SYNTHETIC STUDIES RELATED TO MYCOBACTINS

I. SYNTHESIS OF 2-(2′-HYDROXYPHENYL)-2-OXAZOLINE-4-CARBOXYLIC ACID AND RELATED COMPOUNDS

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Abstract

Several methods for the preparation of 2-(2′-hydroxyphenyl)-2-oxazoline-4-carboxylic acid are described, together with an investigation of the chemical reactivity of 2-(2′-hydroxyphenyl)-2-oxazoline.

Introduction

Mycobactins are naturally occurring sexadentate chelating agents which coordinate with iron(III) and stimulate the growth of mycobacteria. Among these bacteria are various pathogens, including those responsible for leprosy, tuberculosis, and Johne's disease, a condition of chronic enteritis in cattle. Their isolation and structural elucidation has been reviewed recently by Snow,[1] whose group is almost entirely responsible for the work in this field. The detailed structure of mycobactin P, isolated from *Mycobacterium phlei*, was established in 1965,[2] and slight structural variations have been exhibited by mycobactins extracted from a variety of other mycobacterial species.[3] The general structure of mycobactins is shown in Figure 1. In this formula R^1 is a methyl, ethyl, or long-chain alkenyl group, R^2 is a methyl, ethyl, or long-chain alkyl group, and R^3, R^4, and R^5 are hydrogen atoms or methyl groups. There are also stereochemical differences at the asymmetric centres marked with an asterisk; all other asymmetric centres exhibit the stereochemistry of the L-amino acid from which they are derived (i.e. *S* configuration).

Chelation is provided by two hydroxamic acid groups and an *o*-hydroxyphenyl-oxazoline fragment. Although the function of the mycobactins is unknown, it has been suggested[1,2] that they are involved in the transport and metabolism of iron in the bacteria. The chelation appears to be important, as a mycobactin analogue[4] lacking the three hydroxyl groups vital for metal coordination has been found to be biologically inactive. This analogue was synthesized by Carpenter and Moore,[4]

* Department of Chemistry, Monash University, Clayton, Vic. 3168.

[1] Snow, G. A., *Bacteriol. Rev.*, 1970, **34**, 99.

[2] Snow, G. A., *Biochem. J.*, 1965, **94**, 160.

[3] Snow, G. A., *Biochem. J.*, 1961, **81**, 4p; Snow, G. A., *Biochem. J.*, 1965, **97**, 166; White, A. J., and Snow, G. A., *Biochem. J.*, 1968, **108**, 593; White, A. J., and Snow, G. A., *Biochem. J.*, 1969, **111**, 785; White, A. J., and Snow, G. A., *Biochem. J.*, 1969, **115**, 1031.

[4] Carpenter, J. G. D., and Moore, J. W., *J. chem. Soc.* (*C*), 1969, 1610.

making use of standard techniques of peptide synthesis. The incorporation of the three necessary hydroxyl groups greatly compounds the difficulty of the synthetic task.

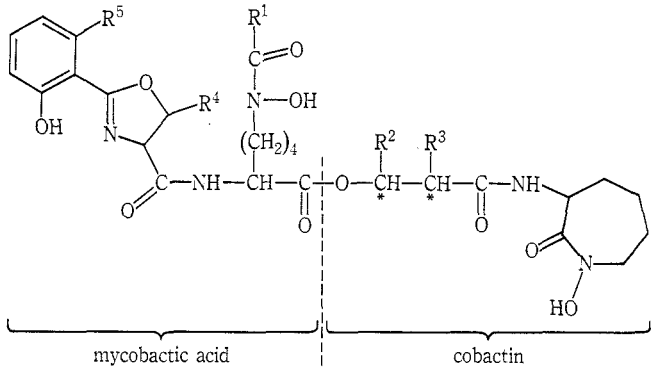
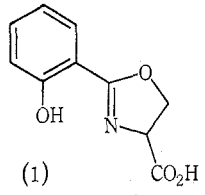


Fig. 1

In view of the possibility[5] that chelate compounds closely related to the mycobactins may exhibit a specific action against mycobacteria, we have initiated a program of research directed towards the synthesis of mycobactins and their chelating analogues. A reasonable synthetic strategy is the combination of a number of smaller fragments in a process which is the reverse of the known hydrolysis of mycobactins. Mild alkaline hydrolysis, for example, results in ester hydrolysis (shown by a dotted line in Fig. 1) with the formation of a mycobactic acid and a cobactin. Further hydrolysis of the amide groups in these molecules leads to the formation of smaller fragments. Early synthetic work therefore deals with the formation of some of these smaller fragments. In this paper, several synthetic routes to a useful *o*-hydroxyphenyl oxazoline derivative (1) are described, together with a general study of the methods of synthesis and chemical properties of simpler oxazolines.



(1)

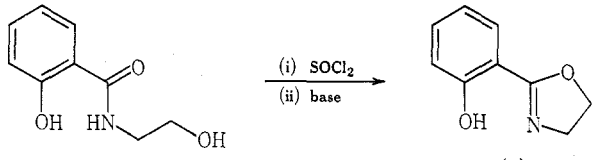
Results and Discussion

(*a*) *The Synthesis of 2-Oxazolines*

A wide variety of methods[6] has been used for the synthesis of 2-oxazolines, but two types of synthesis are most common. One involves cyclization of a hydroxyamide, a chloroamide, or an alkenyl amide: the other is based on the condensation of an alkyl imidate with an ethanolamine. The known compounds 2-(2′-hydroxyphenyl)-2-oxazoline (3)[7,8] and isopropyl 2-phenyl-2-oxazoline-4-carboxylate (6)[9]

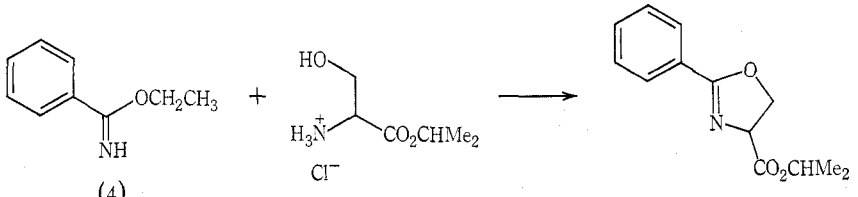
[5] Francis, J., Macturk, H. M., Madinaveitia, J., and Snow, G. A., *Biochem. J.*, 1953, **55**, 596.
[6] Cornforth, J. W., in "Heterocyclic Chemistry." (Ed. R. C. Elderfield.) Vol. 5, p. 298. (Wiley: New York 1957.)
[7] Kalle, A. G., Brit. Pat. 1,152,920 (*Chem. Abstr.*, 1969, **71**, 101841).
[8] Boyer, J. H., and Hamer, J., *J. Am. chem. Soc.*, 1955, **77**, 951.
[9] Elliott, D. F., *J. chem. Soc.*, 1949, 589.

were synthesized for use as model compounds, with respect to the preparative methods used and also the general chemical and physical properties of oxazolines.



(2) (3)

The oxazoline (3) was formed in high yield from 2-hydroxy-*N*-(2′-hydroxyethyl)-benzamide (2).[10] It had an ultraviolet spectrum characteristic[1] of the mycobactins and its nuclear magnetic resonance spectrum showed a symmetrical complex multiplet centred at δ 4·2 p.p.m. caused by the four oxazoline ring protons. Intramolecular hydrogen bonding of the phenolic group was indicated by the infrared spectral data.



