Chemistry of Heterocyclic Compounds, Vol. 33, No. 4, 1997

1- AND 2-(4-HYDROXYCARBONYLPHENYL)-4-OXO-4,5,6,7-TETRAHYDROINDAZOLES

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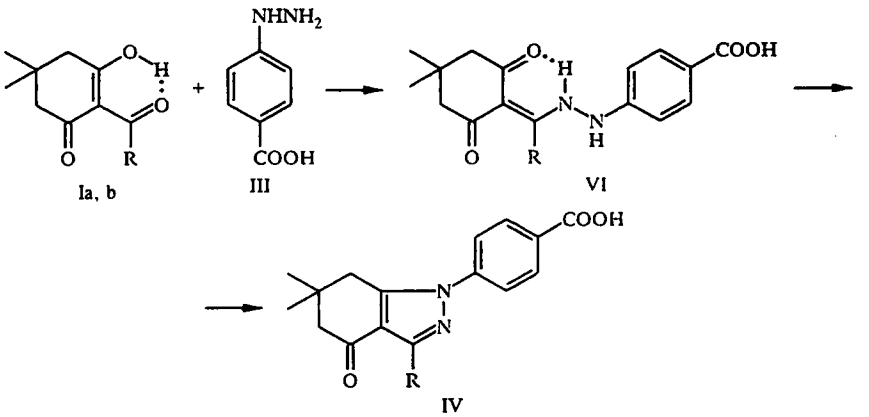
Reactions of 4-hydrazinobenzoic acid with 2-formyl- and 2-acetyldimedones were utilized to synthesize 6,6-dimethyl- and 3,6,6-trimethyl-1-(4-hydroxycarbonylphenyl)-4-oxo-4,5,6,7-tetrahydroindazoles corre-spondingly, and the reaction with 2-cyano-3-ethoxy-5,5-dimethylcyclohex-2-en-1-one gave 2-(4-hydroxycarbonylphenyl)-3-amino-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydroindazole.

In the continuation of work on the biological activity of derivatives of indazole and other pyrazole-containing systems [1-5] and the synthesis and properties of 4,5,6,7-tetrahydroindazoles [6-10], including 3-amino-4-oxo-4,5,6,7-tetrahydroindazoles [11-15], reactions of the 2-acyldimedones (Ia, b) and 2-cyano-3-ethoxy-5,5-dimethylcyclohex-2-en-1-one (II) with 4-hydrazinobenzoic acid (III) were carried out. This resulted in the synthesis of 1-(4-hydroxycarbonylphenyl)- and 2-(4-hydroxycarbonylphenyl)-3-amino-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydroindazoles, (IVa, b) and (V) correspondingly. The reactions of the 2-acyldimedones (Ia, b) with the hydrazine (III) were performed in boiling ethanol under conditions of acid catalysis. In the case of 2-formyldimedone, the mixing of ethanolic solutions of (Ia) and (III), heated to 50°C, led to the isolation of the intermediate hydrazinomethylene derivative (VIa). The boiling of the hydrazinomethylene derivative (VIa) in ethanol in the presence of acids also leads to the indazole (IVa).

Interaction of the enol ether (II) with 4-hydrazinobenzoic acid by boiling in ethanol gives 2-(4-hydroxycarbonylphenyl)-3-amino-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydroindazole (V). The reactions of 4-nitrophenylhydrazine (VIIa) and 4-methoxybenzoylhydrazine (VIIb) with the enol ether (IIb) also afford the corresponding 2-substituted 3-aminoindazoles (VIII). Condensation of the aminoindazoles (V) and (VIII) with 2-formyldimedone leads to the 2-aminomethylenedimedones (IX).

2-Formyl-1,3-indandione and dehydroacetic acid react with 4-hydrazinobenzoic acid to form 2-(4-hydroxycarbonylphenylhydrazinomethylen)-1,3-indandione (X) and 3-[1-[2-(4-hydroxycarbonylphenyl)-hydrazino]ethylidene]-6-methyl-2,4-pyrandione (XI) correspondingly. The conversion of the first of them to 1-(4-hydroxycarbonylphenyl)-4-oxo-4H-indeno[2,3-d]pyrazole under conditions of acid catalysis, employed for the conversion of the hydrazino derivative (VI) to the indazole (IV), was unsuccessful.



