Regioisomerism in the Ritter reaction
1. Synthesis of 3,3,5,6,7-, 3,3,6,7,8-, 3,3,5,7,8-, and 3,3,5,6,8-pentamethyl-3,4-dihydroisoquinolines from 1,2,3- and 1,2,4-trimethylbenzenes

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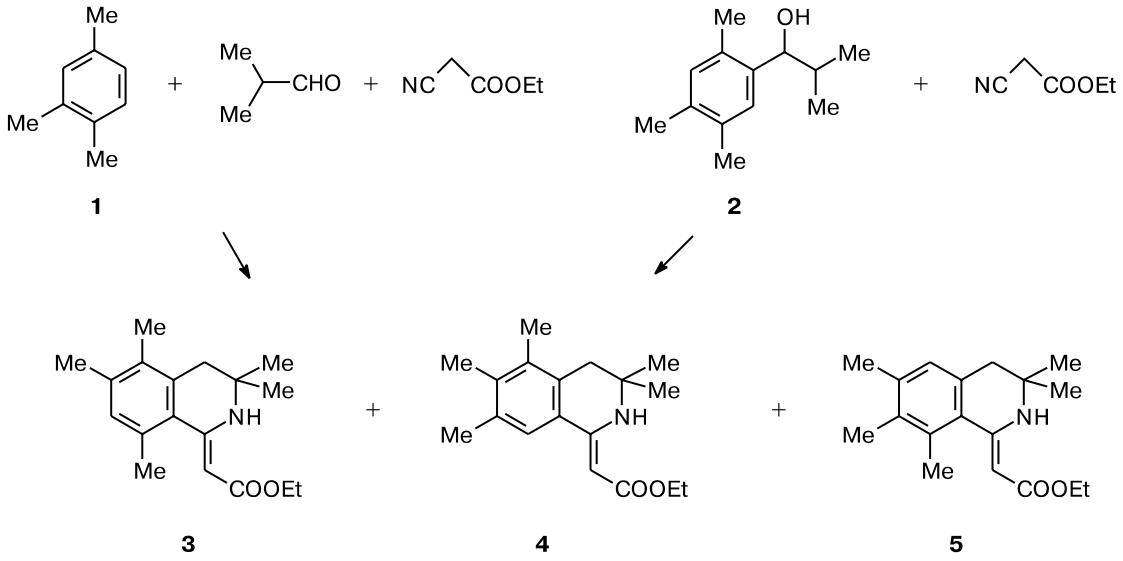
Reactions of 1,2,3- or 1,2,4-trimethylbenzene with isobutyraldehyde and ethyl cyanoacetate (ECA) or reactions of the corresponding 1-aryl-2-methylpropan-1-ols with ECA afforded isomeric 3,3,5,6,7-, 3,3,6,7,8-, 3,3,5,7,8-, and 3,3,5,6,8-pentamethyl-3,4-dihydroisoquinolines. Isomerization is explained as the ring opening of a spiran intermediate in two possible ways followed by the Jacobsen rearrangement.

Key words: Ritter reaction, pseudocumene, 1,2,3-trimethylbenzene, isobutyraldehyde, nitriles, spirocyclization, isomerization.

Reactions of activated arenes with nitriles and isobutyraldehyde in conc. H_2SO_4 are known to yield derivatives of 3,3-dimethyl-3,4-dihydroisoquinoline.[1,2] We found that the reaction of 1,2,4-trimethylbenzene (pseudocumene, **1**), isobutyraldehyde, and ethyl cyanoacetate (ECA) gives a mixture of three products (Scheme 1) in the ≈1 : 5 : 1 ratio determined from the integral signal intensities in the ^{1}H NMR spectrum. According to NOE data, the products obtained are ethyl 3,3,5,6,8-pentamethyl-1,2,3,4-tetrahydroisoquinolyliden-1-acetate (**3**) and its isomeric ethyl 3,3,5,6,7-pentamethyl- (**4**) and 3,3,6,7,8-pentamethyl-1,2,3,4-tetrahydroisoquinolyliden-1-acetates (**5**).

