75. *Derivatives of 6-Aminopenicillanic Acid. Part IV.*[1] *Analogues of 2,6-Dimethoxyphenylpenicillin in the Naphthalene and Quinoline Series.*

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A number of sterically hindered alkoxy-naphthoic and -quinoline-carboxylic acids have been synthesised. Reaction of the acid chlorides with 6-aminopenicillanic acid gave substituted naphthyl- and quinolyl-penicillins which resisted inactivation by penicillinase.

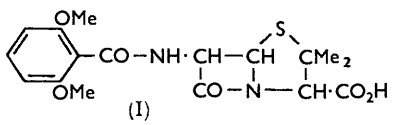
Acylation of 6-aminopenicillanic acid [2] with a series of 2,6-dialkoxybenzoyl chlorides to give 2,6-dialkoxyphenylpenicillins was reported recently.[1] These products were relatively resistant to inactivation by penicillinase and one of them, 2,6-dimethoxyphenylpenicillin (methicillin) (I) has proved clinically valuable, especially in the treatment of resistant staphylococcal infections. Naphthalene and quinoline analogues of this penicillin have

[1] Part III, Doyle, Hardy, Nayler, Soulal, Stove, and Waddington, *J.*, 1962, 1453.
[2] Batchelor, Doyle, Nayler, and Rolinson, *Nature*, 1959, **183**, 257.

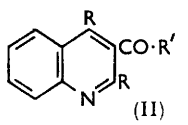
now been prepared by using appropriate sterically hindered alkoxynaphthoic and alkoxyquinolinecarboxylic acids.

The exact analogue of 2,6-dimethoxybenzoic acid in the naphthalene series, namely, 1,3-dimethoxy-2-naphthoic acid, was readily prepared by methylation of the corresponding dihydroxy-acid. In the quinoline series 6,8-dimethoxyquinoline-7-carboxylic acid was obtained in small yield by a Skraup reaction on 3-amino-2,6-dimethoxybenzoic acid, which was itself prepared by nitrating 2,6-dimethoxybenzoic acid and hydrogenating the product.

Analogous acids having the carboxyl group in the pyridine ring were conveniently prepared from ethyl 2,4-dichloroquinoline-3-carboxylate [3] (II; R = Cl, R′ = OEt). Reaction with methanolic sodium methoxide, followed by hydrolysis, gave 2,4-dimethoxyquinoline-3-carboxylic acid (II; R = OMe, R′ = OH), and the corresponding diethoxy-acid (II; R = OEt, R′ = OH), was prepared similarly by using sodium ethoxide. An alternative but less direct synthesis involved mild hydrolysis of the dihydroxy-ester (II; R = OH, R′ = OEt) with barium hydroxide to give 2,4-dihydroxyquinoline-3-carboxylic acid (II; R = R′ = OH) more vigorous treatment with potassium hydroxide was accompanied by decarboxylation to 2,4-dihydroxyquinoline. With phosphorus oxychloride the dihydroxy-acid gave 2,4-dichloroquinoline-3-carbonyl chloride (II; R = R′ = Cl), which proved remarkably resistant to hydrolysis or alcoholysis. The acid chloride was indeed purified by recrystallisation from ethanol, this lack of reactivity towards alcohols recalling the behaviour of 2,4,6-trichlorobenzoyl chloride.[4] By contrast, ammonolysis occurred readily, to give the amide (II; R = Cl, R′ = NH_2). Reaction with ethanolic sodium ethoxide, followed by hydrolysis, gave 2,4-diethoxyquinoline-3-carboxylic acid.



(I)



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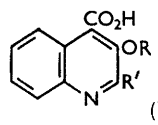

(III)

The hindered acids considered hitherto carry alkoxy-substituents in both *ortho*-positions, but with 1-naphthoic and quinoline-4-carboxylic acid very marked steric hindrance can be achieved by the introduction of only one such substituent since the second fused ring itself contributes a pronounced steric effect. Several 2-alkoxy-1-naphthoic acids were prepared by oxidising the corresponding aldehydes with potassium permanganate in acetone. This procedure, which has been used before for the methoxy-compound,[5] was useful with 2-ethoxy-, 2-n-propoxy-, 2-isopropoxy-, 2-n-butoxy-, and 2-benzyloxy-1-naphthaldehyde but failed for 2-allyloxy- and 2-2′-diethylaminoethoxy-1-naphthaldehyde. The requisite 2-alkoxy-1-naphthaldehydes were prepared by heating 2-hydroxy-1-naphthaldehyde with the appropriate alkyl halide and potassium carbonate in acetone or, in the case of the isopropoxy-compound, in dimethylformamide. Both 2,3- and 2,8-dimethoxy-1-naphthoic acid were similarly prepared through the corresponding aldehydes.

