2,5-DIMETHYL-4-(p-ALKYLBENZYL)PYRIDINES

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1,2,5-Trimethyl-4[p-methyl(ethyl, isopropyl) benzyl]-4-piperidole were obtained and converted to the similarly substituted pyridine bases.

We used 2,5-dimethyl-4-aryl(arylkyl)pyridines, which are comparatively readily obtained from γ-piperidones, to synthesize condensed, nitrogen-containing polycyclic system of the azafluorene and benzoisoquinoline type. The latter type, in particular, includes 3-methyl-6,7-benzoisoquinoline, which is obtained by the dehydrocyclization of 2,5-dimethyl-4-benzylpyridine [1,2].

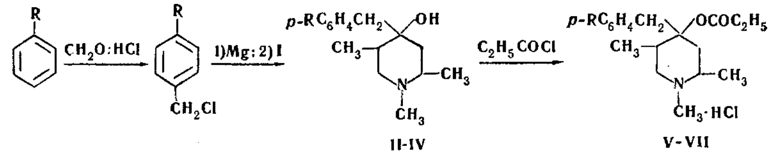
To extend the possibilities with respect to the synthesis of substituted benzoquinolines we had recourse to the preparation of analogous pyridines containing alkyl groups (methyl, ethyl, and isopropyl) in the para position of the aromatic ring.

First of all, we synthesized new tertiary γ-piperidols, viz., 1,2,5-trimethyl-{p-methyl (II) [ethyl (III), isopropyl (IV)]benzyl}-4-piperidols. These alcohols were obtained by the reaction of 1,2,5-trimethyl-4-piperidone (I) with the appropriate alkyl substituted benzylmagnesium chlorides. The starting alkyl-substituted benzyl chlorides were obtained by chloromethylation of toluene, ethylbenzene, and cumene, respectively.

It is well known that the chloromethylation of these hydrocarbon does not proceed unambiguously. It has been shown [3] that in all cases a practically inseparable mixture of o- and p-alkylbenzyl chlorides is formed and that the amount of the ortho isomer increases on passing from cumene to ethylbenzene and toluene (15%, 30%, and 55%). Thus a mixture of isomeric alkylbenzyl chlorides was used in the syntheses of piperidols II, III, and IV. However, only one pure piperidol was isolated in all cases. Considering the predominating amount of the p-alkylbenzyl chloride as well as steric factors which to a certain degree will hinder the reaction of piperidone I with the o-alkylbenzylmagnesium chloride, it could be assumed that the alkyl group in the piperidols obtained is situated in the para position of the aromatic ring. The spectral data confirmed this assumption. The IR spectra of piperidols II, III, and IV contained two bands in the region of the out-of-plane vibrations of the C–H group of the aromatic bonds: 818 and 853 cm^{-1} (II), 828 and 850 cm^{-1} (III), 830 and 855 cm^{-1} (IV); these were due to the vicinal C–H aromatic bonds [4].

The oxidation of piperidols II, III, and IV with chromic anhydride is chemical evidence for the indicated assumption. The terephthalic acid formed in the process was identified as the dimethyl terephthalate.

The propyl esters in the form of hydrochlorides were obtained by the usual route from piperidols II, III, and IV: the hydrochlorides of 1,2,5-trimethyl-4-{p-methyl (V) [ethyl (VI), isopropyl (VII)]benzyl}-4-propionyloxypiperidines.



II,V $R=CH_3$; III,VI $R=C_2H_5$; IV,VII $R=CH(CH_3)_2$

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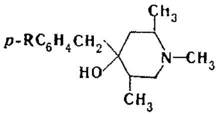
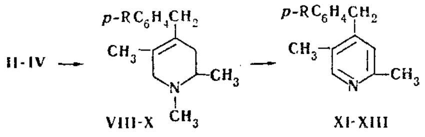
TABLE 1



Compound	R	Mp (from petroleum ether)	Empirical formula	Found, %			Calc., %			Yield, % (based on converted I)	Picrate,* mp (from alcohol)
				C	H	N	C	H	N		
II	CH_3	101—101,5	$C_{16}H_{25}NO$	77,4	10,6	5,5	77,7	10,1	5,7	40	166—167
III	C_2H_5	92—93	$C_{17}H_{27}NO$	78,3	10,5	5,7	78,2	10,3	5,4	42	139—140
IV	$(CH_3)_2CH$	102,5—103	$C_{18}H_{29}NO$	77,7	10,5	4,8	78,5	10,5	5,1	62	152—153

*The composition of the picrates was confirmed by analysis for nitrogen.

The piperidols were subsequently dehydrated with concentrated hydrochloric acid. The 1,2,5-trimethyl-4-{p-methyl (VIII) [ethyl (IX), isopropyl (X)]benzyl}piperidines were isolated in the form of analytically pure substances. However, thin-layer chromatography [activity II aluminum oxide, ether–petroleum ether (1:1)] indicated that they are a mixture of piperideines with the double bond located at different positions; piperideines: VIII R_f 0.36 and 0.48; IX R_f 0.35 and 0.49; X R_f 0.37 and 0.47. The formation of isomeric piperideines was established during a study of the dehydration of 3-methyl-4-aryl-4-piperidols [5]. The position of the double bond in the formula of the piperideines is arbitrarily indicated in the reaction scheme.



