Brief Communications

Spirocyclohexadienones
5*. Synthesis of 2-R-7a-methyl-3-(spirocyclohexa-2,5-dien-4-one)perhydro-1-indolines

V. A. Glushkov, O. G. Ausheva, and Yu. V. Shklyaev*

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

2-R-7a-Methyl-3-(spirocyclohexa-2,5-dien-4-one)perhydro-1-indolines were obtained by the reactions of 1-(4-ethoxyphenyl)-2-methylcyclohexanol with nitriles (RCN) in dichloromethane in the presence of concentrated sulfuric acid.

Key words: spiro compounds, indole, cyclohexa-2,5-dien-1-one, nitriles, the Ritter reaction.

Indole derivatives can be obtained in a variety of ways,[2] whereas the number of synthetic methods for the construction of a perhydroindole system is limited.[3—6] Earlier,[1] we have proposed a synthetic route to spiropyrrolines, namely, 1-substituted 3,3-dimethyl-2-azaspiro[4.5]deca-1,6,9-trien-8-ones. The method is based on the Ritter condensation of 2,2-dialkyl-1-(4-methoxyphenyl)ethanols with nitriles. In the present work, the Ritter reaction was used to obtain 2-R-7a-methyl-3-(spirocyclohexa-2,5-dien-4-one)perhydro-1-indolines **3a—c** from 1-(4-ethoxyphenyl)-2-methylcyclohexanol (**1**) and nitriles RCN **2a—c** (Scheme 1). During the condensation, alcohol **1** undergoes dehydration to give a tertiary benzyl carbocation **A**, which is in equilibrium with tertiary carbocation **B**. Being more reactive, the latter interacts with a nitrile to form a nitrilium ion **C**. An intramolecular *ipso*-attack in the nitrilium ion **C** is a key stage of the synthesis, which affords the target perhydroindolines **3a—c**. Thus, the method affords 2-R-7a-methylperhydro-1-indolines spiro-fused through the C(3) atom with cyclohexa-2,5-dien-1-one.

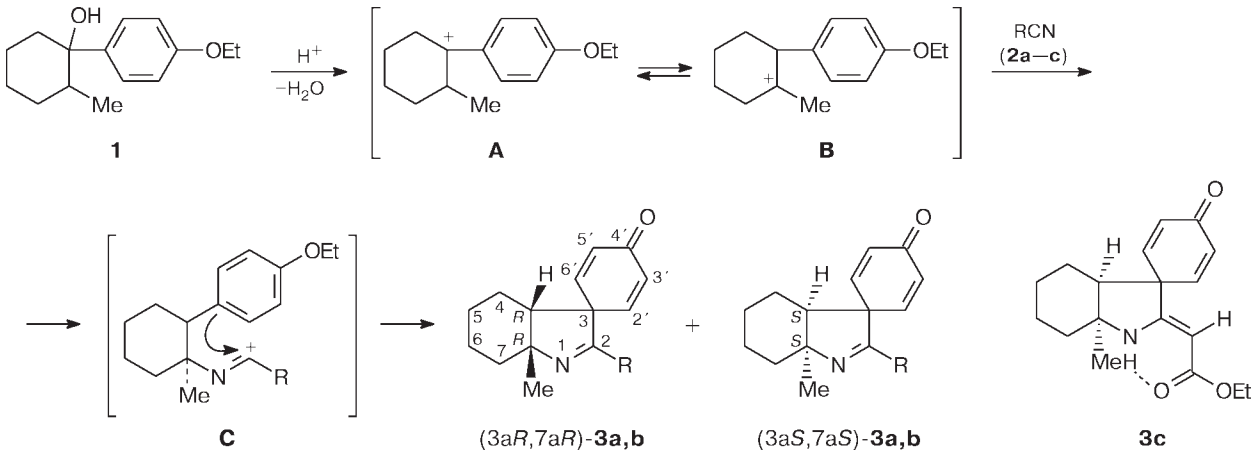
The structures of compounds **3a—c** were confirmed by elemental analysis data and IR, ^{1}H and ^{13}C NMR, and mass spectra. Correlation of ^{13}C chemical shifts for compounds **3b,c** was performed using two-dimensional ^{1}H—^{13}C NMR spectroscopy.

