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SIMPLE SYNTHESIS OF 6-SUBSTITUTED 4a-METHYL-1,2,3,4,4a,10b-HEXA-HYDROPHENANTHRIDINES AND -9,10-BENZOPHENANTHRIDINES

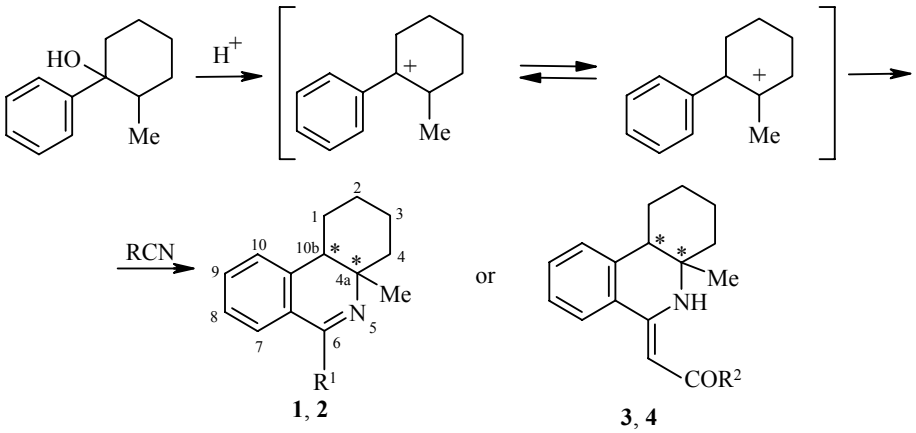
Yu. V. Shklyaev and Yu. V. Nifontov

A route has been developed for the synthesis of 6-substituted 4a-methyl-1,2,3,4,4a,10b-hexahydrophenanthridines and -9,10-benzophenanthridines. The effect has been shown of the nature of the substituent at position 10 of the ring on the chemical shift of the proton at position 10b.

Keywords: 9,10-benzophenanthridines, hexahydrophenanthridines, diastereomers, Ritter reaction.

Aromatic phenanthridines have been studied adequately well [1-4]. However there is only one study on the chemistry and biological activity of hydrogenated phenanthridines, which is probably linked with the absence of convenient methods of synthesizing them [3].

The synthesis of 6-R-4a-methyl-1,2,3,4,4a,10b-hexahydrophenanthridines (R = Me, CH_2COOEt) from 1-methyl-2-phenylcyclohexanol has been described [5]. In spite of its superficial simplicity it requires the use of the difficultly available 2-phenylcyclohexanone and in addition a mixture of all the possible diastereomers is formed.



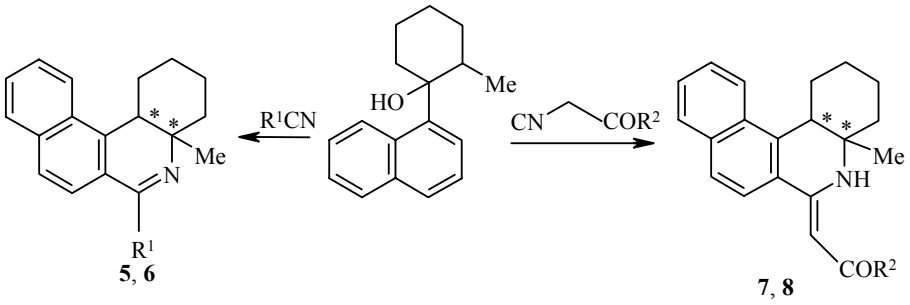
1, **2** **3**, **4**

R = Me, SMe, CH_2COOEt, CH_2CONH_2; **1** R^1 = Me, **2** R^1 = SMe, **3** R^2 = OEt, **4** R^2 = NH_2

Institute of Technical Chemistry, Urals Branch of the Russian Academy of Sciences, Perm 614990; e-mail: cheminst@mpm.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, Vol. 40, No. 5, pp. 706-710, May, 2004. Original article submitted October 23, 2001.

