

## TRITERPENES. XXV.\*

ISOMERISATION OF 20 $\alpha$ ,21 $\alpha$ -EPOXY-28-BENZOYLOXY DERIVATIVES OF TARAXASTANE

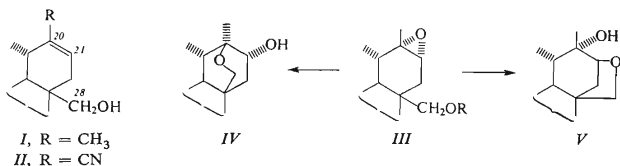
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The participation of the C<sub>(28)</sub>-functional group on the 20 $\alpha$ ,21 $\alpha$ -epoxy group reactions of 20-taraxastene derivatives can be almost completely suppressed by benzoylating the 28-hydroxy group. Without this participation epoxy derivative *VII* isomerises in the presence of boron trifluoride etherate to 21-oxo derivative *XV*, while with hydrogen chloride, it affords chloro derivative *XX*.

In communications<sup>1-3</sup> we have shown that the hydroxy group in the position 28 participates in the reaction of the double bond in derivatives of 20-taraxastene (*I*); in these reactions cyclic ethers are formed, *i.e.* either 20 $\beta$ ,28- or 21 $\beta$ ,28-epoxy derivatives. The first case<sup>1</sup> takes place during acid catalysed cyclisation of 28-hydroxy-20-taraxastene derivatives (*I*), while the second<sup>2</sup> on base catalysed Michael addition of the 28-hydroxy group to the conjugated system of nitrile *II*. A similar participation of the C<sub>(28)</sub> oxygen function was also observed<sup>3</sup> in the reactions of 20 $\alpha$ ,21 $\alpha$ -epoxy derivatives *III*, where in acid medium 20 $\beta$ ,28-epoxy-21 $\alpha$ -hydroxy derivative *IV*, in alkaline medium a mixture of isomeric hydroxy ethers *IV* and *V* is formed. These cyclisations prevail to such an extent that it is impossible to isolate the product corresponding to the normal opening of the epoxide ring (*i.e.* without the participation of the group at C<sub>(28)</sub>), even when 28-hydroxy group is acetylated.

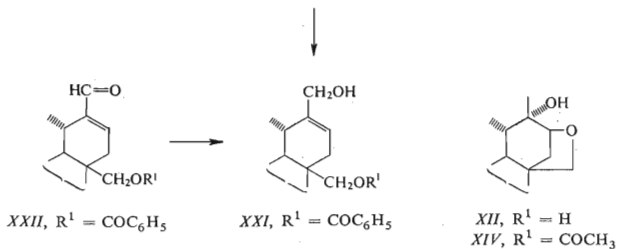
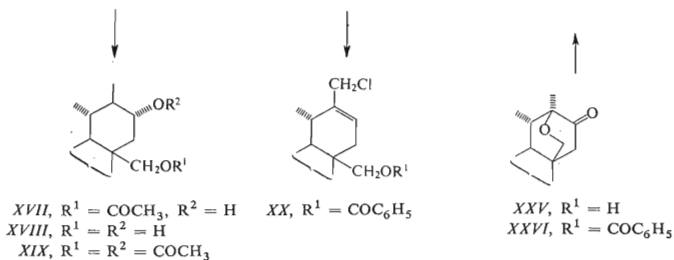
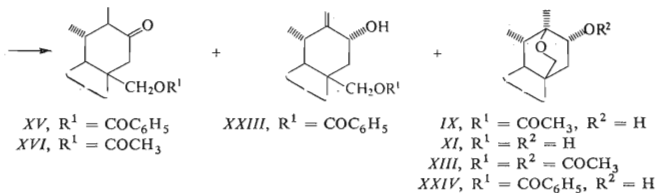
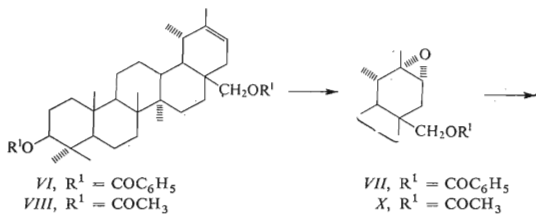


