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# Synthesis, psychotropic and anticancer activity of 2,2-dimethyl-5-[5′-trialkylgermyl(silyl)-2′-hetarylidene]-1,3-dioxane-4,6-diones and their analogues

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**A series of 2,2-dimethyl-5-(5′-R-hetarylidene)-1,3-dioxane-4,6-diones has been synthesized for examing a structure–activity relationship. Furyl and thienyl derivatives of Meldrum's acid possess neurotropic activity comprising both depriming and activating components. Comparison of acute toxicity of carbon, silicon and germanium analogues in the furan series of the compounds has demonstrated that the germanium derivative is 11.5 times less toxic than the carbon analogue and four times less toxic than the silicon derivative. 2,2-Dimethyl-5-(5′-triethylsilyl-2′-thenylidene)-1,3-dioxane-4,6-dione has moderate toxicity with the highest neurotropic and cytotoxic activity Copyright © 2003 John Wiley & Sons, Ltd.**

**KEYWORDS:** 2,2-dimethyl-5-furfurylidene-1,3-dioxane-4,6-dione; 2,2-dimethyl-5-thenylidene-1,3-dioxane-4,6-dione; organogermanium compounds; organosilicon compounds; psychotropic activity; cytotoxicity; toxicity

## INTRODUCTION

Many heterocyclic derivatives of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) have been prepared and well studied from the synthetic and structural points of view,[1–18] whereas their biological properties have scarcely been investigated; only the antimicrobial properties of some nitrofuran derivatives have been reported.[6] On the other hand, compounds that have a multi-substituted heterocycle, like furan or thiophene, as their main framework have exhibited a broad spectrum of biological activity.[19] Their biological activity can be changed or improved by the introduction of an organo-silicon (-germanium) substituent, which increases the lipophilicity and may also change the metabolism of the compound. At the same time, the majority of organogermanium compounds are less toxic than the analogous organosilicon compounds.[20]

Thus, the main idea of the proposed investigation was the search for new effective anticancer and psychotropic substances in a series of heterocyclic compounds with an unsaturated substituent containing a carbonyl group and the determination of the influence of organosilicon and organogermanium substituents on the biological activity.

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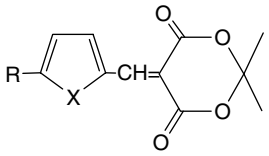
## RESULTS AND DISCUSSION

It is known that Meldrum's acid undergoes standard Knoevenagel condensation with aromatic and heteroaromatic aldehydes to yield the corresponding arylidene derivatives, which are versatile substrates for different kinds of reaction,[21] as well as being useful intermediates for cycloaddition reactions and for the synthesis of heterocyclic compounds with potential pharmacological activity.[22]

Silicon- and germanium-containing heterocyclic aldehydes have been regioselectively prepared by a one-pot procedure[23] from the corresponding furan- and thiophene-carbaldehydes using lithium *N*-methylpiperazide/butyllithium or *sec*-butyllithium/chlorotrialkyl-silanes or -germanes/water as the sequence of reagents. After blocking with a suitable aminolithium compound, the aldehyde function is regenerated by hydrolysis in neutral or weakly acid conditions. Mild

