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2-(3-ACETYLAMINO-2,2-DIMETHYLCYCLOBUTYL)-METHYL-4(3H)-QUINAZOLINONES

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Beckmann rearrangement of N-[3-(1-hydroxyimino)ethyl-2,2-dimethylcyclobutyl]acetylanthranilic acid, and its 5-bromo and 4-chloro derivatives gives the corresponding N-(3-acetylamino-2,2-dimethylcyclobutyl)acetylanthranilic acids. Treatment of these acylanthranilic acids with formamide gives 2-(3-acetylamino-2,2-dimethylcyclobutyl)methyl-4(3H)-quinazoline and its 6-bromo and 7-chloro derivatives.

Keywords: N-[3-(1-hydroxyimino)ethyl-2,2-dimethylcyclobutyl]acetylanthranilic acids, Beckmann rearrangement, 2-(3-acetylamino-2,2-dimethylcyclobutyl)methyl-4(3H)-quinazoline, its 6-bromo and 7-chloro derivatives.

We have extended work [1] describing the synthesis of 4(3H)-quinazolinones with cyclobutylmethyl substituent group in the 2 position. Treatment of pinonoylanthranilic acids **1** (reported in [1]) with hydroxylamine hydrochloride according to the method used in [2] gave 73-89% yield of hydroxyimino derivatives **2**. Beckmann rearrangement of oximes **2** was carried out as described in the method used in [3] by heating with polyphosphoric acid. Heating the mixture of acylanthranilic acids **3** with formamide in the molar ratio 1 : 3 gave 4(3H)-quinazolinones **4**.

The structure of the synthesized compounds was confirmed by IR and ^{1}H NMR spectroscopic data. The ^{1}H NMR spectra of compounds **2-4**, in which α- and β-methyl groups can be well-defined [4], confirmed the presence of cyclobutylmethyl structural fragment, absorbing at 0.81-0.92 and 1.05-1.17 ppm respectively. The IR spectra of oximes **2** showed a broad absorption band at 2600-2500 cm^{-1} and also strong amide NH bond absorption at 3250 cm^{-1}. The ^{1}H NMR spectra also showed the presence of signals for NH (10.18-10.36) and OH (11.01-11.19 and 11.07-13.44 ppm) protons. The IR spectra of the Beckmann rearrangement products (diamides **3**) also revealed two amide functions (ν_{CO} 1691-1680 and 1670-1655 cm^{-1}, ν_{NH} 3380-3350 and 3250-3240 cm^{-1}). The protons of diamide **3** functional groups referred to appeared in the ^{1}H NMR spectra at 6.25-7.76 and 8.65-11.08 (NH) and at 11.15-13.1 ppm (OH). The same applies to the quinazoline derivatives **4** for which the IR and ^{1}H NMR spectra confirm the presence of two NH fragments (ν_{NH} 3320-3270 and 3200-3170 cm^{-1}, δ_{NH} 7.36-7.79 and 8.13-12.33 ppm). Although we have assigned the lower field signal in the ^{1}H NMR spectra of compounds **2** and **3** to the carboxyl group proton, it is quite possible that the signal assignments may be reversed (Scheme 1).

Compounds **3** and **4** show the typical methine proton signals on $C_{(3)}$ of the cyclobutyl fragment at 3.80-3.95 ppm and broad doublets for NH with $^3J_{CHNH}$ = 6.8 Hz.

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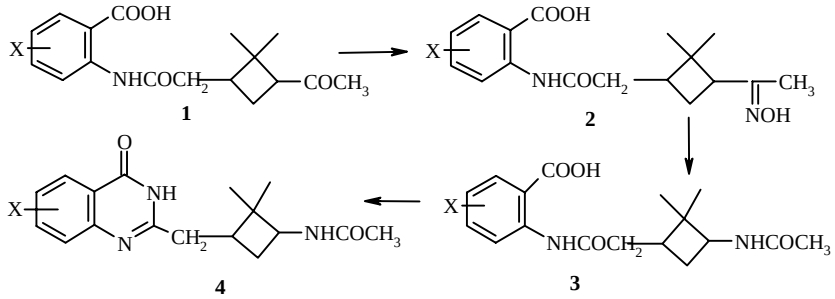
Scheme 1



1–3 a X = H; **b** X = 5-Br; **c** X = 4-Cl
4a X = H; **b** X = 6-Br; **c** X = 7-Cl

EXPERIMENTAL

IR spectra were taken on a Specord 75-IR instrument for suspensions in vaseline oil (1800-1500 cm^{-1}) and hexachlorobutadiene (3600-2000 cm^{-1}, the frequencies of the C–H stretching bands in the region 3050-2800 cm^{-1} are not reported). The ^1H NMR spectra were recorded on a Bruker WH-90/DS (90 MHz) instrument for solutions in $CDCl_3$ or DMSO-d_6 with HMDS as internal standard. Monitoring of the reaction course and the purity of the products was carried out by TLC on Silufol UV-254 plates using the system $CHCl_3$–C_2H_5OH (9: 1) and were revealed in UV light or with chlorine and subsequent treatment with KI-benzidine reagent.