VIII, XI $R = CH_3$; IX, XII $R = C_2H_5$; X, XIII $R = CH(CH_3)_2$

The piperideines were catalytically dehydrated and N-demethylated. Of the 2,5-dimethyl-4-{p-methyl (XI) [ethyl (XII), isopropyrl (XIII)]benzyl}pyridines obtained, only XI was isolated in the crystalline state; XII and XIII are liquids. Their perchlorates were convenient for the isolation and identification of these pyridine bases.

EXPERIMENTAL

1,2,5-Trimethyl-4-(p-alkylbenzyl)-4-piperidols (II-IV). Magnesium, a mixture of o- and p-alkylbenzyl chlorides, and piperidone I in equimolecular amounts were used to obtain piperidols II-IV [6]. The characteristics of the compounds obtained are presented in Table 1.

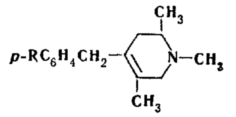
1,2,5-Trimethyl-4-(p-alkylbenzyl)-4-propionyloxypiperidine Hydrochlorides (V-VII). A. A mixture of 2.35 g (9.5 mmole) of piperidol II, 2.35 g (25.4 mmole) of propionyl chloride, and 40 ml of anhydrous benzene was refluxed for 20 h. Recrystallization of the precipitate formed yielded 1.90 g (59%) of hydrochloride V with mp 185-186 deg (from acetone). Found %: N 3.9; Cl 10.3. $C_{19}H_{29}NO_2 \cdot HCl$. Calc. %: N 4.1; Cl 10.5.

B. Hydrochloride VI [2.08 g (51%)] with mp 194-194.5 deg (from acetone) was similarly obtained from 3.0 g (11.5 mmole) of piperidol of III and 3.0 g (32.4 mmole) of propionyl chloride. Found %: N 3.9; Cl 10.1. $C_{20}H_{31}NO_2 \cdot HCl$. Calc. %: N 4.0; Cl 10.0.

C. Hydrochloride VII [2.59 g (97%)] with mp 212-212.5 deg (from acetone) was similarly obtained from 2.0 g (7.3 mmole) of piperidol IV and 1.36 g (14.6 mmole) of propionyl chloride. Found %: N 3.8; Cl 9.8. $C_{21}H_{33}NO_2 \cdot HCl$. Calc. %: N 3.8; Cl 9.7.

Oxidation of 1,2,5-Trimethyl-4-(p-alkylbenzyl)-4-piperidols. Concentrated sulfuric acid (25 ml) was gradually added with cooling to a solution of 4.4 g (0.0178 mole) of piperidol II and 20 g (0.50 mole) of

TABLE 2



Compound	R*	Bp, °C (press., mm)	n_D^{20}	d_4^{20}	MR_D	
					Found	Calc.
VIII	CH_3	115—117 (0,5)	1,5351	0,9616	74,17	73,77
IX	C_2H_5	121—124 (0,5)	1,5310	0,9609	78,24	78,32
X	$CH(CH_3)_2$	112—115 (0,4)	1,5286	0,9482	83,54	82,98

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* The composition of the picrates was confirmed by analysis for nitrogen.

chromic anhydride in 50 ml of acetic acid. The mixture was refluxed for 3 h. The resulting precipitate (1.43 g) was dried and heated for 13 h with 150 ml of methanol and 15 ml of concentrated sulfuric acid. The methanol was removed by distillation, and 70 ml of water was added to the residue. The reaction products were extracted with ether to give 1.26 g (36.5%) of dimethyl terephthalate with mp 140-141 deg (from ether).

Piperidols III and IV were similarly oxidized.

1,2,5-Trimethyl-4-(p-alkylbenzyl)piperideines (VIII-X). Piperidols II, III, and IV were dehydrated with concentrated hydrochloric acid as described in [1]. The characteristics of the compounds obtained are presented in Table 2.

2,5-Dimethyl-4-(p-methylbenzylpyridine (XI). Piperideine VIII was dehydrated and N-demethylated in a quartz tube with a K-16 catalyst (25 g) at 410-430 deg. The catalyst was activated in a gentle air stream at 520 deg for 2 h.

