Studies on fused pyrimidine derivatives. Part 15.[1] Features and mechanistic considerations of the reaction of 5-(alkylaminomethylene)-6-methyleneperhydropyrimidine-2,4-diones with tropone

Takashi Kobayashi,[a] Ken Ikuno,[b] Michihiko Noguchi *[,b] and Akikazu Kakehi[c]

[a] *Phamaceutical Research Division, Ube Laboratory, Corporate Research and Development, Ube Industries Ltd., 1878–5, Kogushi, Ube 755, Japan*

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

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

The reaction of 5-(alkylaminomethylene)-6-methyleneperhydropyrimidine-2,4-dione intermediates **3** with tropone **4** gave 2,5-ethanopyrido[2,3-*f*]quinazolines **5** and/or 6,10a-methanopyrimido[4′,5′:4,5]cyclohepta[1,2-*b*]azocines **6**. The formation of *endo*- and *exo*-[4 + 2] cycloadducts and their transformations into these products **5** and **6** will be discussed using the results of PM3 calculations. The X-ray structure of 1-benzyl-7,9-dimethyl-1,2,*r*-4a,*c*-5,6,7,8,9,10,*c*-10b-decahydro-2,5-ethanopyrido[2,3-*f*]quinazoline-8,10,11-trione and 5-benzyl-1,3-dimethyl-1,2,3,4,*r*-4b,5,*t*-6,7,10,11-decahydro-6,10a-methanopyrimido[4′,5′:4,5]-cyclopenta[1,2-*b*]azocine-2,4,10-trione are described.

Introduction

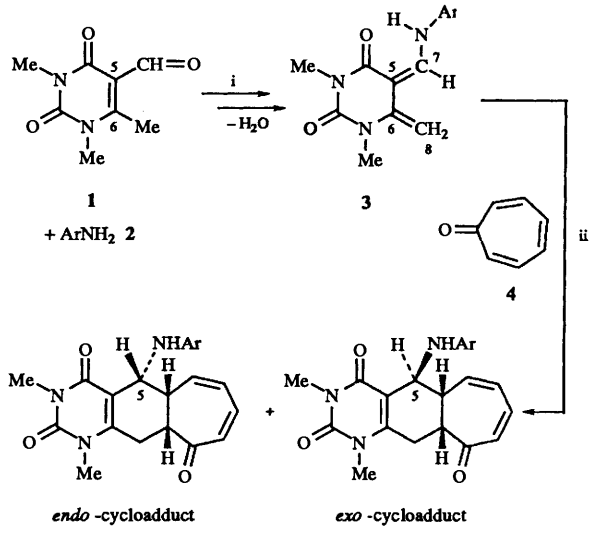
In the preceding paper,[1] we reported that the reaction of 5-(*aryl*aminomethylene)-1,3-dimethyl-6-methyleneperhydropyrimidine-2,4-diones **3** with tropone **4** gave two diastereoisomeric 5-arylamino-1,3-dimethyl-2,3,4,5,5a,10,10a,11-octahydro-1*H*-cyclohepta[*g*]quinazoline-2,4,10-triones in moderate total yields (Scheme 1). The [4 + 2] cycloaddition reaction, therein, proceeded onto the 2,3-double bond of tropone in both an *endo*- and *exo*-approaching manner. The π-electrons of the arylamino moiety in the *endo*-products attacked intramolecularly to the δ-position of the seven-membered α,β,γ,δ-unsaturated ketone moiety to afford acridine derivatives under both neutral and acidic conditions.

Therefore, our next concern was focused on the reaction of 5-(*alkyl*aminomethylene)-1,3-dimethyl-6-methyleneperhydropyrimidine-2,4-diones **3** with tropone **4** and also on the behaviour of the [4 + 2] cycloadducts expected to be formed initially in the reaction. In these reactions none of the [4 + 2] cycloadducts were obtained, but instead tetracyclic products **5** and **6** were formed. The products **5** and **6** were suggested to be secondary ones formed from the *endo*- and *exo*-[4 + 2] cycloadducts.

From considerations of the frontier orbitals of the dione **3** by using the PM3 method, we propose a stepwise process for the [4 + 2] cycloadducts as follows; nucleophilic attack of the 8-position of dione **3** on the 2-position of tropone **4** affords betaine intermediates, which undergo a ring closure to give [4 + 2] cycloadducts. The transformation processes of the [4 + 2] cycloadducts to the final products **5** and **6** will be also discussed.

Results and discussion

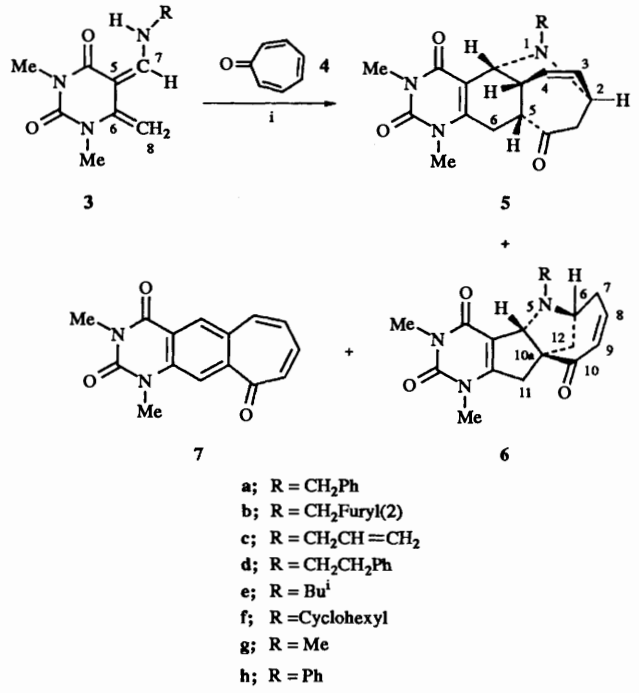
The reaction of 5-(benzylaminomethylene)-1,3-dimethyl-6-methyleneperhydropyrimidine-2,4-dione **3a** with tropone **4** in 1,4-dioxane under reflux for 6 h gave two isomeric products **5a** and **6a** in 34 and 33% yield, respectively (Scheme 2). The molecular formula of the products **5a** and **6a** corresponded to those of 1 : 1 adducts of diene **3a** and tropone **4**. The IR spectra of both products indicated no absorption bands due to NH



Scheme 1 *Reagents:* i, $ArNH_2$ **2**; ii, tropone **4**

stretching. In ^{13}C NMR spectra of both products **5a** and **6a** nine sp^3- and eleven sp^2-carbon signals were observed. These implied that the formation of compounds **5a** and **6a** included processes which involve the reaction of the benzylamino moieties of initially formed adducts. The structure of compound **5a** was assigned as 1-benzylamino-7,9-dimethyl-1,2,*r*-4a,*c*-5,6,7,8,9,10,*c*-10b-decahydro-2,5-ethanopyrido[2,3-*f*]quinazoline-8,10,11-trione by comparison of its ^1H and ^{13}C NMR spectra with those of the *endo*-[4 + 2] cycloadducts[1] of the 5-anilinomethylene dione and tropone **4**.

