SYNTHESIS OF 3-ALKYL-2,4,6-TRIPHENYLPYRIDINES AND 1,3-DIPHENYL-4- AND -2-AZAFLUORENES

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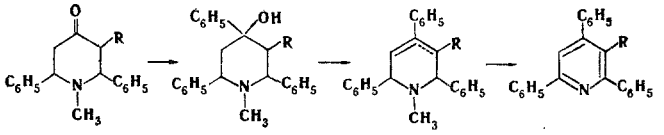
The previously unknown 3-alkyl-2,4,6-triphenylpyridines were obtained from 1-methyl-3-alkyl-2,6-diphenyl-4-piperidones. It was established that a mixture of 1,3-diphenyl-4-azafluorene and 1,3-diphenyl-2-azafluorene is formed in the dehydrocyclization of 3-methyl-2,4,6-triphenylpyridine.

The catalytic dehydrocyclization of 2,5-dimethyl-4-arylpyridines and 2,5-dimethyl-4-arylmethylpyridines is a convenient method for the synthesis of the difficult-to-obtain and as yet little-investigated heterocyclic compounds of the 2-azafluorene [1] and benzo[g]isoquinoline [2] types.

For the study of this reaction it seemed of interest to subject 3-alkyl-2,4,6-triphenylpyridine to dehydrocyclization. In this case dehydrocyclization may proceed both at the phenyl group attached to C_2 and at the phenyl group attached to C_1. In the first case a substituted 4-azafluorene should be formed, whereas in the second case a similarly substituted 2- azafluorene should be formed. The 3-alkyl-2,4,6-triphenylpyridines were obtained by the method described in [3].



I-III IV-VI VII-IX X-XII

I, IV, VII, X R=CH_3; II, V, VIII, XI R=C_3H_7-n; III, VI, IX, XII R=$CH(CH_3)_2$

The reaction of phenyllithium with 1,3-dimethyl- (I), 1-methyl-3-propyl- (II), and 1-methyl-3-isopropyl-2,6-diphenyl-4-piperidone (III) gave, respectively, 1,3-dimethyl- (IV), 1-methyl-3-propyl- (V), and 1-methyl-3-isopropyl-2,4,6-triphenyl-4-piperidol (VI). Each of these piperidols was isolated in the form of one diastereoisomer. Only one isomer was also detected by thin-layer chromatography (TLC) of the reaction products.

The magnitude of the spin–spin coupling constants of the protons attached to C_2 and C_3 and C_5 and C_6 ($J_{2,3}$ and $J_{5,6}$) in the PMR spectra of piperidones I-III and piperidols IV-VI (Table 1) shows that the phenyl groups attached to C_2 and C_6 and the alkyl group attached to C_3 are equatorially oriented. The stereochemistry of addition of organolithium compounds to cyclic ketones containing a substituent in the α position relative to the keto group [4, 5] makes it possible to assume that the phenyl group attached to C_4 in the case of piperidols IV-VI is oriented equatorially, whereas the OH group is axially oriented. The nonequivalence of the methyl groups of the isopropyl group of alcohol VI (the presence in the PMR spectrum of two doublets at 0.70 and 0.14 ppm of three proton units each) indicates the hindered character of rotation of this group.

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TABLE 1. Data from the PMR Spectra of 1-Methyl-3-alkyl-2,6-diphenyl-4-piperidones and 1-Methyl-3-alkyl-2,4,6-triphenyl-4-piperidols

Compound	Chemical shift, δ, ppm multiplicity									Spin–spin coupling constant, Hz				
	ring protons				substituent protons									
	H-2	H-6	H-5a	H-5e	N-CH_3	Ph	CH_3—	CH_2—	CH—	$J_{2,3}$	$J_{5a,6}$	$J_{5e,6}$	$J_{5a,5e}$	J_{3,CH_3}
I	2.90 d	3.33 q	2,77 m	2,40 m	1.67 s	7,28 m	0,65 d	—	—	11,2	12.0	4.2	13,0	6.0
II	3.02 d	3,40 q	2,79 m	2.42 m	1,64 s	7,3 m	0.68 m	0.95–1,60 m	—	11,5	11.5	4.0	13.0	--
III	3.23 d	3,33 q	2,71 m	2,40 m	1.67 s	7,28 m	0,90 d 0,87 d	—	—	11.2	11.2	4.4	13.6	—
IV	3,23 d	3.62 q	1,90–2.40 m		1.72 s	6,88–7,55 m	0,32 d	—	—	10,5	11.0	4.5	*	7.0
V	3,28 d	3,63 q	1.67–2.50 m		1.75 s	6,95–7.70 m		—	—	10.5	12.0	4.5	*	—
VI	3,59 d	3.60 q	1,25–2.50 m		1,66 s	6,97–7,67 m	0,70 d; 0,14 d	—	1.25–2,5 m	11,0	~12.0	*	*	—

