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5-BENZYLIDENE- AND 5-AMINOMETHYL-4-OXO-4,5,6,7-TETRAHYDROINDAZOLES

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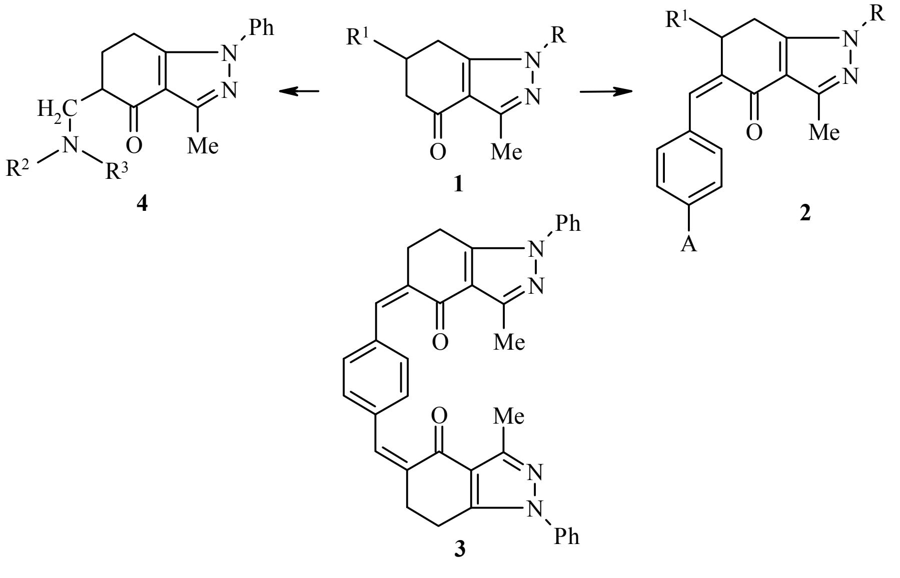
The reaction of 3-methyl-4-oxo-4,5,6,7-tetrahydroindazoles with benzaldehydes gave 5-benzylidene-3-methyl-4-oxo-4,5,6,7-tetrahydroindazoles. Under Mannich conditions, 3-methyl-1-phenyl-4,5,6,7-tetrahydroindazole gave 5-aminomethyl-3-methyl-4-oxo-1-phenyl-4,5,6,7-tetrahydroindazoles.

Keywords: amines; benzaldehydes; 5-benzylidene- and 5-aminomethyl-3-methyl-4-oxo-4,5,6,7-tetrahydroindazoles; Mannich reaction.

Amongst the works on the modification of the carbocyclic part of α-oxocyclohexeno heterocycles (including 4-oxo-4,5,6,7-tetrahydoindazoles as described recently in the article [1]) studies of their reaction with aromatic aldehydes at the β-carbon and their reaction under Mannich conditions have been absent. Hence, within the scope of our work on the modification of 4,5,6,7-tetrahydroindazoles [1-6] we have studied the reaction of 3-methyl-4-oxo-4,5,6,7-tetrahydroindazoles **1** with benzaldehydes under the conditions for the reaction of cyclanones with aromatic aldehydes [7-10]. Heating the oxoindazoles **1a,b** with the benzaldehydes in 85% H_3PO_4 at 120-130°C for 4 h gave the 5-benzylidene-3-methyl-4-oxo-4,5,6,7-tetrahydroindazoles **2a-g**.



1 a R, R^1 = Ph, H; **b** C_5H_4N, H; **c** Ph, Ph; **2 a** R, R^1 A = Ph, H, H; **b** Ph, H, Br;
c Ph, H, NEt_2; **d** Ph, H, NO_2; **e** C_5H_4N, H, Br; **f** C_5H_4N, H, NEt_2; **g** C_5H_4N, H, NO_2;
h Ph, Ph, NO_2; **4 a** R^2R^3= Me, Me; **b** Et, Et; **c** $(CH_2)_4$; **d** $(CH_2)_5$; **e** $(CH_2CH_2)_2O$

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The reaction of oxoindazole **1c** with 4-nitrobenzaldehyde also led to the 5-benzylidene derivative **2h**. Terephthaldialdehyde and the oxoindazole **1a** in the molar ratio 2:1 gave the bis product **3**.

The structure of the benzylidene ketones **2** and **3** was confirmed by IR and ^{1}H NMR spectroscopy. The ^{1}H NMR spectra of all of the compounds **2** showed the presence of a singlet for the C_3 methyl group protons in the range 2.49-2.61 ppm, a multiplet for the protons of the $C_{(6)}H_2$–$C_{(7)}H_2$ group at 2.98-3.34 ppm, and a singlet for the methine =CH– proton at 7.38-8.27 ppm. The IR spectra of compounds **2** and **3** revealed an absorption band for the carbonyl group at 1669-1649 cm^{-1}.