Scheme 1



3 : 4 : 5 = 1 : 5 : 1

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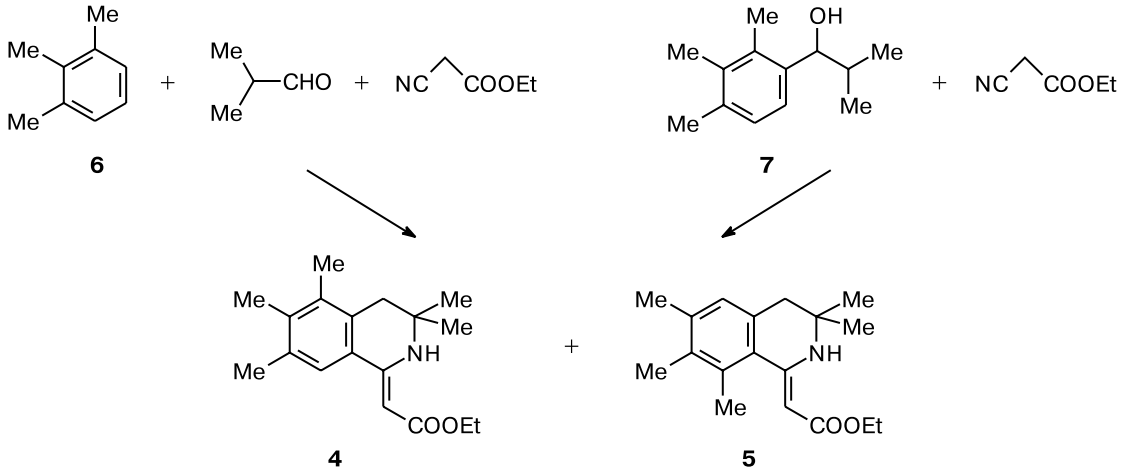
Scheme 2

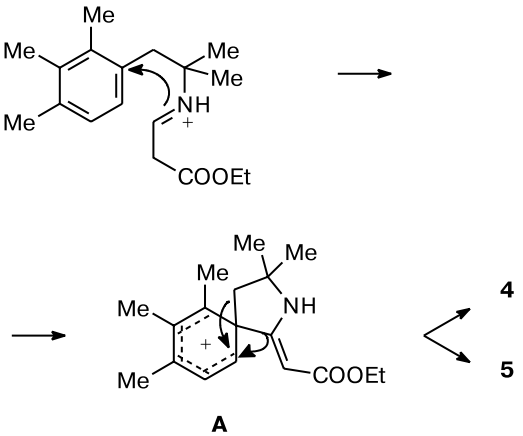


The reaction of ECA with a separately prepared alcohol **2** yielded the same products.

Compounds **4** and **5** were also formed by the three-component synthesis from 1,2,3-trimethylbenzene (**6**), isobutyraldehyde, and ECA or from alcohol **7** (separately prepared from 1-bromo-2,3,4-trimethylbenzene and isobutyraldehyde) and ECA (**4** : **5** = 5 : 1) (Scheme 2).

The formation of products **4** and **5** from arene **6** and alcohol **7** can be explained by the skeleton isomerization of spiro intermediate **A** in two pathways (Scheme 3).

Scheme 3



The structure of the carbon framework of compound **4** was refined from the 2D spectrum (COLOC, Table 1) containing cross peaks between the singlet at δ 7.40 for the aromatic proton and ^{13}C NMR singlet signals at δ 124.2 (C_{ipso}), 138.3 (C_o), and 156.5 (C(1)). The vinylic proton (H(1′), s, δ 5.12) exhibits cross peaks with singlets for the C atoms at the double bond at δ 77.0 and 156.5. The protons of the 4-CH_2 group (s, δ 2.76) show cross peaks with the C atom of the 4-CH_2 group (t, δ 39.1), C(4a) (s, δ 131.2), and C(5) (s, δ 134.2).

The reaction of compound **6** or **7** with methyl thiocyanate proceeds analogously (Scheme 4); in this case, crystallization of the resulting mixture of sulfides **9** and **10** gave pure compound **9**, from which isocarbostyril **11** was obtained. The minor isomers **10** and **12** were identified only spectroscopically (^1H NMR data).