*It was not possible to determine the spin–spin coupling constants because of overlapping of the signals.

Piperidols IV-VI were dehydrated by means of phosphorus tribromide in refluxing benzene and subsequent treatment of the reaction mixture with ammonium hydroxide. This procedure was used to obtain 1,3-dimethyl-(VII), 1-methyl-3-propyl-(VIII)-, and 1-methyl-3-isopropyl-2,4,6-triphenylpiperideine (IX). Piperideine VII is formed as a single Δ^4 isomer, as confirmed by the presence in its PMR spectrum of one signal of an N–CH_3 group at δ 1.72 ppm (3-H) and a broad signal of an olefin proton attached to C_5 with δ 5.50 ppm (1H). However, piperideines VIII and IX are mixtures of Δ^3 and Δ^4 isomers. This is proved by the fact that the PMR spectra of VIII and IX contain two singlets of an N–CH_3 group at 1.73 and 1.84 and 1.73 and 1.88 ppm, respectively. The assignment of these signals was confirmed by their splitting on protonation (CF_3COOH) and conversion to a singlet upon subsequent deuterium exchange. The signal of the olefin proton in the spectra of VIII and IX is found at 5.63 ppm. The signal at 1.73 ppm is due to the N–CH_3 group of the Δ^4 isomer, as follows from the ratio of the integral intensities of this signal and the signal of the olefin proton (3 : 1). The ratio of the Δ^3 and Δ^4 isomers, determined from the integral intensities of the signals of the N–CH_3 groups, is ~ 1 : 2 in the case of IX.

The dehydrogenation and N-demethylation of piperideines VII-IX were accomplished with a K-16 catalyst at 350-420°. 3-Methyl (XII) were obtained in 30, 29, and 1% yields, respectively. The dehydrogenation and N-demethylation of piperideines VII-IX give considerably lower yields than the analogous transformations of piperideines that do not contain phenyl substituents attached to the C_2 and C_6 atoms of the piperidine ring. In all cases we established the formation of up to 60% of substances that do not contain a basic nitrogen atom and are apparently products of deamination and hydrogenolysis of the starting piperideines at the C_6–N or C_2–N bonds. It was established experimentally that the nitrogen atom is split out as ammonia during deamination. However, the catalytic hydrogenolysis of benzylamines, which are analogs of the piperideines under investigation, is the usual method of debenzylation. In the case of the catalytic transformations of piperideines VIII and IX, one observes partial cleavage of the alkyl group and the phenyl group attached to C_2. 2,4,6-Triphenylpyridine (XIII) and 5-isopropyl-2,4-diphenylpyridine (XIV) were isolated from the reaction products. The location of the phenyl groups at C_2 and C_4 in XIV follows unambiguously from the presence in the PMR spectrum of singlets of the α and β protons of the pyridine ring at 9.03 and 7.50 ppm, respectively.

Pyridine base X was subjected to dehydrocyclization on the same K-16 catalyst at 550-560°. In this case we isolated 1,3-diphenyl-4-azafluorene (XV) (with mp 157.5-158° in 27% yield) and 1,3-diphenyl-2-azafluorene (XVI) (with mp 143.5-144.5° in 9.5% yield). In order to confirm structures XV and XVI we carried out the alternative synthesis of XVI. It was obtained by dehydrocyclization of 2.6-diphenyl-4-(o-tolyl)pyridine (XVII) under the same conditions as in the cyclization of X.

