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Synthesis of 5-Aryl-1-methyl-1,2,3,4-tetrahydrobenzo[*a*]phenanthridines

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Abstract—5-Aryl-1-methyl-1,2,3,4-tetrahydrobenzo[*a*]phenanthridines were synthesized by cascade heterocyclization of the corresponding substituted benzaldehydes with 2-methylcyclohexanone and naphthalen-2-amine in a polar solvent in the presence of hydrochloric acid.

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In the preceding communications [1, 2] we described a one-step synthesis of tetrahydrobenzo[*a*]-phenanthridine derivatives having an asymmetric carbon atom via three-component condensation of naphthalen-2-amine, substituted benzaldehyde, and cyclohexanone (or 3- or 4-methylcyclohexanone). In continuation of our studies in this line we examined reaction of naphthalene-2-amine with substituted benzaldehydes and 2-methylcyclohexanone. As a result, we isolated tetrahydrobenzo[*a*]phenanhtridine derivatives whose molecules contain benzoquinoline and cyclohexene fragments. The products attract interest from the viewpoint of synthesis on their base of compounds possessing antitumor [3] and antimicrobial [4] activity, as well as of antibiotics [5]. The presence of a methyl group in the cyclohexene ring makes the product molecules more similar to structural analogs of natural alkaloids [6].

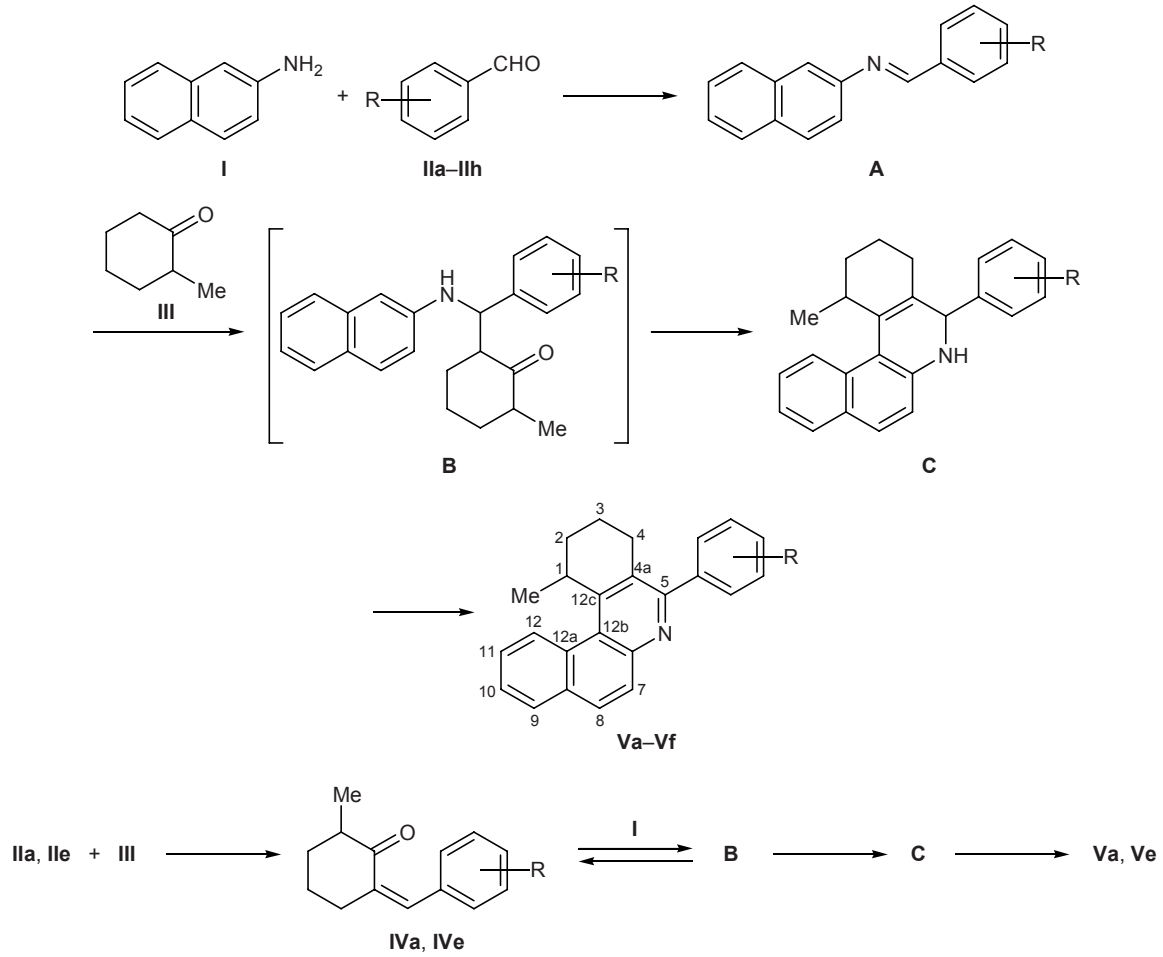
The reactions were carried out by heating equimolar amounts of naphthalen-2-amine (**I**) and substituted benzaldehyde **IIa**–**IIh** and 3 equiv of 2-methylcyclohexanone in boiling ethanol containing a catalytic amount of hydrochloric acid (reaction time 2–6 h). The products were isolated as the corresponding hydrochlorides by treatment of the tarry reaction mixture with diethyl ether, followed by recrystallization of the precipitate from methanol. The hydrochlorides were converted into free bases **Va**–**Vf** by treatment with aqueous ammonia and subsequent repeated recrystallizations.

