# New Acylthiosemicarbazides, Thiazolidinones, and 1,3,4-Oxadiazoles as Possible Anticonvulsants

## Neue Acylthiosemicarbazide, Thiazolidinone und 1,3,4-Oxadiazole mit möglicher antikonvulsiver Wirkung

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Thiazolidinone derivatives have various pharmacological activities such as anesthetic, anticonvulsant, and hypnotic[1]. Several imidazo[1,2-*a*]pyridines exhibit antiinflammatory, analgesic, antipyretic, and antiulcerative action[2].

As a continuation of our programme concerning heterocyclic pharmaceuticals, we synthesized some new thiosemicarbazides and 4-thiazolidinones incorporating a 2-methylimidazo[1,2-*a*]pyridine substituent to screen their anticonvulsant activity.

Ethyl 2-methylimidazo[1,2-*a*]pyridine-3-carboxylate (**1**)[3] reacted with hydrazine hydrate to give the hydrazide **2**[4]. The reaction of appropriate alkyl or arylisothiocyanates with **2** yielded the 1-acylthiosemicarbazide derivatives **3a-g**.

**3a-e** on treatment with ethyl bromoacetate and sodium acetate gave the desired thiazolidinones **4a-e**. Our attempts to prepare the 3-arylsubstituted derivatives of the thiazolidinone from **3f** and **3g** failed and instead 1,3,4-oxadiazoles **5a,b** were obtained (Scheme).

After the reaction with ethyl bromoacetate the products displayed only an additional 2H-singlet at about 4.13-4.07 ppm which proved ring closure in **4a-e**.

The products of **3f** and **3g** were assigned the structure 2-(2-methylimidazo[1,2-*a*]pyridine-3-yl)-5-arylamino-1,3,4-oxadiazole, **5a,b**.

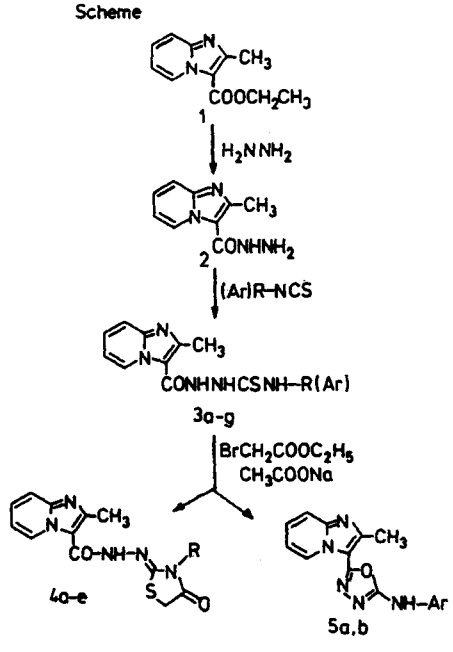
1-Acyl-4-arylthiosemicarbazides undergo desulfuration to afford 1,3,4-oxadiazoles with $I_2$/KI in the presence of NaOH[5]. *N*-aryl groups are likely to be less nucleophilic than *N*-alkyl ones. It seems most likely that after the formation of the *S*-alkyl intermediate the carbonyl group attacks the carbon bearing the S atom and makes the *S*-R group the leaving group affording ring closure. **5a,b** are the amino tautomers (NH, 10.6 ppm). The absence of CO bands in the IR spectra also supports the 1,3,4-oxadiazole structure. Chemical shifts of the protons of the imidazo[1,2-*a*]pyridine ring were in the order of H-5>H-8>H-7>H-6.

All the compounds except **3f,g** exhibit $M^{+\cdot}$ ions of different intensities. Spectral data of representative derivatives are given in the Experimental Part.

### *Anticonvulsant activity*

**2,3a,c,f,g,4a,c,d** and **5b** were tested for anticonvulsant activity at the National Institutes of Health, Division of Convulsive, Developmental and Neuromuscular Disorders, Bethesda, Maryland, USA, but no significant activity was observed.

Scheme




## Experimental Part

M.p.'s:Büchi (Model Tottoli) apparatus, uncorrected. -Elemental analysis: Perkin Elmer 240, values within ±0.4% of calculated values. -IR spectra: Perkin Elmer 577 or Shimadzu spectrophotometer (KBr). -$^1$H-NMR: Bruker AC 300 MHz, DMSO-$d_6$.

*2-Methylimidazo[1,2-a]pyridine-3-carbohydrazide (2)*[4]

0.01 mol of **1** was refluxed with 0.1 mol of $H_2NNH_2 \cdot H_2O$ in 15 ml of EtOH (96%) for 5 h and cooled. The crystals were washed with $H_2O$ and recrystallized from EtOH (96%), m.p. 185 °C, yield 80%.

*1-[(2-Methylimidazo[1,2-a]pyridine-3-yl)carbonyl]-4-alkyl/arylthiosemicarbazides 3a-g*

0.01 mol of **2**, 0.01 mol of the appropriate isothiocyanate and 15 ml of absol. EtOH were refluxed for 3 h. The solid that separated was filtered and recrystallized from EtOH (96%). - **3a**: IR: 3456;3308;3169 (NH),

