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SYNTHESIS OF SPIRO(BENZO[*h*]QUINAZOLINE-5,1′-CYCLOHEXANE) DERIVATIVES

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3-p-Methoxyphenyl-4-oxo-2-mercapto-3,4,5,6-tetrahydrospiro(benzo[h]quinazoline-4,1′-cyclohexane) was synthesized by the reaction of 4-amino-3-ethoxycarbonyl-1,2-dihydrospiro(naphthalene-2,1′-cyclohexane) (I) with p-methoxyphenyl isothiocyanate without separation of the thioureido derivative. Amino ester I is transformed by acetamide and formamide into 2-methyl-4-oxo-3,4,5,6-tetrahydrospiro(benzo[h]quinazoline-5,1′-cyclohexane) and 4-oxo-3,4,5,6-tetrahydrospiro(benzo[h]quinazoline-5,1′-cyclohexane (II), respectively. Alkylation of quinazoline II with methyl iodide results in formation of 3-methyl-4-oxo-3,4,5,6-tetrahydro-spiro(benzo-[h]quinazoline-5,1′-cyclohexane). Amino ester I reacts with caprolactam with formation of 2,3-pentamethylene-4-oxo-3,4,5,6-tetrahydrospiro(benzo[h]quinazoline-5,1′-cyclohexane). 4-Ethoxymethyleneamino-3-ethoxy-carbonyl-1,2-dihydrospiro(naphthalene-2,1′-cyclohexane) was synthesized by the reaction of amino ester I with o-formic ester, and was converted into 3-amino-4-oxo-3,4,5,6-tetrahydro-spiro(benzo[h]quinazoline-5,1′-cyclohexane) (VIII) by hydrazine hydrate. Aminoquinazoline VIII is acylated by acid chlorides with formation of 3-acylamino-4-oxo-3,4,5,6-tetrahydrospiro(benzo[h]quinazoline-5,1′-cyclohexanes) and forms 3-benzyl-ideneamino-4-oxo-3,4,5,6-tetrahydrospiro(benzo[h]quinazoline-5,1′-cyclohexane) with benzaldehyde.

Benzo[*h*]quinazoline derivatives exhibit anti-inflammatory [1] and antineoplastic [2] activity. Centazolone — a therapeutic agent of the benzoquinazoline series — is used in medical practice as an anticonvulsant and also has sedative and tranquillizing actikons [3]. We previously reported synthesis of 4-amino-3-cyano-1,2-dihydrospiro(naphthalene-2,1′-cyclohexane) [4] and its conversion into spiro(benzoquinazoline-5,1-cyclohexane) derivatives [5, 6]. In continuing the research on synthesis of spiroheterocyclic compounds, we report data on the development of methods of obtaining 4-oxo-3,4,5,6-tetrahydro-spiro(benzo[*h*]quinazoline-5,1′-cyclohexanes) based on 4-amino-3-ethoxycarbonyl-1,2-dihydrospiro(naphthalene-2,1′-cyclohexane) (I) whose synthesis is described in [4]. The reaction of amino ester I with *p*-methoxyphenyl isothiocyanate and subsequent cyclization of thiourea II formed in basic medium yields 3-*p*-methoxyphenyl-4-oxo-2-mercapto-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexane) (III).

Thioureido derivative II underwent cyclization without separation from the reaction medium. The second method of synthesis of benzo[*h*]quinazolines is based on the Nimentovskii reaction — condensation of amino ester I with formamide and acetamide with formation of 4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexane) (IV) and 2-methyl-4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexane) (V), respectively. Benzo[*h*]quinazoline derivative VI, condensed in position *b* with perhydroazepine, was synthesized by reaction of amino ester I with caprolactam. The fourth method of synthesis of benzo[*h*]quinazolines is based on the reaction of hydrazine hydrate with 4-ethoxymethyleneamino-3-ethoxycarbonyl-1,2-dihydrospiro(naphthalene-2,1′-cyclohexane) (VII), obtained by reaction of amino ester I with *o*-formic acid ethyl ester.

