a. Diffusion Method. To establish the antimicrobial activity, a sample of compounds I-VII (0.1 g/ml) was placed in a hole of beef-extract or saccharose agar that had previously been seeded by the "lawn" pattern with the approporiate microbial suspension. The dishes were incubated in a thermostat at 37°C for 18 h. The presence of antimicrobial properties was judged by the diameter of the zone of bactericidal action of the compound (Table 2).

The results of the tests indicate that of the compounds tested a distinct antimicrobial activity is shown by compounds V, VI, and VII. Therefore, the antimicrobial activity of these compounds was further tested by the serial dilution method.

b. Method of Serial Dilutions. Compounds V, VI, and VII were used in dilutions of $1:10^{-6}$ to 1:10. Concurrently we carried out tests with antibiotics (benzylpenicillin sodium salt, kanamycin sulfate) and the solvent (dimethyl sulfoxide) (see Table 3).

With regard to activity against pathogens of purulent infection (Salm. typhimurium, Shigella flexner 2a, Proteus), compound V is not inferior to the compounds VI and VII surpass known antibiotics: Penicillin sodium salt by a factor of 10-100 and kanamycin sulfate by a factor of 10-100. The minimal inhibitory concentrations of V, VI, and VII against pathogens of purulent infection is 0.000001-0.0001 g/ml.

LITERATURE CITED

1. Author's Cert. USSR 851914, Otkrytiya, No. 28 (1981).
2. A. G. Makhsumov, F. A. Normatov, and M. S. Ergashev, Third Kazakhstan on Chemical Reagents [in Russian], Vol. 2, Tashkent (1990), p. 208.
3. A. Shukurov and M. N. Bolotova, Works of Young Academic Medical Students of Uzbekistan [in Russian], Vol. 6, Pt. 2, Tashkent (1975), pp. 377-378.

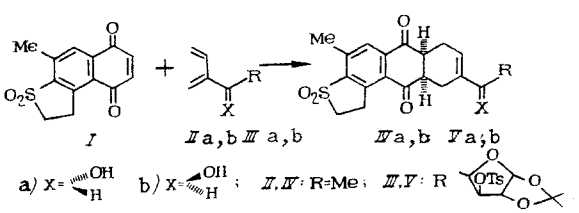
SYNTHESIS AND BIOLOGICAL ACTIVITY OF ANTIBIOTIC ANALOGS FROM THE HYDROGENATED ANTHRAQUINONE SERIES

G. A. Tolstikov, É. É. Shul'ts,
G. F. Vafina, T. G. Tolstikova,
V. A. Davydova, A. F. Ismagilova,
L. V. Spirikhin, F. A. Zarudii,
and D. N. Lazareva

UDC 547.655:547.673.5:609.6

Interest in the quinonoid fungal metabolites is to a significant degree the result of their high and diverse biological activity. In consideration of the influence on the antibacterial and antifungal activity of such derivatives of hydrogenated anthraquinone, such as altersolanol, daktilariol, bostritsin etc. [13-15], we decided to synthesize analogs possessing reduced toxicity. One of the safest approaches providing lowered toxicity of materials is, as we have repeatedly claimed [4], the introduction of the sulfone fragment.

For this reason we suggested the synthesis of new analogs of the natural hydroxyanthraquinones based upon the diene synthesis involving the recently-described 4-methyl-3,3-dioxi-1,2-dihydrothieno[3,2-a]naphthoquinone(I) [7].



I IIa,b III a,b IVa,b Va,b

a) X = OH (H); b) X = OH (H); II, IV: R=Me; III, V: R = OTs

Institute of Chemistry, Bashkir Scientific-Center, Academy of Sciences of the USSR, Urals Branch, UFa. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 25, No. 11, pp. 39-42, November, 1991. Original article submitted October 28, 1990.

