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# PHEROMONES OF COLEOPTERA.

## COMMUNICATION 4. SYNTHESIS OF MULTISTRIATIN WITH THE APPLICATION OF THE THERMAL HYDROXY-COPE REARRANGEMENT UNDER HIGH PRESSURE

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We recently showed that the [3,3]-sigmatropic rearrangement of 1,5-dien-3-ols (the "hydroxy-Cope rearrangement"), in its thermal or catalytic variant, is a simple and preparatively convenient route for the synthesis of the carbon skeleton of brevicomin [1] and frontalin [2] – aggregation pheromones of the bark beetles of the genus Dendroctonus. With the object of clarifying the usefulness of this approach for the isolation of other physiologically active compounds in the 6,8-dioxabicyclo[3.2.1]octane series, we undertook the synthesis of multistriatin (I), an essential component of the aggregation pheromone of bark beetles of the genus Scolytus which are pests of the elm and other greenwood trees [3].

Several synthesis, none of which is completely stereospecific, were described for the racemic multistriatin (I) [3-7]. In the best cases, the mixture of the biologically active α-multistriatin (Iα) with the biologically inactive γ-multistriatin (Iγ) is obtained [4, 5, 7]. In the other cases [3, 6], mixtures of racemates also containing traces of β-multistriatin (Iβ) and δ-multistriatin (Iδ), which likewise attracts some types of bark beetle, are formed [8]. The separation of the mixtures is only achieved using GLC. Since the mixture of all four of the diastereomeric racemates, containing ~35% of the active component (Iα), is sufficiently attractive to the bark beetles [3, 9], it is also utilized in the synthetic pheromone composition "multilure" [9]. In the given work, we were therefore interested, first of all, in the reduction of the number of the stages in the synthesis of multistriatin (I) and the possibility of its preparative simplification.

The key stage of the synthesis was chosen to be the hydroxy-Cope rearrangement of 3-ethyl-2-methyl-1,5-heptadien-3-ol (II) to 4,6-dimethyl-7-octen-2-one (III), from which the transition to multistriatin (I) was previously described [6].

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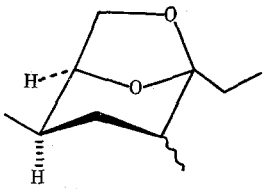
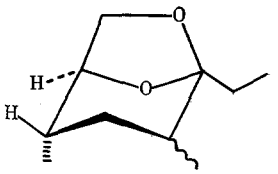


(Iα), (Iγ)



(Iβ), (Iδ)

The compound (IV) (2-methyl-1-penten-3-one), which was obtained from diethyl ketone in 34% yield according to [4], served as the initial substance.

The method of the thermal isomerization of the adducts of allylic organozinc compounds with ketones was utilized for the isolation of (II) [10]. The treatment of the ketone (IV) with crotyl zinc bromide in THF at 0°C and the subsequent boiling for 48 h led to an 88% yield of the carbinol (II). In conformity with the data obtained with other examples [11], the thermal rearrangement of the alcoholate thereby gave the mixture of the E and Z isomers of the carbinol (II), although pure E-crotyl bromide was utilized for the isolation of the organozinc compound. According to the data of GLC and the PMR spectrum, the carbinol (II) is a mixture of two geometrical isomers in the ratio of ≈55:45. By analogy with the data of [11], the E configuration (IIa) was assigned by us to the predominating isomer; the Z configuration (IIb) was assigned to the second isomer. The regioisomeric 3-ethyl-2,4-dimethyl-1,5-hexadien-3-ol (V) was completely absent from the reaction product. This carbinol, as was also anticipated (cf. [10]), was obtained as the only product in the reaction of the ketone (IV) with crotyl magnesium bromide in THF at 0°C; it is the inseparable mixture of the erythro and threo isomers (Va, b) in the ratio of 1:1 (the data of the PMR spectrum).

