SYNTHESIS OF PYRIDINE BASES FROM PIPERIDINE DERIVATIVES

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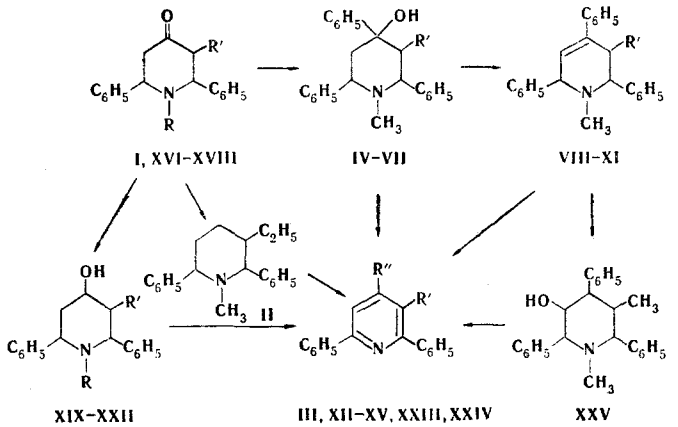
The corresponding substituted pyridines are obtained in 40-90% yields when N-alkyl-substituted piperidines, Δ^4-piperideines, and secondary and tertiary γ-piperidols are heated at 240-270°C with pyridine N-oxide.

Our method for the synthesis of pyridine bases from γ-piperidols is convenient for the preparation of pyridines with substituents in predesignated positions [1, 2]. However, it is less suitable for the preparation of compounds containing phenyl substituents in the 2 and 6 positions [3].

Sdaykov and co-workers [4] have shown that piperidine, N-benzoylpiperidine, the Hantzsch ester, and anabasine undergo dehydrogenation when they are heated at 200-230°C with pyridine N-oxide; the products are obtained in satisfactory yields.

In the present communication we describe the application of this method for the synthesis of 3-alkyl-2,6-diphenyl- and 3-alkyl-2,4,6-triphenylpyridines. We have established that piperidine derivatives undergo dehydration and N-dimethylation in addition to dehydrogenation on reaction with pyridine N-oxide. This made it possible to use N-methyl-substituted piperidines, piperideines, and secondary and tertiary γ-piperidols for the synthesis of pyridine bases.



III, XVII, XVIII, XXI—XXIV R=R″=H; I, XVI, XIX, XX R=CH_3; IV, VIII, XII, XVII, XXI, XXIV R′=CH_3; I, III, V, IX, XIII, XIX R′=C_2H_5; VI, X, XIV, XVI, XVIII, XX, XXII, XXIII, R′=p-C_3H_7; VII, XI, XV R′=i-C_3H_7; XII—XV R″=C_6H_5

The reaction was carried out at 240-270° in a stream of nitrogen at a pyridine N-oxide to piperidine (piperidol) molar ratio of 5:1.

EXPERIMENTAL

The IR spectra of chloroform solutions of the compounds were recorded with a Perkin—Elmer 325 spectrometer. The PMR spectra of deuterochloroform solutions were recorded with a Varian XL-100 spectrometer with tetramethylsilane as the internal standard. The individuality of the compounds was confirmed by thin-layer chromatography on a loose layer of neu-

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TABLE 1. 3-Alkyl-2,6-diphenyl-4-piperidols and 3-Alkyl-2,6-diphenyl- and 3-Alkyl-2,4,6-triphenylpyridines

Compound	mp, °C (from heptane)	bp, °C (mm)	Found, %			Empirical formula	calc., %			Yield, %	Picrate			
			C	H	N		C	H	N		mp, °C (from alcohol)	empirical formula	N, % found	N, % Calc.,
IX	107—109	—	88,0	7,9	4,3	$C_{26}H_{26}N$	88,4	7,6	4,0	60	199—200	$C_{26}H_{26}N \cdot C_6H_3N_3O_7$	10,0	9,6
XII	137—138	—	89,5	6,0	4,2	$C_{24}H_{19}N$	89,7	5,9	4,4	53/53[a]	189—190,5	$C_{24}H_{19}N \cdot C_6H_3N_3O_7$	10,5	10,2
XIII	99—100	—	89,4	6,0	4,2	$C_{25}H_{21}N$	89,6	6,3	4,2	48/62[a, b]	159—160	$C_{25}H_{21}N \cdot C_6H_3N_3O_7$	10,1	10,0
XIV	116—117	—	89,2	6,6	4,1	$C_{26}H_{29}N$	89,4	6,6	4,0	43/63[a]	—	—	—	—
XV	140—141	—	89,4	7,0	4,0	$C_{26}H_{29}N$	89,4	6,6	4,0	—/90[a]	—	—	—	—
XIX	—	212,5—215 (3)	81,5	8,4	4,5	$C_{20}H_{25}NO$	81,4	8,5	4,7	85	—	—	—	—
XX	—	275—280 (3)	81,9	8,5	4,4	$C_{21}H_{27}NO$	81,6	8,7	4,5	77	—	—	—	—
XXI	84—86	250—252 (3)	80,6	7,4	5,1	$C_{18}H_{21}NO$	80,9	7,8	5,2	67	—	—	—	—
XXII[c]	—	225—230 (3)	—	—	—	$C_{20}H_{25}NO$	—	—	—	95	241—243	$C_{20}H_{25}NO \cdot C_6H_3N_3O_7$	10,6	10,7
XXIII	—	275—280 (3)	88,1	7,2	5,1	$C_{20}H_{19}N$	87,9	7,0	5,1	50	160,5—161	$C_{20}H_{19}N \cdot C_6H_3N_3O_7$	11,0	11,1
XXIV	82—84	—	88,0	6,0	5,7	$C_{18}H_{15}N$	88,2	6,1	5,7	67	165—167	$C_{18}H_{15}N \cdot C_6H_3N_3O_7$	12,0	11,8

