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# Synthesis and Anticonvulsant Activity of Some New Arylidenehydrazides and 4-Thiazolidinones

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**Summary.** A number of N,N′-*bis*(arylidene)mono(1-methylpropyl)malonic acid dihydrazides (**3a–c**), 1,1-*bis*[[(2-aryl-4-thiazolidinone-3-yl)amino]carbonyl]-2-methylbutanes (**4a–e**), and 1,1-*bis*[[(3-alkyl/aryl-4-thiazolidinone-2-yl)hydrazono]carbonyl]-2-methylbutanes (**6a–i**) have been synthesized, characterized and evaluated for anticonvulsant activity. All tested compounds showed significant activity (10 to 60% protection) against pentylenetetrazole induced seizures.

**Keywords.** Anticonvulsant activity; Arylidenehydrazides; 4-Thiazolidinones; Synthesis.

**Synthese einiger neuer Arylidenhydrazide und 4-Thiazolidinone sowie Untersuchung ihrer krampflösenden Eigenschaften**

**Zusammenfassung.** Eine Reihe von N,N′-*Bis*(aryliden)mono(1-methylpropyl)malonsäure dihydraziden, (**3a–c**), 1,1-*Bis*[[2-Aryl-4-thiazolidinon-3-yl)amino]carbonyl]-2-methylbutanen (**4a–e**) und 1,1-*Bis*[[3-alkyl/aryl-4-thiazolidinon-2-yl)hydrazono]carbonyl]-2-methylbutanen (**6a–i**) wurden hergestellt, charakterisiert und auf ihre antikonvulsive Wirkung geprüft. Alle getesteten Substanzen zeigen relevante Aktivitäten gegen durch Pentilentetrazol induzierte Krämpfe (10–60% Schutz).

## Introduction

A wide variety of pharmacological properties has been shown to be associated with N-arylidene hydrazide derivatives [1–4]. Various 4-thiazolidinones are also associated with a broad spectrum of biological properties including anticonvulsant activity [5, 6]. In continuation of our work on the synthesis of heterocycles of pharmaceutical interest [7, 8] we report here the synthesis, characterization, and anticonvulsant evaluation of new N,N′-*bis*(arylidene)dihydrazide and *bis*(4-thiazolidinone) derivatives.

