Condensation of β-Dicarbonyl Compounds with Halogenopyridinecarboxylic Acids. A Convenient Synthesis of Some Naphthyridine Derivatives

By **D. E. Ames** * and **W. D. Dodds**, Chemistry Department, Chelsea College of Science and Technology, Manresa Road, London SW3 6LX

Condensation reactions of *o*-halogenopyridinecarboxylic acids with carbanions in the presence of copper or copper salts have been investigated. For example, 2-bromopyridine-3-carboxylic acid reacted with acetylacetone and with ethyl acetoacetate to give 2-acetonylpyridine-3-carboxylic acid and ethyl 3-carboxy-2-pyridylacetate respectively. This bromo-acid condensed similarly with β-diketones and β-keto-esters, and with diethyl malonate, an acyl group being eliminated by ethanolysis in each case. 2-Substituted 1,3-dicarbonyl compounds did not react. Examples of such condensations have been obtained with three of the four possible *o*-halogeno-acid isomers of the pyridine series, 4-halogenopyridine-3-carboxylic acid being the exception. These products are useful intermediates in the synthesis of naphthyridine derivatives. Thus 2-acetonylpyridine-3-carboxylic acid condensed with ammonia to form 7-methyl-1,6-naphthyridin-5(6*H*)-one and with amines, hydroxylamine, and hydrazine to give corresponding 6-substituted compounds, but reaction with methylhydrazine yielded 2,5-dihydro-2,4-dimethylpyrido[3,2-*d*]-[1,2]diazepin-1-one.

HURTLEY [1] showed that the halide ion could be displaced from *o*-bromobenzoic acid by copper-catalysed reactions under basic conditions. Thus in sodium ethoxide solution, in the presence of copper acetate, the anion from β-dicarbonyl compounds will displace halide ion. Since ethyl *o*-bromobenzoate and *p*-bromobenzoic acid do not show similar reactivity, a cyclic intermediate of type (I) is presumably involved. Ethanolysis of an acyl group occurs in some cases, so that although acetylacetone gives the diketone (II; X = Y = Ac), ethyl acetoacetate yields ethyl hydrogen homophthalate (II; X = H, Y = CO_2Et). Adams and his co-workers [2] used cyclohexane-1,3-diones in similar condensation reactions in the synthesis of cannabinol. It has also been shown [3] that both halogeno-substituents in 2,5-dibromoterephthalic acid possess similar reactivity but the process has apparently not been extended further, though the copper-catalysed reaction of *o*-halogenobenzoic acids with amines is well known.[4]

We are now investigating an extension of this reaction to some heterocyclic halogeno-acids, and we report here the use of halogenopyridinecarboxylic acids. The reactions of 2-bromopyridine-3-carboxylic acid with acetylacetone and with ethyl acetoacetate were examined under various conditions (see Experimental section); the best results were obtained when bromo-acid and dicarbonyl compound were heated with ethanolic sodium ethoxide and copper acetate. The results (Table) show that one acyl or ethoxycarbonyl group was eliminated by alcoholysis in each reaction with an aliphatic β-dicarbonyl compound, the order of preference for elimination being Ac > Bz > CO_2Et for unsymmetrical systems. Condensation with 5,5-dimethylcyclohexane-1,3-dione occurred in rather low yield but without either cleavage of an acyl group or formation of an enol lactone, in contrast to the formation of the lactone (IV) from *o*-bromobenzoic acid.[1,2]

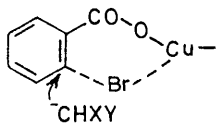
Reactions of halogenopyridinecarboxylic acids with β-dicarbonyl compounds

Acid	Dicarbonyl compound	Product	Yield (%)
(III) R = Br	CH_2Ac_2	(III) R = CH_2Ac	52
	$AcCH_2Bz$	R = CH_2Bz	67
	CH_2Bz_2	R = CH_2Bz	77
	$AcCH_2·CO_2Et$	R = $CH_2·CO_2Et$	78
R = Cl	$AcCH_2·CO_2Et$	R = $CH_2·CO_2Et$	68
R = Br	$BzCH_2·CO_2Et$	R = $CH_2·CO_2Et$	45
	$CH_2(CO_2Et)_2$	R = $CH_2·CO_2Et$	25
	$CO(CH_2·CO_2Et)_2$	R = $CH_2·CO_2Et$	53
	$AcCH_2·CO·NHPh$	R = $CH_2·CO·NHPh$	74
	$CO·CH_2·CMe_2·CH_2·CO·CH_2$	R = $CO·CH_2·CMe_2·CH_2·CO·CH$	20
(VI) R = Br	CH_2Ac_2	(VI) R = $CHAc_2$	33
	$AcCH_2Bz$	R = CH_2Bz	41
	CH_2Bz_2	R = CH_2Bz	54
	$AcCH_2·CO_2Et$	R = $CH_2·CO_2Et$	39
R = I	$AcCH_2·CO_2Et$	R = $CH_2·CO_2Et$	36
(VII) R = I	$AcCH_2·CO_2Et$	(VII) R = $CH_2·CO_2Et$	24

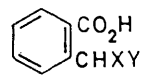
Attempts to condense 2-bromopyridine-3-carboxylic acid with 3-ethylpentane-2,4-dione, ethyl 2-oxocyclohexanecarboxylate, and ethyl 2-oxocyclohexylglyoxylate failed; only 2-ethoxypyridine-3-carboxylic acid was isolated in each case. Ethyl cyanoacetate reacted with displacement of the halogen and addition of ethanol to give a crystalline product which is tentatively formulated as (V) on the basis of spectroscopic evidence (see Experimental section). Condensation of 2-chloropyridine-3-carboxylic acid with ethyl acetoacetate gave the ester (III; R = $CH_2·CO_2Et$) in slightly lower yield than the

