

Cyclisation of α -Acylamino-acids in the Presence of Perchloric Acid to give 5-Oxo- Δ^2 -oxazolinium Perchlorates

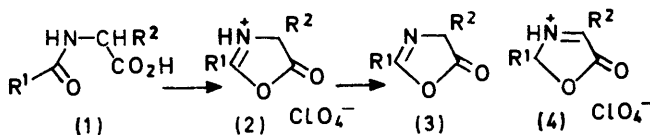
By G. V. Boyd* and P. H. Wright, Department of Chemistry, Chelsea College, London SW3 6LX

The action of acetic anhydride and perchloric acid on simple α -acylamino-acids yields 5-oxo- Δ^2 -oxazolinium perchlorates, which can be deprotonated to the corresponding saturated oxazolin-5-ones. *N*-Benzoyl-L-phenylalanine gave the hydroperchlorate of L-4-benzyl-2-phenyloxazolinone. The salt obtained from hippuric acid undergoes ring opening on treatment with water, methanol, and various amines: it condenses with benzaldehyde to give the hydroperchlorate of the labile geometrical isomer of 4-benzylidene-2-phenyloxazolinone. Ten *N*-substituted oxo-oxazolinium perchlorates were prepared and their reactions with benzaldehyde and amines are reported. The bicyclic perchlorate, obtained from *p*-nitrobenzoyl-L-proline, is easily racemised, probably *via* a mesoionic oxazolium oxide; the corresponding diphenylamino-compound is optically stable.

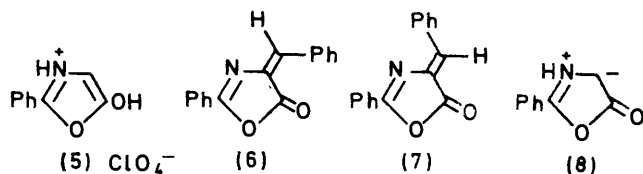
THE constitution of the labile hygroscopic compounds formed by the action of phosphorus halides or thionyl chloride on α -acylamino-acids¹ or from Δ^2 -oxazolin-5-ones and hydrogen chloride² was for many years in doubt. The early view that they were acyl halides became questionable when it was discovered that 'hippuryl chloride' gave 2-phenyl- Δ^2 -oxazolin-5-one (3a) on treatment with diazomethane³ or aqueous sodium acetate,⁴ and it was suggested⁴ that they were hydrohalides of oxazolinones. The matter was finally settled in favour of the salt hypothesis by cryoscopic studies⁵ and, in particular, i.r. spectroscopy, which demonstrated the azlactone structure by the presence of an intense band near 1890 cm^{-1} .⁶ In the course of our studies⁷ of the action of acetic anhydride-perchloric acid on compounds of the general formula $-\text{OC}\cdot\text{X}\cdot\text{Y}\cdot\text{CO}-$ we investigated the behaviour of α -acylamino-acids towards the reagent and found that crystalline perchlorates were produced which were readily identified as 5-oxo- Δ^2 -oxazolinium salts.⁸

Hippuric acid gave the perchlorate (2a) (89%), whose i.r. spectrum exhibited the characteristic high-frequency absorption at 1880 cm^{-1} ; its n.m.r. spectrum contained only aromatic signals and a methylene singlet; the appearance of the latter rules out the alternative Δ^3 -oxazolinium structure (4a). This is in accord with HMO⁹ calculations on the parent ions corresponding to (2) and (4), which predict a greater π -electron energy (12.794 β) for the former than for the latter (12.688 β). The spectral findings also exclude the tautomeric hydroxyoxazolium structure (5). The oxazolinium perchlorate is stable when kept dry; a sample has been kept in a desiccator for 2 years without deterioration. It is rapidly hydrolysed by cold water to hippuric acid. The action of triethylamine on the salt results in deprotonation to give 2-phenyloxazolinone (3a), from which perchloric acid regenerates the salt. Treatment

with cold aqueous sodium carbonate gave a mixture of the oxazolinone and sodium hippurate. Since the oxazolinone is not affected by water or sodium carbonate



- a; R¹ = Ph, R² = H
 b; R¹ = R² = Ph
 c; R¹ = Me, R² = H
 d; R¹ = Ph, R² = PhCH₂
 e; R¹ = Me, R² = Ph



under these conditions we suggest that the ring opening occurs by direct attack on the cyclic cation (see Scheme) rather than through preliminary deprotonation. The oxazolinium perchlorate functions as a highly active acylating agent, yielding methyl hippurate, hippuramide, hippuranilide, *N*-(benzylcarbamoymethyl)benzamide, and benzoylglycylglycine when treated with methanol, aqueous ammonia, aniline, benzylamine, and sodium glycinate, respectively. Treatment with benzaldehyde gave an orange benzylidene derivative which yielded the labile geometrical isomer (6)¹⁰ of 4-benzylidene-2-phenyloxazolinone on treatment with water. The identity of the latter was established by its quantitative conversion^{10a} into the stable form (7) in cold pyridine. Since the benzylidene perchlorate was obtained in low yield it is possible that the other isomer was also produced; but was not detected. The isolation of the hydroperchlorate of the labile isomer is in accord with

¹ E. Fischer, *Ber.*, 1905, **38**, 605.