SCHEME 1

In this paper we wished to determine to what extent the 28-benzoyloxy group (in which the nucleophilicity of the oxygen atom is lower than in the acetyl group) would take part in the reaction of 20 $\alpha$ ,21 $\alpha$ -epoxy group. The lower willingness of the 28-ben-

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zoyloxy group to participate was already manifest during the epoxidation of di-benzoate VI; with hydrogen peroxide in acetic acid under the catalysis of traces



of a mineral acid only epoxy derivative *VII* was obtained, while the same reaction conditions give rise<sup>3</sup> to hydroxy ether *IX* in the case of diacetate *VIII*. In alkaline medium dibenzoyl epoxide *VII* is opened in the same manner as diacetyl epoxide *X*, under formation of hydroxy derivatives *XI* and *XII* with a six-membered and a five-membered oxygen bridged heterocycle, which were separated and then characterised in the form of acetates *XIII* and *XIV*. Different reactivity of 28-O-acylated groups was manifest in reactions with acids. Under the effect of boron trifluoride, *i.e.* under conditions when diacetyl epoxide *X* affords<sup>3</sup> hydroxy ether *IX*, dibenzoyl epoxide *VII* gave 21-oxo derivative *XV* as the sole product. We formulate this oxo derivative as 20 $\alpha$  H isomer with an equatorial 20 $\beta$ -methyl group, although according to the known course of the isomerisations of epoxy derivatives in the presence of boron trifluoride etherate<sup>4-6</sup>, the isomer with the 20 $\alpha$ -methyl group should be formed by rearrangement of the 21 $\beta$  H. For the  $\beta$ -configuration of the 20-methyl group the following facts are indicative: *a*) 21-Oxidibenzoate *XV* has an ORD curve identical with 21-oxodiacetate *XVI* prepared<sup>3</sup> by oxidation of hydroxy derivative *XVII*. *b*) On reduction of 21-oxidibenzoate *XV* with lithium aluminum hydride triol *XVIII* was formed the triacetate of which was identical with the known<sup>3</sup> triacetate *XIX*. Hence, it seems that the originally formed 20 $\beta$  H, 21-oxo derivative is isomerised to 20 $\alpha$  H isomer during the working up of the reaction mixture of epoxy derivative *VII* with boron trifluoride etherate.

When dibenzoyl epoxide *VII* reacted with hydrogen chloride in anhydrous medium, only 17% of 21-oxo derivative *XV* were obtained. The main product (45%) in this case was chloro derivative *XX*. Its structure was proposed on the basis of PMR spectra in which two AB systems of CH<sub>2</sub>—O and CH<sub>2</sub>—Cl groups were found as well as the signal of an olefinic hydrogen (broad doublet, 5.75 p.p.m.,  $J_1 = 7$  Hz,  $J_2 \sim 1-2$  Hz) vicinal to a methylene group. The signal of one hydrogen of this methylene group was also found in the spectrum (doublet of doublets, 2.28 p.p.m.,  $J_{\text{gem}} = 17$  Hz,  $J_{\text{vic}} = 7$  Hz); this signal we assign to the 22 $\beta$  hydrogen on the basis of its  $J_{\text{vic}}$  value. Chloro derivative *XX* changes to hydroxy derivative *XXI* on alumina. The substitution of the chlorine atom takes place completely and without an allylic rearrangement. The formed hydroxy derivative *XXI* has the same structural features (two AB systems of C<sub>(28)</sub>H<sub>2</sub>—O and C<sub>(30)</sub>H<sub>2</sub>—O groups, signals of an olefinic proton, and C<sub>(22)</sub> $\beta$  H) as chloro derivative *XX* according to its PMR spectrum. The structure *XXI* with a primary hydroxy group was proved by the preparation of this hydroxy derivative from aldehyde *XXII* on reduction with sodium borohydride.

Reaction of epoxy derivative *VII* with hydrogen chloride gave further a mixture of polar products (30%) which differed only negligibly from each other on thin-layer chromatography. Repeated crystallisation of this mixture gave hydroxydibenzoate which gave chloro derivative *XX* with hydrogen chloride. Hence, it can be formulated as 21-hydroxy derivative *XXIII*. The isomeric 30-hydroxy derivative *XXI* does not change in the presence of hydrogen chloride under the given conditions. 21 $\alpha$ -Hydroxy

derivative *XXIII* is evidently a primary product of isomerisation of epoxy derivative *VII* with hydrogen chloride and also an intermediary product of the formation of chloro derivative *XX*. In mother liquors after isolation of 21 $\alpha$ -hydroxy derivative *XIII* 30-hydroxy derivative *XXI* was found by thin-layer chromatography, accompanied by traces of hydroxy ether *XXIV*.

