SYNTHESIS AND ANTIVIRAL ACTIVITY OF ADAMANTYLOXIRANES AND THEIR DERIVATIVES

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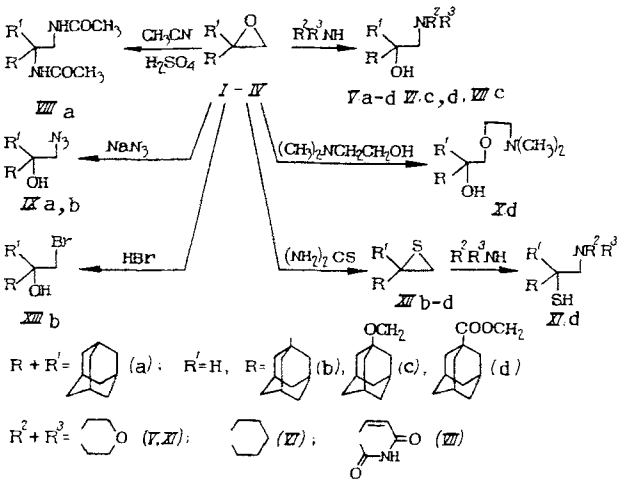
UDC 615.281.8:547.598.7].012.1.07

Adamantane derivatives have a wide spectrum of biological activity [5]. Adamantane amines – amantadine and remantadine [4] – are effective antiviral agents [4], but the mechanism of their antiviral action has not yet been satisfactorily clarified [2]. In searching for new adamantane compounds having virus-inhibiting action, we synthesized epoxy compounds based on adamantane and certain reaction products of the latter.

2-Adamantanespiroxirane (I) and the glycidyl ester of 1-adamantanecarboxylic acid (IV) were synthesized by methods described in [8] and [7], respectively. Unlike the method in [6], 2-(1-adamantyl)oxirane (II) was obtained by reduction of 1-adamantyl bromomethyl ketone with sodium borohydride, followed by dehydrobromination without isolation of the intermediate bromohydrin. 1-Adamantylglycidyl ether (III) was synthesized similarly as tertbutylglycidyl ether [3], but in a higher yield.

Oxiranes I, II react more slowly with secondary amines than do glycidyl ether III and glycidyl ester IV; the initial reaction rates of oxiranes I-IV with piperidine are equal to 0.0058, 0.018, 0.30 and 0.29 mmole/(liter·sec), respectively. The lower reactivity of oxiranes I and II with respect to nucleophilic reagents is probably due to steric, as well as electronic effects of the adamantane fragment on the oxirane ring. The least reactive is spirooxirane I, from which thiirane could not be obtained by reaction with thiourea. However, I can form a fairly stable carbocation, and despite the ease of rearrangement of I into an aldehyde [9], this carbocation is not able to rearrange completely under the Ritter reaction conditions, so that the corresponding diacetylamino derivative VIIIa could be obtained.



The composition and structure of the synthesized compounds were confirmed by data from elemental analysis, and IR and PMR spectroscopy (Tables 1 and 2).

EXPERIMENTAL (CHEMICAL)

The purity of the compounds obtained was monitored by chromatography on "Silufol UV-254" plates. The IR spectra were run on "Specord M-80" and IKS-22 spectrophotometers in a thin lay-

Kuibishev Polytechnical Institute. Belorussian Scientific Research Institute of Epidemiology and Microbiology, Minsk. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 24, No. 5, pp. 23-25, May, 1990. Original article submitted July 27, 1989.

