was obtained with mp 158-160°C from ethanol, and also identical with a tetraacetate of hydroxymeristotropic acid [4] according to IR and UV spectroscopy.

SUMMARY

A pentacyclic triterpenoid isolated from the roots of the plant *Glycyrrhiza triphylla* Fisch. et Mey — triphyllic acid — has the structure of 3β,24-dihydroxy-22-oxooleano-12-en-29-oic acid.

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GLYCOSYLATION OF BETULIN AND ITS ACETATES IN THE PRESENCE OF CADMIUM CARBONATE

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UDC 547.917+547.455+547.918+547.497

The glycosylation of betulin and its acetates by α-acetobromoglucose in toluene in the presence of cadmium carbonate is considered. It has been shown that the reaction is accompanied by Wagner—Meerwein rearrangements of the initial alcohols in rings A and E. This leads to the formation — in addition to acetates of betulin glycosides — of derivatives of allobetulin — A-nor-$\Delta^{3(5)}$-allobetulin and A-nor-$\Delta^{3(5)}$-betulin — as was shown by ^{1}H and ^{13}C NMR spectroscopy.

Betulin — one of the representatives of the pentacyclic triterpenoids of the lupane series most promising for practical use — is widely distributed in the vegetable kingdom [1, 2]. The main source of betulin is the bark of various species of the genus *Betula* [1-5]. Esters of betulin and higher fatty acids have found use as various protective coatings [6]. A number of plant extracts, the main components of which are betulin, betulinic acid, and lupeol, exhibit an antitumoral action [7, 8].

The availability and biological activity of betulin place it among valuable natural sources for use both in the native state and in the form of various transformation products.

Our aim was to study the conditions for the glycosylation of betulin (I) and its acetates (II) and (III) by α-acetobromoglucose (α-ABG) in the presence of cadium carbonate in toluene [12]. We have previously synthesized some acetylated betulin glycosides by the orthoester and other methods [9-11]. The glycosylation conditions used by Conrow and Bern-

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TABLE 1. Conditions and Results of the Glycosylation of Compounds (I-III) in Toluene

Expt.	Starting materials, mmole			Reaction time, h	Yield of products, %		Recovery of the initial alcohol, %
	ROH	α-ABG	$CdCO_3$		acyl glycosides	by-products	
1	II, 4,55	6,8	6,8	3	IV, 41,4	IV, 5,0; IX, 28,6*; XI, 4,2*	3,6
2	III, 2,8	4,2	4,2	3	VII, 61,4; VIII, 2,2	IV, 7,0; XII, 23,1*	1,2
3	I, 5,0	12,5	12,5	1	V, 17,8; X, 52.2*	XI, 25,1*	—

*The yields of compounds (IX-XII) are given on the crystallized substances, and the others of the chromatographically homogeneous substances.

TABLE 2. ^{13}C Chemical Shifts of the Initial Alcohols (I-III) and the Products of Their Transformations (ppm relative to TMS)

