877. *Methylnicotinic Acids. Part III.*[1] *Their Conversion into Pyranopyridines and* 1,6-*Naphthyridines.*

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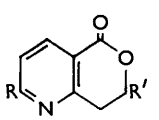
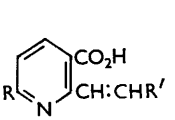
5-Oxopyrano[4,3-*b*]pyridines have been prepared from 2-(2-hydroxyphenethyl)nicotinic lactones, from 2-styrylnicotinic acids, and from ethyl 2-(α-cyano-α-formylmethyl)-6-phenylnicotinate. In two cases the pyranopyridines were converted into 1,6-naphthyridines.

2-METHYLNICOTINIC ACIDS condense with aromatic aldehydes to yield both 2-β-hydroxyphenethylnicotinic acid lactones (7-aryl-7,8-dihydro-5-oxopyrano[4,3-*b*]pyridines) (I; R′ = aryl) and 2-styrylnicotinic acids (II; R′ = aryl). An obvious extension of this work is the conversion of these compounds into 5-oxopyrano[4,3-*b*]pyridines (III). This type of pyranopyridine may be considered as a pyridine analogue of an isocoumarin, the commonest method of synthesis of which is the Dieckmann–Meiser [2] condensation of a homophthalic ester with ethyl formate, followed by cyclisation with acid. 2-*p*-Methoxyphenylisocoumarin has been prepared [3] by heating sodium 2-4′-methoxystyrylbenzoate with bromine in acetic acid at 220°, and the closely related flavones have been obtained by bromination of flavanones with *N*-bromosuccinimide followed by dehydrobromination.[4]


(I)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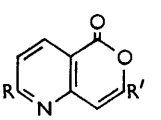
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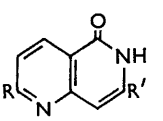
(IV)

Application of these three methods proved successful for the synthesis of pyrano[3,4-*b*]pyridines. Thus, 2-styrylnicotinic acid (II; R = H, R′ = Ph), with bromine in boiling acetic acid, yielded 5-oxo-7-phenylpyrano[4,3-*b*]pyridine (III; R = H, R′ = Ph). The same compound was produced by the action of *N*-bromosuccinimide (and benzoyl peroxide) in boiling acetic acid on 2-β-hydroxyphenethylnicotinic acid lactone, bromination

[1] Part I, *J.*, 1956, 1778; Part II, *J.*, 1958, 3161.
[2] Dieckmann and Meiser, *Ber.*, 1908, **41**, 3253.
[3] Horeau and Jacques, *Bull. Soc. chim. France*, 1948, **15**, 53.
[4] Lorette, Gage, and Wender, *J. Org. Chem.*, 1951, **16**, 930.

and dehydrobromination taking place in the same operation. By similar reactions 6-phenyl-2-styrylnicotinic acid (II; R = R′ = Ph) and 2-β-hydroxyphenethyl-6-phenylnicotinic acid lactone (I; R = R′ = Ph) were both converted into 5-oxo-2,7-diphenylpyrano[4,3-*b*]pyridine (III; R = R′ = Ph); 2-3′-nitrostyryl-6-phenylnicotinic acid (II; R = Ph, R′ = *m*-NO_2·C_6H_4) and 2-(β-hydroxy-3-nitrophenethyl)-6-phenylnicotinic acid lactone (I; R = Ph, R′ = *m*-NO_2·C_6H_4) was converted into the pyranopyridine (III; R = Ph, R′ = *m*-NO_2·C_6H_4); and 2-3′-nitrostyrylnicotinic acid (II; R = H, R′ = *m*-NO_2·C_6H_4) was converted into the pyranopyridine (III; R = H, R′ = *m*-NO_2·C_6H_4). Ethyl 2-cyanomethyl-6-phenylnicotinate [5] resisted alcoholysis to the 2-ethoxycarbonylmethyl derivative, but condensation of the nitrile with ethyl formate in the presence of sodium ethoxide yielded ethyl 2-(α-cyano-α-formylmethyl)-6-phenylnicotinate which was converted, by boiling hydrochloric acid, into the pyranopyridine (III; R = Ph, R′ = H).

