Enamine Chemistry. Part 26.[1] Preparation of Substituted Adamantane-2,4-diones and Bicyclo[2.2.2]octan-2-ones

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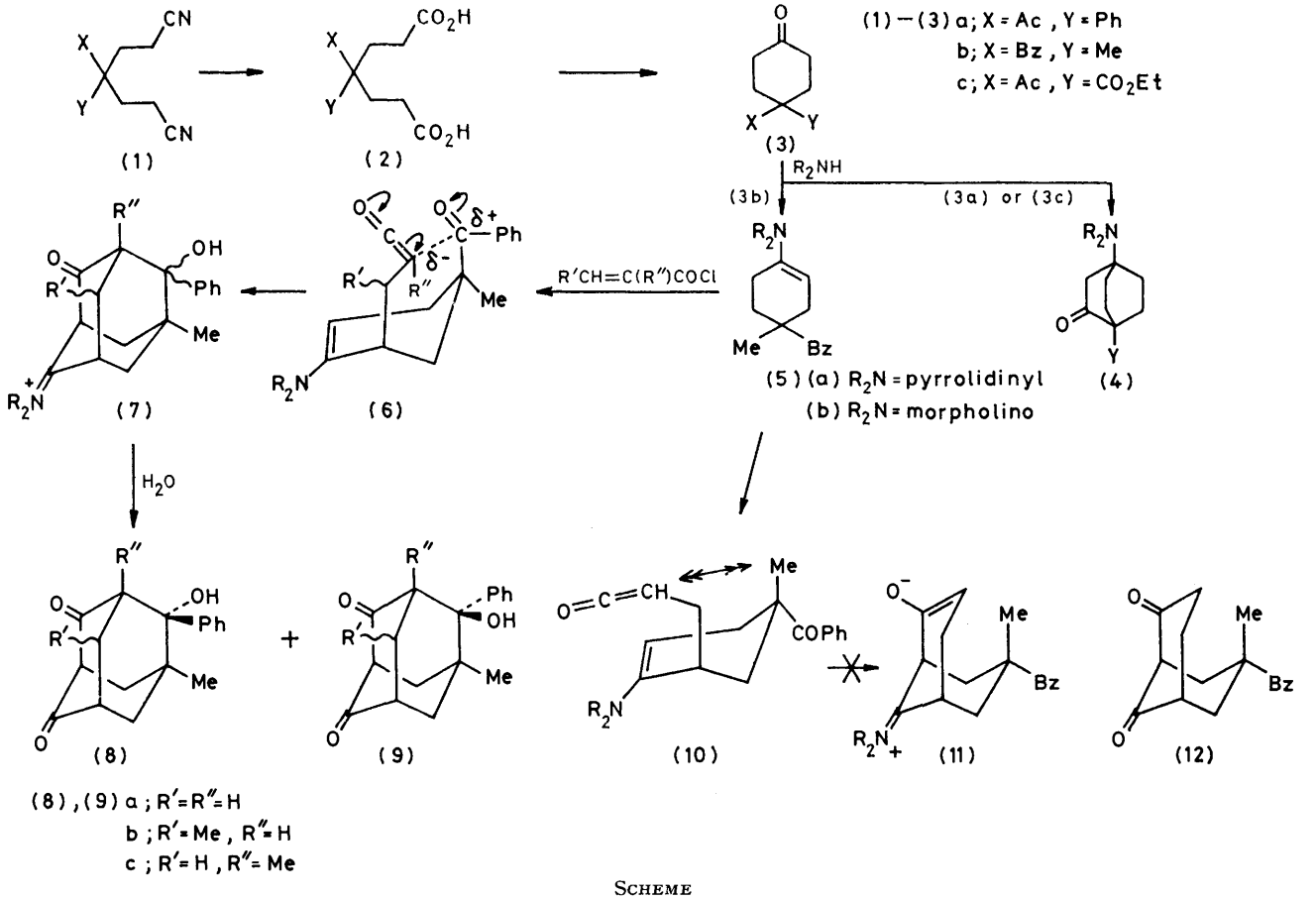
Reaction of αβ-unsaturated acid chlorides with the morpholine or pyrrolidine enamines derived from 4-benzoyl-4-methylcyclohexanone gives the corresponding 6-hydroxy-7-methyl-6-phenyladamantane-2,4-dione in moderate to good yield. Enamines from 4-acetyl-4-phenyl (or 4-ethoxycarbonyl) cyclohexanone could not be isolated owing to their preferential cyclisation into 1-phenyl (or 1-ethoxycarbonyl) 4-substituted aminobicyclo[2.2.2]octan-2-ones.