It was discovered by us that identical products are also formed by the Ritter reaction from 2-methyl-1-phenylcyclohexanol, obtained from phenyl magnesium bromide and 2-methylcyclohexanone. As was shown in [6], when alkyl substituents are present at the second carbon atom of 1-aryl-2,2-dialkylethanols, transposition of the reaction center is observed, and the tertiary carbocation formed in this way, which is not stabilized by a neighboring aryl residue, is the only one which can interact with a nitrile group. 2-Methyl-1-phenylcyclohexanol reacts with nitriles in a similar manner with the formation of phenanthridines **1-4**.

The Ritter reaction proceeds similarly and for 2-methyl-1-(1-naphthyl)cyclohexanol, obtained from 1-naphthylmagnesium bromide and 2-methylcyclo-hexanone, leads to the preparation of the previously unknown 6-substituted 4a-methyl-1,2,3,4,4a,10b-hexahydro-9,10-benzophenanthridines **5-8**.

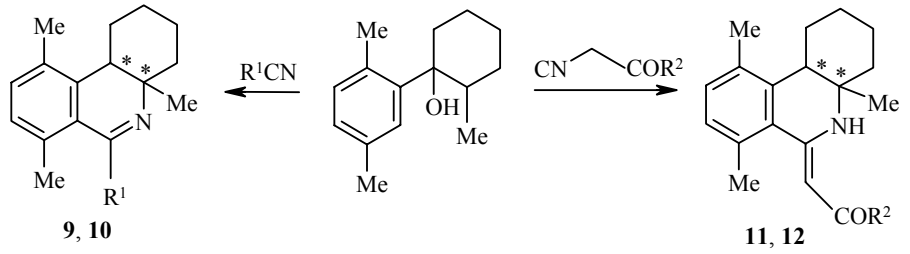


5, **6** **7**, **8**

5 R^1 = Me, **6** R^1 = SMe, **7** R^2 = OEt, **8** R^2 = NH_2

A characteristic feature of compounds **1-8** is the presence of a signal for the 10b proton of the phenanthridine ring in the ^{1}H NMR spectrum. For the 6-R-1,2,3,4,4a,10b-derivatives **1-4** this signal is found at 2.70-2.73 ppm. For compounds **5-8** the signal is displaced to substantially lower field (for **5** to 3.52, for **6** to 3.38, for **7** to 3.50, and for **8** to 3.39 ppm), which, in our view, may be explained by the significant deshielding of this proton due to the π-electrons of the naphthalene ring. In addition this signal is a doublet of doublets, which in combination with the singlet of the methyl group in position 4a of the ring, indicates the presence of only one pair of enantiomers. Additional confirmation is given by the presence of only one signal for the vinyl proton and the heterocyclic NH for compounds **3, 4, 7,** and **8**.

With the aim of clarifying the role of the substituent in position 10 of the phenanthridine ring we studied the behavior in this reaction of 1-(2,5-dimethylphenyl)-2-methylcyclohexanol, obtained from 2,5-xylylmagnesium bromide and 2-methylcyclohexanone. It turned out that in this case the preparation was observed of only one pair of enantiomers of derivatives of 4a,7,10-trimethyl-1,2,3,4,4a,10b-hexahydro-phenanthridines **9-12**. However the signal of the proton at position 10b of the ring at 2.52-2.59 ppm was displaced towards high field in comparison with compounds **1-4**, which is explained by the shielding of this proton by the methyl group at position 10.



