348. *Methylnicotinic Acids. Part I. Condensation of 2-Methyl-6-phenylnicotinic Acid and its Ethyl Ester with Aldehydes.*

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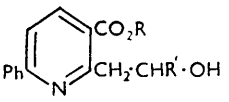
Condensation of benzaldehyde with 2-methyl-6-phenylnicotinic acid and its ethyl ester has been shown to produce a lactone in addition to the styryl derivatives of the acid and its ester. With certain substituted benzaldehydes, however, the lactone was the only product isolated.

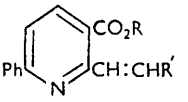
Little information appears in the literature on the condensation of 2- or 4-methylnicotinic acid with aldehydes apart from a report by Koenigs [1] that 4-methylnicotinic acid condenses with formaldehyde and less readily with acetaldehyde when heated in a sealed tube, one of the products from the latter condensation being the lactone of 4-(2-hydroxy-*n*-propyl)nicotinic acid. Since 2-methyl-6-phenylnicotinic acid is readily prepared by Späth and Burger's method,[2] it was chosen as a suitable derivative with which to begin an investigation into these condensations. It was found, however, that under the conditions described by Koenigs no reaction took place between 2-methyl-6-phenylnicotinic acid and formaldehyde or acetaldehyde, but extension of the investigation to include aromatic aldehydes gave positive results. Heating 2-methyl-6-phenylnicotinic acid with benzaldehyde and water in a sealed tube yielded 2-(2-hydroxyphenethyl)-6-phenylnicotinic

[1] Koenigs, *Ber.*, 1901, **34**, 4336.
[2] Späth and Burger, *Monatsh.*, 1928, **49**, 265.

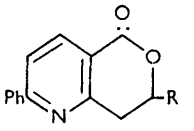
acid (I; R = H, R′ = Ph), whereas in acetic anhydride a mixture of 6-phenyl-2-styrylnicotinic acid (II; R = H, R′ = Ph) and 2-(2-hydroxyphenethyl)-6-phenylnicotinic lactone (III; R = Ph) was obtained.



(I)



(II)



(III)

6-Phenyl-2-styrylnicotinic acid (II; R = H, R′ = Ph) showed normal olefinic reactions towards bromine water and aqueous potassium permanganate. The lactone (III; R′ = Ph) was readily converted into the hydroxy-acid (I; R = H, R′ = Ph) in hot aqueous acetic acid, and re-formation of the lactone was accomplished by heating the acid with acetic anhydride or in a solvent such as ethyl acetate, some of the 6-phenyl-2-styrylnicotinic acid (II; R = H, R′ = Ph) being formed simultaneously. It is not possible, by heating alone, with acetic anhydride or with mineral acid, to convert 6-phenyl-2-styrylnicotinic acid (II; R = H, R′ = Ph) into the lactone (III; R′ = Ph). It thus seems clear that the first product of reaction between benzaldehyde and 2-methyl-6-phenylnicotinic acid, the hydroxy-acid (I; R = H, R′ = Ph), is converted during the reaction into a mixture of the styryl compound (II; R = H, R′ = Ph) and the lactone (III; R′ = Ph).

Substitution of ethyl 2-methyl-6-phenylnicotinate for the acid in reactions with benzaldehyde gave essentially similar results. The first product, ethyl 2-(2-hydroxyphenethyl)-6-phenylnicotinate (I; R = Et, R′ = Ph) was never isolated, but from condensations in sealed tubes under the influence of zinc chloride the major product was ethyl 6-phenyl-2-styrylnicotinate (II; R = Et, R′ = Ph) and was accompanied by the lactone (III; R′ = Ph) or in some experiments the hydroxy-acid (I; R = H, R′ = Ph). Ethyl 6-phenyl-2-styrylnicotinate (II; R = Et, R′ = Ph) and the lactone (III; R = Ph) were also produced when acetic anhydride was used as a condensing reagent and a very small quantity of 6-phenyl-2-styrylnicotinic acid (II; R = H, R′ = Ph) was recovered from the mother-liquors from several experiments.

