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Reaction of Methylcyclohexanones with Substituted Benzaldehydes and 2-Naphthylamine

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Abstract—Cascade heterocyclization of 3(4)-methylcyclohexanone, substituted benzaldehyde, and 2-naphthylamine in a polar solvent in the presence of hydrochloric acid afforded the corresponding 5-aryl-2(3)-methyl-1,2,3,4-tetrahydrobenzo[*a*]phenanthridines and 12-aryl-9(10)-methyl-8,9,10,11-tetrahydrobenz[*a*]acridines having an asymmetric carbon atom in position *2* or *3*.

Despite numerous publications, compounds of the quinoline series persistently attract researchers' interest due to versatile biological activity of quinoline derivatives. A large number of antitumor [1] and antimicrobial agents [2], enzyme inhibitors [3], and antibiotics [4] were obtained therefrom.

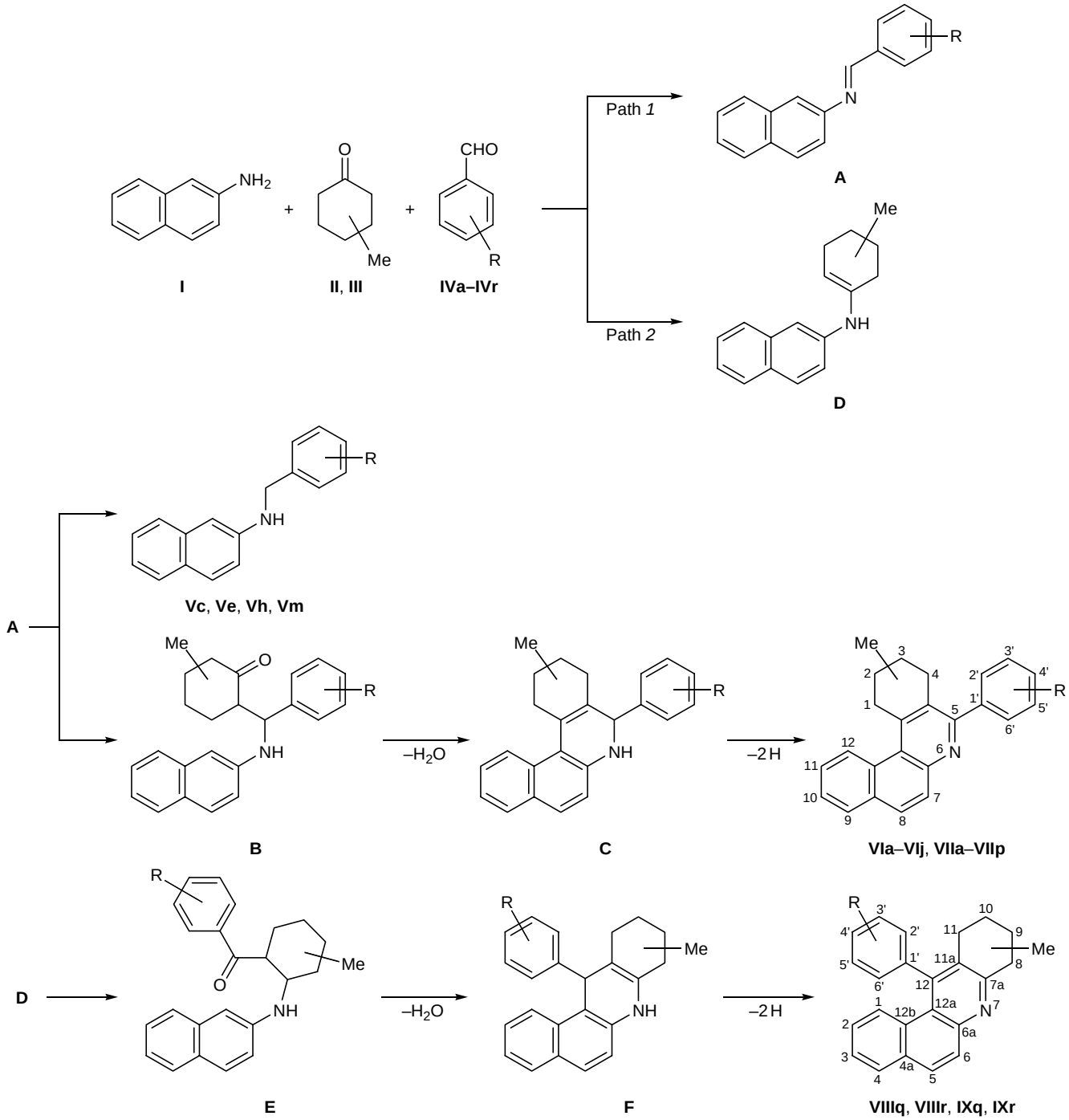
We previously [5] synthesized tetrahydrobenzo[*a*]phenanthridine derivatives having fused benzoquinoline and cyclohexane moieties by condensation of cyclohexanone with Schiff bases of the 2-naphthylamine series in the presence of a catalytic amount of hydrochloric acid. In the present work we were the first to involve in the synthesis of tetrahydrobenzo[*a*]phenanthridine and tetrahydrobenz[*a*]acridine derivatives substituted cyclic ketones, namely unsymmetrical 3-methylcyclohexanone and symmetrical 4-methylcyclohexanone. According to published data [6], these compounds are not isomerically pure. Using ^{1}H and ^{13}C NMR spectroscopy with shift reagents, we determined the fractions of the isomers with axial orientation of the methyl group in the equilibrium mixtures of 3- and 4-methylcyclohexanones: these fractions were 15 and more than 50%, respectively.