The pyranopyridines gave neutral solutions in acetone, but behaved as bases when titrated in acetic acid solution. They were stable to acid but were decomposed by alkali; the resulting orange solutions yielded tarry solids on acidification. Their infrared spectra and those of the hydroxyphenethylnicotinic acid lactones (I) were similar in the carbonyl region (bands at 1709—1724 $cm.^{-1}$), both showing absorption in the expected region for αβ-unsaturated lactones; these bands resembled the carbonyl absorption of other 2- [6] and 4-hydroxyethylnicotinic acid lactones.[7] Both the pyranopyridines and 2-styrylnicotinic acid (but not 2-β-hydroxyphenethylnicotinic acid lactone) absorbed strongly at 1625 $cm.^{-1}$ (conjugated double bond). 5,6-Dihydro-5-oxo-1,6-naphthyridines (IV; R = H, R′ = H and Me) have been prepared by Ikekawa [6] from 2-2′-hydroxyethylnicotinic lactones (I; R = H, R′ = H and Me) by ammonolysis to 2-2′-hydroxyethylnicotinamides followed by oxidation and concurrent cyclisation. By treatment of two pyranopyridines (III; R = H, R′ = Ph; and R = Ph, R′ = *m*-NO_2·C_6H_4) with methanolic ammonia, 5,6-dihydro-5-oxo-1,6-naphthyridines (IV; R = H, R′ = Ph; and R = Ph, R′ = *m*-NO_2·C_6H_4) were obtained. The naphthyridines behaved as monoacidic bases when titrated in acetic acid solution; their infrared spectra showed bands at 3175 (NH), 1653 and 1667 (αβ-unsaturated lactam), and 1626 $cm.^{-1}$ (conjugated double bond).

Experimental

Infrared spectra (KBr disc) were determined by Mr. G. S. Hall, Grubb–Parsons Ltd., Newcastle-upon-Tyne. Equivalent weights were determined, except where otherwise stated, by non-aqueous titration with perchloric acid.

2-Styrylnicotinic Acid (II; R = H, R′ = Ph).—Ethyl 2-methylnicotinate (7·5 g.), benzaldehyde (4·7 g.), and acetic anhydride (3·0 ml.) were refluxed for 14 hr. The resultant brown oil was triturated with ether to give a product (1·9 g.) which on crystallisation from ethyl acetate yielded *2-styrylnicotinic acid* (0·62 g.) in prisms, m. p. 201—202° [Found: C, 74·3; H, 5·1; N, 6·2%; equiv. (direct titration), 225. $C_{14}H_{11}NO_2$ requires C, 74·7; H, 4·9; N, 6·2%; equiv., 225], $\lambda_{max.}$ 308 mμ (log ε 4·10), $\nu_{max.}$ 2500w (OH), 1701m (aryl CO_2H), 1631m $cm.^{-1}$ (aryl-conjugated C=C). The ethyl acetate mother-liquors were concentrated to give a sticky solid which solidified when stirred with 2N-hydrochloric acid. The liberated solid was 2-β-hydroxyphenethylnicotinic lactone hydrochloride, m. p. and mixed m. p. 183—184°. It was converted into the lactone (as described in Part II [1]), $\lambda_{max.}$ 270 mμ (log ε 3·58), $\nu_{max.}$ 1709s $cm.^{-1}$ [lactone (C=O)].

5-Oxo-7-phenylpyrano[4,3-*b*]*pyridine* (III; R = H, R′ = Ph).—(*a*) 2-Styrylnicotinic acid (0·5 g.), bromine (0·6 g.), and acetic acid (10 ml.) were refluxed for 4 hr. (hydrogen bromide evolved). The clear solution was neutralised with 5N-sodium hydroxide to yield the *pyranopyridine* (III; R = H, R′ = Ph) (0·25 g.), prisms (from ethanol), m. p. 128—129° (Found: C, 75·5; H 4·0; N, 6·4%; equiv., 222. $C_{14}H_9NO_2$ requires C, 75·3; H, 4·0; N, 6·3%; equiv., 223), $\lambda_{max.}$ 310 mμ (log ε 4·35), $\nu_{max.}$ 1724s (lactone C=O), 1626s $cm.^{-1}$ (conjugated C=C).