In the quinoline series, 3-ethoxy-2-methylquinoline-4-carboxylic acid (III; R = Et, R′ = Me) was prepared from isatin and ethoxyacetone by the Pfitzinger synthesis [6] and characterised as the amide. 3-Methoxy-2-methyl-, 2-ethyl-3-methoxy-, 3-ethoxy-, and 2-methyl-3-propoxy-quinoline-4-carboxylic acid were prepared by treatment of the corresponding 3-hydroxy-acids with diazomethane or the appropriate alkyl iodide, followed by hydrolysis.

The various alkoxynaphthoic acids were warmed with thionyl chloride to give, after

[3] Grundon, McCorkindale, and Rodger, *J.*, 1955, 4284.
[4] Norris and Ware, *J. Amer. Chem. Soc.*, 1939, **61**, 1418.
[5] Warren, Gindy, and Baddar, *J.*, 1941, 687.
[6] Cross and Henze, *J. Amer. Chem. Soc.*, 1939, **61**, 2730.

removal of the excess of reagent *in vacuo*, the corresponding acid chlorides, which were not purified further. Reaction of the chlorides with 6-aminopenicillanic acid in chloroform containing triethylamine gave substituted naphthylpenicillins which, after removal of triethylamine with dilute acid, were extracted into aqueous sodium hydrogen carbonate. Removal of water at low temperature and pressure gave the sodium salts of the penicillins in sufficient purity for initial antibacterial tests. Further purification by recrystallisation gave the pure sodium salts of 2-methoxy-, 2-ethoxy-, and 2-n-propoxy-1-naphthylpenicillin, but this was not attempted with the other penicillins.

The alkoxyquinolinecarboxylic acids were sensitive towards hot thionyl chloride, so they were treated with this reagent in cold methylene dichloride in the presence of triethylamine, and the resulting acid chlorides were allowed to react with 6-aminopenicillanic acid *in situ*. The resulting substituted quinolylpenicillins were then partially purified as described for the naphthyl analogues.

All the penicillins derived from these highly hindered naphthoic and quinolinecarboxylic acids proved to be essentially stable towards penicillinase, but this valuable property was not shown by related penicillins derived from the less hindered 1-naphthoic acid, 1- and 3-methoxy-2-naphthoic acid, and quinoline-4-carboxylic acid. These observations, together with the essential equivalence of the naphthalene and quinoline nuclei in this respect, provided further support for the view [7] that stability towards the enzyme is governed by the steric properties of the penicillin side-chain rather than its chemical constitution.

Antibacterial tests on the new penicillins were carried out *in vitro* and *in vivo* by Dr. G. N. Rolinson, Mr. D. M. Brown, and their respective colleagues. Some of the compounds, particularly the 2-alkoxy-1-naphthyl- and 3-alkoxy-4-quinolyl-penicillins, exhibited useful activity against penicillinase-producing *Staphylococci*.

Experimental

1,3-Dihydroxy-2-naphthoic Acid.—This was prepared by cyclisation [8] of diethyl phenylacetylmalonate. The latter was obtained by Borsche and Wannagat's method [9] since that of Meyer and Bloch [8] gave, in our hands, chiefly ethyl phenylacetate.

1,3-Dimethoxy-2-naphthoic Acid.—A mixture of 1,3-dihydroxy-2-naphthoic acid (11·6 g.), acetone (200 ml.), methyl sulphate (9·5 ml.), and anhydrous potassium carbonate (7 g.) was refluxed for 48 hr., then evaporated to small bulk. Water (100 ml.) was added and the resulting methyl 1,3-dimethoxy-2-naphthoate was extracted in ether (2 × 50 ml.), washed with dilute sodium hydroxide, and, after removal of ether, hydrolysed with boiling aqueous-alcoholic sodium hydroxide. Evaporation and acidification gave *1,3-dimethoxy-2-naphthoic acid* (40%), which crystallised from dilute alcohol in platelets, m. p. 123—124° (Found: C, 67·2; H, 5·5. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%).