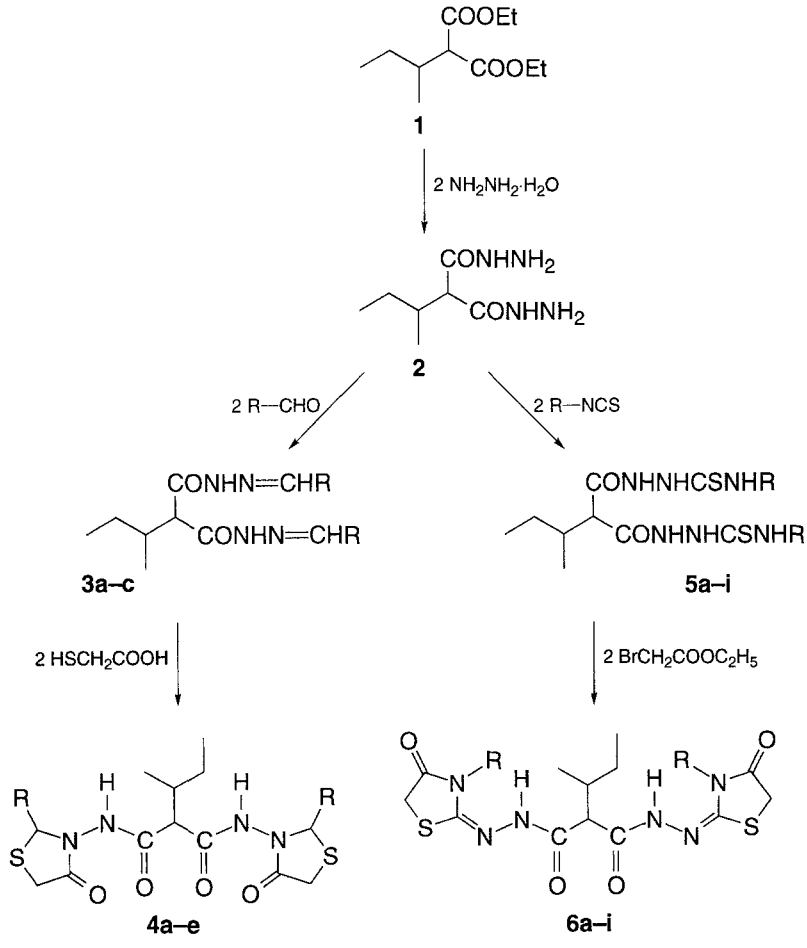
## Results and Discussion

The required compounds were obtained by the reaction sequences outlined in the Scheme. Thus, mono(1-methylpropyl)malonyldihydrazide (**2**) was obtained by re-

fluxing mono(1-methylpropyl)malonic acid diethyl ester (**1**) with hydrazine hydrate in ethanol according to the literature method [9]. Compound **2** was condensed with appropriate aromatic aldehydes to give the corresponding N,N′-*bis*(arylidene) dihydrazides [10] **3a–c**, which on condensation with mercaptoacetic acid [11] afforded the *bis*(4-thiazolidinones) **4a–e**. Mono(1-methylpropyl)malonyl*bis*(4-substituted)thiosemicarbazides **5a–i** were obtained by a method reported previously [7]. On treatment with ethyl bromoacetate and sodium acetate, **5a–i** furnished the 4-thiazolidinones **6a–i** (Table 1). The structures of the compounds were confirmed by spectroscopic methods (IR, $^1$H NMR, EI-MS) and elemental analyses.

The IR spectra of **3**, **4**, **5**, and **6** showed CO bands at 1725–1665 cm$^{-1}$ (CONH-N in **3**, **4**, **6** and CONH-NH in **5**). A new strong band at 1745–1718 cm$^{-1}$ in the spectra of **4** and **6** provided firm support for ring closure [5, 12].

The NMR spectrum of compound **4c** displayed two doublets at $\delta = 3.72$ and 3.88 ppm due to the non-equivalence of the methylene protons [12]. The singlets of N=CH at 7.95 and 8.27 ppm in the spectrum of **3a** were shifted upfield to 5.59–5.82 ppm as the **sp**$^2$ carbon of **3a** was transformed into the **sp**$^3$ carbon of **4c**, verifying the nucleophilic addition to the C=N double bond. Compound **6a**



displayed an additional singlet at 4.04 ppm ($S-CH_2$) which proved ring closure [13].

EI mass spectra of three representative examples (**3a**, **4c**, and **6a**) provided molecular ions at $m/z = 400$, 548, and 414 with different intensities confirming their molecular weights. The major fragmentation pathway in **3a**, **4c**, and **6a** involved the cleavage of the amide linkage, giving fragments with $m/z = 263$ and 138, 337 and 212 and 270 and 145, respectively. Further experimental details are given in the experimental part.

