THE SYNTHESIS OF (3-^{2}H)TRICYCLO[6,2,2,$O^{2,7}$]-3,9-DODECADIENE

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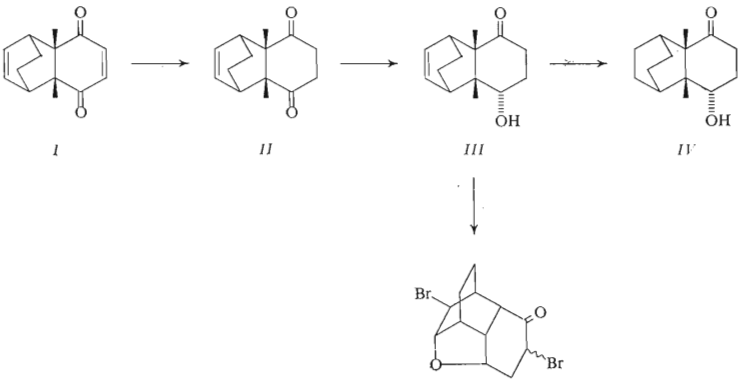
Tricyclo[6,2,2,$0^{2,7}$]-3,9-dodecadiene (dicyclohexadiene) (*XIII*) specifically labelled with deuterium was prepared by an 8 step synthesis. Simultaneously isomeric tricyclo[6,2,2,$0^{2,7}$]-2,9-dodecadiene (*VIII*) (the main product of the synthesis) and tricyclo[6,2,2,$0^{2,7}$]-2(7),9-dodecadiene (*XIV*) were also prepared. The relative configuration of three intermediates was determined.

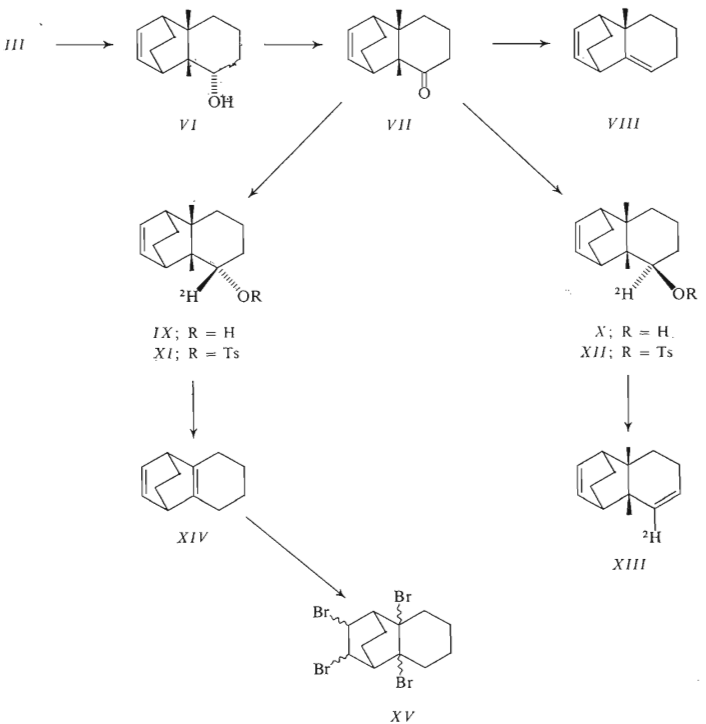
For the study of the course of the retro-Diels–Alder reaction of ionized molecules we needed tricyclo[6,2,2,$0^{2,7}$]-3,9-dodecadiene specifically labelled with deuterium. Tricyclo[6,2,2,$0^{2,7}$]-3,9-dodecadiene (dicyclohexadiene) (*XIII*) is easily accessible either by direct Diels–Alder dimerization of 1,3-cyclohexadiene[1,2] or by thermic isomerization of photochemical dimers of 1,3-cyclohexadiene[3,4]. Neither of these procedures is suitable, however, for the preparation of dicyclohexadiene which would be specifically labelled in one of its cyclohexene subunits, *i.e.* in positions $C_{(2)}$, $C_{(3)}$, $C_{(4)}$, $C_{(5)}$, $C_{(6)}$ $C_{(7)}$ or $C_{(1)}$, $C_{(8)}$, $C_{(9)}$, $C_{(10)}$, $C_{(11)}$, $C_{(12)}$. The synthetic procedure described in this paper (Scheme 1 and 2) starts from the Diels–Alder reaction of 1,3-cyclohexadiene with *p*-benzoquinone[5]. Tricyclo[6,2,2,$0^{2,7}$]-4,9-dodecadiene-3,6-dione (*I*) (ref.[5]) was reduced[6] to tricyclo[6,2,2,$0^{2,7}$]-9-dodecene-3,6-dione (*II*). Partial reduction[7] of dione (*II*) gave 6-hydroxytricyclo[6,2,2,$0^{2,7}$]-9-dodecen-3-one (*III*). The *endo*-configuration of the hydroxyl group was determined on the basis of the formation of the intramolecular hydrogen bridge with the double bond of the skeleton ($\Delta\nu$(OH) = 65 cm^{-1}). In order to exclude the possibility of the existence of an intramolecular hydrogen bond between the hydroxyl and the carbonyl group (at an *exo*-configuration of the hydroxyl), hydroxy ketone *III* was hydrogenated under formation of the saturated derivative *IV*; in its IR spectrum only the absorption band of the free hydroxyl vibration (ν(OH) 3619 cm^{-1}) was found. Further evidence of the *endo*-configuration of the hydroxy group in hydroxy ketone *III* is its reaction with bromine: in its addition phase the *endo*-configuration is involved in intramolecular participation, which is excluded for the *exo*-configuration. The structure of 4,10-dibromo-6,9-epoxytricyclo[6,2,2,$0^{2,7}$]dodecan-3-one has been proposed for compound *V* on the basis of its IR spectrum (1712, 1032, 990, 665 cm^{-1}, the band of the stretching vibration of hydroxyl is absent) and mass spectrum ($C_{12}H_{14}Br_2O_2^+$, (M^+); $C_{12}H_{14}BrO_2^+$, $(M - Br)^+$; $C_{12}H_{14}O_2^+$, $(M - 2\,Br)^+$). Hydroxy ketone *III*