A solution of 8.6 g (37.5 mmole) of piperideine VIII in 40 ml of benzene was passed through the tube at a constant rate in the course of 4 h. A total of 1920 ml of gas (20 deg, 724 mm) was collected. After drying with potassium hydroxide, the condensate yielded a fraction (4.34 g) with bp 160-166 deg (4 mm) and n_D^{20} 1.5630. According to thin layer chromatography [KSK silica gel, methanol–ether (1:10)] the fraction contained a trace of the starting piperideine (R_f 0.18 and 0.35) in addition to pyridine XI (R_f 0.75). This fraction (1.99 g) was treated with 5 ml of alcohol and 10 ml of 30% perchloric acid to give 1.8 g (61%) of the perchlorate of XI in the form of colorless crystals with mp 209-210 deg (from acetone). Found %: N 4.3; Cl 11.5. $C_{15}H_{17}N \cdot HClO_4$. Calc. %: N 4.5; Cl 11.4. Treatment for the perchlorate with saturated aqueous sodium carbonate yielded 1.54 g (93.5%) of XI with mp 110-116 deg (0.5 mm) and mp 46-47 deg. Found %: C 85.4; H 8.0; N 6.4. $C_{15}H_{17}N$. Calc. %: C 85.3; H 8.1; N 6.6. The picrate of XI had mp 131-131.5 deg (from alcohol). Found %: N 12.6. $C_{15}H_{17}N \cdot C_6H_3N_3O_7$. Calc. %: N 12.7. The hydrochloride of XI had mp 163-165 deg (from acetone). Found %: N 5.7; Cl 14.4. $C_{15}H_{17}N \cdot HCl$. Calc. %: N 5.7: Cl 14.3.

2,5-Dimethyl-4-(p-ethylbenzyl)pyridine (XII). Compound IX was dehydrated and N-demethylated on the same catalyst under the same conditions. A total of 1330 ml of gas (20 deg, 724 mm) and a fraction (4.1 g) with bp 125-131 deg (0.5 mm) and n_D^{20} 1.5595 was obtained from 6.26 g (25.8 mmole) of IX (60 ml of benzene, 3 h). This fraction (3.7 g) yielded 2.7 g (50.7%) of the perchlorate of XII with mp 169-171 deg (from acetone). Found %: N 4.1; Cl 11.0. $C_{16}N_{19}N \cdot HClO_4$. Calc. %: N 4.3; Cl 10.9. The perchlorate was used to obtain 1.45 g (77.5%) of XII with bp 120-127 deg (0.5 mm), n_D^{20} 1.0093. Found %: C 85.0; H 8.2; N 6.0; MR_D 72.52. $C_{16}H_{19}N$. Calc. %: C 85.3; H 8.4; N 6.0; MR_D 72.80. The picrate of XII had mp 118-119.5 deg (from alcohol). On the basis of the analytical data obtained after several recrystallizations and thorough drying of the sample, it can be assumed that this picrate contains one molecule of alcohol of crystallization. Found %: N 11.2. $C_{16}H_{19}N \cdot C_6H_3N_3O_7 \cdot C_2H_5OH$. Calc. %: N 11.2. The hydrochloride of XII had mp 151-152 deg (from acetone). Found %: N 5.0; Cl 13.8. $C_{16}H_{19}N \cdot HCl$. Calc. %: N 5.4; Cl 13.5.

Empirical formula	Found, %			Calc., %			Yield, %	Picrate,* mp (from alcohol)
	C	H	N	C	H	N		
$C_{16}H_{23}N$	84,0	10,2	6,1	83,8	10,0	6,1	74	138—139
$C_{17}H_{25}N$	84,3	10,5	5,5	83,9	10,3	5,8	67	105—106
$C_{18}H_{27}N$	83,7	10,5	5,5	84,0	10,5	5,4	63	114—114,5

2,5-Dimethyl-4-(p-isopropylbenzyl)pyridine (XIII). The reaction was run with 6.98 g (27.1 mmole) of piperideine X and 60 ml of benzene. A total of 1350 ml of gas (20 deg, 724 mm) and a fraction (4.6 g) with bp 128-136 deg (0.5 mm) and n_D^{20} 1.5543 were obtained. Thin-layer chromatography [KSK silica gel, ethanol–ether (1:10)] gave R_f values of 0.62, 0.19 and 0.12. The last two R_f values refer to starting piperideine X. This fraction (4.6 g) was used to obtain 4.7 g (71.6%) of the perchlorate of XIII with mp 166-167 deg (from acetone). Found %: N 4.0; Cl 10.4. $C_{17}H_{21}N \cdot HClO_4$. Calc. %: N 4.1; Cl 10.5. The perchlorate was used to obtain 2.21 g (67.0%) of XIII with bp 130-136 deg (0.5 mm), n_D^{20} 1.5600, and d_4^{20} 1.0012. Found %: C 85.5; H 9.0; N 5.9; MR_D 77.19. Calc. %: C 85.3; H 8.8; N 5.9; MR_D 77.4. The picrate of XIII had mp 142-143.5 deg (from acetone). Found %: N 11.6. $C_{17}H_{21}N \cdot C_6H_3N_3O_7$. Calc. %: N 11.9. The hydrochloride of XIII had mp 155.5-156 deg (from acetone). Found %: N 4.9; Cl 13.2. $C_{17}H_{21}N \cdot HCl$. Calc. %: N 5.0; Cl 12.9.

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