0091-150X/91/2511-0800$12.50

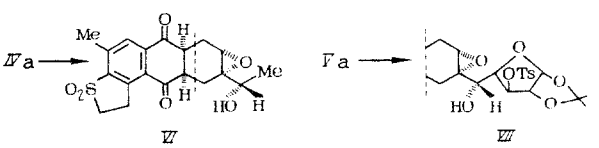
TABLE 1. Properties of the New Sulfone-containing Naphthacenequinones

Compound no.	mp, °C (recrystallization solvent)	Empirical formula	IR spectra, ν, cm^{-1}	^{1}H NMR spectra, δ, ppm.
IVa	87—90 Ethyl acetate	$C_{19}H_{20}O_5S$	830, 1085, 1120, 1135, 1150, 1285, 1310, 1595, 1690, 3345	1,27 d (3H, CH_3, J 6,47 Hz), 1,70 m (1H, H^{10}), 2,30 m (3H, $H^{7,10}$), 2,65 s (CH_3), 3,30 m (2H, H^1), 3,65 m (3H, $H^{2,9a}$), 3,80 ddd (1H, H^{10a}, J 6,5; 4,8; 2,3 Hz); 4,20 q (1H, H^{9a}), 5,80 d (1H, H^7, J 2,0 Hz), 7,91 s (1H, H^5)
IVb	112—115 Ether	$C_{19}H_{20}O_5S$	850, 870, 1065, 1100, 1150, 1315, 1590, 1675, 3340	1,32 d (CH_3, J 6,13 Hz), 1,75 m (H^{10}), 2,32 m (3H, $H^{7,10}$), 2,67 s (CH_3), 3,56 m (4H, $H^{1,2}$), 3,75 m (1H, H^{9a}), 3,82 m (1H, H^{10}), 4,25 q (1H, H^{9a}), 5,82 d (1H, H^7, J 3,8 Hz), 7,90 s (1H, H^5)
Vc	105—108 Ether	$C_{42}H_{56}S_2O_{11}$	770, 780, 830, 870, 880, 920, 970, 1040, 1105, 1190, 1200, 1315, 1600, 1647, 1700, 3500	1,18 s, 1,41 s (2,38 s 2,67 s (CH_3), 3,25 ddd (2H, H^{10}, 14,1, 4,2 and 1,1 Hz), 345 m (2H, H^1), 3,63 ddd (2H, $H^{10a,9a}$, J 4,6, 2,8, 2,0 Hz), 6,83 m (4H, $H^{2,5}$), 4,20 q (1H, H^{9a}), 4,60 m (2H, $H^{1',4'}$), 5,15 m ($H^{3',2'}$), 5,80 d (1H, H^7), 7,80 m (5H, Ph, H^5)
Vd	156—159 Ether	$C_{32}H_{36}S_2O_{11}$	750, 860, 930, 1050, 1120, 1140, 1190, 1200, 1320, 1600, 1670, 3450	1,18, 1,41, 2,38, 2,70 s (CH_3), 2,79 dd (2H, H^7, J 14,0, 7,1 Hz), 2,90 m (2H, H^1), 3,55 dd (1H, H^{9a}, J 6,2 and 4,1 Hz), 3,90 m (2H, H^2), 3,95 dd (1H, H^{10a}, J 6,2 and 3,5 Hz), 4,05 ddd (2H, H^{10}, J 12,1; 3,5; 1,6 Hz), 4,25 q (1H, CH), 4,60 m (2H, $H^{1',4'}$), 5,15 m (2H, $H^{3',2'}$), 5,85 d (1H, H^7), 7,82 m (5H, Ph, H^5)
VI	67—70 Ether	$C_{19}H_{20}O_6S$	1140, 1310, 1595, 1660, 1690, 3350	1,35 d (CH_3, J 6,4 Hz), 2,28 ddd (2H, H^{10}, J 19,6; 7,8 and 5,3 Hz), 2,48 m (2H, H^7), 3,10 dd (1H, H^6, J 5,7 and 3,25 Hz), 3,58 m (3H, $H^{1,10a}$), 3,70 ddd (1H, H^{9a}, J 6,9, 5,8 and 4,2 Hz), 3,90 m (2H H^2), 7,91 s (1H, H^5)
VII	164—168 Ethyl acetate	$C_{42}H_{56}O_{12}S$	870, 1065, 1110, 1150, 1315, 1590, 1675, 3450	1,20, 140 s (CH_3), 2,38; 2,75 s (CH_3), 2,58 m (4H, $H^{7,10}$), 3,20 dd (1H, H^6, J 6,2 and 4,2 Hz), 3,50 m (2H, H^1), 3,80 m (4H, $H^{2,9a,10a}$), 4,05 q (1H, H^{9a}, J 6,9 Hz), 4,52 m (1H, $H^{4'}$), 4,65 m (1H, $H^{3'}$), 5,05 m (2H, $H^{5',2'}$) 7,45 m (4H, Ph), 7,89 s (1H, H^5)
IX	108—112 Ether	$C_{19}H_{22}O_6S$	780, 1140, 1150, 1310, 1590, 1680, 3320, 3480	1,35 dd (3H, CH_3, J 6,5 Hz), 1,52 ddd (2H, H^7, J 15,2; 6,9 and 2,2 Hz), 2,2 m (4H, $H^{8,9}$), 3,60 m (2H, H^1), 3,70 dd (1H, H^{9a}, J 4,8 and 2,2 Hz), 3,95 dd (1H, H^{10a}, J 4,8 and 2,8 Hz, 4,0 q (1H, H^{9a}), 7,91 s (1H, H^5)
X	132—135 Ether	$C_{19}H_{18}O_5S$	1030, 1060, 1120, 1140, 1180, 1245, 1260, 1285, 1300, 1610, 1640, 3350	1,60 d (3H, CH_3, J 6,9), 2,70 s (3H, CH_3), 3,60 m (2H, H^1) 4,0 m (2H, H^2), 5,05 q (1H, H^{9a}), 7,85 dd (1H, H^7, J 8,05 and 1,4 Hz), 8,35 s (1H, H^5), 8,45 d (1H, H^6, J 1,4 Hz), 8,50 d (1H, H^7, J 8,05 Hz)