THE scope of our recent one-step synthesis [2] of alkyl 2,4,6-trioxoadamantane-1-carboxylates, which evolved from the elegant work of Stetter *et al.*,[3] has now been extended. The synthesis involved αα'-annelation of cyclohexanone enamines, with crotonoyl and methacryloyl chlorides, and cyclisation of an enolate anion intermediate onto an axially orientated ester group.[2] We now have found that cyclisation will also occur onto the carbonyl group of an axially orientated ketone. Thus the reaction of acryloyl, crotonoyl, and methacryloyl chlorides with the pyrrolidine enamine (5a) of 4-benzoyl-4-methylcyclohexanone (3b) gave the corresponding 6-hydroxy-7-methyl-6-phenyladamantane-2,4-dione as a mixture of isomers [(8) and (9)] epimeric at C-6, and in the case of crotonoyl chloride at C-9, in moderate to good yield. The structures follow from the analytical data, accurate mass measurements, and the i.r. data which clearly show the presence of a hydroxy-group (Table 1) and the absence of the benzoyl carbonyl group which gives an absorption at 1 680 cm^{-1} in the precursor (3b). This clearly rules out the alternative structure (12). This was confirmed by the ^1H n.m.r. spectrum of the product from methacryloyl chloride which showed, in addition to a hydroxy-signal (τ 7.75), the presence of both methyl signals as singlets. This confirmed the formation of a carbon–carbon bond between the α-position of the acid chloride residue and the benzoyl carbonyl group. Further evidence for the pre-



SCHEME

sence of the hydroxy-group was obtained by the conversion, with some difficulty, of the product from acryloyl chloride into the mono-acetate (13) (see below). The structure of this product was verified by accurate mass measurement, and the absence of hydroxy and the presence of acetyl signals in the i.r. and ^{1}H n.m.r. spectra (see Experimental section).

The assignments of the C-6 stereochemistry (Table 1) follow from the different chemical shifts of the C-7 methyl groups. These differences may be attributed to different preferred orientations of the benzene ring. Models show that in order to minimise steric interactions, the benzene ring will be orientated in such a manner that the C-7 methyl group will lie further into the shielding region of the benzene ring in (9a), (9b), and (8c), and further into the deshielding region in (8a), (8b), and (9c). Similarly, the stereochemistry of the C-9 chiral centre in the product from crotonoyl chloride (9b) follows from the chemical shifts of the C-9 methyl group in the two epimers, that at higher field (τ 9.22) being assigned to the epimer having the *S*-configuration since the C-9 methyl group would then lie in the shielding region of the C-2 and C-4 carbonyl groups. The other epimer is assigned the *R*-configuration at C-9 since the low-field shift of the methyl signal (τ 8.45) can then be attributed to the combined deshielding influence of the C-2 and C-4 carbonyl groups, the C-6 phenyl group, and the nearby axial C-6 hydroxy-group. The configuration at C-9 in (8b) cannot be settled at present since the shielding of the C-9 methyl group could be due to the methyl group lying in the shielding region of the C-2 and C-4 carbonyl groups in the one epimer or the benzene ring in the other C-9 epimer.

