SYNTHESIS OF ARYL(γ-PYRIDYL)METHANES AND THEIR CONVERSION TO SUBSTITUTED BENZO[g]ISOQUINOLINES

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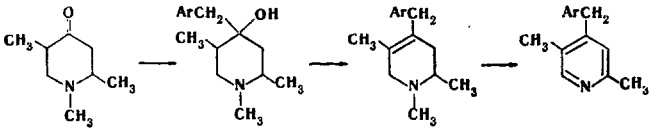
New substituted pyridine bases of the aryl(γ-pyridyl)methane type were obtained from 1,2,5-trimethyl-4-piperidone by successive transformations. The new substituted pyridine bases were catalytically dehydrocyclized to di(tri)methylbenzo[g]isoquinolines.

Like other benzoquinolines, benzo[g]isoquinolines have remained inaccessible compounds in a synthetic respect [1]. We are making a systematic study of a method for the preparation of substituted benzo[g]isoquinolines by catalytic dehydrocyclization of the corresponding pyridine bases [2, 3], which are obtained from γ-piperidones by a series of successive transformations by a method developed in our laboratory [4, 5]. In the present communication we present the synthesis of a new group of tertiary γ-piperidols, which were subsequently converted to aryl(γ-pyridyl)methanes.



I II-VI VII-XI XII-XVI

II, VII, XII Ar = *o,m*-$C_6H_3(CH_3)_2$; III, VIII, XIII Ar = *o,p*-$C_6H_3(CH_3)_2$; IV, IX, XIV Ar = *m,p*-$C_6H_3(CH_3)_2$; V, X, XV Ar = *o,m',p*-$C_6H_2(CH_3)_3$; VI, XI, XVI Ar = *o,o',p*-$C_6H_2(CH_3)_3$.

γ-Piperidols II-VI were obtained from 1,2,5-trimethyl-4-piperidone (I) and organomagnesium compounds from the corresponding di(tri)methylbenzyl chlorides. The latter were synthesized by chloromethylation of isomeric xylenes, pseudocumene, and mesitylene by the method described in [6, 7]. Piperidines VII-XI were obtained from piperidols II-VI by dehydration by means of concentrated hydrochloric acid. The piperidines were converted to pyridine bases (XII-XVI) (colorless crystalline substances) by catalytic dehydrogenation on a K-16 dehydrogenating catalyst at 420-440° C.

Dehydrocyclization of pyridine bases XII-XVI was accomplished on the same catalyst at 560-580°. All of the isolated benzo[g]isoquinolines are yellow crystalline substances with high melting points, and, except for XIX, they are only slightly soluble in nonpolar solvents.

A similar dehydrocyclization reaction has been previously accomplished in only one case – the conversion of 2,5-dimethyl-4-(4-methylbenzyl)pyridine (XVII) to 3,8-dimethylbenzo[g]isoquinoline (XVIII) [3]. In this case the dehydrocyclization proceeds through the β-methyl group of the pyridine ring and the hydrogen in the ortho position of the benzyl group. If it is assumed that the dehydrocyclization of 2,5-dimethyl(2,4-dimethylbenzyl)pyridine (XIII) proceeds in the same way, one must expect the formation of 3,6,8-trimethylbenzo[g]isoquinoline (XIX) from it. However it was experimentally established that benzo[g]isoquinoline XVIII is formed in 40% yield in this case. It is important that, in addition to the principal reaction product (XIII), a mixture of XVIII and XIX, which could be separated by repeated crystallization, is formed in ~1% yield at the stage of preparation of pyridine base XIII from piperideine VIII (at 440°). Considering these experimental data, one may assume that the first step in the catalytic transformations of pyridine base XIII is its dehydrocyclization with the participation of the β-CH_3 group of the pyridine ring and the hydrogen in the ortho position of the dimethylbenzyl group and that the second step is hydrogenolysis accompanied by splitting out of the methyl group attached to the C_6 atom of benzo[g]isoquinoline system XIX. The cyclization of XIII to XVIII with the participation of the β-methyl group of the pyridine ring and the o-CH_3 group of the dimethylbenzyl group of XIII (a different