0091-159X/90/2405-0339$12.50

TABLE 1. Derivatives of Adamantyloxiranes

Compound	Molar excess of the reagent	Time of reaction, h	Yield, %	mp, °C, (n_D^{20})	IR spectrum, cm^{-1}	Empirical formula
Va	10	50	51	238—9	3250, 2570, 1045	$C_{15}H_{26}ClNO_2$
Vb	10	3	53	268—75	3200, 2600, 1060	$C_{16}H_{28}ClNO_2$
Vc	2	0,5	42	148—9	3200, 2600, 1080	$C_{17}H_{30}ClNO_3$
Vd	2	0,5	89	208—10	3300, 2700, 1715, 1090	$C_{18}H_{30}ClNO_4$
VIc	2	0,5	63	156—7	3200, 2700, 1060	$C_{18}H_{32}ClNO_2$
VId	2	0,5	87	176—7	3200, 2650, 1705, 1070	$C_{19}H_{32}ClNO_3$
VIIc	—	5	30	(1,5165)	3400, 1700, 1660, 1090	$C_{17}H_{24}N_2O_4$
VIIIa	—	3	73	106—8	3250, 1675, 1540	$C_{15}H_{24}N_2O_2$
IXa	1,5	20	75	76—7	3300, 2120, 1080	$C_{11}H_{17}N_3O$
IXb	1,5	15	78	63—4	3400, 2110, 1070	$C_{12}H_{19}N_3O$
Xd	5	0,5	65	203—5	3350, 2550, 1720, 1080	$C_{18}H_{32}ClNO_4$
XId	5	1	56	61—3	2650, 1715, 1230, 1100	$C_{18}H_{30}ClNO_3S$
XIIb	5	0,5	28	(1,5470)	667, 620	$C_{12}H_{18}S$
XIId	5	0,5	93	(1,5250)	695, 685, 610	$C_{13}H_{20}OS$
XIId	5	0,5	89	36—7 (1,5320)	1725, 1230, 1080, 670, 610	$C_{14}H_{20}O_2S$
XIIIb	—	3,5	87	52—3	3300, 1090	$C_{12}H_{19}BrO$

TABLE 2. PMR Spectra of Synthesized Compounds

Compound	Chemical shifts, δ, ppp, SSCC, Hz
I	1,86(14H), 2,64(2H)
II	1,54(6H), 1,83(6H), 1,97(3H), 2,57—2,72(3H)
III	1,60(6H), 1,71(6H), 2,13(3H), 2,60(1H, J 5,6 and 1,6), 2,79(1H, J 5,6 and 4,0), 3,10(1H, m), 3,44(1H, J 10,4 and 4,8), 3,61(1H, J 10,4 4,0)
IV	1,71(6H), 1,92(9H), 2,64(1H, J 5,0 3,0), 2,83(1H, J 5,0 and 4,0), 3,18(1H, m), 3,90(1H, J 12,0 and 6,0), 4,40(1H, J 12,0 and 3,0)
Va	1,40—2,10(14H, m), 2,25—2,55(2H, m), 3,24(2H), 3,60—4,40(6H, m)
VIIIa	1,68(14H), 1,98(6H), 4,02(2H)
IXa	1,77(14H), 3,55(2H)
XIIb	1,55(6H), 1,69(6H), 2,00(3H), 2,36(2H, J 6,6), 2,84(1H, T, J 6,6)
XIIc	1,62(6H), 1,76(6H), 2,12(3H), 2,18(1H, J 4,5), 2,53(1H, J 5,4), 3,00(1H, m), 3,26(1H, J 10,0 and 7,2), 3,75(1H, J 10.0 and 4,8)
XIId	1,74(6H), 1,92(6H), 2,03(3H), 2,27(1H, J, 5,8), 2,53(1H, J 6,1), 3,10(1H, m), 4,14 (2H, J 6,4)
XIIIb	1,64(6H), 1,68(6H), 2,00(3H), 3,45(1H, J 10,1 and 6,2), 3,50(1H, J 10,1 and 1,5), 3,73(1H, J 6,2 and 1,5)

er and in KBr tablets. The PMR spectra were recorded on a "Bruker WP-80" spectrometer (80 MHz) in $CDCl_3$ and $(CD_3)_2SO$, using HMDS as an internal standard. The results of the elemental analysis correspond to the calculated values.

