4-H), 4.18 and 4.56 (each 1 H, each d, *J* 17.1, CH_2Ph), 4.32 (1 H, br, 2-H) and 7.3–7.4 (5 H, Ph); δ_C(67 MHz) 17.2 and 20.1 (CHMe_2), 27.9 (6-Me), 29.3 (*C*HMe_2), 32.0, 34.3 and 35.1 (C-9 and -10, and 8-Me), 51.3 (OMe), 54.9 and 55.2 (*C*H_2Ph and C-4), 67.2 (NCH), 77.6 (C-2), 101.0 (C-4a), 126.5, 127.6, 129.0 and 136.5 (Ph C), 152.5 and 152.8 (C-7 and -8a), 161.1 (C-5) and 170.2 (CO_2); *m/z* 426 (M^+).

Isomer **14c** (*minor*) was isolated in a pure form and was obtained as prisms from hexane–benzene; m.p. 161–163 °C (Found: C, 64.8; H, 7.1; N, 13.2%); δ_H(270 MHz) 0.94 and 1.01 (each 3 H, each d, *J* 6.8, CHMe_2), 2.0–2.3 (5 H, ov, 9- and 10-H_2 and C*H*Me_2), 3.23 (1 H, ov, NCHCO$_2$Me), 3.22 and 3.33 (each 3 H, each s, 6- and 8-Me), 3.70 (3 H, s, OMe), 4.28 (1 H, d, *J* 5.9, 4-H), 4.39 and 4.47 (each 1 H, each d, *J* 18.1, CH_2Ph),

5.85 (1 H, d, *J* 9.8, 2-H) and 7.2–7.4 (5 H, Ph); δ_C(67 MHz) 16.6 and 20.1 (CH*Me*$_2$), 27.9 (6-Me), 28.9 (*C*HMe$_2$), 32.0 and 34.3 (C-9 and -10), 35.1 (8-Me), 51.5 (*C*H$_2$Ph), 52.7 (C-4), 54.6 (N*C*HCO$_2$Me), 64.6 (OMe), 76.9 (C-2), 94.4 (C-4a), 125.9, 127.6, 129.0 and 136.3 (Ph C), 152.5 and 152.8 (C-7 and -8a), 161.0 (C-5) and 171.8 (CO_2); *m/z* 426 (M^+) and 335 (M^+ – CH_2Ph).

Methyl α-(1-*benzyl*-6,8-*dimethyl*-5,7-*dioxo*-1,2,3,4,5,6,7,8-*octahydro*-2,4-*ethanopyrimido*[4,5-b]*pyrimidin*-3-*yl*)*propionate* **14d** was obtained as prisms from hexane–ethyl acetate; m.p. 174–178 °C (Found: C, 63.6; H, 6.6; N, 14.3. $C_{21}H_{26}N_4O_4$ requires C, 63.30; H, 6.58; N, 14.06%). This product was obtained as a 64:36 mixture of two diastereoisomers. *Isomer* **14d** (*major*) was isolated pure and was obtained as prisms from hexane–benzene; m.p. 174 °C (Found: C, 63.45; H, 6.7; N, 14.2%); ν_{max}/cm^{-1} 1740 and 1695 (CO); δ_H(270 MHz) 1.41 (3 H, d, *J* 7.0, CH*Me*), 1.9–2.2 (total 4 H, ov, 9- and 10-H), 3.09 (1 H, q, *J* 7.0, C*H*Me), 3.30 and 3.34 (each 3 H, each s, 6- and 8-Me), 3.59 (3 H, s, OMe), 4.08 (1 H, d, *J* 7.0, 4-H), 4.20 and 4.62 (each 1 H, each d, *J* 17.0, C*H*$_2$Ph), 4.38 (1 H, d, *J* 4.4, 2-H) and 7.2–7.5 (5 H, Ph); δ_C(67 MHz) 16.7 (CH*Me*), 27.9 (6-Me), 33.5 (8-Me), 28.8 and 32.9 (C-9 and -10), 52.2 (*C*H$_2$Ph), 54.1 (OMe), 55.2 (C-4), 56.1 (N*C*HMe), 77.8 (C-2), 101.4 (C-4a), 126.5, 127.6, 128.9 and 136.3 (Ph C), 152.7 and 152.8 (C-7 and -8a), 160.9 (C-5) and 174.1 (CO_2).

