1112. Derivatives of 6-Aminopenicillanic Acid. Part VI.¹ Penicillins from 3- and 5-Phenylisoxazole-4-carboxylic Acids and their Alkyl and Halogen Derivatives.

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Condensation of benzohydroxamoyl chloride or its methyl or halogen derivatives with the sodio-derivatives of acylacetic esters gave a series of 3-arylisoxazole-4-carboxylic acids. Corresponding 5-aryl compounds were prepared from α -alkanoyl- α -aroylacetic esters and hydroxylamine. The 3- and 5-aryl acids were conveniently differentiated by means of their ultraviolet absorption spectra. Reaction of the isoxazole acid chlorides with 6-aminopenicillanic acid gave isoxazolylpenicillins with useful antibacterial activity.

In previous Parts of this series 2 it has been shown that acylation of 6-aminopenicillanic acid with the chlorides of sterically hindered carboxylic acids of various types gives penicillins which resist inactivation by penicillinase. If such penicillins are to be effective when given by mouth they should preferably have a fair stability at low pH, a require-



ment met by various 3,5-disubstituted 4-isoxazolyl- $\begin{array}{c} \mathsf{R} & \mathsf{CO} \cdot \mathsf{NH} \cdot \mathsf{CH} - \mathsf{CH} \cdot \mathsf{CMe}_2 \\ \mathsf{N} & \mathsf{CO} - \mathsf{N} - \mathsf{CH} \cdot \mathsf{CO}_2 \mathsf{H} \end{array} \qquad \begin{array}{c} \text{penicillins (I). Syntheses of oxacillin (I; R = Ph, R' = Ph) have been described, 3 and the former compound has been used} \end{array}$ clinically in the oral treatment of resistant staphylo-

coccal infections.⁴ Analogues of these penicillins in which the methyl substituent on the

- ¹ Part V, Doyle, Nayler, Waddington, Hanson, and Thomas, J., 1963, 497.

^{755.}

isoxazole ring has been replaced by hydrogen or a higher alkyl group, or in which the benzene ring carries methyl or halogen substituents, are described in the present paper.

Quilico and Fusco⁵ condensed benzohydroxamoyl chloride (II; R = Ph), prepared by chlorination of benzaldoxime,⁶ with ethyl sodioacetoacetate (III; R' = Me, $R^2 = Et$) to give ethyl 5-methyl-3-phenylisoxazole-4-carboxylate (IV; R = Ph, $R^1 = Me$, $R^2 =$

$$\begin{array}{ccc} R \cdot C \cdot C & & \\ II \\ N \cdot OH \end{array} + \begin{array}{c} N_a \cdot CH \cdot CO_2 R^2 \\ I \\ COR^1 \\ (II) \end{array} \xrightarrow{R} \begin{array}{c} R & CO_2 R^2 \\ N_O \\ R^1 \end{array} \xrightarrow{NH_2 \cdot OH} \begin{array}{c} R \cdot CO \cdot CH \cdot CO_2 R^2 \\ I \\ COR^1 \\ COR^1 \end{array}$$

Et), which was hydrolysed by alkali to the carboxylic acid. Similar syntheses with sodio-derivatives of other acylacetic esters have now given 3-phenylisoxazole-4-carboxylic acid (IV; R = Ph, $R^1 = R^2 = H$) and analogues containing ethyl, propyl, isopropyl, and chloromethyl substituents in the 5-position. Other 5-alkyl-3-arylisoxazole-4-carboxylic acids were synthesised by the same route from substituted benzohydroxamoyl chlorides (II; R = tolyl or halogenophenyl). The condensation stage was best carried out in the alcohol corresponding to the ester group of the starting material (III) when it was desired to isolate the isoxazole ester, but if this intermediate was to be hydrolysed without isolation the possibility of transesterification was no longer important and hence either methanol or ethanol was a suitable solvent. The esters were hydrolysed with alkali except in the preparation of 3-phenylisoxazole-4-carboxylic acid and its 5-chloromethyl derivative, when acid was used to avoid decomposition. Farley and his co-workers ⁷ claim to have prepared 3-p-chlorophenyl-5-methylisoxazole-4-carboxylic acid by this route, but the physical constants given for the intermediates and end-product are grossly different from those found by us.

Turning next to the 5-arylisoxazole-4-carboxylic acids, we synthesised the 5-phenyl compound (IV: $R = R^2 = H$, $R^1 = Ph$) from ethyl α -benzoyl- β -ethoxyacrylate and hydroxylamine by Panizzi's method.⁸ except that the final hydrolysis stage was more conveniently effected by heating the ester with a mixture of acetic and concentrated hydrochloric acid. The non-identity of the product with 3-phenylisoxazole-4-carboxylic acid, here prepared for the first time, confirmed the structure.

The earliest synthesis of 3,5-disubstituted isoxazole-4-carboxylic acids, namely, the condensation of diacylacetic esters (V) with hydroxylamine,⁹ is also capable in theory of giving more than one isomer when the acyl groups are different. The older literature on these compounds ¹⁰ is further confused by reports of another synthesis leading to " unstable isomers" of 3-substituted 5-arylisoxazole-4-carboxylic acids and their derivatives, but these have now been shown 11 to be highly enolised acylisoxazolones and not carboxylic acids. The only authentic 3-methyl-5-phenylisoxazole-4-carboxylic acid is that having m. p. 189°, which is conveniently prepared from α -benzoylacetoacetic ester and hydroxylamine, none of the isomeric 5-methyl-3-phenylisoxazole-4-carboxylic acid being formed.^{12,13} In extending this synthesis to thirteen other α -alkanoyl- α -aroylacetic esters (V) we in no case obtained more than one isoxazolecarboxylic acid, although the 3-isopropyl-5-phenyl compound needed to be purified by way of the amide to remove an unidentified contaminant.

- ⁵ Quilico and Fusco, Gazzetta, 1937, 67, 589.
 ⁶ Werner and Buss, Ber., 1894, 27, 2193; Piloty and Steinbock, Ber., 1902, 35, 3112.
 ⁷ Farley, Rathmann, and Tangen, Proc. N. Dakota Acad. Sci., 1959, 13, 61.

⁸ Panizzi, Gazzetta, 1943, 73, 13.

¹³ Hydorn, McGinn, Moetz, and Schwarz, J. Org. Chem., 1962, 27, 4305.

<sup>Claisen, Annalen, 1893, 277, 174.
¹⁰ Beilstein's 2nd Suppl., "Handbuch der Organischen Chemie," Springer, Vol. XXVII, pp. 382</sup> et seg. ¹¹ Speroni, Gazzetta, 1952, **82**, 691.

¹² Betti and Alessandri, Gazzetta, 1915, 45, 462.

In order to confirm that the new acids were all the 5-aryl isomers it was desirable to demonstrate their non-identity with the corresponding 3-aryl compounds, here prepared unambiguously from benzohydroxamoyl chloride and its derivatives. Melting-point determinations were not always adequate for this purpose, since the values for several isomeric pairs lay close together and the depressions observed on admixture were small. Fortunately, examination of ultraviolet absorption spectra in the range 200-350 mu proved a convenient method.

The major absorption peak of 3-phenylisoxazole-4-carboxylic acid and its various 5-alkyl derivatives is at about 230 m μ , but that of 5-phenylisoxazole-4-carboxylic acid and its 3-alkyl derivatives (which incorporate a diene chain linked head-to-tail with the benzene ring ¹⁴) occurs at about 267 mµ. These results agree well with recent findings for the 3-methyl-5-phenyl and 5-methyl-3-phenyl acids¹³ Introduction of methyl or halogen substituents into the *para*-position of the benzene ring scarcely alters the spectra. but the effect of ortho-substitution is more significant. The carbocyclic and heterocyclic rings in 3-methyl-5-phenylisoxazole-4-carboxylic acid are probably almost co-planar, but when the benzene ring is ortho-substituted this is no longer possible and the chief absorption peak is consequently shifted by 15-30 m μ towards shorter wavelengths with broadening of the band and loss of intensity. In 5-methyl-3-phenylisoxazole-4 carboxylic acid, however, the rings are believed to be already inclined at an appreciable angle 13 so it is not surprising that in this series ortho-substitution produces a hypsochromic shift of only 10-15 mµ.

Heating the various isoxazole-4-carboxylic acids with thionyl chloride gave the acid chlorides, of which some were purified by distillation and most were characterised as amides. Reaction of the chlorides with 6-aminopenicillanic acid occurred readily in aqueous media, and isolation of some of the resulting penicillins (I) as pure sodium salts is described in the Experimental section. The remainder were obtained sufficiently pure 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.

