

1113. *Derivatives of 6-Aminopenicillanic Acid. Part VII.¹ Further 3,5-Disubstituted Isoxazole-4-Carboxylic Acid Derivatives.*

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Various methods have been used to prepare further 3,5-disubstituted isoxazole-4-carboxylic acids as intermediates for the synthesis of penicillins, many of which resisted inactivation by penicillinase.

WE have previously reported the preparation of 3- and 5-phenylisoxazole-4-carboxylic acid and many of their alkyl and halogen derivatives.¹ Reaction of the acid chlorides with 6-aminopenicillanic acid gave isoxazolympenicillins, most of which exhibited useful antibacterial activity, especially against penicillinase-producing strains of staphylococci.^{1,2} We have now prepared, as intermediates for the synthesis of analogous penicillins, other isoxazole-4-carboxylic acids containing a broader selection of 3- and 5-substituents.

Treatment of various aromatic or heteroaromatic aldoximes and of pivalalldoxime with chlorine gave the corresponding hydroxamoyl chlorides (I), which were not usually purified. Conversion of *o*- and *p*-methoxybenzalldoxime into the hydroxamoyl chlorides

¹ Part VI, Doyle, Hanson, Long, Nayler, and Stove, preceding paper.

² Doyle, Long, Nayler, and Stove, *Nature*, 1961, **192**, 1183.

was effected with nitrosyl chloride,³ in order to avoid chlorination of the benzene ring. Condensation of the hydroxamoyl chlorides with the sodio-derivative of methyl or ethyl acetoacetate by the general method of Quilico and Fusco⁴ gave 3-substituted 5-methylisoxazole-4-carboxylic esters. These were mostly hydrolysed to the corresponding acids (II; R' = Me) with alkali, but, when the 3-substituent was nitrophenyl, nitrofuryl, or pyridyl, acid hydrolysis gave a cleaner product. Heating 3-*p*-methoxyphenyl-5-methylisoxazole-4-carboxylic acid with aluminium chloride gave the 3-*p*-hydroxyphenyl compound.

The action of nitric and sulphuric acid on 5-methyl-3-phenylisoxazole-4-carboxylic acid (II; R = Ph; R' = Me) provided a convenient alternative route to the 3-*m*-nitrophenyl acid. Hydrogenation of the nitro-compound in ethanol over Adams catalyst gave 3-*m*-aminophenyl-5-methylisoxazole-4-carboxylic acid together with a by-product, C₁₀H₁₂N₂O, which appears to be the ketone (III) formed by ring-opening and decarboxylation. Esterification of the major product with methanol and hydrogen chloride gave methyl 3-*m*-aminophenyl-5-methylisoxazole-4-carboxylate. Conversion into the diazonium fluoroborate in the usual way, followed by thermal decomposition and hydrolysis of the resulting ester gave 3-*m*-fluorophenyl-5-methylisoxazole-4-carboxylic acid. Diazotisation of the amino-acid (II; R = *m*-H₂N·C₆H₄, R' = Me) in dilute sulphuric acid followed by heating to 100° gave 3-*m*-hydroxyphenyl-5-methylisoxazole-4-carboxylic acid, which, with methyl sulphate and potassium carbonate in acetone, afforded the *m*-methoxy-compound (II; R = *m*-MeO·C₆H₄, R' = Me).

Korte and Störko⁵ recently described the conversion of 3-phenylisoxazol-5-one (IV; R = Ph) into the 4-acetyl derivative (VI; R = Ph) either directly with acetic anhydride or, in better yield, by way of the 1'-ethoxyethylidene derivative (V; R = Ph). On treatment with hot, concentrated alkali the acylisoxazolone (VI; R = Ph) underwent a rearrangement of the type studied by Speroni,⁶ to give 5-methyl-3-phenylisoxazole-4-carboxylic acid (II; R = Ph, R' = Me). By subjecting 3-*p*-methoxyphenylisoxazol-5-one (IV; R = *p*-MeO·C₆H₄) to a similar sequence of reactions we obtained 3-*p*-methoxyphenyl-5-methylisoxazole-4-carboxylic acid (II; R = *p*-MeO·C₆H₄, R' = Me), identical with that synthesised from *p*-methoxybenzohydroxamoyl chloride. Synthesis of 3-2'-furyl-5-methylisoxazole-4-carboxylic acid was similarly accomplished from 3-2'-furylisoxazol-5-one (IV; R = 2-C₄H₃O). In the course of similar syntheses of 5-methyl-3-2'-thienyl- and 3-(3,5-dimethyl-4-isoxazolyl)-5-methylisoxazole-4-carboxylic acids it was observed that the intermediate 1'-ethoxyethylidene compounds (V) were exceptionally readily hydrolysed, being converted into the 4-acetyl compounds (VI) on exposure to moist air.

Condensation of ethyl α-benzoylmalonate with hydroxylamine gave ethyl 4,5-dihydro-5-oxo-3-phenylisoxazole-4-carboxylate (VII). d'Alcontres and his colleagues⁷ were unable to prepare the compound in this way, but they did obtain it from benzo-hydroxamoyl chloride, ethyl malonate, and sodium hydroxide. Treatment with diazomethane gave the *O*-methyl derivative (VIII), as reported by d'Alcontres,⁷ whereas methyl iodide gave the isomeric *N*-methyl derivative (IX). Both methyl derivatives are neutral compounds, whereas the isoxazolones (IV–VII) are strongly acidic. Unfortunately, the ester (VIII) could not be hydrolysed to the acid (II; R = Ph, R' = OMe) because the methoxy-group proved to be more labile than the ester group: mild treatment with alkali or acid gave the isoxazolone ester (VII), whereas more vigorous treatment with these reagents gave the simple isoxazolone (IV; R = Ph) and acetophenone, respectively.

Claisen condensation of diacetylacetic ester with hydroxylamine to give, after hydrolysis of the ester, 3,5-dimethylisoxazole-4-carboxylic acid,⁸ was applied to the

³ Rheinboldt, Dewald, Jansen, and Schmitz-Dumont, *Annalen*, 1926, **451**, 161.

⁴ Quilico and Fusco, *Gazzetta*, 1937, **67**, 589.

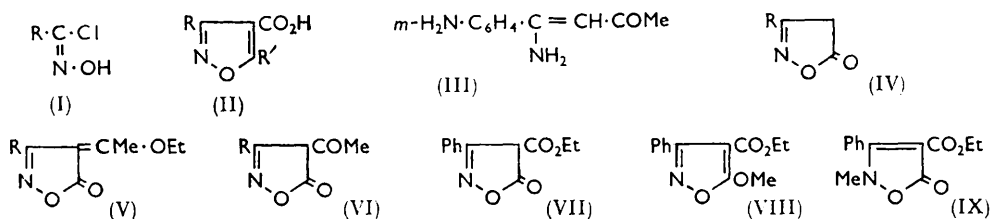
⁵ Korte and Störko, *Chem. Ber.*, 1961, **94**, 1956.