(4) (5a) (6)

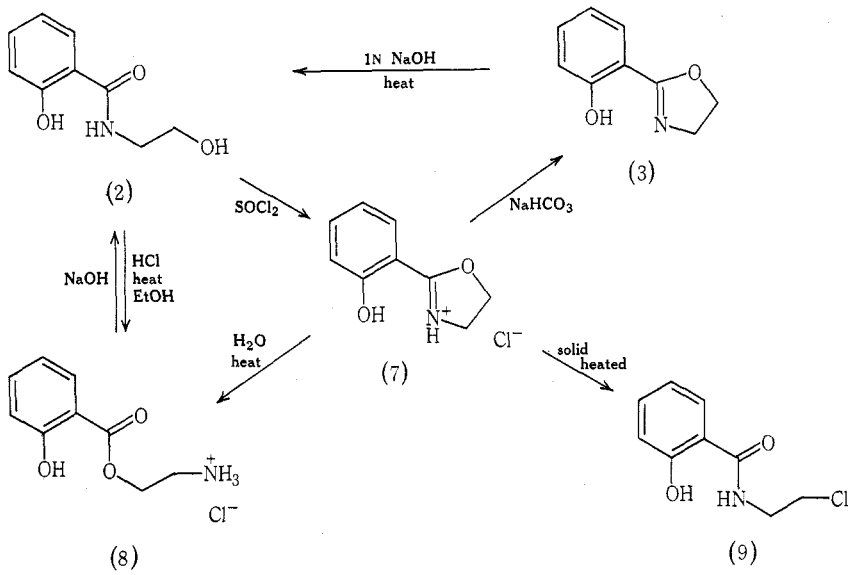
The oxazoline (6) was prepared in 40% yield by the condensation of ethyl benzimidate (4) with serine isopropyl ester hydrochloride (5a) using the two-phase system devised by Elliott.[9] The isopropyl ester was chosen because the serine isopropyl ester hydrochloride (5a) is not hygroscopic. The n.m.r. spectrum of the oxazoline (6) included a complex multiplet at δ 4·7 p.p.m. caused by the oxazoline ring protons and this multiplet overlapped with a septet at δ 5·1 p.p.m. due to the isopropyl methine proton.

(*b*) *Reactions of 2-(2′-Hydroxyphenyl)-2-oxazoline* (*3*)

The oxazoline (3) was submitted to a variety of hydrolytic reactions of the type known[11] to encourage cleavage of the oxazoline ring and the results are summarized in Scheme 1.

The oxazoline (3) was found to be relatively stable to mild alkaline or very mild acidic conditions, but labile when heated in either acid or base. Acid hydrolysis resulted in the cleavage of the C=N bond and formation of the amine hydrochloride (8) whereas base hydrolysis afforded the hydroxy amide (2) as a consequence of C–O bond cleavage. The hydrochloride (8) underwent thermal isomerization[11,12] at *c.* 140° to the chloro amide (9).

[10] Phillips, A. P., and Baltzly, R., *J. Am. chem. Soc.*, 1947, **69**, 200.
[11] Fry, E. M., *J. org. Chem.*, 1949, **14**, 887.
[12] Lusskin, R. M., and Ritter, J. J., *J. Am. chem. Soc.*, 1950, **72**, 5577.



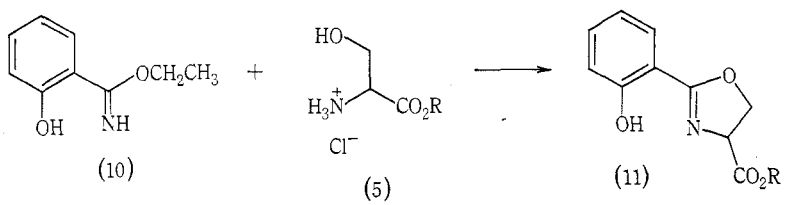
Scheme 1

The oxazoline (3) readily behaved as a bidentate chelating agent, with loss of the phenolic proton. Bis[2-(2′-hydroxyphenyl)-2-oxazolinato] complexes of copper(II), nickel(II), and zinc(II) were formed by reaction of the oxazoline (3) with a methanolic solution of the appropriate metal acetate. The combination of methanolic iron(III) chloride and oxazoline (3) afforded chlorobis[2-(2′-hydroxyphenyl)-2-oxazolinato]-iron(III) as dark purple crystals.

(c) *Synthesis of 2-(2′-Hydroxyphenyl)-2-oxazoline-4-carboxylic Acid (1)*

Method A

Because of the stability of the oxazoline ring under mild hydrolytic conditions, an oxazoline carboxylic acid can be prepared[11] by hydrolysis of a corresponding ester. The series of esters (11) was prepared by reaction of the serine ester hydrochlorides (5)



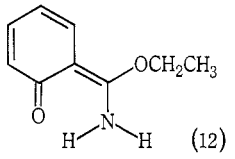
(5a), (11a) R = $CHMe_2$ (*RS*)
(5b), (11b) R = $CHMe_2$ (*S*)
(5c), (11c) R = Me

(11a) $\xrightarrow[\text{2N NaOH}]{\text{cold}}$ (1)

Scheme 2

with ethyl 2-hydroxybenzimidate (10) and the isopropyl ester (11a) was hydrolysed by cold dilute alkali to afford the oxazoline carboxylic acid (1) (Scheme 2).

The imidate (10) was prepared from 2-hydroxybenzonitrile via its hydrochloride salt[13] in a yield of only 27%. The ultraviolet spectrum of the imidate (10) showed absorption maxima at 303 and 362 nm in contrast to the absorption only at 304 nm in the spectrum of the oxazoline (3). Although the two compounds have a similar chromophore, the absorption at 362 nm may be caused by the presence of the structure (12), arising from a tautomeric equilibrium, which is significant in the stronger base (10) but not in the weaker base (3).



(12)

The oxazoline isopropyl ester (11a) was formed in 56% yield, after purification by column chromatography. Its n.m.r. spectrum was similar to that of the model oxazoline (6) and included overlapping multiplets at δ 4·7 p.p.m. (oxazoline ring protons) and 5·1 p.p.m. (isopropyl methine proton).

The corresponding methyl ester (11c) was prepared similarly in 53% yield. Its n.m.r. spectrum contained a complex multiplet at δ 4·7 p.p.m. (oxazoline ring protons), which approximated to an AB_2 multiplet with A *c.* 4·81 p.p.m., B *c.* 4·56 p.p.m., and J_{AB} *c.* 10 Hz.

As the oxazolines present in mycobactins have the *S* configuration at the 4-position, (*S*)-serine isopropyl ester hydrochloride (5b) and the imidate (10) were condensed as for the racemic compound to yield (*S*)-isopropyl 2-(2′-hydroxyphenyl)-2-oxazoline-4-carboxylate (11b) as an oil, which could not be crystallized but which was purified by distillation. The serine ester hydrochloride (5b) and the oxazoline ester (11b) were analytically pure, but their optical purity was not confirmed. An optically active serine ester has been converted previously[14,15] into an oxazoline by this method, without significant racemization.