Theoretically, two reaction paths are possible. The first of these involves initial condensation of naphthalen-2-amine (**I**) with aldehyde **II** to give Schiff base **A** which then reacts with 2-methylcyclohexanone. Unstable intermediate **B** thus formed may undergo reversible decomposition into 6-arylmethylidene-2-methylcyclohexanone **IV** and naphthelen-2-amine or heterocyclization to thermodynamically unstable hexahydrobenzo[*a*]phenanthrifine derivative **C**. Aromatization of the latter with oxygen dissolved in the reaction medium yields 5-aryl-1-methyl-1,2,3,4-tetrahydrobenzo[*a*]phenanthridines **Va**–**Vf** as final products (Scheme 1).

According to the second path, the first step is condensation of 2-methylcyclohexanone (**III**) with aldehyde **II**, leading to 6-arylmethylidene-2-methylcyclohexanone **IV** in which the double bond is activated due to conjugation with the carbonyl group. Intermediate **IV** is capable of taking up naphthalene-2-amine molecule with formation of the same intermediate **B** as in the first path, and the subsequent transformations of **B** (see above) give final products **V**.

We succeeded in isolating 6-arylmethylidene-2-methylcyclohexanones **IVa** and **IVe** by carrying out the reactions of 2-methylcyclohexanone with aldehydes **IIa** and **IIe** in aqueous suspension in the presence of alkali. Compounds **IVa** and **IVe** were brought into reaction with naphthalen-2-amine under the conditions of the three-component condensation. As a result, we obtained 5-phenyl- and 5-(4-ethoxyphenyl)-1-methyl-1,2,3,4-tetrahydrobenzo[*a*]phenanthridines **Va** and **Ve**. We believe that the first path is more probable, since 6-arylmethylidene-2-methylcyclohexanones **IV** are unlikely to be formed in acid medium. Although

Scheme 1.



R = H (**a**), 4-Cl (**b**), 4-Br (**c**), 4-O_2N (**d**), 4-EtO (**e**), 3,4-OCH_2O (**f**), 4-HO (**g**), 3,4-$(HO)_2$ (**h**).

we failed to obtain compounds **IV** in the absence of alkali, the formation of structure **IV** as a result of decomposition of intermediate **B** and the existence of equilibrium **B** ↔ **IV** + **I** seem to be probable.

It should be noted that the yields of compounds **Va**–**Vf** in the examined reactions were lower than the yields of the condensation products of the same aldehydes with naphthalen-2-amine and 3- or 4-methylcyclohexanone [2]. Presumably, the reason is that the presence of methyl group reduces mobility of the hydrogen atom located in the neighboring position to the carbonyl group. The reactions of naphthalen-2-amine with 2-methylcyclohexanone and 4-hydroxy- and 2,4-dihydroxybenzaldehydes **IIg** and **IIh** having electron-donating substituents gave no expected condensation products (unlike analogous reactions with 3- or 4-methylcyclohexanones [2]), whereas the yield of compound **Vf** in the condensation with disubstituted benzaldehyde **IIf** was as low as 11%.