Similar processes were observed earlier in the Bischler—Napieralski cyclization[3] of *N*-phenethyl- and *N*-[2-(6′-methoxynaphth-2′-yl)]ethylbenzamides, which is genetically linked with the Ritter reaction since both involve the formation of the same intermediate.[4]

In the case of pseudocumene **1**, the reaction intermediate seems to be a spiro compound **B** (Scheme 5), which should first lead to isoquinolines **3** and **8**, the latter being dominant. Then, product **8** probably undergoes the Jacobsen rearrangement[5] observed upon heating of tetraalkylbenzenes in H_2SO_4. Insofar as the Jacobsen reaction is characterized by the migration of alkyl from the *ortho*- to *para*-position relative to the electron-withdrawing group, the Me group in the *in situ* protonated isoquinoline **8** apparently migrates predominantly from C(8) to C(6) to give product **4** (minor migration of the Me group from C(5) to C(6) affords product **5**). It is beyond question that isoquinoline **3** containing the Me group in position 6 of the ring, undergoes no rearrangement.

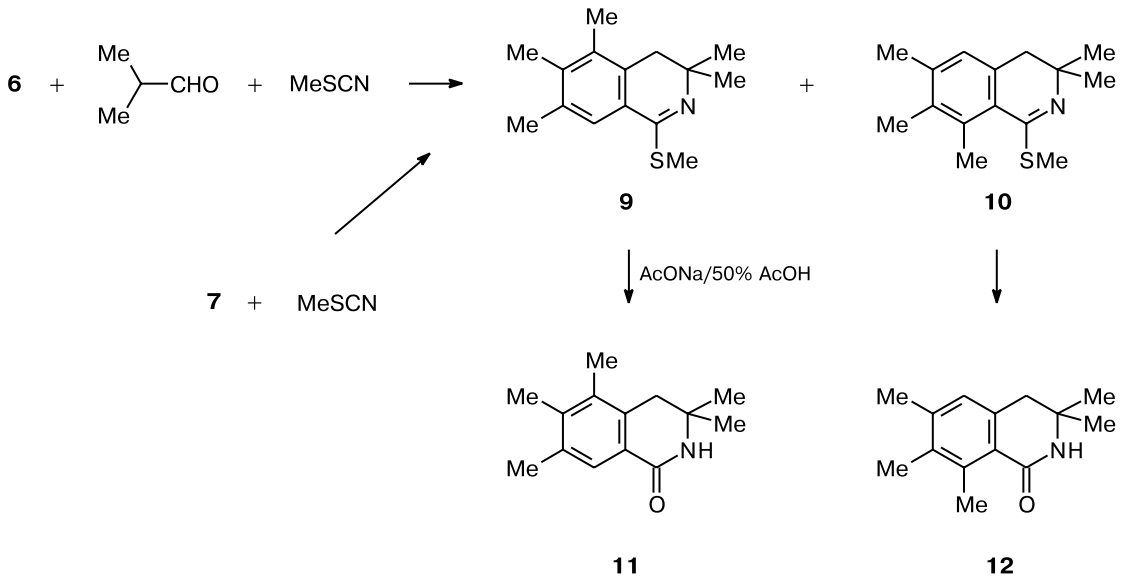
When the reaction time was reduced from 15 to 2 min, product **8** was also isolated; however, the Jacobsen rearrangement of these compounds seems to proceed very rapidly since the yield of isoquinoline **8** at the lowest possible reaction time was no higher than 10%.

Table 1. COLOC 2D NMR spectrum of compound **4** ("+" indicates the presence of a cross peak)*