[1] W. R. H. Hurtley, *J. Chem. Soc.*, 1929, 1870.
[2] R. Adams, D. C. Pease, J. H. Clark, and B. R. Baker, *J. Amer. Chem. Soc.*, 1940, **62**, 2197; R. Adams, C. K. Cain, and B. R. Baker, *ibid.*, p. 2201; R. Adams, B. R. Baker, and R. B. Wearn, *ibid.*, p. 2204.
[3] H. Stetter and E. Siehnhold, *Chem. Ber.*, 1955, **88**, 1223.
[4] A. Albert, ' The Acridines,' Arnold, London, 1966, 2nd edn., p. 75.

bromo-acid. 2-Bromopyridine-3-carboxylic acid *N*-oxide did not react with acetylacetone.



(I)



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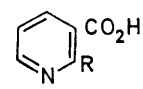

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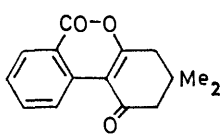

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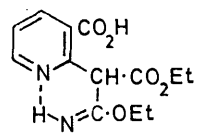

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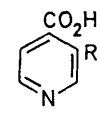

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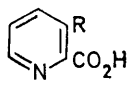

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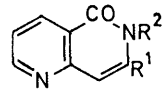

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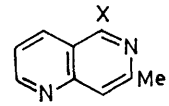

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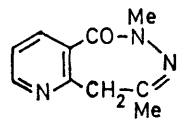

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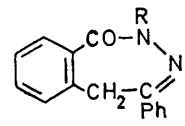

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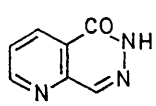

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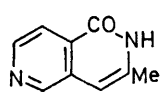

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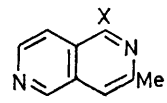

(XV)

Application of this process to other halogenopyridinecarboxylic acids gave less satisfactory results. 3-Bromopyridine-4-carboxylic acid condensed with acetylacetone to give the diketone (VI; R = $CHAc_2$) but in other cases alcoholysis of an acyl group occurred; in each reaction, the yield was lower than that obtained from 2-bromopyridine-3-carboxylic acid. 3-Iodopyridine-2-carboxylic acid reacted with ethyl acetoacetate to give the ester (VII; R = $CH_2{\cdot}CO_2Et$) in rather low yield, but could not be condensed with 1,3-diketones. No condensation products were obtained from 4-chloropyridine-3-carboxylic acid, 6-bromopyridine-3-carboxylic acid, or 2-bromo-3-methylpyridine.

The substituted pyridinecarboxylic acids prepared by this process are useful intermediates for the synthesis of various naphthyridine derivatives. Thus the ester acid (VI; R = $CH_2{\cdot}CO_2Et$) was readily converted into the corresponding diester, which has been used for the preparation of the cyclic imide and other 2,6-naphthyridine derivatives.[5]

Condensation of 2-acetonyl- and 2-phenacyl-pyridine-3-carboxylic acid (III; R = CH_2Ac or CH_2Bz) with ammonia gave 7-methyl- and 7-phenyl-1,6-naphthyridin-5(6*H*)-one (VIII; R^1 = Me or Ph, R^2 = H) in high yields. These products have been prepared previously by multistep syntheses in low overall yields.[6,7] Treatment of 7-methyl-1,6-naphthyridin-5(6*H*)-one with phosphoryl chloride yielded 5-chloro-7-methyl-1,6-naphthyridine (IX; X = Cl), which was converted into the 5-methoxy- and 5-benzylamino-compounds. When the latter (IX; X = $NH{\cdot}CH_2Ph$) was hydrogenated over palladium, reduction (not *N*-debenzylation) occurred to give the tetrahydro-derivative (X).

2-Acetonylpyridine-3-carboxylic acid condensed with methylamine, *NN*-diethylaminoethylamine, and hydroxylamine to give the corresponding naphthyridinones (VIII; R^1 = Me, R^2 = Me, $CH_2{\cdot}CH_2{\cdot}NEt_2$, or OH). Reactions with hydrazine and phenylhydrazine yielded similar products (VIII; R^1 = Me, R^2 = NH_2 or NHPh) but methylhydrazine formed 2,5-dihydro-2,4-dimethylpyrido[3,2-*d*][1,2]diazepin-1-one (XI). 2-Phenacylpyridine-3-carboxylic acid gave analogous compounds in these reactions. The structures of the products were elucidated from spectroscopic evidence (Experimental section). It is of interest to contrast these results with those of Wolbling,[8] who heated hydrazine and 2-phenacylbenzoic acid in ethanol in a sealed tube to obtain 2,5-dihydro-4-phenyl-2,3-benzodiazepin-1-one (XII; R = H); the 2-methyl derivative (XII; R = Me) was then prepared by methylation.[8] We have carried out the reactions with hydrazine and methylhydrazine in a high-boiling solvent to obtain the same compounds, the structures of which were confirmed by spectroscopic evidence.