The IR spectra of compounds **Va**–**Vf** lacked absorption bands typical of stretching vibrations of carbonyl and secondary amino groups (1720–1650 and 3400–3300 cm^{-1}, respectively). Methylene C–H bonds in the cyclohexene ring gave two absorption bands at 2930–2920 and 2880– 2861 cm^{-1}, and bands in the region 3076–2931 cm^{-1} were assigned to stretching vibrations of aromatic C–H bonds. A strong absorption band at 2852–2840 cm^{-1} (C–H bonds in the OC_2H_5 group) was observed in the IR spectra of **IVe** and **Ve**. Compounds **Vb** and **Vc** displayed absorption bands due to stretching vibrations of C–Cl and C–Br bonds, respectively, at 834 and 570 cm^{-1}. Absorption bands at 1350 and 1518 cm^{-1} in the spectrum of 4-nitrophenyl derivative **Vd** belonged to symmetric and antisymmetric vibrations of the nitro group.

In the ^1H NMR spectra of **Va**–**Vf** we observed a doublet at δ 1.50–1.52 ppm from protons in the 1-methyl group; protons in the tetrahydrobenzophen-

anthridine fragment resonated as a doublet at δ 8.79–8.87 ppm and multiplets at δ 7.42–8.02 ppm. Multiplet signals in the regions δ 1.65–2.10, 2.90–3.08, and 4.38–5.00 ppm corresponded to protons in the cyclohexene ring.

The molecular ion peaks in the mass spectra of 6-arylmethylidene-2-methylcyclohexanones **IVa** and **IVe** and tetrahydrobenzophenanthridines **Va**–**Vf** had the maximal intensity, indicating that their molecular ions are fairly stable. In addition, $[M - 1]^+$ ion peaks (I_{rel} 36–64%) were observed in the spectra of **Va**–**Vf**, and the mass spectra of **IVa**, **IVe**, and **Va**–**Vf** contained peaks from $[M - CH_3]^+$ ions (I_{rel} 19–62%). The fragmentation pattern of benzophenanthridines **Vb**–**Ve** having a *p*-substituted phenyl ring involved elimination of the *para*-substituent from the molecular ion ($[M - R]^+$, I_{rel} 13–31%.

EXPERIMENTAL

The IR spectra were recorded in KBr (or films) on a Nicolet Protégé-460 spectrometer with Fourier transform. The ^{1}H NMR spectra were measured on a Bruker AC-500 instrument at 500 MHz from 5% solutions in DMSO-d_6 using tetramethylsilane as internal reference. The mass spectra (electron impact, 70 eV) were obtained on a Chrommas Hewlett-Packard 5890/5972 GC–MS system (HP-5MS capillary column, 30 m× 0.25 mm, stationary phase 5% phenylmethylsilicone, film thickness 0.25 μm; injector temperature 250°C; samples were injected as solutions in CH_2Cl_2).

6-Benzylidene- and 5-(4-ethoxybenzylidene)-2-methylcyclohexan-1-ones **IVa** and **IVe** were synthesized from 2-methylcyclohexanone and benzaldehyde (**IIa**) or 4-ethoxybenzaldehyde (**IIb**), respectively, by stirring the reactants in water in the presence of alkali according to the procedure described in [7].

6-Benzylidene-2-methylcyclohexan-1-one (IVa). Yield 35%, colorless crystals, mp 123°C. IR spectrum, ν, cm^{-1}: 2985, 2961, 2930, 2867, 1830, 1671, ^{1}H NMR spectrum, δ, ppm: 1.22 d (3H, CH_3); 1.63 m, 1.88 m, 2.09 m, 2.47 m, and 2.67 m (6H, CH_2); 3.02 m (1H, CH); 7.32 m (1H, =CH); 7.37–7.40 m (5H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 200 (100), 185 (22), 184 (13). Found, %: C 84.00; H 8.03. $C_{14}H_{16}O$. Calculated, %: C 84.00; H 8.00.