The diene components for the reactions were compounds II and III, obtained in the form of a mixture of diastereoisomeric isomers by reaction of the corresponding 2-(1,3-butadienyl)-magnesium chloride was acetaldehyde or 1,2-O-isopropylidine-3-O-tosyl-a-D-xylopentadialdo-1,4-furan (diene II was isolated by distillation and diene III by column chromatography).

Dienes II and III react with quinone I upon boiling in aqueous dioxane (5:1) to form a mixture of the diastereoisomeric adducts in a yield of 55-65. It should be noted that a significant acceleration of the reaction occurs upon carrying it out in aqueous solution (2-2.5 times). The isomeric ratio of IVa and b to Va and b was 10:3. Significant differences in the ^{1}H NMR spectra of the diastereoisomeric adducts consist of different chemical shifts of the doublet signals for the protons of the methyl group on carbon 9a: (δ 1.27 ppm, J = 6.47 Hz) for IVa and (δ 1.32 ppm, J = 6.13 Hz) for IVb. The IR spectra of the compounds differ in the position of the absorption bands of the quinone carbonyl and the double bond (ν 1690 and 830 cm^{-1} for IVa and 1675 and 850, 870 cm^{-1} for IVb).

Epoxidation of the double bond of compounds IVa and Va by the action of tert-butyl hydroperoxide in the presence of $MoCl_5$ [4, 8] proceeds with the formation of the corresponding cis-oxides VI and VII in a yield of 65-70%.