On the other hand, the ^{13}C NMR spectrum of compound **6a** showed a quaternary sp^3-carbon at δ_C 60.3 and its ^1H–^1H COSY spectrum revealed the alignment of methylene (12-H), methine (6-H), methylene (7-H), olefin (8-H), and olefin protons (9-H) along with the isolated methylene (11-H) and methine protons (4b-H). Therefore, the structure of compound **6a** was assigned to be 5-benzyl-1,3-dimethyl-1,2,3,4,*r*-4b,5,*t*-6,7,10,11-decahydro-6,10a-methanopyrimido[4′,5′:4,5]cyclopenta[1,2-



a; R = CH_2Ph
b; R = CH_2Furyl(2)
c; R = $CH_2CH{=}CH_2$
d; R = CH_2CH_2Ph
e; R = Bu^i
f; R = Cyclohexyl
g; R = Me
h; R = Ph

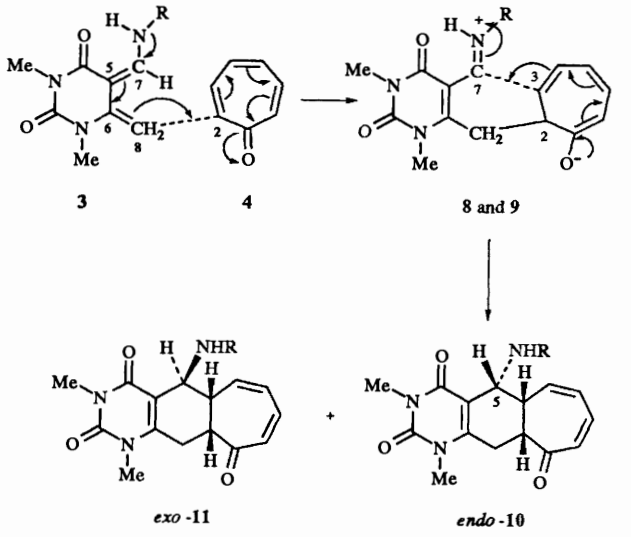
Scheme 2 *Reagents and conditions:* i, RNH_2, tropone **4**, 1,4-dioxane (benzene, acetonitrile or THF), reflux

b]azocine-2,4,10-trione. The structures of compounds **5a** and **6a** were confirmed unambiguously by X-ray crystallographic analyses (see the Experimental section).

Similar reactions of 5-(2-furfurylaminomethylene)- **3b**, 5-(allylaminomethylene)- **3c**, and 5-(phenethylaminomethylene)-substituted dione **3d** with tropone **4** gave 2,5-ethanopyrido-[2,3-*f*]quinazolines **5b–d** and 6,10a-methanopyrimido-[4′,5′:4,5]cyclopenta[1,2-*b*]azocines **6b–d** along with a small amount of 1,3-dimethyl-2,3,4,10-tetrahydro-1*H*-cyclohepta-[*g*]quinazoline-2,4,10-trione **7**.[1] Interestingly, the reactions of 5-(isobutylaminomethylene)- **3e** and 5-(cyclohexylamino-methylene)-substituted dione **3f** with tropone **4** gave 6,10a-methanopyrimidocyclopentaazocines **6e, f** and cycloheptaquin-azoline **7** in moderate total yields (Scheme 2). The ratios of products **5** and **6** seem to depend on the kinds of amino moieties in dione **3** and will be detailed later.

In order to obtain further understanding of the reaction pathway, we carried out semi-empirical molecular orbital (MO) calculations by utilising the PM3 method for 5-(methyl-aminomethylene)- **3g** and 5-(anilinomethylene)-substituted dione **3h** (see the Experimental section). The energy levels and frontier electron densities of the diene moieties of intermediates **3g** and **3h** are demonstrated in Fig. 1 together with the coefficients of the LUMO of tropone **4**.[2] The electronic features of dione **3g** are almost coincident with those of dione **3h**. This means that diene intermediates **3g** and **3h** react with tropone **4** in a similar manner. The frontier electron densities of the diene moieties reveal that these dienes can be regarded as 1,3-diaminobuta-1,3-dienes. This suggests that their cycloaddition onto the 2,3-double bond of tropone **4** proceeds in a stepwise manner; nucleophilic attack of the 8-position in dione **3** occurs in an *endo*- and *exo*-approaching manner at the 2-position of tropone **4** to give betaines *endo*-**8** and *exo*-**9**, which give *endo*-**10** and *exo*-[4 + 2] cycloadducts **11** (Scheme 3). In an early study on tropone chemistry, a similar betaine was proposed as an intermediate in the reaction of 1-(morpholino)cyclohexene with tropone **4**, in which the [2 + 4] and [2 + 8] cycloadducts are formed.[3]

The heats of formation and frontier orbitals of betaines **8g**



Scheme 3 A reaction pathway to *endo*- **10** and *exo*-[4 + 2] cycloadducts **11** by the reaction of diene **3** with tropone **4**

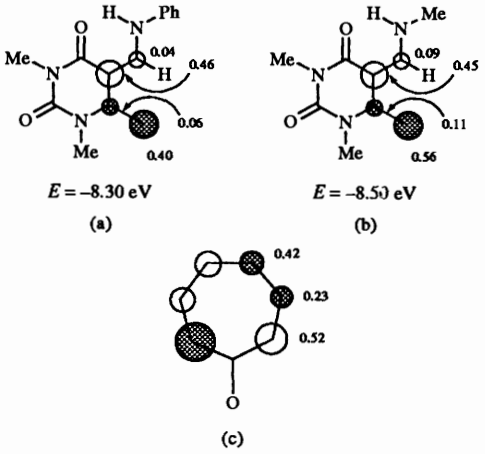
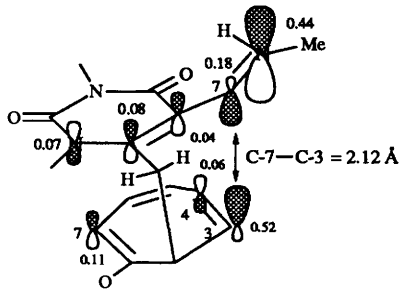