The reaction under study provides the possibility for synthesizing previously unknown compounds which are the nearest structural analogs of natural alkaloids [7]. By condensation of methylcyclohexanones **II** and **III** with 2-naphthylamine (**I**) and substituted benzaldehydes **IVa**–**IVr** we succeeded in introducing for the first time an asymmetric center into phenanthridine and acridine molecules. The presence of asymmetric centers is an important attribute of a biologically active compound, for its effect is essentially determined by the stereochemical structure.

The reactions were carried out by heating equimolar amounts of 2-naphthylamine (**I**) and substituted benzaldehyde **IVa**–**IVr** and 3 equiv of methylcyclohexanone **II** or **III** in boiling ethanol in the presence of a catalytic amount of hydrochloric acid. The reaction time was 1–6 h. The products were isolated as the corresponding hydrochlorides by the following procedure. The tarry reaction mixture was treated with diethyl ether, and the product was repeatedly crystallized from methanol. Treatment of the isolated hydrochlorides with ammonia and subsequent recrystallization gave pure compounds **VIa**–**VIj**, **VIIa**–**VIIp**, **VIIIq**, **VIIIr**, **IXq**, and **IXr** (Scheme 1, Table 1).

Theoretically, two paths of the cascade heterocyclization are possible. According to the first of these (path *1* in Scheme 1), initially formed Schiff base **A** is protonated by hydrochloric acid with retention of its planar configuration. As a result, the C=N carbon atom becomes more electrophilic [8]. In addition, acid medium enhances the nucleophilicity of the carbon atom neighboring to the carbonyl group in the methylcyclohexanone molecule. Therefore, favorable conditions are created for addition of the ketone to the Schiff base with formation of arylaminoketone **B**. The enol form of the latter loses water molecule, yielding thermodynamically unstable 1,2-dihydropyridine derivative **C**, and the subsequent aromatization via oxidation with dissolved atmospheric oxygen leads to

Scheme 1.



II, 3-Me; **III**, 4-Me; **VI**, 2-Me; **VII**, 3-Me; **VIII**, 9-Me; **IX**, 10-Me; **IV**, **V**–**IX,** R = 2-HO (**a**), 3-HO (**b**), 4-HO (**c**), 4-O_2N (**d**), 4-EtO (**e**), 3-pyridyl (**f**), 3,4-$(HO)_2$ (**g**), 3,4-$(MeO)_2$ (**h**), 3,4-CH_2O_2 (**i**), 5-Br-2-HO (**j**), 4-F (**k**), 4-Br (**l**), 4-PrO (**m**), 2-furyl (**n**), 4-MeS (**o**), 4-(2-FC_6H_4 CH_2O) (**p**), 3-Me_2N (**q**), 2,4-$(HO)_2$ (**r**).

final tetrahydrobenzo[*a*]phenanthridines **VIa**–**VIj** and **VIIa**–**VIIp** (Scheme 1). In the reactions with aldehydes **IVc**, **IVe**, **IVh**, and **IVm**, apart from the corresponding tetrahydrobenzo[*a*]phenanthridines, we isolated *N*-(R-benzyl)-2-naphthylamines **Vc**, **Ve**, **Vh**, and **Vm**, which were formed by reduction of intermediate Schiff base **A**.

