Spirocyclohexadienones
4.* Synthesis and dienone-phenolic rearrangement of 1-R-3,3-dialkyl-2-azaspiro[4.5]deca-1,6,9-trien-8-ones

O. G. Ausheva,[a] V. A. Glushkov,[a]★ S. N. Shurov,[b] and Yu. V. Shklyaev[a]

[a]*Institute of Technical Chemistry, Ural Branch of the Russian Academy of Sciences, 13 ul. Lenina, 614600 Perm, Russian Federation. Fax: +7 (342 2) 12 6237. E-mail: cheminst@mpm.ru*
[b]*Department of Chemistry, Perm State University, 15 ul. Bukireva, 614600 Perm, Russian Federation. Fax: +7 (342 2) 39 6367. E-mail: info@psu.ru*

The reactions of 1-(*p*-methoxyphenyl)-2-methylpropan-1-ol or α-cyclohexyl-*p*-methoxybenzyl alcohol with nitriles RCN in concentrated sulfuric acid afforded 1-R-3,3-dialkyl-2-azaspiro[4.5]deca-1,6,9-trien-8-ones. The stability of the latter toward the dienone-phenolic rearrangement depends on the nature of the substituent R. The reaction mechanism was studied by the semiempirical quantum-chemical AM1 method.

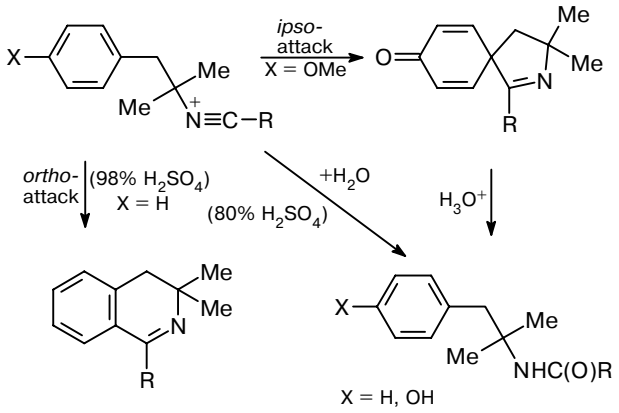
Key words: secondary alcohols, nitriles, Ritter reaction, cyclohexa-2,5-dien-4-one, 1-pyrrolines, spiro compounds, dienone-phenolic rearrangement, amides of carboxylic acids, semiempirical quantum-chemical AM1 calculations.

Heterocyclic systems spiro-fused at position 4 of cyclohexa-2,5-dien-1-one occur in nature[2,3] and serve as intermediates in the synthesis of alkaloids of the *Amaryllidaceae* family.[4] Procedures were developed for the synthesis of cyclohexa-2,5-dienospirolactams,[5] -spiroisoxazolines,[6] and -spirobenzofurans.[7]

Spiro derivatives of cyclohexa-2,5-dien-1-ones have been described in the last few years.[8,9] These compounds were synthesized by intramolecular cyclization catalyzed by Lewis acids through the electrophilic *ipso*-attack on *para*-substituted anisoles. Recently, we have developed a procedure for the synthesis of heterocyclic spirocyclohexadienones, *viz.*, 1-R-3,3-dimethyl-2-azaspiro[4.5]deca-1,6,9-trien-8-ones, based on the Ritter reaction.[10] Possible ways of stabilizing the key product of the Ritter reaction, *viz.*, the nitrilium cation, are shown in Scheme 1.

Depending on the nature of the substituent in the aromatic nucleus and on the concentration of the acid used (in our case, H_2SO_4), the Ritter reaction can take three pathways. Previously, it has been established that if X = H, the reaction performed in 98% sulfuric acid proceeded as the *ortho*-attack to form 3,4-dihydroisoquinolines;[11,12] however, lowering of the H_2SO_4 concentration to 80% resulted in the nucleophilic attack of water on the nitrilium cation to yield amides, which are products of the normal Ritter reaction.[13,14] The peculiar reaction pathway was observed in the case of X = OMe: the nitrilium cation was stabilized through the *ipso*-attack

Scheme 1



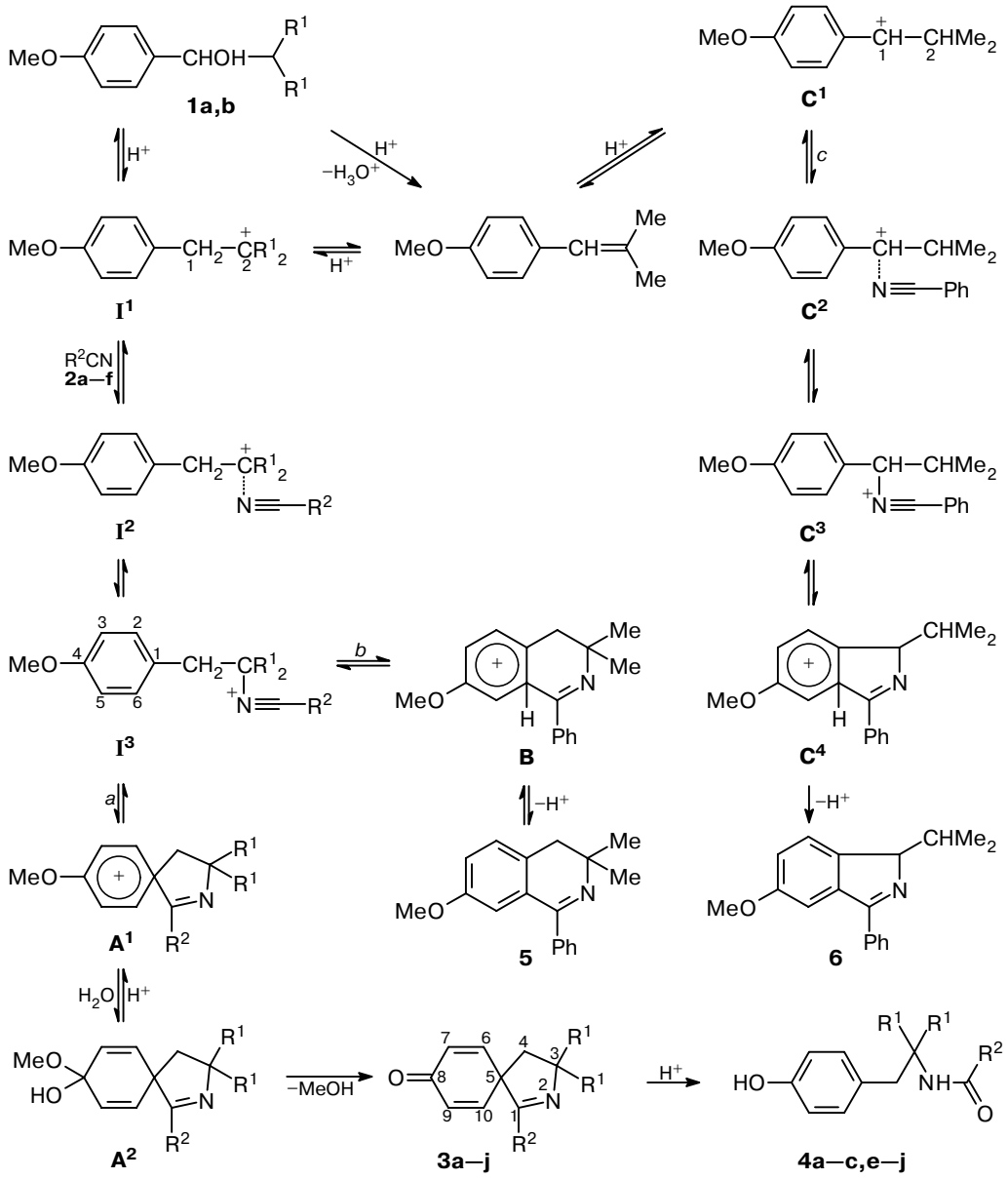
to form 1-R-3,3-dimethyl-2-azaspiro[4.5]deca-1,6,9-trien-8-ones.[10] Analogous spiro compounds have been postulated previously as intermediates in the synthesis of methoxy-substituted isoquinolines;[15,16] however, these compounds have not been isolated. Intermediates with the spiropyrroline structure can either be stabilized through the 1,2-shift to generate 3,4-dihydroisoquinolines[16] or undergo the dienone-phenolic rearrangement to *p*-hydroxyphenylethylamides. In the present study, we synthesized spiroheterocyclic compounds **3a—d**, which were then subjected to the dienone-phenolic rearrangement in an acidic medium to obtain amides **4a—c**,**e—j**. The synthesis of spiranes **3a—f** is detailed in Scheme 2.