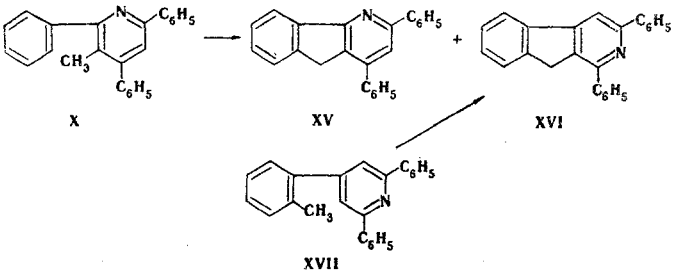
TABLE 2. 1-Methyl-3-alkyl-2,6-diphenyl-4-piperidones, 4-Piperidols, and Piperideines

Compound	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %	Picrate			
			C	H	N	C	H	N		mp, °C	empirical formula	N, % found	N, % calc.
I	130—130,5	$C_{19}H_{21}NO$	82,0	7,8	4,9	81,7	7,6	5,0	46,4	159—161	$C_{19}H_{21}NO \cdot C_6H_3N_3O_7$	11,0	11,0
II	83,5—84,5	$C_{21}H_{25}NO$	82,3	8,5	4,4	82,1	8,2	4,6	59,8	183,5—184	$C_{21}H_{25}NO \cdot C_6H_3N_3O_7$	10,2	10,5
III	108—109	$C_{21}H_{25}NO$	82,3	8,4	4,9	82,1	8,2	4,6	64,0	206—207	$C_{21}H_{25}NO \cdot C_6H_3N_3O_7$	10,4	10,5
IV	151—151,5	$C_{25}H_{27}NO$	84,0	7,4	3,8	84,0	7,6	3,9	94,4	257—257,5	$C_{25}H_{27}NO \cdot C_6H_3N_3O_7$	9,7	9,6
V*	—	—	—	—	—	—	—	—	94,7	240—241	$C_{27}H_{31}NO \cdot C_6H_3N_3O_7$	9,5	9,1
VI	144,5—145	$C_{27}H_{31}NO$	84,0	8,3	3,5	84,1	8,1	3,6	79	248—249	$C_{27}H_{31}NO \cdot C_6H_3N_3O_7$	9,0	9,3
VII	121—122	$C_{25}H_{25}N$	88,6	7,8	4,0	88,5	7,4	4,1	62	190—192	$C_{25}H_{25}N \cdot C_6H_3N_3O_7$	10,1	9,9
VIII†	—	—	—	—	—	—	—	—	78	209,5—211	$C_{27}H_{29}N \cdot C_6H_3N_3O_7$	9,1	9,4
IX	74—75	$C_{27}H_{29}N$	88,3	7,8	3,6	88,5	7,7	3,8	75	185—186,5	$C_{27}H_{29}N \cdot C_6H_3N_3O_7$	9,2	9,4
XVII	116—117	$C_{24}H_{19}N$	89,9	6,1	4,5	89,7	5,9	4,4	10,2	175—176	$C_{24}H_{19}N \cdot C_6H_3N_3O_7$	10,2	10,2
XIX	158—158,5	$C_{25}H_{27}NO$	83,7	7,9	4,0	84,0	7,6	3,9	95	188—189	$C_{25}H_{27}NO \cdot C_6H_3N_3O_7$	9,4	9,6
XX‡	—	$C_{25}H_{25}$	—	—	—	—	—	—	75	161,5—163	$C_{25}H_{25}N \cdot C_6H_3N_3O_7$	9,6	9,9

*This compound had bp 234-235° (2 mm). The hydrochloride had mp 164-166° (from alcohol). Found: C 76.5; H 7.8; N 3.2%. $C_{27}H_{31}ON \cdot HCl$. Calculated: C 76.9; H 7.6; N 3.3%.

† This compound had bp 219-221° (2 mm). The hydrochloride had mp 233-234° (from alcohol). Found: C 80.3; H 7.3; N 3.6%. $C_{27}H_{29}N \cdot HCl$. Calculated: C 80.3; H 7.2; N 3.5%.

‡This compound had bp 219-220° (1.5 mm). The hydrochloride had mp 220-221° (from acetone). Found: C 80.0; H 7.1; N 3.4%. $C_{25}H_{25}N \cdot HCl$. Calculated: C 79.9; H 7.0; N 3.7%.



