DIVERGENT PATHWAYS OF REACTION BETWEEN CYCLOHEXANONE ENAMINES AND α,β-UNSATURATED ACID CHLORIDES

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The reaction of cyclohexanone enamines with α,β-unsaturated acid chlorides and 2- and 3-chloropropanoyl chlorides under various conditions has been investigated. α,α′-Annulation of enamines *Ia–Ie* occurs on treatment with chlorides *IIa–IId* or 3-chloropropanoyl chloride to give bicyclo[3.3.1]nonane-2,9-dione derivatives *III*. The formation of isomeric bicyclononanediones *IIIe* and *IIIh* and chromanones *VIIIa* and *VIIIb* in the reaction of enamines derived from substituted cyclohexanones suggests that the cyclization might proceed also by another pathway than via [3,3] sigmatropic rearrangement. Based on the reaction course and product distribution in these reactions, a parallel reaction pathway involving a *C*-acylation–Michael addition has been suggested.

The reaction of cycloalkanone enamines with α,β-unsaturated electrophiles is one of the most versatile methods of carbocyclization[1]. Products of this process are bicyclic and adamantane ring structures[2]. The dependence of the reaction course on the structure of initial reagents and on the reaction conditions is generally recognized[3]. The proposed cyclization mechanism involves *N*-acylation of the enamine, followed by a [3,3] sigmatropic rearrangement leading to a ketene intermediate, and subsequent cyclization[4]. An alternative explanation for the ring closure leading to bridged or fused bicyclic structures has been suggested that assumes a *C*-acylation of the enamine or a direct interaction between the β-position of the enamine and the β-position of the α,β-unsaturated acid chloride[5]. The evidence for each of the reaction pathways was obtained by structure elucidation of the reaction products or by isolation of reaction intermediates. The sensitivity of the reaction to substituents in both the enamines and the reactants, as well as to the reaction conditions, and discrepancies in the reaction pathways prompted us to study the reaction of cyclic ketone enamines with unsaturated acid chlorides and related electrophiles in order to rationalize the reaction course.

RESULTS AND DISCUSSION

Reaction of Cyclohexanone Enamines with α,β-Unsaturated Acid Chlorides

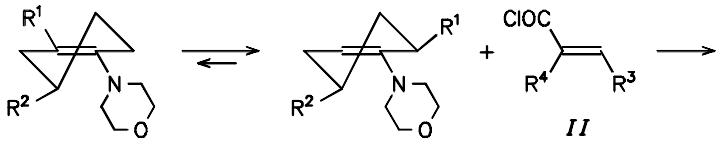
The reaction of cyclohexanone enamines with α,β-unsaturated acid chlorides is a facile route to the bicyclo[3.3.1]nonane-2,9-dione system[6]. Recently[7] we have shown that the reaction of enamine *Ia* with alkyl 3-chloroformyl acrylates *IIa* and *IIb* gives 4,9-dioxobicyclo[3.3.1]nonane-2-carboxylates *IIIa* and *IIIb* (Scheme 1). Proton and ^{13}C NMR spectra indicated that the products were obtained in diastereomerically pure form. Similar results were obtained using compound *IId* as the annulation reagent to give *IIIk*. In addition, the reaction of enamine *Ia* with (1*R*,2*S*,5*R*)-(–)-menthyl-*IIc* afforded the corresponding diastereoisomerically pure (–)-menthyl derivative *IIIc*. The positions and number of signals of keto and ester carbonyl groups (δ 209.1, 207.0 and 172.3) in its ^{13}C NMR spectrum confirm that a single diastereoisomer was formed.

We studied the effect of the reaction temperature, solvent, concentration of enamine, and duration of addition of the chloride on the yield of diones *IIIa* and *IIIb* (Table I). The yield of the bicyclic product increased when the reaction was carried out in an inert atmosphere. As optimum conditions we found: equimolar ratio of the reagents, a nonpolar solvent, slow addition of the acid chloride and a low enamine concentration.

TABLE I
Reaction of cyclohexanone enamine *Ia* with methyl 3-chloroformylacrylate *IIa*

Entry	Enamine equiv.	Addition time, h	Solvent	Temperature °C	Time[a], h	Yield of *IIIa* %
1	1	0.4	C_6H_6	80	20	12
2[b]	1	5	C_6H_6	20	8	32
3[c]	1	1	C_6H_6	20	6	63
4[d]	1	1	C_6H_6	20	6	20
5[e]	1	1	C_6H_6	20	6	28
6	9	1	CCl_4	0 to –5	20	2
7	2.2	1	C_6H_6	20	20	21
8	1	1	$C_6H_5CH_3$	20	6	30
9	1	1	Et_2O	20	6	56
10	1	1	$CHCl_3$	20	6	31

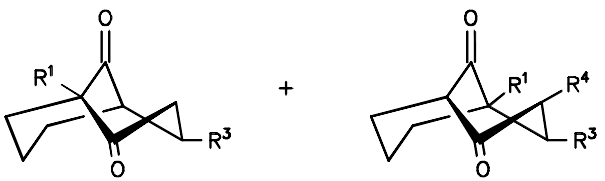
[a] Acid chloride addition time is included. [b] Reaction was performed with ethyl 3-chloroformylacrylate. [c] Entries 3–8 were carried out under inert atmosphere. [d] Pyrrolidine enamine. [e] Piperidine enamine.