A portion of the acid was treated with thionyl chloride (20 minutes' refluxing), the excess of reagent was removed *in vacuo*, and the residual crude acid chloride was treated with concentrated ammonia (*d* 0·88), to give *1,3-dimethoxy-2-naphthamide*, which crystallised from benzene in needles, m. p. 181° (Found: C, 67·6; H, 5·6; N, 6·1. $C_{13}H_{13}NO_3$ requires C, 67·5; H, 5·6; N, 6·1%).

2,6-Dimethoxy-3-nitrobenzoic Acid [With M. J. Soulal].—Powdered 2,6-dimethoxybenzoic acid (36·4 g.) was stirred with concentrated sulphuric acid (100 ml.) until dissolution was complete, then the mixture was cooled and kept at 0—5° whilst concentrated nitric acid (14 ml.; *d* 1·42) was slowly added. The mixture was stirred for 1 hr. more whilst it attained room temperature, then poured on ice (500 g.). The product was collected, washed thoroughly, dried at 40° *in vacuo*, and crystallised from ethyl acetate–light petroleum to give pale yellow needles of *2,6-dimethoxy-3-nitrobenzoic acid* (27·1 g.), m. p. 131·5—132° (Found: C, 47·7; H, 3·9; N, 6·1. $C_9H_9NO_6$ requires C, 47·6; H, 4·0; N, 6·2%).

3-Amino-2,6-dimethoxybenzoic Acid.—A solution of 2,6-dimethoxy-3-nitrobenzoic acid

[7] Doyle, Long, Nayler, and Stove, *Nature*, 1961, **192**, 1183.
[8] Meyer and Bloch, *Org. Synth.*, Coll. Vol. III, p. 637.
[9] Borsche and Wannagat, *Chem. Ber.*, 1952, **85**, 193.

(100 g.) in ethanol (750 ml.) and concentrated hydrochloric acid (90 ml.) was hydrogenated at atmospheric pressure over 10% palladium–charcoal (10 g.). When hydrogen uptake ceased (4 hr.) the catalyst was removed and the filtrate evaporated to dryness *in vacuo*. The residue was dissolved in hot water, treated with sodium hydroxide (17·6 g.) in water, and again evaporated to dryness *in vacuo*. Extraction of the residue with boiling ethanol, followed by concentration and cooling of the extracts, gave pale fawn needles of 3-*amino*-2,6-*dimethoxybenzoic acid* (50 g.), m. p. 182—183° (Found: C, 54·9; H, 5·8; N, 6·8. $C_9H_{11}NO_4$ requires C, 54·8; H, 5·6; N, 7·1%).

6,8-*Dimethoxyquinoline*-7-*carboxylic Acid*.—Acraldehyde (2·1 g.) was added dropwise to a stirred mixture of 3-amino-2,6-dimethoxybenzoic acid (5 g.), arsenic acid (9·5 g.), and phosphoric acid (25 ml.) at 100°. After 30 minutes' heating, the mixture was poured into water (70 ml.), treated with charcoal, filtered, treated with sodium carbonate until it was only weakly acidic, and then continuously extracted with ether for 72 hr. The extracts were dried and evaporated, and the residue was crystallised from acetic acid, to give pale fawn needles of 6,8-*dimethoxyquinoline*-7-*carboxylic acid* (0·47 g.), m. p. *ca.* 230° (decomp.) (Found: C, 62·1; H, 5·1; N, 6·0. $C_{12}H_{11}NO_4$ requires C, 61·8; H, 4·8; N, 6·0%).

2,4-*Dimethoxyquinoline*-3-*carboxylic Acid*.—Ethyl 2,4-dichloroquinoline-3-carboxylate [3] (33·4 g.) was refluxed for 3·5 hr. with a solution prepared from sodium (11·2 g.) and dry methanol (300 ml.). 20% Aqueous sodium hydroxide (100 ml.) was added and the mixture refluxed for 2 hr. to hydrolyse the ester. It was then diluted with water (400 ml.) and concentrated to remove methanol. The aqueous solution was washed with ether and then acidified to pH 2, whereupon 2,4-*dimethoxyquinoline*-3-*carboxylic acid* (26 g.) separated. Recrystallisation from aqueous methanol gave colourless needles, m. p. 153° (Found: C, 61·7; H, 5·0; N, 6·1. $C_{12}H_{11}NO_4$ requires C, 61·8; H, 4·8; N, 6·0%).