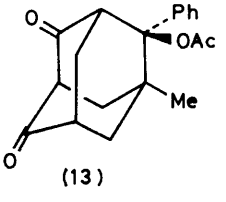
There are several interesting features of this work which deserve comment. First, the best yields of the adamantane derivative were obtained from acryloyl chloride. This is in complete contrast to our previous work [2] which failed to yield any adamantane from acryloyl chloride, although other bicyclic products were obtained.[4] Secondly, we have obtained no evidence for the formation of the bicyclic dione (12). This was an expected product since we have previously shown [5] that the α,α'-annelation process occurs principally from the axial direction, and axial attack on the enamine conformer having the benzoyl group equatorial would give an intermediate (11) having no chance of undergoing cyclisation to an adamantane. The possibility that the dione was formed in low yield, but was not observed by t.l.c. owing to the R_F value being identical to that of the corresponding adamantanedione, has been ruled out in the following way. Acetylation of the crude adamantane (8a) and (9a) (R_F 0.45 using 10% acetone in chloroform on silica) gave the monoacetate as a mixture of isomers [(13): τ 9.08s (C-7 methyl), τ 7.85s ($OCOCH_3$), and (14): τ 8.98 (C-7 methyl), τ 8.05 ($OCOCH_3$); R_F 0.6], the t.l.c. of which showed no component at R_F 0.45. A possible explanation for the dione (12) not being formed is that in order for the keten group [in (6)] to become suitably orientated over the regenerated enamine system for cyclisation to occur, in the presence of a bulky axial substituent at C-4 an electrostatic attraction or a partial bonding interaction must occur between the keten group and the axial substituent as depicted in (6). Certainly an attractive interaction of this type can only aid the cyclisation process, whereas an axial methyl substituent at C-4 can only impede [2] the cyclisation of (10) to (11). Finally the absorptions at 3 570—3 580 cm^{-1} in the i.r. spectra of the adamantanediones (Table 1) are probably due to intramolecular hydrogen bonding of the hydroxy-group, but to the π-electrons of the benzene ring not the carbonyl group.[6] Models indicate that the distance from the oxygen to the middle of the nearest carbon–

TABLE 1

Synthesis and spectral properties of 6-hydroxy-7-methyl-6-phenyladamantane-2,4-diones (8) and (9)

Acid chloride *	Enamine	Yield (%) †	Product	Isomer ratio	M.p. (°C)	Solvent for § crystln.	Found (%) C	Found (%) H		Reqd. (%) C	Reqd. (%) H	^{1}H n.m.r. (τ Me) C-7	^{1}H n.m.r. (τ Me) C-5	^{1}H n.m.r. (τ Me) C-9	$\nu_{max.}$/cm^{-1} ($CHCl_3$)
A	(5a)	54	(8a)	3	162—163	$CHCl_3$–LP	75.4	6.8	$C_{17}H_{18}O_3$	75.55	6.7	8.92			3 577, 3 450 (OH)
A	(5b)	46 ‡	(9a)	2	194—195		*M*$^+$, 270.1256			*M*, 270.1256		9.15			1 737, 1 704 (C=O)
C	(5a)	20	(8b)	2	209—210	$CHCl_3$–LP	75.6	7.3	$C_{18}H_{20}O_3$	75.8	7.0	8.68		9.45	3 570 (OH)
			(9*R*)-(9b)	1	229—230		*M*$^+$, 284.1412			*M*, 284.1412		9.1		8.45	1 735, 1 705 (C=O)
			(9*S*)-(9b)	1	Not isolated							9.14		9.22	
M	(5a)	40	(8c)	1	168—170	$CHCl_3$–LP	*M*$^+$, 284.1412			*M*, 284.1412		9.35	9.13		3 580 (OH)
			(9c)	2	211—221		75.6	7.15	$C_{18}H_{20}O_3$	75.8	7.0	9.3	9.0		1 735, 1 700 (C=O)

* A = Acryloyl chloride C = crotonoyl chloride, M = methacryloyl chloride. † Mixture of (8) and (9) before purification. ‡ Reaction period reduced from 20 to 2 h (see General method). § CH = cyclohexane, LP = light petroleum (b.p. 40—60 °C).



