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Synthesis of new derivatives of 3-(1-methylpyrrole-2-ylmethyl)-4-substituted-1,2,4-triazolin-5-thione

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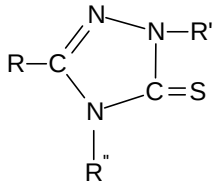
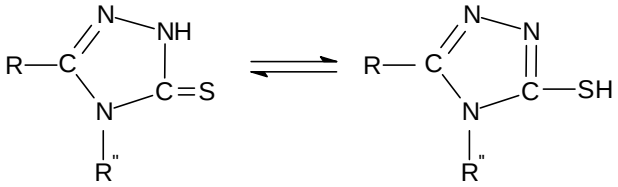
In the reaction of hydrazide of 1-methylpyrrole-2-acetic acid (I) with isothiocyanates the thiosemicarbazide derivatives of 1-methylpyrrole-2--acetic acid (II-IX) were obtained. Cyclization of these compounds in the presence of 2% NaOH led to formation of derivatives of 1,2,4-triazolin-5--thione (X-XVII).

1. INTRODUCTION

1,2,4-Triazolin-5-thione derivatives have the general formula:



were: R, R', R" can be hydrogen, alkyl, aryl, amine group. In the case when R' = H or R" = H, in this type of compounds tautomerism is likely to occur as can be see in the formulae.



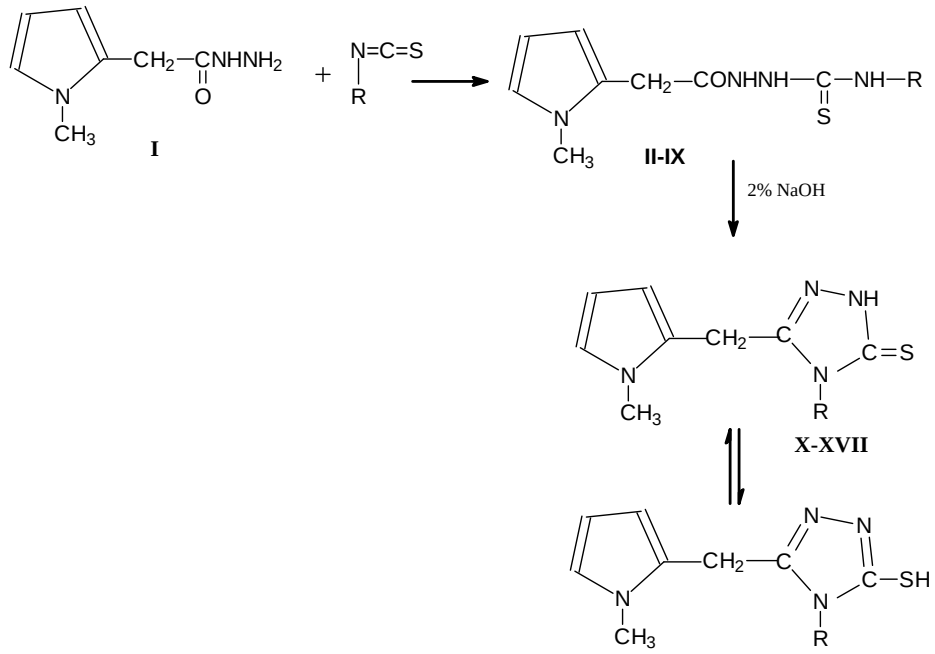
Depending on the type of substituents groups, some derivatives with the 1,2,4-triazole system show a very differentiated pharmacological action. As the former pharmacological have evidenced they should possess bacteriostatic and antivirus properties [1-18], antifungal [19-20], antiphlogistic [21] and hypotensive [22].

One of the methods of synthesis these compounds is the cyclization of acyl derivatives of thiosemicarbazide in alkaline media [23-26]. Using this method 1,2,4-triazolin-5-thione derivatives were obtained earlier [27-28]. These compounds were tested on the experimental animals showed an inhibiting effect on the central nervous system and over twice as large prolongation of hexabarbital sleeping time was found [29]. As these compounds were also slightly toxic, searching new derivatives of similar structure was desirable.

