Cyclisation Reactions of α-Hydroxy-imidates with Oxalyl Chloride and *NN'*-Dicyclohexylcarbodi-imide

By **Mohammed I. Butt, Douglas G. Neilson,*** and **Kathleen M. Watson,** Department of Chemistry, The University, Dundee
Roy Hull, I.C.I. Pharmaceuticals Ltd., Mereside, Alderley Park, Macclesfield, Cheshire

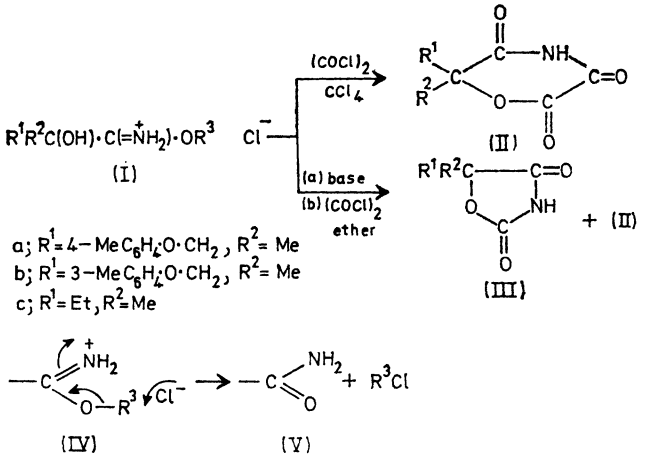
α-Hydroxy-imidate salts reacted with oxalyl chloride to form morpholine-2,3,5-triones, whereas the free bases gave oxazolidine-2,4-diones with the same reagent. Although imidate bases did not react with *NN'*-dicyclohexylcarbodi-imide, their salts gave 2-cyclohexylimino-oxazolidin-4-ones.

IMIDATES and their salts are useful intermediates in the synthesis of a wide variety of heterocyclic systems.[1,2] However, even when a second functional group, *e.g.* an α-hydroxy-group, is present, these cyclisation reactions involve the imidate grouping [–C(=NH)·OR] almost exclusively. Thus, mandelimidates (I; R^1 = Ph, R^2 = H) have been converted into imidazolines [3] and tetrahydropyrimidines [4] by interaction with ethane- and propane-diamines. This paper describes novel cyclisation reactions involving condensation of both the imidate and hydroxy-functions of compounds of type (I) with oxalyl chloride and *NN'*-dicyclohexylcarbodi-imide. The imidate salts (I) are readily available from the corresponding cyanohydrins *via* Pinner syntheses.[1,2]

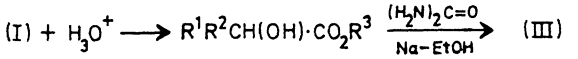
Oxalyl Chloride.—The interaction of oxalyl chloride with imidates led to different products depending on the conditions. Thus the imidate salts (Ia—c), when warmed as a slurry in carbon tetrachloride containing oxalyl chloride, yielded the novel morpholine-2,3,5-triones (IIa—c). These amide-type products (II) can arise by nucleophilic attack of halide ion on the alkoxy-group of the imidate cation [(IV) ⟶ (V)].[1,2] However, attempts to obtain related compounds from the direct action of oxalyl chloride on α-hydroxy-amides were not

[1] R. Roger and D. G. Neilson, *Chem. Rev.*, 1961, **61**, 179.
[2] D. G. Neilson in ' The Chemistry of Amidines and Imidates,' ed. S. Patai, Wiley, New York, 1975, p. 385.
[3] N. W. Bristow, *J. Chem. Soc.*, 1957, 513.
[4] D. G. Neilson, I. A. Khan, and R. S. Whitehead, *J. Chem. Soc.* (*C*), 1968, 1853.

