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SYNTHESIS OF 5-ARYLIDENE-3-(4'-BROMO-BENZYL)THIAZOLIDINE-2,4-DIONES

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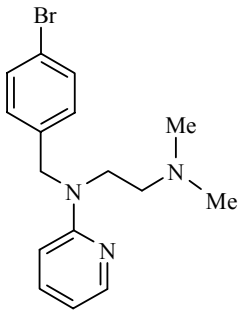
Potential antihistamines 5-arylidene-3-(4'-bromobenzyl)thiazolidine-2,4-diones were synthesized using 5-arylidenethiazolidine-2,4-dione potassium salt and 4-bromobenzyl bromide in dry acetone. The log P values are given for all the synthesized compounds.

Keywords: 5-arylidenethiazolidine-2,4-diones, partition coefficients, N-substitution.

Thiazolidinedione derivatives with a carbonyl group at positions 2 and 4 are an important group of heterocyclic compounds with a diverse array of biological activities [1]. The thiazolidinedione derivatives have been extensively studied chemically as well as biologically [2-4].

The greatest interest today centers around the derivatives of thiazolidine-2,4-dione, which can be used for the treatment of diabetes, hyperlipidemia, hypercholesterolemia, and artherosclerosis [5, 6] as well as antiallergy agents – antihistamines [7].

This paper attempts to obtain new derivatives of thiazolidine-2,4-dione containing the substructure $BrC_6H_4–CH_2–N$. The cited substructure is present the antihistamine Hibernon (**1**), and the substructure $BrC_6H_4–CH_2–X$ can be found in the antihistamines Bromadryl (**2**), Disomer (**3**), and Bromazine (**4**).



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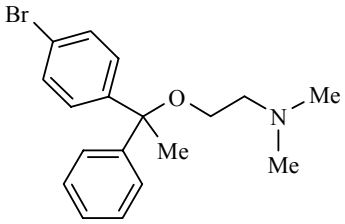

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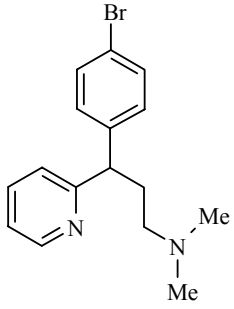

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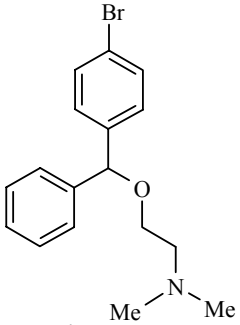

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Several new 5-arylidene-3-(4'-bromobenzyl)thiazolidine-2,4-diones were prepared using Scheme 1.

The synthesis of 5-arylidene-3-(4'-bromobenzyl)thiazolidine-2,4-diones was performed in the following steps. By condensation of 2,4-thiazolidinedione (**5**) with appropriate aldehydes, in the presence of morpholine as a catalyst, 5-arylidenethiazolidine-2,4-diones **6** were obtained [8]. The 5-arylidene derivatives were

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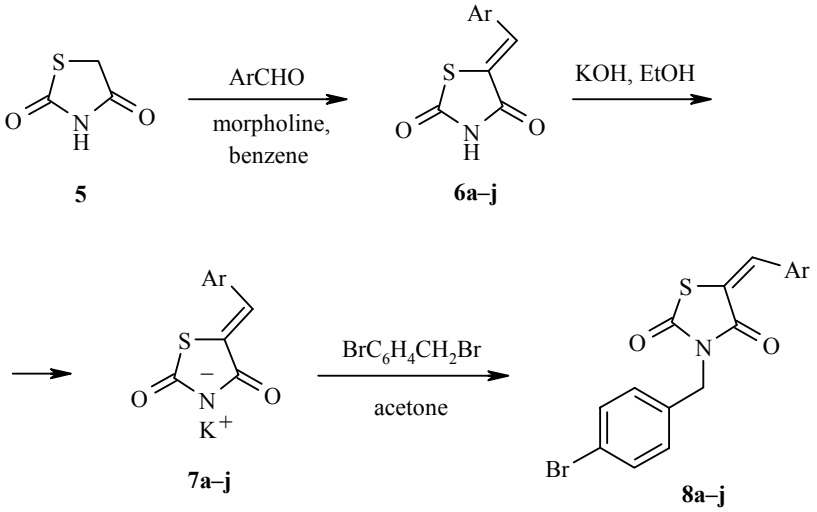
Scheme 1



6-8 a Ar = 4-$MeOC_6H_4$, **b** Ar = 4-$EtOC_6H_4$, **c** Ar = 3,4-$(MeO)_2C_6H_3$, **d** Ar = 3,4-$OCH_2OC_6H_3$, **e** Ar = 4-$PhCH_2OC_6H_4$, **f** Ar = 4-$Me_2NC_6H_4$, **g** Ar = 4-BrC_6H_4, **h** Ar = 5-methyl-2-furyl, **i** Ar = 2-C_4H_3S, **j** Ar = 3-C_4H_3S

transformed into their potassium salts **7** using potassium hydroxide in ethanolic medium [9]. Treatment of salts **7** with 4-bromobenzyl bromide in acetone gave 5-arylidene-3-(4'-bromobenzyl)thiazolidine-2,4-diones **8a-j**.

