Adducts from Acyl Chlorides and 2-Unsubstituted Oxazolines: Formation and Reactions

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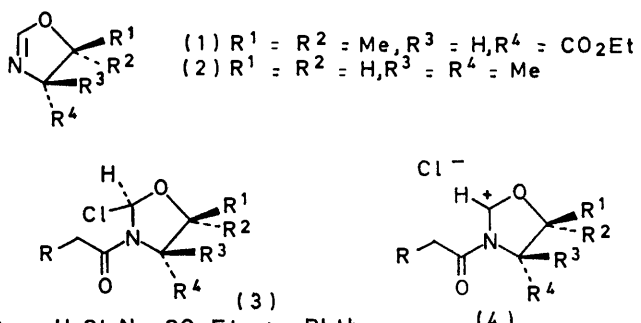
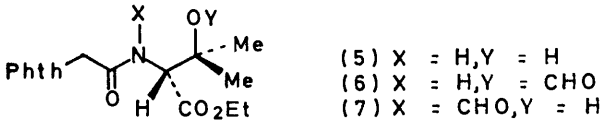
Several acyl chlorides react rapidly with both ethyl 5,5-dimethyl-Δ^2-oxazoline-4-carboxylate (1) and 4,4-dimethyl-Δ^2-oxazoline (2) to give 1:1 adducts [(3) $\rightleftharpoons$ (4)], which readily react with bases or nucleophiles. Products have been characterised from reactions of these adducts with anhydrous triethylamine [*e.g.* (2) ⟶ (12) + (14)], wet triethylamine [*e.g.* (1) ⟶ (5) + (6)], and methanolic triethylamine [*e.g.* (1) ⟶ (8)]. Under a variety of anhydrous conditions, no evidence was obtained for the formation of β-lactams from acyl chlorides with either oxazoline (1) or (2) in the presence of triethylamine.

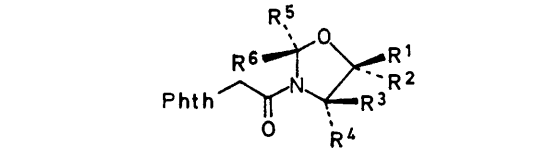
A STANDARD route to β-lactams involves the reaction between an imine and an acyl chloride in the presence of triethylamine.[1] Available evidence [2] favours a non-concerted pathway, *viz.* the intermediacy of a dipolar intermediate. This approach has been used to synthesise 6-*epi*-penicillins from a thiazoline [3] and cephalosporins from a thiazine.[4] An attractive starting material for the synthesis of oxapenams † with penicillin-like substituents in this way is the readily available [5] ethyl 5,5-dimethyl-Δ^2-oxazoline-4-carboxylate (1). We have therefore investigated reactions of this oxazoline and also of 4,4-dimethyl-Δ^2-oxazoline (2) with several acyl chlorides under a variety of conditions.

With rigorous exclusion of water and at high dilution, treatment of the oxazoline (1) or (2) with triethylamine and either phthalimidoacetyl chloride or azidoacetyl chloride failed to give any β-lactam,† as judged by i.r. spectroscopy under the following conditions: (i) addition of the acyl chloride to a mixture of the oxazoline and triethylamine at either room temperature or −80 °C; (ii) addition of triethylamine to a mixture of the acyl chloride and oxazoline at room temperature or −80 °C; (iii) addition of triethylamine to azidoacetyl chloride at −80 °C under nitrogen, and transfer of the resulting solution to a solution of the oxazoline (1) at −80 °C. (*N.B.* 1 mol. equiv. of each reactant was used in the above experiments. In reactions performed at −80 °C the mixture was eventually allowed to warm to room temperature.) We therefore proceeded to examine the chemistry of species formed under the above conditions.

Adducts from the Oxazolines (1) *and* (2) *with Acyl Chlorides.*—When the oxazoline (1) was mixed with an equimolar amount of an acetyl chloride (RCH_2·COCl; R = H, Cl, CO_2Et, N_3, or phthalimido) in $CDCl_3$ or CCl_4 in an n.m.r. tube, a rapid reaction ensued and the resulting n.m.r. spectrum was consistent with the formation of an *N*-acyl-2-chloro-oxazolidine (3) as the principal product [*e.g.* the n.m.r. spectrum of (1) + $ClCH_2$·COCl in CCl_4 shows signals at δ 1·42 (3H, s, ring Me), 1·71 (3H, s, ring Me), 4·33 (2H, s, $ClCH_2$), 4·45 (1H, s, H-4), and 7·67 (1H, s, H-2), and ester signals]. The oxazoline (2) behaved similarly in $CDCl_3$ (with RCH_2·COCl where R = H, Cl, N_3, or phthalimido) [*e.g.* the n.m.r. spectrum of (2) + $ClCH_2$·COCl in $CDCl_3$ shows signals at δ 1·58 (6H, s, Me_2), 4·20 (2H, s, $ClCH_2$), 4·31 (2H, s, 2 × H-4),







N.B. All compounds discussed in this paper are racemic mixtures.

and 7·60 (1H, s, H-2)]. The interpretation given is consistent with the subsequent chemical reactions of the

† We have prepared a simple oxapenam (B. T. Golding and D. R. Hall, *J.C.S. Chem. Comm.*, 1973, 293) and have shown it to be stable to triethylamine under the conditions (*i.e.* temperature and duration) of reactions (i)—(iii).

[1] J. C. Sheehan, E. L. Buhle, E. J. Corey, G. D. Laubach, and J. J. Ryan, *J. Amer. Chem. Soc.*, 1950, **72**, 3828.

[2] R. Gompper, *Angew. Chem. Internat. Edn.*, 1969, **8**, 312; A. Gomes and M. M. Joullié, *Chem. Comm.*, 1967, 935; J. Decazes, J. L. Luche, and H. B. Kagan, *Tetrahedron Letters*, 1970, 3655.

[3] A. K. Bose, G. Spiegelman, and M. S. Manhas, *J. Amer. Chem. Soc.*, 1968, **90**, 4506; *J. Chem. Soc.* (*C*), 1971, 2468.

[4] R. W. Ratcliffe and B. G. Christensen, *Tetrahedron Letters*, 1973, 4645, 4649, 4653.

