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Synthesis and Reactivity of Ethyl 7-Amino-3-*tert*-butyl-4-thioxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carboxylate

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Abstract—Treatment of ethyl 7-amino-3-*tert*-butyl-4-oxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carboxylate with P_2S_5 in pyridine gave ethyl 7-amino-3-*tert*-butyl-4-thioxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carboxylate which was subjected to acylation, decarboxylation, and hydrazinolysis.

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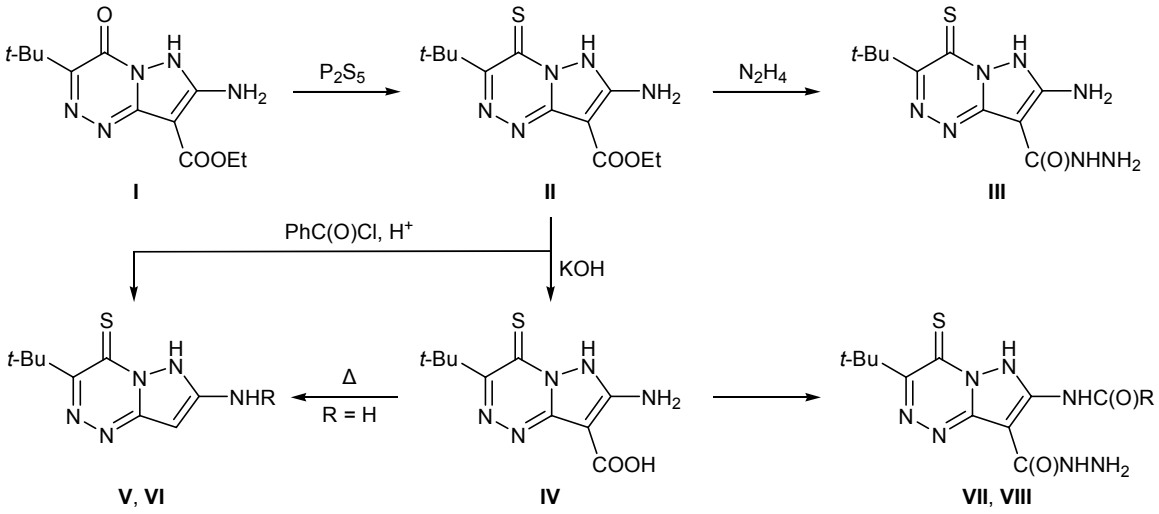
Bicyclic systems based on 1,2,4-triazines attract interest from the synthetic viewpoint. In particular, pyrazolo[1,2,4]triazine derivatives exhibit various kinds of pharmacological activity, e.g., antiviral [1, 2]. We previously [3] synthesized ethyl 7-amino-3-*tert*-butyl-4-oxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carboxylate (**I**) by reaction of 4-amino-6-*tert*-butyl-3-methylsulfonyl-4*H*-1,2,4-triazin-5-one with ethyl cyanoacetate in pyridine. The goal of the present work was to synthesize ethyl 7-amino-3-*tert*-butyl-4-thioxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carboxylate (**II**) and examine its reactivity.

Heating of compound **I** in pyridine with excess phosphorus pentasulfide resulted in replacement of the 4-oxo group by thioxo with formation of ethyl 7-amino-3-*tert*-butyl-4-thioxo-4,6-dihydropyrazolo-[5,1-*c*][1,2,4]triazine-8-carboxylate (**II**). The presence of a thioxo group in the bicyclic system did not affect its reactivity. Compound **II** reacted with excess 100% hydrazine in methanol on heating to afford 7-amino-3-*tert*-butyl-4-thioxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]-triazine-8-carbohydrazide (**III**) (Scheme 1). 7-Amino-3-*tert*-butyl-4-thioxo-4,6-dihydropyrazolo[5,1-*c*]-[1,2,4]triazine-8-carboxylic acid (**IV**) was synthesized by heating ester **II** in boiling propan-1-ol in the presence of potassium hydroxide. Decarboxylation of **IV** on heating in DMF afforded 7-amino-3-*tert*-butyl-6*H*-pyrazolo[5,1-*c*][1,2,4]triazine-4-thione (**VI**).

Scheme 1.



V, R = PhC(O); **VI**, R = H; **VII**, R = Me; **VIII**, R = Ph.