² E. Mohr and F. Stroschein, *Ber.*, 1909, **42**, 2521.

³ P. Karrer and G. Bussmann, *Helv. Chim. Acta*, 1941, **24**, 645.

⁴ J. W. Cornforth, in 'The Chemistry of Penicillin,' ed. H. T. Clarke, Princeton University Press, Princeton, 1949, pp. 731, 746.

⁵ J. L. O'Brien and C. Niemann, *J. Amer. Chem. Soc.*, 1957, **79**, 80.

⁶ C. W. Smith and R. S. Rasmussen, *J. Amer. Chem. Soc.*, 1949, **71**, 1080; H. E. Carter and J. W. Hinman, *J. Biol. Chem.*, 1949, **178**, 403.

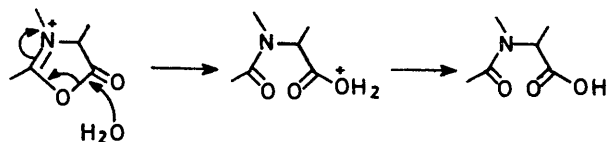
⁷ G. V. Boyd, *Chem. Comm.*, 1969, 1147; G. V. Boyd and S. R. Dando, *J. Chem. Soc. (C)*, 1970, 1397; G. V. Boyd and K. Heatherington, *Chem. Comm.*, 1971, 346.

⁸ G. V. Boyd, *Chem. Comm.*, 1968, 1410.

⁹ We used the hetero-atom parameters recommended by A. Streitwieser, 'Molecular Orbital Theory for Organic Chemists,' Wiley, New York, 1961, p. 135.

¹⁰ (a) H. E. Carter and W. C. Risser, *J. Biol. Chem.*, 1941, **139**, 255; (b) K. Brocklehurst, R. P. Bywater, R. A. Palmer, and R. Patrick, *Chem. Comm.*, 1971, 632.

the report⁵ that a mixture of both isomers results when benzaldehyde is condensed with hippuric acid under acidic conditions. We suggest that the formation of the benzylidene perchlorate occurs by way of a preliminary proton exchange between the cation (2a) and benzaldehyde, followed by attack on the dipolar intermediate (8). Such mesoionic tautomers of saturated azlactones have been detected spectroscopically¹¹ and are invoked to account for their cycloaddition reactions.¹²



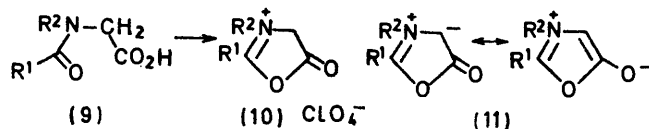
SCHEME

Cyclisation of (\pm)- α -benzamidophenylacetic acid (1b) and *N*-acetylglycine (1c) yielded the perchlorates (2b) and (2c),¹³ respectively. *N*-Benzoyl-L-phenylalanine (1d) gave the optically active salt (2d) from which the laevorotatory oxazolinone (3d) was obtained by deprotonation with aqueous sodium hydrogen carbonate. The perchlorate was hydrolysed by cold water to yield the original acid with high retention of asymmetry. The Δ^2 -oxazolinium structure of the salt (2d), suggested by its optical activity, was confirmed by the n.m.r. spectrum, which exhibited a methylene doublet and a methine triplet. An attempt was made to produce a perchlorate having the tautomeric Δ^3 -oxazolinium structure; the 2-methyl-4-phenyloxazolinium salt (4e) appeared to be a promising candidate since the 3,4-double bond might be stabilised by conjugation with the 4-phenyl substituent. However, the n.m.r. spectrum of the oily perchlorate obtained from (\pm)- α -acetamidophenylacetic acid (1e) showed that the salt existed solely in the Δ^2 -form (2e), since only a singlet methyl resonance was observed.