The thermolysis of the carbinol (II) at 180°C in N-methylpyrrolidone (N-MP), according to the method of Fujita [12], proved to be unsuccessful. A polymeric product was obtained instead of the desired ketone (III). It is probable that the retro-decomposition to 1-butene and the readily polymerized ketone (IV) proceeded at 180°C instead of the rearrangement of (II) to (III). According to the data of GLC, the low-molecular-weight fraction, which was obtained in 15-20% yield from (II), contained eight products; five of these had lower $R_t$ values than the E and Z components of the initial carbinol (IIa, b). The attempt to carry out the rearrangement by the heating of (II) adsorbed on silica gel at 80-180°C also gave no result. The initial (II) was recovered at 80°C, and resinification occurred with the increase in the temperature.

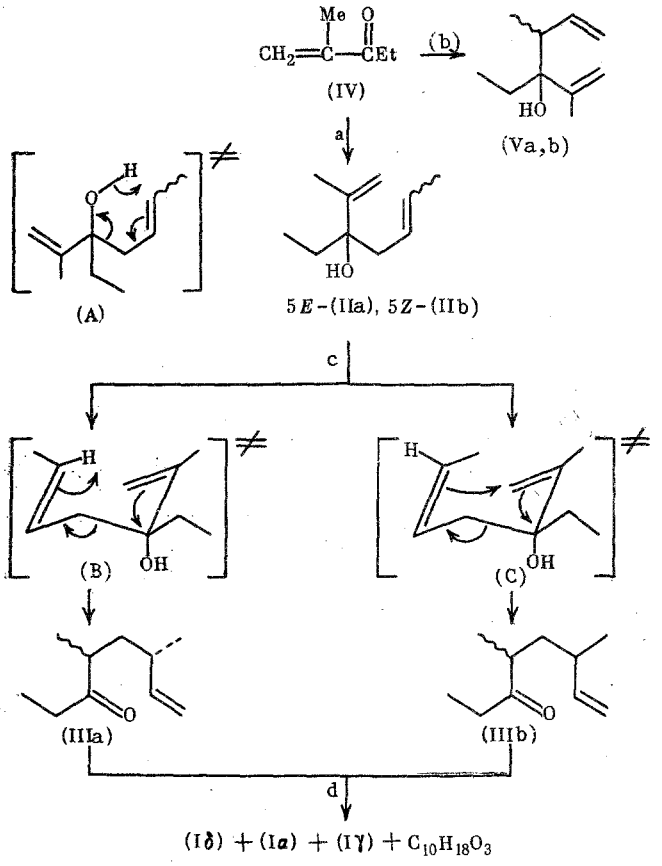
The thermal rearrangement of the carbinol (II) under high pressure was performed with the object of suppressing the concurrent reaction of retrodecomposition, which evidently proceeds via the less sterically hindered intermediate state (A) and leads to the formation of two molecules from one. We previously showed [13] that pressures of the order of 1-10 kbar markedly accelerate the hydroxy-Cope rearrangement of 3,5-dimethyl-1,5-hexadien-3-ol to 6-methyl-6-hepten-2-one. It was assumed that the high pressure should prevent the decomposition of (II) to (IV) and 1-butene and assist in the formation, from (IIa, b), of the transition states (B, C) which are necessary for the rearrangement.

In fact, the conversion of the carbinol (II) in N-MP at 190°C under 10 kbar pressure proceeded entirely differently from that at the normal pressure; the requisite ketone (III) proved to be the only product of the reaction in the conversion of (II) by 75%. Regardless of the fact that the indicated degree of conversion was obtained after 10 h (which indicates the slow course of the rearrangement), polymers were not formed. The ketone (III) and the carbinol (II) were separated by the method of preparative TLC on silica gel. The yield of the ketone (III) comprised 70%; the constants and the spectral characteristics of (III) agreed with the literature values [6]. Therefore, the carrying out of the thermal hydroxy-Cope rearrangement under high pressure permits the extension of this important synthetic reaction to those 1,5-dien-3-ols which do not participate in it under normal conditions.