⁶ Speroni, *Gazzetta*, 1952, **82**, 691.

⁷ d'Alcontres, Lo Vecchio, and Lamonica, *Gazzetta*, 1961, **91**, 1005.

⁸ Claisen, *Annalen*, 1893, **277**, 174.

preparation of the 3,5-di-isopropyl acid (II; $R = R' = \text{Pr}^i$) from di-isobutyrylacetic ester. Various α -acyl derivatives of acetoacetic ester were similarly condensed with hydroxylamine to give 5-substituted 3-methylisoxazole-4-carboxylic acids (II; $R = \text{Me}$). Where the second substituent (R' in II) is aromatic this formulation is in accord with the hitherto invariable conversion of α -alkanoyl- α -aroylacetic esters into 3-alkyl-5-aryl- rather



than 5-alkyl-3-aryl-isoxazole-4-carboxylic acids.¹ The structure of the 5-styryl compound is confirmed by a marked difference in physical properties from those reported for the isomeric 5-methyl-3-styrylisoxazole-4-carboxylic acid.⁹ When the 5-substituent was 2-furyl, 2-thienyl, or 3,5-dimethyl-4-isoxazolyl, the products were shown to differ from the 3-heterocyclic 5-methyl isomers, here obtained by alkaline rearrangement of the appropriate 4-acetylisoxazolones (VI). Finally, the products from the α -hexahydrobenzoyl and the α -phenylacetyl derivative of acetoacetic ester were formulated on the assumption that the hydroxylamine-nitrogen would react first with the less hindered acyl group.

Treatment of the various 3,5-disubstituted isoxazole-4-carboxylic acids with thionyl chloride gave the acid chlorides, some of which were purified by distillation and some characterised as amides. Reaction of the acid chlorides with 6-aminopenicillanic acid gave 3,5-disubstituted 4-isoxazolympenicillins¹⁰ in sufficient purity for initial antibacterial tests, which were carried out *in vitro* by Dr. G. N. Rolinson and his colleagues and *in vivo* by Mr. D. M. Brown and his colleagues. Since none of the products proved to be more active than 3-*o*-chlorophenyl-5-methyl-4-isoxazolympenicillin (cloxacillin¹¹) only two of them were purified completely (see Experimental section). In agreement with earlier work² the penicillins derived from the less hindered 3,5-dimethyl- and 5-benzyl-3-methylisoxazole-4-carboxylic acid were readily inactivated by staphylococcal penicillinase. Those derived from 5-methyl-3-4'-pyridyl-, 3-methyl-5-styryl-, 5-cyclohexyl-3-methyl-, and 3,5-di-isopropyl-isoxazole-4-carboxylic acids were somewhat more stable, while the penicillins from the remaining acids with more hindered carboxyl groups were essentially resistant towards the enzyme.

EXPERIMENTAL

Hydroxamoyl Chlorides.—*p*-Nitrobenzohydroxamoyl chloride, m. p. 113–116° (lit.,³ 123.5–124°) was prepared by passing chlorine into a stirred suspension of *p*-nitrobenzaldehyde in 8*N*-hydrochloric acid.¹¹ Similar chlorination of 5-chloro- and 5-nitro-furfuraldehyde¹² gave the corresponding furohydroxamoyl chlorides in crude form.

m-Nitrobenzohydroxamoyl chloride, m. p. 102–103° (from benzene-cyclohexane) (lit.,³ 99.5–100°) (Found: C, 42.1; H, 2.75; Cl, 17.5; N, 14.3. Calc. for $\text{C}_7\text{H}_5\text{ClN}_2\text{O}_3$: C, 41.9; H, 2.5; Cl, 17.7; N, 14.0%), was obtained by passing chlorine into a solution of *m*-nitrobenzaldehyde in chloroform.¹³ The same method was used to prepare crude hydroxamoyl chlorides from the oximes of α -naphthaldehyde, pyridine-4-aldehyde, and pivalaldehyde.

⁹ Panizzi, *Gazzetta*, 1939, **69**, 332.

¹⁰ Doyle and Nayler, B.P. 905,778.

¹¹ Piloty and Steinbock, *Ber.*, 1902, **35**, 3101.

¹² Gilman and Wright, *J. Amer. Chem. Soc.*, 1930, **52**, 2553; *Rec. Trav. chim.*, 1931, **50**, 833.

¹³ Werner and Buss, *Ber.*, 1894, **27**, 2193; Werner, *ibid.*, p. 2846.

Solutions of *o*- and *p*-methoxybenzaldoxime in ether were treated with nitrosyl chloride (freshly prepared from butyl nitrite and acetyl chloride¹⁴), to give the methoxybenzohydroxamoyl chlorides.³

Condensation of Hydroxamoyl Chlorides with β -Keto-esters.—(a) *5-Methyl-3-p-nitrophenylisoxazole-4-carboxylic acid and its derivatives.* (i) Cold methanolic ethyl sodioacetoacetate [from sodium (7.7 g.), methanol (370 ml.), and ethyl acetoacetate (42.5 ml.)] was added during 30 min. to a stirred solution of *p*-nitrobenzohydroxamoyl chloride (66.8 g.) in methanol (420 ml.) at -5° to 0° , the mixture was held at that temperature for 1 hr., then at room temperature overnight, and filtered, and the solid was made into a slurry with water (500 ml.). 3% Sodium hydroxide solution (500 ml.) was added and the solid was collected and washed with water (3×500 ml.), affording crude *ethyl 5-methyl-3-p-nitrophenylisoxazole-4-carboxylate* (57.5 g.). A sample crystallised successively from benzene–light petroleum, ethanol, and acetic acid had m. p. $143\text{--}144^{\circ}$ (Found: C, 56.5; H, 4.2; N, 10.55. $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_5$ requires C, 56.5; H, 4.35; N, 10.15%). Evaporation of the filtrate from the crude product followed by similar washing of the residue yielded a second crop (16.0 g.) of less pure material.

(ii) The ester (20.0 g.), glacial acetic acid (155 ml.), and concentrated hydrochloric acid (75 ml.) were refluxed for 24 hr., diluted with water (100 ml.), and cooled. The crude product was dissolved in 2% aqueous sodium hydroxide, filtered, and acidified, yielding *5-methyl-3-p-nitrophenylisoxazole-4-carboxylic acid* (16.6 g.), m. p. $238\text{--}239^{\circ}$ (not raised by crystallisation from acetonitrile and then from ethanol) (Found: C, 53.2; H, 3.4; N, 11.4. $\text{C}_{11}\text{H}_8\text{N}_2\text{O}_6$ requires C, 53.2; H, 3.2; N, 11.3%), λ_{max} 218.5 and 271.5 μ (ϵ 13,510 and 12,900).