(*b*) 2-β-Hydroxyphenethylnicotinic acid lactone (0·5 g.), *N*-bromosuccinimide (0·44 g.),

[5] Hurst and Wibberley, *J.*, 1962, 119.
[6] Ikekawa, *Pharm. Bull.* (*Japan*), 1958, **6**, 263.
[7] Govindachari, Nagarajan, and Rajappa, *J.*, 1957, 551.

benzoyl peroxide (0·01 g.) and acetic acid were refluxed for 4 hr. A clear solution was formed almost immediately and a solid separated in 20 min. which redissolved during the next 1·5 hr. with evolution of hydrogen bromide. The solution was neutralised with 5N-sodium hydroxide, to give the pyranopyridine (III; R = H, R′ = Ph) (0·18 g.), m. p. 128—129° (from ethanol) alone and mixed with the above product.

5-Oxo-2,7-diphenylpyrano[4,3-b]pyridine (III; R = R′ = Ph).—(*a*) 6-Phenyl-2-styrylnicotinic acid (0·32 g.), on treatment with bromine (0·6 g.) and acetic acid (20 ml.) as described above for 2-styrylnicotinic acid, yielded the *pyranopyridine* (III; R = R′ = Ph) (0·21 g.), prisms (from 2-ethoxyethanol), m. p. 164—165° [Found: C, 79·9; H, 4·6; N, 4.65%; equiv. (titration against alkali), 0; equiv., 306. $C_{20}H_{13}NO_2$ requires C, 80·3; H, 4·3; N, 4·7%; equiv., 299], $\lambda_{max.}$ 298 (log ε 4·34), 227 mμ (log ε 3·93), $\nu_{max.}$ 1724s (lactone C=O), 1631m cm.$^{-1}$ (conjugated C=C).

(*b*) 2-β-Hydroxyphenethyl-6-phenylnicotinic acid lactone (0·8 g.) on treatment with *N*-bromosuccinimide (0·7 g.), benzoyl peroxide (0·02 g.), and acetic acid (15 ml.), as described above for 2-β-hydroxyphenethylnicotinic acid lactone yielded the pyranopyridine (III; R = R′ = Ph) (0·52 g.), m. p. (from 2-ethoxyethanol) and mixed m. p. 164—165°.

7-3′-Nitrophenyl-5-oxo-2-phenylpyrano[4,3-b]pyridine (III; R = Ph, R′ = *m*-NO_2·C_6H_4).—(*a*) 2-3′-Nitrostyryl-6-phenylnicotinic acid (0·37 g.), bromine (0·38 g.), and acetic acid (10·0 ml.) were refluxed for 1·5 hr. The mixture was cooled, the hydrobromide (0·27 g.), m. p. 257—259° (decomp.), collected and suspended in water (10·0 ml.), the suspension made just alkaline with ammonia, boiled, and cooled, and the *pyranopyridine* (III; R = Ph, R′ = *m*-NO_2·C_6H_4) (0·15 g.) collected and crystallised from acetic acid, to give cream prisms, m. p. 237—238° (Found: C, 69·3; H. 3·6; N, 8·4%; equiv., 354. $C_{20}H_{12}N_2O_4$ requires C, 69·7; H, 3·5; N, 8·1%; equiv., 344), $\lambda_{max.}$ 280 (log ε 4·45), 223 mμ (log ε 4·10), $\nu_{max.}$ 1724s (lactone C=O), 1626m (conjugated C=C), 1527s and 1342s cm.$^{-1}$ (NO_2).

(*b*) 2-(β-Hydroxy-3-nitrophenethyl)-6-phenylnicotinic lactone (1·0 g.), *N*-bromosuccinimide (0·8 g.), benzoyl peroxide (0·02 g.), and acetic acid (20 ml.) were refluxed. When the reaction was stopped after 1 hr. the pyranopyridine hydrobromide, m. p. and mixed m. p. 257—259° (decomp.), remained undissolved. After 4 hr. the clear solution was neutralised as usual, to give the pyranopyridine (III; R = Ph, R′ = *m*-NO_2·C_6H_4) (0·84 g.), m. p. (from acetic acid) and mixed m. p. 237—238°.