It was found that 3-amino-4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexane) (VIII) has weak basic properties and for this reason does not react with alkyl halides, benzyl chloride, and chloroacetic acid ethyl ester but forms Schiff base IX, while it forms amides X-XIII in the reaction with carboxylic acid chlorides. Alkylation of 4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexane) (III) with methyl iodide yields 3-methyl-4-oxo-3,4,5,6-tetrahydrospiro-(benzo[*h*]quinazoline-5,1′-cyclohexane) (XIII).

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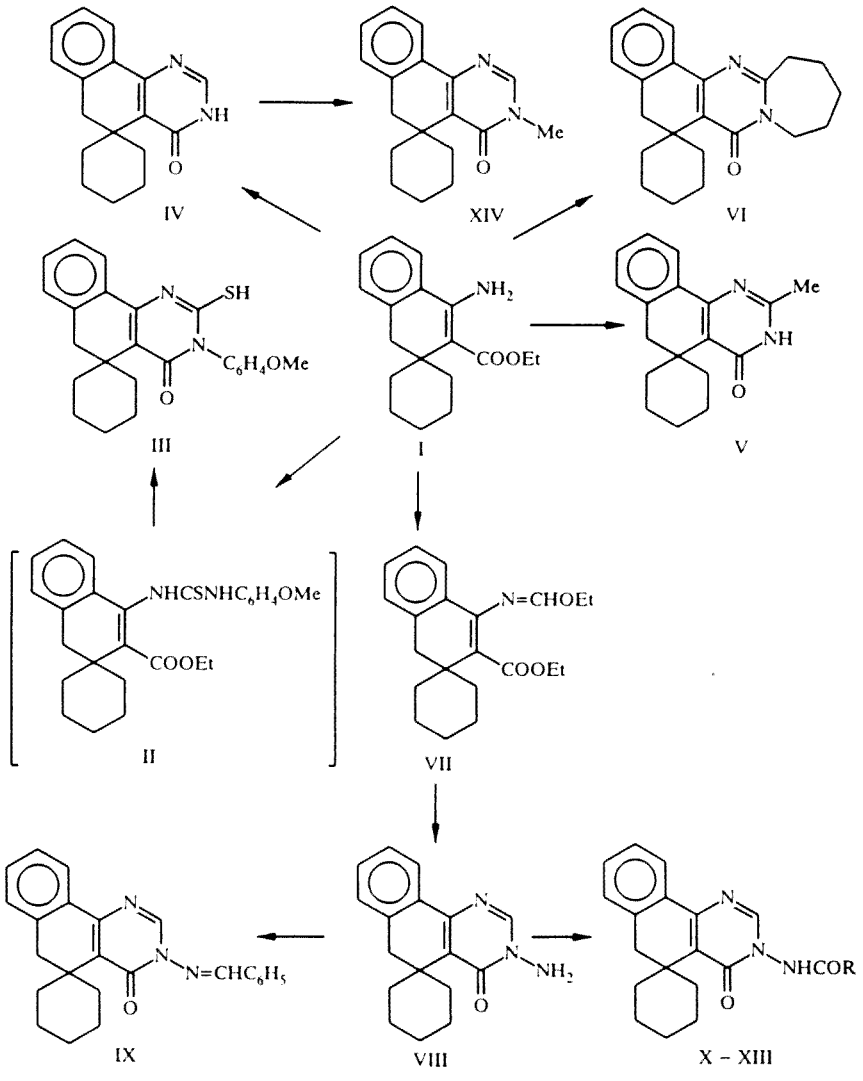

EXPERIMENTAL

The IR spectra were made on a UR-20 instrument (in petrolatum), the PMR spectra were made on a Varian T-60 spectrometer in deuterated solvents, TMS and HMDS internal standards, and the mass spectra were recorded on a MX-1320 spectrometer with direct sample introduction and an ion source with ionizing voltage of 70 eV. TLC was conducted on Silufol UV-254 plates with iodine vapors as developer.

