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PARTICIPATION OF OXYGEN-CONTAINING GROUPS IN POSITION 28 IN THE ADDITION OF BROMINE TO THE DOUBLE BOND OF 20(21)-TARAXASTENE DERIVATIVES

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The oxygen atom from position 28 takes part in the addition of bromine to the double bond of 20(21)-taraxastene derivatives *I*–*IV*. For the 28-hydroxy group the participation is more than 98%, for the 28-acetoxy group it is roughly 50%, while for the benzoyloxy group it is less than 5%. If the reaction takes place with the participation of the 28-functional group 21α-bromo-20β,28-epoxy derivatives *V*, *VII*, *VIII*, and *XVIII* are formed; in the case of diacetate *III* a partial migration of the 19α-methyl group also takes place, resulting in 21α-bromo-19β,28-epoxy derivative *XXVIII*. Without the participation of the 28-functional group mostly allylic bromo derivatives *XVI* and *XXIV* are formed.

In connection with the study of the participation of the 28-functional group in reactions of 20(21)-double bond and 20α,21α-epoxy group in taraxastene skeleton we investigated[1–3] mainly the course of the reactions of 28-hydroxy- and 28-acetoxy derivatives which led, depending on the reaction conditions applied, to the formation of oxygen bridges from $C_{(28)}$ to the positions 19, 20 and 21. We have shown[4] that the nucleophility of the oxygen atom in 28-benzoyloxy derivatives is very low so that the participation of this functional group in the reactions of 20α,21α-epoxy group is practically excluded.

In this paper we wish to compare the participation of the 28-hydroxy, acetoxy, and benzoyloxy group during the reaction of the double bond with bromine. In this reaction the differences in the nucleophility of the 28-oxygen atom should be sufficiently great, as follows from the study of the participation reactions during the addition of halogens to the double bonds[5,6]. The study was carried out with 3-deoxy-heterobetulin (*I*), heterobetulin** (*II*), its diacetate *III*, and dibenzoate *IV*, in acetic acid.

The reaction of bromine with 28-hydroxy compounds *I* and *II* had a uniform course at 10–14°C, while at higher temperature side-reactions occurred. In the case of

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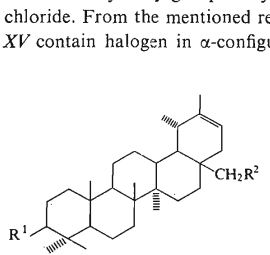
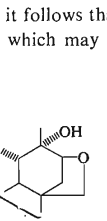
** For the sake of simplicity we use trivial names derived from heterobetulin: 18α,19β*H*-urs-20-ene-3β,28-diol.

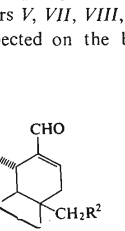
3-deoxyheterobetulin (*I*), where the product formed may be differentiated most easily, the only product formed at 10°C is bromo ether *V*. At 60°C 3-deoxyallo-heterobetulin (*VI*) (formed on isomerisation[1] catalysed with hydrogen bromide formed in the reaction) was isolated as the main product in addition to a small amount of bromo ether *V*. Under the effect of bromine on heterobetulin (*II*) at 14°C bromo ether *VII* was formed which on acetylation under mild conditions gave acetate *VIII*. The bromine atom in bromo ethers *V*, *VII*, and *VIII* is very reactive and easily submits to substitution reactions. On alumina it is substituted by hydroxy group; thus, bromo derivatives *VII* and *VIII* are transformed to known[3] 21α-hydroxy derivatives *IX* and *X*. In acetic acid in the presence of sodium acetate acetoxy derivatives *XI*, *XII*, and the known[3] diacetate *XIII* are formed from bromo derivatives *V*, *VII*, and *VIII*. Diacetate *XIII* was also the sole product during an attempt at reduction of bromo derivative *VIII* with zinc in acetic acid. The increased reactivity of the bromine atom in the mentioned epoxy derivatives indicates the participation of the neighbouring oxygen atom during substitution reactions. The effect of the epoxide oxygen on the reactivity of the substituents in positions 20 and 21 was also observed in subsequent reactions which led to the formation of 21-halo ethers of the given type from 20-hydroxy ether *XIV*. As was shown earlier, in acidic medium the epoxidic bond of hydroxy ether *XIV* migrates* from $C_{(21)}$ to $C_{(20)}$ under formation of 21α-substituted derivatives with a six-membered epoxide ring[3]. When hydrogen bromide was used bromo ether *VIII* was obtained from hydroxy ether *XIV*. Similarly, under the effect of hydrogen chloride or phosphorus oxychloride chloro ether *XV* was prepared. The same chloro ether was also obtained in an attempt at elimination of the 21α-hydroxy group in hydroxy ether *X* under the effect of phosphorus oxychloride. From the mentioned reactions it follows that halo ethers *V*, *VII*, *VIII*, and *XV* contain halogen in α-configuration, which may be also expected on the basis



