Enamine Chemistry. Part XIII.[1] Reaction of αβ-Unsaturated Acid Chlorides with Primary and Secondary Enamines. Synthesis of Tetrahydro-2-oxopyridines and Octahydro-2-oxoquinolines

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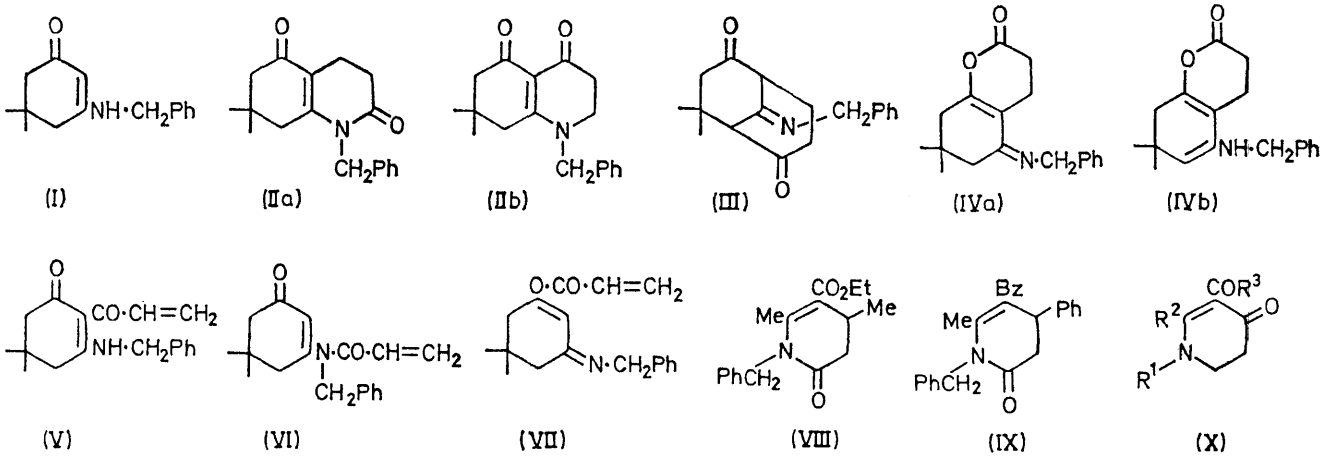
αβ-Unsaturated acid chlorides react with primary and secondary enamines, obtained by condensation of ammonia or primary amines with β-diketones or β-keto-esters, to give tetrahydro-2-oxopyridines or octahydro-2-oxoquinolines. The evidence available from this and previous work suggests that the reaction involves initial *O*- or *N*-acylation followed by a [3,3] sigmatropic rearrangement and cyclisation of the keten intermediate formed on to the nitrogen atom.

ROBINSON demonstrated, in his investigations into the conjugative effects of the amino-group, that alkylation of β-aminocrotonic esters gives *C*-alkyl derivatives.[2] Similarly, it has been shown that primary and secondary enamines, in which the enamine system is stabilised by further conjugation with a carbonyl group, react with electrophilic olefins to give tetrahydro-2-oxopyridines, derived by *C*-alkylation followed by cyclisation.[3] However, in the reaction of such compounds with acid chlorides, the occurrence of both *C*- and *N*-acylation has been reported, depending on the substituents present in the enamine and on the nature of the acylating agent.[4] We have now investigated the corresponding reaction with αβ-unsaturated acid chlorides and find that tetrahydro-2-oxopyridines are again obtained, there being no evidence for appreciable *C*-acylation. This reaction is envisaged as involving initial *O*- or *N*-acylation followed by a [3,3] sigmatropic rearrangement and cyclisation on to the nitrogen atom (Scheme 1, paths A and C).

