Aromatization of Some 4-Substituted 2, 6-Dimethyl-3, 5-diethoxycarbonyl-1, 4-dihydropyridines to Pyridines

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Following the preparation of a series of dihydropyridine compounds[1] it was considered interesting to investigate the possibility of preparing the corresponding piperidines through "hydrogen-transfer." When 2,6-dimethyl-3,5-diethoxycarbonyl-4-phenyl-1,4-dihydropyridine was refluxed in cyclohexene in the presence of 5% palladium/charcoal catalyst with a catalytic amount of glacial acetic acid added to it, the product that was obtained was not the corresponding piperidine, instead 2,6-dimethyl-3,5-diethoxycarbonyl-4-phenylpyridine was obtained in 90% yield. The identity of this product was confirmed by comparison with the authentic sample prepared through oxidation of the corresponding dihydropyridine with nitrous oxide.[2]

Accordingly, all the dihydropyridine compounds reported earlier[1] were subjected to this reaction. Since cyclohexene did not play any part, this reaction was carried out by boiling the dihydropyridines in toluene or benzene, containing a catalytic amount of glacial acetic acid and 5% palladium-charcoal catalyst. In the absence of acetic acid, however, no aromatization could be achieved. It was also interesting to observe that in this reaction aromatization did not proceed at all, if the substituent in the fourth position happened to be a phenol. As for instance 2,6-dimethyl-3,5-diethoxycarbonyl-4-(3-hydroxyphenyl)-1,4-dihydropyridine, 2,6-dimethyl-3,5-diethoxycarbonyl-4-(3-methoxy-4-hydroxyphenyl)-1,4-dihydropyridine and 2,6-dimethyl-3,5-diethoxycarbonyl-4-(4-hydroxyphenyl)-1,4-dihydropyridine failed to give the corresponding pyridine derivatives. However, on methylation of phenolic OH the aromatization with palladium/charcoal proceeded as usual.

Reference to literature reveals that Knoevenagel and Fuchs prepared 2,6-dimethyl-3,5-diethoxycarbonylpyridine by heating 2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine with palladium-black at 200~265°C,[3] and also by heating with concentrated hydrochloric acid when the corresponding pyridine derivative was obtained in 5% yield only.

Since oxidation with nitrous oxide gave invariably poor yields of the corresponding pyridine derivatives, oxidation with potassium permanganate in glacial acetic acid was also tried when the pyridine derivatives were obtained in comparatively high yields. Oxidation in acetone however, failed, the dihydropyridines being recovered unchanged.

Experimental

All melting points are corrected. Ultraviolet absorption spectra were determined with a Beckman spectrophotometer model DB in 95% ethanol.

General Method.—*A) Aromatization of the Dihydropyridine Ring with 5% Palladium/Charcoal-Acetic Acid.*—A dihydropyridine (0.002 mol.) dissolved in toluene (25 ml.) containing palladium-on-charcoal catalyst (5%; 50 mg.) and glacial acetic acid (5 ml.) was refluxed (42 hr.) on a sand bath, filtered and filtrate washed thrice with water and then with aqueous sodium hydrogen carbonate (10%; 2 ml.) followed by water. Drying and removal of the solvent gave the corresponding pyridine.

B) Aromatization of Dihydropyridine Ring through Oxidation with Potassium Permanganate.—A dihydropyridine (0.01 mol.) was dissolved in glacial acetic acid (50 ml.) and powdered potassium permanganate (1 g., 0.006 mol.) added. The mixture was heated on a water bath (about 5 hr.) till almost whole of the permanganate was consumed. The very slight excess of the permanganate was destroyed by heating with a little ethyl alcohol and the solvent was removed in vacuo. Water (25 ml.) was added to the residue and the product was isolated with ethyl acetate and worked up.

The pyridine compounds are generally soluble in acetone, benzene, chloroform, dioxane, ethyl acetate, ethyl and methyl alcohols, sparingly soluble in ether, carbon tetrachloride, light-petroleum (60~80°C) and insoluble in water.

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TABLE I. YIELDS AND PROPERTIES OF 4-SUBSTITUTED 2,6-DIMETHYL-3,5-DIETHOXYCARBONYLPYRIDINES

