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3,6,6-TRIMETHYL-4-OXO-1-(2-PYRIDYL)-4,5,6,7-TETRAHYDROINDAZOLE IN SCHMIDT REACTION AND BECKMANN REARRANGEMENT CONDITIONS FOR THE 4-HYDROXYIMINO DERIVATIVE

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Treatment of 3,6,6-trimethyl-4-oxo-1-(2-pyridyl)-4,5,6,7-tetrahydroindazole with sodium azide in acids gives 3,7,7-trimethyl-5-oxo-1-(2-pyridyl)-5,6,7,8-tetrahydro(4H)pyrazolo[4,3-b]azepine. Heating 1-(2-pyridyl)-3,6,6-trimethyl- and 1-phenyl-6,6-dimethyl-4-hydroxyimino-4,5,6,7-tetrahydroindazoles in polyphosphoric acid gives 1-phenyl-5,6-dimethyl- and 1-(2-pyridyl)-3,5,6-trimethyl-4-aminoindazole respectively. The reactions of the latter with 4-dimethylaminobenzaldehyde gave the 4-(4-dimethylaminobenzalamino) derivative and with 2-formyldimedone the 4-(4,4-dimethyl-2,6-dioxocyclohexylidenemethylamino) derivative.

Keywords: 3,7,7-trimethyl-5-oxo-1-(2-pyridyl)-5,6,7,8-tetrahydro(4H)pyrazolo[4,3-*b*]azepine, 4-amino-3,5,6-trimethyl-1-(2-pyridyl)-indazole.

We continue our work on modification of the carbocyclic part of 1-(2-pyridyl)indazoles [1-4] with a study of the reaction of 3,6,6-trimethyl-4-oxo-1-(2-pyridyl)-4,5,6,7-tetrahydroindazole (**1**) under Schmidt reaction conditions and the Beckmann rearrangement of the 4-hydroxyimino derivative **2**. The Schmidt reaction was carried out using sodium azide in polyphosphoric acid (PPA) using the method in study [5] and in sulfuric acid as described in method [6]. Under both conditions one product was obtained and this was identified by us as 3,7,7-trimethyl-5-oxo-1-(2-pyridyl)-5,6,7,8-tetrahydro(4H)pyrazolo[4,3-*b*]azepine (**3**).

The choice in favor of amide **3** from the two isomeric lactams (**3**, **4**) was made on the basis of ^{1}H NMR spectral data. In the spectrum of the discussed pyrazoloazepine **3** the chemical shift of the 6-CH_2 protons is 2.52 ppm (according to data in [5, 7-9, 12] δ is less than 3 ppm) and the 8-CH_2 protons are at 3.29 ppm (which agrees with values for the signal of an analogous methylene group at 3.22-3.73 ppm) as observed for other 1-(2-pyridyl)indazoles [1-4]. It was found that lactam **3** is stable to hydrolysis in aqueous hydrochloric acid and potassium hydroxide solutions.

Oxime **2** was prepared by refluxing ketone **1** with hydroxylamine hydrochloride in pyridine. Holding oxime **2** for 7 hours at 110-120°C in PPA did not produce either of the lactams **3**, **4**. The structure of the compound **5** obtained was proved by a combination of IR, NMR, and mass spectrometric data. The IR spectrum of the compound showed primary amino group absorption (3440 and 3350 cm^{-1}) and the absence of absorption bands above 1625 cm^{-1}. The ^{1}H NMR spectrum shows a broad, two proton signal at 4.14 ppm (NH_2), the presence of three singlets for the methyl groups at 2.11, 2.43, and 2.76 ppm, protons of the α-pyridyl fragment, and one isolated proton signal on an aromatic carbon. The steric proximity of the primary amine to two of the methyl