Treatment of 3-benzylamino-5,5-dimethylcyclohex-2-enone (I) with acryloyl chloride in boiling benzene gave 1-benzyl-3,4,7,8-tetrahydro-7,7-dimethylquinoline-2(1*H*),5(6*H*)-dione (IIa), identified from analytical and spectral data. The isomeric bicyclic dione (III) and enol lactone (IV) structures were ruled out by the absence of i.r. carbonyl absorptions in the 1760—1700 cm^{-1} region. The formation of *C*-, *N*-, and *O*-acylated products [(V)—(VII)] was ruled out by the absence of olefinic signals in the ^1H n.m.r. spectrum. Similar results were obtained in reactions of acryloyl chloride with 4-benzylaminopent-3-en-2-one, 3-benzylamino-1-phenylbut-2-enone, ethyl 3-aminocrotonate, ethyl 3-cyclohexylaminocrotonate, ethyl 3-benzylaminocinnamate, and ethyl 3-benzylaminocrotonate. In each case the corresponding tetrahydro-2-oxopyridine (XVI) was obtained, in 40—50% yield. Structural confirmation was obtained by showing that the product from ethyl 3-aminocrotonate was identical with the previously reported[3] ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxopyridine-5-carboxylate (XVI; R^1 = H, R^2 = Me, R^3 = OEt). This therefore rules out the isomeric 4-oxotetrahydropyridine and 4-oxo-octahydroquinoline structures (X) and (IIb).



(I) (IIa) (IIb) (III) (IVa) (IVb)

(V) (VI) (VII) (VIII) (IX) (X)

Substituted αβ-unsaturated acid chlorides behave in the same way. Crotonoyl chloride, for example, and ethyl 3-benzylaminocrotonate gave ethyl 1-benzyl-1,2,3,4-tetrahydro-4,6-dimethyl-2-oxopyridine-5-carboxylate (VIII). The same product was obtained by condensation of ethyl 3-benzylaminocrotonate with crotonic acid under the conditions described by Schroll,

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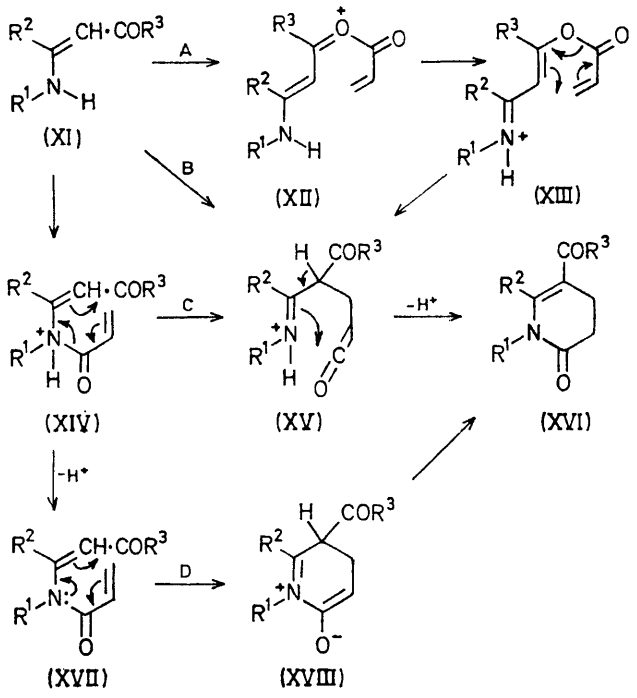
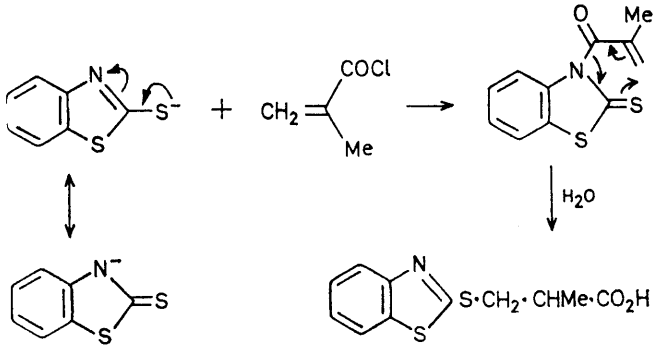
Klemmensen, and Lawesson,[3b] but in much lower yield (14%) and at higher temperatures. The tetrahydro-2-oxopyridine (VIII) contains a centre of asymmetry, and even though this is considerably removed from the benzyl group it was found that the methylene protons were rendered non-equivalent and gave rise to an AB quartet in the ^{1}H n.m.r. spectrum (J 16 Hz). Similar observations by Elguaro and his co-workers [5] indicate that the benzyl group is a very sensitive probe for asymmetry. Treatment of 3-benzylamino-1-phenyl-but-2-enone with cinnamoyl chloride also gave a tetrahydro-2-oxopyridine (IX), again readily recognisable as a cyclic structure by the non-equivalence of the benzyl methylene protons. The C-3 ring methylene protons in structure (IX) are also rendered non-equivalent by the adjacent asymmetric centre (at C-4) and give rise to a clearly defined quartet of doublets in deuteriobenzene [τ 7·58 (dd, J 3·5 and 16 Hz) and 7·1 (dd, J 7 and 16 Hz)].