2-(1-Adamantyl)oxirane (II). A mixture of 25.7 g (0.10 mole) of 1-adamantyl bromomethyl ketone, 2 g (0.05 mole) of sodium borohydride, 50 ml of 2-propanol and 50 ml of a 0.5% solution of sodium hydroxide was stirred for 3 h at 20-25°C, and then for 30 min at 60-70°C. The alcoholic layer was separated, and 8 g (0.2 mole) of sodium hydroxide in 8 ml of water was added to it. The mixture was stirred for 1 h at 35-40°C for 1 h, and then poured into water. The product was extracted with hexane and purified by distillation at 88-89°C (20 mm Hg). Yield, 15.3 g (86%), n_D^{20} 1.5085, IR spectrum, cm^{-1}: 3040 (CH), 2998 (CH), 1248 (COC), 914 (COC), 856 (COC).

1-Adamantylglycidyl Ether (III). A 56 ml portion (0.72 g) of epichlorohydrin was added dropwise in the course of 1 h, with stirring and cooling, to a mixture of 90 g (0.59 mole) of 1-adamantanol, 300 ml of carbon tetrachloride and 4 ml of tin tetrachloride. The reaction mixture was boiled for 30 min, then cooled, washed with a 5% sodium hydroxide solution, and water, the solvent was evaporated, and the chlorohydrin ether was distilled at 160-165°C (10 mm Hg). The ether obtained was dissolved in 200 ml of 2-propanol, and to the solution obtained, a solution of 30 g (0.75 mole) of sodium hydroxide in 30 ml of water was added with stirring and cooling. The reaction mixture was diluted with water, the product was extracted with hexane and purified by distillation at 130-135°C (10 mm Hg). Yield, 75 g (61%), n_D^{20} 1.5092. IR spectrum, cm^{-1}: 3048 (CH), 2994 (CH), 1254 (COC), 898 (COC), 856 (COC), 840 (COC).

TABLE 3. Characteristics of the Antiviral Action of Adamantyloxiranes

Compound	Virus	"Screening test"		Method of reduction		CTI
		toxicity zone mm	suppression of plaque formation, mm	concentration, μg/ml	decrease in the virus titer, compared with control, mm log PFU/ml	
II	HSV	10	12	400	1,15	1
				200	0,65	
				100	0,21	
	CFP	12	20	400	⩾1,49	1
				200	0,71	
				100	0,89	
XIIIb	VSV	14	10	100	⩾1,61	1
				50	0,83	
				25	0,41	
IXa	VSV	0	12	400	⩾1,64	1
				200	0,44	
				100	0,24	
VIIc	SVV	12	10	50	⩾1,68	1
				25	0,53	
				12	0,19	
	VEE	10	10	50	1,34	1
				25	0,23	
				12	0,02	
Va	VEE	0	12	100	1,34	1
				50	0,02	
				25	0,09	
Vd	SVV	0	14	100	⩾1,68	4
				50	⩾1,68	
				25	1,68	
				12	0,42	
	CFP	0	20	100	⩾1,48	8—16
				50	⩾1,48	
				25	⩾1,48	
				12	1,18	
				6	1,18	
Vc	SVV	0	16	100	⩾1,68	2
				50	1,28	
				25	0,78	
	CFP	0	16	100	⩾1,48	1
				50	0,70	
				25	0,48	
Xd	SVV	12	12	50	⩾1,68	2
				25	⩾1,68	
				12	0,64	
Vb	HSV	12	14	50	1,22	1
				25	0,57	
	SVV	10	12	50	⩾1,68	2
				25	⩾1,68	
				12	0,40	
Vb	CFP	16	10	50	⩾1,48	2
				25	⩾1,48	
				12	0,70	
				6	0,93	
XId	SVV	0	18	50	⩾1,58	4
				25	⩾1,58	
				12	⩾1,58	
				6	0,28	
	VEE	8	12	50	⩾1,67	1
				25	0,19	
				12	0,02	

1,2-Aminoalcohols (Va-d, VIc, d, Xd). A mixture of 0.01 mole of oxirane, 0.02-0.10 mole of an amine or 2-(dimethylamino)ethanol and 5 ml of 2-propanol was boiled for 0.5-50 h. The reaction mixture was diluted with 50 ml of benzene, washed with water, and dried over calcium chloride, purged with dry hydrogen chloride, and the precipitate of the 1,2-aminoalcohol hydrochloride was filtered off. 1,2-Aminothiol XId was obtained in a similar way as the 1,2-aminoalcohols.

