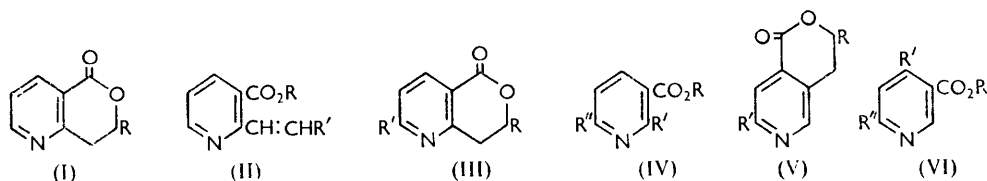


640. *Methylnicotinic Acids. Part II.*¹

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2-Methyl-, 2:6-dimethyl-, and 4:6-dimethyl-nicotinic acid and their ethyl esters have been condensed with benzaldehyde and *m*-nitrobenzaldehyde in the presence of acetic anhydride. In three cases lactones analogous to those reported in Part I were obtained; in others the products were mono- or di-styryl derivatives.

CONDENSATION of aromatic aldehydes with 2-methyl-6-phenylnicotinic acid and its ethyl ester was shown in Part I¹ to give lactones (III; R = R' = Ph). This work has been extended to condensation of 2-methyl-, 2:6-dimethyl-, and 4:6-dimethyl-nicotinic acid and their ethyl esters in the hope that other lactones could be prepared.



Condensations were carried out with benzaldehyde or *m*-nitrobenzaldehyde and with acetic anhydride as catalyst, the intermediate 2- or 4-(2-hydroxyphenethyl)nicotinic acids not being isolated. 2-Methylnicotinic acid, or its ethyl ester, with benzaldehyde yielded 2-(2-hydroxyphenethyl)nicotinic lactone (I; R = Ph) which gave a positive hydroxamic acid test and was recovered unchanged after attempted ozonolysis. With *m*-nitrobenzaldehyde, however, the only product isolated was 2-3'-nitrostyrylnicotinic acid (II; R = H, R' = NO₂·C₆H₄). This gave a negative hydroxamic acid test and on ozonolysis in ethyl acetate yielded an ozonide which was decomposed by aqueous silver nitrate to quinolinic acid. Where only one molecule of aldehyde condensed with the dimethylnicotinic acids or esters the 6-position was always attacked first. Thus 2:6-dimethylnicotinic acid yielded 2-methyl-6-styrylnicotinic acid (IV; R = H, R' = Me, R'' = Ph·CH:CH) with benzaldehyde, 2-methyl-6-3'-nitrostyrylnicotinic acid (IV; R = H, R' = Me, R'' = NO₂·C₆H₄·CH:CH) with *m*-nitrobenzaldehyde, and its ethyl ester the corresponding esters; 4:6-dimethylnicotinic acid gave the four analogous 4:6-compounds. All these styryl derivatives showed typical olefinic reactions. Their orientation was determined by ozonolysis: the acids gave 6-methylpyridine-2:5-dicarboxylic acid which was immediately decarboxylated, to give 2-methylnicotinic acid. Ethyl 4-methyl-6-styryl- and -6-3'-nitrostyryl-nicotinate gave 5-ethoxycarbonyl-4-methylpyridine-2-carboxylic acid, which showed the characteristic deep red coloration of a 2-carboxylic acid with ferrous sulphate solution and was readily decarboxylated to ethyl 4-methylnicotinate. When two molecules of benzaldehyde condensed with 2:6-dimethylnicotinic acid or its ethyl ester only 2-(2-hydroxyphenethyl)-6-styrylnicotinic lactone (III; R = Ph; R' = Ph·CH:CH) was isolated, but with *m*-nitrobenzaldehyde 2-(2-hydroxy-3'-nitrophenethyl)-6-3'-nitrostyrylnicotinic lactone (III; R = R' = NO₂·C₆H₄·CH:CH) was obtained from condensation with the ethyl ester, and 2:6-di-3'-nitrostyrylnicotinic acid (IV; R = H, R' = R'' = NO₂·C₆H₄·CH:CH) from condensation with the acid. In condensation of two molecules of aldehyde with 4:6-dimethylnicotinic acid, the only products obtained were 4:6-distyrylnicotinic acid (VI; R = H, R' = R'' = Ph·CH:CH) with benzaldehyde, and the 3'-nitrostyryl analogue with *m*-nitrobenzaldehyde. No lactone (V) was obtained in any condensation from 4:6-dimethylnicotinic acid or its ethyl ester.