(b) Similarly, *m*-nitrobenzohydroxamoyl chloride gave *5-methyl-3-m-nitrophenylisoxazole-4-carboxylic acid* (89%), m. p. $203\text{--}204^{\circ}$ (from ethanol) (Found: C, 52.95; H, 3.55; N, 11.0. $\text{C}_{11}\text{H}_8\text{N}_2\text{O}_6$ requires C, 53.2; H, 3.2; N, 11.3%), λ_{max} 220 and 260sh μ (ϵ 22,000 and 8380).

(c) 5-Nitro-2-furohydroxamoyl chloride and methyl sodioacetoacetate, condensed at -20° , yielded *methyl 5-methyl-3-(5-nitro-2-furyl)isoxazole-4-carboxylate* (64%), m. p. $125\text{--}126^{\circ}$ (from aqueous ethanol) (Found: C, 48.0; H, 3.5; N, 11.05. $\text{C}_{10}\text{H}_8\text{N}_2\text{O}_6$ requires C, 47.6; H, 3.2; N, 11.1%). Acid hydrolysis of the ester afforded *5-methyl-3-(5-nitro-2-furyl)isoxazole-4-carboxylic acid* (90%), m. p. $196\text{--}198^{\circ}$ (from aqueous ethanol) (Found: C, 46.1; H, 3.1; N, 11.65. $\text{C}_9\text{H}_6\text{N}_2\text{O}_6$ requires C, 45.4; H, 2.5; N, 11.75%), λ_{max} 216 and 322.5 μ (ϵ 11,970 and 11,680).

(d) Crude methyl 5-methyl-3-4'-pyridylisoxazole-4-carboxylate (34%), m. p. $87\text{--}90^{\circ}$ (buff needles from cyclohexane), obtained similarly, gave, after hydrolysis, *5-methyl-3-4'-pyridylisoxazole-4-carboxylic acid* (82%), m. p. $259\text{--}260^{\circ}$ (from acetic acid, then from 50% aqueous ethanol) (Found: C, 58.65; H, 4.0; N, 13.9. $\text{C}_{10}\text{H}_8\text{N}_2\text{O}_3$ requires C, 58.8; H, 3.9; N, 13.75%), λ_{max} 215 and 263 μ (ϵ 12,670 and 2920).

(e) Condensation of *p*-methoxybenzohydroxamoyl chloride and methyl sodioacetoacetate afforded *methyl 3-p-methoxyphenyl-5-methylisoxazole-4-carboxylate* (47%), b. p. $135\text{--}148^{\circ}/0.1$ mm., m. p. $57\text{--}60^{\circ}$ (Found: C, 63.6; H, 5.5; N, 5.35. $\text{C}_{13}\text{H}_{13}\text{NO}_4$ requires C, 63.2; H, 5.25; N, 5.65%). The ester (11.5 g.) and potassium hydroxide (3.1 g.) in 50% aqueous ethanol (50 ml.), when boiled for 2 hr., cooled, and acidified, gave *3-p-methoxyphenyl-5-methylisoxazole-4-carboxylic acid* (10.4 g.), m. p. $194\text{--}195^{\circ}$ (needles from ethanol) (Found: C, 61.9; H, 5.1; N, 6.1. $\text{C}_{12}\text{H}_{11}\text{NO}_4$ requires C, 61.8; H, 4.7; N, 6.0%), λ_{max} 213 and 281 μ (ϵ 11,460 and 9550).

(f) In the same way, *o*-methoxybenzohydroxamoyl chloride gave *3-o-methoxyphenyl-5-methylisoxazole-4-carboxylic acid* (18%), m. p. $212\text{--}213^{\circ}$ (from aqueous ethanol) (Found: C, 62.0; H, 4.75; N, 5.8. $\text{C}_{12}\text{H}_{11}\text{NO}_4$ requires C, 61.8; H, 4.7; N, 6.0%) λ_{max} 213.5 and 282.5 μ (ϵ 14,120 and 2960).

(g) Similarly α -naphthohydroxamoyl chloride yielded *5-methyl-3- α -naphthylisoxazole-4-carboxylic acid* (25%), m. p. $182\text{--}183^{\circ}$ (from benzene–light petroleum, aqueous ethanol, and then toluene) (Found: C, 71.0; H, 4.6; N, 5.35. $\text{C}_{15}\text{H}_{11}\text{NO}_3$ requires C, 71.2; H, 4.35; N, 5.55%), λ_{max} 227.5, 272.5sh, 281, and 288sh μ (ϵ 25,000, 6510, 7540, and 6380).

(h) Pivalohydroxamoyl chloride reacted similarly to give *5-methyl-3-*t*-butylisoxazole-4-carboxylic acid* (30%), m. p. 98° (from cyclohexane) (Found: C, 59.25; H, 7.0; N, 7.7. $\text{C}_9\text{H}_{13}\text{NO}_3$ requires C, 59.0; H, 7.1; N, 7.65%), λ_{max} 217.5 μ (ϵ 6400).

(i) In the same way 5-chloro-2-furohydroxamoyl chloride (decomp. $>5^{\circ}$) gave *methyl 3-(5-*

¹⁴ Franzen and Zimmermann, *Ber.*, 1907, **40**, 2009.

chloro-2-furyl-5-methylisoxazole-4-carboxylate (13%), m. p. 116—117° (from ether) (Found: C, 49.7; H, 3.2; Cl, 14.4; N, 6.1. $C_{10}H_8ClNO_4$ requires C, 49.7; H, 3.3; Cl, 14.7; N, 5.8%). Alkaline hydrolysis yielded *3-(5-chloro-2-furyl)-5-methylisoxazole-4-carboxylic acid* (96%), m. p. 221—222° (from ethanol) (Found: C, 47.7; H, 2.9; Cl, 15.75; N, 6.2. $C_9H_6ClNO_4$ requires C, 47.7; H, 2.65; Cl, 15.65; N, 6.15%), λ_{max} 218 and 268 m μ (ϵ 9870 and 14,670).

3-p-Hydroxyphenyl-5-methylisoxazole-4-carboxylic Acid.—*3-p-Methoxyphenyl-5-methylisoxazole-4-carboxylic acid* (4.2 g.) and anhydrous aluminium chloride (18.5 g.) in benzene (100 ml.) were refluxed together for 90 min., then cooled, and ice (50 g.) was added. The mixture was acidified to pH 1, the precipitate broken up, ether (200 ml.) added, and the mixture filtered. Extraction of the solid, and of the aqueous phase, with ether, evaporation of the combined ether extracts, dissolution of the residue in dilute aqueous sodium hydrogen carbonate, and acidification of the filtered solution afforded pure *3-p-hydroxyphenyl-5-methylisoxazole-4-carboxylic acid* (1.4 g.), m. p. 237—239° (decomp.) (Found: C, 60.15; H, 4.2; N, 6.55. $C_{11}H_9NO_4$ requires C, 60.3; H, 4.1; N, 6.4%), λ_{max} 214 and 252 m μ (ϵ 12,960 and 10,470).

