REACTION OF DAUNOMYCINONE WITH DIOLS

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During the acid catalyzed acetalization of the 13-ketone group of daunomycinone (*I*) by 1,2-ethanediol or 1,3-propanediol its 7-O-alkylation also takes place. The 7-O-ω-hydroxyalkyl derivatives only are formed with 1,4-butanediol, 1,6-hexanediol or 1,4-butynediol. The conformational preference of new compounds is discussed. The (7*S*)-ω-hydroxyalkyl derivatives of daunomycinone are active against *Bacillus subtilis*, on the contrary to *I* and their (7*R*)-epimers.

The carbonyl group at the position 13 of the side chain of daunomycinone, an aglycone of the antitumour antibiotic daunomycin, is its most reactive functional group. Thus it is usually protected by acetalization in the course of various synthetic reactions or biotransformations[1,2]. The dehydration product *III* was described as a side product in the preparation of the ethylene acetal[2] *II*. Reproducing this work, we have isolated another three compounds. This paper is devoted to their structures determination and to the study of the reaction of daunomycinone with several other diols.

One component of the reaction mixture was identified as *II* on the basis of m.p., ^{1}H NMR and mass spectra comparison with the published data[2]. However, in the paper cited, the intense ion *a* (*m*/*z* 87, $C_4H_7O_2$) is not mentioned. This ion is of diagnostic value since it contains all side chain atoms. The acetalization of the 13-carbonyl group is further indicated by the chemical shift changes of the methyl group protons from 2·43 to 1·50 ppm and by the replacement of the carbonyl carbon signal (211·6 ppm) in the ^{13}C NMR spectrum by a signal at 111·8 ppm. The detailed analysis of ^{1}H NMR data (Tables I and II) confirms the same configuration (7*S*) and conformation ($^8H_9$) of the alicyclic ring for *II* and the starting compound[3] (Fig. 1).

The compound of lowest polarity exhibit a molecular ion *m*/*z* 406 ($C_{23}H_{18}O_7$) and ions *m*/*z* 391 ($M-CH_3$) and *a* (87, $C_4H_7O_2$) in its mass spectrum. ^{1}H NMR spectrum contains a three-proton singlet at 1·74 ppm, a four-proton multiplet at 3·88 ppm, a three-proton singlet at 4·10 ppm, multiplets of six aromatic protons in the region of 7·13–8·59 ppm and singlets of two phenolic hydroxyls at 15·27 and 15·97 ppm. That suggests the structure *III*, corresponding to the dehydration product of *II*. The chemical shift of the methyl group agrees with the value 1·72 ppm,

observed with a similar fully aromatized acetal[4]. The aromatization of the last ring is also supported by chemical shift of the phenolic OH groups shifted to the unusually low field[5] with respect to *II*.

The next compound has an elemental composition $C_{25}H_{26}O_{10}$ (high resolution mass spectroscopy). The presence of the ion *a* (*m/z* 87) in its mass spectrum, the three-proton singlet at 1·49 ppm in ^{1}H NMR spectrum and the absence of the ketone carbonyl signal in ^{13}C NMR spectrum (Table III) show that this compound is an acetal. The difference in the molecular formula with respect to *II* is C_2H_4O. These atoms give rise to a four-proton multiplet at 3·85 ppm in the ^{1}H NMR spectrum and to the two methylene carbon signals at 61·5 and 70·0 ppm in the ^{13}C NMR spectrum. The signal of $H_{(7)}$ is shifted 0·21 ppm upfield with respect to *II*, that of $C_{(7)}$ appears 8·9 ppm downfield. These changes can be explained by an ether formation at the position 7. The chemical shifts of carbon atoms of the new substituent agree well with that of ethylene glycol monomethyl ether (73·5 and 61·1 ppm). The analysis of ^{1}H NMR coupling constants (Table II) indicates the configuration

TABLE I

Chemical shifts (±0·005 ppm) and apparent signal multiplicity (different from that given in Table II, based on the decoupling experiments and partially relaxed spectra) of selected protons in daunomycinone derivatives; solvent: deuteriochloroform

Compound	7	8a	8e	10a	10e	14[a]
I	5·29 mt	2·14 dd	2·35 ddd	2·89 d	3·14 dd	2·44 s
II	5·30 mt	1·99 dd	2·46 ddd	2·79 d	3·25 dd	1·49 s
V	5·09 mt	1·81 dd	2·57 ddd	2·85 d	3·27 dd	1·49 s
VI	5·09 t	1·97 dd	2·56 ddd	2·86 d	3·13 dd	1·45 s
VIII	5·00 mt	1·88 dd	2·55 dmt	2·89 d	3·23 d[c]	1·51 s
IX	5·31 mt	n.o.[b]	n.o.[b]	2·84 d	3·25 d[c]	1·51 s
X	5·02 t	n.o.[b]	n.o.[b]	2·85 d	3·15 d[c]	1·47 s
XI	5·04 mt	1·91 dd	2·33 ddd	2·96 d	3·24 dd	2·41 s
XII[d]	4·95 mt	2·56 dd	2·09 dd[c]	3·67 d	3·27 dd	2·33 s
XIII	5·01 mt	1·94 dd	2·38 ddd	2·87 d	3·20 dd	2·41 s
XIV	5·07 t	2·51 dd	2·06 ddd	3·29 d	2·99 dd	2·37 s
XV	5·21 mt	1·99 dd	2·59 ddd	2·95 d	3·26 dd	2·45 s
XVI	5·12 mt	1·93 dd	2·47 ddd	2·91 d	3·24 dd	2·41 s
XVII[d]	5·05 t	2·56 dd	2·17 ddd	3·49 d	3·25 dd	2·31 s
XVIII	5·04 mt	1·98 dd	2·41 ddd	2·96 d	3·26 d[c]	2·43 s
XIX	5·10 mt	n.o.[b]	n.p.[b]	2·71 d	3·17 d[c]	1·28 d
XX	5·04 t	2·13 dd	2·38 ddd	2·85 d	3·17 dd	1·45 s

[a] 3 H; [b] not observed because of overlap; [c] unresolved coupling; [d] $(C^2H_3)_2SO$ added.

