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SYNTHESIS OF METHYL 2-(5-ARYLIDENE-2,4-DIOXOTETRA-HYDROTHIAZOL-3-YL)PROPIONATES

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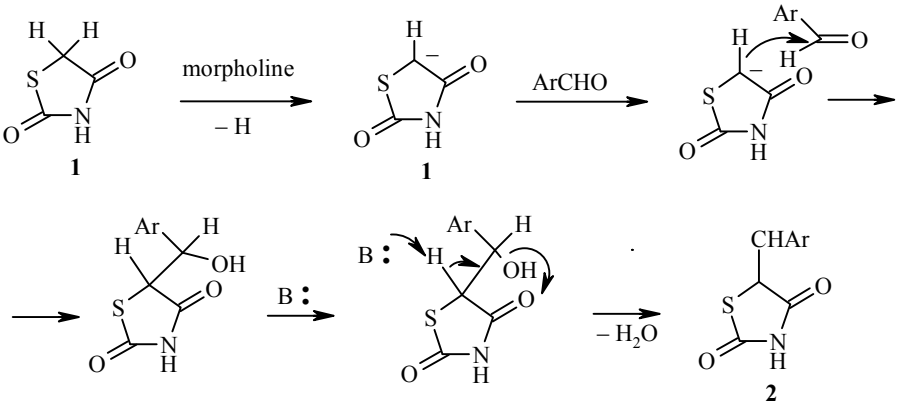
A series of methyl 2-(arylidene-2,4-dioxotetrahydrothiazol-3-yl)propionates were prepared. A study of the 3D structure was performed. The log P values are given for all the synthesized compounds.

Keywords: 5-arylidene-2,4-dioxotetrahydrothiazoles, partition coefficients, 3D analysis, N-substitution.

The structure of 2,4-dioxotetrahydrothiazole, substituted by different substituents, is found in compounds that possess biological activity (antidiabetics [1, 2], anesthetics [3], mydriatics [4], tuberculostatics [5], antirheumatics [6]). For the syntheses of derivatives with potential biological activity, the most interesting centers of reactivity are C(5) and N(3).

In our previous paper [7] we have accomplished substitution at the C(5) atom using the alkali-catalyzed condensation of 2,4-dioxotetrahydrothiazole (**1**) with different aromatic aldehydes. Morpholine was used as a catalyst. It gave high yields of 5-arylidene derivatives **2** and could be very easily removed by water.



The second step was substitution at N(3) with a substituent, which allows one to obtain various derivatives with potential biological activity. Therefore 5-arylidene-2,4-dioxotetrahydrothiazoles (**2a-i**) were transformed in their potassium salts, which further reacted with methyl 2-bromopropionate to yield methyl 2-(5-arylidene-2,4-dioxotetrahydrothiazol-3-yl)propionates (**3a-i**).

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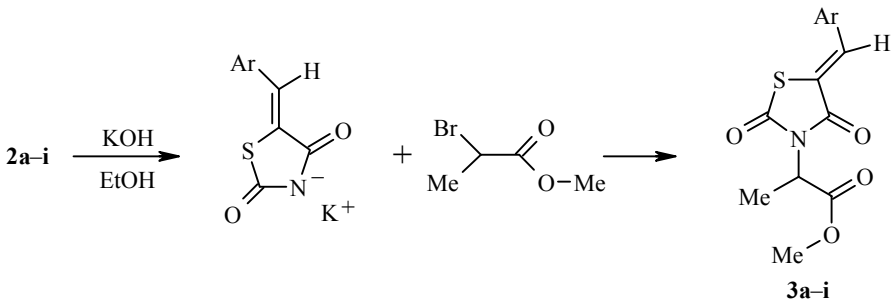

2, **3 a** Ar = Ph, **b** Ar = 3,4-$(MeO)_2C_6H_3$, **c** Ar = 4-$EtOC_6H_4$, **d** Ar = 3,4-$OCH_2OC_6H_3$, **e** Ar = 4-$PhCH_2OC_6H_4$, **f** Ar = 4-$Me_2NC_6H_4$, **g** Ar = 1-$C_{10}H_7$, **h** Ar = 2-C_4H_3S, **i** Ar = 5-methyl-2-furyl

These compounds can possess their own biological activity or can be used as a starting material for the syntheses of more complicated compounds due to the active hydrogen atom at C(2) of the propionic acid substructure or by reactions at the carbomethoxy group.