[a]The yield of pyridine from the corresponding piperidol is presented in the numerator, and the yield from the corresponding piperideine is presented in the denominator. [b]The yield of pyridine in the catalytic dehydrogenation and N-demethylation of piperideine IX was 9.4%. [c]The hydrochloride had mp 286-288° (from alcohol). Found: C 72.1; H 7.4; N 4.1%. $C_{20}H_{25}NO \cdot HCl$. Calculated: C 72.4; H 7.8; N 4.2%.

tral activity II (Brockmann scale) aluminum oxide in a heptane–ethyl acetate system (4:1) with development with iodine vapors.

1-Methyl-3-ethyl-2,6-diphenylpiperidine (II). A mixture of 23.44 g (0.08 mole) of piperidone I, 10 g (0.2 mole) of hydrazine hydrate, and 50 ml of absolute alcohol was heated at 130° for 3 h, after which 8.4 g of potassium hydroxide was added, and the mixture was heated for another 3 h. The alcohol was then removed by distillation, and the residue was extracted with ether. The extract was dried with magnesium sulfate, the ether was removed by distillation, and the residue (20.9 g) was crystallized from heptane to give 10.9 g (40%) of piperidine II with mp 179-182°. Found: C 85.7; H 9.3; N 5.3%. $C_{20}H_{25}N$. Calculated: C 86.0; H 9.0; N 5.0%.

3-Ethyl-2,6-diphenylpyridine (III). A mixture of 8.85 g (0.03 mole) of piperidine II and 14.25 g (0.15 mole) of pyridine N-oxide was heated at 265-270° for 40 min, during which the volatile products were removed by distillation. The residue was dissolved in chloroform, and the chloroform solution was washed with water and dried with magnesium sulfate. The chloroform was removed by distillation, and the residue was extracted with hot heptane. The heptane extract was passed through a layer of aluminum oxide, after which the heptane was removed by distillation to give 5.18 g (66%) of pyridine III with mp 60-62° (from heptane). Found: C 87.7; H 6.6; N 5.4%. $C_{19}H_{17}N$. Calculated: C 88.0; H 6.6; N 5.4%. The picrate had mp 155-157° (from alcohol). Found: N 11.1%. $C_{19}H_{17}N \cdot C_6H_3N_3O_7$. Calculated: N 11.5%.

3-Alkyl-2,4,6-triphenylpyridines (XII-XV). Of the tertiary piperidols used (IV-VII), alcohol V has not been previously described. It was obtained in 79% yield from piperidone I and phenyllithium and had bp 270-280° (3 mm). The hydrochloride had mp 237.5-239° (from alcohol–acetone). Found: C 75.5; H 7.7; N 3.2%. $C_{26}H_{29}NO \cdot HCl$. Calculated: C 75.2; H 7.4; N 3.4%. The picrate had mp 232.234° (from acetone). Found: N 9.2%. $C_{26}H_{29}NO \cdot C_6H_3N_3O_7$. Calculated: N 9.3%. Piperideines VIII-XI were obtained from piperidols IV-VII as described in [5]. The characteristics of the previously undescribed piperideine IX are presented in Table 1. Pyridine bases XII-XV were obtained from piperideines VIII-XI, piperidols, IV-VII, and pyridine N-oxide (at 240-270°) by the method described for the preparation of pyridine III. Their characteristics, which are presented in Table 1, were identical to those previously described [3].

3-Alkyl-2,6-diphenylpyridines (XXIII, XXIV). Secondary piperidols XIX-XXII were obtained by reduction of, respectively, I and XVI, XVIII with sodium in butyl alcohol. The characteristics of alcohols XIX-XXII are presented in Table 1. Pyridine bases III, XXIII, and XXIV were obtained by heating these piperidols with pyridine N-oxide at 250-270°. The characteristics of the last two bases are presented in Table 1.