(7*S*) and conformation ($^8H_9$) identical with that of daunomycinone. Thus, the structure *V* is assigned to this compound.

According to its mass spectrum, the fourth component of the reaction mixture is isomeric with *V*. Both ^1H and ^{13}C NMR spectra (upfield shift of $H_{(7)}$, downfield shift of $C_{(7)}$) confirm the attachment of a $HOCH_2CH_2O$— group at position 7. The proton $H_{(7)}$ in the studied compound appears as a triplet with two large couplings (Table II), a pattern typical for 7*R*-epimers of anthracyclinones[6] existing in the conformation $^8H_9$. A long-range coupling was observed between the downfield member of an AB system of the $C_{(10)}$-protons and the downfield resonating proton $H_{(8)}$. The same coupling occurs in daunomycinone[3] and indicates the pseudoequatorial orientation of the respective protons (*i.e.* $H_{(8e)}$ and $H_{(10e)}$) located in so-called *W*-arrangement. This coupling allows to reject the boat conformation in which such arrangement

TABLE II

Selected coupling constants *J* (Hz) of alicyclic ring protons in daunomycinone derivatives; solvent: deuteriochloroform

Compound	7,8a	7,8e	8a,8e	8e,10e	10a,10e	J^a	configuration at $C_{(7)}$	conformation[b]
I	4·4	2·0	14·2	1·2	18·4	6·4	*S*	$^8H_9$
II	4·9	2·2	14·7	1·2	18·3	7·1	*S*	$^8H_9$
V	3·7	2·4	14·6	1·2	19·5	6·1	*S*	$^8H_9$
VI	7·3	7·3	13·4	1·3	18·3	14·6	*R*	$^8H_9$
VIII	4·9	2·0	14·7	±0	18·8	6·9	*S*	$^8H_9$
IX	[c]	[c]	[c]	±0	18·2	7·0	*S*	$^8H_9$
X	7·4	7·3	[c]	±0	18·3	14·7	*R*	$^8H_9$
XI	3·7	2·4	14·7	1·0	19·0	6·1	*S*	$^8H_9$
XII[d]	3·7	4·9	14·7	1·1	18·9	8·6	*R*	$^9H_8$
XIII	3·7	3·0	14·7	1·0	18·9	6·7	*S*	$^8H_9$
XIV	4·9	4·3	14·6	1·0	16·8	9·2	*R*	$^9H_8$
XV	3·7	2·4	14·7	1·0	19·5	6·1	*S*	$^8H_9$
XVI	3·7	1·8	14·7	1·1	18·3	5·5	*S*	$^8H_9$
XVII[d]	4·9	3·7	14·7	1·0	18·0	8·6	*R*	$^9H_8$
XVIII	3·7	2·2	14·7	1·0	18·9	5·9	*S*	$^8H_9$
XIX	4·9	2·4	[c]	±0	19·5	7·3	*S*	$^8H_9$
XX	7·3	7·3	14·6	1·1	17·1	14·6	*R*	$^8H_9$
XXII[e]	3·5	2·5	15·0	1·0	18·5	6·0	*S*	$^8H_9$

[a] $J_{7,8a} + J_{7,8e}$ in Hz; [b] conformation nomenclature using the usual anthracyclinone numbering; [c] not determined because of signal overlap; [d] C^2HCl_3 with $(C^2H_3)_2SO$ added; [e] ref.[3].

is impossible. Therefore, our compound has a reversed configuration at $C_{(7)}$ with respect to *V* (*i.e.* 7R) and exists in the conformation $^8H_9$ (Fig. 1), similarly to *I*, *II*, and *V*; its structure is *VI*.

Compound of the lowest polarity from the reaction of *I* with 1,3-propanediol yields a molecular ion *m/z* 420 ($C_{24}H_{20}O_7$) in its mass spectrum, accompanied by an intense ion *a* (*m/z* 101, $C_5H_9O_2$), characteristic for an acetal. A three-proton

TABLE III

^{13}C NMR chemical shifts (±0·06 ppm) of daunomycinone derivatives

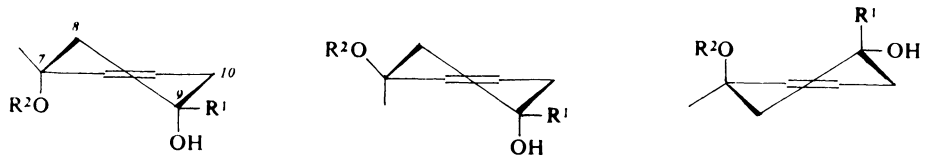
Carbon	*I*[a,b]	*II*[c]	*V*[a]	*VI*[a]	*VIII*[a]	*XIII*[a]	*XV*[d]
1	119·6	119·8	119·2	119·3	119·7	119·7	118·5
2	135·3	135·7	135·3	135·3	135·5	135·5	135·8
3	118·3	118·4	118·0	118·0	118·3	118·3	117·7
4	160·9	160·6	160·4	160·8	160·8	160·0	155·9
5	186·0	186·7	186·0	186·4	187·1	186·6	185·6
6	155·0	156·2	155·8	155·7	156·1	155·9	154·5
7	61·9	62·4	71·3	71·6	70·4	69·3	68·1
8	34·3	33·4	31·7	34·2	32·2	33·8	32·6
9	78·5	71·3	73·9	75·8	73·9	70·8	73·3
10	33·1	31·3	28·5	30·3	32·2	32·6	32·0
11	156·0	156·6	156·1	156·7	156·5	156·6	156·1
12	186·0	187·0	186·2	186·0	187·1	187·0	188·7
13	211·6	111·8	111·4	112·0	117·0	212·9	211·6
14	24·5	19·0	18·3	19·0	18·7	25·0	23·9
4a	122·2	121·1	120·2	120·4	121·5	120·9	121·0
5a	110·3	111·0	110·6	111·4	111·8	111·2	110·2
6a	133·3	135·0	133·8	134·9	134·6	134·1	132·9
10a	133·5	135·4	134·8	134·9	134·6	134·8	133·9
11a	110·4	111·4	110·7	111·6	111·9	111·2	110·9
12a	134·0	137·0	136·3	136·5	136·7	135·5	134·3
OCH_3	56·6	56·8	56·3	56·4	56·7	56·7	55·6
1′[c]	—	—	70·0	70·6	68·0	69·3	57·8
2′[c]	—	—	61·5	61·6	29·0	32·0	91·6
3′[e]	—	—	—	—	60·1	25·7	85·5
4′[e]	—	—	—	—	—	25·3	48·9
5′[e]	—	—	—	—	—	29·8	—
6′[e]	—	—	—	—	—	62·9	—
α[f]	—	65·6[g]	65·2[g]	65·4[g]	72·1[g]	—	—
β[f]	—	—	—	—	32·2	—	—

