Enamine Chemistry. Part 29.[1] Synthesis of Adamantane Derivatives from α,β-Unsaturated Acid Chlorides and 4,4-Disubstituted Cyclohexanone Enamines. Multiple [3,3] Sigmatropic Rearrangement Transition State Stereochemistry. *X*-Ray analysis

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Chemical, spectroscopic and *X*-ray crystallographic evidence has confirmed that the three isomers of 6-hydroxy-7,9-dimethyl-6-phenyladamantane-2,4-dione, obtained by the reaction of crotonoyl chloride with the pyrrolidine enamine of 4-benzoyl-4-methylcyclohexanone, have the 9α-methyl-6α-phenyl (**4**), 9β-methyl-6α-phenyl (**2**), and 9β-methyl-6β-phenyl (**3**) configurations. The mechanism of their formation has been investigated and the evidence available indicates that the stereochemistry of the C-6 and C-9 chiral centres is determined largely by the stereochemistry of the [3,3] sigmatropic rearrangement leading to them. A chair-like transition state for the rearrangement, occurring from the same side of the cyclohexene ring as the benzoyl group (chair-*syn*) in the intermediate *N*-acylated enamine (**9a**) must lead to the 9α-Me,6α-Ph configuration as in (**4**), whereas the same process from the opposite side (chair-*anti*) followed by inversion of the substituted ring carbon could lead to the 9β-Me,6α-Ph configuration as in (**2**) and the 9β-Me,6β-Ph configuration as in (**3**). However, the main isomer (**3**), having the more crowded 9β-Me,6β-Ph configuration, is more likely to be derived by a [3,3] sigmatropic rearrangement having a boat-like transition state, but again occurring from the same side of the cyclohexene ring as the benzoyl group (boat-*syn*). An *X*-ray crystallographic analysis of 6β-hydroxy-7,9α-dimethyl-6α-phenyladamantane-2,4-dione (**4**) and of 3-(5-benzoyl-5-methyl-2-oxocyclohexyl)-butanoic acid (**34**), isolated at an intermediate stage in the above reaction, has been carried out. The corresponding reaction of αβ-unsaturated acid chlorides with enamines of 4-benzoyl-4-phenylcyclohexanone (**9c**) and ethyl 1-benzoyl-4-oxocyclohexane-1-carboxylate (**9b**) has been carried out and shown to lead to 6-hydroxy-6,7-diphenyladamantane-2,4-diones and ethyl 2-hydroxy-4,6-dioxo-2-phenyladamantane-1-carboxylates respectively, as a mixture of stereoisomers. A similar multiplicity in the stereochemistry of the transition state of the [3,3] sigmatropic rearrangement is evident from the structures of the adamantane derivatives produced.

Previous work has shown that the reaction of crotonoyl chloride with the pyrrolidine enamine of 4-benzoyl-4-methylcyclohexanone gives 6-hydroxy-7,9-dimethyl-6-phenyladamantane-2,4-dione as a mixture of three of the four possible isomers (**2**)—(**4**)[2] shown in Scheme 1.‡ Surprisingly, the main product obtained was assigned[3] the most sterically crowded structure (**3**), in which the bulky 6-phenyl and 9-methyl groups are in a mutually 1,3-diaxial disposition, and the other two isomers were assigned[2] structures (**2**) and (**4**) (Scheme 1). Since the stereochemical assignments of the 6 and 9 chiral centres were to some extent tentative, and since the preferred formation of the more crowded isomer has interesting theoretical implications, the object of the present work has been to obtain more compelling evidence for the structures of the isomers produced and to investigate the mechanism of their formation.

Confirmation that the above structural assignments were, in fact, correct has now been obtained as follows. Since the 9-methyl group lies in the shielding region of the 2- and 4-carbonyl groups in isomer (**4**), reduction of these carbonyl groups should exchange a shielding influence for a deshielding one and therefore cause a lowfield shift in the 9-methyl signal. Conversely in (**2**) and (**3**), where the 9-methyl group lies in the deshielding region of the 2- and 4-carbonyl groups, reduction should remove this long range deshielding influence and thereby cause a highfield shift of the 9-methyl doublet.§ These predictions have been fully confirmed by borohydride reduction (Scheme 1). Mixtures of adamantane triols were of course produced, so the 9-methyl signal of reduction product (**5**) appeared as two doublets, and that of (**6**) as four doublets, but in every case the doublets were highfield to that of the adamantanedione precursor [(**2**) and (**3**), respectively]. Furthermore the number of isomers produced also reflects the stereochemistry of the 6- and 9-substituents. For example in (**3**) the two carbonyl groups can be reduced from either direction thus producing four isomers. However, in (**2**) reduction of the 4-carbonyl group appears to be hindered by the phenyl group from what we have termed the α-direction.¶ Reduction of the

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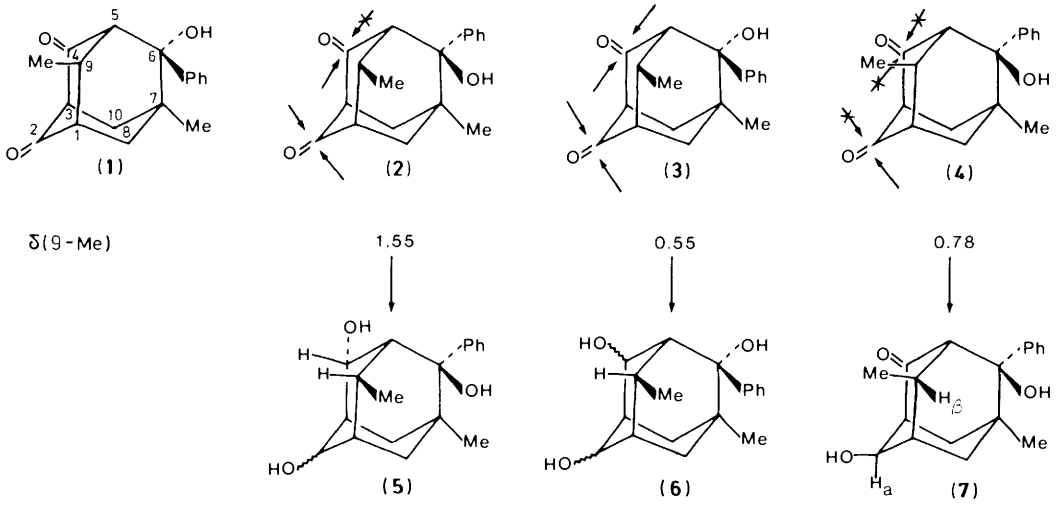
‡ All substrates and products are racemic; only one enantiomer is illustrated in the diagrams.

§ Admittedly the HO groups thus introduced are also deshielding, but their deshielding influence appears to be much more localised than that of a carbonyl group.

¶ In order to differentiate between the isomers the α,β-system has been employed with reference to the 195 678 ring. Substituents at C-6 or C-9 which are equatorial to this ring are designated α, and axial substituents at C-6 or C-9 are designated β. Thus isomer (**2**) is 6β-OH, 9β-Me, 6α-Ph. In the case of isomers (**35**)—(**38**), (**40**), and (**48**)—(**49**), these same chiral centres are numbered C-2 and C-10 respectively.



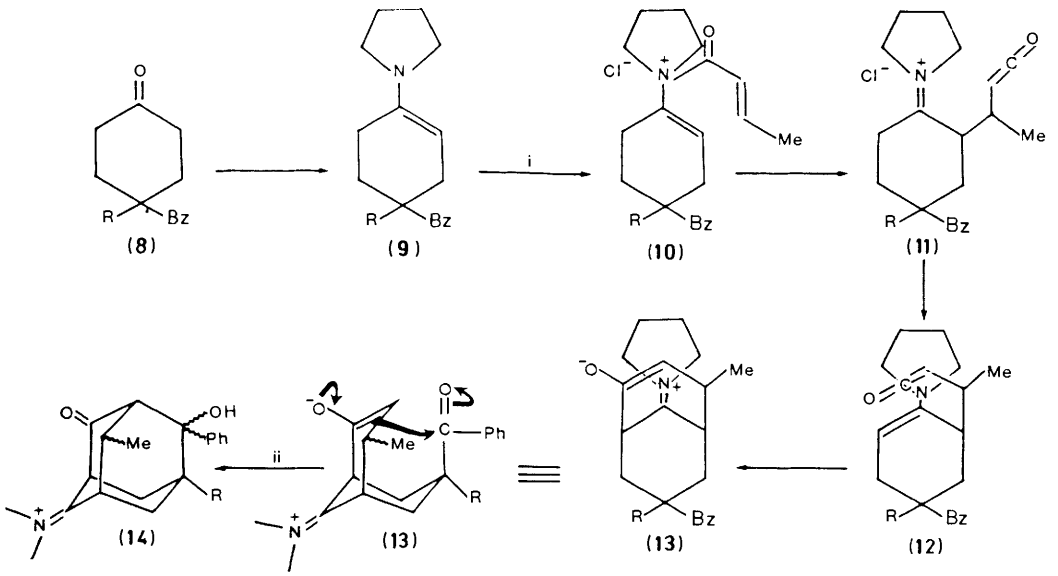
Number of isomers:	Two	Four	One
Predicted shift of 9-Me:	To highfield	To highfield	To lowfield
Observed chemical shift of 9-Me:	δ 1.44, 1.4	δ 0.45, 0.4, 0.35, 0.3	δ 1.22

Scheme 1.

2-carbonyl group then produces two isomeric triols (**5**). In the case of (**4**), reduction of the 4-carbonyl group appears to be hindered from both directions and reduction of the 2-carbonyl group only occurs from below, thus producing one diol (**7**), the stereochemistry of which is confirmed by the observation of W coupling between H_a and H_β ($J_{2,9}$ 2.9 Hz). Additionally, the 9-methyl signal shows the predicted shift to lowfield.

Finally, *X*-ray analysis has confirmed the structure of (**2**)[4] and in order to differentiate unequivocally between structures (**1**) and (**4**), we carried out an *X*-ray analysis (*vide infra*) which fully confirms structure (**4**). Unfortunately, we were unable to grow suitable crystals of isomer (**3**), but there can now be no doubt as to the correctness of the stereochemical assignments.