2,5-Dimethyl-4-phenylpyridine [6] was similarly obtained from 1,2,5-trimethyl-4-phenyl-4-piperidol.

1,3-Dimethyl-2,4,6-triphenyl-5-piperidol (XXV) and Its Conversion to 3-Methyl-2,4,6-triphenylpyridine (XII). A solution of 4.5 g (0.013 mole) of piperideine VIII in 15 ml of absolute diglyme was added in a stream of dry nitrogen to a solution of 0.84 g (0.022 mole) of sodium borohydride in 10 ml of absolute diglyme, after which a solution of 4.2 g (0.03 mole) of boron trifluoride etherate in 9 ml of absolute diglyme was added with vigorous stirring in the course of 35 min, and the mixture was stirred at 20° for 1 h and at 160° for 25 min. It was then cooled, and 1.5 ml of water, 7 ml of concentrated hydrochloric acid, and 13 ml of 40% sodium hydroxide solution were added successively, after which 11 ml of 30% Perhydrol was added in the course of 10 min. The mixture was stirred for 3 h, and the reaction products were extracted with chloroform. The extract was treated with an ether solution of hydrogen chloride until it was acidic (with respect to Congo red), after which it was evaporated to dryness. The residue was made alkaline with 40% sodium hydroxide solution and extracted with chloroform. The chloroform extract was dried with potassium carbonate, the chloroform was removed by distillation, and the residue was chromatographed with a column filled with aluminum oxide by successive elution with heptane and ethyl acetate–heptane (10:1) to give 1.4 g (30%) of piperidol XXV with mp 207-209° (from heptane). Found: C 83.7; H 7.8; H 3.8%. $C_{25}H_{27}NO$. Calculated: C 84.0; H 7.6; N 3.9%. IR spectrum: 3555 (free OH), 3450 (associated OH), 2780 (N-CH_3), and 952 cm^{-1} (δ_{OH}). PMR spectrum: 0.48 (d, CH_3), 1.78 (s, N-CH_3), 1.32 (s, OH), 2-2.3 (m, 3-H), 2.52 (t, 4-H), 2.94 (d, 2-H, $J_{2,3}$ = 9 Hz), 3.15 (d, 6-H, $J_{6,5}$ = 9 Hz), and 3.90 ppm (t, 5-H).

A mixture of 0.8 g (0.224 mmole) of piperidol XXV and 1.06 g (1.12 mmole) of pyridine N-oxide was heated in a Claisen flask at 245-250° for 15 min, during which the volatile re-

action products were removed by distillation. The mixture was then worked up as in the preparation of pyridine III to give 0.12 g (17%) of pyridine XII with mp 136-137°. No melting-point depression was observed for a mixture of a sample of this product with an authentic sample.

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UTILIZATION OF IR SPECTROSCOPY FOR THE STUDY OF THE MECHANISM OF THE CYCLIZATION OF β-(2-CARBOXYARYLAMINO)PROPIONIC ACIDS

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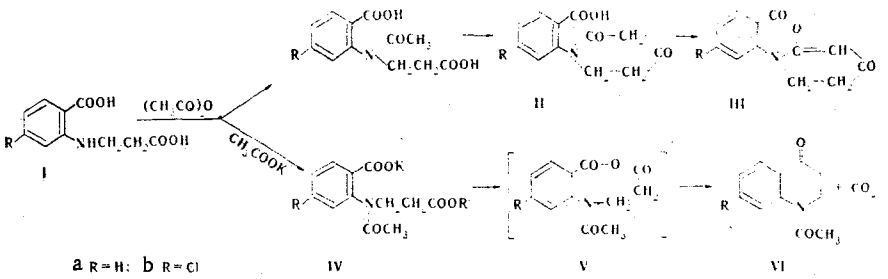
It was established by IR spectroscopy that the cyclization of β-(2-carboxylaryl-amino)propionic acids to 2,3-dihydroquinoline-4(1H)-ones in acetic anhydride in the presence of an alkali metal acetate proceeds through an intermediate step involving the formation of an eight-membered cyclic anhydride. In the case of β-(2-carboxy-5-chlorophenylamino)propionic acid the presence of an intermediate in the reaction mixture was established by the IR spectra of samples of the mixtures selected at various temperatures and was illustrated by the IR spectrum obtained by differential spectroscopy.

It has been previously shown [1, 2] that the cyclization of β-(2-carboxyarylamino)-propionic acids (I) in acetic anhydride may proceed in two directions, depending on the presence or absence of an alkali metal acetate in the reaction medium:



a R=H; b R=Cl

It has been established that in the presence of potassium acetate a reaction with splitting out of carbon dioxide leads to N-acetyl-2,3-dihydroquinolin-4(1H)-one (VI), and the acetyl derivative (IV) of the monopotassium salt of the starting acid was isolated as an intermediate. It was later assumed that the latter is converted to a cyclic anhydride (V), which undergoes decomposition to give carbon dioxide and a quinoline (VI).

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