Nitration of 5-Methyl-3-phenylisoxazole-4-carboxylic Acid.—*5-Methyl-3-phenylisoxazole-4-carboxylic acid* (5.0 g.) was added to a mixture of concentrated sulphuric acid (70 ml.) and fuming nitric acid (50 ml.) at 0°. The temperature was raised to 20° for 2 hr., the mixture was poured into water (3 l.), and the crude product was collected and crystallised twice from ethanol, to give *5-methyl-3-m-nitrophenylisoxazole-4-carboxylic acid* (2.25 g.), m. p. 202—203° undepressed on admixture with the acid obtained from *m*-nitrobenzohydroxamoyl chloride (Found: C, 53.1; H, 3.45; N, 11.0. Calc. for $C_{11}H_8N_2O_5$: C, 53.2; H, 3.2; N, 11.3%).

3-m-Aminophenyl-5-methylisoxazole-4-carboxylic Acid.—*5-Methyl-3-m-nitrophenylisoxazole-4-carboxylic acid* (20 g.) was hydrogenated in ethanol (100 ml.) without heating and at atmospheric pressure in the presence of Adams catalyst (0.28 g.) for 3 hr. (5.93 l. absorbed). The mixture was filtered while hot and some solvent was evaporated. The crude product (11.0 g.), m. p. 168—169°, separated from the cooled solution. Pure *3-m-aminophenyl-5-methylisoxazole-4-carboxylic acid*, m. p. 171—172°, crystallised from ethanol (Found: C, 60.5; H, 4.9; N, 12.65. $C_{11}H_{10}N_2O_3$ requires C, 60.55; H, 4.6; N, 12.85%) and had λ_{max} 217.5 and 305 m μ (ϵ 24,090 and 2180). It gave a *hydrochloride* as needles, m. p. 260—265° (decomp.) (Found: C, 52.15; H, 4.75; Cl, 14.0; N, 11.2. $C_{11}H_{11}ClN_2O_3$ requires C, 51.85; H, 4.3; Cl, 13.95; N, 11.0%).

The ethanolic mother-liquor from the hydrogenation was evaporated and the residue washed with dilute sodium hydroxide, then crystallised from ethanol to give *4-amino-4-m-aminophenyl-but-3-en-2-one*, m. p. 176—178° (Found: C, 68.25; H, 6.85; N, 15.45. $C_{10}H_{12}N_2O$ requires C, 68.2; H, 6.8; N, 15.9%), λ_{max} 210sh, 232.5, and 324 m μ (ϵ 9120, 18,920, and 18,130).

3-m-Hydroxyphenyl-5-methylisoxazole-4-carboxylic Acid.—*3-m-Aminophenyl-5-methylisoxazole-4-carboxylic acid* (10.9 g.) was suspended in water (100 ml.), treated with concentrated sulphuric acid (4 ml.), and stirred at 0—5° whilst sodium nitrite (3.45 g.) in water (8 ml.) was added slowly. After 2 hr. at 0—5°, the diazonium solution was heated at 100° until gas evolution had ceased, then cooled and extracted with ether (3 \times 200 ml.). The ether solution was extracted with *N*-sodium hydrogen carbonate (2 \times 75 ml.), and these extracts were acidified, yielding the hydroxy-acid (11.5 g.). Crystallisation from hot water gave *3-m-hydroxyphenyl-5-methylisoxazole-4-carboxylic acid monohydrate*, m. p. 201—203° (Found: C, 55.75; H, 4.55; N, 5.75. $C_{11}H_9NO_4 \cdot H_2O$ requires C, 55.7; H, 4.65; N, 5.9%), λ_{max} 215 and 287.5 m μ (ϵ 16,930 and 2390).

3-m-Methoxyphenyl-5-methylisoxazole-4-carboxylic Acid.—The hydroxy-acid monohydrate (6.7 g.), dimethyl sulphate (7.8 g.), anhydrous potassium carbonate (8.6 g.), and acetone (30 ml.) were heated together under reflux for 3 hr. The mixture was filtered, the solid was dissolved in water, the solution was extracted with ether (2 \times 50 ml.), and the extracts were combined with the acetone filtrate. Evaporation of the organic phase left a brown oil which was dissolved in ethanol (60 ml.). The solution was treated with potassium hydroxide (4.2 g.) in water (24 ml.), and boiled for 2 hr. Evaporation of most of the ethanol, dilution of the residual solution with water (100 ml.), extraction with ether (3 \times 50 ml.), and acidification of the aqueous phase precipitated the crude product (7.2 g.). Crystallisation from 50% aqueous ethanol gave *3-m-methoxyphenyl-5-methylisoxazole-4-carboxylic acid* (4.2 g.), m. p. 134—135° as orange crystals (Found: C, 62.0; H, 4.95; N, 5.85. $C_{12}H_{11}NO_4$ requires C, 61.8; H, 4.7; N, 6.0), λ_{max} 216.5 and 285 m μ (ϵ 19,200 and 2490).

3-m-Fluorophenyl-5-methylisoxazole-4-carboxylic Acid.—(a) 3-m-Aminophenyl-5-methylisoxazole-4-carboxylic acid (10.9 g.), suspended in methanol (110 ml.), was saturated with hydrogen-chloride and set aside for 72 hr., then evaporated *in vacuo*. The residue was made alkaline and extracted with ether, from which *methyl 3-m-aminophenyl-5-methylisoxazole-4-carboxylate* (9.5 g.), m. p. 116°, crystallised (Found: C, 61.9; H, 5.85; N, 11.6. $C_{12}H_{12}N_2O_3$ requires C, 62.0; H, 5.2; N, 12.05%).

(b) The methyl ester (9.5 g.), in concentrated hydrochloric acid (12 ml.) and water (40 ml.), was diazotised at 0° with sodium nitrite (2.98 g.) in water (5.5 ml.). The mixture was kept at 0° for 30 min., then 40% fluoroboric acid (11 g.) was added and the whole was stirred at 0° for a further 30 min. The precipitated fluoroborate (13.4 g.) was collected, washed with ice-water (100 ml.), and dried *in vacuo*. The dry salt (10.4 g.) was decomposed by heating it gently and the crude product was distilled, to give *methyl 3-m-fluorophenyl-5-methylisoxazole-4-carboxylate* (3 g.), b. p. 114–116°/0.4 mm., m. p. 76–78°.