I, $R^1 = H$, $R^2 = OH$
II, $R^1 = R^2 = OH$
III, $R^1 = R^2 = OCOCH_3$
IV, $R^1 = R^2 = OCOC_6H_5$



XIV, $R^1 = OCOCH_3$

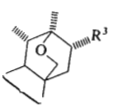


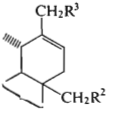
XXVI, $R^1 = R^2 = OCOCH_3$
XXX, $R^1 = R^2 = OCOC_6H_5$

* A more detailed discussion of an analogous rearrangement in steroid compounds was published recently in paper[7].

of a better steric accessibility of the double bond from the α-side during the reaction with bromine. The α-configuration is also corroborated by PMR spectrum of chloroether *XV* in which the doublet of the 19α-methyl group is shifted downfield (+0·36 p.p.m.) in comparison with that of 3-deoxyalloheterobetulin (*VI*). According to the analogy in steroid chemistry[8] this corresponds to the 1,3-diaxal position of 19α-methyl group and 21-chlorine atom. The retention of the α-configuration of the substituents on $C_{(21)}$ during substitution reactions is caused by the participation of the vicinal epoxide oxygen[7,9].

The reaction of bromine with ester *III* and *IV* led to the formation of a mixture of bromo derivatives the separation of which was difficult both owing to small differences in adsorptivity and to the appreciable reactivity of some components. The reactive bromo derivatives were isolated only in the case of dibenzoate *IV*. Chromatography on silica gel gave a mixture of dibenzoylbromo derivatives *XVI* and *XVII* and monobenzoate *XVIII* which according to IR spectrum contained a six-membered epoxide ring (1047 cm^{-1}). In agreement with the above mentioned reactivity of halogen in this type of compounds bromo ether *XVIII* afforded under the effect of sodium acetate acetyl derivative *XIX*, while it is transformed by contact reaction with alumina to the known[4] hydroxy ether *XX*. From the chromatographically inseparable mixture of dibenzoylbromo derivatives *XVI* and *XVII*, derivative *XVI* was obtained by repeated crystallisation. Two AB systems of CH_2—O and CH_2—Br groups were found in its PMR spectrum in addition to a signal of an olefinic proton and the 22β-H signal coupled with it (2·265 p.p.m., J_{gem} = 17 Hz, J_{vic} = 6·5), similarly as in the earlier[4] described analogous chloro derivative *XXI*. The reactivity



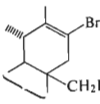


V, $R^1 = H$, $R^3 = Br$
VI, $R^1 = R^3 = H$
VII, $R^1 = OH$, $R^3 = Br$
VIII, $R^1 = OCOCH_3$, $R^3 = Br$
IX, $R^1 = R^1 = R^3 = OH$
X, $R^1 = OCOCH_3$, $R^3 = OH$
XI, $R^1 = H$, $R^3 = OCOCH_3$
XII, $R^1 = OH$, $R^3 = OCOCH_3$
XIII, $R^1 = R^3 = OCOCH_3$
XV, $R^1 = OCOCH_3$, $R^3 = Cl$
XVIII, $R^1 = OCOC_6H_5$, $R^3 = Br$
XIX, $R^1 = OCOC_6H_5$, $R^3 = OCOCH_3$
XX, $R^1 = OCOC_6H_5$, $R^3 = OH$

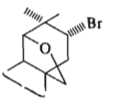
XVI, $R^1 = R^2 = OCOC_6H_5$, $R^3 = Br$
XXI, $R^1 = R^2 = OCOC_6H_5$, $R^3 = Cl$
XXII, $R^1 = R^2 = OCOC_6H_5$, $R^3 = OH$
XXIII, $R^1 = R^2 = OCOC_6H_5$, $R^3 = OCOCH_3$
XXIV, $R^1 = R^2 = OCOCH_3$, $R^3 = Br$
XXV, $R^1 = R^2 = R^3 = OCOCH_3$
XXVII, $R^1 = R^2 = OCOCH_3$, $R^3 = OH$
XXIX, $R^1 = R^2 = OCOC_6H_5$, $R^3 = OCOH$

of the bromine atom is in accordance with structure *XVI*: by contact reaction on alumina the known[4] hydroxy derivative *XXII* is formed from bromo derivative *XVI*; under the effect of sodium acetate, acetate *XXIII* is formed which was also obtained on acetylation of hydroxy derivative *XXII*. Hence both substitution reactions take place without an allylic rearrangement. On reaction of bromine with diacetate *III* reactive bromo derivatives of the same type as from dibenzoate *IV* are formed, *i.e.* bromoether *VIII* and the allylic bromo derivative *XXIV*. These derivatives could not be isolated, but their presence was proved by their transformation to acetates *XIII* and *XXV* when the crude mixture of bromo derivatives was allowed to react with sodium acetate. For comparison triacetate *XXV* was also prepared by reduction of the unsaturated aldehyde *XXVI* with sodium borohydride and acetylation of the diacetyl alcohol *XXVII* formed.