I *II* *III* *IV* *V*

SCHEME 1

was reduced according to Huang–Minlon to tricyclo[6,2,2,$0^{2,7}$]-9-dodecen-3-ol (*VI*) which was oxidized[8] to tricyclo[6,2,2,$0^{2,7}$]-9-dodecen-3-one (*VII*). Applying the Bamford–Stevenson reaction[9] to the *p*-toluenesulfonylhydrazone of ketone *VII* tricyclo[6,2,2,$0^{2,7}$]-2,9-dodecadiene (*VIII*) was obtained. The same product was formed when tosylation of alcohol VI at room temperature was attempted. The position of the double bond in diene *VIII* was determined on the basis of its ^{1}H-NMR spectrum from differing chemical shifts of protons on $C_{(1)}$ ($\delta = 2{\cdot}83$ ppm) and on $C_{(8)}$ ($\delta = 2{\cdot}43$ ppm) and from the shape of the XY-part of the ABXY multiplet (protons on $C_{(1)}$, $C_{(8)}$, $C_{(9)}$ and $C_{(10)}$). Ketone *VII* was further reduced with lithium aluminum deuteride under formation of isomeric (3-^{2}H)tricyclo[6,2,2,$0^{2,7}$]--9-dodecen-3-ols (*IX*, or *X*, 8 : 1). The configuration of the hydroxyl group in alcohol *IX* or *X* was determined from their IR spectra on the basis of the formation of an intramolecular hydrogen bond (isomer *IX*, $\Delta\nu(\mathrm{OH}) = 37\ \mathrm{cm}^{-1}$). On tosylation of alcohols *IX* and *X* at low temperature (3-^{2}H)tricyclo[6,2,2,$0^{2,7}$]-9-dodecen-3-yl *p*-toluenesulfonates *XI* or *XII*, respectively, were obtained. Elimination of the *p*-toluenesulfonyl group from these tosylates was carried out using potassium tert-butoxide; tosylate *XII* was thus converted to (3-^{2}H)tricyclo[6,2,2,$0^{2,7}$]-3,9-dodecadiene (*XIII*) in good yield. Its double bond was characterized unambiguously by ^{1}H-NMR spectrum (multiplet, $\delta = 5{\cdot}94$ ppm, 2 H; broad singlet, $\delta = 5{\cdot}50$ ppm, 1 H). In contrast to this tosylate *XI* did not afford the expected 3-^{2}H-analogue of diene *VIII*, but tricyclo[6,2,2,$0^{2,7}$]-2(7),9-dodecadiene (*XIV*) was obtained as the main product (90%) in addition to diene *XIII* (10%). Under the effect of the base used an almost



