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SHORT COMMUNICATIONS

Three-Component Synthesis of 1-Substituted 6',7'-Dimethoxy-4'*H*-spiro[adamantane-2,3'-isoquinolines]

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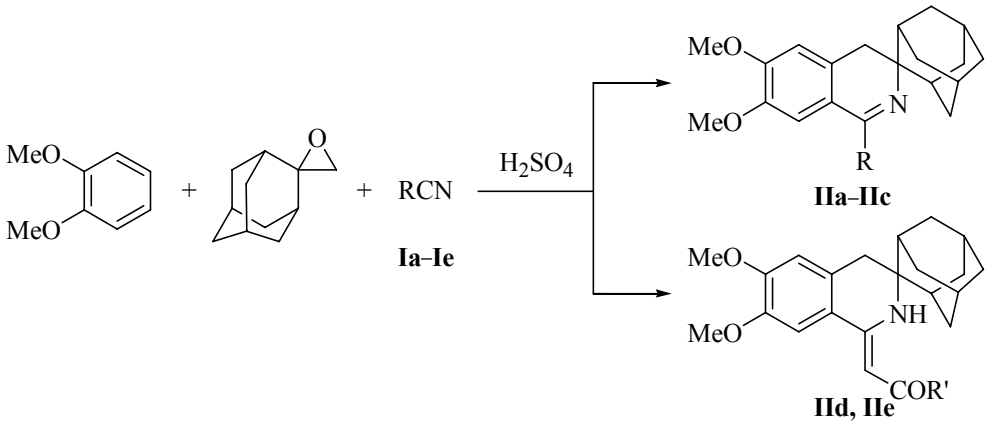
Adamantane derivatives like amantadine and rimantadine exhibit antiviral activity. They also proved to be efficient in the treatment of Alzheimer's and Parkinson's disease, the disorders of the central nervous system [1, 2]. In search for new analogs of the amantadine and rimantadine synthetic procedures were developed for quite a number of spiroadamantane derivatives including both carbocycles [3] and versatile heterocycles [4–6]. Interestingly some of these compounds proved to be more effective than rimantadine and amantadine. We report on the development of the preparation method of spiro[adamantane-2,3'-isoquinolines].

Ritter reaction as one among traditional synthetic procedures for 3,4-dihydroisoquinoline derivatives involves the use as the source of carbocations of alcohols from the series of 2-methyl-1-phenylpropan-2-ol [7], 2-methyl-1-phenylpropan-1-ol, or the corresponding styrenes [8]. In [9] a simple method was developed for the synthesis of 1-substituted 3,4-dihydroisoquinolines by a three-component condensation of an activated arene (1,2- or 1,4-dimethoxybenzene), isobutylene oxide, and a nitrile in a concentrated sulfuric acid. Here the necessary carbocation formed in situ by the acid-catalyzed alkylation of the arene with the isobutylene oxide.

In this study we explored the possibility to apply 2-epoxymethyleneadamantane to the synthesis of 4'*H*-spiro[adamantane-2,3'-isoquinoline] derivatives by the three-component condensation. We established that the reaction of 2-epoxymethyleneadamantane with 1,2-dimethoxybenzene and nitriles **Ia–Ie** in the concentrated sulfuric acid afforded 6',7'-dimethoxy-4'*H*(or 2'*H*,4'*H*)-spiro-[adamantane-2,3'-isoquinolines] **IIa–IIe** in 38–70% yields.



I, R = SMe (**a**), Me (**b**), Ph (**c**), CH_2COOEt (**d**), CH_2CONH_2 (**e**); **II**, R = SMe (**a**), Me (**b**), Ph (**c**), R' = OEt (**d**), NH_2 (**e**).

The composition and structure of compounds **IIa–IIe** were confirmed by the elemental analyses, mass and ^{1}H NMR spectra.

The developed method is a simple and efficient procedure of the preparation of spiro[adamantane-2,3'-isoquinolines]. These structures undoubtedly are interesting from the viewpoint of biological action for they combine the fragments of adamantane and 3,4-dihydroisoquinoline.