In order to obtain further components from the mixtures of acetyl- and benzoyl-bromo derivatives we transformed the reactive bromo derivatives (*VIII* and *XXIV*, or *XVI* and *XVIII*) to acetates (*XIII* and *XXV*, or *XIX* and *XXIII*, respectively) using sodium acetate. The acetates could be separated from the unreacted bromo derivatives (*XXVIII* or *XVII*) chromatographically. From the mixture of acetyl-bromo derivatives monobromo derivative *XXVIII* was isolated in this manner, having a five-membered epoxy ring (1032 cm^{-1}), in the PMR spectrum of which the doublet of the 19α-methyl group is absent, but the singlet 19α-H (3·72 p.p.m., $J_{vic} \sim 0$), characteristic of the 19β,28-epoxy-18α-oleanane derivatives[10] was present; the signals of the 28-methylene group also correspond to this skeleton. The hydrogen atoms in the position 21 give a doublet of doublets (4·18 p.p.m., $J_1 \sim 7$ Hz, $J_2 \sim 11{\cdot}5$ Hz), the coupling constants of which correspond according to the molecular model to the axial β-configuration. Hence, the bromine atom must have the equatorial α-configuration. Evidently, a rearrangement of the 19α-methyl group into position 20 must have taken place. Such a rearrangement was already observed during acid catalysed isomerisation of heterobetulin derivatives[11], where it took place to a substantially smaller extent. The possibility that bromo ether *XXVIII* was formed by a subsequent rearrangement of bromo ether *VIII* under the influence of hydrogen bromide was excluded because such an isomerisation could not be performed even with a higher concentration of hydrogen bromide and a prolonged reaction time. The non-reactive fraction from the mixture of dibenzoylbromo derivatives was chromatographically pure, but it could not be obtained in a crystalline state. In the



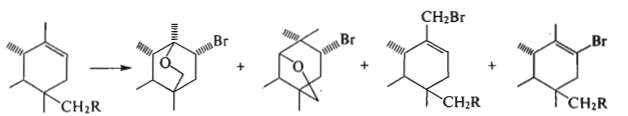
XVII, $R^1 = R^2 = OCOC_6H_5$



XXVIII, $R^1 = OCOCH_3$

PMR spectrum the signal of a methyl group on the double bond was present, while the 22β-H showed, in contrast to the allylic bromo derivative *XVI*, only a geminal coupling (doublet, J_{gem} = 17 Hz). According to the intensities of the given signals and according to the complex nature of the spectrum in the 4–5 p.p.m. region it is probably a mixture of dibenzoylbromo derivatives in which the predominant component is the vinylic bromo derivative *XVII*. On the basis of the PMR spectrum the presence of bromo ether of the type *XXVIII* and of the compounds with a hydrogen on a double bond may be excluded. It is interesting that in no case dibromo derivative was obtained; it is probably due to the hindrance of the β-side of the cycle E by the functional group in position 28 which prevents an attack of the external nucleophile at $C_{(20)}$. The adduct with the double bond could not be obtained even when the reaction was carried out in dimethylformamide, which, according to the analogies with di- and trisubstituted double bonds, takes place with the participation of dimethylformamide under formation of O-formyl derivatives of halohydrins[12,13]. On reaction of bromine with heterobetulin dibenzoate (*IV*) in dimethylformamide in the presence of one mol of silver perchlorate[12], derivatives *XVI* and *XVII* were obtained as the main products in addition to a small amount of bromo ether *XVIII*, formate *XXIX* (the structure of which was determined on the basis of its PMR spectrum), and aldehyde *XXX*.

In order to enable the comparison of the participation of oxygenated functions in the position 28 in the reaction of the double bond with bromine in acetic acid it was necessary to determine the quantitative composition of the mixtures obtained. In the case of less reactive bromo derivatives *XVII* and *XXVIII* and in bromo ether *VII* the yield after the isolation from the reaction mixture is taken as content; in the case of reactive derivatives (*VIII* and *XXIV*; *XVI* and *XVIII*) the content and the ratio was determined after the reaction with sodium acetate on the basis of optical rotations of the obtained mixtures of the acetyl derivatives (*XIII* and *XXV*; or *XIX* and *XXIII*, resp.). In the acetate series the ratio of both components, *i.e.* of the diacetate *XIII* and triacetate *XXV* is approximately 1 : 1, in the mixture prepared from benzoyl derivatives the allylic acetate *XXIII* greatly predominated; ether acetate *XIX* was demonstrated by thin-layer chromatography, but its amount did not exceed 5%, because the optical rotation of the mixture corresponded to the pure allylic acetyl derivative *XXIII* within the limits of experimental error. The course of the reaction with bromine and the results obtained are given in Scheme 1. In view of difficult

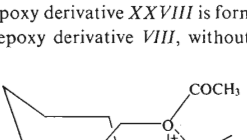


R = OH	>98%	—	—	—
$OCOCH_3$	~42%	~12%	~44%	—
$OCOC_6H_5$	< 5%	—	~60%	~37%

SCHEME 1

separation and appreciable reactivity of some components the given data are only approximate although they give a good overall idea of the participation of the investigated substituents.

