CYCLIZATION OF ISOPRENOID COMPOUNDS

COMMUNICATION 21. CYCLIZATION OF FARNESYLIC ESTERS UNDER THE ACTION OF CATIONOID INITIATORS

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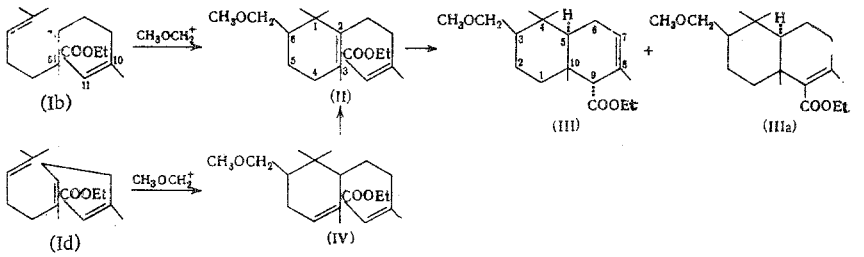
We have shown previously on the basis of several examples in the monoterpene series that reagents of the $R^+BF_4^-$ type are able to bring about cyclization with simultaneous introduction of the group R into the cyclic molecule [1]. In the present work we studied the applicability of this reaction in the sesquiterpene series for the case of the stereoisomeric farnesylic esters, the cyclization of which under the action of acids has been studied in fair detail [2].

As cyclization agent we chose $CH_3OCH_2^+BF_4^-$. The ethyl farnesylates required [6,7-trans-10,11-trans (Ia), 6,7-trans-10,11-cis (Ib), 6,7-cis-10,11-trans (Ic), and 6,7-cis-10,11-cis (Id)] were prepared by the reactions of the individual geranylacetones [3] with ethyl ethynyl ether in presence of boron trifluoride ether complex [4]. The geometric isomers with respect to the 10- and 11-positions then obtained were separated by distillation through a column, which proved to be very much more effective than the methods used previously [2, 5]. The cyclization was effected by a procedure which we have developed [6]. The compositions of the mixtures of reaction products were determined by means of GLC.

Our investigation showed that the cyclization of (Ia)-(Id) under the action of $CH_3OCH_2^+$ leads to the formation of cyclic products containing the CH_3OCH_2 group. As in the case of proton initiation [2], the reaction goes in two stages: the formation of a monocyclic product, and its conversion into a bicyclic compound. Thus, in the cyclization of the 6,7-trans-10,11-cis ester (Ib) at −60° the monocyclic product (II) is formed almost exclusively (Expt. 4), at −24 to −26° a mixture of (II) and the bicyclic ester (III) is formed (2 : 1, Expt. 5), while at 0° only a mixture of the bicyclic products (III) and (IIIa) is formed (Expt. 6).*



The structure of (II) as the 6-CH_3OCH_2 derivative of β-monocyclofarnesylic ester follows from NMR data (Table 1). The NMR spectrum of the ester (III) also points unequivocally to the structure of α-bicyclofarnesylic acid (Fig. 1), which is confirmed by data on the stability of (III) to alkaline hydrolysis (under the conditions of the hydrolysis of monocyclic products [8]).

The cyclization of the other isomers of (I) goes analogously. Thus, at −60° the 6,7-cis-10,11-cis isomer (Id) forms only the monocyclic products (IV) and (II) (Expt. 8), while at −25° it forms a mixture of the monocyclic product (II) and the bicyclic product (III) (Expt. 7). In the cyclization of (Id) at the stage of

*The transformation (II) → (III) can also be effected by treating the mixture of (II) and (III) with H_2SO_4 in nitropropane solution under the conditions for the preparation of bicyclifarnesylic acid [2, 7]. We were unable to isolate the isomeric bicyclic ester (IIIa) in the pure state, and its structure was assumed on analogy with [2].

