

Interaction of Alkyl Pyridines with Aldehydes and Phthalic Anhydride

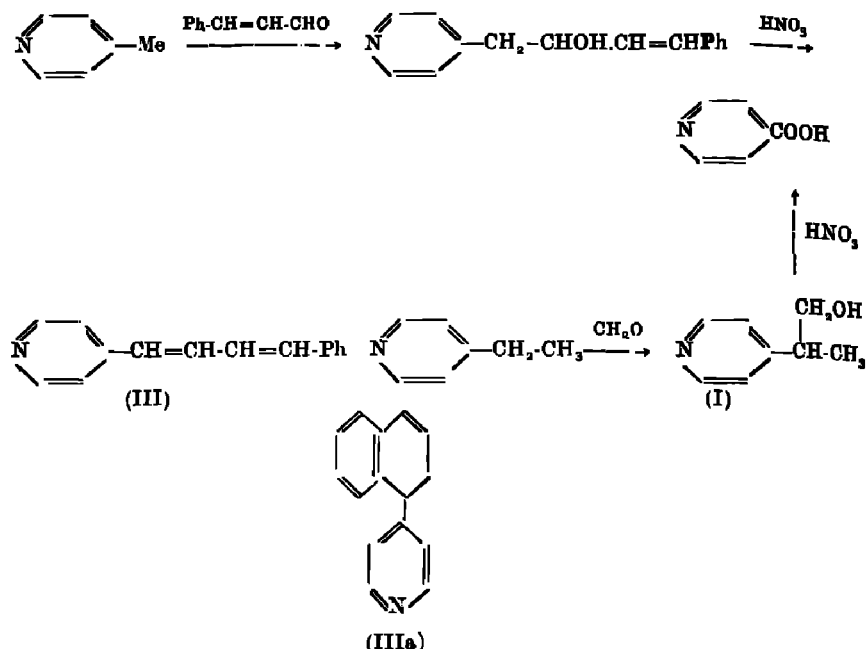
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4-Ethylpyridine readily reacts with formaldehyde to form 2-(4'-pyridyl)propanol(I) and γ -picoline with cinnamic aldehyde affords 1-(4'-pyridyl)-2-hydroxy-4-phenyl- Δ^3 -butylene (II) and 1-(4'-pyridyl)-4-phenyl-butadiene(III). (I) and (III) are easily oxidised to isonicotinic acid, whereas 4-ethylpyridine fails to react; γ -picoline and 2, 6-lutidine condense with phthalic anhydride, catalysed by fused zinc chloride or acetic anhydride to afford 4-pyrophthalone (VI), 6-methylpyrophthalone (IV), and 2, 6-bis-pyrophthalone (V).

The physico-chemical characteristics of pyridine nucleus induce alkylpyridines to react with aldehydes to afford aldol like condensation products¹⁻³. In an extended investigation in this direction it has now been possible to condense 4-ethylpyridine with formaldehyde to afford 2-(4'-pyridyl) propanol (I) in a satisfactory yield and γ -picoline with cinnamic aldehyde to furnish 1-(4'-pyridyl)-2-hydroxy-4-phenyl- Δ^3 -butylene (II). The carbinol (I) in presence of hydrochloric acid polymerises to a resinous mass, possibly through the intermediate formation of the corresponding stillbazole, but with moderately dilute nitric acid (I) is oxidised to isonicotinic acid. Under similar condition(II) the compound also provides isonicotinic acid and cinnamic acid. Dehydration of compound (II) with acetic anhydride leads to formation of 1-(4'-pyridyl)-4-phenylbutadiene (III) which can also be prepared by condensing γ -picoline with cinnamic aldehyde in presence of acetic anhydride.