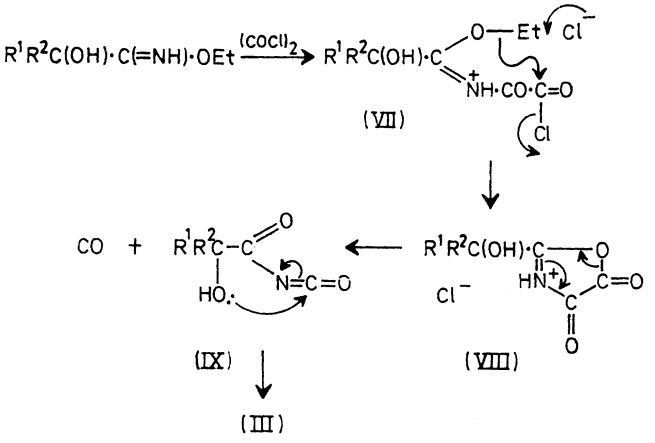
generally successful, although *N*-phenylmandelamide yielded 4,6-diphenylmorpholine-2,3,5-trione.



On the other hand, when an imidate free base (Ia; as base) was treated with oxalyl chloride in ether, the main product was the oxazolidine-2,4-dione (IIIa), and compound (IIa) was a minor component. The dione (IIIa) was unambiguously synthesised [5] by the action of urea on the ester (VIa) obtained by hydrolysis of the imidate salt (Ia). Imidates are known to yield acyl isocyanates [6] on treatment with oxalyl chloride. One possible



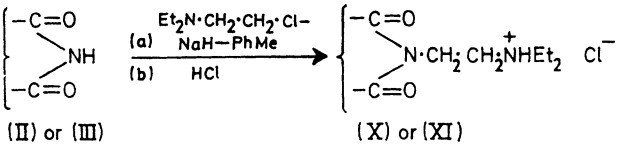
mechanistic route to products of type (III) based on this fact [6] and on related reactions on amides studied by Speziale and his co-workers [7-9] is detailed in Scheme 1.



SCHEME 1

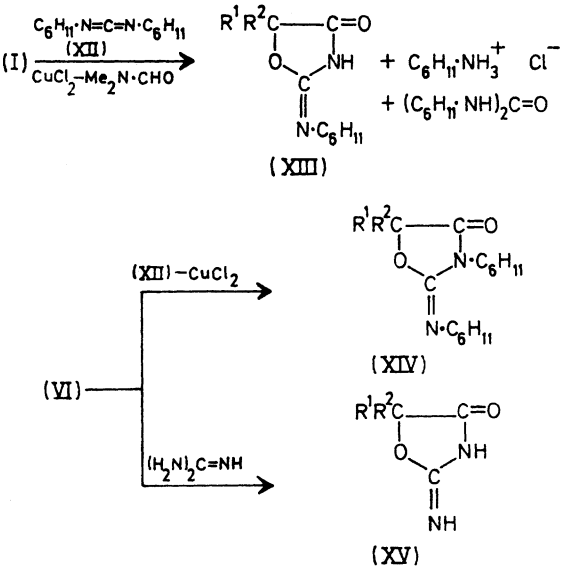
This involves acylation of the imidate to yield a salt of type (VII), which decomposes *via* a cyclic intermediate (VIII) into an acyl isocyanate (IX) with loss of carbon monoxide. The isocycanate (IX) then undergoes intramolecular cyclisation to give an oxazolidine-2,4-dione (III).

As expected, the 4-imino-group of the 2,3,5-trione (IIa) could be readily alkylated, *e.g.* with β-diethylaminoethyl chloride in toluene containing sodium hydride; a related reaction was carried out on the oxazolidine-2,4-diones (IIIa and b) (see Scheme 2).