For the synthesized compounds we have established the value of log *P*, which is based on the octanol–water partition coefficient. These coefficients correlate with permeation through membranes and with biological potency. The obtained values are given in Table 1.

The synthesized derivatives can be divided in two groups: 3,4-dimethoxybenzylidene, 2-thenylidene, and 2-(5-methylfurfurylidene) derivatives with lower values of log *P* and easier permeation through membranes, and other derivatives with moderate values of log *P*.

Computer-aided 3D analyses of the synthesized compounds have given the following results. The thiazolidine ring and the aromatic ring are practically in the same plane in all the synthesized derivatives with the exception of the 2-thenylidene derivative, where the torsion angle between both rings is 48.263°. This exception can be explained by the presence of the relatively bulky sulfur atom in the thiophene ring, which causes space arrangement. In the case of the 4-benzyloxybenzylidene derivative the two benzene rings exist in two almost parallel planes.

The C(5)=CH–C_{arom} bond angles for benzylidene, 3,4-dimethoxybenzylidene, 4-ethoxybenzylidene, 3,4-methylenedioxybenzylidene, 4-dimethylaminobenzylidene, and 1-naphthylidene derivatives are in the range 124.7-125.7°. For 4-benzyloxybenzylidene, 2-5-methylfurfurylidene, and 2-thenylidene derivatives these bond angles are 123.9, 123.2, and 121.1° respectively.

TABLE 1. Log *P* Values of Methyl 2-(5-Arylidene-2,4-dioxotetrahydro-thiazol-3-yl)propionates

Compound	Arylidene	log P
3a	Benzylidene	3.97
3b	3,4-Dimethoxybenzylidene	2.68
3c	4-Ethoxybenzylidene	4.44
3d	3,4-Methylenedioxybenzylidene	3.97
3e	4-Benzyloxybenzylidene	4.45
3f	4-Dimethylaminobenzylidene	4.08
3g	1-Naphthylidene	4.08
3h	2-Thenylidene	2.53
3i	2-(5-Methylfurfurylidene)	2.47

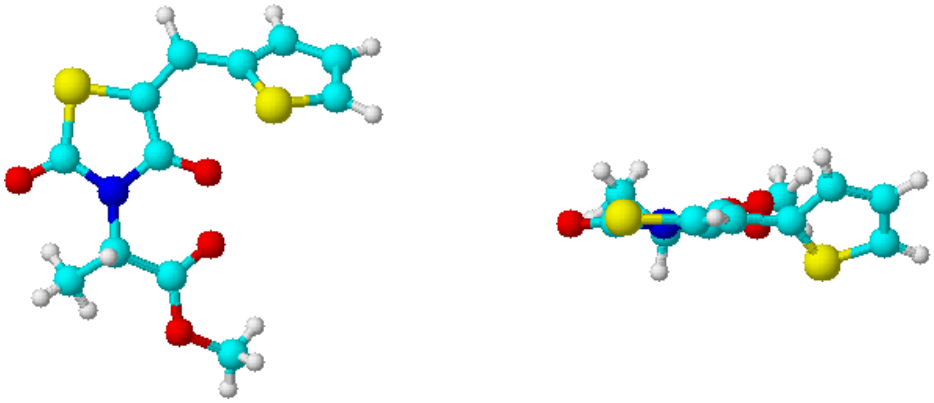

Fig. 1. Methyl 2-[5-(2-thenylidene)-2,4-dioxotetrahydro-1,3-thiazolyl-3]propionate (**3h**).

The lengths of bonds in the substructure C(5)=CH–C_{arom} for all derivatives differ from standard values. The double bond is longer (1.34 Å), and the single bond is shorter (1.47-1.48 Å). These differences can be explained by the delocalization of π-electrons through the whole substructure. This delocalization is the reason why attempts to carry out some addition reactions, which are normal for the double bond, were unsuccessful.