The same products as in the reaction with anhydrous hydrogen chloride were also formed from epoxy derivative *VII* under the influence of aqueous hydrochloric acid. In addition to oxo derivative *XV* and chloro derivative *XX* polar compounds were also formed which in this case made up more than 50% of the mixture of products. In addition to 30-hydroxy derivative *XXI* another component was isolated from this mixture in 13% yield, identified as a monobenzoate with a free hydroxy group. As a band at 1050  $\text{cm}^{-1}$ , characteristic of a six-membered oxygen-containing ring, was present in the IR spectrum of this compound, we assigned it structure *XXIV* (with a 21 $\alpha$ -hydroxy group and an oxygen bridge between  $\text{C}_{(28)}$  and  $\text{C}_{(20)}$ ) on the basis of the analogy with the reactions of epoxy diacetate *X*<sup>3</sup>. This structure was also corroborated by the preparation of hydroxy ether *XXIV* from the known<sup>3</sup> 3 $\beta$ -hydroxy-21-oxo derivative *XXV* by benzylation and reduction of the oxobenzoate *XXVI* with sodium borohydride.

From the experiments mentioned it follows that the benzylation of 28-hydroxy group suffices to prevent its participation in the acid catalysed reactions of 20 $\alpha$ ,21 $\alpha$ -epoxy group. The sole product formed by this participation, hydroxy ether *XXIV*, was obtained only in a low yield and only when the possibility of an acid catalysed hydrolysis of 28-benzoyloxy group could not be excluded.

## EXPERIMENTAL

The melting points were determined on a Kofler block. Optical rotation was measured in chloroform on an automatic polarimeter ETL-NPL (Bendix Ericsson), with a  $\pm 1$ –2% error. The infrared spectra were measured in 5–8% chloroform solutions in a model spectrometer of ÚPT ČSAV (Brno). The PMR spectra were measured in deuteriochloroform on a Varian HA-100 apparatus at 100 MHz, using tetramethylsilane as the internal standard. ORD was measured on a spectropolarimeter Jasco ORD/UV-5. For chromatography neutral alumina Reanal (act. II) and neutral silica gel (Spolana) were used. Samples for analysis were dried over phosphorus pentoxide at 100°C and 2 Torr for 8–12 hours.

### 3 $\beta$ ,28-Dibenzoyloxy-20 $\alpha$ ,21 $\alpha$ -epoxy-18 $\alpha$ ,19 $\beta$ H-ursane (*VII*)

To a solution of heterobetulin dibenzoate (*VI*; 0.37 g) in benzene (6.5 ml) a 30% solution of hydrogen peroxide (6 ml) in acetic acid (39 ml) and a drop of sulfuric acid were added and the mixture was allowed to stand at room temperature for 30 hours. It was diluted with water and extracted with chloroform. The chloroform layer was washed with 5% sodium hydrogen carbonate and water and dried by filtration through a layer of alumina. After evaporation of the solvent dibenzoyl epoxide *VII* (0.29 g), m.p. 243–244°C (chloroform–methanol), was isolated;  $[\alpha]_{\text{D}} + 30.5^\circ$  (*c* 0.68). For  $\text{C}_{44}\text{H}_{58}\text{O}_5$  (667.3) calculated: 79.24% C, 8.77% H; found: 78.92% C, 8.78% H. IR spectrum: 1717, 1608, 1588, 1282  $\text{cm}^{-1}$  ( $\text{C}_6\text{H}_5\text{COO}$ ).