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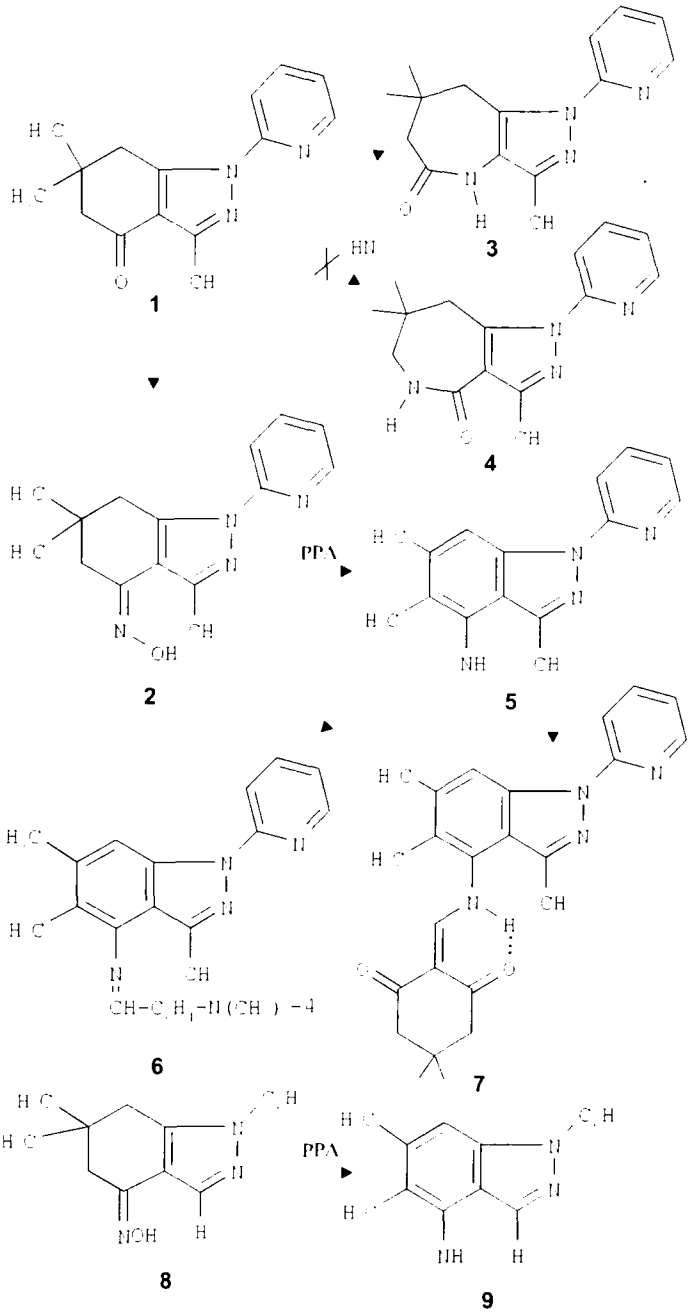
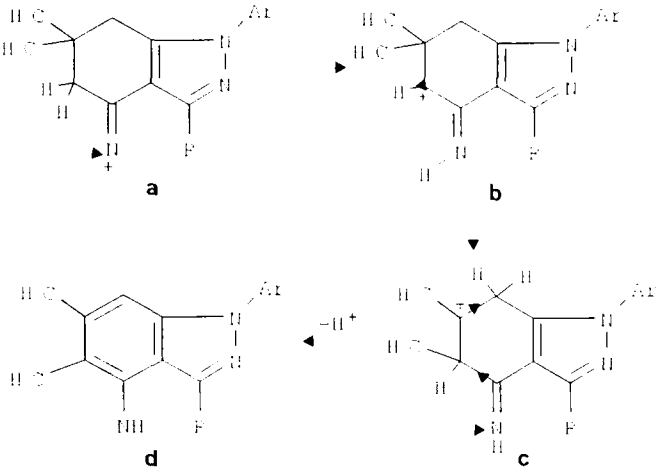
groups (2.11 and 2.76 ppm) and also that of the aromatic proton at 8.02 ppm to the methyl group at δ 2.43 ppm was shown by difference ^{1}H NMR spectroscopy (NOE). The ^{13}C NMR spectrum of compound **5** shows signals for all 15 carbon atoms (see Experimental) and the mass spectrum is characterized by a molecular ion peak (*m/z* 252), the intensity of which confirms the conjugated system of compound **5** together with low intensity peaks for the $[M\text{-}CH_3]^+$ and pyridine $C_5H_4N^+$ ions. The data given confirms the structure of compound **5** as 4-amino-3,5,6-trimethyl-1-(2-pyridyl)indazole, the amino group of which was established by reaction with 4-dimethylaminobenzaldehyde and with 2-formyldimedone. The structures of the obtained compound **6** and **7** were confirmed by ^{1}H NMR spectral data, which are given in the Experimental.

Scheme 1



Heating 4-hydroxyimino-6,6-dimethyl-1-phenyl-4,5,6,7-tetrahydroindazole (**8**) in PPA led to a similar carbocycle aromatization to give 4-amino-5,6-dimethyl-1-phenylindazole (**9**). The mechanism of formation of amines **5** and **9** is given in Scheme 2.

Scheme 2



The initially formed cation **a**, being an intermediate molecule in the Beckmann rearrangement, is converted to cation **b** and then to **c** as a result of migration of a methyl group. Deprotonation of this carbocation and conversion to the tautomeric aromatic form then gives **d**.