* For Part 3, see Ref. 1.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 9, pp. 1571—1579, September, 2001.

1066-5285/01/5009-1648 $25.00

Scheme 2



Compound	R^1 or $R^1{}_2$	Compound	R^2	Compound 3, 4:	R^1 or $R^1{}_2$	R^2
1a	Me	**2a**	SMe	**3a, 4a**	Me	SMe
1b	$(CH_2)_5$	**2b**	SBn	**3b, 4b**	Me	SBn
		2c	CH_2CO_2Et	**3c, 4c**	$(CH_2)_5$	SMe
		2d	Ph	**3d**	$(CH_2)_5$	SBn
		2e	Bn	**3e, 4e**	Me	CH_2CO_2Et
		2f	CH_2Cl	**3f, 4f**	Me	Ph
				3g, 4g	$(CH_2)_5$	CH_2CO_2Et
				3h, 4h	$(CH_2)_5$	Ph
				3i, 4i	$(CH_2)_5$	Bn
				3j, 4j	$(CH_2)_5$	CH_2Cl

Note: only for $\mathbf{I^2}$—$\mathbf{A^2}$: R^1 = Me, R^2 = Ph.

Table 1. Characteristics and data of elemental analysis of compounds **3**, **4**, and **7**

Compound	Yield (%)	M.p./°C (solvent for crystallization)	Found / Calculated (%)			Molecular formula
			C	H	N	
3a	52	95—97 [95—97[10]] (EtOH—water)	65.33 / 65.12	6.74 / 6.83	6.41 / 6.33	$C_{12}H_{15}NOS$
3b	13	115—116 (ether)	72.58 / 72.69	6.36 / 6.44	5.15 / 4.71	$C_{18}H_{19}NOS$
3c	14	104—106 (ether)	69.12 / 68.93	7.40 / 7.33	5.25 / 5.36	$C_{15}H_{19}NOS$
3d	17	140—142 (ether)	74.47 / 74.74	7.08 / 6.87	4.38 / 4.15	$C_{21}H_{23}NOS$
4a	97	139—140 (CH_2Cl_2—hexane)	60.19 / 60.22	7.16 / 7.16	5.77 / 5.85	$C_{12}H_{17}NO_2S$
4b	27	131—132 (EtOH—water)	68.44 / 68.54	6.56 / 6.71	4.60 / 4.44	$C_{18}H_{21}NO_2S$
4c	17	177—178.5 (AcOEt—hexane)	64.67 / 64.48	7.49 / 7.58	5.09 / 5.01	$C_{15}H_{21}NO_2S$
4e	64	100—102 (toluene—hexane)	64.75 / 64.50	7.39 / 7.58	5.18 / 5.01	$C_{15}H_{21}NO_4$
4f	58	141—142 (dichloroethane)	75.88 / 75.81	7.05 / 7.11	5.27 / 5.20	$C_{17}H_{19}NO_2$
4g	15	119—121 (toluene)	67.54 / 67.69	7.85 / 7.89	4.60 / 4.38	$C_{18}H_{25}NO_4$
4h	38	148—150 (EtOH—water)	77.77 / 77.64	7.33 / 7.49	4.50 / 4.52	$C_{20}H_{23}NO_2$
4i	29	158—160 (toluene)	78.05 / 77.98	7.83 / 7.79	4.62 / 4.33	$C_{21}H_{25}NO_2$
4j	28	140—141 (CH_2Cl_2—hexane)	64.09 / 63.94	7.17 / 7.15	5.11 / 4.97	$C_{15}H_{20}ClNO_2$
7	72	109—110	76.52 / 76.27	7.40 / 7.47	5.16 / 4.94	$C_{18}H_{21}NO_2$

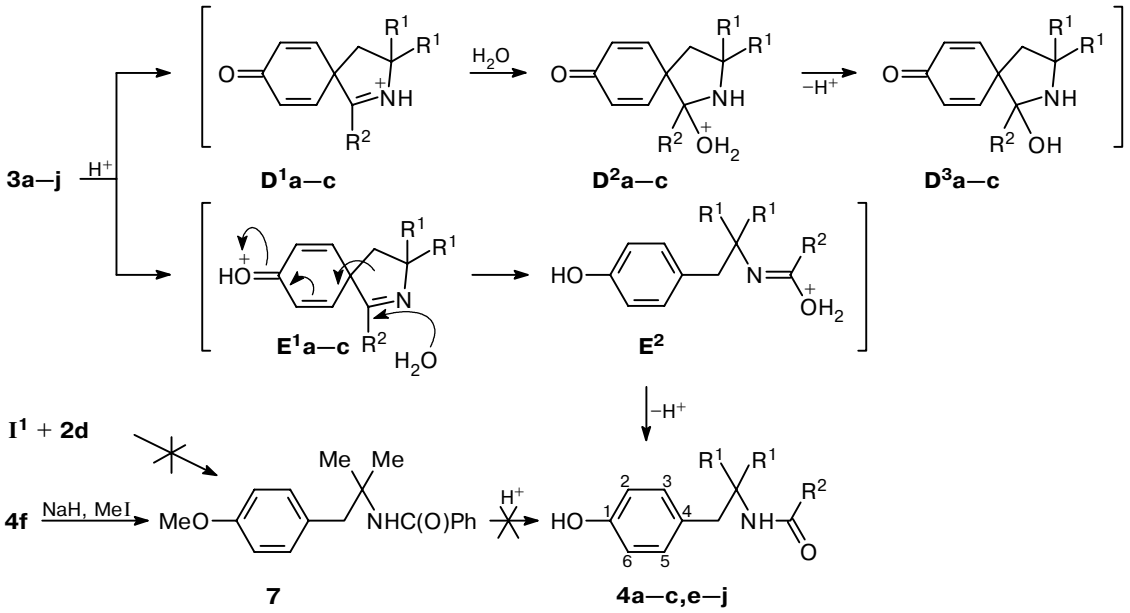
In these reactions, both carbinols **1a,b** and 1-(*p*-methoxyphenyl)-2-methylprop-1-ene, which is generated from carbinol **1a** in the course of the reaction in the presence of 98% H_2SO_4, can be used as a source of carbocations.