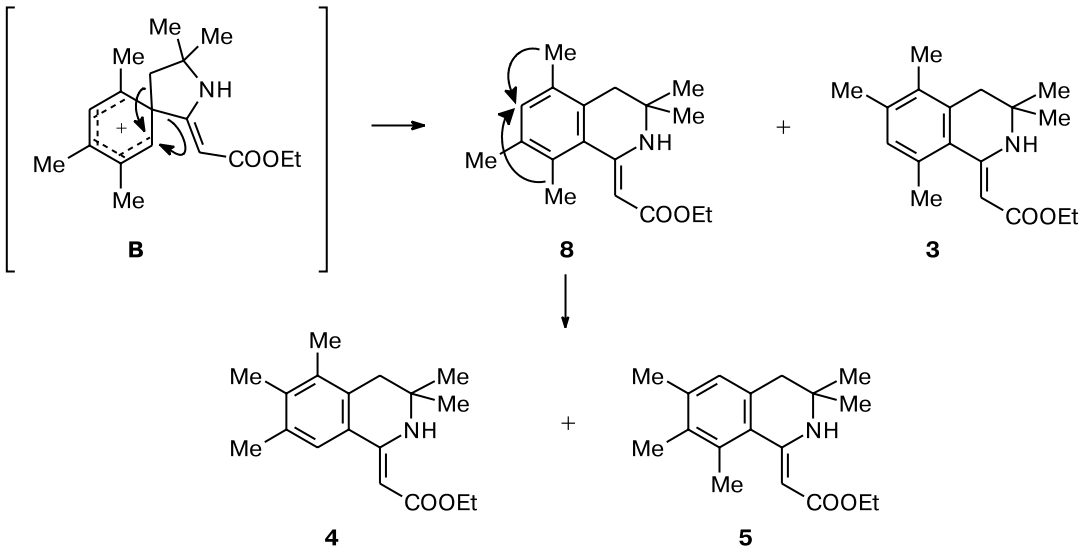
δ_{13C}	δ_{1H}							
	1.28 (3′,3′-Me_2)	2.20 (5′-Me)	2.23 (6′-Me)	2.34 (7′-Me)	2.76 (C(4)H_2)	5.12 (C(1′)H)	7.40 (C(8)H)	9.00 (NH)
15.4 (5′-Me)	—	+	—	—	—	—	—	—
16.3 (6′-Me)	—	—	+	—	—	—	—	—
20.9 (7′-Me)	—	—	—	+	—	—	+	—
28.9 (3′,3′-Me_2)	+	—	—	—	+	—	—	—
39.1 (C(4)H_2)	+	—	—	—	+	—	—	—
49.0 (C(3))	+	—	—	—	+	—	—	—
77.0 (C(1′)H)	—	—	—	—	—	+	—	—
124.2 (C(8)H)	—	—	—	+	—	—	+	—
125.7 (C(8a))	—	+	—	—	+	+	—	+
131.2 (C(4a))	—	+	+	—	+	—	+	—
134.2 (C(5))	—	+	+	—	+	—	—	—
134.3 (C(6))	—	—	+	+	—	—	—	—
138.3 (C(7))	—	—	—	+	—	—	+	—
156.5 (C(1))	—	—	—	—	—	+	+	—

* The data for the ethoxycarbonyl group are not included.

Scheme 4



Scheme 5



Experimental

Melting points were determined on a PTP instrument and are given noncorrected. IR spectra were recorded on a UR-20 spectrophotometer (Nujol). ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 at 303 K on Bruker DRX-500 (500.13 MHz) and Bruker AM-300 instruments (75.470 MHz), respectively. The residual signal for protons in DMSO-d_6 (δ 2.50) was used as a reference signal in ^{1}H NMR spectra; the chemical shift of the signal for DMSO-d_6 in ^{13}C NMR spectra was δ 39.5. 2D spectra were recorded according to Bruker standard procedures. The mixing time in NOESY spectra was 500 ms. The HMBC experiment was optimized for a spin-spin coupling constant of 8 Hz. Mass spectra were recorded on a Finnigan MAT instrument under standard conditions (EI, 70 eV). The course of the reaction was monitored and the purity of the compounds obtained was checked by TLC on Silufol UV-254 plates in $CHCl_3$—Me_2CO (9 : 1); spots were visualized with 0.5% chloranil in toluene.

Three-component synthesis from 1,2,4-trimethylbenzene. A mixture of pseudocumene (1.2 g, 10 mmol), isobutyraldehyde (0.72 g, 10 mmol), and ECA (1.13 g, 10 mmol) was added dropwise at 5 to 10 °C for 1 min to stirred 95% H_2SO_4 (15 mL). Stirring was continued for 3 to 5 min and the mixture was poured into crushed ice (100 g). The organic material was extracted with benzene (25 mL), the benzene was separated, and the aqueous layer was neutralized with ammonium carbonate to pH 8—9. The product that formed was extracted with $CHCl_3$ (2×50 mL) and dried over $MgSO_4$. The solvent was removed in a rotary evaporator to give a mixture of products (2.3 g). Column chromatography of the mixture (silica gel 30/50 deactivated with triethylamine, benzene—ether (35 : 1)) gave pure compound **4** (1.5 g, 52%), m.p. 83—84 °C (hexane) and isoquinoline **5** (170 mg), m.p. 71—72 °C (hexane). The purity of compound **3** was 85% (content of isoquinoline **4** was 15%), and the purity of compound **5** was 80% (isoquinoline **4**, 20%) (^{1}H NMR data).