The mechanistic implications of these results are interesting. In the related synthesis of bicyclo[3.3.1]nonane-2,9-diones from the reaction of αβ-unsaturated acid chlorides with cyclohexanone enamines, in which two carbon–carbon bonds are formed sequentially, we have shown that initial *N*-acylation of the enamine occurs as the first step, followed by a [3,3] sigmatropic rearrangement leading to a ketene intermediate which subsequently cyclised to a bicyclic iminium salt.[5,6] The indications are that the same mechanism also applies to the present work. Evidence for the involvement of the *N*-acylated enamine (**10**) was obtained by varying the amine moiety of the enamine. This should affect the propensity for *N*-acylation and be reflected in the yield of adamantanedione produced, *if N*-acylation is a necessary prerequisite to adamantane formation. The results of this investigation are summarised in Table 1 and

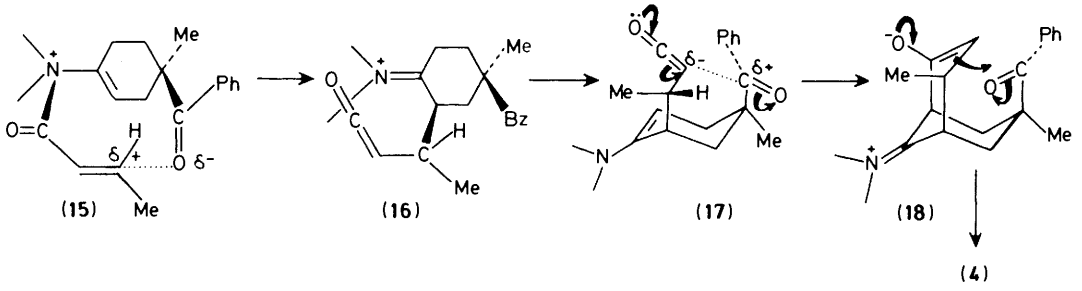


a; R = Me
b; R = CO_2Et
c; R = Ph

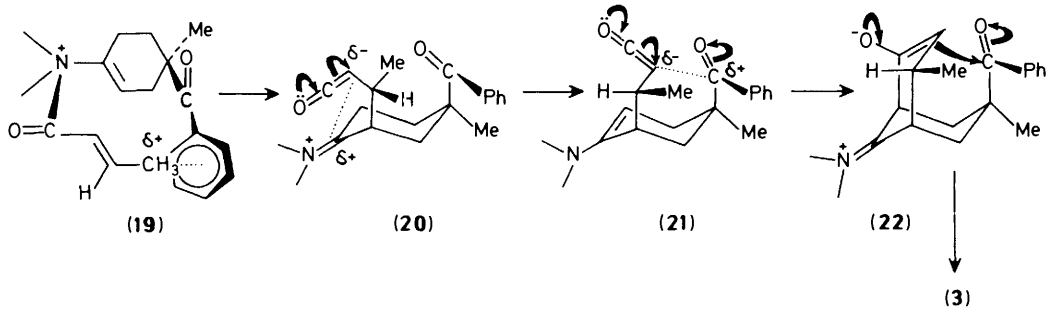
Scheme 2. *Reagents:* (i) Crotonoyl chloride, benzene, 80 °C; (ii) H^+

are quite unequivocal. When a sterically hindered enamine[7] derived from dibutylamine or di-isobutylamine is used, *N*-acylation is prevented and the yield of adamantanedione falls to zero. We have previously shown in other work that the reactivity of the β-carbon atom is not affected by these bulky alkyl groups attached to the nitrogen atom of the enamine.[6] The conversion of the *N*-acylated enamine (**10**) into the ketene (**11**) could occur by an intramolecular process ([3,3] sigmatropic rearrangement) or an intermolecular Michael addition or S_N2' reaction with a second molecule of enamine. However, the latter alternatives are unlikely to lead to adamantane formation for several reasons,*† not least of which is that attempted alkylation of the enamine (**9a**) with methyl crotonate failed completely.[8] Clearly intermolecular attack at the β-position of the enamine by a bulky electrophile is sterically impeded by the bulky axial 4-substitutent (Bz or Me). So formation of the *N*-acylated enamine, which is a kinetically favoured process anyway, is favoured even more by the presence of an axial 4-substituent. Furthermore, the situation is now ideally set up for a [3,3] sigmatropic rearrangement, the activation energy of which will be lowered by the positively charged nitrogen.

The formation of the more crowded isomer can now be explained. The preferred transition state conformation for a [3,3] sigmatropic rearrangement is normally the chair form[9] and if this process occurs from the axial direction with respect to the cyclohexene moiety, and from the same side as the axial benzoyl group, then the less crowded 9α-methyl configuration will be produced, as in isomer (**4**) (Scheme 3). Conversely, if the rearrangement occurs *via* a boat conformation (Scheme 4) from the axial direction, the more crowded 9β-methyl configuration is produced, as in (**2**) and (**3**). Furthermore, an attractive interaction between the electron deficient methyl hydrogens of the crotonoyl residue and the π-electrons of the benzene ring [*i.e.* ····· in (**19**), Scheme 4] could then account for the preferred formation of the 6β-phenyl configuration in the major isomer (**3**) (*vide infra*).‡ However, it is also possible that the [3,3] sigmatropic rearrangement occurs *via* a chair transition state but from the face of the enamine *anti* to the benzoyl group, followed by epimerisation of the alkylated ring carbon [(**24**)→(**25**); Scheme 5], and this would also lead to the 9β-methyl configuration. However, we consider that this process is unlikely to lead to the major isomer (**3**) for several reasons (*vide infra*). (See footnote § on next page.) Primarily we reject it because the epimerisation process would involve formation of a tetrasubstituted enamine double bond as in (**27**) and this would engender an $A^{(1,3)}$ strain[11] between the α-methylene group of the pyrrolidine ring and the ketene methylene residue when these are coplanar. In order to appreciate the relevance of this we must digress briefly. We have previously shown[12] that in the reaction with the pyrrolidine enamine of diethyl 4-oxocyclohexane-1,1-dicarboxylate (**28**), both crotonoyl chloride and, to a lesser extent, methacryloyl chloride cyclised to the adamantane derivative (**29**), whereas acryloyl chloride gave the bicyclic derivative (**30**). This is not an isolated observation (see



Scheme 3.

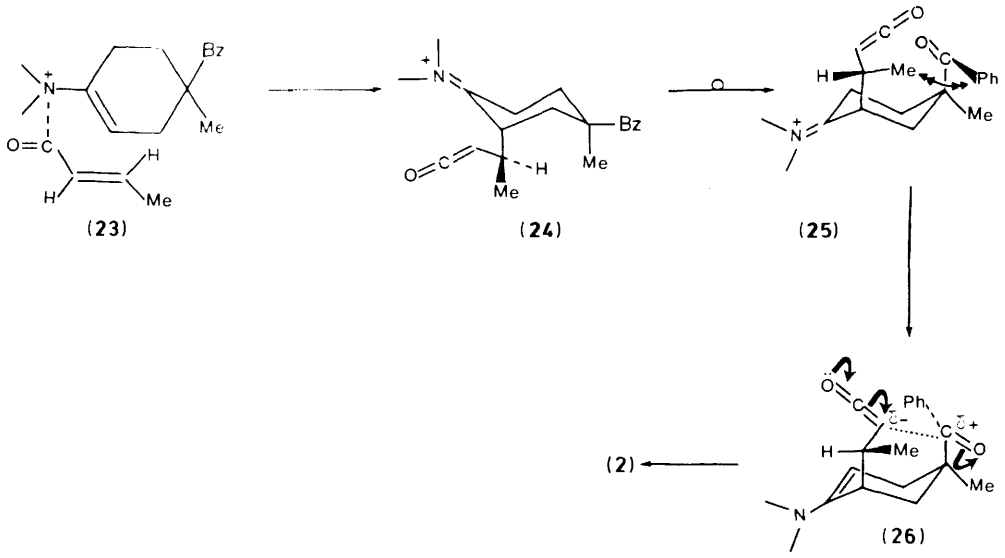


Scheme 4.

* Cross-over experiments are unreliable for distinguishing between intra- and inter-molecular reactions in the present work owing to the reversible formation of the *N*-acylated enamine which can therefore undergo exchange with an added second enamine or *N*-acylated enamine.

† There is no precedent in the literature for conjugate addition of amines to acryloyl chloride let alone crotonoyl chloride, which will be less reactive at the β-position. Furthermore reaction of αβ-unsaturated acid chloride–triethylamine adducts with enamines results in *C*-acylation not *C*-alkylation of the enamine.[6]

‡ Since the *N*-acylated enamine (**19**) and the iminium salt (**20**) are both positively charged, the transition state for this interconversion must also be highly polarised and there could well be an electrostatic attraction between the terminal position of the developing ketene and the developing iminium group, as depicted in the product of this process [*i.e.* ···· in (**20**)], which could account for the slight preference for a six-centre boat transition state over the normal four-centre chair transition state for the [3,3] sigmatropic rearrangement.

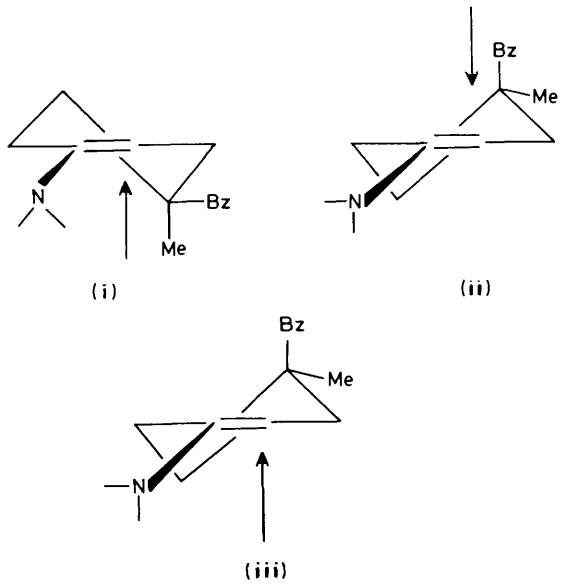


Scheme 5.

also footnote† on p. 2569) and we have attributed the change in the course of the reaction to differential steric effects. That is, the $A^{(1,3)}$ strain in (**27**) (Z = X = CO_2Et, R or R′ = Me) must be greater than the 1,3-diaxial interactions between the substituted ketene methylene group and the axial 4-ethoxycarbonyl group in (**31**) or (**32**) (Z = X = CO_2Et, R or R′ = Me). The substituted ketene methylene group must then stay axially orientated and is thus available to cyclise onto the regenerated enamine system in (**32**) and with the axial ester group [X in (**32**)] to give (**29**). In the case of acryloyl chloride the steric interactions are changed and we proposed that the 1,3-diaxial interactions in (**31**) or (**32**) (R = R′ = H) now outweigh the $A^{(1,3)}$ strain in (**27**; R = R′ = H) so that the ketene methylene group is forced into an equatorial orientation and cannot cyclise onto the regenerated enamine system in (**32**). Instead, decarboxylation occurs, generating an anionic centre at C-4 and removing the steric impediment previously preventing the ketene methylene group from adopting an axial orientation. Cyclisation onto the anionic centre at C-4 then yields (**30**).[12a] Returning to the present situation, if this argument is correct, then it follows that chair-*anti* attack followed by epimerisation *via* the tetrasubstituted enamine (**27**; Z = Me, X = PhCO, R = Me, R′ = H) would generate steric interactions which are greater than those resulting from chair-*syn* or boat-*syn* attack. It follows therefore that chair-*anti* attack, irrespective of whether axial or equatorial approach is involved, is a higher energy route and is, therefore, less likely to be involved in product formation. In fact the most likely result of chair-*anti* attack would seem to be regression to an *N*-acylated enamine, as shown for example in (**33**), except for a small proportion of more energised molecules having sufficient kinetic energy to surmount the energy barrier to (**27**) and hence epimerise and subsequently cyclise to the adamantane. Even then we do not regard this as a route to the major isomer (**3**) since the methyl group of the crotonoyl residue would be involved in a repulsive steric interaction with the phenyl group [see structure (**25**)] thus favouring conformation (**26**) leading to the less crowded 6α-phenyl configuration. Consequently we consider that only the minor isomer (**2**) could be formed by chair-*anti* attack.*

The different processes depicted in Schemes 3, 4, and 5 leading

§ Axial attack *anti* to the benzoyl group would be impeded by the axial methyl group [conformation (i)]. Conversely, axial attack *syn* to the benzoyl group [conformation (ii)] could be favoured by attractive interactions as indicated in (**15**) and (**19**) (Schemes 3 and 4). Equatorial attack *anti* to the benzoyl group [conformation (iii)] would not be expected to contribute significantly to the course of the reaction unless



the transition state was reactant-like.[10] Previous investigations of related systems (P. W. Hickmott, P. J. Cox, and G. A. Sim, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2544) have shown that axial attack of the acid chloride residue is favoured over equatorial attack by at least 4:1. Similar conclusions have been reached for the Claisen rearrangement of conformationally-rigid diosphenol allyl ethers (A. A. Ponaras, *Tetrahedron Lett.*, 1983, 3).