According to the change of nucleophility in the substances investigated the participation of the 28-hydroxy group is practically quantitative (more than 98% of the products), 28-acetoxy group took part in the reaction only to 50%, while the benzoyloxy group to less than 5%. The difference in the participations of the acetoxy and benzoyloxy groups is also illustrated by bromo derivatives *XVII* and *XXVIII*. The vinylic bromo derivative *XVII* may be formed from the transition ion most easily if the resulting electron deficit at $C_{(20)}$ is not compensated by the 28-ester group, *i.e.*, the benzoyloxy group. On the other hand the formation of bromo derivative *XXVIII*, which requires the rearrangement of the 19α-methyl group during the addition of bromine from the α-side, may be better explained on the supposition that the oxygen atom from $C_{(28)}$ stabilises the cation at $C_{(20)}$; the boat like transition state thus originating, also has better sterical conditions for the migration of the 19α-methyl group. Thus, either 19β,28-epoxy derivative *XXVIII* is formed via the stage *XXXI*, or, to a greater extent, 20β,28-epoxy derivative *VIII*, without any rearrangement.



XXXI

EXPERIMENTAL

Melting points were determined on a Kofler block. Optical rotation was measured in chloroform on an automatic polarimeter ETL-NPL (Bendix-Ericsson) with a ± 1—2° error. Infrared spectra were measured in 5—8% solutions in chloroform on a model spectrograph of ÚTP ČSAV (Brno). PMR spectra were measured in deuteriochloroform on a Varian HA-100 apparatus (100 MHz) using tetramethylsilane as internal reference. For chromatography neutral alumina (Reanal, act. II) and neutral silica gel (Spolana) were used. For thin-layer chromatography we used silica gel according to Stahl (Spolana) and the same silica gel with the addition of 4% of silver nitrate. Samples for analysis were dried at 100°C/2 Torr over phosphorus pentoxide for 8—12 hours.

Reaction of 3-Deoxyheterobetulin (*I*) with Bromine

a) *At* 10°C: Excess bromine (96 mg) in acetic acid (3 ml) was added dropwise and under stirring to a cooled solution (10°C) of substance *I* (0·11 g) in chloroform (2·5 ml) and acetic acid (10 ml) and after five minutes stirring the precipitated bromo ether *V* (0·12 g), m.p. 262—266°C (decomp.) was filtered off with suction. IR spectrum: 1047 cm^{-1} (C—O—C). For $C_{30}H_{49}BrO$ (505·6) calculated: 71·26% C, 9·76% H; found: 70·93% C, 9·73% H. The residue of the reaction mixture after the elimination of bromo ether *V* by filtration was extracted with chloroform and the extract was washed with sodium hydrogen carbonate and water, and dried over sodium sulfate. This gave another 0·01 g of bromo ether *V* which according to thin-layer chromatography on silica gel contained traces of 3-deoxyalloheterobetulin (*VI*).

b) *At* 60°C: To a solution of substance *I* (0·11 g) in chloroform (2·5 ml) and acetic acid (10 ml) excess bromine (96 mg) in acetic acid (3 ml) was added at 60°C. After 5 minutes reacting the mixture was cooled to room temperature and the separated bromo ether *V* was filtered off (0·02 g; m.p. 264—267°C, decomp.). Its IR spectrum was identical with that of the sample obtained by the preceding procedure. The filtrate was worked up as described under *a*) and the obtained mixture (0·10 g) was refluxed for 30 minutes with sodium acetate (0·15 g) in acetic acid (7 ml). On addition of water the separated product was filtered off under suction and chromatographed on alumina (5 g). Light petroleum–benzene mixture eluted substance *VI* (0·07 g), m.p. 229—231°C, which according to its IR spectrum and mixture melting point was identical with an authentic sample. Benzene eluted acetate *XI* (0·01 g), m.p. 213—215°C (chloroform–methanol). IR spectrum: 1735, 1259 (CH_3COO), 1051 cm^{-1} (C—O—C). For $C_{32}H_{52}O_3$ (484·7) calculated: 79·28% C, 10·81% H; found: 79·62% C, 10·91% H.

Reaction of Heterobetulin (*II*) with Bromine

To a suspension of substance *II* (0·40 g) in acetic acid (30 ml) a solution of bromine (192 mg) in acetic acid (6 ml) was added at 14°C over 10 minutes. After 10 minutes additional stirring the reaction mixture was diluted with water and the precipitate filtered off, dissolved in ether, and the solution was filtered through a layer of silica gel. The residue (0·46 g, 98%) was chromatographically pure and on crystallisation from n-heptane it afforded bromo ether *VII*, m.p. 245—248°C. (decomp.) (benzene–n-heptane); $[\alpha]_D$ −19·5° (*c* 0·7), IR spectrum: 3610 (OH), 1048 cm^{-1} (C—O—C). For $C_{30}H_{49}BrO_2$ (521·6) calculated: 69·07% C, 9·46% H; found: 68·87% C, 9·52% H.