4'*H*-Spiro[adamantane-2,3'-isoquinolines IIa–IIe. General procedure. A mixture of 1 mmol of 2-epoxymethyleneadamantane, 1 mmol of nitrile **Ia–Id**, and 1 mmol of 1,2-dimethoxybenzene in 1 ml of CH_2Cl_2 was added dropwise to 4 ml of 96% H_2SO_4 at vigorous stirring and cooling with ice water. The mixture was stirred for 20 min at room temperature, then it was poured in water and neutralized with aqueous ammonia till pH 8–9. The products were extracted into CH_2Cl_2 (3×15 ml). The combined extracts were dried with $MgSO_4$, the solvent was distilled off, the residue was recrystallized.

1'-Methylthio-6',7'-dimethoxy-4'*H*-spiro-[adamantane-2,3'-isoquinoline] (**IIa**). Yield 0.25 g (70%), mp 173.5–175.5°C (2-propanol). IR spectrum, ν, cm^{-1}: 1636 (C=N), 1600, 1570, 1514. ^{1}H NMR spectrum, δ, ppm: 1.40–1.51 m (2H, H_{Ad}), 1.60–1.75 m (6H, H_{Ad}), 1.81–2.00 m (4H, H_{Ad}), 2.47 s (3H, SCH_3), 2.53 br.s (2H, H_{Ad}), 2.86 s (2H, CH_2), 3.89 s (3H, OCH_3), 3.90 s (3H, OCH_3), 6.66 s (1H, H^5), 7.14 s (1H, H^8). Mass spectrum, m/z (I_{rel}, %): 357 (46.1) $[M]^+$, 342 (100) $[M – Me]^+$, 324 (7.1), 310 (3.0) $[M – SMe]^+$, 262 (3.8), 222 (4.2), 176 (7.1), 150 (1.4), 115 (1.1), 91 (4.1), 79 (3.8), 67 (1.8). Found, %: C 70.49; H 7.62; N 3.86; S 8.89. $C_{21}H_{27}NO_2S$. Calculated, %: C 70.55; H 7.61; N 3.92; S 8.97. M 357.18.

1'-Methyl-6',7'-dimethoxy-4'*H*-spiro[adamantane-2,3'-isoquinoline] (IIb). Yield 0.14 g (43%), mp 144–148°C (2-propanol). IR spectrum, ν, cm^{-1}: 1624 (C=N), 1601, 1573, 1510. ^{1}H NMR spectrum, δ, ppm: 1.41–1.48 m (2H, H_{Ad}), 1.59–1.76 m (6H, H_{Ad}), 1.81–2.00 m (4H, H_{Ad}), 2.36 s (3H, CH_3), 2.41–2.51 m (2H, H_{Ad}), 2.82 s (2H, CH_2), 3.89 s (3H, OCH_3), 3.91 s (3H, OCH_3), 6.67 s (1H, H^5), 6.97 s (1H, H^8). Mass spectrum, *m/z* (I_{rel}, %): 325 (100) $[M]^+$, 310 (10.0) $[M – Me]^+$, 296 (4.1), 282 (20.7), 268 (5.5), 256 (5.3), 244 (15.2), 230 (23.3), 217 (19.9), 204 (19.9), 176 (1.4), 160 (2.1), 141 (2.2), 115 (2.3), 79 (3.5), 41 (1.8). Found, %: C 77.61; H 8.36; N 4.23. $C_{21}H_{27}NO_2$. Calculated, %: C 77.50; H 8.36; N 4.30. M 325.20.

1'-Phenyl-6',7'-dimethoxy-4'H-spiro[adamantane-2,3'-isoquinoline] (IIc). Yield 0.19 g (49%), mp 190–192°C (ethyl acetate). IR spectrum, ν, cm^{-1}: 1601 (C=N), 1559, 1512. ^{1}H NMR spectrum, δ, ppm: 1.48–2.22 m (12H, H_{Ad}), 2.59–2.66 m (2H, H_{Ad}), 2.91 s (2H, CH_2), 3.70 s (3H, OCH_3), 3.90 s (3H, OCH_3), 6.75 s (1H, H^5), 6.81 s (1H, H^8), 7.32–7.40 m (3H, Ph), 7.62–7.69 m (2H, Ph). Mass spectrum, m/z (I_{rel}, %): 387 (100) $[M]^+$, 370 (3.8), 344 (14.8), 318 (3.3), 306 (10.8), 292 (16.3), 279 (14.2), 266 (12.6), 250 (2.8), 239 (5.2), 208 (1.6), 165 (2.3), 115 (1.1), 79 (2.1), 41 (1.1). Found, %: C 80.51; H 7.46; N 3.60. $C_{26}H_{29}NO_2$. Calculated, %: C 80.59; H 7.54; N 3.61. M 387.22.