SCHEME 2

complete exchange of deuterium for hydrogen took place in diene *XIV*, so that it contained about 10% of the corresponding ^{2}H-analogue only. The structure of diene *XIV* was proposed on the basis of its mass spectrum, *m/e* 160, $(M^{\pm})$; *m/e* 132 $(M - C_2H_4)^{\pm}$; *m/e* 104 $(M - 2\,C_2H_4)^{\pm}$), which permits either the presence of another double bond, or of a new cycle; the structures with a cyclopropane ring and with a double bond $C_{(4)}$—$C_{(5)}$ were excluded on the basis of the ^{1}H-NMR spectrum (multiplet, $\delta = 6{\cdot}00$ ppm, 2 H). The bromine addition was also in accordance with the proposed structure: tetrabromo derivative *XV* was obtained in the mass spectrum of which the ionic species $C_{12}H_{16}Br_3^+$ $(M - Br)^+$ were abundant, while the ions

$C_{12}H_{16}Br_2^+$ almost did not appear. The presence of a tetrasubstituted double bond in diene *XIV* is also consistent with the order on increasing retention of isomeric dienes *XIV*, *VIII* and *XIII* on GE-XE-60 and GE-SE-30.

EXPERIMENTAL

The melting points were determined on a Boetius melting point apparatus. The IR spectra were measured on a UR-10, Zeiss (Jena) spectrophotometer in tetrachloromethane. The region of valence vibrations ν(O—H) was measured on a Pye-Unicam SP-700 spectrophotometer in tetrachloromethane, at $5 \cdot 10^{-3}$M concentration. The ^{1}H-NMR spectra were measured with a JEOL JNM-PS-100 (100 MHz) instrument, using tetramethylsilane as internal reference. Chemical shifts are given in ppm, δ-scale. The mass spectra were measured on a spectrometer JEOL D-100, 75 eV, either using the direct inlet method (compounds *I*—*XII*, *XV*), or in connection with gas chromatography (GE-SE-30, column temperature 80°C, evaporator 150°C, separator 150°C, substances *VIII*, *XIII*, *XIV*). Gas chromatographic analyses were carried out on a CHROM 31 chromatograph, Laboratorní přístroje, Praha, using the following columns: A, GE-SE-30, 6% on Chromaton NAW-DMCS, 2·40 m × 6 mm; B, GE-XE-60, 11% on Chromaton NAW-DMCS, 2·40 m × 6 mm. Purity of the compounds and the course of the reactions were checked by thin-layer chromatography on Silufol plates, Kavalier, Votice, using a potassium permanganate solution in 50% aqueous acetic acid for detection. The phrase "worked up as usual" means that the extract was dried over magnesium sulfate, filtered and evaporated on a rotatory evaporator.

Tricyclo[6,2,2,$0^{2,7}$]-9-dodecene-3,6-dione (*II*)

Tricyclo[6,2,2,$0^{2,7}$]4,9-dodecadiene-3,6-dione (*I*) (6 g, m.p. 96—97°C, ref.[5] gives 98°C) was reduced[6] with zinc (7·5 g) in 40 ml of 50% acetic acid. After ten minutes' stirring at 60°C the inorganic material was filtered off and 450 ml of 5% sodium hydrogen carbonate were added. The product was extracted with three 50 ml portions of ether and further worked up as usual. The ketone *II* obtained was purified by column chromatography on silica gel (elution with ether), affording 3·6 g (60%) of ketone *II*, m.p. 55—56° (heptane). For $C_{12}H_{14}O_2$ (190·2) calculated: 75·77% C, 7·42% H; found: 75·45% C, 7·69% H. IR spectrum: 1705, 1610, 1460, 1420, 1370, 1295, 1255, 1232, 1166, 1130, 985 cm^{-1}. Mass spectrum: *m/e* 190, (M^+).

