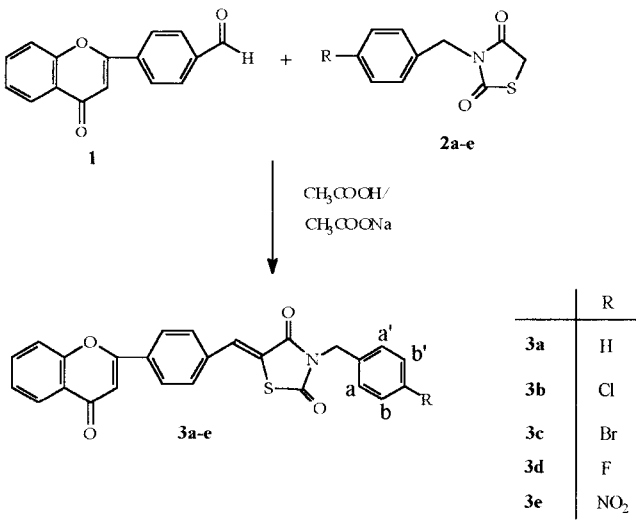
Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ankara University, Tandoğan, Ankara, Turkey

Studies on the synthesis of some substituted flavonyl thiazolidinedione derivatives, II

O. BOZDAĞ, M. TUNÇBİLEK, G. AYHAN-KILCIGİL and R. ERTAN

Thiazolidinediones possess potential biological activity. Depending on the substituents, this heterocycle can induce different pharmacological properties such as antibacterial, antifungal [1], antidiabetic [2], cardiotonic [3], anti-oedamatous and analgesic [4], anticonvulsant [5], cyclooxygenase and lipoxygenase inhibitory [6]. Flavonoids also show interesting pharmacological activities including spasmolytic [7], capillary resistance activity [8], coronary dilatory effect [9], antibacterial [10] and antidiabetic [11] activities. In our previous papers, we described the synthesis pathway of substituted flavonyl thiazolidinediones [12, 13]. The present manuscript reports the synthesis of the 3-*p*-substituted benzyl-5-[4′(4*H*-4-oxo-1-benzopyran-2-yl)-benzylidene]-2,4-thiazolidinediones **3a**–**e**. The thiazolidine-2,4-dione was prepared by cyclisation of equimolar quantities of chloroacetic acid and thiourea [3]. The thiazolidine-2,4-dione was N-alkylated with five appropriate benzylhalides in alcaline medium [3]. Compounds **3a**–**e** were synthesized by Knoevenagel condensation of flavone-4′-carboxaldehyde (**1**) and 3-*p*-substituted benzyl-2,4-thiazolidinediones **2a**–**e** using a glacial acetic acid/anhydrous sodium acetate mixture (Scheme).

Scheme



The structure of the compounds was confirmed on the basis of IR, ^{1}H NMR spectral data, mass and elemental analysis. In the ^{1}H NMR spectra C-3, C-5, C-6, C-7 and C-8 protons of the 4 H-benzopyran ring and the flavone B ring protons were observed between 6.97–8.30 ppm. Benzylic protons were seen at 4.80–5.10 ppm as a singlet. In MS all the compounds have molecular ion peaks ($M^{+\cdot}$). The ion peak (m/z = 278) is the base peak for R = Br (**3c**) and R = NO_2 (**3e**), the benzyl cation peak is the base peak for R = H (**3a**) (m/z = 91), R = Cl (**3b**) (m/z = 125), R = F (**3d**) (m/z = 109).

It is known from the literature that unsubstituted imidazolidinediones and benzaldehydes in acidic medium gave mainly the *Z*-isomer [14]. The coupled ^{13}C NMR study of arylidine thiazolidinediones and imidazolidinediones also shown that only the *Z*-isomer was formed [15, 16]. In this study, ^{13}C NMR analysis could not performed because of the poor solubility of the compounds but in view of the literature findings it was assumed that the synthesized compounds had *Z* configuration.

Experimental

1. Equipment and chemicals

Melting points were determined with a Buchi SMP 20 capillary apparatus and are uncorrected. IR spectra were recorded on a Jasco FT/IR 420 Spectrophotometer as KBr pellets. Instrumental analysis were performed by TÜBİTAK (Instrumental Analyse Lab. Ankara). The ^{1}H NMR spectra were measured with a Bruker GmbH DPX-400, 400 MHz instrument using TMS as internal standard and DMSO-d_6. All chemical shifts were reported as δ (ppm) values. MS were recorded on a VG Platform II LC-MS spectrometer (70 eV) with Electron Ionisation (EI) method. Elementary analysis were performed on a Leco 932 CHNS-O analyser. All values of C, H, N were within ±0.4% of the calculated data. All the chemical reagents used in the synthesis were purchased from E. Merck (Darmstadt, FRG) or Aldrich (Milwaukee, WI, USA).