EXPERIMENTAL

^{1}H NMR spectra were obtained with a Varian Gemini 200 (200 MHz) instrument, and chemical shifts (δ) are given relative to TMS. IR spectra were measured using a Perkin–Elmer FTIR 1725X instrument in KBr pellets. Mass spectra were obtained on a Finnigan MAT-8230 BE spectrometer with EI-CI source at 200°C. EI: 70 eV, 0.5 mA; CI: 1 m Torr of isobutane, 150 eV, 0.2 mA.

The condensation reaction between 2,4-dioxotetrahydrothiazole and aromatic aldehydes was described in our paper [7], and their transformation to potassium salts – in our paper [8].

General Synthetic Procedure. The 5-arylidene-2,4-dioxotetrahydrothiazole potassium salt (0.1 mol) was poured into dry acetone (20 ml) in a round-bottom flask equipped with a reflux condenser, and methyl 2-bromopropionate (0.1 mol) was added. The reaction mixture was then refluxed for 2 h and filtered. Acetone was evaporated and the crude reaction product was purified by recrystallization from an ethanol–water mixture.

Methyl 2-(5-benzylidene-2,4-dioxotetrahydrothiazol-3-yl)-propionate (3a). Yield 48.9%, mp 218°C. IR spectrum, ν, cm^{-1}: 1160 (C–O ester). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.55 (d, 3H, *J* = 7.2); 3.74 (s, 3H); 5.10 (q, 1H, *J* = 7.2); 7.45-7.75 (m, 5H_{arom}); 8.00 (s, 1H). Log *P* 3.97. Found, %: C 57.66; H 4.39; N 4.60; S 10.97. $C_{14}H_{13}NO_4S$ (291.3, M^+ 291). Calculated, %: C 57.72; H 4.50; N 4.81; S 11.01.

Methyl 2-[5-(3,4-Dimethoxybenzylidene)-2,4-dioxotetrahydrothiazol-3-yl]propionate (3b). Yield 42.7%; mp 168°C. IR spectrum, ν, cm^{-1}: 1166 (C–O ester). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.55 (d, 3H, *J* = 7.2); 3.75 (s, 3H); 3.94 (s, 3H); 3.95 (s, 3H); 5.41 (q, 1H, *J* = 7.2); 7.00-7.35 (m, 3H_{arom}); 7.95 (s, 1H). Log *P* 2.68. Found, %: C 54.47; H 4.81; N 3.73; S 9.07. $C_{16}H_{17}NO_6S$ (351.3, M^+ 351). Calculated, %: C 54.69; H 4.88; N 3.99; S 9.13.

Methyl 2-[5-(4-Ethoxybenzylidene)-2,4-dioxotetrahydrothiazol-3-yl]propionate (3c). Yield 52.7%; mp 155°C. IR spectrum, ν, cm^{-1}: 1216 (alkoxy group), 1165 (C–O ester). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.45 (t, 3H, *J* = 7.1); 1.65 (d, 3H, *J* = 7.2); 3.70 (s, 3H); 4.10 (q, 2H, *J* = 7.1); 5.07 (q, 1H, *J* = 7.2); 6.98-7.45 (m, 4H_{arom}); 7.87 (s, 1H). Log P 4.44. Found, %: C 57.11; H 5.03; N 4.01; S 9.40. $C_{16}H_{17}NO_5S$ (335.3, M^+ 335). Calculated, %: C 57.30; H 5.11; N 4.18; S 9.56.

Methyl 2-[5-(3,4-Methylenedioxybenzylidene)-2,4-dioxotetrahydrothiazol-3-yl]propionate (3d). Yield 47.9%; mp 221°C. IR spectrum, ν, cm^{-1}: 1156 (C–O ester). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.50 (t, 3H, *J* = 7.2); 3.72 (s, 3H); 5.15 (q, 1H, *J* = 7.2); 5.98 (m, 2H); 7.10-7.27 (m, $3H_{arom}$); 7.73 (s, 1H). Log *P* 3.97. Found, %: C 53.61; H 3.95; N 4.03; S 9.39. $C_{15}H_{13}NO_6S$ (335.3, M^+ 335). Calculated, %: C 53.73; H 3.91; N 4.18; S 9.56.