SCHEME 2

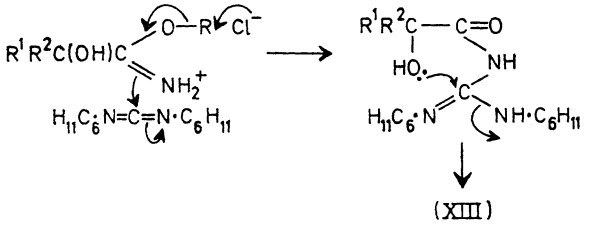
NN′-*Dicyclohexylcarbodi-imide*.—The imidate hydrochlorides (Ia and b) when treated with the di-imide (XII) and catalytic amounts of copper(II) chloride yielded a mixture of *NN*′-dicyclohexylurea, cyclohexylamine hydrochloride, and the corresponding 2-cyclohexyliminooxazolidin-4-one (XIIIa or b). Imidate free bases did not react with compound (XII) under similar conditions.



That the condensation of an imidate salt and the di-imide (XII) involved the loss of a cyclohexylimino-group from (XII) was clearly illustrated by the isolation of cyclohexylamine hydrochloride and by synthesis [10] of the dicyclohexyl compound (XIVa) from the ester (VIa) and the di-imide (XII). The related compound (XVa) was also prepared [11] from guanidine and the ester (VIa) for spectral comparison. Thus the reaction of an α-hydroxy-imidate salt with the di-imide appears to parallel closely that described for an amino-alcohol and

[5] R. W. Stoughton, *J. Amer. Chem. Soc.*, 1941, **63**, 2376.
[6] L. I. Samarai, V. P. Belaya, O. V. Vishnekskii, and G. I. Derkach, *Zhur. org. Khim.*, 1970, **6**, 85.
[7] A. J. Speziale and L. R. Smith, *J. Org. Chem.*, 1962, **27**, 3742.
[8] A. J. Speziale and L. R. Smith, *J. Org. Chem.*, 1963, **28**, 1805.
[9] A. J. Speziale, L. R. Smith, and J. E. Fedder, *J. Org. Chem.*, 1965, **30**, 4306.
[10] E. Schmidt and W. Carl, *Annalen*, 1961, **639**, 24.
[11] W. Traube and R. Ascher, *Ber.*, 1913, **46**, 2080.

the di-imide,[12] as this also results in loss of amine from the di-imide. One possible mechanistic pathway involving amide formation [1,2] from the imidate salt, attack on the di-imide, and subsequent cyclisation of a guanidine intermediate, is illustrated in Scheme 3.



SCHEME 3

EXPERIMENTAL

N.m.r. spectra were determined with a Varian A60 instrument (tetramethylsilane as internal reference). I.r. spectra for Nujol mulls were recorded with a Perkin-Elmer 157 spectrophotometer.

Preparation of Imidate Hydrochlorides (I).—4-Tolyloxyacetone (82 g, 0.5 mol), b.p. 125—130° at 20 mmHg (lit.,[13] 108—112° at 6 mmHg), sodium hydrogen sulphite solution (40% w/w; 150 ml), and ether (200 ml) were stirred at room temperature for 12 h. The hydrogen sulphite adduct was filtered off, washed with ether, and dissolved in a solution of sodium cyanide (25 g, 0.5 mol) in water (200 ml) at 0 °C. The cyanohydrin (63.7 g, 67%) was extracted with ether, dried ($MgSO_4$), and used without further purification (after removal of ether *in vacuo*) to give the imidate hydrochloride (Ia; R^3 = Et) (45.6 g, 67%), m.p. 153—154°, by a Pinner synthesis.[1,2] The imidate salt (Ib; R^3 = Et), m.p. 138—139°, was prepared similarly from 3-tolyloxyacetone. The imidate hydrochloride (Ic; R^3 = Et) had m.p. 93° (lit.,[14] 98°).