I *II*

I	R^1	R^2
a	H	H
b	H	CO_2Me
c	H	OCOPh
d	Me	H
e	Bn	H

II	R^3	R^4
a	CO_2Me	H
b	CO_2Et	H
c	CO_2–menthyl	H
d	H	CH_2CO_2Bn
e	H	H



IIIa–IIIf *IIIh–IIIk*

III	R^1	R^3
a	H	CO_2Me
b	H	CO_2Et
c	H	CO_2–menthyl
d	Me	CO_2Me
e	Me	H
f	Bn	H

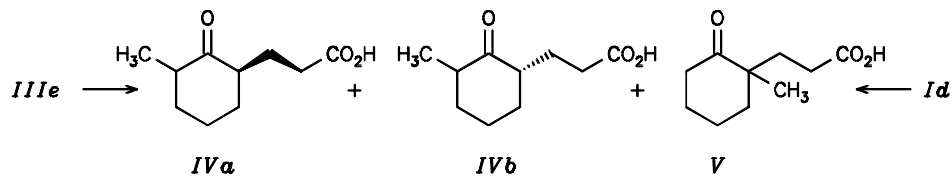
III	R^1	R^3	R^4
h	Me	H	H
i	Me	CO_2Me	H
j	H	H	H
k	H	H	CH_2CO_2Bn

SCHEME 1

The effect of the enamine moiety on the yield of the diketo ester *IIIa* followed the same trend as in the reaction of *Ia* with acryloyl chloride *IIe*, i.e., the yield of *IIIa* decreased in the order morpholine > piperidine > pyrrolidine enamines[4].

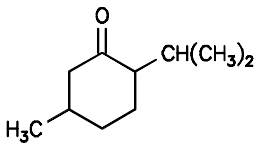
The annulation reagents *IIa–IId* introduce functional groups into the final bicyclononane skeleton in one operation. Using the conditions developed for the synthesis of *IIIa–IIIc*, we examined the reactions of enamines derived from substituted cyclohexanones. Reaction of 2-methylcyclohexanone enamine *Id* with chloride *IIa* was expected to produce a single structure, *IIId*, because the transition state for the intermediate sigmatropic rearrangement of the less reactive enamine with more substituted double bond, *I′*, would be impeded by the methyl group from both the axial and equatorial side of the enamine. However, the reaction gave a mixture of two compounds that could not be separated. The ^{1}H NMR spectrum of the reaction product showed two singlets at δ 3.63 and 3.59 due to methyl protons of the ester group, overlapping singlets of methyl protons at δ 1.05–1.08 and no signals in the region of olefinic and carboxylic protons. The ^{13}C NMR spectrum showed four signals of keto carbonyl and two of ester carbonyl groups. According to the spectral and analytical data we suggest the structures *IIId* and *IIIi* for the components of the mixture (Scheme 1).

It has been reported that the reaction of the same enamine *Id* with acryloyl chloride *IIe* leads to 1-methyl-2,9-dione[6] *IIIe*. In order to get more evidence for the structural assignment and the cyclization path, this reaction was reexamined. To our surprise, it did not give a single isomer under various conditions employed, i.e. addition of the acid chloride to a boiling solution of the enamine or addition at room temperature. Both the ^{1}H NMR and ^{13}C NMR spectra indicated that this reaction gave rise to a mixture of bicyclic diketones. Gated ^{13}C NMR spectrum showed two doublets at δ 72.4 and 63.5 that could be assigned to the tertiary carbon atoms C-1 and C-5 in *IIIe* and *IIIh*, respectively, and consequently the mixture consisted of two structural isomers, *IIIe* and *IIIh*. The same conclusion was drawn from the results of hydrolysis of the reaction product. Hydrolysis of the bicyclic dione *IIIe* should give acid *IVb*, however, a mixture of isomeric acids was isolated (Scheme 2). It was reported that Michael addition of ethyl acrylate to enamine *Id* in dioxane gave a mixture of 2,2- and 2,6-substituted cyclohexanone derivatives *IV* and *V*, respectively, the ratio of the product *V* to stereoisomers *IVa* and *IVb* being approximately one to one[8]. As shown by GLC and spectral data, the latter mixture was identical with that obtained by hydrolysis of bicyclic diones. Contrary to the reported results[6], no pure *cis*-acid, melting at 72–73 °C, was obtained.

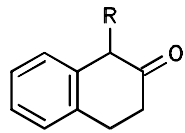


SCHEME 2

The series of annulation reactions with enamines derived from substituted cyclohexanones *Ib*, *Ic*, *Ie*, *VI* and *VIIa* gave mixtures of compounds from which an appreciable amount of the bicyclic dione was isolated in the case of the 2-benzylcyclohexanone enamine[9] *Ie*. Attempted cyclization of the enamine of tetrahydronaphthalen-2-one *VIIa* was unsuccessful both with acryloyl chloride *IIe* and chloride *IIa*. The only product obtained from a vast amount of tar was the unsaturated diketone *VIIb* that quickly decomposed on air. Enamines of (–)-menthone *VI* were very reactive and tetrahydrochromanone derivative *VIIIb* was obtained in a low yield.