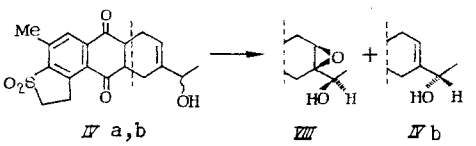
VI VII

It should be noted that the diastereoselectivity of the epoxidation may be explained by both steric factors and complex formation with the catlayst by the hydroxyl group in the α-position [4]. Analogous control by the hdyroxyl group of a stereoselective epoxidation was observed in the chiral epoxidation of Sharpless [12]. Under conditions of kientic control of the reaction (−30°C, 4 Å sieves) with a ratio of tetraisoproposytitanium:(+)-diethyl tartrate:t-butyl hdyroperoxide (TBHP) of 2:2:1 in a period of 4h (followed by TLC),

TABLE 2. Biological Activity of the Synthesized Compounds

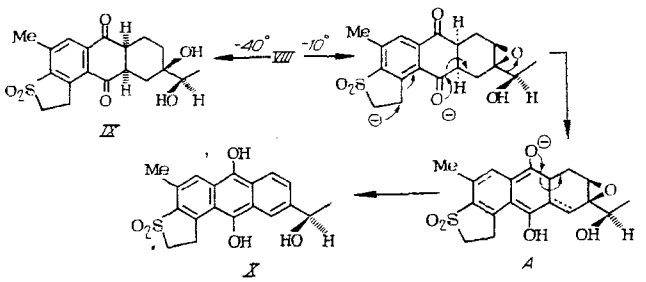
Compound	Toxicity, mg/kg	Antimicrobial activity				Action on Central Nervous System				
		Proteus vulgaris	Escherichia coli	Staphylococcus aureus	Bacillus pyocyaneus	motor activity	sleep prolongation, min		apomorphine stereotype, min	dose, mg/kg
						quantity of motion	from hexenal	from chloral hydrate		
IV a	442,8±49,0	++	+++	+++	–	25,10±2,1	48,50±9,8	49,20±3,6	90,00±0,15	5,0
Va	234,4±25,4	+++	+++	–	+++	29,20±4,9	154,70±30,6	322,80±1,68	86,00±0,15	5,0
VI	625±95,6	+++	+++	+++	+++	24,90±3,6	189,30±31,0	260,40±28,0	97,00±0,15	5,0
VII	364,7±49,0	–	–	–	-	27,20±2,45	48,50±9,8	49,20±3,6	100,00±0,15	5,0
Tetracycline		+++	+++	–	+++	–	–	–	–	–
Streptomycin		–	–	+++	–	–	–	–	–	–
Seduxen	455,0	–	–	–	–	9,45±2,8	196,60±1,7	390,00±0,17	86,00±0,17	2,5
Imizine	80,0	–	–	–	–	18,20±2,75	69,70±5,4	228,00±19,9	89,00±0,17	5,0
Control		–	–	–	–	29,45±2,1	47,70±3,7	90,20±8,1	82,00±0,15	

a mixture of epoxide (–) VIII, $[\alpha]_D^{25}$ –13.26°(c 1.0, $CHCl_3$) and nonreacted alcohol (+) IVa, $[\alpha]_D^{25}$ + 27.05° (c 0.8, $CHCl_3$) was obtained.



IV a,b VIII IV b

The reduction of epoxide VIII by $LiAlH_4$ at –40°C proceeded over 2 h and gave diol IX, $[\alpha]_D^{25}$ + 44.1°(c 1.0, $CHCl_3$). Cleavage of the epoxide ring at –10° by treatment with $LiAlH_4$ or at 0°C by the action of 20% aqueous $NaHCO_3$ lead to the formation of hydroquinone X. It is proposed that the cleavage in this case proceeds through the formation of the quinone methide intermediate A, reduction to the corresponding hydroquinone, and aromatization by dehydration.