* Isomer (**2**) could also have been derived by epimerisation of the C-6 chiral centre in (**3**) since acid catalysed equilibration studies clearly demonstrated the greater thermodynamic stability of the 6α-phenyl-6β-hydroxy configuration in (**2**) (see Experimental section). However, we consider this unlikely since there was no interconversion of any of the isomers (**2**), (**3**), and (**4**) under conditions which approximated as closely as possible to those of the reaction conditions employed (*i.e.* presence of both basic and acid catalysts; see Experimental section). There was no conversion of (**2**) or (**3**) into (**4**), or *vice versa*, under any of the conditions we tried.

Table 1. Effect of the amine moiety on the reaction between 4-benzoyl-4-methylcyclohexanone enamines and crotonoyl chloride

Enamine	Adamantanedione[a] Yield (%)[b]
Pyrrolidine	35
Piperidine	30
Morpholine	29
Dibutylamine	0
Di-isobutylamine	0

[a] Total yield of (2) + (3) + (4). [b] Without allowance being made for recovered 4-benzoyl-4-methylcyclohexanone.

Table 2. Influence of reaction time on product yield and isomer distribution[a]

Addition time (h)	0.1	0.1	1	1	1	1
Reaction time (h)	0.1	1	10	15	20	140
Isomer (2)	0	51	66	70	91	65
Isomer (4)	148	174	120	223	215	78
Isomer (3)	31	53	271	241	352	165
Ketone (8a)	496	341	71	68	80	18
Total yield (2) + (3) + (4)	179	278	457	534	658	308
%Yield[b]	18	23	29	34	44	25

[a] Weight quoted in mg. [b] After allowing for ketone (8a) recovered from unchanged enamine (9a).

to isomers (4), (3), and (2), respectively, would of course be expected to occur at different rates and this should be reflected in a variation in product distribution with change in reaction time; this expectation was confirmed (Table 2). In fact the product distribution changes quite dramatically with time. At short reaction times the less crowded isomer (4) is the main product. The more crowded isomer (3) only begins to become the main product after *ca.* 10 h. However, this is readily explicable if the rate constants for the three sigmatropic rearrangements are in the order $K_{boat\text{-}syn} > K_{chair\text{-}syn} > K_{chair\text{-}anti}$* and the rate constants for the cyclisations to the adamantane diones are in the order $K_4 > K_2 > K_3$. It then follows that (2) is the minor isomer formed because the rate of formation of the ketene (24) is low, being impeded by the axial methyl group, and (3) becomes the main product over a longer reaction time because the ketene (20) is formed most rapidly initially. Isomer (4) is the main product at short reaction times because, although there is less of ketene (16) compared to ketene (20), its cyclisation rate is much faster than that leading to (3) or (2) because in the former case (3) cyclisation is sterically impeded and in the latter case, (2), cyclisation to the adamantane has to be preceded by initial epimerisation of the alkylated ring carbon, (24)→(25). We have attempted to obtain evidence of this by trapping the intermediate ketenes (16), (20), and (24). Unfortunately the addition of methanol to the reaction mixture, in order to convert the ketene into the corresponding 3-substituted methyl butanoate led to a complex mixture which we could not purify. Although the addition of water to the reaction mixture at various intermediate reaction times did convert the ketenes into the corresponding 3-(5-benzoyl-5-methyl-2-oxocyclohexyl)butanoic acid, unfortunately either the reaction conditions (boiling water) or the isolation procedure (strong alkali) caused epimerisation of the substituted ring α-carbon and only the one stereoisomer was isolated (see Experimental section), the stereochemistry being established by *X*-ray analysis.† However, this result does serve as confirmatory evidence for the intermediacy of the ketenes in these reactions.

Finally, we have looked briefly at the reaction of crotonoyl chloride with cyclohexanone enamines carrying other substituents at C-4. For this purpose we have used pyrrolidine enamines of 4-benzoyl-4-phenylcyclohexanone, and ethyl 1-benzoyl-4-oxocyclohexane-1-carboxylate. In each case mixtures of isomeric adamantane diones or triones were produced which were separated where possible. The stereochemistry of the chiral centres at C-6 and C-9 (or C-2 and C-10) of all the isomers was assigned by the spectroscopic methods used previously for the assignments of isomers (2), (3), and (4).[2,3] The results are summarised in Table 3 together with the stereochemistry (chair-*syn*, boat-*syn*, and chair-*anti*) of the transition state of the [3,3] sigmatropic rearrangement *via* which we suggest the various isomers are derived. The corresponding reaction with the pyrrolidine enamine of 4-benzoyl-4-methylcyclohexanone, to give (2), (3), and (4), is included for comparison purposes. Although these results can probably only be regarded as circumstantial evidence, the results do fit remarkably well into the mechanistic scheme which we have developed, and some definite conclusions can be drawn.

For example, in the case of the enamine of ethyl 1-benzoyl-4-oxocyclohexane-1-carboxylate (9b), if *anti* attack occurs on conformation (39), with the ester group axially orientated, then

* *syn* or *anti* Refers to the direction of axial attack on the enamine β-carbon relative to the benzoyl group [*i.e.* ⟶ in conformations (ii) and (i) respectively, see footnote § on previous page].

† The stereochemistry of the butanoic acid (34) corresponds to the enantiomer of that which would be expected from hydrolysis of ketene (24), but this is the thermodynamically most stable acid and could equally well have been derived from ketene (20) under the reaction conditions employed.

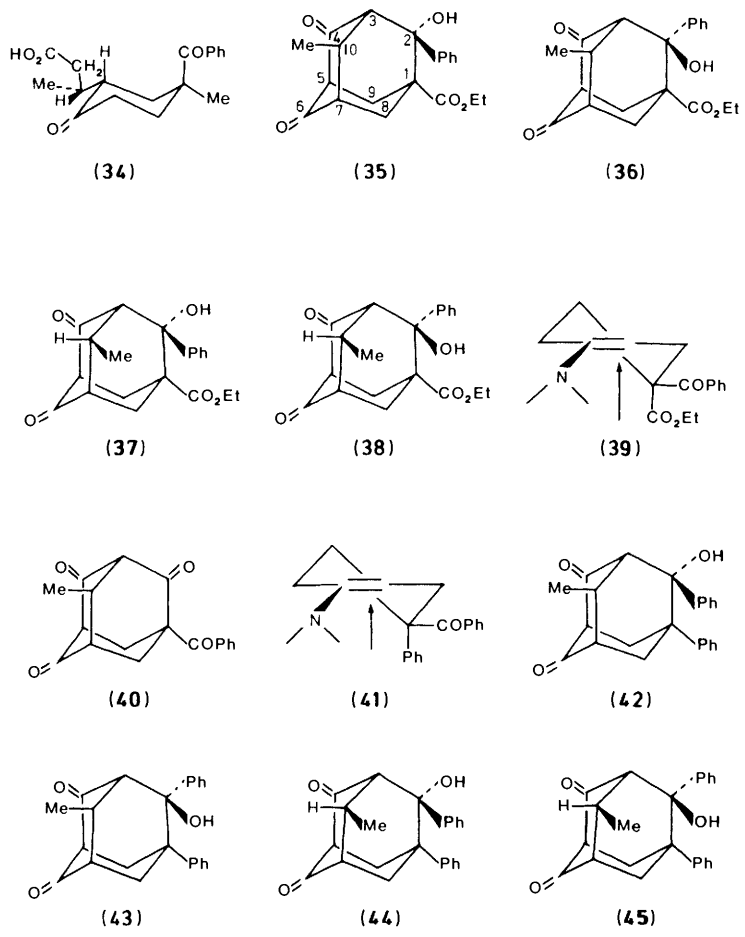


Table 3. Transition state stereochemistry of the [3,3] sigmatropic rearrangement leading to isomeric adamantanediones from crotonoyl chloride

Transition state / Isomer produced / From enamine of	Chair-*syn*[a] 9α-Me, 6β-Ph (% Yield)[b]	Chair-*syn*[a] 9α-Me, 6α-Ph (% Yield)	Boat-*syn*[a] 9β-Me, 6β-Ph (% Yield)	Chair-*anti*[a] 9β-Me, 6α-Ph (% Yield)
Ethyl 1-benzoyl-4-oxocyclohexane-1-carboxylate (**8b**)[d]	(**35**)(15)	(**36**)(50)	(**37**)(25)	(**38**)(0)[c]
4-Benzoyl-4-methylcyclohexanone (**8a**)	(**1**)(0)	(**4**)(25)	(**3**)(50)	(**2**)(25)
4-Benzoyl-4-phenylcyclohexanone (**8c**)	(**42**)(17)	(**43**)(17)	(44)(66)	(**45**)(0)

[a] See Footnote * on previous page. [b] Relative percent. [c] Instead of this isomer we obtained 10%[b] of 1-benzoyl-10-methyladamantane-2,4,6-trione (**40**). [d] The numbering changes in the adamantane derivatives produced from this precursor, so the chiral centres now occur at C-2 and C-10 instead of C-6 and C-9.

cyclisation of the ketene would be expected to occur onto the ester group thus leading to the adamantanetrione (**40**), rather than cyclisation onto the benzoyl group to give the adamantanedione (**38**) since the latter would involve initial inversion of the ring carbon carrying the ketene substituent, with concomitant increase in the activation energy for the process owing to the $A^{(1,3)}$ strain engendered in the intermediate tetrasubstituted enamine, *i.e.* (**27**; Z = Bz, X = CO_2Et, R = Me, R′ = H). The fact that none of (**38**) is formed suggests that the 9β-Me, 6α-Ph configuration is normally derived by a chair-*anti* transition state, as indicated in Table 3, when there is no other electrophilic group at C-4 which can trap the ketene substituent prior to inversion. Again since the more hindered isomer (**37**) is still formed, albeit in reduced yield, this suggests it is derived by the boat-*syn* route rather than the chair-*anti* inversion route. Similarly with the enamine from 4-benzoyl-4-phenylcyclohexanone (**9c**), *anti* attack on conformation (**41**) appears to be blocked by the axial phenyl group, or at least sufficiently hindered to favour exclusive *syn* attack, since none of the 9β-Me, 6α-Ph isomer (**45**) is formed. However, the more crowded 9β-Me, 6β-Ph isomer (**44**) is still formed from the enamine (**9c**), in *increased* relative yield, and this has to be regarded as strong confirmatory evidence for the involvement of the boat-*syn* route rather than the alternative chair-*anti* inversion route. The only example we have in which the 9β-Me, 6α-Ph configuration is formed, (**2**), presumably involves conformation (i) of enamine (**9a**). In this case although the axially orientated methyl group will certainly hinder *anti* attack, the steric impediment would be expected to be less than that of a bulky axial phenyl group and some *anti* attack could occur.