2,4-*Dimethoxyquinoline*-3-*carboxamide*.—Thionyl chloride (0·5 ml.) in chloroform (2 ml.) was added dropwise to a solution of 2,4-dimethoxyquinoline-3-carboxylic acid (1·5 g.) in chloroform (10 ml.) and triethylamine (1·8 ml.) at −20°. The mixture was stirred for 30 min., then gaseous ammonia was bubbled in for 5 min. Water (20 ml.) and ether (50 ml.) were added and the layers were separated. The organic layer was washed with dilute sodium hydroxide, then dried and evaporated. Recrystallisation of the residue from benzene gave colourless needles of 2,4-*dimethoxyquinoline*-3-*carboxamide* (1·1 g.), m. p. 177—178° (Found: C, 62·2; H, 5·1; N, 12·0. $C_{12}H_{12}N_2O_3$ requires C, 62·1; H, 5·2; N, 12·1%).

2,4-*Dihydroxyquinoline*-3-*carboxylic Acid*.—Ethyl 2,4-dihydroxyquinoline-3-carboxylate [3] (30 g.) was treated with an aqueous solution of barium hydroxide octahydrate (61·5 g.). The mixture was refluxed for 2 hr. and then cooled. The barium salt of the acid was collected by filtration, suspended in water, and treated with hydrochloric acid to liberate the acid, which was collected, washed with water, and dried. Recrystallisation from acetic acid (1·5 l.) gave yellow needles of 2,4-*dihydroxyquinoline*-3-*carboxylic acid* (18 g.), m. p. *ca.* 360° (decomp.) (Found: C, 58·8; H, 3·7; N, 6·5. $C_{10}H_7NO_4$ requires C, 58·5; H, 3·4; N, 6·8%).

2,4-*Dichloroquinoline*-3-*carbonyl Chloride*.—2,4-Dihydroxyquinoline-3-carboxylic acid (7·6 g.) and phosphorus oxychloride (70 ml.) were refluxed for 2 hr., then evaporated *in vacuo*. Trituration of the residual gum with ethanol gave 2,4-*dichloroquinoline*-3-*carbonyl chloride* (2·6 g.) which crystallised from ethanol in colourless platelets, m. p. 83—84° (Found: C, 46·1; H, 1·2; N, 5·4. $C_{10}H_4Cl_3NO$ requires C, 46·1; H, 1·5; N, 5·4%).

A portion treated with ammonia in chloroform gave the *amide* as needles (from ethanol), m. p. 245—246° (Found: C, 49·4; H, 2·9; Cl, 29·6; N, 11·6. $C_{10}H_6Cl_2N_2O$ requires C, 49·8; H, 2·5; Cl, 29·5; N, 11·6%).

2,4-*Diethoxyquinoline*-3-*carboxylic Acid*.—(*a*) Ethyl 2,4-dichloroquinoline-3-carboxylate [3] (3·8 g.) was refluxed for 1 hr. with a solution prepared from ethanol (40 ml.) and sodium (1·95 g.), then treated with 40% aqueous sodium hydroxide (15 ml.) and refluxed for a further 2 hr. to hydrolyse the ester. Water (50 ml.) was added, ethanol was removed under reduced pressure, and the aqueous solution was washed with ether and acidified to pH 2. 2,4-*Diethoxyquinoline*-3-*carboxylic acid* (3·4 g.) was collected and recrystallised from acetic acid as colourless needles, m. p. 159—161° (Found: C, 64·6; H, 6·0; N, 5·0. $C_{14}H_{15}NO_4$ requires C, 64·4; H, 5·8; N, 5·4%).

(*b*) 2,4-Dichloroquinoline-3-carbonyl chloride (3·1 g.) was treated (exothermic reaction) with a solution prepared from ethanol (15 ml.) and sodium (1 g.). Hydrolysis of the resulting ester as in (*a*) gave 2,4-diethoxyquinoline-3-carboxylic acid (1·24 g.), identified by mixed m. p.

Alkylation of 2-Hydroxy-1-naphthaldehyde.—(*a*) *General method.* A solution of 2-hydroxy-1-naphthaldehyde (1 mol.) in dry acetone was refluxed for 48 hr. with the appropriate alkyl halide (1·1 mol.) and anhydrous potassium carbonate (1 mol.), then the mixture was filtered and the filtrate evaporated. The residual 2-alkoxy-1-naphthaldehyde was purified by recrystallisation.