1-[3-(1-Adamantyloxy)-2-hydroxypropyl]uracil (VIIc). A mixture of 3 g (0.014 mole) of 1-adamantylglycidyl ether, 1 g (0.009 mole) of uracil, 1 ml of pyridine and 10 ml of 2-propanol was boiled for 5 h. The reaction mixture was diluted with 30 ml of benzene, washed with 5% sulfuric acid and water, and dried over calcium chloride. A 30 ml portion of heptane was added, the solution was clarified by activated carbon, the solvent was evaporated and 1 g (30%) of the product was obtained, R_f 0.52 (2-propanol).

1,2-Azidoalcohols (IXa, b). A mixture of 0.02 mole of oxirane, 2 g (0.03 mole) of sodium azide, 2 g (0.04 mole) of ammonium chloride and 20 ml of 2-propanol was boiled up to the cessation of the ammonia evolution (15-20 h). The reaction mixture was poured into water, the product was extracted with ether, and recrystallized from hexane.

Thiiranes (XIIb-d). A mixture of 0.01 mole of oxirane, 0.05 mole of thiourea and 10 ml of 2-propanol was boiled for 30 min (for III and IV) or 5 h (for II). The reaction mixture was diluted with water, extracted with hexane, the hexane solution was decolorized by activated carbon, and the solvent was evaporated.

2-Acetylamino-2-(acetylaminomethyl)adamantane (VIIIa). A solution of 3.2 g (0.02 mole) of 2-adamantylspiroxirane 1 in 10 ml of acetonitrile was added dropwise at 5-10°C to 25 ml of 94-96% sulfuric acid. The mixture was stirred for 3 h, poured onto ice and neutralized by sodium carbonate. The product was extracted from the solid residue with benzene and recrystallized from hexane. Yield, 3.2 g (73%)

1-(1-Hydroxy-2-bromoethyl)adamantane (XIIIb). A mixture of 25.7 g (0.10 mole) of 1-adamantyl bromomethyl ketone, 2 g (0.05 mole) of sodium borohydride, 50 ml of 2-propanol, and 50 ml of a 0.5% sodium hydroxide solution was stirred for 3 h at 20-25°C and then for 30 min at 60-70°C. The alcoholic layer was separated, evaporated under vacuum, and the residue was recrystallized from hexane. Yield, 22.5 g (87%) of the product. Bromohydrin XIIIb is also formed in the reaction of oxirane II with a 48% hydrobromic acid in alcohol.

The initial rates of the reaction of adamantyloxiranes I-IV with piperidine were determined by withdrawing 0.5 ml samples after 5-60 min from the boiling mixture of 0.01 mole of oxirane and 5 ml of 2 M benzene solution of piperidine. The sample was diluted with 5 ml of benzene, the unreacted piperidine was extracted with water (3 × 10 ml), and the aqueous solution was titrated with 0.2 N HCl. The initial reaction rate (R_0) was calculated from the linear dependence (at up to 30% of conversion) of the volume of HCl spent on titration (V, ml) on time (t, sec), according to the formula

$$R_0 = C_0 V/(V_0 t),$$

where V_0, ml is the volume of 0.2 N HCl consumed in the titration of 0.5 ml of a benzene solution of piperidine at a concentration C_0, mole/liter. The error of the measurements did not exceed 10%.