VI



VIIa, R = H

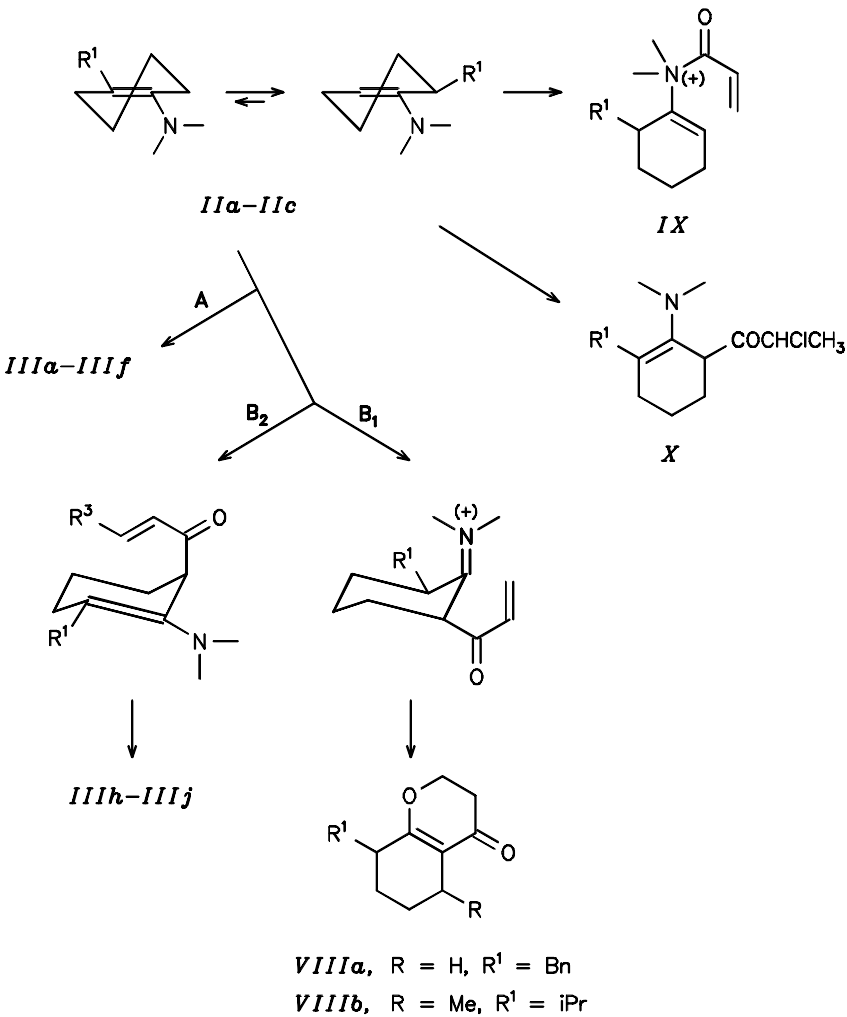
VIIb, R = $COCH{=}CH_2$

Notably, the formation of isomeric bicyclic diones *IIIe* and *IIIh* and tetrahydrochromanones in the reaction of enamines with α,β-unsaturated acid chlorides suggests that divergent reaction mechanisms might operate in the reaction. The main reasons for this assumption are the transition state structure and the stereoelectronic requirements for [3,3] sigmatropic rearrangement that leads to a single structural isomer of bicyclononanedione. Secondly, the tetrahydrochromanone must arise by *C*-acylation of the enamine followed by cyclization of the enol tautomer.

Reactions of Enamines with Chloropropanoyl Chlorides

We next turned our attention to the reaction of enamines with annulation reagents that could react in other way than through a [3,3] sigmatropic rearrangement. It seemed likely that 3-chloropropanoyl chloride could be such a reagent. Reaction of this chloride with enamine *Ia* was carried out under conditions developed[10b] for acid chlorides *II* and afforded bicyclononane-2,9-dione[10] *IIIj*. Its spectra were identical with those of the reaction product formed from enamine *Ia* and acryloyl chloride. Best yields were obtained with 1 equivalent of *N*-ethylmorpholine in boiling benzene. With triethylamine as external base, the yield of the bicyclic product decreased and additional uncharacterized products were formed. Triethylamine probably was too strong a base. Reaction of 3-chloropropanoyl chloride with *N*-ethylmorpholine under the cyclization conditions produced almost quantitatively the salt $Cl^-(R^+–CH_2CH_2COR^+)Cl^-$, where *R* = *N*-ethylmorpholine. Attempts to obtain the cyclization product by reaction of the enamine with this salt failed.

Regeneration of the enamine before the last cyclization step might lead to isomer with the most substituted double bond since it seems to be stabilized by conjugation with the adjacent carbonyl group. This should be true for pyrrolidine but not for the morpholine enamine[11]. Therefore, the results suggest that the enamine reacts with 3-chloropropanoyl chloride by a *C*-acylation–*C*-alkylation pathway without formation of double bond or intermediate *IX* (Scheme 3). If this suggestion is not true and the reaction involves formation of the double bond at any step of this transformation, the



SCHEME 3

reaction with 2-chloropropanoyl chloride should lead to the bicyclic dione as well. In order to test this hypothesis we carried out the reaction of enamine *Ia* with 2-chloropropanoyl chloride. Since with this chloride the elimination of hydrogen chloride requires more vigorous conditions, triethylamine in boiling benzene was used as additional base. As predicted, no bicyclic dione was found in the reaction mixture and we obtained the acylated enamine *X* (Scheme 3) as the reaction product. Reaction of 2-chloropropanoyl chloride with triethylamine under the cyclization conditions produced the salt $CH_3CH(N^+R_3Cl^-)CON^+R_3Cl^-$ (R = C_2H_5) quantitatively and again formation of a double bond was not observed. These results are in agreement with the proposed reaction pathway. The only role of the additional base is to bind hydrogen chloride and to facilitate the regeneration of free enamine. Since the reaction with 3-chloropropanoyl chloride seems to proceed through a different pathway than with acryloyl chloride, the product of the reaction with the enamine *Id* should be the isomeric bicyclononanedione *IIIh*. However, the reaction of enamine *Id* and 3-chloropropanoyl chloride afforded a mixture of bicyclic compounds and ^{1}H NMR spectrum showed the same peaks as found for the reaction product from enamine *Id* with acryloyl chloride. These data indicate that the cyclization with 3-chloropropanoyl chloride was not regioselective. The reaction involved both isomers of the enamine and, in accord with the acyl–alkyl pathway, the attack on the more substituted enamine double bond should also give bicyclic dione (as already mentioned, this is impossible if the reaction proceeds through a [3,3] sigmatropic rearrangement because of steric hindrance by the methyl group).