¹ Part I, Tittensor and Wibberley, *J.*, 1956, 1778.

EXPERIMENTAL

2-(2-Hydroxyphenethyl)nicotinic Lactone.—Ethyl 2-methylnicotinate² (5.5 g.), benzaldehyde (4.8 g.), and acetic anhydride (3.1 c.c.) were refluxed for 14 hr. The resultant brown oil was triturated with 2N-hydrochloric acid to give a sticky solid which on crystallisation from ethanol gave 2-(2-hydroxyphenethyl)nicotinic lactone hydrochloride (1.5 g.), m. p. 183—184° (Found: C, 59.7; H, 5.2; N, 5.3; Cl, 12.85. $C_{14}H_{12}O_2NCl \cdot H_2O$ requires C, 60.1; H, 5.0; N, 5.0; Cl, 12.7%). The hydrochloride (0.17 g.) was suspended in water (4.0 c.c.), the suspension made alkaline with ammonia (*d* 0.88), boiled, and then cooled, and the lactone (0.11 g.) collected. Crystallisation from ethanol gave needles, m. p. 142—143° (Found: C, 74.4; H, 5.1; N, 6.3. $C_{14}H_{11}O_2N$ requires C, 74.6; H, 4.9; N, 6.2%). Basification of the acid layer yielded unchanged ethyl 2-methylnicotinate (1.2 g.).

The same lactone hydrochloride was isolated in 31% yield after condensation of 2-methylnicotinic acid.

2:3'-Nitrostyrylnicotinic Acid.—Similar condensation of ethyl 2-methylnicotinate (1.65 g.) with *m*-nitrobenzaldehyde (1.81 g.) in the presence of acetic anhydride (0.93 c.c.) (10 hr. reflux) yielded 2:3'-nitrostyrylnicotinic acid (0.99 g.), crystallising from 2-ethoxyethanol in prisms, m. p. 230—232° [Found: C, 61.9; H, 3.8; N, 10.4%; equiv., 263 (titration). $C_{14}H_{10}O_4N_2$ requires C, 62.2; H, 3.7; N, 10.4%; equiv., 270]. Bromination in carbon tetrachloride gave 2-(1:2-dibromo-3'-nitrophenethyl)nicotinic acid in prisms (from ethanol), m. p. 176—177° (Found: Br, 36.6. $C_{14}H_{10}O_4N_2Br_2$ requires Br, 37.2%). Basification of the acid washings yielded unchanged ethyl 2-methylnicotinate (0.3 g.). Condensation of 2-methylnicotinic acid gave the same styryl derivative as the sole product in 54% yield, but no unchanged starting material.

2-(2-Hydroxyphenethyl)-6-styrylnicotinic Lactone.—Ethyl 2:6-dimethylnicotinate³ (2.8 g.) and benzaldehyde (2.4 g.) in acetic anhydride (1.4 c.c.) (10 hr. reflux) yielded the lactone (0.4 g.) in needles (from ethyl acetate), m. p. 200—201° (Found: C, 81.0; H, 5.2; N, 4.5. $C_{22}H_{17}O_2N$ requires C, 80.7; H, 5.2; N, 4.3%). 6-(1:2-Dibromophenethyl)-2-(2-hydroxyphenethyl)nicotinic lactone was obtained, by bromination of the lactone, in pale yellow needles, m. p. 236—238° (from 2-ethoxyethanol) (Found: N, 3.3; Br, 32.2. $C_{22}H_{17}O_2NBr_2$ requires N, 2.9; Br, 32.8%).