By acylation of **II** with benzoyl chloride in ethyl acetate in the presence of a catalytic amount of hydrochloric acid we obtained *N*-(3-*tert*-butyl-4-thioxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazin-7-yl)benzamide (**V**). The reaction was accompanied by hydrolysis of the ester group and subsequent decarboxylation. Acylation of **IV** with acetic anhydride under solvent-free conditions led to the formation of 7-acetylamino-3-*tert*-butyl-4-thioxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]-triazine-8-carboxylic acid (**VII**), while the reaction of **IV** with benzoyl chloride produced 7-benzoylamino-3-*tert*-butyl-4-thioxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]-triazine-8-carboxylic acid (**VIII**) (Scheme 1).

The structure of compounds **II**–**VIII** was determined on the basis of their elemental compositions and IR, ^{1}H NMR, and mass spectra. Unlike initial compound **I**, the IR spectra of **II**–**VIII** contained an absorption band at 1215–1238 cm^{-1} due to stretching vibrations of the thioxo group. Carbonyl absorption in the region 1660–1689 cm^{-1} was conserved in the IR spectra of **II**–**IV**, **VII**, **VIII**, while compounds **V**, **VI**, and **VIII** displayed a new carbonyl absorption band at 1697–1717 cm^{-1} (C=O) due to acyl group on the nitrogen. The ^{1}H NMR spectra of **II**–**VIII** also confirmed the assumed structure. All compounds were characterized by a singlet at δ 1.19–1.38 ppm from protons in the *tert*-butyl group, and the 8-H proton resonated in the spectrum of **VI** at δ 8.2 ppm.

The obtained compounds showed selective antimicrobial activity against Gram-positive bacteria (*Staphylococcus aureus*, *Micrococcus luteus*).

EXPERIMENTAL

The IR spectra were recorded in KBr on a UR-10 spectrometer. The ^{1}H NMR spectra were measured on a Varian Mercury VX-200 instrument at 200 MHz from solutions in DMSO-d_6 using hexamethyldisiloxane as internal reference. The mass spectra were run on an MS-1302 mass spectrometer. The purity of the products was checked by TLC on Silufol UV-254 plates using chloroform–methanol (9 : 1) as eluent. Compound **I** was synthesized according to the procedure reported in [3]; mp 242–244°C (decomp.).

Ethyl 7-amino-3-*tert*-butyl-4-thioxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carboxylate (II). A mixture of 0.279 g (1 mmol) of ethyl 7-amino-3-*tert*-butyl-4-oxo-4,6-dihydropyrazolo[5,1-*c*]triazine-8-carboxylic acid (**I**) and 0.695 g (3.5 mmol) of phosphorus pentasulfide in 10 ml of pyridine was heated for 3.5 h under reflux. The mixture was filtered while hot and diluted with distilled water (1 : 1), the solvent was removed, the residue was dissolved in DMF, the solution was diluted with distilled water (1 : 1), and the precipitate was filtered off, dried in air, and recrystallized from dioxane. Yield 0.257 g (87%), yellow crystals, mp 145–150°C (with tarring). IR spectrum, ν, cm^{-1}: 3433 (NH_2), 2956, 2927, 1665 (C=O), 1630, 1606, 1540, 1480, 1457, 1389, 1362, 1230 (C=S), 1144, 1008, 973, 941, 831, 745, 661. ^{1}H NMR spectrum, δ, ppm: 1.27 t (3H, $CH_2C\mathbf{H}_3$, J = 7.2 Hz), 1.35 s (9H, *t*-Bu), 4.27 q (2H, $C\mathbf{H}_2CH_3$, J = 7.0 Hz), 6.25 s (2H, NH_2), 13.20 s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 295 (100) $[M]^+$, 293 (12), 256 (17), 234 (10), 213 (61), 211 (12), 160 (15), 128 (24), 109 (16), 97 (23), 96 (40), 76 (45), 73 (20), 72 (24), 69 (15), 62 (26), 59 (15), 44 (18), 41 (28). Found, %: C 48.82; H 5.79; N 23.73. $C_{12}H_{17}N_5O_2S$. Calculated, %: C 48.80; H 5.80; N 23.71.