*Alkaline hydrolysis:* Epoxy derivative *VII* (0.13 g) was refluxed in a mixture of benzene (5 ml) and 5% sodium hydroxide in ethanol (5 ml) for 2 hours. After dilution with water the mixture was

extracted with chloroform and the extract was washed with water and dried by filtration through a layer of alumina. On evaporation of the solvent a mixture of hydroxy derivatives *XI* and *XII* (0.12 g) was obtained which was acetylated with acetic anhydride in pyridine (1 : 1) at room temperature for 24 hours. The mixture was decomposed with water and the separated product (0.11 g) was filtered off and chromatographed on alumina (7 g). With benzene-ether 10 : 1 mixture diacetate *XIII* (0.03 g) was eluted, m.p. 282.5–283°C (chloroform-methanol),  $[\alpha]_D^{25} - 23.5^\circ$  (c 0.92), according to IR spectra identical with an authentic sample. With ether hydroxy-acetate *XIV* (0.08 g) was eluted, m.p. 340–341°C (chloroform-methanol), according to IR spectra identical with an authentic sample.

### Reactions of Epoxy Derivative *VII*

a) *With boron trifluoride etherate.* A solution of epoxy derivative *VII* (0.65 g) in benzene (30 ml) added with freshly distilled boron trifluoride etherate (3 ml) was allowed to stand at room temperature for 18 hours. The reaction mixture was decomposed with water and extracted with chloroform. The extract was washed with 5% sodium carbonate solution and water and dried over sodium sulfate. Oxo derivative *XV* was obtained (0.54 g), melting at 205–205.5°C (chloroform-methanol);  $[\alpha]_D^{25} + 86.5^\circ$  (c 0.93). For  $C_{44}H_{58}O_5$  (667.3) calculated: 79.24% C, 8.77% H; found: 79.11% C, 8.65% H. IR spectrum: 1715, 1605, 1590, 1285  $cm^{-1}$  ( $C_6H_5COO$ ). ORD: (c 0.061, dioxane):  $[\Phi]_{400} + 2100^\circ$ ,  $[\Phi]_{350} + 4300^\circ$ ,  $[\Phi]_{320} + 9700^\circ$ ,  $[\Phi]_{315} + 10200^\circ$ ,  $[\Phi]_{312} + 9900^\circ$ ,  $[\Phi]_{308} + 10200^\circ$ ,  $[\Phi]_{288} 0^\circ$ ,  $[\Phi]_{271} - 3600^\circ$ ,  $[\Phi]_{258} 0^\circ$ . (ORD of diacetate *XVI* (c 0.022, dioxane):  $[\Phi]_{400} + 840^\circ$ ,  $[\Phi]_{350} + 2400^\circ$ ,  $[\Phi]_{320} + 5600^\circ$ ,  $[\Phi]_{315} + 6270^\circ$ ,  $[\Phi]_{310} + 6270^\circ$ ,  $[\Phi]_{290} 0^\circ$ ,  $[\Phi]_{270} - 4200^\circ$ ,  $[\Phi]_{258} - 3100^\circ$ .)

b) *With anhydrous hydrogen chloride:* Hydrogen chloride gas was introduced into a solution of epoxy derivative *VII* (0.17 g) in benzene (15 ml) at room temperature for 5 minutes. After another 5 minutes standing the mixture was poured into ice-cold water. The product was extracted with ether and the extract was washed with 5% solution of sodium hydrogen carbonate and water and dried over sodium sulfate. After evaporation of the solvent the residue (0.17 g) was chromatographed on silica gel (17 g). Cyclohexane-ether mixture (100 : 4) eluted chloro derivative *XX* (0.08 g, 47%), m.p. 196–199°C (n-heptane);  $[\alpha]_D^{25} + 20^\circ$  (c 0.89). For  $C_{44}H_{57}ClO_4$  (685.3) calculated: 77.10% C, 8.38% H, 5.17% Cl; found: 77.24% C, 8.55% H, 4.95% Cl. IR spectrum: 1715, 1605, 1587, 1280  $cm^{-1}$  ( $C_6H_5COO$ ). PMR spectrum: 0.93, 1.015, 1.04, 1.12, 1.13 (6 ×  $CH_3$ ), 2.28 (doublet of doublets,  $J_{gem} = 17$  Hz,  $J_{vic} = 7$  Hz,  $C_{(22)}$  βH), 4.08 and 4.68 (two doublets,  $J = 11$  Hz,  $C_{(28)}$  H<sub>2</sub>—O), 4.24 and 3.96 (two doublets,  $J = 11.5$  Hz,  $C_{(30)}$  H<sub>2</sub>Cl), 4.74 (multiplet, 3αH), 5.75 (broad doublet,  $J_1 = 7$  Hz,  $J_2 \sim 1-2$  Hz,  $C_{(21)}$  H), 7.25–7.65 and 7.95–8.15 p.p.m. (multiplets, aromatic H).