Ethyl 2-(6',7'-dimethoxy-2'H,4'H-spiro[adamantane-2,3'-isoquinolin]-1'-ylidene)acetate (IId). Yield 0.19 g (48%), mp 196–198°C (2-propanol–ethyl acetate). IR spectrum, ν, cm^{-1}: 3273 (NH), 1738 (C=O), 1634 (C=N), 1601, 1573, 1515. ^{1}H NMR spectrum, δ, ppm: 1.30 t (3H, OCH_2CH_3), 1.60–1.77 m (8H, H_{Ad}), 1.83–2.02 m (4H, H_{Ad}), 2.12–2.22 m (2H, H_{Ad}), 3.01 s (2H, CH_2), 3.88 s (3H, OCH_3), 3.90 s (3H, OCH_3), 4.18 q (2H, OCH_2CH_3), 5.04 s (1H, =CH–), 6.34 s (1H, H^5), 7.11 s (1H, H^8), 9.66 br.s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 325 (100) $[M – COOEt + H]^+$, 310 (10.1), 296 (4.1), 282 (21.4), 268 (5.8), 256 (5.5), 244 (16.1), 230 (25.9), 217 (22.2), 204 (22.2), 188 (3.3), 160 (2.3), 115 (3.0), 91 (5.0), 79 (5.2). Found, %: C 72.56; H 7.93; N 3.49. $C_{24}H_{31}NO_4$. Calculated, %: C 72.52; H 7.86; N 3.52. M 397.23.

2-(6',7'-Dimethoxy-2'H,4'H-spiro[adamantane-2,3'-isoquinolin]-1'-ylidene)acetamide (IIe). 0.084 g (1 mmol) of cyanoacetamide was dissolved in 4 ml of 96% H_2SO_4. Then a mixture was added of 0.16 g (1 mmol) of 2-epoxymethyleneadamantane and 0.11 g (1 mmol) of 1,2-dimethoxybenzene in 1 ml of CH_2Cl_2. Further the reaction mixture was worked up as described in the general procedure. Yield 0.14 g (38%), mp 227–230°C (2-propanol–dichloromethane). IR spectrum, ν, cm^{-1}: 3473 (NH_{free}), 3278 (NH_{bound}), 3143 (NH_{bound}), 1631 (C=O), 1619 (C=N), 1604, 1571, 1513. ^{1}H NMR spectrum, δ, ppm: 1.55–2.04 m (12H, H_{Ad}), 2.15–2.25 m (2H, H_{Ad}), 3.00 s (2H, CH_2), 3.89 s (3H, OCH_3), 3.91 s (3H, OCH_3), 4.84 br.s (1H, $CONH_2$), 4.95 s (1H, =CH–), 6.64 s (1H, H^5), 7.06 s (1H, H^8), 10.39 s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 325 (100) $[M – CONH_2 + H]^+$, 310 (9.7), 296 (3.8), 282 (19.3), 268 (5.6), 256 (5.3), 244 (15.5), 230 (24.5), 217 (20.8), 204 (21.8), 188 (3.2), 160 (2.1), 115 (2.8), 91 (4.0), 79 (4.3). Found,

%: C 71.66; H 7.74; N 7.56. $C_{22}H_{28}N_2O_3$. Calculated, %: C 71.71; H 7.66; N 7.60. M 368.21.

2-Epoxymethyleneadamantane was synthesized as described in [10]. IR spectra of compounds as mulls in mineral oil were recorded on a Fourier-spectrophotometer IFS-66 (Bruker). ^{1}H NMR spectra of solutions in $CDCl_3$ were registered on a spectrometer Varian Mercury Plus (operating frequency 300.06 MHz, internal reference HMDS). Mass spectra were taken on a GC-MS instrument Agilent Technologies 6890N/5975B, column HP-5ms, 30 m × 0.25 mm, 0.25 μm, carrier gas helium, ionizing electrons energy 70 eV. Elemental analysis was carried out on an analyzer CHNS-932 Leco Corporation. Reactions progress was monitored and the purity of compounds obtained was checked by TLC on Sorbfil UV-254 plates, development with 5% solution of chloranil in toluene. The melting poits were measured on PPP device and were reported uncorrected.

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