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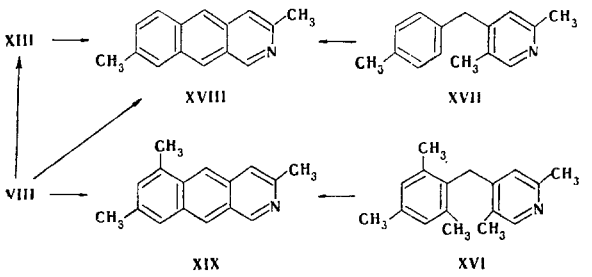
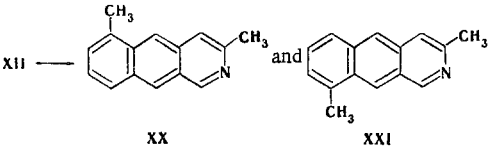
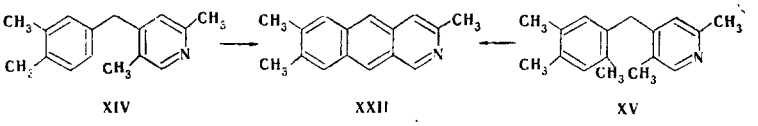
chemical mechanism for the demethylation) is unlikely, since it has been established that benzo[g]isoquinoline XIX is formed in less than 1% yield from pyridine base XVI under similar conditions.



The dehydrocyclization of 2,5-dimethyl-4-(2,5-dimethylbenzyl)pyridine (XII) is also accompanied by demethylation. Instead of the possible 3,6,9-trimethylbenzo[g]isoquinoline, a mixture of 3,6-dimethyl- and 3,9-dimethylbenzo[g]isoquinolines (XX and XXI) was obtained in 8% yield in this case; this mixture could not be separated, but its composition was confirmed by spectral data. It is essential that in this case, as in the case of the dehydrocyclization of XIII, the methyl group in the ortho position of the benzene ring of the possible intermediate trimethylbenzo[g]isoquinoline is split out.



Demethylation does not occur in the dehydrocyclization of 2,5-dimethyl-4-(3,4-dimethylbenzyl)pyridine (XIV); 3,7,8-trimethylbenzo[g]isoquinoline (XXIII) was obtained in 40% yield. Compound XXII was obtained in low yield (4%) in the analogous catalytic conversion of 2,5-dimethyl-4-(2,4,5-trimethylbenzyl)pyridine (XV).



The problem of the position of the methyl groups in aryl(γ-pyridyl)methanes XII-XVI and benzo[g]isoquinolines XVIII-XXII was solved on the basis of data from their PMR spectra (see Tables 1 and 2, respectively). The conclusion that a mixture of benzo[g]isoquinolines XX and XXI is formed in the dehydrocyclization of XII was drawn on the basis of the fact that two groups of signals – 8.97 and 9.08 and 8.61 and 8.53 ppm – related to the protons attached to C_5 and C_{10}, respectively, are observed in the PMR spectrum of a solution in CF_3COOH; the ratio of the integral intensities of these signals is ~1:2, whereas the signals of the remaining protons have identical chemical shifts – triplet at 7.72 (J = 9.0 Hz) and doublet at 9.60 (J = 8.0 Hz) – and the resonance lines of the methyl groups at 2.70 ppm have almost merged (Fig. 1). The signals of the methyl group

