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Adamantane Derivatives IV:** Unexpected Debenzylation on Ring Closure of 1-(1-Adamantylcarbonyl)-4-benzylthiosemicarbazide with Sulphuric Acid***

A. A. El-Emam and **J. Lehmann***

Pharmazeutisches Institut, Universität Bonn, D-53121 Bonn, Federal Republic of Germany

Summary. Cyclization of 1-(1-adamantylcarbonyl)-4-substituted thiosemicarbazides **2a–e** with sulphuric acid at ambient temperature or by heating with phosphorus oxychloride yielded the corresponding 2-(1-adamantyl)-5-amino-1,3,4-thiadiazoles **3a–e**. Cyclization of 1-(1-adamantylcarbonyl)-4-benzylthiosemicarbazide **2f** with sulphuric acid gave the debenzylated product 2-(1-adamantyl)-5-amino-1,3,4-thiadiazole **4**. On the other hand, cyclization of **2f** using phosphorus oxychloride yielded 2-(1-adamantyl)-5-benzylamino-1,3,4-thiadiazole **3f**.

Keywords. Adamantanes; Debenzylation; 1,3,4-Thiadiazoles.

Adamantan Derivate, 4. Mitt.: Unerwartete Debenzylierung bei der Cyclisierung von 1-(1-Adamantylcarbonyl)-4-benzylthiosemicarbazid mit Schwefelsäure

Zusammenfassung. Die 4-substituierten 1-(1-Adamantylcarbonyl)-thiosemicarbazide **2a–e** cyclisieren mit Schwefelsäure bei Raumtemperatur oder durch Erhitzen mit Phosphoroxytrichlorid zu den entsprechenden N-substituierten 2-(1-Adamantyl)-5-amino-1,3,4-thiadiazolen **3a–e**. Unter gleichen Reaktionsbedingungen cyclisiert das 4-Benzylthiosemicarbazid **2f** mit Phosphoroxytrichlorid zum 5-Benzylamino-1,3,4-thiadiazol **3f**, während in Schwefelsäure eine Cyclisierung unter Debenzylierung zum 5-Amino-1,3,4-thiadiazol **4** erfolgt.

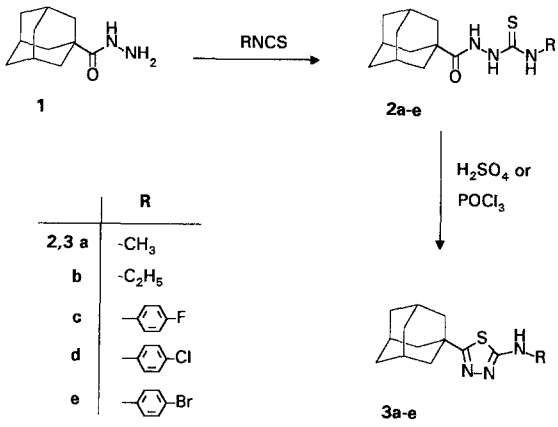
Introduction

A number of adamantane derivatives have long been known for their antiviral [1–4] and central nervous activities [4–6]. Moreover, adamantane derivatives are now receiving continuous interest for their antiinflammatory activity [7–12]. Furthermore, several 1,3,4-thiadiazole derivatives were also reported to possess antiviral activity [13]. In view of these observations and in continuation of our studies in adamantane chemistry [12, 14, 15], it was considered of interest to synthesize a series of 2-(1-adamantyl)-5-substituted amino-1,3,4-thiadiazoles as potential antiviral and/or central nervous agents.

** For part III, see Ref. [15]. *** We would like to dedicate this paper to Prof. Dr. E. Röder, Bonn, on the occasion of his 65th birthday

Results and Discussion

The starting material adamantane-1-carboxylic acid hydrazide **1** was prepared from the corresponding carboxylic acid following the previously described procedure [16]. Treatment of **1** with certain alkyl or arylisothiocyanates in ethanol yielded the corresponding 1-(1-adamantylcarbonyl)-4-substituted thiosemicarbazides **2a–f** [12, 17]. Several procedures were reported for the dehydrative cyclization of substituted thiosemicarbazides to their 1,3,4-thiadiazole analogs utilizing a variety of dehydrating agents, e.g. sulphuric acid, phosphorus oxychloride, or polyphosphoric acid [13, 17, 18]. Accordingly, treatment of compounds **2a–e** with sulphuric acid at ambient temperature for 24 hours yielded the corresponding 2-(1-adamantyl)-5-substituted amino-1,3,4-thiadiazoles **3a–e** in good yield (66%) in case of compounds **3a, b** and moderate yields (51–55%) in case of compounds **3c–e**. Relatively higher yields (65–68%) of compounds **3c–d** were obtained on carrying out the cyclization by heating with phosphorus oxychloride. The lower yields of compounds **3c–e** in case of cyclization with sulphuric acid may be attributed to partial aromatic ring sulphonation as previously reported [19] (Scheme 1).