EXPERIMENTAL

IR spectra were taken on a Specord-75 IR spectrometer for suspensions in vaseline oil (1800-1500 cm^{-1}) and hexachlorobutadiene (3600-2000 cm^{-1}); the frequencies of the C–H stretching vibrations in the region 3050-2800 cm^{-1} are not given. ^1H NMR spectra were recorded on Varian Mercury BB (200 MHz) and Bruker WH-90/DS (90 MHz) instruments for $CDCl_3$ solutions using HMDS as internal standard. ^{13}C NMR spectra were taken on a Varian Mercury BB spectrometer at a frequency of 50.03 MHz. The mass spectrum of compound **5** was taken on a Hewlett Packard HP 6890 chromatographic mass spectrometer.

3,7,7-Trimethyl-5-oxo-1-(2-pyridyl)-5,6,7,8-tetrahydro(4H)pyrazolo[4,3-b]azepine (3). A. Ketone **1** (0.60 g, 2.4 mmol) was dissolved with stirring at 80-100°C in PPA (10 g) [10]. After formation of a homogenous solution, sodium azide (0.16 g, 2.4 mmol) was added in small portions. The product was heated for 5 h at 80-100°C, cooled, poured into about 100 g of crushed ice, and diluted with a 1:1 solution of ammonium hydroxide to pH 7-8. After one day the precipitated **3** was filtered off and recrystallized from petroleum ether–ethyl acetate (1:3) to give compound **3** (0.35 g, 54%); mp 196-198°C. IR spectrum: 1681, 1631, 1587, 3155, 3055 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): 1.18 (6H, s, $2CH_3$); 2.27 (3H, s, CH_3); 2.52 (2H, s, CH_2); 3.29 (2H, s, 8-H); 7.18 (1H, m, C_5H_4N); 7.49 (1H, br. s, NH); 7.76 (2H, m, C_5H_4N); 8.41 ppm (1H, m, C_5H_4N). Found, %: C 66.48; H 6.50; N 20.51. $C_{15}H_{18}N_4O$. Calculated, %: C 66.67; H 6.67; N 20.74.

B. Lactam **3** was also obtained in 46% yield by dissolving ketone **1** (2 mmol) in concentrated sulfuric acid (6 ml), addition of sodium azide (2 mmol), and holding the solution at 70-80°C for 4 h. The separation was carried out as described before in Section A. The precipitated **3** was purified using column chromatography on Aeros silica gel (pore diameter 6 nm) eluent ethyl acetate–toluene (7: 3); R_f = 0.35.

4-Hydroxyimino-3,6,6-trimethyl-1-(2-pyridyl)-4,5,6,7-tetrahydroindazole (2). Compound **1** (0.50 g, 2.0 mmol) and hydroxylamine hydrochloride (0.14 g, 2.0 mmol) were refluxed in pyridine (10 ml) for 3 h. The product was cooled, poured into water (50 ml) and, after one day, the precipitated oxime was filtered off and

recrystallized from ethanol to give compound **2** (0.47 g, 87%); mp 188-190°C. IR spectrum: 1645, 1639, 1587, 1561, 1515, 3250-3000 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): 1.05 (6H, s, $2CH_3$); 2.45 (3H, s, CH_3); 2.62 (2H, s, CH_2); 3.09 (2H, s, CH_2); 7.27 (1H, m, C_5H_4N); 7.95 (2H, m, C_5H_4N); 8.6 (1H, m, C_5H_4N); 8.77 ppm (1H, br. s, OH). Found, %: C 66.82; H 6.50; N 20.51. $C_{15}H_{18}N_4O$. Calculated, %: C 66.67; H 6.67; N 20.74.

4-Hydroxyimino-6,6-dimethyl-1-phenyl-4,5,6,7-tetrahydroindazole (8) was prepared similarly as before from 6,6-dimethyl-4-oxo-1-phenyl-4,5,6,7-tetrahydroindazole [11]. Yield 85%; mp 178-180°C. IR spectrum, 1661, 1597, 1541, 3347 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): 1.03 (6H, s, $2CH_3$); 2.33 (2H, s, CH_2); 2.65 (2H, s, CH_2); 7.43 (6H, m, C_6H_5, OH); 8.38 ppm (1H, s, =CH–). Found, %: C 70.40; H 6.49, N 16.50. $C_{15}H_{17}N_3O$. Calculated, %: C 70.59; H 6.67; N 16.47.