9, **10** **11**, **12**

9 R^1 = Me, **10** R^1 = SMe, **11** R^2 = OEt, **12** R^2 = NH_2

TABLE 1. Spectral Characteristics of Compounds **1-12**

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)				
		3H, s, 4a-Me	8H, complex. m, $(CH_2)_4$	1H, dd, 10b-H*	H arom.	Other protons
1-HOC_6H_4COOH*[2]	—	0.73	1.35-2.00	2.70	6.80-7.78 (8H, m)	2.47 (3H, s, 6-CH_3)
2	1620, 1580, 1500, 1320	0.80	1.12-1.96	2.72	7.10-7.56 (4H, m)	2.54 (3H, s, 6-SCH_3)
3	3280, 1735, 1605, 1580	0.83	1.16-2.01	2.73	7.02-7.49 (4H, m)	1.20 (3H, t, CH_3 ester); 4.10 (2H, q, OCH_2); 5.19 (1H, s, CH); 8.80 (1H, s, NH)
4	3440, 3360, 3190, 1650, 1610	0.82	1.21-2.00	2.72	7.13-7.71 (4H, m)	5.21 (1H, s, CH); 6.32 (2H, br. s, NH_2); 8.60 (1H, s, NH)
5	1620, 1580, 1500	0.75	1.00-2.00	3.52	7.50-7.93 (5H, m); 8.20 (1H, d, 7-H)	2.40 (3H, s, 6-CH_3)
6	1622, 1585, 1510	0.80	0.99-2.10	3.38	7.60-7.95 (5H); 8.25 (1H, d, 7-H)	2.47 (3H, s, SCH_3)
7	3250, 1725, 1610	0.97	1.43-1.92	3.50	7.60-7.99 (5H, m); 8.23 (1H, d, 7-H)	1.22 (3H, t, CH_3 ester); 4.10 (2H, q, OCH_2); 5.23 (1H, s, CH); 8.90 (1H, s, NH)
8	3310, 3245, 1645, 1610	0.95	1.20-1.80	3.39	7.50-7.80 (5H, m); 8.15 (1H, d, 7-H)	5.23 (1H, s, CH); 6.25 (2H, br. s, NH_2); 9.40 (1H, s, NH)
9-HOC_6H_4COOH*[2]	—	0.73	1.22-1.99	2.52	6.93-7.66 (6H, m)	2.43 (3H, s, 6-CH_3); 2.31 (3H, s, 7-CH_3); 2.28 (3H, s, 10-CH_3)
10	1620, 1585, 1510	0.58	1.30-2.05	2.55	6.88 (1H, d); 6.93 (1H, d)	2.27 (3H, s, 10-CH_3); 2.34 (3H, s, 7-CH_3); 2.60 (3H, s, 6-SCH_3)
11	3280, 1735, 1605, 1580	0.86	1.30-1.90	2.53	7.05(1H, d); 7.12 (1H, d)	1.22 (3H, t, *J* = 7.4, CH_3 ester); 2.27 (3H, s, 10-CH_3); 2.48 (3H, s, 7-CH_3); 4.08 (2H, q, *J* = 7.3, OCH_2); 4.73 (1H, s, CH); 9.03 (1H, s, NH)
12	3440, 3355, 3190, 1650, 1605	0.81	1.20-1.80	2.59	7.00 (1H, d); 7.04 (1H, d)	2.26 (3H, s, 10-CH_3); 2.47 (3H, s, 7-CH_3); 4.79 (1H, s, CH); 6.20 (2H, br. s, NH_2); 9.60 (1H, s, NH)

* *J* = 8.3 Hz.

*[2] Compounds **1** and **9** were identified as salicylates.