Oxo-oxazolinium perchlorates, because of their stability and ease of preparation, are recommended as precursors for the sensitive saturated oxazolinones for use in syntheses.^{13,14}

N-Substituted oxo-oxazolinium salts, previously unknown, were produced in high yields by the action of acetic anhydride and perchloric acid on *N*-alkyl- and *N*-phenyl- α -acylamino-acids. *N*-Benzoylsarcosine (9a) gave the perchlorate (10a) (ν_{max} , 1883 cm^{-1}); the appearance of a methylene singlet in its n.m.r. spectrum establishes the position of the double bond. Analogous crystalline hygroscopic Δ^2 -oxazolinium salts (10b–f)* were prepared from the corresponding acids, the preparation of some of which is described in the Experimental section. The *p*-nitrophenyloxazolinium per-

chlorate (10g) was obtained as a syrup. *N*-(Diphenylcarbamoyl)sarcosine (9h) yielded the exceptionally stable diphenylamino-derivative (10h). All the salts exhibited methylene singlets in their n.m.r. spectra.

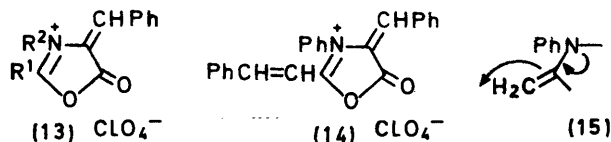


- a; R¹ = Ph, R² = Me
 b; R¹ = R² = Ph
 c; R¹ = Me, R² = Ph
 d; R¹ = *p*-O₂N·C₆H₄, R² = Ph
 e; R¹ = *p*-MeO·C₆H₄, R² = Ph
 f; R¹ = *p*-ClC₆H₄, R² = Me
 g; R¹ = *p*-O₂N·C₆H₄, R² = Me
 h; R¹ = Ph₂N, R² = Me

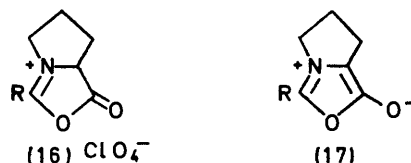


(12)

- | | R ¹ | R ² | R ³ |
|----|--|----------------|-------------------|
| a; | Ph | Ph | PhCH ₂ |
| b; | <i>p</i> -MeO·C ₆ H ₄ | Ph | Ph |
| c; | <i>p</i> -ClC ₆ H ₄ | Me | Ph |
| d; | <i>p</i> -O ₂ N·C ₆ H ₄ | Me | Ph |
| e; | Ph ₂ N | Me | PhCH ₂ |



- a; R¹ = Ph, R² = Me
 b; R¹ = R² = Ph



- a; R = *p*-O₂N·C₆H₄
 b; R = Ph₂N

The *N*-substituted oxazolinium salts are of special interest because deprotonation leads to the formation of mesoionic oxazolones (11), the 'münchnones',¹⁵ whose properties are described in the following paper.

The diphenyloxazolinium perchlorate (10b) was rapidly hydrolysed by water to yield the original acid, the reaction mixture remaining colourless throughout; addition of the salt to benzylamine, or to a mixture of benzylamine and triethylamine, however, resulted in a transient yellow colouration and the formation of the benzylamide (12a). We suggest that the hydrolysis of this salt, like that of the *N*-H analogue (2a), proceeds by attack of water on the cation (see Scheme) but that

¹² H. O. Bayer, H. Gotthardt, and R. Huisgen, *Chem. Ber.*, 1970, **103**, 2356, 2368.

¹³ A. M. Knowles, A. Lawson, G. V. Boyd, and R. A. Newb, *J. Chem. Soc. (C)*, 1971, 598.

¹⁴ G. V. Boyd and S. R. Dando, *J.C.S. Perkin I*, 1972, 777.

¹⁵ R. Huisgen, in 'Aromaticity,' *Chem. Soc. Special Publ.* No. 21, p. 51.

¹¹ G. Kille and J. P. Fleury, *Bull. Soc. chim. France*, 1968, 4636; H. Gotthardt, R. Huisgen, and H. O. Bayer, *J. Amer. Chem. Soc.*, 1970, **92**, 4340.

the aminolysis occurs, at least partly, *via* preliminary deprotonation to the yellow oxazolium oxide (11b), which then yields the benzylamide as in the reaction of the isolable 3-methyl-2,4-diphenyloxazolium-5-oxide with *p*-toluidine.¹⁶ Treatment of the salts (10e–g) with aniline in the presence of triethylamine similarly afforded the anilides (12b–d), respectively; the benzylamide (12e) was obtained from the perchlorate (10h).