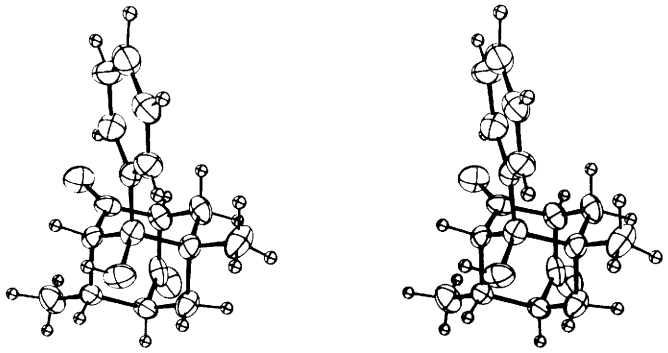


Figure 1. ORTEP stereoscopic drawing of (4). Ellipsoids are of 50% probability.

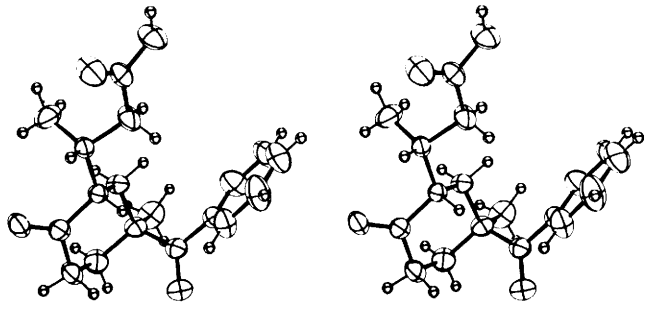
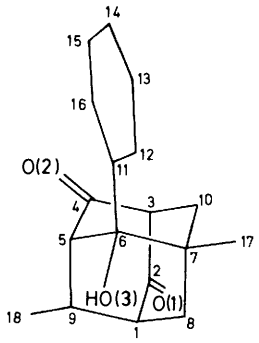
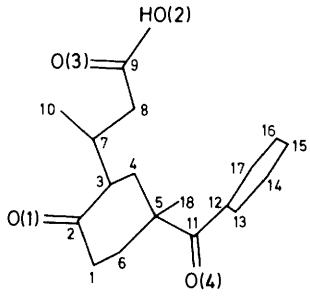


Figure 2. ORTEP stereoscopic drawing of (34). Ellipsoids are of 50% probability.



(I)



(II)

Since the axial methyl group will also presumably hinder cyclisation of the ketene group onto the regenerated enamine system from the same side as the methyl group, then inversion of the ring carbon carrying the ketene residue can occur, followed by cyclisation onto the regenerated enamine and benzoyl group to give (2).

Returning to consideration of the boat-*syn* process (Scheme 4), the methyl group of the crotonoyl residue is vinylogous to, and activated by, the carbonyl group. As mentioned earlier there could therefore be an attractive interaction between the electron deficient methyl hydrogens of the crotonoyl residue and the π-electrons of the benzene ring [*i.e.* ···· in (**19**), Scheme 4] which could account for the preferred formation of the 6β-phenyl configuration in the major isomer (**3**). Once the [3,3] sigmatropic rearrangement has occurred to give (**20**), the bulky ketene side chain would make free rotation about the C(4)–COPh carbon–carbon bond difficult. Since there is a significant mesomeric displacement of electrons towards the terminal carbon atom of a ketene,[13] once the enamine system has been regenerated [in (**21**)] an attractive electrostatic interaction between the ketene group and the axial C(4) substitutent can ensue [as depicted by ···· in (**17**), (**21**), and (**26**)] which would tend to prevent ring-flipping or ring-flattening and again prevent rotation about the C(4)–COPh bond. In this way the benzoyl group could be held in the same conformation as that induced by the initial interaction shown in structure (**19**) (Scheme 4). It is also interesting to note that the attractive interactions shown in (**17**), (**21**), and (**26**) could also serve to position the ketene carbonyl group over the regenerated enamine double bond and to line up the orthogonal orbitals of the ketene group in such a way that synchronous bonding interactions could occur between the enamine β-carbon and the ketene carbonyl group, and between the ketene carbon–carbon double bond and the benzoyl group. So the conversion of (**12**)→(**14**) could occur without the intermediacy of the enolate anion (**13**) (Scheme 2), the presumed formation of which had been the driving force for this investigation!

Table 4. Crystallographic data and refinement details for structures (**4**) and (**34**)

	(4)	(34)
Formula	$C_{18}H_{20}O_3$	$C_{18}H_{22}O_4$
Formula weight (*M*)	284.3	302.4
F(0,0,0)	608	648
a	13.802(5)	16.912(6)
b	12.966(5)	8.675(4)
c (Å)	8.020(4)	11.435(5)
β (°)	—	106.78(5)
V (Å^3)	1 435	1 606
Z	4	4
Space group	$P2_12_12_1$	$P2_1/n$
D_c (g cm^{-3})	1.316	1.251
Radiation	Mo-*Kα*	Mo-*Kα*
Scan mode	ω/2θ	ω/2θ
Scan speed (in ω° min^{-1})	1.5	1.5
Scan width (in ω)	1.3	1.2
Angular range (in 2θ deg.)	5—45	5—46
Background time at each side of the peak (min)	10	10
No. of unique reflections	1 090	2 171
No of unobserved reflections	32	259
No of reflections at the final refinement stage	927	1 662
Cut off criterion	$F_o > 1.5\ \sigma(F_o)$	$F_o > 1.5\ \sigma(F_o)$
No. of refined parameters	270	285
R	0.049	0.073
R_w	0.051	0.069
Weighting scheme (w)	$0.784/(\sigma^2(F_o) + 0.003(F_o)^2)$	$1.452/(\sigma^2(F_o) + 0.001(F_o)^2)$

ORTEP[14] stereoscopic views of molecules (**4**) and (**34**) are displayed in Figures 1 and 2 and their numbering systems are shown in (**I**) and (**II**) respectively.

The scatter of the C–C bond distances, as tabulated in Table 7, reveals a noteworthy deviation of the adamantane skeleton from exact point group *Td*, as expected in a 2,4-dione. Here, all C(sp^2)–C(sp^3) bond lengths involving the sp^2 hybridised carbonyl carbons C(2) and C(4) are shorter by 0.04 Å from the C–C mean value as found for instance in adamantane-1,3-dicarbonyl chloride[15] and in (*E*)- and (*Z*)-2-chloro-2-ethynyl-5-phenyladamantane.[16] On the other hand, the bond angles C(1)–C(2)–C(3) and C(3)–C(4)–C(5) are larger by 4° than the mean value of 109.5°. Deviations from ideal tetrahedral geometry are even extended to C(3) and C(5) as vicinal atoms to the deformation centres at C(2) and C(4). Beyond this

Table 5. Noteworthy bond lengths (in Å) and angles (in °) for (**4**). E.s.d.'s are shown in parentheses

C(1)–C(2)	1.487(9)	C(14)–C(15)	1.38(1)
C(1)–C(8)	1.519(9)	C(15)–C(16)	1.374(9)
C(1)–C(9)	1.545(8)	C(1)–H(1)	0.96(5)
C(2)–C(3)	1.518(9)	C(3)–H(3)	0.98(7)
C(2)–O(1)	1.215(7)	C(5)–H(5)	1.04(4)
C(3)–C(4)	1.514(9)	C(8)–H1(8)	1.04(5)
C(3)–C(10)	1.552(9)	C(8)–H2(8)	0.84(7)
C(4)–C(5)	1.488(8)	C(9)–H(9)	1.02(5)
C(4)–O(2)	1.219(7)	C(10)–H1(10)	1.04(6)
C(5)–C(6)	1.558(8)	C(10)–H2(10)	1.04(6)
C(5)–C(9)	1.564(8)	C(12)–H(12)	1.02(6)
C(6)–C(7)	1.563(8)	C(13)–H(13)	1.00(8)
C(6)–C(11)	1.536(8)	C(14)–H(14)	1.09(7)
C(6)–O(3)	1.420(7)	C(15)–H(15)	0.96(8)
C(7)–C(8)	1.547(9)	C(16)–H(16)	0.82(5)
C(7)–C(10)	1.548(8)	C(17)–H1(17)	1.03(7)
C(7)–C(17)	1.515(9)	C(17)–H2(17)	0.97(7)
C(9)–C(18)	1.52(1)	C(17)–H3(17)	0.94(7)
C(11)–C(12)	1.387(8)	C(18)–H1(18)	1.09(7)
C(11)–C(16)	1.397(8)	C(18)–H2(18)	0.97(8)
C(12)–C(13)	1.376(9)	C(18)–H3(18)	0.89(9)
C(13)–C(14)	1.39(1)	O(3)–HO(3)	0.9(1)
C(2)–C(1)–C(8)	107.9(5)	C(11)–C(6)–O(3)	109.5(4)
C(2)–C(1)–C(9)	108.0(5)	C(6)–C(7)–C(8)	108.7(4)
C(8)–C(1)–C(9)	110.2(5)	C(6)–C(7)–C(10)	109.7(4)
C(1)–C(2)–C(3)	113.6(5)	C(6)–C(7)–C(17)	113.4(5)
C(1)–C(2)–O(1)	125.1(6)	C(8)–C(7)–C(10)	107.2(5)
C(3)–C(2)–O(1)	121.2(6)	C(8)–C(7)–C(17)	109.5(5)
C(2)–C(3)–C(4)	105.9(5)	C(10)–C(7)–C(17)	108.1(5)
C(2)–C(3)–C(10)	108.0(5)	C(1)–C(8)–C(7)	112.3(5)
C(4)–C(3)–C(10)	108.0(5)	C(1)–C(9)–C(5)	108.6(4)
C(3)–C(4)–C(5)	113.3(5)	C(1)–C(9)–C(18)	112.2(5)
C(3)–C(4)–O(2)	121.4(6)	C(5)–C(9)–C(18)	112.0(5)
C(5)–C(4)–O(2)	124.7(5)	C(3)–C(10)–C(7)	111.8(5)
C(4)–C(5)–C(6)	114.6(4)	C(6)–C(11)–C(12)	124.2(5)
C(4)–C(5)–C(9)	104.8(4)	C(6)–C(11)–C(16)	120.3(5)
C(6)–C(5)–C(9)	110.3(4)	C(12)–C(11)–C(16)	115.6(5)
C(5)–C(6)–C(7)	106.8(4)	C(11)–c(12)–C(13)	123.3(6)
C(5)–C(6)–C(11)	112.7(4)	C(12)–C(13)–C(14)	119.8(6)
C(5)–C(6)–O(3)	108.9(4)	C(13)–C(14)–C(15)	118.3(6)
C(7)–C(6)–C(11)	113.4(4)	C(14)–C(15)–C(16)	120.9(6)
C(7)–C(6)–O(3)	105.2(4)	C(11)–C(16)–C(15)	122.2(6)

environment, the adamantane skeleton remains unaffected by substitution at carbons C(6), C(7), and C(9).