With a mixture of cyclohexane-ether 9 : 1 oxo derivative *XV* (0.03 g, 17%) was eluted, m.p. 201–203°, identical with the above mentioned preparation. Cyclohexane-ether (2 : 1) mixture eluted 0.05 g (29.5%) of a mixture which according to thin-layer chromatography on silica gel impregnated with silver nitrate contained hydroxy derivatives with slightly different  $R_f$  values and also traces of hydroxy ether *XXIV*. Repeated crystallisation from a chloroform-methanol mixture gave hydroxy derivative *XXIII*, m.p. 257–261°C; for  $C_{44}H_{58}O_5$  (666.9) calculated: 79.24% C, 8.77% H; found: 79.40% C, 8.89% H. IR spectrum: 3600 (OH), 1715, 1606, 1589, 1285 ( $C_6H_5COO$ ), 920  $cm^{-1}$  ( $C=CH_2$ ). The mother liquors of this hydroxy derivative were dissolved in benzene and saturated with hydrogen chloride gas and then worked up as in the case of the isomerisation of epoxy derivative *VII*. Chloro derivative *XX* was obtained as the main product, accompanied by 30-hydroxy derivative *XXI* and a trace of hydroxy ether *XXIV*. Under the same conditions a sample of pure 21-hydroxy derivative *XXIII* gave a chromatographically pure chloro derivative *XX*, while the sample of pure 30-hydroxy derivative *XXI* remained unchanged.

c) *With hydrochloric acid.* To a solution of epoxy derivative VII (0.65 g) in chloroform (20 ml) and methanol (8 ml) 35% hydrochloric acid (2.5 ml) was added and the mixture was allowed to stand at room temperature for 24 hours. It was then diluted with water and extracted with chloroform. The extract was washed with 5% sodium carbonate solution and water, and dried over sodium sulfate. The residue (0.58) was separated chromatographically on alumina (30 g). Light petroleum-ether mixture (9:1) eluted oxo derivative XV (0.1 g, 17%), m.p. 203–205°C (chloroform-methanol), which according to its IR spectrum was identical with the oxo derivative obtained by preceding reactions. A light petroleum-ether mixture (10:3) eluted 0.28 g (48%) of a mixture of hydroxy derivatives XXI and XXIII and also pure hydroxy derivative XXI (0.05 g, 8.5%), m.p. 229–231°C (chloroform-methanol):  $[\alpha]_D +51^\circ$  (c 0.66). For  $C_{44}H_{58}O_5$  (666.9) calculated: 79.24% C, 8.77% H; found: 79.08% C, 8.91% H. IR spectrum: 1715, 1606, 1588, 1284 ( $C_6H_5COO$ ),  $3640\text{ cm}^{-1}$  (OH). PMR spectrum: 0.92, 0.99, 1.02, 1.08 ( $6 \times CH_3$ ), 2.18 (doublet of doublets,  $J_{gem} = 16\text{ Hz}$ ,  $J_{vic} = 7\text{ Hz}$ ,  $C_{(22)}\beta H$ ), 4.14 and 3.99 (two doublets,  $J \sim 12\text{ Hz}$ ,  $C_{(30)}H_2-OH$ ), 4.45 and 4.27 (two doublets,  $J \sim 11\text{ Hz}$ ,  $C_{(28)}H_2-O$ ), 4.73 (multiplet,  $3\alpha H$ ), 5.55 (broad doublet,  $J_1 \sim 7\text{ Hz}$ ,  $J_2 \sim 1-2\text{ Hz}$ ,  $C_{(21)}H$ ), 7.25–7.65 and 7.90–8.15 p.p.m. (multiplets, aromatic H). The same solvent mixture also eluted hydroxy ether XXIV (0.08 g, 13%); m.p. 288–289°C (chloroform-methanol);  $[\alpha]_D +38^\circ$  (c 0.59). For  $C_{37}H_{54}O_4$  (563.7) calculated: 78.96% C, 9.67% H; found: 78.68% C, 9.45% H. IR spectrum: 3630 (OH), 1710, 1610, 1594, 1285 ( $C_6H_5COO$ ),  $1050\text{ cm}^{-1}$  (six-membered ether ring). If silica gel was used for the separation of the products of this reaction (0.05 g), chloro derivative XX (0.02 g) was obtained, m.p. 188–192°C (n-heptane). Oxo derivative XV and hydroxy derivatives XXI and XXIV were also isolated, as in the case when alumina was employed.

