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4-Functionally-Substituted 3-Heterylpyrazoles: XVII.* 3-Aryl-1-phenyl-4-pyrazolmethylsulfanyl(sulfinyl, sulfonyl)acetic Acids

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Abstract—3-Aryl-1-phenyl-4-mercaptomethylpyrazoles reacted with monochloroacetic acid to give 3-aryl-1-phenyl-4-pyrazolylmethylsulfanylacetic acids whose oxidation with hydrogen peroxide in acetone or acetic acid solution led to 3-aryl-1-phenyl-4-pyrazolylmethylsulfinyl- and sulfonylacetic acids, respectively.

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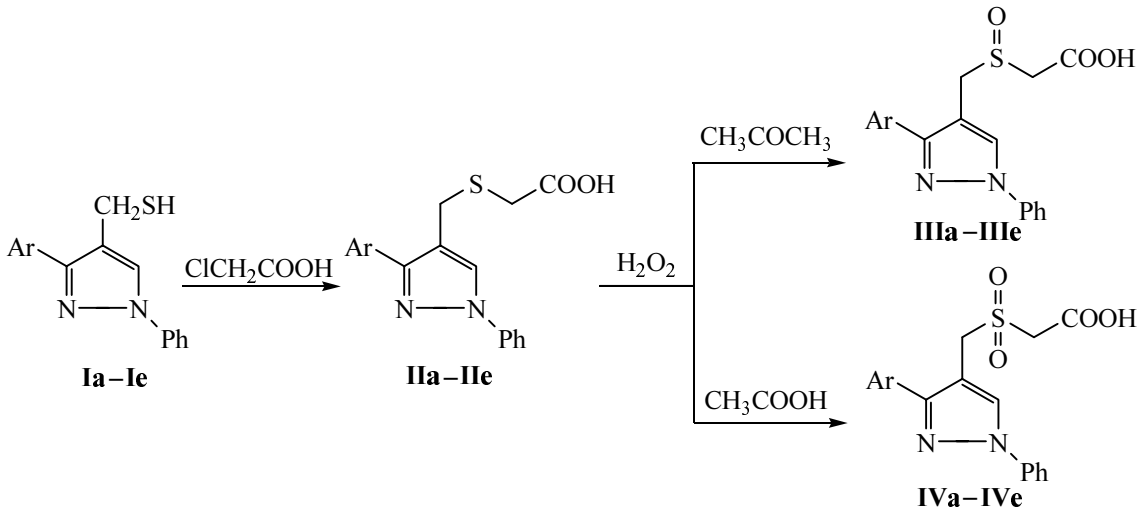
Sulfur-containing acetic acids possessing versatile synthetic possibilities and useful properties are a matter of rapt attention of chemists. By now a thorough investigation was carried out on transformations of a series of benzylsulfanylacetic acids into their sulfinyl and sulfonyl derivatives [2–8]. The benzylsulfinylacetic acids proper turned out to be convenient models for studying the optical properties of sulfoxide systems [6–8], and benzylsulfonylacetic acids found the use as important blocks in the synthesis of α,β-unsaturated sulfones [9, 10].

We report here on the results of the study on the synthesis of previously unkhown heterocyclic analogs of the above mentioned sulfur-containing compounds, 4-pyrazolylmethylthioacetic acids and their oxidation products. We chose as initial compounds 4-mercaptomethylpyrazoles **Ia–If** that we had synthesized previously [11]. These substances in the presence of alcoholic alkali were readily alkylated with the monochloroacetic acid to afford 4-pyrazolylmethylsulfanylacetic acids **IIa–IIf** in 62–73% yields. The latter were identified based on IR,



Ia–Ie **IIa–IIe** **IIIa–IIIe** **IVa–IVe**

Ar = Ph (**a**), 4-FC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 4-BrC_6H_4 (**d**), 4-$MeOC_6H_4$ (**e**), 3,4-$Me_2C_6H_3$ (**f**).

* For Communication XVI, see [1].

^{1}H NMR spectra, and elemental analysis. In particular, the ^{1}H NMR spectra contained characteristic singlets belonging to the methylene protons of the carboxymethyl (3.17–3.26) and pyrazolemethyl (3.88–3.92 ppm) fragments.

