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SYNTHESIS AND CHARACTERIZATIONS OF SOME ARYLIDENE DERIVATIVES OF BARBITURIC, THIOBARBITURIC ACIDS AND THIOHYDANTOIN

BARBİTÜRİK VE TİYOBARBİTÜRİK ASİDLERLE TİYOHİDANTOİNİN BAZI ARİLİDEN TÜREVLERİNİN SENTEZİ VE YAPI TAYİNİ

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*5-(4-Carboxybenzylidene)barbituric acid (**2a**), 5-(4-carboxybenzylidene)-2-thiobarbituric acid (**3a**) and 5-(4-carboxybenzylidene)-2-thiohydantoin (**4a**) were synthesized by the condensation of barbituric acid (**2**), 2-thiobarbituric acid (**3**) and 2-thiohydantoin (**4**) with p-carboxybenzaldehyde (**1**), respectively. Analytical and spectral data [IR, ^{1}H-NMR, CIMS(CH_4)] confirmed the proposed structures. Compounds **2a** and **4a** were examined for anticonvulsant activity in the MES (Maximal Electroshock Seizure) test and in the scMet (subcutaneous pentetrazole seizure) screen. A dose range of 30-3000 mg/kg was utilized. Anticonvulsant properties were not observed.*

*Barbitürik asid (**2**), 2-tiyobarbitürik asid (**3**) ve 2-tiyohidantoinin (**4**) p-karboksibenzaldehid (**1**) ile kondensasyonuyla sırasıyla 5-(4-karboksibenziliden) barbitürik asid (**2a**), 5-(4-karboksibenziliden)-2-tiyobarbitürik asid (**3a**) ve 5-(4-karboksibenziliden)-2-tiyohidantoin (**4a**) sentezlenmiştir. Analitik ve spektral veriler [IR, ^{1}H-NMR, CIMS(CH_4)] amaçlanan yapıları doğrulamaktadır. **2a** ve **4a** maddelerinin antikonvülsan aktiviteleri MES (Maksimal elektroşok nöbeti) testi ve scMet (subkutan pentetrazol nöbeti) taramalarıyla incelenmiştir. 30-3000 mg/kg arasında dozlar kullanılmıştır. Antikonvülsan özellikler gözlenmemiştir.*

Keywords: *Arylidenebarbituric acid; Arylidene 2-thiobarbituric acid; Arylidene 2-thiohydantoin; Synthesis; Anticonvulsant activity*

Anahtar kelimeler: *Arilidenbarbitürik asid; Ariliden 2-tiyobarbitürik asid ; Ariliden 2-tiyohidantoin; Sentez; Antikonvülsan aktivite*

Introduction

In previous papers [1-3] we reported the synthesis and the characteristics of some arylidene derivatives of barbituric acids, hydantoin and their thio analogs. Many derivatives of barbituric and thiobarbituric acids, bearing aryl groups at C-5 are known to possess anticonvulsant activity.

Materials and Methods

All m.ps were determined on a Buchi Flawil apparatus and were uncorrected. IR spectra were recorded on Perkin Elmer 577 Grating Spectrophotometer. ^{1}H-NMR spectra were run on Bruker AC 200 and Bruker AC 300 using TMS as an internal standard. CIMS(CH_4) and elemental analyses were performed at Sittingbourne Research Centre, UK. Anticonvulsant screening was undertaken by the Anticonvulsant Screening Project conducted by the National Institute of Neurological and Communicative Disorders and Stroke, Bethesda, MD, USA.

*1. Synthesis of 5-(4-carboxybenzylidene)barbituric acid (**2a**), and 5-(4-carboxybenzylidene)-2-thiobarbituric acid (**3a**)*

A solution containing 0.01 mol of barbituric acid (**2**) [or 2-thiobarbituric acid (**3**)] and 0.015 mol of p-carboxybenzaldehyde (**1**) in ethanol (150 ml) was heated under reflux for 2h, in a water bath. The reaction mixture was cooled and the yellow product was isolated and crystallized from ethanol.

2a: IR (cm^{-1}): 3200, 3060 (NH, OH, CH), 1740, 1670 (C=O). ^{1}H-NMR (δ ppm): 13.30 (1H, bs, OH), 11.46 (1H, s, NH), 11.29 (1H, s, NH), 8.30 (1H, s, =CH), 8.03-7.93 (4H, m, ArH).CIMS (CH_4) [m/z (%)]: 261 (MH^+, 55), 129 (100).

3a: IR (cm^{-1}) : 3060, 2900 (NH, OH, CH), 1715, 1675 (C=O), 1200 (C=S). ^{1}H-NMR (δ ppm): 13.30 (1H,bs,OH) 12.52 (1H,s,NH), 12.39 (1H,s,NH), 8.30 (1H,s,=CH), 8.08-7.94 (4H, m, ArH). CIMS(CH_4) [m/z (%)]: 277 (MH^+, 55), 145 (100).