All the 4-isoxazolylpenicillins showed considerable activity against most Grampositive bacteria, but only the 3,5-disubstituted types were effective against penicillinaseproducing strains of staphylococci. Evidently in 3- or 5-phenyl-4-isoxazolylpenicillin the phenyl group alone does not exert sufficient steric influence to prevent inactivation by penicillinase. The different behaviour of 2-biphenylylpenicillin,¹⁵ which exhibits considerable stability towards the enzyme, must be attributed to the differing geometry of the five-membered isoxazole and six-membered benzene rings.

Among the disubstituted isoxazolylpenicillins the 5-alkyl-3-aryl compounds were generally more active than the corresponding 3-alkyl-5-aryl isomers. In both series the preferred alkyl substituent was methyl, the higher homologues being less active. Halogenation in the benzene ring had relatively little influence on antibacterial activity. but sometimes resulted in improved absorption into the human bloodstream after oral administration. This effect was particularly marked in cloxacillin (I; R = o-Cl·C₆H₄, $R^1 = Me$),¹⁶ which has proved clinically effective in the treatment of resistant staphylococcal infections.¹⁷

EXPERIMENTAL

Representative experiments are described; other compounds, further details, and analyses appear in the Tables.

Ultraviolet absorption spectra of dilute methanolic solutions were measured on a Hilger ¹⁴ Del Re, J., 1962, 3324.

¹⁶ Dolan, Bondi, Hoover, Tumilowicz, Stewart, and Ferlauto, in "Antimicrobial Agents and Chemo-therapy—1961," ed. M. Finland and G. M. Savage, Amer. Soc. Microbiology, Detroit, p. 648; Goure-vitch, Holdrege, Hunt, Minor, Flanigan, Cheney, and Lein, Antibiotics and Chemotherapy, 1962, 12, 318.

¹⁶ Nayler, Long, Brown, Acred, Rolinson, Batchelor, Stevens, and Sutherland, Nature, 1962, 195, 1264; Knudsen, Brown, and Rolinson, Lancet, 1962, II, 632.
 ¹⁷ A Report from Six Hospitals, Lancet, 1962, II, 634.

"Uvispek" instrument and we are indebted to Dr. H. D. C. Rapson and his staff for these results.

Substituted Benzaldehydes and Benzaldoximes. - o- and p-Bromo-, and o- and p-fluoro-benzaldehyde, were prepared as described by Coleman and Honeywell ¹⁸ for the p-bromo-compound; o-tolualdehyde was prepared from o-toluidine by Beech's method.¹⁹ Oximes were made by standard methods.20

p-Fluorobenzoic Acid.—Solid potassium permanganate (720 g.) was added portionwise during 3 hr. to a stirred mixture of p-fluorotoluene (110 g.), pyridine (485 ml.), and water (1100 ml.) at 100°. Heating and stirring were continued for 1 hr. longer, then the mixture was set aside overnight. The manganese dioxide was filtered off and washed with water, and the filtrate was decolourised with sulphur dioxide and extracted with ether (1.5, 1.0 l.). Evaporation of the dried extracts left p-fluorobenzoic acid (120 g., 86%), m. p. 185-187° (lit.,²¹ 186°).

Ethyl Alkanoylacetates.-Ethyl formylacetate was obtained as the sodio-derivative by Deuschel's method.²² Ethyl propionyl-, butyryl-, and isobutyryl-acetate were prepared as described by Brändström,²³ and ethyl chloroacetylacetate was prepared from ethyl chloroacetate by Alexandrow's method.²⁴

Ethyl α -Alkanoyl- α -aroylacetates.—(a) Ethyl α -aroylacetoacetates were prepared as their sodio-derivatives as described by Burton and Ingold ²⁵ for ethyl sodio-p-chlorobenzoylacetoacetate. Treatment of the sodio-derivatives with dilute hydrochloric acid liberated the free diketo-esters which were extracted into ether. The extracts were washed with water and dried, and the solvent was evaporated, to give materials of sufficient purity for the next reaction.

(b) Ethyl α -propionyl-, α -butyryl-, and α -isobutyrylbenzoylacetate were prepared by acylation of ethyl sodiobenzoylacetate with the appropriate acid chloride in benzene under the conditions described by Shriner, Schmidt, and Roll ²⁶ for ethyl benzoylacetoacetate.

5-Alkyl-3-arylisoxazole-4-carboxylic Acids and their Derivatives.—(a) 3-o-Chlorophenyl-5methylisoxazole-4-carboxylic acid derivatives. (i) A stirred solution of o-chlorobenzaldoxime (89 g.) in chloroform (500 ml.) was treated at -10° to 0° with chlorine (45 g.) in chloroform (300 ml.), and the mixture was allowed to attain room temperature overnight. Removal of the solvent in vacuo left crude o-chlorobenzohydroxamoyl chloride (107 g., 98%) as a pale yellow oil which partially solidified. A sample, crystallised from ethanol, had m. p. 54-56° (lit.,27 56°).

(ii) A solution of methyl sodioacetoacetate [from sodium $(13 \cdot 4 \text{ g.})$, methanol (400 ml.), and methyl acetoacetate (64 ml.)] was added slowly to a stirred solution of o-chlorobenzohydroxamoyl chloride (107 g.) in methanol (400 ml.) at 0°, the mixture was allowed to warm to room temperature overnight, and the solvent was evaporated in vacuo. The residue was shaken with water (200 ml.) and ether (200 ml.), the aqueous phase was extracted with more ether $(2 \times 200 \text{ ml.})$, the combined ether extracts were washed with 5% sodium hydroxide solution, then with water, dried, and distilled to give methyl 3-o-chlorophenyl-5-methylisoxazole-4-carboxylate (88.3 g.), b. p. 120-134°/0.05 mm., m. p. 57-58°.

(iii) The ester (85 g.), dissolved in ethanol (500 ml.), was treated with potassium hydroxide (32 g.) in water (70 ml.) and refluxed for 2 hr. After distillation of most of the ethanol, water (400 ml.) was added, and the solution was clarified by ether-extraction, and acidified to precipitate crude pale yellow 3-o-chlorophenyl-5-methylisoxazole-4-carboxylic acid (75.2 g.), m. p. 194—196°.

(iv) When the acid (75.2 g.) and thionyl chloride (40 ml.) had been boiled together for 1 hr. and the excess of thionyl chloride removed in vacuo, distillation of the residue yielded 3-o-chlorophenyl-5-methylisoxazole-4-carbonyl chloride (73.5 g., 91%), b. p. 130°/0.5 mm., which solidified.

¹⁸ Coleman and Honeywell, Org. Synth., Coll. Vol. II, p. 89.

 Beech, J., 1954, 1297.
 Linstead and Weedon, "A Guide to Qualitative Organic Chemical Analysis," Butterworths Scientific Publns., London, 1956, p. 27.

²¹ Schiemann and Winkelmüller, Org. Synth., Coll. Vol. II, p. 299.

- ²² Deuschel, Helv. Chim. Acta, 1952, 35, 1587.
 ²³ Brändström, Acta. Chem. Scand., 1951, 5, 820.
 ²⁴ Alexandrow, Ber., 1913, 46, 1022.

- ²⁵ Burton and Ingold, J., 1928, 919.
 ²⁶ Shriner, Schmidt, and Roll, Org. Synth., Coll. Vol. II, p. 266.
- 27 Rheinboldt, Dewald, Jansen, and Schmitz-Dumont, Annalen, 1926, 451, 161.