The IR spectra of compounds **3a—c** show absorption bands from the cyclohexadienone ring at 1660—1665 (C=O) and 1600—1625 cm^{-1} (C=C); the bands from the indoline C=N bond (for **3a,b**) appear at 1575—1600 cm^{-1}. The ^{13}C NMR spectra of compounds **3a,b** contain a signal from the spiro C atom at δ 72—77 (δ 57 for **3c**).

* For Part 4, see Ref. 1.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 4, pp. 654—656, April, 2002.

Scheme 1



2, **3**: R = SMe (**a**); Ph (**b**); CH_2CO_2Et (**c**)

According to the ^1H NMR data, compounds **3a—c** were isolated as a racemic mixture of diastereomers (3a*RS*, 7a*RS*)-**3** with *cis*-juncture of the rings.

^1H NMR spectrum of compound **3c**, as distinct from the spectra of other products, contains signals from the olefin proton at δ 4.01 and from the NH group at δ 8.32, which suggests its enamino form stabilized by an intramolecular hydrogen bond, as was earlier determined for structurally close 1-ethoxycarbonylmethylidene-(*Z*)-3,3-dimethyl-2-azaspiro[4.5]deca-6,9-dien-8-one.[7] Such a structure of compound **3c** is also confirmed by its IR spectrum, in which the absorption band from the ester group is shifted toward the low-frequency range (1640 cm^{-1}). Because of this, compounds **3a—c** follow different fragmentation pathways in mass spectra. Thus, indolines **3a,b** easily lose the original nitrile under electron impact, while the decomposition of compound **3c** includes gradual detachment of the ethoxycarbonyl group and breaking of the cyclohexane ring (see Experimental).

Experimental

IR spectra were recorded on a UR-20 instrument (suspensions in Vaseline oil). ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX 500 instrument (500 and 125.76 MHz) with HMDS and $CDCl_3$ as the internal standards, respectively. The mass spectra of compounds **3a—c** were taken on a Finnigan MAT instrument (EI, 70 eV). The course of the reactions was monitored and the purity of the products was checked by TLC on Silufol plates in toluene — AcOEt (1 : 1), spots were visualized with a 3% solution of chloranil in toluene with heating the plates to 70 °C (the spot color was recognized immediately during the heating). Methylene chloride (Lancaster Co., Great Britain) was used.

7a-Methyl-2-methylthiospiro[3a,4,5,6,7,7a-hexahydro-1*H*-indole-3,4′-cyclohexa-2′,5′-dien]-1′-one (3a). A solution of alcohol **1**[8] (11.7 g, 0.05 mol) (obtained by the reaction of 4-ethoxyphenylmagnesium bromide with 2-methylcyclohexanone in ether in 53% yield, b.p. 155—165 °C (7 Torr)) and MeSCN (3.44 mL, 0.05 mol) in 40 mL of CH_2Cl_2 was added dropwise at ~15 °C to vigorously stirred 96% H_2SO_4 (12 mL, 0.22 mol). The reaction mixture was stirred for 40 min and poured into a mixture of ice (300 mL) and 20% aqueous ammonia (pH ~8) (45 mL). The aqueous layer was separated, and the organic material was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with water and dried over $MgSO_4$. The solvent was removed, and the residue was treated with hexane. The precipitate that formed was recrystallized from hexane. Yield 4.42 g (34%), m.p. 86—88 °C. R_f 0.46 (a gray spot with a light blue-green contour). Found (%): C, 68.89; H, 7.30; N, 5.18. $C_{15}H_{19}NOS$. Calculated (%): C, 68.93; H, 7.33; N, 5.36. IR, ν/cm^{-1}: 1665 (C=O); 1625 (C=C); 1575 (C=N); 1270, 1245, 1220 (w); 1200, 1180, 1140, 1110, 1045, 920, 905, 890, 860. ^1H NMR (DMSO-d_6), δ: 1.20 (m, 2 H, CH_2); 1.26 (m, 2 H, CH_2); 1.35 (s, 3 H, Me); 1.38 (m, 1 H, CH); 1.55 (m, 1 H, CH); 1.65 (m, 1 H, CH); 1.88 (m, 1 H, CH); 2.34 (s, 3 H, SMe); 2.47 (d, 1 H, CH, J = 7 Hz); 6.27 (dd, 1 H, C(3′)H, ^3J = 10 Hz, ^4J = 2 Hz); 6.32 (dd, 1 H, C(5′)H, ^3J = 10 Hz, ^4J = 2 Hz); 6.85 (dd, 1 H, C(2′)H, ^3J = 10 Hz, ^4J = 2 Hz); 7.40 (dd, 1 H, C(6′)H, ^3J = 10 Hz, ^4J = 2 Hz). ^{13}C NMR (DMSO-d_6), δ: 184.36 (C=O); 166.45 (C=N); 150.82 and 147.50 (C(2′) and C(6′), respectively), 129.50 and 129.21 (C(5′) and C(3′), respectively); 73.18 (C(3)); 65.23 (C(7a)); 53.62 (C(3a)); 36.47 (Me); 27.12, 21.80, 21.21, and 20.99 (C(7), C(4), C(5), and C(6)); 12.95 (SMe). MS (EI, 70 eV), m/z (I_{rel} (%)): 261 $[M]^+$ (7), 188 $[M - MeSCN]^+$ (100), 173 (10), 159 (12), 145 (17), 131 (19), 121 (32), 107 (18), 91 (30).