6-Hydroxytricyclo[6,2,2,$0^{2,7}$]-9-dodecen-3-one (*III*)

A solution of sodium borohydride (180 mg) in methanol (20 ml) was added to a mixture of diketone *II* (2 g), ammonium chloride (600 mg) and methanol (100 ml) under stirring and at 0·C. The reaction course was followed by thin-layer chromatography (ether). After one hour's reaction ether (40 ml) was added and the precipitated salts filtered off, the solution was concentrated *in vacuo* and chromatographed on a silica gel column (elution with ether). Yield 1·53 g (76%) of hydroxyketone *III*, m.p. 96°C (heptane). For $C_{12}H_{16}O_2$ (192·2) calculated: 74·97% C, 8·39% H; found: 74·69% C, 8·20% H. IR spectrum: 3625, 3562 (measured at a $5 \cdot 10^{-3}$M concentration), 1700, 1610, 1450, 1410, 1375, 1300, 1235, 1050, 940 cm^{-1}. Mass spectrum: *m/e* 192 (M^+).

6-Hydroxytricyclo[6,2,2,$0^{2,7}$]dodecan-3-one (*IV*)

Hydroxy ketone *III* (83 mg) was hydrogenated on 10% palladium on charcoal (15 mg) in ethanol (10 ml). After 1 h the conversion was complete, the catalyst was filtered off and ethanol evaporated

under reduced pressure. Yield 90 mg (96%) of hydroxy ketone *IV*, m.p. 105—106° (heptane). For $C_{12}H_{18}O_2$ (194·2) calculated: 74·18% C, 9·33% H; found: 74·43% C, 9·44% H. IR spectrum: 3619 (measured at $7 \cdot 10^{-3}$M concentration), 3440, 1695, 1450, 1410, 1085, 1065, 1045, 1030 cm^{-1}. Mass spectrum: $C_{12}H_{18}O^+$ (M^+).

4,10-Dibromo-6,9-epoxytricyclo[6,2,2,$0^{2,7}$]dodecan-3-one (*V*)

A solution of hydroxy ketone *III* (75 mg, 0·41 mmol) in chloroform (5 ml) was added at −78°C to a solution of bromide (160 mg, 1 mmol) in chloroform (10 ml). After 30 minutes stirring at −30°C chloroform was distilled off in a vacuum and the residue purified by chromatography on a silica gel column (elution with chloroform). Yield 95 mg (88%) of dibromo derivative *V*, m.p. 119—120° (tetrachloromethane). For $C_{12}H_{14}Br_2O_2$ (350·1) calculated: 41·17% C, 4·03% H, 45·66% Br; found: 41·29% C, 4·11% H, 45·22% Br. IR spectrum: 1712, 1460, 1440, 1195, 1180, 1160, 1032, 990 cm^{-1}. Mass spectrum: $C_{12}H_{14}O_2Br_2^+$ (M^+); $C_{12}H_{14}O_2Br^+$ ($M - Br$)$^+$; $C_{12}H_{14}O^+$ ($M - 2\,Br$)$^+$.

Tricyclo[6,2,2,$O^{2,7}$]-9-dodecen-3-ol (*VI*)

A solution of hydroxy ketone *III* (1·5 g) and 100% hydrazine hydrate (600 mg) in diethylene glycol (20 ml) was heated at 140°C for 4 hours. Potassium hydroxide (600 mg) was then added and the mixture heated under argon for 4 hours at 200°C. After cooling the mixture was poured into water (150 ml), the product extracted with pentane (3 × 30 ml) and worked up in the usual manner. Distillation at 95°C/0·6 Torr (bath temperature) gave 1·10 g (79%) of alcohol *VI*. For $C_{12}H_{18}O$ (178·3) calculated: 80·84% C, 10·17% H; found: 80·60% C, 10·10% H. IR spectrum: 3619, 3600, 3460, 1600, 1050, 1010 cm^{-1}. Mass spectrum: *m/e* 178 (M^+).