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$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Сснаст Сснас Сснаст Сснаст Ссна Сснаст Сснаст Ссна Сснаст Сснаст Ссна Сснаст Сснаст Ссна	1.1.1.1.8 1.21.1.8 1.21.1.8 1.21.1.8 1.21.1.8 1.21.23 1.01.0.7 1.01.0.2 1.	Р-С; А; Р-С; А-D А-D А-D; В-Е А-D; В-Е В-Е В-Е С; В-Е С; В-Е С; В-Е С; В-Е С; В-Е С; В-Е С; В-Е С С; В-Е С С; В-Е	759 945 950 960 960 960 971 45 759 94 92 759 94 95 759 950 960 960 97 759 950 90 759 950 950 90 759 950 950 950 950 950 950 950 950 950 9	1 255 395 40 40 50 50 50 50 50 50 50 50 50 50 50 50 50	55 15-0 55 15-0 55 14-1 55 14-4 55 15-20	5 9.5 6.0 7.9 7.9 7.9 7.9 7.9 7.4 7.4 7.4 7.7 7.9 7.9 7.9 7.9 7.9 7.9 7.9	Clarkino Cla	60.35 66.35 66.35 66.35 66.35 66.35 66.35 89.45 89.45 89.45 89.45 89.45 89.45 89.45 89.45 89.45 89.45 89.45 89.45 89.45 80.45	0.00 0.00	2. 2. 2. 2. 2. 2. 2. 2. 2. 2. 2. 2. 2. 2	e \$\$ \$ 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	. (11,440) (6.5 (12,260) (6.13,730) (6.11,090) (6 (11,090) (6 (10,340) (6 (10,340) (9 (12,780) (13,430)
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	CH ₃ CI Me Me Me CO ₃ H Me CO ₃ Me Me CO ₃ Me CO ₃ Me Me CO ₃ Me Me CO ₃ Me Me CO ₃ Me Me CO ₃ Me CO ₃ Me Me CO ₃ Me CO ₃ Me Me CO ₃ Me CO ₃ Me Me CO ₃ Me CO ₃ Me Me CO ₃ Me CO ₃	$\begin{array}{c} 143\\ 143\\ 160\\ 160\\ 160\\ 160\\ 160\\ 194\\ 194\\ 192\\ 192\\ 192\\ 192\\ 192\\ 193\\ 173\\ 59\\ -60\\ 195\\ 196\\ 1155\\ 196\\ 1155\\ 196\\ 1155\\ 106\\ 1155\\ 106\\ 1155\\ 106\\ 1156\\ 106\\ 1156\\ 106\\ 106\\ 105\\ 106\\ 106\\ 106\\ 106\\ 106\\ 106\\ 106\\ 100\\ 100$	А-D, А-D, А, B-E В В Е В В Е С В В Е С С В В Е С С В В Е В В Е В В Е С В В Е В В В Е В В В Е В	114 224 669 669 57 995 667 57 667 57 667 57 57 57 57 57 57 57 57 57 57 57 57 57	1 2.5 3 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	55 15.0 25 15.0 26 14.1 55 15.2(14.4 57 15.2(56 14.1	5 11 11 11 11 11 11 11 11 11 11 11 11 11	Cliffic Cliffi	55.6 66.35 66.35 66.35 66.35 59.75 59.75 57.2 68.975 57.2 57.2	3 3 4 4 4 4 4 9 3 9 5 5 7 7 1 9 7 9 7 9 7 9 7 9 7 9 7 9 7 9 7 9	4.95 4.95 5.05 4.45 5.05	6 8 9 9 9 7 3 3 3 9 7 9 9 7 9 9 7 9 9 9 9 9	6 (13,730) 6.5 (12,260) 66 (11,090) 7.5 (12,240) 6 (10,340) 9 (12,780) 9 (13,430)
	Me CO ₂ H Me CO ₂ H CO ₂ Me CO ₂ Me CO ₂ Me CO ₂ Me CO ₂ Me CO ₂ Me CO ₂ Me CO ₂ Me	$\begin{array}{c} 160-160\cdot 5\\ 66-67\\ 66-67\\ 194-195\\ 1120-122/0\cdot 5\\ 1120-122/0\cdot 5\\ 1120-122/0\cdot 5\\ 1120-122/0\cdot 5\\ 1120-122/0\cdot 5\\ 1120-122/0\cdot 5\\ 1120-128/0\cdot 1\\ 1120-128/0\cdot 1\\ 1120-128/0\cdot 1\\ 165-166\\ 1120-166\\ $	А; В-Е В-Е Е С; В-Е С; В-Е С; В-Е С; В-Е С; В-С С; В-Е С С; В-Е С С; В-С С; В-Е С С; В-Е С С; В-Е С С; В-Е С С; В-Е С В-Е С; В-Е С В-Е С В-Е С В-Е С В-Е С В-Е С В-Е С В-Е С В-Е С С В-Е С С В-Е С С В-Е С С В-Е С С С В-Е С С В-Е С С С В-Е С В-С С В-Е С С В-Е С С В-С С В-С С В-Е С С В-С С В-С С В-С С С В-С С С В-С С С В-С С В-С С В-С С В-С С С В-С С С В-С С В-С С В-С С С В-С С С В-С С С В-С С С В-С С С В-С С С В-С С С В-С С С В-С С С В-С С С В-С С С В-С С С В-С С С В-С С С С	224 66 69 67 59 66 57 60 57 57 57 57 57 57 57 57 57 57 57 57 57	6 5 5 5 775 6 6 5 5 115 5 3 5 3 5 0 3 9 6 6 5 5 3 5 <td></td> <td>5 12 5 5 5 5 5 5 5 5 5 5 5 5 5</td> <td>C12H11NO C12H11NO C12H11NO C12H11NO C12H11NO C14H8FNO C14H8FNO C14H8FNO C14H10FNO C14H10FNO C14H10FNO C11H6CINO C11H6CINO</td> <td>66.35 67.5 66.35 66.35 59.75 59.75 57.2 68.95 57.2</td> <td>3.34.04 3.44.05 3.40.44 3.40.44 3.40.44 3.40.44 3.40.44 3.40.44 3.40.44 3.40.44 3.40.44 3.40.44 3.40.44 3.40.44 3.40.44 3.40.44 5.40.440.44 5.40.44 5.40.440 5.40.440 5.40.440 5.40.440 5.40.440 5.40.440 5.40.440 5.40.440 5.40.4400 5.40.440000000000</td> <td>8886 69 64 64 64 66 66 66 66 66 66 66 66 66 66</td> <td>6 6 22 21 22 22 22 23 24 25 21 24 25 21 25 25 25 25 25 25 25 25 25 25 25 25 25</td> <td>$\begin{array}{l} 6\cdot 5 & (12,260) \\ (6 & (11,090) \\ 7\cdot 5 & (12,240) \\ (6 & (10,340) \\ 6 & (12,780) \\ 9 & (12,780) \\ 0 & (13,430) \end{array}$</td>		5 12 5 5 5 5 5 5 5 5 5 5 5 5 5	C12H11NO C12H11NO C12H11NO C12H11NO C12H11NO C14H8FNO C14H8FNO C14H8FNO C14H10FNO C14H10FNO C14H10FNO C11H6CINO C11H6CINO	66.35 67.5 66.35 66.35 59.75 59.75 57.2 68.95 57.2	3.34.04 3.44.05 3.40.44 3.40.44 3.40.44 3.40.44 3.40.44 3.40.44 3.40.44 3.40.44 3.40.44 3.40.44 3.40.44 3.40.44 3.40.44 3.40.44 5.40.440.44 5.40.44 5.40.440 5.40.440 5.40.440 5.40.440 5.40.440 5.40.440 5.40.440 5.40.440 5.40.4400 5.40.440000000000	8886 69 64 64 64 66 66 66 66 66 66 66 66 66 66	6 6 22 21 22 22 22 23 24 25 21 24 25 21 25 25 25 25 25 25 25 25 25 25 25 25 25	$\begin{array}{l} 6\cdot 5 & (12,260) \\ (6 & (11,090) \\ 7\cdot 5 & (12,240) \\ (6 & (10,340) \\ 6 & (12,780) \\ 9 & (12,780) \\ 0 & (13,430) \end{array}$