Behun and Levine [9] showed that treatment of acetonylpyrazine with potassium hypochlorite gave 2-dichloromethylpyrazine instead of the expected carboxylic acid. 2-Acetonylpyridine-3-carboxylic acid reacted similarly, forming 2-dichloromethylpyridine-3-carboxylic acid (III; R = $CHCl_2$), which condensed with hydrazine to give pyrido[2,3-*d*]pyridazin-5(6*H*)-one (XIII). This has been prepared previously from quinolinimide.[10]

3-Acetonyl- and 3-phenacyl-pyridine-4-carboxylic acids are similarly useful intermediates for the synthesis of derivatives of the relatively inaccessible 2,6-naphthyridine system. The former acid (VI; R = CH_2Ac), obtained in high yield by action of ethanolic ammonia on 3-(1-acetylacetonyl)pyridine-4-carboxylic acid (VI; R = $CHAc_2$), condensed with ammonia–ammonium acetate solution to give 3-methyl-2,6-naphthyridin-1(2*H*)-one (XIV). Conversion into the chloro-compound (XV; X = Cl) and the hydrazine derivative (XV; X = $NH{\cdot}NH_2$), followed by oxidation with copper sulphate,

[5] F. Alhaique and F. M. Riccieri, *Ann. Chim.* (*Italy*), 1970, **60**, 791.
[6] N. Ikekawa, *Chem. and Pharm. Bull.* (*Japan*), 1958, **6**, 263, 269.
[7] D. G. Wibberley, *J. Chem. Soc.*, 1962, 4528.
[8] H. Wolbling, *Ber.*, 1905, **38**, 3846.
[9] J. D. Behun and R. Levine, *J. Org. Chem.*, 1958, **23**, 406.
[10] S. Kakimoto and S. Tonooka, *Bull. Chem. Soc. Japan*, 1967, **40**, 153.

yielded 3-methyl-2,6-naphthyridine (XV; X = H). This base differed from that isolated from *Antirrhinum majus* [11] and formulated as 4-methyl-2,6-naphthyridine.

EXPERIMENTAL

Evaporations were carried out under reduced pressure; petrol refers to light petroleum (b.p. 60—80°). ^{1}H N.m.r. spectra were measured on a Perkin-Elmer R10 spectrometer at 60 MHz. Where possible deuteriochloroform was used as solvent, with tetramethylsilane as internal standard; with [$^2H_6$]dimethyl sulphoxide or trifluoroacetic acid as solvent sodium 3-trimethylsilylpropane-1-sulphonate was used. U.v. spectra were recorded on a Perkin-Elmer 137 spectrophotometer with ethanol as solvent.

Condensation of 2-Bromopyridine-3-carboxylic Acid (III; R = Br) *with 1,3-Dicarbonyl Compounds.—General procedure.* Sodium (1·44 g, 62·6 mg atom) was dissolved in absolute ethanol (30 ml) and the solution was cooled to room temperature. The dicarbonyl compound (37·5 mmol) and then a mixture of 2-bromopyridine-3-carboxylic acid (5·03 g; 25 mmol) and copper acetate (0·2 g) were added to the stirred mixture, which was heated under reflux for 2 h. The cooled solution was acidified with acetic acid (25 ml), evaporated, and treated with water (25 ml). When the product crystallised it was filtered off; in other cases it was isolated with chloroform.

The following compounds were prepared by this process (reactions and yields are shown in the Table): *2-acetonylpyridine-3-carboxylic acid* (III; R = CH_2Ac), m.p. 140—141° (from benzene–petrol) (Found: C, 59·9; H, 5·0; N, 7·9. $C_9H_9NO_3$ requires C, 60·3; H, 5·1; N, 7·8%), $\lambda_{max.}$ 267 and 220infl nm (ε 2900 and 9500); *2-phenacylpyridine-3-carboxylic acid* (III; R = CH_2Bz), m.p. 175—177° (from ethyl acetate–methanol) (Found: C, 69·8; H, 4·7; N, 6·0. $C_{14}H_{11}NO_3$ requires C, 69·7; H, 4·6; N, 5·8%); *ethyl 3-carboxy-2-pyridylacetate* (III; R = CH_2·CO_2Et), m.p. 130—131° (from benzene–petrol) (Found: C, 57·6; H, 5·4; N, 6·9. $C_{10}H_{11}NO_4$ requires C, 57·4; H, 5·3; N, 6·7%); *3-carboxy-2-pyridylacetanilide* (III; R = CH_2·CO·NHPh), m.p. 203—205° (decomp.) (from ethyl acetate–methanol) (Found: C, 65·6; H, 4·7; N, 10·9. $C_{14}H_{12}N_2O_3$ requires C, 65·6; H, 4·7; N, 10·9%); *2-(4,4-dimethyl-2,6-dioxocyclohexyl)pyridine-3-carboxylic acid* (III; R = CO·CH_2·CMe_2·CH_2·CO·CH) pale yellow, m.p. 177—178° (from ethanol) (Found: C, 64·4; H, 5·7; N, 5·3. $C_{14}H_{15}NO_4$ requires C, 64·4; H, 5·8; N, 5·4%), $\lambda_{max.}$ 370 and 271 nm (ε 4800 and 12,400).

When condensation was attempted with 3-ethylpentane-2,4-dione, ethyl 2-oxocyclohexanecarboxylate, or ethyl 2-oxocyclohexylglyoxylate, the product isolated was *2-ethoxypyridine-3-carboxylic acid* (III; R = OEt), m.p. 87·5—89° (from benzene–petrol) (Found: C, 57·1; H, 5·4; N, 8·5. $C_8H_9NO_3$ requires C, 57·5; H, 5·4; N, 8·4%), in 50—70% yield. The same product (77%) was obtained when no β-dicarbonyl compound was used.