[5] D. Hoppe and U. Schollkopf, *Annalen*, 1972, **763**, 1.

mixtures (see below). Furthermore, the formation of covalent and/or ionic adducts from acyl chlorides and simple imines, as well as characterisation of *N*-acyloxazolinium fluoroborates from cyclisation of 2-(diacylamino)-ethyl chlorides with silver tetrafluoroborate, has been reported.[6,7] However, the actual situation may be more complex for the following reasons. (i) The diastereotopic methylene protons and *gem*-dimethyl group in the adduct from the oxazoline (2) should have different chemical shifts. In no case is this observed, whereas in the spectra of compounds (10) and (11) the expected spectral non-equivalence of their diastereotopic methylene protons and methyl groups is observed. (ii) The resonance due to H-2 in the spectra of *N*-acyl-2-methoxyoxazolidines [*e.g.* (8) and (11)] appears at *ca.* δ 6·2. On the *rough* basis of Shoolery's Effective Shielding Constants (for Cl, $\sigma_{eff} = 2{\cdot}53$ p.p.m.; for OR, $\sigma_{eff} = 2{\cdot}36$ p.p.m.)[8] the resonance due to H-2 in *N*-acyl-2-chloro-oxazolidines (3) ought not to be as low as δ 7·6—7·7. These points may be explained by postulating that the oxazolidine (3) is in equilibrium with a small amount of ionic adduct (4).

On mixing acyl chlorides with the oxazoline (2) in CCl_4, a white precipitate appeared, so no n.m.r. measurements were made. Adducts of oxazolines (1) and (2) with cyanoacetyl chloride and benzoyl chloride were also investigated, but the n.m.r. spectra are not readily interpretable.

Heating to 60 °C a solution (in $CDCl_3$) of the adduct from chloroacetyl chloride and the oxazoline (2) caused irreversible changes in the n.m.r. spectrum, which we ascribe to the formation of 2-(2-chloro-*N*-formylacetamido)-2-methylpropyl chloride.[9]

Reactions of the Adducts of the Oxazolines (1) *and* (2) *with Acyl Chlorides.*—The adducts from the oxazolines (1) and (2) with acyl chlorides are very susceptible to hydrolysis, especially in the presence of triethylamine, giving products derived from kinetically controlled attack of water (or hydroxide ion) at C-2, followed by irreversible prototropy. For example, treating the adduct from the oxazoline (1) and phthalimidoacetyl chloride with 1 mol. equiv. each of water and triethylamine gave the acylamino-alcohol (5) and its *O*-formate (6) (ratio 27 : 73). The structure of each compound follows from its spectral properties (see Experimental section). The former compound probably originates from deformylation of the *N*-formylacylamino-alcohol (7), since the pure *O*-formate (6) is stable to conditions used to produce (5). Even though the n.m.r. spectrum of the adduct(s) formed from the oxazoline (1) and benzoyl chloride cannot be interpreted, hydrolysis of the mixture does give products analogous to (5) and (6). When a mixture of acyl chloride and the oxazoline (1) or (2) is treated with 1 mol. equiv. each of methanol and triethylamine, the sole product is the corresponding *N*-acyl-2-methoxyoxazolidine. These compounds have been fully characterised (see Experimental section) with phthalimidoacetyl chloride as the acyl chloride. The oxazoline (1) gives a mixture of epimeric methoxy-compounds [(8) and (9)] from which one pure epimer was obtained by fractional crystallisation.

These reactions support the assignment of equilibrating structures (3) and (4) to the adducts obtained from the oxazoline (1) or (2) with acyl chlorides (see above).

Addition of 1 mol. equiv. of triethylamine to a dilute solution containing equimolar amounts of phthalimidoacetyl chloride and the oxazoline (2) in CH_2Cl_2 at room temperature gave, after 30 min, triethylamine hydrochloride (100%) and another product separated by fractional crystallisation into two compounds. One of these (a 2 : 1 adduct; see below, 10 mol %) is formally derived from two molecules of phthalimidoketen and one molecule of oxazoline; the other (a 1 : 2 adduct; see below, 16 mol %) formally comes from one molecule of phthalimidoketen and two of oxazoline. When a mixture containing 1 mol. equiv. each of phthalimidoacetyl chloride and the oxazoline (2) was treated with a mixture of 1 mol. equiv. each of triethylamine and the oxazoline (2), the yields of products were 0 (2 : 1 adduct) and 52 mol % (isolated 1 : 2 adduct). By treating 2 mol. equiv. of phthalimidoacetyl chloride and 1 mol. equiv. of the oxazoline (2) with 2 mol. equiv. of triethylamine, 28 mol % of 2 : 1 adduct was obtained, accompanied by a trace of 1 : 2 adduct. Analogous reactions involving the oxazoline (1) gave a 2 : 1 adduct, but a corresponding 1 : 2 adduct was not obtained.

Structure of the 1 : 2 *adduct from the oxazoline* (2). The 1 : 2 adduct derived from the oxazoline (2) is 2-(4,4-dimethyl-Δ^2-oxazolin-2-yl)-4,4-dimethyl-*N*-phthalimidoacetyloxazolidine (12) as shown by spectral data (see Experimental section; *e.g.* its n.m.r. spectrum clearly shows the presence of an oxazoline and an oxazolidine ring) and its degradation in methanolic sulphuric acid. This reaction gave a small amount of methyl phthalimidoacetate and a moderate yield of an ester to which is assigned structure (10). A study of the temperature-dependence of the n.m.r. spectrum of (10) shows the presence of rotamers (10*a* and *b*) at −20 °C, but an averaged spectrum at + 60 °C (data in Experimental section) due to sufficiently rapid rotation about the N–CO bond at this temperature.

Structure of 2 : 1 *adducts* (13) *from the oxazoline* (1); (14) *from the oxazoline* (2). The n.m.r. spectrum of the 2 : 1 adduct (14) derived from the oxazoline (2) shows, in addition to different phthalimido multiplets (total 8H), singlet resonances for the *gem*-dimethyl group (6H), ring methylene protons (2H), and phthalimido-CH_2CO protons (2H), and a one-proton singlet at δ 7·21. The i.r. spectrum shows a very strong band at 1725 and a weaker band at 1775 cm^{-1} due to the phthalimido-groups. There is also a very weak absorption at

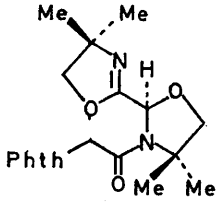
[6] T. C. James and C. W. Judd, *J. Chem. Soc.*, 1914, **105**, 1427; H. Böhme, S. Ebel, and K. Hartke, *Chem. Ber.*, 1965, **98**, 1463; A. K. Bose, G. Spiegelman, and M. S. Manhas, *Tetrahedron Letters*, 1971, 3167; D. A. Nelson, *J. Org. Chem.*, 1972, **37**, 1447.