3-Methyl-2-phenyloxo-oxazolinium perchlorate (10a) was condensed with benzaldehyde in hot acetic acid to yield the yellow benzylidene derivative (13a), of undetermined configuration; the diphenyl analogue (10b) similarly gave the salt (13b). These reactions must

isolation it was found to be optically inactive. The first experiment demonstrates that cyclisation and hydrolysis do not proceed by way of the mesoionic oxazolone (17a), and supports the arguments already advanced for the mechanism of the hydrolytic ring-opening (see Scheme) of the two types, (2) and (10), of oxo-oxazolinium salts. The observed racemisation of the perchlorate (16a) in solution is attributed to equilibration between the salt and its conjugate base (17a). Cyclisation of *N*-(diphenylcarbonyl)-*L*-proline gave the crystalline optically active perchlorate (16b), which, like its monocyclic analogue (10h), had such little tendency to be deprotonated that hydrolysis, even under

TABLE I
5-Oxo- Δ^2 -oxazolinium perchlorates

Acylamino-acid	Oxazolinium perchlorate	Yield (%)	M.p. (°C) (decomp.)	Found (%)			Required (%)			$\nu_{\max.}/\text{cm}^{-1}$	τ				
(1a)	(2a)	88.8	171–172 ^a	C	H	N	Formula	C	H	N					
(1b)	(2b)	68.6	137 ^c	40.9	3.1	3.4	$\text{C}_{16}\text{H}_{12}\text{ClNO}_6$	41.3	3.1	5.35	3200(w), 1880, 1662, 1600, 1115	1.65–2.35 (m, Ph), 4.98 (s, CH_2)			
(9a) *	(10a)	96	167	43.35	3.7	5.0	$\text{C}_{16}\text{H}_{12}\text{ClNO}_6$	43.55	3.65	5.1	1883, 1666, 1090	1.9–2.4 (m, Ph), 4.90 (s, CH_2), 6.1 (s, Me)			
(9b) †	(10b)	74	165	53.3	3.6	4.0	$\text{C}_{16}\text{H}_{12}\text{ClNO}_6$	53.35	3.6	4.15	1890, 1618, 1090	2.1–2.6 (m, 2 × Ph), 4.61 (s, CH_2)			
(9c) ‡	(10c)	84.5	143	43.25	3.85	5.1	$\text{C}_{16}\text{H}_{12}\text{ClNO}_6$	43.55	3.65	5.1	1920, 1880, 1650, 1100	2.22–2.5 (m, Ph), 4.78 (s, CH_2), 7.72 (s, Me)			
(9d) ^e	(10d)	90	169	<i>f</i>			$\text{C}_{16}\text{H}_{12}\text{ClNO}_6$				1887, 1625, 1090	1.67–2.36 (m, Ar), 2.63 (s, Ph), 5.01 (s, CH_2)			
(9e) ^g	(10e)	85 ^h	131–132				$\text{C}_{16}\text{H}_{12}\text{ClNO}_6$				3.8	2.16–3.05 (m, Ar), 2.28 (s, Ph), 4.70 (s, CH_2), 6.02 (s, Me)			
(9f) ⁱ	(10f)	93.5 ^h	110–113				$\text{C}_{16}\text{H}_{12}\text{Cl}_2\text{NO}_6$				4.5	1.9–2.35 (m, Ar), 4.87 (s, CH_2), 6.08 (s, Me)			
(9g) [§]	(10g)	Oil					$\text{C}_{16}\text{H}_{12}\text{ClNO}_6$				52.4	4.1	7.6	1916, 1892, 1665, 1100	2.45br (s, 2 × Ph), 5.18 (s, CH_2), 7.16 (s, Me)
(9h)	(10h)	92 ^a	170–173 ^h	52.4	4.1	7.5	$\text{C}_{16}\text{H}_{12}\text{ClNO}_6$	52.4	4.1	7.6	1890, 1676, 1090				

^a From acetonitrile. ^b 0.01 mol scale. ^c Unstable. ^d Found: ClO_4 , 29.1. Required: 29.45%. ^e This acid (48.3 g, 80.5%), m.p. 193–193.5° (from ethanol), $\nu_{\max.}$ 2400–2700, 1740, and 1620 cm^{-1} (Found: C, 59.9; H, 4.0; N, 9.35. $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_6$ requires C, 60.0; H, 4.05; N, 9.3%). ^f This acid (48.3 g, 80.5%), m.p. 193–193.5° (from ethanol), $\nu_{\max.}$ 2400–2700, 1740, and 1620 cm^{-1} (Found: C, 59.9; H, 4.0; N, 9.35. $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_6$ requires C, 60.0; H, 4.05; N, 9.3%). ^g This acid (48.3 g, 80.5%), m.p. 193–193.5° (from ethanol), $\nu_{\max.}$ 2400–2700, 1740, and 1620 cm^{-1} (Found: C, 59.9; H, 4.0; N, 9.35. $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_6$ requires C, 60.0; H, 4.05; N, 9.3%). ^h This acid (48.3 g, 80.5%), m.p. 193–193.5° (from ethanol), $\nu_{\max.}$ 2400–2700, 1740, and 1620 cm^{-1} (Found: C, 59.9; H, 4.0; N, 9.35. $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_6$ requires C, 60.0; H, 4.05; N, 9.3%). ⁱ This acid (48.3 g, 80.5%), m.p. 193–193.5° (from ethanol), $\nu_{\max.}$ 2400–2700, 1740, and 1620 cm^{-1} (Found: C, 59.9; H, 4.0; N, 9.35. $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_6$ requires C, 60.0; H, 4.05; N, 9.3%). ^{||} This acid (48.3 g, 80.5%), m.p. 193–193.5° (from ethanol), $\nu_{\max.}$ 2400–2700, 1740, and 1620 cm^{-1} (Found: C, 59.9; H, 4.0; N, 9.35. $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_6$ requires C, 60.0; H, 4.05; N, 9.3%).