Ethyl 2-Methyl-6-styrylnicotinate.—Concentration of the alcoholic mother-liquors remaining after isolation of 2-(2-hydroxyphenethyl)-6-styrylnicotinic lactone yielded ethyl 2-methyl-6-styrylnicotinate hydrochloride (1.07 g.), needles (from 2-ethoxyethanol), m. p. 222—223° (decomp.) (Found: C, 67.25; H, 6.1; N, 5.0; Cl, 11.7. $C_{17}H_{18}O_2NCl$ requires C, 67.2; H, 5.9; N, 4.6; Cl, 11.7%). This with aqueous ammonia yielded ethyl 2-methyl-6-styrylnicotinate, which separated from ethanol in prisms, m. p. 68—69° (Found: C, 75.7; H, 6.2; N, 5.4. $C_{17}H_{17}O_2N$ requires C, 76.3; H, 6.35; N, 5.2%). Bromination in carbon tetrachloride gave ethyl 6-(1:2-dibromophenethyl)-2-methylnicotinate, needles (from ethanol), m. p. 138—139° (Found: N, 3.1; Br, 37.5. $C_{17}H_{17}O_2NBr_2$ requires N, 3.3; Br, 37.5%).

2:6-Dimethylnicotinic Acid.—Ethyl 2:6-dimethylnicotinate (5 g.) and 6.5N-sodium hydroxide (15.3 c.c.) were refluxed for 2 hr. The cooled solution was adjusted to pH 4.5 with 5N-hydrochloric acid and evaporated to dryness. The residue was extracted with ethanol, and the extract concentrated to give the acid (2.2 g.) which separated from ethanol in prisms, m. p. 170—171° (Found: C, 63.9; H, 6.1; N, 9.5. $C_8H_9O_2N$ requires C, 63.6; H, 6.0; N, 9.3%). Weiss⁴ gives m. p. 160° for a hemihydrate.

2-Methyl-6-styrylnicotinic Acid.—(a) 2:6-Dimethylnicotinic acid (2.0 g.) and benzaldehyde (1.6 c.c.) in acetic anhydride (1.3 c.c.) (10 hr. reflux) gave a first crop of 2-(2-hydroxyphenethyl)-6-styrylnicotinic lactone (0.63 g.), m. p. and mixed m. p. 200—201°. 2-Methyl-6-styrylnicotinic acid (0.66 g.) was isolated from the methanolic mother-liquors and recrystallised from ethyl acetate as plates, m. p. 192—194° (Found: C, 75.0; H, 5.6; N, 6.05%; equiv., 236. $C_{15}H_{13}O_2N$ requires C, 75.3; H, 5.4; N, 5.9%; equiv., 239).

(b) Ethyl 2-methyl-6-styrylnicotinate (0.43 g.) and 5N-sodium hydroxide (10 c.c.) were refluxed for 1 hr. The cooled solution was neutralised with acetic acid to give 2-methyl-6-styrylnicotinic acid (0.34 g.), m. p. and mixed m. p. 192—193° (from ethanol).

² Tsuda, Satch, Ikekawa, and Mishima, *J. Org. Chem.*, 1956, **21**, 800.

³ Rabe, *Ber.*, 1912, **45**, 2120.

⁴ Weiss, *Ber.*, 1886, **19**, 1308.

2-(2-Hydroxy-3'-nitrophenethyl)-6-3'-nitrostyrylnicotinic Lactone.—Ethyl 2:6-dimethylnicotinate (3.6 g.) and *m*-nitrobenzaldehyde (9.0 g.) in acetic anhydride (1.86 c.c.) (14 hr. reflux) gave the crude lactone (3.0 g.; m. p. 196—210°), which separated from acetic acid in pale yellow prisms, m. p. 230—232° [Found: C, 63.2; H, 3.8; N, 9.7%; equiv., 425 (hydrolysis). $C_{22}H_{15}O_6N_3$ requires C, 63.3; H, 3.6; N, 10.1%; equiv., 417].