Ethyl 3,3,5,6,8-pentamethyl-1,2,3,4-tetrahydroisoquinolylidene-1-acetate (3). ^{1}H NMR, δ: 1.22 (s, 6 H, Me_{gem}); 1.30 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.2 Hz); 2.19 (s, 3 H, 5′-Me); 2.32 (s, 3 H, 6′-Me); 2.51 (s, 3 H, 8′-Me); 2.78 (s, 2 H, C(4)H_2); 4.20 (q, 2 H, OCH_2Me, J = 7.2 Hz); 4.81 (s, 1 H, H_{vinyl}); 6.97 (s, H, H(7) arom.); 9.11 (br.s, 1 H, NH).

Ethyl 3,3,5,7,8-pentamethyl-1,2,3,4-tetrahydroisoquinolylidene-1-acetate (8), m.p. 71—72 °C (hexane). Found (%): C, 75.19; H, 8.72; N, 4.93. $C_{18}H_{25}NO_2$. Calculated (%): C, 75.26; H, 8.71; N, 4.88. IR, ν/cm^{-1}: 3250, 2960, 2850, 1640, 1600, 1370. ^{1}H NMR, δ: 1.22 (s, 6 H, Me_{gem}); 1.29 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.2 Hz); 2.22 (s, 3 H, 5′-Me); 2.26 (s, 3 H, 7′-Me); 2.44 (s, 3 H, 8′-Me); 2.67 (s, 2 H, 4-CH_2); 4.15 (q, 2 H, $OC\underline{H}_2Me$, J = 7.2 Hz); 4.76 (s, 1 H, H_{vinyl}); 7.01 (s, 1 H, H arom.); 9.12 (br.s, 1 H, NH).

Ethyl 3,3,5,6,7-pentamethyl-1,2,3,4-tetrahydroisoquinolylidene-1-acetate (4) (three-component synthesis). A mixture of 1,2,3-trimethylbenzene (1.2 g, 10 mmol), isobutyraldehyde (0.72 g, 10 mmol), and ethyl cyanoacetate (1.13 g, 10 mmol) was added dropwise at 5 to 10 °C for 3 min to stirred 95% H_2SO_4 (15 mL). Stirring was continued for 15 min and the mixture was poured into crushed ice (100 g) and treated as described above for the synthesis from pseudocumene. Column chromatography (silica gel 30/50 deactivated with triethylamine, benzene—ether (35 : 1)) gave pure compound **4** (1.5 g, 52%; m.p. 83—84 °C (hexane)) and an inseparable mixture of esters **4** and **5** (**5** : **4** = 4 : 1, ^{1}H NMR data).

Ester 4. Found (%); C, 75.13; H, 8.62; N, 4.95. $C_{18}H_{25}NO_2$. Calculated (%): C, 75.26; H, 8.71; N, 4.88. IR, ν/cm^{-1}: 3260, 2960, 2850, 1630, 1600, 1380. ^{1}H NMR, δ: 1.28 (s, 6 H, 2 Me_{gem}); 1.30 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.1 Hz); 2.20 (s, 3 H, 5′-Me); 2.23 (s, 3 H, 6′-Me); 2.34 (s, 3 H, 7′-Me); 2.76 (s, 2 H, C(4)H_2); 4.16 (q, 2 H, $OC\underline{H}_2CH_3$, J = 7.1 Hz); 5.12 (s, 1 H, H_{vinyl}); 7.40 (s, 1 H, H(8)); 9.00 (br.s, 1 H, NH). ^{13}C NMR, δ: 14.8 ($CH_2\underline{C}H_3$); 15.4 (5′-Me); 16.3 (6′-Me); 20.9 (7′-Me); 28.9 (Me_{gem}); 39.1 (C(4)H_2); 49.0 (C(3)); 58.4 ($\underline{C}H_2Me$); 77.0 (C_{vinyl}); 124.2 (C(8)); 125.7 (C(8a)); 131.2

(C(4a)); 134.2 (C(5)); 134.3 (C(6)); 138.3 (C(7)); 156.5 (C(1)); 171.3 (C=O).