As can be seen from Scheme 2, the key stage of the synthesis of spiropyrrolines **3a—d** involves the *ipso*-attack on the nitrilium cation at the *para* position with respect to the MeO group in intermediate **I**[3]. The resulting compounds **3a—d** and **4a—c**,**e—j** are presented in Table 1. The low yields of spiropyrrolines **3b—d** (13—17%) are, apparently, accounted for by side processes involving both the initial carbinols **1a,b** and thiocyanates **2a,b** in acidic media.

It should be noted that only spiranes **3a—d** with sulfur-containing substituents can be prepared by these reactions. Under the reaction conditions, spiropyrrolines **3e—h** containing electron-withdrawing substituents at the C(1) atom (Ph or CH_2COOEt) and spiranes **3i,j** were found to undergo the dienone-phenolic rearrangement even upon isolation giving rise to the corresponding amides **4e—j**. In this case, the dienone-phenolic rearrangement can be considered as a peculiar kind of hydrolysis of spiranes at the C(1)—C(5) bond. Apparently, the fact that spiranes containing electron-withdrawing groups at the C(1) atom of the pyrroline ring readily underwent hydrolysis is associated with an increase in the partial positive charge on the C(1) atom, which promotes the attack of a water molecule (Scheme 3). Spiranes **3a—c** with sulfur-containing substituents appeared to be more stable toward hydrolysis due, apparently, to the positive mesomeric effect of the sulfur atom.

It has been possible to carry out the dienone-phenolic rearrangement of sulfur-containing spiranes **3a,b** by heating their aqueous-ethanolic solutions with 10% H_2SO_4. The reactions proceeded smoothly to form the corresponding amides **4a,b** (see the Experimental section). Since *p*-methoxy-substituted amides of type **7** can be normal products of the Ritter reaction (Scheme 1), the question arose of whether amides **4a—c,e—j** can be formed by the classical Ritter reaction[13,14] accompanied by acidic elimination of the MeO group in the course of treatment, *i.e.*, by the direct reaction without intermediate formation of spiranes **3**. According to the published data, this is not possible;[16] however, we carried out methylation of compound **4f** at the hydroxyl group of the aryl fragment and treated the resulting amide **7** with concentrated H_2SO_4 followed by dilution with water and extraction with toluene, thus simulating the condi-

Scheme 3



Only for $\mathbf{D^1}$—$\mathbf{D^3}$, $\mathbf{E^1}$, and $\mathbf{E^2}$: R^1 = Me; R^2 = Ph (**a**); R^2 = SMe (**b**); R^2 = CH_2CO_2Et (**c**).

tions of isolation of amides **4**. The starting amide **7**, which was identified based on the TLC data, the melting point, and the IR spectrum, was regenerated in 73% yield. Hence, the cleavage of the *p*-methoxy group by acid hydrolysis in H_2SO_4 did not occur. We attempted to direct the Ritter reaction toward the classical formation of amides of type **7** (see Scheme 1) by performing the reaction in 90% or 70% H_2SO_4. However, the reactions afforded exclusively *p*-hydroxyamides **4**, *i.e.*, elimination of the *p*-methoxy group from the aromatic ring occurred through the formation of spiranes **3** followed by their subsequent decomposition. In our opinion, the results of the experiments provided support for the conclusion that *p*-hydroxyamides **4** were formed exclusively *via* spiranes **3** and their dienone-phenolic rearrangement (Scheme 3).

The characteristics of spiranes **3a—d** and amides **4a—c**,**e—j** and **7** are given in Table 1. Their structures were confirmed by the results of elemental analysis, the IR and ^{1}H NMR spectral data (Table 2), and by the ^{13}C NMR and mass spectra (Tables 3 and 4).

The IR spectra of spiranes **3a—d** in Nujol mulls have strong absorption bands of the cyclohexadienyl fragment at 1660—1700 (C=O) and 1620—1660 cm^{-1} (C=C) and medium intensity bands at 1585—1620 cm^{-1} (C=N) (the shoulder at 1630 cm^{-1} in the spectrum of compound **3b**). The IR spectra of amides **4a—c,e—j** have signals at 1620—1660 cm^{-1} (C=O) along with a narrow band at 3350—3405 cm^{-1} (NH) and a broad band of the OH groups, which occur in the associated form in the crystalline state, with the absorption maximum at 3150—3330 cm^{-1}. The latter band is absent in the spectrum of methoxy derivative **7**. In the spectra of dilute solutions of compounds **4b,h** in CCl_4, this band is observed at 3612 cm^{-1}, which indicates that the OH groups in the crystals are involved in intermolecular association. In the spectra of solutions in CCl_4, the NH stretching vibrations are observed at 3430—3445 cm^{-1}. The spectra of amides **4a—c,e—j** have also bands at 1605—1615 cm^{-1} (C=C of the aromatic ring). The IR spectrum of amide **7** shows also asymmetric and symmetric stretching vibration bands of the C—O—CH_3 bond at 1250 and 1070 cm^{-1}, respectively.

The distinguishing feature of the ^{1}H NMR spectra of spiranes **3a—d** is the presence of doublets of the H(7) and H(9) protons of the cyclohexadiene ring at δ 6.17—6.23. The NMR spectra of amides **4a—c,e—j** have doublets of the corresponding H(2) and H(6) protons at δ 6.57—6.70. In the ^{1}H NMR spectra, amides **4c,g—j** containing the cyclohexane ring give, in addition to multiplets of the CH_2 groups at δ 1.15—1.65, a characteristic signal at δ 2.00—2.25. The latter can be assigned to two protons of the CH_2 groups, which are adjacent to the quaternary carbon atom and experience the anisotropic influence of the amide carbonyl group.