The crude yields in condensations of substituted benzaldehydes with 2-methyl-6-phenylnicotinic acid and its ethyl ester in acetic anhydride were in the expected order *p*-NO_2 > *m*-NO_2 > H > *p*-MeO > *o*-OH. *p*-Nitrobenzaldehyde yielded the lactone (III; R′ = *p*-NO_2·C_6H_4) only, but both the stilbazole (II; R = H) and the lactone were obtained where R′ = *m*-NO_2·C_6H_4. *p*-Anisaldehyde and salicylaldehyde yielded, apart from intractable material, only the lactones (III; R′ = *p*-MeO·C_6H_4, R′ = *o*-HO·C_6H_4) and unchanged starting material in condensations with the ethyl ester. With the free acid salicylaldehyde yielded no product and *p*-acetamidobenzaldehyde gave only dark tars from reactions with both the acid and its ethyl ester.

Experimental

Condensation of 2-Methyl-6-phenylnicotinic Acid and Benzaldehyde.—(a) *In the presence of water.* 2-Methyl-6-phenylnicotinic acid (0·75 g.), benzaldehyde (0·3 c.c.), and water (0·2 c.c.) were heated in a sealed tube at 180° for 10 hr. The product was stirred with water and dissolved in the minimum of hot aqueous ethanol (1 : 1), to yield 2-(*2-hydroxyphenethyl*)-6-*phenylnicotinic acid* (I; R = H, R′ = Ph) (0·5 g.) which, on recrystallisation from aqueous ethanol, formed colourless needles, m. p. 176—177° (Found: C, 74·9; H, 4·7; N, 4·3. $C_{20}H_{17}O_3N$ requires C, 75·2; H, 5·3; N, 4·4%).

(b) *In the presence of acetic anhydride.* 2-Methyl-6-phenylnicotinic acid (4·26 g.), benzaldehyde (2·21 c.c.), and acetic anhydride (1·88 c.c.) were refluxed for 8 hr. Water (20 c.c.) was added and the gum which separated was stirred with ethanol (20 c.c.), to yield the crude product (4·1 g.), m. p. 132—147°. This crude product was boiled with ethanol (70 c.c.), the mixture cooled rapidly and the insoluble 2-(*2-hydroxyphenethyl*)-6-*phenylnicotinic lactone* (1·3 g.), m. p. 188—190°, collected. Recrystallisation from ethanol gave colourless plates, m. p. 194—195°

(Found: C, 79·5; H, 5·0; N, 4·9. $C_{20}H_{15}O_2N$ requires C, 79·7; H, 5·0; N, 4·7%). The filtrate was concentrated to 25 c.c., to yield *6-phenyl-2-styrylnicotinic acid* (0·95 g.), m. p. 189—191°. Recrystallisation from benzene and then ethanol gave colourless prisms, m. p. 202—203° (Found: C, 79·7; H, 5·3; N, 4·7. $C_{20}H_{15}O_2N$ requires C, 79·7; H, 5·0; N, 4·7%).

Condensation of Ethyl 2-Methyl-6-phenylnicotinate and Benzaldehyde.—(a) *In the presence of zinc chloride.* Ethyl 2-methyl-6-phenylnicotinate (24 g.), benzaldehyde (15·2 c.c.), and zinc chloride (6·8 g.) were heated in a sealed tube at 180° for 18 hr. The resultant brown oil was triturated with 2N-hydrochloric acid (100 c.c.), to yield a pale yellow sticky solid which on crystallisation from ethanol gave *ethyl 6-phenyl-2-styrylnicotinate* (13·5 g.), m. p. 100—102°. Recrystallisation from ethanol gave colourless needles, m. p. 106—107° (Found: C, 80·0; H, 5·7; N, 4·7. $C_{22}H_{19}O_2N$ requires C, 80·2; H, 5·8; N, 4·3%). Concentration of the mother-liquors gave a second crop which on recrystallisation from ethanol and ethyl acetate gave the lactone (3·1 g.), m. p. 194—195°.

