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Alkylation of 2,6-Lutidine

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For a study of the intramolecular oxidative coupling of phenolic compounds, we tried to prepare 2,6-bis(*p*-hydroxyphenyl)alkyl- and alkenylpyridine.

Attempts to condense 2,6-lutidine with cinnamaldehyde and hydrocinnamaldehyde by heating or with acetic anhydride were unsuccessful.

Some reactions of 6-methyl-2-picolyllithium have been reported, but discrepancies are found in literature regarding the possibility of generating and using a dilithium derivative of 2,6-lutidine.[1]

The reaction of lutidyllithium with cinnamaldehyde afforded no simple reaction products. 1-(6-Methyl-2-pyridyl)-4-phenyl-2-butanol (Ia) was formed by the action of hydrocinnamaldehyde along with 3,3-di(6-methyl-2-pyridylmethyl)-1-phenylpropane (II), which was formed from two moles of lutidine with one mole of aldehyde. Further treatment of lithium derivative of tetrahydropyranyl ether Ib with aldehyde gave no

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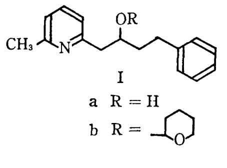
[1] K. Schofield, "Hetero-Aromatic Nitrogen Compounds," Butterworth & Co. Ltd., London (1967), p. 381.

reaction products, only the starting material Ib and Ia being recovered.

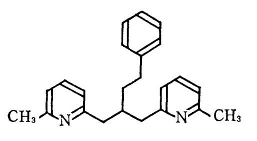
The product obtained from 2,6-lutidine and benzyl chloride with two equivalents of phenyllithium has been reported as 2-dibenzylmethyl-6-methylpyridine.[2]

The same results were obtained by the action of lutidyllithium on cinnamyl chloride. The product ($C_{25}H_{25}N$) was assigned to 2-dicinnamylmethyl-6-methylpyridine by NMR spectra (2.50 ppm, 3H singlet of α-methyl proton of pyridine).

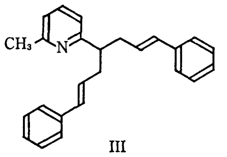
On the other hand, symmetrical dialkylation occurred by using γ-phenylpropyl bromide. The product IVa ($C_{25}H_{29}N$) showed no absorption at 2.50 ppm in NMR spectra. This prompted us to try the reaction with γ-(*p*-methoxyphenyl)-propyl bromide. The structure of IVb is supported by NMR and MS which has a parent ion peak at *m/e* 403. Fragmentation peaks at *m/e* 255, 121, and 107 are assigned to ions $[CH_3O\text{-}C_6H_4\text{-}(CH_2)_4\text{-}C_5H_4N\text{-}CH_2]^+$, $[CH_3O\text{-}C_6H_4\text{-}CH_2]^+$ and $[CH_3\text{-}C_5H_4N\text{-}CH_2]^+$ respectively. Phenolic compound IVc was produced by boiling IVb with 48% hydrobromic acid.



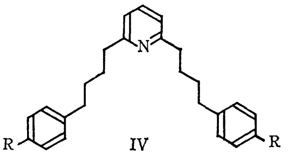
I
a R = H
b R =



II



III



IV
a R = H
b R = OCH₃
c R = OH

Experimental

Reaction of 2,6-lutidine with hydrocinnamaldehyde.

1) To a solution of phenyllithium (0.2 mol) in ether (200 m*l*) was added dropwise 2,6-lutidine (21.4g, 0.2 mol) at room temperature and stirred for 3 hr. A solution of hydrocinnamaldehyde (26.8g, 0.2 mole) in ether (30 m*l*) was then added and the reaction mixture was stirred overnight at room temperature. The cooled reaction mixture was decomposed by addition of ice-water. The aqueous layer was extracted with ether and the ethereal extracts were washed with water, and dried. The residual oil obtained by evaporation of the solvent was distilled to give 37g (78%) of Ia, bp 137—142°C/0.001 mmHg. NMR: δ (CCl_4) 1.75 (m, 2), 2.52 (s, 3), 2.60-3.00 (broad, 4), 3.92 (quintet, 1, *J*=*ca.* 6 Hz), 4.97 (broad s, 1), 6.8—7.6 ppm (8). IR: 3400, 1600, 1585 cm^{-1}.

Found: C, 79.74; H, 7.96; N, 5.84%. Calcd for $C_{16}H_{19}ON$: C, 79.63; H, 7.94; N, 5.80%.

Tetrahydropyranyl ether of Ia, bp 170—175°C/0.001 mmHg.

Found: C, 77.47; H, 8.39; N, 4.23%. Calcd for $C_{21}H_{27}O_2N$: C, 77.50; H, 8.36; N, 4.30%.

2) The reaction was effected by 0.05 mol of 2,6-lutidine and 0.18 mol of hydrocinnamaldehyde and the product was extracted with ether. The organic layer was extracted with 6N hydrochloric acid and the acidic extract was made basic with sodium carbonate and then reextracted with ether. The ethereal extracts were washed with sodium hydrogen sulfite solution and water, and dried. The solvent was removed and the residual oil was distilled at 180—190°C/0.001 mmHg, 2.2 g. The oil showed two spots (R_f 0.60, 0.69: ethyl acetate) on TLC (silica gel G). One (R_f 0.69) was identical with that of Ia. Chromatography over 40 g of silica gel and elution with benzene-ether (99: 1) afforded 700 mg of II: R_f 0.60, bp 220—250°C/0.001 mmHg. NMR: δ(CCl_4) 1.37—1.77 (broad, 3), 2.45 (s, 6), 2.48—2.90 (broad, 6), 6.65—7.42 ppm (11).