2. Synthesis of 5-(4-carboxybenzylidene)-2-thiohydantoin (4a)

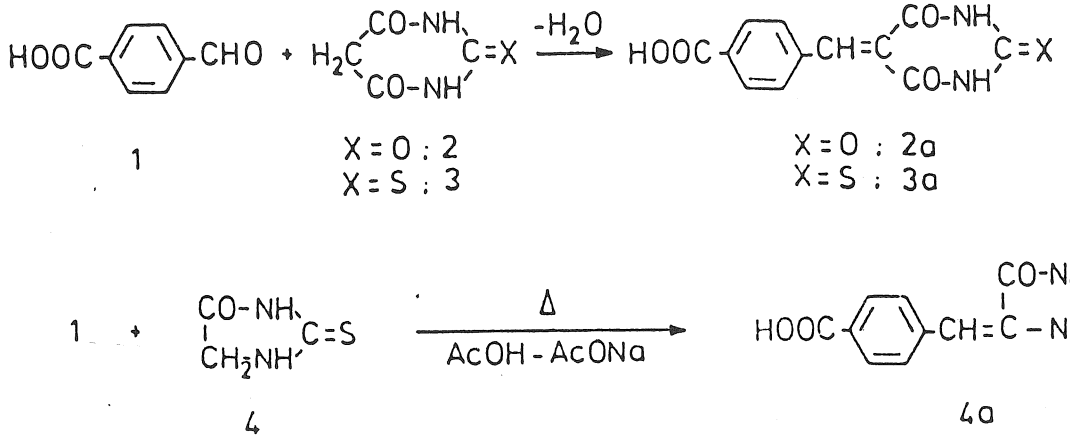
A mixture of 2-thiohydantoin (**4**) (0.01 mol), p-carboxybenzaldehyde (**1**) (0.015 mol), fused sodium acetate (0.04 mol) and glacial acetic acid (12.5 ml) was refluxed for 4h in an oil bath at 140°C. The hot reaction mixture was then poured into water. The precipitated solid was filtered, washed with water, ethanol and ether.

4a: IR (cm^{-1}): 3300, 3100 (NH,OH,CH), 1730, 1690 (C=O), 1200 (C=S). ^{1}H-NMR (δ ppm): 13.06 (1H, bs,OH), 12.47 (1H,s,NH), 12.27 (1H,s,NH), 7.95-7.82 (4H,m,ArH),6.52 (1H,s,=CH). CIMS (CH_4) [m/z (%)]: 249 (MH^+, 100).

Results and Discussion

The reaction of 4-carboxybenzaldehyde (**1**) with barbituric acid (**2**) and 2-thiobarbituric acid (**3**) gave 5 - (4 - carboxybenzylidene) barbituric acid (**2a**) and 5 - (4 - carboxybenzylidene) - 2 - thiobarbituric acid (**3a**), respectively [4]. On the other hand 5-(4-carboxybenzylidene) - 2 -thiohydantoin (**4a**) was prepared by condensing (**1**) with 2-thiohydantoin (**4**) in glacial acetic acid in the presence of sodium acetate [5]. After purification of the crude products, compounds **2a**, **3a** and **4a** were obtained (Scheme and Table).

The synthesized compounds were characterized by their elementary analysis, m.ps and TLC analysis on silicagel. For structural determination, spectroscopic methods (IR, NMR and mass spectrometry) were used. The IR spectra of compounds **2a**, **3a** and **4a** showed bands in the 3300-2900 cm^{-1} region attributed



Scheme

Table. Physical data of the synthesized compounds

Compound	M.p. (°C)	Yield (%)	Molecular formula (molecular mass)	Elemental analyses calcd./found		
				C	H	N
2a	>300	56.92	$C_{12}H_8N_2O_5$ (260.20)	55.39 55.30	3.09 3.30	10.76 10.90
3a	> 300	24.63	$C_{12}H_8N_2O_4S$ (276.26)	52.17 51.90	2.91 3.20	10.13 10.10
4a	>300	90.48	$C_{11}H_8N_2O_3S$ (248.25)	53.22 53.40	3.24 3.60	11.28 11.50

to the bonded OH (carboxyl), bonded NH and aromatic CH absorptions. The presence of carbonyl functionality was confirmed by the bands observed in the 1740-1715 and 1690-1670 cm^{-1}regions where the former was assigned to the ring C=O. In compounds **3a** and **4a,** C=S stretching of the rings was characterized by the strong absorption band at 1200 cm^{-1} [6]. In the ^{1}H-NMR spectra of compounds **2a**, **3a** and **4a,** the carboxylic acid protons showed broad singlets at 13.06-13.30 ppm. The NH protons displayed two separate singlets at 11.29-12.39 and 11.46-12.52 ppm due to the nonequivalance of the NH protons [6]. The olefinic proton of Ar-CH=C- was observed as a singlet at 8.30 ppm in **2a**, **3a** and at 6.52 ppm in **4a** [7]. Aromatic protons resonated at 7.82-8.08 ppm as multiplets. Quasi-molecular ions at m/z 261, 277 and 249 corresponding to $(MH)^+$ observed in CIMS of compounds **2a**, **3a** and **4a** respectively, confirm their molecular weights. Compounds **2a** and **3a** showed the characteristic fragment as base peak at m/z 129 and 145, respectively. The quasi-molecular ion of **4a** coincides with the base peak at m/z 249. The fragmentation pattern observed in the CI mass spectra of compound **2a**, **3a** and **4a** was in accordance with the fragmentation mode proposed for aryl substituted barbituric and arylidenethiobarbituric acids [6,8].

Compounds **2a** and **4a** were examined for anticonvulsant activity in the MES (Maximal Electroshock Seizure) test and in the scMet (subcutaneous pentetrazole seizure) screen. A dose range of 30-3000 mg/kg was utilized. Anticonvulsant properties were not observed.

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