**Table 1.** Analytical data for




| Compound | R | X | M.p. (°C) | Molecular formula | Yield (%) | Anal. Found (Calc.) (%) C | H | S | $^1$H NMR ($\delta$, ppm; $J$, Hz) |
|---|---|---|---|---|---|---|---|---|---|
| **1** | H | O[8] | 90–91 | $C_{11}H_{10}O_5$ | 80 | 59.45 (59.45) | 4.55 (4.54) | — | 1.77 (6H, s, C–$CH_3$), 6.76 (1H, ddd, $H^4$), 7.86 (1H, ddd, $H^3$), 8.37 (1H, ddd, CH═), 8.48 (1H, ddd, $H^5$), $J_{3,4}$ 3.9, $J_{3,5}$ 0.7, $J_{4,5}$ 0.2, $J_{3\text{-CH=}}$ 1.6, $J_{4\text{-CH=}}$ 0.8, $J_{5\text{-CH=}}$ 1.4 |
| **2** | Me | O[8] | 99–100 | $C_{12}H_{12}O_5$ | 62 | 61.04 (61.01) | 5.11 (5.12) | — | 1.76 (6H, s, C–$CH_3$), 2.46–2.50 (3H, m, $CH_3$) 6.40–6.45 (1H, m, $H^4$), 8.29–8.3 (1H, m, CH═), 8.44–8.49 (1H, m, $H^3$), $J_{3,4}$3.8 |
| **3** | $Me_3C$ | O | 85–86 | $C_{15}H_{18}O_5$ | 54 | 64.76 (64.74) | 6.61 (6.52) | — | 1.27 (9H, s, C–$CH_3$), 1.73 (6H, s, C–$CH_3$), 6.31 (1H, d, $H^4$), 8.24 (1H, s, CH═), 8.40 (1H, d, $H^3$), $J_{3,4}$ 3.4 |
| **4** | $Me_3Si$ | O | 65–66 | $C_{14}H_{18}O_5Si$ | 52 | 57.10 (57.12) | 6.17 (6.17) | — | 0.35 (9H, s, Si–$CH_3$), 1.77 (6H, s, C–$CH_3$), 6.91 (1H, d, $H^3$), 8.42 (1H, d, $H^4$) 8.47 (1H, s, CH═), $J_{3,4}$ 3.7 |
| **5** | $Me_3Ge$ | O | 68–70 | $C_{14}H_{18}O_5Ge$ | 45 | 49.65 (49.62) | 5.34 (5.35) | — | 0.49 (9H, s, Ge–$CH_3$), 1.78 (6H, s, C–$CH_3$), 6.86 (1H, d, $H^3$), 8.43 (1H, s, CH═) 8.47 (1H, d, $H^4$), $J_{3,4}$ 3.8 |
| **6** | $Et_3$ Si | O | Oil | $C_{17}H_{24}O_5Si$ | 42 | — | — | — | 0.51–1.24 (15H, m, Si–$C_2H_5$), 1.74 (6H, s, C–$CH_3$), 6.91 (1H, dd, $H^3$), 8.43 (1H, dd, $H^4$) 8.46–8.50 (1H, m, CH═), $J_{3,4}$ 3.8, $J_{3\text{-CH=}}$ 0.9, $J_{4\text{-CH=}}$ 0.3 |
| **7** | $HOCH_2$ | O | 104–105 | $C_{12}H_{12}O_6$ | 72 | 57.23 (57.14) | 4.83 (4.80) | — | 1.67 (6H, s, C–$CH_3$), 2.44 (1H, bs, OH), 4.67 (2H, s, $CH_2$), 6.56 (1H, d, $H^4$), 8.18 (1H, s, CH═), 8.31 (1H, d, $H^3$), $J_{3,4}$ 3.9 |