Reaction of Oxalyl Chloride with Imidate Hydrochlorides.—Oxalyl chloride (1.3 g, 0.01 mol) in carbon tetrachloride (20 ml) was added to a stirred suspension of the imidate salt (Ia) (2.7 g, 0.01 mol) in carbon tetrachloride (20 ml). The mixture was warmed at 55 °C for 2 h. Removal of solvent *in vacuo* left 6-*methyl*-6-(4-*tolyloxymethyl*)*morpholine*-2,3,5-*trione* (IIa) (1.2 g, 51%), m.p. 147—148° [from petrol (b.p. 40—60°)–chloroform], $\nu_{max.}$ 3 170, 3 070 (NH), 1 775, and 1 710 cm^{-1} (C=O), δ (CD_3OD), 1.75 (3 H, s, 6-Me), 2.2 (3 H, s, ArMe), 4.1—4.4 (2 H, dd, CH_2, prochiral), and 6.7—7.1 (4 H, dd, Aryl) (Found: C, 59.1; H, 4.9; N, 5.3. $C_{13}H_{13}NO_5$ requires C, 59.2; H, 4.9; N, 5.3%).

The trione (IIb) was obtained as a sticky solid when the imidate salt Ib was treated similarly; *m/e* 263 (M^+), $\nu_{max.}$ 3 200, 3 070 (NH), 1 775, and 1 725 cm^{-1} (C=O), δ ($CDCl_3$) 1.7 (3 H, s, 6-Me), 2.25 (3 H, s, ArMe), 3.95—4.4 (2 H, dd, CH_2, prochiral), 6.5—7.4 (4 H, m, ArH), and 9.9 (1 H, s, NH).

Similar treatment of the salt (Ic) yielded the *trione* (IIc) (56%), m.p. 133—134° [from petrol (b.p. 60—80°)–ethyl acetate], $\nu_{max.}$ 3 170, 3 070 (NH), 1 760, and 1 720 cm^{-1} (C=O), δ [$(CD_3)_2CO$] 1.0 (3 H, t, $CH_2{\cdot}CH_3$), 1.75 (3 H, s, CH_3), and 1.9—2.3 (2 H, m, CH_2, prochiral) (Found: C, 48.9; H, 5.2; N, 8.1. $C_7H_9NO_4$ requires C, 49.1; H, 5.3; N, 8.2%).

Reaction of Oxalyl Chloride with the Imidate Base (Ia; *as base*).—The imidate salt (Ia) (2.4 g, 0.01 mol) was stirred with triethylamine [2] (1.0 g, 0.01 mol) in dry ether (25 ml) at room temperature for 5 min. Solid was then filtered off and oxalyl chloride (1.3 g, 0.01 mol) in dry ether (20 ml) was added slowly to the imidate base so formed. The mixture was stirred at room temperature (2 h) and the resultant precipitate (1.3 g) filtered off. This proved to be the imidate salt (Ia). The filtrate was then evaporated *in vacuo* to an oil which yielded a solid, m.p. 127—128° [from petrol (b.p. 40—60°)–ether], shown to be a mixture of compounds (IIa) and (IIIa) (1 : 10) [mixed m.p. with authentic (IIIa) (m.p. 131—132°; see below) 128—129°]. The mass spectrum of compound (IIa) (M^+ 263) included a peak at *m/e* 235 which represented less than 10% of the parent ion, whereas the spectrum of the product of this reaction gave a peak at *m/e* 235 ten times as intense as that at *m/e* 263.

Reaction of Oxalyl Chloride with Amides.—*N*-Phenylmandelamide (2.3 g, 0.01 mol) reacted with oxalyl chloride (1.4 g, 0.01 mol) in ethylene chloride under conditions analogous to those for the imidate salt, to give 4,6-*diphenylmorpholine*-2,3,5-*trione* (2.1 g, 76%), m.p. 207—208° (from acetone), $\nu_{max.}$ 1 760 and 1 690 cm^{-1} (C=O), δ[$(CD_3)_2SO$] 6.55 (1 H, s, CH) and 7.2—7.9 (10 H, m, ArH) (Found: C, 68.6; H, 3.9; N, 5.0. $C_{16}H_{11}NO_4$ requires C, 68.3; H, 3.9; N, 5.0%).

Mandelamide under similar conditions did not react with oxalyl chloride in carbon tetrachloride.