The racemic oxazolinecarboxylic acid (1) had typical ultraviolet and n.m.r. spectra. Its infrared spectrum showed a sharp absorption at 3310 cm^{-1}, presumably due to the carboxylic acid hydroxyl group, which is possibly held in a rigid hydrogen-bonded conformation.

Although the optically active oxazoline ester (11b) has not been hydrolysed to the acid (1), similar experiments[14,15] have shown that little or no racemization occurs.

The above sequence is suitable for the synthesis of an optically active oxazoline, but the overall yield is not high.

Method B

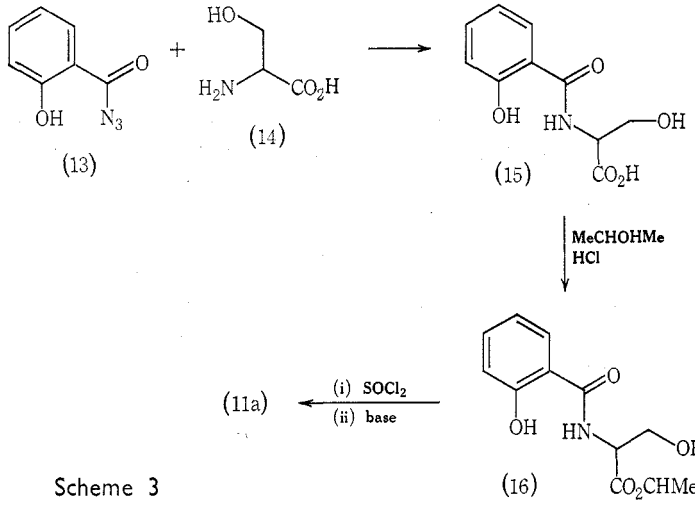
This alternative route, involving cyclization[11] of the hydroxy amide (15), was devised for the preparation of the oxazoline isopropyl ester (11a). The amide (15) was obtained in high yield by the reaction of 2-hydroxybenzoyl azide (13) with serine (14). It was then converted into its isopropyl ester (16), which was cyclized by reaction with thionyl chloride to afford the oxazoline ester (11a) (Scheme 3).

[13] Easson, A. P. T., and Pyman, F. L., *J. chem. Soc.*, 1931, 2991.

[14] Stammer, C. H., Wilson, A. N., Spencer, C. F., Bachelor, F. W., Holly, F. W., and Folkers, K., *J. Am. chem. Soc.*, 1957, **79**, 3236.

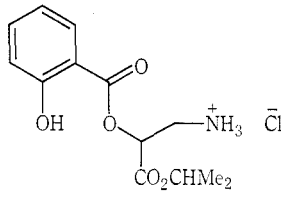
[15] Fry, E. M., *J. org. Chem.*, 1950, **15**, 438.

It was necessary to protect the carboxyl group of the amide (15) during the cyclodehydration step. The isopropyl ester (16) was formed by the addition of dry hydrogen chloride to the amide (15) in isopropanol at room temperature. When the above esterification was carried out at the reflux temperature of isopropanol, a small amount of *O*-2-hydroxybenzoyl serine isopropyl ester hydrochloride (17) was formed by the known rearrangement[10] of 2-hydroxyethyl amides to 2-aminoethyl esters.



Scheme 3

The n.m.r. spectrum of compound (17) shows a quartet at δ 1·3 p.p.m. rather than a doublet, indicating the effect[16] of the nearby asymmetric centre on the isopropyl methyl protons. A similar n.m.r. splitting pattern should also be observed for the ester (16), but apparently in this case the diastereotopic methyl groups have similar chemical shifts.



(17)

The isopropyl ester (16) was crystallized only with difficulty, so the highly crystalline *p*-bromophenacyl ester was prepared from the acid (15) and was fully characterized. However, the yield of this preparation, only 33%, limited the synthetic utility of the *p*-bromophenacyl ester.

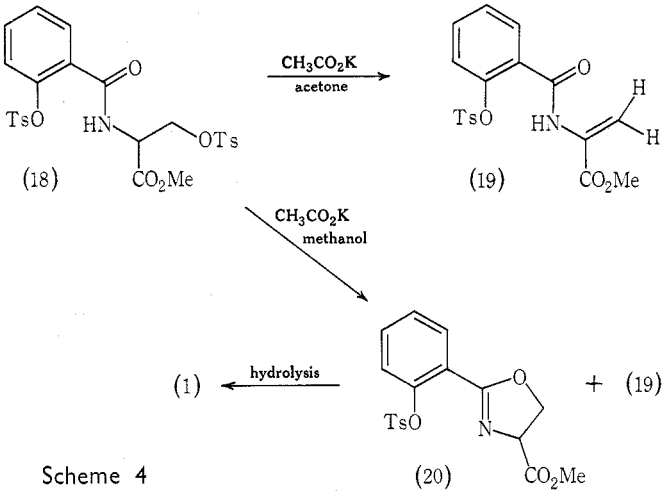
The conversion of the ester (16) into the hydrochloride of the oxazoline (11a) was most effectively carried out by treatment with thionyl chloride in boiling ether, in contrast to earlier reports[9,11] that reaction temperatures above 0° are unsuitable. The two samples of oxazoline (11a) derived from preparative methods A and B were shown to have identical structures.

[16] Whitesides, G. M., Holtz, D., and Roberts, J. D., *J. Am. chem. Soc.*, 1964, **86**, 2628.

Although route B provides an efficient and high-yield synthesis of the oxazoline carboxylic acid (1), it would be undesirable for the formation of optically active oxazolines, because the use of strong base in the preparation of the acid (15) would lead to racemization.

Method C

There was some initial difficulty in carrying out a clean conversion of the ester (16) into the oxazoline (11a) using thionyl chloride, so a milder procedure was investigated. This involved the preparation of the *p*-toluenesulphonyl (tosyl) derivative (18) and its subsequent treatment[17] with base to afford the tosyl oxazoline (20), which underwent hydrolysis to the desired oxazoline acid (1) (Scheme 4).



Scheme 4

The ditosylate (18) was obtained as a crystalline solid by treatment of *N*-2-hydroxybenzoylserine methyl ester with tosyl chloride in pyridine. When a solution of the ditosylate (18) in acetone was heated under reflux with potassium acetate, methyl *N*-2′-tosyloxybenzoyl-2-aminopropenoate (19) was obtained in 100% yield. However, when acetone was replaced by the more polar methanol as the reaction solvent, a 3 : 2 mixture of the tosyl oxazoline (20) and alkene (19) was obtained. Assuming that no interconversion of (19) and (20) occurs under the above conditions, there would appear to be competition between an intramolecular S_N2 displacement leading to (20) and an elimination of the E_2 or E_1cb type leading to (19). In such an elimination, the methine proton could be lost before or simultaneously with the tosylate anion and the elimination process could be facilitated by the stabilizing effect of the adjacent methoxycarbonyl group on the incipient carbanion or double bond. The observation that the less polar solvent favours elimination is compatible with the postulate that the above behaviour is due to competing $E2$ and S_N2 processes.