[7] D. A. Tomalia and J. N. Paige, *J. Org. Chem.*, 1973, **38**, 422.

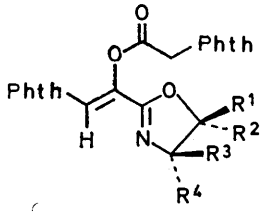
[8] L. M. Jackman, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' MacMillan, New York, 1959, p. 59.

[9] E. M. Fry, *J. Org. Chem.*, 1950, **15**, 802.

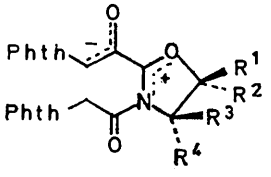
1640 and a pronounced shoulder at 1790 cm^{-1} on the higher frequency phthalimido-band. Comparison of the spectrum of (14) with spectra of known phthalimidoacetyl amides and esters at comparable concentrations



(12)



(13) R^{1-4} as in (1)
(14) R^{1-4} as in (2)



(13a)
(14a)

[taking into account the two phthalimido-groups in (14)] suggests that the higher frequency phthalimido-absorption is stronger than normal in the spectrum of (14) and therefore that it masks a second carbonyl band.

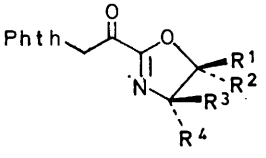
The 2 : 1 adduct (13) from the oxazoline (1) has an i.r. spectrum almost identical with that of (14) except for the presence of a shoulder at 1740 cm^{-1} on the stronger phthalimido-band, due to the ester carbonyl group. The n.m.r. spectrum of (13) shows the signals expected for an analogue of (14), including those for two phthalimido-groups, and also a one-proton singlet at δ 4·52 (C*H*·CO_2Et).

On addition of a slight excess of benzylamine to a solution of the adduct (14) in dichloromethane, an equimolar mixture of *N*-phthalimidoacetylbenzylamine [identified by comparison with authentic material] and 2-phthalimidoacetyl-4,4-dimethyl-Δ^2-oxazoline (15) [identified by spectral data and chemical transformations described below] was rapidly formed. Methyl phthalimidoacetate and the ketone (15) were formed slowly from the adduct (14) in methanol [57% conversion of (14) (0·04 mmol) with methanol (0·15 mmol) in $CDCl_3$ (0·35 ml) after 14 h at 37°]. The reaction between the adduct (14) and benzylamine can be used to advantage in purification of the 1 : 2 adduct (12). If the crude product from the reaction of equimolar quantities of phthalimidoacetyl chloride, the oxazoline (2) and triethylamine is treated with benzylamine to destroy the 2 : 1 adduct (14), isolation of the 1 : 2 adduct (12) is easier.

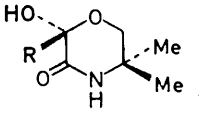
The 2 : 1 adduct (13) derived from the oxazoline (1) also reacted with benzylamine and methanol to give the same derivatives of phthalimidoacetic acid as obtained from the adduct (14), but the ketone (16) analogous to (15) decomposed during chromatography and was only characterised by an n.m.r. spectrum.

From the evidence presented so far, there are two possible structures for the 2 : 1 adduct from the oxazoline (2): the dipolar compound (14a) and the enol ester (14). Similarly, possible structures for the 2 : 1 adduct from the oxazoline (1) are (13a) and (13). Both structures (13) and (14), as well as (13a) and (14a), would be expected to give the observed products with benzylamine and methanol and to have a low-field vinylic singlet in their n.m.r. spectra. The i.r. absorptions of phthalimidoacetate esters are typically *ca.* 10 cm^{-1} to higher wavenumber than normal (*e.g.* methyl phthalimidoacetate: $\nu_{max.}$ 1755 cm^{-1}) and 1780—1790 cm^{-1} would not be an unreasonable value for the enol ester carbonyl absorptions of (13) and (14).

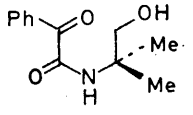
The positions of the resonances corresponding to the C-4 methyl groups and the methylene protons of the oxazoline ring of (14) are very similar to those of the ketone (15). In the presence of an excess of trifluoroacetic acid these signals of (14) are shifted downfield to positions similar to those of corresponding protons in the spectrum of the trifluoroacetate of 4,4-dimethyl-Δ^2-oxazoline. These observations support the enol ester structures (13) and (14) if one assumes that they are *N*-protonated in trifluoroacetic acid. The dipolar structures (13a) and (14a) should suffer *O*-protonation in



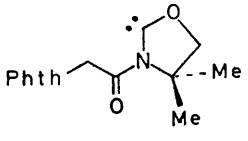
(15) R^{1-4} as in (2)
(16) R^{1-4} as in (1)



(17) R = PhthCH$_2$
(18) R = Ph



(18a)



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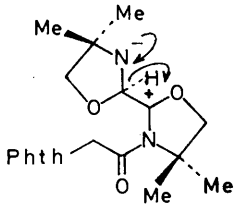

(20)

trifluoroacetic acid, causing n.m.r. shifts different from those observed.

Formation of 2 : 1 adducts from a ketene and an imine has been described,[10] but none of these compounds is

[10] J. C. Martin, V. A. Hoyle, and K. C. Brannock, *Tetrahedron Letters*, 1965, 3589; S. A. Proctor and G. A. Taylor, *J. Chem. Soc.*, 1965, 5877; *J. Chem. Soc.* (*C*), 1967, 1937; R. Huisgen, B. A. Davis, and M. Morikawa, *Angew. Chem. Internat. Edn.*, 1968, **7**, 826; J. C. Martin, K. C. Brannock, R. D. Burpitt, P. Glenn Gott, and V. A. Hoyle, *J. Org. Chem.*, 1971, **36**, 2211; A. Hassner, M. J. Haddadin, and A. B. Levy, *Tetrahedron Letters*, 1973, 1015; M. J. Haddadin and A. Hassner, *J. Org. Chem.*, 1973, **38**, 2650; P. Y. Johnson and J. W. Caldwell, *ibid.*, p. 4465.

structurally analogous to the 2 : 1 adducts described here. We have also investigated a product from treating the oxazoline (2) with azidoacetyl chloride followed by triethylamine. This is probably a 2 : 1 adduct having a structure of different type from (13) or (14) (see ref. 11 for details).