(c) Methyl 3-m-fluorophenyl-5-methylisoxazole-4-carboxylate (2.15 g.) and potassium hydroxide (0.8 g.) in ethanol (20 ml.) and water (5 ml.) were refluxed for 3 hr. The ethanol was distilled off and the residue was diluted with water (15 ml.), extracted with ether (2 × 10 ml.), and acidified, to precipitate the acid (1.7 g.), m. p. 178°. Pure 3-m-fluorophenyl-5-methylisoxazole-4-carboxylic acid, crystallised from 50% aqueous ethanol, had m. p. 176–177° (Found: C, 59.55; H, 3.45; N, 6.35. $C_{11}H_8FNO_3$ requires C, 59.75; H, 3.6; N, 6.3%), λ_{\max} 218 and 270 μ (ϵ 12,040 and 1410).

Ethyl β -(3,5-dimethylisoxazol-4-yl)- β -oxopropionate.—Ethyl acetoacetate (90.0 g.), sodium wire (16.0 g.), and dry benzene (1400 ml.) were heated together under reflux for 12 hr., then cooled, and the resulting suspension was treated with 3,5-dimethylisoxazole-4-carbonyl chloride (103.3 g.). The mixture was held at 50° for 2 hr., then cooled, 5N-hydrochloric acid was added to give an acidic aqueous phase, the layers were separated, the benzene solution was washed with water, and the solvent was distilled off. The residue was taken up in ethanol (100 ml.), aqueous ammonia (100 ml.; d 0.88) was added, and the mixture was stirred at 15–20° for 3 hr., then acidified. The product was extracted into ether, the extract was washed with N-sodium hydrogen carbonate, then with water, dried, and distilled, to give *ethyl β -(3,5-dimethylisoxazol-4-yl)- β -oxopropionate* (57.4 g.), b. p. 116–120°/0.25–0.5 mm., m. p. 48–49° (Found: C, 56.9; H, 6.15; N, 6.5. $C_{10}H_{13}NO_4$ requires C, 56.85; H, 6.15; N, 6.65%).

3-Substituted Isoxazol-5-ones.—(a) 3-(3,5-Dimethylisoxazol-4-yl)isoxazol-5-one. Ethyl β -(3,5-dimethylisoxazol-4-yl)- β -oxopropionate (57.0 g.), ethanol (60 ml.), hydroxylamine hydrochloride (21.0 g.), and water (25 ml.) were heated together under reflux until all the solid had dissolved (*ca.* 1 hr.), cooled to room temperature, and diluted with water (170 ml.). This precipitated the crude product (22.75 g.) as an oil which solidified. Crystallisation from benzene gave pure 3-(3,5-dimethylisoxazol-4-yl)isoxazol-5-one, m. p. 95–97° (Found: C, 53.5; H, 4.3; N, 15.3. $C_8H_8N_2O_3$ requires C, 53.35; H, 4.45; N, 15.55%).

(b) 3-2'-Thienylisoxazol-5-one, m. p. 135–137° (lit.¹⁵ m. p. 133.5–137°), was prepared similarly.

4-Acetylisoxazol-5-ones.—(a) 3-p-Methoxyphenylisoxazol-5-one¹⁶ (2.0 g.), sodium acetate (2.0 g.), and acetic anhydride (15 ml.) were refluxed for 90 min., cooled, diluted with water (20 ml.), washed with ether, and acidified with 5N-hydrochloric acid, giving an oil which solidified. Extraction of the crude product with hot water yielded, after treatment with charcoal, 4-acetyl-3-p-methoxyphenylisoxazol-5-one (0.62 g.) as needles, m. p. 101–103° (Found: C, 61.85; H, 4.35; N, 6.5. $C_{12}H_{11}NO_4$ requires C, 61.8; H, 4.7; N, 6.0%), λ_{\max} 211, 217.5sh, 247.5, and 283 μ (ϵ 14,280, 13,070, 11,400, and 14,450).

(b) 3-2'-Furylisoxazol-5-one¹⁷ (51.0 g.), ethyl orthoacetate (60.5 g.), and toluene (100 ml.) were heated together at 110° for 1 hr., then cooled. The product was collected (57.5 g.) and crystallised from benzene-cyclohexane, yielding 4-1'-ethoxyethylidene-3-2'-furylisoxazol-5-one, m. p. 131–132° (Found: C, 59.65; H, 5.0; N, 6.0. $C_{11}H_{11}NO_4$ requires C, 59.7; H, 4.95; N, 6.3%), λ_{\max} 221.5, 255sh, and 290 μ (ϵ 11,710, 9880, and 13,370). This intermediate (44.1 g.) was heated at 90–100° for 1 hr. with sodium hydroxide (9.0 g.) in water (100 ml.), then cooled, and the solution was adjusted to pH 1, affording 4-acetyl-3-2'-furylisoxazol-5-one (29.2 g.), m. p. 172° (decomp.). The pure compound, crystallised from ethanol-ethyl acetate

¹⁵ Homeyer, U.S.P. 2,630,437 (*Chem. Abs.*, 1954, **48**, 2116).

¹⁶ Katritzky, Øksne, and Boulton, *Tetrahedron*, 1962, **18**, 777.

¹⁷ Posner and Sichert, *Ber.*, 1930, **63**, 3078.

(1:1), had m. p. 173° (decomp.) (Found: C, 56.0; H, 3.8; N, 6.95. $C_9H_7NO_4$ requires C, 55.95; H, 3.6; N, 7.25%) and λ_{\max} . 210sh, 224, 255, and 280 m μ (ϵ 6680, 10,540, 11,330, and 11,910).

(c) Treatment of 3-2'-thienylisoxazol-5-one with triethyl orthoacetate as in (b) yielded impure 4-1'-ethoxyethylidene-3-2'-thienylisoxazol-5-one. Hydrolysis of this moisture-sensitive compound was completed by treatment with dilute aqueous sodium hydroxide for 90 min. at 60–75°. Acidification, followed by crystallisation from benzene and then from 50% aqueous ethanol, gave 4-acetyl-3-2'-thienylisoxazol-5-one, m. p. 144° (decomp.) (Found: C, 52.1; H, 3.5; N, 6.5; S, 15.3. $C_9H_7NO_3S$ requires C, 51.65; H, 3.35; N, 6.7; S, 15.3%), λ_{\max} . 210sh, 235, 253.5, and 287.5 m μ (ϵ 5830, 10,260, 12,160, and 11,540).

(d) In the same way, 3-(3,5-dimethylisoxazol-4-yl)isoxazol-5-one and triethyl orthoacetate yielded the moisture-sensitive 4-1'-ethoxyethylidene-3-(3,5-dimethylisoxazol-4-yl)isoxazol-5-one, which was hydrolysed as in (c) to 4-acetyl-3-(3,5-dimethylisoxazol-4-yl)isoxazol-5-one which

5-Substituted 3-methylisoxazole-4-carboxylic acids.