2. General synthesis of substituted flavonyl thiazolidinedione derivatives **3a**–**e**

A mixture of flavone-4′-carboxaldehyde (**1**) (0.01 mol) and 3-substituted benzyl 2,4-thiazolidinediones **2a**–**e** (0.01 mol) was heated at 140–150 °C in the presence of 1 ml glacial acetic acid and sodium acetate (0.01 mol) for 12 h. The crude product was crystallized from DMF.

2.1. 3-Benzyl-5-[4′-(4 H-4-oxo-1-benzopyran-2-yl)-benzylidene]-2,4-thiazolidinedione (**3a**)

Yield: 81.4%, m.p: 218 °C. IR (KBr) cm^{-1}: 1655 (C=O, γ-pyron), 1682, 1745 (C=O, thiazolidinedione ring). ^{1}H NMR (DMSO-d_6): δ = 4.87 (s, 2 H, CH_2), 7.15 (s, 1 H, 3-H), 7.28–7.42 (m, 5 H, $-C_6H_5$), 7.52 (ddd, 1 H, 6-H), 7.72–7.90 (m, 4 H, 7,8,3′,5′-H), 8.07 (d, 2 H, 2′,6′-H), 8.22 (s, 1 H, =CH), 8.27 (dd, 1 H, 5-H). MS (EI): m/z (%) = 439 (11.58) $[M]^{+\cdot}$, 278 (23.84), 221 (2.62), 120 (9.59), 102 (0.61), 101 (0.63), 92 (12.16), 91 (100), 63 (6.88).
$C_{26}H_{17}NO_4S$ (439)

2.2. 3-(4-Chlorobenzyl)-5-[4′-(4 H-4-oxo-1-benzopyran-2-yl)-benzylidene]-2,4-thiazolidinedione (**3b**)

Yield: 66.0%, m.p: 280 °C. IR (KBr) cm^{-1}: 1648 (C=O, γ-pyron), 1681, 1744 (C=O, thiazolidinedione ring). ^{1}H NMR (DMSO-d_6): δ = 4.85 (s, 2 H, CH_2), 7.16 (s, 1 H, 3-H), 7.30–7.50 (m, 7 H, 6,7,8,a,a′b,b′-H)), 7.82 (d, 2 H, 3′, 5′-H), 8.05 (d, 2 H, 2′,6′-H), 8.26 (s, 1 H, =CH), 8.30 (dd, 1 H, 5-H). MS (EI): m/z (%) = 473.5 (25.72) $[M]^{+\cdot}$, 278 (45.03), 221 (4.69), 125 (100), 120 (7.05), 102 (2.68), 101 (3.48), 92 (18.60), 63 (21.61).
$C_{26}H_{16}ClNO_4S$ (473.5)

2.3. 3-(4-Bromobenzyl)-5-[4′-(4 H-4-oxo-1-benzopyran-2-yl)-benzylidene]-2,4-thiazolidinedione (**3c**)

Yield: 83.0%, m.p: 274 °C. IR (KBr) cm^{-1}: 1648 (C=O, γ-pyron), 1684, 1744 (C=O, thiazolidinedione ring). ^{1}H NMR (DMSO-d_6): δ = 4.80 (s, 2 H, CH_2), 6.98 (s, 1 H, 3-H), 7.26 (d, 2 H, a,a′-H), 7.44 (d, 2 H, b,b′-H)), 7.62 (ddd, 1 H, 6-H), 7.68 (dd, 1 H, 8-H), 7.72 (ddd, 1 H, 7-H), 7.94–8.10 (m, 4 H, 2′, 3′,5′,6′-H), 8.12 (s, 1 H, =CH), 8.17 (d, 1 H, 5-H). MS (EI): m/z (%) = 519 (5.67) $[M]^{+\cdot}$, 278 (100), 221 (7.02), 170 (10.01), 169 (98.34), 120 (5.18), 92 (13.57), 63 (9.90).
$C_{26}H_{16}BrNO_4S$ (519)

2.4. 3-(4-Fluorobenzyl)-5-[4′-(4 H-4-oxo-1-benzopyran-2-yl)-benzylidene]-2,4-thiazolidinedione (**3d**)