Chemical Studies of 4,4-*Dimethyl*-2-*phthalimidoacetyl*-Δ^2-*oxazoline* (15).—Spectral data supporting structure (15) are given in the Experimental section. The ketone (15) was initially isolated by column chromatography. During a subsequent isolation this compound was left for 48 h on a silica gel plate and on recovery was found to have undergone hydration and rearrangement to 2-hydroxy-5,5-dimethyl-2-phthalimidomethylmorpholin-3-one (17). To confirm this structure the analogue (18) was synthesised from methyl phenylglyoxylate and 2-amino-2-methylpropanol. This compound has been reported [12] to exist in a cyclic structure (18) in the solid state, but tautomerises to the acyclic amide (18a) in methanolic solution. We have found compound (18)/(18a) to dissolve in $CDCl_3$ only on warming: the resultant n.m.r. spectrum reveals only the acyclic form (18a). The compound is more soluble in [$^2H_4$]methanol, and the resulting n.m.r. spectrum is initially that of the cyclic form (18) [AB pattern for methylene protons similar to that observed with (17)]. During 70 min at 37 °C compound (18) is converted into an equilibrium mixture of (18) and (18a) (ratio 71 : 29). The i.r. spectrum of (18)/(18a) taken immediately in CH_2Cl_2 shows the cyclic structure (18) exclusively (no amide II band; ν_{CO} 1675 cm^{-1}), but after being left overnight shows the acyclic form (18a) (amide II band at 1515 cm^{-1}; ν_{CO} 1668 cm^{-1}). Compound (17) exists solely as the cyclic form under all conditions described above.

2-Acyloxazolines such as (15) have not been described before, except for an isolated report [13] of 2-benzoyloxazoline. Attempted synthesis of (15) by treating the 2-anion of 4,4-dimethyl-Δ^2-oxazoline with phthalimidoacetyl chloride gave only 2-isocyano-2-methylpropyl phthalimidoacetate, formed by preferential capture of the acyclic tautomer of the anion by the acyl chloride.

Mechanism of Formation of the Adducts (12)—(14).—We believe that the adduct (14) [and similarly (13)] arises by deprotonation at C-2 of an intermediate *N*-phthalimidoacetyloxazolinium ion [*cf.* (4)] followed by reaction of the derived nucleophilic carbene (19) with a molecule of phthalimidoketen. This reaction gives (14a), which by intramolecular N ⟶ O transfer of a phthalimidoacetyl group produces (14). This behaviour could explain the failure of the reaction between 2-unsubstituted thiazolines and ketens to give good yields of β-lactams, whereas 2-substituted thiazolines, which cannot give a carbenoid species from deprotonation at C-2, do give good yields of β-lactams.[14]

The 1 : 2 adduct (12) may arise by a reaction between the carbene (19) and the oxazoline (2) giving an intermediate (20), which rearranges to (12) by a 1,2-hydride shift.

EXPERIMENTAL

Materials.—Reagent grade dichloromethane was dried over calcium sulphate, distilled from phosphorous pentoxide under nitrogen, and stored in darkness under nitrogen. Tetrahydrofuran (THF) was refluxed over $LiAlH_4$ and distilled from $LiAlH_4$ under nitrogen. Ether, benzene, chloroform (2% ethanol), and ethyl acetate were reagent grade, freshly redistilled. Methanol was AnalaR grade.

Acetyl, benzoyl, and chloroacetyl chloride were commercial products redistilled within 7 days of use.

Ethyl 2-(chloroformyl)acetate was obtained by heating ethyl hydrogen malonate with thionyl chloride (1·2 equiv.) at 60—70 °C for 2 h, followed by fractionation (72%; b.p. 60° at 8 mmHg).

Cyanoacetyl chloride was prepared by adding phosphorus pentachloride (15 g, 75 mmol) in small portions to a stirred, cooled solution of cyanoacetic acid (4·25 g, 50 mmol; predried *in vacuo* over P_2O_5) in dry ether (40 ml), followed by stirring at room temperature until nearly all solid had gone into solution (4 h); after removal of ether, cyanoacetyl chloride was obtained by distillation (67%; b.p. 32—35° at 0·15 mmHg; decomposes within 8 days at 0 °C).

Azidoacetyl chloride was obtained by stirring overnight crude azidoacetic acid [15] with thionyl chloride (1·5 equiv.), followed by fractionation (*caution*!) (72%; b.p. 57—59° at 30 mmHg).

Phthalimidoacetyl chloride was prepared by refluxing phthalimidoacetic acid with thionyl chloride (2·5 equiv.) for 45 min, followed by evaporation of the excess of thionyl chloride and recrystallisation (twice) of the residue from benzene–petroleum (70%; m.p. 84—85°) (stable for at least 6 months over silica gel in desiccator).

Ethyl 5,5-dimethyl-Δ^2-oxazoline-4-carboxylate [5] (1) and 4,4-dimethyl Δ^2-oxazoline [16] (2) were prepared essentially as described (yields 50 and 30%, respectively).

Triethylamine was reagent grade redistilled from Na–Pb alloy. Methyl phthalimidoacetate was prepared as described.[17]

Unless stated otherwise, n.m.r. spectra were taken for 5—10% solutions in $CDCl_3$ and i.r. spectra for 1% solutions in CH_2Cl_2. T.l.c. analyses were carried out on silica gel G/UV_{254} (Machery, Nagel, and Co.). M.p.s were determined for samples in open capillary tubes.

Recording n.m.r. spectra of acyl chloride–oxazoline adducts. N.B. Best results were obtained by preparing reaction mixtures in a dry-box using $CDCl_3$ immediately pre-treated with basic alumina. All liquid compounds were transferred by microsyringes through serum caps: *ca.* 0·5 mmol of the oxazoline was syringed into an n.m.r. sample tube, followed by 0·5 ml of the appropriate solvent ($CDCl_3$ or CCl_4). An equimolar quantity of the acyl chloride was added from a syringe slowly down the side of the tube, the reactants were mixed by partially inverting the tube, and the spectrum was recorded immediately. The spectra in several examples were unchanged after 4 h at 37 °C.

Phthalimidoacetyl chloride was handled by weighing out

[11] D. R. Hall, Ph.D. Thesis, Warwick, 1972, p. 134.
[12] E. Biekert and J. Sonnenbichler, *Chem. Ber.*, 1961, **94**, 2785.
[13] T. Sasaki, T. Yoshioka, and Y. Suzuki, *Bull. Chem. Soc. Japan*, 1971, **44**, 185.
[14] J. C. Sheehan and E. J. Corey, *Org. Reactions*, 1957, **9**, 388.
[15] M. O. Forster and H. E. Fierz, *J. Chem. Soc.*, 1908, **93**, 72.
[16] A. I. Meyers and E. W. Collington, *J. Amer. Chem. Soc.*, 1970, **92**, 6676.
[17] G. B. Crippa and P. Galimberti, *Gazzetta*, 1933, **63**, 81 (*Chem. Abs.*, 1933, **27**, 3463).

rapidly into a sample vial, which was then fitted with a serum cap. The appropriate amount of solvent was added with a syringe, and the solution withdrawn with the same syringe and transferred to the reaction mixture.