A computer-assisted examination (with ACDLabs software: ChemSketch 5.0 and 3D Viewer) of the structure of the synthesized compounds has given the following results.

The lengths of bonds in the substructure $C_{(5)}$=CH–$C_{arom.}$ for all derivatives differ from standard values. The double bond is longer (1.35-1.37Å), while the single bond is shorter (1.46-1.47Å). These differences can be explained by the delocalization of π-electrons through the whole substructure.

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 membrane permeation and biological potential. The obtained values are given in Table 1. Log P values of known antihistamines are given in Table 2.

By comparing log P values of synthesized 3-(4'-bromobenzyl) derivatives with known antihistamines **1-4**, it can be observed that log P values of compounds **8c**,**h**,**i** and **j** are in the area of log P values of known antihistamines.

TABLE 1. Log P Values of 5-Arylidene-3-(4'-bromobenzyl)thiazolidine-2,4-diones

Compound	Arylidene	log P
8a	4'-Methoxybenzylidene	4.89
8b	4'-Ethoxybenzylidene	5.43
8c	3',4'-Dimethoxybenzylidene	4.78
8d	3',4'-Methylenedioxybenzylidene	4.81
8e	4'-Benzyloxybenzylidene	6.55
8f	4'-Dimethylaminobenzylidene	5.06
8g	4'-Bromobenzylidene	5.72
8h	5'-Methyl-2'-furfurylidene	4.57
8i	2'-Thenylidene	4.63
8j	3'-Thenylidene	4.63

TABLE 2. Log P Values of Known Antihistamines

Compound	Antihistamines	log P
1	Hibernon	4.12
2	Bromadryl	4.78
3	Disomer	3.57
4	Bromazine	4.43

EXPERIMENTAL

IR spectra (KBr) were recorded on Perkin–Elmer 457 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained with Bruker AC 250E spectrometer (250 MHz) in $CDCl_3$ solution.

The potassium salts of the synthesized compounds were prepared according to our previous paper [9].

General Synthetic Procedure. 5-Arylidenethiazolidine-2,4-dione potassium salt (1 mmol) was suspended in dry acetone (20 cm^3) and 4-bromobenzyl bromide (1mmol) was added. The reaction mixture was heated under reflux for 2 h, and after that filtered. Acetone was evaporated to dryness. The obtained crystals of 5-arylidene-3-(4'-bromobenzyl)thiazolidine-2,4-diones are recrystallized from 95% ethanol.

3-(4'-Bromobenzyl)-5-(4'-methoxybenzylidene)thiazolidine-2,4-dione (8a). Yield 28.44% (0.1051 g); mp 161°C. IR spectrum, ν, cm^{-1}: 3440, 1735, 1670, 1595, 1515, 1425, 1380, 1335, 1260, 1185, 1140. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.81 (3H, s, OCH_3); 4.83 (2H, s, CH_2N); 6.97 (2H, m AA', J_1 = 8.8, J_2 = 0.4); 7.31 (2H, m AA', J_1 = 8.5, J_2 = 0.4); 7.44 (2H$_{arom,}$ m BB', J_1 = 8.7, J_2 = 0.4); 7.45 (2H$_{arom,}$ m BB', J_1 = 8.4, J_2 = 0.4); 7.85 (1H, s, =CH). ^{13}C NMR spectrum, δ, ppm: 44.5 (1C, NCH_2), 55.5 (1C, OCH_3), 114.8 (2C), 118.1, 122.3, 125.8, 130.6 (2C), 131.8 (2C), 132.2 (2C), 134.2 (2C), 161.6 (1C, qC), 166.2 (1C, C=O), 167.8 (1C, C=O). Found, %: C 53.41; H 3.42; N 3.39; S 7.73. $C_{18}H_{14}BrNO_3S$. Calculated, %: C 53.48; H 3.49; N 3.46; S 7.93.