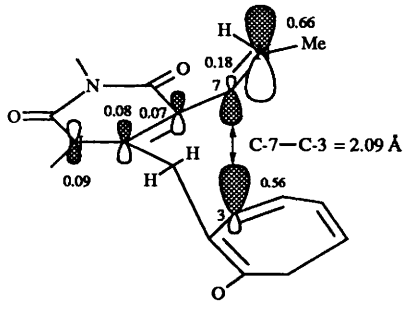
Fig. 1 (*a*) Energy level and frontier electron densities of diene moiety of compound **3h**; (*b*) energy level and frontier electron densities of diene moiety of compound **3g**; (*c*) coefficients of LUMO of tropone **4**

and **9g** are demonstrated in Fig. 2. Therein, the newly formed carbon–carbon single bonds are postulated to be 1.50 Å long and the structure optimisations were performed on the assumption that the distances between the terminals are ~2.0 Å long (see the Experimental section), in which an interaction between both terminals would be expected. The heats of formation are estimated to be −27.58 for **8g** and −31.62 kcal mol^{-1} † for **9g**. This means that the betaine **9g** due to an *exo*-approaching mode is thermodynamically favourable to **8g**. Cyclisation of betaines **8g** and **9g** to *endo*- **10g** and *exo*-[4 + 2] cycloadducts **11g** is expected to proceed smoothly; in these betaines both cyclisation terminals are able to co-locate closely and they also have orbital phases convenient for the next cyclisation process. The heats of formation of the *endo*- **10g** and *exo*-[4 + 2] cycloadducts **11g** are estimated to be −63.19 and −63.92 kcal mol^{-1}. Those of tricycles **10h** and **11h** are also estimated to be −34.34 and −38.54 kcal mol^{-1}, respectively (Fig. 3). These values mean that the formation of *exo*-[4 + 2] cycloadduct **11** is thermodynamically equal or favourable to that of *endo*-adduct **10**. It seems reasonable that the competitive formation of tricycles **10** and **11** will be expected in the reactions of 5-(alkylaminomethylene)-substituted dione systems **3a–f**

† 1 cal = 4.184 J.

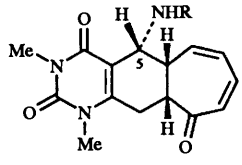


8g: *endo*-approaching mode
Heat of formation = –27.58 kcal mol^{-1}

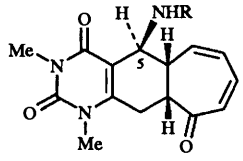


9g: *exo*-approaching mode
Heat of formation = –31.62 kcal mol^{-1}

Fig. 2 Energy levels and frontier orbitals of betaines **8g** and **9g**



Heats of formation for *endo*-adducts
10g R = Me –63.19 kcal mol^{-1}
10h R = Ph –34.34 kcal mol^{-1}

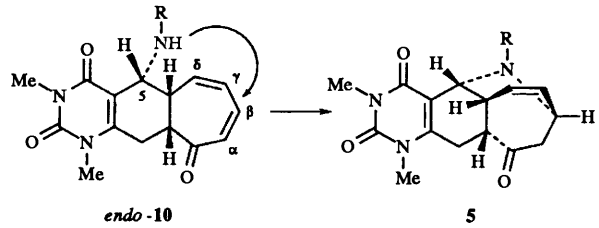


Heats of formation for *exo*-adducts
11g R = Me –63.92 kcal mol^{-1}
11h R = Ph –38.54 kcal mol^{-1}

Fig. 3 Heats of formation for *endo*- **10** and *exo*-[4 + 2] cycloadducts **11**

with tropone **4** as well as in those of 5-arylaminomethylene ones.[1]

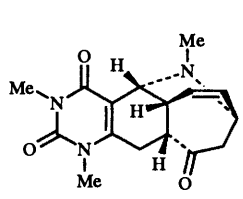
Taking the stereochemistry of products **5** into consideration, a reasonable pathway to compounds **5** was demonstrated; the *endo*-[4 + 2] cycloaddition of 5-(alkylaminomethylene)-1,3-dimethyl-6-methyleneperhydropyrimidine-2,4-dione **3** with the 2,3-bond of tropone **4** gave a cyclohepta[*g*]quinazoline derivative **10**. The alkylamino moiety at the 5-position in product **10** attacked nucleophilically at the β-position of the seven-membered α,β,γ,δ-unsaturated ketone system, leading to tetracycle **5** (Scheme 4). The transformation of *endo*-[4 + 2]



endo-**10** **5**

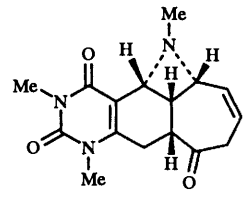
Scheme 4 A pathway from *endo*-cycloadducts **10** to pyridoquinazolines **5**

cycloadduct **10** to 2,5-ethanopyridoquinazoline **5** was also supported by the results of PM3 calculations; the heat of formation of 1,7,9-trimethyl-1,*r*-2,4a,*c*-5,6,7,8,9,10,*c*-11b-



Heat of formation
–75.65 kcal mol^{-1}

5g



Heat of formation
–67.44 kcal mol^{-1}

Fig. 4 Heats of formation for the intramolecular cyclisation products from *endo*-cycloadducts **10**

Table 1 Reaction of 5-(alkylaminomethylene)-1,3-dimethyl-6-methyl-eneperhydropyrimidine-2,4-diones **3** with tropone **4**

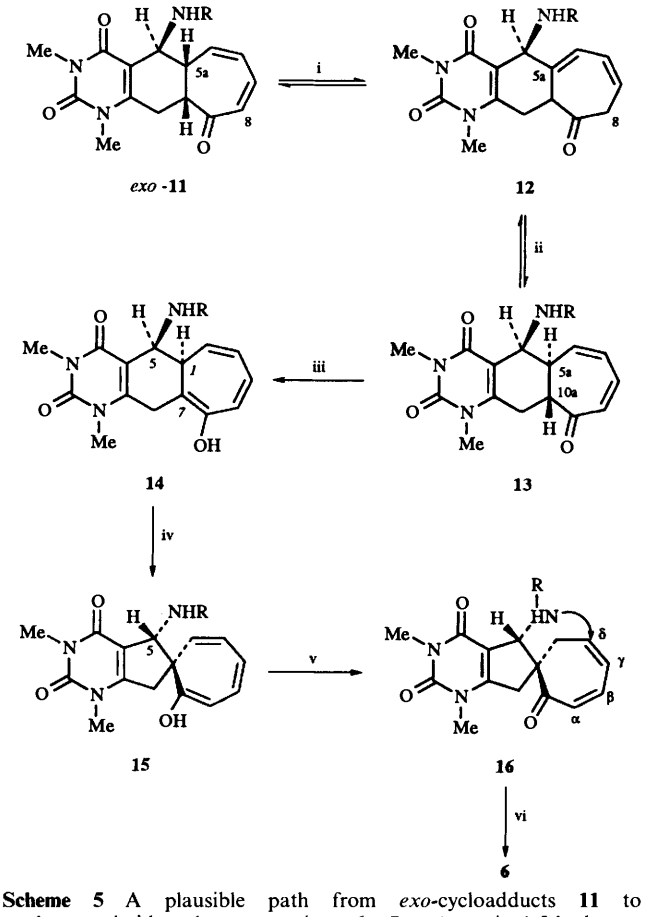
Run	R	Solvent	Time (*t*/h)	Products (Yield[a]/%)		
1	$PhCH_2$	1,4-dioxane	6	**5a** (34)	**6a** (33)	
3	$PhCH_2$	benzene	6	**5a** (21)	**6a** (21)	
3	$PhCH_2$	MeCN	6	**5a** (21)	**6a** (11)	
4	$PhCH_2$	THF[b]	10	**5a** (13)	**6a** (39)	
5	Furfuryl	1,4-dioxane	6	**5b** (25)	**6b** (26)	
6	CH_2=$CHCH_2$	1,4-dioxane	6	**5c** (23)	**6c** (40)	**7** (4)
7	$PhCH_2CH_2$	1,4-dioxane	6	**5d** (16)	**6d** (38)	**7** (4)
8	Bu^i	1,4-dioxane	6		**6e** (50)	**7** (8)
9	Bu^i	THF	6		**6e** (38)	**7** (6)
10	Cyclohexyl	1,4-dioxane	6		**6f** (35)	**7** (15)