7-Amino-3-*tert*-butyl-4-thioxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carbohydrazide (III). A mixture of 0.279 g (1 mmol) of compound **II** and 0.096 g (3 mmol) of 100% hydrazine in methanol was heated for 10 h under reflux. The mixture was filtered while hot, the filtrate was evaporated to dryness, the residue was dissolved in DMF, the solution was diluted with distilled water (1 : 2), and the precipitate was filtered off, dried in air, and purified by reprecipitation from dioxane with water (1 : 1). Yield 0.230 g (82%), yellow crystals, mp 188–193°C (decomp.). IR spectrum, ν, cm^{-1}: 3435, 2921, 1660 (C=O), 1630, 1540, 1490, 1458, 1390, 1352, 1215 (C=S), 1144, 1100, 960, 740, 666. ^{1}H NMR spectrum, δ, ppm: 1.36 s (9H, *t*-Bu), 5.57 s (2H, $NHN\mathbf{H}_2$), 6.60 s (2H, NH_2), 8.79 s (1H, $N\mathbf{H}NH_2$), 12.86 s (1H, NH). Found, %: C 42.71; H 5.40; N 34.89. $C_{10}H_{15}N_7OS$. Calculated, %: C 42.69; H 5.37; N 34.85.

7-Amino-3-*tert*-butyl-4-thioxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carboxylic acid (IV). A mixture of 0.279 g (1 mmol) of ester **II** and 0.112 g (2 mmol) of potassium hydroxide in 10 ml of propan-2-ol was heated for 6 h under reflux. The mixture was evaporated to dryness, the residue was dissolved in 15 ml of distilled water, the solution was filtered, the filtrate was acidified with 5% aqueous HCl to pH 5–6, and the precipitate was filtered off and recrystallized from methanol. Yield 0.229 g (86%), brown crystals, mp >300°C (decomp.). IR spectrum, ν, cm^{-1}: 3419, 2965, 2927, 1680 (C=O), 1622, 1538, 1479, 1460, 1393, 1363, 1220 (C=S), 1129, 1034, 745. ^{1}H NMR spectrum, δ, ppm: 1.27 s (9H, *t*-Bu), 6.15 s (2H, NH_2), 12.80 s (1H, COOH), 13.25 br.s (1H, NH). Found, %:

C 44.95; H 4.92; N 26.17. $C_{10}H_{13}N_5O_2S$. Calculated, %: C 44.93; H 4.90; N 26.20.

***N*-(3-*tert*-Butyl-4-thioxo-4,6-dihydropyrazolo-[5,1-*c*][1,2,4]triazin-7-yl)benzamide (V).** A mixture of 0.279 g (1 mmol) of compound **II**, 0.562 g (4 mmol) of benzoyl chloride, and 2–3 drops of hydrochloric acid in 10 ml of ethyl acetate was heated for 18 h under reflux. The mixture was cooled, the solvent was removed, the residue was dissolved in DMF, the solution was diluted with distilled water (1:1), and the precipitate was filtered off and dried in air. The product was chromatographically pure. Yield 0.268 g (82%), brown crystals, mp 207–210°C (decomp.). IR spectrum, ν, cm^{-1}: 3457, 3170, 3088, 2958, 2934, 2887, 1697 (C=O), 1583, 1547, 1484, 1476, 1393, 1386, 1297, 1279, 1238 (C=S), 1224, 1195, 1152, 1095, 1026, 937, 887, 853, 788, 776, 734, 714, 688, 661, 537, 485. ^{1}H NMR spectrum, δ, ppm: 1.38 s (9H, *t*-Bu), 7.44–7.67 m (3H, *m*-H, *p*-H), 7.93 d.d (2H, *o*-H, J = 8.2 Hz), 8.20 s (1H, CH), 13.77 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 324 (3) $[M]^+$, 203 (11), 202 (14), 201 (98), 200 (23), 168 (14), 142 (13), 141 (9), 110 (5), 109 (12), 105 (100), 85 (56), 84 (9), 83 (83), 82 (26), 77 (31), 60 (7), 57 (20), 56 (12), 55 (15), 51 (7), 41 (13). Found, %: C 58.72; H 5.21; N 21.40. $C_{16}H_{17}N_5OS$. Calculated, %: C 58.70; H 5.23; N 21.39.