3-*p*-Methoxyphenyl-2-mercapto-4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexane) (III). A mixture of 5.7 g (0.02 mole) of amino ester I, 2.3 g (0.02 mole) of *p*-methoxyphenyl isothiocyanate, and 20 ml of ethanol was boiled with a reflux condenser for 10 h. The mixture was cooled, a solution of 2.24 g (40 mmole) of potassium hydroxide and 20 ml of water was added and boiled for 6 h. It was cooled, 4 ml of 36% hydrochloric acid was added, the precipitated crystals were filtered off, washed with water, and recrystallized from *n*-butanol, yielding 4.2 g (52%) of quinazoline III. mp = 268-270°C, R_f 0.65 (ethyl acetate–nonane, 2:1). IR spectrum: 1570, 1600 (arom. C=C), 1625 (C=N), 1680 cm^{-1} (C=O). PMR spectrum (pyridine-D_5): 1.2-2.8 [10H, m, $(CH_2)_5$], 3.03 (2H, s, 6-CH_2), 3.6 (3H, s, OCH_3), 7.0-8.3 ppm [8H, m, $(C_6H_4)_2$]. Found, %: C 71.44, H 6.13, N 6.84. $C_{24}H_{24}N_2O_2S$. Calculated, %: C 71.26, H 5.98, N 6.92.

4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexane) (IV). A mixture of 5.7 g (0.02 mole) of amino ester I and 20 ml of formamide was heated for 2 h at 150°C, the temperature was raised to 185-190°C, and it was held for

another 2 h. It was cooled, water was added, the precipitated crystals were filtered off, recrystallized from ethanol–water mixture, 2:1, and 1.8 g (34%) of quinazoline IV was obtained. mp 258-260°C, R_f 0.57 (ether–hexane, 5:1). IR spectrum: 1590 (arom. C=C), 1625 (C=N), 1650 (C=O), 3170 cm^{-1} (NH). PMR spectrum ($CDCl_3$): 1.0-2.65 [10H, m, $(CH_2)_5$], 2.96 (2H, s, 6-CH_2), 6.96-8.20 (4H, m, C_6H_4), 8.0 ppm (1H, s, 2-H). Mass spectrum, *m/z* (>1%): M^+ 266(100), 249(26), 237(17), 223(69), 210(89), 197(29). Found, %: C 76.79, H 6.98, N 10.41. $C_{17}H_{18}N_2O$. Calculated, %: C 76.66, H 6.81, N 10.52.

2-Methyl-4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexane) (V). A mixture of 5.7 g (0.02 mole) of amino ester I and 4.7 g (0.08 mole) of acetamide was heated with a reflux condenser at 200°C for 6 h, the mixture was cooled, and 20 ml of water was added to it. The precipitated crystals were filtered, washed with water, and recrystallized from ethanol, yielding 1.5 g (27%) of quinazoline V. mp 53-355°C. IR spectrum: 1590 (arom. C=C), 1620 (C=N), 1650 (C=O), 3180 cm^{-1} (NH). PMR spectrum (DMSO-D_6): 0.86-2.70 [10H, m, $(CH_2)_5$], 2.97 (2H, s, 6-CH_2), 3.40 (3H, s, CH_3), 7.43-8.40 ppm (4H, m, C_6H_4). Found, %: C 76.97, H 7.36, N 9.88. $C_{18}H_{20}N_2O$. Calculated, %: C 77.11, H 7.19, N 9.99.

2,3-Pentamethylene-4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexane) (VI). Here 4 ml of phosphorus oxychloride was added to a solution of 5 g (44 mmole) of caprolactam in 20 ml of dichloroethane with cooling with ice water, maintaining the temperature of the reaction mixture in the 5-10°C range. The temperature was raised to 35-40°C, the mixture was stirred for 10 min, and a solution of 11.4 g (0.04 mole) of amino ester I in 30 ml of dichloroethane was added at the same temperature. The reaction mixture was boiled for 6 h. It was cooled, a solution of 5 g of sodium acetate in 30 ml of water was added, and the mixture was boiled for 20 min. The organic layer was separated, and the aqueous layer was extracted with dichloroethane. The extract was washed with water and dried with magnesium sulfate. After distillation of the solvent, the residue was recrystallized from ethanol, and 3 g (22%) of quinazoline VI was obtained. mp 181-183°C, R_f 0.59 (ethyl acetate–nonane, 1:1). IR spectrum: 1599 (arom. C=C), 1650 cm^{-1} (C=O). Mass spectrum, *m/z* (>1%): M^+ 334(97), 317(5), 305(11), 291(100), 278(57), 265(16), 240(83), 198(12). Found, %: C 79.17, H 7.66, N 8.53. $C_{22}H_{26}N_2O$. Calculated, %: C 79.00, H 7.84, N 8.38.