The oxazoline (20) was isolated by preparative thin-layer chromatography but could not be crystallized. It was characterized by its spectral properties and by hydrolysis to the oxazolinecarboxylic acid (1).

[17] Attenburrow, J., Elliott, D. F., and Penny, G. F., *J. chem. Soc.*, 1948, 310.

Experimental

Microanalyses were performed by the Australian Microanalytical Service, Melbourne. Ultraviolet spectra of solutions in 95% ethanol were measured with a Unicam S.P. 800 spectrophotometer. Infrared spectra refer to Nujol mulls or liquid films, as stated, and were measured with a Perkin–Elmer 257 spectrophotometer. Nuclear magnetic resonance spectra were recorded with a Varian A56/60 spectrometer. Chemical shifts are reported in p.p.m. relative to tetramethyl silane (δ 0·00) as an internal standard and the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; sp, septet; m, complex multiplet; b, broad resonance. The relative areas of signals are consistent with the assigned structures. Signals due to OH and NH disappeared on proton exchange with D_2O. In cases where there is more than one exchangeable proton assignments are made by analogy. Mass spectra were recorded with a Hitachi Perkin–Elmer RMU-6E spectrometer. Optical rotations were measured with a Stanley photoelectric polarimeter. Unless otherwise stated, compounds containing an asymmetric centre are in the racemic form. Melting points are uncorrected.

(*a*) *Synthesis of Model Oxazoline Compounds*

*2-Hydroxy-*N*-(2′-hydroxyethyl)benzamide* (*2*)

This compound was prepared by a modification of the method of Phillips.[10] Methyl salicylate (83 g, 0·55 mol) and ethanolamine (33·5 g, 0·55 mol) were heated together under reflux for 2 hr and the resulting methanol was evaporated under reduced pressure. The residual oil crystallized on the addition of benzene with cooling. Recrystallization from ethyl acetate gave the amide as white crystals (73 g, 65%), m.p. 115–117° (lit.[10] 113–114°). λ_{max} (ε) 237 (8100), 301 nm (4200); ν_{max} (Nujol) 3380, 3290, 1630, 1595, 1545, 1235, and 755 cm^{-1}. N.m.r. spectrum (DMSO-d_6): 3·5, m, 4H (CH_2CH_2); 5·1, b, 2H (OH); 7·4, m, 4H (aromatic protons); 8·8, b, 1H (NH). Mass spectrum: 181 (22%, M), 122 (12), 121 (100), 120 (26), 93 (15), 92 (14), 65 (26).

2-(2′-Hydroxyphenyl)-2-oxazoline Hydrochloride

Thionyl chloride (74 g, 0·62 mol) was slowly added to a solution of 2-hydroxy-*N*-(2′-hydroxyethyl)benzamide (50 g, 0·28 mol) in chloroform (500 ml) at 0°. The pale yellow crystals of the oxazoline hydrochloride which had formed after 18 hr were collected, m.p. 140–143° (lit.[7] 159°) (Found: Cl, 18·1. Calc. for $C_9H_{10}ClNO_2$: Cl, 17·8%). λ_{max} (ε) 242 (7900), 248 (8400), 257sh (5200), 305 nm (4000); ν_{max} (Nujol): 3150, 1630, 1255, 1095, and 750 cm^{-1}. The mass spectrum was identical to that of 2-(2′-hydroxyphenyl)-2-oxazoline.

2-(2′-Hydroxyphenyl)-2-oxazoline (*3*)

A solution of the above oxazoline hydrochloride (50 g) in water was basified with aqueous sodium bicarbonate and extracted with ether. The ether extract was washed, dried (Na_2SO_4), and concentrated to give a reddish oil which solidified on cooling. This was distilled to give large, colourless crystals of the oxazoline (29·3 g, 85% based on 2-hydroxy-*N*-(2′-hydroxyethyl)-benzamide), b.p. 106–107°/0·05 mm, m.p. 42–43°. λ_{max} (ε) 242 (8200), 249 (8100), 257sh (3800), 304 nm (4500): ν_{max} (Nujol) 1640, 1615, 1235, 1065, 945, and 755 cm^{-1}. N.m.r. spectrum: ($CDCl_3$) 4·2, m, 4H (CH_2CH_2); 7·2, m, 4H (aromatic protons); 12·1, b, 1H (OH). Mass spectrum: 164 (12%), 163 (100, M), 147 (14), 133 (10), 121 (18), 120 (23), 119 (88), 105 (10), 92 (26), 91 (23), 78 (10), 77 (11), 64 (14), 63 (16), 62 (14). The picrate (from ethanol) had m.p. 165–167° (lit.[8] 158°).

Ethyl Benzimidate Hydrochloride

This compound was prepared from benzonitrile by the method of Pinner[18] (54 g, 99%), m.p. 118° (dec.) (lit.[18] 118° (dec.)). ν_{max} 1630, 1275, 1075, 1065, 880, 865, and 705 cm^{-1}. N.m.r. spectrum (D_2O): 1·7, t, 3H (CH_3, *J* 7 Hz); 4·7, q, 2H (CH_2, *J* 7 Hz); 7·8, m, 5H (aromatic protons).

[18] Pinner, A., *Ber. dt. chem. Ges.*, 1883, **16**, 1643.

Ethyl Benzimidate (4)

A solution of ethyl benzimidate hydrochloride (20 g) in water was basified with aqueous sodium carbonate. The mixture was extracted with ether and the dried (Na_2SO_4) ether extract was concentrated to give ethyl benzimidate as a clear mobile oil (15·3 g, 95%). λ_{max} (ϵ) 231 nm (9100); ν_{max} (liquid film) 3330, 2980, 1630, 1375, 1325, 1075, and 690 cm^{-1}. N.m.r. spectrum ($CDCl_3$): 1·35, t, 3H (CH_3, J 7 Hz); 4·3, q, 2H (CH_2, J 7 Hz); 7·6, m, 5H (aromatic protons).

Serine Isopropyl Ester Hydrochloride (5a)

This compound was prepared by the method of Elliott[9] (16 g, 92%), m.p. 135–139° (lit.[9] 142–143°). ν_{max} (Nujol) 3390, 1730, 1505, 1250, 1155, 1115, 1095, and 1035 cm^{-1}. N.m.r. spectrum (D_2O): 1·3, d, 6H ($CH(CH_3)_2$, J, 6 Hz); 4·1, m, 3H (CH_2CH); 5·1, sp, 1H ($CH(CH_3)_2$, J 6 Hz).

Isopropyl 2-Phenyl-2-oxazoline-4-carboxylate (6)

This compound was prepared by the method of Elliott[9] (2·6 g, 40%), b.p. 106–108°/0·05 mm, m.p. 39–40° (lit.[9] 41–41·5°). λ_{max} (ϵ) 243 nm (8900); ν_{max} (Nujol) 1730, 1630, 1205, 1090, and 695 cm^{-1}. N.m.r. spectrum ($CDCl_3$): 1·3, d, 6H ($CH(CH_3)_2$, J 6 Hz); 4·7, m, 3H ($CHCH_2$); 5·1, sp, 1H ($CH(CH_3)_2$, J 6 Hz); 7·7, m, 5H (aromatic protons). Mass spectrum: 233 (4%, M), 147 (15), 146 (100), 118 (20), 105 (13), 91 (25), 77 (17), 51 (9). The picrate had m.p. 134–135° (lit.[9] 134–135°).