SCHEME 1

Although these products may be regarded as formally derived by ring closure of the N-acyl derivative [(XVII) ⟶ (XVIII)] (path D, Scheme 1) this mechanism is ruled out by our previous work [6] on the reactions of αβ-unsaturated acid chlorides with imines. The N-acyl enamines obtained were shown to be very inert and all attempts to initiate their ring closure were unsuccessful. We have not been able to differentiate between paths A, B, and C, but the first seems probable for the following reasons. First, tertiary enamino-ketones are well known to give O-protonated salts [7] and, under conditions of kinetic control, O-alkylated derivatives.[8] The reversible nature of the O-alkylation process has been demonstrated by Meyers and his co-workers,[8] who have shown that C-alkylation is favoured under conditions of thermodynamic control. Similarly, in their reactions with acid chlorides, O-acylation of tertiary enamino ketones has been observed by Hünig [9] and, indirectly, by Alt and Speziale.[10] When C-acylation has been observed this has been attributed to the reversible nature of the O-acylation process.[10b] We therefore suggest that, in the reaction between αβ-unsaturated acid chlorides and primary and secondary enamines, the kinetically favoured O-acylation occurs [(XI) ⟶ (XII) ⟶ (XIII)], and that this is rendered irreversible by the [3,3] sigmatropic rearrangement which follows [(XIII) ⟶ (XV)].

Path B, involving a nucleophilic attack by C-β of the enamine on C-β of the acid chloride (an S_N2' reaction), is unlikely, since this would involve initial reaction at the least reactive positions of both the enamine and the acid chloride. Although acryloyl chloride reacts at the β-carbon atom with thiols [11] and sodium thiolates,[12] these reagents, unlike enamines, are strong nucleophiles, and might be expected to attack the less reactive position of the acid chloride to some extent. Even so, in the reaction of acryloyl chloride with sodium benzothiazole-2-thiolate, the proposed mechanism for the formation of (benzothiazolylthio)propionic acid [12] involves N-acylation followed by a [3,3] sigmatropic rearrangement (Scheme 2). Also, reactions with alcohols,[13] primary [13a] and secondary amines,[14] and urea [15] all involve preferential attack at the carbonyl carbon atom of the acid



SCHEME 2

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chloride, while in other cases of ambiguity the mechanism does not seem to have been established.[16] The greater reactivity of the carbonyl group in crotonoyl chloride has been demonstrated in its reactions with aldehyde enamines,[17] thiols,[11] phosphorous ylides,[18] and sodioacetophenone,[19] while with cinnamoyl chloride this fact requires no exemplification. The fact that we have shown that both these acid chlorides give heterocyclic products with secondary enamines, and bridged bicyclic products from the corresponding reaction with tertiary enamines derived from cyclic ketones,[20] in the same way as acryloyl chloride, argues against initial reaction between C-β of the enamine and C-β of the acid chloride (path B) but is in accordance with *O*- (or *N*-) acylation followed by a [3,3] sigmatropic rearrangement.