The stereochemistry at C(6) and C(9) can be nicely compared with that in the more crowded isomer (**2**) studied by Redhouse.[4] In (**2**) the methyl group attached to C(9) and the β-orientated hydroxy group at C(6) are involved in a 1,3-diaxial interaction, the nonbonded distance between them being 2.89 Å. Comparison between dihedral angles involving bond C(6)–C(7) in both isomers shows that the environment around the substituted atoms C(6) and C(7) is unaffected by moving the methyl group attached to C(9) from a β to an α orientation. However, remarkable differences are observed around bond C(9)–C(1) as atoms C(18) and H(9) interchange substitution sites. The dihedral angles H(9)–C(9)–C(1)–C(8) = 56.7°, H(9)–C(9)–C(1)–H(1) = 67° and C(18)–C(9)–C(1)–H(1) = 54.8° in (**4**) differ from the corresponding values 75, 45, and 68° given for the crowded isomer (**2**), where H(9) is replaced by CM9 and C(18) by H91 (see Figure 2; Ref. 4).

The oxocyclohexyl moiety of molecule (**34**) assumes the normal chair conformation. Here, bond lengths C(1)–C(2) and C(2)–C(3) as presented in Table 8 are shorter by 0.04 Å and the angle C(1)–C(2)–C(3) is larger by 6° than the corresponding mean values in cyclohexane due to the sp^2 hybridised carbon

Table 6. Noteworthy bond lengths (in Å) and angles (in °) for (**34**). E.s.d.'s are shown in parentheses

C(1)–C(2)	1.493(6)	C(16)–C(17)	1.371(7)
C(1)–C(6)	1.526(7)	C(1)–H1(1)	1.04(5)
C(2)–C(3)	1.500(5)	C(1)–H2(1)	0.97(4)
C(2)–O(1)	1.225(5)	C(3)–H(3)	0.98(4)
C(3)–C(4)	1.536(6)	C(4)–H1(4)	0.99(5)
C(3)–C(7)	1.542(5)	C(4)–H2(4)	0.98(3)
C(4)–C(5)	1.541(5)	C(6)–H1(6)	0.95(4)
C(5)–C(6)	1.532(6)	C(6)–H2(6)	0.99(6)
C(5)–C(11)	1.535(7)	C(7)–H(7)	0.96(4)
C(5)–C(18)	1.550(7)	C(8)–H1(8)	0.92(5)
C(7)–C(8)	1.514(6)	C(8)–H2(8)	0.96(6)
C(7)–C(10)	1.510(8)	C(10)–H1(10)	0.90(5)
C(8)–C(9)	1.498(6)	C(10)–H2(10)	0.98(4)
C(9)–O(2)	1.324(5)	C(10)–H3(10)	0.97(6)
C(9)–O(3)	1.187(6)	C(13)–H(13)	0.93(5)
C(11)–C(12)	1.505(6)	C(15)–H(15)	0.86(6)
C(11)–O(4)	1.213(5)	C(16)–H(16)	1.01(4)
C(12)–C(13)	1.374(6)	C(17)–H(17)	0.91(4)
C(12)–C(17)	1.369(7)	C(18)–H1(18)	0.94(5)
C(13)–C(14)	1.385(7)	C(18)–H2(18)	1.01(7)
C(14)–C(15)	1.37(7)	C(18)–H3(18)	0.99(5)
C(15)–C(16)	1.357(8)	O(2)–HO(2)	0.86(5)
C(2)–C(1)–C(6)	113.3(5)	C(8)–C(7)–C(10)	110.7(5)
C(1)–C(2)–C(3)	115.8(3)	C(7)–C(8)–C(9)	114.4(4)
C(1)–C(2)–O(1)	121.4(4)	C(8)–C(9)–O(2)	111.9(4)
C(3)–C(2)–O(1)	122.8(4)	C(8)–C(9)–O(3)	125.0(5)
C(2)–C(3)–C(4)	108.9(3)	O(2)–C(9)–O(3)	123.1(4)
C(2)–C(3)–C(7)	115.3(3)	C(5)–C(11)–C(12)	119.9(4)
C(4)–C(3)–C(7)	114.4(4)	C(5)–C(11)–O(4)	121.4(4)
C(3)–C(4)–C(5)	113.1(3)	C(12)–C(11)–O(4)	118.7(3)
C(4)–C(5)–C(6)	107.9(3)	C(11)–C(12)–C(13)	124.2(4)
C(4)–C(5)–C(11)	111.0(3)	C(11)–C(12)–C(17)	117.3(4)
C(4)–C(5)–C(18)	110.4(4)	C(13)–C(12)–C(17)	118.4(5)
C(6)–C(5)–C(11)	110.1(4)	C(12)–C(13)–C(14)	120.5(5)
C(6)–C(5)–C(18)	109.0(4)	C(13)–C(14)–C(15)	119.7(6)
C(11)–C(5)–C(18)	108.5(3)	C(14)–C(15)–C(16)	119.9(6)
C(1)–C(6)–C(5)	113.3(4)	C(15)–C(16)–C(17)	120.1(5)
C(3)–C(7)–C(8)	110.1(3)	C(12)–C(17)–C(16)	121.3(5)
C(3)–C(7)–C(10)	114.0(4)		

Table 7. Final fractional atomic co-ordinates for (**4**). Co-ordinates are $\times 10^4$ for C and O and $\times 10^3$ for H. Equivalent temperature factors are $\times 10^3$ and $U_{iso} \times 10^2$. E.s.d.'s are shown in parentheses.

Atom	*x*	*y*	*z*
C(1)	6 544(5)	3 139(5)	6 352(8)
C(2)	5 873(5)	3 528(5)	7 657(8)
C(3)	4 869(5)	3 788(5)	7 004(8)
C(4)	5 022(4)	4 575(5)	5 635(9)
C(5)	5 616(4)	4 181(4)	4 224(7)
C(6)	5 219(4)	3 179(4)	3 396(7)
C(7)	5 102(4)	2 364(5)	4 818(8)
C(8)	6 106(5)	2 166(5)	5 614(9)
C(9)	6 640(4)	3 978(5)	4 996(8)
C(10)	4 438(5)	2 800(5)	6 203(8)
C(11)	4 283(4)	3 365(4)	2 405(7)
C(12)	3 644(5)	4 169(5)	2 709(9)
C(13)	2 818(5)	4 333(5)	1 787(9)
C(14)	2 576(5)	3 654(6)	512(9)
C(15)	3 199(5)	2 844(6)	179(8)
C(16)	4 026(5)	2 704(5)	1 103(8)
C(17)	4 675(7)	1 352(6)	4 224(11)
C(18)	7 096(7)	4 958(6)	5 664(12)
O(1)	6 075(4)	3 633(4)	9 121(6)
O(2)	4 768(3)	5 470(4)	5 803(6)
O(3)	5 939(3)	2 768(4)	2 321(6)

Table 8. Final fractional atomic co-ordinates of (**34**). Co-ordinates are $\times 10^4$ for C and O and 10^3 for H. Equivalent temperature factors are $\times 10^4$ and $U_{iso} \times 10^2$. E.s.d.'s are shown in parentheses

Atom	*x*	*y*	*z*
C(1)	4 546(3)	5 400(6)	7 038(5)
C(2)	4 069(3)	4 325(5)	6 070(4)
C(3)	3 221(2)	4 854(5)	5 366(4)
C(4)	3 279(3)	6 496(5)	4 895(4)
C(5)	3 672(3)	7 650(5)	5 925(4)
C(6)	4 538(3)	7 053(7)	6 599(6)
C(7)	2 729(3)	3 719(5)	4 385(4)
C(8)	1 826(3)	4 174(6)	3 974(6)
C(9)	1 269(3)	2 997(6)	3 194(4)
C(10)	3 063(4)	3 548(9)	3 302(5)
C(11)	3 149(3)	7 799(5)	6 816(4)
C(12)	2 221(3)	7 817(5)	6 335(4)
C(13)	1 782(3)	8 783(7)	5 427(5)
C(14)	929(4)	8 677(9)	5 001(5)
C(15)	524(4)	7 564(8)	5 459(6)
C(16)	955(4)	6 620(7)	6 365(6)
C(17)	1 797(3)	6 761(6)	6 810(5)
C(18)	3 745(4)	9 264(7)	5 383(6)
O(1)	4 356(2)	3 082(4)	5 886(3)
O(2)	625(2)	3 640(4)	2 398(3)
O(3)	1 374(2)	1 643(4)	3 274(3)
O(4)	3 466(2)	7 855(4)	7 911(3)

C(2). The butanoic acid residue and the benzoyl group take the equatorial and axial sites at C(3) and C(5) respectively. The arrangement of atoms around the chiral site at C(7) is clearly illustrated in Figure 2. Substitution sites at C(5) are occupied by bulky groups, but crowding is avoided by rotation of the carbonyl group at C(11) away from C(18). This leads to disposition of the phenyl ring above the butanoic acid residue.

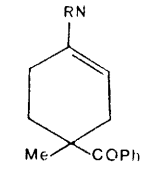
Experimental

General Procedures.—I.r. spectra were run on a Perkin-Elmer 257 grating spectrophotometer and calibrated against the 1 602 cm^{-1} band of a polystyrene film. ^1H N.m.r. spectra were recorded on Perkin-Elmer R32 and R34 instruments, operating at 90 MHz and 220 MHz respectively, in $CDCl_3$ solutions using tetramethylsilane as internal standard. ^{13}C N.m.r. spectra were determined on a Varian Associates CFT 20 instrument operating at 20 MHz in $CDCl_3$ solutions. Chemical shifts are in p.p.m. relative to $SiMe_4$; 'obnm' refers to signals observed (by decoupling) but not measurable. Mass spectral data were obtained on a Kratos MS 30 spectrometer and high resolution spectra on an AEI MS 9 spectrometer operating at 70 eV. Melting points were taken by the capillary tube method and are uncorrected. Elemental analyses were obtained at Buttersworth Laboratories Ltd., Middlesex, U.K., or the analytical department of Glaxo Group Research, Ware, U.K.

Silica gel (0.25 mm) 'Polygram' plates, supplied by Macherey-Nagel were used for t.l.c. and silica gel (Art 9385) supplied by Merck was used for Flash chromatography.[17] All solvents were distilled before use.

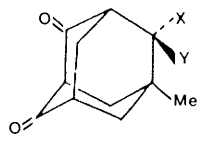
Preparation of 4,4-Disubstituted Cyclohexanones.—4-Benzoyl-4-methylcyclohexanone was prepared by the literature method.[18]

(*a*) *4-Benzoyl-4-phenylcyclohexanone* (**8c**). A mixture of 4-benzoyl-4-phenylheptanedioic acid[19] (11.2 g, 0.03 mol) and acetic anhydride (9.18 g, 0.09 mol) was heated under reflux for 15 min. The excess of acetic anhydride and acetic acid produced was then removed by distillation at atmospheric pressure and the residual viscous mass was distilled under reduced pressure to give 4-benzoyl-4-phenylcyclohexanone (5 g, 73%), b.p. 180—



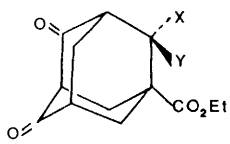
(**46**)

a; RN = morpholino
b; RN = piperidino
c; RN = butylamino
d; RN = isobutylamino

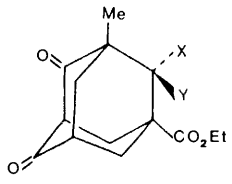


(**47**)

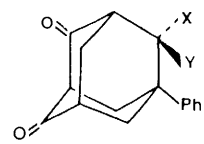
a; X = Ph, Y = OH
b; X = OH, Y = Ph



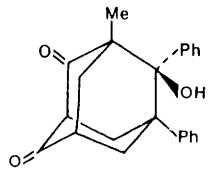
(**48**)



(**49**)



(**50**)



(**51**)

a; X = Ph, Y = OH; **b**; X = OH, Y = Ph

200 °C/0.2 mmHg, which solidified on cooling, m.p. 94—95 °C (from ethanol); δ($CDCl_3$) 7.40 (m, Ph) and 2.95—2.0 (m, CH_2); $\nu_{max.}$(Nujol) 1 710 and 1 675 cm^{-1} (CO) (Found: C, 82.1; H, 6.6%; M^+, 278.1304. $C_{19}H_{18}O_2$ requires C, 82.0; H, 6.5%; *M*, 278.1306).