In another approach it was considered possible that 1-(4'-pyridyl)-4-phenyl butadiene (III) on cyclisation would give rise to 4-(4'-pyridyl)-1,2-dihydronaphthalene (IIIa). Accordingly the butadiene (III), m.p. 160°, was treated with polyphosphoric acid at 80° under stirring for one hour to furnish product which was purified by sublimation at 280°/5 m.m.p. It had m.p. 121°, $\lambda_{\text{max}}^{\text{EtOH}}$ 260m μ (log ϵ , 2.97), whereas compound (III) showed absorption maxima at 234 and 331 m μ (log ϵ , 4.04 and 4.64 respectively). The dihydronaphthalene derivative formed was proved to be a mixture by TLC. The ease of cyclisation was hindered possibly by the *trans* configuration of the butadiene chain when compared with the favoured *cis* configuration. Cyclisation of the open chain reduced the basicity to such an extent that compound (IIIa) afforded a very unstable picrate. To obtain a pure naphthalene derivative, (IIIa) was subjected to dehydrogenation over Pd-C and also by sulphur but without any success. During dehydrogenation strong smell of γ -picoline proved the existence of an open chain in the cyclised product.

1. Meisenheimer, *Annalen*, 420, 202.
2. Ladenburg, *Ber.*, 1899, 22, 2583.
3. Dutta, *et al.*, unpublished work.



Much information are available in literature regarding 2-pyrophthalone⁴⁻⁶ condensation product of α -picoline and phthalic anhydride. In view of the relatively scanty data about other pyrophthalones, condensation of γ -picoline, 2,6-lutidine and 4-ethylpyridine with phthalic anhydride have now been studied. Whereas 4-ethylpyridine fails to react possibly due to steric hindrance, 2,6-lutidine furnishes two products, 6-methyl-2-pyrophthalone (IV) and 2,6-bis-pyrophthalone (V), depending on the molecular proportions of the reactants, in presence of anhydrous zinc chloride or acetic anhydride as catalyst. In a similar way γ -picoline affords 4-pyrophthalone (VI). The yields of these condensation products are comparatively fair in presence of zinc chloride as a catalyst. A liquid by-product (A) is obtained along with compound (VI) when γ -picoline is condensed with commercial phthalic anhydride (contaminated with phthalic acid) or with phthalic acid in presence of zinc chloride and (A) is the main reaction product in case of phthalic acid.

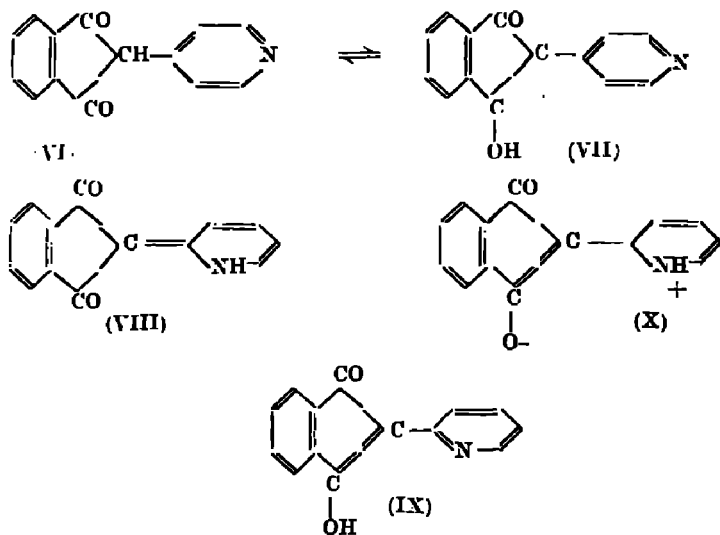
These pyrophthalones are insoluble in mineral acids and are resistant to alkaline hydrolysis. Caustic soda solution provides orange or red coloured crystalline salts which on treatment with acetic acid afford the original condensation products. Acetic anhydride in acetic acid medium affords the corresponding acetyl derivatives. Nitric acid oxidises (VI) to isonicotinic acid and phthalic acid. The formation of (VI) can be utilised in separation of beta picoline from a mixture of beta gamma picolines.

4. Huber, *Ber.*, 1903, 36, 165.

5. Kuhn and Bar, *Annalen*, 1935, 516, 155.

6. Jacobsen and Reimer, *Ber.*, 1883, 16, 2602.

The properties of these pyrophthalones differ in a few respects from those of 2-pyrophthalone(VIII) as found in literature. Huber⁴ has claimed to have isolated mono-phenylhydrazones from 2-pyrophthalone. But now it has been observed that 4-pyrophthalone and its analogues from 2,6-lutidine do not afford phenylhydrazones or oximes. Kuhn and Bar's⁵ interpretation regarding the structure of 2-pyrophthalone is still now accepted. According to Kuhn, (IX) & (X) are tautomeric forms of (VIII). (VIII) would presumably be oxidised to 2-pyridone. Since 4-pyridone is not one of the products of oxidation and because of the facile formation of acetoxy derivative, 4-pyrophthalone seems to exist in the tautomeric forms (VI) and (VII), though, however, no test for ketonic group could be achieved. From this structural analogy with 4-pyrophthalone it appears that other pyrophthalones from 2,6-lutidines also possibly exist in two tautomeric forms.