Alkylation with n-propyl iodide gave *2-n-propoxy-1-naphthaldehyde* (74%) which crystallised from light petroleum in prisms, m. p. 63—64° (Found: C, 78·9; H, 6·4. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·5%).

n-Butyl bromide similarly gave *2-n-butoxy-1-naphthaldehyde* (59%), plates (from ethanol), m. p. 59—61° (Found: C, 79·2; H, 7·0. $C_{15}H_{16}O_2$ requires C, 78·9; H, 7·0%).

Allyl bromide gave *2-allyloxy-1-naphthaldehyde* (63%), needles (from ethanol), m. p. 76—78° (Found: C, 79·2; H, 6·3. $C_{14}H_{12}O_2$ requires C, 79·2; H, 5·6%).

Benzyl bromide gave 2-benzyloxy-1-naphthaldehyde (61%), needles (from ethanol), m. p. 120—121° (lit.,[10] m. p. 126°) (Found: C, 82·7; H, 5·8. Calc. for $C_{18}H_{14}O_2$: C, 82·5; H, 5·3%).

2-Diethylaminoethyl chloride gave 2-2′-diethylaminoethoxy-1-naphthaldehyde (46%), needles (from light petroleum) m. p. 49—51° (lit.,[11] m. p. 53·5—54·5°) (Found: C, 75·5; H, 7·9; N, 5·4. Calc. for $C_{17}H_{21}NO_2$: C, 75·2; H, 7·8; N, 5·2%).

(*b*) *2-Isopropoxy-1-naphthaldehyde.* This was obtained in only poor yield by method (*a*). Therefore 2-hydroxy-1-naphthaldehyde (1 mol.) was heated with anhydrous potassium carbonate (1·1 mol.) in dimethylformamide for 1·5 hr. (bath-temperature 130°) under nitrogen. After cooling, isopropyl iodide (4 mol.) was added and the mixture again heated in a bath at 130° for 7 hr., filtered, and evaporated to dryness *in vacuo*. The residue was treated with water and ether, the layers were separated, and the bright red ether layer was washed with dilute sodium hydroxide and dried. After removal of solvent, the residue was crystallised from methanol, to give *2-isopropoxy-1-naphthaldehyde* (80%) as plates, m. p. 66—68° (Found: C, 78·3; H, 6·7. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·5%).

2,3-Dimethoxy-1-naphthaldehyde.—A solution of 2,3-dihydroxy-1-naphthaldehyde [12] (1 mol.) in dry acetone was refluxed for 48 hr. with methyl iodide (2·2 mol.) and anhydrous potassium carbonate (2 mol.), then the mixture was filtered and evaporated. Recrystallisation of the residue from ethanol gave colourless needles of 2,3-dimethoxy-1-naphthaldehyde (65%), m. p. 77—79° (lit.,[13] m. p. 79°).

Alkoxy-substituted 1-Naphthoic Acids.—The appropriate naphthaldehydes were oxidised with potassium permanganate in acetone according to the general procedure of Warren *et al.*,[5] to give the *acids* detailed in the Table. 2,8-Dimethoxy-1-naphthaldehyde was prepared by the method of Adams and Burney.[14]

TABLE

Alkoxy-substituted 1-naphthoic acids.

Substituents	M. p.	Yield (%)	Crystalline form and solvent *	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
2-Ethoxy	141—142°	58	Benzene	$C_{13}H_{12}O_3$	71·9	5·5	72·2	5·6
2-n-Propoxy ...	89—90	47	Et_2O–Pet	$C_{14}H_{14}O_3$	73·2	5·9	73·1	6·1
2-Isopropoxy ...	153—154	64	Needles, Benzene	$C_{14}H_{14}O_3$	73·3	6·4	73·1	6·1
2-n-Butoxy ...	93—95	64	Needles, Pet	$C_{15}H_{16}O_3$	73·4	6·8	73·7	6·6
2-Benzyloxy ...	128—130	55	Plates, Benzene	$C_{18}H_{14}O_3$	77·5	5·4	77·7	5·2
2,3-Dimethoxy	153—155	79	Prisms, Toluene	$C_{13}H_{12}O_4$	67·0	5·5	67·2	5·2
2,8-Dimethoxy	160—161	47	Needles, Toluene	$C_{13}H_{12}O_4$	67·5	5·4	67·2	5·2

* Pet = Light petroleum.