It should be noted that the mixture of the E and Z isomers of the carbinol (IIa, b) were utilized for the rearrangement in all cases. The hypothesis that the predominant component of the mixture has the E configuration is confirmed by the fact that it declines more rapidly than the Z isomer in the thermolysis under high pressure. The latter declines more slowly, and therefore it prevails in the carbinol which is regenerated from the reaction mixture. It

is known [14] that the Z isomers react significantly more slowly than the E isomers in [3,3]-sigmatropic rearrangements of 1,5-diene systems; therefore, the second component undergoing slow rearrangement should be the Z isomer (IIa). In its turn, the product of the rearrangement is the 2.5:1 mixture (the data of GLC and the PMR spectrum) of the two diastereomers (IIIa, b). Since the configuration at $C^4$ in the ketones (IIIa) and (IIIb) is unstable owing to the enolization of the ketone, the mixture of (IIIa, b) was utilized without separation for the conversion to multistriatin.

The epoxidation of the ketone (III) with t-butyl hydroperoxide (TBHP) in toluene at 95-100°C in the presence of a catalytic amount of molybdenyl acetylacetonate gave a 27% yield (not optimized) of the 36:28:16:20 mixture (in the order of increase in the $R_t$ values) of four compounds.




Reagents: a: $MeCH = CHCH_2ZnBr$/THF, 65°, 48 h; b: $MeCH = CHCH_2MgBr$/THF, 0°, 3 h; c: 190°, 10 kbar, N-MP, 10 h; d: TBHP/$MoO_2(acac)_2$, toluene 95—100°, 48 h.

The IR spectrum of this mixture contained all the bands characteristic of the multistriatins [4-7], in particular the strong bands of the vibrations of the C—O of the ketal grouping (ν 1170-1180, 1120, and 1030-1050 $cm^{-1}$) as well as the moderately intense bands of the vibrations of C=O and C—O of the ester group (ν 1740 and 1245 $cm^{-1}$). The analysis of the mixture by the method of GLC-mass spectrometry (MS) showed that the first three components give the molecular ion at m/z 170 and contain characteristic ions of multistriatin at m/z 57, 71, 128, and 140 (cf. [3, 15]) in the mass spectrum. According to the retention time, the main and most volatile component of the mixture was characterized as δ-multistriatin (Iδ); the components following it were characterized as α-multistriatin (Iα) and γ-multistriatin (Iγ). The fourth, least volatile, component gives the molecular ion at m/z 186; this corresponds to the addition of two atoms of oxygen to the ketone (III). This component is evidently the product of the Baeyer—Villiger oxidation of (III), and is responsible for the characteristic absorption bands of the ester group in the IR spectrum of the mixture (cf. [6]). It appears that the hydroperoxide oxidation of the monosubstituted olefin (III) proceeds worse than the oxidation using a per acid, as utilized in [6]. Due to the low yield at the last stage, the total yield of the mixture (Iα, γ, δ) from the ketone (IV) comprises ~13% for the three stages (or 4.4% based on the diethyl ketone). The total number of stages is less than that in the majority of the known syntheses.

Therefore, the approach, which we previously proposed, to the synthesis of derivatives of 6,8-dioxa[3.2.1]bicyclooctane using the hydroxy-Cope rearrangement [1, 2] was extended to the synthesis of multistriatin. In the given case, the thermolysis in N-MP under high pressure proved to be a successful variant in carrying out the rearrangement. As far as we know, this is the first case of the preparative utilization of the high pressure method which is applicable to the [3,3]-sigmatropic rearrangement of 1,5-dien-3-ols.

## EXPERIMENTAL

The experiments under high pressure were performed in thin-walled Teflon ampuls placed in the cylinder of the high-pressure unit with heating (cf. [16]). The analysis of the reaction mixtures was performed by the method of TLC on silica gel L 40-100 μm (Chemapol, Czechoslovakia) and the method of GLC on a "Biokhrom-1" instrument with a 100 × 0.3 cm glass column with 5% XE-60 on Chromaton N-AW-HMDS, a nitrogen flow rate of 40 ml/min, a column temperature of 90°C, and the temperature of the vaporizer and the detector set at 140-160°C. For the preparative TLC, we utilized the same silica gel L on 24 × 36 cm glass plates with a 1 mm thickness of the layer. The IR spectra were taken in $CCl_4$ on a UR-20 instrument. The PMR spectra were taken in $CDCl_3$ on a "Tesla BS-497" (100 MHz) instrument relative to HMDS, and a "Bruker WM-497" (250 MHz) instrument. The analysis of the mixture of multistriatins by the method of GLC-MS was performed on an LKB-9000 instrument (1.50 × 0.3 cm column with 3% XE-30 on Chromaton N-AW-HMDS, 90-110°C, 1°/min). Compound (IV) (2-methyl-1-penten-3-one) was obtained from diethyl ketone according to [4]; it had bp 37-38°C (30 mm).