3-(4'-Bromobenzyl)-5-(4'-ethoxybenzylidene)thiazolidine-2,4-dione (8b). Yield 30.88% (0.1123 g); mp 142°C. IR spectrum, ν, cm^{-1}: 3410, 1740, 1685, 1590, 1510, 1355, 1330, 1260, 1180. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.44 (3H, t, *J* = 7.1, CH_3); 4.08 (2H, q, *J* = 7.1, CH_2); 4.83 (2H, s, CH_2N); 6.97 (2H, m AA', J_1 = 6.75, J_2 = 0.4); 7.32 (2H, m AA', J_1 = 6.7, J_2 = 0.4); 7.38-7.45 (4H$_{arom,}$ m 2 × BB'); 7.85 (1H, s, =CH). ^{13}C NMR spectrum, δ, ppm: 14.6 (1C, CH_3), 44.4 (1C, NCH_2), 63.8 (1C, OCH_2), 115.2 (2C), 117.9, 122.3, 125.5, 130.6 (2C), 131.8 (2C), 134.2, 134.3, 161.0 (1C, qC), 166.2 (1C, C=O), 167.9 (1C, C=O). Found, %: C 54.28; H 3.88; N 3.14; S 7.39. $C_{19}H_{16}BrNO_3S$. Calculated, %: C 54.55, H 3.86, N 3.35, S 7.67.

3-(4'-Bromobenzyl)-5-(3',4'-dimethoxybenzylidene)thiazolidine-2,4-dione (8c). Yield 33.33% (0.1066 g); mp 167°C. IR spectrum, ν, cm^{-1}: 3460, 2940, 1735, 1685, 1590, 1515, 1450, 1425, 1380, 1330, 1275, 1175. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.92 (3H, s, OCH_3); 3.93 (3H, s, OCH_3); 4.84 (2H, s, CH_2N); 6.95 (1H, d, *J* = 8.4); 6.99 (1H, d, *J* = 2.0); 7.12 (1H, dd, J_1 = 8.4, J_2 = 2.0); 7.32 (2H, m AA', J_1 = 6.7, J_2 = 0.4); 7.45 (m BB', 2H$_{arom}$); 7.85 (1H, s, =CH). ^{13}C NMR spectrum, δ, ppm: 44.5 (1C, NCH_2), 55.9 (1C, OCH_3), 56.0 (1C, OCH_3), 111.4, 112.3, 118.3, 122.4, 124.8, 126.0, 130.6 (2C), 131.9 (2C), 134.2, 134.5, 149.6, 151.3 (1C, qC), 166.1 (1C, C=O), 167.8 (1C, C=O). Found, %: C 52.34; H 3.65; N 3.07; S 7.08. $C_{19}H_{16}BrNO_4S$. Calculated, %: C 52.54; H 3.71; N 3.23; S 7.38.

3-(4'-Bromobenzyl)-5-(3',4'-methylenedioxybenzylidene)thiazolidine-2,4-dione (8d). Yield 39.23% (0.1427 g); mp 174°C. IR spectrum, ν, cm^{-1}: 3420, 1740, 1675, 1595, 1510, 1490, 1455, 1375, 1335, 1270, 1110. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.84 (2H, s, CH_2N); 6.05 (2H, s, OCH_2O); 6.89 (1H, d, *J* = 8.1); 6.96 (1H, d, *J* = 1.7); 7.03 (1H, dd, J_1 = 8.1, J_2 = 1.7); 7.31 (2H, m AA', J_1 = 8.4, J_2 = = 0.4); 7.46 (2H, m BB', J_1 = 8.4, J_2 = 0.4); 7.80 (1H, s, =CH). ^{13}C NMR spectrum, δ, ppm: 44.5 (1C, NCH_2), 101.2 (1C, O–CH_2–O), 109.4 (2C), 118.8, 122.4, 126.7, 127.4, 130.7 (2C), 131.9 (2C), 134.1, 134.3, 148.6, 149.9 (1C, qC), 166.1 (1C,

C=O), 167.7 (1C, C=O). Found, %: C 51.48; H 3.08; N 3.19; S 7.43. $C_{18}H_{12}BrNO_4S$. Calculated, %: C 51.69; H 2.89; N 3.35; S 7.67.