7a-Methyl-2-phenylspiro[3a,4,5,6,7,7a-hexahydro-1*H*-indole-3,4′-cyclohexa-2′,5′-dien]-1′-one (3b) was obtained analogously from alcohol **1** (11.7 g, 0.05 mol) and PhCN (5.15 g, 0.05 mol). The solvent was removed, and the residue was treated with a small amount of cold MeOH and crystallized from MeOH. Yield 2.34 g (16%), m.p. 165—166 °C. R_f 0.58 (a green spot). Found (%): C, 82.40; H, 7.25; N, 4.62. $C_{20}H_{21}NO$. Calculated (%): C, 82.44; H, 7.26; N, 4.81. IR, ν/cm^{-1}: 1665 (C=O); 1625 (C=C); 1600 (C=N); 1320, 1270 (w), 1260,

1240 (w), 1220, 1190, 1175, 1140, 1010, 915, 890, 860. ^{1}H NMR (DMSO-d_6), δ: 1.25 (m, 2 H, CH_2); 1.37 (m, 2 H, CH_2); 1.48 (m, 1 H, CH); 1.50 (s, 3 H, Me); 1.56 (m, 1 H, CH); 1.68 (m, 1 H, CH); 1.95 (m, 1 H, CH); 2.45 (d, 1 H, CH, J = 7 Hz); 6.32 (dd, 1 H, C(3′)H, ^3J = 10 Hz, ^4J = 2 Hz); 6.36 (dd, 1 H, C(5′)H, ^3J = 10 Hz, ^4J = 2 Hz); 7.00 (dd, 1 H, C(2′)H, ^3J = 10 Hz, ^4J = 2 Hz); 7.33 (m, 3 H, H_{arom}); 7.65 (m, 2 H, H_{arom}); 7.40 (dd, 1 H, C(6′)H, ^3J = 10 Hz, ^4J = 2 Hz). ^{13}C NMR (DMSO-d_6), δ: 184.18 (C=O); 165.08 (C=N); 152.88 and 149.10 (C(2′) and C(6′), respectively), 129.46 and 128.27 (C(3′) and C(5′), respectively); 133.89, 130.36, 128.12, 127.14 (Ph); 72.18 (C(3)); 63.97 (C(7a)); 53.44 (C(3a)); 36.37 (Me); 26.93, 21.98, 21.28, and 20.46 (C(7), C(4), C(5), and C(6)). MS (EI, 70 eV), m/z (I_{rel} (%)): 291 $[M]^+$ (1), 189 $[M + H - C_6H_5CN]^+$ (14), 188 $[M - C_6H_5CN]^+$ (100), 173 (12), 159 (18), 152 (18), 146 (19), 131 (22), 121 (44), 107 (52), 91 (35).