Tricyclo[6,2,2,$0^{2,7}$]-9-dodecen-3-one (*VII*)

A solution of alcohol *VI* (940) mg in dichloromethane (10 ml) was added to a mixture of pyridinium chlorochromate[8] (1·5 g) and dichloromethane (30 ml) under stirring. The oxidation course was followed by thin-layer chromatography (light petroleum–ether 1 : 1). After 1 h the solution was filtered through a silica gel column (10 g), dichloromethane was evaporated *in vacuo* and the residue distilled. Yield 825 g (88%) of ketone *VII*, b.p. 95°C/1 Torr. For $C_{12}H_{16}O$ (176·2) calculated: 81·80% C, 9·15% H; found: 81·36% C, 9·14% H. IR spectrum: 1705, 1610, 1460, 1452, 1410, 1150, 715 cm^{-1}. Mass spectrum: *m/e* 176, (M^+). Oxime: m.p. 114—116°C (heptane).

Tricyclo[6,2,2,$0^{2,7}$]-2,9-dodecadiene (*VIII*)

A) *From ketone* VII: A mixture of ketone *VII* (250 mg, 1·42 mmol), *p*-toluenesulfonylhydrazide (300 mg), tetrahydrofuran (5 ml) and methanol (1 ml) was refluxed for 5 h. Methanol (5 ml) was then added and the mixture refluxed for another 5 h. The reaction course was followed by thin-layer chromatography (light petroleum–ether 3 : 2). The solvents were then distilled off in vacuo, and a solution of sodium methoxide (5 mmol) in diethylene glycol dimethyl ether (10 ml) was added to the residue. The mixture was refluxed under argon for 16 h, cooled and poured into water (150 ml). The product was extracted with pentane (3 × 20 ml) and worked up as usual. After distillation at 100°C/10 Torr (bath temperature) 112 mg (49%) of diene *VIII* were obtained, which when chromatographed on columns *A*, *B* (80°C) was pure. For $C_{12}H_{16}$ (160·2) calculated: 89·97% C, 10·07% H; found: 89·35% C, 9·92% H. IR spectrum: 1670, 1635,

1460, 1446, 935, 900, 845 cm^{-1}. Mass spectrum: *m/e* 160 ($M^{\pm}$). ^{1}H-NMR spectrum: 1·31, 1·63 mt, total 8 H; 2·00 mt, 3 H; 2·43 mt, 1 H; 2·83 mt, 1 H; 5·12 mt, 1 H; 6·10 mt, 2 H.

B) *From alcohol* VI: Alcohol *VI* (200 mg, 1·12 mmol) in pyridine (2 ml) was allowed to stand in the presence of *p*-toluenesulfonyl chloride (228 mg, 1·20 mmol) at 20°C for 120 h. The reaction course was followed by thin-layer chromatography in chloroform. When the reaction was terminated the mixture was poured into water (50 ml), the product extracted with pentane (3 × 10 ml) and worked up as usual. After distillation 126 mg (70%) of diene *VIII* were obtained, which was identified by comparison of its retention data (columns *A*, *B*), mass and infrared spectra with those of the diene obtained under *A*).

(3-^{2}H)Tricyclo[6,2,2,$0^{2,7}$]-9-dodecen-3-ol (*IX*, *X*)

Ketone *VII* (930 mg) was reduced with lithium aluminum deuteride (160 mg) in ether (15 ml). After the conventional work-up a mixture of alcohols was obtained which was separated on a silica gel column (elution with a mixture of light petroleum and ether, 3 : 2), yielding 750 mg of alcohol *IX*, m.p. 25–27°C; for $C_{12}H_{17}{}^2HO$ (179·3) calculated: 80·39% C, 10·68% (H + ^{2}H); found: 80·60% C, 10·10% (H + ^{2}H). IR spectrum: 3588 (measured at 4 . 10^{-3}M concentration), 2120, 1090, 1610, 1460, 1075 cm^{-1}; mass spectrum: *m/e* 179 ($M^{\pm}$). Further elution gave 90 mg of alcohol *X*, m.p. 51–52°C; for $C_{12}H_{17}{}^2HO$ (179·3) calculated: 80·39% C, 10·68% (H + ^{2}H); found 80·51% C, 10·65% (H + ^{2}H). IR spectrum: 3625 (measured at 6 . 10^{-3}M concentration), 2120, 1610, 1460, 1095, 1080, 1070 cm^{-1}. Mass spectrum: *m/e* 179 ($M^{\pm}$).