5-Subst.	M. p.	Cryst. from ‡	Yield (%)	Found (%)			Formula	Required (%)			λ_{\max} . (m μ) (ϵ in parentheses)
				C	H	N		C	H	N	
Cyclohexyl	165–168°	C_6H_{12} ; C_6H_{12} ; EtOAc	63	63.1	7.0	6.85	$C_{11}H_{13}NO_3$	63.15	7.2	6.7	222.5 (7960)
Ph·CH ₂	139–140	Aq. EtOH; C_6H_5 -Pet	69	66.1	5.3	6.1	$C_{12}H_{11}NO_3$	66.35	5.05	6.45	223.5 (9760)
Ph·CH ₂ ·CH	218–220	EtOH; AcOH; C_6H_5 -Pet	46	68.5	4.65	6.4	$C_{13}H_{11}NO_3$	68.1	4.8	6.1	230 (11,500); 318 (29,770) †
<i>p</i> -MeO·C ₆ H ₄	178–180	PhMe; EtOH	48	62.0	4.9	6.25	$C_{12}H_{11}NO_4$	61.8	4.7	6.0	289 (18,830) †
2,6-(MeO) ₂ C ₆ H ₃	193	Aq. EtOH; C_6H_5 ; MeCN	32	59.65	5.2	4.7	$C_{13}H_{13}NO_5$	59.3	4.95	5.3	267.5 (5970) †
<i>p</i> -Me·SO ₂ ·C ₆ H ₄	198–200	Aq. EtOH; EtOH	41	51.0	3.6	4.65	$C_{12}H_{11}NO_5S$ §	51.25	3.9	5.0	275 (16,020) †
<i>o</i> -O ₂ N·C ₆ H ₄	190–192 *	AcOH; aq. AcOH	42	53.15	3.35	11.75	$C_{11}H_8N_2O_5$	53.2	3.2	11.3	230 (14,460); 290sh (2980) †
<i>m</i> -O ₂ N·C ₆ H ₄	183–184	PhMe; aq. EtOH	63	53.5	3.25	11.55	$C_{11}H_8N_2O_5$	53.2	3.2	11.3	259 (17,560) †
<i>p</i> -O ₂ N·C ₆ H ₄	226–228	AcOH	73	53.2	3.45	10.9	$C_{11}H_8N_2O_5$	53.2	3.2	11.3	233 (8090); 298.5 (12,080) †
2-Furyl	222–224	Aq. MeOH; AcOH; EtOH	61	56.1	3.75	7.05	$C_9H_7NO_4$	55.95	3.6	7.25	222.5sh (2840); 296.5 (17,810) †
2-Thienyl	200–201	EtOH	70	51.7	3.6	6.5	$C_9H_7NO_3S$ ¶	51.65	3.35	6.7	304.5 (15,800) †
3,5-Dimethyl-4-isoxazolyl	187–187.5	H ₂ O; aq. EtOH	58	54.15	4.6	12.65	$C_{10}H_{10}N_2O_4$	54.05	4.5	12.6	248 (7880)

* Khromov and Porai-Koshits [*J. Gen. Chem. (U.S.S.R.)*, 1947, **17**, 1816] report m. p. 185–186°. † These acids also show absorption in the region 205–215 m μ (ϵ 6500–16,600). ‡ Pet = light petroleum. § Found: S, 11.1. Reqd.: S, 11.4%. ¶ Found: S, 14.9. Reqd.: S, 15.3%.

crystallised from water as the *monohydrate*, m. p. 151–152° (Found: C, 49.5; H, 5.2; N, 11.7. $C_{10}H_{10}N_2O_4 \cdot H_2O$ requires C, 50.0; H, 5.0; N, 11.6%), λ_{\max} . 229 and 285 m μ (ϵ 10,280 and 10,880).

4-1'-Ethoxyethylidene-3-*p*-methoxyphenylisoxazol-5-one.—3-*p*-Methoxyphenylisoxazol-5-one ¹⁸ (22.5 g.) and triethyl orthoacetate (37.8 g.) were heated together for 30 min. at 110°, then cooled, and the product was collected, yielding 4-1'-ethoxyethylidene-3-*p*-methoxyphenylisoxazol-5-one (26.7 g.), which crystallised from ethyl acetate as pale yellow needles, m. p. 133–134° (Found: C, 64.4; H, 5.85; N, 5.15. $C_{14}H_{15}NO_4$ requires C, 64.3; H, 5.75; N, 5.35%).

Rearrangement of 3-Substituted 4-Acetylisoxazol-5-ones and Related Compounds.—(a) 4-1'-Ethoxyethylidene-3-*p*-methoxyphenylisoxazol-5-one (1.0 g.) and sodium hydroxide (10.0 g.) in water (10 ml.) were refluxed at 160° for 4 hr., cooled, and poured into water (100 ml.), the solution was acidified and extracted with ether (2 × 50 ml.), the extracts were evaporated, and the product (0.75 g.) was crystallised from ethanol, yielding 3-*p*-methoxyphenyl-5-methylisoxazole-4-carboxylic acid as needles, m. p. 192–194° undepressed on admixture with the acid prepared from *p*-methoxybenzohydroxamoyl chloride.

(b) 4-Acetyl-3-2'-thienylisoxazol-5-one (10.0 g.) and potassium hydroxide (45 g.) in water (90 ml.) were boiled under reflux for 4 hr. (bath-temperature 125°) and worked up in similar manner, yielding 5-methyl-3-2'-thienylisoxazole-4-carboxylic acid (9.2 g.), m. p. 173–174° (from benzene) (Found: C, 51.7; H, 3.65; N, 6.6; S, 15.6. $C_9H_7NO_3S$ requires C, 51.65; H, 3.35; N, 6.7; S, 15.3%), λ_{\max} . 217.5, 258, and 267 m μ (ϵ 9510, 9030, and 8670).

(c) 4-Acetyl-3-2'-furylisoxazol-5-one (29.2 g.), potassium hydroxide (129 g.), and water (120 ml.) were heated under reflux for 1 hr. (bath-temperature 145–150°), cooled, diluted

with water (200 ml.), and extracted with ether. The aqueous phase, adjusted to pH 8, was filtered and acidified to pH 2. This yielded 3-2'-furyl-5-methylisoxazole-4-carboxylic acid (24.8 g.), m. p. 219—220° (from ethanol) (Found: C, 55.95; H, 3.6; N, 7.6. $C_9H_7NO_4$ requires C, 55.95; H, 3.6; N, 7.25%), λ_{\max} 216 and 262 m μ (ϵ 10,710 and 13,120).