4-Ethoxymethyleneamino-3-ethoxycarbonyl-1,2-dihydrospiro(naphthalene-2,1′-cyclohexane) (VII). Here 10.4 g (0.07 mole) of *o*-formic ester and 5-6 drops of acetic anhydride were added to a solution of 4.3 g (15 mmole) of amino ester I in 20 ml of benzene. The mixture was boiled for 7 h, cooled, and the solvent and excess *o*-formic ester were distilled off. The crystals were recrystallized from ethanol–water mixture, 2:1, yielding 3.9 g (64%) of ester VII. mp 43-45°C, R_f 0.61 (ethyl acetate–nonane, 1:1). IR spectrum: 1605 (arom. C=C), 1665 (C=N), 1710 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 1.03-1.90 [16H, m, $(CH_2)_5$, $(OCH_2\underline{CH_3})_2$], 2.86 (2H, s, 1-$CH_2$), 3.90-4.50 [4H, m, $(O\underline{CH_2}CH_3)_2$], 7.06-7.43 (4H, m, C_6H_4), 7.57 ppm (1H, s, CH). Found, %: C 74.03, H 8.08, N 4.22. $C_{21}H_{27}NO_3$. Calculated, %: C 73.87, H 7.97, N 4.10.

3-Amino-4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexane) (VIII). A mixture of 3 g (0.06 mole) of hydrazine hydrate, 4 g (0.012 mole) of compound VII, and 15 ml of abs. ethanol was boiled with a reflux condenser for 5 h. It was cooled, the precipitated crystals were filtered, washed with ethanol, and recrystallized from benzene, yielding 3 g (89%) of aminoquinazoline VIII. mp 200-202°C. R_f 0.47 (ether–benzene, 1:1). IR spectrum: 1600 (arom. C=C), 1655 (C=O), 3170, 3280 cm^{-1} (NH_2). PMR spectrum ($CDCl_3$): 1.13-2.70 [(10H, m, $(CH_2)_5$], 3.03 (2H, s, 6-CH_2), 3.66 (2H, s, NH_2), 7.13-8.23 (4H, m, C_6H_4), 8.33 ppm (1H, s, 2-H). Mass spectrum, *m/z* (>1%): M^+ 281(100), 265(16), 250(16), 238(34), 253 (12), 225(45), 221(66), 209(19), 196(36), 172(34), 154(12). Found, %: C 72.72, H 6.97, N 14.80. $C_{17}H_{19}N_3O$. Calculated, %: C 72.57, H 6.81, N 14.93.

3-Benzylideneamino-4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexane) (IX). A mixture of 5.6 g (0.02 mole) of quinazoline VIII, 2.6 g (0.025 mole) of benzaldehyde, 10 ml of toluene, and 10 mg of *p*-toluenesulfonic acid was boiled with Dean–Stark packing for 5 h. It was cooled, the precipitated crystals were filtered and washed with toluene, and 7.2 g (98%) of imine IX was obtained. mp 230-232°C. IR spectrum: 1585 (arom. C=C), 1625 (C=N), 1670 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 1.20-2.90 [10H, m $(CH_2)_5$], 3.03 (2H, s, 6-CH_2), 7.10-8.33 (9H, m, C_6H_4 and C_6H_6), 8.43 (1H, s, 2-CH), 9.57 ppm (1H, s, CH). Found, %: C 78.11, H 6.43, N 11.28. $C_{24}H_{23}N_3O$. Calculated, %: C 78.02, H 6.27, N 11.38.

3-Acylamino-4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexane) (X-XIII). Here 2 mmole of the corresponding acid chloride was added to a solution of 5.6 g (0.02 mole) of aminoquinazoline VIII in 15 ml of benzene. The mixture was boiled with a reflux condenser for 5 h, cooled, and the precipitated crystals were filtered off and recrystallized.