[a] C^2HCl_3; [b] ref.[7]; [c] $C^2HCl_3 + C^2H_3O^2H$; [d] $C^2HCl_3 + (C^2H_3)_2SO$; [e] $C_{(7)}$-side chain; [f] acetal rest; [g] 2 C.

singlet at 1·74 ppm in ^{1}H NMR spectrum, a two-proton multiplet at 1·88 ppm, a four-proton multiplet at 3·88 ppm, a three-proton singlet at 4·10 ppm, multiplets of six aromatic protons (7·21–8·20 ppm) and two extremely downfield resonating phenolic hydroxyls (15·29 and 15·99 ppm) lead to a conclusion that this compound is a dehydration product of the expected acetal possessing the structure *VII*, as with the compound *IV*.

The main reaction product displays in its mass spectrum an ion with the highest mass at *m/z* 420 ($C_{24}H_{20}O_7$). The presence of a trimethylene acetal group in the molecule is indicated by an intense ion *a* (*m/z* 101) and by loss of a methyl from the *m/z* 420 ion. It is further supported by the methyl singlet at 1·51 ppm in ^{1}H NMR spectrum, by absence of the ketone carbonyl signal in ^{13}C NMR spectrum instead of which a new signal of the —O—C—O— type carbon at 117·0 ppm appears (Table III). Elemental analysis and both NMR spectra are in variance with the mass spectroscopic results. According to them the compound contains more protons and aliphatic type carbons than follows from the composition of the *m/z* 420 ion. That can be explained by a fast loss of water and propanediol under electron-impact. The interpretation of coupling constants among protons of the alicyclic aglycone ring by the way used above (Table II) allows a conclusion that there is no change of the conformation with respect to *I*. The upfield shift of $H_{(7)}$ signal (Table I) and the marked downfield shift of $C_{(7)}$ (Table III) indicate a substitution of the $C_{(7)}$

(7*S*) (7*R*) (7*R*)



$^8H_9$ $^8H_9$ $^9H_8$

R^1 = $COCH_3$
or —$C(CH_3)O(CH_2)_nO$—,
n = 2, 3
R^2 = H, $HO(CH_2)_n$—,
n = 2, 3, 4, 6,
$HOCH_2C{\equiv}CCH_2$—

R^1 = $COCH_3$ and R^2 = H
or —$C(CH_3)O(CH_2)_nO$—,
n = 2, 3
R^2 = H, $HO(CH_2)_n$—,
n = 2, 3, 4, 6,
$HOCH_2C{\equiv}CCH_2$—

R^1 = $COCH_3$
R^2 = $HO(CH_2)_n$—, *n* = 2, 4, 6

FIG. 1

Conformation of the alicyclic ring in anthracyclinones (conformational nomenclature of sugars[8] plus the usual anthracyclinone numbering)

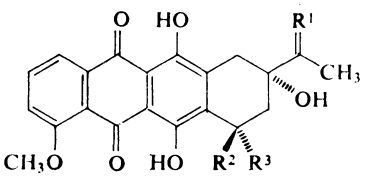
hydroxyl by a propylene glycole residue which explains the additional signals in both NMR spectra. So we obtain the formula *VIII*.

Next compound found in the discussed mixture has a molecular composition $C_{24}H_{24}O_9$ (high resolution mass spectroscopy). It also produces the ion *m/z* 101(*a*). There is a singlet at 1·51 ppm (3 H) in its ^{1}H NMR spectrum. Therefore, this compound is an acetal, too. Chemical shift of the $H_{(7)}$ proton (5·31 ppm) indicates a free hydroxyl group at the position 7. From the results given in Table II it follows that the configuration at $C_{(7)}$ is 7S and that the alicyclic ring adopts the conformation $^8H_9$, similarly to *I*. Thus, this compound might be formulated as *IX*.

The last compound, $C_{27}H_{30}O_{10}$ (high resolution mass spectrum), is also an acetal (*m/z* 101, *a*, δ_H 1·47 (3 H). The integral of ^{1}H NMR spectrum shows several protons of the OCH type that can be again explained by the presence of a $OCH_2CH_2CH_2OH$ group. Chemical shift of the $H_{(7)}$ (5·02 ppm) indicates the ether formation at $C_{(7)}$. Long-range coupling between H_{8e} and H_{10e} (Table II) is an evidence for the usual conformation ($^8H_9$) of the alicyclic ring. Two large coupling constants $J_{7,8a}$ and $J_{7,8e}$ (Table II) indicate the reversed configuration (*i.e.* 7*R*) with respect to its isomer *VIII*. This compound therefore has the structure *X*.

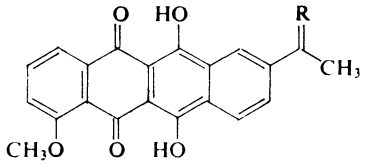
The reaction mixture of *I* with 1,4-butanediol contains besides the unreacted *I* two main components only. In the mass spectrum, both provide a molecular ion *m/z* 470 ($C_{25}H_{26}O_9$) indicating the attachment of one diol molecule. Their mass spectra differ in the peak intensities only, as can be expected for isomers. From the chemical shifts of $H_{(14)}$ and $H_{(7)}$ protons (Table I) it follows that both compounds retain a CH_3CO group and that the $C_{(7)}$ hydroxyl is etherified. The magnitudes of coupling constants $J_{7,8a}$ and $J_{7,8e}$ (Table II) for the first compound approach that of daunomycinone; therefore, this compound has 7*S* configuration and formula *XI*. The width of the $H_{(7)}$ multiplet (8·6 Hz) in the ^{1}H NMR spectrum of the other isomer also indicates its pseudoequatorial position. However, the pair of equatorial protons H_{8e} and H_{10e}, identified on the basis of their mutual long-range coupling, resonates in the higher field (instead in the lower field as in daunomycinone) than their axial counterparts. These facts are compatible either with the (7*R*,9*R*)-configuration in the conformation $^9H_8$ or with the (7*S*,9*S*)-configuration in the conformation $^8H_9$. With respect to the way of its formation and using the arguments presented below we prefer the former possibility (formula *XII*).