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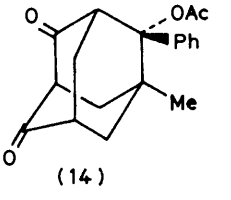

(14)

carbon double bond is < 3.0 Å in both C-6 epimers and, in fact, is nearer to 2.5 Å in (9) if the benzene ring is orientated so as to minimise 1,3-diaxial interactions. Although the 1 735—1 737 carbonyl band is at higher frequency than is normal [7] (in chloroform) the carbonyl doublet at 1 700—1 705 and 1 735—1 737 cm^{-1} is, nevertheless, characteristic of bicyclic β-diketones [6,7] and has been attributed to vibrational coupling.

Attempted formation of 1-methyl-4-(pyrrolidin-1-yl)cyclohex-3-enyl methyl ketone by condensation of pyrrolidine with 4-acetyl-4-phenylcyclohexanone (3a) failed to give the enamine. Instead 1-phenyl-4-(pyrrolidin-1-yl)bicyclo[2.2.2]octan-2-one (4) was produced, presumably arising by proton abstraction from the acetyl group by the initially formed enamine and cyclisation of the resulting enolate anion onto the iminium group thus formed. In the hope that the less reactive morpholine enamine might be sufficiently stable to be isolated [8] the condensation of (3a) with morpholine was carried out, but again only the bicyclo-[2.2.2]octanone (4) was isolated. The structure followed from the i.r. spectrum which showed the disappearance of the two carbonyl absorptions at 1 700 and 1 730 cm^{-1} in the starting material (3a), and the appearance of a new carbonyl absorption at 1 720 cm^{-1}. The ^1H n.m.r. spectrum ($CDCl_3$) also showed signals at τ 2.75 (m, Ph), 6.3 (t, CH_2OCH_2), 7.41 (t, CH_2NCH_2), 7.54 (s, 3-CH_2), 7.9 (m, 2 × CH_2), and 8.15 (m, 2 × CH_2). There were no olefinic signals and the singlet due to the acetyl group in the starting material at τ 8.04 was also missing. Similar results were obtained on condensation of (3a) with piperidine and *N*-methylpiperazine and (3c) with pyrrolidine (Table 2).

EXPERIMENTAL

The 4,4-disubstituted cyclohexanones (3a, b) [9] and their precursors (1a, b) and (2a, b) [10] were prepared by the literature methods.

Ethyl 1-Acetyl-4-oxocyclohexane-1-carboxylate (3c).—A mixture of 4-acetyl-4-ethoxycarbonylpimelonitrile [11] (1c) (190 g) and concentrated hydrochloric acid (350 ml) was heated under reflux for 25 min. The reaction mixture was cooled and the solid collected and dissolved in the minimum of water (100 ml). The aqueous solution was extracted with diethyl ether (4 × 150 ml) and the ether extracts combined, dried ($MgSO_4$), and evaporated to dryness. Recrystallisation of the gummy residue [chloroform–light petroleum (b.p. 40—60 °C)] gave 4-acetyl-4-ethoxycarbonylpimelic acid (2c) (90 g, 41%), m.p. 113—114 °C (Found: C, 52.5; H, 6.8. $C_{12}H_{18}O_7$ requires C, 52.55; H, 6.6%), $\nu_{max.}$ (Nujol) 1 735, 1 720, and 1 710 cm^{-1}; τ[$(CD_3)_2$-SO] −2.0 br (2 × CO_2H), 5.82 (q, CH_2), 7.90 (s, $COCH_3$), 7.97 (s, 4 × CH_2), and 8.82 (t, CH_3). A mixture of the dicarboxylic acid (2c) (20 g), acetic anhydride (59 ml), and pyridine (6.2 ml) was heated under reflux for 2 h. The mixture was cooled, concentrated *in vacuo*, and distilled to give ethyl 1-acetyl-4-oxocyclohexane-1-carboxylate (3c) (7.5 g, 48%) as an oil, b.p. 101—102 °C/0.3 mmHg (Found: C, 62.0; H, 7.5. $C_{11}H_{16}O_4$ requires C, 62.3; H, 7.5%), $\nu_{max.}$ (film) 1 725br; τ($CDCl_3$) 5.72 (q, CH_2), 7.65 (m, 4 × CH_2), 7.79 (s, $COCH_3$), and 8.7 (t, CH_3).