Methyl 2-[5-(4-Benzyloxybenzylidene)-2,4-dioxotetrahydrothiazol-3-yl]propionate (3e). Yield 51.3%; mp 111°C. IR spectrum, ν, cm^{-1}: 1149 (C–O ester). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.66 (t, 3H, *J* = 7.2); 3.74 (s, 3H); 5.06 (q, 1H, *J* = 7.2); 5.11 (s, 2H); 7.21-7.67 (m, $9H_{arom}$); 7.76 (s, 1H). Log *P* 4.45. Found, %: C 63.30; H 4.73; N 3.38; S 7.87. $C_{21}H_{19}NO_5S$ (397.4, M^+ 397). Calculated, %: C 63.46; H 4.82; N 3.52; S 8.07.

Methyl 2-[5-(4-Dimethylaminobenzylidene)-2,4-dioxotetrahydrothiazol-3-yl]propionate (3f). Yield 87.1%; mp 134°C. IR spectrum, ν, cm^{-1}: 1161. ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.49 (d, 3H, *J* = 7.2); 3.03 (s, 6H, 2 × Me–N); 3.66 (s, 3H); 5.13 (q, 1H, *J* = 7.2); 6.91, 7.50 (2 × d, AA'BB', $4H_{arom}$); 7.89 (s, 1H). Log *P* 4.08. Found, %: C 57.22; H 5.39; N 8.26; S 9.44. $C_{16}H_{18}N_2O_4S$ (334.3, M^+ 334). Calculated, %: C 57.47; H 5.43; N 8.38; S 9.59.

Methyl 2-[5-(1-Naphthylidene)-2,4-dioxotetrahyrothiazol-3-yl]propionate (3g). Yield 48.06%; mp 185°C. IR spectrum, ν, cm^{-1}: 1151 (C–O ester). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.69 (d, 3H, *J* = 7.2); 3.79 (s, 3H); 5.05 (q, 1H, *J* = 7.2); 7.48-8.15 (m, $7H_{napthyl}$); 8.61 (s, 1H). Log *P* 4.08. Found, %: C 63.20; H 4.26; N 3.89; S 9.18. $C_{18}H_{15}NO_4S$ (341.3, M^+ 341). Calculated, %: C 63.33; H 4.43; N 4.10; S 9.39.

Methyl 2-[5-(2-Thenylidene)-2,4-dioxotetrahydro-1,3-thiazol-3-yl]propionate (3h). Yield 41.2%; mp 223°C. IR spectrum, ν, cm^{-1}: 1162 (C–O ester). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.05 (t, 3H, *J* = 7.2); 3.82 (s, 3H); 5.08 (q, 1H, *J* = 7.2); 7.25, 7.67, 8.07 (m, $3H_{thiophene}$); 8.27 (s, 1H). Log *P* 2.53. Found, %: C 48.19; H 3.66; N 4.58; S 21.44. $C_{12}H_{11}NO_4S_2$ (297.3, M^+ 297). Calculated, %: C 48.47; H 3.73; N 4.71; S 21.57.

Methyl 2-[5-(5-Methyl-2-furfurylidene)-2,4-dioxotetrahydrothiazol-3-yl]propionate (3i). Yield 42.3%; mp 185°C (decomp.). IR spectrum, ν, cm^{-1}: 1167 (C–O ester). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.64 (d, 3H, *J* = 7.2); 2.43 (s, 3H); 3.74 (s, 3H); 5.04 (q, 1H, *J* = 7.2); 6.20, 6.73 (2 × d, *J* = 3.4, $2H_{furyl}$); 7.49 (s, 1H). Log *P* 2.47. Found, %: C 52.71; H 4.42; N 4.58; S 10.67. $C_{13}H_{13}NO_5S$ (295.3, M^+ 295). Calculated, %: C 52.87; H 4.44; N 4.74; S 10.86.

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