2-Ethoxycarbonylmethylidene-*Z*-7a-methylspiro[perhydroindole-3,4′-cyclohexa-2′,5′-dien]-1′-one (3c) was obtained analogously from alcohol **1** (11.7 g, 0.05 mol) and $CNCH_2CO_2Et$ (5.65 g, 0.05 mol). The solvent was removed, and the residue was crystallized from EtOH. Yield 3.53 g (25%), m.p. 177—179 °C. R_f 0.62 (a gray spot with a green contour). Found (%): C, 71.68; H, 7.65; N, 4.52. $C_{18}H_{23}NO_3$. Calculated (%): C, 71.73; H, 7.69; N, 4.65. IR, ν/cm^{-1}: 3340 (NH); 1660 (C=O); 1640 (O—C=O); 1600 (br, C=C and C=N); 1275 (w); 1260 (w); 1235, 1215 (w); 1195 (w); 1145, 1075, 1060, 1015, 925, 910, 865. ^{1}H NMR (DMSO-d_6), δ: 1.16 (t, 3 H, $CH_2\underline{Me}$, J = 7 Hz); 1.25 (m, 2 H, CH_2); 1.32 (m, 1 H, CH); 1.43 (s, 3 H, Me); 1.45 (m, 1 H, CH); 1.60 (m, 2 H, CH_2); 1.67 (m, 1 H, CH); 1.92 (m, 1 H, CH); 2.38 (d, 1 H, CH, J = 7 Hz); 3.97 (t, 2 H, OCH_2, J = 7 Hz); 4.01 (s, 1 H, CH=); 6.17 (dd, 1 H, C(3′)H, ^3J = 10 Hz, ^4J = 2 Hz); 6.25 (dd, 1 H, C(5′)H, ^3J = 10 Hz, ^4J = 2 Hz); 6.80 (dd, 1 H, C(2′)H, ^3J = 10 Hz, ^4J = 2 Hz); 7.20 (dd, 1 H, C(6′)H, ^3J = 10 Hz, ^4J = 2 Hz); 8.32 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 184.39 (C=O); 168.44* (C(O)—O); 160.60* (=C—N); 151.13 (C(2′)) and 148.37 (C(6′)), 128.84 (C(5′)) and 127.48 (C(3′)); 77.08 (=$\underline{C}$HC(O)); 61.31 (C(7a)); 57.60* (C(3)), 57.24* (OCH_2); 49.35 (C(3a)); 37.19 (Me); 26.12, 21.57, 21.50, and 20.57 (C(7), C(4), C(5), and C(6)); 14.39 ($CH_2\underline{Me}$). MS (EI, 70 eV), m/z (I_{rel} (%)): 301 $[M]^+$ (97), 286 $[M - Me]^+$ (22), 255 $[M - EtOH]^+$ (32), 244 $[M - C_4H_9]^+$ (86), 240 $[M - Me - OEt - H]^+$ (72), 228 $[M - CO_2Et]^+$ (28), 216 $[M - CHCO_2Et]^+$ (100), 212 (40), 200 (25), 184 (28), 170 (88), 144 (43), 132 (31), 117 (48), 107 (61), 91 (68).

* Assignments of the signals may have to be interchanged.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 01-03-96479).

References

1. V. A. Glushkov, O. G. Ausheva, S. N. Shurov, and Yu. V. Shklyaev, *Izv. Akad. Nauk, Ser. Khim.*, 2001, 1571 [*Russ. Chem. Bull. Int. Ed.*, 2001, **50**, 1648 (Engl. Transl.)].
2. R. T. Brown and G. A. Jouli, in *Comprehensive Organic Chemistry*, Eds. D. Barton and W. D. Ollis, V. **4**: *Heterocyclic Compounds*, Ed. P. G. Sammes, Pergamon Press, Oxford—New York—Toronto—Sydney—Paris—Frankfurt, 1978.
3. B. A. Trofimov and A. I. Mikhaleva, *N-Vinilpirroly* [*N-Vinylpyrroles*], Nauka, Novosibirsk, 1984, 260 pp. (in Russian).
4. B. F. Kukharev, V. K. Stankevich, and V. A. Kukhareva, *Abstrs., I Vsesoyuznaya konferentsiya po "Khimii, biokhimii i farmakologii proizvodnykh indola"* [*I All-Union Conf. on "The Chemistry, Biochemistry, and Pharmacology of Indole Derivatives"*], Tbilisi, 1986, 89 (in Russian).
5. D. Bland, G. Chambournier, V. Dragan, and D. J. Hart, *Tetrahedron*, 1999, **55**, 8953.
6. A. Padwa, M. A. Brodney, K. Satake, and C. S. Straub, *J. Org. Chem.*, 1999, **64**, 4617.
7. V. A. Glushkov, O. G. Ausheva, S. N. Shurov, and Yu. V. Shklyaev, *Izv. Akad. Nauk, Ser. Khim.*, 2002, 822 [*Russ. Chem. Bull., Int. Ed.*, 2002, **51**, No. 5].
8. H. Bergs, *Ber. Deutsch. Chem. Ges.*, 1934, **67**, 238.

Received June 28, 2001;
in revised form December 17, 2001