**Table 1.** Physical data of compounds **3a–c**, **4a–e**, and **6a–i**

| | *R* | Yield (%) | m.p. (°C) | Molecular formula[a] Molecular weight |
|---|---|---|---|---|
| **3a** | *p*-$C_6H_4F$ | 90 | 247–248 | $C_{21}H_{22}F_2N_4O_2$ 400.44 |
| **3b** | *p*-$C_6H_4Cl$ | 91 | 261–262 | $C_{21}H_{22}Cl_2N_4O_2$ 433.34 |
| **3c** | *p*-$C_6H_4Br$ | 91 | 258–259 | $C_{21}H_{22}Br_2N_4O_2$ 522.26 |
| **4a** | $C_6H_5$ | 83 | 209–210 | $C_{25}H_{28}N_4O_4S_2 \cdot 2H_2O$ 548.68 |
| **4b** | *p*-$C_6H_4OCH_3$ | 54 | 247–248 | $C_{27}H_{32}N_4O_6S_2 \cdot \frac{1}{2}H_2O$ 581.71 |
| **4c** | *p*-$C_6H_4F$ | 83 | 270–271 | $C_{25}H_{26}F_2N_4O_4S_2$ 548.64 |
| **4d** | *p*-$C_6H_4Cl$ | 91 | 257–258 | $C_{25}H_{26}Cl_2N_4O_4S_2$ 581.54 |
| **4e** | *p*-$C_6H_4Br$ | 90 | 230–231 | $C_{25}H_{26}Br_2N_4O_4S_2$ 670.46 |
| **6a** | $CH_3$ | 76 | 266–267 | $C_{15}H_{22}N_6O_4S_2$ 414.51 |
| **6b** | $C_2H_5$ | 67 | 215–217 | $C_{17}H_{26}N_6O_4S_2 \cdot H_2O$ 460.58 |
| **6c** | $C_3H_7$ | 57 | 169–170 | $C_{19}H_{30}N_6O_4S_2$ 470.61 |
| **6d** | $C_4H_9$ | 92 | 189–190 | $C_{21}H_{34}N_6O_4S_2$ 498.66 |
| **6e** | $CH_2$-CH=$CH_2$ | 86 | 190–191 | $C_{19}H_{26}N_6O_4S_2$ 466.58 |
| **6f** | $C_6H_5$ | 76 | 281–282 | $C_{25}H_{26}N_6O_4S_2$ 538.65 |
| **6g** | *p*-$C_6H_4CH_3$ | 95 | 280–281 | $C_{27}H_{30}N_6O_4S_2$ 566.70 |
| **6h** | *p*-$C_6H_4Cl$ | 91 | 280–281 | $C_{25}H_{24}Cl_2N_6O_4S_2$ 607.53 |
| **6i** | *p*-$C_6H_4Br$ | 95 | 281–282 | $C_{25}H_{24}Br_2N_6O_4S_2$ 696.45 |

[a] All compounds gave satisfactory elemental analyses (C, H, N)

**Table 2.** Anticonvulsant activity of compounds **3a–c**, **4a–e**, and **6a–i**

| | Protection (%) | Pentylenetetrazole mortality (%) |
|---|---|---|
| **3a** | 40 | 60 |
| **3b** | 60 | 40 |
| **3c** | 20 | 80 |
| **4a** | 50 | 50 |
| **4b** | 40 | 60 |
| **4c** | 10 | 90 |
| **4d** | 20 | 80 |
| **4e** | 20 | 80 |
| **6a** | 30 | 70 |
| **6b** | 60 | 40 |
| **6c** | 60 | 40 |
| **6d** | 30 | 70 |
| **6e** | 60 | 40 |
| **6f** | 40 | 60 |
| **6g** | 60 | 40 |
| **6h** | 40 | 60 |
| **6i** | 30 | 70 |

The anticonvulsant activity of **3**, **4**, and **6** was determined against pentylenetetrazole induced seizures. As can be seen from Table 2, **3b**, **4a**, and most of **6** showed significant protection.

## Experimental

Melting points: Büchi 530, uncorrected; IR (KBr): Perkin Elmer 1600 FTIR; $^1$H NMR (*DMSO*-$d_6$, *TMS*): Bruker DP × 400 (400 MHz); EI-MS: VG Zab Spec (70 eV); elemental analyses: Carlo Erba 1106 and Leco CHNS-932.

*N,N'-Bis(arylidene)mono(1-methylpropyl)malonic acid dihydrazides* (**3a–c**)

A mixture of **2** (0.005 mol) in EtOH (40 ml) and the appropriate aromatic aldehyde (0.01 mol) was heated under reflux for 3 h. The precipitate obtained from the hot ethanolic solution was purified either by washing with hot EtOH (**3b**, **3c**) or by recrystallization from EtOH (**3a**).

**3a**: IR (KBr): $\nu_{max} = 1670\,cm^{-1}$ (CO); $^1$H NMR: $\delta = 0.87$–$0.99$ (m, 6H, $2CH_3$), 1.20–1.26, 1.53–1.56 (m, 1H, m, 1H, $CH_2$), 2.24–2.26 (m, 1H, CH), 3.87–3.89, 4.92 (m, d, $J = 8.39$ Hz, 1H, CO-CH-CO), 6.97–7.28, 7.66–7.77 (2m, 8H, Ar-H), 7.95, 8.27 (2s, 2H, 2N=CH), 11.37, 11.53 (2s, 2H, 2NH) ppm; EI-MS: $m/z$ (%) = 400 ($M^+$, 22) 344 (26), 263 (100), 235 (24), 207 (79), 179 (24), 165 (66), 138 (73), 122 (77), 57 (26).