2-(2-*Chloro*-N-*formylacetamido*)-2-*methylpropyl Chloride*.—On warming to 60°, the n.m.r. spectrum of a mixture of chloroacetyl chloride and 4,4-dimethyl-Δ^2-oxazoline in $CDCl_3$ changed to that expected for the above-named compound [δ 1·60 (6H, s), 3·91 (2H, s), 4·58 (2H, s), and 8·72 (1H, s)].

Reactions of Acyl Chloride–Oxazoline Adducts with Triethylamine.—*General procedure*. A flask fitted with reflux condenser, nitrogen bubbler, and stirrer was flamed out under a rapid stream of dry nitrogen, then allowed to cool, and the nitrogen flow rate was reduced. The oxazoline (1) or (2) was added by syringe. Triethylamine (1 mmol) and acyl chloride (1 mmol) were weighed into or transferred by syringe to separate vials fitted with serum caps. Dry dichloromethane (10 ml) was added (syringe) to each vial and the resulting solutions were transferred (syringe) to the reaction vessel (first the acyl chloride, then triethylamine). Reactions were monitored by i.r. or t.l.c. analysis. On completion, evaporation left a residue which was extracted with benzene. Filtration removed triethylammonium chloride and evaporation of the filtrate gave crude product which was crystallised or chromatographed.

Great difficulty was experienced over intrusion of moisture in earlier experiments, but by using the above procedure, reaction mixtures were invariably free of acyclic hydrolysis products (no O·CHO singlet at δ *ca.* 8).

2-*Methoxy*-4,4-*dimethyl*-N-*phthalimidoacetyloxazolidine* (11).—The foregoing procedure was used. 4,4-Dimethyl-Δ^2-oxazoline (103 μl, 1 mmol) was added (syringe) to the flask, followed by dichloromethane (10 ml). Phthalimidoacetyl chloride (224 mg, 1 mmol) was quickly weighed into a vial fitted with a serum cap. Dichloromethane (10 ml) was added to the vial by syringe and the solution was withdrawn (syringe) and transferred dropwise to the stirred solution of the oxazoline during *ca.* 3 min. Triethylamine (139 μl, 1 mmol) was placed (syringe) in a vial in a dry box. The vial was fitted with a serum cap and removed from the dry box. Dichloromethane (10 ml) was added, followed by methanol (40 μl, 1 mmol). This mixture was added from a syringe to the stirred acyl chloride–oxazoline mixture dropwise during *ca.* 15 min. The mixture was stirred for 10 min at room temperature, although t.l.c. indicated that reaction occurred almost immediately giving a single product (R_F 0·6 in EtOAc–PhH, 1 : 1). The mixture was evaporated to small bulk, extracted with benzene (25 ml), and filtered through a weighed sinter. Small portions of benzene were used for washing through, and the white crystalline residue was sucked dry [Et_3N,HCl (130 mg, 96%)]. The filtrate was evaporated to give the *oxazolidine* (11), which was crystallised from benzene–petroleum (yield 226 mg, 71%; m.p. 152—155°). A sample twice recrystallised from CCl_4 had m.p. 156°, $\nu_{max.}$ 1775w, 1720vs, and 1680s cm^{-1}; δ 1·44 (3H, s, CH_3), 1·53 (3H, s, CH_3), 3·48 (3H, s, OMe), 3·76 (1H, d, *J* 8·0 Hz, H-5 *cis* to OMe), 3·93 (1H, d with each signal slightly broadened owing to W-coupling to H-2, J_{gem} 8·0 Hz, H-5 *trans* to OMe), 4·29 and 4·47 (2H, AB, *J* 16·7 Hz, $PhthCH_2$), 6·07 (1H, s, H-2), and 7·91 (4H, m, ArH); *m/e* 287 (14%, M^+ — OMe), 188 (15), 161 (45), and 160 (100) (Found: C, 60·2; H, 5·55; N, 8·65. $C_{16}H_{18}N_2O_5$ requires C, 60·35; H, 5·7; N, 8·8%).

Ethyl 2-*Methoxy*-5,5-*dimethyl*-N-*phthalimidoacetyloxazolidine*-4-*carboxylate* [(8) *and* (9)].—These compounds were prepared in a similar manner to compound (11), but from ethyl 5,5-dimethyl-Δ^2-oxazoline-4-carboxylate (1) (158 μl, 1 mmol). The n.m.r. spectrum of the crude product (400 mg) showed two OCH_3 signals, just resolvable at 60 MHz (ratio 5 : 1), but after one crystallisation (benzene–petroleum) only one signal (120 mg, 30%). This *product* [probably (8)] had m.p. 156°, $\nu_{max.}$ 1776w, 1740s(sh), 1720vs, and 1688s cm^{-1}; δ 1·26 (3H, t, *J* 7 Hz, $CH_3{\cdot}CH_2O$), 1·33 and 1·58 (6H, 2 × s, *gem*-Me_2), 3·52 (3H, s, OMe), 4·24 (2H, q, *J* 7 Hz, $CH_3{\cdot}CH_2O$), 4·42 (1H, s, H-4), 4·41 and 4·78 (2H, ABq, *J* 16·7 Hz, $PhthCH_2$), 6·22 (1H, s, H-2), and 7·90 (4H, m, ArH); *m/e* 390 (0·12%, M^+), 359 (7, M^+ — OMe, $C_{18}H_{19}N_2O_6$), and 160 (100) (Found: C, 57·85; H, 5·5; N, 6·95. $C_{19}H_{22}N_2O_7$ requires C, 58·45; H, 5·7; N, 7·2%).

Ethyl 2-[$^2H_3$]*Methoxy*-5,5-*dimethyl*-N-*phthalimidoacetyloxazolidine*-4-*carboxylate*.—This was prepared like (8) and (11), but by using [$^2H_4$]methanol (45 μl, 1 mmol); m.p. 159—160°. The n.m.r. spectrum is identical to that of (8), except it lacks a signal at δ 3·52 (Found: C, 57·95; H, 5·6; N, 7·05. Calc. for $C_{19}H_{19}N_2O_7D_3$: C, 58·0; H, 5·65; N, 7·1%).