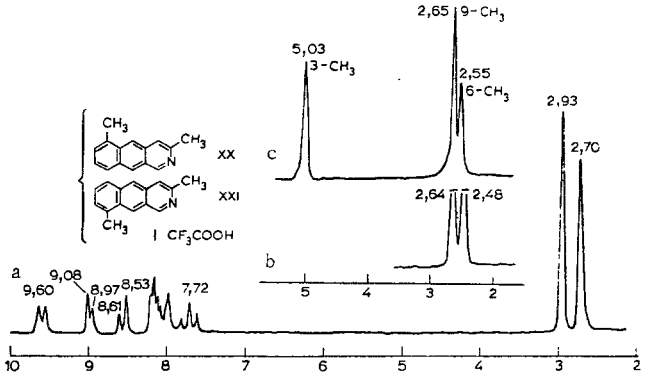


Fig. 1. PMR spectrum of a mixture of 3,6-dimethyl- and 3,9-dimethylbenzo[g]isoquinolines (XX and XXI): a) in trifluoroacetic acid; b) in $CDCl_3$; c) in $CDCl_3$ with $Eu(DPM)_3$.

TABLE 1. Data from the PMR Spectra of Polymethyl-Substituted Aryl(γ-pyridyl)methanes XII-XVI *

Compound	6-H	3′-H	4′-H	5′-H, 6′-H	5′-H	6′-H	3′-H, 5′-H	2′-H	3-H	CH_2	2-CH_3	5-CH_3, 2′-CH_3, 5′-CH_3	5-CH_3, 2′-CH_3, 4′-CH_3	5-CH_3, 3′-CH_3, 4′-CH_3	5-CH_3, 2′-CH_3, 4′-CH_3, 5′-CH_3	2-CH, 5-CH_3, 2′-CH, 4′-CH_3, 6′-CH_3
XII	8,05, 1H, s	6,94, 1H,d,8,0	6,82 1H,d,8,0	—	—	6,60, 1H, s	—	—	6,40, 1H, s	3,65, 2H, s	2,28, 3H, s	2,06—2,17, 9H	—	—	—	—
XIII	8,02, 1H, s	6,83, 1H, s	—	—	6,78, 1H,d,8,0	6,62, 1H,d,8,0	—	—	6,39, 1H, s	3,64, 2H, s	2,24, 3H, s	—	2,04—2,18, 9H	—	—	—
XIV	8,05, 1H, s	—	—	—	6,89, 1H,d,8,0	6,67, 1H,d,8,0	—	6,71, 1H, s	6,62, 1H, s	3,67, 2H, s	2,31, 3H, s	—	—	2,03—2,11, 9H	—	—
XV	8,04, 1H, s	6,80, 1H, s	—	—	—	6,54, 1H, s	—	—	6,37, 1H, s	3,63, 2H, s	2,27, 3H, s	—	—	—	2,02—2,12, 12H	—
XVI	8,05, 1H, s	—	—	—	—	—	6,76, 2H, s	—	6,09, 1H, s	3,66, 2H, s	- -	—	—		—	2,01—2,22, 15H

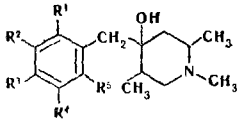
* The solvent was CCl_4, and the internal standard was hexamethyldisiloxane.

TABLE 2. Data from the PMR Spectra of Polymethyl-Substituted Benzo[g]isoquinolines XVIII-XXII*

Compound	Chemical shifts, δ, ppm (multiplicity, integral intensity, J, Hz)														
	1-H	5-H	10-H	4-H	6-H	6-H, 9-H	4-H, 6-H, 8-H	9-H	7-H	3-CH_3	8-CH_3	6-CH_3	7-CH_3	6-CH_3, 9-CH_3
XVIII	9,62, 1H,d, 8,0	8,95, 1H, s	8,58, 1H,s	8,16, 1H,s	8,12, 1H,d, 8,0	—	—	8,01, 1H,d, 2,0	7,76, 1H,d, 8,0	2,90, 3H,s	2,66, 3H,s	—	—	—
XIX	9,65, 1H,d, 8,0	9,0, 1H,s	8,83, 1H,s	8,30, 1H,s	—	—	—	7,92, 1H,s	7,68, 1H, s	2,95, 3H,s	2,65, 3H,s	2,93, 3H,s	—	—
Mixture of XX and XXI	9,60, 1H,d, 3,0	8,97, s 9,08, s	8,61, s 8,53, s	—	—	—	7,92-8,23, 3Hm	—	7,72, 1H, t, 9,0	2,93, 3H,s	—	—	—	2,70, 3H, s
XXII	9,58, 1H,d, 8,0	8,92, 1H,s	8,50, 1H, s	8,17, 1H,s	—	7,98, 2H,s	—	—	—	2,93, 3H,s	2,64, 3H,s	—	2,62, 3H,s	—

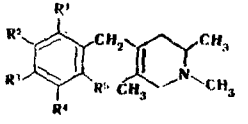
* The solvent was CF_3COOH, and the internal standard was tetramethylsilane.