In this paper we present the results of our studies on the cyclization reaction of thiosemicarbazide derivatives of 1-methylpyrrole-2-acetic acid in alkaline media. We expected to obtain the new 1,2,4-triazolin-5-thione derivatives with promising pharmacological activity as the survey of literature revealed [30-33].

In our experiments the methyl ester of 1-methylpyrrole-2-acetate was used as starting material to preparation of hydrazide of 1-methylpyrrole-2-acetic acid (I). Next, in the reaction of the hydrazide with isothiocyanates, the respective thiosemicarbazide derivatives (II-IX) were obtained. Cyclization of these compounds led to new derivatives (X-XVII) composed of two heterocyclic systems linked through a methylene group. This compounds possess aliphatic or aromatic group in position 4 of the formed 1,2,4-triazolin-5-thione system.

The cyclization processes run according to the Scheme:



R= C_2H_5, C_6H_{11}, C_6H_5, 4-$CH_3OC_6H_4$, 4-BrC_6H_4, $CH_2C_6H_5$, 4-$CH_3C_6H_4$, $CH_2COOC_2H_5$, CH_2COOH

2. EXPERIMENTAL

Melting points were determined in a Fisher-Johns block without corrections. IR spectra were recorded in KBr using Specord IR-75 spectrophotometer. The ^1H NMR spectra were recorded on Tesla BS-567 A spectrometer (100 MHz) in DMSO-d_6 with TMS as internal standard. Chemicals were purchased from Merck Co. or Fluca Ltd. and used without purification.

1. Hydrazide of 1-methylpyrrole-2-acetic acid (I)

0.01 Mole (1.4g) of the methyl 1-methylpyrrole-2-acetate, 5 cm^3 anhydride ethanol and 0.8 cm^3 (0.02 mole) 100% hydrazine hydrate was heated while boiling for 3h under reflux condenser. After cooling the precipitated was filtered off, dried and crystallized from ethanol.
m.p.= 112^0C. Yield 1.38g (90%).
Analysis for $C_7H_{11}N_3O$ (153.18) – calcd: 54.88 %C, 7.24 %H, 27.43 %N;
found: 54.91 %C, 7.12 %H, 27.33 %N.
IR (cm^{-1}): 3280 NH, 3039 CH arom. 1631 C=O, 1428 CH_2.

^{1}H NMR (DMSO-d_6 ppm): 3.33 (s, 3H, CH_3), 3.53 (s, 2H, CH_2), 4.18 (s, 2H, NH_2), 5.80; 5.81 (2d, 2H, 2CH) J=2, 6.57 (d, 1H, CH) J=2, 9.04 (s, 1H, NH).

2. Thiosemicarbazide derivatives of 1-methylpyrrole-2-acetic acid (II-IX)

General procedure for (II-VIII):

A solution of hydrazide (1.5 g, 0.01 mole) and isothiocyanate (0.01 mole) was heated at the 70–90^{0}C for 15 h. The product was washed with diethyl ether to remove the unreacted isothiocyanate, dried and crystallized from ethanol.

4-Ethyl-1-(1-methylpyrrol-2-ylacetyl)thiosemicarbazide (II), m.p. 170–171^{0}C. Yield 1.99 g (83 %).
Analysis for $C_{10}H_{16}N_4OS$ (240.61) – calcd: 49.91 %C, 6.70 %H, 23.41 %N;
found: 50.01 %C, 6.83 %H, 23.68 %N.
IR (cm^{-1}): 3289 NH, 3027 CH arom., 2975, 1493 CH aliph., 1690 C=O, 1379 C=S.
^{1}H NMR (DMSO-d_6, ppm): 1.05–1.09 (t, 3H, CH_3), 3.40–3.46 (q, 2H, CH_2), 3.51 (s, 2H, CH_2), 5.85;5.86 (2d, 2H, 2CH) J=2, 6.61 (d, 1H, CH) J=2, 7.89; 9.14; 9.79 (3s, 3H, 3NH).