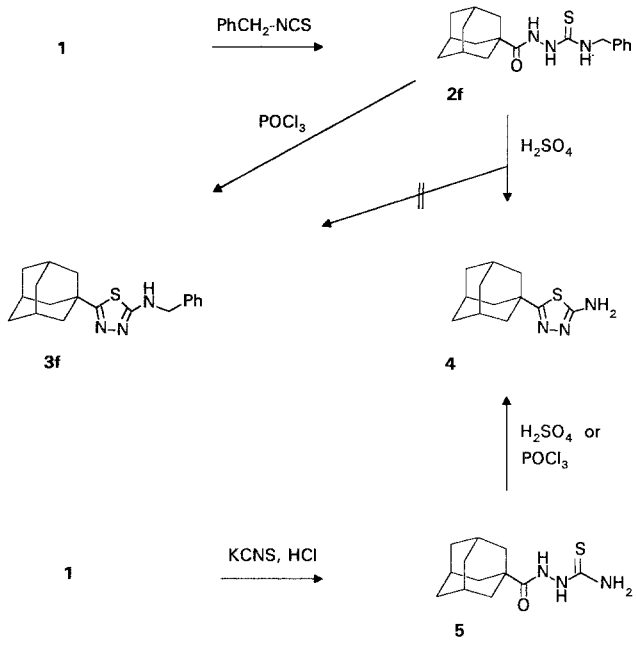


Scheme 1

Attempted cyclization of 1-(1-adamantylcarbonyl)-4-benzylthiosemicarbazide **2f** by the action of sulphuric acid did not yield the target compound **3f**; the debenzylated product 2-(1-adamantyl)-5-amino-1,3,4-thiadiazole **4** was obtained instead. On the other hand, cyclization of **2f** using phosphorus oxychloride yielded the target product **3f** (Scheme 2). The structure of the debenzylated product **4** was based on the ^{1}H NMR spectrum lacking the aromatic protons, the mass spectrum and on the elemental analysis.

A further confirmation of the structure of debenzylated product **4** was based on an independent synthesis *via* the reaction of **1** with potassium thiocyanate and hydrochloric acid to yield 1-(1-adamantylcarbonyl)thiosemicarbazide **5** [12], and subsequent cyclization with either sulphuric acid or phosphorus oxychloride to yield **4** whose spectral and analytical data are identical with the product obtained by the action of sulphuric acid on **2f**.

Although the literature contains numerous reports on the cleavage of the NH-benzyl bond under the influence of various reagents, to our knowledge,



Scheme 2

debenzylation by the action of sulphuric acid at ambient temperature is unusual and previously unreported. The cleavage of the NH-benzyl bond has been reported to take place usually by catalytic hydrogenation with Pd-C [20], by the action of sodium or lithium and ammonia [21, 22], *tert*-butyl lithium in *THF* [23], aqueous HBr [24], 95% formic acid [25], phenol and orthophosphoric acid [26], and trifluoroacetic acid [27, 28].

Experimental Part

Melting points (°C, uncorrected) were recorded on a Gallenkamp melting point apparatus. ^{1}H NMR spectra were carried out on a Bruker WH 90 (90 MHz) instrument using *TMS* as an internal standard (chemical shifts in δ, ppm). Mass spectra were obtained on a Kratos MS50 instrument at 70 eV. Analytical data (C, H, N) were within $\pm 0.4\%$ of the theoretical values.

1-(1-Adamantylcarbonyl)-4-substituted thiosemicarbazides **2a–f** [12, 17]

The appropriate alkyl or arylisothiocyanate (0.01 mol) was added to a solution of adamantane-1-carboxylic acid hydrazide **1** (1.9 g, 0.01 mol) in ethanol (30 ml) and the mixture was heated under reflux for 1 h. On cooling, the precipitated solid was filtered, washed with ethanol and dried. The products were pure enough to be used in the next step without further purification.

2-(1-Adamantyl)-5-substituted amino-1,3,4-thiadiazoles **3a–e**

Method A: Concentrated sulphuric acid (15 ml) was added dropwise to the appropriate thiosemicarbazide **2a–e** (0.005 mol) and the mixture was stirred at ambient temperature for 24 h. The mixture was then poured into crushed ice (100 g) and the separated solid (in case of compounds **3c–e**) was filtered, washed with dilute ammonium hydroxide solution and water, dried and crystallized from

ethanol. In case of compounds **3a, b** the products were not precipitated upon addition to crushed ice and it was necessary to neutralize the mixture with ammonium hydroxide solution where the products were precipitated, washed with water, dried and crystallized from aqueous ethanol. Yields: **3a, b**: 66%, **3c**: 51%, **3d, e**: 55%.