The exact nature of the by-product (A) could not be ascertained but phthalic acid seems to be the constituent part of its molecule. Further work is in progress regarding the identification of the material.

EXPERIMENTAL

2-(4'-Pyridyl)propanal (I).—4-Ethylpyridine (5 g.) and formalin (38% w/w, 15ml) were thoroughly mixed and heated to brisk refluxing for 18 hours. The reaction mixture was then diluted with water (50 ml) and the unchanged 4-ethylpyridine was distilled. The residual liquid was concentrated under reduced pressure on a water bath, distilled under reduced pressure and the fraction boiling at 140°-50°C/10mm was collected, yield 2.5 g. The material was characterised as picrate, crystallised from ethanol in yellow needles m.p. 156°. (Found: N, 15.4, $C_8H_{11}OH$, $C_6H_3O_7N_3$ requires N, 15.3%)

1-(4'-Pyridyl)-2-hydroxy-4-phenyl- Δ^3 -butylene (II).— γ -Picoline (0.3 g) and cinnamic aldehyde (freshly distilled, 10 g.) were mixed and the mixture was heated in an oil bath at

130°-40° for 16 hrs. The reaction mixture was then poured in ice and acidified with HCl to pH 2-3. The oil, separated, was extracted with benzene and the extract was washed with water and dried with sodium sulphate. The oil (about 2 g.), left after removal of the benzene, could not be distilled under vacuum. It was converted to its picrate from ethanolic solution in beautiful yellow needles, yield 2 g., m.p. 152° (Found: N, 11.9. $C_{13}H_{13}ON$, $C_6H_3N_3O_7$, requires N, 12.3%).

*1-(4'-Pyridyl-4-phenylbutadiene (III).—*The preceding compound (II) (3.2g.) was mixed with acetic anhydride (6 ml) and was heated to brisk refluxing on a sand bath for 6 hrs. The reaction mixture was then treated with icecooled water under stirring and finally basified with ammonia. The semisolid mass separating became solid on scratching. It was filtered and crystallised from ethanol as light cream-coloured solid. The solid was dried in vacuum over calcium chloride, m.p. 160-61°, yield 1.6g., (Found: N, 6.3. $C_{15}H_{15}N$ requires N, 6.8%).

*Cyclisation of (III) with Polyphosphoric Acid.—*Phosphorus pentoxide (32 g.) was mixed thoroughly with phosphoric acid (22 ml.) and heated under stirring on an oil bath at 100° for 1hr. The reaction mixture was cooled to the room temperature and compound (III) (2.5g.) was added to it. The mixture was then heated under stirring at 80° for 1 hr., cooled, and decomposed with icecold water. The solution was adjusted to pH 7 with dilute alkali when a light brown solid separated. It was filtered, washed with icecold water and air dried, m.p. 121°-22°, yield 0.7 g. The solid could not be crystallised from usual solvents and was proved to be a mixture by TLC. The compound furnished a picrate which was very unstable.

*Oxidation of (I) to Isonicotinic Acid.—*Compound (I) (2.5g.) was mixed with 50% nitric (50 ml) in a flask fitted with an upright condenser and heated on a wire gauze to brisk boiling. Oxidation took place with evolution of nitrous fumes. When the evolution of nitrous fumes had subsided the mass was refluxed for further 2 hr. and the excess of nitric acid removed by distillation. The residual liquid (about 10 ml) was diluted with water (10 ml) and cooled in ice and then the pH was adjusted to 3.2-3.4 with dilute NaOH solution. Isonicotinic acid separating was isolated by filtration and purified by crystallisation, m.p. 316° (decomp.), yield 2g. mixed m.p. with an authentic sample was not depressed.