The ^{13}C NMR spectra measured with complete suppression of spin-spin ^{1}H—^{13}C coupling also confirmed the structures of compounds **3** (Table 3) and **4** (Table 4). The atomic numbering schemes for spiranes **3** and amides **4** are shown in Schemes 2 and 3, respectively. The ^{13}C NMR spectra of compounds **3a,b,d** have a characteristic signal of the C(5) spiro-atom at δ 74.4—77.8, which is absent in the spectra of compounds **4c,f—h**. The signals of the carbonyl groups in the spectra of ketones **3a,b,d** are observed at

Table 2. IR[a] and ^{1}H NMR spectra of spiranes **3a—d** and amides **4a—c,e—j** and **7**

Compound	IR, ν/cm^{-1}	^{1}H NMR, δ (J/Hz)
3a	1700 (C=O), 1660 (C=C), 1620 (C=N)	1.43 (s, 6 H, 2 Me); 2.23 (s, 2 H, C(4)H_2); 2.38 (s, 3 H, SMe); 6.22 (d, 2 H, H(7), H(9), J = 10.0); 6.75 (d, 2 H, H(6), H(10), J = 10.0)
3b	1660 (C=O), 1630 (C=N and C=C)	1.41 (s, 6 H, 2 Me); 2.21 (s, 2 H, C(4)H_2); 4.19 (s, 2 H, SCH_2); 6.17 (d, 2 H, H(7), H(9), J = 10.0); 6.81 (d, 2 H, H(6), H(10), J = 10.0); 7.20—7.35 (m, 5 H, Ph)
3c	1660 (C=O), 1620 (C=C), 1585 (C=N)	1.34—1.83 (m, 10 H, $(CH_2)_5$); 2.19 (s, 2 H, C(4)H_2); 2.35 (s, 3 H, SMe); 6.23 (d, 2 H, H(7), H(9), J = 10.1); 6.92 (d, 2 H, H(6), H(10), J = 10.1)
3d	1660 (C=O), 1620 (C=C), 1585 (C=N)	1.40—1.85 (m, 10 H, $(CH_2)_5$); 2.20 (s, 2 H, C(4)H_2); 4.22 (s, 2 H, SCH_2); 6.21 (d, 2 H, H(7), H(9), J = 10.0); 6.89 (d, 2 H, H(6), H(10), J = 10.0); 7.20—7.40 (m, 5 H, H arom.)
4a	3400 (NH), 3220 (OH), 1650 (C=O), 1610	1.24 (s, 6 H, 2 Me); 2.27 (s, 3 H, SMe); 2.85 (s, 2 H, CH_2Ar); 5.46 (br.s, 1 H, NH); 6.70 (d, 2 H, H(2), H(6), J = 9.2); 6.92 (d, 2 H, H(3), H(5), J = 9.2); 8.62 (s, 1 H, OH)
4b	3400 (NH), 3320 (OH), 1660 (C=O), 1605	1.20 (s, 6 H, 2 Me); 2.83 (s, 2 H, CH_2Ar); 4.04 (s, 2 H, SCH_2); 6.57 (d, 2 H, H(2), H(6), J = 9.3); 6.82 (d, 2 H, H(3), H(5), J = 9.3); 7.20—7.40 (m, 6 H, Ph + NH); 8.88 (s, 1 H, OH)
4c	3370 (NH), 3330 (OH), 1650 (C=O), 1610	1.20—1.60 (m, 10 H), 1.95 and 2.05 (both s, 1 H each, $(CH_2)_5$); 2.22 (s, 3 H, SMe); 2.80 (s, 2 H, CH_2Ar); 6.62 (d, 2 H, H(2), H(6), J = 9.0); 6.84 (d, 2 H, H(3), H(5), J = 9.0); 6.98 (br.s, 1 H, NH); 8.85 (br.s, 1 H, OH)
4e	3390 (NH), 3240 (OH), 1735 (O—C=O), 1640 (C=O), 1615	1.20 (s, 6 H, 2 Me); 1.27 (t, 3 H, Me, J = 7.0); 2.85 (s, 2 H, CH_2Ar); 3.13 (s, 2 H, CH_2CO); 4.13 (κ, 2 H, OCH_2, J = 7.0); 6.62 (d, 2 H, H(2), H(6), J = 9.0); 6.90 (d, 2 H, H(3), H(5), J = 9.0); 7.29 (s, 1 H, NH); 8.87 (s, 1 H, OH)
4f	3405 (NH), 3385 (OH), 3190 (br., NH), 1630 (C=O), 1610	1.34 (s, 6 H, 2 Me); 3.00 (s, 2 H, CH_2Ar); 6.60 (d, 2 H, H(2), H(6)); 6.92 (d, 2 H, H(3), H(5), J = 10.0); 7.38—7.48 (m, 5 H, Ph); 7.73 (s, 1 H, NH); 8.84 (s, 1 H, OH)
4g	3350 (NH), 3150 (br., OH), 1720 (O—C=O), 1660 (C=O), 1610	1.16—1.55 (m, 8 H), 1.95 and 2.05 (both s, 1 H each, $(CH_2)_5$); 1.28 (t, 3 H, Me, J = 7.6); 2.80 (s, 2 H, CH_2Ar); 3.18 (s, 2 H, CH_2CO); 4.11 (q, 2 H, OCH_2, J = 7.6); 6.60 (d, 2 H, H(2), H(6), J = 9.8); 6.88 (d, 2 H, H(3), H(5), J = 9.8); 7.00 (s, 1 H, NH); 8.80 (s, 1 H, OH)
4h	3365 (NH), 3170 (br., OH), 1620 (C=O), 1610	1.25—1.65 (m, 8 H), 2.20 and 2.25 (both s, 1 H each, $(CH_2)_5$); 2.98 (s, 2 H, CH_2Ar); 6.59 (d, 2 H, H(2), H(6), J = 10.1); 6.88 (d, 2 H, H(3), H(5), J = 10.1); 6.96 (s, 1 H, NH); 7.35—7.50 (m, 5 H, Ph); 8.85 (s, 1 H, OH)
4i	3400 (NH), 3160 (OH), 1635 (C=O), 1610	1.15—2.00 (m, 10 H, $(CH_2)_5$); 2.80 (s, 2 H, CH_2Ar); 3.39 (s, 2 H, CH_2Ph); 6.57 (d, 2 H, H(2), H(6), J = 10.0); 6.73 (d, 2 H, H(3), H(5), J = 10.0); 6.83 (s, 1 H, NH); 7.19—7.30 (m, 5 H, Ph); 8.83 (s, 1 H, OH)
4j	3400 (NH), 3170 (br., OH), 1650 (C=O), 1610	1.15—2.02 (m, 10 H, $(CH_2)_5$); 2.83 (s, 2 H, CH_2Ar); 3.93 (s, 2 H, CH_2Cl); 6.62 (d, 2 H, H(2), H(6), J = 10.1); 6.85 (d, 2 H, H(3), H(5), J = 10.1); 7.10 (s, 1 H, NH); 8.87 (s, 1 H, OH)
7	3350 (NH), 1630 (C=O), 1605, 1575	1.37 (s, 6 H, 2 Me); 3.05 (s, 2 H, CH_2); 3.75 (s, 3 H, OMe); 6.75 (d, 2 H, H(3), H(5), J = 10.0); 7.05 (m, 2 H, H arom.); 7.38 (s, 1 H, NH); 7.43 (m, 3 H, H arom.); 7.74 (d, 2 H, H(2), H(6), J = 10.0)

[a] For suspensions in Nujol mulls.