Path *2* includes initial formation of enamine **D** by reaction of 2-naphthylamine with methylcyclohexanone. The β-carbon atom in molecule **D** becomes

Table 1. Yields, melting points, and elemental analyses of 5-aryl-2(3)-methyl-1,2,3,4-tetrahydrobenzo[*a*]phenanthridines **VIa**–**VIj** and **VIIa**–**VIIp** and 5-aryl-9(10)-methyl-1,2,3,4-tetrahydrobenz[*a*]acridines **VIIIq**, **VIIIr**, **IXq**, and **IXr**

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
VIa	60	282	84.97	6.22	4.10	$C_{24}H_{21}NO$	84.95	6.19	4.13
VIb	63	300	84.98	6.17	4.15	$C_{24}H_{21}NO$	84.95	6.19	4.13
VIc	34	264–265	84.97	6.18	4.14	$C_{24}H_{21}NO$	84.95	6.19	4.13
VId	62	172–174	78.25	5.44	7.62	$C_{24}H_{20}N_2O_2$	78.26	5.43	7.61
VIe	45	175	85.00	6.84	3.80	$C_{26}H_{25}NO$	85.01	6.82	3.82
VIf	58	126–130	85.18	6.17	8.65	$C_{23}H_{20}N_2$	87.37	5.83	6.80
VIg	55	268–270	81.10	5.93	3.96	$C_{24}H_{21}NO_2$	81.12	5.91	3.94
VIh	23	148–150	81.42	6.55	3.65	$C_{26}H_{25}NO_2$	81.46	6.53	3.66
VIi	45	160	81.77	5.70	3.81	$C_{25}H_{21}NO_2$	81.74	5.75	3.81
VIj	30	260	68.90	4.77	3.35	$C_{24}H_{20}BrNO$[a]	68.89	4.78	3.35
VIIa	72	270	84.96	6.20	4.14	$C_{24}H_{21}NO$	84.95	6.19	4.13
VIIb	76	286	84.93	6.21	4.13	$C_{24}H_{21}NO$	84.95	6.19	4.13
VIIc	28	278	84.3	6.26	4.10	$C_{24}H_{21}NO$	84.95	6.19	4.13
VIId	72	218–220	78.29	5.39	7.64	$C_{24}H_{20}N_2O_2$	78.26	5.43	7.61
VIIe	46	190	85.00	6.84	3.80	$C_{26}H_{25}NO$	85.01	6.82	3.82
VIIf	62	210	85.18	6.17	8.65	$C_{23}H_{20}N_2$	87.37	5.83	6.80
VIIg	60	180	81.12	5.93	3.94	$C_{24}H_{21}NO_2$	81.12	5.91	3.94
VIIh	29	140–142	81.43	6.50	3.65	$C_{26}H_{25}NO_2$	81.46	6.53	3.66
VIIi	52	176	81.77	5.70	3.84	$C_{25}H_{21}NO_2$	81.74	5.72	3.81
VIIj	39	168–170	68.67	4.80	3.34	$C_{24}H_{20}BrNO$[b]	68.68	4.78	3.35
VIIk	44	206–208	–	–	4.11	$C_{24}H_{20}FN$[c]	84.45	5.87	4.11
VIIl	36	234	71.66	5.00	3.49	$C_{24}H_{20}BrN$[d]	71.64	4.98	3.48
VIIm	13	188–190	85.07	7.06	3.65	$C_{27}H_{27}NO$	85.04	7.09	3.67
VIIn	60	130	84.34	6.07	4.47	$C_{22}H_{19}NO$	84.45	6.75	4.10
VIIo	85	192	81.32	6.24	3.81	$C_{25}H_{23}NS$	81.30	6.23	3.79
VIIp	64	188	–	–	3.15	$C_{31}H_{26}FNO$[e]	83.22	5.82	3.13
VIIIq	45	210–212	85.27	7.13	7.67	$C_{26}N_{26}N_2$	85.25	7.10	7.65
VIIIr	50	330	81.16	5.87	3.95	$C_{24}H_{21}NO_2$	81.12	5.91	3.94
IXq	37	218–220	85.27	7.09	7.64	$C_{26}H_{26}N_2$	85.25	7.10	7.65
IXr	52	190	81.10	5.92	3.94	$C_{24}H_{21}NO_2$	81.12	5.91	3.94