3-(4'-Bromobenzyl)-5-(4'-benzyloxybenzylidene)thiazolidine-2,4-dione (8e). Yield 42.33% (0.2033 g); mp 165°C. IR spectrum, ν, cm^{-1}: 3410, 1745, 1685, 1600, 1515, 1365, 1340, 1260, 1185, 1000. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.83 (2H, s, CH_2N); 5.12 (2H, s, CH_2O); 7.05 (2H, m AA', J_1 = 8.8, J_2 = 0.8); 7.31 (2H, m AA', J_1 = 8.4, J_2 = 1.4); 7.35-7.47 (m, $9H_{arom}$); 7.85 (1H, s). ^{13}C NMR (DEPT), δ, ppm: 44.5 (1C, NCH_2), 70.2 (1C, OCH_2), 115.7 (2C), 118.2, 122.4 (1C), 125.0, 127.4 (2C), 128.3, 128.7(2C), 130.7 (CH, Ar), 131.9 (2CH, Ar), 132.3 (2C), 134.2, 136.1, 160.7, 166.2 (1C, C=O), 167.9 (1C, C=O). Found, %: C 59.84; H 3.87; N 2.80; S 6.46. $C_{24}H_{18}BrNO_3S$. Calculated, %: C 60.01; H 3.78; N 2.92; S 6.68.

3-(4'-Bromobenzyl)-5-(4'-dimethylaminobenzylidene)thiazolidine-2,4-dione (8f). Yield 45.41% (0.1852 g); mp 194°C. IR spectrum, ν, cm^{-1}: 3440, 1730, 1680, 1590, 1530, 1495, 1435, 1380, 1340, 1310, 1200, 1140. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.06 (6H, s, $N(CH_3)_2$); 4.83 (2H, s, CH_2N); 6.72 (2H, m AA', J_1 = 8.8, J_2 = 1.8); 7.31 (2H, m AA', J_1 = 8.4, J_2 = 1.4); 7.37-7.50 (2 × d BB', $4H_{arom}$); 7.83 (1H, s). ^{13}C NMR spectrum, δ, ppm: 40.0 (2C, $N(CH_3)_2$), 44.5 (1C, NCH_2), 111.9 (2C), 120.5 (1C), 130.6 (2CH, Ar), 131.8 (2CH, Ar), 132.6 (2C), 134.5, 135.3, 160.7, 166.5 (1C, C=O), 168.4 (1C, C=O). Found, %: C 54.50; H 4.18; N 6.59; S 7.47. $C_{19}H_{17}BrN_2O_2S$. Calculated, %: C 54.68; H 4.11; N 6.71; S 7.68.

3-(4'-Bromobenzyl)-5-(4'-bromobenzylidene)thiazolidine-2,4-dione (8g). Yield 48.76% (0.2194 g); mp 179°C. IR spectrum, ν, cm^{-1}: 3420, 1740, 1680, 1610, 1585, 1490, 1425, 1380, 1340, 1145, 1110. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.85 (2H, s, CH_2N); 7.32 (2H, m AA', J_1 = 8.5, J_2 = 1.4); 7.35 (2H, m AA', J_1 = 8.4, J_2 = 1.4); 7.47 ($2H_{arom,}$ m BB', J_1 = 8.4, J_2 = 1.4); 7.61 ($2H_{arom,}$ m BB', J_1 = 8.5, J_2 = 1.4); 7.83 (1H, s, =CH). ^{13}C NMR (DEPT), δ, ppm (*J*, Hz): 44.7 (1C, NCH_2), 122.0 (1C), 122.5, 125.2, 130.7 (CH, Ar), 131.4 (CH, Ar), 131.9 (CH, Ar), 132.0, 132.5 (CH, Ar), 132.9 (CH), 133.9, 165.8 (1C, C=O), 167.2 (1C, C=O). Found, %: C 44.92; H 2.34; N 3.01; S 6.73. $C_{17}H_{11}Br_2NO_2S$. Calculated, %: C 45.06; H 2.45; N 3.09; S 7.08.

3-(4'-Bromobenzyl)-5-(5'-methyl-2'-furfurylidene)thiazolidine-2,4-dione (8h). Yield 51.52 % (0.1970 g); mp 195°C. IR spectrum, ν, cm^{-1}: 3420, 3040, 2920, 1735, 1680, 1620, 1570, 1520, 1490, 1435, 1380, 1330, 1200, 1140, 1110. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.40 (3H, s, CH_3); 4.81 (2H, s, CH_2N); 6.19 ($1H_{furyl}$, d, J = 3.4,); 6.71 ($1H_{furyl}$, d, J = 3.4); 7.30 ($2H_{arom,}$ m AA', J_1= 8.4, J_2 = 1.4); 7.45 ($2H_{arom,}$ m BB', J_1= 8.4, J_2 = 1.4); 7.56 (1H, s).^{13}C NMR spectrum, δ, ppm: 14.2 (1C, CH_3), 44.2 (1C, NCH_2), 110.0, 116.8, 119.9, 125.0, 120.1, 122.3, 130.6 (2CH, Ar), 131.8 (2CH, Ar), 134.3, 148,3, 157.9, 166.0 (1C, C=O), 168.9 (1C, C=O). Found, %: C 50.62; H 3.27; N 3.49; S 8.23. $C_{16}H_{12}BrNO_3S$. Calculated, %: C 50.81; H 3.20; N 3.70; S 8.48.