Acetylation of bromo ether *VII* with acetic anhydride and pyridine at room temperature for 30 minutes gave 3-acetate *VIII*, m.p. 242—245°C (decomp.) (benzene–n-heptane), $[\alpha]_D$ −27° (*c* 0·69). IR spectrum: 1731, 1259 (CH_3COO), 1051 cm^{-1} (C—O—C). For $C_{32}H_{51}BrO_3$ (563,6) calculated: 68·18% C, 9·12% H; found: 68·16% C, 9·15% H.

Reaction of Heterobetulin Diacetate (*III*) with Bromine

Ester *III* (0·38) was dissolved in warm acetic acid (20 ml) and the solution was cooled to 14°C; diacetate *III* partly crystallised out. To the supension bromine (180 mg) solution in acetic acid (3·2 ml) was added under stirring over 10 minutes. During the addition the solid phase went completely into solution. After an additional 15 minutes the reaction mixture was diluted with water and the precipitated product was filtered off, dissolved in benzene and dried over sodium sulfate. After distilling off of the solvent a mixture of substances was obtained (0·42 g) which did not differ in their mobility on a thin layer of silica gel; on a thin layer of silica gel containing silver nitrate decomposition products were formed corresponding by their mobility to hydroxy ether *X* and diacetyl derivative *XXVII*. The main fraction consisted of two spots with very similar R_F values. A part of the crude mixture (0·2 g) was refluxed with sodium acetate (0·3 g) in acetic acid (20 ml) for 30 minutes. The product (0·19 g) was precipitated by the addition of water, then filtered off under suction and chromatographed on alumina (100 g). Bromo derivative *XXVIII* (0·024 g, 12%), m.p. 277—282°C (chloroform–methanol, decomp.) was eluted with benzene–ether 9 : 1. IR spectrum: 1732, 1263 (CH_3COO), 1034 cm^{-1} (C—O—C). PMR: 1·085; 0·97, 0·92, 0·875, 0·845 (5 × CH_3), 2·02 (CH_3COO), 3·42 and 3·81 (two doublets $C_{28}H_2$, $J \sim 8$ Hz), 3·72 ($C_{(19)}\alpha$-H), 4·18 (doublet of doublets $C_{(21)}\beta$-H, $J_1 \sim 7$Hz, $J_2 \sim 11{\cdot}5$ Hz), 4·50 (3α-H) p.p.m. For $C_{32}H_{51}BrO_3$ (563·6) calculated: 68·18% C, 9·12% H; found: 68·13% C 9·07% H. With ether a mixture (0·16 g) of diacetate *XIII* and triacetate *XXV* was eluted with $[\alpha]_D + 7° \pm 2°$ (*c* 0·58) corresponding to a content of 48% of diacetete *XIII* in the mixture of acetyl derivatives (*i.e.* approximately 42% with respect to the original mixture of bromo derivatives) and 52% of triacetate *XXV* (corresponding to approx. 45% of bromo derivative *XXIV* in the original mixture).

Hydrolysis of the mentioned mixture of acetates (2 hours boiling in 5% potassium hydroxide in a mixture of benzene and ethanol 1 : 1) gave a mixture of two hydroxy derivatives which after chromatography on alumina and acetylation gave diacetate *XIII*, m.p. 274—276°C, and triacetate *XXV*, m.p. 180—182°C. According to their IR spectra both were identical with authentic samples.