Compound (II) was oxidised exactly as above. From the reaction mixture after removal of excess nitric acid and dilution with water, cinnamic acid was isolated by cooling in ice. From the filtrate isonicotinic acid was isolated by adjustment of pH as above.

*6-Methyl-2-pyrophthalone (IV).—*2,6-Lutidine (freshly distilled, 5g.) phthalic anhydride (purified by sublimation 3.8 g.) and zinc chloride (fused, 1.2 g.) were mixed and heated in an oil bath at 200° for 18 hr. The reaction mixture was then treated with water and scratched, when it solidified. The solid was filtered and crystallised from dilute acetic acid in fine orange crystals, m.p. 210° (decomp.), yield 3g. (Found: N, 5.60. $C_{13}H_{11}O_4N$ requires N, 5.90%)

2,6-bis-pyrophthalone (V) was obtained in fine orange yellow crystals, m.p. 180°-181° (decomp.), exactly as (IV), using double the quantity of phthalic anhydride for the same amount of 2,6 lutidine as in (IV). (Found: N, 3.81. $C_{23}H_{15}O_6N$ requires N, 3.95%)

Acetylation of 6-Methyl-2-pyrophthalone.—Mixture of 6-methyl-2-pyrophthalone (1 g. distilled acetic anhydride (1 g.), and glacial acetic acid (5 ml) was heated to reflux with a small flame over a wire gauze for 3 hr., affording a clear solution. The solid separating on cooling was crystallised from acetic acid in fine yellow crystals. The original mother liquor on concentration provided a little more solid which was also crystallised from acetic acid. Total yield of solid-0.5 g., m.p. 220° (Found: N, 4.8. $C_{17}H_{13}O_3N$, requires N, 5.0%).

Acetyl derivative of 2,6-bis pyrophthalone was prepared exactly as above in orange yellow flaky crystals, m.p. 211—12° (Found: N, 2. $C_{27}H_{17}O_6N$ requires N, 3.1%)

Formation of 4-pyrophthalone (VI) was achieved in fine orange red crystals (from glacial acetic acid), m.p. 318-19° (decomp.) from the reaction mixture of γ -picoline (25 g.), phthalic anhydride (30 g.) and fused zinc chloride (5 g.), following the procedure as in (IV), yield 32 g. (Found: N, 6.15. $C_{14}H_9O_2N$ requires N, 6.28%).

The m.p. of the acetyl derivative of (VI), prepared as in the case of other two pyrophthalones, was 308-10° (Found: N, 5.3. $C_{16}H_{12}O_3N$ requires N, 5.26%)

Formation of 4-Pyrophthalone (VI) and a Liquid Product Designated (A).— γ -picoline (distilled, 25g.), commercial phthalic anhydride (contaminated with phthalic acid, 30 g.), and anhydrous zinc chloride were mixed and heated in an oil bath at 200° for 18 hr. The reaction mixture was cooled and treated with water and scratched; the solid separating was filtered and finally crystallised from glacial acetic acid to yield (VI), yield 12 g., m.p. 318-19° (decomp.); mixed m.p. with an authentic sample of (VI) showed no depression. The filtrate from the reaction mixture was adjusted to pH-7 with alkali when an oil separated (A, about 8 g.) which was converted to its hydrochloride with HCl (conc.) and finally crystallised from water in beautiful yellow crystals, m.p. 205-206°, yield 10g. If γ -picoline (distilled 9.3 g.) and phthalic acid (16.6 g) were mixed and treated at the same temperature and for the same period of time as above and worked up exactly in the identical manner, the main condensation product was the oily liquid (A), yield 6 g. which was converted to its hydrochloride m.p. 205-206° (Found: Cl content, 1.8%).

Oxidation of 4-Pyrophthalone to Isonicotinic Acid.—4-pyrophthalone (16 g.) was added gradually to a boiling mixture of nitric acid (35 ml, 70% w/w) and water (28 ml) and heated to reflux for 6 hr. From the reaction mixture phthalic acid separated on cooling and the aqueous liquor after separation of phthalic acid (6 g.) was concentrated. Adjustment of pH to 3.2 to 3.4 afforded isonicotinic acid (5g. after crystallisation), m.p. 315°-16° (decomp.).

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