[a] Isolation yield. [b] Tetrahydrofuran.

decahydro-2,5-ethanopyrido[2,3-*f*]quinazoline-8,10,11-trione **5g** was estimated to be –75.65 kcal mol^{-1} (Fig. 4). This means that compound **5g** is more stable than the *endo*-[4 + 2] adduct **10g** by 12.46 kcal mol^{-1} and that the transformation of **10g** to **5g** is theoretically possible.

On the other hand, it is reasonable to postulate the *exo*-[4 + 2] cycloadduct **11** as an intermediary product for the formation of the azocine **6**. The formation of fully conjugated cycloheptaquinazoline **7** in entries 5–10 of Table 1 also suggested the formation of *exo*-[4 + 2] cycloadducts **11**.[1] Although there is no obvious evidence for the transformation of the *endo*-[4 + 2] cycloadduct **11** into the azocine **6**, we here propose a plausible pathway; 1,5-shift of 5a-H in compound **11** gives a cycloheptaquinazoline **12**. A second 1,5-shift, of 8-H, in compound **12** proceeds to afford the starting material **11** and 5a,10a-*trans*-fused product **13**, respectively. The latter undergoes a 1,7-sigmatropic rearrangement to afford a spiro enolised product **15**, which isomerises to spiro system **16** bearing a seven-membered α,β,γ,δ-unsaturated ketone system. The rearrangement is expected to proceed with the inversion of the configuration on the immigrating carbon atom, if it is a concerted process. The amino group in compound **16** attacks nucleophilically at the δ-position of the ketone system to give the final product **6** (Scheme 5).

The ratios of products **5** and **6**, consequently, might reflect the facility of formation of betaines **8** and **9** as well as that of their cyclisation to *endo*- **10** and *exo*-[4 + 2] cycloadducts **11**. The heats of formation of betaines **8g** and **9g** and adducts **10g** and **11g** suggested that the formation of [4 + 2] cycloadducts might proceed somewhat *exo*-selectively. The reaction of 5-(isobutylaminomethylene) **3e** and 5-(cyclohexylaminomethyl-ene)-substituted dione **3f** with tropone **4** gave only azocines **6e** and **6f** along with cycloheptaquinazoline **7** (Table 1, entries 8–10), which are suggested to be the secondary products from *exo*-[4 + 2] cycloadducts **11e** and **11f**. Although the formation of *exo*-cycloadduct **11h** is more favourable than that of *endo*-adduct **10h** based on the heats of formation, a similar reaction of compound **3h** gave a 1:1 mixture of diastereoisomers **10h**



Scheme 5 A plausible path from *exo*-cycloadducts **11** to methanopyrimidocyclopentaazocines **6**. *Reactions:* i, 1,5-hydrogen shift; ii, 1,5-hydrogen shift; iii, enolisation; iv, 1,7-sigmatropic rearrangement; v, isomerisation to ketone; vi, nucleophilic attack of amino nitrogen.

Table 2 Crystal data for compounds **5a** and **6a**

	5a	**6a**
Molecular formula	$C_{22}H_{23}N_3O_3$	$C_{22}H_{23}N_3O_3$
Relative molecular mass	377.44	377.44
Crystal system	Orthorhombic	Orthorhombic
Space group	*Pbca* (#61)	*Pbca* (#61)
Cell constants		
a/Å	19.669(4)	20.759(2)
b/Å	20.573(5)	18.961(3)
c/Å	9.181(4)	9.687(3)
V/Å^3	3715(2)	3813(2)
Z	8	8
D_c (g cm^{-3})	1.349	1.315

and **11h** as described in the preceding paper.[1] The reactions of 5-(benzylaminomethylene) **3a**, 5-(2-furfurylaminomethylene) **3b**, 5-(allylaminomethylene) **3c** and 5-(phenylethylaminomethylene)-substituted dione **3d** with tropone **4** afforded also compounds **5** and **6** derived from the *endo*-**10** and *exo*-[4 + 2] cycloadducts **11**, respectively. The *endo*-selectivity of the reaction seems to decline as the π-electron system is remote from the amino nitrogen. Although no clear interpretation is at hand, we suggest that the *endo* selectivity would result from a negative interaction between the π-electron systems of the amino substituents and the tropone moiety in the *exo*-approaching mode during the formation of betaine and/or cyclisation from the betaine.

Conclusions

We have described the features of the reaction of 6-methylene-5-(substituted aminomethylene)perhydropyrimidine-2,4-dione intermediates **3** with tropone **4**. The 5-(alkylaminomethylene)-substituted diones **3** added to the 2,3-double bond of tropone **4** nucleophilically to give betaine intermediates **8** and **9**. These were cyclised to [4 + 2] cycloadducts **10** and **11**, which were transformed into final products **5** and **6**, respectively. It should be noted that the results of PM3 calculations provided a good understanding of this reaction pathway.

Experimental

For general details of apparatus and procedures, see the preceding paper.[1] Overlapping splitting patterns in ^{1}H NMR spectra are indicated as ov.

Reaction of diene 3a with tropone 4; typical procedures

To a refluxing solution of tropone **4** (1.16 g, 10.0 mmol) in 1,4-dioxane (5 cm^3) were added solutions of 1,3,6-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde **1** (0.182 g, 1.0 mmol) and benzylamine (0.131 cm^3, 1.2 mmol) each in 1,4-dioxane (2.5 cm^3), *via* a double-barrelled micro feeder over a period of 3 h. The reaction mixture was heated under reflux for an additional 6 h and the solvent was then evaporated off. The residue was subjected to column chromatography on a silica gel with hexane–ethyl acetate (4:1) to give the 2,5-ethanopyrido-[2,3-*f*]quinazoline **5a** (0.128 g, 34%) and the 6,10a-methanopyrido[4′,5′:4,5]cyclopenta[1,2-*b*]azocine **6a** (0.123 g, 33%).