4-Cyclohexyl-1-(1-methylpyrrol-2-ylacetyl)thiosemicarbazide (III), m.p. 169––170^{0}C. Yield 2.50g (85 %).
Analysis for $C_{14}H_{22}N_4OS$ (294.70) – calcd: 57.05 %C, 7.52 %H, 19.11 %N;
found: 56.98 %C, 7.32 %H, 19.22 %N.
IR (cm^{-1}): 3299 NH, 3011 CH arom., 2935,1469 CH aliph., 1694 C=O, 1546, 1356 C=S, 715 $(CH_2)_5$.
^{1}H NMR (DMSO-d_6, ppm): 1.03 (m, 10H, $5CH_2$), 3.52 (s,3H,CH_3), 4.05 (s, 2H, CH_2), 5.85; 5.87 (2d, 2H, 2CH) J=2, 6.61 (d, 1H, CH) J=2, 9.06; 9.16; 9.78 (3s, 3H, 3NH).

1-(1-Methylpyrrol-2-ylacetyl)-4-phenylthiosemicarbazide (IV), m.p. 173––175^{0}C. Yield 2.36g (82 %).
Analysis for $C_{14}H_{16}N_4OS$ (288.65) – calcd: 58.25 %C, 5.58 %H, 19.51 %N;
found: 58.30 %C, 5.43 %H, 19.70 %N.
IR (cm^{-1}): 3239 NH, 3011 CH arom., 2940, 1472 CH aliph., 1690 C=O, 1356 C=S.
^{1}H NMR (DMSO-d_6 ppm): 3.54 (s,3H, CH_3), 3.58 (s, 2H, CH_2), 5.87; 5.89 (2d, 2H, 2CH) J=2, 6.62 (d, 1H, CH) J=2, 7.13–7.45 (m, 5H, ar. benzene), 9.60; 10.04 (2s, 3H, 3NH).

4-(4-Methoxyphenyl)-1-(1-methylpyrrol-2-ylacetyl)thiosemicarbazide (V), m.p. 145–147^{0}C. Yield 2.58 g (81 %).
Analysis for $C_{15}H_{18}N_4O_2S$ (318.70) – calcd: 56.53 %C, 5.69 %H, 17.67 %N;
found: 56.66 %C, 5.51 %H, 17.80 %N.
IR (cm^{-1}): 3181 NH, 3005 CH arom., 2938, 1469 CH aliph., 1693 C=O, 1356 C=S.
^{1}H NMR (DMSO-d_6, ppm): 3.52 (s,3H,CH_3), 3.75 (s, 2H, CH_2), 5.8 7; 5.89 (2d, 2H, 2CH) J=2, 6.61 (d, 1H, CH) J=2, 7.00-7.40 (m, 4H, ar. benene), 9.49; 9.51; 10.00 (3s, 3H, 3NH).

4-(4-Bromophenyl)-1-(1-methylpyrrol-2-ylacetyl)thiosemicarbazide (VI), m.p. 173–174^{0}C. Yield 3.12g (85 %).
Analysis for $C_{14}H_{15}N_4OSBr$ (367.56) – calcd: 45.74 %C, 4.11 %H, 15.32 %N;
found: 45.78 %C, 4.31 %H, 15.12 %N.
IR (cm^{-1}): 3268 NH, 3091 CH arom., 2942, 1458 CH aliph., 1688 C=O, 1349 C=S.
^{1}H NMR (DMSO-d_6, ppm): 3.53 (s, 3H, CH_3), 3.70 (s, 2H, CH_2), 5.85; 5.88 (2d, 2H, 2CH) J=2, 6.58 (d, 1H, CH) J=2, 7.24–7.73 (m, 4H, ar. benzene), 9.06; 9.68; 10.06 (3s, 3H, 3NH).

4-Benzyl-1-(1-methylpyrrol-2-ylacetyl)thiosemicarbazide (VII), m.p. 108––110^{0}C. Yield 2.54g (84 %).
Analysis for $C_{15}H_{18}N_4OS$ (302.68) – calcd: 59.52 %C, 5.99 %H, 18.61 %N;
found: 59.83 %C, 6.01 %H, 18.73 %N.
IR (cm^{-1}): 3279 NH, 3028 CH arom., 2937, 1453 CH aliph., 1682 C=O, 1383 C=S.
^{1}H NMR (DMSO-d_6, ppm): 3.50 (s,3H,CH_3), 4.72 (s, 2H, CH_2), 4.93 (s, 2H, CH_2), 5.84; 5.86 (2d, 2H, 2CH) J=2, 6.61 (d, 1H, CH) J=2, 7.18-7.45 (m, 5H, ar, benzene), 9.35; 9.46; 9.90 (3s, 3H, 3NH).