^{1}H NMR difference spectrum of ethyl 3,3,6,7,8-pentamethyl-1,2,3,4-tetrahydroisoquinolyliden-1-acetate (**5**), δ: 1.22 (s, 6 H, 2 Me_{gem}); 1.29 (t, 3 H, $OCH_2C\underline{H}_3$, J = 7.2 Hz); 2.21 (s, 3 H, 6′-Me); 2.30 (s, 3 H, 7′-Me); 2.48 (s, 3 H, 8′-Me); 4.15 (q, 2 H, $OC\underline{H}_2Me$, J = 7.2 Hz); 4.77 (s, 1 H, C(4)H_2); 6.81 (s, 1 H, H(5)); 9.12 (br.s, 1 H, NH).

1-Bromo-2,3,4-trimethylbenzene. Water (100 mL) was added to 1,2,3-trimethylbenzene (60 g, 0.5 mol) in 400 mL of CCl_4. Then Br_2 (80 g, 0.5 mol) was added dropwise to the stirred solution so that it remained slightly colored. After the addition was completed, the reaction mixture was stirred for 30 min. The aqueous layer was separated and the organic layer was washed with water (2×200 mL), saturated $NaHCO_3$ (200 mL), and again water to pH 7. The solvent was removed in a rotary evaporator and ethanol (200 mL) and solid KOH (20 g) were added to the residue. The solution was stirred for 20 min, heated in the boiling solvent for 30 min, and poured into water (700 mL). The product was extracted with *tert*-butyl methyl ether (2×300 mL) and dried with $MgSO_4$. The solvent was removed in a water bath and the residue was distilled *in vacuo*. A fraction with b.p. 110—115 °C (15 Torr) was collected. The yield of 1-bromo-2,3,4-trimethylbenzene was 65 g (65%). The ^{1}H NMR spectrum was identical with that described earlier.[6]

2-Methyl-1-(2′,3′,4′-trimethylphenyl)propan-1-ol (7). Freshly distilled isobutyraldehyde (15 g, 0.21 mol) in 50 mL of dry THF was added dropwise to a cooled (water + ice) solution of 2,3,4-trimethylphenylmagnesium bromide (0.2 mol) prepared from 1-bromo-2,3,4-trimethylbenzene (40 g, 0.2 mol) and magnesium (5 g, 0.21 mol) in 150 mL of dry THF. The stirred reaction mixture was heated for 30 min, cooled, and treated with saturated NH_4Cl. The organic layer was separated and the product was extracted from the aqueous layer with *tert*-butyl methyl ether (2×150 mL). The combined organic layers were washed with water and dried over $MgSO_4$. The solvent was removed in a water bath and the residue was distilled *in vacuo*. A fraction with b.p. 140—145 °C (5 Torr) was collected. The yield of compound **7** was ≈30 g (77%). Found (%): C, 81.33; H, 10.61. $C_{13}H_{20}O$. Calculated (%): C, 81.20; H, 10.48.

Reaction of compound 7 with ethyl cyanoacetate. A mixture of compound **7** (1.92 g, 0.01 mol) and ethyl cyanoacetate (1.13 g, 0.01 mol) was added dropwise to conc. H_2SO_4 (15 mL). The reaction mixture was treated as described above for the three-component synthesis. The total yield and the ratio between products **4** and **5** were identical with those obtained in the three-component synthesis.

Three-component synthesis involving methyl thiocyanate (compounds 9 and 10). The synthesis was carried out as described for compound **4**. An oil obtained from 1,2,3-trimethylbenzene (1.2 g, 10 mmol), isobutyraldehyde (0.72 g, 10 mmol), and methyl thiocyanate (0.73 g, 10 mmol) was distilled *in vacuo*. A fraction with b.p. 150—160 °C (5 Torr) was collected. The yield was 1.9 g (77%). Found (%): C, 73.0; H, 8.59; N, 5.58; S, 13.01. $C_{15}H_{21}NS$. Calculated (%): C, 72.87; H, 8.50; N, 5.67; S, 12.95. On prolonged storage, the mass solidified and double crystallization from MeOH gave pure 3,3,5,6,7-pentamethyl-1-methylthio-3,4-dihydroisoquinoline (**9**)[7] in 52% yield, m.p. 55—56 °C. Found (%): C, 72.99; H, 8.60; N, 5.50; S, 12.90. $C_{15}H_{21}NS$. Calculated (%): C, 72.87; H, 8.50; N, 5.67; S, 12.96. IR, ν/cm^{-1}: 1610, 1580, 1500. ^{1}H NMR, δ: 1.15 (s, 6 H, 2 Me_{gem}); 2.18 (s, 3 H, 5-Me); 2.22 (s, 3 H, 6-Me); 2.28 (s, 3 H, 7-Me); 2.35 (s, 3 H, SMe); 2.61 (s, 2 H, C(4)H_2); 7.90 (s, 1 H, H(8) arom.).