1,4-Disubstituted Bicyclo[2.2.2]octan-2-ones (4): *General Method.*—A mixture of the 4-acetylcyclohexanone (3a) or (3c) (0.01 mol), secondary amine (0.013 mol), and toluene-*p*-sulphonic acid (40 mg) in benzene (30 ml) was heated under reflux for the time stated (Table 2) using a Dean and Stark head to collect the water which was eliminated. The solution was cooled and concentrated *in vacuo*. Distillation of the residual oil gave the bicyclo[2.2.2]octan-2-one (4) as an oil which in most cases solidified with time. Preparative and analytical data are summarised in Table 2.

1-Phenyl-4-(pyrrolidin-1-yl)bicyclo[2.2.2]octan-2-one was converted into the oxime, m.p. 254 °C (decomp.) [M^+, 284.188 7. $C_{18}H_{24}N_2O$ requires *M*, 284.188 9] and semicarbazone, m.p. 235 °C (decomp) [M^+, 326.211 1. $C_{19}H_{26}N_4O$ requires *M*, 326.210 7].

TABLE 2

1,4-Disubstituted bicyclo[2.2.2]octan-2-ones (4): preparative and analytical data *

R_2N	Y	Reflux time (h)	Yield (%)	B.p. (°C/mmHg)	M.p. (°C)	Found (%) C	H	N		Required (%) C	H	N
Pyrrolidinyl	Ph	6	44	168—182/0.2	137—138	80.0	8.5	5.2	$C_{18}H_{23}NO$	80.3	8.55	5.2
Morpholino	Ph	17	36	160—180/0.2	164—165	75.3	8.2	4.8	$C_{18}H_{23}NO_2$	75.8	8.1	4.9
Piperidino	Ph	17	53	172—180/0.4	160—161	80.3	8.5	4.95	$C_{19}H_{25}NO$	80.6	8.8	4.9
4-Methylpiperazinyl	Ph	17	50	160—180/0.4	146—147	76.3	8.5	9.2	$C_{19}H_{26}N_2O$	76.5	8.7	9.4
Pyrrolidinyl	CO_2Et	6	38	138—140/0.2		*M*+, 265.1679			$C_{15}H_{23}NO_3$	*M*, 265.1678		

* All structures are supported by i.r. and n.m.r. data, the significant aspects of which are discussed in the text.

1-Methyl-4-(pyrrolidin-1-yl)cyclohex-3-enyl Phenyl Ketone (5a).—A mixture of 4-benzoyl-4-methylcyclohexanone (3b) (2.16 g, 0.01 mol), pyrrolidine (0.013 mol), and toluene-*p*-sulphonic acid (40 mg) in benzene (25 ml) was heated under reflux under a Dean and Stark head for 5 h. The solution was cooled and concentrated *in vacuo* to give the crude product which was used without further purification since extensive decomposition occurred on distillation (56%; b.p. 156—158 °C/0.1 mmHg). The crude product showed: M^+, 269.177 9 ($C_{18}H_{23}NO$ requires *M*, 269.177 9); $\nu_{max.}$ (benzene) 1 680 (CO) and 1 645 (C=C) cm^{-1}; τ($CDCl_3$) 2.50 (m, C_6H_5), 5.85 (t, =CH), 7.00 (t, CH_2NCH_2), 7.72 (m, 2- and 5-CH_2), 8.19 (m, β-CH_2 and 6-CH_2), 8.61 (s, CH_3).