Yield: 66.0%, m.p: 268 °C. IR (KBr) cm^{-1}: 1649 (C=O, γ-pyron), 1683, 1746 (C=O, thiazolidinedione ring). ^{1}H NMR (DMSO-d_6): δ = 4.82 (s, 2 H, CH_2), 7.23 (m, 3 H, 3,b,b′-H)), 7.38–7.45 (m, 2 H, a,a′-H), 7.55 (ddd, 1 H, 6-H), 7.80–7.92 (m, 4 H, 7,8,3′,5′-H), 8.08 (d, 2 H, 2′,6′-H), 8.28–8.33 (m, 1 H, =CH, 5 H). MS (EI): m/e (%) = 457 (14.29) $[M]^{+\cdot}$, 278 (15.97), 221 (2.02), 120 (9.19), 109 (100), 102 (0.54), 92 (11.71), 63 (11.92).
$C_{26}H_{16}FNO_4S$ (457)

2.5. 3-(4-Nitrobenzyl)-5-[4′-(4 H-4-oxo-1-benzopyran-2-yl)-benzylidene]-2,4-thiazolidinedione (**3e**)

Yield: 52.0%, m.p: 287 °C. IR (KBr) cm^{-1}: 1644 (C=O, γ-pyron), 1683, 1738 (C=O, thiazolidinedione ring). ^1H NMR (DMSO-d_6): δ = 5.10 (s, 2 H, CH_2), 6.97 (s, 1 H, 3-H), 7.46 (ddd, 1 H, 6-H), 7.57–8.17 (m, 10 H, 7,8,2′,3′,5′,6′,a,a′,b,b′-H)), 8.18 (s, 1 H, =CH), 8.22 (d, 1 H, 5-H). MS (EI): m/z (%) = 484 (5.00) $[M]^{+\cdot}$, 278 (100), 221 (12.34), 136 (10.53), 120 (27.80), 102 (5.63), 101 (5.55), 92 (83.55), 63 (88.82).
$C_{26}H_{16}N_2O_4S$ (484)

Acknowledgement: This work was supported by the Research Organisation of the Ankara University, Turkey (No: 97030002) and TÜBİTAK (No: SBAG-AYD-158).

References

1 DeLima, M. C. A.; Costa, D. L. B.; Goes, A. J. S.; Galdino, S. L.; Pitta, I. R.; Luu-Duc, C.: Pharmazie **47**, 182 (1992)
2 Cantello, B. C. C.; Cawthorne, M. A.; Cottam, G. P.; Duff, P. T.; Haigh, D.; Hindley, R. M.; Lister, C. A.; Smith, S. A.; Thurlby, P. L.: J. Med. Chem. **37**, 3977 (1994)
3 Andreani, A.; Rambaldi, M.; Locatelli, A.; Leoni, A.; Bossa, R.; Chiericozzi, M.; Galatulas, I.; Salvatore, G.: Eur. J. Med. Chem. **28**, 825 (1993)
4 De Lima, J. D.; Perrissin, M.; Chantegrel, J.; Luu-Duc, C.; Rousseau, A.; Narcisse, G.: Arzneim.-Forsch./Drug Res. **44**, 831 (1994)
5 El-Feky, S. A. H.: Pharmazie **48**, 894 (1993)
6 Boschelli, D. H.; Connor, D. T.; Kuipers, P. J.; Wright, C. D.: Bioorg. Med. Chem. Lett. **2**, 705 (1992)
7 Bradley, D. V.; Cazort, R. J.: J. Clin. Pharmacol. 65 (1970)
8 Gabor, M.: Arzneim.-Forsch./Drug Res. **31**, 442 (1981)
9 Nitz, R. E.; Pötzsch, E.: Arzneim.-Forsch./Drug Res. **13**, 243 (1963)
10 Mori, A.; Nishino, C.; Enoki, N.; Tawata, S.; Phytochemistry **26**, 2231 (1987)
11 Hii, C. S.; Howell, S. L.: J. Endocrinol. **107**, 1 (1985)
12 Ertan, R.; Bozdağ, O.: Acta Pharm. Turc. **XXXIX**, 33 (1997)
13 Bozdağ, O.; Ayhan-Kılcıgil, G.; Tunçbilek, M.; Ertan, R.: T. J. Chem. submitted
14 Tan, S. F.; Ang, K. P.; Fong, Y. Y.: J. Chem. Soc. Perkin Trans. II **12**, 1941 (1986)
15 Vögeli, U.; Philipsborn, W.: Helv. Chim. Acta **61**, 607 (1978)
16 Albuquerque, J. F. C.; Albuquerque, A.; Azevedo, C. C.; Thomasson, F.; Galdino, L. S.; Chante-Grel, J.; Catanho, M. T. J.; Pitta, I. R.; Luu-Duc, C.: Pharmazie **50**, 387 (1995)

Received August 10, 1998
Accepted October 7, 1998

Prof. Dr. Rahmiye Ertan
University of Ankara
Faculty of Pharmacy
06100-Tandoğan
Ankara
Turkey