δ 183.9—184.3, whereas these signals in the spectra of amides **4c,f—h** are observed at δ 164.8—167.1. In addition, the spectra of the spiranes have signals of the C(1) atom at the C=N bond at low field (δ 164.3—165.7). The quaternary carbon atom adjacent to the nitrogen atom gives a signal at δ 53.5—62.0, this signal in the spectra of the spiranes being shifted downfield by 3—7 ppm. The same is true for the methyl groups at this carbon atom (signals at δ 26.7—30.8). The pentamethylene ring is manifested as three signals at δ 21.0—23.0, 25.3—26.0, and 33.8—34.6. The ^{13}C NMR spectra of amides **4e,g** containing the ethoxycarbonyl groups have additional low-intensity signals at δ 160.0—160.1, which are apparently attributable to one of the rotational conformers with respect to the amide C—N bond. The ^{13}C NMR spectra of compounds **3** and **4** show also signals characteristic of the cyclohexadiene ring (**3a,b,d**) and the *p*-hydroxy-substituted aromatic ring (**4c,e,f—h**) as well as of the functional groups R^2 (see Tables 3 and 4, respectively).

The structures of compounds **3** and **4** were confirmed by the mass spectra (see Tables 3 and 4, respectively) although the fragmentation paths for spiranes **3** and amides **4** are somewhat different. All spectra have low-intensity molecular ions peaks, which are in agreement with the calculated values. Fragmentation of spiranes **3a,b,d** under the action of electron impact occurred predominantly with the cleavage of the

Table 3. ^{13}C NMR spectra (δ) and mass spectra of compounds **3a,b,d**

Compound	C(5)	C(6), C(10)	C(7), C(9)	C(8)	C(1)	C(4)	C(3)	R^1	R^2	MS, *m/z* (I_{rel} (%))
3a	74.5	150.6	128.4	184.3	165.7	48.2	62.9	30.8	13.7 (SMe)	221 $[M]^+$ (2), 149 (16), 148 (100), 133 (75), 107 (19), 106 (26), 105 (25)
3b	74.4	150.0	128.3	184.0	164.4	47.8	61.8	30.5	137.1, 28.7, 128.2, 127.0 (Ph); 34.5 (SCH_2)	297 $[M]^+$ (9), 197 (28), 148 (24), 133 (14), 105 (10), 100 (12), 91 (100)
3d	77.8	150.6	128.3	184.1	164.3	45.8	61.0	23.0; 26.0; 34.6	137.5, 129.0, 128.8, 128.7, 127.1 (Ph)*	337 $[M]^+$ (2), 197 (11), 188 (28), 107 (40), 91 (100), 81 (29)

* The signal of SCH_2 overlaps with the signal of DMSO.

Table 4. ^{13}C NMR spectra (δ) and mass spectra of compounds **4c,e—h**

Compound	C(1)	C(2), C(6)	C(3), C(5)	C(4)	C=O	CH_2	$N\underline{C}(R^1)_2$	R^1	R^2	MS, *m/z* (I_{rel} (%))
4c	155.7	114.6	127.6	131.2	164.8	42.8	57.6	21.3, 25.3, 34.0	11.6 (SMe)	279 $[M]^+$ (32), 172 (100), 144 (25), 129 (18), 107 (28), 75 (13)
4e	155.6	114.5	128.2	131.2	164.8	42.7	53.5	26.7	160.0 (C=O); 168.0 (C=O); 60.2 (CH_2O); 43.3 (CH_2N); 14.0 (Me)	279 $[M]^+$ (5), 172 (38), 148 (14), 107 (7), 58 (100)
4f	155.7	114.6	128.0*	131.1	166.8	43.0	53.9	26.9	136.1; 130.6; 128.4*; 127.3 (Ph)*	269 $[M]^+$ (13), 162 (53), 148 (21), 105 (100), 77 (22)
4g	155.6	114.5	127.6	131.2	164.9	42.3	55.8	21.0, 25.3, 33.8	160.1 (C=O); 168.1 (C=O); 60.2 (CH_2O); 43.3 (CH_2N); 14.0 (Me)	319 $[M]^+$ (23), 212 (85), 188 (25), 107 (23), 98 (100)
4h	155.6	114.5	127.9*	131.2	167.1	42.4	56.2	21.5, 25.5, 34.0	136.5, 130.5, 127.4 (Ph)*	309 $[M]^+$ (23), 202 (65), 188 (18), 107 (10), 105 (100), 77 (28)

* Assignments of the signals may be interchanged.

C(1)—C(5) and N—C(3) bonds and then of the C(3)—C(4) bond in the pyrroline ring. Compounds **3b,d** are also characterized by the detachment of the benzyl carbocation (*m/z* 91).

Under the action of electron impact, fragmentation of amides **4c,e,g,i,j** occurred at the amide C—N bond with elimination of the *p*-hydroxybenzyl carbocation (*m/z* 107). Compounds **4i,j** containing the pentamethylene ring produced additionally the (1*H*)- or (3*H*)-tetrahydroazepinium cations (*m/z* 98). Substituted benzamides **4f,h** eliminated the C_6H_5CO group (*m/z* 105). The mass spectra of **4i,j** are given in the Experimental section.

The structure of compound **3a** has been established previously[10] by X-ray diffraction analysis.

Possible conversion pathways for carbinols **1a,b** and 1-(*p*-methoxyphenyl)-2-methylprop-1-ene and the formation of assumed intermediates $\mathbf{I^1}$—$\mathbf{I^3}$, $\mathbf{A^1}$, $\mathbf{A^2}$, **B**, and $\mathbf{C^1}$—$\mathbf{C^4}$ under the reaction conditions *via* the paths *a*, *b*, and *c* are presented in Scheme 2. Under the reaction conditions, alcohol **1a** was, evidently, dehydrated to 1-(*p*-methoxyphenyl)-2-methylprop-1-ene, which added a proton to give cation $\mathbf{I^1}$ of the *tert*-butyl type. The reaction of the latter with a molecule of nitrile R^2CN (**2a—f**) afforded initially ion-dipole complex $\mathbf{I^2}$ and then intermediate $\mathbf{I^3}$. The latter underwent intramolecular cyclization through the electrophilic *ipso*-attack on the aromatic ring to form intermediate $\mathbf{A^1}$, thus giving rise to the spiro system. The subsequent stages involved the addition of water to the C(8) atom and deprotonation.

Finally, elimination of methanol from neutral intermediate **A²** afforded spirane **3**.

With the aim of confirming the proposed scheme, we simulated particular reaction stages by the semiempirical AM1 SCF MO LCAO method[17] and calculated the enthalpies of formation (ΔH_f) and the total energies (E_{total}) of the possible intermediates, which can be involved in the process under consideration. According to the results of our calculations, the C(1) and C(2) atoms in 1-(*p*-methoxyphenyl)-2-methylprop-1-ene bear the charges $q = -0.135$ and -0.095 a.u., respectively. The attachment of a proton to the C(1) atom (according to the Markovnikoff rule) gives rise to cation **I¹** of the *tert*-butyl type (ΔH_f = 664.3 kJ mol^{-1}, E_{total} = −1927.1 eV), whereas the attachment of a proton to the C(2) atom affords cation **C¹** of the benzyl type (ΔH_f = 620.0 kJ mol^{-1}, E_{total} = −1927.6 eV). The subsequent conversions of these cations are described by the paths *a*, *b*, and *c* (Scheme 2). A comparison of the ΔH_f and E_{total} values demonstrated that benzyl cation **C¹** should be more stable than substituted *tert*-butyl cation **I¹** and, hence, the formation of the former should be considered as more favorable. However, we did not detect products of the conversion of cation **C¹** (isoindoles of type **6**) (see Scheme 2) in the reaction mixture, *i.e.*, the reaction did not actually take the path *c*.