3-(4'-Bromobenzyl)-5-(2'-thenylidene)thiazolidine-2,4-dione (8i). Yield 54.65% (0.2086 g); mp 195°C. IR spectrum, ν, cm^{-1}: 3440, 1740, 1670, 1600, 1490, 1420, 1385, 1335, 1230, 1140, 1110. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.83 (2H, s, CH_2N); 7.19 ($1H_{thenyl}$, dd, J_1 = 4.9, J_2 = 3.4); 7.31 ($2H_{arom,}$ m AA', J_1 = 8.4, J_2 = 1.4); 7.40 ($1H_{thenyl}$, dd, J_1=3.4, J_2 = 0.4); 7.45 ($2H_{arom,}$ m BB', J_1 = 8.4, J_2 = 1.4); 7.66 ($1H_{thenyl}$, dd, J_1 = 4.9, J_2 = 0.4); 8.07 (1H, s). ^{13}C NMR spectrum, δ, ppm: 44.6 (1C, NCH_2), 110.0, 119.0, 122.4, 126.9, 128.6, 130.6 (2CH, Ar), 131.8 (2CH, Ar), 132.2, 133.5, 134.1, 137.5, 157.9, 165.4 (1C, C=O), 167.2 (1C, C=O). Found: C 47.19; H 2.57; N 3.57; S 16.63. $C_{15}H_{10}BrNO_2S_2$. Calculated, %: C 47.38; H 2.65; N 3.68; S 16.86.

3-(4'-Bromobenzyl)-5-(3'-thenylidene)thiazolidine-2,4-dione (8j). Yield 55.48% (0.2118 g); mp 173°C. IR spectrum, ν, cm^{-1}: 3440, 1740, 1675, 1610, 1490, 1430, 1380, 1330, 1265, 1185, 1145, 1110. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.84 (2H, s, CH_2N); 7.27 ($1H_{thenyl}$, dd, J_1 = 4.9, J_2 = 3.4); 7.31 ($2H_{arom}$, m AA', J_1 = 8.4, J_2 = 1.4); 7.40 ($1H_{thenyl}$, dd, J_1 = 3.4, J_2 = 0.4); 7.46 ($2H_{arom}$, m BB', J_1=8.4, J_2=1.4); 7.61 ($1H_{thenyl}$, dd, J_1 = 4.9, J_2 = 0.4); 7.90 (1H, s). ^{13}C NMR spectrum, δ, ppm: 44.6 (1C, NCH_2), 120.2, 122.4, 127.4, 127.6, 127.9, 130.4, 130.7 (2CH, Ar), 131.5, 131.9 (2CH, Ar), 134.1, 135.4, 157.9, 166.1 (1C, C=O), 167.4 (1C, C=O). Found: C 47.45; H 2.72; N 3.61; S 16.66. $C_{15}H_{10}BrNO_2S_2$. Calculated, %: C 47.38; H 2.65; N 3.68; S 16.86.

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REFERENCES

1. S. P. Singh, S. S. Parmar, K. Raman, and V. I. Stenberg, *Chem. Rev.*, **81**, 175 (1981).
2. G. R. New Kome, and A. Nayak, *Advances in Heterocyclic Chemistry*, Acad. Press Inc., New York, 1979, **25**, p. 83.
3. F. G. Brown, *Chem. Rev.*, **61**, 463 (1961).
4. Hong Woo Lee, Bok Young Kim, Joong Bok Ahn, Hoe Joo Son, Jae Wook Lee, Soon Kil Ahn, and Chung Il Hong, *Heterocycles*, **57**, 2163 (2002).
5. P. Druzgala, P. G. Milner, and J. R. Pfister, US Pat. 2003027798; *Chem. Abstr*., **138**, 153526 (2003).
6. N. A. Cetenko, D. T. Conor, R. J. Sorenson, A. C. Unangst, and S. R. Stabler, Eur. Pat. 0343643; *Chem. Abstr*., **112**, 235298 (1990).
7. K. Popov-Pergal, Z. Cekovic, and M. Pergal, *Zh. Obshch. Khim.*, **61**, 2112 (1991).
8. K. Popov-Pergal, Z. Cekovic, and M. Pergal, *Sulfur Lett.*, **9**, 95 (1989).