Mechanistic Considerations

The mechanistic implications of the obtained results are interesting. The formation of mixtures of bicyclic diones, tetrahydrochromanones and unsaturated diketones, together with the results obtained with 3-chloropropanoyl chloride, suggest that, in addition to the [3,3] sigmatropic route, another reaction pathway should exist in cyclization reactions of enamines with α,β-unsaturated acid chlorides, leading to bicyclononanediones. This might be a *C*-acylation–Michael addition pathway. The regio- and stereoselectivity of unsubstituted enamine annulations with 3-chloroformylacrylates *IIa* and *IIb* can be reasonably explained by the [3,3] sigmatropic rearrangement mechanism proposed by Hickmott[4,12]. Although the preferred transition state conformation for a [3,3] sigmatropic rearrangement is normally the chair form, an examination of molecular models shows that a boat transition state appears to be sterically equivalent. The involvement of a boat transition state is supported by formation of diastereoisomerically pure keto esters *IIIa*, *IIIb* with *exo*-configuration of the ester group at C-2. These findings were also substantiated by MM2 molecular mechanics calculations, indicating that the lowest energy form of *III* is the chair–boat conformation with *exo*-configuration of the ester group[13]. Finally, the X-ray analysis (Fig. 1) fully proves the chair–boat conformation of *IIIa* as presented in Scheme 1, with bond lengths and angles given in Table II.

Another possible reaction pathway that would explain formation of mixtures of bicyclic isomers, tetrahydrochromanones and unsaturated diketones might be a *C*-acylation followed by Michael addition. *C*-Acylation may occur by direct attack of the acid chloride at the nucleophilic carbon atom of the enamine double bond or it may be the result of a further reaction after the attack on nitrogen. Direct attack by the acid chloride at the double bond should produce a stable iminium salt and the cyclization should fail. Two paths of the second alternative could be anticipated from the study of a similar reaction of acylated tertiary amines with nucleophiles[14]. The cyclization might occur if the enamine is regenerated with the less substituted double bond and this should be true for the morpholine enamine. The subsequent Michael addition might occur from either side of the double bond of the attached fragment. The topological rule for the stereochemistry of Michael addition reactions to enamines predicts that *E*-isomers of enamines (i.e. enamines with the less substituted double bond) should give *syn*-products in reaction with electrophilic olefins[15]. Thus, a bicyclic dione with the *endo*-ester group is expected to predominate in this reaction.

In conclusion, the general course of the reaction can be outlined as paths A or B in Scheme 3. The products obtained depend on the ratio A/B_2 (B_1). As it appears from the experimental data, the reactions proceed by both mechanisms and mixtures of products are obtained. Bicyclic diones *IIIa–IIIf* with the substituent closer to the newly formed carbonyl group are produced by [3,3] rearrangement while the isomeric diones *IIIh–IIIk*, chromanones *VIII* and unsaturated diketones are formed by an initial *C*-acylation pathway. The ratios of products from 2(6)-substituted enamines indicate that the relative

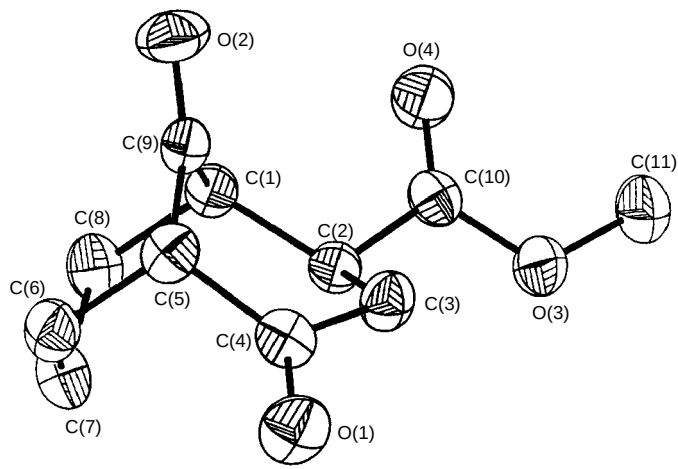


FIG. 1
Molecular structure of *IIIa*

amount of bicyclononanediones *IIIa–IIIf*, arising through the [3,3] sigmatropic shift increases with increasing substituent size. This could be attributed to higher reactivity of the ketene intermediates compared with that of electrophilic double bond of the acylated enamine intermediate which is more sensitive to steric requirements. Reaction of 3-chloroformylacrylates *IIa* and *IIb* with unsubstituted cyclic enamines appears to proceed through the A pathway since only a single isomer with the *exo*-ester group was obtained, but the path B cannot be completely excluded either. When this reaction was applied to enamines of substituted ketones, both mechanisms operated and product mixtures were obtained.