Evaporation of the ether extract yielded 3-2'-furyl-5-methylisoxazole (1.0 g.), m. p. 39—40° (Found: C, 64.2; H, 4.9; N, 9.3. $C_8H_7NO_2$ requires C, 64.45; H, 4.7; N, 9.4%).

(d) 4-Acetyl-3-(3,5-dimethylisoxazol-4-yl)isoxazol-5-one (10.3 g.) and potassium hydroxide (20 g.) in water (40 ml.) were refluxed for 4 hr. and worked up similarly, affording 3-(3,5-dimethylisoxazol-4-yl)-5-methylisoxazole-4-carboxylic acid (8.0 g.), m. p. 190° (after successive crystallisations from aqueous ethanol, isobutyl methyl ketone, and ethanol) (Found: C, 53.8; H, 4.5; N, 12.3. $C_{10}H_{10}N_2O_4$ requires C, 54.05; H, 4.5; N, 12.6%), λ_{\max} 218 m μ (ϵ 11,080).

Ethyl 4,5-Dihydro-5-oxo-3-phenylisoxazole-4-carboxylate.—A solution of ethyl α -benzoylmalonate¹⁸ (10 g.) and hydroxylamine hydrochloride (3 g.) in ethanol (40 ml.) was refluxed for 3 hr., then evaporated *in vacuo*. The residue was boiled with benzene (160 ml.). After filtration from unchanged hydroxylamine hydrochloride (0.86 g.), the extracts were allowed to cool. The crystals (3.94 g.) were collected and recrystallised from ethyl acetate to give colourless needles of ethyl 4,5-dihydro-5-oxo-3-phenylisoxazole-4-carboxylate, m. p. 147—149° [lit.⁷ 139° (decomp.)] (Found: C, 61.5; H, 5.1; N, 6.1. Calc. for $C_{12}H_{11}NO_4$: C, 61.8; H, 4.8; N, 6.0%). Concentration of the benzene mother-liquors gave 3-phenylisoxazol-5-one (1.63 g.) which, recrystallised from ethanol, had m. p. 148—149° (decomp.), not depressed on admixture with an authentic specimen.¹⁹

Methylation of Ethyl 4,5-Dihydro-5-oxo-3-phenylisoxazole-4-carboxylate.—(a) The isoxazolone ester (10 g.) was added portionwise to diazomethane (from 8 g. of methylnitrosourea) in ether and, after 30 min., the excess of diazomethane was destroyed with acetic acid. A white solid was collected and a second crop obtained by evaporating the filtrate and triturating the residual oil with a small volume of light petroleum (b. p. 40—60°). Crystallisation of the combined crops from light petroleum (350 ml.; b. p. 60—80°) gave almost pure ethyl 5-methoxy-3-phenylisoxazole-4-carboxylate (8.92 g.), m. p. 92—93°, which on recrystallisation from alcohol formed needles, m. p. 94—95° (lit.⁷ m. p. 93.5°) (Found: C, 63.3; H, 5.4; N, 5.5. Calc. for $C_{13}H_{13}NO_4$: C, 63.2; H, 5.3; N, 5.7%).

(b) A stirred mixture of the isoxazolone ester (1 g.), methyl iodide (1 ml.), potassium carbonate (1 g.), and acetone (20 ml.) was refluxed for 3 hr., cooled, filtered, and evaporated, yielding an oil, which solidified on trituration with light petroleum containing a little ether. The solid was collected and crystallised from 30% aqueous alcohol (15 ml.) to give almost pure ethyl 4,5-dihydro-2-methyl-5-oxo-3-phenylisoxazole-4-carboxylate (0.7 g.), m. p. 137—138°, which on recrystallisation from the same solvent mixture formed laths, m. p. 138—139° depressed on admixture with the starting material (Found: C, 62.9; H, 5.4; N, 5.7. $C_{13}H_{13}NO_4$ requires C, 63.2; H, 5.3; N, 5.7%).

Ethyl α -Di-isobutyrylacetate.—Ethyl isobutyrylacetate²⁰ (55.5 g.) was added dropwise to a stirred suspension of sodium (8.1 g.) in benzene (500 ml.) to give a clear solution which was then boiled under reflux for 1 hr., cooled, treated with isobutyryl chloride (40.5 ml.), and refluxed for 3 hr. Next morning, the mixture was washed successively with water, *N*-sodium hydrogen carbonate, and water again, dried, and distilled, to give ethyl α -di-isobutyrylacetate (41.7 g.), b. p. 122—128°/15 mm., n_D^{23} 1.4578 (Found: C, 63.55; H, 9.05. $C_{12}H_{20}O_4$ requires C, 63.15; H, 8.75%).

Reaction of Diketo-esters with Hydroxylamine.—(a) Ethyl di-isobutyrylacetate (41.5 g.) in ethanol (150 ml.) was treated with hydroxylamine hydrochloride (23.8 g.) in water (30 ml.), and the mixture was boiled for 10 min. The following day, the mixture was diluted with water and the precipitated oil was extracted into ether (3 \times 100 ml.). The combined ether extracts were washed with 10% aqueous sodium hydroxide (until the alkaline extracts gave no precipitate when acidified), then with water, dried, and distilled, giving ethyl 3,5-di-isopropylisoxazole-4-carboxylate (25 g., 61%), b. p. 81°/0.01 mm., n_D^{24} 1.4581. The ester was refluxed in ethanol (150 ml.) for 2 hr. with potassium hydroxide (9.6 g.) in water (60 ml.), the bulk of the solvent was distilled off, and the residue diluted with water, extracted with ether, and acidified, affording 3,5-di-isopropylisoxazole-4-carboxylic acid (17.0 g.). Crystallisation from light

¹⁸ King, King, and Thompson, *J.*, 1948, 552.

¹⁹ Dains and Griffin, *J. Amer. Chem. Soc.*, 1913, **35**, 959.

²⁰ Brändström, *Acta Chem. Scand.*, 1951, **5**, 820.

petroleum (b. p. 60—80°) gave the pure acid, m. p. 102—103° (Found: C, 61.05; H, 7.9; N, 7.05. $C_{10}H_{15}NO_3$ requires C, 60.9; H, 7.6; N, 7.1%), λ_{\max} , 218.5 m μ (ϵ 7680).

(b) The 5-substituted 3-methylisoxazole-4-carboxylic acids listed in the Table were obtained in similar manner except that, for the nitro-compounds, hydrolysis of the esters was best carried out with equal volumes of glacial acetic and concentrated hydrochloric acids (24 hr. under reflux).

For these syntheses, ethyl *o*-, *m*-, and *p*-nitro- and *p*-methylsulphonyl-benzoylacetoacetate were obtained as described by McCluskey²¹ for the *o*-nitro-compound; crude preparations of the remaining intermediate diketo-esters were made as described by Shriner, Schmidt, and Roll²² for ethyl benzoylacetoacetate.