4-Substituent	Solvents for crystallization. Shape and color of crystals	Yield, % Method A	Yield, % Method B	M.p. or b.p.	Analysis Found	Analysis Calcd. for	UV Absorption λ_{max} (log ε)
H	Light-petroleum* Colorless needles	43.0	49.0	72°C Lit.[3] 72~73°C		$C_{13}H_{17}O_4N$ C, 62.24 62.14 H, 6.72 6.82 O, 25.51 25.47 N, 5.52 5.57	265(4.02) 206(4.55)
Methyl-	Golden yellow oil	27.0	64.0	222°C/2 mmHg Lit. b.p. 308~310°C[4]		$C_{14}H_{19}O_4N$ C, 63.30 63.38 H, 6.56 7.22 O, 24.38 24.12 N, 5.66 5.28	270(3.32) 208(3.92)
Propyl-	Brown oil n_D^{22} 1.498	63.0	51.5	132°C/0.5 mmHg Lit. 308°C/714 mmHg[5]		$C_{16}H_{23}O_4N$ C, 65.07 65.51 H, 7.65 7.90 O, 21.81 21.82 N, 4.91 4.78	270(3.45) 208(4.37)
Hexyl-	Yellow oil	67.4	74.5	200°C/1.5 mmHg $(C_{19}H_{29}NO_4)_2H_2PtCl_6$ m.p. 140°C Lit.[5] 141°C		$C_{19}H_{29}O_4N$ C, 67.73 68.03** H, 8.45 8.71 O, 19.41 19.08 N, 4.90 4.18	232(4.16) 208(4.37)
Styryl-	Benzene-light petroleum* Long colorless needles	49.7	—	39°C Lit.[6] 39°C		$C_{21}H_{23}O_4N$ C, 71.42 71.37 H, 6.26 6.56 O, 17.98 18.11 N, 3.72 3.96	287(4.30) 208(4.26)
Phenyl-	Benzene-light petroleum* Microscopic hexagonal plates	90.0	68.8	65°C Lit.[2] 66~67°C		$C_{19}H_{21}O_4N$ C, 69.32 69.70 H, 6.40 6.47 O, 19.49 19.55 N, 4.49 4.28	267(3.90) 206(4.50)
4-Methoxyphenyl-	Benzene Microscopic colorless plates	42.8	64.8	52°C Lit.[7] 51~53°C		$C_{20}H_{23}O_5N$ C, 67.20 67.21 H, 6.48 6.49 O, 22.43 22.38 N, 4.05 3.92	272(4.06) 206(4.54)

TABLE I. (Continued)

4-Substituent	Solvents for crystallization. Shape and color of crystals	Yield, % Method A	Yield, % Method B	M.p. or b.p.	Analysis Found	Analysis Calcd. for	UV Absorption λ_{max} (log ε)
3,4-Dimethoxyphenyl-	Benzene Microscopic colorless needles	41.5	35.4	98°C		$C_{21}H_{25}O_6N$	
					C, 65.12	65.10	272(4.11)
					H, 6.53	6.50	204(4.66)
					O, 24.19	24.78	
					N, 4.05	3.62	
Propenyl-	Red oil	65.2	—	230°C/1.5 mmHg Hydroiodide m.p. 140°C (decomp.) Lit.[8] 137～140°C (decomp.)		$C_{16}H_{21}O_4N$**	
					C, 64.14	65.95	208(4.16)
					H, 7.10	7.27	203(4.12)
					O, 21.25	21.97	
					N, 4.81	4.81	
2-Nitrophenyl-	Ether-ligroin Microscopic needles	76.0	47.7	73°C Lit.[9] 75°C		$C_{19}H_{20}O_6N_2$	
					C, 61.32	61.28	268(3.72)
					H, 5.52	5.41	205(4.49)
					O, 25.45	25.78	
					N, 7.36	7.52	
3-Nitrophenyl-	Benzene-ligroin Microscopic prisms	60.4	58.0	60～61°C Lit.[10] 65°C		$C_{19}H_{20}O_6N_2$	
					C, 61.06	61.28	256(4.19)
					H, 5.63	5.41	206(4.65)
					O, 25.97	25.78	
					N, 7.54	7.52	
4-Nitrophenyl-	Ether-light petroleum* Microscopic needles	83.0	56.4	115°C Lit.[7] 117°C		$C_{19}H_{20}O_6N_2$	
					C, 61.21	61.28	270(4.21)
					H, 5.30	5.41	205(4.56)
					O, 25.60	25.78	
					N, 7.61	7.52	
2-Chlorophenyl-	Yellow oil	80.3	34.6	62°C 225°C/1.5 mmHg Lit.[11] 62°C		$C_{19}H_{20}O_4NCl$	
					C, 62.18	62.80	272(3.51)
					H, 5.79	5.54	210(4.30)
					O, 17.65	17.74	
					N, 4.26	3.97	
α-Furyl-	Oil n_D^{22} 1.532	66.0	45.0	40～41°C 180°C/1.5 mmHg Lit.[12] 40～41°C		$C_{17}H_{19}O_5N$	
					C, 63.60	64.34	281(4.13)
					H, 5.79	6.04	212(4.22)
					O, 26.02	25.21	
					N, 4.62	4.41	

* Light petroleum b.p. 60～80°C ** Requires