The reaction of daunomycinone with 1,6-hexanediol also provides two isomeric products of molecular formula $C_{27}H_{30}O_9$ (high resolution mass spectrometry). Chemical shifts of $H_{(14)}$ and $H_{(7)}$ (Table I) show that both 7-$O(CH_2)_6OH$ derivatives have an unchanged methylketo group. According to ^{1}H NMR spectra, they differ in the arrangement of the alicyclic ring. The appropriate proton-proton coupling constants (Table II) in the major product are similar to those of daunomycinone. Therefore, it is assigned the structure *XIII*. The NMR properties of the minor pro-

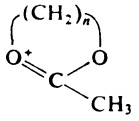


	R^1	R^2	R^3
I	=O	H	OH
II	$-O(CH_2)_2O-$	H	OH
V	$-O(CH_2)_2O-$	H	$O(CH_2)_2OH$
VI	$-O(CH_2)_2O-$	$O(CH_2)_2OH$	H
VIII	$-O(CH_2)_3O-$	H	$O(CH_2)_3OH$
IX	$-O(CH_2)_3O-$	H	OH
X	$-O(CH_2)_3O-$	$O(CH_2)_3OH$	H
XI	=O	H	$O(CH_2)_4OH$
XII	=O	$O(CH_2)_4OH$	H
XIII	=O	H	$O(CH_2)_6OH$
XIV	=O	$O(CH_2)_6OH$	H
XV	=O	H	$OCH_2C{\equiv}CCH_2OH$
XVI	=O	H	$O(CH_2)_2OH$
XVII	=O	$O(CH_2)_2OH$	H
XVIII	=O	H	$O(CH_2)_3OH$
XIX	H, OH	H	$O(CH_2)_2OH$
XX	$-O(CH_2)_2O-$	$O(CH_2)_4OH$	H
XXI	=O	OH	H
XXII[a]	=O	H	OCH_3

[a] OCH_3 instead of OH at $C_{(6)}$ and $C_{(11)}$.



III, R = =O
IV, R = $-O(CH_2)_2O-$
VII, R = $-O(CH_2)_3O-$



ion *a*

$n = 2$ m/z 87
$n = 3$ m/z 101

duct are similar to those of compound *XII*; the width of the $H_{(7)}$ multiplet is 9·2 Hz, equatorial protons H_{8e} and H_{10e} (coupled by a long-range coupling) resonate contrary to *I* at higher field than the axially disposed protons H_{8a} and H_{10a}. That means that the alicyclic ring exists in the conformation $^9H_8$ (Fig. 1) with a pseudoaxial substituent at $C_{(7)}$ (*i.e.* with the configuration 7*R*). The structure of this compound is thus *XIV*.

Only one compound of molecular formula $C_{25}H_{22}O_9$ (high resolution mass spectrometry) was isolated from the reaction of daunomycinone with 1,4-butyndiol. A three-proton singlet δ_H 2·45 and the signal δ_C 211·6 in its ^1H and ^{13}C NMR spectra are the proof of the presence of an unchanged methylketo group. From the chemical shift of $C_{(7)}$ (68·1 ppm) it is clear that the reaction took place at this position. The coupling constants (Table II) show that this compound has both the configuration (7*S*) and the conformation ($^8H_9$) identical to daunomycinone. Its structure is expressed by the formula *XV*.

To be able to compare the biological activity of newly prepared compounds, the acetal group in compounds *V*, *VI* and *VIII* was removed by hydrogen chloride hydrolysis. Compounds *XVI*, *XVII* and *XVIII* were obtained in this way. Reduction of compound *XVI* by $NaBH_4$ produced its 13ξ-dihydro derivative *XIX*, an authentic specimen for the study of biotransformations[13]. Mass and ^1H NMR spectra of compounds *XVI*–*XIX* agree with the supposed structures. An interesting effect was observed in *XVII* having a (7*R*)-OCH_2CH_2OH substituent. The width of the $H_{(7)}$ multiplet changes from 14·6 Hz to 8·6 Hz after removing the acetal group, what indicates the change of conformation from $^8H_9$ to $^9H_8$ (Fig. 1). Since the (7*R*)-epimers *XII* and *XIV* also exist in this conformation, a hypothesis can be advanced that only those (7*R*)-derivatives of daunomycinone having a $C_{(9)}$ substituent bulky enough to force the equatorial position and so stabilize the conformation adopt the $^8H_9$ conformation. The sole methylketo group has not evidently the sufficient size and is able to take the axial position or even to stabilize the conformation $^9H_8$ by interaction of its carbonyl with the $C_{(7)}$-oxygen atom. To confirm this hypothesis, we prepared the ethylene acetal *XX* from *XII*. In its ^1H NMR spectrum (Tables I and II), $H_{(7)}$ gives a triplet with coupling constant of 7·3 Hz and equatorial protons H_{8e} and H_{10e} resonate in lower field than their axial counterparts. Therefore, this compound exists in the „normal" conformation $^8H_9$. An evident exception is 7-epidaunomycinone *XXI*, for which the width of the $H_{(7)}$ multiplet of 17 Hz was reported[9,10]. In this case, the conformation $^8H_9$ is most probably stabilized by a hydrogen bridge between the $C_{(9)}$—OH and $C_{(7)}$—OH. CD spectra of pairs *XIII*–*XIV* and *XVI* to *XVII* are mirror images (*XIII* $\Delta\varepsilon_{290}$ −3·78, $\Delta\varepsilon$ +1·55, $\Delta\varepsilon_{345}$ +1·49; *XIV* $\Delta\varepsilon_{290}$ +3·87, $\Delta\varepsilon_{350}$ −0·64, $\Delta\varepsilon_{415}$ +0·41; *XVI* $\Delta\varepsilon_{284}$ −2·96, $\Delta\varepsilon_{310}$ +1·61, $\Delta\varepsilon_{345}$ +1·40; *XVII* $\Delta\varepsilon_{290}$ +4·23, $\Delta\varepsilon_{350}$ −0·65, $\Delta\varepsilon_{415}$ +0·55), similarly to the pairs of epimers existing in conformation $^8H_9$. Our conclusions concerning the conformation of daunomycinone (7*R*)-epimers agree with the results on (7*R*)-alkoxy derivatives of another

anthracyclinone antibiotic nogalarol for which the conformation ${}^{9}H_{8}$ was also proposed[12].