1-*Benzyl*-7,9-*dimethyl*-1,2,r-4a,c-5,6,7,8,9,10,c-10b-*decahydro*-2,5-*ethanopyrido*[2,3-f]*quinazoline*-8,10,11-*trione* **5a** was obtained as pale yellow plates from hexane–benzene; mp 183–184 °C (Found: C, 70.1; H, 6.1; N, 10.8. $C_{22}H_{23}N_3O_3$ requires C, 70.01; H, 6.14; N, 11.13%); ν_{max}/cm^{-1} 1690 and 1650 (CO); δ_H(270 MHz) 2.35 (1 H, ddd, *J* 0.7, 2.9 and 17.6, 12-H), 2.57–2.74 (4 H, ov, 4a-, 5-, 6- and 12-H), 3.31–3.36 (4 H, ov, NMe and 2-H), 3.44–3.51 (4 H, ov, NMe and 6-H), 3.67 (1 H, d, *J* 13.9, C*H*$_2$Ph), 3.88 (1 H, d, *J* 5.1, 10b-H), 4.71 (1 H, d, *J* 13.9, C*H*$_2$Ph), 6.45–6.58 (2 H, ov, 3- and 4-H), 7.16–7.27 (5 H, ov, Ph); δ_C(68 MHz) 28.4 (7-Me), 30.6 (C-6), 31.1 (9-Me), 34.0 (C-4a), 48.5, 50.0 and 55.3 (C-2, -5 and -10b), 49.7 (C-12), 61.7 (*C*H$_2$Ph), 113.0 (C-10a), 126.7, 128.1, 128.6 and 140.7 (phenyl-C), 132.4 and 135.4 (C-3 and -4), 147.1 (C-6a), 151.8 (C-8), 163.0 (C-10) and 211.3 (C-11); *m*/*z* 377 (M$^+$) and 286 (M$^+$ − CH$_2$Ph).

5-*Benzyl*-1,3-*dimethyl*-1,2,3,4,r-4b,5,t-6,7,10,11-*decahydro*-6,10a-*methanopyrimido*[4′,5′:4,5]*cyclopenta*[1,2-b]*azocine*-2,4,10-*trione* **6a** was obtained as plates from ethanol; mp 206–208 °C (Found: C, 70.4; H, 6.2; N, 11.3%); ν_{max}/cm^{-1} 1700, 1660 and 1640 (CO); δ_H(270 MHz) 2.12 (1 H, ddd, *J* 3.7, 6.6 and 20.9, 7-H), 2.35 (1 H, dd, *J* 6.2 and 12.8, 12-H), 2.44 (1 H, d, *J* 12.8, 12-H), 2.60 (1 H, dd, *J* 1.5 and 18.0, 11-H), 2.96 (1 H, td, *J* 2.6 and 20.9, 7-H), 3.33 and 3.39 (each 3 H, each s, 1- and 3-Me), 3.54 (1 H, m, 6-H), 3.76 (1 H, d, *J* 14.3, C*H*$_2$Ph), 3.99 (1 H, d, *J* 18.0, 11-H), 4.55 (1 H, d, *J* 1.5, 4b-H), 5.19 (1 H, d, *J* 14.3, C*H*$_2$Ph), 6.04 (1 H, d, *J* 12.8, 9-H), 6.49 (1 H, ddd, *J* 2.6, 3.7 and 12.8, 8-H) and 7.17–7.36 (5 H, ov, Ph); δ_C(68 MHz) 28.1 (1-Me), 32.0 (C-3), 32.5 (3-Me), 37.4 (C-11), 39.9 (C-12), 53.3 (*C*H$_2$Ph), 56.8 (C-6), 60.3 (C-10a), 75.3 (C-4b), 112.3 (C-4a), 126.7, 128.2, 128.3 and 139.7 (phenyl-C), 128.0 (C-9), 143.9 (C-8), 152.7 (C-11a), 153.7 (C-2), 160.9 (C-4) and 199.2 (C-10); *m*/*z* 377 (M$^+$).

The structures of compounds **5a** and **6a** were confirmed by X-ray crystal-structure analyses and the crystal data are summarised in Table 2.

1-(2-*Furfuryl*)-7,9-*dimethyl*-1,2,r-4a,c-5,6,7,8,9,10,c-10b-*hexahydro*-2,5-*ethanopyrido*[2,3-f]*quinazoline*-8,10,11-*trione* **5b** was obtained as prisms from hexane–benzene; mp 144–146 °C (Found: C, 65.0; H, 5.7; N, 11.25. $C_{20}H_{21}N_3O_4$ requires C, 65.38; H, 5.76; N, 11.44%); ν_{max}/cm^{-1} 1690 and 1650 (CO); δ_H(270 MHz) 2.45 (1 H, dd, *J* 2.6 and 17.6, 12-H), 2.56–2.72 (3 H, ov, 4a-, 5- and 6-H), 2.84 (1 H, dd, *J* 4.8 and 17.6, 12-H), 3.37

(3 H, s, NMe), 3.43–3.50 (4 H, ov, NMe and 6-H), 3.63 (1 H, m, 2-H), 3.95 (1 H, d, *J* 4.8, 10b-H), 4.16 and 4.27 (each 1 H, each d, *J* 14.7, CH_2-furyl), 6.24–6.43 (4 H, ov, 3- and 4-H and furan) and 7.34 (1 H, br s, furan); δ_C(68 MHz) 28.3 (7-Me), 30.4 (C-6), 31.0 (9-Me), 33.8 (C-4a), 48.2, 51.6, 53.2 and 53.3 (C-2, -5 and C-10b and CH_2-furyl), 49.5 (C-12), 108.7, 110.0, 141.7 and 153.1 (furan-C), 112.5 (C-10a), 131.1 and 135.3 (C-3 and -4), 147.5 (C-6a), 151.7 (C-8), 163.0 (C-10) and 211.0 (C-11); *m*/*z* 367 (M^+).