7-Amino-3-*tert*-butyl-6*H*-pyrazolo[5,1-*c*][1,2,4]-triazine-4-thione (VI). A mixture of 0.267 g (1 mmol) of acid **IV** and 10 ml of DMF was heated for 6 h under reflux. The solvent was removed, the precipitate was dissolved in methanol, the solution was diluted with distilled water (1:1), and the precipitate was filtered off, dried in air, and purified by reprecipitation from propan-2-ol with water (1:1). Yield 0.163 g (73%), brown crystals, mp 139–143°C (with tarring). IR spectrum, ν, cm^{-1}: 3447 (NH_2), 2969, 2932, 2891, 2806, 1635, 1543, 1533, 1480, 1475, 1393, 1365, 1334, 1273, 1235 (C=S), 1206, 1196, 1144, 1127, 1072, 1049, 1040, 1007, 958, 937, 897, 778, 743, 666, 620. ^{1}H NMR spectrum, δ, ppm: 1.38 s (9H, *t*-Bu), 5.62 s (2H, NH_2), 8.41 s (1H, CH), 13.77 s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 223 (3) $[M]^+$, 202 (13), 201 (100), 200 (32), 170 (17), 168 (20), 141 (9), 128 (11), 109 (17), 100 (9), 99 (14), 83 (25), 82 (11), 72 (10), 69 (15), 68 (17), 67 (9), 45 (14), 44 (16), 41 (25). Found, %: C 48.43; H 5.89; N 31.39. $C_9H_{13}N_5S$. Calculated, %: C 48.41; H 5.87; N 31.36.

7-Acetylamino-3-*tert*-butyl-4-thioxo-4,6-dihydro-pyrazolo[5,1-*c*][1,2,4]triazine-8-carboxylic acid (VII). A mixture of 0.267 g (1 mmol) of compound **IV** and 5 ml of acetic anhydride was heated for 6 h under reflux. The mixture was cooled, the solvent was removed, the residue was dissolved in methanol, the solution was diluted with distilled water (1:1), and the precipitate was filtered off and dried in air. The product was chromatographically pure. Yield 0.181 g (59%), yellow crystals, mp 120–125°C (decomp.). IR spectrum, ν, cm^{-1}: 3448, 3199, 3094, 2960, 2930, 2880, 1717 (C=O), 1689 (C=O), 1598, 1549, 1483, 1451, 1393, 1367, 1273, 1243, 1226 (C=S), 1151, 1039, 897, 778, 661, 592, 545, 471. ^{1}H NMR spectrum, δ, ppm: 1.20 s (3H, CH_3), 1.40 s (9H, *t*-Bu), 13.0 s (1H, NH), 13.32 s (1H, OH). Mass spectrum, *m*/*z* (I_{rel}, %): 307 (4) $[M]^+$, 294 (2), 291 (2), 258 (16), 256 (41), 249 (12), 225 (10), 224 (100), 201 (28), 200 (12), 192 (29), 186 (14), 185 (83), 184 (18), 183 (12), 170 (36), 162 (13), 160 (70), 130 (19), 128 (67), 127 (23), 126 (18), 115 (7), 98 (10), 97 (13), 96 (46), 83 (17), 69 (10), 68 (13), 66 (11), 64 (100), 60 (25), 59 (16), 57 (20), 43 (44), 41 (14). Found, %: C 46.58; H 4.90; N 22.62. $C_{12}H_{15}N_5O_3S$. Calculated, %: C 46.59; H 4.89; N 22.64.

7-Benzoylamino-3-*tert*-butyl-4-thioxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carboxylic acid (VIII). A mixture of 0.267 g (1 mmol) of compound **IV**, 0.422 g (3 mmol) of benzoyl chloride, and one drop of hydrochloric acid in 10 ml of ethyl acetate was heated for 6 h under reflux. The mixture was cooled, the solvent was removed, the residue was dissolved in propan-2-ol, the solution was diluted with distilled water (1:5), and the precipitate was filtered off and dried in air. The product was chromatographically pure. Yield 0.241 g (65%), mp 265–267°C (decomp.). IR spectrum, ν, cm^{-1}: 3437, 3269, 3080, 2968, 2932, 2892, 1700 (C=O), 1665 (C=O), 1630, 1595, 1547, 1481, 1393, 1363, 1276, 1226 (C=S), 1140, 1107, 959, 765, 713, 553, 520. ^{1}H NMR spectrum, δ, ppm: 1.29 s (9H, *t*-Bu), 7.24 t (2H, *m*-H, *p*-H, J = 6.9 Hz), 7.43 d (3H, *o*-H, J = 7.4 Hz), 7.93 s (1H, NH), 10.61 s (1H, NH), 13.45 s (1H, OH). Found, %: C 54.96; H 4.63; N 18.87. $C_{17}H_{17}N_5O_3S$. Calculated, %: C 54.97; H 4.61; N 18.86.

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