$ \begin{array}{ccccc} Me & COMe & 60-07 & F & F & 60 & 67.75 & 6-0 & 5-86 & 6-05 & 6-05 & 5-55 & 6-05 & 6-05 & 5-10 & 1000 \\ CONH & 104-195 & E & 104-195 & 104-1$	Me CO ₂ Me Me Me CO ₂ Me Me CO ₂ Me Me CO ₂ Me Me Me Me CO ₂ Me M	$\begin{array}{c} 66-67\\ 206-207\\ 194-195\\ 120-122\\ 120-122\\ 120-122\\ 203-204\\ 173-173\cdot 5\\ 59-60\\ 195-196\\ 115-196\\ 115-146\\ 115-146\\ 115-146\\ 115-16\\ 115-16\\ 115-$	н в в в в в в в с ; в с ; в с ; в с в в е с с ; в с в н с с ; в с с ; в с с ; в с с ; с с ; с с ; с ;	669 95 95 95 66- 75 94 75 75 75 77 75 77 75 77 75 77 75 77 75 77 75 77 75 77 75 77 75 77 75 75	1 25 3 3 5 4 5 3 5 6 0 25 4 5 3 5 5 6 0 25 3 5 5 5 5 6 0 2 5 5 5 5 5 6 0 2 5 5 5 5 5 6 0 2 5 5 5 5 5 5 6 0 2 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	55 14-1 55 14-1 55 15-24	5 12 5 5 5 5 5 5 5 5 5 5 5 5 5	C11413NO3 C12413NO3 C12412NO3 C1445NO3 C1445NO3 C1445NO3 C1445NO3 C1445NO3 C1445CNO3 C1445CNO3 C1445CNO3 C1445CNO3	67.5 66.35 66.65 59.75 59.75 68.95 57.2 57.2	55.65 5.75 5.75 5.75 5.75 5.75 5.75 5.75	6 8 8 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6	05 05 05 05 05 05 05 05 05 05	6 (11,090) 6 (10,340) 6 (10,340) 9 (12,780) 0 (13,430)
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	CO ₂ H CO ₂ Me CO ₂ Me CO ₂ Me Me CO ₂ Me Me CO ₂ Me	$\begin{array}{c} 206-207\\ 194-195\\ 120-122/0.5\\ 191-192\\ 203-204\\ 173-173.5\\ 59-60\\ 195-196\\ 1145-196\\ 1145-128/0.1\\ 165-166\\ 165-166\\ 165-166\\ 165-166 \end{array}$	В-Е Е 6; C; B-E 9-E; G; B-E Н В-E G; B-E G; B-E C, -	95 66- 95 66- 92 759 66- 92 557 60- 178 557 50- 5557 50- 178 557 50- 5557 50- 50057 50- 50057 50- 50057 50- 50057 50057 50057 50057 50057 50057 50057 50057 500500000000	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	55 14-1 55 14-1 55 15-24	5 11.5.4 12.95 5 0.0 5 0.0 1.5.7 1.5.7 1.5.7 1.5.7 1.5.7 1.5.7 1.5.7 1.5.7 1.5.7 1.5.7 1.5.7 1.5.95 1.5.555 1.5.555 1.5.555 1.5.555 1.5.55	C ₁₂ H ₁₁ NO ₂ C ₁₂ H ₁₂ N ₂ O ₂ C ₁₁ H ₆ FNO ₃ C ₁₁ H ₆ CNO ₂ C ₁₁ H ₆ CNO ₂ O ₂	66-35 66-65 59-75 59-75 59-75 68-95 57-2 57-2	55.1 5.55 3.6 3.6 5.55 5.55 5.55 5.55 5.55 5	6 8.6 6.4 6.4 1.1 5.0 11.1 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	6 6 6 6 6 7 5 5 5 5 5 5 6 6 6 6 6 7 5 5 5 5	6 (11,090) 6 (10,340) 6 (10,340) 9 (12,780) 0 (13,430)
$ \begin{array}{ccccc} {\rm CONH} & 190-192 \\ {\rm We} & {\rm CONH} & 190-192 \\ {\rm COMH} & 120-122 \\ {\rm Me} & {\rm COMH} & 120-122 \\ {\rm COMH} & 120-122 \\ {\rm Me} & {\rm COMH} & 120-120 \\ {\rm Me} & {\rm COMH} & 145-146 \\ {\rm G} & {\rm G} & {\rm B-E} & {\rm G} & {\rm F} & {\rm G} & {\rm G} & {\rm S} & {\rm S} & {\rm H} & {\rm H} & {\rm S} & {\rm G} & {\rm S} & {\rm S} & {\rm H} & {\rm H} & {\rm S} & {\rm S} & {\rm S} & {\rm H} & {\rm H} & {\rm S} & {\rm S} & {\rm S} & {\rm H} & {\rm H} & {\rm S} & {\rm S} & {\rm S} & {\rm H} & {\rm H} & {\rm S} & {\rm S} & {\rm S} & {\rm S} & {\rm H} & {\rm H} & {\rm S} & {\rm $	Me CO·NH ² Me CO ₂ Me CO ₂ Me Me CO ₂ H Me CO ₂ Me Me CO ₂ Me	$\begin{array}{c} 194-195\\ 120-122/0.5\\ 120-122/0.5\\ 173-173.5\\ 59-60\\ 195-196\\ 1155-196\\ 1145-128/0.1\\ 165-166\\ 165-166\\ 165-166\end{array}$	E G; C; B-E B-E; G; B-C E E B-E G; B-E G; B-E	55 57 57 57 57 57 57 57 57 57	4 0.0 4 0.0 2 5 4.5 2 5 3.5 2 5 3.5 1 3.9 1 3	5 14-1 55 14-1 55 15-24	12:95 6:0 11:5:7:4:2 11:5:7:4:2 11:5:7:4:2 11:5:7:4:2 11:5:7:4:2 11:5:7:4:2 11:5:7:4:2 11:5:7:4:2 11:5:7:4:2 11:5:7:4:2 11:5:7:4:2 11:5:7:7:7:7:7:7:7:7:7:7:7:7:7:7:7:7:7:7	C11H12N202 C11H8FN03 C11H8FN03 C11H8FN03 C11H18FN03 C11H101N03 C11H0CIN03 C11H0CIN03 C11H0CIN03 C11H0CIN03	66-65 59-75 59-75 59-75 68-95 57-2	5.55 3.6 3.6 3.6 4.4 4.4 1 3.8 1 3.8 1	12 8-6 6-4 6-4 6-4 9 6-4 9 1 5 6-4 9 1 1 5 7 1 1 7 7 8-1 7 8-6 8-6 6 6 6 6 6 6 6 6 7 8-6 6 6 6 8-6 6 6 6 8-6 6 6 6 6 6 6 6 6	6 6 6 7 7 7 7 7 7 7 7 6 7 7 7 7 7 7 7 7	(10,340) (10,340) (12,780) (13,430) (13,430)
$ \begin{array}{cccccc} Me & CO_{M} & 191-192 (0.5 \\ CO_{H} & 191-192 (0.1 \\ H_{1}-146 & 15-16 \\ CO_{H} & 191-196 & 1-E \\ CO_{H} & 195-196 & 1-E \\ CO_{H} & 195-196 & 1-E \\ CO_{H} & 191-196 & 1-E \\ CO_{H} & 191-196 & 1-16 \\ CO_{H} & 191-132 & 1-16 \\ DE_{I} & 1$	Me CO ₂ Me Me CO ₂ H Me CO ₂ H Me CO ₂ Me Me	$\begin{array}{c} 120-122/0.5\\ 191-192\\ 173-173.5\\ 59-60\\ 195-196\\ 195-196\\ 195-1146\\ 1124-128/0.1\\ 165-166\\ 105-16$	G; C; B-E B-E; G; B-E E E H B-E G; B-E G; B-E	59 93 60- 62 57- 56 77- 55 77- 55- 77- 55- 77- 55- 77- 55- 77- 55- 77- 55- 77- 55- 77- 55- 77- 55- 77- 55- 57- 57	1 25 35 25 35 25 25 35 25 25 25 25 25 25 25 25 25 25 25 25 25	55 14-1 55 14-1 55 15-2;	5 11.5 1.5 1.5 1.5 1.5 1.5 1.5 1.5 1.5 1	C ₁₁ H ₆ FNO ₃ C ₁₁ H ₆ FNO ₃ C ₁₇ H ₁₈ FN ₂ O ₂ C ₁₇ H ₁₈ FN ₂ O ₂ C ₁₁ H ₁₀ CINO ₃ C ₁₁ H ₆ CINO ₃ C ₁₁ H ₆ CINO ₃	59-75 59-75 68-95 57-2	8 8 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9	8.6 8.6 6.4 95.0 11 7 7.0 11 7 7 7 7 11 7 7 7 11 7 7 7 7 7 7 7 7	ခ်င်္နှင့် 22 ခြင်္နှင့် 22 ခြင်္နှင့် 22	. (12,240) (6 (10,340) (12,780) (13,430) (0 (13,430)
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Me CO ₂ H Me CO ₂ H Me CO ₂ Me Me CO ₂ Me	$\begin{array}{c} 191-192\\ 203-204\\ 173-173\cdot 5\\ 59-60\\ 59-196\\ 1145-146\\ 124-128/0\cdot 1\\ 125-166\\ 165-166 \end{array}$	GG; C; B-E B-E; G; B-C H B-E G; B-E G; B-E	93 60- 27 60- 62 57- 94 55- 73 55- 73 57- 78 57- 78 57- 77	1 25 3:60 3:9 25 3:65 3:8 25 3:65 3:6	55 14-1 55 14-4 55 15-27 50 15-27	5 11 5 11 5 7 4 7 7 7 6 0 0 8 0 9 8 0 8 9 9 8 9 9 9 9 9 9 9 9 9	C ₁₁ H ₈ FNO ₃ C ₁₁ H ₈ FNO ₃ C ₁₇ H ₁₃ FN ₉ O ₂ C ₁₂ H ₁₀ CINO ₃ C ₁₁ H ₆ CINO ₃ C ₁₁ H ₆ CINO ₃	59-75 59-75 68-95 57-2 55-6	3.6 3.4 3.8 4.0 4.0 5 8 1 1 1	886 866 866 866 866 86 86 86 86 86 86 86	ခဲ့မှ ခွဲမှ မှ မ ်းခဲ့ခဲ့ ၁၂ ၁၂ ၁၂ ၁၂ ၁၂ ၁၂ ၁၂ ၁၂ ၁၂ ၁၂ ၁၂ ၁၂ ၁၂ ၁	$\begin{array}{c} 7.5 \ (12,240) \\ (6 \ (10,340) \\ 9 \ (12,780) \\ 0 \ (13,430) \end{array}$