* Ref. 5. † G. Rebuffat, *Gazzetta*, 1887, 17, 232. ‡ A. Lumière, L. Lumière, and P. Barbier, *Bull. Soc. chim. France*, 1880, 33, 786. § W. B. Wright, D. B. Cosulich, M. J. Fahrenbach, C. W. Waller, J. M. Smith, and M. E. Hultquist, *J. Amer. Chem. Soc.*, 1949, 71, 3014.

involve attack by the protonated aldehyde on mesoionic intermediates (11) as postulated previously for the formation of the hydroperchlorate of compound (6). Heating benzaldehyde with the 2-methyl-3-phenyloxazolinium perchlorate (10c) produced the dibenzylidene derivative (14); activation of the methyl group can be rationalised in terms of the partial structure (15). Attempts to prepare a monobenzylidene compound failed. The diphenylamino-oxazolinium salt (10h) could not be condensed with benzaldehyde or *p*-dimethylaminobenzaldehyde; this may be attributed to the reluctance of the highly stabilised cation to undergo deprotonation.

In order to gain some insight into the course of the cyclisation reaction we submitted *N-p*-nitrobenzoyl-*L*-proline¹⁷ to the action of acetic anhydride-perchloric acid below 0°; addition of ether after 1 h precipitated the oily optically active perchlorate (16a), which was hydrolysed by water to yield the original acid with 97.5% retention of optical activity. However, when the perchlorate was left in the reaction mixture for 24 h before

alkaline conditions, gave the parent acylamino-acid with complete retention of optical activity.

EXPERIMENTAL

Perchloric acid was of 70% strength. M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra refer to Nujol mulls. N.m.r. spectra were recorded for trifluoroacetic acid solutions at 60 MHz on a Perkin-Elmer R10 spectrometer.

5-Oxo- Δ^2 -oxazolinium Perchlorates (2) and (10).—Perchloric acid (12.5 ml) was slowly added to a stirred suspension of an acylamino-acid (1) or (9) (0.1 mol) in acetic anhydride (70 ml), the temperature being kept below 30° by external cooling. The product usually crystallised during the addition; if it did not ether was added to incipient turbidity and the mixture was cooled to 0°. The oxazolinium perchlorates are listed in Table I.

Reactions of 5-Oxo-2-phenyl-3H- Δ^2 -oxazolinium Perchlorate (2a).—The salt (1.0 g) was stirred with water (10 ml); the resulting hippuric acid (0.53 g, 77.5%) was identified by direct comparison with an authentic specimen. A suspension of the perchlorate (2.62 g) in benzene (45 ml) was treated

¹⁶ H. O. Bayer, R. Huisgen, R. Knorr, and F. Schaefer, *Chem. Ber.*, 1970, 103, 2581.

¹⁷ M. W. Williams and G. T. Young, *J. Chem. Soc.*, 1964, 3701.

with triethylamine (1.01 g, 1 mol. equiv.) and the mixture was shaken for 5 min. The benzene layer was decanted from the oily triethylammonium perchlorate and the oil was washed with benzene (20 ml). The benzene solutions were combined and evaporated; the residual 2-phenyl- Δ^2 -oxazolin-5-one (3a) was recrystallised from light petroleum (b.p. 60—80°); yield 1.30 g (81.5%), m.p. 88—90.5° (lit.,¹⁸ 91°). The oxazolinone was recovered quantitatively after being stirred with water or *N*-sodium carbonate for 1 min.

A solution of the oxazolinone (3a) (0.3 g) in acetic acid (2 ml) was treated with perchloric acid (0.3 ml), followed by ether (2 ml); the oxazolinium perchlorate (2a) (0.38 g, 78%), identified by its i.r. spectrum, separated.

The perchlorate (2a) (1.0 g) was added to *N*-sodium carbonate (20 ml) with stirring. The mixture was filtered after 1 min; the residue was washed with water and recrystallised from light petroleum (b.p. 60—80°) to give the oxazolinone (3a) (0.12 g, 19.5%), m.p. and mixed m.p. 87—89.5°. The combined filtrate and washings on acidification yielded hippuric acid (0.41 g, 60%).