4,4-*Dimethyl*-2-(1-*phthalimidoacetoxy*-2-*phthalimidovinyl*) *oxazoline* [*the* 2 : 1 *Adduct* (14)].—Phthalimidoacetyl chloride (447 mg, 2 mmol) was added to 4,4-dimethyl-Δ^2-oxazoline (103 μl, 1 mmol) in dichloromethane (2 × 10 ml) as described above (general procedure). The resulting solution showed $\nu_{max.}$ (CH_2Cl_2) 1802m, 1775w, 1725s, 1685m, and 1640vw cm^{-1}. Triethylamine (278 μl, 2 mmol) in dichloromethane (10 ml) was added dropwise from a syringe to the stirred mixture during *ca.* 15 min. After stirring for a further 15 min at room temperature, the mixture was evaporated to small bulk, extracted with benzene, and filtered. The residue was washed with water, removing Et_3N,HCl (270 mg, 100%), and leaving insoluble polymeric (?) matter (70 mg). The benzene filtrate was evaporated. An n.m.r. spectrum of the residue showed the ratio of 2 : 1 adduct (14) to 1 : 2 adduct (12) to be 5 : 2 (integration of the singlet resonances at δ 7·21 and 5·91, respectively). The mixture was extracted with ether (4 × 20 ml). The material insoluble in ether (160 mg) contained no 1 : 2 adduct (12) (by n.m.r.). It was dissolved in the minimum amount of dichloromethane (*ca.* 2 ml) and set aside for 12 h to give the 2 : 1 adduct (50 mg), m.p. 219—221°. The material soluble in ether (230 mg) contained (14) and (12) in the ratio 57 : 43 (by n.m.r.). It was dissolved in the minimum of dichloromethane and set aside to give crystals (35 mg), m.p. 219°. All the residues were combined and dissolved in a little dichloromethane, and small portions of ether were added to give several small crops of crystals (total 47 mg), m.p. 210—219°; total yield of (14) 132 mg (0·28 mmol); yield of (12) (by n.m.r.) 0·16 mmol. A sample of (14) obtained by two recrystallisations from dichloromethane formed white *crystals*, m.p. 221°, $\nu_{max.}$ 1790w(sh), 1777m, 1720vs, 1680w, and 1640w cm^{-1}; δ 1·32 (6H, s, Me_2), 4·07 (2H, s, ring CH_2), 4·71 (2H, s, $PhthCH_2$), 7·21 (1H, s, =CH), and 7·75 and 7·84 (8H, 2 × m, ArH); *m/e* 473 (4%, M^+), 285 (61, M^+ —$PhthCH_2CO$), and 160 (100) (Found: C, 63·8; H, 3·95; N, 8·6. $C_{25}H_{19}N_3O_7$ requires C, 63·4; H, 4·05; N, 8·9%).

2-(4,4-*Dimethyl*-Δ^2-*oxazolin*-2-*yl*)-4,4-*dimethyl*-N-*phthalimidoacetyloxazolidine* [*the* 1 : 2 *Adduct* (12)].—By the general procedure (see above), phthalimidoacetyl chloride (224 mg, 1 mmol) in dichloromethane (10 ml) was added to 4,4-dimethyl-Δ^2-oxazoline (103 μl, 1 mmol) in dichloromethane (10 ml), followed by triethylamine (139 μl, 1 mmol)

and 4,4-dimethyl-Δ^2-oxazoline (103 μl, 1 mmol) in dichloromethane (10 ml). The mixture was evaporated to dryness, extracted with benzene, and filtered to give Et_3N,HCl (130 mg, 95%). The filtrate was evaporated, and an n.m.r. spectrum of the residue showed no 2 : 1 adduct (14) (no signal at δ 7·21). It was extracted with ether (4 × 10 ml). Analysis (n.m.r.) of the ether-soluble fraction (300 mg) showed the presence of almost pure 1 : 2 adduct (12). It was purified by preparative layer chromatography (p.l.c.) (two 100 cm × 20 cm × 0·5 mm plates, developed twice in EtOAc–PhH, 1 : 1) to give compound (12) (175 mg). The ether-insoluble fraction (100 mg) was purified on a short silica gel column (5 g) (elution, with PhH and 15% EtOAc–PhH) to give the adduct (12) [24 mg; total yield (crude) 199 mg (0·52 mmol)]. This product was crystalline, but very difficult to recrystallise and to free from traces of the acyclic acylamino-alcohol *O*-formate (see below). A *sample* obtained by low temperature recrystallisation from ether had m.p. 130°, $\nu_{max.}$ 1773w, 1720vs, and 1672s cm^{-1}; δ 1·38 (6H, s), 1·50 (3H, s), and 1·57 (3H, s) (4 × ring Me), 4·11 (2H, s, ring CH_2), 3·88 and 4·16 (2H, ABq, *J* 8·0 Hz, ring CH_2), 4·27 and 4·56 (2H, ABq, *J* 16·0 Hz, PhthCH$_2$), 5·91 (1H, s, H-2), and 7.76 (4H, m, ArH); *m/e* 385 (14%, M^+, $C_{20}H_{23}N_3O_5$), 287 (11), 259 (14), 258 (47), 245 (26), 225 (20), 197 (43), 188 (14), 183 (17), 161 (47), and 160 (100) (Found: C, 61·4; H, 5·95; N, 10·65. $C_{20}H_{23}N_3O_5$ requires C, 62·3; H, 6·0; N, 10·9%).

Use of the above reactants in a 1 : 1 : 1 ratio gave 333 mg of crude product after removal of Et_3N,HCl (126 mg, 93%). Recrystallisation from dichloromethane gave (14) (42 mg, 0·089 mmol). The residue (230 mg) contained little (14), and was purified on a silica gel column; (12) was eluted with 15% EtOAc–PhH (62 mg, 0·16 mmol). Adducts (12) and (14) both have R_F 0·3 on t.l.c. (EtOAc–PhH, 1 : 1), but on a column (12) is eluted with 15% and (14) with 25% EtOAc–PhH.