TABLE 3. Aryl(1,2,5-trimethyl-4-hydroxy-4-piperidyl)methanes



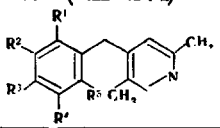
Compound	R¹	R²	R³	R⁵	R⁶	mp, °C (from petroleum ether)	Empirical formula	Found, %			Calculated, %			IR spectra		Yield based on converted I, %	Picrate		
								C	H	N	C	H	N	ν_{OH}, cm⁻¹	aromatic δ(C-H), cm⁻¹		mp, °C	N, % found	N, % calc.
II	CH_3	H	H	CH_3	H	72–73	$C_{17}H_{27}NO$	78,3	10,4	5,1	78,1	10,4	5,4	3350	807 (s) 855 (w)	23	165,5–166,5	11,2	11,4
III	CH_3	H	CH_3	H	H	68,5–70,5	$C_{17}H_{27}NO$	78,1	10,8	5,1	78,1	10,4	5,4	3230	822 (s) 850 (w)	21	171–173	11,2	11,4
IV	H	CH_3	CH_3	H	H	89–90	$C_{17}H_{27}NO$	77,9	10,3	5,2	78,1	10,4	5,4	3250	822 (s) 848 (w)	37	203	11,7	11,4
V	CH_3	H	CH_3	CH_3	H	103–104	$C_{18}H_{29}NO$	78,3	10,2	5,0	78,6	10,5	5,1	3190	880 (s)	32	174—175	10,9	11,1
VI	CH_3	H	CH_3	H	CH_3	90–91,5	$C_{18}H_{29}NO$	78,6	10,8	5,1	78,6	10,5	5,1	3290	854 (s)	26	208–210	11,1	11,1

TABLE 4. Aryl(1,2,5-trimethyl-Δ^4-piperidein-4-yl)methanes (VII-XI)



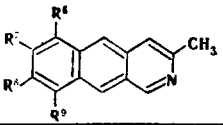
Compound	R¹	R²	R³	R⁵	R⁶	bp, °C (mm)	Yield, %	Picrate		
								mp, °C	N, % found	N, % calc.
VII	CH_3	H	H	CH_3	H	152—156(2)	53	135—136	12,0	11,9
VIII	CH_3	H	CH_3	H	H	156—160(2)	63	153—155	12,1	11,9
IX	H	CH_3	CH_3	H	H	149—150(2)	59	140—142	11,6	11,9
X	CH_3	H	CH_3	CH_3	H	174—180(4)	83	128—129	11,5	11,5
XI	CH_3	H	CH_3	H	CH_3	170—174(3)	89	179—181	11,4	11,5

TABLE 5. Aryl(2,5-dimethyl-4-pyridyl)methanes (XII-XVI)