The perchlorate (1.3 g) was added to a solution of triethylamine (1.2 ml) in methanol (15 ml). The resulting solution was evaporated; the oily residue solidified in contact with 0.5*N*-hydrochloric acid to give methyl hippurate (0.65 g, 67.4%), m.p. 79—81° (lit.,¹⁹ 85°).

The perchlorate (4.04 g) was added in small portions to aqueous ammonia (*d* 0.88; 23 ml); the precipitated hippuramide (1.64 g, 59.7%) was collected and washed with water; m.p. 181—183° (lit.,¹ 185°).

The perchlorate (2.5 g) was added to a solution of aniline (1.0 g) and triethylamine (1.0 g) in ethanol (10 ml). After 10 min the solution was poured into water and the precipitated hippuranilide was recrystallised from aqueous ethanol; yield 1.3 g (51%), m.p. 208—210° (lit.,²⁰ 208.5°).

A similar reaction of the salt (2.5 g) with benzylamine gave *N*-(benzylcarbamoylmethyl)benzamide (2.13 g, 83%), m.p. 158.5° (from ethanol), ν_{\max} 3280br, 1666, 1640, and 1603 cm^{-1} (Found: C, 71.3; H, 6.0; N, 10.6. $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2$ requires C, 71.6; H, 6.0; N, 10.45%).

The salt (2.62 g) was added to a solution of glycine (0.94 g) in 2*N*-sodium hydroxide (5 ml). The precipitated benzylglycylglycine (1.62 g, 68.6%) was washed with ice-cold water, followed by ethanol; m.p. 199—203° (decomp.) (lit.,¹ 208°).

A mixture of benzaldehyde (1.3 g), the perchlorate (2.62 g), and acetonitrile (20 ml) was heated under reflux for 1 h. The resulting red solution was cooled and ether was added to incipient turbidity, whereupon 4-benzylidene-2-phenyl- Δ^2 -oxazolin-5-one hydroperchlorate crystallised (0.3 g, 8.5%); m.p. 198° (decomp.), ν_{\max} 3160w, 1835sh, 1810, 1630, and 1120br cm^{-1} (Found: ClO_4 , 28.1. $\text{C}_{16}\text{H}_{12}\text{ClNO}_6$ requires ClO_4 , 28.4%). Addition of ether to the mother liquor gave an intractable yellow gum. Similar results were obtained when the condensation was carried out in acetic acid or acetic anhydride. The benzylidene perchlorate (0.2 g) was stirred with water (10 ml); the resulting labile geometrical isomer of 4-benzylidene-2-phenyloxazolinone (6) (0.14 g, 98%), m.p. 143—145°, after one crystallisation from ethanol, had m.p. 146—148° (lit.,^{10a} 146—148°). The labile isomer (0.05 g) was dissolved in pyridine (1 ml); the solution was poured into ice-cold 0.5*N*-hydrochloric acid after 1 min; the m.p. of the precipitated product (0.04 g) was 161—164°,

showing no depression on admixture with an authentic sample of the stable isomer of benzylidene-phenyloxazolinone of m.p. 165°. The i.r. spectra of the two isomers were almost identical.

L-4-Benzyl-5-oxo-2-phenyl-3H- Δ^2 -oxazolinium Perchlorate (2d).—*N*-Benzoyl-*L*-phenylalanine (1d) [$[\alpha]_{\text{D}}^{25} + 37.52^\circ$ (*c* 1.47 in dioxan) (lit.,²¹ +38.74°)] (5.4 g) was suspended in acetic anhydride (20 ml) and perchloric acid (4 ml) was slowly added below 5°. The resulting salt (5.34 g, 76%) was collected and washed with ether; m.p. 129—131° (decomp.), $[\alpha]_{\text{D}}^{25} - 37.8^\circ$ (*c* 2.4 in MeCN), ν_{\max} 3200w, 1880, 1648, 1600, and 1115 cm^{-1} , τ 1.85—2.67 (m, 2 × Ph), 4.5 (t, CH), and 6.36 (d, CH_2) (Found: C, 54.45; H, 4.15; N, 4.1. $\text{C}_{16}\text{H}_{14}\text{ClNO}_6$ requires C, 54.6; H, 4.0; N, 4.0%). The perchlorate (0.9 g) was stirred with ice-cold saturated aqueous sodium hydrogen carbonate solution (10 ml); the residue (0.35 g, 54.5%), m.p. 79—82°, was dissolved in ether; light petroleum (b.p. 40—60°) was added and the solution was cooled to -40° whereupon *L*-4-benzyl-2-phenyl- Δ^2 -oxazolin-5-one (3d) (0.05 g) separated, m.p. 86—87°, $[\alpha]_{\text{D}}^{25} - 70.27^\circ$ (*c* 0.37 in dioxan) (lit.,²¹ m.p. 86.6—87.2°, $[\alpha]_{\text{D}}^{25} - 71.20^\circ$). The i.r. spectrum was the same as that reported.²¹ When the perchlorate (1.0 g) was stirred with water (22 ml) *N*-benzoyl-*L*-phenylalanine (1d) (0.72 g, 94%) was rapidly formed, $[\alpha]_{\text{D}}^{25} + 35.14^\circ$ (*c* 1.48 in dioxan), *i.e.* 93.7% retention of optical activity. The acid was identified by m.p., mixed m.p., and i.r. spectrum.