Reaction of Heterobetulin Dibenzoate *IV* with Bromine

a) *In acetic acid*: To a solution of ester *IV* (0·81 g) in chloroform (5 ml) and acetic acid (20 ml) excess bromine (0·4 g) in acetic acid (8·5 ml) was added at 10°C and the mixture was allowed to stand for 3 hours without further cooling. After dilution of the reaction mixture with water the product was extracted with ether and the extract washed with 5% sodium hydrogen carbonate solution and water, and then dried over sodium sulfate. The residue weighed 0·9 g. A part of it (0·45 g) was separated chromatographically on silica gel (25 g). Benzene–ether mixture (1 000 : 1) eluted a mixture (0·3 g) from which bromo derivative *XVI* (0·11 g) was isolated by crystallisation, m.p. 196—199°C (n-heptane), $[\alpha]_D$ +62° (*c* 0·66); IR spectrum: 1718, 1610, 1594, 1284 cm^{-1} (C_6H_5COO). PMR: 0·94 (2 × CH_3), 1·015, 1·04, 1·13 (3 × CH_3), 1·08 (doublet, J = 7 Hz, 19α-CH_3), 4·09 and 4·69 (two doublets, $J \sim 11$ Hz, $C_{(28)}H_2$), 4·18 and 3·94 (two doublets, $J \sim 10$ Hz, $C_{(30)}H_2$), 4·73 (multiplet 3α-H), 5·83 (broad doublet, J_1 = 6·5 Hz, $J_2 \sim 1-2$ Hz, 21-H), 2·26 (doublet of doublets, J_1 = 17 Hz, J_2 = 6·5 Hz, 22β-H), ~ 8·04 and ~ 7·40 (multiplets of aromatic hydrogens) p.p.m. For $C_{44}H_{57}BrO_4$ (729·6) calculated: 72·67% C, 7·81% H; found: 72·75% C, 7·98% H. On elution with benzene–ether mixtures 100 : 1 to 10 : 1 substance mixtures were obtained from which on repeated chromatography on silica gel bromo-ether *XVIII* (approx. 3 mg) was eluted, m.p. 258—260°C (benzene–n-heptane), identical according to IR spectrum with the sample obtained under *b*). Elution with ether gave mixtures of more polar substances (0·13 g) which according to chromatography on a thin layer of silica gel were not present in the mixture before the chromatographic separation.

The second part of the original crude mixture of products (0·45 g), in which according to chromatography on thin layers of silica gel and silica gel impregnated with silver nitrate only bromo derivatives (*XVI*, *XVII* and *XVIII*) were present, was refluxed in acetic acid (40 ml) and in the presence of sodium acetate (0·6 g) for 30 minutes. The product was separated on addition of water, then filtered off, dissolved in chloroform, and the solution was filtered through a layer of alumina. The residue (0·43 g) was chromatographed on 25 g of alumina. Cyclohexane–ether mixture (100 : 3) eluted bromo derivative *XVII* (0·16 g, 37%) which would not crystalise; $[\alpha_D]$ +42° (*c* 0·74), IR spectrum: 1720, 1612, 1594, 1284 (C_6H_5COO) cm^{-1}. PMR: 0·93 (2 × CH_3), 1·01 (2 × CH_3), 1·11 (CH_3) 1·80 ($C_{(30)}H_3$), 1·00 (doublet, $J \sim 8$ Hz, 19α-CH_3), 2·72 (doublet, J = 17 Hz, 22β-H), 3·80 to 5·00 (unresolved overlapping multiplets), ~7·48 and ~8·05 (multiplets, aromatic H) p.p.m. For $C_{44}H_{57}BrO_4$ (729·6) calculated: 72·67% C, 7·81% H, 10·95% Br; found: 72·42% C, 8·00% H, 10·53% Br. With cyclohexane–ether mixture (10 : 1) a mixture of acetyl derivatives *XIX* and *XXIII* was eluted, the $[\alpha]_D$ +32° (0·84) of which is in agreement with the $[\alpha]_D$ of the allylic acetyl derivative *XXIII*. By hydrolysis with refluxing 5% potassium hydroxide solution a triol was obtained which according to thin-layer chromatography was accompanied by a small amount of dihydroxyether *IX* which on acetylation gave triacetate *XXV*, m.p. 178—180°C, identical according to its IR spectrum with an authentic specimen.

b) *In dimethylformamide*: to a solution of ester *IV* (0·91 g) in chloroform (30 ml) a solution of silver perchlorate (0·37 g; 1·2 mol) in dimethylformamide (10 ml) was added. To this mixture, cooled to 10°C a solution of bromine (0·27 g; 1·2 mol) in dimethylformamide (2·95 ml) was added dropwise and under stirring over 15 minutes. After an additional 15 minutes stirring the separated silver bromide was filtered off, the filtrate diluted with water and extracted with chloroform. The extract was washed with a 5% sodium hydrogen carbonate solution and water, and dried over