(b) *In the presence of acetic anhydride.* Ethyl 2-methyl-6-phenylnicotinate (9·6 g.), benzaldehyde (5·1 g.), and acetic anhydride (4·5 g.) were refluxed for 10 hr. The solution was cooled and stirred with 2N-hydrochloric acid. Basification of the acid layer yielded ethyl 2-methyl-6-phenylnicotinate (3·4 g.), m. p. 44—46°. The residual sticky solid was stirred with water and then with alcohol, to give a crude product (4·5 g.), m. p. 98—128°, which was dissolved in the minimum of hot ethanol and cooled rapidly, to yield 2-(2-hydroxyphenethyl)-6-phenylnicotinic lactone (1·2 g.), m. p. 194—195°. The filtrate after concentration yielded ethyl 6-phenyl-2-styrylnicotinate (1·9 g.), m. p. 106—107°.

Reaction of the Hydroxy-acid (I; R = H, R′ = Ph) *with Acetic Anhydride.*—2-(2-Hydroxyphenethyl)-6-phenylnicotinic acid (1·0 g.) was refluxed with acetic anhydride (10 c.c.) for 2·5 hr. The mixture was cooled and boiled with ethanol (20 c.c.) and the solvents were evaporated, to leave a product (0·95 g.), m. p. 178—187°, which, recrystallised from ethanol, yielded 2-(2-hydroxyphenethyl)-6-phenylnicotinic lactone (0·26 g.), m. p. and mixed m. p. 194—195°. The alcohol was distilled from the filtrate, and the residue recrystallised from ethyl acetate, to give 6-phenyl-2-styrylnicotinic acid (0·29 g.), m. p. and mixed m. p. 202—203°.

Reaction of the Lactone (III; R′ = Ph) *with Aqueous Acetic Acid.*—2-(2-Hydroxyphenethyl)-6-phenylnicotinic lactone (0·5 g.) was refluxed with acetic acid–water (4 : 1; 10 c.c.) for 1 hr. and the solution left for 4 days. The crude product which separated was collected and recrystallised from aqueous alcohol, to give 2-(2-hydroxyphenethyl)-6-phenylnicotinic acid (0·34 g.), m. p. and mixed m. p. 176—177°.

Condensation of 2-Methyl-6-phenylnicotinic Acid and its Ethyl Ester with Substituted Benzaldehydes.—(a) p-*Nitrobenzaldehyde.* Ethyl 2-methyl-6-phenylnicotinate (2·41 g.), *p*-nitrobenzaldehyde (1·8 g.), and acetic anhydride (1·1 g.) were heated together for 8 hr. at 170—180°. The resulting semi-solid residue was stirred with 2N-hydrochloric acid, to give the crude product (3·6 g.), m. p. 208—212°. Crystallisation from ethyl acetate and from ethanol yielded *2-(2-hydroxy-4′-nitrophenethyl)-6-phenylnicotinic lactone* (III; R′ = *p*-NO_2·C_6H_4) (1·67 g.) as yellow needles, m. p. 237—239° (Found: C, 69·1; H, 3·6; N, 8·4. $C_{20}H_{14}O_4N_2$ requires C, 69·4; H, 4·0; N, 8·1%).

2-Methyl-6-phenylnicotinic acid (4·3 g.), *p*-nitrobenzaldehyde (3·6 g.), and acetic anhydride (2·0 g.) were heated together under reflux for 6 hr. at 200—210°. The mixture, which had solidified after the first 2 hr., was allowed to cool and then ground with water (20 c.c.), and the crude 2-(2-hydroxy-4′-nitrophenethyl)-6-phenylnicotinic lactone (III; R′ = *p*-NO_2·C_6H_4) (6·8 g.), m. p. 220—224°, collected. Crystallisation from ethanol yielded yellow needles (5·9 g.), m. p. and mixed m. p. 237—239°.