Isomer **14d** (*minor*): δ_H(270 MHz) 1.37 (3 H, d, *J* 6.8, CH*Me*), 1.85–2.3 (total 4 H, ov, 9- and 10-H), 3.23 and 3.33 (each 3 H, each s, 6- and 8-Me), 3.38 (1 H, q, *J* 6.8, NC*H*Me), 3.74 (3 H, s, OMe), 4.35–4.4 (total 3 H, ov, 2- and 4-H, and C*H*HPh), 4.42 (1 H, d, *J* 17.1, CH*H*Ph) and 7.25–7.4 (5 H, Ph); δ_C(67 MHz) 17.7 (CHMe), 27.8 (6-Me), 34.1 (8-Me), 32.0 and 35.0 (C-9 and -10), 52.2 (OMe), 53.7 and 54.8 (*C*H$_2$Ph and N*C*HMe), 55.0 (C-4), 76.3 (C-2), 94.9 (C-4a), 126.1, 127.8, 129.2 and 136.4 (Ph C), 152.6 and 152.9 (C-7 and -8a), 161.0 (C-5) and 174.2 (CO_2).

Reaction of Formyl Dione **1a** *with Diethyl Aminomalonate* **15**.—A mixture of formyl dione **1a** (1.0 mmol) diethyl aminomalonate hydrochloride (1.0 mmol), and diisopropylethylamine (1.3 mmol) in 1,4-dioxane (5 cm^3) was heated under reflux for 17 h. The resultant precipitates were filtered off and the filtrate was evaporated to dryness. The residue was subjected to column chromatography on silica gel with dichloromethane–ethyl acetate (5:2) and (2:1) to give compounds **16** (0.141 g, 30%) and **17** (0.254 g, 54%), respectively.

Diethyl 5-*benzyl*-6,8-*dimethyl*-7,9-*dioxo*-2,3,r-3a,4,5,6,7,8,9,c-9b-*decahydro*-1H-*pyrrolo*[2′,3′:4,5]*pyrido*[2,3-d]*pyrimidine*-2,2-*dicarboxylate* **16** was obtained as prisms from benzene–hexane; m.p. 127–128 °C (Found: C, 61.5; H, 6.45; N, 12.0. $C_{24}H_{30}N_4O_6$ requires C, 61.26; H, 6.43; N, 11.91%); ν_{max}/cm^{-1} 3350 (NH), 1735, 1685 and 1630 (CO); δ_H(270 MHz) 1.21 (3 H, t, *J* 7.3, CH$_2$*Me*), 1.29 (3 H, t, *J* 7.3, CH$_2$*Me*), 2.10 (1 H, ov, 3a-H), 2.13 (1 H, dd, *J* 2.0 and 14.2, 3-H), 2.57 (1 H, dd, *J* 8.3 and 14.2, 3-H), 3.02 (total 2 H, ov, 4-H$_2$), 3.36 (6 H, s, 6- and 8-Me), 3.88 (1 H, br s, NH), 4.1–4.3 (total 6 H, ov, OC*H*$_2$Me and C*H*$_2$Ph) and 7.35 (5 H, Ph); δ_C(67 MHz) 13.9 and 14.1 (CH$_2$*Me*), 27.8 (6-Me), 29.6 (C-3a), 33.1 (C-3), 34.7 (8-Me), 49.1 (*C*H$_2$Ph), 53.0 (C-9b), 55.2 (C-4), 61.9 and 62.0 (O*C*H$_2$Me), 70.7 (C-2), 98.6 (C-9a), 126.8, 128.0, 129.1 and 135.1 (Ph C), 152.6 (C-5a), 154.0 (C-7), 163.5 (C-9) and 170.3 and 172.0 (CO_2); *m/z* 470 (M^+) and 397 (M^+ – $CO_2C_2H_5$).