**Table 1.** (*Continued*)

| Compound | R | X | M.p. (°C) | Molecular formula | Yield (%) | Anal. Found (Calc.) (%) | | | $^1$H NMR ($\delta$, ppm; $J$, Hz) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | S | |
| **8** | $O_2N$ | O[6,8] | 154–155 | $C_{11}H_9NO_7$ | 69 | 49.48 (49.45) | 3.35 (3.40) | 5.30 (5.24)[a] | 1.81 (6H, s, C–$CH_3$), 7.45 (1H, dd, $H^3$), 8.29 (1H, dd, CH═), 8.44 (1H, dd, $H^4$), $J_{3,4}$ 3.4, $J_{3\text{-CH}}$= 0.7, $J_{4\text{-CH}}$= 0.5 |
| **9** | H | S[11] | 187–188 | $C_{11}H_{10}O_4S$ | 80 | 55.29 (55.45) | 13.50 (13.46) | 4.07 (4.21) | 1.78 (6H, s, C–$CH_3$) 7.28 (1H, ddd, $H^4$), 7.92 (1H, ddd, $H^3$), 8.03 (1H, ddd, $H^5$), 8.68 (1H, ddd, CH═), $J_{3,4}$ 3.9, $J_{3,5}$ 1.3, $J_{4,5}$ 5.0, $J_{3\text{-CH}}$= 0.5, $J_{4\text{-CH}}$= 0.2, $J_{5\text{-CH}}$=1.1 |
| **10** | Me | S | 116–117 | $C_{12}H_{12}O_4S$ | 73 | 57.63 (57.13) | 12.94 (12.71) | 4.62 (4.79) | 1.76 (6H, s, C–$CH_3$), 2.64 (3H, dd, $CH_3$), 6.98 (1H, dq, $H^4$), 7.74 (1H, ddq, $H^3$) 8.56 (1H, d, CH═), $J_{3,4}$ 3.9, $J_{4-CH_3}$ 0.9, $J_{3\text{-}CH_3}$ 0.5, $J_{3\text{-CH}}$= 0.5 |
| **11** | Et | S[11] | 108–109 | $C_{13}H_{14}O_4S$ | 76 | 58.69 (58.63) | 5.33 (5.30) | 12.28 (12.04) | 1.39 (3H, t, $CH_3$), $J_{CH_3}$ 8.0, 1.76 (6H, s, C–$CH_3$), 2.94–3.02 (2H, m, $CH_2$), 7.02 (1H, dt, $H^4$), 7.76 (1H, dd, $H^3$), 8.57 (1H, d, CH═), $J_{3,4}$ 4.0, $J_{3\text{-CH}}$= 0.5, $J_{4\text{-}CH_2}$= 0.9 |
| **12** | *n*-Pr | S | 68–70 | $C_{14}H_{16}O_4S$ | 64 | 59.94 (59.98) | 5.79 (5.75) | 11.60 (11.43) | 1.01 (3H, t, $CH_3$), $J_{CH_3-CH_2}$ 7.5, 1.68–1.92 (2H, m, $CH_2$, 6H, m, C–$CH_3$), 2.88 (2H, dt, $CH_2$), $J_{CH_2-CH_2}$ 7.6 7.00 (1H, dt, $H^4$), 7.77 (1H, dd, $H^3$), 8.57 (1H, d, CH═) $J_{3,4}$ 3.9, $J_{4\text{-}CH_2}$ 0.8, $J_{3\text{-CH}}$= 0.55 |
| **13** | $Me_3Si$ | S | 100–101 | $C_{14}H_{18}O_4SSi$ | 65 | 54.17 (54.17) | 5.83 (5.84) | 10.21 (10.33) | 0.39 (9H, s, Si–$CH_3$), 1.77 (6H, s, C–$CH_3$), 7.37 (1H, d, $H^3$), 7.94 (1H, d, $H^4$) 8.65 (1H, s, CH═), $J_{3,4}$ 3.8 |

**Table 1.** (*Continued*)

| Compound | R | X | M.p. (°C) | Molecular formula | Yield (%) | Anal. Found (Calc.) (%) C | H | S | $^1$H NMR ($\delta$, ppm; $J$, Hz) |
|---|---|---|---|---|---|---|---|---|---|
| **14** | $Me_3Ge$ | S | 82–83 | $C_{14}H_{18}O_4GeS$ | 54 | 47.43 (47.37) | 5.08 (5.11) | 9.27 (9.03) | 0.53 (9H, s, Ge–$CH_3$), 1.77 (6H, s, C–$CH_3$), 7.32 (1H, dd, $H^3$), 7.92 (1H, d, $H^4$), 8.65 (1H, d, CH═), $J_{3,4}$ 3.8, $J_{3\text{-CH}=}$ 0.9 |
| **15** | $Et_3Si$ | S | 46–45 | $C_{17}H_{24}O_4SSi$ | 57 | 57.80 (57.92) | 6.97 (6.86) | 9.08 (9.10) | 0.91–1.02 (15H, m, Si–$C_2H_5$), 1.78 (6H, s, C–$CH_3$), 7.33 (1H, dd, $H^3$), 7.96 (1H, d, $H^4$) 8.67 (1H, d, CH═), $J_{3,4}$3.8, $J_{3\text{-CH}=}$ 0.6 |
| **16** | Cl | S | 116–117 | $C_{11}H_{10}O_4SCl$ | 74 | 48.54 (48.27) | 3.35 (3.68) | 11.58 (11.71) | 1.77 (6H, s, C–$CH_3$), 7.13 (1H, d, $H^4$), 7.37 (1H, s, CH═), 7.67 (1H, d, $H^3$), $J_{3,4}$4.3 |

[a] For nitrogen.

conditions for the hydrolysis are required to preserve the $R_3M$ (M = Si, Ge; R = Me, Et) group bound to the heterocycle.

In the case of 2-furaldehyde and 2-thiophenecarbaldehyde, this procedure gives regiospecifically the 5-metallated derivatives in good yield. The protection of the aldehyde function has been carried out by lithium *N*-methylpiperazide, but the lithium morpholide, also used for the preparation of 5-trimethylgermylfuran-2-carbaldehyde, gave the same result. In each case the only detectable impurity was the starting aldehyde, which is easily separated by chromatography on silica gel.