(b) Reactions of 2-(2′-Hydroxyphenyl)-2-oxazoline

Thermal Treatment of 2-(2′-Hydroxyphenyl)-2-oxazoline Hydrochloride

2-(2′-Hydroxyphenyl)-2-oxazoline hydrochloride (3·2 g) was heated until it melted. The solid which formed on cooling was recrystallized from chloroform to yield *N-(2′-chloroethyl)-2-hydroxybenzamide* (9) as white needles (2·6 g, 82%), m.p. 131–132° (Found: C, 54·0; H, 5·1; Cl, 18·0; N, 7·0. $C_9H_{10}ClNO_2$ requires C, 54·2; H, 5·1; Cl, 17·8; N, 7·0%). λ_{max} (ϵ) 237 (8800), 301 nm (4200); ν_{max} (Nujol) 3360, 1640, 1590, 1540, 1495, 1260, 1240, and 755 cm^{-1}. N.m.r. spectrum ($CDCl_3$): 3·8, m, 4H (CH_2CH_2); 7·0, m, 5H (aromatic protons, NH); 12·1, b, 1H (OH). Mass spectrum: 201 (10%, M(^{37}Cl)), 199 (29%, M(^{35}Cl)), 163 (15), 149 (13), 121 (100), 120 (77), 119 (16), 93 (16), 92 (28), 91 (10), 65 (35), 64 (12), 63 (16), 53 (10).

Acid Hydrolysis of 2-(2′-Hydroxyphenyl)-2-oxazoline

A solution of 2-(2′-hydroxyphenyl)-2-oxazoline hydrochloride (150 mg) in water was heated at 100° for 15 min. The cooled solution was concentrated to yield a white solid, m.p. 168–171°. This had an identical infrared spectrum to an authentic sample of 2′-aminoethyl-2-hydroxybenzoate hydrochloride (8) prepared by the method of Phillips,[10] m.p. 176–178° (lit.[10] 189–190°). ν_{max} (Nujol) 1680, 1615, 1600, 1300, 1230, 960 and 775 cm^{-1}.

Base Hydrolysis of 2-(2′-Hydroxyphenyl)-2-oxazoline

A solution of 2-(2′-hydroxyphenyl)-2-oxazoline (200 mg) in 1N sodium hydroxide was heated at 100° for 15 min. The solution was cooled and neutralized by the addition of 2N hydrochloric acid. The white crystals that precipitated were collected, m.p. 115–117°. This compound had an infrared spectrum identical to that of an authentic sample of 2-hydroxy-*N*-(2′-hydroxyethyl)benzamide.

(c) Metal Complexes of 2-(2′-Hydroxyphenyl)-2-oxazoline

The complexes were prepared by mixing filtered methanolic solutions of the metal acetate (0·005 mol) and 2-(2′-hydroxyphenyl)-2-oxazoline (0·01 mol). The complexes which precipitated immediately on mixing, or after a few minutes, were collected and washed thoroughly with methanol.

Bis[2-(2'-hydroxyphenyl)-2-oxazolinato]copper(II)

This *complex* was prepared as dull green crystals (100%) (Found: C, 55·1; H, 4·2; Cu, 16·6; N, 7·4. $C_{18}H_{16}CuN_2O_4$ requires C, 55·7; H, 4·2; Cu, 16·4; N, 7·2%).

Bis[2-(2'-hydroxyphenyl)-2-oxazolinato]nickel(II)

This *complex* was prepared as grey crystals (100%) (Found: C, 56·6; H, 4·1; N, 7·0. $C_{18}H_{16}N_2NiO_4$ requires C, 56·4; H, 4·2; N, 7·3%).

Bis[2-(2'-hydroxyphenyl)-2-oxazolinato]zinc(II)

This *complex* was prepared as white crystals (30%) (Found: C, 54·8; H, 4·2; N, 6·9. $C_{18}H_{16}N_2O_4Zn$ requires C, 55·5; H, 4·1; N, 7·2%).

Chlorobis[2-(2'-hydroxyphenyl)-2-oxazolinato]iron(III)

Filtered dry methanolic solutions of ferric chloride (0·005 mol) and 2-(2'-hydroxyphenyl)-2-oxazoline (0·015 mol) were mixed. Dark purple crystals of the *complex* precipitated during 1 hr (30%) (Found: C, 51·9; H, 3·9; N, 6·2. $C_{18}H_{16}ClFeN_2O_4$ requires C, 52·0; H, 3·9; N, 6·7%).

(d) Synthesis of Acid (1) by Method A

2-Hydroxybenzonitrile

This compound was prepared from salicylaldehyde by the method of Van Es[19] (40 g, 78%), m.p. 93–95° (lit.[19] 98°). ν_{max} (Nujol) 3220, 2260, 1600, 1590, 1310, 1270, 1245, 1165, 765, and 755 cm^{-1}.

Ethyl 2-Hydroxybenzimidate (10)

A solution of 2-hydroxybenzonitrile (27·8 g) in a mixture of ethanol (11 ml), ether (25 ml), and benzene (6 ml) was treated with dry hydrogen chloride at 0°. After 6 weeks the reaction mixture was poured into ether and the red precipitate of crude ethyl 2-hydroxybenzimidate hydrochloride was collected. Impure 2-hydroxybenzonitrile (17·6 g) was recovered from the filtrate. A solution of the imidate hydrochloride in water was basified with aqueous sodium bicarbonate and extracted with ether; the washed and dried (Na_2SO_4) ether extract was concentrated to yield a solid. This was recrystallized from hexane to give cream-coloured needles of the *imidate* (10·3 g, 27%), m.p. 69–70·5° (Found: C, 65·5; H, 6·8; N, 8·8. $C_9H_{11}NO_2$ requires C, 65·4; H, 6·7; N, 8·5%). λ_{max} (ϵ) 237sh (6800), 244sh (5500), 257sh (1900), 303 (2900), 362 nm (1650); ν_{max} (Nujol) 3300, 1640, 1600, 1500, 1275, 1155, 1095, 840, and 760 cm^{-1}. N.m.r. spectrum (CCl_4): 1·3, t, 3H (CH_3, *J* 7 Hz); 3·9, q, 2H (CH_2, *J* 7 Hz); 7·2, m, 4H (aromatic protons); 10·0, b, 2H (NH, OH). Mass spectrum: 165 (26%, M), 164 (11), 121 (26), 120 (100), 119 (21), 93 (13), 92 (61), 91 (26), 77 (12), 69 (19), 65 (29), 64 (21), 63 (16), 51 (13). The *picrate* (from ethanol) had m.p. 146–148° (Found: C, 45·9; H, 3·6; N, 14·0. $C_{15}H_{14}N_4O_9$ requires C, 45·7; H, 3·6; N, 14·2%).