Ethyl 5,5-Dimethyl-2-(1-phthalimidoacetoxy-2-phthalimidovinyl)-Δ²-oxazoline-4-carboxylate [the 2 : 1 Adduct (13)].—The procedure was as for (14), but with ethyl 5,5-dimethyl-Δ^2-oxazoline-4-carboxylate (158 μl, 1 mmol). The evaporated mixture, extracted with benzene, and filtered, left a solid mostly water-soluble (290 mg; theoretical Et_3N,HCl 273 mg). The filtrate was evaporated to give the crude product, which was purified twice by p.l.c. (3 × with EtOAc–PhH, 1 : 1). The resulting chromatographically pure (13) was crystallised from benzene–petroleum at room temperature to give a *sample* of m.p. 160° (softens 140°), $\nu_{max.}$ 1790w(sh), 1775m, 1735s(sh), 1723vs, 1680w(sh), and 1630w cm^{-1}; δ 1·26 (3H, t, *J* 7 Hz, CH_3·CH_2O), 1·37 and 1·58 (6H, 2 × s, Me_2), 4·23 (2H, q, *J* 7 Hz, CH_3·CH_2O), 4·52 (1H, s, H-4), 4·72 (2H, s, PhthCH$_2$), 7·28 (1H, s, =CH), and 7·77 and 7·86 (8H, 2 × m, ArH); *m/e* 545 (8%, M^+, $C_{28}H_{23}N_3O_9$) and 160 (100) (Found: C, 61·35; H, 4·45; N, 7·65. $C_{28}H_{23}N_3O_9$ requires C, 61·65; H, 4·25; N, 7·7%).

The n.m.r. spectra of crude products in this series showed no signals in the δ 6 region expected for a 1 : 2 adduct analogous to (12).

Reactions of the 2 : 1 Adducts (13) *and* (14) *and the 1 : 2 Adduct* (12).—*Reaction of* (14) *with benzylamine.* To a solution of the 2 : 1 adduct (14) (70 mg, 0·15 mmol) in dichloromethane (4 ml) was added benzylamine (20 μl, 0·2 mmol). T.l.c. after 5 min showed only two new spots (5% MeOH–$CHCl_3$; R_F 0·6 and 0·3). The mixture was evaporated (90 mg) and chromatographed on a short silica gel column (5 g) made up in chloroform and eluted with 1 and 2% methanol–chloroform. The first fraction was pure (15) (12 mg, 28%); the second was mainly *N*-phthalimidoacetylbenzylamine and the third pure *N*-phthalimidoacetylbenzylamine (total 51 mg). [Repetition of the experiment in an n.m.r. sample tube showed that reaction was complete within 4 min at 37 °C and that equimolar amounts of (15) and *N*-phthalimidoacetylbenzylamine were the only products.] The *N*-phthalimidoacetylbenzylamine was identified by comparison with an authentic sample (see below). The white crystals of 4,4-dimethyl-2-phthalimidoacetyl-Δ^2-oxazoline (15) had m.p. 148° (from benzene–petroleum); $\nu_{max.}$ 1775w, 1722vs, and 1631w cm^{-1}; δ 1·41 (6H, s, Me_2), 4·16 (2H, s, ring CH_2), 5·09 (2H, s, PhthCH$_2$), and 7·92 (4H, m, ArH); *m/e* 286 (53%, M^+, $C_{15}H_{14}N_2O_4$) and 160 (100).

N-Phthalimidoacetylbenzylamine. Sodium carbonate (200 mg, 2 mmol) was added to benzylamine (107 mg, 1 mmol) in dry dichloromethane (5 ml). The mixture was cooled in ice, and phthalimidoacetyl chloride (224 mg, 1 mmol) in dichloromethane (5 ml) was added dropwise with stirring. After stirring for 30 min at room temperature, the suspension was filtered and the filtrate washed with small portions of saturated Na_2CO_3 solution, N-HCl, and water, and then dried and evaporated. The residue was recrystallised from methanol giving the *product*, m.p. 221°; $\nu_{max.}$ 3425w, 1775m, 1720vs, 1700s(sh), and 1615m cm^{-1}; δ 4·33 (2H, s, PhthCH$_2$), 4·42 (2H, d, *J* 5·0 Hz, PhCH$_2$), 6·10br (1H, NH), 7·24 (5H, s, Ph), and 7·75 (4H, m, ArH) (Found: C, 69·6; H, 4·85; N, 9·45, $C_{17}H_{14}N_2O_3$ requires C, 69·35; H, 4·8; N, 9·5%).

Reaction of (13) *with benzylamine.* Following this reaction by n.m.r. spectroscopy showed that the 2 : 1 adduct (13) reacted rapidly with 1·5 mol. equiv. of benzylamine to give equimolar amounts of *N*-phthalimidoacetylbenzylamine and another product, probably ethyl 2-phthalimidoacetyl-5,5-dimethyl-Δ^2-oxazoline-4-carboxylate (16). After 10 h at 37 °C, the n.m.r. spectrum showed appreciable decomposition of (16), and attempted isolation by p.l.c. gave only *N*-phthalimidoacetylbenzylamine and small amounts of several other unidentified products.

Reactions of the 2 : 1 adducts (13) *and* (14) *with methanol and ethanol.* By n.m.r. spectroscopy it was shown that with 5·4 mol. equiv. of methanol in 0·5 ml of $CDCl_3$, the adduct (14) (14 mg, 0·030 mmol) was 80% converted to a mixture of (15) and methyl phthalimidoacetate after 27·5 h at 37° (*cf.* other data in text). Adduct (13) with ethanol (5·8 mol. equiv.) showed 24% reaction after 67 h at 37 °C.

2-Hydroxy-5,5-dimethyl-2-phthalimidomethylmorpholin-3-one (17). To a solution of the 2 : 1 adduct (14) (34 mg, 0·072 mmol) in dichloromethane (3 ml), was added methanol (40 μl, 1 mmol); the mixture was set aside for 24 h at room temperature, then evaporated and separated by p.l.c. (3 × with 2% MeOH–$CHCl_3$) to give only two bands corresponding to methyl phthalimidoacetate and (15). The plate was left for 48 h, and the band corresponding to (15) was then extracted, giving crystalline (17) (16 mg, 0·053 mmol), R_F 0·15 in 5% MeOH–$CHCl_3$. Recrystallisation from benzene gave a *sample* of m.p. 148°; $\nu_{max.}$ 3370m, 3500—3270w, 1775m, 1706vs, and 1680s cm^{-1}; δ 1·18 and 1·34 (6H, 2 × s, Me_2), 3·42 and 4·00 (2H, ABq, *J* 12·0 Hz, ring CH_2), 4·22 (2H, s, PhthCH$_2$), 6·35br (1H, NH), and 7·84 (4H, m, ArH); *m/e* 304 (1%, M^+), 287 (2), 273 (20, $M-CH_2OH$, $C_{14}H_{13}N_2O_4$), 162 (17), 161 (100), and 160 (53).