4-Amino-3,5,6-trimethyl-1-(2-pyridyl)indazole (5). Oxime **2** (0.54 g, 2.0 mmol) was heated for 7 h at 110-120°C in PPA (15 g). After cooling, it was poured onto crushed ice and diluted with a concentrated solution of ammonium hydroxide to pH 7-8. After 1 day the precipitate was filtered off and purified by column chromatography (ethyl acetate–toluene, 7: 3, R_f = 0.64) to give amine **5** (0.30 g, 60%); mp 124-126°C. IR spectrum: 1621, 1583, 1513, 3450, 3350 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): 2.11 (3H, s, CH_3); 2.42 (3H, s, CH_3); 2.76 (3H, s, CH_3); 4.14 (2H, br. s, NH_2); 7.05 (1H, m, C_5H_4N); 7.74 (1H, m, C_5H_4N); 7.93 (1H, m, C_5H_4N); 8.02 (1H, s, =CH–); 8.49 ppm (1H, m, C_5H_4N). ^{13}C NMR spectrum ($CDCl_3$): 12.12 (CH_3); 15.31 (CH_3); 22.2 (CH_3); 105.8 (=CH–); 112.2; 113.06 (=CH–); 113.6; 118.8 (=CH–); 137.9 (=CH–); 137.9; 138.9; 139.7; 143.6; 147.6 (=CH–); 154.3 ppm ($C_{(3)}$). Mass spectrum, *m/z*, %: 252 (100, $[M]^+$), 237 (18, $[M\text{-}CH_3]^+$), 78 (21, $[C_5H_4N]^+$), 51 (14, $[C_4H_3]^+$). Found, %: C 71.5; H 6.53, N 21.98. $C_{15}H_{16}N_4$. Calculated, %: C 71.43; H 6.35, N 22.22.

4-Amino-5,6-dimethyl-1-phenylindazole (9) was prepared similarly to the above from oxime **8**. Yield 32%; mp 89-91°C. IR spectrum: 1643, 1595, 1573, 1503, 3460, 3350, 3230 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): 2.16 (3H, s, CH_3); 2.40 (3H, s, CH_3); 4.12 (2H, br. s, NH_2); 7.04 (1H, s, =CH–); 7.33 (1H, m, C_6H_5); 7.52 (2H, m, C_6H_5); 7.73 (2H, m, C_6H_5); 8.06 ppm (1H, s, =CH–). Found, %: C 75.75; H 6.11; N 17.48. $C_{15}H_{15}N_3$. Calculated, %: C 75.95; H 6.33; N 17.72.

4-(4-Dimethylaminobenzylideneamino)- 3,5,6-trimethyl-1-(2-pyridyl)indazole (6). A solution of amine **5** (0.10 g, 0.4 mmol) in ethanol (5 ml) heated to 60-70°C was added to 4-dimethylaminobenzaldehyde (0.10 g, 0.6 mmol), a catalytic amount of *p*-toluenesulfonic was added, and the product was allowed to stand at 20°C for 48 h. The precipitate was filtered off and recrystallized from ethanol to give compound **6** (0.09 g, 60%); mp 208-210°C. IR spectrum: 1635, 1599, 1580, 1554, 1530, 1510 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): 2.19 (3H, s, CH_3); 2.48 (6H, s, $2CH_3$); 3.08 (6H, s, $2CH_3$); 6.79 (2H, m, C_6H_4); 7.07 (1H, m, C_5H_4N); 7.72-7.82 (1H, m, C_5H_4N); 7.84 (2H, m, C_6H_4); 7.95 (1H, m, C_5H_4N); 8.17 (1H, s, =CH–); 8.35 (1H, s, =CH–); 8.50 ppm (1H, m, C_5H_4N). Found, %: C 74.98; H 6.40; N 18.18. $C_{24}H_{25}N_5$. Calculated, %: C 75.19; H 6.53; N 18.28.

4-(4,4-Dimethyl-2,6-dioxocyclohexylidenemethylamino)-3,5,6-trimethyl-1-(2-pyridyl)indazole (7). A solution of amine **5** (0.10 g, 0.4 mmol) in ethanol (5 ml) heated to 60-70°C was added to 2-formyldimedone (0.10 g, 0.6 mmol) in ethanol (5 ml), a catalytic amount of *p*-toluenesulfonic acid was added, and the product was allowed to stand at 20°C for 24 h. The precipitate was filtered off and recrystallized from ethanol to give compound **7** (0.10 g, 63%); mp 175-177°C. IR spectrum: 1671, 1595, 1575, 1562, 1520 cm^{-1}. ^1H NMR spectrum ($CDCl_3$): 1.01 (6H, s, $2CH_3$); 2.29 (3H, s, CH_3); 2.44 (2H, s, CH_2); 2.48 (3H, s, CH_3); 2.52 (2H, s, CH_2); 2.54 (3H, s, CH_3); 7.12 (1H, m, C_5H_4N); 7.79 (1H, m, C_5H_4N); 7.96 (1H, m, C_5H_4N); 8.22 (1H, d, ^3J = 13.7 Hz, =CH–); 8.51 (1H, m, C_5H_4N); 8.62 (1H, s, =CH–); 12.70 ppm (1H, d, ^3J = 13.7 Hz, NH). Found, %: C 71.51; H 6.28; N 13.77. $C_{24}H_{26}N_4O_2$. Calculated, %: C 71.64; H 6.47; N 13.93.

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