Found: C, 82.84; H, 8.01; N, 8.15%. Calcd for $C_{23}H_{26}N_2$: C, 83.59; H, 7.93; N, 8.48%.

Picrate: mp 174°C (from ethanol).

Found: C, 53.45; H, 4.13; N, 14.23%. Calcd for $C_{35}H_{32}O_{14}N_8$: C, 53.30; H, 4.09; N, 14.21%.

2-Dicinnamylmethyl-6-methylpyridine (III). To a stirred solution of lutidyllithium (0.06 mol) in ether was added dropwise cinnamyl chloride (21.2 g, 0.16 mol) at −15°C during a period of 2.5 hr. After standing overnight at 0°C, the reaction mixture was refluxed for 1 hr. The product obtained in the usual way was distilled to give 9.8 g (48%) of III, bp 215—217°C/0.001 mmHg. NMR: δ (CCl_4), 2.50 (s, 3), *ca.* 6.2 (2), 6.7—7.4 ppm (15).

Found: C, 88.33; H, 7.35; N, 4.12%. Calcd for $C_{25}H_{25}N$: C, 88.45; H, 7.42; N, 4.13%.

2,6-Bis-(δ-phenylbutyl)pyridine (IVa). To a stirred solution of lutidyllithium (0.05 mol) in ether (100 m*l*) was added a solution of γ-phenylpropyl bromide (20 g, 0.1 mol) in ether (50 m*l*) at 0°C. After stirring for 2 hr at room temperature and for 30 min under reflux, the reaction was quenched by addition of water. The separated ethereal layer was washed with water and dried. The residue obtained by evaporation of the solvent was distilled to give two kinds of oily products. The first fraction amounted to 5.1 g (45%) of 6-methyl-2-(δ-phenylbutyl)pyridine, bp 107°C/0.1 mmHg. NMR: δ (CCl_4) 1.7 (m, 4), 2.5 (s, 3), 2.65 (m, 4), 6.67—7.6 (8).

Found: C, 84.95; H, 8.56; N, 6.03%. Calcd for $C_{16}H_{19}N$: C, 85.28; H, 8.50; N, 6.22%.

The second fraction was 8.3 g (48%) of IVa, bp 183°C/0.1 mmHg. NMR: δ (CCl_4) 1.7 (m, 8), 2.65 (m, 8), 6.67—7.6 ppm (13).

Found: C, 87.14; H, 8.48; N, 4.10%. Calcd for $C_{25}H_{29}N$: C, 87.41; H, 8.51; N, 4.08%.

*2,6-Bis[δ-(*p*-methoxyphenyl)butyl]pyridine (IVb).* To a stirred solution of lutidyllithium (0.1 mol) in ether (170 m*l*) was added a solution of γ-(*p*-methoxyphenyl)propyl bromide[3] (45.8 g, 0.2 mol) in ether (100 m*l*) at 0°C. After further stirring for 3 hr at 0°C, 2 hr at room temperature and 1 hr under reflux, the reaction was quenched by addtion of water and the products obtained in the usual way were fractionally distilled. The main fraction was 17.3 g (43%) of IVb, bp 230—235°C/0.001 mmHg. NMR: δ (CCl_4), 1.3—2.0 (broad, 8), 2.3—2.9 (broad, 8), 3.65 (s, 6), 6.5—7.5 ppm (11). IR: 1610, 1585, 1580 cm^{-1}. MS: *m/e* 403(3), 268 (5), 255(21), 121(100), 120(75), 107(48), 91(9), 79(5), 78(9), 77(12%).

Found: C, 80.14; H, 8.26; N, 3.47%. Calcd for $C_{27}H_{33}O_2N$: C, 80.36; H, 8.24; N, 3.47%.

The low boiling fraction (bp 132—135°C/0.001 mmHg) was 6.1 g of 2-[δ-(*p*-methoxyphenyl)butyl]-6-methylpyridine.

Found: C, 79.83; H, 8.22; N, 5.53%. Calcd for $C_{17}H_{21}ON$: C, 79.96; H, 8.29; N, 5.49%.

Further treatment of the lithium derivative of this compound with equimolecular amount of bromide yielded IVb, 60%.

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[2] J.I. de Jong and J.P. Wibaut, *Rec. Trav. Chim.*, **70**, 962 (1951).

[3] Ki-U Kim, *J. Pharm. Soc. Japan*, **63**, 376 (1943).

*2,6-Bis[δ-(*p*-hydroxyphenyl)butyl]pyridine (IVc).* IVa (26 g) was dissolved in 48% hydrobromic acid (1 *l*) and heated for 8 hr under reflux. The residue obtained by evaporation of the solution *in vacuo* was crystallized from alcoholic water to give 16 g(54 %) of IVc-hydrobromide, mp 181—182°C.

Found: C, 65.74; H, 6.54; N, 3.02; Br, 17.30%. Calcd for $C_{25}H_{30}O_2NBr$: C, 65.79; H, 6.65; N, 3.07; Br, 17.51%.

The solution of IVc-hydrobromide in methanol was treated with sodium carbonate solution and evaporated to dryness *in vacuo*. The residue was extracted with hot ethyl acetate. The crystal obtained by evaporation of the solvent was recrystallized from ethanol, mp 124—126°C. NMR: δ (pyridine-d_5), 1.5—2.0 (broad, 8), 2.56 (t, 4, *J*=*ca.* 7 Hz), 2.82 (t, 4, *J*=*ca.* 6 Hz), 7.02 (s, 8), 6.8—7.9 (t, 3), 8.6 ppm (broad s, 2). IR: 3320—2300 cm^{-1}.

Found: C, 79.89; H, 7.77; N, 3.68%. Calcd for $C_{25}H_{29}O_2N$: C, 79.96; H, 7.79; N, 3.73%.