[a] Found Br, %: 19.16. Calculated Br, %: 19.14.
[b] Found Br, %: 19.18. Calculated Br, %: 19.14.
[c] Found F, %: 5.59. Calculated F, %: 5.57.
[d] Found Br, %: 19.97. Calculated Br, %: 19.90.
[e] Found F, %: 4.27. Calculated F, %: 4.25.

Table 2. ^{1}H NMR spectra of compounds **VIa**, **VIIp**, and **VIIIr**, δ, ppm (*J*, Hz)

Atom	**VIa**	**VIIp**	**VIIIr**	Atom	**VIa**	**VIIp**	**VIIIr**
1-H	–	–	7.83, 7.81 ($J_{1,2}$ = 6)	10-H	7.87 ($J_{10,11}$ = 7)	7.69	–
1-H$_{eq}$	3.72 ($J_{1,1}$ = 18)	3.57 ($J_{1,1}$ = 17)	–	10-H$_{eq}$	–	–	1.90
1-H$_{ax}$	3.52 ($J_{1\text{-}ax,2\text{-}eq}$ = 9)	3.67	–	10-H$_{eq}$	–	–	1.43
2-H	1.78 ($J_{2,1\text{-}eq}$ = 3)	–	7.42 ($J_{2,3}$ = 8)	11-H	7.90 ($J_{11,12}$ = 8)	7.69 ($J_{11,12}$ = 8)	2.67
2-H$_{eq}$	–	2.01 ($J_{2,2}$ = 14)	–	12-H	8.93	8.83	–
2-H$_{ax}$	–	1.29 ($J_{2\text{-}ax,3}$ = 10)	–	3'-H	7.28 ($J_{3',4'}$ = 8)	–	6.71, 6.70
3-H	–	1.92	7.66 ($J_{3,4}$ = 8)	4'-H	7.48 ($J_{4',5'}$ = 8)	–	–
3-H$_{eq}$	1.94	–	–	5'-H	7.06 ($J_{5',6'}$ = 7)	–	6.53 6.51
3-H$_{ax}$	1.57	–	–	6'-H	7.46	–	6.75, 6.73
4-H	2.58	–	8.10	2'-H, 6'-H	–	7.51 ($J_{2',3'}$ = 8)	–
4-H$_{eq}$	–	2.97 ($J_{4,4}$ = 16)	–	3'-H, 5'-H	–	7.15 ($J_{5',6'}$ = 8)	–
4-H$_{ax}$	–	2.42 ($J_{4\text{-}ax,3}$ = 10)	–	3''-H	–	7.28 ($J_{3'',4''}$ = 8)	–
5-H	–	–	8.40 ($J_{5,6}$ = 8)	4''-H	–	7.45 ($J_{4'',5''}$ = 8)	–
6-H	–	–	8.37	5''-H	–	7.28 ($J_{5'',6''}$ = 7)	–
7-H	8.23 ($J_{7,8}$ = 9)	7.82 ($J_{7,8}$ = 9)	–	6''-H	–	7.61 ($J_{6'',F}$ = 7)	–
8-H	8.39	8.01	–	CH_3	1.17 ($J_{Me,2}$ = 7)	1.02 ($J_{Me,3}$ = 7)	1.11 ($J_{Me,9}$ = 7)
8-H$_{ax}$	–	–	2.99, 2.95 ($J_{8\text{-}ax,7}$ = 18)	OH	10.5	–	9.60
8-H$_{eq}$	–	–	3.56 ($J_{8,8}$ = 18)	OCH_2	–	5.23	–
9-H	8.23 ($J_{9,10}$ = 7)	8.06 ($J_{9,10}$ = 7)	2.03 ($J_{9,8\text{-}ax}$ = 9)				

nucleophilic due to conjugation, and its addition to substituted benzaldehyde yields aryl amino ketone **E**. Cyclization of the latter with elimination of water molecule leads to thermodynamically more stable 1,4-dihydropyridine derivative **F** which is oxidized with atmospheric oxygen to give tetrahydrobenz[*a*]-acridines **VIIIq**, **VIIIr**, **IXq**, and **IXr** (Scheme 1).