3-Ethoxy-2-methylquinoline-4-carboxamide.—Thionyl chloride (1 ml.) in methylene dichloride (4 ml.) was added dropwise to a stirred solution of 3-ethoxy-2-methylquinoline-4-carboxylic acid [6] (2·9 g.) and triethylamine (3·6 ml.) in methylene chloride (20 ml.). The mixture was stirred at room temperature for 1 hr., gaseous ammonia was bubbled in for 5 min., then the whole was evaporated to dryness. The residual solid was washed with water, dried,

[10] Buu-Hoï, Xuong, and Binon, *J.*, 1956, 713.
[11] Goodson, Moffett, Stafford, and Hoehm, U.S.P. 2,711,428/1955.
[12] Morgan and Vining, *J.*, 1921, 77.
[13] Buu-Hoï and Lavit, *J. Org. Chem.*, 1956, **21**, 21.
[14] Adams and Burney, *J. Amer. Chem. Soc.*, 1941, **63**, 1103.

and crystallised from ethyl acetate, to give colourless needles of *3-ethoxy-2-methylquinoline-4-carboxamide*, m. p. 235° (decomp.) (Found: C, 68·2; H, 6·5; N, 12·3. $C_{13}H_{14}N_2O_2$ requires C, 68·0; H, 6·1; N, 12·2%).

2-Ethyl-3-methoxyquinoline-4-carboxylic Acid.—2-Ethyl-3-hydroxyquinoline-4-carboxylic acid [15] (21·7 g.) was added in portions to a stirred solution of diazomethane (from 35 g. of nitrosomethylurea) in ether (650 ml.). The solution was stirred at room temperature for 18 hr., concentrated to half its volume, washed with sodium carbonate solution and then with water, dried, and distilled. *Methyl 2-ethyl-3-methoxyquinoline-4-carboxylate* (10·3 g.) was collected at 118—122°/0·05 mm. and subsequently crystallised in needles, m. p. 93° (Found: C, 68·6; H, 6·1; N, 5·7. $C_{14}H_{15}NO_3$ requires C, 68·6; H, 6·1; N, 5·7%). Hydrolysis with dilute sodium hydroxide (1 hr. under reflux) gave *2-ethyl-3-methoxyquinoline-4-carboxylic acid* (75%) as needles (from ethyl acetate), m. p. 214—216° (decomp.) (Found: N, 6·0. $C_{13}H_{13}NO_3$ requires N, 6·1%).

A portion was converted into the *amide* as described for the 3-ethoxy-2-methyl analogue, giving needles (from benzene), m. p. 183° (Found: C, 68·4; H, 6·4; N, 12·2. $C_{13}H_{14}N_2O_2$ requires C, 68·0; H, 6·1; N, 12·2%).

3-Methoxy-2-methylquinoline-4-carboxylic Acid.—Methylation of 3-hydroxy-2-methylquinoline-4-carboxylic acid [16] with diazomethane as described for the 2-ethyl homologue, followed by alkaline hydrolysis of the resulting ester, gave *3-methoxy-2-methylquinoline-4-carboxylic acid* (69%), which crystallised from aqueous ethanol in colourless needles, m. p. 236° (decomp.) (Found: C, 66·4; H, 5·0; N, 6·5. $C_{12}H_{11}NO_3$ requires C, 66·4; H, 5·1; N, 6·5%).

2-Methyl-3-n-propoxyquinoline-4-carboxylic Acid.—A mixture of 3-hydroxy-2-methylquinoline-4-carboxylic acid [16] (1 mol.), n-propyl iodide (4 mol.), anhydrous potassium carbonate (1·1 mol.), and acetone was refluxed for 48 hr., filtered, and evaporated. The residual ester was refluxed with sodium hydroxide solution for 1 hr., then the mixture was cooled and acidified, to give *2-methyl-3-n-propoxyquinoline-4-carboxylic acid* (80%), which crystallised from aqueous ethanol in colourless needles, m. p. 225—226° (decomp.) (Found: C, 68·4; H, 6·0; N, 5·7. $C_{14}H_{15}NO_3$ requires C, 68·6; H, 6·1; N, 5·7%).

3-Ethoxyquinoline-4-carboxylic Acid.—3-Hydroxyquinoline-4-carboxylic acid [17] was similarly alkylated with an excess of ethyl iodide to give, after hydrolysis of the ester, *3-ethoxyquinoline-4-carboxylic acid* (30%) which crystallised from aqueous ethanol in colourless plates, m. p. 205—206° (decomp.) (Found: C, 66·4; H, 5·3; N, 6·4. $C_{12}H_{11}NO_3$ requires C, 66·4; H, 5·1; N, 6·5%).