The structure of compounds X followed from spectral data. The ^1H NMR spectrum was characterized by a set of signals corresponding to the protons of the anthracene skelton at δ 8.50 d (J = 8.05 Hz, H^7), 8.45 d (J = 1.4 Hz, H^{10}), 8.35 s (H^5), 7.85 dd (H^8); the methine proton at C(9a) was a quartet at 5.05 ppm (J = 6.9 Hz), in agreement with the proposed structure. The ^{13}C NMR spectrum was found to be four doublets at 72.06, 124.10, 127.82, and 130.28 ppm: the singlet signalt for C(6) and C(11) occurred at 153.06 and 153.45 ppm. Analysis of the NMR spectra and comparing the chemical shifts and the spin-spin constants with literature data for substituted naphthalene-9,10-hydroquinones showed that substituents in ring C of compound X are positioned on C(9). Thus the reaction of the substituted quinones I with 2-hydroxy-containing butadienes is characterized by regiospecificity, where the regiocontrol is brought about by the sulfur-containing substituent in the naphthoquinone ring. Influence by the polar effect of the subsituent on the regiochemical cycloaddition in the reaction of juglone with sulfer-containing dienes is recoded in [16], where regiocontrol also is brought about by a sulfer-containing substituent. The direct effects by the substituents on the naphthoquinone C(6) on regiochemical cycloaddition reactions was substituted butadienes was studied in [10] using kinetic calculations.

EXPERIMENTAL

The NMR spectra were determined with a Bruker WM-360 spectrometer using TMS as internal standard. The IR spectra were recorded with an UR-20 spectrometer in Vaseline oil, and

specific rotations were determined with a Perkin-Elmer 141 polarimeter. TLC was carried out on Silufol UV-254 plates, eluted with benzene:ethyl acetate (9:1), or chloroform: methanol (10:1). Dienes II and III were obtained by the method of [5]. The properties of the quinone adducts are presented in Table 1. The elemental analyses data corresponded with the calculated values.

EXPERIMENTAL (CHEMISTRY)

2-[(3-O-Tosyl-1,2-O-isopropylidine-α-D-xylopentafuranoso)-1-hydroxymethyl]-1,3-butadiene (III), oil, $[\alpha]_D^{25}$ − 19° (c 1.2, $CHCl_3$), $C_{19}H_{24}O_7S$.

(6aRS, 9aRS, 10aRS)- and (6aRS, 9aRS, 10aRS)-9-(1-Hydroxyethyl)-4-methyl-1,2,6a,7,10,10a-hexahydrothieno[3,2-a]anthracene-3,3,6,11-tetraones (IVa, IVb). A solution of 1.1 g of quinone I (4.2 mmoles) and 0.6 g (6.12 mmoles) of dienes IIa and IIb (ratio = 10:3) was boiled with a mixture of 50 ml of dioxane and 9 ml of H_2O for 5 h. The reaction mass was evaporated, the residue was dried azeotropically with benzene, and the resulting oil was chromatographed on a column of SiO_2 (in chloroform–methanol). The chromatographically homogeneous products were crystallized from ether to give 0.76 g (50%) of IVa and 0.23 g (15%) of adduct IVb. The ^{13}C NMR spectrum of IVa, δ, ppm: 17.36 q, 21.41 q (Me), 22.78 t C(7) 25.46 t C(1) 46.54 t C(10), 47.26 d, 47.39 d C(6a, 10a), 50, 15 t C(2), 71.21 d C(9a), 128.65 d C(5), 137.41 s, 139.49 s, 139.62 s, 141.65 s, 143.02 s C(3a, 4, 5a, 11a, 11b) 197.02 s, 198.14 s C(6, 11).