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Me CO ₂ H CO-NHPh Me CO ₂ Me	$\begin{array}{c} 203-204\\ 173-173\cdot 5\\ 59-60\\ 145-146\\ 145-146\\ 124-128/0\cdot 1\\ 165-166\end{array}$	B-E; G; B-C E B-E G; B-E G; B-E	27 60. 62 57 94 55 7 56 7 7 8 7 7	1 25 3 5 4 5 25 3 5 5 25 3 5 5 25 3 5 5 25 3 5 5 2 5 2 5 2 5 2 5 5 5 5 5 5 5 5 5 5 5	2 14-1 55 14-4 35 15-27 15-27	5 11.57.4.2.2 11.57.4.2.2 11.57.4.2.2 11.57.4.2.2.2 11.57.4.2.2.2.2.2.2.2.2.2.2.2.2.2.2.2.2.2.2.	CuH ⁸ FNO ₃ Cr ¹ H ₁₃ FN ₂ O ₃ CuH ₁₆ CNO ₃ CuH ₈ CINO ₃ CuH ₈ CINO ₃	59-75 68-95 57-2 55-6	33.6 4.4 3.3 3.4 0.4 0.4 0.4 0.4 0.4 0.4 0.4 0.4 0.4 0	8.6 6.4 6.4 9 5.0 11 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	6 (10,340) 9 (12,780) 0 (13,430)
$ \begin{array}{cccccc} {\rm CONPTP} & {\rm CONPT} & {\rm F} & {\rm F} & {\rm C} & {\rm C} & {\rm H} & {\rm F} & {\rm C} & {\rm C} & {\rm H} & {\rm F} & {\rm C} & {\rm F} & {\rm F} & {\rm F} & {\rm C} & {\rm H} & {\rm F} & {\rm F} & {\rm C} & {\rm H} & {\rm F} & {\rm F} & {\rm C} & {\rm H} & {\rm F} & {\rm F} & {\rm C} & {\rm H} & {\rm F} & {\rm F} & {\rm C} & {\rm H} & {\rm F} & {\rm F} & {\rm C} & {\rm H} & {\rm F} & {\rm F} & {\rm C} & {\rm H} & {\rm F} & {\rm F} & {\rm F} & {\rm C} & {\rm H} & {\rm F} & {\rm C} & {\rm H} & {\rm F} & {\rm H} & {\rm F} & {\rm F} & {\rm F} & {\rm H} & {\rm F} & {\rm F} & {\rm F} & {\rm F} & {\rm H} & {\rm F} & {\rm F} & {\rm F} & {\rm F} & {\rm H} & {\rm F} & {\rm F} & {\rm F} & {\rm F} & {\rm H} & {\rm F} & {\rm H} & {\rm H} & {\rm F} & {\rm F} & {\rm F} & {\rm F} & {\rm H} & {\rm H} & {\rm F} & {\rm F} & {\rm F} & {\rm F} & {\rm H} & {\rm H} & {\rm F} & {\rm F} & {\rm F} & {\rm H} & {\rm H} & {\rm H} & {\rm F} & {\rm F} & {\rm H} & {\rm$	Me CO ₂ Me	$\begin{array}{c} 173 - 173 \cdot 5 \\ 59 - 60 \\ 195 - 196 \\ 145 - 146 \\ 124 - 128 / 0 \cdot 1 \\ 165 - 166 \end{array}$	н н В-в G; В-е С С В-е С С С С	62 57- 62 57- 94 55- 55- 55- 55- 55- 55- 55- 55- 55- 55-	55 4-2 9 3-5 25 3-6 1 3-9	2 14-1 55 14-4 35 15-28	9.2 5.4 11.5 11.5	C ₁₇ H ₁₃ FN ₂ O ₂ C ₁₂ H ₁₆ CINO3 C ₁₁ H ₆ CINO3 C ₁₁ H ₉ CIN ₂ O2	68-95 57-2 55-6	4.4 4.6 3.4 3.8 1 1	6.4 9 4.1 5 4.95 5 5.0 11 7.1 5	6 22 21 21 21 21 21 21 21 21 21 21 21 21	9 (12,780) 0 (13,430)
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Me CO ₂ Me	59-60 195-196 145-146 124-128/0·1 165-166	H B-E G; B-E T. P.C. A.D	62 57-1 94 55- 55-1 55- 57- 78 57-	1 25 3 6 4 2 25 3 6 4 2 3 9 6 2 1 3 6	2 14·1 55 14·4 35 15·2	5 11.5 7.7 7.7	C ₁₁ H ₁₀ CINO C ₁₁ H ₆ CINO C ₁₁ H ₉ CIN ₂ O	57-2 55-6	3.8 1 3.8 1 3.8 1	4.1 5 4.95 5 5.0 11 4.1 5	6 22 21 21 21 21 21 21 21 21 21 21 21 21	9 (12,780) 0 (13,430)
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		195-196 145-146 124-128/0.1 165-166	B-E G; B-E A-D R-C A-D	94 55- 	1 3.0 3.0 1 3.0 1	55 14·4 55 15·2(75 15·2(5 11.5 5 11.5 5 5	C ₁₁ H ₆ CINO ₅ C ₁₁ H ₆ CIN ₂ O ₂	55.6	3.4 3.8 1	4.95 5 5.0 11 4.1 5	6	9 (12,780) 0 (13,430)
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	CO.H	$\frac{145-146}{124-128/0.1}$ $165-166$	G; B-E G n· B-C· A-D	55- 55- 78 57-	25 36 1 3.9	35 15-2(br 19.6	5 11.5	C ₁₁ H,CIN ₂ O		3.8	5.0 11 4.1 5	85 9 9 7 8 7	0 (13,430)
Et $CO_{0}Et$ 122-128[01 0. 0.10+5 A-D; B-E; A-D 78 571 4.45 14.35 11.05 C_{12}H_{11}CIN_{0}C_{3} 577 4.4 14.2 11.2 50 (13,430) CO_{0}H 165-166 G-D; B-C; A-D 78 571 4.45 14.35 11.06 C_{12}H_{11}CIN_{0}C_{3} 575 4.4 14.2 11.2 50 (13,430) Pr CO_{0}H 136-137 019 B-C; A-D 78 571 4.45 14.35 11.06 C_{12}H_{12}CIN_{0}C_{3} 5885 4.5 134 5.22 (13,800) Pr CO_{0}H 138-137 019 B-C; A-D 49 587 5.4 13.7 10.5 C_{12}H_{12}CIN_{0}C_{3} 5885 4.5 134 5.22 (13,800) Pr CO_{1}H 108-109 B-C; A-D - 587 5.4 13.7 10.5 C_{12}H_{12}CIN_{0}C_{3} 5885 4.5 134 5.52 210 (13,130); Me CO_{1}H 128-137 D - 49 134 10.6 20 (13,130); Me CO_{1}H 140-142 B-E; A-D - 566 3.8 14.8 5.8 C_{11}H_{9}CIN_{0}^{2} 58.6 4.5 134 5.52 218 (10,130); Me CO_{1}H 140-142 B-E; A-D - 566 3.8 14.8 5.8 C_{11}H_{9}CIN_{0}^{2} 55.8 3.8 150 11.86 5.9 216 (13,130); Me CO_{2}H 174-175 B-C; G; F 63 5.8 14.8 5.8 (1.6, 2.0) (1.6, 2.0) (1.0, 2.0) (1.6, 2	CONH	124-128/0.1 165-166	ית_ח. א_רו ב	59 78 57.	1 3.0	19.0 19.0	յ հ։ ւ հ։ ւ	CHCINO.	55.85	5	4·1 2	• • • • •	0 (13,430)
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Ft CO.Ft	165-166	ת_ה. א_ית ית	78 57.	1 3.9	NE 19.0	հ	C., H., CINO,			4.1 5	.6 22	0 (13,430)
$ \begin{array}{ccccc} \mathrm{Pr}^{\mathrm{r}} & \mathrm{iop} = 1095 & \mathrm{A-D}^{\mathrm{r}} \mathrm{B-E} & \mathrm{D-1} \mathrm{B-1} $	CO.H				, ,	0.01 04	с. с		57.2	4.0 1		 	(and fact a
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	CO NH	109-109-5	A-D. B-F.	. 57.	1 4.4	14-3	5 11-05	C. H. CIN O	57.5	4.4	4.9 11		
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Pra CO.Ff	136-142/0-02		64	, H				5	H H		1	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	CO.H	136-137	H: A: I	53 58.	7 4.8	3 13.5	5.35	CHCINO.	58.85	4.5 1	3.4 5	-25 22	0 (13,800)
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	CO·NH.	108-109	B-C: A-D	8. 26. 27.	7 5.4	13.7	10.5	C.,H.,CIN,O.	59-0	4.9	3.4 10	¦ ¦Ģ	(000 101) 0