EXPERIMENTAL

Enamines were prepared by published methods. Preparative and spectral data are summarised in the Table.

Secondary enamines: preparative and spectral data

Compound	Yield (%)	M.p. *T*/°C	*M*+	Relevant spectral data ν (CCl$_4$)/cm^{-1}	^{1}H N.m.r. (τ; CCl$_4$)
(I)	90	128 *	229	3220, 1585, 1500br †	2·66 (Ph), 4·35 (NH), 4·85 (=CH), 5·73 (d, CH$_2$·N), 7·75 and 7·88 (s, 2 × CH$_2$), 8·96 (Me$_2$C) ‡
(XI; R^1 = PhCH$_2$, R^2 = R^3 = Me)	73	Oil	189	1617, 1580br	−1·25 (NH), 2·72 (Ph), 5·06 (=CH), 5·58 (d, CH$_2$·N), 8·08 and 8·18 (2 × Me)
(XI; R^1 = PhCH$_2$, R^2 = Me, R^3 = OEt)	69	Oil	219	1658, 1610	0·9 (NH), 2·72 (Ph), 5·54 (=CH), 5·56 (d, CH$_2$·N), 5·93 (q, CH$_2$), 8·15 (MeC=), 8·78 (t, Me)
(XI; R^1 = PhCH$_2$, R^2 = Ph, R^3 = OEt)	10	64 §	281	1658, 1613, 1600	0·9 (NH), 2·66 and 2·75 (2 × Ph), 5·34 (=CH), 5·75 (d, CH$_2$·N), 5·86 (q, CH$_2$), 8·73 (t, Me)
(XI; R^1 = PhCH$_2$, R^2 = Me, R^3 = Ph)	31	54—55 §	251	1607, 1588	−1·9 (NH), 2·7 (Ph), 4·31 (=CH), 5·5 (d, CH$_2$·N), 8·04 (Me)
(XI; R^1 = C$_6$H$_{11}$, R^2 = Me, R^3 = OEt)	73	Oil	211	3275, 1650, 1608 ¶	1·2 (NH), 5·55 (=CH), 5·84 (q, CH$_2$), 6·65 (m, CH·N), 8·02 (MeC=), 7·8—8·9 (m, ring CH$_2$), 8·72 (t, Me) ‡

* From benzene. † Nujol mull. ‡ In CDCl$_3$. § From light petroleum (b.p. 60—80°). ¶ Film.

Synthesis of Heterocycles.—Method (*A*). The αβ-unsaturated acid chloride (0·01 mol) in dry benzene (25 ml) was added to the enamine (0·01 mol) in boiling dry benzene (50 ml) during 1 h, and the mixture was heated under reflux for 48 h, or until evolution of hydrogen chloride had ceased. The solvent was removed *in vacuo* and the residual oil was purified by preparative t.l.c. on silica, with 5% acetone–benzene as solvent system unless stated otherwise.

Method (*B*). A solution of the αβ-unsaturated acid (0·05 mol) and the enamine (0·05 mol) in chlorobenzene (100 ml) was heated under reflux for the time stated. The solvent was removed *in vacuo* and the residue was purified as in method (A).

1-Benzyl-3,4,7,8-tetrahydro-7,7-dimethylquinoline-2(1H),5(6H)-dione (IIa) was obtained (47%) from acryloyl chloride and compound (I) [method (A)] (Found: C, 76·0; H, 7·6; N, 5·0%; *M*+, 283. $C_{18}H_{21}NO_2$ requires C, 76·4; H, 7·4; N, 5·0%; *M*, 283); $\nu_{max.}$ (film) 1690 and 1655 (C=O) and 1620 cm^{-1} (C=C), $\lambda_{max.}$ (MeOH) 298 nm (ε 11,600), τ (C$_6$D$_6$) 9·37 (6H, s, 2 × Me), 8·05 (2H, t, *J* 1·5 Hz, 8-H$_2$), 8·0 (2H, s, 6-H$_2$), 7·9—7·2 (4H, m, 3- and 4-H$_2$), 5·16 (2H, s, PhC*H*$_2$), and 2·85 (s, Ph).