Contrary to ref.[3], we found that several minutes of heating are necessary for the completion of the reaction of daunomycinone with 1,2-ethylene glycol to give *II* when a catalytic amount of *p*-toluenesulfonic acid is used. The proportion of products *V* and *VI* increases with prolonged reaction time. The same results is achieved when using a stochiometric amount of the acid or its excess. All that suggests that the reaction goes through the formation of 7-O-esters with *p*-toluenesulfonic acid (similarly to rhodomycinones[11]) that are then solvolysed by the glycol. The described reaction represents a novel way of daunomycinone functionalization, in which the secondary alcoholic group is replaced by the more reactive primary alcoholic one.

Whereas daunomycinone itself is devoid of biologic activity in common tests, its derivatives having a free carbonyl group at the position 13 and "natural" (7*S*)-configuration (*XI*, *XIII*, *XV*, *XVI*, and *XVIII*) are active against *Bacillus subtilis*.

EXPERIMENTAL

Melting points were determined using a Kofler apparatus. Optical rotation values (in chloroform) were obtained on a Bendix–Ericson instrument. CD spectra were measured in dioxan on a Rousel Jouan CD 185 Dichrograph. ^{1}H and ^{13}C NMR spectra were studied on a FT NMR spectrometer Jeol FX-60 (59·797 and 15·036 MHz) in deuteriochloroform at 25°C. Chemical shifts are given in the δ-scale with accuracy $\pm 0{\cdot}005$ and $\pm 0{\cdot}06$ ppm (^{1}H and ^{13}C, respectively). Protons at $C_{(7)}$ and $C_{(8)}$ were analyzed as an ABX system in the decoupled spectrum (H_{10e} irradiated); protons at $C_{(10)}$ were treated as an AB system (H_{8e} irradiated). The assignment of ^{13}C NMR signals is based on the off-resonance decoupling and on the comparison with the literature. Mass spectra were measured on a Varian MAT 311 spectrometer (70 eV, ionization current 1 mA, ion source temperature 200°C, direct inlet temperature is given together with the actual spectra below). Elemental composition of ions was measured (with accuracy ± 5 ppm) using a peak-matching technique with perfluorokerosene standard. Daunomycinone was prepared by acid hydrolysis of rubomycin (Medexport, USSR). Column chromatography was performed on silica gel Herrmann (GFR), 80–200 mesh. Further purification was carried out on Silufol R^{20} plates (Kavalier, Votice, Czechoslovakia). Following chromatographic systems were used: S_1 chloroform–methanol 97 : 3, S_2 heptane–chloroform–methanol 70 : 20 : 10, S_3 benzene–chloroform–methanol 25 : 65 : 10, S_4 benzene–chloroform–methanol 40 : 50 : 10, S_5 heptane–chloroform–methanol 30 : 60 : 10, S_6 benzene–chloroform–ethyl acetate–methanol 7 : 7 : 3 : 1, S_7 benzene–ethyl acetate–methanol 30 : 60 : 10.

Reaction of Daunomycinone (*I*) with 1,2-Ethanediol

Mixture of *I* (160 mg, 0·4 mmol), *p*-toluenesulfonic acid (35 mg) and 1,2-ethanediol (2 ml) was heated 3 h to 130°C in 50 ml of benzene, diluted with water (100 ml) and extracted with chloroform. The extract was dried over Na_2SO_4 and the solvent was removed. The residue was subjected to column chromatography on silica gel in the system S_1. The first fraction was chromatographed on Silufol in the system S_2. Crystallization has provided 12 mg (7%) of compound *IV*, m.p. 233–235°C (chloroform–ethanol). Purification of the second fraction on Silufol in the system S_5 yielded 45 mg (25%) of compound *II*, m.p. 238–239°C (ref.[2] gives 245–247°C)

From the most polar fraction, 82 mg (42%) of compound *V*, m.p. 198°C (chloroform–ethanol) and 15 mg (8%) of compound *VI*, m.p. 213—215°C (methanol) were isolated after chromatography on Silufol in the systems S_4 and S_6.

IV: Mass spectrum (160°C) *m/z* (% of relative intensity, composition): 406 (57, $C_{23}H_{18}O_7$, M^+), 391 (100, $C_{22}H_{15}O_7$), 347 (24, $C_{20}H_{11}O_6$), 319 (18, $C_{19}H_{11}O_5$), 301 (10, $C_{19}H_9O_4$), 291 (7, $C_{18}H_{11}O_4$), 273 (6, $C_{18}H_9O_3$), 87 (59, $C_4H_7O_2$, *a*), 43 (56, C_2H_3O). For $C_{23}H_{18}O_7$ (406·4) was calculated: 67·98% C, 4·46% H; found: 68·10% C, 4·41% H.

II: $[\alpha]_D$ +108·3° (*c* = 0·12, chloroform). Mass spectrum (190°C (*m/z* (% of relative intensity, composition): 442 (0·3, $C_{23}H_{22}O_9$, M^+), 426 (0·4, $C_{23}H_{22}O_8$), 422 (1·4, $C_{23}H_{18}O_8$), 406 (3·4, $C_{23}H_{18}O_7$), 391 (5·2, $C_{22}H_{15}O_7$), 87 (100, $C_4H_7O_2$, *a*), 43 (23, C_2H_3O). For $C_{23}H_{22}O_9$ (442·4) was calculated: 62·44% C, 5·01% H; found: 62·67% C, 5·15% H.