^{1}H NMR difference spectrum of 3,3,6,7,8-pentamethyl-1-methylthio-3,4-dihydroisoquinoline (**10**), δ: 1.11 (s, 6 H, 2 Me_{gem}); 2.15 (s, 3 H, 6-Me); 2.26 (s, 3 H, 7-Me); 2.32 (s, 3 H, 8-Me); 2.47 (s, 3 H, SMe); 2.54 (s, 2 H, 4-CH_2); 6.33 (s, 1 H, H(5) arom.).

3,3,5,6,7-Pentamethyl-3,4-dihydroisocarbostyril (11). One to two scales of dry NaOH were added to a solution of compound **9** (2.47 g, 0.01 mol) in 50% AcOH (10 mL). The reaction mixture was heated for 1 h and worked up as described earlier[8] to give compound **11** (2.1 g). Crystallization from benzene gave pure isocarbostyril **11** (1.9 g, 88%), m.p. 219—220 °C. Found (%): C, 77.54; H, 8.84; N, 6.55. $C_{14}H_{19}NO$. Calculated (%): C, 77.42; H, 8.76; N, 6.45. IR, ν/cm^{-1}: 3195, 1660, 1595, 1510. ^{1}H NMR, δ: 1.25 (s, 6 H, Me_{gem}); 2.20 (s, 3 H, 5-Me); 2.24 (s, 3 H, 6-Me); 2.33 (s, 3 H, 7-Me); 2.77 (s, 2 H, C(4)H_2); 7.31 (br.s, 1 H, NH); 7.72 (s, 1 H, H(8) arom.).

^{1}H NMR difference spectrum of 3,3,6,7,8-pentamethyl-3,4-dihydroisocarbostyril (**12**), δ: 1.20 (s, 6 H, Me_{gem}); 2.18 (s, 3 H, 6-Me); 2.24 (s, 3 H, 7-Me); 2.29 (s, 3 H, 8-Me); 2.73 (s, 2 H, C(4)H_2); 6.77 (s, 1 H, H(5) arom.); 7.20 (br.s, 1 H, NH).

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References

1. Yu. V. Shklyaev and Yu. V. Nifontov, *Izv. Akad. Nauk, Ser. Khim.,* 2002, 780 [*Russ. Chem. Bull., Int. Ed.*, 2002, **51**, 844].
2. Yu. V. Shklyaev, R. R. Ismagilov, Yu. V. Nifontov, I. B. Abdrakhmanov, and A. G. Tolstikov, *Khimiya i komp´yuternoe modelirovanie. Butlerovskie soobshcheniya* [*Chemistry and Computer Modeling. Butlerov Communications*], 2002, **6**, 67 (in Russian).
3. S. Doi, N. Shirai, and Y. Sato, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2217.
4. G. Fodor and S. Nagubandi, *Tetrahedron*, 1980, **36**, 1297.
5. L. I. Smith, in *Organic Reactions*, Ed. R. Adams, Wiley, New York, 1942, **1**.
6. R. H. Mitchell, Y. Lai, and R. V. Williams, *J. Org. Chem.*, 1979, **44**, 4733.
7. Yu. V. Nifontov, Ph.D. (Chem.) Thesis, Inst. Tekhn. Khim., Ural Otd., Ross. Akad. Nauk, Perm, 2001, p. 74; 133.
8. Yu. V. Shklyaev, V. A. Glushkov, N. B. Belogub, and I. L. Misyura, *Khim. Geterotsikl. Soedin.*, 1996, 800 [*Chem. Heterocycl. Compd.*, 1996 (Engl. Transl.)].

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