4-(4-Methylphenyl)-1-(1-methylpyrrol-2-ylacetyl)thiosemicarbazide (VIII), m.p. 130–132^{0}C. Yield 2.48 g (82 %).
Analysis for $C_{15}H_{18}N_4OS$ (302.68) – calcd: 59.52 %C, 5.99 %H, 18.61 %N;
found: 59.63 %C, 5.81 %H, 18.53 %N.
IR (cm^{-1}): 3245 NH, 3028 CH arom., 2941, 1465 CH aliph., 1690 C=O, 1350 C=S.
^{1}H NMR (DMSO-d_6 ppm): 2.28 (s,3H,CH_3), 3.53 (s,3H,CH_3), 3.79 (s, 2H, CH_2), 5.86; 5.88 (2d, 2H, 2CH) J=2, 6.63 (d, 1H, CH) J=2, 7.08-7.44 (m, 4H, ar, benzene), 9.54; 9.69; 10.01 (3s, 3H, 3NH).

Procedure for (IX)

A mixture of hydrazide (I) (1.4 g, 0.01 mole) and ethoxycarbonylmethyl isothiocyanate (1.4 g, 0.01 mole) in 10 cm^3 of anhydrous diethyl ether was kept at room temperature for 24h. Then the formed compound was filtered off, washed with diethyl ether and crystallized from ethanol.

4-Ethoxycarbonylmethyl-1-(1-methylpyrrol-2-ylacetyl)thiosemicarbazide (IX), m.p. 134–135^{0}C. Yield 2.38g (80 %).
Analysis for $C_{12}H_{18}N_4O_3S$ (298.65) – calcd: 48.26 %C, 6.07 %H, 18.88 %N;
found: 48.11 %C, 6.13 %H, 18.64 %N.
IR (cm^{-1}): 3279 NH, 2983 CH arom., 2939, 1451 CH aliph., 1728 C=O ester, 1687 C=O amide, 1547, 1376 C=S.
^{1}H NMR (DMSO-d_6, ppm): 1.19-1.22 (t, 3H, CH_3) J=3, 3.52 (s,3H,CH_3), 4.08-4.10 (q,2H,CH_2) J=3, 4.19 (s, 2H, CH_2), 5.81; 5.87 (2d, 2H, 2CH) J=2, 6.62 (d, 1H, CH) J=2, 8.24; 9.50; 9.97 (3s, 3H, 3NH).

3. 3,4 –Disubstituted-1,2,4-triazolin-5-thione (X-XVII)

General procedure:

A mixture of thiosemicarbazide (II-IX) (0.01 mole) and 40-50 cm^3 of 2% solution of sodium hydroxide was boiled for 2h. After cooling, the solution was neutralized with dilute hydrochloric acid. The precipitate was filtered off and then crystallized from ethanol.

4-Ethyl-3-(1-methylpyrrol-2-ylmethyl)-1,2,4-triazolin-5-thione (X), m.p. 174––176 ^{0}C. Yield 1.66g (75%).
Analysis for $C_{10}H_{14}N_4S$ (222.31) – calcd: 54.02 %C, 6.34 %H, 25.20 %N;
found: 53.91 %C, 6.28 %H, 25.14 %N.
IR (cm^{-1}): 3044 CH arom., 2946, 1461 CH aliph., 1572 C=N, 1503 C-N.
^{1}H NMR (DMSO-d_6, ppm): 1.00-1.05 (t, 3H, CH_3) J=7, 3.50 (s,3H,CH_3), 3.89–3.96 (q,2H,CH_2), J=7, 4.10 (s, 2H, CH_2), 5.84, 5.90, 6.67 (3d, 3H, 3CH) J=2, 13.48 (s, 1H, NH).