(*b*) *Ethyl 1-benzoyl-4-oxocyclohexane-1-carboxylate* (**8b**). A mixture of 4-benzoyl-4-ethoxycarbonylheptanedinitrile[20] (39.5 g) and concentrated hydrochloric acid (135 ml) was heated under reflux for 7.25 h. The mixture was cooled and the solid which separated was collected and dissolved in water (50 ml). The aqueous solution was extracted with chloroform (3 × 75 ml) and the chloroform extracts were combined, dried ($MgSO_4$), and evaporated to dryness. Recrystallisation of the residue from chloroform–light petroleum (b.p. 40—60 °C) gave

4-benzoyl-4-ethoxycarbonylheptanedioic acid (36.7 g, 82%), m.p. 81—83 °C; δ($CDCl_3$) 10.87 (s, CO_2H), 7.7 and 7.35 (m, Ph), 4.10 (q, OCH_2), 3.0—1.92 (m, CH_2), and 1.02 (t, CH_2Me); $\nu_{max.}$(Nujol) 1 740 (CO_2Et), 1 710 (CO_2H), and 1 690 (PhCO) cm^{-1}. A mixture of this dicarboxylic acid (11.76 g) and acetic anhydride was distilled slowly at atmospheric pressure to remove the acetic acid formed and the excess of acetic anhydride. The residue was then distilled under reduced pressure to give ethyl 1-benzoyl-4-oxocyclohexane-1-carboxylate (6.9 g, 71%), b.p. 132—134 °C/0.15 mmHg; δ($CDCl_3$) 7.85 and 7.42 (m, Ph), 4.13 (q, OCH_2), 2.8—2.05 (m, CH_2), and 1.02 (t, CH_2Me); $\nu_{max.}$(film) 1 735, 1 720, and 1 680 cm^{-1} (Found: C, 69.9; H, 6.6%; M^+, 274.1206. Calc. for $C_{16}H_{18}O_4$: C, 70.1; H, 6.6%; *M*, 274.1205).

Preparation of Enamines: General Method.—A mixture of the 4,4-disubstituted cyclohexanone (0.01—0.05 mol) and a slight excess of secondary amine (0.011—0.06 mol) and toluene-*p*-sulphonic acid (0.01—0.2 g) in benzene (25—125 ml) was heated under reflux under a Dean and Stark head for 16 h. On cooling, the solvent and excess of amine were removed under reduced pressure and the crude enamine used without further purification since extensive decomposition occurred on distillation. In this way the following were obtained:

1-*Methyl*-4-*pyrrolidin*-1-*ylcyclohex*-3-*enyl phenyl ketone* (**9a**), δ 4.12; $\nu_{max.}$ 1 680 and 1 645 cm^{-1} (Found: *M*, 269.1779. Calc. for $C_{18}H_{23}NO$: M^+, 269.1779).

1-*Methyl*-4-*morpholinocyclohex*-3-*enyl phenyl ketone* (**46a**), δ 4.50; $\nu_{max.}$ 1 680 and 1 655 (Found: *M*, 285.1731. Calc. for $C_{18}H_{23}NO_2$ *M*, 285.1729).

1-*Methyl*-4-*piperidinocyclohex*-3-*enyl phenyl ketone* (**46b**), δ 4.55; $\nu_{max.}$ 1 680 and 1 650 (Found: M^+, 283.1934. Calc. for $C_{19}H_{25}NO$: *M*, 283.1935).

4-*Dibutylamino*-1-*methylcyclohex*-3-*enyl phenyl ketone* (**46c**), δ 4.20; $\nu_{max.}$ 1 680 and 1 640 (Found: *M*, 327.2557. Calc. for $C_{22}H_{33}NO$: *M*, 327.2560).

4-*Di-isobutylamino*-1-*methylcyclohex*-3-*enyl phenyl ketone* (**46d**), δ 4.30; $\nu_{max.}$ 1 680 and 1 640 (Found: *M*, 327.2560. Calc. for $C_{22}H_{33}NO$: *M*, 327.2560).

1-*Phenyl*-4-*pyrrolidin*-1-*ylcyclohex*-3-*enyl phenyl ketone* (**9c**), δ 4.25; $\nu_{max.}$ 1 675 and 1 640 (Found: M^+, 331.1933. Calc. for $C_{23}H_{25}NO$: *M*, 331.1935).

Ethyl 1-*benzoyl*-4-*pyrrolidin*-1-*ylcyclohex*-3-*ene*-1-*carboxylate* (**9b**), 4.13; $\nu_{max.}$ 1 730, 1 680, and 1 645 (Found: M^+, 327.1828. Calc. for $C_{20}H_{25}NO_3$: *M*, 327.1833).

6-*Hydroxy*-7,9-*dimethyl*-6-*phenyladamantane*-2,4-*diones* (**2**), (**3**), *and* (**4**): *Procedure A.*—This, a modification of our previously reported method, has resulted in improved yields and purity, and the isolation of a third stereoisomer whose presence had previously only been inferred from the ^1H n.m.r. spectral data of the product mixture.[2] To a boiling solution of 1-methyl-4-pyrrolidin-1-ylcyclohex-3-enyl phenyl ketone (**9a**)[2] (5.42 g, 0.02 mol) in sodium dried benzene (150 ml) was added dropwise a solution of crotonoyl chloride (2.1g, 0.02 mol) in dry benzene (30 ml). The mixture was then heated under reflux for 20 h, and cooled and the precipitated solid washed with dry benzene and stirred with cold water (100 ml) for 18 h. The crude product was isolated by extraction with chloroform (5 × 100 ml), and the chloroform extracts dried ($MgSO_4$). After filtration and removal of the chloroform under reduced pressure the oily solid was purified by elution down a 50 mm diameter flash column packed with 200 mm of silica using acetone–light petroleum (60—80 °C) (3:17) as eluant; 140 10-ml fractions were collected. Fractions 8—20 were combined to give unchanged starting material (**8a**) (0.356 g). Fractions 31—39 gave (**2**) (0.234 g, 4.5%*), fractions 40—49 gave a mixture of (**2**) and (**4**) (0.242 g; ratio 1 : 3 respectively), fractions 50—58 gave (**4**) (0.462 g, 9%*), and fractions 86—100 gave (**3**) (1.12 g, 21.5%*). The total combined yield of the adamantane isomers, including the mixed fraction, was 2.058 g (40%*). Each isomer was recrystallised from chloroform–light petroleum (b.p. 60—80 °C) and gave the following physical, analytical, and spectroscopic data:

Compound (**2**), m.p. 238—239 °C (lit.,[2] 229—230 °C); δ_C† ($CDCl_3$) 207.1(s) 206.75(s), 144.27(1), 127.8(d), 128.28(d), 127.2(d), 79.83(s), 65.43(d), 61.88(d), 50.3(d), 40.9(t), 37.1(s), 36.24(t), 34.78(d), 22.06(q), and 18.3(q) (Found: C, 75.96; H, 7.23. Calc. for $C_{18}H_{20}O_3$: C, 76.05; H, 7.04%).

Compound (**4**), m.p. 210—211 °C; δ($CDCl_3$)‡ 7.54, 7.36 (m, Ph), 3.40 (m, 3-H, $J_{3,10a}$ 2.8, $J_{3,10e}$ 3.8 Hz, $J_{1,3}$ and $J_{3,5}$ obnm), 3.15 (m, 9-H, J_{9Me} 7.0, $J_{1,9}$ 2.8, $J_{5,9}$ 2.5 Hz), 2.90 (m, 5-H, $J_{1,5}$ obnm), 2.81 (dt, 8e-H, $J_{8a,8e}$ 13.5, $J_{1,8e}$ 3.5, $J_{8e,10e}$ 3.6 Hz), 2.56 (m, 1-H, $J_{1,8a}$ 2.8 Hz), 2.06 (s, OH), 1.96 (dt, 10e-H, $J_{10a,10e}$ 14.0 Hz), 1.83 (dd, 10a-H), 1.80 (dd, 8a-H), 0.86 (s, 7-Me), and 0.81 (d, 9-Me); δ_C($CDCl_3$) 208.25(s), 206.7(s), 143.84(s), 127.9(d), 127.4(d), 79.34(s), 67.5(d), 63.47(d), 51.05(d), 41.45(t), 41.1(t), 36.7(s), 30.12(d), 21.72(q), and 16.82(q); $\nu_{max.}$(Nujol) 3 475, 1 710, and 1 695 cm^{-1} (Found: C, 76.1; H, 7.1%; M^+, 284.1411. Calc. for $C_{18}H_{20}O_3$: C, 76.05; H, 7.04%; *M*, 284.1411).

Compound (**3**), m.p. 219—220 °C (lit.,[2] 209—210 °C); δ_C† 207.37(s), 204.96(s), 144.62(s), 128.4(d), 127.9(d), 127.52(d), 78.82(s), 65.65(d), 63.7(d), 49.64(d), 47.1(t), 37.82(s), 37.1(t), 32.45(d), 20.87(q), and 15.2(q) (Found: C, 76.1; H, 7.15. Calc. for $C_{18}H_{20}O_3$: C, 76.05; H, 7.04%).

7,9β-*Dimethyl*-6β-*phenyladamantane*-2,4,6α-*triol* (**6**).—The adamantane dione (**3**) (173 mg, 0.6 mmol) was added to a solution of sodium borohydride (112 mg, 3 mmol) in ethanol (5 ml) and the mixture was stirred for 48 h. The ethanol was removed under reduced pressure and the residue dissolved in water (1.5 ml) and the resulting solution extracted with ether (6 × 5 ml). The combined extracts were dried ($MgSO_4$) and the ether removed to give the crude triol (100 mg, 57%). Purification by means of preparative t.l.c. on silica using 15% acetone in chloroform as eluant gave 7,9β-dimethyl-6β-phenyladamantane-2,4,6α-triol (**6**), m.p. 179—181 °C, as a mixture of four isomers epimeric at C-2 and C-4: δ($CDCl_3$) 7.68, 7.25 (m, Ph), 4.4, 4.06, 3.73 (m, C*H*-OH), 3.0—0.7 (complex), 1.22 (s, 7-Me), and 0.45, 0.4, 0.35, 0.3 (d, 9-Me); $\nu_{max.}$(Nujol) 3 300 cm^{-1} (Found: M^+, 286.1507. Calc. for $C_{18}H_{22}O_3$: *M*, 286.1507.)