C atom	Compound							
	I	II	III	VI	IX	X	XI	XII
1	38,9	38,4	38,8	38,4	38,6	39,0	42,0	41,9
2	27,2	23,7	27,4	23,7	23,7	26,0	27,4	27,5
3	79,0	81,0	78,7	80,8	80,8	90,6	136,2	136,3
4	38,9	37,8	38,8	37,8	37,8	39,0	26,3	26,4
5	55,4	55,4	55,4	55,4	55,6	55,8	140,0	140,0
6	18,4	18,2	18,3	18,1	18,1	18,1	19,8	19,8
7	34,4	34,2	34,2	34,2	34,1	34,2	34,7	34,7
8	41,0	40,9	40,9	40,9	40,6	40,7	40,9	41,3
9	50,6	50,4	50,4	50,3	51,0	51,1	50,2	50,0
10	37,2	37,1	37,1	37,1	37,2	37,0	49,9	49,6
11	21,0	20,9	20,8	20,9	21,0	21,1	23,7	23,7
12	25,3	25,2	25,2	25,1	26,3	26,3	26,3	25,5
13	37,4	37,3	37,6	37,8	36,7	36,8	36,8	38,2
14	42,8	42,7	42,6	42,7	41,5	41,5	41,5	42,7
15	27,2	27,1	27,1	27,1	26,4	26,4	26,6	27,5
16	29,3	29,2	29,6	29,4	26,4	26,4	26,8	29,8
17	47,9	47,8	46,3	47,1	40,6	40,7	40,6	46,5
18	48,9	48,8	48,8	48,7	46,8	46,9	46,9	48,9
19	47,9	47,8	47,6	48,0	87,9	87,9	88,0	47,8
20	150,7	150,4	149,9	150,3	36,3	36,3	36,3	150,2
21	29,8	29,8	29,8	29,6	32,7	32,8	32,6	29,8
22	34,0	34,0	34,5	34,0	33,9	34,0	32,8	32,9
23	28,0	27,9	28,0	27,9	27,9	27,6	21,8	21,9
24	15,5	16,5	15,4	16,5	16,5	16,2	21,3	21,3
25	16,2	16,0	16,1	16,1	15,7	15,7	19,2	19,2
26	16,2	16,2	16,1	16,1	16,5	16,4	14,3	14,7
27	14,8	14,8	14,8	14,8	13,5	13,5	13,5	14,7
28	60,1	60,4	62,8	68,6	71,7	71,2	71,3	62,9
29	109,6	109,7	109,8	109,7	24,5	24,6	24,6	109,8
30	19,2	19,1	19,2	19,0	28,8	28,9	28,9	19,0
OAc	—	21,3	20,9	21,3	21,3	—	—	20,9
		170,9	171,4	170,9	170,9			171,4

stein [12] attracted our attention because of the availability of the initial reactants and the simplicity of performing the experiment. The literature has information on the use of this method for the synthesis of triterpenoid glycosides [11, 13].

The present work is distinguished by a more complete analysis of the glycosylation products, which permits an objective evaluation possibility of this modification. Since it is planned subsequently to study the glycosylation reaction of a number of other representatives of the triterpenoids of the lupane series, we decided to dwell in detail on the proof by NMR spectroscopy of the structures of the compounds obtained. The ^{13}C chemical shifts of the initial alcohols and the products of their glycosylation are given in Tables 2 and 3.

The glycosylation of 3-O-acetylbetulin (II) (Table 1, experiment 1) led to the formation of the glucoside pentaacetate (VI) [10], with the β configuration of the glycosidic bond, and the diacetate (IV) [11], and also of two nonpolar compounds (IX) and (XI).

The structure of compound (IX) as allobetulin acetate was shown on the basis of an absence of a depression of the melting point of a mixed sample with the authentic substance

TABLE 3. ^{13}C Chemical Shifts of the Sugar Components of the Glycosides (VI) and (VII) (ppm relative to TMS)*

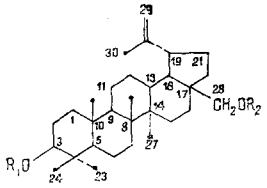
Compound	C atom					
	1	2	3	4	5	6
VI	101,6	71,3	72,9	68,6	71,7	62,1
VII	102,9	71,6	72,9	68,8	71,7	62,3

*The ^{13}C signals of the acetate groups of the sugar components of glycosides (VI) and (VII) appear in the 20.6-20.8 ppm (CH_3) and 169.0-171.0 ppm (C=O) regions.

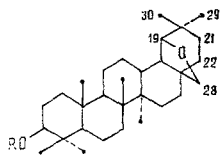
obtained as described in [14]. The selection of (IX) as the basic compound permitted an unambiguous determination of the structures of compounds (X-XII) by a comparison of spectral characteristics.

The absence of a signal from olefinic protons at 4.6-4.7 ppm in the ^1H spectrum of (IX), while such signals were observed in this region in the ^1H spectrum of compound (II), showed that changes had been undergone by the double bond of the initial acetate. The appearance in the ^{13}C spectrum of (IX) of the signal of a methine carbinyl carbon atom at 87.9 ppm and a shift of the signal of the C^{28} atom downfield by 11.3 ppm as compared with the signal of the corresponding atom in the spectrum of (II) showed the participation of the hydroxymethyl group at C^{17} in the observed rearrangement of the acetate (II).