X XV XVI

XVII

The position of the nitrogen atom in the pyridine ring of azafluorenes XV and XVI is also in agreement with the PMR spectra. The signal of the β proton (relative to the nitrogen atom) in the spectrum of XVI is found at 7.77 ppm, as compared with 7.42 ppm in the spectrum of XV. The weak-field shift of the signal of the β proton in XVI is associated with steric interaction of the H-4 and H-5 protons [6]. 1,3-Diphenyl-4-aza-9-fluorenone (XVIII) was obtained by oxidation of azafluorene XV with potassium permanganate in acetone at 20°; this is confirmed by the presence in the IR spectrum of the product of a carbonyl band at 1714 cm^{-1}. Pyridine base XVII was obtained via the scheme presented above from 1-methyl-2,6-diphenyl-4-piperidone with isolation of the intermediates – 1-methyl-2,6-diphenyl-4-(o-tolyl)-4-piperidol (XIX) and 1-methyl-2,6-diphenyl-4-(o-tolyl)piprideine (XX).

EXPERIMENTAL METHOD

Chromatography was carried out on a loose layer of activity II aluminum oxide in ethyl acetate hexane (1 : 4). The PMR spectra of carbon tetrachloride solutions of the compounds were recorded with a D-60 spectrometer with hexamethyldisiloxane as the internal standard.

1-Methyl-3-alkyl-2,6-diphenyl-4-piperidones (I-III). Piperidones I-III were obtained by the method in [7] from benzaldehyde and methylamine (solution in glacial acetic acid) and, respectively, methyl ethyl ketone, methyl butyl ketone, and methyl isobutyl ketone at a benzaldehyde–ketone–methylamine molar ratio of 1.5 : 1 : 1. The characteristics of piperidones I-III are presented in Table 2.

1-Methyl-3-alkyl-2,4,6-triphenyl-4-piperidols (IV-VI). A 0.3-mole sample of the appropriate piperidone was added in the course of 1.5 h to a cooled (to 0°) solution of phenyllithium, obtained from 14 g (2.2 g-atom) of lithium and 1.57 g (1 mole) of bromobenzene in 500 ml of absolute ether, after which the mixture was heated for 30 min, cooled, and decomposed with water. The ether layer was separated, and hydrogen chloride was passed through it. The resulting precipitate of the hydrochloride was washed repeatedly with ether, after which it was decomposed with 25% ammonium hydroxide. The organic bases were extracted with ether, and the extract was dried with magnesium sulfate. The residue obtained after removal of the ether by distillation was crystallized from heptane in the case of piperidols IV and VI, whereas it was vacuum fractionated in the case of V. The characteristics of piperidols IV-VI are presented in Table 2.

1-Methyl-1-3-alkyl-2,4,6-triphenylpiperideines (VII-IX). Piperidols V and VI were dehydrated by means of phosphorus tribromide as described in [8]. The characteristics of the products are presented in Table 2.

3-Methyl-2,4,6-triphenylpyridine (X). The dehydrogenation and N-demethylation were carried out in a flow system on a K-16 catalysts (25 g); the temperature in the contact zone was 400-410°.

A solution of 20 g (0.05 mole) of piperideine VII in 100 ml of benzene was passed through a contact tube at a constant rate in the course of 5 h. A total of 3.3 liters of gas (21°, 755 mm) was collected. The catalyzate was dried with sodium hydroxide, the benzene was removed by distillation, and the residue (17 g) was dissolved in ether. A stream of hydrogen chloride was passed through the ether solution, and the precipitated hydrochloride was triturated repeatedly with ether, after which it was decomposed with 25% ammonium hydroxide. The organic bases were extracted with ether, and the extracts were dried with magnesium sulfate. The residue (9 g) from the ether extract was crystallized from hexane to give 6.1 g (30%) of X with mp 136-137° and R_f 0.77. Found: C 89.4; H 6.2; N 4.1%. $C_{24}H_{19}N$. Calculated: C 89.7; H 5.9; N 4.4%. The picrate of X had mp 183-184° (from acetone). Found: N 10.3%. $C_{24}H_{19}N \cdot C_6H_3N_3O_7$. Calculated: N 10.2%.