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Pri CO.H	132 - 134	L L	49 58-	4 4.6	13.2	5.0	C. H. CINO.	58.85	4.5	3.4	25 21	8.5 (15.270)
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	CO'NH.	140 - 142	B-E: A-D	29.	1 4-8-	35 13.68	5 10.4	C.,H.,CIN,O.	59-0	4·9	3.4 10	i 9	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Me CO.H	174 - 175	B-C; G: F	63 55.	6 3.8	3 14·8	5.8	C, H.CINO,	55.6	3.4 1	4.95 5	-9 21	6 (13.130):
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	3							•					228sh (10,330
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	CO·NH ₂ 2	200 - 201	н	- 26.	0 3.8	55	11.55	C ₁₁ H ₆ CIN ₂ O ₃	55-85	3.8 1	5.0 11	·85	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Me CO ₂ Me	63 - 64	A	90 ‡ 27-1	5 4.3		2.6	C ₁₂ H ₁₀ CINO ₃	57.2	4·0 I	4·1 5	9	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$CO_{2}Et$	59 - 60	A	93 ‡ 29.]	1 4·9	_	5.0	C ₁₃ H ₁₂ CINO ₃	58-85	4·5 1	3.4 5	·25	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	CO ₂ H	213-214	A; B-E	65 55.	5 3.6	15.3	5.6	C ₁₁ H _s CINO ₃	55.6	3.4 1	4.95 5	-9 23	2(14,600)
$ \begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	COCI	146/0.25		95 51-6	85 3·1	5 28.2	5.2	C ₁₁ H,CI,NO,	51.55	2.75 2	7.75 5	-45	
Et $CO_{2}H$ 187–188 C; G; E 30 57.3 4.1 14.45 5.35 $C_{12}H_{10}CINO_{3}$ 57.2 4.0 14.1 5.6 232.5 (15,220) CO.NH ₂ 179–180 E; G $-$ 57.5 4.4 14.3 10.95 $C_{12}H_{11}CIN_{2}O_{3}$ 57.5 4.4 14.2 11.2 Me $CO_{2}Me$ 66–67 D; H 58 48.5 3.65 27.25 4.5 $C_{12}H_{10}BNO_{3}$ 48.65 3.4 27.0 4.75 CO.NH 196.5–197.5 G; B–E 93 46.85 2.95 28.45 4.95 $C_{11}H_{3}BNO_{3}$ 48.65 3.4 27.0 4.75 CO.NH 195–220 A; G; B–E $-$ 47.45 2.2 28.2 9.95 $C_{11}H_{3}BNO_{3}$ 46.8 2.85 28.35 4.95 Me $CO_{4}H$ 219-2 28.45 4.70 3.2 28.2 5 4.6 $C_{11}H_{3}BNO_{3}$ 46.8 2.85 28.35 4.95 Me $CO_{4}H$ 219-220 A; G; B–C $-$ 47.42 3.2 28.2 9.95 $C_{11}H_{3}BNO_{3}$ 46.8 2.85 28.35 4.95 Me $CO_{4}H$ 219-220 A; G; B–C $-$ 57.0 3.6 22.55 7.5 $C_{11}H_{3}BNO_{3}O_{3}$ 57.15 3.65 22.4 7.85	CO-NH.	207 - 208	ਜ	55.	65 3.9	5 14-9f	5 12·1	C,H,CIN,O	55.85	3.8 1	5.0 11	·85	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Et CO ₈ H ⁻]	187—188	С; G; E	30 57.	3 4·1	14-45	5.35	C, H, CINO,	57.2	4·0 1	4·1 5	·6 23	2.5 (15,220)
$ \begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	CO-NH.	179 - 180	E. G.	57-4	5 4.4	14·3	10.95	C, H, CIN, O,	57.5	4·4 1	4·2 11	ş	•
$ \begin{array}{ccccc} {\rm CO}_{0}^{\rm H} & 196\cdot5-197\cdot5 & {\rm G}_{\rm i}^{\rm j} {\rm B}{\rm -E} & 93 & 46\cdot85 & 2\cdot95 & 28\cdot45 & 4\cdot95 & {\rm Cu}^{\rm H}{_{0}} {\rm B}{\rm FN}{\rm O}_{0}^{\rm s} & 46\cdot8 & 2\cdot85 & 28\cdot35 & 4\cdot95 & 217\cdot5 (13,200) \\ {\rm CO}{\rm \cdot NH}_{\rm s} & 133-134 & {\rm E} & & 47\cdot45 & 3\cdot2 & 28\cdot2 & 9\cdot95 & {\rm Cu}^{\rm H}{_{0}} {\rm B}{\rm FN}{\rm N}_{0}{\rm O}_{\rm s} & 47\cdot0 & 3\cdot2 & 28\cdot45 & 9\cdot95 \\ {\rm Me} & {\rm CO}_{\rm s}{\rm H} & 219\cdot5-220 & {\rm A}; {\rm G}; {\rm B}{\rm -C} & 25 & 47\cdot2 & 2\cdot9 & 28\cdot25 & 4\cdot8 & {\rm Cu}^{\rm H}{_{0}} {\rm B}{\rm EN}{\rm O}_{\rm s} & 46\cdot8 & 2\cdot85 & 28\cdot35 & 4\cdot95 & 237 (14,180) \\ {\rm Me} & {\rm CO}{\rm \cdot NHPh} & 185-185\cdot5 & {\rm E} & & 57\cdot0 & 3\cdot6 & 22\cdot55 & 7\cdot5 & {\rm C}{\rm \cdot 7}{\rm H}_{\rm s} {\rm B}{\rm EN}_{\rm s}{\rm O}_{\rm s} & 57\cdot15 & 3\cdot65 & 22\cdot4 & 7\cdot85 \\ \end{array}$	Me CO _° Me É	66-67	D; H	58 48·8	5 3.6	5 27-25	5 4.5	C, H. BrNO	48.65	3.4 2	7.0 4	.75	
$ \begin{array}{ccccc} {\rm CO}^{\rm \bullet}{\rm NH}_{\rm a} & 133-134 & {\rm E} & & 47\cdot45 & 3\cdot2 & 28\cdot2 & 9\cdot95 & {\rm Cu}_{\rm H}_{\rm a}{\rm BFN}_{\rm a}{\rm O}_{\rm a} & 47\cdot0 & 3\cdot2 & 28\cdot45 & 9\cdot95 & {\rm O}_{\rm a} \\ {\rm Me} & {\rm CO}_{\rm a}{\rm H} & 219\cdot5-220 & {\rm A}; \ {\rm G}; \ {\rm B}-{\rm C} & 25 & 47\cdot2 & 2\cdot9 & 28\cdot25 & 4\cdot8 & {\rm Cu}_{\rm H}_{\rm a}{\rm BFN}_{\rm O}_{\rm a} & 46\cdot8 & 2\cdot85 & 28\cdot35 & 4\cdot95 & 237 & (14,180) \\ {\rm CO}_{\rm a}{\rm Me} & {\rm CO}_{\rm a}{\rm Me} & {\rm B}_{\rm c}{\rm B}_{\rm c}{\rm O}_{\rm a} & 46\cdot8 & 2\cdot85 & 28\cdot35 & 4\cdot95 & 237 & (14,180) \\ {\rm CO}_{\rm a}{\rm Me} & {\rm B}_{\rm c}{\rm D}_{\rm c}{\rm B}_{\rm c}{\rm D}_{\rm c} & 57\cdot15 & 3\cdot65 & 22\cdot4 & 7\cdot85 \\ \end{array} $	CO [*] H 19	96·5 —197·5	G; B-E	93 46·8	85 2.9	5 28.45	5 4.95	C,H,BrNO,	46.8	2.85 2	8.35 4	-95 21	7.5 (13.200)
$ \begin{array}{rclcrcl} Me & CO_{4}H & 219\cdot5-220 & A; \ G; \ B-C & 25 & 47\cdot2 & 2\cdot9 & 28\cdot25 & 4\cdot8 & C_{11}H_{8}BrNO_{8}, & 46\cdot8 & 2\cdot85 & 24\cdot95 & 237 & (14,180) \\ CO^{1}HPh & 185-185\cdot5 & E &57\cdot0 & 3\cdot6 & 22\cdot55 & 7\cdot5 & C_{17}H_{18}BrN_{8}O_{2} & 57\cdot15 & 3\cdot65 & 22\cdot4 & 7\cdot85 \\ \end{array} $	CO'NH,	133-134	́. Э	- 47.4	45 3.2	28.2	9.95	C,H,BrN,Ö,	47-0	3.2	8.45 9.	-95	
$\begin{array}{ccccc} \text{CO-NHPh} & 185 \hline 185 \hline 185 \hline 185 \hline 185 \hline 195 \hline $	Me CO ₆ H 21	19-5-220	A; G; B-C	25 47.5	2 2.9	28.25	5 4·8	C,H,BrNO.	46.8	2.85 2	8.35 4	.95 23	7(14.180)
	CONHPh	$185 - 185 \cdot 5$	'	- 57.(0 3.6	22.55	5 7.5	C ₁₇ H ₁₃ BrN ₂ O ₂	a 57.15	3.65 2	2·4 7·	-85	