Compound	R¹	R²	R³	R⁴	R⁵	mp, °C (from hexane)	M⁺	Empirical formula	Found, %			Calculated, %			IR spectra, aromatic δ(C-H), cm⁻¹	Yield, %	Picrate		
									C	H	N	C	H	N			mp, °C	N, % found	N, % calc.
XII	CH_3	H	H	CH_3	H	63—64	—	$C_{16}H_{19}N$	85,1	8,2	6,5	85,3	8,5	6,2	810 s, 858 w	29	156,5—157,5	12,1	12,3
XIII	CH_3	H	CH_3	H	H	82,5—83,5	225	$C_{16}H_{19}N$	85,1	8,8	6,0	85,3	8,5	6,2	832 s, 857 w	28	185—186	12,3	12,3
XIV	H	CH_3	CH_3	H	H	69—70,5	—	$C_{16}H_{19}N$	85,1	8,3	6,1	85,3	8,5	6,2	837 s, 852 w	28	182,5—183,5	12,3	12,3
XV	CH_3	H	CH_3	CH_3	H	80—81,5	239	$C_{17}H_{21}N$	85,1	9,0	6,0	85,4	8,8	5,8	867 m, 880 m	37	177—178	12,2	12,0
XVI	CH_3	H	CH_3	H	CH_3	124—125	—	$C_{17}H_{21}N$	85,7	8,8	5,7	85,4	8,8	5,8	858 s, 863 w	32	222—223	11,5	12,0

TABLE 6. Polymethyl-Substituted Benzo[g]soquinolines (XVIII-XXII)



Compound	R⁶	R⁷	R⁸	R⁹	mp, °C (from hexane)	M⁺	Empirical formula	Found, %			Calc., %			IR spectra, aromatic δ(C-H), cm⁻¹	UV spectra, λmax, nm	Yield, %	Picrates		
								C	H	N	C	H	N				mp, °C	N, % found	N, % calc.
XVIII	H	H	CH_3	H	245—246	207	$C_{15}H_{13}N$	87,0	6,6	6,5	87,0	6,3	6,8	910 s, 810 w	233, 256, 312, 327, 345, 365, 384, 406	40	241—242	12,9	12,8
XIX	CH_3	H	CH_3	H	163	221	$C_{16}H_{15}N$	86,9	7,1	6,1	86,9	6,8	6,3	900 s	236, 254, 314, 324, 342, 366, 390, 410	1	245—246	12,3	12,4
XX and XXI	CH_3 H	H H	H H	H CH_3	218—219	207	$C_{15}H_{13}N$	84,5	6,4	6,4	87,0	6,3	6,8	908 s, 805 w	234, 256, 315, 332, 348, 364, 382, 404	8	232—233	12,6	12.8
XXII	H	CH_3	CH_3	H	256—257	221	$C_{16}H_{15}N$	84,6	6,9	6,5	86,9	6,8	6,3	910 s	236, 257, 318, 333, 349, 365, 383, 403	40	247—248	12,4	12.4

attached to $C_{(3)}$ of XX and XXI in the PMR spectrum of a mixture of XX and XXI in $CDCl_3$ containing the paramagnetic shift reagent $Eu(DPM)_3$ (Fig. 1) is shifted sharply to weak field at 5.03 ppm, whereas the signals at 2.55 ppm [methyl group attached to $C_{(6)}$ of XX] and 2.65 ppm [methyl group attached to $C_{(9)}$ of XXI] remain at strong field, but their intensity ratio is ~1:2. The large induced shift of the signal of the methyl group of XXI, which predominates in the mixture, constitutes evidence that the methyl group in structure XXI is attached to $C_{(9)}$, i.e., it is closer to the coordination center than the methyl group attached to $C_{(6)}$ of benzo[g]-isoquinoline XX.

The position of the methyl group attached to $C_{(8)}$ of the benzene ring of isoquinoline XVIII was determined on the basis of assignment of the signals of the aromatic protons. The signals of the protons of this ring show up as a doublet (J = 9.0 Hz), a quartet (J = 9.0 Hz, J = 2.0 Hz), and a broad singlet (Table 2). The J constant of 9.0 Hz attests to spin–spin coupling of the protons in the ortho position, whereas the J constant of 2.0 Hz constitutes evidence for spin–spin coupling of the protons in the meta position. The broad singlet at 7.98 ppm with an intensity of two proton units in the PMR spectrum of XXII is related to the protons attached to $C_{(6)}$ and $C_{(9)}$, whereas the signals at 7.68 and 7.92 ppm in the analogous spectrum of isoquinoline XIX are due to the protons attached to $C_{(7)}$ and $C_{(9)}$, respectively.