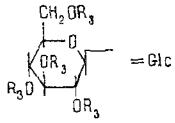
Since the comparison of the ^{13}C spectra of compounds (II) and (IX) with the spectra of 3β-acetyl derivatives of tetra- and pentacyclic triterpenoids [15-17] shows good agreement of the ^{13}C chemical shifts (CSs) of rings A, B, and C in (II) and (IX) and the triterpenoids mentioned, it may be concluded that the rearrangement affected only rings D and E of the initial acetate (II).



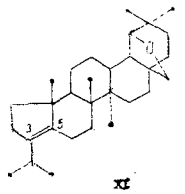
I. $R_1=R_2=H$;
II. $R_1=Ac$, $R_2=H$;
III. $R=H$, $R_2=Ac$;
IV. $R_1=R_2=Ac$;
V. $R_1=R_2=Glc$, $R_3=Ac$;
VI. $R_1=R_3=Ac$, $R_2=Glc$;
VII $R_1=-Glc$, $R_2=R_3=Ac$
VIII. $R_1=-Glc$, $R_2=R_3=Ac$
XIV. $R_1=R_2=Glc$, $R_3=H$;
XV. $R_1=R_3=H$, $R_2=Glc$;
XVI. $R_1=R_3=H$, $R_2=Glc$;



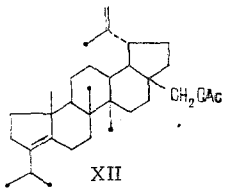
IX. R = Ac;
X. R = Glc, R_3=Ac;
XVII. R = Glc, R_3=H;



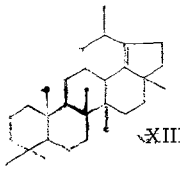
=Glc



XI



XII



XIII

The appearance in the ^1H spectrum of (IX) of another two singlet signals of methyl groups [$C^{20}-(CH_3)_2$] in the 0.80-0.91 ppm region as compared with the spectrum of (II), and also of the signal of a quaternary carbon atom in the ^{13}C spectrum at 36.3 ppm (C^{20}) as compared with

the spectrum of (II), together with the facts presented above, permits compound (IX) quite definitely to be ascribed the structure of allobetulin acetate.

The complete assignment of the signals in the ^{13}C spectra of IX was made by comparing the spectra of (II) and (IX), by the use of ^{13}C experiments with off-resonance decoupling of protons, and by the calculation of the ^{13}C CSs of rings D and E by the method of Beierbeck et al. [18]. Another of the by-products formed in the glycosylation of (II) was ascribed the structure of A-nor-$\Delta^{3(5)}$-allobetulin or "α-apoallobetulin" (XI), the formation of which obviously took place as the result of a Wagner–Meerwein rearrangement [2, 19] in ring A of compound (IX). The formation of α-apoallobetulin has been observed previously when allobetulin was treated with various dehydrating agents [1]. The spectral characteristics of (XI) did not differ from those for α-apoallobetulin.

A comparison of the ^{13}C spectra of compounds (IX) and (XI) showed good agreement of the signals of the atoms of rings C, D, and E and the C^7 signal of ring B. Consequently, (IX) and (XI) differed by the structure of ring A. The ^1H spectrum of (XI) showed two doublet signals of methyl groups at 0.92 and 0.98 ppm with the same spin–spin coupling constants (SSCCs) (J ≈ 6.7 Hz), and a regular septet with unit intensity at 2.65 ppm and the same SSCC value, which shows the presence in ring A of (XI) of an isolated isopropyl group formed as the result of the contraction of ring A. The ^{13}C spectrum of (XI) contained two signals of the quaternary carbon atoms at 136.2 and 140 ppm, showing the presence of a tetrasubstituted double bond in (XI). Since a tetrasubstituted double bond in ring A of (XI) can be located only in the 3(5) position, compound (XI) has the structure of A-nor-$\Delta^{3(5)}$-allobetulin.

The presence of $\Delta^{3(5)}$ double bond in (XI) was confirmed by the downfield shift of the signals of the C^{10} quaternary atom in the ^{13}C spectrum of (XI) (49.9 ppm) as compared with its position in the spectrum of (IX) (37.2 ppm), since in (XI) this atom is present in the allyl position to a double bond. This was also shown by the downfield shift of the C^{25} signal (19.2 ppm) in the ^{13}C spectrum of (XI) as compared with the position of the corresponding signal in the spectrum of (IX) (15.7 ppm), due to its homoallyl position in (XI) [20]. The assignment of the signals of the carbon atom of ring A in the ^{13}C spectrum of (XI) was made by comparing the ^{13}C CSs of ring E in 20,29-dihydrolup-18-ene (XII) [17], modeling ring A in (XI), with the CSs of the corresponding atoms of (XI).