Compounds **VIa**–**VIj** and **VIIa**–**VIIp** are regio-isomeric to **VIIIq**, **VIIIr**, **IXq**, and **IXr**, and rigorous determination of their structure is very difficult. Using two-dimensional COSY (assignment of proton signals), HSQC (assignment of signals from carbon atoms attached to protons), and HMBC NMR techniques (assignment of signals from quaternary carbon atoms), as well as NOESY spectra (for **VIa**, **VIIp**, and **VIIIr)**, we succeeded in unambiguously establishing the structure of the products. The results showed that the reaction under study can give both phenanthridine (**VIa**–**VIj** and **VIIa**–**VIIp**) and acridine derivatives (**VIIIq**, **VIIIr**, **IXq**, and **IXr**). Table 2

Table 3. ^{13}C NMR spectra of compounds **VIa**, **VIIp**, and **VIIIr** (10% solutions in DMSO-d_6), δ_C, ppm (J, Hz)

Atom no.	**VIa**	**VIIp**	**VIIIr**
1	41.5	32.4	125.9, 126.1
2	28.1	30.8	128.1
3	28.4	27.7	128.1
4	26.2	36.7	129.7
4a	132.6	128.6	138.1
5	152.3	158.1	135.6
6	–	–	118.3
6a	138.3	130.3	138.7
7	119.1	128.6	–
7a	–	–	152.0, 152.2
8	134.9	129.6	35.9
8a	132.6	132.8	–
9	129.8	128.8	26.7
10	128.3	126.3	29.2, 29.5
11	128.2	126.0	25.5, 26.4
11a	–	–	133.5
12	128.5	128.2	154.3
12a	127.8	145.8	128.7
12b	125.3	134.8	124.3
12c	154.5	144.3	–
1'	150.9	133.6	115.8
2'	155.0	–	153.8, 154.2
3'	116.3	–	103.8
4'	131.9	157.9	159.7
5'	119.1	–	108.5
6'	130.2	–	128.2
Me	21.1	21.8	20.80, 20.85
OCH_2	–	63.6	–
2',6'	–	130.3	–
3',5'	–	114.2	–
1"	–	123.8 (J = 27)[a]	–
2"	–	160.2 (J = 26)[a]	–
3"	–	115.3 (J = 21)[a]	–
4"	–	130.4	–
5"	–	124.5	–
6"	–	130.7	–

[a] ^{13}C–^{19}F coupling constants, Hz.

contains the ^1H NMR parameters of compounds **VIa**, **VIIp**, and **VIIIr** as examples. On the basis of these data, we formulated some criteria which allowed us to identify compounds **VIa**–**VIj** and **VIIa**–**VIIp** as 5-aryl-1,2,3,4-tetrahydrobenzo[*a*]phenanthridines, and compounds **VIIIq**, **VIIIr**, **IXq**, and **IXr**, as tetrahydrobenz[*a*]acridines.

The ^1H NMR spectra of **VIa**–**VIj** and **VIIa**–**VIIp** are characterized by the presence of a doublet at δ 8.75–8.90 ppm from the 12-H proton, while the spectra of **VIIIq**, **VIIIr**, **IXq**, and **IXr** lack that signal. Due to shielding by the aryl substituent, the 1-H signal in the spectra of **VIIIq**, **VIIIr**, **IXq**, and **IXr** shifts upfield by about 1 ppm. The chemical shifts of protons on C^4, depending on the orientation of the methyl group, are also indicative: in the spectra of **VIa**–**VIj**, the difference in the chemical shifts of 4-H_{eq} and 4-H_{ax} does not exceed 0.2 ppm (δ 2.8–3.1 ppm), while the corresponding difference for compounds **VIIa**–**VIIp** is 0.5–0.6 ppm [δ, ppm: 2.9–3.1 (4-H_{eq}), 2.4–2.5 (4-H_{ax})]. An analogous pattern is observed in the variation of the chemical shift of 11-H in the spectra of **VIIIq**, **VIIIr**, **IXq**, and **IXr**.