The synthesis of carbon analogues of these aldehydes having the t-butyl group at the furan and thiophene rings was rather difficult, because only a limited number of methodologies for the regioselective alkylation of these heterocycles are available. The target aldehyde was prepared in the following way: alkylation of furan by t-butanol[24] followed by subsequent metallation with *n*-butyllithium and formylation with dimethylformamide to give 5-t-butyl-2-furaldehyde in 43% yield.[25]

The aldehydes synthesized were involved in a condensation reaction with Meldrum's acid, giving the 2,2-dimethyl-5-(5′-R-hetarylidene)-1,3-dioxane-4,6-diones (**1**–**16**; Fig. 1). For the determination of the role of the silicon- and germanium-containing substituents in the heterocycle on the psychotropic and antitumour activity, we prepared silyl (**4**, **6**, **13**, **15**) and germyl (**5**, **14**) derivatives.

For the comparison of biological properties we have also synthesized a series of similar 1,3-dicarbonyl derivatives (**1**–**3**, **7**–**12**, **16**) with different organic substituents at the heterocycle

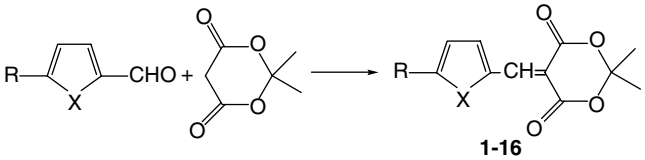



**Figure 1.** Condensation reaction of aldehydes with Meldrum's acid to give **1**–**16**: X = O, R = H (**1**), Me (**2**), $Me_3C$ (**3**), $Me_3Si$ (**4**), $Me_3Ge$ (**5**), $Et_3Si$ (**6**), $HOCH_2$ (**7**), $O_2N$ (**8**); X = S, R = H (**9**), Me (**10**), Et (**11**), *n*-Pr (**12**), $Me_3Si$ (**13**), $Me_3Ge$ (**14**), $Et_3Si$ (**15**), Cl (**16**).

(Me, Et, Pr, t-Bu, $HOCH_2$, Cl, $NO_2$). Yields, melting points, element analysis and $^1$H NMR data for the compounds synthesized are summarized in Table 1.

The experimental evaluations of the acute toxicity and neurotropic properties are presented in Tables 2 and 3. The compounds investigated have a wide range of biological activities. The toxicity depends strongly on the type of heterocycle and on the substituent at the heterocyclic ring. It has been shown that furan derivatives ($LD_{50}$ = 178–515 mg kg$^{-1}$) are more toxic than the thiophene analogues ($LD_{50}$ = 325–3550 mg kg$^{-1}$) (Table 2). The 5-trimethylgermyl derivative **5**, having acute toxicity $LD_{50}$ = 2050 mg kg$^{-1}$, is the sole exception. The introduction of a chlorine, *n*-propyl- or $R_3Si$(Me, Et)-substituent in position 5 of the thiophene ring increases the toxicity for the thiophene derivatives (Table 2). In the furan series, the influence of a silicon substituent is not expressed much in the case

**Table 2.** Acute toxicity and psychotropic activity of 2,2-dimethyl-5-(5′-R-hetarylidene)-1,3-dioxane-4,6-diones

| Compound | $LD_{50}$ (mg $kg^{-1}$) | $EC_{50}$ (mg $kg^{-1}$) | | | | |
|---|---|---|---|---|---|---|
| | | Rotating-rod | Tube | Traction | Hypothermia | Analgesia |
| **1** | 515 (362–692) | >250 | 51.5 (36.2–69.2) | >250 | 346 (120–562) | 224 (144–285) |
| **2** | 239 (124–383) | >200 | 141 (92–209) | >200 | 112 (64.8–163.9) | >200 |
| **3** | 178 (136–230) | 89 (63–120) | 56 (34–81) | 81 (57–111) | 65 (34–81) | 45 (31–60) |
| **4** | 447 (313–596) | 258 (168–357) | 224 (144–285) | >500 | 447 (413–596) | >500 |
| **5** | 2050 (1460–2880) | >500 | >500 | >500 | >500 | >500 |
| **6** | 224 (144–285) | >200 | >200 | >200 | 65 (44–89) | 103 (67–138) |
| **7** | 447 (313–596) | 205 (146–288) | 45 (31–60) | 45 (31–60) | 69 (24–130) | 45 (31–60) |
| **8** | 194 (119–273) | >100 | 118 (65–182) | 141 (117–183) | 108 (79–139) | 118 (65–181) |
| **9** | >2500 | >500 | 447 (313–596) | >500 | >500 | >500 |
| **10** | 3550 (2490–4610) | 447 (313–596) | 447 (313–596) | >500 | >500 | 224 (144–285) |
| **11** | 4100 (2680–5520) | 410 (268–552) | 300 (158–481) | 258 (145–431) | 346 (120–662) | 447 (413–596) |
| **12** | 410 (268–552) | 141 (68–209) | 89 (63.1–119.7) | 224 (144–285) | 205 (146–288) | >250 |
| **13** | 1200 (730–1910) | >500 | 244 (144–285) | >500 | 447 (313–596) | >500 |
| **15** | 1120 (790–1474) | >500 | 258 (145–404) | >500 | >500 | >500 |
| **16** | 325 (219–455) | >250 | 89 (67–113) | 154 (101–211) | 141 (117–183) | 97 (62–132) |