The glycosylation of 28-O-acetylbetulin (III) (Table 1, experiment 2) led to the formation of a mixture of the α and β anomers of the glycosides (VIII) and (VII) with a predominance of the latter.

The α configuration of the glycosidic bond in (VIII) was established in [11] and the β configuration of the glycosidic bond in (VII) was confirmed by the CS of the signal of the anomeric proton in its ^1H spectrum (4.53 ppm) and the SSCC of this proton (J = 8.0 Hz). In addition to the glycosides (VII) and (VIII), the formation of the diacetate (XII) and of a nonpolar compound, to which the structure of 28-O-acetyl-A-nor-$\Delta^{3(5)}$-betulin (XII) was assigned, was observed. A comparison of the ^{13}C spectra of (III) with (XII) showed a good agreement of the signals of the atoms of ring C, D, and E and the signal of C^7 of ring B, as in the case of the pair (IX) and (XII), showing a difference between them only in the structure of ring A. The presence in the ^1H spectrum of (XII) of two doublet signals of methyl groups at 0.92 and 0.98 ppm (J = 6.7 Hz) and of a regular septet of unit intensity at 2.65 ppm (J = 6.7 Hz) and also of two signals of quaternary carbon atoms at 136.3 and 140.0 in the ^{13}C spectrum of (XII) confirmed the identity of the structures of rings A in compounds (XII) and (XI) and, therefore, the suggested structure of compound (XII).

The glycosylation of betulin (I) (Table 1, experiment 3) led to the formation of a nonpolar compound (XI) and of two glucosides (V) and (X). The β configurations of both glycosidic bonds in the 3,28-bisglucoside (V) was established in [9]. The presence of an acetylated sugar component in (X) was confirmed by the presence in the ^1H spectrum of (X) of the signals of the protons of four acetate groups in the 2.00-2.07 ppm region and the signals of six protons in the 3.39-5.33 ppm region. A comparison of the ^{13}C spectra of (IX) and (X) revealed good agreement of almost all the signals of the carbon atoms with the exception of C^2, C^3, and C^4 (Table 3). Compounds (IX) and (X) therefore have the same skeleton and differ only by the nature of the substituent at C^3, as is shown in the different effects of the acetate and glycosyl groupings on the CSs of the carbon atoms of ring A.

The β configuration of the glycosidic bond in (X) was determined by the CS value of the signal of the anomeric proton in the ^1H spectrum (4.54 ppm) and the SSCC of this proton (J = 7.6 Hz).

Thus, compound (X) was assigned the structure of 3-O-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl)allobetulin.

It must be mentioned that the prolonged heating of betulin and its monoacetates under the conditions given by Conrow and Bernstein [12] in the absence of α-acetobromoglucose did not lead to any appreciable change in them. In order to obtain free glucosides of betulin and of allobetulin, we deacetylated the acetates (V, VI, VII, and X) under the action of 0.1 N CH_3ONa in methanol. The yields of the glucosides (XIV-XVII) amounted to 90-95%.

An analysis of the experimental results (Table 1) showed that the glycosylation of betulin and its monoacetates with α-acetobromoglucose in toluene in the presence of $CdCO_3$ is accompanied by fairly well-defined Wagner–Meerwein rearrangements affecting rings A and E of the initial triterpenoids.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Bruker HX-90E spectrometer in the Fourier regime at 30°C using 8% solution of the substances in $CDCl_3$ at a working frequency of 90.0 MHz for ^1H and 22.63 MHz for ^{13}C. The accuracy of the measurements was ±0.15 Hz for ^1H and ±1.5 Hz for ^{13}C. Optical rotations were determined in a Perkin-Elmer 141 polarimeter at 20°C in a cell 10 cm long, and melting points on a Boëtius stage.