*1,1-Bis[[2-aryl-4-thiazolidinone-3-yl)amino]carbonyl]-2-methylbutanes* (**4a–e**)

A mixture of **3** (0.005 mol) and mercaptoacetic acid (0.01 mol) was refluxed in dry benzene (30 ml) using a *Dean-Stark* water separator. Excess benzene was evaporated *in vacuo*. The resulting residue was

triturated with saturated $NaHCO_3$ solution until $CO_2$ evolution ceased and was allowed to stand overnight. The solid thus obtained was washed with water, dried, and recrystallized from EtOH.

**4c**: IR (KBr): $\nu_{max} = 1727$ (CO, thiazolidinone), 1684 (NHCO) $cm^{-1}$; $^1H$ NMR: $\delta = 0.51–0.70$ (m, 6H, $2CH_3$), 0.73–0.84, 0.86–1.24 (m, 1H, m, 1H, $CH_2$), 1.75–1.90 (m, 1H, CH), 2.76 (d, $J = 9.58$ Hz, 1H, CO-CH-CO), 3.72, 3.88 (2H each, 2d, $J = 15.9$ Hz, $2CH_2$-S), 5.59–5.82 (m, 2H, 2N-CH-S), 7.14–7.22, 7.41–7.50 (2m, 8H, Ar-H), 9.83–10.08 (m, 2H, 2NH) ppm; EI-MS: $m/z$ (%) = 548 ($M^+$, 0.6), 352 (3), 337 (3), 263 (42), 212 (41), 196 (100), 165 (29), 122 (48), 74 (6), 57 (8).

*1,1-Bis[ [3-alkyl/aryl-4-thiazolidinone-2-yl)hydrazono]carbonyl]-2-methylbutanes* (**6a–i**)

An appropriate thiosemicarbazide **5a–i** (0.005 mol) and ethyl bromoacetate (0.01 mol) were refluxed in 40 ml absolute EtOH in the presence of 0.04 mol anhydrous $CH_3COONa$ for 3 h. The reaction mixture was cooled, diluted with water, and allowed to stand overnight. The solid thus obtained was washed with water, dried, and recrystallized from EtOH (**6a–e**) or washed with hot EtOH (**6f–i**).

**6a**: IR (KBr): $\nu_{max} = 1720$ (CO, thiazolidinone), 1670 (NHCO) $cm^{-1}$; $^1H$ NMR: $\delta = 0.85–0.93$ (m, 6H, $2CH_3$), 1.12–1.24, 1.44–1.50 (m, 1H, m, 1H, $CH_2$), 2.08–2.10 (m, 1H, CH), 3.07 (s, 6H, 2N-$CH_3$), 3.09 (d, $J = 9.17$ Hz, 1H, CO-CH-CO), 4.04 (s, 4H, $2SCH_2$), 10.1 (s, 2H, 2NH) ppm; EI-MS: $m/z$ (%) = 414 ($M^+$, 4), 358 (19), 270 (72), 242 (14), 172 (25), 145 (56), 57 (40), 42 (100).

*Anticonvulsant Activity* [8, 14]

The anticonvulsant activity of compounds **3–6** was determined against pentylenetetrazole induced seizures in albino Swiss mice of either sex weighing 20–30 g. They were housed in groups of 10 and acclimated to their environment for at least 2 days before the experiments were done. The animals were allowed free access to food and water before being tested. The test compounds were suspended in 5% aqueous suspension of gum acacia and administered to a group of 10 animals at a dose of 100 mg/kg intraperitoneally. 2 hours after the administration, pentylenetetrazole (90 mg/kg) was injected subcutaneously. This dose of pentylenetetrazole has been shown not only to produce convulsions in almost all untreated mice, but also to exhibit 100% mortality during 24 hours in the control group. The mice were observed for the next 60 min for the occurence of seizures. Animals devoid of a threshold convulsion were considered protected. The mortality within 24 hours was also recorded (Table 2).

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