5-(2-*Furfuryl*)-1,3-*dimethyl*-1,2,3,4,r-4b,5,t-6,7,10,11-*decahydro*-6,10a-*methanopyrimido*[4′,5′:4,5]*cyclopenta*[1,2-b]*azocine*-2,4,10-*trione* **6b** was obtained as pale orange needles from ethanol; mp 191–193 °C (Found: C, 65.2; H, 5.8; N, 11.1%); ν_{max}/cm^{-1} 1700, 1660 and 1640 (CO); δ_H(270 MHz) 2.27 (1 H, ddd, *J* 3.7, 6.6 and 21.3, 7-H), 2.38 (1 H, dd, *J* 6.2 and 12.8, 12-H), 2.48 (1 H, d, *J* 12.8, 12-H), 2.60 (1 H, dd, *J* 1.5 and 18.3, 11-H), 3.22 (1 H, dt, *J* 2.6 and 21.3, 7-H), 3.33 and 3.36 (each 3 H, each s, 1- and 3-Me), 3.65 (1 H, m, 6-H), 3.92 (1 H, d, *J* 14.6, CH_2-furyl), 3.99 (1 H, d, *J* 18.3, 11-H), 4.49 (1 H, d, *J* 1.5, 4b-H), 5.09 (1 H, d, *J* 14.6, CH_2-furyl), 6.02 (1 H, d, *J* 12.8, 9-H), 6.24 (1 H, d, *J* 3.3, furan), 6.29 (1 H, dd, *J* 1.8 and 3.3, furan), 6.49 (1 H, ddd, *J* 2.6, 3.7 and 12.8, 8-H) and 7.34 (1 H, d, *J* 1.8, furan); δ_C(68 MHz) 28.1 (1-Me), 32.0 (C-7), 32.5 (3-Me), 37.6 (C-11), 39.9 (C-12), 45.7 (CH_2-furyl), 58.4 (C-6), 60.2 (C-10a), 74.7 (C-4b), 107.8, 110.0, 141.9 and 152.9 (furan-C), 111.8 (C-4a), 127.8 (C-9), 143.9 (C-8), 152.7 (C-11a), 154.3 (C-2), 161.0 (C-4) and 198.9 (C-10); *m*/*z* 367 (M^+).

1-*Allyl*-7,9-*dimethyl*-1,2,r-4a,c-5,6,7,8,9,10,c-10b-*decahydro*-2,5-*ethanopyrido*[2,3-f]*quinazoline*-8,10,11-*trione* **5c** was obtained as prisms from hexane–benzene; mp 107–109 °C (Found: C, 66.1; H, 6.4; N, 12.8. $C_{18}H_{21}N_3O_3$ requires C, 66.03; H, 6.47; N, 12.84%); ν_{max}/cm^{-1} 1690, 1680 and 1650 (CO); δ_H(270 MHz) 2.49 (1 H, ddd, *J* 0.7, 2.9 and 17.6, 12-H), 2.57–2.75 (3 H, ov, 4a-, 5- and 6-H), 2.82 (1 H, dd, *J* 5.1 and 17.6, 12-H), 3.35 and 3.43 (each 3 H, each s, 7- and 9-Me), 3.29–3.51 (2 H, ov, 6-H and CH_2CH=), 3.54 (1 H, m, 2-H), 3.78 (1 H, d, *J* 5.1, 10b-H), 3.92 (1 H, dd, *J* 2.9 and 14.3, CH_2CH=), 5.06–5.19 (2 H, ov, =CH_2), 5.87 (1 H, m, –CH=) and 6.46–6.54 (2 H, ov, 3- and 4-H); δ_C(68 MHz) 28.3 (7-Me), 30.5 (C-6), 31.1 (9-Me), 34.1 (C-4a), 48.4, 50.5 and 54.5 (C-2, -5 and -10b), 49.7 (C-12), 60.6 (NCH$_2$CH=), 112.5 (C-10a), 117.0 (=CH_2), 132.1 and 135.6 (C-3 and -4), 136.8 (CH=) 147.4 (C-6a), 151.8 (C-8), 163.0 (C-10) and 211.1 (11-C); *m*/*z* 327 (M^+) and 286 ($M^+ - C_3H_5$).

5-*Allyl*-1,3-*dimethyl*-1,2,3,4,r-4b,5,t-6,7,10,11-*decahydro*-6,10a-*methanopyrimido*[4′,5′:4,5]*cyclopenta*[1,2-b]*azocine*-2,4,10-*trione* **6c** was obtained as plates from hexane–benzene; mp 172–173 °C (Found: C, 66.1; H, 6.4; N, 12.9%); ν_{max}/cm^{-1} 1690, 1660 and 1640 (CO); δ_H(270 MHz) 2.24 (1 H, ddd, *J* 3.7, 6.6 and 20.9, 7-H), 2.38 (1 H, dd, *J* 6.6 and 13.2, 12-H), 2.50 (1 H, d, *J* 13.2, 12-H), 2.60 (1 H, dd, *J* 1.5 and 18.0, 11-H), 3.03 (1 H, td, *J* 2.6 and 20.9, 7-H), 3.30 and 3.36 (each 3 H, each s, 1- and 3-Me), 3.36 (1 H, br d, *J* 14.3, NCH_2CH=), 3.78 (1 H, m, 6-H), 3.98 (1 H, d, *J* 18.0, 11-H), 4.38 (1 H, d, *J* 1.5, 4b-H), 4.55 (1 H, ddd, *J* 1.8, 4.0 and 14.3, NCH_2CH=), 5.11 (1 H, td, *J* 1.8 and 10.3, =CH_2), 5.26 (1 H, d, *J* 17.2, =CH_2), 5.89 (1 H, m, CH=), 6.00 (1 H, d, *J* 13.2, 9-H) and 6.48 (1 H, ddd, *J* 2.6, 3.7 and 13.2, 8-H); δ_C(68 MHz) 28.0 (1-Me), 31.8 (C-7), 32.5 (3-Me), 37.5 (C-11), 40.0 (C-12), 52.6 (NCH$_2$CH=), 58.1 (C-6), 60.1 (C-10a), 74.9 (C-4b), 111.8 (C-4a), 116.5 (=CH_2), 127.8 (C-9), 136.3 (–CH=), 144.1 (C-8), 152.7 (C-11a), 154.2 (C-2), 160.8 (C-4) and 198.9 (C-10); *m*/*z* 327 (M^+) and 271 ($M^+ - NHC_3H_5$).