TABLE II
Bond lengths (Å) and angles (°) in *IIIa*

Atoms	Bond length	Atoms	Angle
C(1)–C(2)	1.548(5)	C(2)–C(1)–C(8)	113.2(3)
C(1)–C(9)	1.501(4)	C(8)–C(1)–C(9)	106.8(3)
C(2)–C(3)	1.543(4)	C(1)–C(2)–C(3)	113.5(3)
C(4)–C(5)	1.514(5)	C(2)–C(3)–C(4)	112.9(3)
C(5)–C(6)	1.542(5)	C(3)–C(2)–C(10)	110.0(3)
C(6)–C(7)	1.515(5)	C(4)–C(5)–C(6)	109.9(3)
C(9)–O(2)	1.211(4)	C(6)–C(5)–C(9)	107.9(3)
C(10)–O(4)	1.196(4)	C(6)–C(7)–C(8)	112.5(3)
C(1)–C(8)	1.540(5)	C(1)–C(9)–C(5)	112.0(3)
C(2)–O(1)	1.516(5)	C(5)–C(9)–O(2)	123.5(3)
C(3)–C(4)	1.504(5)	C(2)–C(10)–O(4)	125.9(3)
C(4)–C(10)	1.210(4)	C(10)–O(3)–C(11)	116.1(3)
C(5)–C(9)	1.502(4)	C(2)–C(1)–C(9)	110.4(3)
C(7)–C(8)	1.508(5)	C(1)–C(2)–C(10)	110.8(3)
C(10)–O(3)	1.330(4)	O(1)–C(4)–C(3)	122.9(3)
O(3)–C(11)	1.436(4)	C(3)–C(4)–C(5)	116.2(3)
		C(5)–C(4)–O(1)	120.8(3)
		C(5)–C(6)–C(7)	110.9(3)
		C(1)–C(8)–C(7)	113.0(3)
		C(1)–C(9)–O(2)	124.4(3)
		C(4)–C(10)–O(3)	110.9(3)
		O(3)–C(10)–O(4)	123.2(3)

EXPERIMENTAL

All purchased reagents were purified immediately before use. The solvents were dried by conventional methods and distilled. The reactions were performed in dried glassware in an atmosphere of nitrogen. The IR spectra were measured as liquid films in Nujol (unless stated otherwise) on a Specord M80 spectrophotometer. Proton and carbon-13 NMR spectra were recorded in deuteriochloroform (unless stated otherwise) on a BS 487 C Tesla spectrometer (80 MHz for protons and 20 MHz for ^{13}C). Chemical shifts are given in ppm (δ-scale) relative to tetramethylsilane as internal standard. GLC analyses were performed on a Chrom 5 instrument. Thin-layer chromatography was carried out on Silufol aluminium sheets coated with silica gel, column chromatography on silica gel L 40/100 (Lachema, Czech Republic). Melting points were determined on a Kofler block; the boiling and melting points are uncorrected.

Materials

Methyl 3-chloroformylacrylate (*IIa*), b.p. 67–69 °C/1.9 kPa, m.p. 16 °C (reported[16] b.p. 69.6 °C/14 mm Hg) and ethyl 3-chloroformylacrylate (*IIb*), b.p. 77–78 °C/1.6 kPa (reported[17] b.p. 90–92 °C/19 mm Hg) were prepared according to a published procedure[17].

(1*R*,2*S*,5*R*)-(–)-Menthyl 3-chloroformylacrylate (*IIc*) was synthesized by adding dry (–)-menthol (4.3 g, 0.03 mol) to cooled (10 °C) freshly distilled fumaroyl dichloride in a two-necked flask equipped so that dry nitrogen could be introduced and reduced pressure could be applied during the reaction. The mixture was gently shaken until the menthol dissolved, and then heated at 70 °C for 30 min until the vigorous evolution of gas ceased. Then the heating bath was removed and hydrogen chloride was completely blown out by introducing dry nitrogen under reduced pressure for 15 min. The product *IIc* was obtained in 60% yield and was used without further purification.

Benzyl 3-chloroformyl-3-butenoate (*IId*) was prepared from 3-methylenebutanedioyl dichloride according to the method described above for *IIc*, m.p. 82 °C. For $C_{12}H_{12}O_4$ (220.2) calculated: 65.45% C, 5.49% H; found: 65.43% C, 5.79% H. ^1H NMR spectrum (CCl_4): 10.3 s, 1 H (OH); 7.15 s, 5 H (arom. H); 6.33 and 5.68 m, 2 H (=CH); 4.98 s, 2 H (CH_2Ph); 3.23 s, 2 H (CH_2CO).

2-Benzylcyclohexanone was prepared as described[18], b.p. 136–137 °C/0.3 kPa (ref.[18] states b.p. 137–138 °C/2 mmHg). 4-Oxocyclohexyl benzoate was obtained from 1,4-cyclohexanediol by a described method[19]; m.p. 62 °C (reported[19] m.p. 62 °C). Methyl 4-oxocyclohexylcarboxylate was synthesized according to a published procedure[20]; b.p. 127 °C/1.6 kPa, n_D^{20} 1.4658 (reported[20] b.p. 104–105 °C/2 mmHg, n_D^{20} 1.4589). 3,4-Dihydro-2(1*H*)-naphthalenone (*VIIa*) was prepared from 2-naphthol as described[21]; b.p. 131 °C/1.5 kPa.

