

Enamine Chemistry. Part XVI.¹ Reaction of $\alpha\beta$ -Unsaturated Acid Chlorides with 1,4-Dimorpholinocyclohexa-1,3-diene. Synthesis of 7-Morpholino- and 4,7-Dimorpholino-indan-1-ones

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The reaction of acryloyl chloride with 1,4-dimorpholinocyclohexa-1,3-diene has been shown to give 7-morpholinoindan-1-one. In a similar way methacryloyl, crotonoyl, and cinnamoyl chlorides gave the corresponding 2-methyl-, 3-methyl-, and 3-phenyl-7-morpholinoindan-1-one, respectively, and β -chloroacryloyl chloride gave 4,7-dimorpholinoindan-1-one. Yields were low owing to competing formation of 1,4-dimorpholinobenzene and the corresponding $\alpha\beta$ -unsaturated acid morpholide.

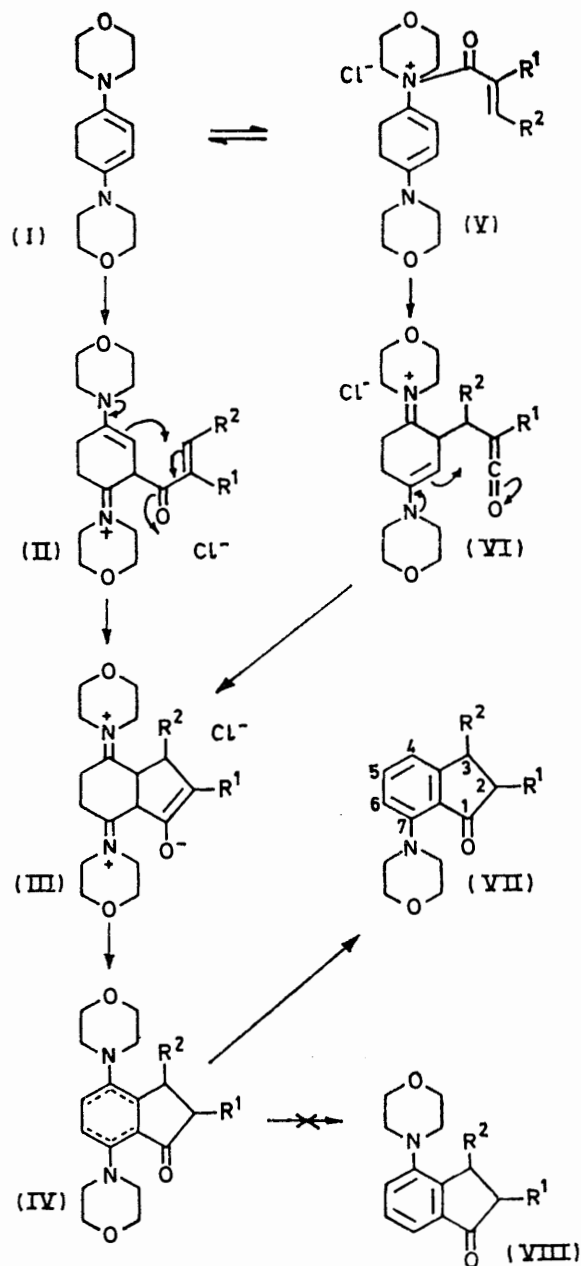
THE formation of six-membered carbocycles and heterocycles by the reactions of $\alpha\beta$ -unsaturated acid chlorides with enamines and imines has been reported previously.² In an attempt to extend the scope of this reaction to the synthesis of five-membered rings we have investigated

the reaction of $\alpha\beta$ -unsaturated acid chlorides with 1,4-dimorpholinocyclohexa-1,3-diene (I).

¹ Part XV, P. W. Hickmott and C. T. Yoxall, *J.C.S. Perkin II*, 1972, 890.

² N. F. Firrell and P. W. Hickmott, *J. Chem. Soc. (C)*, 1968, 2320; J. R. Hargreaves, P. W. Hickmott, and B. J. Hopkins, *ibid.*, 1969, 592; P. W. Hickmott, B. J. Hopkins, and C. T. Yoxall, *Tetrahedron Letters*, 1970, 2519; P. W. Hickmott and G. Sheppard, *J. Chem. Soc. (C)*, 1971, 2112, and references therein.