(6aRS, 9aSR, 10aRS)- and (6aRS,9aRS, 10aRS)-9-[2-[(3-O-Tosyl-1,2-O-isopropylidin-α-D-xylopentafuranoso)-1-hydroxyethyl]-4-methyl-1,2,6a,7,10,10a-hexahydrothieno[3,2-a]-anthracen-3,3,6,11-tetraones (Va and Vb). A mixture of 1.0 g (3.81 mmoles) of quinoine I and 1.8 g (4.55 mmoles) of dienes IIIa and IIIb was boiled in aqueous dioxane (5:1) for 3 h. The reaction mixture was evaporated and dried azeotropically with benzene. Chromatographic purification on SiO_2 gave 1.42 g (55%) of a mixture of Va and Vb. Isolation gave 0.45 g of pure Va, $[\alpha]_D^{25}$ − 17.1° (c 1.5, $CHCl_3$), and 0.15 g of Vb, $[\alpha]_D^{25}$ + 7.7° (c 2.1, $CHCl_3$).

(6aRS, 8R, 9aSR, 10aRS)-9-(1-Hydroxyethyl)-4-methyl-8,9-epoxy-1,2,6a,7,8,9,10,10a-octahydrothieno[3,2-a]anthracen-3,3,6,11-tetraone (VI). To a suspension of 0.6 g of adduct IVa and 0.005 g of $MoCl_5$ in 50 ml of benzene was added 10 ml of 90% t-butylhydroperoxide and the mixture was boiled for 3 h. The reaction mass was cooled, treated with 50 ml of benzene, washed with water, dried, and concentrated under vacuum. The residue was crystallized from ether to give 0.42 g (70%) of a single epoxide VI.

Epoxidation of adduct Va under the described conditions lead to (6aRS, 8SR, 9aSR, 10aRS)-9-[2-(3-O-Tosyl-1,2-O-isopropylidin-α-D-xylopentafuranoso)-1-hydroxyethyl]-4-methyl-8,9-epoxy-1,2,6a,7,8,9,10,10a-octahydrothieno[3,2-a]anthracen-3,3,6,11-tetraone (VII), $[\alpha]_D^{25}$ −33.3° (c 0.9, $CHCl_3$).

Sharpless Epoxidation of IVa and IVb Mixture. A three-necked flask containing 25 ml of CH_2Cl_2 and 2 g of 0.4 nm molecular sieves was cooled under a stream of argon to −30°C. Then 0.64 g (2.26 mmoles) of tetraisopropoxytitanium and 0.46 g (2.26 mmoles) of (+)diethyl tartrate we added, followed by 0.4 g (1.13 mmoles) of adducts IVa and IVb (ratio = 1:2 by NMR) in 5 ml of CH_2Cl_2 over several minutes. This was followed by 0.32 ml of a 3.86 M solution of t-butyl hydroperoxide in CH_2Cl_2. The reaction mixture was stirred for 4 h at −30° C, treated with 5 ml of 10% aqueous tartaric acid, and stirred for 30 min at this temperature and then for 1 h at room temperature. The layers were separated, the aqueous layer was extracted with chloroform, and the combined chloroform layers were washed with water, dried with Na_2SO_4 and concentrated under vacuum. The residue was chromatographed on SiO_2 to give 0.11 g (26%) of epoxide (−) VIII and 0.18 g (39%) of alcohol (+) IVa.

(6aRS, 9SR, 9aSR, 10aRS)-9-Hydroxy-9-(1-hydroxyethyl)-4-methyl-1,2,6a,7,8,9,10,10a-octdahydrothieno[3,2-a]anthracene (IX). To a mixture of 30 mg (0.8 mmole) of $LiAlH_4$ in 15 ml of anhydrous ether was added at −30°C a solution of 150 mg (0.5 mmole) of (−)VIII in 10 m of ether. After stirring at this temperature for 2 h, 0.5 ml of $NaHCO_3$ was added, and the usual workup gave 0.12 g (80%) of (+)IX. Compound X was shown to be present in the residue by TLC.

9-(1-Hydroxyethyl)-4-methyl-1,2-dihydrothieno[3,2-a]naphthacen-6,11-diol-3,3-dione (X) was obtained in 85% yield by reduction of VI by the described method at 0°C or by chromatographic workup of the solution of epoxide VI after treatment with 20% soda at room temperature. The yield in this case did not exceed 50%.