The ^{13}C (Table 3) and HMBC spectra of **VIa**, **VIIp**, and **VIIIr** confirm the assumed structures. The NOESY spectrum of **VIa** contains correlation peaks 12-H/1-H_{ax} and 12-H/1-H_{eq}, while in the HMBC spectrum we observed correlation peaks 1-H_{ax}/C^{12c} and H–Me/C^1. These data indicate localization of the methyl group on C^2. Among other spatial contacts between protons, which are important for determination of steric structure, we should note similar chemical shifts of the 6'-H and 4-H protons. The correlation peaks 12-H/1-H_{ax} and 12-H/1-H_{eq} on the one hand and 2'-H, 6'-H/4-H_{ax} and 2'-H, 6'-H/4-H_{eq}, on the other, in the NOESY spectrum of **VIIp** unambiguously indicate the mode of junction of the heteroaromatic and aliphatic rings. The above noted similarity in the chemical shifts of the OCH_2 protons and 3'-H, 5'-H, and 6"-H is also important.

The correlation peaks 8a-H/C^{7a} and 8a-H/C^{Me} in the HMBC spectrum of **VIIIr** suggest localization of the methyl group on C^9. The presence of double sets of signals from some protons and carbon atoms is likely to result from rotational isomerism with respect to the C^{12}–$C^{1'}$ bond. This follows from the two-dimensional NOESY spectrum which shows correlations between 1-H and 3'-H and between 1-H and 5'-H simultaneously.

Our results led us to conclude that the reaction direction and the yield of the final product are largely determined by electronic nature of the substituent in the benzaldehyde molecule. Strong electron-donor substituents in the *meta* (aldehyde **IVq**) or *ortho*

position (**IVr**) reduce the nucleophilicity of the carbonyl group so strongly that the reaction of methylcyclohexanone with 2-naphthylamine to give enamine **F** becomes the predominant path. As a result, acridine derivatives **VIIIq**, **VIIIr**, **IXq**, and **IXr** are formed. The reaction with aldehydes **IVa**–**IVp** takes path *1* involving formation of Schiff base **A**. Here, electron-acceptor substituents in the *para* position facilitate addition of methylcyclohexanone anion. Therefore, the product yields are appreciably greater than in the reactions with aldehydes containing electron-donor substituents. On the other hand, electron-donor substituents in the *meta* position of the benzene ring do not affect the reaction direction, but the yield of the target product increases, presumably due to negative inductive effect. For example, the yield of 2-methyl-5-(3-hydroxyphenyl)-1,2,3,4-tetrahydrobenzo[*a*]phenanthridine (**VIb**) is greater by 29% than that of 2-methyl-5-(4-hydroxyphenyl)-1,2,3,4-tetrahydrobenzo[*a*]phenanthridine (**VIc**).

Disubstituted benzaldehydes require more severe conditions to be converted into fused phenanthridine derivatives. Thus the reactions with 3,4-dimethoxy- and 5-bromo-2-hydroxybenzaldehydes **IVh** and **IVj** were carried out over a period of 6 h in the presence of increased amount of the catalyst. The position of the methyl group in cyclohexanones **II** and **III** has no appreciable effect on the product yield.

The structure of tetrahydrobenzo[*a*]phenanthridines **VIa**–**VIj** and **VIIa**–**VIIIp** and tetrahydrobenz[*a*]-acridines **VIIIq**, **VIIIr**, **IXq**, and **IXr** was also confirmed by IR spectroscopy and gas chromatography–mass spectrometry. The IR spectra of **VIa–VIj**, **VIIa**–**VIIp**, **VIIIq**, **VIIIr**, **IXq**, and **IXr** lack absorption bands in the regions 1725–1650 cm^{-1}, which are typical of carbonyl stretching vibrations, and 3400–3300 cm^{-1} (νNH), in keeping with their cyclic structure. Two absorption bands at 2920–2880 cm^{-1} belong to C–H stretching vibrations of the methylene groups in the cyclohexane ring, and aromatic C–H bonds give rise to absorption at 3065–3050 cm^{-1}. The IR spectra of **VIh** and **VIIh** contain a strong absorption band at 2860 cm^{-1} due to C–H stretching vibrations in the methoxy group. Compounds **VId** and **VIId** show in the spectra absorption bands at 1365 and 1530 cm^{-1}, which correspond to symmetric and antisymmetric stretching vibrations of the nitro group.