Mixture of the E- and Z-Carbinols (IIa, b). To the solution of crotyl zinc bromide, obtained from 5.85 g (0.09 g-atom) of a degreased zinc cutting and 6.075 g (45 mmole) of crotyl bromide in 50 ml of THF at 0-5°C, was added the solution of 2.9 g (30 mmole) of the ketone (IV) in 5 ml of abs. THF under Ar. After this, the mixture was gradually heated to boiling, and was stirred while boiling for 48 h. The reaction mixture was decanted from the residues of the zinc cutting, decomposed with ice water, saturated with dry $NH_4Cl$ until the separation into layers was achieved, and extracted with ether (4 portions of 30 ml). The extract was dried with $K_2CO_3$, and the ether was distilled through a small fractionating column at atmospheric pressure (bath temperature of 40-45°C). The residue was distilled in vacuo. The mixture of the two carbinols (IIa, b) was obtained; it had bp 86-86.5°C (26 mm) and the 55:45 ratio of the E isomer ($R_t$ 31.4 min) and the Z isomer ($R_t$ 24.0 min). The yield was 4.0 g (88%). The IR spectrum (ν, $cm^{-1}$) was as follows: 3600, 3070, 1640, 970, and 910. The PMR spectrum (100 MHz, δ, ppm) was as follows: 0.76 triplet (3H, J = 6.5 Hz), 1.14-1.67 [double set quartet (2H), singlet (3H) and doublet (3H), 55:45], 2.20 multiplet (2H), 3.60 broad singlet (1H), and 4.88-5.45 [double set broad singlet (1H), doublet (1H), multiplet (2H), 55:45].

Mixture of the Erythro- and Threo-Carbinols (Va-b). To the solution of crotyl magnesium bromide, prepared from 2.16 g (0.08 g-atom) of an Mg cutting and 10.8 g (80 mmole) of crotyl bromide in 100 ml of THF, were added 3.0 g (30 mmole) of the ketone (IV) at 0°C with energetic stirring. At the conclusion of the reaction (stirring for 4 h at 0°C), the mixture was decomposed with ice water, saturated with dry $NH_4Cl$, and extracted with ether. The extract was dried with $K_2CO_3$, and the ether was distilled. The extract yielded the mixture of the carbinols (Va, b) with bp 96-97°C (50 mm) and the yield of 2.90 g (64%). The IR spectrum (ν, $cm^{-1}$) was as follows: 3600, 3060, 1640, 950, and 915. The PMR spectrum (100 MHz, δ, ppm) was as follows: 0.85 and 0.89 [two triplets (3H), 1:1], 0.98 and 1.06 [two doublets (3H), 1:1], 2.05-2.26 [double set quartet (2H) and multiplet (1H), 1:1], 3.64 broad singlet (1H), 4.95-5.75 [doubly, partially overlapping set, broad singlet (1H), doublet (1H), and multiplet (3H), 1:1].