To account for this fact, we simulated the addition of benzonitrile (ΔH_f = 223.5 kJ mol^{-1}, E_{total} = −1170.9 eV) to cations **I¹** and **C¹** by the reaction coordinate method. We used the interatomic distances $l_{C(1)...N}$ and $l_{C(2)...N}$, respectively, as such a reaction coordinate. The curves on the ΔH_f—$l_{C(1\text{ or }2)...N}$ coordinates each have two minima. One of them corresponds to possible ion-dipole complexes **I²** (ΔH_f = 842.2 kJ mol^{-1}, E_{total} = −3098.4 eV) and **C²** (ΔH_f = 813.3 kJ mol^{-1}, E_{total} = −3098.7 eV), respectively, which are responsible for the character of the approach of the reagents. The second minimum corresponds to cations **I³** (ΔH_f = 798.1 kJ mol^{-1}, E_{total} = −3098.9 eV) and **C³** (ΔH_f = 791.4 kJ mol^{-1}, E_{total} = −3099.0 eV), respectively. The maxima in the curves are assigned to the reaction transition states **I³TS** (ΔH_f = 887.4 kJ mol^{-1}, E_{total} = −3098.0 eV) and **C³TS** (ΔH_f = 870.0 kJ mol^{-1}, E_{total} = −3098.2 eV). The activation barrier of the reaction **I²** → **I³**, which is determined as the difference between the ΔH_f values for the activated and the starting ion-dipole complexes, is 45.6 kJ mol^{-1}; the activation barrier of the reaction **C²** → **C³** is 56.7 kJ mol^{-1}. However, if the formation of cations **I³** and **C³** is reversible, the activation barriers of the back reactions **I³** → **I²** and **C³** → **C²** are equally important. According to the results of calculations, these barriers are 89.3 and 78.6 kJ mol^{-1}, respectively. Assuming a supermolecule, whose ΔH_f is equal to the sum of the enthalpies of formation of the constituent species, as the starting point of the reaction, the reaction **I¹** + PhCN → **I³** is activationless to within the accuracy of the AM1 method, whereas the reaction **C¹** + PhCN → **C³** has the activation barrier of 26.5 kJ mol^{-1}. Hence, the conversion **I¹** + PhCN ⇌ **I³** is characterized by the lower energy barrier (or the absence of this barrier) of the forward reaction and the higher energy barrier of the back reaction, which can provide accumulation of cations **I³** in the reaction mixture. It is also probable that under the conditions of the real process, the activation barrier of the reaction **I¹** + PhCN → **I³** decreases, whereas the barrier of the reaction **C¹** + PhCN → **C³** increases due to specific solvation, which was not taken into account in calculations of the isolated species.

The possible path of the conversion of a cation of type **C³** (path *c*, Scheme 2) involves the intramolecular electrophilic attack of the *sp*-hybridized carbon atom on one of the *ortho* positions of the methoxyphenyl group, which should give rise to a σ-adduct of type **C⁴** (ΔH_f = 934.4 kJ mol^{-1}, E_{total} = −3097.5 eV). However, on the one hand, this species, is characterized by the large ΔH_f and E_{total} values and, hence, its formation requires substantial expenditure of energy and, on the other hand, its conversion into the reaction product, *viz.*, into indole **6**, should involve the proton abstraction, which does not occur in a strongly acidic reaction medium. Apparently, it is because of these facts that the path *c* is, on the whole, unfavorable.

In connection with the fact that cation **I³** is the key intermediate in both the paths *a* and *b*, we carried out calculations of the geometry of **I³** and the electron density distribution. Intermediate **I³** appeared to have the structure of the nitrilium cation formed through the unoccupied 2p orbital of the carbon atom of carbocation **I¹** and the lone electron pair of the nitrogen atom of nitrile, the hybridizations of the nitrogen and carbon atoms of the C≡N group in **I³** remaining virtually unchanged compared to those in benzonitrile. The $Me_2C—N≡C$ and $N≡C—C_{Ph}$ bond angles are 176.4° and 179.4°, respectively. The N≡C and $C—C_{Ph}$ bond lengths (1.161 and 1.410 Å, respectively) are also similar to those in the starting nitrile (1.163 and 1.422 Å).

The largest positive charge (q = +0.282 a.u.) in cation **I³** is localized on the *sp*-hybridized carbon atom. The nitrogen atom bears a negative charge (q = −0.060 a.u.). The carbon atoms of the aromatic ring containing the methoxy group, except for the C(4) atom, are electron-excessive. The charges on the C(1), C(2), and C(6) atoms of the ring are −0.166, −0.073, and −0.109 a.u., respectively. It is these reaction centers that can be subjected to the electrophilic attack by the *sp*-hybridized carbon atom (the corresponding interatomic distances are 3.46, 4.33, and 3.41 Å). The attack on the C(2) atom, which is more remote and bears a lower negative charge, seems to be the least probable. The attack on the C(1) atom should give rise to cation **A¹** with the spiro structure (ΔH_f = 869.5 kJ mol^{-1}, E_{total} = −3098.2 eV), and the attack on the C(6) atom should afford cation **B** (ΔH_f = 870.6 kJ mol^{-1}, E_{total} = −3098.2 eV) whose deprotonation may produce substituted 3,4-dihydroisoquinoline **5** (in reality, compounds

of type **5** were formed in trace amounts and were detected in the reaction mixtures only by TLC; previously, it has been established that 3,3-dialkyl-substituted 3,4-dihydroisoquinolines, regardless of the substituent in the aromatic portion of the molecule, gave characteristic bright colors with chloranil, the color of the spot being dependent on the character of the substituent at position 1 of isoquinoline[18]). It follows from the above-considered data that cations $\mathbf{A^1}$ and **B** have similar energy characteristics. Simulation of their formation by the reaction coordinate method and localization of the corresponding transition states gave similar activation barriers (99.1 and 101.6 kJ mol^{-1}, respectively). Apparently, the regioselectivity of the process under study is governed by the low basicity of the medium in which cation **B** does not undergo deprotonation rather than is determined by the energies of the formation of cations $\mathbf{A^1}$ and **B**.