Cyclisation of the $\alpha\beta$ -unsaturated acid chloride across the 2,3-bond of the dienamine occurred with formation of a five-membered ring as expected. This was followed by aromatisation of the intermediate cycloadduct, with elimination of a morpholine residue, to give the corresponding 7-morpholinoindan-1-one (VII) (Scheme 1).

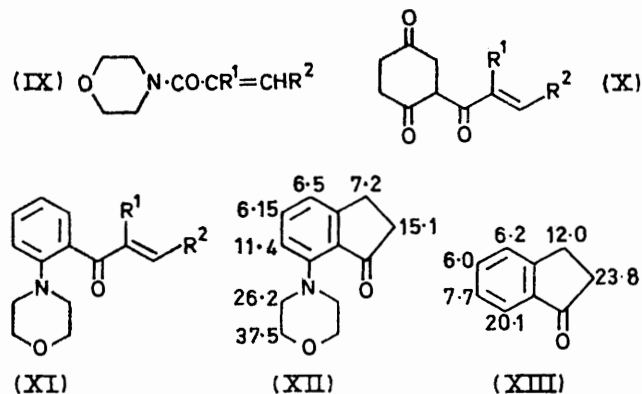


SCHEME 1

The yield of indanone was low (10–20%) owing to competing aromatisation of the dienamine (I) to give 1,4-dimorpholinobenzene, and formation of the $\alpha\beta$ -unsaturated amide (IX). Indanone formation presumably occurs primarily *via* the intermediacy and

rearrangement of the *N*-acylated dienamine [(I) \rightleftharpoons (V) \rightarrow (VI) \rightarrow (III)] rather than by initial *C*-acylation [(I) \rightarrow (II) \rightarrow (III)] by analogy with our previous work² and since we have not isolated any products [such as (X) or (XI)] formed by hydrolysis or aromatisation of the *C*-acylated intermediate (II).

The isomeric structure (VIII) for the indanone is ruled out by the spectral data (Table 2). The assignment of the ¹H n.m.r. signals of 7-morpholinoindan-1-one (VII; R¹ = R² = H) was confirmed as follows. The signals centred at τ 7.40 were removed on deuteration, thus confirming their assignment to the protons α to the carbonyl group. The multiplet at τ 6.94 must therefore be due to the methylene protons at C-3, α to the benzene ring. Irradiation at the frequency of the methylene protons α to the nitrogen atom of the morpholine ring (at τ 6.79), resulted in an increase of 10.5% in the integral of the high-field aromatic doublet (at τ 3.22) (nuclear Overhauser effect), confirming its assignment to the C-6 proton *ortho* to the morpholine ring.³ The assignment of the other doublet (at τ 3.00) to the C-4 proton of structure (VII; R¹ = R² = H) rather than the C-7 proton of structure (VIII; R¹ = R² = H) was confirmed by the decoupling observed on irradiation at



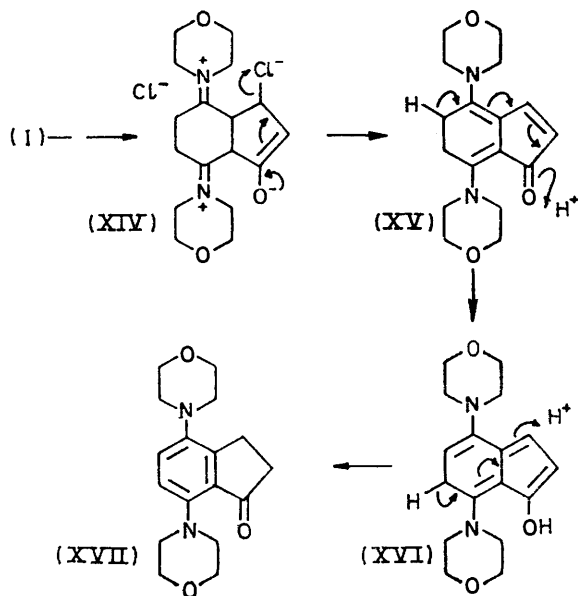
τ 6.94. The doublets at τ 3.00 and (to a lesser extent) τ 3.22 were sharpened, but there was no observable effect on the triplet at τ 2.49 assigned to the C-5 proton. The unequivocal assignment of the n.m.r. signals to 7-morpholinoindan-1-one (VII; R¹ = R² = H) rather than 4-morpholinoindan-1-one (VIII; R¹ = R² = H) was substantiated by the ytterbium-induced shifts to lower field. The extrapolated values (in p.p.m.) at equimolar proportions of tris(dipivaloylmethanato)ytterbium⁴ and the indanone, are summarised in formula (XII). These values are similar to those reported⁵ for indan-1-one (XIII), the main difference being the absence of the large shift of 20.1 p.p.m. for the C-7 proton which would have been anticipated in 4-morpholinoindan-1-one but not in 7-morpholinoindan-1-one.