The Ketone (III). To 500 mg of the carbinol (IIa, b) was added dry, freshly distilled N-MP to the volume of 4.8 ml. The solution was transferred to the Teflon ampuls of 1.2 ml capacity and placed in the high-pressure unit with heating. After the heating (10 h at 190°C) under the pressure of 10 kbar, the contents of the ampuls were diluted with 25 ml of pentane; the solution obtained was carefully washed free from the N-MP with distilled water. The organic layer was dried with $MgSO_4$. The pentane was distilled at atmospheric pressure through a small fractionating column (bath temperature of 40-45°C). The residue, obtained from four experiments, was combined and chromatographed on preparative plates with silica gel in the 3:1 system of hexane–ether. After elution with dry ether, (III) was obtained from the zone with $R_f$ 0.56 in the form of a colorless oil which was discrete on TLC. The yield was 350 mg (70%); it had the bp 80-82°C (22 mm). According to the data of GLC, (III) consisted of two components with $R_t$ values of 34.5 and 39.5 min in the ratio of 28:72. The IR spectrum

($\nu$, $cm^{-1}$) was as follows: 3080, 2980, 2940, 1712, 1640, 1380, 1110, 995, and 910. The PMR spectrum (250 MHz, $\delta$, ppm) was as follows: 0.93 triplet (3H, J = 7 Hz), 0.98 and 1.04 [double set doublet (3H, J = 7 Hz), 1:2.5], 1.10 and 1.13 [double set, doublet (3H, J = 6 Hz), ~2.5:1], 1.28-1.35 [double set, multiplet (2H)], 1.90-2.10 [double set, multiplet (1H) and triplet (2H), J = 7 Hz, ~2.5:1], 2.60-2.70 multiplet (1H), and 4.90-6.00 multiplet (3H) (overlapping double set of the signals of the $CH_2CH$ group). All the constants of the sample of (IIIa, b) were close to the literature values (cf. [6]). The initial carbinol (IIa, b) (210 mg) was obtained from the zone with $R_f$ 0.45 after the elution with ether. According to the data of GLC, it had the 4:1 ratio of the components with $R_t$ values of 8.0 and 10.5 min.

Multistriatin (I). To the solution of 154 mg (1 mmole) of the ketone (III) in 5 ml of toluene were added 0.20 ml of 95% t-BuOOH (~2 mmole) and 100 mg of molybdenyl acetylacetonate. The mixture was gradually heated with a reflux condenser to 95-100°C and was maintained at this temperature for 48 h. After cooling to 20°C, the mixture was washed with $Na_2SO_3$ solution, 25% aqueous NaOH solution, and water; it was dried with $MgSO_4$. The toluene and t-BuOH were distilled in vacuo. The residue was distilled in a flanged flask at 90-100°C (20 mm). We obtained a colorless oil which, according to the analytical data of the GLC-MS method, contained $\delta$-multistriatin (I$\delta$) ($R_t$ 24.5 min), $\alpha$-multistriatin (I$\alpha$) ($R_t$ 28.5 min), and $\gamma$-multistriatin (I$\gamma$) ($R_t$ 32.0 min) as well as the ester $C_{10}H_{18}O_3$ ($R_t$ 46.5 min) in the ratio of 36:28:16:20. The yield was 42 mg (~27%). The components (I$\delta$), (I$\alpha$), and (I$\gamma$) gave practically the same spectra containing peaks of the ions with the following values of m/z: 170 (0.10-0.12) $M^+$, 140 (0.55-0.62) $[M - CH_2O]^+$, 128 (0.70-0.79) $[M - C_3H_3CH{=}CH_2]^+$, 71 (0.45-0.48) $[C_4H_7O]^+$, and 57 (1.0) $[C_2H_5{=}O]$. The component with $R_t$ 46.5 min contained the peaks of the ions with m/z 186 $M^+$ and 112 $[M - C_2H_5COOH]^+$ in the mass spectrum. The IR spectrum ($\nu$, $cm^{-1}$) was as follows: 2970, 2935, 2880, 1460, 1380, 1370, 1360, 1180, 1170, 1130, 1120, 1050, 1030, 915, and 895 (absorption characteristic of multistriatin) as well as 1740 and 1245 (the admixture of the ester).

## CONCLUSION

The synthesis of multistriatin (in the form of the $\alpha$, $\gamma$, and $\delta$ isomers) was accomplished in three stages from 2-methyl-1-penten-3-one (IV) with the total yield of 13%. The thermal hydroxy-Cope rearrangement of 3-ethyl-2-methyl-1,5-heptadien-3-ol (II) at the pressure of 10 kbar was utilized at the key stage of the synthesis.

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