  0365-6233/92/0808-623 $ 3.50 + .25/0

**Table**

| Compounds | R/Ar | Mp. [°C] | Yield [%] | Formula (molecular mass) | Analysis(calcd./found) C | H | N | MS(CI,$CH_4$) (rel.int.%) |
|---|---|---|---|---|---|---|---|---|
| 3a | $CH_3$ | 222 | 91 | $C_{11}H_{13}N_5OS.H_2O$ (263.3) | 46.7<br>46.9 | 5.4<br>5.2 | 24.8<br>24.7 | 264($MH^+$,68) |
| 3b | $C_2H_5$ | 215 | 97 | $C_{12}H_{15}N_5OS$ (277.4) | 52.0<br>52.1 | 5.5<br>5.6 | 25.3<br>25.7 | 277[a] ($M^{+\cdot}$,73) |
| 3c | $C_3H_5$ | 180-182 | 95 | $C_{13}H_{15}N_5OS.H_2O$ (289.4) | 50.8<br>50.8 | 5.6<br>5.5 | 22.8<br>22.8 | 289[a] ($M^{+\cdot}$,2) |
| 3d | $C_3H_7$ | 105-108 | 90 | $C_{13}H_{17}N_5OS$ (291.4) | 53.4<br>53.3 | 6.9<br>6.8 | 20.8<br>21.2 | 292($MH^+$,48) |
| 3e | $C_4H_9$ | 92-95 | 99 | $C_{14}H_{19}N_5OS.1.5H_2O$ (305.4) | 50.6<br>50.3 | 6.7<br>6.3 | 21.1<br>20.8 | 305[a] ($M^{+\cdot}$,12) |
| 3f | $C_6H_5$ | 220 | 96 | $C_{16}H_{15}N_5OS$ (325.4) | 59.1<br>58.5 | 4.6<br>4.6 | 21.5<br>21.8 | $MH^+$ (not observed) |
| 3g | $C_6H_4CH_3$(p) | 207 | 99 | $C_{17}H_{17}N_5OS$ (339.4) | 60.2<br>59.8 | 5.0<br>5.0 | 20.6<br>20.9 | $MH^+$ (not observed) |
| 4a | $CH_3$ | 216-218 | 81 | $C_{13}H_{13}N_5O_2S$ (303.3) | 47.3<br>47.7 | 4.9<br>4.7 | 21.2<br>21.4 | 304($MH^+$,63) |
| 4b | $C_2H_5$ | 207-209 | 57 | $C_{14}H_{15}N_5O_2S.H_2O$ (317.4) | 50.1<br>50.1 | 5.1<br>5.3 | 20.9<br>20.6 | 318($MH^+$,100) |
| 4c | $C_3H_5$ | 210-213 | 74 | $C_{15}H_{15}N_5O_2S$ (329.4) | 54.6<br>54.4 | 4.6<br>4.7 | 21.3<br>21.2 | 330($MH^+$,66) |
| 4d | $C_3H_7$ | 203-205 | 41 | $C_{15}H_{17}N_5O_2S$ (331.4) | 54.4<br>54.5 | 5.2<br>5.3 | 21.1<br>21.2 | 332($MH^+$,57) |
| 4e | $C_4H_9$ | 192 | 71 | $C_{16}H_{17}N_5O_2S$ (345.4) | 55.6<br>55.9 | 5.5<br>5.8 | 20.3<br>20.2 | 346($MH^+$,100) |
| 5a | $C_6H_5$ | 250 | 82 | $C_{16}H_{13}N_5O$ (291.3) | 66.0<br>66.4 | 4.5<br>4.7 | 24.0<br>23.8 | 292($MH^+$,100) |
| 5b | $C_6H_4CH_3$(p) | 115 | 88 | $C_{17}H_{15}N_5O$ (305.4) | 67.9<br>67.3 | 5.0<br>5.1 | 22.9<br>22.9 | 306($MH^+$,100) |

[a] $M^{+\cdot}$, obtained by EI (70 eV)

1649 (CO) $cm^{-1}$. -$^1$H-NMR: (δ ppm) = 9.61 (1H,s,$N^1$H), 9.37 (1H,s,$N^2$H), 8.99 (1H,d,J = 6.9 Hz, H-5), 8.08 (1H,q,J = 4.2 Hz, $N^4$H), 7.60 (1H,d,J = 7 Hz, H-8), 7.43 (1H,t,J = 7 Hz, H-7), 7.06 (1H,t,J = 6.9 Hz, H-6), 2.90 (3H,d,J = 4.5 Hz, $CH_3$), 2.63 (3H,s,C-2-$CH_3$).

*2-[(2-Methylimidazo[1,2-a]pyridine-3-yl)carbonyl]hydrazono-3-alkylthiazolidin-4-one* ***4a-e***

0.01 mol of the appropriate thiosemicarbazide **3a-e** and 0.011 mol of ethyl bromoacetate were refluxed in 30 mol of absol. EtOH in the presence of 0.04 mol of anhydrous $CH_3COONa$ for 2-4 h. After 15 h the crystalline product was washed with $H_2O$ and recrystallized from EtOH. - **4a**: IR:3530; 3408 (NH), 1712; 1635 (CO) $cm^{-1}$. - $^1$H-NMR:(δ ppm) = 10.36 (1H,s, NH), 8.96 (1H,d,J = 6.9 Hz, H-5), 7.60 (1H,d,J = 8.9 Hz, H-8), 7.40 (1H,t,J = 6.9 Hz, H-7), 7.05 (1H,t,J = 6.9 Hz, H-6), 4.07 (2H,s,$CH_2$), 3.17 (3H,s,$CH_3$), 2.62 (3H,s, C-2-$CH_3$).

*2-(2-Methylimidazo[1,2-a]pyridine-3-yl)-5-arylamino-1,3,4-oxadiazole* ***5a,b***

**5a,b** were obtained from **3f,3g** as described for **4a-e**. **5a**: IR: 3408 (NH) $cm^{-1}$. -$^1$H-NMR: (δ ppm) = 10.6 (1H,s,NH), 9.23 (1H,d,J = 6.9 Hz, H-5) 7.72-7.06 (7H,m, phenyl, H-8 and H-7), 7.03 (1H,t,J = 7.3 Hz, H-6), 2.69 (3H,s, C-2-$CH_3$).

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