We found conditions for a selective conversion of acids **IIa–IIf** into 4-pyrazolylmethylsulfinylacetic acids **IIIa–IIIf** and 4-pyrazolylmethyl-sulfonyl-acetic acids **IVa–IVf**. It was shown that the treatment of acetone solutions of compounds **IIa–IIf** with 30% hydrogen peroxide at room temperature furnished in 78–92% yields acids **IIIa–IIIf**. In their turn, acids **IVa–IVf** were obtained in 85-98% yields by oxidation of compounds **IIa–IIf** with 30% hydrogen peroxide in acetic acid at 60°C.

The characteristic feature of acids **III** is the nonequivalence of the protons in both methylene groups caused by the pyramidal structure of the sulfoxide moiety. In the ^{1}H NMR spectra these protons give rise to quartets of *AB* systems in the range 3.63–3.98 and 4.15–4.36 ppm respectively. At the same time the methylene groups of acids **IVa-IVf** appear in the ^{1}H NMR spectra as two singlets: CH_2COOH at 4.30–4.35, $PyrCH_2$ at 4.66–4.70 ppm. In general the oxidation of sulfides **II** into sulfoxides **III** and sulfones **IV** tends to increase the acid character of the methylene groups that is revealed in the ^{1}H NMR spectra by their successive downfield shift by approximately 0.4–0.6 ppm.

EXPERIMENTAL

IR spectra of compounds were recorded on a spectrophotometer UR-20 from KBr pellets. ^{1}H NMR spectra were registered from solutions of compounds in $(CD_3)_2SO$ on a spectrometer Varian Gemini (300 MHz), internal reference TMS.

3-Aryl-1-phenyl-4-pyrazolylmethylsulfanylacetic acid IIa–IIf. A mixture of 10 mmol of 4-mercaptomethylpyrazole **Ia–If**, 1 g (10.6 mmol) of monochloroacetic acid, and 10 ml of 20% water solution of NaOH in 10 ml of ethanol was boiled for 2 h, cooled, then 50 ml of water was added, and the solution was filtered. The filtrate was acidified with 6 N hydrochloric acid, the arising oily substance get solid within 24 h and was recrystallized from 80% aqueous ethanol.

1,3-Diphenyl-4-pyrazolylmethylsulfanylacetic acid (IIa). Yield 63%, mp 87–88°C. IR spectrum, cm^{-1}: 1720 (C=O), 2650–2940 (OH). ^{1}H NMR spectrum, δ, ppm: 3.23 s (2H, CH_2COOH), 3.91 s (2H, $PyrCH_2$), 7.26–7.85 m (10H_{arom}), 8.44 s (1H, H^5_{Pyr}), 12.51 br.s (1H, COOH). Found, %: C 66.42; H 4.81; N 8.56. $C_{18}H_{16}N_2O_2S$. Calculated, %: C 66.67; H 4.94; N 8.64.

1-Phenyl-3-(4-fluorophenyl)-4-pyrazolylmethylsulfanylacetic acid (IIb). Yield 71%, mp 108–111°C. IR spectrum, cm^{-1}: 1725 (C=O), 2680–2950 (OH). ^{1}H NMR spectrum, δ, ppm: 3.26 s (2H, CH_2COOH), 3.91 s (2H, PσrCH$_2$), 7.25–7.87 m (9H_{arom}), 8.45 s (1H, H^5_{Pyr}), 12.47 br.s (1H, COOH). Found, %: C 63.40; H 4.51; N 7.98. $C_{18}H_{15}FN_2O_2S$. Calculated, %: C 63.16; H 4.39; N 8.19.

1-Phenyl-3-(4-chlorophenyl)-4-pyrazolylmethylsulfanylacetic acid (IIc). Yield 68%, mp 119–120°C. IR spectrum, cm^{-1}: 1720 (C=O), 2650–2930 (OH). ^{1}H NMR spectrum, δ, ppm: 3.17 s (2H, CH_2COOH), 3.88 s (2H, $PyrCH_2$), 7.27–7.88 m (9H_{arom}), 8.45 s (1H, H^5_{Pyr}), 12.40 br.s (1H, COOH). Found, %: C 60.03; H 3.99; N 7.67. $C_{18}H_{15}ClN_2O_2S$. Calculated, %: C 60.25; H 4.18; N 7.81.

3-(4-Bromophenyl)-1-phenyl-4-pyrazolylmethylsulfanylacetic acid (IId). Yield 73%, mp 138–140°C. IR spectrum, cm^{-1}: 1725 (C=O), 2700–2980 (OH). ^{1}H NMR spectrum, δ, ppm: 3.26 s (2H, CH_2COOH), 3.92 s (2H, $PyrCH_2$), 7.30–7.90 m (9H_{arom}), 8.46 s (1H, H^5_{Pyr}), 12.52 br.s (1H, COOH). Found, %: C 53.33; H 3.60; N 6.81. $C_{18}H_{15}BrN_2O_2S$. Calculated, %: C 53.60; H 3.72; N 6.95.