Enamines were prepared from cyclic ketones (0.1 mol) and secondary amines (0.12 mol) in the presence of catalytic amount of *p*-toluenesulfonic acid (0.02 g) in dry benzene (250 ml) by a described procedure[22]. The following enamines were obtained:

N-(2(6)-Methylcyclohexen-1-yl)morpholine (*Id*) (mixture of isomers), b.p. 128–130 °C/1.7 kPa, n_D^{20} 1.543 (reported[22] b.p. 125–127 °C/12 mmHg, n_D^{20} 1.545). ^1H NMR spectrum: 4.60 m, 1 H (CH=); 3.63 t, 4 H; 2.70 t, 4 H; 2.4–1.3 m, 7 H; 1.0–0.85 m, 3 H (CH_3). *N*-(2(6)-Benzylcyclohexen-1-yl)morpholine (*Ie*) (mixture of isomers), b.p. 163 °C/0.3 kPa. ^1H NMR spectrum: 7.0 s, 5 H (arom. H); 4.5–4.6 m, 1 H (CH=); 3.4 t, 4 H; 3.1–2.45 m, 2 H (CH_2Ph); 2.3 t, 4 H; 2.0–1.9 m, 7 H. 1-(*N*-morpholino)cyclohexen-1-yl benzoate (*Ic*), viscous liquid, decomposing upon distillation. ^1H NMR spectrum: 7.9 and 7.35 m, 5 H (arom. H); 5.25 m, 1 H (CHO); 4.45 m, 1 H (CH=); 3.6 t, 4 H; 2.8 t, 4 H; 2.6–1.8 m, 6 H ($3 \times CH_2$).

General Procedure for Reaction of Enamines with Alkyl 3-Chloroformylacrylates

A solution of *IIa* or *IIb* in benzene (10 ml) was added dropwise at 20 °C during 5–6 h to a stirred solution of freshly distilled enamine (0.06 mol) in benzene (400 ml). The reaction mixture was stirred at room temperature for an additional hour under exclusion of moisture and then filtered. The crystalline precipitate was washed with dry hexane and dissolved in ice-cold water (200 ml). The aqueous solution was allowed to stand overnight and then extracted with methylene chloride. The combined organic extracts were dried over magnesium sulfate, filtered and concentrated at reduced pressure. The crude bicyclic products were purified by recrystallization from anhydrous solvents or chromatographed on a silica gel column in benzene–acetone (9 : 1).

Methyl (IIIa) *and ethyl* (IIIb) *4,9-dioxobicyclo[3.3.1]nonane-2-carboxylates* were obtained as described[7].

(–)-*Menthyl 4,9-dioxobicyclo[3.3.1]nonane-2-carboxylate* (IIIc); yield 53%, m.p. 71 °C (ether). For $C_{20}H_{30}O_4$ (334.4) calculated: 71.83% C, 9.04% H; found: 71.80% C, 9.04% H. ^{1}H NMR spectrum (CCl_4): 4.5 m, 1 H (CHCO); 3.05–2.3 m, 5 H; 2.3–1.0 m, 14 H (methylene envelope); 1.0–0.5 m, 9 H ($3 \times CH_3$). ^{13}C NMR spectrum: 209.1 and 207.1 (ketone C=O), 172.3 (ester C=O), 75.6 (C-11), 63.1 (C-5), 47.9 (C-1), 46.6 (C-2), 42.0, 40.7, 40.3 (C-3, C-12, C-16), 35.5, 35.3, 33.9, 31.1 (C-6, C-15, C-14), 25.9, 23.0, 21.7, 20.5, 18.6, 15.9.

Methyl 1- and 5-methyl-4,9-dioxobicyclo[3.3.1]nonane-2-carboxylates (IIId *and* IIIi); yield 56%, pale yellow oil. For $C_{12}H_{16}O_4$ (224.2) calculated: 64.28% C, 7.19% H; found: 63.71% C, 6.84% H. ^{1}H NMR spectrum: 3.7–3.55 m and 3.63 s and 3.59 s, 3.6 H (OMe and CHαCO); 3.4–2.5 m, 4.7 H (CHαCO and COCHCHCOOR); 2.4–1.3 m, 4.6 H; 1.05–0.8 m, 3 H (CH_3). ^{13}C NMR spectrum: 209.6, 208.4, 207.1, 204.5 (all ketone CO), 173.3, 173.1 (both ester CO), 71.1, 69.3 (αCCO), 62.7, 62.5, 52.3, 47.3, 46.7, 43.5, 42.7, 41.7, 41.6, 40.5, 33.2, 30.9, 28.0, 25.1, 24.4, 20.4.

Benzyl 4,9-Dioxobicyclo[3.3.1]nonan-3-ylacetate (*IIIk*)

Freshly prepared compound *IId* (4.5 g, 0.019 mol) was diluted with dry benzene (10 ml) and the solution was added during 45 min to a stirred solution of *Ia* (3.3 g, 0.019 mol) in dry benzene (135 ml) at room temperature. The resulting solution was stirred overnight. Benzene was decanted and the oily residue was hydrolyzed with ice-cold water (30 ml) for 3 h. The aqueous solution was extracted with diisopropyl ether (2×50 ml) and the combined extracts were dried over magnesium sulfate. Removal of the solvent afforded 2.8 g of pale yellow viscous oil. A part of this mixture (300 mg) was chromatographed on a silica gel column (tetrachloromethane–acetone 4.5 : 1) to give 100 mg (16%) of the title product as a colourless oil. For $C_{18}H_{18}O_4$ (298.3) calculated: 71.99% C, 6.71% H; found: 71.98% C, 6.88% H. ^{1}H NMR spectrum: 7.25 s, 5 H (ArH); 5.05 s, 2 H (CHαCOOBn); 3.3 m, 1 H (CHαCO); 2.9–2.1 m, 4 H (H adjacent to CO); 2.1–1.25 m, 6 H.