4-Cyclohexyl-3-(1-methylpyrrol-2-ylmethyl)-1,2,4-triazolin-5-thione (XI), m.p. 260–262 ^{0}C. Yield 2.07g (74%).
Analysis for $C_{14}H_{20}N_4S$ (276.40) – calcd: 60.83 %C, 7.29 %H, 20.27 %N;
found: 60.94 %C, 7.18 %H, 20.34 %N.
IR (cm^{-1}): 3041 CH arom., 2937, 1447 CH aliph., 1561 C=N, 1504 C-N, 723 $(CH_2)_5$.

^{1}H NMR (DMSO-d_6, ppm): 1.10-1.77 (m, 10H, 5CH_2), 3.32 (s, 1H, CH), 3.49 (s, 3H, CH_3), 4.14 (s, 2H, CH_2), 5.82; 5.88; 6.66 (3d, 3H, 3CH) J=2, 13.48 (s, 1H, NH).

3-(1-Methylpyrrol-2-ylmethyl)-4-phenyl-1,2,4-triazolin-5-thione (XII), m.p. 183–185 ^{0}C. Yield 2.05 g (76%).
Analysis for $C_{14}H_{14}N_4S$ (270.35) – calcd: 62.19 %C, 5.22 %H, 20.72 %N;
found: 62.01 %C, 5.18 %H, 20.84 %N.
IR (cm^{-1}): 3041 CH arom., 2932, 1494 CH aliph., 1571 C=N, 1455 C-N, 776 1-subst. benzene.
^{1}H NMR (DMSO-d_6, ppm): 3.30 (s, 3H, CH_3), 3.81 (s, 2H, CH_2), 5.44, 5.78, 6.55 (3d, 3H, 3CH) J=2, 7.25-7.53 (m, 5H, ar.benzene), 13.77 (s, 1H, NH).

4-(4-Methoxyphenyl)-3-(1-methylpyrrol-2-ylmethyl)-1,2,4-triazolin-5-thione (XIII), m.p. 144–145^{0}C. Yield 2.10g (70%).
Analysis for $C_{15}H_{16}N_4OS$ (300.37) – calcd: 59.97 %C, 5.34 %H, 18.65 %N;
found: 60.02 %C, 5.38 %H, 18.74 %N.
IR (cm^{-1}): 3040 CH arom., 2922, 1477 CH aliph., 1566 C=N, 1442 C-N, 1241 C-O-C, 822 p-disubst. benzene
^{1}H NMR (DMSO-d_6 ppm): 3.38 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 5.25 (s, 2H, CH_2), 5.71, 5.83, 6.62 (3d, 3H, 3CH) J=2, 7.20-7.33 (m, 4H, ar.benzene), 13.70 (s, 1H, NH).

4-(4-Bromophenyl)-3-(1-methylpyrrol-2-ylmethyl)-1,2,4-triazolin-5-thione (XIV), m.p. 99–100 ^{0}C. Yield 2.76g (79 %).
Analysis for $C_{14}H_{13}N_4SBr$ (349.26) – calcd: 48.14 %C, 3.75 %H, 16.04 %N;
found: 48.22 %C, 3.68 %H, 16.14 %N.
IR (cm^{-1}): 3098 CH arom., 2926, 1493 CH aliph., 1572 C=N, 1409 C-N, 831 p-disubst. benzene
^{1}H NMR (DMSO-d_6, ppm): 3.34 (s, 3H, CH_3), 3.84 (s, 2H, CH_2), 5.45; 5.85; 6.56 (3d, 3H, 3CH) J=2, 7.18-7.80 (m, 4H, ar.benzene), 13.81 (s, 1H, NH).

4-Benzyl-3-(1-methylpyrrol-2-ylmethyl)-1,2,4-triazolin-5-thione (XV), m.p. 119-121 ^{0}C. Yield 2.16g (76 %).
Analysis for $C_{15}H_{16}N_4S$ (284.40) – calcd: 63.35 %C, 5.67 %H, 19.70 %N;
found: 63.42 %C, 5.58 %H, 19.76 %N.
IR (cm^{-1}): 3042 CH arom., 2927, 1493 CH aliph., 1576 C=N, 1465 C-N, 770 1-subst. benzene
^{1}H NMR (DMSO-d_6, ppm): 3.33 (s, 3H, CH_3), 3.71 (s, 2H, CH_2), 3.81 (s, 2H, CH_2), 5.48; 5.79; 6.57 (3d, 3H, 3CH) J=2, 7.03-7.39 (m, 5H, ar.benzene), 13.70 (s, 1H, NH).