Cyclisation of DL- α -Acetamidophenylacetic Acid (1e).—Treatment of the acid (3.86 g) with acetic anhydride (15 ml) and perchloric acid (3 ml) gave a solution from which ether precipitated the oily perchlorate (2e) (3.0 g), ν_{\max} (film) 1885, 1650, and 1120 cm^{-1} , τ 0.3br (d, *J* 6 Hz, NH), 2.55 (m, Ph), 4.15 (d, *J* 6 Hz, CH), and 7.3 (s, Me).

Hydrolysis of 5-Oxo-2,3-diphenyl- Δ^2 -oxazolinium Perchlorate (10b).—The salt (1.23 g) was added to water (15 ml); the resulting gum soon solidified to yield *N*-benzoyl-*N*-phenylglycine: b) (0.8 g, 87%), identified by mixed m.p. and i.r. spectrum. The reaction mixture remained colourless throughout the experiment.

Reaction of N-Substituted Oxazolinium Salts with Amines.—The oxazolinium perchlorate (10) (0.01 mol) was added in small portions to a stirred solution of benzylamine or aniline (0.011 mol) and triethylamine (1.5 g) in dichloromethane (15 ml); a transient yellow or orange colour was observed during the addition. Stirring was continued for 15 min and the solvent was then removed. The residue was warmed briefly with 50% aqueous ethanol and the solid product (12) was collected. The benzylamides and anilides are listed in Table 2.

Condensation of N-Substituted Oxazolinium Salts with Benzaldehyde (Table 3).—A mixture of the appropriate salt (0.01 mol), benzaldehyde (1.2 g), and the appropriate solvent was boiled under reflux for 1 h; the yellow or orange benzylidene derivative separated on cooling or on adding ether.

*Experiments with N-p-Nitrobenzoyl-*L*-proline.*—*p*-Nitrobenzoyl-*L*-proline was characterised as its cyclohexylammonium salt, m.p. 177—179°, $[\alpha]_{\text{D}}^{25} - 69.11^\circ$ (*c* 1.85 in EtOH) (lit.,¹⁷ m.p. 175—176°, $[\alpha]_{\text{D}}^{25} - 73^\circ$). The acid (5.28 g, 0.02 mol) in acetic anhydride (15 ml) was slowly treated with perchloric acid (4 ml) below 0°. The solution was kept at -10° for 1 h and then treated with ether; the precipitated

¹⁸ P. Karrer and R. Widmer, *Helv. Chim. Acta*, 1925, **8**, 203.

¹⁹ 'Dictionary of Organic Compounds', 4th edn., Eyre and Spottiswoode, London, 1965, vol. 3, p. 1622.

²⁰ T. Curtius, *J. prakt. Chem.*, 1895, **52**, 243.

²¹ M. Goodman and L. Levine, *J. Amer. Chem. Soc.*, 1964, **86**, 2918.

oily perchlorate (1 was washed several times with ether by decantation; ν_{\max} 1894, 1648, 1605, and 1095 cm^{-1} , $[\alpha]_{\text{D}}^{25} -11.95^\circ$ (c 6.4 in MeCN). The oily perchlorate was stirred with water, the mixture was extracted three times with ethyl acetate, and the extracts were combined, dried (MgSO_4), and treated with cyclohexylamine to give the

cipitated 3-diphenylamino-5,6,7,7a-tetrahydro-1-oxo-1H-pyrrolo[1,2-c]oxazolium perchlorate (16b) (3.5 g, 89%) was collected and washed with ether; m.p. 165–166° (decomp.) (from acetonitrile), $[\alpha]_{\text{D}}^{25} +234^\circ$ (c 1.0 in MeCN), ν_{\max} 1888, 1660, and 1095 cm^{-1} , τ 2.35 (s, NPh), 2.47 (s, NPh), 4.86 (t, CH), 6.6–7.0 (m, CH_2), 7.4–7.7 (m, $2 \times \text{CH}_2$)