3-(4-Methoxy)-1-phenyl-4-pyrazolylmethylsulfanylacetic acid (IIe). Yield 65%, mp 110–111°C. IR spectrum, cm^{-1}: 1720 (C=O), 2670–2920 (OH). ^{1}H NMR spectrum, δ, ppm: 3.26 s (2H, CH_2COOH), 3.81 s (3H, CH_3O), 3.90 s (2H, $PyrCH_2$), 6.99 d (2H_{arom}), 7.26 t (1H_{arom}), 7.46 t (2 H_{arom}), 7.74 d (2H_{arom}), 7.86 d (2H_{arom}), 8.39 s (1H, H^5_{Pyr}), 12.57 br.s (1H, COOH). Found, %: C 64.16; H 4.91; N 7.78. $C_{19}H_{18}N_2O_3S$. Calculated, %: C 64.41; H 5.08; N 7.91.

3-(3,4-Dimethylphenyl)-1-phenyl-4-pyrazolylmethylsulfanylacetic acid (IIf). Yield 62%, mp 99–101°C. IR spectrum, cm^{-1}: 1725 (C=O), 2650–2950 (OH). ^{1}H NMR spectrum, δ, ppm: 2.28 s (3H, CH_3), 2.31 s (3H, CH_3), 3.23 s (2H, CH_2COOH), 3.88 s (2H, PσrCH$_2$), 7.21–7.59 m (6H_{arom}), 7.86 d (2H_{arom}), 8.40 s (1H, H^5_{Pyr}), 12.40 br.s (1H, COOH). Found, %: C 68.44; H 5.56; N 7.81. $C_{20}H_{20}N_2O_2S$. Calculated, %: C 68.18; H 5.68; N 7.95.

3-Aryl-1-phenyl-4-pyrazolylmethylsulfinylacetic acids IIIa–IIIf. To a solution of 5 mmol of acid **IIa–IIf** in 20 ml of acetone was added 3 ml of 30% solution of

hydrogen peroxide, and the mixture was stirred for 3 days at room temperature. The solution was evaporated, the residue was recrystallized from 75% acetic acid.

1,3-Diphenyl-4-pyrazolylmethylsulfinylacetic acid (IIIa). Yield 83%, mp 138–140°C. IR spectrum, cm^{-1}: 1730 (C=O), 2750–2920 (OH). ^1H NMR spectrum, δ, ppm: 3.64 d (1H, CH_2COOH, ^2J 13 Hz), 3.97 d (1H, CH_2COOH, ^2J 13 Hz), 4.17 d (1H, $PyrCH_2$, ^2J 14 Hz), 4.30 d (1H, $PyrCH_2$, ^2J 14 Hz), 7.28–7.89 m ($10H_{arom}$), 8.57 s (1H, H^5_{Pyr}), 13.03 br.s (1H, COOH). Found, %: C 63.80; H 4.68; N 8.42. $C_{18}H_{16}N_2O_3S$. Calculated, %: C 63.53; H 4.71; N 8.23.

1-Phenyl-3-(4-fluorophenyl)-4-pyrazolylmethylsulfinylacetic acid (IIIb). Yield 90%, mp 183–185°C. IR spectrum, cm^{-1}: 1735 (C=O), 2720–2950 (OH). ^1H NMR spectrum, δ, ppm: 3.63 d (1H, CH_2COOH, ^2J 14 Hz), 3.93 d (1H, CH_2COOH, ^2J 14 Hz), 4.16 d (1H, $PyrCH_2$, ^2J 14 Hz), 4.28 d (1H, $PyrCH_2$, ^2J 14 Hz), 7.24–7.87 m ($9H_{arom}$), 8.53 s (1H, H^5_{Pyr}), 12.87 br.s (1H, COOH). Found, %: C 60.07; H 4.32; N 8.03. $C_{18}H_{15}FN_2O_3S$. Calculated, %: C 60.34; H 4.19; N 7.82.