7,9-*Dimethyl*-1-(*phenethyl*)-1,2,r-4a,c-5,6,7,8,9,10,c-10b-*decahydro*-2,5-*ethanopyrido*[2.3-f]*quinazoline*-8,10,11-*trione* **5d** was obtained as prisms from hexane; mp 130–133 °C (Found: C, 70.5; H, 6.7; N, 10.5. $C_{23}H_{25}N_3O_3$ requires C, 70.57; H, 6.44; N, 10.74%); ν_{max}/cm^{-1} 1690 and 1650 (CO); δ_H(270 MHz) 2.45–2.71 (5 H, ov, 4a-, 5-, 6- and 12-H and CH_2Ph), 2.79–2.97 (2 H, ov, 12-H and CH_2Ph), 3.09 (1 H, ddd, *J* 4.8, 8.4 and 13.6, NCH_2CH$_2$), 3.31 and 3.37 (each 3 H, each s, 7- and 9-Me), 3.21–3.51 (3 H, ov, 2- and 6-H and NCH_2CH$_2$), 3.89 (1 H, d, *J* 4.0, 10b-H), 6.45–6.57 (2 H, ov, 3- and 4-H) and 7.09–7.23 (5 H, ov, Ph); δ_C(68 MHz) 28.3 (7-Me), 29.9 (C-6), 30.9 (9-Me), 34.8 and 34.9 (C-4a and CH_2Ph), 48.0, 52.7 and 53.9 (C-2, -5 and -10b), 50.5 (C-12), 58.7 (NCH_2CH$_2$), 113.4 (C-10a), 125.6, 127.9, 129.1 and 140.6 (phenyl-C), 132.3 and 135.4 (C-3 and -4), 147.6 (C-6a), 151.7 (C-8), 162.7 (C-10) and 210.5 (C-11); *m*/*z* 391 (M^+).

1,3-*Dimethyl*-1-(*phenethyl*)-1,2,3,4,r-4b,5,t-6,7,10,11-*decahydro*-6,10a-*methanopyrimido*[4′,5′:4,5]*cyclopenta*[1,2-b]*azocine*-2,4,10-*trione* **6d** was obtained as pale yellow plates from ethanol–chloroform; mp 210–211 °C (Found: C, 70.6; H, 6.5; N, 10.6%); ν_{max}/cm^{-1} 1690 and 1660 (CO); δ_H(270 MHz) 2.27–2.42 (2 H, ov, 7- and 12-H), 2.54 (1 H, d, *J* 12.8, 12-H), 2.58 (1 H, dd, *J* 1.4 and 18.3, 11-H), 2.74–3.03 (4 H, ov, 7-H and NCH$_2$CH_2Ph), 3.32 and 3.35 (each 3 H, each s, 1- and 3-Me), 3.89 (1 H, m, 6-H), 3.97 (1 H, d, *J* 18.3, 11-H), 4.14 (1 H, m, NCH_2CH$_2$), 4.38 (1 H, d, *J* 1.4, 4b-H), 6.00 (1 H, td, *J* 1.8 and 13.2, 9-H), 6.45 (1 H, td, *J* 4.0 and 13.2, 8-H) and 7.17–7.29 (5 H, ov, Ph); δ_C(67 MHz) 28.1 (1-Me), 31.6 (C-7), 32.4 (3-Me), 35.7 (CH_2Ph), 37.5 (C-11), 40.1 (C-12), 50.1 (NCH_2CH$_2$), 57.4 (C-6), 59.8 (C-10a), 75.5 (C-4b), 111.9 (C-4a), 126.1, 128.3, 128.7 and 140.0 (phenyl-C), 128.0 (C-9), 143.6 (C-8), 152.7 (C-11a), 153.9 (C-2), 160.7 (C-4) and 199.0 (C-10); *m*/*z* 391 (M^+) and 300 ($M^+ - CH_2Ph$).

5-*Isobutyl*-1,3-*dimethyl*-1,2,3,4,r-4b,5,t-6,7,10,11-*decahydro*-6,10a-*methanopyrimido*[4′,5′:4,5]*cyclopenta*[1,2-b]*azocine*-2,4,10-*trione* **6e** was obtained as plates from ethanol; mp 169–171 °C (Found: C, 66.5; H, 7.4; N, 12.3. $C_{19}H_{25}N_3O_3$ requires C, 66.45; H, 7.34; N, 12.24%); ν_{max}/cm^{-1} 1700, 1660 and 1650 (CO); δ_H(270 MHz) 0.90 and 0.93 (each 3 H, each d, *J* 6.6, CH*Me*$_2$), 1.63 (1 H, m, C*H*Me$_2$), 2.24 (1 H, ddd, *J* 3.7, 6.6 and 20.9, 7-H), 2.31–2.51 (2 H, ov, 12-H$_2$), 2.56 (1 H, dd, *J* 1.5 and 18.0, 11-H), 2.65 (1 H, dd, *J* 3.7 and 12.8, NCH_2CHMe$_2$), 2.95 (1 H, td, *J* 2.6 and 20.9, 7-H), 3.31 and 3.36 (each 3 H, each s, 1- and 3-Me), 3.42 (1 H, d, *J* 12.8, NCH_2CHMe$_2$), 3.71 (1 H, m, 6-H), 3.94 (1 H, d, *J* 18.0, 11-H), 4.32 (1 H, d, *J* 1.5, 4b-H), 5.99 (1 H, d, *J* 12.8, 9-H) and 6.46 (1 H, ddd, *J* 2.6, 3.7 and 12.8, 8-H); δ_C(68 MHz) 20.0 (Me), 27.4 (*C*HMe$_2$), 28.1 (1-Me), 31.8 (C-7), 32.4 (3-Me), 37.4 (C-11), 40.1 (12-C), 56.6 (NCH_2CHMe$_2$), 57.0 (C-6), 59.8 (C-10a), 75.8 (C-4b), 112.4 (C-4a), 127.9 (C-9), 144.0 (C-8), 152.8 (C-11a), 153.5 (C-2), 160.7 (C-4) and 199.4 (C-10); *m*/*z* 343 (M^+) and 300 ($M^+ - CHMe_2$).

5-*Cyclohexyl*-1,3-*dimethyl*-1,2,3,4,r-4b,5,t-6,7,10,11-*deca*-6,10a-*methanopyrimido*[4′,5′:4,5]*cyclopenta*[1,2-b]*azocine*-2,4,10-*trione* **6f** was obtained as prisms from hexane–benzene; mp 136–137 °C (Found: C, 68.1; H, 7.25; N, 11.2. $C_{21}H_{27}N_3O_3$ requires C, 68.27; H, 7.37; N, 11.37%); ν_{max}/cm^{-1} 1700, 1650 and 1640 (CO); δ_H(270 MHz) 1.06–1.84 (9 H, ov, cyclohexyl-H), 2.26–2.44 (4 H, ov, 7-H, 12-H and cyclohexyl-H), 2.56 (1 H, dd, *J* 1.1 and 18.3, 11-H), 3.02 (1 H, br d, *J* 17.6, 7-H), 3.31 and 3.35 (each 3 H, each s, 1- and 3-Me), 3.59 (1 H, m, 6-H), 3.94–4.01 (2 H, ov, 11-H and cyclohexyl-H), 4.84 (1 H, s, 4b-H), 6.04 (1 H, br d, *J* 12.8, 9-H) and 6.46 (1 H, td, *J* 4.0 and 12.8, 8-H); δ_C(68 MHz) 26.2, 26.6 and 26.8 (cyclohexyl-C), 28.2 and 28.8 (1-Me and cyclohexyl-C), 32.4 (C-7), 32.8 (3-Me), 37.5 (C-11), 40.0 (C-12), 38.7 (cyclohexyl-C), 56.3 and 56.6 (C-6 and cyclohexyl-C), 59.5 (C-10a), 69.5 (C-4b), 112.3 (C-4a), 128.1 (C-9), 144.5 (C-8), 152.8 (C-11a), 154.3 (C-2), 160.0 (C-4) and 199.3 (C-10); *m*/*z* 369 (M^+) and 341 ($M^+ - CO$).