Other experiments. The condensation with ethyl acetoacetate was attempted under various conditions. Use of potassium t-butoxide in t-butyl alcohol yielded ethyl 3-carboxy-2-pyridylacetate (50%), m.p. and mixed m.p. 130—131°. Attempted condensations in the presence of sodium hydride in dimethoxyethane or *NN*-dimethylformamide or of triethylamine–acetonitrile gave mixtures from which no crystalline product could be isolated.

When 2-chloropyridine-3-carboxylic acid and ethyl acetoacetate reacted according to the general procedure, ethyl 3-carboxy-2-pyridylacetate (68%) was obtained. Condensation of the bromo-acid with ethyl acetoacetate in presence of mercury(II) acetate (0·3 g) or copper bronze (0·2 g) gave the same product (59 and 74%, respectively).

Condensation of 2-Bromopyridine-3-carboxylic Acid (III; R = Br) *with Ethyl Cyanoacetate.*—The reaction was carried out by the general procedure, with 4·2 g of ethyl cyanoacetate. Isolation with chloroform furnished a red oil which was dissolved in benzene (20 ml) and applied to a column of alumina (100 g, type O). The column was eluted with benzene until the effluent was no longer yellow; evaporation gave a red gum (100 mg). Elution with ethyl acetate and evaporation, followed by crystallisation from benzene–petrol, gave *ethyl 3-carboxy-2-pyridyl(ethoxyformimidoyl)acetate* (V) (1·2 g), m.p. 111—112° (Found: C, 55·9; H, 5·7; N, 9·9. $C_{13}H_{16}N_2O_5$ requires C, 55·7; H, 5·8; N, 10·0%); τ ($CDCl_3$) 1·35 (1H, H-6), 1·70 (1H, H-4), 2·68 (1H, H-5), 4·56 (1H, CH), 5·63 (2H, q, CH_2), 5·82 (2H, q, CH_2), 8·62 (3H, t, Me), 8·88 (3H, t, Me), and 2·32 and 4·06 (exchangeable NH and CO_2H); $\nu_{max.}$ 3410 (NH), 3270 and 3210 (OH), 1720 (CO_2Et), 1680 (CO_2H), and 1600 cm^{-1} (C:N); $\lambda_{max.}$ 266 and 220infl nm (ε 2000 and 6300); u.v. spectrum very similar to that of 2-acetonylpyridine-3-carboxylic acid.

2-Bromopyridine-3-carboxylic Acid N*-Oxide.*[12]—A solution of 2-bromopyridine-3-carboxylic acid (5 g) in concentrated sulphuric acid (5 ml) and acetic acid (15 ml) was cooled at 0° while hydrogen peroxide (30%; 15 ml) was added dropwise. The mixture was then stirred at 46—48° for 48 h, treated with water (25 ml), and cooled. The N*-oxide* (2·3 g), which was filtered off, had m.p. 180° (decomp.), unchanged by crystallisation from ethanol (Found: C, 33·3; H, 2·0; N, 6·5. $C_6H_4BrNO_3$ requires C, 33·1; H, 1·9; N, 6·4%). Unchanged bromo-acid (1 g) was isolated from the filtrate with chloroform.

Condensation of 3-Bromopyridine-4-carboxylic Acid (VI; R = Br) *with β-Dicarbonyl Compounds.*—The same general procedure was used except that the volume of solvent was increased (to 50 ml). The following compounds were obtained: *3-(1-acetylacetonyl)pyridine-4-carboxylic acid* (VI; R = $CHAc_2$), m.p. 213° (decomp.) (from ethanol) (Found: C, 59·7; H, 5·0; N, 6·2. $C_{11}H_{11}NO_4$ requires C, 59·7; H, 5·0; N, 6·3%); $\nu_{max.}$ 1720 cm^{-1}; $\lambda_{max.}$ 283 nm (ε 10,600); *3-phenacylpyridine-4-carboxylic acid* (VI; R = CH_2Bz), m.p. 206·5—208° (from ethanol) (Found: C, 69·7; H, 4·5; N, 5·7. $C_{14}H_{11}NO_3$ requires C, 69·7; H, 4·6; N, 5·8%); $\nu_{max.}$ 1678 cm^{-1}; $\lambda_{max.}$ 280 and 242·5 nm (ε 5200 and 15,600); and *ethyl 4-carboxy-3-pyridylacetate* (VI; R = CH_2·CO_2Et), m.p. 189° (Found: C, 57·2; H, 5·3; N, 6·6. $C_{10}H_{11}NO_4$ requires C, 57·4; H, 5·3; N, 6·7%); $\nu_{max.}$ 1725 cm^{-1}; $\lambda_{max.}$ 277 nm (ε 3900).

Condensation of 3-Iodopyridine-2-carboxylic Acid (VII; R = I) *with Ethyl Acetoacetate.*—The reaction was carried out according to the general procedure; isolation with chloroform and crystallisation from benzene gave *ethyl 2-carboxy-3-pyridylacetate* (VII; R = CH_2·CO_2Et) (1·2 g), m.p. 138—138·5° (Found: C, 57·4; H, 5·3; N, 6·6. $C_{10}H_{11}NO_4$ requires C, 57·4; H, 5·3; N, 6·7%); $\lambda_{max.}$ 268 and 218 nm (ε 3700 and 7500).