The reaction of β -chloroacryloyl chloride with 1,4-dimorpholinocyclohexa-1,3-diene differed from those of

⁴ K. J. Eisentraut and R. E. Sievers, *J. Amer. Chem. Soc.*, 1965, **87**, 5254; *Inorg. Synth.*, 1968, **11**, 94.

⁵ Z. W. Wolkowski, *Tetrahedron Letters*, 1971, 821.

³ P. W. Hickmott and G. Sheppard, *J.C.S. Perkin I*, 1972, 1038.



SCHEME 2

the other acid chlorides in that aromatisation occurred without expulsion of a morpholine residue, to give 4,7-dimorpholinoindan-1-one (XVII) (Scheme 2). The

structure follows from the spectral data, particularly from the close similarity of the u.v. data to those of the other indanones (Table 2). This was further confirmed by the loss of the n.m.r. signals due to the C-2 methylene group [τ (CDCl₃) 7.32] on deuteration, and by use of the nuclear Overhauser effect. Irradiation (solution in C₆D₆) at τ 7.33 (4-N[CH₂]₂) resulted in a 6% increase in the integral of the 5-H signal (τ 3.08), and irradiation at τ 6.93 (7-N[CH₂]₂) gave a 16% increase in the integral of the 6-H signal (τ 3.57). These results rule out the isomeric structure (XV), which may however be an intermediate in the formation of 4,7-dimorpholinoindan-1-one, as shown in Scheme 2.

EXPERIMENTAL

U.v. and i.r. spectra were determined with Unicam SP 800A and Perkin-Elmer 257 spectrophotometers, respectively, and ¹H n.m.r. and mass spectra with Varian A60 and A.E.I. MS12 instruments, respectively. The ytterbium-induced shifts and the effects of double irradiation were investigated with the Varian HA 100 spectrometer.

Reaction of $\alpha\beta$ -Unsaturated Acid Chlorides with 1,4-Dimorpholinocyclohexa-1,3-diene.—*General method.* The $\alpha\beta$ -unsaturated acid chloride (0.01 mol) in dry benzene (20 ml)

TABLE 1

Reaction of $\alpha\beta$ -unsaturated acid chlorides with 1,4-dimorpholinocyclohexa-1,3-diene

Acid chloride	1,4-Dimorpholinobenzene Yield (%)	$\alpha\beta$ -Unsaturated amide (IX) Yield (%)	7-Morpholinoindan-1-one (VII)		Yield (%)	M.p.* (°C)	Analysis (mass measurement)			Required (%)			
			R ¹	R ²			Found (%)	C	H	N	C	H	N
Acryloyl chloride	26	28	H	H	21	96—98	72.2	7.1	6.2	C ₁₃ H ₁₅ NO ₂	71.9	6.9	6.45
Crotonoyl chloride	8 †	37	H	Me	9	(Oil)	(m/e 231.1258)			(231.1259)			
Methacryloyl chloride	14 †	35	Me	H	10	(Oil)	(m/e 231.1258)			(231.1259)			
Cinnamoyl chloride	15 †	36	H	Ph	11	121—122	77.9	6.5	4.4	C ₁₉ H ₁₉ NO ₂	77.8	6.5	4.8
β -Chloroacryloyl chloride	—	—	H	H	12 ‡	157—159	67.6	7.25	8.9	C ₁₇ H ₂₂ N ₂ O ₅ ‡	67.6	7.3	9.3

* Recrystallised from light petroleum (b.p. 60—80°)—benzene. † Isolated from the benzene layer only, the precipitated hydrochloride being discarded (see General method). ‡ 4,7-Dimorpholinoindan-1-one (XVII).