Riga Technical University, Riga LV-1658. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 516-519, April, 1997. Original article submitted June 12, 1996.

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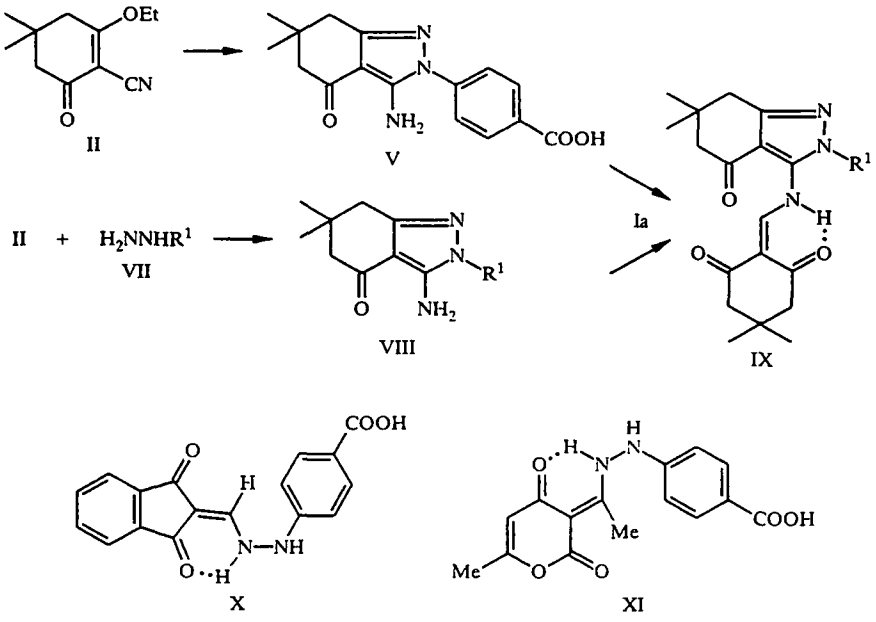

I, IV a R = H, b R = CH_3; VII, VIII a R^1 = $C_6H_4NO_2$-4, b R^1 = $COC_6H_4OCH_3$-4
IX a R^1 = C_6H_4COOH-4, b R^1 = $C_6H_4NO_2$-4

The structure of the compounds synthesized is confirmed by PMR and IR spectral data. Shifts of the signals of the protons of the $C_{(5)}$ and $C_{(7)}$ methylene groups in the case of the 2-substituted indazoles (V), (VIII), and (IX) differ by 0.30-0.35 ppm; in the case of the 1-substituted compounds (IV), they differ by 0.60-0.65 ppm. The amino group in compounds (V) and (VIII) is characterized by the δ 6.75-7.33 ppm in the PMR spectra, and by stretching vibrations at 3430-3410 and 3330-3310 cm^{-1} in the IR spectra. The hydroxycarbonyl group in the compounds (IV), (V), (VIa), (IXa), (X), and (XI) is characterized by two absorption maxima in the IR spectra, taken in hexachlorobutadiene, in the region of 2680-2540 cm^{-1}. The chelated proton in the hydrazino derivatives (VIa), as well as the compounds (IX), is detected at the δ 12.38-13.24 ppm; it is detected in compound (XI) at 15.58 ppm.

EXPERIMENTAL

The IR spectra were taken on the Specord 75-IR spectrometer using suspensions of the substances in Nujol (1800-1500 cm^{-1}) and hexachlorobutadiene (3600-2000 cm^{-1}); the frequencies of stretching vibrations of the C–H bonds in the region of 3050-2800 cm^{-1} were not presented. The ^1H NMR spectra were obtained on the Bruker 90/DS (90 MHz) and Bruker AM-360 (360 MHz) spectrometers using the impulse regime with subsequent Fourier transformation. The internal standard was TMS.

1-(4-Hydroxycarbonylphenyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydroindazole (IVa). A. The hydrazinomethylene derivative (VI) (0.76 g, 2.5 mmole) is boiled for 3 h in the solution of 25 ml of ethanol and 1 ml of conc. hydrochloric acid. After 24 h, the indazole (IVa) is filtered off and recrystallized from ethanol. The yield is 0.39 g (55%). The mp is 110-112°C.