Column chromatography was performed on silica gel L 100/160 (Chemapol, Czechoslovakia). The substances were eluted with petroleum ether–acetone systems. TLC was performed on a fixed layer of SiO_2 in the following systems: 1) hexane–acetone (2:1), and 2) benzene–chloroform–methanol (3:2:1). The TLC plates were revealed with 10% H_2SO_4 in MeOH at 120-150°C. Grade kh.ch. ["chemically pure"] toluene was purified by redistillation over Na. Betulin was isolated from the bark of the birch *Betula platyphylla* [21], mp 250-252°C (benzene). The acetates (II) and (III) were obtained as described by Ruzicka et al. [21].

General Procedure for the Glycosylation of (I-III). A solution of α-acetobromoglucose in toluene (10-20 ml) was added dropwise over 30 min to a boiling suspension of the initial alcohol and cadmium carbonate in toluene (50-100 ml). After the end of the reaction (monitoring by TLC in system 1), the mixture was cooled, the solid matter was filtered off, and the filtrate was evaporated to dryness under reduced pressure. The residue was chromatographed on a column of SiO_2. The chromatographically individual substances were purified additionally by crystallization from ethanol. The yields of the glycosylation products are given in Table 1.

Experiment 1. From 2.205 g of (II) we obtained: 1.51 g of (VI), mp 140-142°C (lit. [10]: 140-143°C); 0.8 g of (II); 0.12 g of (IV), mp 217-219°C (lit. [21]: 217-219°C); 0.63 g of (IX), mp 284-284.5°C (lit. [14]: 281-283°C); and 0.081 g of (XI), mp 203-206°C (lit. [1]: 200-201°C).

Experiment 2. From 1.38 g of (III) we obtained 1.4 g of (VII), mp 162-164°C (lit [10]: 177-179°C); 0.04 g of (VIII), mp 113-114°C (lit. [11]: 111-114°C); 0.02 g of (III); 0.10 g of (IV), 0.35 g of (XII), $C_{32}H_{50}O_2$, mp 57-60°C, $[\alpha]_D^{20}$ +27.0° (c 0.5; chloroform).

Experiment 3. From 2.21 g of (I) we obtained: 0.85 g of (V), mp 230-231°C (lit. [10]: 230-231°C); 1.86 g of (X), $C_{44}H_{68}O_{11}\cdot C_2H_5OH$, mp 230-231°C, $[\alpha]_D^{20}$ +41.2° (c 1.0; chloroform); and 0.54 g of (XI).

General Procedure for the Saponification of the Acetylated Glucosides (V-VIII) and (X). The initial glucoside (1 mmole) was treated at room temperature with 50 ml of a 0.1 N solution of MeONa in MeOH. The completeness of deacylation was checked by the TLC method in system 2. After neutralization of the solution with KU-2 resin (H^+ form) and separation of the resin, the filtrate was evaporated to dryness under reduced pressure. The residue was crystallized from methanol.

3,28-Di-O-β-D-glucopyranosylbetulin (IV), amorphous powder $C_{42}H_{70}O_{12}\cdot H_2O$, $[\alpha]_D^{20}$ +6.62° (c 0.73, methanol).

28-O-β-D-Glucopyranosylbetulin (XV), $C_{36}H_{60}O_7\cdot 3CH_3OH$, mp 155-157°, $[\alpha]_D^{20}$ +1.1°(c 0.09, methanol).

3-O-β-D-Glucopyranosylbetulin (XVI), $C_{36}H_{60}O_7\cdot 4CH_3OH$, mp 192-195°, $[\alpha]_D^{20}$ +9.5° (c 0.5, methanol).

3-O-β-D-Glucopyranosylallobetulin (XVII), $C_{36}H_{60}O_7 \cdot CH_3OH$, mp 256-260°, $[\alpha]_D^{20}$ +16.7° (c 1.0, pyridine).

SUMMARY

1. The interaction of betulin and its monoacetates at C^3 and C^{28} with α-acetobromoglucose on heating with toluene in the presence of cadmium carbonate has been studied. It has been found that these conditions can be used for the synthesis of the tetraacetate of allobetulin β-D-glucoside and pentaacetates of betulin β-D-glucosides.

2. It has been shown that the glycosylation of betulin and its monoacetates is accompanied by Wagner–Meerwein rearrangements in rings A and E of the initial alcohols with the formation of derivatives of allobetulin, of A-nor-$\Delta^{3(5)}$-betulin, and of A-nor-$\Delta^{3(5)}$-allobetulin.

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