Compound X. mp 199-201°C (nonane), R_f 0.52 (benzene–ether, 1:7). IR spectrum: 1595 (arom. C=C), 1640 (C=O), 1715 (C=O), 3190 cm^{-1} (NH). PMR spectrum ($CDCl_3$): 1.03-2.66 [10H, m, $(CH_2)_5$], 2.17 (3H, s, CH_3), 2.93 (2H,

s, 6-CH_2), 6.93-8.20 (4H, m, C_6H_4), 8.06 (1H, s, 2-CH), 9.60 ppm (1H, br. s, NH). Found, %: C 70.41, H 6.35, N 13.12. $C_{19}H_{21}N_3O_2$. Calculated, %: C 70.57, H 6.54, N 12.99.

Compound XI. mp 198-200°C (benzene). R_f 0.47 (benzene–ether, 1:2). IR spectrum: 1585 (arom. C=C), 1635 (C=O), 1705 (C=O), 3230 cm^{-1} (NH). PMR spectrum ($CDCl_3$): 1.0-2.70 [12H, m, $(CH_2)_5$, $COCH_2$], 1.13 (3H, t, $COCH_2CH_3$), 2.90 (2H, s, 6-CH_2), 7.07-8.33 (4H, m, C_6H_4), 8.17 (1H, s, 2-CH), 9.30 ppm (1H, br. s, NH). Found, %: C 71.34, H 7.03, N 12.52. $C_{20}H_{23}N_3O_2$. Calculated, %: C 71.19, H 6.87, N 12.45.

Compound XII. mp 166-168°C (benzene), R_f 0.58 (benzene–ether, 1:2). IR spectrum: 1590 (arom. C=C), 1635 (C=N), 1670 (C=O), 1705 (C=O), 3240 cm^{-1} (NH). PMR spectrum ($CDCl_3$): 0.8-2.66 [17H, m, $(CH_2)_5$, $COCH_2CH_2CH_3$)], 2.93 (2H, s, 6-CH_2), 7.0-8.20 (4H, m, C_6H_4), 8.06 ppm (1H, s, 2-CH). Found, %: C 71.58, H 7.24, N 12.15. $C_{21}H_{25}N_3O_2$. Calculated, %: C 71.77, H 7.17, N 11.96.

Compound XIII. mp 241-243°C (butanol), R_f 0.53 (benzene–ether, 3:1). IR spectrum: 1600 (arom. C=C), 1655 (C=O), 1680 (C=O), 3260 cm^{-1} (NH). PMR spectrum ($CDCl_3$): 1.0-2.70 [10H, m, $(CH_2)_5$], 2.96 (2H, s, 6-CH_2), 3.73 (1H, br. s, NH), 7.06-8.10 (9H, m, C_6H_4, C_6H_5), 8.13 ppm (1H, s, 2-CH). Found, %: C 74.70, H 6.13, N 10.79. $C_{24}H_{23}N_3O_2$. Calculated, %: C 74.78, H 6.01, N 10.90.

3-Methyl-4-oxo-3,4,5,6-tetrahydrospiro(benzo[*h*]quinazoline-5,1′-cyclohexane) (XIV). A mixture of 2.7 g (0.01 mole) of quinazoline IV, 0.56 g (0.01 mole) of potassium hydroxide, and 30 ml of abs. ethanol was boiled until the components dissolved. Then 2.8 g (0.02 mole) of methyl iodide was added and the mixture was boiled for 7 h, cooled, 30 ml of water was added, and the precipitated crystals were filtered and recrystallized from ethanol, yielding 2 g (71%) of quinazoline XIV. mp 187-190°C, R_f 0.54 (ethyl acetate–nonane, 3:1). IR spectrum: 1595 (arom. C=C), 1655 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 1.10-2.90 [10H, m, $(CH_2)_5$], 3.03 (2H, s, 6-CH_2), 3.50 (3H, s, N–CH_3), 7.10-8.33 (4H, m, C_6H_4), 8.13 ppm (1H, s, 2-CH). Found, %: C 77.06, H 7.22, N 10.16. $C_{18}H_{20}N_2O$. Calculated, %: C 77.11, H 7.19, N 9.99.

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