Ethyl 2-Methyl-6-3'-nitrostyrylnicotinate Hydrochloride.—Repetition of the last experiment with less *m*-nitrobenzaldehyde (3.6 g.) and refluxing for 10 hr. yielded, after trituration with 2*N*-hydrochloric acid, *ethyl 2-methyl-6-3'-nitrostyrylnicotinate hydrochloride* (2.04 g.), m. p. 238—239° (Found: C, 58.3; H, 4.9; N, 8.2; Cl, 10.3. $C_{17}H_{17}O_4N_2Cl$ requires C, 58.4; H, 4.9; N, 8.0; Cl, 10.2%).

2-Methyl-6-3'-nitrostyrylnicotinic Acid.—(a) 2:6-Dimethylnicotinic acid (1.5 g.), *m*-nitrobenzaldehyde (1.8 g.), acetic anhydride (0.93 c.c.), and nitrobenzene (15 c.c.) were refluxed for 6.5 hr. The clear brown solution was cooled to give *2-methyl-6-3'-nitrostyrylnicotinic acid* (1.2 g.), m. p. 230—232°. Recrystallisation from 2-ethoxyethanol gave cream needles, m. p. 238—239° (Found: C, 63.3; H, 4.0; N, 10.3%; equiv., 282. $C_{15}H_{12}O_4N_2$ requires C, 63.4; H, 4.2; N, 9.8%; equiv., 284).

(b) Ethyl 2-methyl-6-3'-nitrostyrylnicotinate hydrochloride (0.9 g.) and 3*N*-sodium hydroxide (30 c.c.) were refluxed for 2 hr. The mixture was diluted to 100 c.c. to give a clear solution. Hydrochloric acid was added to adjust to pH 5.0 and the mixture left for 2 hr. at 0°, to yield 2-methyl-6-3'-nitrostyrylnicotinic acid (0.47 g.), m. p. 227—230°, and on recrystallisation from 2-ethoxyethanol, m. p. and mixed m. p. 238—239°.

2:6-Di-3'-nitrostyrylnicotinic Acid.—2:6-Dimethylnicotinic acid (0.71 g.) and *m*-nitrobenzaldehyde (2.1 g.) in acetic anhydride (0.6 c.c.) and nitrobenzene (15 c.c.) yielded the *distyryl acid* (0.71 g.) in pale yellow prisms (from 2-ethoxyethanol), m. p. 228—230° (Found: C, 62.9; H, 3.9; N, 10.3%; equiv., 406. $C_{22}H_{15}O_6N_3$ requires C, 63.3; H, 3.6; N, 10.1%; equiv., 417).

4:6-Dimethylnicotinonitrile.—2-Chloro-4:6-dimethylnicotinonitrile⁵ (35 g.), granulated tin (35 g.), concentrated hydrochloric acid (280 c.c.), and water (370 c.c.) were heated on the water-bath for 8 hr. The clear solution was made alkaline with sodium hydroxide, and the mixture extracted with chloroform. The extract was dried and distilled and the residual damp solid recrystallised directly from methanol, to give the *nitrile* (23.1 g.) in prisms, m. p. 54—56°. Recrystallisation from methanol raised the m. p. to 56—57° (Found: C, 71.9; H, 6.0; N, 20.7. $C_8H_8N_2$ requires C, 72.7; H, 6.05; N, 21.2%).

4:6-Dimethylnicotinic Acid.—2:6-Dimethylnicotinonitrile (15 g.) and 5*N*-potassium hydroxide were refluxed for 2 hr. The solution was acidified with concentrated hydrochloric acid, then concentrated *in vacuo*, and the dry residue extracted with ethanol (3 × 40 c.c.). The alcoholic extract was distilled, to leave 18.6 g., m. p. 247—253° (decomp.). A portion was recrystallised directly from ethanol to give *4:6-dimethylnicotinic acid hydrochloride*, m. p. 257—259° (decomp.) (Found: C, 50.7; H, 5.3; N, 7.1. $C_8H_{10}O_2NCl$ requires C, 51.2; H, 5.3; N, 7.5%).