2-Methoxy-1-naphthylpenicillin.—(a) *Sodium salt.* 2-Methoxy-1-naphthoyl chloride (16·3 g.) in chloroform (110 ml.) was slowly added to a stirred mixture of 6-aminopenicillanic acid (16 g.), chloroform (110 ml.), and triethylamine (16 g.) at 0°. The mixture was stirred at room temperature for 2 hr., then filtered. The filtrate was cooled to 0°, washed with N- and then with 0·1N-hydrochloric acid (74 ml. of each), and then extracted with two portions (74 ml. and 7·4 ml.) of N-sodium hydrogen carbonate. The combined alkaline extracts were washed with ether (100 ml.) and evaporated at low temperature and pressure to give the crude sodium salt of the penicillin as a yellow solid (26·3 g.). A portion (25 g.) was dissolved in water (25 ml.) at 30° and stirred whilst propan-1-ol (225 ml.) at the same temperature was added. Slow cooling to 0° gave colourless needles of *sodium 2-methoxy-1-naphthylpenicillin sesquihydrate* which, after a second similar crystallisation, had m. p. 180—185° (decomp.) $[\alpha]_D^{22}$ +204° (*c* 5 in H_2O) (Found: C, 53·6; H, 4·9; N, 6·2; S, 7·4; Na, 5·2; H_2O, 6·1. $C_{20}H_{19}N_2NaO_5S,1{\cdot}5H_2O$ requires C, 53·5; H, 4·9; N, 6·2; S, 7·1; Na, 5·1; H_2O, 6·0%).

(b) *NN'-Dibenzylethylenediamine salt.* Concentrated aqueous solutions of the sodium salt (1·08 g.) and of *NN'*-dibenzylethylenediamine diacetate (0·46 g.) were mixed, to give an oily precipitate which quickly crystallised. The hydrated *salt* was collected, washed with water, dried, and recrystallised from hot ethanol (30 ml.); it had m. p. 132—133° (decomp.) (Found: C, 61·1; H, 6·5; N, 7·8; S, 5·5. $C_{56}H_{60}N_6O_{10}S_2,3H_2O$ requires C, 61·4; H, 6·1; N, 7·7; S, 5·8%).

2-Ethoxy-1-naphthylpenicillin [with K. Utting].—Acylation of 6-aminopenicillanic acid (12·6 g.) with 2-ethoxy-1-naphthoylchloride (13·8 g.) as described for the methoxy-compound gave the crude sodium salt of the penicillin as a yellow powder (20·3 g.). This was dissolved

[15] Blanchard, *Bull. Johns Hopkins Hosp.*, 1952, **91**, 330.
[16] Marshall and Blanchard, *J. Pharmacol.*, 1949, **95**, 185.
[17] Cragoe, Robb, and Bealor, *J. Org. Chem.*, 1953, **18**, 552.

in water (20 ml.) at 30° and diluted with butan-1-ol (180 ml.), also at 30°, with stirring. Slow cooling to 0° gave colourless needles of *sodium 2-ethoxy-1-naphthylpenicillin monohydrate*, $[\alpha]_D^{23}$ +198° (*c* 1·2 in H_2O), m. p. indefinite (Found: N, 6·0; S, 6·7; Na, 4·8; H_2O, 3·8. $C_{21}H_{21}N_2NaO_5S,H_2O$ requires N, 6·2; S, 7·1; Na, 5·1; H_2O, 4·0%).

2-n-Propoxy-1-naphthylpenicillin [with H. R. J. WADDINGTON].—The crude sodium salt (2 g.) of this penicillin, similarly prepared from 6-aminopenicillanic acid and 2-n-propoxy-1-naphthoyl chloride, was dissolved in dry acetone (30 ml.), and the solution clarified by filtration. Acetone was removed *in vacuo* and the residual gum was triturated with dry ether. The resulting solid was dissolved in a mixture of propan-1-ol (13 ml.) and water (0·7 ml.), and the solution was chilled to give colourless needles of *sodium 2-n-propoxy-1-naphthylpenicillin* (Found: C, 58·4; H, 5·3; S, 7·1. $C_{22}H_{23}N_2NaO_5S$ requires C, 58·7; H, 5·1; S, 7·1%).

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