Department of Pharmaceutical Chemistry, Pharmaceutical Faculty, University of J. A. Komenský, Bratislava, Slovak Republic

The kinetics of alkaline hydrolysis of 1-methyl-2-piperidinoethyl esters of alkyloxyphenylcarbamic acid

M. Stankovičová, M. Pokorná and J. Čižmárik

The 1-methyl-2-piperidinoethyl esters of phenylcarbamic acid, substituted at the positions 2, 3 or 4 of the benzene ring by an alkyloxy substituent – 2-hexyloxy- (**1**), 2-heptyloxy- (**2**), 3-heptyloxy (**3**), and 4-heptyloxy (**4**) have been prepared by Pokorná et al. [1]. These substances possess high local anaesthetic activity, comparable with that of heptacaine (*N*-[2-(2-heptyloxyphenylcarbamoyloxy)-ethyl]-piperidine chloride, (**5**) and carbisocaine (*N*-[2-methyl-2-(2-heptyloxyphenylcarbamoyloxy)-ethyl]-diethylamonium chloride, (**6**) [2, 3]. The aim of this work was to determine the rate constants of alkaline hydrolysis of the new potential local anaesthetic drugs **1–4** at increased temperature and to compare these values with the rate constants of hydrolysis of **5** and **6** [4], as well as the study of hydrolysis of **2** in buffer solutions. In alkaline media, these substances decompose to final products – substituted aniline, basic alcohol, and carbon dioxide. The studied substances possess the branched connecting chain between the carbamate functional group and the basic part of the molecule. This is the difference to piperidinoethyl esters of phenylcarbamic acid. Substance **2** differs from **6** in the basic part of the molecule. In the Table the values for second order rate constants at 60, 65, 70 and 75 °C and values of activation parameters E_A, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are presented. It follows from the results that the rate constants decrease depends on the size of the alkyloxy substituent. The 4-substituted derivative shows the slowest rate of hydrolysis. The influence of the position of the substituent on the benzene ring on the rate of hydrolysis is more distinct at higher temperature. The values of rate constants of hydrolysis of the studied substances at 60 °C are significantly higher than those of the piperidinoethyl esters [4, 5]. The rate of hydrolysis of **1** is approximately six times slower than that of its analogue. The rate of hydrolysis of **2** is approximately five times slower than that of **5**. The branching in the connecting chain – the methyl in α-position is advantageous in view of stability, because the methyl group protects the carbamate functional group sterically. In contrary, the rate of hydrolysis of **2** is approximately two times higher than that of **6**. These substances differ in the basic part of the molecule.

The values of activation parameters of the compounds are in accordance with values of other derivatives of phenylcarbamic acid esters [4].

Hydrolysis of compound **2** was also studied in media of different pH values at equal ionic strength of the reaction medium ($\mu = 0.1\ mol \cdot l^{-1}$). As reaction media for stability testing [6], buffers were chosen with different concentrations of sodium hydroxide, where the presence of ethanol was required because of the low basic solubility of compounds. In all cases the ethanol concentration was equal to 50% (v/v). The dependence of log k on sodium hydroxide concentration at 70 °C is shown in the Fig. It follows from the results that **2** is stable in aqueous-ethano-

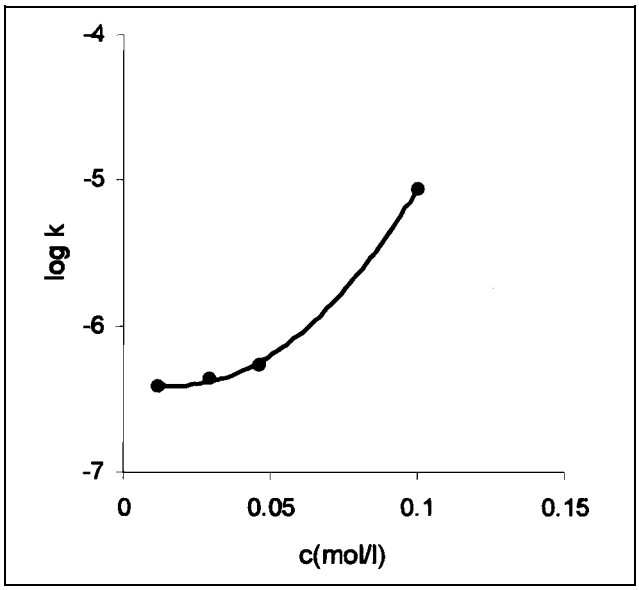


Fig.: Dependence of log k(s^{-1}) of compound **2** on sodium hydroxide concentration at 70 °C. Ionic strength μ = 0.1 mol/l