The remainder of the hydrochloride (17.4 g.) was stirred with the calculated amount of *N*-sodium hydroxide, and the solution concentrated on the water-bath *in vacuo*. The dry residue was extracted with boiling ethanol (3 × 40 c.c.), and the extract concentrated to 40 c.c. and cooled, to give the free *acid* in prisms, m. p. 193—194° (Found: C, 63.0; H, 6.1; N, 8.8. $C_8H_9O_2N$ requires C, 63.6; H, 6.0; N, 9.3%).

Ethyl 4:6-Dimethylnicotinate.—4:6-Dimethylnicotinic acid (5.0 g.), absolute ethanol (100 c.c.), and concentrated sulphuric acid (4 c.c.) were refluxed for 16 hr. The ethanol was removed by distillation from a water-bath. Water (100 c.c.) was added, the solution made alkaline with sodium hydroxide solution, and the liberated oil extracted with chloroform. The extract was dried and the chloroform distilled, to leave the *ester* (3.2 g.) (Found: N, 7.5. $C_{10}H_{13}O_2N$ requires N, 7.8%).

Ethyl 4-Methyl-6-styrylnicotinate Hydrochloride.—Ethyl 4:6-dimethylnicotinate (1.2 g.) and benzaldehyde (0.85 g.) in acetic anhydride (0.62 c.c.) (12 hr. reflux) gave the hydrochloride (1.3 g.), separating in cream needles (from ethanol), m. p. 203—204° (Found: C, 66.8; H, 6.3; N, 4.8; Cl, 11.5%; equiv., 314. $C_{17}H_{18}O_2NCl$ requires C, 67.2; H, 5.9; N, 4.6; Cl, 11.7%; equiv., 303.5). Condensation with excess of benzaldehyde gave the same compound as the sole product.

4-Methyl-6-styrylnicotinic Acid.—(a) 4:6-Dimethylnicotinic acid (3.0 g.) and benzaldehyde

⁵ Mariella and Leech, *J. Amer. Chem. Soc.*, 1949, **71**, 332.

(2.54 g.) in acetic anhydride (1.86 c.c.) (11.5 hr. reflux) yielded the pale yellow *hydrochloride* (2.45 g.), m. p. 249—251° on recrystallisation from 2-ethoxyethanol (Found: C, 61.0; H, 5.7; N, 4.9; Cl, 12.1; H₂O, 7.0. C₁₅H₁₄O₂NCl.H₂O requires C, 61.3; H, 5.45; N, 4.8; Cl, 12.1; H₂O, 6.1%).

(b) Ethyl 4-methyl-6-styrylnicotinate hydrochloride (0.1 g.), potassium hydroxide (1.0 g.), and water (3.0 c.c.) were refluxed for 2 hr. The cooled solution was acidified with concentrated hydrochloric acid to give the hydrochloride, m. p. 246—249° alone and 248—250° with the product obtained in (a). The hydrochloride (0.5 g.) was dissolved in aqueous ammonia and the pH of the solution adjusted to 5.0 with acetic acid. The liberated 4-methyl-6-styrylnicotinic acid (0.32 g.) was collected and recrystallised from methanol, to give needles, m. p. 215—216° (Found: C, 74.8; H, 5.5; N, 6.0. C₁₅H₁₃O₂N requires C, 75.3; H, 5.4; N, 5.9%).

4 : 6-Distyrylnicotinic Acid.—4 : 6-Dimethylnicotinic acid (2.0 g.) and benzaldehyde (5.1 g.) in acetic anhydride (1.28 c.c.) (12 hr. reflux) gave the *distyryl acid* (1.3 g.) in needles (from 2-ethoxyethanol), m. p. 233—234° (Found: C, 80.4; H, 5.1; N, 4.6. C₂₂H₁₇O₂N requires C, 80.7; H, 5.2; N, 4.3%).