In the mass spectra of 5-aryl-2-methyl-1,2,3,4-tetrahydrobenzo[*a*]phenanthridines **VIa**–**VIj** and 12-aryl-9-methyl-8,9,10,11-tetrahydrobenz[*a*]acridines **VIIIq** and **VIIIr**, the molecular ion peaks were the most abundant (I_{rel} = 100%), indicating that their molecules are stable to electron impact. In addition, $[M - 1]^+$ (I_{rel} = 80–95%) and $[M - CH_3]^+$ ion peaks (I_{rel} = 20–35%) were present. In the mass spectra of **VIIa**–**VIIp**, **IXq**, and **IXr**, the most intense peak was that from the $[M - CH_3]^+$ ion, while their molecular ion peaks $[M]^+$ had relative intensities of 60 to 80% ($[M - 1]^+$, I_{rel} = 28–51%). Phenanthridine derivatives **VIa**–**VIf**, **VIIa**–**VIIf**, and **VIIk**–**VIIp**, which were obtained from monosubstituted benzaldehydes, showed in the mass spectra a peak corresponding to the $[M - R]^+$ ion (I_{rel} = 9–25%), whereas no such peak was observed in the spectra of disubstituted (in the phenyl ring) phenanthridine derivatives **VIg**–**VIj** and **VIIg**–**VIIj** and acridine derivatives **VIIIq**, **VIIIr**, **IXq**, and **IXr**.

EXPERIMENTAL

The IR spectra were recorded on a Nicolet Protege-460 Fourier spectrometer. The ^1H and ^{13}C NMR spectra were measured on Tesla BS-567A (100 MHz) and Bruker AC-500 (500 MHz) spectrometers from 2–5% solutions in DMSO-d_6 using tetramethylsilane as internal reference. The mass spectra were run on a Chrommas Hewlett–Packard HP 5890/5972 GC–MS system using an HP-5MS column (70 eV).

5-Aryl-2(3)-methyl-1,2,3,4-tetrahydrobenzo[*a*]-phenanthridines VIa–VIj and VIIa–VIIp (*general procedure***).** A mixture of 0.01 mol of substituted benzaldehyde **IVa**–**IVp**, 0.01 mol of 2-naphthylamine (**I**), 0.03 mol of 3- or 4-methylcyclohexanone **II** or **III**, 5–8 drops of hydrochloric acid, and 60 ml of ethanol was heated for 1–6 h under reflux (on a water bath). The resulting tarry material was treated with diethyl ether under stirring. After 1–2 h, the precipitate was filtered off and recrystallized from methanol at least twice. We thus isolated R-benzyl-2-naphthylamines **Vc**, **Ve**, **Vh**, and **Vm**. Below are given compound no., yield (%), mp (°C), and ν(NH) (cm^{-1}): **Vc**, 45, 143, 3390; **Ve**, 32, 128, 3386; **Vh**, 50, 118, 3395; **Vm**, 48, 140, 3380. The filtrate was left to stand for 24 h and more, and the precipitate was filtered off, washed with warm (30–40°C) 25% aqueous ammonia, and recrystallized in succession from 1-butanol and benzene (or toluene) until the product purity was no less than 95%. In some cases, no product precipitated upon treatment of the tarry mixture with diethyl ether. Then the mixture was treated with ammonia as described above and stirred for 6–10 h. The precipitate was filtered off

and recrystallized. Compounds **VIe**, **VIi**, **VIj**, **VIIe**, **VIIi**, and **VIIj** were thus isolated.

12-Aryl-9(10)-methyl-8,9,10,11-tetrahydrobenz-[*a*]acridines VIIIq, VIIIr, IXq, and IXr were synthesized in a similar way from benzaldehydes **IVq** and **IVr**, respectively.

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