3-Arylisoxazole-4-carboxylic acids and their derivatives.

TABLE I.

Doyle, Hanson, Long, Nayler, and Stove:

Subst.	at posi	tion	3-Alk	yl-5-arylisox	azole-4	-carbox	tylic ad Found	cids an 1 (%)	d their	· derivatives.	щ	equire	(%) P		
ณ	m	4	M. p. or b. p./mm.	Cryst. from *	Yield (%)	ပြ		Hal	ſz	Formula	lυ		Hal	⊎ ∫Z	λ_{\max} . (m μ) § in parenthesis)
Ч	, E	CO2Et CO2H CO-NH2	$130^{\circ}/0.5$ 179^{-180} 181^{-182}	A; I E	57 83	66-5 67-45	5.45 5.95		5.9 13.15	C ₁₂ H ₁₁ NO ₃ C ₁₂ H ₁₂ N ₂ O ₂	66-35 66-65	5.1 5.55		6-45 2 12-95	67 (13,130)
	LT N	CO_H CO_H CO_NH	150-158/1.0 115-117 162-163	B-С; I; Н Е	22 2 2 2 2 2	67-25 68-15	5-65 6-35		$5.7 \\ 12.15$	C ₁₃ H ₁₃ NO ₃ C ₁₃ H ₁₄ N ₂ O ₂	67.5 67.8	5·65 6·1		6-05 2 12-2	67 ·5 (13,380)
۰ March H	M	CO_H CO_H CO_NH		B−E B−E	8 8 8 8	66-4 66-85	5.9		$6.2 \\ 13.35$	${}^{\mathrm{C}_{12}}_{\mathrm{C}_{12}}\mathrm{H}_{11}\mathrm{NO_3}_{\mathrm{C}_{22}}\mathrm{O}_2$	66-35 66-65	5-1 5-55		6-45 12-95	47·5 (8030)
p-™-on4	Me	CO ² E1 CO ² H CO ² H	132/0~2 185 213—214 194 196/0.4	ы Б	888	6-99 96-0	5·1 5·75		6·3 13·0	C ₁₂ H ₁₁ NO ₃ C ₁₂ H ₁₂ N ₂ O ₂	66-35 66-65	5·1 5·55		6-45 12-95	12-5 (15,650)
w-FC.H.	Me	CO_H	123-5-120/07 183-5-184 118-190/0.9	B-E; G	96 10	59.6	3.8		6.2	C ₁₁ H ₈ FNO ₃	59-75	3.6	8.6	6.3	53 (9860)
м-F.C.H.	Me Me	CO.H	182 - 183 182 - 183 190 - 191 / 0.1	Е; I Е;	96 	59-65 59-7	$3.2 \\ 4.15$		$\begin{array}{c} 6.1\\ 12.6\end{array}$	C ₁₁ H ₈ FNO ₃ C ₁₁ H ₉ FN ₂ O ₂	59-75 60-0	3·6 4·1	8.65 8.65	6-3 12-75	67 (12,640)
F ~ 8 · · · 4		CO ₂ H CO ² H	191.5-192 203-204	A; B-E E: C	86	60.2 59.4	3·8 4·1		6.0 12.8	C ₁₁ H ₈ FNO3 CH ₆ FN ₂ O2	59-75 60-0	3·6 4·1	8.6 8.65	6-3 2 12-75	67 (12,660)
o-CI-C ₆ H ₄	Me	CO ₂ H	159-160	A A	77	55.5	3.6	14-9	5.95	C ₁₁ H ₈ CINO ₃	55.6	3.4	14.95	2.9	240 br. sh. (7110)
m-Cl·C.H.	Me	CO-NH ₃ CO.Et	140-141 140-147/0.01	н	- 11	55.8	4.05	14-7	11-6	$C_{11}H_9CIN_2O_2$	55-85	3.8	15-0	11-85	
ь-СІ-С.Н.	Me	CO.Ft CO.Ft	176-178	н Н Н	97 86 87	55-55 55-65	$3.65 \\ 4.05$	15.0 15.2	5.511.85	C ₁₁ H ₈ CINO3 C ₁₁ H ₉ CIN2O2	55-6 55-85	3.4 3.8	14-95 15-0	5-9 2 11-85	.67 (13,440)
		CO.NH _a	204-205 227-228	G; I; E B-C; C	86 1	55-4 55-65 70-1	3.1 3.8	14.6	5.6 11.4	C ₁₁ H ₈ CINO ₈ C ₁₁ H ₉ CIN ₂ O ₂	55.6 55.85	3.8 4.8 2.8	14-95 15-0	5.9 5 11.85	73 (16,800)
^የ ጠፄጋ. 10-0	am	CO ² ET CO ² H	120134/0.4 175176 159161	A; B-E B-F	98 98	20-7 46-95 46-7	4-0 2-95	20.80 28.4 28.1	4 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8	C ₁₁ H ₁₂ BrNO ₃ C ₁₁ H ₈ BrNO ₃ C ₁ H ₈ PrNO ₃	00-3 46-8 47-0	2.82 5.82	20-8 28-35 98-45	4-95 9-95 9-95	(45br.sh (6350)
$p ext{-Br-C_6H_4}$	Me	CO ₂ H	195 195		85	47-0	9.0 9.0 8	28.4 99.55	4.6 0.75	C ₁₁ H ₈ BrNO ₃	46.8	2.85	28.35	4.95	275 (18,360)
o-I·C ₆ H ₄	Me	CO2H	171-172	A, A	45	40.3	2.65	38.7	4.25	C ₁₁ H ₈ INO ₃	40.15	2.45	38.6	4.25	27.5 (14,410). 255 v br. sh
		CO·NH ₂	205-206.5	Е; С		40.1	2.95	38.8	8-35	C ₁₁ H,IN2O2	40.25	2.75	38-7	8.55	
* See foot acids also she	motes to ow abso	o Table 1. vrption in th	† Needles, m. p. e region 210-22	$47-48^{\circ}$. \ddagger] 5 m μ (ε 4000-	Khromo -11,000	v and P).	orai-K	oshits [J. Gen.	Chem. (U.S.S.H	2.), 1947,	17, 18	16] give	em. p.	176°. § These

Тавье 2.

5843

5844 Derivatives of 6-Aminopenicillanic Acid. Part VI.

(v) Treatment of the acid chloride in acetone solution with an excess of aqueous ammonia $(d \ 0.88)$ afforded 3-o-chlorophenyl-5-methylisoxazole-4-carboxamide.

(b) The other 3-arylisoxazole-4-carboxylic acids and their derivatives listed in Table 1, were obtained similarly, except that ethyl 3-phenylisoxazole-4-carboxylate and its 5-chloromethyl derivative were both hydrolysed with a mixture of equal volumes of acetic and concentrated hydrochloric acids (5 hours' refluxing) rather than with alkali.