General Procedure for Reaction of Enamines with Acryloyl Chloride

Freshly distilled acryloyl chloride (*IIe*; 21.1 g, 0.3 mol) in dry benzene (10 ml) was added to a solution of the enamine (0.3 mol) in dry benzene (150 ml) at room temperature. After heating at reflux for 6 h, the mixture was cooled and the precipitate was filtered, washed with dry hexane and stirred with ice-cold water (50 ml). The aqueous phase was extracted several times with ether and the combined extracts were dried over magnesium sulfate. After removal of the solvent, the residue was purified by column chromatography. The following compounds were obtained:

Bicyclo[3.3.1]nonane-2,9-dione (IIIj), yield 70%, m.p. 118 °C (reported[5] m.p. 117 °C). For $C_9H_{12}O_2$ (152.1) calculated: 71.02% C, 7.94% H; found: 70.99% C, 7.87% H. IR spectrum (CCl_4): two bands in the region 1 700–1 730 cm^{-1} (C=O). ^{1}H NMR spectrum: 3.10 m, 1 H; 2.75–1.45 m,

11 H (methylene envelope). ^{13}C NMR spectrum: 211.9 (C-2), 210.2 (C-9), 64.1 (C-1), 44.3 (C-5), 39.1 (C-3), 35.65, 34.95, 22.18, 18.6.

1(5)-Methylbicyclo[3.3.1]nonane-2,9-dione (IIIe *and* IIIh), yield 71%, waxy solid, m.p. 36–37 °C (reported m.p. 37 °C). For $C_{10}H_{14}O_2$ (166.2) calculated: 72.26% C, 8.49% H; found: 72.10% C, 8.51% H. IR spectrum (CCl_4): two bands in the region 1 710–1 735 cm^{-1} (C=O). ^{1}H NMR spectrum: 3.1 m, 1 H (CHCO); 3.0–1.50 m, 10 H (methylene envelope); 0.9 m, 3 H (CH_3). ^{13}C NMR spectrum: 211.3, 210.2, 72.41 (d, C-1), 70.59 (C-1), 63.5 (d, C-5), 44.1, 43.9, 43.7, 42.5, 41.3, 39.4, 38.9, 33.6, 28.4, 25.1, 23.4, 20.7, 19.2, 18.2.

Benzylbicyclo[3.3.1]nonane-2,9-dione (IIIf), yield 40%, m.p. 58 °C. For $C_{16}H_{18}O_2$ (242.3) calculated: 79.31% C, 7.49% H; found: 79.20% C, 7.41% H. ^{1}H NMR spectrum: 7.0 s, 5 H (arom. H); 3.1–2.2 m, 5 H (CH_2Ph and HαCO); 2.2–1.45 m, 8 H (methylene envelope). ^{13}C NMR spectrum: 212.1, 209.3, 130.8, 127.7, 126.0, 44.8 (C-1), 43.0 (C-3), 41.2 (C-4), 37.5 (C-10), 37.0 (C-8), 21.1 (C-6), 18.42 (C-7).

8-Benzyl-5,6,7,8-tetrahydrochromanone-4 (VIIIa), yield 12%, yellow oil, decomposing on distillation. For $C_{16}H_{18}O_2$ (242.3) calculated: 79.31% C, 7.49% H; found: 78.99% C, 7.39% H. ^{13}C NMR spectrum: 213.2 (C=O), 171.6 (O–C=C), 140.2, 128.9, 128.1, 125.7, 125.9, 66.6, 52.7, 50.2.

8-Isopropyl-5-methyl-5,6,7,8-tetrahydrochromanone-4 (VIIIb), pale yellow liquid, decomposing when exposed to air and moisture; yield 18%. For $C_{13}H_{20}O_2$ (208.3) calculated: 74.99% C, 9.68% H; found: 74.80% C, 8.55% H. n_D^{20} 1.455. ^{1}H NMR spectrum: 3.75 m, 2 H (OCH_2); 3.15–1.25 m, 8 H (alicyclic H); 1.03–0.75 m, 9 H (3 × CH_3).

1-Acryloyl-1,2,3,4-tetrahydronaphthalen-2-one (VIIb), pale yellow quickly decomposing oil; yield 10%. ^{1}H NMR spectrum (CD_2Cl_2): 7.3–7.0 m, 6 H (ArH and =CH); 5.2 m, 1 H (COCH=); 5.1 s, 1 H (COCHCO); 2.8 t, 2 H (CH_2CO); 2.3 t, 2 H (CH_2).

General Procedure for Reaction of Enamines with 3- and 2-Chloropropanoyl Chlorides

A solution of the acyl chloride (3.81 g, 0.03 mol) in dry benzene (10 ml) was added dropwise to a boiling and stirred solution of the enamine (0.03 ml) and the tertiary amine (0.06 mol) in dry benzene (150 ml). The reaction mixture was refluxed for 6 h. After cooling, the precipitate was filtered, washed with hexane and hydrolyzed with ice-cold water overnight. The aqueous solution was extracted several times with ether and the combined extracts were dried over magnesium sulfate. The solvent was evaporated and the remaining oil was purified by column chromatography.

Bicyclo[3.3.1]nonane-2,9-dione (IIIj), waxy solid (yield 69%), m.p. 118 °C. Analytical and spectral data corresponded in all respects with those of the sample obtained from *Ia* and acryloyl chloride.