EXPERIMENTAL (BIOLOGY)

The antimicrobial activity of compounds IVa, Va, and VI was determined using disks impregnated with the test materials [6]. The disks were equally spaced in Petri dishes (6 pieces) upon 1 ml of microbe cell culture suspension. The microbes used were Proteus vulgaris, Bacillus pyocyaneus, Escherichia coli, and Staphylococcus aureus. The disks were kept in a thermostate maintained at 37°C for 18 h. The results were calculated by measuring the zone of microbe growth around the disks. Disks containing tetracycline and streptomycin were used as controls for the tests. The results are presented in Table 2.

The acute toxicity and antidepressant activity of IVa, Va, VI, and VII were determined with white mice by intraperitoneal injection. The action of the compounds on the central nervous system was studied by means of a motor activity test [1], by the prolongation of the soporific action of hexenal (75 mg/kg) and chloral hydrate (300 mg/kg), and by the apomorphine stereotype [11]. The toxicity was determined according to Kerber [2].

As Table 2 shows, the studied compounds possessed high antimicrobial activity, analogous to that of tetracycline and streptomycin.

The LD_{50} of the compounds was found to be in the range of 625 ± 95 to 234 ± 28 mg/kg. Epoxidation of the double bonds of the compounds leads to a significant decrease of the toxicity. Materials containing glycoside residues are more toxic than the methyl substituted compounds.

The compounds in a dose of 5 mg/kg did not change the motor activity of the animals. Materials containing glycoside fragments possess a sedative effect, less effective than seduksen, which is increased by epoxidation of the double bond. All compounds (especially the epoxides) potentiated the action of apomorphine.

The significant sedative effects of the new hydrogenated derivatives of anthraquinone probably are connected with an influence on the benzodiazepinone receptors, and the potentiation of apomorphine action with a simulation effect on the D_2 receptor [3]. Adduct IVa posssesses a stimulating action on the central nervous system, as indicated by its antagonism to the soporific effect of hexenal and chloral hydrate.

Analysis of the above data shows that the new sulfolane-containing hydrogenated anthraquinones possess antidepressant properties, one with significant sedative effect, and others with stimulant effects.

We noticed the sedative effect of the sulfolane ring in the quinone structure earlier [9].

LITERATURE CITED

1. E. S. Balynina and I. V. Berezovskaya, Farmakol. Toksikol., No. 5, 635-638 (1976).
2. O. M. Elizarova, Determination of the Threshhold Dose of Industrial Poisons by Peroral Introduction [in Russian], Moscow (1971), pp. 47-49.
3. É. F. Lavretskaya, Pharmocological Regulation of Psychiatric Processes [in Russian], Moscow (1985), pp. 128-130.
4. D. N. Lazareva, V. A. Davydova, É. G. Kamalova, et al., Farmakol. Toksikol., No. 4, 482-484 (1981).
5. L. A. Pashanyan, S. A. Vorskanyan, Zh. A. Chobanyan, and Sh. O. Babanyan, Arm. Khim. Zh., 34, No. 2, 133-137 (1981).
6. M. O. Birgera, ed., Handbook of Microbiological and Virological Methods of Investigation , Moscow (1973), p. 180.
7. G. A. Tolstikov, E. E. Shul'ts, G. F. Vafina, et al., Zh Org. Khim., 25, No. 6, 1231-1245 (1989).
8. G. A. Tolstikov, Hydroperoxide Oxidation Reactions [in Russian], Moscow (1976), pp. 76-95.
9. T. G. Tolstikova, V. A. Davydova, É. É. Shul'ts, et al., Khim.-farm. Zh., No. 7, 27-30 (1990).
10. R. K. Boeckman, T. M. Dolak, and K. O. Culos, J. Am. Chem. Soc., 100, 7098-7100 (1978).
11. A. M. Ernst, Psychopharmacologia (Berlin), 100, 316 (1967).
12. V. S. Martin, S. S. Woodward, T. Katsuki, et al., J. Am. Chem. Soc., 103, 6237-6255 (1981).