3,5-Disubstituted Isoxazole-4-carboxamides.—(a) 3,5-Di-isopropylisoxazole-4-carboxylic acid (12.2 g.) and thionyl chloride (25 ml.) were boiled together for 90 min., the excess of thionyl chloride was removed *in vacuo*, and the residue distilled. This gave 3,5-di-isopropylisoxazole-4-carbonyl chloride (12.0 g.), b. p. 117—119°/15 mm. In acetone, with an excess of aqueous ammonia (*d* 0.88), this gave 3,5-di-isopropylisoxazole-4-carboxamide, m. p. 137—138° (from toluene, then acetonitrile) (Found: C, 61.5; H, 8.1; N, 14.05. $C_{10}H_{16}N_2O_2$ requires C, 61.2; H, 8.15; N, 14.3%).

(b) In the same way 5-cyclohexyl-3-methylisoxazole-4-carboxamide, m. p. 140—143° (from aqueous ethanol, benzene, and aqueous acetic acid), was obtained from the acid (Found: C, 63.55; H, 7.5; N, 13.55. $C_{11}H_{16}N_2O_2$ requires C, 63.45; H, 7.7; N, 13.45%).

(c) 3-*o*-Methoxyphenyl-5-methylisoxazole-4-carboxamide, m. p. 140—141° (from ethanol) (Found: C, 62.3; H, 5.5; N, 12.2. $C_{12}H_{12}N_2O_3$ requires C, 62.05; H, 5.25; N, 12.05%), was prepared similarly.

(d) Similar reactions yielded 5-methyl-3-*t*-butyl-, m. p. 175—176° (from aqueous ethanol) (Found: C, 59.25; H, 7.6; N, 15.35; $C_9H_{14}N_2O_2$ requires C, 59.35; H, 7.7; N, 15.4%), and 5-methyl-3- α -naphthylisoxazole-4-carboxamide, m. p. 147—148° (from acetonitrile) (Found: C, 71.45; H, 5.05; N, 11.3. $C_{18}H_{12}N_2O_2$ requires C, 71.4; H, 4.75; N, 11.1%).

3-*m*-Hydroxyphenyl-5-methylisoxazole-4-carboxanilide.—3-*m*-Hydroxyphenyl-5-methylisoxazole-4-carboxylic acid (0.44 g.) and thionyl chloride (2.0 ml.), warmed together for 30 min. at 40° and then for 30 min. at 60°, gave a crude chloride which was added in acetone (4.0 ml.) to a stirred mixture of *N*-sodium hydrogen carbonate (8.0 ml.), acetone (4.0 ml.), and aniline (0.2 ml.). After 2 hr. the pale orange precipitate (0.56 g.) was recrystallised twice from 50% aqueous ethanol, dissolved in warm *N*-sodium hydroxide (2.0 ml.), reprecipitated by *N*-hydrochloric acid (2.0 ml.), and crystallised from 50% aqueous ethanol, giving the *anilide monohydrate* (0.2 g.), needles, m. p. 141—143° (decomp.) (Found: C, 65.55; H, 5.4; N, 8.85. $C_{17}H_{14}N_2O_3 \cdot H_2O$ requires C, 65.4; H, 5.15; N, 8.95%). Drying at 100°/2 mm. for 1 hr. gave the *anhydrous anilide*, m. p. 172—174° (Found: C, 69.2; H, 5.1; N, 9.2. $C_{17}H_{14}N_2O_3$ requires C, 69.4; H, 4.75; N, 9.5%).

3-Substituted 5-Methyl-4-isoxazolylpenicillins.—(a) 3-2'-Furyl-5-methylisoxazole-4-carboxylic acid (14.66 g.) and thionyl chloride (14.0 ml.) were refluxed together for 2 hr. and the excess of thionyl chloride removed *in vacuo*, yielding a solid chloride (15.64 g.). This (14.0 g.) was added in isobutyl methyl ketone (200 ml.) to a stirred solution of 6-aminopenicillanic acid (14.4 g.) in water (132 ml.) and *N*-sodium hydroxide (66.3 ml.). The mixture was stirred for 1 hr. at room temperature, then filtered. The organic layer was washed with saturated brine (66 ml.) which was also used to wash a second isobutyl methyl ketone extract (66 ml.) of the aqueous phase. The combined organic extracts were filtered and treated with 2*N*-sodium 2-ethylhexanoate in propan-2-ol (34 ml.). Sodium 3-2'-furyl-5-methyl-4-isoxazolylpenicillin monohydrate (27.9 g.) [α]_D²⁰ 230.4° (*c* 1 in H_2O), was collected, washed with isobutyl methyl ketone (100 ml.), and dried in air or, for analysis, over phosphorus pentoxide at 20° *in vacuo* for 90 min. (Found: C, 47.2; H, 4.8; N, 9.9; S, 7.55; Na, 5.4. $C_{17}H_{16}N_3NaO_6S \cdot H_2O$ requires C, 47.35; H, 4.15; N, 9.75; S, 7.4; Na, 5.35%).

(b) 3-*p*-Hydroxyphenyl-5-methylisoxazole-4-carboxylic acid (3.3 g.) and thionyl chloride (16.0 ml.) were allowed to react at room temperature for 9 days. The excess of thionyl chloride was removed *in vacuo* and the residual oil was dried azeotropically with benzene. Exposure of the oil to moist air caused it to lose sulphur dioxide and solidify, to give 3-*p*-hydroxyphenyl-5-methylisoxazole-4-carbonyl chloride (3.22 g.), m. p. 103—104° (decomp.) (Found: C, 55.4; H,

²¹ McCluskey, *J. Amer. Chem. Soc.*, 1922, **44**, 1573.

²² Shriner, Schmidt, and Roll, *Org. Synth.*, Coll. Vol. II, p. 266.

3.75; Cl, 15.05; N, 5.65. $C_{11}H_8ClNO_3$ requires C, 55.6; H, 3.35; Cl, 14.95; N, 5.8%). This intermediate reacted with 6-aminopenicillanic acid as described in (a), to give *sodium 3-p-hydroxyphenyl-5-methyl-4-isoxazolylpenicillin monohydrate* (Found: C, 49.6; H, 4.9; N, 9.6; S, 7.15; Na, 4.7. $C_{19}H_{18}N_3NaO_6S \cdot H_2O$ requires C, 49.8; H, 4.4; N, 9.2; S, 7.0; Na, 5.05%).

The authors are indebted to Miss R. Martin for ultraviolet absorption measurements and acknowledge the skilled experimental assistance of Mr. R. Ridler.

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[Received, June 6th, 1963.]