Attempted Preparation of 6-Acetonylpyridine-3-carboxylic Acid.—Acetylacetone and 6-bromopyridine-3-carboxylic

[11] K. J. Harkiss and D. Swift, *Tetrahedron Letters*, 1970, 4773.
[12] G. E. Chivers and H. Suschitzky, *Chem. Comm.*, 1971, 28; *J. Chem. Soc.* (*C*), 1971, 2867.

acid were treated according to the general procedure (copper bronze catalyst; reflux for 20 h). Isolation gave 6-bromopyridine-3-carboxylic acid (80%), m.p. and mixed m.p. 193—194° (lit.,[13] 193—193·9°), and 6-ethoxypyridine-3-carboxylic acid (15%), m.p. 183—183·5° (lit.,[14] 183°).

7-Methyl-1,6-naphthyridin-5(6H)-one (VIII; R^1 = Me, R^2 = H).—A solution of 2-acetonylpyridine-3-carboxylic acid (1 g) in aqueous ammonia (*d* 0·88; 10 ml) was heated under reflux for 15 h, then concentrated to a small volume by heating at atmospheric pressure on an oil-bath (120°). Addition of more ammonia (1 ml) and re-evaporation yielded a brown solid, which was crystallised from methanol (charcoal) to give 7-methyl-1,6-naphthyridin-5(6*H*)-one (0·8 g, 80%), m.p. 244·5—246° (lit.,[6] 245°), $\lambda_{max.}$ 331·5, 292·5, and 240·5 nm (ε 4000, 9600, and 7100). The naphthyridinone (0·1 g) was suspended in water (5 ml) and concentrated hydrochloric acid (5 drops) was added. The resulting solution was evaporated to give *7-methyl-1,6-naphthyridin-5(6H)-one hydrochloride* as yellow crystals, m.p. 258—260° (from ethanol) (Found: C, 55·2; H, 4·7; N, 14·6. $C_9H_8N_2O$,HCl requires C, 55·0; H, 4·6; N, 14·3%).

7-Phenyl-1,6-naphthyridin-5(6*H*)-one (VIII; R^1 = Ph, R^2 = H) (80%), prepared similarly, had m.p. 229—230° (from ethanol) (lit.,[7] 228—229°), $\lambda_{max.}$ 317 and 242·5 (ε 19,100 and 18,500).

5-Chloro-7-methyl-1,6-naphthyridine (IX; X = Cl).—7-Methyl-1,6-naphthyridin-5(6*H*)-one (1·75 g) was heated with phosphoryl chloride (35 ml) in a sealed tube at 135° for 26 h. The solvent was removed by distillation under reduced pressure and ice–water (25 ml) was added. Basification with sodium carbonate and isolation with chloroform yielded a sticky red solid which was shaken with ether (300 ml). Evaporation of the filtered solution gave 5-chloro-7-methyl-1,6-naphthyridine (1·5 g), m.p. 107—108°, which was used without further purification (lit.,[6] m.p. 112—113°).

5-Methoxy-7-methyl-1,6-naphthyridine (IX; X = OMe).—Sodium (60 mg) was dissolved in absolute methanol (5 ml) and 5-chloro-7-methyl-1,6-naphthyridine (0·33 g) was added. The solution was heated under reflux for 15 min and poured into water; isolation with chloroform yielded a yellow oil which was dissolved in benzene (10 ml) and applied to a column of alumina (15 g; type O). Elution with benzene gave a little yellow gum; when the column was eluted with benzene–ethyl acetate (10 : 1), *5-methoxy-7-methyl-1,6-naphthyridine* was obtained as the *hemihydrate* (0·27 g; 80%), m.p. 58—59° [from light petroleum (b.p. 40—60°) at −10°] (Found: C, 65·5; H, 5·7; N, 15·4. $C_{10}H_{10}N_2O,0{\cdot}5H_2O$ requires C, 65·6; H, 6·0; N, 15·3%); τ ($CDCl_3$) 2·82 (1H, s, H-8), 5·95 (3H, s, OMe), and 7·45 (3H, s, CMe).

5-Benzylamino-7-methyl-1,6-naphthyridine (IX; X = $PhCH_2$·NH).—5-Chloro-7-methyl-1,6-naphthyridine (0·3 g) was dissolved in freshly distilled benzylamine (3 ml) and heated for 4 h under nitrogen (bath at 145°). Benzylamine was removed by steam distillation and sodium carbonate was added; isolation with chloroform and crystallisation from benzene–petrol gave *5-benzylamino-7-methyl-1,6-naphthyridine* (0·25 g), m.p. 144·5—145° (Found: C, 77·1; H, 6·0; N, 16·7. $C_{16}H_{15}N_3$ requires C, 77·1; H, 6·1; N, 16·9%); τ ($CDCl_3$) 3·0 (1H, s, H-8), 4·5 (1H, s, NH, exchanges with D_2O), 5·2 (2H, d, collapses to s with D_2O, CH_2), and 7·45 (3H, s, CMe).

5-Benzylamino-1,2,3,4-tetrahydro-7-methyl-1,6-naphthyridine (X).—The benzylamino-compound (0·28 g) in methanol (25 ml) was hydrogenated in presence of 5% palladised charcoal (0·5 g) [illegible] until absorption ceased and the filtered solution was then evaporated. The residue in chloroform was washed with sodium carbonate solution (10 ml); evaporation and crystallisation from benzene–petrol yielded *5-benzylamino-1,2,3,4-tetrahydro-7-methyl-1,6-naphthyridine* (0·22 g), m.p. 136—136·5° (Found: C, 75·8; H, 7·4; N, 16·4. $C_{16}H_{19}N_3$ requires C, 75·9; H, 7·6; N, 16·6%), τ ($CDCl_3$) 4·24 (1H, s, H-8), 6·02 (2H, s, 2 × NH, exchange with D_2O), 6·77 (2H, m, CH_2), and 7·9 (4H, m, 2 × CH_2).