6-(4-Ethoxybenzylidene)-2-methylcyclohexan-1-one (IVe). Yield 22%, colorless crystals, mp 131°C. IR spectrum, ν, cm^{-1}: 3076, 2920, 2860, 2852, 1730, 1703, 1664, 1635, 1527, 1482, 1317, 1302, 1219. ^{1}H NMR spectrum, δ, ppm: 1.29 d (3H, CH_3), 1.42 t (3H, $CH_2C\mathbf{H}_3$), 1.70–2.04 m (4H, CH_2), 2.98 m (2H, CH_2), 3.07 m (1H, CH), 4.06 (2H, OCH_2), 6.97 m (1H, =CH), 7.02 d (2H, H_{arom}), 8.70 d (2H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 228 (100), 213 (19), 212 (10), 139 (15), 140 (27). Found, %: C 84.22; H 8.76. $C_{16}H_{20}O$. Calculated, %: C 84.21; H 8.78.

5-Aryl-1-methyl-1,2,3,4-tetrahydrobenzo[*a*]-phenanthridines Va–Vf (*general procedure*). *a*. A mixture of 0.01 mol of substituted benzaldehyde **IIa**–**IIf**, 0.01 mol of naphthalen-2-amine (**I**), 0.03 mol of 2-methylcyclohexanone (**III**), and 5–8 drops of hydrochloric acid in 60 ml of ethanol was heated for 2–6 h under reflux (on a water bath). The resulting tarry material was treated with diethyl ether. After ~24 h a solid separated from the ether solution; it was filtered off, washed with warm (30–40°C) 25% aqueous ammonia, and repeatedly recrystallized from 1-butanol and benzene until no less than 95% purity of the product.

b. A mixture of 0.01 mol of 6-arylmethylidene-2-methylcyclohexan-1-one **IVa** or **IVe**, 0.01 mol of naphthalen-2-amine, and 8 drops of hydrochloric acid in 50 ml of ethanol was heated for 5 h under reflux (on a water bath). The products were isolated as described above in *a*.

1-Methyl-5-phenyl-1,2,3,4-tetrahydrobenzo[*a*]-phenanthridine (Va). Yield 52%, colorless crystals, mp 170°C. IR spectrum, ν, cm^{-1}: 3443, 3035, 2930, 1543, 1422, 1371, 1313, 1005, 764, 704. ^{1}H NMR spectrum, δ, ppm: 1.51 d (3H, CH_3), 1.65–1.98 m (4H, 2-H, 3-H), 2.90–3.01 m (2H, 4-H), 4.38–4.82 m (1H, 1-H); 7.48 m, 7.60 m, and 7.72 m (7H, H_{arom}); 7.84 m, 7.90 m, and 7.94 m (3H, H_{arom}); 8.87 d (1H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 323 (100), 322 (36), 308 (40), 246 (31), 231 (46). Found, %: C 89.19; H 6.47; N 4.32. $C_{24}H_{21}N$. Calculated, %: C 89.16; H 6.50; N 4.33.

5-(4-Chlorophenyl)-1-methyl-1,2,3,4-tetrahydrobenzo[*a*]phenanthridine (Vb). Yield 60%, colorless crystals, mp 200°C. IR spectrum, ν, cm^{-1}: 3426, 2931, 2864, 1710, 1556, 1439, 1087, 1012, 834, 738. ^{1}H NMR spectrum, δ, ppm: 1.53 d (3H, CH_3), 1.70–2.10 m (4H, 2-H, 3-H), 2.91–3.04 m (2H, 4-H), 4.41–5.00 m (1H, 1-H); 7.48 m and 7.60 m (6H, H_{arom}); 7.80 m, 7.89 m, and 7.96 m (3H, H_{arom}); 8.82 d (1H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 357 (100), 356 (52), 342 (51), 322 (13), 246 (22), 231 (38). Found, %: C 80.65; H 5.59; Cl 9.82; N 3.89. $C_{24}H_{20}ClN$. Calculated, %: C 80.67; H 5.60; Cl 9.80; N 3.92.

