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SYNTHESIS AND ANTITUMOR PROPERTIES OF 10-HYDRAZINOCARBONYLMETHYL-4a,8:6,10-DIMETHANO-4,4a,5,6,7,8,9,10-OCTAHYDROPYRIDAZINO[4,3-e][1,3]DIAZOCIN-3(2*H*)-ONE[1]

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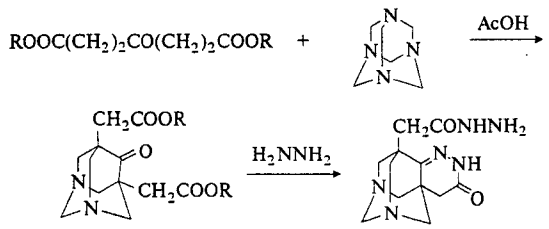
Of the possible heterocyclic compounds containing a heterocyclic ring fused to a 1,3-diazaadamantane system, only one derivative – 1,4,6,8,9,9a-hexahydro-9-phenylthio-3a,7:5,9-dimethano-pyrazolo[4,3-e][1,3]diazocine – has been reported [1]. However, no information is available about its biological activity.

We found that the reaction of 5,7-di(alkoxycarbonylmethyl)-6-oxo-1,3-diazaadamantanes (Ia, b) with hydrazine hydrate in an ethanol solution yields 10-hydrazinocarbonylmethyl-4a,8:6,10-dimethano-4,4a,5,6,7,8,9,10-octahydropyr idazino[4,3-e][1,3]diazocin-3(2*H*)-one (II). The starting 1,3-diazaadamantanes Ia,b were obtained by the reaction of corresponding dialkyl esters of 3-oxo-1,5-pentanedicarboxylic acid with hexamethylene tetramine in butanol in the presence of acetic acid, similarly to the reaction of dialkyl ketones with hexamethylene tetramine [2].



Ia: R=Et, Ib: R= *i*–Pr II

The structure of the compounds synthesized was determined by elemental analysis, IR, PMR, and mass spectra. The purity was confirmed by TLC.

The chemotherapeutic studies showed that diazaadamantane Ia was a slightly toxic compound (LD_{100} = 2500 mg/kg, MTD = 2000 mg/kg) and the synthesized compound pyridazinone II had LD_{100} > 5000 mg/kg.

According to the data given in Table 1, Ia exhibits weak activity with respect to sarcoma 45, stimulates the growth of sarcoma 180, and exerts no antitumor effect on Shvets leukemia. Pyridazinone II shows the highest activity against sarcoma 37 (in grafted tumors in mice) and inhibits the growth of tumor by 62% at a dose of 500 mg/kg with no visible toxic effects on the test animals. Compound II (500 mg/kg) exhibits weak antitumor activity with respect to sarcoma 180, thus suppressing tumor growth by 46% and prolonging the lifespan of the test mice with ascitic Ehrlich carcinoma by 28% ($\alpha > 98$) in comparison with the control. However, it has no therapeutic effect on sarcoma 45, Walker carcinosarcoma, Shvetz leukemia, and the solid form of Ehrlich carcinoma.

CHEMICAL EXPERIMENTAL PART

IR spectra were recorded using Vaseline oil on a Specord UR-20 (DDR) spectrophotometer. PMR spectra were obtained on a Varian T-60 (USA) spectrometer with TMS used as the internal standard. Mass spectra were recorded on an MKh-1320 spectrometer (USSR). TLC was performed on Silufol UV-254 (ChSFR) plates with a 10% ethanol solution of ninhydrin as a visualizing agent.

5,7-Di(ethoxycarbonylmethyl)-6-oxo-1,3-diazaadamantane (Ia). A mixture of diethyl ester of 3-oxo-1,5-pentanedicarboxylic acid (3.9 g, 17 mmole), hexamethyleneamine (2.45 g, 17 mmole), AcOH (2.4 g, 40 mmole), and 50 ml of butanol was refluxed for 10 h. The solvent was distilled off under vacuum, and the oily residue was extracted with benzene (3 × 50 ml). The extract was transferred through a layer of anhydrous aluminum oxide (5 g, activity II) placed on a

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TABLE 1. Antitumor Activity of Compounds Ia and II

Tumor strain	Diazaadamantane Ia			Pyridazinone II		
	Daily dose, mg/kg	*I*, %	K_g, %	Daily dose, mg/kg	*I*, %	K_g, %
Sarcoma 180	250	Stimulates		500	46	−1.7
Sarcoma 37	–	–	–	500	62	−0.3
Sarcoma 45	120	50	+9.9	250	0	–
Walker carcinosarcoma	–	–	–	250	0	–
Ascite Ehrlich carcinoma	–	–	–	500	28*	
Solid Ehrlich carcinoma	–	–	–	500	0	–
Shvets leukemia	120	23**	+10.9	250	0	–

* PLT, %.
** Unreliable.