4-(4-Methylphenyl)-3-(1-methylpyrrol-2-ylmethyl)-1,2,4-triazolin-5-thione (XVI), m.p. 170–172 ^{0}C. Yield 2.10g (74 %).
Analysis for $C_{15}H_{16}N_4S$ (284.40) – calcd: 63.35 %C, 5.67 %H, 19.70 %N;
found: 63.43 %C, 5.62 %H, 19.68 %N.
IR (cm^{-1}): 3040 CH arom., 2921, 1493 CH aliph., 1573 C=N, 1493 C-N, 824 p-disubst. benzene.
^{1}H NMR (DMSO-d_6, ppm): 2.27 (s, 3H, CH_3), 3.32 (s, 3H, CH_3), 3.79 (s, 2H, CH_2), 5.47; 5.79; 6.56 (3d, 3H, 3CH) J=2, 7.13–7.33 (m, 4H, ar.benzene), 13.73 (s, 1H, NH).

3-(1-methylpyrrol-2-ylmethyl)-1,2,4-triazolin-5-thione-4-acetic acid (XVII), m.p. 150-153 ^{0}C. Yield 1.76g (70 %).
Analysis for $C_{10}H_{12}N_4O\,S_2$ (252.30) – calcd: 47.60 %C, 4.79 %H, 22.21 %N;
found: 47.52 %C, 4.71 %H, 22.28 %N.
IR (cm^{-1}): 3100 CH arom., 2938, 1494 CH aliph., 1614 C=O, 1576 C=N, 1443 C-N
^{1}H NMR (DMSO-d_6, ppm): 3.47 (s, 3H, CH_3), 3.98 (s, 2H, CH_2), 4.41 (s, 2H, CH_2), 4.54 (s, 1H, OH), 5.81; 5.88; 6.65 (3d, 3H, 3CH) J=2, 13.49 (s, 1H, NH).

3. RESULTS AND DISCUSSION

Hydrazide of 1-methylpyrrole-2-acetate (I) was obtained in the reaction of methyl 1-methyl- pyrrole-2-acetate with 100% hydrazine hydrate.

New thiosemicarbazide derivatives (II-IX) were obtained by the reaction of the hydrazide (I) with isothiocyanates.

The reaction medium was anhydrous diethyl ether and the reaction was carried out at room temperature or by heating substrates in the melt for 15 h. The conditions of the reactions were established experimentally.

Thiosemicarbazide (II-IX) were cyclized in 2% solution hydroxide. Cyclization of these derivatives in this medium led to formation 1,2,4-triazolin-5-thione system. During cyclization of thiosemicarbazide derivatives with ethoxycarbonylmethyl group, hydrolysis of ester group took place as well. The compounds (X-XVII) possess aliphatic or aromatic group in position 4 of the formed ring.

The structure of all new compounds was confirmed by elemental analysis as well as the IR and ^{1}H NMR spectra.

In IR spectra of thiosemicarbazide derivatives (II-IX) the characteristic absorption bands were observed: about 1690 cm^{-1} corresponding to C=O group and 3200–3300 cm^{-1} corresponding to NH group. In the cyclic compounds

containing 1,2,4-triazole system (X-XVII) were observed the absorption bands of the group C-N 1500cm^{-1} and C=N group 1600cm^{-1}.

^{1}H NMR spectra of thiosemicarbazide derivatives (II-IX) gave 3 protons signals typical of NH group in the range from δ 7.89-10.06. In ^{1}H NMR spectra of 1,2,4-triazolin-5-thione derivatives (X-XVII) gave proton signals for –N-C=S group in the range from δ 13.48-13.80.

Taking into account the possibility of existing of thiol-thione isomerism in the obtained products of cyclization reaction, we have established that all compounds exist in the thione form.

4. REFERENCES

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