of the trimethylsilyl derivative (compound **4**), whereas the introduction of a triethylsilyl group (compound **6**) increases the toxicity by 2.3 times compared with the unsubstituted derivative **1**. The introduction of a trimethylgermyl group (compound **5**) decreases the toxicity by four times compared with the unsubstituted furan derivative **1**. 2,2-Dimethyl-5-(5′-t-butyl-2′-furfurylidene)-1,3-dioxane-4,6-dione (**3**) was the most toxic derivative in this series of compounds ($LD_{50}$ = 178 mg $kg^{-1}$). A comparison of the acute toxicity of the three analogues (carbon compound **3**, silicon compound **4** and germanium compound **5**) has demonstrated that the germanium analogue is 11.5 times less toxic than the carbon analogue and four times less toxic than the silicon derivative.

The effect of the synthesized compounds **1**–**13**, **15** and **16** on the locomotor coordination parameters and muscle tone is insignificant. Thus, compound **3** in rotating-rod, tube and traction tests had an $ED_{50}$ in the 56–89 mg $kg^{-1}$ range. Compound **7** was active in the tube and traction tests (45 mg $kg^{-1}$). The other compounds tested, in doses up to 200 mg $kg^{-1}$, do not entirely cause skeletal muscle relaxation and disturbance of locomotor coordination. Hypothermic action of the compounds synthesized is expressed for compounds **3** ,**6** and **7**; for other compounds it is expressed little and this is revealed in doses of more than 100 mg $kg^{-1}$. Derivatives **3**, **7** and **16** exhibit some analgesic activity in doses of 45–97 mg $kg^{-1}$ (Table 2).

Furan derivatives **2**–**4** and thiophene derivatives **13**, **15** and **16** prolong the life of animals under hypoxia by 25–63%. Concerning the action of the anaesthetic thiopental, it has been found that the silicon-containing thiophene derivatives **13** and **15** substantially increase the duration of anaesthesia by 276% and 238% respectively. The anaesthetic action of ethanol is increased (by 40–154%) under the influence of compounds **2**, **6**, **7**, **9** and **12**. Compounds **3**, **5**, **13**, **15** and **16** considerably reduce the duration of ethanol anaesthesia. It is interesting to note that some compounds have an opposite influence on the action caused by different anaesthetic agents. For example, compounds **8**, **13**, **15** and **16**