Two bands at 908-910 and 805-810 cm^{-1}, which are related to the out-of-plane deformation vibrations of two adjacent and one solitary aromatic C-H bond, are present in the IR spectra of a mixture of XX and XXI, and in the spectrum of XVIII, whereas in the spectra of XIX and XXII there is only one band at 900-910 cm^{-1}, which is due to solitary aromatic C–H bonds (Table 6).

The UV spectra of benzo[g]isoquinolines XVIII-XXII are in quite good agreement with the UV spectra of analogous compounds described in [8-10].

EXPERIMENTAL

The PMR spectra of CF_3COOH (tetramethylsilane internal standard) and $CDCl_3$ (hexamethyldisiloxane internal standard) solutions of the compounds were recorded with HA-100 and BS-487C spectrometers. The IR spectra of KBr pellets were recorded with a UR-20 spectrometer. The electronic spectra were measured with a Hitachi spectrophotometer.

Aryl(1,2,5-trimethyl-4-hydroxy-4-piperidyl)methanes (II-VI). These compounds were obtained by the method described in [5]. The characteristics of the products are presented in Table 3.

Aryl-1,2,5-trimethyl-Δ^4-piperidein-4-yl)methanes (VII-XI). These compounds were obtained by the method in [5]. Their characteristics are presented in Table 4.

Aryl(2,5-dimethyl-4-pyridyl)methanes (XII-XVI). These compounds were obtained by the method described in [4]. Their characteristics are presented in Table 5.

The following preparation of 3,7,8-trimethylbenzo[g]isoquinoline (XXII) (is presented as an example of the synthesis of benzo[g]isoquinolines XVIII-XXII. A solution of 5.0 g (0.022 mole) of XIV in 10 ml of benzene was passed at a constant rate in the course of 2 h over a K-16 catalyst (10 ml). The temperature in the catalyst zone was 560-580°. At the end of the experiment, 50 ml of benzene was passed through the contact tube at the same temperature. The catalyzate was dried with fused potassium hydroxide, and the benzene was removed by distillation. Petroleum ether (15 ml) was added to the residue, and the resulting precipitate was recrystallized from petroleum ether to give 2 g of isoquinoline XIX as a yellow powdery substance. Compounds XVIII-XXI, the characteristics of which are presented in Table 6, were similarly obtained. The results of analysis of the carbon content of the mixture of XX and XXI and of XXII differed from the theoretical values. This is evidently explained by the fact that they contain strongly bonded crystallization water that could not be completely removed by various drying methods. The broad band at 3450 cm^{-1} in the IR spectra of these benzo[g]isoquinolines provides evidence for the presence of water.

LITERATURE CITED

1. N. S. Prostakov, Usp. Khim., 38, 1710 (1969).
2. N. S. Prostakov, L. M. Kirillova, Dkharvar Pkhal'gumani, L. A. Shakhparonova, and V. P. Zvolinskii, Khim. Geterotsikl. Soedin., No. 6, 1068 (1967).
3. N. S. Prostakov and V. V. Dorogov, Khim. Geterotsikl. Soedin., No. 3, 373 (1971).
4. N. S. Prostakov and L. A. Gaivoronskaya, Zh. Obshch. Khim., 32, 76 (1962).
5. N. S. Prostakov, L. A. Gaivoronskaya, N. M. Mikhailova, and L. M. Kirillova, Zh. Obshch. Khim., 33, 2573 (1963).
6. V. D. Shein, M. I. Farberov, and G. S. Mironov, Zh. Prikl. Khim., 40, 2006 (1967).
7. V. Braun and Nelles, Ber., 67, 1094 (1934).
8. A. Etienne and M. Legrand, Bull. Soc. Chim. France, 108 (1953).
9. J. Badger, R. S. Pearce and R. Petit, J. Chem. Soc., 3199 (1961).
10. C. N. Rao, Electronic Spectra in Chemistry [Russian translation], Mir, Moscow (1964), p. 70.