Workup of the ether solution remaining after isolation of the hydrochloride gave 8.5 g of substances that did not contain a basic nitrogen atom.

3-Propyl-2,4,6-triphenylpyridine (XI). A solution of 29 g (0.08 mole of a mixture of isomers of piperideine VIII in 100 ml of benzene was passed through a contact tube (405-410°) for 5 h. The evolved gas was passed through a Tishchenko bottle filled with distilled water. A total of 3.8 liters of gas (21°, 759 mm; H 47.3%, CH_4 41.7%, C_2H_6 1.5%, C_2H_4 1.0%, and C_3H_8 8.52%) was collected. The residue (24.7 g) isolated from the catalyzate was worked up as in the preparation of X to give 7.6 g (29%) of XI with mp 116.5-117.5° (from heptane) and R_f 0.78. Found: C 89.4; H 6.8; N 3.8%. $C_{26}H_{23}N$. Calculated: C 89.4; H 6.6; N 4.0%. The picrate of XI had mp 160.5-161-5° (from alcohol–acetone). Found: N 9.9%. $C_{26}H_{23}N \cdot C_6H_3N_3O_7$. Calculated: N 9.7%. A total of 13 g of substances that did not contain a basic nitrogen atom was isolated. A total of 0.19 g of ammonia identified as ammonium chloride) was absorbed in the Tishchenko bottle.

3-Isopropyl-2,4,6-triphenylpyridine (XII). A solution of 27.6 g of a mixture of isomeric piperideines IX in 100 ml of benzene was passed through a contact tube (380-400°) for 5 h. A total of 3.2 liters of gas (26°, 756 mm; 49% CH_4, 32.2% H_2, and 18.8% C_3H_8) was collected. The catalyzate was worked up as in preparation of X to give 9.86 g of organic bases. A solution of the bases in heptane was passed through a column filled with activity II aluminum oxide with elution by heptane to give 1.12 g (5%) of colorless crystals of XIII with mp 137-138° [9] (from heptane) and R_f 0.77, Found: C 89.7; H 5.6; N 4.3%. $C_{23}H_{17}N$. Calculated: C 90.0; H 5.6; N 4.6%. The picrate of XIII had mp 190-190.5° (from alcohol–acetone). Found: N. 10.3%. $C_{23}H_{17}N \cdot C_6H_3N_3O_7$. Calculated: N 10.5%. Subsequent elution gave 0.9 g of colorless crystals

of XII with mp 141-142° (from hexane) and R_f 0.78. Found: C 89.2; H 6.5; N 4.1%. $C_{26}H_{23}N$. Calculated: C 89.2; H 6.7; N 4.0%. PMR spectrum, δ, ppm: 0.93 (d, CH_3), 3.2 (septet, CH) and 7.1-8.2 (m, aromatic H). The picrate of XII had mp 234-236° (from alcohol–acetone). Found: N 9.9%. $C_{26}H_{23}N \cdot C_6H_3N_3O_7$. Calculated: N 9.7%. The uncrystallizable residue (3.38 g) isolated at the end of chromatography was converted to a picrate. Fractional crystallization of the picrates from alcohol-acetone gave 1.02 g of the picrate of 5-isopropyl-2,4-diphenylpyridine with mp 225-228°, from which 0.49 g of XIV, with mp 97.5-98.3° (from hexane) and R_f 0.77, was obtained by decomposition with a column filled with activity II aluminum oxide and elution by chloroform. Found: C 88.4; H 6.5; N 5.0%. $C_{20}H_{19}N$. Calculated: C 87.9; H 7.9; N. 5.1% PMR spectrum, δ, ppm: 1.13 (d, CH_3), 3.08 (q, CH), and 7.2-8.2 (m, aromatic H).