**Table 3.** Neurotropic activity of 2,2-dimethyl-5-(5′-R-hetarylidene)-1,3-dioxane-4,6-diones

| Compound | Activity (% of control) | | | | | Memory enhancement(s); RA (%) |
|---|---|---|---|---|---|---|
| | Hypoxia | Corazole spasms | Phenamine stereotype | Ethanol anaesthesia | Thiopental anaesthesia | |
| **1** | 112.5 | 224.5 | 212.3 | 108.4 | 130 | 128.5 ± 8.9; 83.3 |
| **2** | 129 | 83 | 104.5 | 183 | 103 | 136.7 ± 10.8; 100 |
| **3** | 147 | 133 | 107 | 64 | 84 | 55.8 ± 17.2; 20 |
| **4** | 124.8 | 140.5 | — | 117.2 | 160 | 24.1 ± 13.0; 66.7 |
| **5** | 91.7 | 205.1 | 44.5 | 83.5 | 79 | 75.2 ± 21.6; 50 |
| **6** | 112 | 120 | 69 | 254 | 128 | 154.8 ± 10.1; 100 |
| **7** | 104 | 134 | 60 | 204 | 108 | 166.2 ± 1.8; 100 |
| **8** | 132 | 120 | 27 | 60 | 133 | 133.6 ± 9.1; 83.3 |
| **9** | 109.1 | 102.5 | 98.3 | 166.7 | 113.8 | 152.5 ± 12.6; 100 |
| **10** | 100 | 102 | 115.4 | 117.3 | 128.5 | 61.6 ± 18.1; 33.3 |
| **11** | 103.6 | 99 | 148.7 | 92.8 | 114.5 | 120.2 ± 15.4; 83.3 |
| **12** | 101.1 | 158.5 | 52.8 | 139.7 | 161.3 | 94.2 ± 19.8; 66.7 |
| **13** | 163 | 183.4 | 104 | 83 | 376 | 88.2 ± 22.5; 66.7 |
| **15** | 156 | 159.2 | 68.6 | 90 | 338 | 57.8 ± 12.4; 16.7 |
| **16** | 134 | 166.7 | 252 | 70 | 180 | 144.5 ± 3.4; 100 |

shorten (by 10–40%) the duration of ethanol anaesthesia and, at the same time, substantially prolong (by 33–276%) the action of thiopental (Table 3). For the duration of phenamine stereotype behaviour, the compounds examined, in both the furan and thiophene series, showed different potencies. Compounds **5**–**8**, **12** and **15** decreased the duration of phenamine stereotype behaviour by 31–73%, whereas 2,2-dimethyl-5-(2′-furfurylidene)-1,3-dioxane-4,6-dione (**1**) and 2,2-dimethyl-5-(5′-chloro-2′-thenylidene)-1,3-dioxane-4,6-dione (**16**) were the strongest phenamine potentiators (Table 3).

All Meldrum's acid derivatives tested, except **2** and **9**–**11**, possess anti-Corazole activity, with the germanium derivative **5** being more active than the silicon analogue **4**.

Furan and thiophene derivatives of Meldrum's acid enhance, to some extent, memory processes and decrease the degree of retrogradal amnesia (RA) induced by maximal electric shock (Table 3). Compounds **2**, **6**, **7**, **9** and **16** completely prevented animals from RA caused by electric shock (RA 100%) and considerably increased the difference in latent periods $\Delta t$ for passage from a darkened chamber after 24 h from 24 to 166 s.

Some regularities have been observed in the furan series of Meldrum's acid derivatives. Carbon derivative **3** is more active than the silicon and germanium analogues **4** and **5** against hypoxia, but the germanium derivative **5** exhibited higher anti-Corazol activity than the silicon and carbon analogues (Table 3).

Thus, furyl and thienyl derivatives of Meldrum's acid possess neurotropic activities comprising both depriming and activating components. 2,2-Dimethyl-5-(5′-triethylsilyl-2′-thenylidene)-1,3-dioxane-4,6-dione (**15**) has a moderate toxicity with the highest neurotropic activity.

The antitumour activity has been studied *in vitro* on two monolayer tumour cell lines: HT-1080 (human fibrosarcoma) and MG-22A (mouse hepatoma). The experimental evalution of cytotoxicity is presented in Table 4. The 2,2-dimethyl-5-(5′-trimethylgermyl-2′-thenylidene)-1,3-dioxane-4,6-dione (**14**) exhibited the highest antitumour activity on mouse hepatoma MG-22A. The silicon derivative **15** possesses good antitumour activity and NO-induction ability. It has the highest cytotoxic effect on HT-1080 (human fibrosarcoma) cell line and high NO-generation activity (400%). The triethylsilyl derivative **15** was also remarkably active on melanoma B16 cells: $IC_{50}$ 0.2 μg ml$^{-1}$ (crystal violet, CV), 2 μg ml$^{-1}$ (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, MTT), NO 150%.

## EXPERIMENTAL

### 2,2-Dimethyl-5-(5′-trimethylgermyl-2′-furfurylidene)-1,3-dioxane-4,6-dione (5)

A mixture of Meldrum's acid (4.25 mmol) and 5-trimethylgermyl-2-furfural (4.5 mmol) in dry benzene (8 ml) with 0.02 ml of dry piperidine and 0.06 ml $CH_3COOH$ was stirred at 95 °C for 2 h. After cooling to 5 °C, the solid product (0.65 g, 45%) was filtered off. The purification from traces of the starting aldehyde was performed by crystallization from petroleum ether. Melting point, element analysis and $^1$H NMR data are summarized in Table 1. Compounds **1**–**4** and **6**–**16** were synthesized analogously. After recrystallization, the compounds had the properties shown in Table 1.