Method B: Phosphorus oxychloride (15 ml) was added to the appropriate thiosemicarbazide **2a–e** (0.005 mol) and the mixture was heated under reflux for 2 h. The mixture was then evaporated *in vavuo* and the residue was washed with dilute ammonium hydroxide solution and water, dried and crystallized from aqueous ethanol (**3a, b**) or ethanol (**3c–e**). Yields: **3a, b**: 68%, **3c**: 66%, **3d**: 68%, **3e**: 65%.
3a: m.p.: 168–70 °C; $C_{13}H_{19}N_3S$ (249.36); ^{1}H NMR ($CDCl_3$): $\delta = 1.80$ (s, 6H, Adamantyl-H), 2.05 (s, 9H, Adamantyl-H), 3.05 (s, 3H, CH_3), 5.30 (s, 1H, NH, D_2O-exchang.); MS, *m/z* (Rel. Int.): 251 ($M^+ + 2$, 6.1), 250 ($M^+ + 1$, 16.5), 249 (M^+, 100), 234 (3.1), 192 (12.8), 135 (13.6), 88 (27.1).
3b: m.p.: 158–60 °C; $C_{14}H_{21}N_3S$ (263.39); ^{1}H NMR ($CDCl_3$): $\delta = 1.20$–1.40 (t, 3H, CH_3), 1.75 (s, 6H, Adamantyl-H), 2.15 (s, 9H, Adamantyl-H), 3.20–3.50 (q, 2H, CH_2CH_3), 5.35 (s, 1H, NH, D_2O-exhang.).
3c: m.p.: 247–9 °C; $C_{18}H_{20}FN_3S$ (329.42); ^{1}H NMR (*DMSO*-d_6): $\delta = 1.75$ (s, 6H, Adamantyl-H), 2.0 (s, 9H, Adamantyl-H), 7.05–7.30 (m, 2H, *Ar*-H), 7.50–7.75 (m, 2H, *Ar*-H), 10.25 (s, 1H, NH, D_2O-exhang.).
3d: m.p.: 265–7 °C; $C_{18}H_{20}ClN_3S$ (345.88); ^{1}H NMR (*DMSO*-d_6): $\delta = 1.70$ (s, 6H, Adamantyl-H), 2.05 (s, 9H, Adamantyl-H), 7.25–7.45 (d, 2H, *Ar*-H), 7.60–7.75 (d, 2H, *Ar*-H), 10.30 (s, 1H, NH, D_2O-exchang.).
3e: m.p.: 263–5 °C; $C_{18}H_{20}BrN_3S$ (390.33); ^{1}H NMR (*DMSO*-d_6): $\delta = 1.75$ (s, 6H, Adamantyl-H), 2.05 (s, 9H, Adamantyl-H), 7.35–7.65 (m, 4H, *Ar*-H), 10.35 (s, 1H, NH, D_2O-exchang.).

2-(1-Adamantyl)-5-benzylamino-1,3,4-thiadiazole **3f**

A mixture of **2f** (1.7 g, 0.005 mol) and phosphorus oxychloride (15 ml) was heated under reflux for 2 h and treated as given for compounds **3a–e** (*method B*). Yield: 61%; m.p. (aqueous ethanol): 185–7 °C; $C_{19}H_{23}N_3S$ (325.45); ^{1}H NMR ($CDCl_3$): $\delta = 1.70$ (s, 6H, Adamantyl-H), 2.0 (s, 9H, Adamantyl-H), 4.50 (s, 2H, $C_6H_5CH_2$), 4.65 (br. s, 1H, NH, D_2O-exchang.), 7.35 (s, 5H, Ar-H); MS, *m/z* (Rel. Int.): 326 ($M^+ + 1$, 25.3), 325 (M^+, 100), 324 (48.1), 248 (1.1), 164 (8.2), 135 (13.3), 106 (16.1), 91 (35.8).

2-(1-Adamantyl)-5-amino-1,3,4-thiadiazole **4**

Method A (Debenzylation): Concentrated sulphuric acid (15 ml) was added dropwise to compound **2f** (1.7 g, 0.005 mol) and the mixture was stirred at ambient temperature for 24 h. The mixture was then poured into crushed ice (100 g), neutralized with ammonium hydroxide solution and the precipitated solid was filtered, washed with water, dried and crystallized from aqueous ethanol. Yield: 48%; m.p.: 201–3 °C; $C_{12}H_{17}N_3S$ (235.34); ^{1}H NMR ($CDCl_3$): $\delta = 1.80$ (s, 6H, Adamantyl-H), 2.10 (s, 9H, Adamantyl-H), 5.30 (br. s, 2H, NH_2, D_2O-exchang.); MS, *m/z* (Rel. Int.): 236 ($M^+ + 1$, 17.3), 235 (100), 178 (14.7), 135 (16.3), 102 (3.9).

Method B: A suspension of compound **1** (1.9 g, 0.01 mol), potassium thiocyanate (1.9 g, 0.02 mol) and hydrochloric acid (10 ml) in water (50 ml) was heated under reflux for 2 h. On cooling, the separated solid was filtered, washed with water, dried and crystallized from ethanol to yield compound **5**. m.p.: 172–4 °C [12]; yield 75%. Treatment of compound **5** with sulphuric acid or phosphorus oxychloride as mentioned under compounds **3a–e** (*methods A* and *B*, respectively) yielded compound **4** whose physical and spectral data were identical with the product obtained by the action of sulphuric acid on compound **2f**.

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