Isopropyl 2-(2'-Hydroxyphenyl)-2-oxazoline-4-carboxylate (11a)

Solutions of ethyl 2-hydroxybenzimidate (2·0 g, 0·012 mol) and serine isopropyl ester hydrochloride (2·2 g, 0·012 mol) in isopropanol were mixed and kept at 65° for 12 hr. The reaction mixture was concentrated and the residual oil was partitioned between chloroform and water. The chloroform layer was washed, dried (Na_2SO_4), and concentrated to yield a reddish oil. Column chromatography (silica gel, 25 g), with benzene elution, gave an oil that yielded colourless needles of the *oxazoline* when crystallized from light petroleum (1·7 g, 56%), m.p. 30–31° (Found: C, 62·9; H, 6·0; N, 5·6. $C_{13}H_{15}NO_4$ requires C, 62·6; H, 6·1; N, 5·6%). λ_{max} (ϵ) 242 (9300), 248 (10000), 257sh (5300), 305 nm (4800): ν_{max} (liquid film) 2980, 1725, 1490, 1370, 1260, 1235, 1205, 1105, and 750 cm^{-1}. N.m.r. spectrum ($CDCl_3$): 1·3, d, 6H ($CH(CH_3)_2$, *J* 6 Hz); 4·7, m, 3H

[19] Van Es, T., *J. chem. Soc.*, 1965, 1564.

(C**H**CH$_2$); 5·1, sp, 1H (C**H**(CH$_3$)$_2$, J 6 Hz); 7·2, m, 4H (aromatic protons); 11·6, b, 1H (OH). Mass spectrum: 249 (46%, M), 207 (13), 163 (11), 162 (100), 134 (24), 121 (13), 107 (18), 92 (10). The *picrate* (from aqueous ethanol) had m.p. 134–135° (Found: N, 11·6. $C_{19}H_{18}N_4O_{11}$ requires N, 11·7%).

(S)-*Serine Isopropyl Ester Hydrochloride* (*5b*)

A suspension of (*S*)-serine (2·0 g) in isopropanol (75 ml) was heated under reflux. Dry hydrogen chloride was passed into the suspension for 1·5 hr during which time the serine dissolved. The solution was cooled and concentrated to yield a solid which on recrystallization from isopropanol gave the *ester hydrochloride* as long colourless needles (3·6 g, 99%), m.p. 150–151° (Found: C, 39·2; H, 7·6; N, 7·6. $C_6H_{14}ClNO_3$ requires C, 39·3; H, 7·7; N, 7·6%). $[\alpha]_D^{20·5}$ −12·3° (*c*, 0·195 in water). The infrared spectrum was identical to that of the racemic compound.

(S)-*Isopropyl 2-(2′-Hydroxyphenyl)-2-oxazoline-4-carboxylate* (*11b*)

Solutions of ethyl 2-hydroxybenzimidate (0·9 g, 0·0055 mol) and (*S*)-serine isopropyl ester hydrochloride (1·0 g, 0·0055 mol) in isopropanol were treated as for the racemic compound. Chromatography gave the oxazoline as an oil (0·85 g, 62%), which could not be crystallized but was further purified by distillation at 110–112° (bath)/0·01 mm (Found: C, 62·5; H, 6·4; N, 5·6. $C_{13}H_{15}NO_4$ requires C, 62·6; H, 6·1; N, 5·6%). $[\alpha]_D^{20·5}$ +63·6° (*c*, 0·349 in chloroform). The infrared and n.m.r. spectra are identical to those of the racemic compound. This compound was unstable and slowly decomposed.

Serine Methyl Ester Hydrochloride (*5c*)

Dry hydrogen chloride was passed into a suspension of serine (2·1 g) in dry methanol. The resultant solution was kept at 0° overnight and concentrated to yield the ester as a hygroscopic solid (3·1 g, 100%), m.p. 110–115° (lit.[9] 134°). ν_{max} (Nujol) 3380, 1735, 1590, 1255, and 1050 cm^{-1}.

Methyl 2-(2′-Hydroxyphenyl)-2-oxazoline-4-carboxylate (*11c*)

Solutions of ethyl 2-hydroxybenzimidate (1·0 g, 0·006 mol) and serine methyl ester hydrochloride (1·0 g, 0·0065 mol) in dry methanol were mixed and heated under reflux for 6 hr. The reaction mixture was concentrated and the residue was partitioned between chloroform and water. The chloroform layer was washed, dried (Na_2SO_4), and concentrated to yield an oil. Column chromatography (silica gel, 25 g), with benzene elution, yielded an oil which gave colourless needles of the *oxazoline* when crystallized from light petroleum (0·7 g, 53%), m.p. 71–72° (Found: C, 59·7; H, 5·1; N, 6·2. $C_{11}H_{11}NO_4$ requires C, 59·7; H, 5·0; N, 6·3%). λ_{max} (ϵ) 243 (9700), 248 (10500), 257sh (5500), 305 nm (4900); ν_{max} (Nujol) 1745, 1635, 1615, 1265, 1215, 760 cm^{-1}. N.m.r. spectrum ($CDCl_3$): 3·8, s, 3H (CH_3); 4·7, m, 3H (C**H**C**H**$_2$); 7·2, m, 4H (aromatic protons); 11·0, b, 1H (OH). Mass spectrum: 221 (47%, M), 163 (10), 162 (100), 134 (89), 121 (17), 120 (12), 107 (87), 92 (29), 91 (14), 78 (14), 77 (27), 65 (21), 64 (19), 63 (18), 51 (16).

2-(2′-Hydroxyphenyl)-2-oxazoline-4-carboxylic Acid (*1*)

A solution of isopropyl 2-(2′-hydroxyphenyl)-2-oxazoline-4-carboxylate (0·30 g) in 2N sodium hydroxide at 0° was acidified with cold 2N hydrochloric acid to pH 3. The solution was extracted with ethyl acetate and the washed and dried (Na_2SO_4) ethyl acetate extract was concentrated to give an oil. This was dissolved in chloroform and the crystals of the *oxazoline* which were deposited during 48 hr were collected (0·18 g, 72%), m.p. 157–158° (Found: C, 57·6; H, 4·3; N, 6·5. $C_{10}H_9NO_4$ requires C, 58·0; H, 4·4; N, 6·8%). λ_{max} (ϵ) 243 (10400), 248 (11000), 257sh (5800), 305 nm (5300); ν_{max} (Nujol): 3310, 1690, 1635, 1265, 1245, and 760 cm^{-1}. N.m.r. spectrum (DMSO-d_6): 4·8, m, 3H (C**H**C**H**$_2$); 7·3, m, 4H (aromatic protons); 9·5, b, 2H (OH). Mass spectrum: 207 (31%, M), 162 (56), 134 (81), 133 (11), 121 (37), 120 (19), 107 (100), 105 (16), 104 (11), 93 (13), 92 (41), 91 (22), 79 (13), 78 (19), 77 (34), 76 (10), 69 (13), 65 (34), 64 (34), 63 (34), 53 (13), 52 (12), 51 (26), 50 (15).

(e) Synthesis of Acid (1) by Method B

2-Hydroxybenzohydrazide

This compound was prepared by the method of Baker[20] (54 g, 95%), m.p. 147–148° (lit.[20] 147°). ν_{max} (Nujol): 3320, 3260, 1640, 1585, 1240, 760 cm^{-1}.