Subsequent conversions of cation $\mathbf{A^1}$ are associated with the irreversible addition of water to the electron-deficient C(4) atom (q = +0.317 a.u.) followed by deprotonation, which gives rise to neutral intermediate $\mathbf{A^2}$, and elimination of methanol. Previously, it has been demonstrated[10] that the stability of spiropyrrolines **3a—f** toward hydrolysis depends on the nature of the substituent R^2. If R^2 = SMe (**3a,c**) or SBn (**3b,d**), the corresponding compounds are stable under the experimental conditions and can be isolated. On the contrary, 3,3-dimethyl-1-R^2-2-azaspiro[4.5]deca-1,6,9-trien-8-ones with $R^2 = CH_2COOEt$ (**3e**) or Ph (**3f**) underwent the dienone-phenolic rearrangement accompanied by the addition of water to the C(1) atom and the cleavage of the C(1)—C(5) bond (Scheme 3). *A priori* both the neutral molecule of compound **3** and its *O*- or *N*-protonated form can be involved in the process.

We carried out simulation of the attack of water on the C(1) atom in neutral molecules **3e,f** and their *N*- and *O*-protonated forms $\mathbf{D^1a—c}$ and $\mathbf{E^1a—c}$ by the reaction coordinate method using the interatomic $l_{C(1)...OH_2}$ distance as the coordinate (Scheme 3). It appeared that only the attack on the *O*-protonated forms is accompanied by an increase in the interatomic C(1)—C(5) distance up to the cleavage of the bond in the molecules of spiranes **3e,f** as the nucleophile comes closer. Therefore, only the *O*-protonated form can be converted (through an intermediate of type $\mathbf{E^2}$) into amide **4**.

Hence, the results of semiempirical quantum-chemical calculations did not provide an unambiguous answer to the question concerning the causes of the specific formation of 1-R-3,3-dialkyl-2-azaspiro[4.5]deca-1,6,9-trien-8-ones **3a—d** in these reactions but demonstrated that hydrolysis (accompanied by the dienone-phenolic rearrangement) of compounds **3e,f** containing electron-withdrawing substituents can proceed through the formation of the *O*-protonated forms.

To summarize, we developed a procedure for the synthesis of 1-R-3,3-dialkyl-2-azaspiro[4.5]deca-1,6,9-trien-8-ones and studied their dienone-phenolic rearrangements in acidic media. The results of the present investigation showed that compounds of this type must be isolated under conditions precluding acid hydrolysis to prevent their rearrangements.

Experimental

The IR spectra were measured on a UR-20 instrument in Nujol mulls. The ^1H NMR spectra were recorded on a Bruker AM-300 instrument (300 MHz) in DMSO-d_6 with HMDS as the internal standard. The ^{13}C NMR spectra were measured on a Bruker AC-200 instrument (50.32 MHz) in DMSO-d_6. The mass spectra were obtained on a Finnigan MAT instrument (EI, 70 eV). The course of the reactions and the purities of the products were monitored by TLC on Silufol plates (Czech Republic) using a toluene—AcOEt system (1 : 1); spots were visualized with a 2% solution of chloranil in toluene. Ethyl acetate was washed with water and a saturated $NaHCO_3$ solution, dried over $MgSO_4$, and distilled. Monoglyme was dried over solid KOH and distilled over sodium. Dichloromethane was purchased from Lancaster (UK). Toluene of analytical grade, $ClCH_2CN$, MeSCN, PhCN, and $CNCH_2CO_2Et$ (all compounds were domestic reagents), and BnSCN (Chemapol, Czech Republic) were used without additional purification. Carbinol **1a** and 1-(*p*-methoxyphenyl)-2-methylprop-1-ene were prepared according to a known procedure.[19] Quantum-chemical calculations were carried out on a Pentium-133 computer with the use of the MOPAC 7.0 program package.[20]

3,3-Dimethyl-1-methylthio-2-azaspiro[4.5]deca-1,6,9-trien-8-one (3a). This compound was synthesized according to a procedure reported previously.[10]

1-Benzylthio-3,3-dimethyl-2-azaspiro[4.5]deca-1,6,9-trien-8-one (3b). A mixture of 1-(*p*-methoxyphenyl)-2-methylprop-1-ene (4.05 g, 25 mmol) and BnSCN (2.98 g, 20 mmol) in CH_2Cl_2 (50 mL) was added dropwise with intense stirring to 98% sulfuric acid (6 mL, 110 mmol) for 0.5 h at the temperature not exceeding −15 °C. The reaction mixture was stirred for 0.5 h and poured into a mixture of NH_4Cl (25 g), a concentrated aqueous NH_3 solution (25 mL), and ice (300 g). Then the reaction mixture was stirred (pH ~8), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with water (50 mL) and dried with anhydrous $MgSO_4$. The solvent was distilled off and the residue was recrystallized from ether upon cooling to −10 °C. Compound **3b** was obtained in a yield of 0.8 g (13%).

1-Methylthio-3,3-(pentane-1,5-diyl)-2-azaspiro[4.5]deca-1,6,9-trien-8-one (3c) was prepared analogously from racemic α-cyclohexyl-*p*-methoxybenzyl alcohol **1b**[21] (5.5 g, 25 mmol) [m.p. 86—87.5 °C; *cf.* lit. data[21]: m.p. 92 °C); IR, ν/cm^{-1}: 3460 (OH). ^1H NMR, δ: 0.85—1.73 (m, 10 H, $(CH_2)_5$); 1.90 (d, 1 H, CH); 3.75 (s, 3 H, OMe); 4.13 (t, 1 H, OCH, J = 7.2 Hz); 4.70 (d, 1 H, OH); 6.80 (d, 2 H, H(3), H(5), J = 9.1 Hz); 7.14 (d, 2 H, H(2), H(6), J = 9.1 Hz) and MeSCN (1.46 g, 1.37 mL, 20 mmol). Compound **3c** was obtained in a yield of 0.73 g (14%).

1-Benzylthio-3,3-(pentane-1,5-diyl)-2-azaspiro[4.5]deca-1,6,9-trien-8-one (3d) was prepared analogously from carbinol **1b** (5.5 g, 25 mmol), BnSCN (2.98 g, 20 mmol), and concentrated H_2SO_4 (6 mL) in CH_2Cl_2 (30 mL). Compound **3d** was obtained in a yield of 1.15 g (17 %).

Thiomethyl *N*-[1-(4-hydroxyphenyl)-2-methylprop-2-yl]carbamate (4a). *A.* The synthesis from carbinol **1a** was

carried out analogously to the synthesis of compound **4c**; the yield was 97%.

B. Acid hydrolysis of compound **3a**. Spirane **3a** (0.3 g, 1.35 mmol) was refluxed in 10% H_2SO_4 (10 mL) for 1 h. Then the reaction mixture was cooled and the precipitate that formed was separated, washed with water (3 mL), dried, and recrystallized. Amide **4a** was obtained in a yield of 0.29 g (90%).

Thiobenzyl *N*-[1-(4-hydroxyphenyl)-2-methylprop-2-yl]carbamate (4b). ***A.*** The synthesis from carbinol **1a** was carried out analogously to the synthesis of compound **4c**; the yield was 27%.