Diethyl 5-*benzyl*-6,8-*dimethyl*-7,9-*dioxo*-2,3,r-3a,4,5,6,7,8,9-t-9b-*decahydro*-1H-*pyrrolo*[2′,3′:4,5]*pyrido*[2,3-d]*pyrimidine*-2,2-*dicarboxylate* **17** was obtained as prisms from benzene–hexane; m.p. 192–194 °C (Found: C, 61.5; H, 6.5; N, 11.95%); ν_{max}/cm^{-1} 3350 (NH), 1725, 1690 and 1630 (CO); δ_H(270 MHz) 1.24 and 1.26 (each 3 H, each t, *J* 7.3, CH$_2$*Me*), 1.68 (1 H, dd, *J* 12.2 and 12.7, 3-H), 2.18 (1 H, m, 3a-H), 2.81 (1 H, dd, *J* 6.4 and 12.7, 3-H), 3.03 (1 H, dd, *J* 12.2 and 12.2, 4-H), 3.28 (1 H, dd, *J* 3.4 and 12.2, 4-H), 3.31 and 3.34 (each 3 H, each s, 6- and 8-Me), 3.68 (1 H, dd, *J* 3.9 and 10.3, 9b-H), 4.0–4.3 (total 6H, ov, OC*H*$_2$Me and C*H*$_2$Ph), 4.36 (1 H, d, *J* 3.9, NH) and 7.2–7.4 (5 H, Ph); δ_C(67 MHz) 13.9 and 14.1 (CH$_2$*Me*), 27.7 (6-Me), 34.2 and 34.8 (C-3 and 8-Me), 38.8 (C-3a), 50.7 (*C*H$_2$Ph), 57.5 (C-4), 58.7 (C-9b), 61.9 and 62.0 (O*C*H$_2$Me), 72.0 (C-2), 97.7 (C-9a), 126.5, 127.9, 129.1 and 135.5 (Ph C), 153.0 (C-5a), 154.8 (C-7), 161.9 (C-9) and 170.1 and 172.0 (CO_2); *m/z* 470 (M^+), 441 (M^+ – C_2H_5) and 397 (M^+ – $CO_2C_2H_5$).

Single-crystal X-Ray Structure Determinations.—Single crystals (prisms) of compounds **5a**, **10a** and **11a** for X-ray diffraction studies were recrystallised from ethanol. A crystal of approximate dimensions 0.200 × 0.120 × 0.280 mm was used for data collection of compound **5a**, one of 0.280 × 0.400 × 0.880 mm of compound **10a**, and one of 0.260 × 0.400 × 0.640 mm of compound **11a**. All measurements were made on a Rigaku AFC5S diffractometer by employing graphite-monochromated Mo-Kα radiation. The unit-cell dimensions were obtained by least-squares analysis of 25 reflections within the range 26.6 < 2θ < 37.4° for compound **5a**, 35.87 < 2θ < 39.84° for compound **10a**, and 38.27 < 2θ < 39.69° for compound **11a**, respectively. Summaries of the crystal data for compounds **5a**, **10a** and **11a** are given in Table 3. The ω–2θ scan technique to a maximum 2θ-value of 55° was used. Scans of (1.05 + 0.30 tan θ)° were made at a speed of 16°/min (in omega) for compound **5a**, of (1.21 + 0.30 tan θ)° at a speed of 32°/min for compound **10a**, and of (1.31 + 0.30 tan θ)° at a speed of 32°/min for compound **11a**. A total of 5159