sodium sulfate. After the evaporation of chloroform under reduced pressure the residue (1·1 g) was chromatographically separated on silica gel (30 g). Elution with mixtures of cyclohexane and ether (100 : 1 to 3 : 1) gave mostly mixtures from which the following substances were isolated in addition to mixed fractions: *1.* bromo derivative *XVI* (0·17 g), m.p. 197–200°C (n-heptane), identical according to IR spectra with the preparation obtained under a). It was obtained by fractional crystallisation of a mixture (0·45 g) of bromo derivatives *XVI* and *XVII*; *2.* From the mother liquors after bromo derivative *XVI* non-crystalline bromo derivative *XVII* was obtained after the reaction with sodium acetate and the conventional working up which according to its specific rotation ($[\alpha]_D$ +38° (*c* 0·76)), elemental analysis, IR spectrum, and thin-layer chromatography data was identical with the sample obtained under *a*); *3.* bromo ether *XVIII* (0·01 g), m.p. 259–260°C (benzene–heptane), IR spectrum: 1718, 1612, 1593, 1258 (C_6H_5COO), 1050 (C–O–C) cm^{-1}. For $C_{37}H_{52}BrO_3$ (625·7) calculated: 71·01% C, 8·53% H; found: 70·81% C, 8·73% H. *4.* Formate *XXIX* (0·04 g), m.p. 210–213°C (n-heptane), $[\alpha]_D$ +33° (*c* 1·68); IR spectrum: 1725, 1615, 1597, 1284 (C_6H_5COO), 1183 (HCOO) cm^{-1}; PMR: 0·87 (2 × CH_3), 0·94, 0·97, 1·05 (3 × CH_3), 1·02 (doublet, J = 6·5 Hz, 19α-CH_3), 2·23 (doublet of doublets, J_1 = = 17 Hz, J_2 = 6 Hz, 22β-H), 4·02, 4·42, 4·57, and 4·73 (four doublets, $J \sim 12$ Hz, $C_{(28)}H_2$ and $C_{(30)}H_2$), 5·54 (doublet, J_1 = 6 Hz, $J_2 \sim 1$ Hz, 21-H), ~7·39 and ~7·98 (multiplets aromatic H), 8·01 (HCOO) p.p.m. For $C_{45}H_{58}O_6$ (694·9) calculated: 77·77% C, 8·41% H, found: 77·82% C, 8·52% H. *5.* Aldehyde *XXX* (0·008 g), m.p. 236–239°C (n-heptane), according to its IR spectrum identical with an authentic sample. 6. From the original chromatographic separation and from the rechromatographies of single fractions polar components were also obtained (approximately 0·2 g) which according to thin-layer chromatography contained hydroxy derivative *XXII* accompanied by a small amount of hydroxy ether *XX*. None of these polar compounds occurred in the mixture before chromatographic separation.

Reaction of Halo Derivatives *VII*, *VIII*, *XV*, *XVI* and *XVIII*

a) *With sodium acetate*: A solution of halo derivative in acetic acid was refluxed with excess sodium acetate for 30 minutes. The product was precipitated on addition of water, then dissolved in chloroform and the solution was filtered through a layer of alumina. From bromo derivative *VIII* and chloro derivative *XV* diacetate *XIII* was obtained in 98% yield. From bromo derivative *VII* (0·15 g) a mixture (0·14 g) was formed from which chromatography on alumina gave diacetate *XIII* (0·01 g) and monoacetate *XII* (0·12), m.p. 240–242°C (chloroform–methanol), $[\alpha]_D$ −34·5° (*c* 0·96). IR spectrum: 3610 (OH), 1729, 1254 (CH_3COO), 1062 (C–O–C) cm^{-1}. For $C_{32}H_{52}O_4$ (500·7) calculated: 76·75% C, 10·47% H; found: 76·72% C, 10·42% H. Acetylation of monoacetate *XII* with a mixture of acetic anhydride and pyridine gave diacetate *XIII*, m.p. 273–275°C, identical according to its IR spectrum with an authentic specimen. From benzoylbromo derivative *XVIII* (0·008 g) acetate *XIX* (0·007 g) was formed, m.p. 287–290°C (chloroform–methanol), $[\alpha]_D$ −1·6° ± 2° (*c* 0·61); IR spectrum: 1724, 1612, 1594, 1285, 1255 (C_6H_5COO and CH_3COO), 1065 (C–O–C) cm^{-1}. For $C_{39}H_{56}O_5$ (604·8) calculated: 77·44% C, 9·33% H; found: 77·32% C, 9·35% H. From bromo derivative *XVI* (0·1 g) non-crystalline acetyl derivative *XXIII* (0·09 g) was obtained, $[\alpha]_D$ +32° (*c* 1·1), IR spectrum: 1609, 1593, and broad bands 1720 and 1280 (C_6H_5COO and CH_3COO) cm^{-1}. For $C_{46}H_{60}O_6$ (708·9) calculated: 77·93% C, 8·53% H; found; 77·64% C, 8·69% H.

b) *On alumina*: Bromo derivative was adsorbed on alumina from a benzene solution and the product was eluted from the column after 24 hours. From bromo derivative *VIII* and chloro derivative *XV* hydroxyether *X*, m.p. 303–304°C, was obtained, identical with an authentic specimen. From bromoether *XVIII* hydroxy derivative *XX*, m.p. 288–289°C was formed, which according to its IR spectrum was also identical with an authentic sample. From dibenzoyl-

bromo derivative *XVI* (0·1 g) hydroxy derivative *XXII* (0·09 g) was formed, m.p. 230—232°C, identical with an authentic sample (IR spectrum); on acetylation with a mixture of acetic anhydride and pyridine hydroxy derivative *XXII* gave acetate *XXIII*, $[\alpha]_D$ +31° (*c* 0·72), according to its IR spectrum identical with a sample obtained as under *a*).