1(5)-Methylbicyclo[3.3.1]nonane-2,9-dione (IIIe *and* IIIh), waxy solid (yield 61%), m.p. 35–37 °C. Analytical and spectral data corresponded in all respects with those of the sample obtained from *Id* and chloride *IIe*.

[2-(N-Morpholinyl)cyclohex-1-en-3-yl]-2-chlorobutan-1-one (X, R^1 = H), yellow oil, qickly decomposing on air. ^{1}H NMR spectrum: 5.0 q, 1 H (CHCl); 3.27 t, 4 H; 2.7 t, 4 H; 2.5 m, 2 H; 2.35 m, 9 H (3 × CH_2 and CH_3).

Acid Hydrolysis of Mixture of *IIIe* and *IIIh*

To a mixture of *IIIe* and *IIIh* (2 mmol), dissolved in a minimum amount of methanol (5 ml), was added 1 M HCl and the mixture was refluxed for 8 h. After cooling, the mixture was several times extracted with ether. The solvent was evaporated and the residue was chromatographed on a silica gel column in ether–acetone (1 : 1) to give a mixture of *IVa*, *IVb* and *V* (about 1 : 1) as a colourless oil, yield 72%. Analytical GLC and spectral data corresponded to those of the sample obtained from *Id*

and ethyl acrylate. Several recrystallizations from ether afforded an acid, melting at 95 °C (for 3-(1-methyl-2-oxocyclohexyl)propanoic acid reported[23] m.p. 49–50 °C, for *cis*-3-(3-methyl-2-oxocyclohexyl)propanoic acid reported[8] m.p. 72 °C). IR spectrum: 1 704, 1 720 cm^{-1}. ^1H NMR spectrum: 10.8 s, 1 H; 2.4–1.2 m, 12 H (methylene envelope); 0.95 d, 3 H (CH_3).

3-(3-Methyl- and 1-methyl-2-oxocyclohexyl)propanoic acids (IVa *and* IVb). Ethyl acrylate (2.3 g, 0.022 mol) was added to a stirred solution of *Id* (3.0 g, 0.017 mol) in dioxane (7 ml). The solution was heated at reflux for 3 h and a buffered acetic acid hydrolysis mixture (25 ml of acetic acid, 25 ml of water and 12.5 g of sodium acetate) was added. The mixture was refluxed for an additional hour, poured into water, and extracted three times with ether. The combined ethereal extracts were concentrated, the residue was mixed with 20% KOH (10 ml) and the mixture was refluxed for 8 h. The aqueous solution was neutralized with HCl, the resulting mixture was extracted with ether and the combined ethereal extracts were dried over magnesium sulfate. Removal of the solvent gave 2.0 g (76%) of a colourless oil. For $C_{10}H_{16}O_3$ (184.2) calculated: 65.20% C, 8.75% H; found: 65.64% C, 8.71% H. ^1H NMR spectrum: 10.95 s, 1 H (OH); 2.5–1.05 m, 12 H (methylene envelope); 1.05–0.85 m, 3 H (CH_3).

Tertiary Amine Salts with 2- and 3-Chloropropanoyl Chlorides

To a refluxing solution of the tertiary amine (0.06 mol) in dry benzene (150 ml) was added dropwise 2- or 3-chloropropanoyl chloride (3.81 g, 0.03 mol) and the mixture was refluxed for 1 h. The white precipitate was filtered and washed with hexane.

N-Ethyl-N-(3-propanoyl-N-ethylmorpholinium chloride) morpholinium chloride; yield 99%, colourless crystals, decomposing > 200 °C. ^1H NMR spectrum: 3.83–3.89 m, 10 H (methylenes adjacent to O); 2.85–3.3 m, 14 H (methylenes at N and of ethyl group); 1.25 t, 6 H (CH_3).

N-Triethyl-N-(2-propanoyl-N-triethylammonium chloride) ammonium chloride, yield 98%, decomposing >200 °C. ^1H NMR spectrum: 4.2 m, 1 H (CH); 3.8 m, 6 H (methylenes at CO); 2.9 q, 6 H (CH_2); 1.2 m, 21 H ($7 \times CH_3$).

X-Ray Crystallography of *IIIa*

Colourless needle, 0.1 × 0.1 × 0.6 mm, $C_{11}H_{14}O_4$, m.w. = 210.2. Monoclinic (space group $P2/n$); a = 6.461(1) Å, b = 8.913(1) Å, c = 17.367(3) Å, $\alpha = \gamma = 90°$, β = 92.40(1)°; V = 999.2(3) $Å^3$, Z = 4, D_{calc} = 1.40 g/cm^3, T = 24 °C, radiation MoKα (λ = 0.71069 Å), μ = 1.0 cm^{-1}, $F(000)$ = 448, R = 0.047, R_w = 0.047, S = 1.24, 137 parameters. The intensity data were taken as $\theta/2\theta$ scans on a Nicolet R3mE four circle diffractometer for 2 931 unique reflections in the range $4° < 2\theta < 60°$, of which 961 with $I > 3\sigma(I)$ were used for the structure solution and refinement. The data were corrected for Lorentz and polarization effects. No absorption or extinction corrections were needed. The structure was solved by direct methods and non-hydrogen atoms were refined by block-cascade least-squares with anisotropic thermal parameters, using statistic weighing. The crystallographic calculations were done with the SHELXTL program package by Sheldrick Siemens Analytical X-Ray Instruments, Madison, Wi, U.S.A. The calculated hydrogen positions were used for the structure refinement after all hydrogens had been located on different maps, and a common isotropic thermal parameter was refined for all hydrogens, U = 0.046(3) $Å^2$.

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