6,7-Dimethyl-1,6-naphthyridin-5(6H)-one (VIII; R^1 = R^2 = Me).—A solution of 2-acetonylpyridine-3-carboxylic acid (0·5 g) and methylamine hydrochloride (0·5 g) in ethanol (8 ml) and concentrated hydrochloric acid (3 drops) was heated under reflux overnight; on cooling, the product separated. Recrystallisations from ethanol yielded *6,7-dimethyl-1,6-naphthyridin-5(6H)-one* as its *hydrochloride* (0·35 g), m.p. 235° (decomp.) (Found: C, 57·0; H, 5·2; N, 13·1. $C_{10}H_{10}N_2O$,HCl requires C, 57·0; H, 5·3; N, 13·3%). The filtrate was evaporated and treated with sodium carbonate solution; isolation with chloroform yielded *6,7-dimethyl-1,6-naphthyridin-5(6H)-one* (0·11 g), m.p. 127·5—128° (from petrol) (Found: C, 68·8; H, 5·8; N, 9·5. $C_{10}H_{10}N_2O$ requires C, 68·9; H, 5·8; N, 9·2%), $\lambda_{max.}$ 297·5 and 244 nm (ε 9000 and 9700). In another experiment, the base was isolated in 76% yield by evaporating the reaction mixture, adding sodium carbonate solution, and isolating with chloroform.

6-(2-Diethylaminoethyl)-7-methyl-1,6-naphthyridin-5(6H)-one (VIII; R^1 = Me, R^2 = CH_2·CH_2·NEt_2).—2-Acetonylpyridine-3-carboxylic acid (0·5 g), *NN*-diethylethylenediamine (1 ml), ethanol (5 ml), and concentrated hydrochloric acid (0·5 ml) were heated under reflux for 16 h. Evaporation, addition of sodium carbonate solution, and isolation with chloroform yielded a brown oil. This was dissolved in benzene and the solution was evaporated. The residue in dry ether was treated with hydrogen chloride to give a yellow precipitate which, on crystallisation from methanol–ethyl acetate, gave *6-(2-diethylaminoethyl)-7-methyl-1,6-naphthyridin-5(6H)-one dihydrochloride hydrate* (0·95 g), m.p. 224° (decomp.) (Found: C, 51·7; H, 7·3; N, 11·8. $C_{15}H_{21}N_2O$,2HCl,H_2O requires C, 51·4; H, 7·2; N, 12·0%), $\lambda_{max.}$ 293 and 244 nm (ε 11,500 and 10,400).

6-Hydroxy-7-methyl-1,6-naphthyridin-5(6H)-one (VIII; R^1 = Me, R^2 = OH).—2-Acetonylpyridine-3-carboxylic acid (0·5 g), hydroxylamine hydrochloride (0·5 g), concentrated hydrochloric acid (2 drops), and ethanol (10 ml) were heated under reflux overnight. The mixture was then evaporated and the residue treated with water (10 ml). Sodium carbonate was added until effervescence ceased and acetic acid (10 ml) was also added. Isolation with chloroform and crystallisations from methanol–ethyl acetate gave *6-hydroxy-7-methyl-1,6-naphthyridin-5(6H)-one* (0·45 g), m.p. 161—162° (Found: C, 61·4; H, 4·6; N, 15·8. $C_9H_8N_2O_2$ requires C, 61·4; H, 4·6; N, 15·9%); $\nu_{max.}$ 1635 cm^{-1}; $\lambda_{max.}$ 302·5 and 248 nm (ε 9900 and 17,100); τ [$(CD_3)_2SO$] 3·34 (1H, H-8) and 7·5 (3H, Me). Similarly prepared was *6-hydroxy-7-phenyl-1,6-naphthyridin-5(6H)-one* (85%), m.p. 204—204·5° (Found: C, 70·4; H, 4·3; N, 11·7. $C_{14}H_{10}N_2O_2$ requires C, 70·6; H, 4·2; N, 11·8%).

6-Amino-7-methyl-1,6-naphthyridin-5(6H)-one (VIII; R^1 = Me, R^2 = NH_2).—A solution of 2-acetonylpyridine-3-carboxylic acid (0·5 g), hydrazine hydrate (0·4 ml), and

[13] H. C. Bradlow and C. A. Vanderwerf, *J. Org. Chem.*, 1949, **14**, 512.
[14] A. Reissert, *Ber.*, 1895, **28**, 119.

concentrated hydrochloric acid (0·1 ml) in ethanol (5 ml) was heated under reflux overnight. The solution was evaporated and water (5 ml) was added; basification (Na_2CO_3), filtration, and crystallisation from ethanol yielded the *naphthyridinone* (0·45 g), m.p. 193—194° (Found: C, 61·7; H, 5·1; N, 23·6. $C_9H_9N_3O$ requires C, 61·7; H, 5·2; N, 24·0%); $\nu_{max.}$ 3290, 3190, 1620, and 1590 cm^{-1}; $\lambda_{max.}$ 304 and 251·5 nm (ε 10,300 and 15,800); τ ($CDCl_3$) 3·37 (1H, H-8), 4·96 (2H, NH_2), and 7·44 (3H, Me).

6-*Amino*-7-*phenyl*-1,6-*naphthyridin*-5(6H)-*one* (VIII; R^1 = Ph, R^2 = NH_2) (82%), prepared similarly, had m.p. 188—191° (from ethanol) (Found: C, 70·7; H, 4·8; N, 17·5. $C_{14}H_{11}N_3O$ requires C, 70·9; H, 4·7; N, 17·7%); $\lambda_{max.}$ 310 and 252 nm (ε 9700 and 14,400).