TABLE 2. Physicochemical Properties of Compounds **1-12**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
1-HOC_6H_4COOH*	$C_{22}H_{25}NO_3$	75.33 / 75.21	7.03 / 7.12	4.11 / 3.99	123-124 (ethyl acetate)	39
2	$C_{15}H_{19}NS$	73.60 / 73.47	7.85 / 7.76	5.84 / 5.71	85-86 (hexane)	50
3	$C_{18}H_{23}NO_2$	75.50 / 75.79	8.12 / 8.07	5.00 / 4.91	64-65 (hexane)	61
4	$C_{16}H_{20}N_2O$	75.31 / 75.00	8.01 / 7.81	10.80 / 10.94	129-130 (benzene)	66
5	$C_{19}H_{21}N$	86.83 / 86.69	8.05 / 7.98	5.12 / 5.33	117-118 (hexane)	49
6	$C_{19}H_{21}NS$	77.00 / 77.29	7.20 / 7.12	4.84 / 4.75	69-70 (hexane)	62
7	$C_{22}H_{25}NO_2$	78.61 / 78.81	7.55 / 7.46	4.31 / 4.18	115-116 (hexane)	81
8	$C_{20}H_{22}N_2O$	78.21 / 78.43	7.30 / 7.19	9.31 / 9.15	210-211 (ethanol)	83
9-HOC_6H_4COOH*	$C_{24}H_{29}NO_3$	75.85 / 75.99	7.72 / 7.65	3.79 / 3.69	127-128 (ethanol)	39
10	$C_{17}H_{23}NS$	74.83 / 74.67	8.37 / 8.48	5.20 / 5.13	102-103 (hexane)	53
11	$C_{20}H_{27}NO_2$	76.80 / 76.68	8.54 / 8.63	4.60 / 4.47	89-90 (hexane)	59
12	$C_{18}H_{24}N_2O$	75.91 / 76.06	8.53 / 8.51	10.00 / 9.86	119-120 (ethyl acetate)	62

* Compounds **1** and **9** were identified as salicylates.

EXPERIMENTAL

The IR spectra were taken on a UR 20 spectrophotometer in nujol. The ^1H NMR spectra were recorded on a Bruker AM 300 spectrophotometer (300 MHz) in DMSO-d_6, internal standard was TMS.

The progress of reactions and the purity of the compounds obtained were checked by TLC on Silufol UV 254 plates (chloroform–acetone, 9:1), visualizer was a 0.5% solution of chloranil in toluene.

2-Methylcyclohexanone (from Lancaster) was used without preliminary purification. Synthesis of the initial carbinols was effected by a standard procedure from 2-methylcyclohexanone and the appropriate arylmagnesium bromide in diethyl ether. After distillation in vacuum the obtained mixture of carbinol and the corresponding styrene (~3 : 1, according to data of ^1H NMR and liquid chromatography) was used in the reaction without further purification allowing for the molar content of the components.

6-Substituted 4a-Methyl-1,2,3,4,4a,10b-hexahydrophenanthridines and Ethyl Esters of (4a-Methyl-1,2,3,4,4a,5,6,10b-octahydro-6-phenanthridinylidene)acetic Acid (1-3, 5-7, 9-11) (General Procedure). A mixture of carbinol (0.1 mol) and nitrile (0.1 mol) was added dropwise with stirring and cooling (0-10°C) to conc. H_2SO_4 (50 ml). The mixture was stirred for 30 min, diluted with water (300 ml), and extracted with toluene (50 ml). The organic layer was rejected, and the remainder was made alkaline with aqueous ammonia to pH 8-9. The separated solid (for compounds **2**, **3**, **5-7**, **10**, **11**) was removed, washed with water, dried in the air, and recrystallized from an appropriate solvent.

Compounds **1** and **9** were oils and were identified as salicylates. A solution of salicylic acid (1.38 g, 0.01 mol) in dry ether (20 ml) was added in one portion to a solution of substituted 4a-methyl-1,2,3,4,4a,10b-hexahydrophenanthridine **1** or **9** (0.01 mol) in dry diethyl ether. The mixture was stirred for 1 min and left for 30 min. The separated solid was removed, washed on the filter with ether (20 ml), and recrystallized.

Amides of (4a-Methyl-1,2,3,4,4a,5,6,10b-octahydro-6-phenanthridinylidene)acetic Acids (4, 8, 12) (General Procedure). Cyanoacetamide (1.68 g, 0.02 mol) was dissolved with stirring in cold conc. H_2SO_4 (15 ml) and the appropriate carbinol (4.28 g, 0.02 mol) was added rapidly in one portion. The mixture was stirred for 15 min, diluted with water (100 ml), and extracted with benzene (20 ml). The organic layer was rejected, and the aqueous layer made alkaline to pH 8-9. The precipitated solid was filtered off, washed with water, dried in the air, and recrystallized.

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