5-(4-Bromophenyl)-1-methyl-1,2,3,4-tetrahydrobenzo[*a*]phenanthridine (Vc). Yield 20%, colorless crystals, mp 190–192°C. IR spectrum, ν, cm^{-1}: 3062, 3058, 2860, 1724, 1517, 1409, 1392, 1237, 822, 570. ^{1}H NMR spectrum, δ, ppm: 1.52 d (3H, CH_3), 1.68–2.00 m (4H, 2-H, 3-H), 2.90–3.00 m (2H, 4-H), 4.41–4.89 m (1H, 1-H); 7.42 m and 7.60 m (6H, H_{arom}); 7.84 m, 7.89 m, and 7.93 m (3H, H_{arom}); 8.80 d (1H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 402 (100), 401 (63), 387 (42), 322 (24), 246 (29), 231 (22), 166 (27). Found, %: C 71.64; H 5.00; Br 19.93; N 3.49. $C_{24}H_{20}BrN$. Calculated, %: C 71.64; H 4.98; Br 19.90; N 3.48.

1-Methyl-5-(4-nitrophenyl)-1,2,3,4-tetrahydrobenzo[*a*]phenanthridine (Vd). Yield 25%, colorless crystals, mp 187–188°C. IR spectrum, ν, cm^{-1}: 2933, 2861, 1750, 1600, 1518, 1439, 1350, 1313, 1105, 858, 833, 735, 701. ^{1}H NMR spectrum, δ, ppm: 1.52 d (3H, CH_3), 1.70–2.09 m (4H, 2-H, 3-H), 2.90–3.08 m (2H, 4-H), 4.42–4.45 m (1H, 1-H), 7.60–7.73 m (2H, H_{arom}), 7.80–8.00 m (5H, H_{arom}), 8.39 d (2H, H_{arom}), 8.84 d (1H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 368 (100), 367(60), 353 (62), 322 (31), 246 (33), 231 (25). Found, %: C 78.25; H 5.40; N 7.64. $C_{24}H_{20}N_2O_2$. Calculated, %: C 78.26; N 5.43; N 7.61.

5-(4-Ethoxyphenyl)-1-methyl-1,2,3,4-tetrahydrobenzo[*a*]phenanthridine (Ve). Yield 37%, colorless crystals, mp 178°C. IR spectrum, ν, cm^{-1}: 3050, 2910, 2880, 2840, 1730, 1613, 1549, 1436, 1452, 1325, 1371, 1239, 847. ^{1}H NMR spectrum, δ, ppm: 1.47 t (3H, $CH_2C\mathbf{H}_3$), 1.50 d (3H, CH_3), 1.70–2.08 m (4H, 2-H, 3-H), 2.90–3.00 m (2H, 4-H), 4.10 q (2H, OCH_2), 4.40–4.48 m (1H, 1-H), 7.52–7.63 m (2H, H_{arom}), 7.75–8.02 m (5H, H_{arom}), 8.37 d (2H, H_{arom}), 8.79 d (1H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 367 (100), 366 (50), 352 (47), 322 (24), 307 (11), 246 (49), 231 (34). Found, %: C 85.00; H 6.80; N 3.84. $C_{26}H_{25}NO$. Calculated, %: C 85.01; H 6.82; N 3.82.

5-(1,3-Benzodioxol-5-yl)-1-methyl-1,2,3,4-tetrahydrobenzo[*a*]phenanthridine (Vf). Yield 11%, colorless crystals, mp 175°C. IR spectrum, ν, cm^{-1}: 3061, 3050, 2920, 2878, 2710, 1810, 1754, 1531, 1406, 1372, 1203, 865. ^{1}H NMR spectrum, δ, ppm: 1.51 d (3H, CH_3), 1.70–2.08 m (4H, 2-H, 3-H), 2.91–3.02 m (2H, 4-H), 3.62 s (2H, OCH_2O), 4.63 m (1H, 1-H); 7.48 m and 7.60 m (6H, H_{arom}); 7.80 m, 7.89 m, and 7.96 m (3H, H_{arom}); 8.82 d (1H, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 367 (100), 366 (64), 352 (32), 246 (43), 231 (12). Found, %: C 81.76; H 5.71; N 3.84. $C_{25}H_{21}NO_2$. Calculated, %: C 81.74; H 5.72; N 3.81.

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