2,5-*Dihydro*-2,4-*dimethylpyrido*[3,2-d][1,2]*diazepin*-1-*one* (XI).—2-Acetonylpyridine-3-carboxylic acid (0·5 g) was suspended in ethanol (5 ml) and methylhydrazine (0·4 ml), was added; the solid dissolved immediately and the solution was heated under reflux for 7 h. Evaporation gave a yellow oil which was taken up in benzene (30 ml) and applied to a column of alumina (15 g; type O). Elution with ethyl acetate–benzene (1 : 9) gave the *dimethylpyridodiazepinone* (0·37 g), m.p. 84° (from petrol) (Found: C, 63·4; H, 5·7; N, 22·1. $C_{10}H_{11}N_3O$ requires C, 63·5; H, 5·9; N, 22·2%); $\nu_{max.}$ 1640 and 1585 cm^{-1}; the u.v. spectrum showed no max. above 220 nm; τ ($CDCl_3$) 6·2 (2H, CH_2), 6·49 (3H, NMe), and 7·8 (3H, CMe). 2,5-*Dihydro*-2-*methyl*-4-*phenylpyrido*[3,2-d]-[1,2]*diazepin*-1-*one* (60%), prepared similarly, had m.p. 114·5—115° (from petrol) (Found: C, 72·0; H, 5·2; N, 16·6. $C_{15}H_{13}N_3O$ requires C, 71·7; H, 5·2; N, 16·7%); $\nu_{max.}$ 1640, 1585, and 1565 cm^{-1}; τ ($CDCl_3$) 5·75 (2H, CH_2) and 6·33 (3H, NMe).

Treatment of 2-acetonylpyridine-3-carboxylic acid with phenylhydrazine in a similar manner gave 6-*anilino*-7-*methyl*-1,6-*naphthyridin*-5(6H)-*one* (VIII; R^1 = Me, R^2 = PhNH) (81%), m.p. 188—189° [from benzene–light petroleum (b.p. 80—100°)] (Found: C, 71·8; H, 5·2; N, 16·6. $C_{15}H_{13}N_3O$ requires C, 71·7; H, 5·2; N, 16·7%); $\nu_{max.}$ 3240, 1660, and 1625 cm^{-1}; $\lambda_{max.}$ 291 and 227 nm (ε 12,900 and 23,300); τ ($CDCl_3$) 2·6—3·4 (8H, NPh, H-8, H-3, and NH) and 7·5 (3H, Me).

Ethyl 3-*Ethoxycarbonyl*-2-*pyridylacetate*.—Ethyl 3-carboxy-2-pyridylacetate (15 g) was dissolved in absolute ethanol (220 ml) and the solution was cooled (ice-bath) while dry hydrogen chloride was passed in for 30 min. The solution was left overnight at room temperature and then heated under reflux for 8 h; excess of sodium carbonate was added and ethanol (150 ml) was removed by distillation under reduced pressure. Addition of water and isolation with ethyl acetate gave *ethyl* 3-*ethoxycarbonyl*-2-*pyridylacetate* (9·5 g), b.p. 102° at 0·1 mmHg, m.p. 34° (Found: C, 60·6; H, 6·5; N, 5·8. $C_{12}H_{15}NO_4$ requires C, 60·8; H, 6·4; N, 5·9%).

Similarly ethyl 4-carboxy-3-pyridylacetate gave ethyl 4-ethoxycarbonyl-3-pyridylacetate, b.p. 123° at 2 mmHg; picrate, m.p. 107—108·5° (lit.,[15] 104—106°).

In an attempt to prepare the corresponding imide, a solution of the diester (1 g) in aqueous ammonia (*d* 0·88; 10 ml) was slowly heated and allowed to evaporate at atmospheric pressure (bath 150°). Vacuum sublimation (0·1 mmHg) yielded 2-methylnicotinic acid (0·25 g), m.p. 221—222° (lit.,[16] 226—227°); τ [$(CD_3)_2SO$] 7·33 (3H, Me).

2-*Dichloromethylpyridine*-3-*carboxylic Acid* (III; R = $CHCl_2$).—Sodium hypochlorite solution [freshly prepared from sodium hydroxide (1·3 g) in water (10 ml)] was stirred while 2-acetonylpyridine-3-carboxylic acid (0·5 g) was added over 10 min. The solution was stirred for 1·5 h, acidified (to pH 2) with concentrated hydrochloric acid, and extracted with chloroform. Evaporation gave 2-*dichloromethylpyridine*-3-*carboxylic acid* (0·36 g), m.p. 183—185° (from chloroform) (Found: C, 40·6; H, 2·7; N, 6·8. $C_7H_5Cl_2NO_2$ requires C, 40·8; H, 2·5; N, 6·8%).

Pyrido[2,3-d]*pyridazin*-5(6H)-*one* (XIII).—2-Dichloromethylpyridine-3-carboxylic acid (0·3 g) was dissolved in ethanol (3 ml) and hydrazine hydrate (0·3 ml) was added. The solution was heated under reflux for 3 h, during which time crystallisation occurred. Water (2 ml) and sodium carbonate (0·1 g) were added and the precipitate (90 mg) was collected. More solid (60 mg) was isolated from the filtrate with chloroform. The solids were combined and crystallised from ethanol to give pyrido[2,3-*d*]pyridazin-5(6*H*)-one (140 mg), m.p. 261—262° (lit.,[10] 261—263°).