The participation of α-oxocyclohexene heterocycles in the Mannich reaction has already been reported [11. 12]. Refluxing the oxoindazole **1a** with an excess of the secondary amine salt and paraformaldehyde gave the 5-aminomethyl-4-oxo derivative **4**. The IR spectra of the latter showed a carbonyl group absorption band at 1662-1656 cm^{-1} but the majority of the proton signals at the tetrahedral carbon atoms in the ^{1}H NMR spectra at 0.98-2.95 ppm could not be assigned with certainty.

EXPERIMENTAL

IR spectra were taken on a Specord 75 IR spectrometer for suspensions in nujol (1800-1500 cm^{-1}) and in hexachlorobutadiene (3600-2000 cm^{-1}). The frequencies for the C–H absorption bands in the region 3050-2800 cm^{-1} are not given. ^{1}H NMR spectra were recorded in $CDCl_3$ (DMSO-d_6 for compound **2d**) on a Bruker WH-90/DS (90 MHz) spectrometer with TMS as internal standard.

5-Benzylidine- (2a), 5-(4-bromobenzylidene)- (2b), and 5-(4-diethylaminobenzylidene- (2c), 3-methyl-4-oxo-1-phenyl-4,5,6,7-tetrahydroindazoles and 5-(4-nitrobenzylidene)-3-methyl-4-oxo-1-phenyl-4,5,6,7-tetrahydroindazole (2d). A mixture of indazole **1a** (2 mmol) and the corresponding benzaldehyde (2 mmol) in 85% H_3PO_4 (10 ml) was heated in a flask with reflux condenser on an oil bath at 120-130°C (bath temperature). The reaction mixture was cooled, water (40 ml) was added, and the precipitate was recrystallized from ethanol. Basification of the acid filtrate permitted recovery of part of the unreacted indazole **1a**.

2a. Yield 33%; mp 119-120°C. IR spectrum, ν, cm^{-1}: 1651, 1593, 1549, 1511. ^{1}H NMR spectrum, δ, ppm: 2.61 (3H, s, CH_3); 3.05 (4H, m, CH_2CH_2); 7.43 (10H, centre m, 2 × C_6H_5); 7.74 (1H, s, =CH–). Found, %: C 80.02; H 5.60; N 8.70. $C_{21}H_{18}N_2O$. Calculated, %: C 80.23; H 5.77; N 8.91.

2b. Yield, 38%; mp 162-164°C. IR spectrum, ν, cm^{-1}: 1659, 1609, 1595, 1549, 1509. ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 2.58 (3H, s, CH_3); 2.98 (4H, m, CH_2CH_2); 7.18 (2H, m, ^3J = 8, C_6H_4); 7.43 (5H, m, C_6H_5); 7.54 (2H, m, ^3J = 8, C_6H_4); 7.69 (1H, s, =CH–). Found, %: C 63.89; H 4.30; Br 20.10; N 7.20. $C_{21}H_{17}BrN_2O$. Calculated, %: C 64.13; H 4.36; Br 20.32; N 7.12.

2c. Yield 58%; mp 170-172°C. IR spectrum, ν, cm^{-1}: 1649, 1609, 1583, 1549, 1513. ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 1.16 (6H, t, ^3J = 7, 2 × $\underline{CH_3}CH_2$); 2.61 (3H, s, CH_3); 2.92-3.18 (4H, m, CH_2CH_2); 3.36 (4H, q, *J* = 7, 2 × $CH_3\underline{CH_2}$); 6.67 (2H, m, ^3J = 8, C_6H_4); 7.38 (2H, m, ^3J = 8, C_6H_4); 7.43 (5H, m, C_6H_5); 7.72 (1H, s, =CH–). Found, %: C 77.95; H 6.92; N 10.85. $C_{25}H_{27}N_3O$. Calculated, %: C 77.89; H 7.06; N 10.90.

2d. Yield 42%; mp 186-187°C. IR spectrum, ν, cm^{-1}: 1669, 1625, 1593, 1545, 1513. ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 2.49 (3H, s, CH_3); 2.96 (4H, centre m, CH_2CH_2); 7.54 (1H, s, =CH–); 7.56-7.68 (7H, m, C_6H_4, C_6H_5); 8.27 (2H, m, ^3J = 8, C_6H_4). Found, %: C 70.02, H 4.70; N 11.50. $C_{21}H_{17}N_3O_3$. Calculated, %: C 70.18; H 4.77; N 11.69.