1-Phenyl-3-(4-chlorophenyl)-4-pyrazolylmethylsulfinylacetic acid (IIIs). Yield 92%, mp 178–180°C. IR spectrum, cm^{-1}: 1735 (C=O), 2700–2930 (OH). ^1H NMR spectrum, δ, ppm: 3.68 d (1H, CH_2COOH, ^2J 13 Hz), 3.95 d (1H, CH_2COOH, ^2J 13 Hz), 4.18 d (1H, $PyrCH_2$, ^2J 14 Hz), 4.33 d (1H, $PyrCH_2$, ^2J 14 Hz), 7.32–7.53 m ($5H_{arom}$), 7.79 d ($2H_{arom}$), 7.88 d ($2H_{arom}$), 8.56 s (1H, H^5_{Pyr}), 13.09 br.s (1H, COOH). Found, %: C 57.94; H 4.17; N 7.68. $C_{18}H_{15}ClN_2O_3S$. Calculated, %: C 57.68; H 4.01; N 7.48.

3-(4-Bromophenyl)-1-phenyl-4-pyrazolylmethylsulfinylacetic acid (IIId). Yield 89%, mp 189–191°C. IR spectrum, cm^{-1}: 1730 (C=O), 2700–2900 (OH). ^1H NMR spectrum, δ, ppm: 3.64 d (1H, CH_2COOH, ^2J 12 Hz), 3.94 d (1H, CH_2COOH, ^2J 12 Hz), 4.15 d (1H, $PyrCH_2$, ^2J 13 Hz), 4.31 d (1H, $PyrCH_2$, ^2J 13 Hz), 7.32–7.93 m ($9H_{arom}$), 8.55 s (1H, H^5_{Pyr}), 13.01 br.s (1H, COOH). Found, %: C 51.79; H 3.51; N 6.60. $C_{18}H_{15}BrN_2O_3S$. Calculated, %: C 51.55; H 3.58; N 6.68.

3-(4-Methoxyphenyl)-1-phenyl-4-pyrazolylmethylsulfinylacetic acid (IIIe). Yield 81%, mp 156–157°C. IR spectrum, cm^{-1}: 1725 (C=O), 2680–2900 (OH). ^1H NMR spectrum, δ, ppm: 3.65 d (1H, CH_2COOH , ^2J 14 Hz), 3,82 s (3H, CH_3O), 3.98 d (1H, CH_2COOH, ^2J 14 Hz), 4.19 d (1H, $PyrCH_2$, ^2J 15 Hz), 4.33 d (1H, $PyrCH_2$, ^2J 15 Hz), 7.03 d ($3H_{arom.}$), 7.30 t ($1H_{arom}$), 7.51 t ($2H_{arom}$), 7.65 d ($2H_{arom}$), 7.83 d ($2H_{arom}$), 8.52 s (1H, H^5_{Pyr}), 12.93 br.s (1H, COOH). Found, %: C 61.60; H 3.59; N 7.50. $C_{19}H_{18}N_2O_4S$. Calculated, %: C 61.61; H 4.90; N 7.56.

3-(3,4-Dimethylphenyl)-1-phenyl-4-pyrazolylmethylsulfinylacetic acid (IIIf). Yield 78%, mp 141–143°C. IR spectrum, cm^{-1}: 1725 (C=O), 2650–2890 (OH). ^1H NMR spectrum, δ, ppm: 2.28 C (3H, CH_3), 2,31 C (3H, CH_3), 3.64 d (1H, CH_2COOH, ^2J 14 Hz), 3.96 d (1H, ^2J 14 Hz), 4.20 d (1H, $PyrCH_2$, ^2J 14 Hz), 4.36 d (1H, $PyrCH_2$, ^2J 14 Hz), 7.28–7.64 d ($6H_{arom}$), 7.87 d ($2H_{arom}$), 8.59 C (1H, H^5_{Pyr}), 12.94 br.s (1H, COOH). Found, %: C 65.35; H 5.40; N 7.50. $C_{20}H_{20}N_2O_3S$. Calculated, %: C 65.20; H 5.47; N 7.60.

3-Aryl-1-phenyl-4-pyrazolylmethylsulfanylacetic acids IVa–IVf. To a solution of 5 mmol of acid **IIa–IIf** in 20 ml of acetic acid was added 6 ml of 30% solution of hydrogen peroxide, and the mixture was stirred for 2 h at room temperature, then 2 h more at 60°C. The reaction mixture was cooled, diluted with 50 ml of water, the separated precipitate was filtered off and recrystallized from 20% acetic acid.