(b) m-*Nitrobenzaldehyde.* 2-Methyl-6-phenylnicotinic acid (12·8 g.), *m*-nitrobenzaldehyde (10·0 g.), and acetic anhydride (6·0 g.) were refluxed for 8 hr. The semi-solid residue was ground with water (50 c.c.), filtered, washed with ethanol (20 c.c.), and then dissolved in the minimum of hot ethanol (600 c.c.). The solution was cooled rapidly, to give *2-(2-hydroxy-3′-nitrophenethyl)-6-phenylnicotinic lactone* (III; R′ = *m*-NO_2·C_6H_4) (7·3 g.), m. p. 178—181°. Recrystallisation from ethanol gave 6·4 g., m. p. 178—179° (Found: C, 69·1; H, 3·9; N, 8·4%). The filtrate was concentrated to 200 c.c. and left for several hours, to yield *2-3′-nitrostyryl-6-phenylnicotinic acid* (II; R = *m*-NO_2·C_6H_4) (7·95 g.), m. p. 201—204°. Recrystallisation from ethyl acetate gave 6·4 g., m. p. 209—210° (Found: C, 69·7; H, 4·2; N, 8·2. $C_{20}H_{14}O_4N_2$ requires C, 69·4; H, 4·0; N, 8·1%).

The lactone and stilbazole were also obtained in lower yields (21·7 and 9·8% respectively) in a similar condensation of ethyl 2-methyl-6-phenylnicotinate.

(c) p-*Anisaldehyde.* Ethyl 2-methyl-6-phenylnicotinate (2·41 g.), *p*-anisaldehyde (1·7 g.),

and acetic anhydride (1·1 g.) were refluxed for 8 hr. The residual brown oil was dissolved in ether, and the ether solution extracted with 2N-hydrochloric acid. Basification of the acid extract yielded ethyl 2-methyl-6-phenylnicotinate (1·9 g.). 2-(2-*Hydroxy*-4′-*methoxyphenethyl*)-6-*phenylnicotinic lactone* (III; R′ = *p*-MeO·C_6H_4) (0·23 g.), m. p. 155—157°, separated gradually from the ether extract. Recrystallisation from butan-1-ol gave colourless plates, m. p. 170·5—171·5° (Found: C, 75·6; H, 5·2; N, 4·4. $C_{21}H_{17}O_3N$ requires C, 76·1; H, 5·1; N, 4·2%).

The same product was also obtained in higher yield (14%) in a condensation of 2-methyl-6-phenylnicotinic acid.

(d) *Salicylaldehyde.* Ethyl 2-methyl-6-phenylnicotinate (2·41 g.), salicylaldehyde (1·46 g.), and acetic anhydride (1·0 g.) were heated at 180° for 8 hr. 2N-Hydrochloric acid (20 c.c.) was added and the insoluble dark brown oil extracted into ether. The acid extract was basified, giving ethyl 2-methyl-6-phenylnicotinate (0·9 g.). The ether extract was concentrated to give a brown oil (1·92 g.) which on trituration with methanol yielded 2-(2-*hydroxy*-2′-*hydroxyphenethyl*)-6-*phenylnicotinic lactone* (0·4 g.), m. p. 91—94°, and on recrystallisation from ethanol gave plates, m. p. 98—99° (Found: C, 75·5; H, 5·3; N, 4·4. $C_{20}H_{15}O_3N$ requires C, 75·7; H, 4·7; N, 4·4%).

Ethyl 2-(1 : 2-*Dibromophenethyl*)-6-*phenylnicotinate.*—Bromine (0·9 g.) was added to a solution of ethyl 6-phenyl-2-styrylnicotinate (1·6 g.) in acetic acid (20 c.c.). Decoloration was almost immediate; the mixture was refluxed for 0·5 hr. and left for 3 days; the product (0·65 g.), m. p. 176—178° (decomp.), was then collected. The filtrate was diluted with water and extracted with ether, and the ether evaporated to yield, after trituration with alcohol, crude unchanged ethyl 6-phenyl-2-styrylnicotinate. The solid *ester*, m. p. 176—178°, was recrystallised from ethanol, to give colourless prisms, m. p. 180—182° (Found: N, 3·0; Br, 30·7. $C_{22}H_{19}O_2NBr_2$ requires N, 2·9; Br, 32·8%).

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