1,3-Diphenyl-4-azafluorene (XV). A solution of 20 g (0.06 mole of pyridine X was passed through a contact tube filled with K-16 catalyst (V = 40 ml) at 550-560° at a constant rate for 5 h. A total of 1.8 liters of gas (21.5°, 747 mm) was collected. The residue (17.8 g) after removal of the benzene from the catalyzate by distillation was converted to the picrate. The resulting mixture of picrates was crystallized from acetone to give 10.86 g of a picrate with mp 234-235°, which was decomposed on activity II aluminum oxide with elution with chloroform to give 5.36 g (27%) of greenish crystals of XV with mp 157.5-158° (from hexane). Found: C 90.2; H 5.7; N 4.7%. $C_{24}H_{17}N$. Calculated: C 90.3; H 5.3; N 4.4%. PMR spectrum δ, ppm: 3.87 (s, CH_2) and 7.42 (s, H-2). The picrate of XV had mp 237-238° (from acetone). Found: 9.9%. $C_{24}H_{17}N \cdot C_6N_3O_7$. Calculated: N 10.2%. The mother liquor obtained after isolation of the picrate of XV was evaporated to give 3.43 g of a picrate with mp 191-193°, which was decomposed on activity II aluminum oxide with elution by chloroform to give 1.9 g (9.5%) of 1,2-diphenyl-2-azafluorene (XVI) as yellowish crystals with mp 143-144° (from heptane). Found: C 90.5; H 5.6; N 4.3%. $C_{24}H_{17}N$. Calculated: C 90.3; H 5.3; N 4.4%. A mixture of this product with a sample of XVI obtained as described below had mp 143-144°.

1,3-Diphenyl-2-azafluorene (XVI). A solution of 2.25 g (7.0 mmole) of XVII in 30 ml of benzene was passed through a contact tube containing 15 ml of K-16 catalyst at 530-540° for 1 h. A total of 0.32 liter of gas (20°, 756 mm) was collected. The residue (1.55 g) obtained after removal of the benzene from the catalyzate by distillation was converted to the picrate. Fractional crystallization of the mixture of picrates from acetone gave 0.2 g of a picrate with mp 193-194°, which was decomposed on activity II aluminum oxide with elution by chloroform to give 0.11 g (5%) of XVI with mp 143.5-144.5° (from alcohol). Found: C 89.9, H 5.7; N 4.4% $C_{24}H_{17}N$. Calculated: C 90.3; H 5.3; N 4.4%. A mixture of this product with XV had mp 125-146°. PMR spectrum, δ, ppm: 3.87 (s, CH_2) and 7.77 (s, H-4). The picrate of XVI had mp 193-194° (from alcohol–acetone). Found: N 10.1%. $C_{24}H_{17}N \cdot C_6H_3N_3O_7$. Calculated: N 10.2%.

1,3-Diphenyl-2-aza-9-fluorenone (XVIII). A 0.49-g (3.1 mmole) sample of potassium permanganate was added in portions with constant stirring to a solution of 0.5 g (1.56 mmole) of XV in 150 ml of acetone. after which the precipitated manganese dioxide was removed by filtration and washed repeatedly with acetone. The residue (0.28 g) obtained after removal of the acetone by distillation was crystallized from heptane to give 0.24 g (57%) of yellow crystals XVIII with mp 163-164.5°. Found: C 86.5; H 4.8; N 4.5%. $C_{24}H_{15}NO$. Calculated: C 86.5; H 4.5; N 4.2%. The picrate of XVIII had mp 224-226° (from acetone). Found: C 9.6%. $C_{24}H_{15}NO \cdot C_6H_2N_2O_7$. Calculated: N 9.9%.

LITERATURE CITED

1. N. S. Prostakov, K. John Matthew, and V. A. Kurichev, Khim. Geterotsikl. Soedin., 876 (1967).
2. N. S. Prostakov and V. V. Dorogov, Khim. Geterotsikl. Soedin., 373 (1971).
3. N. S. Prostakov, L. M. Kirillova, Dkharvar Pkhal'gumani, L. A. Shakhparonova, and V. P. Zvolinskii, Khim. Geterotsikl. Soedin., 1068 (1967).
4. J. Ficini and A. Maujean, Bull. Soc. Chim. France, 219 (1971).
5. M. Cense, A. Sevin, and W. Chodkiewicz, Compt. Rend., C272, 229 (1971).
6. C. Reid, J. Mol. Spectr., 1, 19 (1957).
7. C. R. Noller and V. Baliah, J. Amer. Chem. Soc., 70, 3853 (1948).
8. N. S. Prostakov and A. V. Varlamov, Khim. Geterotsikl. Soedin., 1637 (1970).
9. J. Wislicenus and F. H. Newmann, Ann., 302, 236 (1898).