(3-^{2}H)Tricyclo[6,2,2,$0^{2,7}$]-9-dodecen-3-yl *p*-toluenesulfonates (*XI*, *XII*)

Alcohols *IX* and *X* were tosylated with equivalent amounts of *p*-toluenesulfonyl chloride in pyridine at −5°C, for 72 h. The reaction course was followed by thin-layer chromatography in light petroleum–ether, 3 : 2. The reaction mixtures were poured into ice-cold water, the crystalline tosylates *XI* or *XII*, respectively, were suction-dried and dissolved in chloroform. The solutions were dried over calcium chloride, filtered and evaporated under reduced pressure. The residues were crystallized from pentane. *XI*: m.p. 65–66°C (decomposition), for $C_{19}H_{23}{}^2HO_3S$ (333·5) calculated: 68·43% C, 7·55% (H + ^{2}H); found: 68·71% C, 7·70 (H + ^{2}H). XII: m.p. 101 to 102°C, for $C_{19}H_{23}{}^2HO_3S$ (333·5) calculated: 68·43% C, 7·55% (H + ^{2}H); found: 68·48% C, 7·74% (H + ^{2}H).

(3-^{2}H)Tricyclo[6,2,2,$0^{2,7}$]-3,9-dodecadiene (*XIII*)

A solution of tosylate *XII* (140 mg, 0·42 mmol) and potassium tert-butoxide (112 mg, 1 mmol) in dimethoxyethane (10 ml) was refluxed for 2 h under argon. Water (50 ml) was then added and the product extracted with pentane (3 × 10 ml) and worked up in the usual manner. Distillation at 110°C/10 Torr (bath temperature) gave 40 mg (59%) of diene *XIII* which contained about 5% of a by-product, the retention of which (on columns *A* and *B*) corresponded to that of diene *VIII*. ^{1}H-NMR spectrum: 1·14 mt, total 7 H; 1·88 mt, 2·00 mt, total 5 H; 5·50 mt, 1 H; 5·94 mt, 2 H. Mass spectrum: *m/e* 161 ($M^{\pm}$).

Tricyclo[6,2,2,$0^{2,7}$]-2(7),9-dodecadiene (*XIV*)

A solution of tosylate *XI* (780 mg, 2·34 mmol) and potassium tert-butoxide (800 mg, 7·1 mmol) in 1,2-dimethoxyethane (25 ml) was refluxed under argon for 6 h. The mixture was worked up as in the case of diene *XIII*, and after distillation at 110°C/15 Torr (bath temperature) 126 mg

(33%) of a mixture of 90% diene *XIV* and 10% diene *XIII* (column *B*, 80°C) were obtained. IR spectrum: 1600, 1495, 1445, 1345, 1086, 840, 710, 685 cm^{-1}. Mass spectrum: *m/e* 161,160, 1 : 10 ($M^{+\cdot}$), *m/e* 132, 104. ^{1}H-NMR spectrum: 1·25—2·63 mt, total 14 H; 6·00 mt, 2 H.

2,7,9,10-Tetrabromotricyclo[6,2,2,$0^{2,7}$]-dodecane (*XV*)

A solution of diene *XIV* (20 mg) in tetrachloromethane (5 ml) was added at −78°C to a solution of bromine (25 mg) in chloroform (5 ml). After 30 min at −20°C the solvent was evaporated under reduced pressure and the semicrystalline bromo derivative *XV* was analysed by mass spectrometry without further purification. The mass spectrum displayed a group of ions C_{12}·$H_{16}Br_4^{+\cdot}$ of low abundance and an abundant group of ions $C_{12}H_{16}Br_3^{+}$.

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