3-Alkyl-5-arylisoxazole-4-carboxylic Acids and their Derivatives.—(a) 5-o-Bromophenyl-3methylisoxazole-4-carboxylic acid derivatives. (i) Crude ethyl α -o-bromobenzoylacetoacetate (46.5 g.), in ethanol (150 ml.) was treated with hydroxylamine hydrochloride (21.5 g.) in water (24 ml.), and the mixture was boiled for 10 min., cooled to room temperature overnight, diluted with water (300 ml.), and extracted with ether (2 \times 250 ml.). The ether solution was washed with dilute sodium hydroxide solution until the alkaline extracts gave no precipitate upon acidification, then with water, dried, and distilled, to give ethyl 5-o-bromophenyl-3-methylisoxazole-4-carboxylate (25 g.).

(ii) The ester (24.5 g.) in ethanol (150 ml.) containing potassium hydroxide (7 g.) and water (45 ml.) was refluxed for 2 hr., the bulk of the solvent was removed, and the residual solution was diluted with water, extracted with ether, and acidified, to precipitate crude 5-o-bromophenyl-3-methylisoxazole-4-carboxylic acid (22 g.).

(iii) The acid (16 g.) and thionyl chloride (12 ml.) were refluxed together for 2 hr., the excess of thionyl chloride removed *in vacuo*, and the residual oil dried azeotropically with benzene and then distilled, gave 5-o-bromophenyl-3-methylisoxazole-4-carbonyl chloride (15.1 g., 89%), b. p. 118—120°/0.75 mm.

(iv) The chloride, when treated in acetone with aqueous ammonia ($d \ 0.88$), afforded the *amide*.

(b) 3-Isopropyl-5-phenylisoxazole-4-carboxylic acid derivatives. (i) Crude ethyl α -isobutyrylbenzoylacetate (106 g.), ethanol (350 ml.), hydroxylamine hydrochloride (52 g.), and water (70 ml.), when boiled for 10 min., cooled to room temperature overnight and worked up as in (i) above, yielded an ester (42 g.), b. p. 142-152°/1·3 mm.

(ii) Hydrolysis of the ester (42 g.) with potassium hydroxide (13.5 g.), ethanol (250 ml.), and water (65 ml.) under reflux for $2\frac{1}{2}$ hr., removal of most of the solvent, dilution with water, clarification by ether-extraction, and acidification precipitated the crude acid (26.2 g., 67%), m. p. 140—150°. Crystallisation from light petroleum (b. p. 100—120°), aqueous acetic acid, and benzene-light petroleum failed to improve the m. p. of the product, which, however, gave the expected elemental analysis (Found: C, 67.5; H, 5.85; N, 5.65. C₁₃H₁₃NO₃ requires C, 67.5; H, 5.65; N, 6.05%) and had λ_{max} . 217, 235, and 267 mµ (ε 7800, 7500, and 8920).

(iii) The impure acid (17.8 g.) and thionyl chloride (20 ml.) were refluxed together for 4 hr., the excess of thionyl chloride was removed *in vacuo*, and the residue was distilled, giving 3-isopropyl-5-phenylisoxazole-4-carbonyl chloride (17.5 g., 91%), b. p. $115^{\circ}/0.3$ mm.

(iv) The chloride (17.5 g.), gave, as above, in acetone, the *amide* (15.8 g., 97%), m. p. 155—160°. Crystallisation from aqueous ethanol, benzene-light petroleum (b. p. 80—100°), ethanol, and isobutyl methyl ketone raised the m. p. to 168—169°. The amide had λ_{max} 216 and 262 mµ (ε 7060 and 14,810) (Found: C, 68.05; H, 6.4; N, 12.2. C₁₃H₁₄N₂O₂ requires C, 67.8; H, 6.1; N, 12.2%).

(v) The amide (8.5 g.) and potassium hydroxide (20 g.) in 50% aqueous ethanol (100 ml.) were refluxed for 7 days, most of the solvent was distilled off, and the aqueous residue was diluted with water (100 ml.), extracted with ether (2 \times 100 ml.), adjusted to pH 6.3 with 5N-hydrochloric acid, filtered, and acidified strongly to precipitate the crude product (6.9 g.), m. p. 148—155°. Crystallisation from benzene, ethanol, and then aqueous ethanol gave pure 3-isopropyl-5-phenylisoxazole-4-carboxylic acid (4.7 g.), m. p. 159—160°, λ_{max} 213 and 265 mµ (ϵ 8660 and 13,700) (Found: C, 67.8; H, 5.8; N, 6.05. C₁₃H₁₃NO₃ requires C, 67.5; H, 5.65; N, 6.05%).

(c) The other 3-alkyl-5-arylisoxazole-4-carboxylic acids and their derivatives listed in Table 2 were prepared as described for the o-bromo-compound in (a) above.

3-Aryl-5-methyl-4-isoxazolylpenicillins.—(a) A stirred suspension of 6-aminopenicillanic acid (216 g.) in water (2 l.) was adjusted to pH 7·1 with N-sodium hydroxide, and the resulting solution was treated with 3-o-chlorophenyl-5-methylisoxazole-4-carbonyl chloride (256 g.) in isobutyl methyl ketone (3 l.). The mixture was stirred vigorously for 90 min., then the organic layer was separated, washed with saturated brine (1 l.), and treated with 2N-sodium

2-ethylhexanoate in propan-2-ol (500 ml.), whereupon the sodium salt of the penicillin (414 g., 87%) crystallised. A portion was dissolved in propan-2-ol containing 20% of water, diluted with propan-2-ol to a water content of 5%, and chilled, and the salt was collected and crystallised again in similar fashion, made into a slurry with dry acetone, finally collected, and dried at 40° in air, to give colourless sodium 3-o-chlorophenyl-5-methyl-4-isoxazolylpenicillin monohydrate, m. p. 170° (decomp.), $[\alpha]_{p}^{20} + 163°$ (c 1 in H₂O) (Found: C, 47.75; H, 4.05; Cl, 7.7; N, 8.65; S, 6.75; Na, 5.0; H₂O, 3.9. C₁₉H₁₇ClN₃NaO₅S, H₂O requires C, 47.95; H, 4.0; Cl, 7.45; N, 8.85; S, 6.75; Na, 4.85; H₂O, 3.8%).

In similar fashion were prepared sodium 3-o-fluoro- (90%), $[\alpha]_{D}^{20} + 187^{\circ}$ (c l in H₂O) (Found: C, 50·3; H, 4·4; N, 9·15; S, 7·0; Na, 4·8. C₁₉H₁₇FN₃NaO₅S,H₂O requires C, 49·7; H, 4·15; N, 9·15; S, 6·95; Na, 5·0%), and 3-m-chloro-phenyl-5-methyl-4-isoxazolylpenicillin monohydrate (86%), m. p. 170° (decomp.), $[\alpha]_{D}^{21} + 179^{\circ}$ (c l in H₂O) (Found: C, 48·15; H, 4·5; Cl, 7·35; N, 8·45; S, 6·4; Na, 4·5. C₁₉H₁₇ClN₃NaO₅S,H₂O requires C, 47·95; H, 4·0; Cl, 7·45; N, 8·85; S, 6·75; Na, 4·85%).

(b) A stirred suspension of 6-aminopenicillanic acid (64·8 g.) in water (600 ml.) was adjusted to pH 7·2 with N-sodium hydroxide. The resulting solution was diluted with acetone (300 ml.) and then 3-p-chlorophenyl-5-methylisoxazole-4-carbonyl chloride (76·8 g.) in acetone (600 ml.) was added in one lot, crystallisation of the product beginning almost immediately. The mixture was stirred for 1 hr. at room temperature and then 2 hr. at 0°, and the hydrated penicillin acid was collected, washed with 50% aqueous acetone and then with water; a solution of this product was dissolved in isobutyl methyl ketone (1·5 l.), washed with saturated brine (750 ml.), filtered, and treated with 2N-sodium 2-ethylhexanoate in propan-2-ol (150 ml.), and the resulting colourless platelets of the penicillin sodium salt were collected and dried in air at room temperature and then at 65°. A solution of this product (111·4 g.) in acetone (110 ml.) and water (55 ml.) was diluted with acetone (1 l.), filtered rapidly, and treated with more acetone (1 l.), to give pure *sodium* 3-p-chlorophenyl-5-methyl-4-isoxazolylpenicillin monohydrate (93·6 g.), m. p. 192° (decomp.), $[\alpha]_p^{20} + 187°$ (c 1 in H₂O) (Found: C, 48·2; H, 4·25; Cl, 7·45; N, 9·0; S, 6·6; Na, 4·8; H₂O, 4·0. C₁₉H₁₇ClN₃NaO₅S,H₂O requires C, 47·95; H, 4·0; Cl, 7·45; N, 8·85; S, 6·75; Na, 4·85; H₂O, 3·8%).

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