N-*2-Hydroxybenzoylserine* (*15*)

A solution of 2-hydroxybenzohydrazide (30 g, 0·20 mol) in hydrochloric acid (400 ml of 1N) was cooled in ice and a solution of sodium nitrite (16·5 g, 0·24 mol) in water was added dropwise during 1 hr so that the temperature was maintained at 3–5°. The resulting precipitate of 2-hydroxybenzoyl azide was kept at 5° for 0·5 hr and was then collected and washed with ice-water. The damp azide (caution: lachrymator) was added to a solution of serine (30 g, 0·29 mol) in sodium hydroxide (200 ml of 1N) cooled to 0°. Further sodium hydroxide (210 ml) was added and the mixture was allowed to come to room temperature. The mixture was stirred for 2·5 hr during which time the azide dissolved. The solution was extracted with ether, acidified with 2N hydrochloric acid, and then extracted with ethyl acetate (2 × 200 ml). The ethyl acetate extract was washed, dried (Na_2SO_4), and concentrated to yield the *amide* (32 g, 72%), which was recrystallized from ethyl acetate as small white crystals, m.p. 156–158° (Found: C, 53·6; H, 5·1; N, 6·1. $C_{10}H_{11}NO_5$ requires C, 53·3; H, 4·9; N, 6·2%). λ_{max} (ϵ) 236 (8800), 301 nm (3300); ν_{max} (Nujol) 3340, 3310, 1715, 1620, 1560, 1235, 755 cm^{-1}. N.m.r. spectrum (DMSO-d_6): 3·9, d, 2H (CH_2, *J* 5 Hz); 4·5, m, 1H (CH); 4·8, b, 2H (exchangeable protons); 7·5, m, 4H (aromatic protons); 8·9, bd, 1H (NH); 11·8, b, 1H (exchangeable proton). Mass spectrum: 225 (19%, M), 148 (14), 121 (100), 120 (32), 93 (17), 92 (17), 65 (30).

N-*2-Hydroxybenzoylserine* p-*Bromophenacyl Ester*

A suspension of *N*-2-hydroxybenzoylserine (0·5 g, $2·2 \times 10^{-3}$ mol) in water was neutralized with 2N sodium hydroxide. A solution of *p*-bromophenacyl bromide (0·5 g, $1·8 \times 10^{-3}$ mol) in ethanol was added to the resulting solution and the mixture was heated under reflux for 1 hr. The solution was cooled overnight and the solid which had formed was collected and recrystallized from aqueous ethanol to yield the *ester* as white crystals (0·25 g, 33%), m.p. 124–126° (Found: C, 51·2; H, 3·7; Br, 19·2; N, 3·3. $C_{18}H_{16}BrNO_6$ requires C, 51·2; H, 3·8; Br, 18·9; N, 3·3%). λ_{max} (ϵ) 259 (22500), 303sh nm (3100); ν_{max} (Nujol) 3470, 3290, 1745, 1675, 1635, 1585, 1075, 760 cm^{-1}. N.m.r. spectrum (DMSO-d_6): 4·0, bd, 3H (CHC**H**$_2$, OH); 4·9, m, 1H (CH); 5·6, s, 2H (CH_2CO); 7·5, m, 8H (aromatic protons); 9·1, bd, 1H (NH); 11·9, b, 1H (OH). The chemical shift of the exchangeable proton at 4·0 is based only on integration. Mass spectrum: 423 (4%, M(^{81}Br)), 421 (4, M(^{79}Br)), 185 (25), 177 (26), 157 (10), 155 (10), 148 (34), 121 (100), 120 (20), 93 (10), 92 (11), 76 (12), 75 (10), 65 (18).

N-*2-Hydroxybenzoylserine Isopropyl Ester* (*16*)

A solution of *N*-2-hydroxybenzoylserine (5·0 g) in isopropanol was saturated with dry hydrogen chloride at room temperature. After 24 hr the solution was concentrated to yield an oil which slowly crystallized (5·65 g, 95%). Recrystallization from methylene chloride–n-pentane gave the *isopropyl ester* as white crystals, m.p. 99–101° (Found: C, 58·3; H, 6·3; N, 5·2. $C_{13}H_{17}NO_5$ requires C, 58·4; H, 6·4; N, 5·2%). λ_{max} (ϵ) 236 (8900), 300 nm (4100); ν_{max} (Nujol) 3470, 3360, 1720, 1615, 1220, 1105, 760 cm^{-1}. N.m.r. spectrum ($CDCl_3$): 1·3, d, 6H ($CH(CH_3)_2$, *J* 6 Hz); 2·4, b, 2H (OH, NH); 4·1, d, 2H (CH_2, *J* 4 Hz); 4·8, m, 1H (NCH); 5·1, sp, 1H (C**H**$(CH_3)_2$, *J* 6 Hz); 7·2, m, 4H (aromatic protons); 11·9, b, 1H (OH). Mass spectrum: 267 (10%, M), 180 (10), 121 (100), 120 (20), 93 (16), 92 (14), 65 (29), 60 (10).

O-*2-Hydroxybenzoylserine Isopropyl Ester Hydrochloride* (*17*)

N-2-Hydroxybenzoylserine (1·4 g) was suspended in isopropanol and dry hydrogen chloride was rapidly bubbled into the suspension until the isopropanol boiled and the solid dis-

[20] Baker, W., Haksar, C. N., and McOmie, J. F. W., *J. chem. Soc.*, 1950, 170.

solved. The hydrogen chloride stream was moderate and the solution was heated under reflux for 1 hr. The reaction mixture was concentrated and the oily residue was dissolved in ethyl acetate–benzene and cooled for 24 hr. The *product* was deposited as a white solid (0·2 g, 11%), m.p. 141° (Found: C, 50·9; H, 6·0. $C_{13}H_{18}ClNO_5$ requires C, 51·4; H, 6·0%). λ_{max} (ϵ) 240 (9300), 309 nm (4100); ν_{max} (Nujol): 3250, 2660, 1740, 1700, 1250, 770, and 710 cm^{-1}. N.m.r. spectrum (DMSO-d_6): 1·3, q, 6H ($CH(CH_3)_2$); 4·6, m, 1H (NCH); 4·8, d, 2H (CH_2, J 4 Hz); 5·1, sp, 1H ($CH(CH_3)_2$, J 6 Hz); 7·5, m, 4H (aromatic protons); 9·2, b, 4H ($^+NH_3$, OH). Mass spectrum: 267 (14%, M−36), 180 (39), 121 (100), 120 (10), 88 (13), 74 (16), 65 (12), 60 (10). The remaining product appeared to be crude *N*-2-hydroxybenzoylserine isopropyl ester.

Isopropyl 2-(2′-Hydroxyphenyl)-2-oxazoline-4-carboxylate Hydrochloride

Thionyl chloride (4·9 g, 0·041 mol) was added to a suspension of *N*-2-hydroxybenzoylserine isopropyl ester (2·0 g, 0·0075 mol) in dry ether. The mixture was heated under reflux for 1 hr and the resulting *oxazoline hydrochloride* was collected (1·7 g, 80%), m.p. 133–134°. ν_{max} 1735, 1630, 1260, 1230, 1090, 765 cm^{-1}. This compound was not purified further.