B. Formyldimedone (0.84 g, 5 mmole) and 0.76 g (5 mmole) of 4-hydrazinobenzoic acid are boiled for 3 h in the solution of 30 ml of ethanol and 1 ml of conc. hydrochloric acid. After 24 h, the indazole (IVa) is filtered off and recrystallized from ethanol. The yield is 0.59 g (41%). The IR spectrum is as follows: 1682 cm^{-1}, 1610 cm^{-1}, 1565 cm^{-1}, 1550 cm^{-1}, 1520 cm^{-1}, 2680 cm^{-1}, and 2560 cm^{-1}. The PMR spectrum in DMSO-D_6 is as follows: 1.03 ppm (6H, s, $2CH_3$), 2.39 ppm (2H, s, CH_2), 3.00 ppm (2H, s, CH_2), 7.75-8.17 ppm (4H, m, C_6H_4), 8.06 ppm (1H, s, =CH–), and 13.11 ppm (1H, s, OH). Found, %: C 67.49, H 5.60, and N 9.97. $C_{16}H_{16}N_2O_3$. Calculated, %: C 67.59, H 5.67, and N 9.85.

1-(4-Hydroxycarbonylphenyl)-3,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindazole (IVb). 2-Acetyldimedone (0.91 g, 5 mmole) and 0.76 g (5 mmole) of 4-hydrazinobenzoic acid are boiled for 3 h in the solution of 25 ml of ethanol and 1 ml of

conc. hydrochloric acid. After 24 h, the indazole (IVb) is filtered off and recrystallized from ethanol. The yield is 0.57 g (39%). The mp is 231-232°C. The IR spectrum is as follows: 1700 cm^{-1}, 1675 cm^{-1}, 1665 cm^{-1}, 1615 cm^{-1}, 1595 cm^{-1}, 1570 cm^{-1}, 1545 cm^{-1}, 1520 cm^{-1}, 2670 cm^{-1}, and 2550 cm^{-1}. The PMR spectrum in DMSO-D_6 is as follows: 1.05 ppm (6H, s, $2CH_3$), 2.34 ppm (2H, s, CH_2), 2.44 ppm (3H, s, CH_3), 3.01 ppm (2H, s, CH_2), 7.75-8.13 ppm (4H, m, C_6H_4), and 12.90 ppm (1H, broad s, OH). Found, %: C 68.30, H 6.01, and N 9.51. $C_{17}H_{18}N_2O_3$. Calculated, %: C 68.44, H 6.08, and N 9.39.

2-(4-Hydroxycarbonylphenylhydrazinomethylene)-5,5-dimethyl-1,3-cyclohexanedione (VI). The solution of 0.84 g (5 mmole) of 2-formyldimedone in 15 ml of ethanol is added to the solution, taken to boiling, of 0.76 g (5 mmole) of 4-hydrazinobenzoic acid in 80 ml of ethanol. After 24 h, the residue of the product (VI) is filtered off and recrystallized from ethanol. The yield is 1.04 g (67%). The mp is 234-236°C. The IR spectrum is as follows: 1675 cm^{-1}, 1650 cm^{-1}, 1600 cm^{-1}, 1555 cm^{-1}, 1525 cm^{-1}, 3280 cm^{-1}, 3200 cm^{-1}, 3100 cm^{-1}, 2680 cm^{-1}, and 2560 cm^{-1}. The PMR spectrum in $CDCl_3$ is as follows: 1.11 ppm (6H, s, $2CH_3$), 2.33 ppm (2H, s, CH_2), 2.47 ppm (2H, s, CH_2), 6.82-7.91 ppm (4H, m, C_6H_4), 8.29 ppm (1H, d, J = 8 Hz, =CH-), 9.02 ppm (1H, broad s, OH), and 12.38 ppm (1H, d, J = 8 Hz, NH). Found, %: C 63.47, H 5.92, and N 9.20. $C_{16}H_{18}N_2O_4$. Calculated, %: C 63.56, H 6.00, and N 9.27.