V: $[\alpha]_D$ +84·0° (*c* = 0·35, chloroform). Mass spectrum (180°C) *m/z* (% of relative intensity, composition): 486 (0·06, $C_{23}H_{26}O_{10}$, M^+), 426 (0·8, $C_{23}H_{22}O_8$), 406 (20, $C_{23}H_{18}O_7$), 391 (27, $C_{22}H_{15}O_7$), 347 (5, $C_{20}H_{11}O_6$), 319 (5, $C_{19}H_{11}O_5$), 301 (2, $C_{19}H_9O_4$), 291 (2, $C_{18}H_{11}O_4$), 273 (1, $C_{18}H_9O_3$), 87 (100, $C_4H_7O_2$, *a*), 43 (19, C_2H_3O), 31 (16, CH_3O). For $C_{25}H_{26}O_{10}$ (486·5) was calculated: 61·72% C, 5·39% H; found: 61·59% C, 5·31% H.

VI: $[\alpha]_D$ −231·4° (*c* = 0·07, chloroform). Mass spectrum (180°C) *m/z* (% of relative intensity, composition): 486 (0·2, $C_{25}H_{26}O_{10}$, M^+), 426 (0·5, $C_{23}H_{22}O_8$), 406 (10, $C_{23}H_{18}O_7$), 391 (14, $C_{22}H_{15}O_7$), 347 (3, $C_{20}H_{11}O_6$), 319 (3, $C_{19}H_{11}O_5$), 301 (1, $C_{19}H_9O_4$), 291 (1, $C_{18}H_{11}O_4$), 273 (1, $C_{18}H_9O_3$), 87 (100, $C_4H_7O_2$, *a*), 43 (19, C_2H_3O). For $C_{25}H_{26}O_{10}$ (486·5) was calculated: 61·72% C, 5·39% H; found: 61·80% C, 5·35% H.

Reaction of Daunomycinone (*I*) with 1,3-Propanediol

Mixture of *I* (80 mg, 0·2 mmol), *p*-toluenesulfonic acid (20 mg), and 1,3-propanediol (1 ml) in benzene (30 ml) was heated 6 h to 130°C, diluted by water and extracted by chloroform.. After evaporation, the residue was subjected to preparative chromatography on Silufol in the system S_3. The nonpolar fraction was precipitated by hexane and provided the compound *VII* (7 mg, 8%, m.p. 223°C (chloroform–light petroleum), optically inactive). Mass spectrum (170°C) *m/z* (% of relative intensity, composition): 420 (100, $C_{24}H_{20}O_7$, M^+), 405 (91, $C_{23}H_{17}O_7$), 347 ($C_{20}H_{11}O_6$), 319 (23, $C_{19}H_{11}O_5$), 301 (6, $C_{19}H_9O_4$), 101 (83, $C_5H_9O_2$, *a*), 43 (22, C_2H_3O). The second fraction was purified by chromatography in the system S_7; crystallization yielded compound *IX* (11·5 mg, 11%, m.p. 141—142°C (ethanol), $[\alpha]_D$ +67·3° (*c* = 0·11, chloroform)). Mass spectrum (170°C) *m/z* (% of relative intensity, composition): 456 (0·2, $C_{24}H_{24}O_9$, M^+), 420 (24, $C_{24}H_{20}O_7$), 405 (27, $C_{23}H_{17}O_7$), 364 (5, $C_{20}H_{12}O_7$), 362 (4, $C_{21}H_{14}O_6$), 347 (29, $C_{20}H_{11}O_6$), 319 (10, $C_{19}H_{11}O_5$), 301 (4, $C_{19}H_9O_4$), 101 (100, $C_5H_9O_2$, *a*), 43 (85, C_2H_3O). The third fraction was puried by chromatography on Silufol in the system S_6. Crystallization from chloroform–light petroleum provided compound *VIII* (48 mg, 47%, m.p. 105°C, $[\alpha]_D$ +153·3° (*c* = 0·15, chloroform)). Mass spectrum (170°C) *m/z* (% of relative intensity, composition): 420 (100, $C_{24}H_{20}O_7$, M−94), 405 (80, $C_{23}H_{17}O_7$), 347 (72, $C_{20}H_{11}O_6$), 319 (21, $C_{19}H_{11}O_5$), 301 (7, $C_{19}H_9O_4$), 101 (51, $C_5H_9O_2$, *a*), 43 (85, C_2H_3O). For $C_{27}H_{30}O_{10}$ (514·5) was calculated: 63·03% C, 5·88% H; found: 62·95% C, 5·91% H. During the preparative chromatography of the above mentioned fraction was also obtained the compound *X* (15 mg, 16%, m.p. 172°C (ethanol), $[\alpha]_D$ −76·4$_c$ (*c* = 0·11, chloroform)). Mass spectrum (180°C) *m/z* (% of relative intensity, composition): 514 (0·1, $C_{27}H_{30}O_{10}$, M^+), 420 (12, $C_{24}H_{20}O_7$), 405 (14, $C_{23}H_{17}O_7$), 347 (16, $C_{20}H_{11}O_6$), 319 (6, $C_{19}H_{11}O_5$), 301 (3, $C_{19}H_9O_4$), 101 (100, $C_5H_9O_2$, *a*), 43 (58, C_2H_3O).