3-*Acetonylpyridine*-4-*carboxylic Acid* (VI; R = CH_2Ac).—3-(1-Acetylacetonyl)pyridine-4-carboxylic acid (0·4 g) and aqueous ammonia (*d* 0·88; 12 ml) were heated under reflux for 1·5 h. Evaporation yielded a sticky solid which was triturated with methanol (4 ml) to give 3-*acetonylpyridine*-4-*carboxylic acid* (0·26 g), m.p. 212—213° (from ethanol) (Found: C, 60·5; H, 5·1; N, 7·8. $C_9H_9NO_3$ requires C, 60·3; H, 5·1; N, 7·8%); $\lambda_{max.}$ 281 nm (ε 2900).

3-*Methyl*-2,6-*naphthyridin*-1(2H)-*one* (XIV).—A solution of 3-(1-acetylacetonyl)pyridine-4-carboxylic acid (1·5 g) in aqueous ammonia (*d* 0·88; 15 ml) and acetic acid (4 ml) was heated under reflux for 24 h. The *naphthyridinone* (0·9 g) which separated from the cooled solution had m.p. 254—255°, unchanged by crystallisation from ethanol (Found: C, 67·5; H, 5·1; N, 17·4. $C_9H_8N_2O$ requires C, 67·5; H, 5·0; N, 17·5%); $\lambda_{max.}$ 352 and 282 nm (ε 9200 and 17,000). 3-Acetonylpyridine-4-carboxylic acid reacted similarly.

3-*Phenyl*-2,6-*naphthyridin*-1(2H)-*one*, prepared in the same manner, had m.p. 269—270° (from ethanol) (82% yield) (Found: C, 75·6; H, 4·6; N, 12·4. $C_{14}H_{10}N_2O$ requires C, 75·6; H, 4·5; N, 12·6%), $\lambda_{max.}$ 360 and 306 nm (ε 9000 and 17,400).

1-*Chloro*-3-*methyl*-2,6-*naphthyridine* (XV; X = Cl).—3-Methyl-2,6-naphthyridin-1(2*H*)-one (1·5 g) and phosphoryl chloride (30 ml) were heated at 135° in a sealed tube for 20 h. The solution was concentrated to small bulk and ice–water (20 ml) was added. Basification with sodium carbonate and isolation with chloroform gave a dark brown gum which was extracted with petrol (2 × 25 ml). Evaporation and crystallisation from petroleum yielded 1-*chloro*-3-*methyl*-2,6-*naphthyridine* (1·3 g), m.p. 70—71° (Found: C, 60·8; H, 4·2; N, 15·4. $C_9H_7ClN_2$ requires C, 60·5; H, 4·0; N, 15·7%); $\lambda_{max.}$ 345, 333, 272infl, 262, and 252infl nm (ε 5100, 5300, 7600, 8600, and 6400).

3-*Methyl*-2,6-*naphthyridine* (XV; X = H).—The chloro-compound (0·5 g) and hydrazine hydrate (80%; 1·2 ml) in ethanol (2·5 ml) were heated under reflux. After 5 min, crystallisation suddenly occurred; the mixture was heated for a further 5 min and allowed to cool. The crude hydrazino-compound (0·28 g) was collected and dissolved in acetic acid (0·8 ml) and water (2·2 ml); copper sulphate solution (10%; 7·5 ml) was added to the stirred solution and after 15 min the mixture was heated on a steam-bath for 15 min and then stirred at room temperature for 1·5 h.

[15] G. Giacomello, F. Gualtieri, F. M. Riccieri, and M. L. Stein, *Tetrahedron Letters*, 1965, 1117.
[16] P. Baumgarten and A. Dornow, *Ber.*, 1939, **72**, 563.

Basification and isolation with chloroform yielded a sticky solid. Sublimation (60° at 0·4 mmHg) gave *3-methyl-2,6-naphthyridine* (0·12 g) as white crystals, m.p. 55·5—56° (Found: C, 74·8; H, 5·7; N, 19·3. $C_9H_8N_2$ requires C, 75·0; H, 5·6; N, 19·4%); $\lambda_{max.}$ 341, 327·5, 266infl, 256·5, and 247infl nm (ε 4000, 4300, 5600, 6700, and 5300); τ ($CDCl_3$) 0·8 (2H, s, H-1 and H-5), 1·4 (1H, d, H-7), 2·3 (1H, d, H-8), 2·42 (1H, s, H-4), and 7·2 (3H, s, Me).

2,5-Dihydro-4-phenyl-2,3-benzodiazepin-1-one (XII; R = H).—2-Phenacylbenzoic acid (1 g), hydrazine hydrate (100%; 0·75 ml) and 2-ethoxyethanol (20 ml) were heated at 105—107° for 16 h. Evaporation and trituration with ethyl acetate gave the diazepine (1·6 g), m.p. 203—204°, unchanged by crystallisation from ethanol (lit.,[8] 202°); $\nu_{max.}$ 3210, 1645, and 1605 cm^{-1}; τ [$(CD_3)_2SO$] 1·22 (1H, s, NH, exchanges with D_2O) and 5·90 (2H, s, CH_2).

Similar reaction with methylhydrazine gave 2,5-dihydro-2-methyl-4-phenyl-2,3-benzodiazepin-1-one (87%), m.p. 139—140° [from light petroleum (b.p. 80—100°)] (lit.,[8] 133°); $\nu_{max.}$ 1630 cm^{-1}; τ ($CDCl_3$) 6·03 (2H, s, CH_2) and 6·63 (3H, s, NMe).

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