Reaction of Esters with Urea.[5]—The imidate hydrochloride (Ia) (10 g) was warmed in water (30 ml) at 50 °C for 5 min, and the solution was extracted with ether. The dried extract ($MgSO_4$) gave the ester (VIa) (8.0 g, 0.033 mol), which was refluxed for 11 h with urea (2.0 g, 0.033 mol) in ethanol (25 ml) in which sodium (0.8 g, 0.033 mol) had been dissolved. Most of the ethanol was then removed *in vacuo* and the residue diluted with water before extraction with ether to remove unchanged ester. The aqueous solution was acidified, then extracted with ether to give 5-*methyl*-5-(4-*tolyloxymethyl*)*oxazolidine*-2,4-*dione* (IIIa) (4.2 g, 52%), m.p. 132—133° (from methanol) (Found: C, 61.1; H, 5.6; N, 6.0. $C_{12}H_{13}NO_4$ requires C, 61.3; H, 5.6; N 6.0%).

The ester (VIb), similarly treated, yielded the *dione* (IIIb) (51%), m.p. 94—95° (from toluene) (Found: C, 61.4; H, 5.6; N, 5.9%).

Alkylation of Morpholine and Oxazolidone Imino-groups.—The morpholinetrione (IIa) (0.6 g, 0.025 mol) and *N*-(2-chloroethyl)diethylamine hydrochloride (0.4 g, 0.025 mol) were refluxed in dry toluene containing sodium hydride (0.2 g) for 18 h. Undissolved solid was then filtered off and toluene distilled off under vacuum. Treatment of the residual oil in ether solution with hydrogen chloride gave the *N-alkyl product* (Xa) (0.5 g, 55%), m.p. 148—149° (from ethyl acetate–methanol), $\nu_{max.}$ 2 450 (+NH), 1 770, 1 700, and 1 630 cm^{-1} (C=O), δ [$(CD_3)_2SO$] 1.25 (6 H, t, $CH_3{\cdot}CH_2$), 1.5 (3 H, s, Me), 2.2 (3 H, s, ArMe), 2.9—4.4 (13 H, m, 5 × CH_2 and of $CH_3{\cdot}OH$), and 6.7—7.3 (4 H, dd, ArH) (Found: C, 56.1; H, 7.3; N, 6.4. $C_{19}H_{27}ClN_2O_5,CH_3OH$ requires C, 55.7; H, 7.2; 6.5%).

Similar treatment of the oxazolidinediones (IIIa and b) yielded the corresponding *N-alkyl diones* (XIa) (50%), m.p. 149—150° (Found: C, 58.6; H, 7.3; N, 7.5%) and (XIb) (62%), m.p. 148—149° (Found: C, 58.5; H, 7.3; N, 7.5. $C_{18}H_{27}ClN_2O_4$ requires C, 58.6; H, 7.3; N, 7.6%). Com-

[12] B. Aldcock, A. Lawson, and D. H. Myles, *J. Chem. Soc.*, 1961, 5120.

[13] A. M. Dowell, jun., H. S. McCullough, and P. R. Calaway, *J. Amer. Chem. Soc.*, 1948, **70**, 226.

[14] A. B. Sen and K. Shanker, *J. prakt. Chem.*, 1965, **29**, 309.

pound (XIb) had $\nu_{max.}$ 2 400 ($^{+}$NH), 1 820, and 1 730 cm^{-1} (C=O), δ [$(CD_3)_2SO$] 1.25 (6 H, t, CH_3·CH_2), 1.65 (3 H, s, Me), 2.25 (3 H, s, ArMe), 2.9—3.5 (8 H, m, N·CH_2), 3.7—4.1 (2 H, dd, O·CH_2, prochiral), and 6.6—7.0 (4 H, m, ArH).