5-Acetyl-1-benzyl-3,4-dihydro-6-methyl-2(1H)-pyridone (XVI; R^1 = PhCH$_2$, R^2 = R^3 = Me) was obtained (44%) from acryloyl chloride and the enamine (XI; R^1 = PhCH$_2$, R^2 = R^3 = Me) [method (A)] (Found: C, 74·3; H, 7·5; N, 5·5%; *M*+, 243. $C_{15}H_{17}NO_2$ requires C, 74·1; H, 7·0; N, 5·8%; *M*, 243), $\nu_{max.}$ (film) 1680br and 1600br cm^{-1}, $\lambda_{max.}$ 294·5 nm (ε 9800), τ (CCl$_4$) 7·86 and 7·8 (6H, s, 2 × Me), 7·46 (4H, s, 2 × CH$_2$), 5·03 (2H, s, PhC*H*$_2$), and 2·75 (5H, m, Ph).

Ethyl 1-benzyl-1,2,3,4-tetrahydro-6-methyl-2-oxopyridine-5-carboxylate (XVI; R^1 = PhCH$_2$, R^2 = Me, R^3 = OEt) was obtained (42%) from acryloyl chloride and the enamine (XI; R^1 = PhCH$_2$, R^2 = Me, R^3 = OEt) [method (A)], m.p. 74—75° [from light petroleum (b.p. 60—80°)] (Found: C, 70·4; H, 6·8; N, 4·6%; *M*+, 273. $C_{16}H_{19}NO_3$ requires C, 70·3; H, 7·0; N, 5·1%; *M*, 273), $\nu_{max.}$ (Nujol) 1700, 1690, and 1625 cm^{-1}, $\lambda_{max.}$ (MeOH) 280 nm (ε 12,000), τ (CCl$_4$) 8·72 (3H, t, *J* 7 Hz, C*H*$_3$·CH$_2$), 7·65 (3H, s, MeC=), 7·42 (4H, s, 2 × CH$_2$), 5·85 (2H, q, *J* 7 Hz, CH$_3$·C*H*$_2$), 5·0 (2H, s, PhC*H*$_2$), and 2·75 (5H, m, Ph).

Ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxopyridine-5-carboxylate (XVI; R^1 = H, R^2 = Me, R^3 = OEt) was obtained (39%) yield from acryloyl chloride and ethyl 3-aminocrotonate [method (A)], m.p. and mixed m.p. 154—156° (from benzene) (lit.,[3b] 156°).

5-Benzoyl-1-benzyl-3,4-dihydro-6-methyl-2(1H)-pyridone (XVI; R^1 = PhCH$_2$, R^2 = Me, R^3 = Ph) was obtained (47%) from acryloyl chloride and the enamine (XI; R^1 = PhCH$_2$, R^2 = Me, R^3 = Ph) [method (A)], m.p. 83° [from light petroleum (b.p. 60—80°)–benzene] (Found: C, 78·6; H, 6·3; N, 4·4%; *M*+, 305. $C_{20}H_{19}NO_2$ requires C, 78·7; H, 6·2; N, 4·6%; *M*, 305), $\nu_{max.}$ (Nujol) 1690, 1650, and 1605 cm^{-1}, τ (CCl$_4$) 8·1 (3H, s, MeC=), 7·4 (4H, s, 2 × CH$_2$), 5·0 (2H, s, PhC*H*$_2$), and 2·9—2·2 (10H, m, 2 × Ph).