2-(4-Hydroxycarbonylphenyl)-3-amino-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydroindazole (V). 2-Cyano-3-ethoxy-5,5-dimethylcyclohex-2-en-1-one (II) (0.39 g, 2 mmole) and 0.30 g (2 mmole) of 4-hydrazinobenzoic acid are boiled for 3 h in 30 ml of ethanol. A rotor is utilized to distil off 20 ml of ethanol. After 24 h, the residue of the product (V) is filtered off and recrystallized from ethanol. The yield is 0.34 g (53%). The mp is 252-254°C. The IR spectrum is as follows: 1720 cm^{-1}, 1650 cm^{-1}, 1630 cm^{-1}, 1620 cm^{-1}, 1560 cm^{-1}, 1545 cm^{-1}, 1520 cm^{-1}, 3420 cm^{-1}, 3310 cm^{-1}, 3220 cm^{-1}, 2750 cm^{-1}, and 2620-2500 cm^{-1}. The PMR spectrum in DMSO-D_6 is as follows: 1.03 ppm (6H, s, $2CH_3$), 2.22 ppm (2H, s, CH_2), 2.53 ppm (2H, s, CH_2), 6.75 ppm (2H, broad s, NH_2), 7.69-8.08 ppm (4H, m, C_6H_4), and 12.94 ppm (1H, broad s, OH). Found, %: C 64.01, H 5.58, and N 13.88. $C_{16}H_{17}N_3O_3$. Calculated, %: C 64.20, H 5.73, and N 14.04.

2-(4-Nitrophenyl)- and 2-(4-Methoxybenzoyl)-3-amino-4-oxo-4,5,6,7-tetrahydroindazoles (VIIIa) and (VIIIb). These compounds were obtained by analogy with the preceding account in reactions of equimolar amounts of the enol ether of 2-cyanodimedone with 4-nitrophenylhydrazine and 4-methoxybenzoylhydrazine.

(VIIIa). The yield is 41%. The mp is 220-222°C (from ethanol). The IR spectrum is as follows: 1650 cm^{-1}, 1635 cm^{-1}, 1600 cm^{-1}, 1555 cm^{-1}, 1525 cm^{-1}, 3410 cm^{-1}, 3320 cm^{-1}, and 3220-3150 cm^{-1}. The PMR spectrum in DMSO-D_6 is as follows: 1.04 ppm (6H, s, $2CH_3$), 2.22 ppm (2H, s, CH_2), 2.53 ppm (2H, s, CH_2), 6.95 ppm (2H, s, NH_2), and 7.86-8.37 ppm (4H, m, C_6H_4). Found, %: C 59.80, H 5.30, and N 18.51. $C_{15}H_{16}N_4O_3$. Calculated, %: C 59.99, H 5.37, and N 18.66.

(VIIIb). The yield is 48%. The mp is 139-140°C (from ethanol). The IR spectrum is as follows: 1700 cm^{-1}, 1640 cm^{-1}, 1575 cm^{-1}, 1545 cm^{-1}, 1535-1525 cm^{-1}, 3480 cm^{-1}, 3330 cm^{-1}, and 3200 cm^{-1}. The PMR spectrum in $CDCl_3$ is as follows: 1.13 ppm (6H, s, $2CH_3$), 2.33 ppm (2H, s, CH_2), 2.62 ppm (2H, s, CH_2), 3.89 ppm (3H, s, $-O-CH_3$), 7.33 ppm (2H, broad s, NH_2), and 7.00-8.24 ppm (4H, m, C_6H_4). Found, %: C 64.95, H 5.98, and N 13.40. $C_{17}H_{19}N_3O_3$. Calculated, %: C 65.16, H 6.11, and N 13.41.

2-[2-(4-Hydroxycarbonylphenyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydroindazol-2-ylaminomethylene]-5,5-dimethyl-1,3-cyclohexanedione (IXa). The aminoindazole (V) (0.30 g, 1 mmole) and 0.17 g (1 mmole) of 2-formyldimedone are boiled for 2 h in 15 ml of ethanol. After 24 h, the residue of the product (IXa) is filtered off and recrystallized from ethanol. The yield is 0.18 g (40%). The mp is 261-262°C. The IR spectrum is as follows: 1685 cm^{-1}, 1670 cm^{-1}, 1610 cm^{-1}, 1580 cm^{-1}, 1545 cm^{-1}, 1525 cm^{-1}, 3100 cm^{-1}, 2670 cm^{-1}, and 2540 cm^{-1}. The PMR spectrum in DMSO-D_6 is as follows: 0.97 ppm (6H, s, $2CH_3$), 1.13 ppm (6H, s, $2CH_3$), 2.38 ppm (4H, s, $2CH_2$), 2.41 ppm (2H, s, CH_2), 2.73 ppm (2H, s, CH_2), 7.76-8.16 ppm (4H, m, C_6H_4), 9.23 ppm (1H, d, J = 11 Hz, =CH-), 13.11 ppm (1H, d, J = 11 Hz, NH), and 13.24 ppm (1H, broad s, OH). Found, %: C 66.63, H 5.95, and N 9.34. $C_{25}H_{27}N_3O_5$. Calculated, %: C 66.80, H 6.06, and N 9.35.