5-(4-Bromobenzylidene)- (2e), 5-(4-diethylaminobenzylidene)- (2f), and 5-(4-nitrobenzylidene)- (2g) 3-methyl-4-oxo-1-(2-pyridyl)-4,5,6,7-tetrahydroindazoles were prepared similarly to compounds **2a-d** from equimolar amounts of 3-methyl-4-oxo-1-(2-pyridyl)-4,5,6,7-tetrahydroindazole **1b** and the corresponding benzaldehyde.

2e. Yield 19%; mp 169-170°C (ethanol). IR spectrum, ν, cm^{-1}: 1657, 1609, 1589, 1562, 1549, 1540. ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 2.58 (3H, s, CH_3); 3.05 (2H, t, ^3J = 7, CH_2); 3.49 (2H, t, ^3J = 7, CH_2); 7.21-8.36 (9H, m, C_6H_4, C_5H_4N, =CH–). Found, %: C 60.98; H 4.01; Br 20.40; N 10.49. $C_{20}H_{16}BrN_3O$. Calculated, %: C 60.92; H 4.09; Br 20.27; N 10.66.

2f. Yield 64%; mp 139-140°C (ethanol). IR spectrum, ν, cm^{-1}: 1649, 1610, 1589, 1560, 1551, 1521. ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 1.18 (6H, t, ^3J =7, 2 × $\underline{CH}_3CH_2$); 2.61 (3H, s, CH_3); 3.38 (8H, centre m, 2 × $N\underline{CH}_2CH_3$, CH_2CH_2); 6.65 (2H, m, ^3J = 8, C_6H_4); 7.21 (1H, m, C_5H_4N); 7.38 (2H, m, ^3J = 8, C_6H_4); 7.69 (1H, br. s, =CH–); 7.76-7.96 (2H, m, C_5H_4N); 8.43 (1H, ddd, ^3J = 5, ^4J = 1.5, ^5J = 1.5, C_5H_4N). Found, %: C 72.70; H 7.15; N 15.55. $C_{24}H_{26}N_4O$. Calculated, %: C 72.90; H 7.23; N 15.46.

2g. Yield 55%; mp 216-217°C (ethanol–DMF, 3:1). IR spectrum, ν, cm^{-1}: 1667, 1619, 1594, 1577, 1549, 1511. ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 2.53 (3H, s, CH_3); 3.03 (2H, t, ^3J = 7, CH_2); 3.51 (2H, t, ^3J = 7, CH_2); 7.27 (1H, m, C_5H_4N); 7.52 (2H, m, ^3J = 8, C_6H_4); 7.65-7.92 (3H, m, C_5H_4N, =CH–); 8.21 (2H, m, ^3J = 8, C_6H_4); 8.36 (1H, ddd, ^3J = 5, ^4J = 1.5; ^5J = 1.5, C_5H_4N). Found, %: C 66.49; H 4.50; N 15.38. $C_{20}H_{16}N_4O_3$. Calculated, %: C 66.66; H 4.48; N 15.55.

3-Methyl-5-(4-nitrobenzylidene)-4-oxo-1,6-diphenyl-4,5,6,7-tetrahydroindazole (2h) was prepared similarly to compounds **2a-d** from equimolar amounts of **1c** and 4-nitrobenzaldehyde. Yield 23%; mp 230-232°C (ethanol–DMF, 5:1). IR spectrum, ν, cm^{-1}: 1661, 1619, 1549, 1541, 1517. ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 2.61 (3H, s, CH_3); 3.34 (2H, m, CH_2); 4.72 (1H, m, H-C_6); 7.27 (12H, center m, 2 × C_6H_5, C_6H_4); 7.87 (1H, s, =CH–); 8.14 (2H, m, ^3J = 8, C_6H_4). Found, %: C 74.24; H 4.90; N 9.50. $C_{27}H_{21}N_3O_3$. Calculated, %: C 74.47; H 4.86; N 9.65.