Isopropyl 2-(2′-Hydroxyphenyl)-2-oxazoline-4-carboxylate (11a)

Isopropyl 2-(2′-hydroxyphenyl)-2-oxazoline-4-carboxylate hydrochloride (1·7 g) was partitioned between chloroform and aqueous sodium bicarbonate and the washed and dried (Na_2SO_4) chloroform layer was concentrated to yield an oil. Crystallization from light petroleum (charcoal) gave the oxazoline as colourless needles (1·25 g, 85%), m.p. 30–31°. The infrared spectrum of this compound was identical to that of an authentic sample of isopropyl 2-(2′-hydroxyphenyl)-2-oxazoline-4-carboxylate.

(f) Synthesis of Acid (1) by Method C

N-*2-Hydroxybenzoylserine Methyl Ester*

A solution of *N*-2-hydroxybenzoylserine (2·0 g) in methanol was saturated with dry hydrogen chloride. After 24 hr at room temperature the solution was concentrated to yield the *ester* as an oil (2·15 g, 100%) which was partly purified by column chromatography (silica gel, 20 g), with chloroform elution, but could not be crystallized or distilled. N.m.r. spectrum ($CDCl_3$): 3·8, s, 3H (CH_3); 4·1, d, 2H (CH_2, J 4 Hz); 4·8, m, 1H (NCH); 7·2, m, 5H (aromatic protons, NH); 11·3, b, 1H (OH). The assignments of the exchangeable protons are tentative.

O-*Tosyl*-N-(*2-tosyloxybenzoyl*)*serine Methyl Ester (18)*

A solution of 2-hydroxybenzoylserine methyl ester (0·75 g, $3·1 \times 10^{-3}$ mol) in dry pyridine (15 ml) was cooled to 0°. *p*-Toluenesulphonyl chloride (2·2 g, $11·6 \times 10^{-3}$ mol) was then added. After 36 hr at −10° the mixture was poured into ice-water and stirred for 15 min to yield a white gum. The mixture was extracted with ether and the combined ether extracts were washed with 5N hydrochloric acid, then water, dried (Na_2SO_4/K_2CO_3), and concentrated to yield the *ditosylate* as a white solid (1·2 g, 71%). This was crystallized from chloroform–ether as colourless crystals, m.p. 125·5–126° (Found: C, 55·0; H, 4·7; N, 2·7; $C_{25}H_{25}NO_9S_2$ requires C, 54·8; H, 4·6; N, 2·6%). λ_{max} (ϵ) 226 nm (12400): ν_{max} (Nujol) 3370, 1755, 1645, 1200, 1180, 860, and 730 cm^{-1}. N.m.r. spectrum ($CDCl_3$): 2·3, s, 3H ($C_6H_4CH_3$); 2·4, s, 3H ($C_6H_4CH_3$); 3·8, s, 3H (OCH_3); 4·5, d, 2H (CH_2, J 3 Hz); 4·8, m, 1H (NCH); 7·5, m, 12H (aromatic protons); 9·8, b, 1H (NH). Mass spectrum: 316 (11%), 311 (24), 168 (23), 161 (28), 155 (47), 117 (13), 105 (20), 99 (23), 92 (15), 91 (100), 85 (13), 83 (21), 78 (12), 77 (20), 74 (41), 69 (10), 65 (24), 63 (14), 59 (73), 51 (10).

Treatment of O-*Tosyl*-N-(*2-tosyloxybenzoyl*)*serine Methyl Ester with Potassium Acetate in Acetone*

Anhydrous potassium acetate (0·20 g, $2·0 \times 10^{-3}$ mol) was added to a solution of *O*-tosyl-*N*-(2-tosyloxybenzoyl)serine methyl ester (0·20 g, $3·7 \times 10^{-4}$ mol) in acetone and the mixture was heated under reflux for 3 hr. The reaction mixture was concentrated and the residue was partitioned between chloroform and water. The dried (Na_2SO_4) chloroform layer was concentrated to yield *methyl 2-amino*-N-(*2′-tosyloxybenzoyl*)*propenoate* (19) as a white solid (0·14 g, 100%).

Recrystallization from hexane gave colourless plates, m.p. 121–123° (Found: C, 57·3; H, 4·7; N, 3·6. $C_{19}H_{17}NO_6S$ requires C, 57·6; H, 4·6; N, 3·7%). λ_{max} (ϵ) 229 (21200), 262 nm (7500); ν_{max} (Nujol) 3380, 1715, 1670, 1520, 1340, 1200, 1185, 1085, 790, 650 cm^{-1}. N.m.r. spectrum ($CDCl_3$): 2·4, s, 3H ($C_6H_4CH_3$); 3·9, s, 3H (OCH_3); 5·9, d, 1H (HNC=CH (*E*), *J* 1·5 Hz); 6·6, s, 1H (HNC=CH (*Z*)); 7·4, m, 8H (aromatic protons); 8·7, b, 1H (NH). Mass spectrum: 375 (9%, M), 275 (30), 220 (20), 155 (45), 121 (24), 120 (15), 92 (37), 91 (100), 65 (49), 64 (14), 63 (13).

Treatment of O-*Tosyl*-N-(*2-tosyloxybenzoyl*)*serine Methyl Ester with Potassium Acetate in Methanol*

O-Tosyl-*N*-(2-tosyloxybenzoyl)serine methyl ester (0·27 g, $5·0 \times 10^{-4}$ mol) and anhydrous potassium acetate (0·20 g, $2·0 \times 10^{-3}$ mol) were dissolved in dry methanol and heated together under reflux for 3 hr. The reaction mixture was concentrated and the residue was partitioned between chloroform and water. The dried (Na_2SO_4) chloroform layer was concentrated to yield an oil. The n.m.r. spectrum of this indicated that it was a mixture of *methyl 2-(2′-tosyloxyphenyl)-2-oxazoline-4-carboxylate* (20) and methyl 2-amino-*N*-(2′-tosyloxybenzoyl)propenoate (19) in a 3 : 2 ratio. These were separated by preparative thin-layer chromatography (R_F 0·2 and 0·6 respectively, chloroform). The alkene was obtained as a solid (27 mg, 14%), m.p. 114–117°. The oxazoline was obtained as an oil (73 mg, 39%) which could not be crystallized and was not further purified. N.m.r. spectrum ($CDCl_3$): 2·4, s, 3H ($C_6H_4CH_3$); 3·8, s, 3H (OCH_3); 4·5, m, 3H ($CHCH_2$); 7·5, m, 8H (aromatic protons). ν_{max} (thin film) 2950, 1740, 1375, 1200, 1175, 860, and 780 cm^{-1}.

2-(2′-Hydroxyphenyl)-2-oxazoline-4-carboxylic Acid (*1*)

Methyl 2-(2′-tosyloxyphenyl)-2-oxazoline-4-carboxylate (67 mg) was dissolved in 2N sodium hydroxide. After 12 hr at room temperature the solution was acidified with 2N hydrochloric acid, extracted with ethyl acetate, and the dried (Na_2SO_4) ethyl acetate extract was concentrated to yield an oil. This oil was dissolved in the minimum amount of chloroform and allowed to stand at room temperature. During 48 hr a solid was deposited (7 mg, 19%), m.p. 149–150°. This had an infrared spectrum identical to that of an authentic sample of 2-(2′-hydroxyphenyl)-2-oxazoline-4-carboxylic acid.