Pyridine-2 : 4 : 5-tricarboxylic Acid.—A solution of 4 : 6-distyrylnicotinic acid (0.1 g.) in ethyl acetate (20 c.c.) was treated with ozonised oxygen for 40 min. The solution was evaporated at room temperature and the ozonide decomposed by boiling dilute silver nitrate solution. The solid was collected and crystallised from methanol, to give the acid (0.04 g.) as the *hemihydrate*, m. p. 230—232° (decomp.) (Found: C, 43.1; H, 3.1; N, 6.5. C₈H₅O₆N, $\frac{1}{2}$ H₂O requires C, 43.5; H, 2.7; N, 6.4%). Mumm and Hüneke⁶ give m. p. 243° for the dihydrate. The acid, in dilute acetic acid, gave a strong red-brown colour with ferrous sulphate.

4 : 6-Di-3'-nitrostyrylnicotinic Acid.—4 : 6-Dimethylnicotinic acid (1.0 g.), *m*-nitrobenzaldehyde (3.6 g.), acetic anhydride (0.7 c.c.), and nitrobenzene (20 c.c.) were refluxed for 12 hr. The mixture was diluted with ether, to give the *product* (1.9), m. p. >330°, insoluble in common solvents. It was boiled with 2-ethoxyethanol, the hot mixture filtered, and the insoluble solid dried and analysed directly (Found: C, 63.0; H, 3.8; N, 10.1. C₂₂H₁₅O₆N₃ requires C, 63.3; H, 3.6; N, 10.1%). The acid gave a negative hydroxamic acid test. The same acid was also isolated in 90% yield by reaction of the ethyl ester with *m*-nitrobenzaldehyde (3.0 mol.).

Ethyl 4-Methyl-6-3'-nitrostyrylnicotinate.—Ethyl 4 : 6-dimethylnicotinate (1.5 g.) and *m*-nitrobenzaldehyde (1.5 g.) in acetic anhydride (0.77 c.c.) (3 hr. reflux) gave a crude product (1.9 g.), m. p. 190—>330°. The product was boiled with 2-ethoxyethanol, and the hot mixture filtered, to leave 4 : 6-di-3'-nitrostyrylnicotinic acid (0.48 g.), m. p. >330°. The filtrate, on cooling, yielded *ethyl 4-methyl-6-3'-nitrostyrylnicotinate hydrochloride* (1.15 g.) in prisms (from 2-ethoxyethanol), m. p. 211—212° (Found: C, 58.5; H, 4.7; N, 8.0%; equiv., 362. C₁₇H₁₇O₄N₂Cl requires C, 58.4; H, 4.9; N, 8.0%; equiv., 348.5). Treatment with aqueous ammonia gave *ethyl 4-methyl-6-3'-nitrostyrylnicotinate* in prisms (from ethanol), m. p. 130—131° (Found: C, 65.6; H, 4.9; N, 9.3. C₁₇H₁₆O₄N₂ requires C, 65.3; H, 5.1; N, 9.0%).

4-Methyl-6-3'-nitrostyrylnicotinic Acid.—(a) 4 : 6-Dimethylnicotinic acid (3.0 g.) and *m*-nitrobenzaldehyde (3.6 g.) in acetic anhydride (1.85 c.c.) (11 hr. reflux) yielded 4-methyl-6-3'-nitrostyrylnicotinic acid (5.9 g.), m. p. 298—300° (from nitrobenzene) (Found: C, 62.8; H, 4.1; N, 10.0. C₁₆H₁₃O₂N requires C, 63.4; H, 4.2; N, 9.8%).

(b) The same acid, m. p. 295—297° alone and 297—299° when mixed with the product from (a), was obtained by hydrolysis of ethyl 4-methyl-6-3'-nitrostyrylnicotinate hydrochloride with 6*N*-potassium hydroxide.