c) *Reaction of bromo derivative* VIII *with zinc*: A solution of bromo derivative *VIII* (0·06 g) in acetic acid (20 ml) was refluxed in the presence of zinc powder (300 mg) for 2 hours. The powder was added to the mixture gradually, in several portions. The product was extracted with chloroform and the extract washed with a 5% sodium carbonate solution, then water, and dried by filtration through a layer of alumina. Yield 0·04 g of a product, m.p. 277—278°C, according to IR spectrum identical with diacetate *XIII*.

d) *Reaction of bromo ether* VIII *with hydrogen bromide*: To a solution of bromo ether *VIII* (15 mg) in benzene (1 ml) and acetic acid (4 ml) a 25% hydrogen bromide solution in acetic acid (4 ml) was added and allowed to stand for 4 hours at room temperature. Excess sodium acetate was added to the mixture, benzene was distilled off, and the mixture refluxed for 30 minutes. After working up as under *a*) diacetate *XIII* was obtained, which according to thin-layer chromatography did not contain bromo ether *XXVIII*.

Preparation of Halo Derivative *VIII* and *XV* from Hydroxy Ethers *XIV* and *X*

a) *With hydrogen bromide*: Into a solution of hydroxy ether *XIV* (0·05 g) in benzene (10 ml) hydrogen bromide was introduced at room temperature for 5 minutes. After 15 minutes standing the mixture was poured into an ice-cold solution of sodium hydrogen carbonate and then extracted with ether. After washing of the extract with water and drying over sodium sulfate and evaporation of the solvent bromo ether *VIII* (0·04) was obtained, m.p. 245—248°C (decomp., crystallised from benzene–light petroleum). It was identical (IR spectrum) with the authentic preparation described above.

b) *With hydrogen chloride*: Introduction of hydrogen chloride into a solution of hydroxy ether *XIV* (0·06 g) in benzene (10 ml) and working up of the reaction mixture as in the preceding case gave chloro derivative *XV* (0·048 g), m.p. 280—281°C (chloroform–methanol); IR spectrum: 1728, 1264 (CH_3COO), 1055 (C—O—C) cm^{-1}. PMR: 0·845 (2 × CH_3), 0·875, 0·93, 0·985, 1·275 (4 × CH_3), 1·165 (doublet, J = 7 Hz, 19α-CH_3), 2·03 (CH_3COO), 4·07 (multiplet, 21-H), 4·48 (multiplet, 3α-H), 3·29 (doublet of doublets, J_1 = 8·8 Hz, $J_2 \sim 1$ Hz, $C_{(28)}H_2$) and 4·11 (doublet of doublets, J_1 = 8·8 Hz, $J_2 \sim 2{\cdot}4$ Hz, $C_{(28)}H_2$) p.p.m. For $C_{32}H_{51}ClO_3$ (519·2) calculated: 74·02% C, 9·92% H; found: 74·18% C, 9·99% H.

c) *With phosphorus oxychloride*: A solution of hydroxy ether *XIV* (0·12 g) and phosphorus oxychloride (1·5 ml) in pyridine (10 ml) was allowed to stand at room temperature for 3 days. The reaction mixture was decomposed with ice and the product was extracted with ether. The extract was washed with a 5% sodium carbonate solution and water, and dried over sodium sulfate. The obtained chloro derivative *XV* (0·08 g) had m.p. 278—280°C (chloroform–methanol), and according to its IR spectrum it was identical with a sample obtained as under *b*).

d) *From hydroxy ether* X: A mixture of hydroxy ether *X* (0·26 g) and phosphorus oxychloride (2 ml) in pyridine (20 ml) was allowed to stand at room temperature for 20 hours. It was then poured onto ice and extracted with ether. The etheral solution was washed with sodium carbonate solution and water, and dried over sodium sulfate. The product (0·11 g), m.p. 281—282°C was according to IR spectra identical with chloro ether *XV* obtained by the preceding procedure.

Triacetate *XXV*

Diacetaldehyde *XXVI* (0·2 g) was mixed with sodium borohydride (0·08 g) in chloroform (10 ml and ethanol (10 ml), and stirred at room temperature for 40 minutes. After the decomposition of the reaction mixture with water the product was extracted with chloroform, the chloroform extract was washed with water and then dried over sodium sulfate. Diacetylhydroxy derivative *XXVII* was thus obtained, m.p. 244–246°C (chloroform–n-heptane), $[\alpha]_D$ +34° (*c* 0·69). For $C_{34}H_{54}O_5$ (542·8) calculated: 75·23% C, 10·03% H; found: 75·15% C, 10·06% H. Acetylation of hydroxy derivative *XXVII* with a mixture of acetic anhydride and pyridine gave triacetate *XXV*, m.p. 180–182°C (chloroform–methanol), $[\alpha]_D$ +36° (*c* 0·87), IR spectrum: 1740, 1264 (CH_3COO) cm^{-1}. For $C_{36}H_{56}O_6$ (584·8) calculated: 73·93% C, 9·65% H; found: 74·22% C, 9·76% H.

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