Reaction of Dicyclohexylcarbodi-imide with Imidate Salts.—The imidate hydrochloride (Ia) (2.7 g, 0.01 mol), dicyclohexylcarbodi-imide (XII) (4.1 g, 0.02 mol) and copper(II) chloride (0.1 g) were stirred together in dry dimethylformamide (25 ml) for 3 days at room temperature. Solid (1.1 g), removed by filtration, proved to be dicyclohexylurea. Most of the dimethylformamide was removed *in vacuo* and dry ether was added. The resultant solid mixture on recrystallisation from ethyl acetate–methanol gave cyclohexylamine hydrochloride (0.5 g) and *2-cyclohexylimino-5-methyl-5-(4-tolyloxymethyl)oxazolidin-4-one* (XIIIa) (1.1 g, 35%), m.p. 202—203° (Found: C, 68.2; H, 7.6; N, 8.8. $C_{18}H_{24}N_2O_3$ requires C, 68.4; H, 7.6; N, 8.9%), $\nu_{max.}$ 1 750 (C=O) and 1 660 cm^{-1} (amidine), δ [$(CD_3)_2SO$] 1.4 (3 H, s, Me), 1.0—2.0 (11 H, m, C_6H_{11}), 2.2 (3 H, s, ArMe), 4.1 (2 H, s, CH_2), and 6.6—7.3 (4 H, dd, ArH).

Similar treatment of compound (Ib) gave the *oxazolidone* (XIIIb) (33%), m.p. 167—168° (Found: C, 68.5; H, 7.8; N, 7.0%), $\nu_{max.}$ 1 740 (C=O) and 1 660 cm^{-1} (amidine).

No useful products were characterised from the interaction of imidate bases and compound (XII).

Reaction of Dicyclohexylcarbodi-imide and the Ester (VIa).—The imidate hydrochloride (Ia) was warmed in water as above. The resultant ester (VIa) (5.6 g, 0.025 mol), compound (XII) (10.3 g, 0.05 mol), and copper(II) chloride (0.1 g) in dry acetone (40 ml) were stirred at room temperature for 24 h. Volatile material was removed by distillation *in vacuo* and the residue recrystallised from methanol to give *3-cyclohexyl-2-cyclohexylimino-5-methyl-5-(4-tolyloxymethyl)oxazolidin-4-one* (XIVa) (2.9 g, 32%), m.p. 110—111° (Found: C, 72.3; H, 8.5; N, 7.1. $C_{24}H_{34}N_2O_3$ requires C, 72.3; H, 8.6; N, 7.0%), $\nu_{max.}$ 1 755sh (C=O), 1 690br, and 1 650sh cm^{-1} (amidine), δ (CCl_4) 1.45 (3 H, s, Me), 1.0—2.0 (22 H, m, C_6H_{11}), 2.3 (3 H, s, ArMe), 4.0—4.2 (2 H, dd, O·CH_2, prochiral), and 6.7—7.2 (4 H, dd, ArH).

Reaction of Guanidine with the Ester (VIa).—The ester (VIa) (17.9 g, 0.08 mol) obtained from the imidate salt (Ia) (see above) was refluxed with guanidine hydrochloride (7.7 g, 0.08 mol) and potassium hydroxide (4.5 g, 0.08 mol) in ethanol (100 ml) for 1 h. Water (300 ml) was then added and the mixture kept at 0 °C for 18 h to precipitate *2-imino-5-methyl-5-(4-tolyloxymethyl)oxazolidin-4-one* (XVa) (3.0 g, 15%), m.p. 233—235° (from aqueous ethanol) (Found: C, 61.7; H, 6.0; N, 12.0. $C_{12}H_{14}N_2O_3$ requires C, 61.5; H, 6.0; N, 12.0%), $\nu_{max.}$ 3 150sh (NH) and 1 660 cm^{-1} (amidine), δ [$(CD_3)_2SO$] 1.4 (3 H, s, Me), 2.25 (3 H, s, ArMe), 4.2 (2 H, s, CH_2), 6.7—7.3 (4 H, dd, ArH), and 8.5 (1 H, s, NH).

One of us (M. I. B.) is indebted to the S.R.C. for a C.A.P.S. studentship. We thank the Physical Methods Section, I.C.I. Ltd., Pharmaceuticals Division, Alderley Park, for analytical determinations.

[5/1843 *Received*, 24*th September*, 1975]