TABLE 2

Anilides and benzylamides of *N*-substituted α -acylamino-acids

Oxazolium perchlorate	Product	Yield (%)	M.p. ($^\circ\text{C}$)	Found (%)			Formula	Required (%)			$\nu_{\max}/\text{cm}^{-1}$
				C	H	N		C	H	N	
(10b)	(12a)	88 ^a	162–162.5 ^b	76.6	5.7	8.1	$\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_2$	76.7	5.85	8.1	3275br, 1657, 1643, 1593
(10e)	(12b)	92	151 ^c	73.2	5.8	7.9	$\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_2$	73.3	5.6	7.8	3100–3300, 1676, 1625
(10f)	(12c)	76	165 ^b	63.1	5.0	9.1	$\text{C}_{16}\text{H}_{15}\text{ClN}_2\text{O}_2$	63.5	5.0	9.3	3050–3250, 1670, 1633
(10g)	(12d)	84.5	209–211 ^b	61.2	4.9	13.75	$\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}_4$	61.3	4.8	13.4	3080–3260, 1670, 1633
(10h)	(12e)	86.5 ^d	138 ^c	74.0	6.2	11.3	$\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_2$	74.0	6.2	11.25	3302, 1672, 1639

^a Prepared in tetrahydrofuran. A similar result was obtained when the triethylamine was omitted and an excess of benzylamine used. ^b From ethanol. ^c From aqueous ethanol. ^d 0.005 mol scale.

TABLE 3

4-Benzylidene-5-oxo- Δ^2 -oxazolium perchlorates

Com-pound	Yield (%)	M.p. ($^\circ\text{C}$) ^a	Found (%)			Formula	Required (%)			$\nu_{\max}/\text{cm}^{-1}$	τ
			C	H	N		C	H	N		
(13a)	81 ^b	232–235	56.1	3.9	3.55	$\text{C}_{17}\text{H}_{14}\text{ClNO}_6$	56.1	3.9	3.85	1840, 1633, 1100	1.5–2.5 (m, 11H, $2 \times \text{Ph}$, and =CH), 5.77 (s, Me)
(13b)	72.4 ^c	196.5–198	62.1	3.8	3.5	$\text{C}_{22}\text{H}_{16}\text{ClNO}_6$	62.05	3.8	3.3	1830, 1630, 1090	1.75–2.65(m)
(14)	48.7 ^d	225–228	64.1	4.0	3.35	$\text{C}_{24}\text{H}_{18}\text{ClNO}_6$	63.8	4.0	3.1	1840, 1817, 1630, 1095	1.5–2.65(m)

^a Recrystallised from acetic acid. ^b Prepared from the salt (10a) in acetic acid (30 ml). ^c Prepared from the salt (10b) in a mixture of acetonitrile (15 ml) and acetic anhydride (2 ml). ^d Prepared from the salt (10c) and benzaldehyde (2.4 g) in a mixture of acetonitrile (20 ml) and acetic anhydride (2 ml); 2 h reflux.

cyclohexylammonium salt of *p*-nitrobenzoyl-L-proline, identified by m.p., mixed m.p., and i.r. spectrum, $[\alpha]_{\text{D}}^{25} -67.35^\circ$ (c 2.03 in EtOH), *i.e.* 97.5% retention of optical activity.

The cyclisation experiment was repeated but the reaction mixture was kept at room temperature for 24 h before ether was added. The resulting oily perchlorate was optically inactive: its i.r. spectrum was identical with that of the first salt. The racemic perchlorate was converted into the cyclohexylammonium salt of *p*-nitrobenzoyl-DL-proline, m.p. 169–177°, $[\alpha]_{\text{D}}^{25} 0.00^\circ$, identified by its i.r. spectrum.

*Cyclisation of N-(Diphenylcarbamoyl)-L-proline.*²²—The proline derivative had $[\alpha]_{\text{D}}^{25} +291^\circ$ (c 1.1 in EtOH); it (3.1 g) was stirred with acetic anhydride (9 ml) and perchloric acid (1.2 ml) was added drop by drop. The pre-

(Found: C, 54.5; H, 4.4; N, 6.9. $\text{C}_{18}\text{H}_{17}\text{ClN}_2\text{O}_6$ requires C, 55.0; H, 4.4; N, 7.1%).

The perchlorate (16b) (0.5 g) was stirred with aqueous 10% sodium hydroxide (10 ml). The solution was acidified with hydrochloric acid, the oily suspension was kept at 0° overnight, and the resulting diphenylcarbamoyl-L-proline (0.36 g, 90%) was collected; m.p. and mixed m.p. 163–165° (lit.,²² 165–166°), $[\alpha]_{\text{D}}^{25} +291^\circ$ (c 1.0 in EtOH).

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²² D. E. Rivett and J. F. K. Wilshire, *Austral. J. Chem.*, 1965, 18, 1667.