TABLE 2

7-Morpholino- and 4,7-dimorpholinoindan-1-ones: spectral data

Compound	$\nu_{\max.}/\text{cm}^{-1}$	$\lambda_{\max.}$ (MeOH)/nm (ϵ)	M ⁺	¹ H N.m.r. (τ values)
(VII; R ¹ = R ² = H)	1695 (C=O) * 1593 (C=C) 1580 (C—O—C) 1118 (C—O—C)	364 (3590), 331sh (2400), 207.5 (5350), 237 (17,780), 210 (8500)	217	2.49 (t, 5-H), 3.00 (d, 4-H), 3.22 (d, 6-H), 6.04 (m, CH ₂ ·O·CH ₂), 6.79 (m, CH ₂ ·N·CH ₂), 6.94 (m, 3-H ₂), 7.40 (m, 2-H ₂) †
(VII; R ¹ = H, R ² = Me)	1695br (C=O) ‡ 1580 (C=C) 1118 (C—O—C)	364 (3530), 331sh (2410), 260 (5240), 237 (17,480), 209 (11,000)	231	2.48 (t, 5-H), 2.97 (d, 4-H), 3.22 (d, 6-H), 6.08 (m, CH ₂ ·O·CH ₂), 6.80 (m, CH ₂ ·N·CH ₂ and 3-H), 7.11 (dd, J 18 and 7.5 Hz, 2-H), 7.88 (dd, J 18 and 3.5 Hz, 2-H), 8.63 (d, J 7 Hz, 3-Me) †
(VII; R ¹ = Me, R ² = H)	1700br (C=O) ‡ 1590 (C=C) 1118 (C—O—C)	357 (2560), 331 (2310), 268 (4480), 234 (17,360), 210 (8000)	231	2.52 (t, 5-H), 3.03 (d, 4-H), 3.23 (d, 6-H), 6.08 (m, CH ₂ ·O·CH ₂), 6.80 (m, CH ₂ ·N·CH ₂), 6.30—7.70 (m, 2-H and 3-H ₂), 8.68 (d) and 8.72 (d) (2-Me epimers, J 7 Hz) †
(VII; R ¹ = H, R ² = Ph)	1690 (C=O) * 1585 (C=C) 1570 (C—O—C) 1125 (C—O—C)	364 (3470), 336sh (2550), 270 (5030), 235 (15,560), 212 (16,000)	293	2.4—3.4 (m, aromatic), 5.53 (dd, 3-H), 6.05 (m, CH ₂ ·O·CH ₂), 6.8 (m, CH ₂ ·N·CH ₂ and 2-H), 7.38 (dd, J 19 and 4.5 Hz, 2-H) †
(XVII)	1705 (C=O) * 1560 (C=C) 1115 (C—O—C)	378 (3350), 340sh (1790), 273 (6040), 245 (20,290), 215sh (11,000)	302	3.08 (d, 5-H), 3.57 (d, 6-H), 6.08 (m) and 6.30 (m) (2 × CH ₂ ·O·CH ₂), 6.93 (m) and 7.33 (m) (2 × CH ₂ ·N·CH ₂), 6.7—7.8 (m, 2- and 3-H ₂) §

* Nujol mull. † CDCl₃. ‡ Liquid film. § C₆D₆.

was added dropwise to a solution of 1,4-dimorpholinocyclohexa-1,3-diene⁶ (0.01 mol) in boiling dry benzene (50 ml) under nitrogen during 30 min. The mixture was heated under reflux for 18 h, cooled, and filtered; the precipitate of 1,4-dimorpholinobenzene hydrochloride was discarded. The filtrate was evaporated *in vacuo* and the residue purified by preparative t.l.c. on silica with 10% acetone in benzene as the solvent system. The fastest running band [fluorescent under u.v. light] contained the indanone, the next 1,4-dimorpholinobenzene [intense blue in iodine vapour], m.p. 189–190° (lit.,⁶ 191°), and the third the amide (IX). In the case of β -chloroacryloyl chloride⁷ the first band was an unidentified oil and the 4,7-dimorpholinoindan-1-one was obtained from the second band. 14-

⁶ W. Ried and W. Kappeler, *Annalen*, 1965, **687**, 183.

⁷ E. Gryszkiewicz-Trochimowski, W. Schmidt, and O. Gryszkiewicz-Trochimowski, *Bull. Soc. chim. France*, 1948, 593.

Dimorpholinobenzene, present in the third band, was not isolated.

Preparative and analytical data are summarised in Table 1 and spectral data in Table 2.

Deuteriation of 7-Morpholinoindan-1-one and 4,7-Dimorpholinoindan-1-one.—The indanone (0.15 g) was dissolved in dry pyridine (5 ml), deuterium oxide (5 ml) was added, and the mixture was heated on a steam-bath for 4 h. Evaporation *in vacuo* and extraction with ether gave in each case the 2,2-dideuterio-derivative; for ¹H n.m.r. spectra see Discussion section.

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