#### Reduction of 21-Oxodibenzoate XV with Lithium Aluminium Hydride

A mixture of oxo derivative XV (0.15 g) and lithium aluminium hydride (0.12) in ether (20 ml) was refluxed for 5 hours, then decomposed with water and dilute hydrochloric acid and extracted with ether. The extract was washed with water and dried over sodium sulfate. Weakly soluble triol XVIII (0.11 g) was obtained, m.p. 278–280°C, which was acetylated with a mixture of acetic anhydride and pyridine (1:1) at room temperature. The triacetate XIX formed (0.08 g), m.p. 250–251°C (chloroform-methanol),  $[\alpha]_D -19^\circ$  (c, 0.72), was identical with an authentic specimen (IR spectrum).

#### 3 $\beta$ ,28-Dibenzoyloxy-30-hydroxy-18 $\alpha$ ,19 $\beta$ H-urs-20-ene (XXI)

a) Chloro derivative XX (0.25 g) in benzene solution was adsorbed on alumina (5 g) and after 24 hours standing the product formed was eluted with chloroform, m.p. 229–230°C (chloroform-methanol), which according to its IR spectrum was identical with hydroxy derivative XXI obtained from epoxide VII.

b) A solution of oxo derivative XXII (0.25 g) in chloroform (20 ml) and ethanol (10 ml) was shaken with sodium borohydride (0.1 g) at room temperature for 5 minutes. The reaction mixture was decomposed with water and acetic acid and the chloroform solution was washed with 5% sodium carbonate and water, and dried over sodium sulfate. According to IR spectra the obtained hydroxy derivative XXI (0.18 g), m.p. 230–231°C, was identical with an authentic sample.

#### 3 $\beta$ -Benzoyloxy-21 $\alpha$ -hydroxy-20 $\beta$ ,28-epoxy-18 $\alpha$ ,19 $\beta$ H-ursane (XXIV)

a) Oxo derivative XXV (0.48 g) and benzoyl chloride (2 ml) in pyridine (20 ml) were mixed and allowed to stand at room temperature for 4 days. The reaction mixture was decom-

posed with icecold water and after 4 hours standing the product was extracted with chloroform. The extract was washed with a sodium hydroxide solution, 2M-HCl, and water, and then filtered through a layer of alumina. Derivative *XXVI* was obtained (0.39 g), m.p. 308–308.5°C (chloroform-methanol);  $[\alpha]_D +61^\circ$  (*c* 0.82). For  $C_{37}H_{54}O_4$  (562.7) calculated: 78.94% C, 9.35% H, found: 79.01% C, 9.08% H. IR spectrum: 1 732 (keto group), 1 710, 1 605, 1 589, 1 285 ( $C_6H_5COO$ ), 1 050  $cm^{-1}$  (six-membered cyclic ether).

*b*) A solution of oxo derivative *XXVI* (0.25 g) in pyridine (11 ml) was heated on a water bath with sodium borohydride (0.1 g) for 30 minutes. The reaction mixture was allowed to stand for 3 days at room temperature. On addition of aqueous methanol the product crystallised out. The obtained hydroxy ether *XXIV* (0.18 g) had m.p. 288–289°C (chloroform-methanol);  $[\alpha]_D +38^\circ$  (*c* 0.62). According to its IR spectrum it was identical with the hydroxy ether obtained from epoxy derivative *VII*.

*Elemental analyses were carried out by Mrs J. Čečrdlová and the IR spectra were measured by Mrs M. Podzimeková of the analytical department of our laboratories, (head Dr J. Zelinka). For the measurement of the PMR spectra we thank Dr M. Buděšinský, Institute of Organic Chemistry, and Biochemistry, Czechoslovak Academy of Sciences, Prague. For the measurement of ORD our thanks are due to Dr I. Frič.*

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