Single-crystal X-ray structure determinations

Single crystals (prisms) of compounds **5a** and **6a** for X-ray diffraction studies were recrystallised from ethanol. A crystal of approximate dimensions 0.140 × 0.420 × 0.800 mm was used for data collection of compound **5a**, and one of 0.240 × 0.460 × 0.520 mm of compound **6a**. All measurements

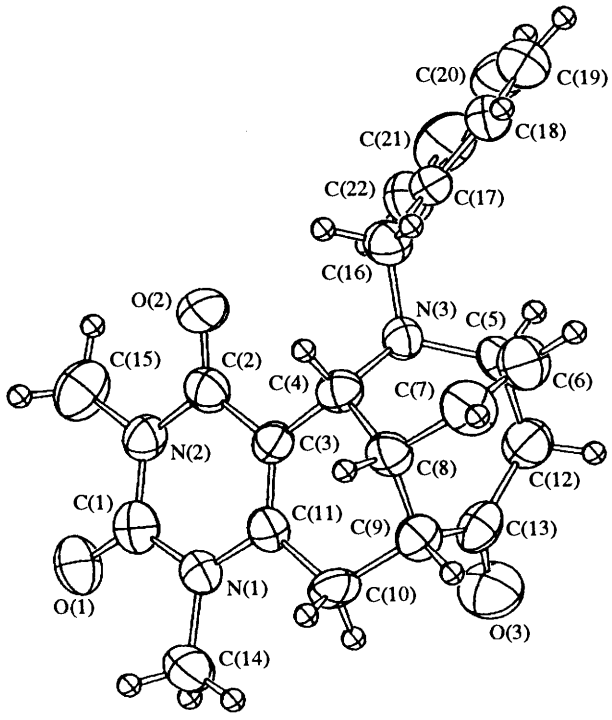


Fig. 5 ORTEP drawing of compound **5a** with crystallographic numbering scheme

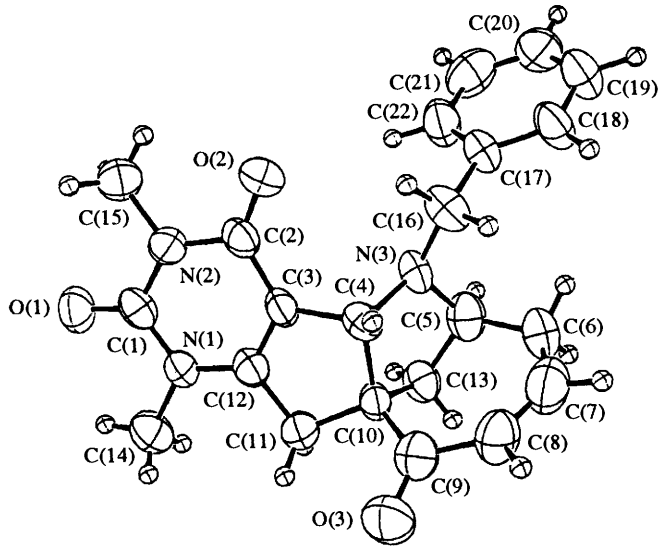


Fig. 6 ORTEP drawing of compound **6a** with crystallographic numbering scheme

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 $22.49 < 2\theta < 37.96°$ for compound **5a** and $26.0 < 2\theta < 36.51°$ for compound **6a**, respectively. Summaries of the crystal data for compounds **5a** and **6a** are given in Table 2. The ω–2θ scan technique to a maximum 2θ-value of 55° was used. Scans of $(0.89 + 0.30 \tan\theta)°$ were made at a speed of 32.0° min^{-1} in omega (2 rescans) for compound **5a** and of $(1.63 + 0.30 \tan\theta)°$ for compound **6a**. A total of 3997 observed reflections (unique: 4620; R_{int} 0.082) for compound **5a**, 4861 for compound **6a**, were collected. All calculations were performed using the TEXSAN program.[4] Atoms other than hydrogen were refined anisotropically. The structures were solved by direct methods (MITHRIL)[5] and refined by least squares to R 0.052 (compound **5a**), 0.059 (compound **6a**). ORTEP[6] drawings of compounds **5a** and **6a** are shown in Figs. 5 and 6, respectively.‡

Computational procedure

The structures **3g**, **3h** were fully optimised and the information on their molecular orbitals was attained by the PM3 method[7] using the MOPAC program (Version 6.00).[8] The heats of formation of compounds **10g**, **10h**, **11g**, **11h** and **5g** were also calculated using the structural data for the *endo*- and *exo*-[4 + 2] cycloadducts[1] and the 2,5-ethanopyrido[2,3-*f*]quinazoline **5a** obained by X-ray structure analyses. The structure optimisation for betaines **8g** and **9g** was carried out by using the structures of dione **3g** and tropone **4** as initial geometries. The carbon–carbon bond newly formed between C-8 of dione **3g** and C-2 of tropone **4** was postulated to be 1.50 Å. The structure optimisations were examined in the cases where the distances between both terminals were 4.0, 3.0 and 2.0 Å long, respectively. In every case, betaine **9g** was thermodynamically favourable over betaine **8g**. These calculations were performed on the VAX 4000 in Ube Laboratory, Corporate Research & Development, Ube Industries Ltd. The calculated results are summarised in Figs. 1–4.

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‡ Supplementary data (tables of atomic coordinates, bond lengths and angles) have been deposited at the Cambridge Crystallographic Data Centre (see *Instructions for Authors*, in the January issue).

References

1 Part 14, K. Ikuno, T. Kobayashi, T. Harada, M. Noguchi and A. Kakehi, preceding paper.
2 L. Salem, *J. Am. Chem. Soc.*, 1968, **90**, 543.
3 M. Oda, M. Funamizu and Y. Kitahara, *Chem. Commun.*, 1969, 737.
4 Texan TEXRAY, Structure Analysis Package, Molecular Structures Corporation, The Woodland, Texas, 1985.
5 C. J. Gilmore, *J. Appl. Crystallogr.*, 1984, **17**, 42.
6 C. K. Johnson, ORTEP II, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.
7 J. J. P. Stewart, *J. Comput. Chem.*, 1989, **10**, 209, 221.
8 J. J. P. Stewart, Frank J. Seiler Research Laboratory, U.S. Air Force Academy, Colorado Springs, Colorado 80840, USA.

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