The general methods of synthesis of compounds **2**, **3**, and **4** are presented.

N-[3-(1-Hydroxyimino)ethyl-2,2-dimethylcyclobutyl]acetylanthranilic Acids (2). Pinonoylanthranilic acid **1** (17.0 mmol), hydroxylamine hydrochloride (22.0 mmol), and sodium acetate (22.0 mmol) were stirred in ethanol (50 ml) for 3 h at 20°C. The product was left overnight, diluted with water (200 ml), and the precipitated compound **2** was filtered and recrystallized.

Compound 2a. Yield 79%; mp 184-185°C (nitromethane). IR spectrum: 1700, 1681, 1607, 1589, 1533; 3260, 2620-2500 cm^{-1}. ^1H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 0.81 (3H, s, β-CH_3); 1.17 (3H, s, α-CH_3); 1.65 (3H, s, CH_3); 1.92-2.40 (6H, m, –CH_2CHCH_2CH–); 7.05 (1H, t, ^3J = 8.5 Hz, C_6H_4); 7.55 (1H, td, ^3J = 8.5 Hz, ^4J = 1, C_6H_4); 7.94 (1H, dd, ^3J = 8.5 Hz, ^4J = 1, C_6H_4); 8.51 (1H, d, ^3J = 8.5, C_6H_4); 10.35 (1H, br. s, NH); 11.1 (1H, br. s, OH); 13.44 (1H, br. s, OH). Found, %: C 63.93; H 6.90, N 8.59. $C_{17}H_{22}N_2O_4$. Calculated, %: C 64.13; H 6.96; N 8.80.

Compound 2b. Yield 73%; mp 185-186°C (acetonitrile). IR spectrum: 1705, 1683, 1647, 1600, 1573, 1500; 3250, 2600-2500 cm^{-1}. ^1H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 0.81 (3H, s, β-CH_3); 1.19 (3H, s, α-CH_3); 1.67 (3H, s, CH_3); 1.58-2.48 (6H, m, –CH_2CHCH_2CH–); 7.71 (1H, dd, ^3J = 9, ^4J = 1.5, C_6H_3); 8.05 (1H, d, ^4J = 1.5, C_6H_3); 8.43 (1H, d, ^3J = 9, C_6H_3); 10.36 (1H, br. s, NH); 11.01 (1H, br. s, OH); 11.07 (1H, br. s, OH). Found, %: C 51.18; H 5.20; Br 20.00; N 7.17. $C_{17}H_{21}BrN_2O_4$. Calculated, %: C 51.40; H 5.33; Br 20.11; N 7.05.

Compound 2c. Yield 87%; mp 171-172°C (acetonitrile). IR spectrum: 1705, 1686, 1655, 1602, 1580, 1520; 3250, 3120, 2600-2500 cm^{-1}. ^1H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 0.81 (3H, s, β-CH_3); 1.18 (3H, s, α-CH_3); 1.64 (3H, s, CH_3); 1.89-2.58 (6H, m, –CH_2CHCH_2CH–); 7.16 (1H, dd, ^3J = 8, ^4J = 1, C_6H_3); 7.96 (1H, d, ^3J = 8, C_6H_3); 8.59 (1H, d, ^4J = 1, C_6H_3); 10.18 (1H, br. s, NH); 11.19 (1H, br. s, OH); 12.9 (1H, br. s, OH). Found, %: C 57.66; H 5.88; Cl 9.90, N 7.83. $C_{17}H_{21}ClN_2O_4$. Calculated, %: C 57.87; H 6.00; Cl 10.05; N 7.94.

N-(3-Acetylamino-2,2-dimethylcyclobutyl)acetylanthranilic Acids (3). Oxime **2** (7 mmol) was heated for 2 h at 80-90°C in PPA (10 ml). After cooling, it was suspended in water (30 ml), and aqueous ammonium hydroxide solution (25%) was added to pH 3-4. The product was then extracted with ethyl acetate (3 × 20 ml), dried over anhydrous magnesium sulfate, ethyl acetate distilled off in vacuo on a water pump, and the residue was recrystallized.

Compound 3a. Yield 39%; mp 221-223°C (nitromethane). IR spectrum: 1680, 1670, 1617, 1591, 1561, 1524; 3350, 3250, 3200, 2650-2500 cm^{-1}. ^1H NMR spectrum, (DMSO-d_6), δ, ppm, *J* (Hz): 0.86 (3H, s, β-CH_3); 1.05 (3H, s, α-CH_3); 1.52-2.47 (5H, m, –CH_2CHCH_2–); 3.80 (1H, m, CH); 7.13 (1H, t, ^3J = 8.5, C_6H_4); 7.52 (1H, t, ^3J = 8.5, C_6H_4); 7.76 (1H, d, ^3J = 6, NH); 7.99 (1H, d, ^3J = 8.5, C_6H_4); 8.49 (1H, d, ^3J = 8.5, C_6H_4); 11.08 (1H, br. s, NH); 13.1 (1H, br. s, OH). Found, %: C 64 03; H 7.04; N 8.62. $C_{17}H_{22}N_2O_4$. Calculated, %: C 64.13; H 6.96; N 8.80.