7,9β-*Dimethyl*-6β-*phenyladamantane*-2,4,6β-*triol* (**5**).—Reduction of the adamantanedione (**2**) (100 mg, 0.35 mmol) in the same way gave the crude triol (60 mg, 60%) as a viscous oil. Purification by preparative t.l.c. as above gave 7,9β-dimethyl-6α-phenyladamantane-2,4,6β-triol as a mixture of two stereoisomers: δ($CDCl_3$) 7.75, 7.27 (m, Ph), 4.1, 3.7 (m, C*H*-OH), 3.0—0.7 (complex), 1.44, 1.4 (d, 9-Me), and 1.16 (s, 7-Me) (Found: M^+, 286.1507. Calc. for $C_{18}H_{22}O_3$: *M*, 286.1507).

2,6β-*Dihydroxy*-7,9α-*dimethyl*-6α-*phenyladamantan*-4-*one* (**7**). Similar treatement of adamantanedione (**4**) (100 mg) with sodium borohydride (68 mg, 1.8 mmol) in ethanol (5 ml) gave a solid which was purified by flash chromatography using 125 mm of silica in a 15 mm column with ethyl acetate–light petroleum (b.p. 60—80 °C) (3:2) as eluant. Forty 5-ml fractions were collected and fractions 14—26 were combined and evaporated to give 7,9α-dimethyl-4-oxo-6α-phenyladamantane-2,6β-diol (33 mg, 33%), m.p. 168—169 °C, δ($CDCl_3$)‡ 7.58, 7.32

* Asterisked yields refer to yield after allowance for the recovered starting ketone (**8a**).

† ^1H N.m.r. data were identical with previously published values.[3]

‡ Ha and He refer to axial and equatorial hydrogens respectively, attached to ring numbered 1,2,3,10,7,8.

(m, Ph), 4.37 (overlaid dt, 2-H, $J_{1,2}$ 2.4, $J_{2,3}$ 2.5, $J_{2,9}$ 2.9 Hz), 3.34 (m, 9-H, J_{9Me} 7.9 Hz, $J_{5,9}$ and $J_{1,9}$ obnm), 2.67 (m, 3-H, $J_{3,10a}$ 2.4, $J_{3,10e}$ 3.5 Hz, $J_{1,3}$ and $J_{3,5}$ obnm), 2.62 (m, 5-H), 2.58 (dt, 8e-H, $J_{8a,8e}$ 13.0, $J_{1,8e}$ 3.5, $J_{8e,10e}$ 4.0 Hz), 2.14 (s, 6-OH), 2.05 (m, 1-H, $J_{1,8a}$ 2.9, $J_{1,9}$ 2.4 Hz) 1.95 (s, 2-OH), 1.62 (dt, 10e-H, $J_{10a,10e}$ 13.9 Hz), 1.52 (dd, 8a-H), 1.47 (dd, 10a-H), 1.22 (d, 9-Me), and 0.87 (s, 7-Me); $\nu_{max.}$(Nujol) 3 410br and 1 700 cm^{-1} (Found: M^+, 286.1564. Calc. for $C_{18}H_{22}O_3$: *M*, 286.1569).

Effect of Variation of Reaction Time on the Yield and Isomer Distribution of 6-Hydroxy-7,9-dimethyl-6-phenyladamantane-2,4-diones (**2**—**4**).—Procedure A was scaled down to that required for 5.6 mmol of enamine (**9a**). Flash chromatography was omitted and the reaction times varied as shown in Table 2. The yield of each isomer was determined by integration of the ^1H n.m.r. spectrum of the crude reaction product using s-trioxane as an internal standard.

Effect of Variation of the Amine Component of the Enamine on the Yield of Adamantanediones (**2**—**4**).—The crude enamines (0.01 mol) were each separately dissolved in dry benzene (80 ml) and treated with a solution of crotonoyl chloride (1.05 g, 0.01 mol) as in Procedure A. The flash chromatographic purification step was omitted and the crude products were analysed by ^1H n.m.r. spectroscopy.* The results are given in Table 1.

3-(5-*Benzoyl*-5-*methyl*-2-*oxocyclohexyl*)*butanoic Acid* (**34**).—The reaction between crotonoyl chloride and the enamine (**9a**) was carried out as in Procedure A (0.03 mol scale) but heating was confined to intermediate times of 0.5, 3, and 12 h instead of 20 h. Water (30 ml) was then added to each reaction and the mixture heated under reflux for 1 h in order to hydrolyse any uncyclised ketene intermediate [*viz.* (**16**), (**20**), (**24**)] and to the corresponding butanoic acid. Each reaction mixture was then cooled, and basified with concentrated aqueous sodium hydroxide. The aqueous layers were separated, washed with chloroform (4 × 50 ml), acidified with concentrated hydrochloric acid, and extracted with chloroform (4 × 50 ml). The chloroform extracts were combined, dried ($MgSO_4$), and evaporated and the residues thus obtained were purified by flash chromatography. The only identifiable products isolated were crotonic acid (identified by comparison with authentic material) and the butanoic acid (**34**), m.p. 122—123 °C; δ($CDCl_3$) 11.0 (s, CO_2H), 7.3—8.1 (m, Ph), 2.0—2.9 (m, CH and CH_2), 1.58 (s, 5-Me), 0.84 (d, Me); δ_C($CDCl_3$) 210.83 (s), 206.65(s), 177.96 (s), 137.41 (s), 128.38 (d), 128.15 (d), 127.44 (d), 49.90 (d), 48.23 (s), 38.3 (t), 38.1 (t), 37.75 (t), 36.48 (t), 26.86 (q), 27.6 (d), and 15.5 (q); $\nu_{max.}$(Nujol) 3 100br, 1 715, 1 705, and 1 680 cm^{-1} (Found: C, 70.95; H, 7.35%; M^+, 302.1517. Calc. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33%; *M*, 302.1517).

Attempted Interconversion of 6-Hydroxy-7,9-dimethyl-6-phenyladamantane-2,4-dione Isomers.—(*a*) A mixture of the isomer (**3**) (50.6 mg, 0.178 mmol), pyrrolidine (12.7 mg, 0.178 mmol), and toluene-*p*-sulphonic acid (34 mg, 0.178 mmol) in benzene (15 ml) was heated under reflux for 20 h, the condensate being passed through a molecular sieve (4 Å) before being returned to the reaction mixture. The solvent was removed under reduced pressure and the residue stirred with cold water (15 ml) for 18 h. The aqueous solution was extracted with ether (4 × 10 ml) and the combined extracts dried ($MgSO_4$) and evaporated to yield unchanged isomer (**3**) (48.9 mg) as indicated by t.l.c. and ^1H n.m.r. There was no evidence for any conversion to isomers (**2**) or (**4**).

(*b*) The same procedure was repeated with 89 mg of the mixed fraction of (**2**) and (**4**) isolated by flash chromatography. The mixture of (**2**) and (**4**) (86.5 mg) was recovered unchanged. T.l.c. and ^1H n.m.r. showed no conversion into isomer (**3**).

(*c*) Each isomer (0.1 g) was dissolved in deuterioacetone (5 ml) and a crystal of toluene-*p*-sulphonic acid added to each solution. The solutions were heated in a sealed n.m.r. tube in an oven at 110 °C for ten days, the ^1H n.m.r. spectrum being recorded at 24 h intervals. These results showed unequivocally that isomer (**3**) was converted under these conditions only into (**2**) and decomposition products, whereas isomer (**2**) was not epimerised into isomer (**3**) but merely decomposed. In the case of isomer (**4**) a new signal at δ 1.15 appeared which could be due to the C(7) methyl group of (**1**), but this was not isolated and the signal intensity never accounted for more than 20% of the corresponding signal for (**4**). Decomposition was again observed.

In parallel experiments it was shown that the two pure C(6) epimers obtained from the corresponding reaction of acryloyl chloride and the enamine (**9**)[2] [(**47a**) and (**47b**)] each epimerised into a 4:1 equilibrium mixture of (**47a**)—(**47b**) over a period of 7—9 days at 110 °C. These results clearly demonstrated that the 6α-phenyl isomer (**47a**) was the thermodynamically more stable isomer. Decomposition and deuterium incorporation at C-3 also occurred as shown by the diminishing intensity of the C-7 methyl and the 3-H signals respectively.[8]

Synthesis of Ethyl 2-Hydroxy-4,6-dioxo-2-phenyladamantane-1-carboxylates: Procedure B.—The αβ-unsaturated acid chloride (0.05 mol) in dry benzene (60 ml) was added dropwise to the enamine (**9b**) (0.05 mol) in dry benzene (60 ml) during 1 h. During the addition a solid was slowly precipitated from the reaction mixture. The mixture was then heated under reflux overnight (*ca.* 20 h), and cooled, and the precipitated iminium salt was collected, washed with dry benzene, and hydrolysed by stirring with ice cold water (100 ml) for 5 h. The crude adamantane derivatives were isolated by extraction with diethyl ether (5 × 30 ml) and purified by preparative t.l.c. on silica using 10—15% acetone in chloroform as eluant. No attempt was made to optimise yields since we were only interested in determining which products were formed. The following results were obtained:

Acryloyl chloride gave a 30% yield of a mixture of (**48a**) and (**48b**) in a ratio of 3:2.† Recrystallisation from acetone–light petroleum (40—60 °C) gave a sample of pure (**48b**), m.p. 150—151 °C; δ‡ ($CDCl_3$) 7.53, 7.36 (Ph), 4.52 (OH), 4.26 (CO_2CH_2Me), 3.52 (5-H, $J_{5,9e}$ 3.5, $J_{5,9a}$ 2.7 Hz, $J_{3,5}$ and $J_{5,7}$ obnm), 3.26 (3-H, $J_{3,10\beta}$ and $J_{3,10\alpha}$ obnm), 3.17 (9e-H, $J_{9e,9a}$ 12.5 Hz, $J_{8e,9e}$ obnm), 2.88 (8e-H and 8a-H), 2.82 (7-H, $J_{7,10\alpha}$ and $J_{7,10\beta}$ obnm), 2.35 (9a-H), 1.64 (10α-H and 10β-H), 1.26 (CO_2CH_2Me); $\nu_{max.}$($CHCl_3$) 3 540, 3 480, 1 740, and 1 710 cm^{-1} (Found: C, 69.7; H, 6.25%; M^+, 328. Calc. for $C_{19}H_{20}O_5$: C, 69.5; H, 6.1%; *M*, 328); dioxime, m.p. 194—195 °C (from aqueous ethanol); $\nu_{max.}$(Nujol) 3 440, 1 725, and 1 670 cm^{-1}. (Found: C, 63.5; H, 6.2; N, 7.5%; M^+, 358.1526. Calc. for $C_{19}H_{22}N_2O_5$: C, 63.7; H, 6.15; N, 7.8%; *M*, 358.1527).

Evaporation of the mother liquors and repeated recrystallisation of the residue from acetone–light petroleum ether (40—

* The same isomer distributions were obtained as those given in Table 2.