EXPERIMENTAL (BIOLOGICAL)

The antiviral properties of the compounds were determined in experiments on tissue cultures with respect to herpes simplex virus type I (HSV), smallpox vaccine virus (SVV), classical fowl plague virus (CFP), respiratory-syncytial virus (RSV), vesicular stomatitis virus (VSV), the Venezuela equine encephalomyelitis virus (VEE), and the ECHO virus by six "screening test" methods and reduction of plaques under agar coating. With the ECHO virus, the investigations were carried out on single layer cultures of passivated skin-muscular cells of a human embryo, with RSV on a culture of grafted cells of rabbit lungs (PI), and with the remaining viruses, on primarily trypsinized chicken embryo fibroblasts.

The presence of a suppression zone of plaque formation during the investigation by the "screening test" method and decrease in the titer of the virus compared with untreated control served as the effectiveness criteria. The chemotherapeutic index (CTI) was calculated as a ratio between the maximal concentration tolerated by a cell culture to a minimal concentration ensuring a decrease in the titer of the virus by a value corresponding to 1.25 PFU/ml.

The methods of investigation and the evaluation of the results obtained have been described in detail in [1].

The results obtained show that the compounds studied are characterized by low toxicity for the cell culture. The maximally tolerated concentration of the chicken embryo fibroblasts was from 50 to 400 μg/ml. Most of the compounds exhibited weak activity with respect to the HSV, SVV, VSV, VEE and CFP viruses. Compounds Vd and XId displayed a high inhibiting activity with respect to the SVV and CFP viruses.

It should be noted that with the introduction of morpholine, piperidine and dimethylamine fragments into the structure, the compounds acquire an inhibiting action with respect to the smallpox vaccine and classical fowl plague viruses. While compounds Vc, VIc and Vb have weak activity, a more pronounced inhibiting effect with respect to these viruses is observed in compounds Vd and XId.

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SYNTHESIS OF SUBSTITUTED 2-ANTHRAQUINONESUCCINAMIC ACID AMIDES AND STUDY OF THEIR PHARMACOLOGICAL ACTIVITY

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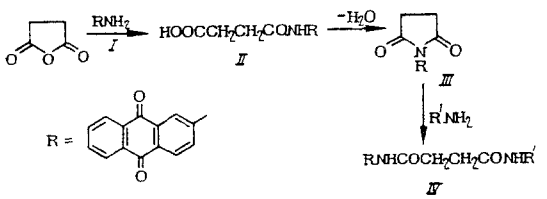
UDC 244.012.1.07

The problem of pharmacotherapeutic correction of liver diseases still remains unsolved because of the polyetiology of the mechanisms of the defects of the liver, and the variety of disturbances of its function [1]. Analysis of the data shows that a favorable clinical effect is observed when drugs with anti-inflammatory, anti-oxidant and membrane-stabilizing action are used [4]. However, there is no information on any research trend on new hepatoprotectors combining the above mentioned types of activity.

We have previously established [2] the presence of antioxidant and membrane-stabilizing activity in several anthraquinone-succinamic acid derivatives. In continuation of this investigation, we synthesized substituted amides of 2-anthraquinonesuccinamic acid and examined their pharmacological activity. The reaction of 2-aminoanthraquinone (I) with succinic anhydride in a glacial acetic acid medium gave 2-anthraquinonesuccinamic acid (II), which was cyclized with Ac_2O to form 2-anthraquinonesuccinimide (III). In the reaction of III with fatty amines, substituted amides of anthraquinonesuccinamic acid (IV a-j) were formed.



These compounds are in the form of yellow crystalline substances, which are soluble in dioxane, DMFA and insoluble in water. The structure and purity of the compounds was controlled by means of elemental analysis, TLC, and IR and UV spectral data.

The structures of the R^1 substituents and the physicochemical characteristics of compounds IVa-j are given in Table 1.

Compounds IVa-j were examined for anti-inflammatory, antioxidant, membrane-stabilizing, and choleretic activity.

Pharmaceutical Institute, Khar'kov. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 24, No. 5, pp. 25-27, May, 1990. Original article submitted July 5, 1989.

0091-159X/90/2405-0343$12.50