1,4-Bis[(3-methyl-4-oxo-1-phenyl-4,5,6,7-tetrahydroindazol-5-ylidene)methyl]benzene (3). A mixture of indazole **1a** (4 mmol) and terephthalaldehyde (2 mmol) in 85% H_3PO_4 (15 ml) was heated in a flask with reflux condenser on an oil bath at 120-130°C (bath temperature). The reaction mixture was cooled, diluted with water to 60 ml, and the precipitate was filtered off and recrystallized (DMF–water, 2:1). Yield 20%; mp 311-314°C. IR spectrum, ν, cm^{-1}: 1657, 1650, 1595, 1549, 1511. ^{1}H NMR spectrum, δ, ppm: 2.61 (6H, s, 2 × CH_3); 3.07 (8H, center m, 2 × CH_2CH_2); 7.45 (14H, center m, 2 × C_6H_5, C_6H_4); 7.72 (2H, s, =CH–). Found, %: C 78.30; H 5.50; N 10.01. $C_{36}H_{30}N_4O_3$. Calculated, %: C 78.52; H 5.49; N 10.18.

5-(Dimethylamino)methyl- (4a), 5-(diethylamino)methyl- (4b), 5-(1-pyrrolidyl)methyl- (4c), 5-(1-piperidyl)methyl- (4d), and 5-(4-morpholyl)methyl- (4e) 3-methyl-4-oxo-1-phenyl-4,5,6,7-tetrahydroindazoles. Paraformaldehyde (1.5 g) was added portionwise over 4 h to a refluxing solution of the oxoindazole **1a** (5 mmol) and the amine hydrochloride (10 mmol) (in the case of **4c-e** the amine and an equimolar amount of conc. HCl were added separately). Refluxing was continued for a further 12 h, the product was cooled, water (50 ml) added, and it was filtered and basified with a concentrated aqueous solution of NH_4OH. In the case of compound **4d** the solution was additionally saturated with NaCl. The precipitated aminomethylated **4** was filtered off and recrystallized from hexane.

4a. Yield 71%; mp 99-100°C. IR spectrum, ν, cm^{-1}: 1659, 1597, 1549, 1509. ^{1}H NMR spectrum, δ, ppm: 2.28 (6H, s, $N(CH_3)_2$); 2.60-2.95 (7H, m, CH_2–CH_2–CH–CH_2); 2.67 (3H, s, CH_3); 7.43 (5H, m, C_6H_5). Found, %: C 72.22; H 7.50; N 14.66. $C_{17}H_{21}N_3O$. Calculated, %: C 72.05; H 7.47; N 14.83.

4b. Yield, 75%; mp 65-66°C. IR spectrum, ν, cm^{-1}: 1656, 1600, 1550, 1514. ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 0.98 (6H, t, ^3J = 7, $N(CH_2–\underline{CH}_3)_2$); 2.54 (3H, d, CH_3); 2.50-2.92 (11H, m, CH_2–CH_2–CH, 3 × $N(CH_2)$; 7.41 (5H, m, C_6H_5). Found, %: C 73.45; H 8.18; N 13.50. $C_{19}H_{25}N_3O$. Calculated, %: C 73.28; H 8.09; N 13.49.

4c. Yield 83%; mp 119-120°C. IR spectrum, ν, cm^{-1}: 1662, 1595, 1545, 1507. ^{1}H NMR spectrum, δ, ppm: 1.72 (4H, m, CH_2CH_2); 2.54 (3H, s, CH_3); 2.40-2.98 (11H, m, CH_2–CH_2–CH, $N(CH_2)_3$); 7.42 (5H, m, C_6H_5). Found, %: C 73.30; H 7.55; N 13.41. $C_{19}H_{23}N_3O$. Calculated, %: C 73.75; H 7.49; N 13.58.

4d. Yield 25%; mp 81-82°C. IR spectrum, ν, cm^{-1}: 1660. 1602, 1548, 1510. ^{1}H NMR spectrum, δ, ppm: 1.42 (6H, m, $(CH_2)_3$); 2.38 (3H, s, CH_3); 2.20-2.92 (11H, m, CH_2–CH_2–CH, $N(CH_2)_3$); 7.41 (5H, m, C_6H_5). Found, %: C 74.11; H 7.90; N 13.13. $C_{20}H_{25}N_3O$. Calculated, %: C 74.27; H 7.79; N 12.99.

4e. Yield 50%; mp 127-128°C. IR spectrum, ν, cm^{-1}: 1661, 1595, 1545, 1507. ^{1}H NMR spectrum, δ, ppm: 1.98-2.92 (11H, m, CH_2–CH_2–CH, $N(CH_2)_3$); 2.47 (3H, s, CH_3); 3.67 (4H, m, CH_2–O–CH_2); 7.41 (5H, m, C_6H_5). Found, %: C 69.90; H 7.15; N 12.77. $C_{19}H_{23}N_3O_2$. Calculated, %: C 70.13; H 7.12; N 12.91.

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