Compound 3b. Yield 47%; mp 188-190°C (acetonitrile). IR spectrum: 1680-1665, 1611, 1587, 1547, 1510; 3380, 3250-3200, 2720, 2650, 2500 cm^{-1}. ^1H NMR spectrum ($CDCl_3$ + DMSO-d_6), δ, ppm, *J* (Hz): 0.85 (3H, s, β-CH_3); 1.07 (3H, s, α-CH_3); 1.54-2.56 (5H, m, –CH_2CHCH_2–); 1.86 (1H, s, CH_3); 3.93 (1H, m, CH); 6.25 (1H, d, ^3J = 6, NH); 7.50 (1H, dd, ^3J = 9, ^4J = 2, C_6H_3); 8.15 (1H, d, ^3J = 2, C_6H_3); 8.54 (1H, d, ^3J = 9, C_6H_3); 9.23 (1H, br. s, NH); 11.15 (1H, br. s, OH). Found, %: C 51.28; H 5.17; Br 20.00; N 6.96. $C_{17}H_{21}BrN_2O_4$. Calculated, % C 51.40; H 5.33; Br 20.11; N 7.05.

Compound 3c. Yield 52%; mp 232-233°C (acetonitrile). IR spectrum: 1691, 1653, 1603, 1578, 1553, 1509; 3380, 3240, 2600 cm^{-1}. ^1H NMR spectrum, (DMSO-d_6), δ, ppm, *J* (Hz): 0.89 (3H, s, β-CH_3); 1.09 (3H, s, α-CH_3); 1.53-2.52 (5H, m, –CH_2CHCH_2–); 3.83 (1H, m, CH); 7.16 (1H, dd, ^3J = 8.5, ^4J = 2, C_6H_3); 7.76 (1H, d, ^3J = 7, NH); 7.98 (1H, d, ^3J = 8.5, C_6H_3); 8.60 (1H, d, ^4J = 2, C_6H_3); 8.65 (1H, br. s, NH); 11.52 (1H, br. s, OH). Found, %: C 57.67; H 5.87; Cl 9.99; N 7.81. $C_{17}H_{21}ClN_2O_4$. Calculated, %: C 57.87; H 6.00; Cl 10.05, N 7.94.

2-(3-Acetylamino-2,2-dimethylcyclobutyl)methyl-4(3H)-quinazolinones (4). Mixture of acid **3** (3.0 mmol) and formamide (9.0 mmol) was heated for 4 h at 170-180°C. After cooling, it was suspended in water (20 ml) containing sodium bicarbonate (12.0 mmol), left for 24 h, filtered, dried, and recrystallized.

Compound 4a. Yield 39%; mp 232-233°C (acetonitrile). IR spectrum: 1687, 1609, 1561, 1506; 3270, 3200 cm^{-1}. ^1H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 0.92 (3H, s, β-CH_3); 1.05 (3H, s, α-CH_3); 1.56-2.58 (5H, m, –CH_2CHCH_2–); 3.86 (1H, m, CH); 7.36-8.13 (6H, m, C_6H_4, 2NH). Found, %: C 68.00; H 6.93; N 13.90. $C_{17}H_{21}ClN_3O_2$. Calculated, %: C 68.21; H 7.07; N 14.03.

Compound 4b. Yield 41%; mp 238-240°C (acetonitrile). IR spectrum: 1685, 1617, 1549; 3320, 3180 cm^{-1}. ^1H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 0.91 (3H, s, β-CH_3); 1.05 (3H, s, α-CH_3); 1.57-2.74 (5H, m, –CH_2CHCH_2–); 3.89 (1H, m, CH); 7.48 (1H, d, ^3J = 9, C_6H_3); 7.87 (1H, dd, ^3J = 9, ^4J = 2, C_6H_3); 7.90 (1H, d, ^3J = 8, NH); 8.14 (1H, d, ^4J = 2, C_6H_3); 12.33 (1H, br. s, NH). Found, %: C 53.77; H 5.14; Br 21.30; N 10.92. $C_{17}H_{20}BrN_3O_2$. Calculated, %: C 53.98; H 5.33; Br 21.12; N 11.11.

Compound 4c. Yield 45%; mp 253-255°C (acetonitrile). IR spectrum: 1679, 1649, 1627; 1605; 1557; 3290, 3170 cm^{-1}. ^1H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 0.87 (3H, s, β-CH_3); 1.03 (3H, s, α-CH_3); 1.61-2.58 (5H, m, –CH_2CHCH_2–); 1.78 (3H, s, CH_3); 3.84 (1H, m, CH); 7.43 (1H, dd, ^3J = 8, ^4J = 2, C_6H_3); 7.58 (1H, d, ^4J = 2, C_6H_3); 7.69 (1H, d, ^3J = 7, NH); 8.02 (1H, d, ^3J = 8, C_6H_3); 12.25 (1H, br. s, NH). Found, %: C 60.95; H 6.00; Cl 10.50; N 12.41. $C_{17}H_{20}ClN_3O_2$. Calculated, %: C 61.17; H 6.04; Cl 10.61; N 12.59.

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