Ethyl 1-benzyl-1,2,3,4-tetrahydro-2-oxo-6-phenylpyridine-5-carboxylate (XVI; R^1 = PhCH$_2$, R^2 = Ph, R^3 = OEt) was obtained (50%) from acryloyl chloride and the enamine (XI; R^1 = PhCH$_2$, R^2 = Ph, R^3 = OEt) [method (A)],

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[19] B. O. Linn and C. R. Hauser, *J. Amer. Chem. Soc.*, 1956, **78**, 6066.
[20] P. W. Hickmott and J. R. Hargreaves, *Tetrahedron*, 1967, **23**, 3151.

m.p. 84—85° [from light petroleum (b.p. 60—80°)–benzene] (Found: N, 3·8%; M^+, 335. $C_{21}H_{21}NO_3$ requires N, 4·2%; M, 335), $\nu_{max.}$ (Nujol) 1680br, 1620, and 1600 cm^{-1}, τ ($CDCl_3$) 9·17 (3H, t, J 7 Hz, $CH_3{\cdot}CH_2$), 7·2 (4H, s, 2 × CH_2), 6·1 (2H, q, J 7 Hz, $CH_3{\cdot}CH_2$), 5·35 (2H, s, $PhCH_2$), and 3·2—2·5 (10H, m, 2 × Ph).

Ethyl 1-benzyl-1,2,3,4-tetrahydro-4,6-dimethyl-2-oxopyridine-5-carboxylate (VIII) was obtained (50%) from crotonoyl chloride and the enamine (XI; R^1 = $PhCH_2$, R^2 = Me, R^3 = OEt) [method (A)], m.p. 85—86° [from light petroleum (b.p. 60—80°)] (Found: N, 4·8%; M^+, 287. $C_{17}H_{21}NO_3$ requires N, 4·9%; M, 287), $\nu_{max.}$ (Nujol) 1690, 1675, and 1610 cm^{-1}, $\lambda_{max.}$ (MeOH) 283 nm (ε 10,900), τ (CCl_4) 8·93 (3H, d, J 7 Hz, $CH_3{\cdot}CH$), 8·72 (3H, t, J 7 Hz, $CH_3{\cdot}CH_2$), 8·3—6·8 (complex, methylene envelope), 7·63 (s, MeC=), 5·83 (q, J 7 Hz, $CH_3{\cdot}CH_2$), 5·25 and 4·73 (d, J 16 Hz, $PhCH_2$), and 2·75 (s, Ph).

The same product was obtained in 14% yield by method (B); the enamine was heated under reflux for 18 h with crotonic acid in chlorobenzene. When benzene was used as solvent, only unchanged starting material was isolated.

5-Benzoyl-1-benzyl-3,4-dihydro-6-methyl-4-phenyl-2(1H)-pyridone (IX) was obtained (30%) from cinnamoyl chloride and the enamine (XI; R^1 = $PhCH_2$, R^2 = Me, R^3 = Ph) [method (A)] (Found: N, 3·5%; M^+, 381. $C_{26}H_{23}NO_2$ requires N, 3·7%; M, 381), $\nu_{max.}$ (Nujol) 1649, 1625, and 1600 cm^{-1}, τ (CCl_4) 7·83 (s, MeC=), 7·28 (m, CH_2), 5·9 and 5·05 (d, J 16·5 Hz, $PhCH_2$), 5·35 (m, PhCH), and 2·78 (3 × Ph).

Ethyl 1-cyclohexyl-1,2,3,4-tetrahydro-6-methyl-2-oxopyridine-5-carboxylate (XVI; R^1 = C_6H_{11}, R^2 = Me, R^3 = OEt) was obtained (61%) from acryloyl chloride and the enamine (XI; R^1 = C_6H_{11}, R^2 = Me, R^3 = OEt) [method (A)], m.p. 56—58° (Found: N, 5·1%; M^+, 265. $C_{15}H_{23}NO_3$ requires N, 5·3%; M, 265), $\nu_{max.}$ (film) 1700sh, 1680, and 1615 cm^{-1}, τ ($CDCl_3$) 8·7 (t, $CH_3{\cdot}CH_2$), 9·0—7·9 (m, ring CH_2), 7·53 (s, MeC=), 6·37 (m, CH·N), and 5·75 (q, $CH_3{\cdot}CH_2$).

U.v. and i.r. spectra were determined with Unicam SP 800A and Perkin-Elmer 257 spectrophotometers, respectively, and ^{1}H n.m.r. and mass spectra with Varian A60 and A.E.I. MS12 instruments, respectively.

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