Schott filter, and the solvent was distilled off under vacuum. The solid residue was recrystallized from hexane. The yield of Ia was 0.8 g (16%), m. p. 53.5 – 55°C, R_f = 0.57 (propanol – water, 7 : 3). IR (ν, cm^{-1}): 1690 (CO), 1725 (COOR). PMR ($CDCl_3$) (δ, ppm): 1.23 t (6H, CH_3, J = 7 Hz); 12.3 s (4H, CH_2); 3.34 d (4H_a, CH_2N, J = 13 Hz); 3.53 d (4H_e, CH_2N, J = 13 Hz); 4.01 s (2H, NCH_2N); 4.01 q (4H, CH_2CH_3, J = 7 Hz). MS, *m/z* (%): M^+ 324 (100), 296 (17.1), 281 (53.3), 251 (10), 211 (28.5), 208 (19). $C_{16}H_{24}N_2O_5$.

5,7-Di(isopropoxycarbonylmethyl-6-oxo-1,3-diazaadamantane (Ib). Ib was synthesized from diisopropyl ester of 3-oxo-1,5-pentanedicarboxylic acid (5.2 g, 17 mmole) by a procedure similar to that used for the Ia synthesis. The yield of Ib was 1.46 g (23.6%), m. p. 68 – 65°C, R_f = 0.58 (propanol – water, 7 : 3). PMR ($CDCl_3$) (δ, ppm): 1.23 d (12H, $(CH_3)_2CH$, J = 7 Hz); 2.3 s (4H, CH_2); 3.34 d (4H_a, CH_2N, J = 13 Hz); 3.53 d (4H_e, CH_2N, J = 13 Hz); 4.01 s (2H, NCH_2N); 5.0 d (2H, $CH(CH_3)_2$, J = 7 Hz). $C_{18}H_{28}N_2O_5$.

10-Hydrazinocarbonylmethyl-4a,8:6,10-dimethano-4,4a,5,6,7,8,9,10-octahydropyridazino[4,3-e][1,3]diazocin-3(2*H*)-one (II). To a solution of Ia (13 g, 40 mmole) or Ib (12.25 g, 40 mmole) in 60 ml of ethanol 85% hydrazine hydrate (30 ml, 510 mmole) was added; the mixture was heated in a water bath for 5 h. Then the solution was concentrated to 1/3 of the starting volume and cooled. The precipitate formed was filtered off and recrystallized from methanol. The yields of II were 7.0 g (62.8%) and 6.1 g (54.7%), respectively, m. p. 242 – 245°C, R_f = 0.28 (methanol – water, 1 : 1). IR spectrum (ν_{max}, cm^{-1}): 1640 (C=N), 1660 (CO), 3240, 3340 (NH). PMR (D_2O) (δ, ppm): 2.40 s (2H, CH_2), 2.43 s (2H, CH_2), 3.4 d (4H_a, CH_2N, J = 13 Hz), 3.34 d (4H_e, CH_2N, J = 13 Hz), 4.2 s (2H, NCH_2N). MS, *m/z* (%): M^+ 278 (73.4), 247 (100), 235 (24.5), 221 (36.7), 204 (36.7), 189 (28.5), 188 (42.8), 178 (34.7), 161 (22.4), 149 (10.5), 42 (40.8). $C_{12}H_{18}N_6O_2$.

The elemental analysis data for the obtained compounds match the calculated data.

BIOLOGICAL EXPERIMENTAL PART

The toxicity and antitumor activity of diazaadamantane Ia and pyridazinone II were examined in male and female white mongrel mice weighing 17 – 21 g and male and female rats weighing 90 – 120 g. The animals were kept in under conventional laboratory conditions on a basic mixed diet.

The toxicity (LD_{100}) and MTD of the compounds were determined in mice by intraperitoneal administration. The antitumor activity of the compounds was studied by the conventional procedure [3] in rats and mice grafted with the strains of the following tumors: sarcoma 180, 37, and 45, Walker carcinosarcoma, Shvets leukemia, and Ehrlich carcinosarcoma in the ascitic and solid forms. The substances were administered intraperitoneally to the test rats daily for 8 days and to the mice for 6 days in 1/20 and 1/10 LD_{100} doses, respectively after dissolution in an isotonic solution of sodium chloride. The therapeutic effect was estimated by the efficacy of the inhibition of growth (*I*, %) of solid tumors by mass, determined a day after the last administration of the compounds, or by the prolongation of the lifespan of the test mice with ascitic (PLT, %). The total toxic effect was evaluated by the growth coefficient (K_g, %).

The results of the experiments were statistically processed by the Student – Fisher method, and the data are reliable with ($\alpha \geq 0.95$).

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