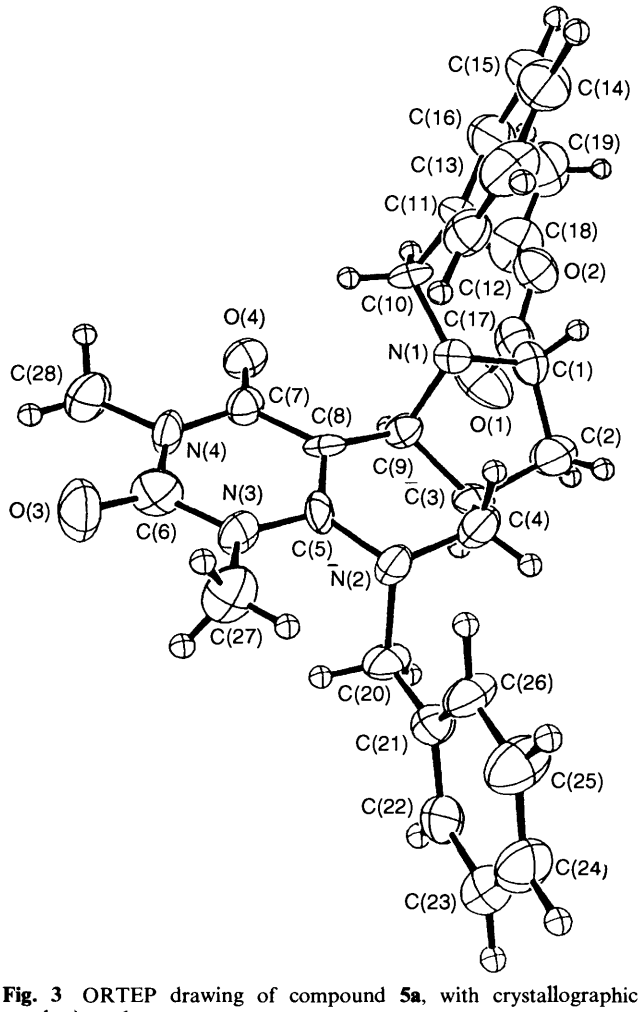


Fig. 3 ORTEP drawing of compound **5a**, with crystallographic numbering scheme

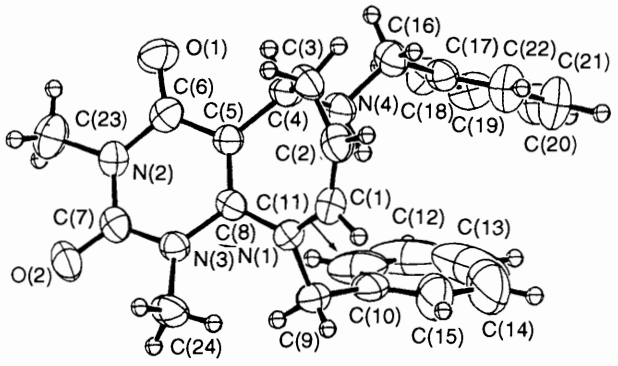


Fig. 4 ORTEP drawing of compound **10a** with crystallographic numbering scheme

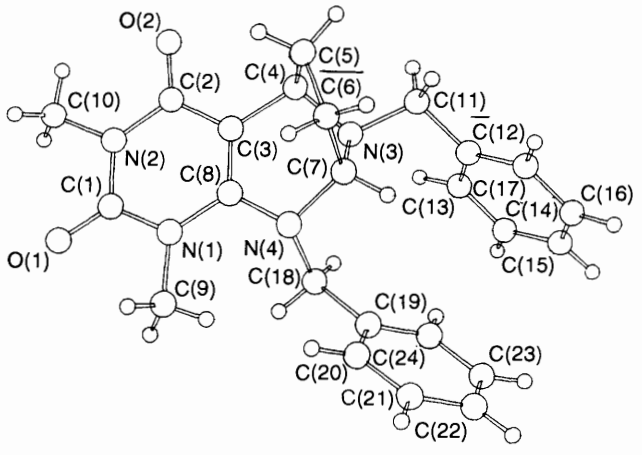


Fig. 5 PLUTO drawing of compound **11a** (one of two independent molecules contained in the single crystal of compound **11a**), with crystallographic numbering scheme

observed reflections (unique: 4854; R_{int} 0.072) for compound **5a**, 5214 (unique: 5002; R_{int} 0.049) for compound **10a**, and 9999 (unique: 9627; R_{int} 0.028) for compound **11a** was collected. All calculations were performed using the TEXSAN program.[11] Atoms other than hydrogen were refined anisotropically. The structures were solved by direct methods (MITHRIL)[12] and refined by least squares to R 0.053 (compound **5a**), 0.054 (compound **10a**) and 0.055 (compound **11a**). ORTEP[13] drawings of compounds **5a** and **10a** are shown in Figs. 3 and 4. The crystal structure of compounds **11a** contains two independent molecules.* One of these corresponds to the ethanopyrimidopyrimidine **11a** and its PLUTO[14] drawing is shown in Fig. 5.

Tables of fractional coordinates, bond lengths and angles, thermal parameters and hydrogen-atom coordinates for compounds **5a**, **10a**, and **11a** have been deposited with the Cambridge Crystallographic Database Centre.

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