7-3′-Nitrophenyl-5-oxo-pyrano[3,4-b]pyridine (III; R = H, R′ = *m*-NO_2·C_6H_4).—2-3′-Nitrostyrylnicotinic acid (1·0 g.), bromine (0·71 g.), and acetic acid (7·5 ml.) were refluxed until the evolution of hydrogen bromide had ceased (9·0 hr.). Neutralisation of the solution gave the *pyranopyridine* (III; R = H, R′ = *m*-NO_2·C_6H_4) (0·41 g.), pale fawn prisms (from 2-ethoxyethanol), m. p. 201—202° (Found: C, 62·55; H, 3·2; N, 10·0%; equiv., 265. $C_{14}H_8N_2O_4$ requires C, 62·7; H, 3·0; N, 10·4%; equiv., 268), $\lambda_{max.}$ 306 mμ (log ε 4·34).

Ethyl 2-(α-Cyano-α-formylmethyl)-6-phenylnicotinate.—Ethyl 2-cyanomethyl-6-phenylnicotinate (0·5 g.) and ethyl formate (3·2 ml.) were added to sodium ethoxide (0·13 g.), and the resulting deep red mixture was refluxed for 2 hr. The excess of ethyl formate was evaporated off and the residue triturated with water and 2N-hydrochloric acid (pH 7·0), to yield the *formyl derivative* (0·47 g.), yellow plates (from ethanol), m. p. 174—176° (decomp.) (Found: C, 69·0; H, 4·8; N, 9·75. $C_{17}H_{14}N_2O_3$ requires C, 69·4; H, 4·8; N, 9·5%).

5-Oxo-2-phenylpyrano[4,3-b]pyridine (III; R = Ph, R′ = H).—The preceding preparation was repeated but with acidification of the residue by concentrated hydrochloric acid (excess) after removal of the ethyl acetate. The acid mixture was then refluxed for 30 min. The crude product (0·31 g.), crystallised from nitrobenzene to give the *pyranopyridine* (III; R = Ph, R′ = H), pale fawn needles (from nitrobenzene), m. p. 321—323° (Found: C, 75·0; H, 3·9; N, 6·1. $C_{14}H_9NO_2$ requires C, 75·3; H, 4·0; N, 6·3%).

5,6-Dihydro-5-oxo-7-phenyl-1,6-naphthyridine (IV; R = H, R′ = Ph).—A solution of the pyranopyridine (III; R = H, R′ = Ph) (0·1 g.) in absolute ethanol (20 ml.) was treated with anhydrous ammonia (2·0 g.) at 0°, stirred for 12 hr. and left at room temperature for 3 days. The solution was filtered, concentrated to 2·0 ml., and cooled, to yield the *naphthyridine* (IV; R = H, R′ = Ph) (0·056 g.), pale yellow needles (from ethanol), m. p. 228—229° (Found: C, 75·2; H, 4·5; N, 12·5. $C_{14}H_{10}N_2O$ requires C, 75·7; H, 4·5; N, 12·6%), $\nu_{max.}$ 3175w (lactam NH), 1667s (amide I), 1626m cm.$^{-1}$ (conjugated C=C).

5,6-Dihydro-5-oxo-7-m-nitrophenyl-2-phenyl-1,6-naphthyridine (IV; R = Ph, R′ = *m*-NO_2·C_6H_4).—A suspension of the pyranopyridine (III; R = Ph, R′ = *m*-NO_2·C_6H_4) (0·1 g.)

in absolute ethanol (20 ml.) was treated with anhydrous ammonia (2·0 g.) at 0°, and the suspension was stirred for 12 hr. and left at room temperature for 3 days. Unchanged starting material (0·06 g.; m. p. 237—238°) was collected, the filtrate evaporated to dryness, and the residue crystallised from acetic acid, to give the *naphthyridine* (IV; R = Ph, R′ = *m*-NO_2·C_6H_4) (0·018 g.), yellow needles, m, p, 343—345° (Found: C, 69·2; H, 3·9; N, 12·1%; equiv., 357. $C_{20}H_{13}N_3O_3$ requires C, 69·9; H, 3·8; N, 12·2%; equiv., 343), $\nu_{max.}$ 3175w (lactam NH), 1653s (amide I), 1626m (conjugated C=C), 1538s and 1342m $cm.^{-1}$ (NO_2).

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