Reaction of Daunomycinone (*I*) with 1,4-Butanediol

Mixture of *I* (60 mg, 0·15 mmol), *p*-toluenesulfonic acid (25 mg), 1,4-butanediol (1·5 ml), and benzene (25 ml) was allowed to react 2 h at 130°C and then was worked-up as above. The residue after evaporation of the extraction solvent was subjected to chromatography on Silufol in the system S_3. This procedure removed the unreacted *I* (20 mg). The second, nonpolar fraction, contained the compound *XI* (42· mg, 59%, m.p. 107°C (ethanol–chloroform), $[\alpha]_D$ +109·7° (*c* = 0·3, chloroform)) as the main product. Mass spectrum (180°C) *m/z* (% of relative intensity, composition): 470 (2, $C_{25}H_{26}O_9$, M^+), 382 (10, $C_{21}H_{18}O_7$), 362 (100, $C_{21}H_{14}O_6$), 344 (62, $C_{21}H_{12}O_5$), 339 (28, $C_{19}H_{15}O_6$), 337 (32, $C_{19}H_{13}O_6$), 329 (15, $C_{20}H_9O_5$), 321 (21, $C_{19}H_{13}O_5$), 319 (20, $C_{19}H_{11}O_5$), 309 (14, $C_{18}H_{13}O_5$), 301 (38, $C_{19}H_9O_4$), 43 (48, C_2H_3O), 31 (69, CH_3O). The most polar fraction was purified by chromatography in the system S_7; the compound *XII* was obtained (11 mg, 16%, m.p. 201° (chloroform–ethanol), $[\alpha]_D$ −58·1° (*c* = 0·18, chloroform)). Mass spectrum (180°C) *m/z* (% of relative intensity, composition): 470 (0·5, $C_{25}H_{26}O_9$, M^+), 382 (6, $C_{21}H_{18}O_7$), 362 (100, $C_{21}H_{14}O_6$), 344 (60, $C_{21}H_{12}O_5$), 339 (18, $C_{19}H_{15}O_6$), 337 (20, $C_{19}H_{13}O_6$), 329 (13, $C_{20}H_9O_5$), 319 (14, $C_{19}H_{11}O_5$), 309 (11, $C_{18}H_{13}O_5$), 301 (31, $C_{19}H_9O_4$), 43 (22, C_2H_3O), 31 (26, CH_3O).

Reaction of Daunomycinone (*I*) with 1,4-Butyndiol

Mixture of *I* (100 mg, 0·25 mmol), *p*-toluenesulfonic acid (25 mg), 1,4-butyndiol (800 mg, 9·3 mmol), and benzene (40 ml) was boiled 2 h at 130°C and worked up as described above. The residue after the evaporation of the extraction solvent was chromatographed on Silufol in the system S_6. Unreacted *I* (22 mg) and the compound *XV* (72 mg, 62%, m.p. 215°C (methanol), $[\alpha]_D$ +62·8° (*c* = 0·2, chloroform)) were obtained. Mass spectrum (180°C) *m/z* (% of relative intensity, composition): 466 (0·2, $C_{25}H_{22}O_8$, M^+), 450 (0·2, $C_{25}H_{22}O_8$), 398 (0·6, $C_{21}H_{18}O_8$), 382 (4, $C_{21}H_{18}O_7$, 362 (100, $C_{21}H_{14}O_6$), 344 (64, $C_{21}H_{12}O_5$), 339 (10, $C_{19}H_{15}O_6$), 337 (6, $C_{19}H_9O_5$), 316 (12, $C_{20}H_{12}O_4$), 309 (5, $C_{18}H_{13}O_5$), 301 (34, $C_{19}H_9O_4$), 43 (23, C_2H_3O), 31 (CH_3O).

Reaction of Daunomycinone (*I*) with 1,6-Hexandiol

Mixture of *I* (100 mg, 0·25 mmol), *p*-toluenesulfonic acid (35 mg), 1,6-hexanediol (900 mg, 7·6 mmol), and benzene (50 ml) was worked up similarly to the previous experiments. The residue after extraction was separated by preparative chromatography on Silufol in the system S_6 and gave the compound *XII* (66 mg, 53%, m.p. 147—149°C (benzene), $[\alpha]_D$ +214·3° (*c* = 0·28, chloroform)). Mass spectrum (170°C) *m/z* (% of relative intensity, composition): 498 (0·04, $C_{27}H_{30}O_9$, M^+), 382 (2, $C_{21}H_{18}O_7$), 362 (33, $C_{21}H_{14}O_6$), 344 (20, $C_{21}H_{12}O_5$), 339 (5, $C_{19}H_{15}O_6$), 329 (4, $C_{20}H_9O_5$), 319 (5, $C_{19}H_{11}O_5$), 317 (4, $C_{19}H_9O_5$), 316 (4, $C_{20}H_{12}O_4$), 301 (11, $C_{11}H_9O_4$), 82 (22, C_6H_{10}), 70 (43, C_5H_{10}), 67 (77, C_5H_7), 57 (50, C_3H_5O), 55 (54, C_4H_7), 54 (42, C_4H_6), 43 (31, C_3H_7), 42 (100), 41 (96), 39 (19), 31 (88, CH_3O). The most polar fraction was purified using the same solvent system and gave unreacted *I* (5 mg) and the compound *XIV* (9 mg), 7%, m.p. 165—166°C (benzene–methanol), $[\alpha]_D$ −145·8° (*c* = 0·11, chloroform)). Mass spectrum (170°C) *m/z* (% of relative intensity, composition): 498 (0·1, $C_{27}H_{30}O_9$, M^+), 382 (3, $C_{21}H_{18}O_7$), 362 (77, $C_{21}H_{14}O_6$), 344 (55, $C_{21}H_{12}O_5$), 339 (8, $C_{19}H_{15}O_6$), 329 (14, $C_{20}H_9O_5$), 319 (11, $C_{19}H_{11}O_5$), 317 (10, $C_{19}H_9O_5$), 316 (12, $C_{20}H_{12}O_4$), 301 (32, $C_{19}H_9O_4$), 82 (22, C_6H_{10}), 70 (40, C_5H_{10}), 67 (82, C_5H_7), 57 (52, C_3H_5O), 55 (61, C_4H_7), 43 (46, C_3H_7), 42 (100), 41 (100), 39 (25), 31 (84, CH_3O).