1-Methyl-4-morpholinocyclohex-3-enyl Phenyl Ketone (5b).—The condensation of (3b) with morpholine was carried out in the same way but required a longer reflux time (18 h). The crude product (57%; b.p. 168—170 °C/0.1 mmHg) was used without further purification and showed: M^+, 285.173 1 ($C_{18}H_{23}NO_2$ requires *M*, 285.172 9); $\nu_{max.}$ (benzene) 1 680 (CO), 1 655 (C=C) cm^{-1}; τ($CDCl_3$) 2.50 (m, C_6H_5), 5.45 (t, =CH), 6.30 (t, CH_2OCH_2), 7.25 (t, CH_2NCH_2), 7.84 (m, 2- and 5-CH_2), 8.2 (m, 6-CH_2), and 8.64 (s, CH_3).

Synthesis of 6-Hydroxy-7-methyl-6-phenyladamantane-2,4-diones: General Method.—The αβ-unsaturated acid chloride

(0.056 mol) in dry benzene (60 ml) was added dropwise to the enamine (5a) or (5b) (0.056 mol) in boiling dry benzene (350 ml) during 1.5 h. The mixture was then heated under reflux overnight (*ca.* 20 h), and cooled, and the precipitated iminium salt (7) was collected, washed with dry benzene, and hydrolysed by stirring with cold water (100 ml) for 10 h. The adamantanedione was isolated by extraction with diethyl ether (5 × 30 ml) and purified by preparative t.l.c. on silica [15% for (8a)/(9a) or 5% for (2b,c)/(9b,c) acetone in chloroform]. The mixture of adamantanediones (8) and (9) thus obtained were separated as follows. Isomers (9a) and (9c) were obtained by repeated recrystallisation (see Table 1). Isomers (8a) and (8c) were obtained by repeating the t.l.c. purification (twice) and removing only the trailing edge of the adamantanedione band. Trace amounts of (9a) or (9c), if present, were removed by recrystallisation from benzene. In the case of the three-component mixture obtained from the reaction of (5a) with crotonoyl chloride, the one isomer [(9*S*)-(9b)] had first to be removed by repeated recrystallisation (see Table 1). T.l.c. (as above) of the two-component mixture remaining then gave pure samples of (9*R*)-(11b) (from the leading edge of the adamantane band) and (8b) (from the trailing edge).

Preparative, analytical, and spectral data are summarised in Table 1.

6-*Acetoxy*-7-*methyl*-6-*phenyladamantane*-2,4-*dione*.—To a mixture of 6-hydroxy-7-methyl-6-phenyladamantane-2,4-dione (9a) (0.1 g) and acetyl chloride (0.1 g) was added dry pyridine (3 drops) followed by dry chloroform (2 ml). The mixture was heated gently under reflux for 5.5 h, and cooled and poured into ice–water. The precipitated acetate was collected, washed with water, and dried (0.08 g, 69%), m.p. 147—148 °C [from chloroform–light petroleum (b.p. 40—60 °C)] (M^+, 312.135 9. $C_{19}H_{20}O_4$ requires M, 312.136 1; $\nu_{max.}$ ($CHCl_3$) 1 740 and 1 705 cm^{-1}). The ^1H n.m.r. spectrum showed the absence of OH signals (D_2O) and the presence of signals at τ 7.85 (s, $OCOCH_3$) and 9.08 (s, 7-CH_3). Attempted acylation of (8a) and (9a) by heating with acetic anhydride in glacial acetic acid gave only unchanged starting material.

I.r. spectra were determined with a Perkin-Elmer 257 spectrometer, ^1H n.m.r. spectra with a Perkin-Elmer R32 spectrometer at 90 MHz in chloroform solutions, and accurate mass measurements with an AEI MS 9 mass spectrometer operating at 70 eV.

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