2-[2-(4-Nitrophenyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydroindazol-2-ylaminomethylene]-5,5-dimethyl-1,3-cyclohexanedione (IXb). This compound was obtained by analogy with the preceding (IXa) from the aminoindazole (VIIIa) and 2-formyldimedone. The yield is 35%. The mp is 205-206°C (from ethanol). The IR spectrum is as follows: 1680 cm^{-1}, 1610-1590 cm^{-1}, 1555 cm^{-1}, 1540 cm^{-1}, 1515 cm^{-1}, 3140 cm^{-1}, 3100 cm^{-1}, and 3060 cm^{-1}. The PMR spectrum in DMSO-D_6 is as follows: 1.00 ppm (6H, s, $2CH_3$), 1.11 ppm (6H, s, $2CH_3$), 2.38 ppm (2H, s, CH_2), 2.40 ppm (4H, s, $2CH_2$), 2.72 ppm (2H, s, CH_2), 7.97-8.42 ppm (4H, m, C_6H_4), 9.08 ppm (1H, d, J = 11 Hz, =CH−), and

13.02 ppm (1H, d, J = 11 Hz, NH). Found, %: C 63.86, H 5.80, and N 12.50. $C_{24}H_{26}N_4O_5$. Calculated, %: C 63.99, H 5.82, and N 12.44.

2-(4-Hydroxycarbonylphenylhydrazinomethylene)-1,3-indandione (X). The solution of 0.44 g (2.5 mmole) of 2-formyl-1,3-indandione in 20 ml of ethanol is added to the solution, brought to boiling, of 0.38 g (2.5 mmole) of 4-hydrazinobenzoic acid in 40 ml of ethanol. After 24 h, the residue of the product (X) is filtered off and recrystallized from ethanol. The yield is 0.60 g (78%). The mp is 275-277°C. The IR spectrum is as follows: 1715 cm^{-1}, 1665 cm^{-1}, 1590 cm^{-1}, 1525 cm^{-1}, 3250 cm^{-1}, 3100 cm^{-1}, 2680 cm^{-1}, and 2580 cm^{-1}. The PMR spectrum in DMSO-D_6 is as follows: 6.83-7.81 ppm (8H, m, $2C_6H_4$), 7.47 ppm (1H, s, =CH−), and 11.86 ppm (3H, broad s, 2NH + OH). Found, %: C 66.02, H 3.99, and N 9.01. $C_{17}H_{12}N_2O_4$. Calculated, %: C 66.23, H 3.93, and N 9.09.

3-[1-(2-(4-Hydroxycarbonylphenyl)hydrazino)ethylidene]-6-methyl-2,4-pyrandione (XI). Dehydroacetic acid (0.42 g, 2.5 mmole) and 0.38 g (2.5 mmole) of 4-hydrazinobenzoic acid are boiled in 30 ml of ethanol for 2 h. After 24 h, the residue of the product (XI) is filtered off and recrystallized from ethanol. The yield is 0.62 g (82%). The mp is 234-235°C. The IR spectrum is as follows: 1690 cm^{-1}, 1680 cm^{-1}, 1610 cm^{-1}, 1585 cm^{-1}, 1535 cm^{-1}, 3270 cm^{-1}, 3090 cm^{-1}, 2680 cm^{-1}, and 2560 cm^{-1}. The PMR spectrum in DMSO-D_6 is as follows: 2.17 ppm (3H, s, CH_3), 2.67 ppm (3H, s, CH_3), 5.97 ppm (1H, s, =CH−), 6.92-7.86 ppm (4H, m, C_6H_4), 9.63 ppm (1H, s, CH), 12.36 ppm (1H, broad s, NH), and 15.58 ppm (1H, broad s, NH). Found, %: C 59.49, H 4.55, and N 9.20. $C_{15}H_{14}N_2O_5$. Calculated, %: C 59.60, H 4.67, and N 9.27.

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