Hydrolysis of Compound *V*

Hydrogen chloride (2%, 3 ml) was added to the solution of *V* (25 mg, 0·05 mmol) in methanol–acetone 1 : 1 (30 ml). The mixture was heated 2 h to 65°C and then allowed to stand 2 h at room temperature. The solvents were evaporated, the residue dissolved in water and extracted with chloroform. The yield was 22 mg (97%) of compound *XVI*, m.p. 115—116°C (methanol), $[\alpha]_D$ +79·3° (*c* = 0·02, chloroform). Mass spectrum (170°C) *m/z* (% of relative intensity, composition): 442 (1, $C_{23}H_{22}O_9$, M^+), 424 (0·3, $C_{23}H_{20}O_8$), 406 (1, $C_{23}H_{18}O_7$), 382 (6, $C_{21}H_{18}O_7$), 362 (70, $C_{21}H_{14}O_6$), 344 (49, $C_{21}H_{12}O_5$), 339 (19, $C_{19}H_{15}O_6$), 329 (12, $C_{20}H_9O_5$), 321 (9, $C_{19}H_{13}O_5$), 319 (14, $C_{19}H_{11}O_5$), 309 (14, $C_{18}H_{13}O_5$), 301 (30, $C_{19}H_9O_4$), 43 (53, C_2H_3O), 31 (100, CH_3O).

Hydrolysis of Compound *VI*

The same procedure applied to compound *VI* (12 mg, 0·025 mmol) yielded quantitatively 10·9 mg of compound *XVII*, m.p. 226—228°C (methanol), $[\alpha]_D$ −107·6° (*c* = 0·07, chloroform). Mass spectrum (200°C) *m/z* (% of relative intensity, composition): 442 (3, $C_{23}H_{22}O_9$, M^+), 424 (1, $C_{23}H_{20}O_8$), 406 (1, $C_{23}H_{18}O_7$), 382 (9, $C_{21}H_{18}O_7$), 362 (82, $C_{21}H_{14}O_6$), 344 (32, $C_{21}H_{12}O_5$), 339 (40, $C_{19}H_{15}O_6$), 337 (100, $C_{19}H_{13}O_6$), 329 (5, $C_{20}H_9O_5$), 321 (29, $C_{19}H_{13}O_5$), 319 (24, $C_{19}H_{11}O_5$), 309 (39, $C_{18}H_{13}O_5$), 301 (20, $C_{19}H_9O_4$), 43 (41, C_2H_3O), 31 (13, CH_2O).

Hydrolysis of Compound *VIII*

Hydrogen chloride (2%, 2 ml) was added to the solution of *VIII* (15 mg) in methanol–acetone 1 : 1 (30 ml). The same procedure as described for *VI* provided 13 mg of compound *XVIII*, m.p. 121—122°C (chloroform), $[\alpha]_D$ +223·3° (*c* = 0·06, chloroform). Mass spectrum (180°C) *m/z* (% of relative intensity. composition): 456 (0·6, $C_{24}H_{24}O_9$, M^+), 420 (1, $C_{24}H_{20}O_7$), 405 (1, $C_{23}H_{17}O_7$), 382 (5, $C_{21}H_{18}O_7$), 362 (100, $C_{21}H_{14}O_6$), 344 (44, $C_{21}H_{12}O_5$), 339 (17, $C_{19}H_{15}O_6$), 337 (17, $C_{19}H_{17}O_6$), 329 (8, $C_{20}H_9O_5$), 319 (15, $C_{19}H_{11}O_5$), 309 (9, $C_{18}H_{13}O_5$), 301 (25, $C_{19}H_9O_4$), 58 (52), 57 (43), 43 (37, C_2H_3O), 31 (39, CH_3O).

Reduction of Compound *XVI*

The suspension of *XVI* (35 mg, 0·08 mmol) was stirred in water (25 ml) with added 2M-NaOH until dissolution and then was added sodium borohydride (15 mg). The mixture was stirred 1 h at 22°C, acidified by 0·2M-HCl and extracted with chloroform. The yield was 31 mg (88%) of compound *XIX*, m.p. 127°C (methanol), $[\alpha]_D$ +117·6° (*c* = 0·09, chloroform). Mass spectrum (180°C) *m/z* (% of relative intensity, composition): 444 (0·5, $C_{23}H_{24}O_9$, M^+), 382 (29, $C_{21}H_{18}O_7$), 364 (100, $C_{21}H_{16}O_6$), 348 (25, $C_{21}H_{16}O_5$), 346 (54, $(C_{21}H_{14}O_5)$), 338 (55, $C_{19}H_{14}O_6$), 331 (25, $C_{20}H_{11}O_5$), 323 (24, $C_{18}H_{11}O_6$), 321 (26, $C_{19}H_{13}O_5$), 310 (27, $C_{18}H_{14}O_5$), 306 (18, $C_{18}H_{10}O_5$), 303 (30, $C_{19}H_{11}O_4$). ^1H NMR (C^2HCl_3): 1·28 d (*J* = 6·1 Hz, 3 H), 1·80—2·60 mt (2 H), 2·71 and 3·17 AB system (*J* = 19·5 Hz), 3·80 mt (3 H), 4·08 s (3 H), 5·10 mt (1 H), 7·35 dd, (*J* = 7·3 and 1·8 Hz, 1 H), 7·79 t (*J* = 7·3 Hz, 1 H), 8·06 dd (*J* = 7·3 and 1·8 Hz, 1 H), 13·55 s (1 H), 14·21 s (1 H).

Ethylene Acetal of Compound *XII*

Mixture of *XII* (6 mg), *p*-toluenesulfonic acid (1 mg), 1,2-ethanediol (1 ml), and benzene (5 ml) was heated 6 min to 130°C. After cooling, water was added and the mixture was extracted with chloroform. Repeated chromatography on Silufol in the system S_6 gave 4 mg of compound *XX*,

m.p. 147°C, $[\alpha]_D$ −170° (c = 0·18, chloroform). Mass spectrum (165°C) m/z (% of relative intensity, composition: 514 (0·1, $C_{27}H_{30}O_{10}$, $M^{+\cdot}$), 406 (5, $C_{23}H_{18}O_7$), 391 (7, $C_{22}H_{15}O_7$), 362 (1, $C_{21}H_{14}O_6$), 347 (2, $C_{20}H_{11}O_6$), 338 (2, $C_{19}H_{14}O_6$), 319 (2, $C_{19}H_{11}O_5$), 301 (1, $C_{19}H_9O_4$), 217 (1, $C_{12}H_9O_4$), 87 (100, $C_4H_7O_2$).

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