B. Acid hydrolysis of compound **3b**. Spirane **3b** (100 mg, 0.3 mmol) was refluxed in a mixture of 10% H_2SO_4 (10 mL) and EtOH (3 mL) for 2.5 h. Then the reaction mixture was poured into water (50 mL) and made alkaline with solid $(NH_4)_2CO_3$ to pH ~7—8. The precipitate that formed was separated, dried, and recrystallized. Amide **4b** was obtained in a yield of 38 mg (40%).

Thiomethyl *N*-[2-(4-hydroxyphenyl)-1,1-(pentane-1,5-diyl)ethyl]carbamate (4c). A solution of carbinol **1b** (11 g, 50 mmol) and MeSCN (3.66 g, 50 mmol) in toluene (100 mL) was added with intense stirring to concentrated H_2SO_4 (50 mL) at 20—25 °C. The reaction mixture was stirred for 1 h, poured into cold water (300 mL), and neutralized with a 25% aqueous NH_3 solution to pH 7—8. The resulting resinous product was triturated with CH_2Cl_2 and the precipitate of compound **4c** that formed was separated. The aqueous layer was extracted with toluene (60 mL). The combined toluene extracts were washed with water and dried with $MgSO_4$. The toluene was distilled off to 1/3 of the initial volume and the residue was kept in the cold (−10 °C). The crystals that precipitated were combined with the compound isolated previously and recrystallized. The total yield of compound **4c** was 2.42 g (17%).

Ethyl 2-{[1-(4-hydroxyphenyl)-2-methylprop-2-yl]aminocarbonyl}acetate (4e), *N*-[1-(4-hydroxyphenyl)-2-methylprop-2-yl]benzamide (4f), ethyl 2-{[2-(4-hydroxyphenyl)-1,1-(pentane-1,5-diyl)ethyl]aminocarbonyl}acetate (4g), and *N*-[2-(4-hydroxyphenyl)-1-(pentane-1,5-diyl)ethyl]benzamide (4h) were prepared analogously from carbinols **1a,b** and the corresponding nitriles **2c,d**.

***N*-[2-(4-Hydroxyphenyl)-1,1-(pentane-1,5-diyl)ethyl]phenylacetamide (4i)** was prepared analogously from carbinol **1b** (11 g, 50 mmol) and BnSCN (5.85 g, 5.75 mL, 50 mmol) in concentrated H_2SO_4 (60 mL); the yield was 4.72 g (29%). MS, m/z (I_{rel} (%)): 323 $[M-2]^+$ (1), 216 (43), 107 (20), 98 (100), 91 (25).

***N*-[2-(4-Hydroxyphenyl)-1,1-(pentane-1,5-diyl)ethyl]chloroacetamide (4j)** was prepared analogously from carbinol **1b** (11 g, 50 mmol) and $ClCH_2CN$ (3.78 g, 50 mmol) in H_2SO_4 (50 mL). MS, m/z (I_{rel} (%)): 281 $[M]^+$ (1), 188 (25), 177 (29), 174 (100), 107 (28), 98 (55), 81 (38). Unlike the remaining amides, compound **4j** was additionally isolated as a precipitate from the aqueous layer; the total yield was 4.0 g (28%).

***N*-[1-(4-Methoxyphenyl)-2-methylprop-2-yl]benzamide (7).** Sodium hydride (90 mg; from 150 mg of a 60% suspension of NaH in mineral oil) and MeI (0.55 mL, 8.3 mmol) in monoglyme (3 mL) were successively added to a solution of amide **4f** (1 g, 3.7 mmol) in dry monoglyme (30 mL). The reaction mixture was stirred for 2 h and the solvent was distilled off to the volume of 10 mL. Then an equal volume of water was added and the precipitate that formed was filtered off and dried. Amide **5** was obtained in a yield of 0.75 g (72%).

References

1. V. A. Glushkov, O. G. Ausheva, G. A. Postanogova, and Yu. V. Shklyaev, *Khim. Geterotsikl. Soedin.*, 2000, 1559 [*Chem. Heterocycl. Compd.,* 2000 (Engl. Transl.)].
2. P. Balczewski, J. A. Joule, C. Estévez, and M. Alvarez, *J. Org. Chem.*, 1994, **59**, 4571.
3. E. V. Sadanandan, S. K. Pillai, M. V. Lakshmikantham, A. D. Billimoria, J. S. Culpepper, and M. P. Cava, *J. Org. Chem.*, 1995, **60**, 1800.
4. Y. Kita, T. Takada, M. Gyoten, H. Tohma, M. H. Zenk, and J. Eichhorn, *J. Org. Chem.*, 1996, **61**, 5857.
5. N. A. Braun, M. A. Ciufolini, K. Peters, and E.-M. Peters, *Tetrahedron Lett.*, 1998, **39**, 4667.
6. S. Hirotani and E. Kaji, *Tetrahedron*, 1999, **55**, 4255.
7. G. V. Gavrilova, D. P. Krut´ko, A. A. Gavrilov, and K. P. Butin, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 1015 [*Russ. Chem. Bull.*, 1997, **46**, 975 (Engl. Transl.)].
8. A. M. Fivush and S. R. Strunk, *Synth. Commun.*, 1996, **26**, 1623.
9. Y. Nagao, W. S. Lee, I. Y. Jeong, and M. Shiro, *Tetrahedron Lett.*, 1995, **36**, 2799.
10. V. A. Glushkov, Yu. V. Shklyaev, V. I. Sokol, V. S. Sergienko, and V. V. Davidov, *Mendeleev Commun.*, 1998, 227; 1999, 170.
11. V. S. Shklyaev, B. B. Aleksandrov, G. I. Legotkina, M. I. Vakhrin, M. S. Gavrilov, and A. G. Mikhailovskii, *Khim. Geterotsikl. Soedin.*, 1983, 1560 [*Chem. Heterocycl. Compd.,* 1983, 1242 (Engl. Transl.)].
12. H. Wollweber and R. Hiltman, *Angew. Chem.*, 1960, **72**, 1001.
13. L. I. Krimen and D. J. Cota, *Org. React.*, 1969, **17**, 213.
14. J. J. Ritter and J. K. Minari, *J. Am. Chem. Soc.*, 1948, **70**, 4045.
15. J. P. Gavin and R. D. Waigh, *J. Chem. Soc., Perkin Trans. 1*, 1990, 503.
16. S. Doi, N. Shirai, and Y. Sato, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2217.
17. M. J. S. Dewar, E. G. Zoeblisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.
18. M. S. Gavrilov, B. B. Aleksandrov, V. S. Shklyaev, and Yu. V. Shklyaev, *Materialy Vtoroi Regional´noi konferentsii "Enaminy v organicheskom sinteze"* [*Abstracts of Papers, II Regional Conference on Enamines in Organic Synthesis*], Perm, Russia, 1991, 31 (in Russian).
19. F. A. Carroll and G. S. Hammond, *Isr. J. Chem.*, 1972, **10**, 613.
20. J. J. P. Stewart, *MOPAC, Version 7.0*, Frank J. Seiler Research Laboratory, US Air Force Academy, QCPE 175.
21. J. Schmidlin and R. V. Escher, *Ber.*, 1912, **45**, 889.

Received April 24, 2000;
in revised form May 14, 2001