Reaction of the 1 : 2 adduct (12) *with methanolic sulphuric acid.* To a solution of the 1 : 2 adduct (12) (36 mg, 0·093 mmol) in methanol (2 ml) was added concentrated sulphuric

acid (0·2 ml) and the mixture was refluxed for 12 h. Water (6 ml) was added, followed by solid sodium carbonate until there was no further effervescence. Extraction with ether gave material (29 mg) which was separated by p.l.c. (3 × with dichloromethane) into two bands only. Extraction of the first gave methyl phthalimidoacetate (4·5 mg) and of the second methyl 4,4-dimethyl-*N*-phthalimidoacetyloxazolidine-2-carboxylate (10) (14 mg, 0·04 mmol) as an oil that slowly crystallised; $\nu_{max.}$ 1778m, 1750s, 1725vs, 1675s, and 1657s cm^{-1}; δ (+60 °C) 1·54 and 1·58 (6H, 2 × s, Me_2), 3·82 (3H, s, OMe), 3·90 (1H, d, *J* 9 Hz, H-5 *cis* to CO_2Me), 4·08 (1H, d, with each signal slightly broadened due to W-coupling to H-2, J_{gem} 9 Hz, H-5 *trans* to CO_2Me), 4·39br (2H, s, $PhthCH_2$) and 5·67 (1H, s, H-2) [at room temperature all signals were unresolved; at −20 °C there were present the expected signals from two rotamers (about N–CO, ratio 54 : 46), *e.g.* δ 5·76 and 5·62 (H-2)].

Hydrolysis Products of the Adducts from Acyl Chlorides and the Oxazoline (1) *or* (2).—Hydrolysis by wet triethylamine of the acyl chloride–oxazoline adducts leads to a mixture of an acylamino-alcohol (5) and its *O*-formate (6). Three such compounds have been crystallised and fully characterised: (i) *ethyl 2-benzamido-3-hydroxy-3-methylbutyrate* [from benzoyl chloride and (1)], m.p. 85° (from petroleum); $\nu_{max.}$ 3575m(br), 3430m, 1725s, 1664s, and 1508m cm^{-1}; δ 1·29 (3H, t, *J* 7 Hz, $CH_3{\cdot}CH_2O$), 1·34 (6H, s, Me_2), 3·29br (1H, OH), 4·20 (2H, q, *J* 7 Hz, $CH_3{\cdot}CH_2O$), 4·71 (1H, d, *J* 9 Hz, CH), 7·40 (4H, m, NH and ArH), and 7·85 (2H, m, ArH); *m/e* 250 (3%, *M* − Me, $C_{13}H_{16}NO_4$) and 161 (100) (Found: C, 63·15; H, 7·15; N, 5·45. $C_{14}H_{19}NO_4$ requires C, 63·4; H, 7·2; N, 5·3%); (ii) *ethyl 3-hydroxy-3-methyl-2-phthalimidoacetamidobutyrate* [from phthalimidoacetyl chloride and (1)], m.p. 141—142° (from benzene) (Found: C, 58·7; H, 5·8; N, 7·65. $C_{17}H_{20}N_2O_6$ requires C, 58·6; H, 5·8; N, 8·05%); (iii) *2-methyl-2-phthalimidoacetamidopropyl formate* (6) [from phthalimidoacetyl chloride and (2)], m.p. 202° (decomp.) (from benzene); $\nu_{max.}$ 3415w, 1773w, 1718vs, 1700s(sh), and 1610w cm^{-1}; δ 1·37 (6H, s, Me_2), 4·28 (4H, s, 2 × CH_2), 6·05br (1H, s, NH), 7·80 (4H, m, ArH), and 8·09 (1H, s, CHO); *m/e* 303 (3%, M^+) and 160 (100) (Found: C, 59·0; H, 5·3; N, 9·1. $C_{15}H_{16}N_2O_5$ requires C, 59·2; H, 5·3; N, 9·2%).

In addition, *O*-formates from reactions (i) and (ii) and azidoacetyl chloride with (2) were spectrally characterised.

2-Isocyano-2-methylpropyl Phthalimidoacetate.—This *compound* was obtained by converting (Bu^nLi in THF at −80 °C) 4,4-dimethyl-Δ^2-oxazoline into its 2-anion and treating this with 1 equiv. of phthalimidoacetyl chloride in THF (−80 °C or room temperature) or ether (−80 °C); m.p. 96·5° (2 × from petroleum); $\nu_{max.}$ 2135m, 1776m, 1758s, and 1723vs cm^{-1}; δ 1·45 (6H, t, *J* 1·6 Hz, Me_2), 4·15 (2H, t, *J* 1·5 Hz, CH_2), 4·54 (2H, s, $PhthCH_2$), and 7·86 (4H, m, ArH) (*N.B.* coupling of H to N through three bonds characteristic of isonitriles); *m/e* 286 (6%, M^+) and 160 (100) (Found: C, 62·85; H, 5·0; N, 9·8. $C_{15}H_{14}N_2O_4$ requires C, 62·95; H, 4·95; N 9·8%).

2-Hydroxy-5,5-dimethyl-2-phenylmorpholin-3-one (18).—Methyl phenylglyoxylate was mixed with 1 equiv. of freshly distilled 2-amino-2-methylpropanol and left overnight at room temperature to give a semi-crystalline mass. This was washed with ether and recrystallised from benzene to give compound (18), m.p. 121·5° (lit.,[12] 122°), $\nu_{max.}$ 3545w, 3365w, and 1673s (18) and 3365m, 1668s, 1595w, and 1615m cm^{-1} (18a); δ (CD_3OD) 1·23 and 1·43 (6H, 2 × s, Me_2), 3·57 and 4·13 (2H, ABq, *J* 12 Hz, CH_2), and 7·26 and 7·60 (5H, 2 × m, ArH) [these signals pertain to (18)]; δ ($CDCl_3$) 1·39 (6H, s, Me_2), 3·48br (1H,), 3·68 (2H, s, CH_2), and 7·50 and 8·26 (5H, 2 × m, ArH) [these signals are for (18a); see text].

We thank the S.R.C. for a C.A.P.S. award (to D. R. H.) in association with Pfizer, Dr. M. S. Tute for his interest in this work, and the P.C.M.U., Harwell, for mass spectral and n.m.r. measurements. Analyses were done by Dr. F. B. Strauss, Oxford.

[5/017 *Received*, 6*th January*, 1975]