13. A. Stoesse, G. H. Umoin, and J. B. Stathers, Can. J. Chem., 61, 372-375 (1983).
14. T. R. Kelly, J. K. Saha, and R. R. Whittle, J. Org. Chem., 50, 3679-3685 (1985).
15. K. Krohn, H. Markus, A. P. Kraemer, and W. Frank, Liebigs Ann. Chem., 1033-1041 (1988).
16. B. M. Trost, W. C. Vladuchick, and A. J. Bridges, J. Am. Chem. Soc., 102, No. 10, 3554-3572 (1980).

AMIDES OF ANTHRACYCLINE ANTIBIOTICS AND N-CARBOXYMETHYLASCORBIGEN

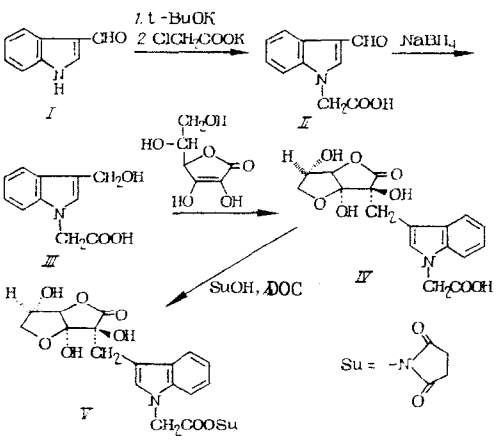
A. M. Korolev, É. I. Lazhko, M. N. Preobrazhenskaya, Ya. Bal'zarini, and É. De Klerk

UDC 615.33:577.182.540].012.6

Compounds with high antitumor activity occur among the N-acylated derivatives of anthracycline antibiotics, in spite of a significant decrease of affinity of these materials of DNA [3].

Some of the ascorbigens, i.e., indole containing derivatives of L-ascorbic acid, are biologically-active compounds possessing antitumor properties or immunomodulating activity, capable of undergoing diverse transformations in the organism. They may interact with different nucleophilic (thio-, amino-) groups or cleave nonenzymatically into L-ascorbic acid and 3-hydroxymethylindole or their derivatives [1, 7]. An increase in the level of L-ascorbic acid after introduction of the preparations may promote the sensitivity of the cells to chemotherapeutic agents [6], and 3-hydroxymethylindole, being an active alkylating fragment, may interact with diverse targets [2, 5, 7]. The wide spectrum of biological activity of these compounds induced an interest in the synthesis and study of the antitumor activity of derivatives of anthracycline antibiotics covalently bonded to ascorbigen, i.e., potential cytostatic agents and the depo-form of ascorbic acid.

The present work undertook the synthesis of derivatives of ascorbigen and anthracycline antibiotics, to produce acylation of the amino groups of the antibiotic by N-carboxymethylascorbigen. N-carboxymethylascorbigen (IV) was synthesized in three stages: alkylation of 3-formylindole with chloroacetic acid in tert-butanol in the presence of potassium tert-butoxide to give 1-(carboxymethyl)-3-formylindole (II). Reduction of II with $NaBH_4$ gave the 3-hydroxymethyl derivative (III), and subsequent condensation of III with L-ascorbic acid in a phosphate-citrate buffer to give IV, which was transformed into the N-hydroxysuccinimide ester (V) with N-hydroxysuccinimide in the presence of dicyclohexylcarbodiimide.



Scientific-Research Institute for Research on New Antibiotics, Academy of Medical Sciences of the USSR, Moscow. Rega Institute, Catholic University of Louvain, Louvain, Belgium. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 25, No. 11, pp. 42-45, November, 1991. Original article submitted February 26, 1991.

0091-150X/91/2511-0805$12.50