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# CHEMICAL MODIFICATION OF GROSSHEMIN IN THE LACTONE RING

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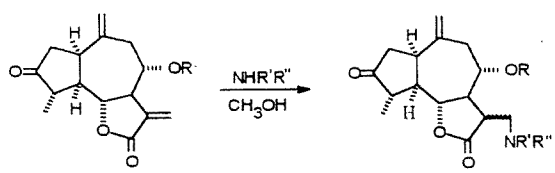
*Results are given on the antitumoral activity of grosshemin derivatives. A new grosshemin derivative has been obtained by the interaction of its acetate with hydroxylamine.*

Grosshemin (**1**) is a natural sesquiterpene lactone isolated from *Chartolepis intermedia* with a yield of 5.8% calculated on the sum of the extractive substances [1]. The presence in grosshemin (**1**) molecule of an exomethylene double bond conjugated with the lactone carbonyl is responsible for manifestation of reactivity in relation to nucleophilic reagents, especially nitrogen-containing reagents: ammonia, pyridine, morpholine, cyclohexylamine, and dimethylamine [2-4]. Many of these amino derivatives possess pronounced bactericidal and antitumoral activities and, moreover, they give water-soluble salts, which is of practical importance.

With the aim of finding new biologically active compounds in the grosshemin series, we have obtained a number of its amino derivatives (**3-6**), which have been studied for antitumoral activity. It was found that substances with maximum tolerable doses (MTDs) of from 50 to 150 mg/kg inhibit the growth of transplantable tumors in mice and rats. The highest antitumoral activity in relation to five types of tumoral strains was possessed by grosshemin acetate [**2**]. This compound inhibits the growth of sarcoma-45 by 71.1%, that of Walker's sarcoma by 82.1%, that of sarcoma M-1 by 89.4%, that of Pliss's lymphosarcoma by 36.0%, and that of P-388 leukemia (USPZh) by 92.1%.




1. R=H
2. R=Ac
3. R=Ac, R'=OH, R"=H
4. R=H, R'=R"=$CH_3$
5. R=H, R'=$CH_2$-$CH_2$-O-$CH_2$-$CH_3$
6. R=H, R'=H, R"= 

The 13-morpholine derivative of grosshemin (**5**) inhibited the growth of sarcoma-45 by 81.0%, that of sarcoma M-1 by 94.2%, and that of leukemia P-388 (USPZh) by 114.1% (Table 1). The 13-cyclohexylamino derivative of grosshemin (**6**) and the hydrochloride of the dimethylamino derivative of grosshemin (**4**) exhibited no high antitumoral activity.

On interacting with hydroxylamine, by a reaction analogous to Michael addition grosshemin acetate gave the corresponding hydroxylamino derivative (**3**).

The PMR spectrum of (**3**) lacked the signals characteristic for the exomethylene protons H13 and H13′ at the double bond, which showed addition of the hydroxylamine to the double bond conjugated with the lactone carbonyl.

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TABLE 1. Antitumoral Activities of Grosshemin and Its Derivatives

| Name of the sesquiterpene lactone and its derivatives | Dose, mg/kg | Inhibition of the growth of tumor strains, % | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Pliss's lymphosarcoma | Walker's carcinosarcoma | Guerin's carcinoma | Sarcoma 45 | Sarcoma M-1 | PC-1 alveolar cancer of the liver | Leukemia P-388 USPZh |
| Grosshemin | 70 | 68.6 | | 40.3 | 41.4 | 13.2 | 52.5 | 59.3 |
| 8-Acetylgrosshemin | 50 | 36.0 | 82.1 | | 71.1 | 89.4 | 48.0 | 92.1 |
| | 70 | 42.3 | | | 76.4 | | 51.3 | |
| 13-Morpholinogrosshemin | 50 | 41.0 | 24.0 | | 81.0 | 94.2 | 40.0 | 114.2 |
| | 70 | 46.3 | 32.1 | | | | | |
| 13-Cyclohexylaminogrosshemin | 50 | 34.0 | | 12.14 | 13.0 | 51.3 | 16.0 | 20.4 |
| Dimethylaminogrosshemin hydrochloride | 100 | 0.0 | 10.0 | | 25.0 | | 15.0 | |
| | 150 | 27.0 | 32.0 | | 27.0 | | 37.0 | |
| Dimethylaminoacetogrosshemin hydrochloride | 100 | 18.0 | 22.0 | | 16.0 | | 0.0 | |
| | 150 | 42.0 | 29.0 | | 34.0 | | 26.0 | |