1,3-Diphenyl-4-pyrazolylmethylsulfonylacetic acid (IVa). Yield 93%, mp 156–157°C. IR spectrum, cm^{-1}: 1730 (C=O), 2560–2850 (OH). ^1H NMR spectrum, δ, ppm: 4.31 s (2H, CH_2COOH), 4.69 d (2H, $PyrCH_2$), 7.29–7.83 m ($10H_{arom}$), 8.53 s (1H, H^5_{Pyr}), 13.03 br.s (1H, COOH). Found, %: C 60.91; H 4.63; N 7.99. $C_{18}H_{16}N_2O_4S$. Calculated, %: C 60.67; H 4.49; N 7.86.

1-Phenyl-3-(4-fluorophenyl)-4-pyrazolylmethylsulfonylacetic acid (IVb). Yield 97%, mp 178–179°C. IR spectrum, cm^{-1}: 1730 (C=O), 2590–2820 (OH). ^1H NMR spectrum, δ, ppm: 4.33 s (2H, CH_2COOH), 4.68 s (2H, $PyrCH_2$), 7.26–7.89 m ($9H_{arom}$), 8.55 s (1H), 13.03 br.s (1H, COOH). Found, %: C 57.43; H 4.20; N 7.26. $C_{18}H_{15}FN_2O_4S$. Calculated, %: C 57.75; H 4.01; N 7.49.

1-Phenyl-3-(4-chlorophenyl)-4-pyrazolylmethylsulfonylacetic acid (IVc). Yield 95%, mp 183–185°C. IR spectrum, cm^{-1}: 1725 (C=O), 2550–2860 (OH). ^1H NMR spectrum, δ, ppm: 4.34 s (2H, CH_2COOH), 4.69 s (2H, $PyrCH_2$), 7.34–7.69 m ($5H_{arom}$), 7.69 d ($2H_{arom}$), 7.86 d ($2H_{arom}$), 8.59 s (1H, H^5_{Pyr}), 12.99 br.s (1H, COOH). Found,%: C 55.06; H 3.97; N 7.34. $C_{18}H_{15}ClN_2O_4S$. Calculated,%: C 55.31; H 3.84; N 7.17.

3-(4-Bromophenyl)-1-phenyl-4-pyrazolylmethylsulfonylacetic acid (IVd). Yield 98%, mp 195–197°C. IR spectrum, cm^{-1}: 1730 (C=O), 2580–2900 (OH). ^1H NMR spectrum, δ, ppm: 4.35 s (2H, CH_2COOH),

4.70 s (2H, $PyrCH_2$), 7.33–7.64 m ($5H_{arom}$), 7.74 d ($2H_{arom}$), 7.89 d ($2H_{arom}$), 8.57 s (1H, H^5_{Pyr}), 13.07 br.s (1H, COOH). Found,%: C 49.95; H 3.28; N 6.61. $C_{18}H_{15}BrN_2O_4S$. Calculated,%: C 49.66; H 3.45; N 6.44.

3-(4-Methoxyphenyl)-1-phenyl-4-pyrazolylmethylsulfonylacetic acid (IVe). Yield 89%, mp 164–165°C. IR spectrum, cm^{-1}: 1730 (C=O), 2580–2910 (OH). ^1H NMR spectrum, δ, ppm: 3.81 s (3H, CH_3O), 4.30 s (2H, CH_2COOH), 4.68 s (2H, $PyrCH_2$), 6.99 d ($2H_{arom}$), 7.31 t ($1H_{arom}$), 7.50 t ($2H_{arom}$), 7.70 d ($2H_{arom}$), 7.90 d ($2H_{arom}$), 8.57 s (1H, H^5_{Pyr}), 13.07 br.s (1H, COOH). Found,%: C 49.95; H 3.28; N 6.61. $C_{18}H_{15}BrN_2O_4S$. Calculated,%: C 49.66; H 3.45; N 6.44.

3-(3,4-Dimethylphenyl)-1-phenyl-4-pyrazolylmethylsulfonylacetic acid (IVf). Yield 85%, mp 148–150°C. IR spectrum, cm^{-1}: 1730 (C=O), 2610–2890 (OH). ^1H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 2.28 s (3H, CH_3), 4.32 s (2H, CH_2COOH), 4.67 s (2H, $PyrCH_2$), 7.21–7.59 m ($6H_{arom}$), 7.90 d ($2H_{arom}$), 8.52 s (1H, H^5_{Pyr}), 12.93 br.s (1H, COOH). Found,%: C 62.75; H 5.04; N 7.47. $C_{20}H_{20}N_2O_4S$. Calculated,%: C 62.50; H 5.21; N 7.29.

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