† The failure of acryloyl chloride and, to a lesser extent, methacryloyl chloride, to cyclise onto an axial ester substituent has been referred to earlier in the text and has been attributed to differential steric effects [*i.e.* $A^{(1,3)}$-strain (which forces the ketene residue into an axial orientation) *vs.* 1,3-diaxial strain (which forces the ketene residue into an equatorial orientation and, if dominant, prevents intramolecular cyclisation onto the regenerated enamine from taking place)].[12] As a consequence, adamantanetriones analogous to (**40**) were not obtained with acryloyl or methacryloyl chlorides.

‡ As footnote † on previous page.

60 C) gave a small sample of isomer (**48a**) m.p. 120—121 C; δ($CDCl_3$) 7.36, 7.27 (Ph), 4.69 (OH), 4.09 (CO_2CH_2Me), 3.48 (5-H, $J_{5,9e}$ 3.0, $J_{5,9a}$ 2.7 Hz, $J_{3,5}$ and $J_{5,7}$ obnm), 3.23 (3-H, $J_{3,10\beta}$ 2.5 Hz, $J_{3,10\alpha}$ and $J_{3,7}$ obnm), 3.11 (8e-H, $J_{8a,8e}$ 13, $J_{8e,9e}$ 3.5 Hz, $J_{7,8e}$ obnm), 3.01 (10β-H, $J_{10\alpha,10\beta}$ 13 Hz), 2.80 (7-H, $J_{7,8a}$ 2.5 $J_{7,10\alpha}$ obnm), 2.65 (9e-H, $J_{9a,9e}$ 14 Hz), 2.55 (9a-H), 2.13 (8a-H, $J_{8a,10\alpha}$ obnm), 1.56 ($H_{10\alpha}$), and 1.10 (CO_2CH_2Me); $\nu_{max.}$($CHCl_3$) 3 550, 3 470, 1 740, and 1 705; M^+ *m/z* 328.

Methacryloyl chloride gave a (3:2)* mixture of (**49a**) and (**49b**) (37% yield). Recrystallisation from chloroform–light petroleum (40—60 °C) gave a pure sample of (**49a**), m.p. 149—150 C; δ($CDCl_3$) 7.28 (Ph), 4.71 (OH), 3.99 (CO_2CH_2Me), 3.70 5-H, $J_{5,9e}$ 3.5, $J_{5,9a}$ 2.5 Hz, $J_{5,7}$ obnm), 3.12 (8e-H, $J_{8a,8e}$ 13, $J_{7,8e}$ 3.5, $J_{8e,9e}$ 4.0 Hz), 2.92 (10β-H, $J_{10\alpha,10\beta}$ 13, $J_{7,10\beta}$ 2.5 Hz), 2.88 (7-H, $J_{7,8a}$ and $J_{7,10\alpha}$ obnm), 2.83 (9e-H), 2.38 (9a-H), 2.09 (8a-H, $J_{8a,10\alpha}$ obnm), 1.26 (10α-H), 0.99 (3-Me), 0.88 (CO_2CH_2Me); $\nu_{max.}$($CHCl_3$) 3 540, 3 460, 1 740, and 1 700 cm^{-1} (Found: C, 70.3; H, 6.5%; M^+, 342. Calc. for $C_{20}H_{22}O_5$: C, 70.2; H, 6.4%; *M*, 342).

Crotonoyl chloride gave a 12% yield of a mixture of (**35**), (**36**), (**37**), and (**40**) in a ratio of 15:50:25:10.† Recrystallisation from chloroform–light petroleum ether (40—60 °C) gave a pure sample of (**36**), m.p. 142—143 °C; δ($CDCl_3$) 7.43, 7.31 (Ph), 4.74 (OH), 4.15 (CO_2CH_2Me), 3.41 (5-H, $J_{5,9a}$ 2.7 Hz, $J_{3,5}$, $J_{5,7}$ and $J_{5,9e}$ obnm), 3.28 (10β-H, $J_{3,10\beta}$ and $J_{7,10\beta}$ obnm), 3.15 (8e-H, $J_{8a,8e}$ 13 Hz, $J_{7,8e}$ and $J_{8e,9e}$ obnm), 3.13 (3-H), 2.70 (9e-H), 2.66 (7-H), 2.59 (9a-H), 2.18 (8a-H), 1.14 (CO_2CH_2Me), 0.84 (10-Me); $\nu_{max.}$($CHCl_3$) 3 500, 1 740, and 1 705 cm^{-1} (Found: C, 70.4; H, 6.2%; M^+, 342.1465. Calc. for $C_{20}H_{22}O_5$: C, 70.2; H, 6.4%; *M*, 342.1466). Evaporation of the mother liquors and repeated recrystallisation of the residue from chloroform–light petroleum (b.p. 40—60 °C) gave a small sample of (**40**), m.p. 165—166 °C; δ‡ ($CDCl_3$) 7.5 (Ph), 3.7 (3-H and 5-H), 1.0 (10-Me); $\nu_{max.}$($CHCl_3$) 1 745, 1 720, and 1 680 cm^{-1} (Found: M^+, 296.1048. Calc. for $C_{18}H_{16}O_4$: *M*, 296.1048).

Synthesis of 6-Hydroxy-6,7-diphenyladamantane-2,4-diones.—The reaction of the αβ-unsaturated acid chlorides with an equimolar amount of enamine (**9c**) was carried out under the same conditions as given in Procedure B, but using 5% acetone in chloroform as eluant for the t.l.c. purification. The following results were obtained:

Acryloyl chloride gave a 1:1 mixture of (**50a**) and (**50b**) in 36% yield which could not be separated by t.l.c. or fractional crystallisation; m.p. 220—222 °C; $\nu_{max.}$($CHCl_3$) 3 580, 1 740, and 1 705 cm^{-1} (Found: C, 79.4; H, 5.9%; M^+, 332. Calc. for $C_{22}H_{20}O_3$: C, 79.5; H, 6.0%; *M*, 332); dioxime (of the isomer mixture), m.p. 157—160 °C; $\nu_{max.}$(Nujol) 3 470 and 1 660 cm^{-1} (Found: M^+, 362.1629. Calc. for $C_{22}H_{22}N_2O_3$: *M*, 362.1629).

Methacryloyl chloride gave a 14% yield of the one isomer (**51a**), m.p. 199—200 °C; δ($CDCl_3$) 7.05, 6.9 (m, Ph), 3.74 (3-H, $J_{3,10a}$ 2.7 Hz, $J_{1,3}$ and $J_{3,10e}$ obnm), 3.52 (m, 8e-H, $J_{8e,8a}$ 13 Hz, $J_{1,8e}$ and $J_{8e,10e}$ obnm), 2.88 (1-H, 9β-H, and 10e-H, $J_{1,9\alpha}$ 3.0, $J_{9\alpha,9\beta}$ 13, $J_{10a,10e}$ 13.5 Hz, $J_{1,8a}$ and $J_{3,10e}$ obnm), 2.30 (OH), 2.20 (10a-H), 2.06 (8a-H, $J_{8a,9\alpha}$ obnm), 1.32 (9α-H), 1.08 (5-Me); $\nu_{max.}$($CHCl_3$) 3 580, 1 735, 1 700 cm^{-1} (Found: C, 79.4; H, 6.7%; M^+, 346. Calc. for $C_{23}H_{22}O_3$: C, 79.8; H, 6.4%; *M*, 346).

Crotonoyl chloride gave a 19% yield of a mixture of (**44**), (**42**), and (**43**) in a ratio of 66:17:17.§ Recrystallisation from chloroform–light petroleum (40—60 °C) gave a sample of pure (**44**), m.p. 195—196 °C; δ($CDCl_3$) 7.68, 7.48, 7.2 (Ph), 3.43 (3-H, $J_{3,10a}$ 2.0 Hz, $J_{3,5}$ and $J_{3,10e}$ obnm), 3.30 (5-H, 8e-H, 10e-H, $J_{8a,8e}$ 14.5, $J_{10a,10e}$ 12.5 Hz, $J_{5,9\alpha}$ and $J_{1,8e}$ obnm), 2.83 (8a-H), 2.80 (OH), 2.61 (1-H, $J_{1,8a}$ obnm), 2.08 (10a-H), 2.0 (9α-H, $J_{8a,9\alpha}$ obnm), and 0.54 (9-Me); $\nu_{max.}$($CHCl_3$) 3 570, 1 735, and 1 705 cm^{-1} (Found: C, 79.8; H, 6.2%; M^+, 346. Calc. for $C_{23}H_{22}O_3$: C, 79.8; H, 6.4%; *M*, 346).

Data Collection and X-ray Structure Analyses of (**4**) *and* (**34**).—Transparent prismatic crystals of compounds (**4**) and (**34**) were mounted on the Philips 1100/20 four circle diffractometer and accurate cell dimensions were derived from 25 carefully centred reflections. These and other pertinent data are listed in Table 4.

Intensities were collected with graphite monochromated Mo-Kα radiation under the measuring conditions described in Table 4. Apparatus instability was monitored by three standard reflections, which showed intensity fluctuations no larger than 5% throughout the measurements. Background, Lorentz and polarization corrections were applied to the measured intensities and these were reduced to unique sets of structure factors.

The structures of (**4**) and (**34**) were solved by MULTAN.[21] *E* Maps revealed the positions of all nonhydrogen atoms, and these were refined by the SHELX 77 program package least squares routine.[22] Scattering factor tables for C and O were taken from Cromer and Mann[23] and for H from Stewart, Davidson, and Simpson.[24] Hydrogens were located from difference Fourier maps after all nonhydrogen atoms were refined anisotropically. The structure was further refined by allowing the hydrogens to shift isotropically until convergence was reached. Unit weights were introduced at the initial stages and statistical weights at the final stages of the refinement. Inspection of the difference Fourier maps revealed at this stage, peaks having electron densities no higher than 0.3 e $Å^{-3}$.

Final atomic co-ordinates are presented in Tables 5 and 6 and noteworthy bonds and angles are summarised in Tables 7 and 8. Thermal parameters for structures (**4**) and (**34**) are available as Supplementary material, SUP. No. 56344 (7 pp).¶ The structure factors are available on request from the editorial office.

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* See footnote † on previous page.

† The ^{1}H n.m.r. spectrum (90 MHz; $CDCl_3$) of the crude mixture showed three hydroxy groups (singlets at δ 4.74, 4.48, and 4.3), three ester groups (quartets at δ 4.25, 4.23, and 4.14; triplets at δ 1.24, 1.22, and 1.14), and four C-10 methyl groups (doublets at δ 1.0, 0.84, 0.72, and 0.52). Isomer (**38**) is ruled out by the absence of a methyl doublet at *ca.* δ 1.55. The two isomers not isolated were assigned their C-2 and C-10 stereochemistry on the basis of the chemical shifts of their C-10 methyl signals as follows: (**35**), δ 0.72; (**37**), δ 0.52.

‡ Determined at 90 MHz. Complete proton assignment is not possible owing to overlap of signals.

§ The ^{1}H n.m.r. spectrum (90 MHz; $CDCl_3$) of the crude mixture showed three C-9 methyl signals at δ 0.88, 0.83, and 0.54. The first two signals were assigned to isomers (**43**) and (**42**) respectively. and the last to isomer (**44**), since (**45**) would have been expected to give a signal to much lower field (about δ 1.55).

¶ For details of the Supplementary Publications scheme, see Instructions for Authors (1985), *J. Chem. Soc., Perkin Trans. 1*, 1985, Issue 1.

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