TABLE 2. Physicochemical Characteristics of Grosshemin and Its Derivatives (2-6)

| Name of the lactone and its derivatives | Empirical formula | mp, °C | $[\alpha]_D$, degrees | Details of the PMR spectrum, 400 mHz, δ, $(CD_3)_2CO$ | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | H-13 | H-13′ | Me-4 | H-14 | H-6 | H-8 | other protons |
| Grosshemin (1) | $C_{15}H_{18}O_4$ | 200–202 | +159.9 (c 1.14; $CHCl_3$) 20°C | 6.18(1H, q) $J_1$=1, $J_2$=3, $J_3$=8 | 6.33(1H, q) $J_1$=1, $J_2$=3, $J_3$=8 | 1.15(3H, d) J=7 | 4.75(1H, s) 5.08(1H, s) | 4.08(1H, t) J=9.5 | 3.80 (1H, m) | |
| Grosshemin acetate (2) | $C_{17}H_{20}O_5$ | 163–164 | +122.7 (c 0.43; $(CH_3)_2CO$) | 5.85(1H, d) J=3 | 6.14(1H, d) J=3 | 1.17(3H, d) J=6 | 4.89(1H, s) 5.10(1H, s) | 4.27 (1H, dd) $J_1$=10, $J_2$=9 | 5.00 (1H, m) | |
| 8-Acetoxy-13-hydroxylamino-11,13-dihydrogrosshemin (3)* | $C_{17}H_{23}NO_6$ | 160–165 | – | 3.21 (1H, dd) $J_1$=12, $J_2$=2 | 3.08 m | 1.25(3H, d) J=7 | 4.80(1H, s) 5.07(1H, s) | 3.95(1H, t) J=8 | 4.88 (1H, td) $J_1$=5, $J_2$=9 | 2.08(3H, s) $CH_3CO$ 6.57 br.s) N–H 8.72 O–H br.s) |
| Dimethylamino-grosshemin hydrochloride (4) | $C_{17}H_{24}O_3$ | HCl 190–193 | +6.25 (c 0.1; $H_2O$) | 3.45 (1H, m) | 3.27 (1H, m) | 1.18(3H, d) J=6.5 | 4.70(1H, s) 5.06(1H, s) | 4.05(1H, t) J=9 | 3.87 (1H, m) | |
| 13-Morpholino-grosshemin (5) | $C_{19}H_{27}NO_5$ | 175–177 | +57 (c 0.43; $CHCl_3$) | 3.77(1H, br.s) | 3.92(1H, br.s) | 1.27(3H, d) J=6 Hz | 4.86(1H, br.s) 5.16(1H, br.s) | 3.86 (1H, m) | 3.86 (1H, m) | |
| 13-Cyclohexyl-aminogrosshemin (6) | $C_{21}H_{31}NO_4$ | 151–152 | +68.0 (c 0.6; $CHCl_3$) | 3.44 (1H, br.s) | 3.62 (1H, br.s) | 1.21(3H, d) J=6 | 4.76(1H, br.s) 5.06(1H br.s) | 4.01(1H, t) | 4.62 (1H, m) | |

*Solvent $CDCl_3$.

## EXPERIMENTAL

IR spectra were taken on a UR-20 spectrophotometer in KBr tablets, and PMR spectra on a Bruker instrument with a working frequency of 400 MHz using $CDCl_3$ and $(CD_3)_2CO$ as solvents.

The physicochemical constants and spectral characteristics of the compounds are given in Table 2.

Grosshemin (**1**) — $C_{15}H_{18}O_4$, mp 200-202°C, $[\alpha]_D^{20}$ +159.9° (*c* 1.14; $CDCl_3$) was isolated from *Chartolepis intermedia* Boiss. by a method described previously [1].

The amination of the α-methylene-γ-lactone was carried out at room temperature by the addition of a primary or secondary amine to a methanolic solution of grosshemin and its acetate followed by keeping the mixture at the same temperature for a day.

The course of the reaction was monitored by TLC in the ether system, the revealing agent being a saturated solution of $KMnO_4$. The reaction mixture was extracted with chloroform. The chloroform layer, which contained the desired substance, was separated off, dried over $MgSO_4$, and evaporated under vacuum, and the residue was chromatographed on a column of silica gel.

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