$^1$H NMR spectra were obtained on a Varian 200 (200 MHz) spectrometer with $CDCl_3$ as solvent and tetramethylsilane

**Table 4.** Anticancer activity of 2,2-dimethyl-5-(5′-R-hetarylidene)-1,3-dioxane-4,6-diones[a]

| | HT-1080 | | | MG-22A | | |
|---|---|---|---|---|---|---|
| | $IC_{50}$ (μg $ml^{-1}$) | | | $IC_{50}$ (μg $ml^{-1}$) | | |
| Compound | CV | MTT | NO (%) | CV | MTT | NO (%) |
| **2** | nce | nce | 2 | nce | nce | 3 |
| **3** | 52 | 62 | 450 | 42 | 42 | 250 |
| **4** | 58 | 48 | 43 | 27 | 39 | 83 |
| **5** | nce | nce | 4 | ~10 | nce | 10 |
| **7** | 48 | 59 | 700 | 65 | 72 | 142 |
| **8** | 59 | 56 | 29 | 55 | 36 | 38 |
| **9** | nce | nce | 3 | nce | nce | 4 |
| **10** | nce | nce | 2 | nce | nce | 3 |
| **11** | 73 | 62 | 200 | 44 | 57 | 100 |
| **12** | 59 | 61 | 100 | 55 | 75 | 16 |
| **13** | 67 | 66 | 12 | nce | nce | 8 |
| **14** | 100 | 100 | 35 | 10 | 1 | 142 |
| **15** | 9 | 10 | 400 | 7 | 9 | 150 |
| **16** | 36 | 47 | 117 | 100 | nce | 15 |

[a] nce: no cytotoxic effect. $IC_{50}$ (μg $ml^{-1}$) providing 50% cell killing effect (CV: coloration; MTT: coloration); NO concentration (CV: coloration).

as internal standard. Melting points were determined on a Boetius melting point apparatus and are uncorrected.

## Psychotropic activity

The compounds synthesized were studied for neurotropic activity on BALB/c mice of both sexes weighing 18–23 g in the autumn season.[26] The room temperature was maintained within the limits $22 \pm 1.5\,^{\circ}C$. The trials were performed on groups of animals consisting of six individuals. The substances investigated were administrated at dosages of 5 mg $kg^{-1}$ in the form of dimethylsulfoxide solutions and were injected intraperitoneally 45 min before the test was set up. The control animals were injected in the abdominal cavity with the same volume of solvent. The acute toxicity was determined by intraperitoneal introduction of the substances investigated and by establishing the lethal dose ($LD_{50}$).

The experimental data were treated statistically. The mean $LD_{50}$ and $ED_{50}$ values were determined by a rapid method given in Ref. 27. Average values and standard deviations ($M \pm m$) were calculated to assess the average duration of the anaesthetic effect of the thiopental, ethanol and phenamine stereotype, the protective properties in the Corazol spasms and hypoxia, and the degree of hypothermia. The significance of differences between mean values was assessed by Student's criterion: differences were considered as significant at a probability level $p < 0.05$.

## Cytotoxicity *in vitro*

Monolayer tumour cell lines MG-22A (mouse hepatoma), HT-1080 (human fibrosarcoma) and B16 (mouse melanoma) were cultivated for 72 h in standard Dulbecco's modified Eagle's medium (Sigma) without an indicator and antibiotics.[28] After the ampoule was defrosted, no more than four passages were performed. The control cells and cells with test substances in the range of $(2–5) \times 10^4$ cell $ml^{-1}$ concentration (depending on line nature) were placed on separate 96-well plates. Solutions containing test compounds were diluted and added in wells to give the final concentrations of 50, 25, 12.5 and 6.25 μg $ml^{-1}$. Control cells were treated in the same manner only in the absence of test compounds. Plates were cultivated for 72 h. The quantity of surviving cells was determined using CV or MTT coloration, which was assayed by multiscan spectrophotometer. The quantity of living cells on the control plate was taken in calculations for 100%.[28,29] The concentration of NO was determined according to Ref. 29.

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