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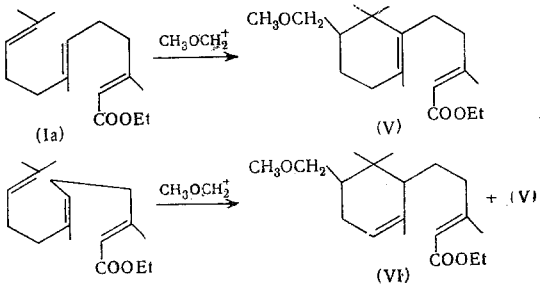
TABLE 1. Chemical Shifts of Protons of Characteristic Groups in the NMR Spectra of (II) and (V)

	A	B	C	D*	E	F	G
(II), cis-2^3, 2^4	0,85 1,08	1,21 (triplet)	1,64	1,87	3,20	4,04 (quadruplet)	5,50
(V), trans-2^3, 2^4	0,76 1,02	1,19 (triplet)	1,55	2,09	3,17	3,97 (quadruplet)	5,47

*The difference in the chemical shifts of the 2^3-CH_3 groups in (II) and (V) (0.22 ppm) is fully in accord with data in the literature [5].

the formation of monocyclic derivatives the primary product is probably the ester (IV), a derivative of α-monocyclofarnesylic acid. The formation of the ester (II) at the same time is probably to be explained, in the main, by the isomerization (IV) → (II) (cf. Expts. 8 and 7). The ease of the conversion of α-monocyclic products into the β-isomers under acidic conditions has been noted earlier in a number of cases [9]. The bicyclic ester formed from (Id) is identical to the above-described α-bicyclic ester (III) (according to GLC on various stationary phases under the conditions for the separation of geometric isomers). The stagewise and nonstereospecific formation of the bicyclic product from isomers differing with respect to the 6,7-bond is a characteristic feature of the cyclization of isoprenoids with a conjugated double bond in the 10,11-position [2]. Since in the proton cyclization of the farnesylic esters (Ib) and (Id) a bicyclofarnesylic acid is formed with trans annelation of the rings and an axial disposition of the carboxyl [2], it may be assumed that the product (III) formed with the nonproton initiation of the cyclization of both (Ib) and (Id) has the same stereochemistry, since the stage of the conversion of the monocyclic product into the bicyclic product is identical for the two types of initiation.



In the case of derivatives of the 10,11-trans series the formation of bicyclic products goes less readily and is accompanied by the formation of unidentified high-boiling substances. Hence, for the 6,7-trans-10,11-trans (Ia) and 6,7-cis-10,11-trans (Ic) isomers we studied only the stage of the formation of monocyclic products. As in the case of the isomers of the 10,11-cis series (Ib) and (Id), the conversion of (Ia) and (Ic) into derivatives of monocyclofarnesylic esters goes in accordance with the relations found earlier for proton initiation of the reaction [2, 9], i.e., the 6,7-trans isomer [(Ia); cf. with (Ib)] gives exclusively the β-monocyclic product (V) (Expt. 1), while the 6,7-cis isomer [(Ic); cf. with (Id)] gives a mixture of the α-(VI)* and β-(V) isomers (Expt. 2), and, probably in this case also, the formation of the β-product is largely the result of the transformation $\alpha \rightarrow \beta$ (cf. Expts. 2 and 3).

The structure of (V) follows from the NMR spectrum (Table 1). The ester (VI) [like (IV)] was not isolated in the pure state, and its identification as an α-cyclic derivative is based on the appearance in the NMR spectrum of a mixture of (V) and (VI) [or (II) and (IV)] of a signal at 5.25 p.p.m. (proton at C-4), the intensity of which corresponds approximately to the content of (VI) [or (IV)] in the mixture according to GLC data, and it is also based on its conversion into the corresponding β-isomer (see above). In a number of

*According to the IR (898 cm^{-1}) and NMR (δ = 4.65 p.p.m.) spectra, the mixture also contains the γ-isomer with a semicyclic double bond, the exact amount of which could not be determined.

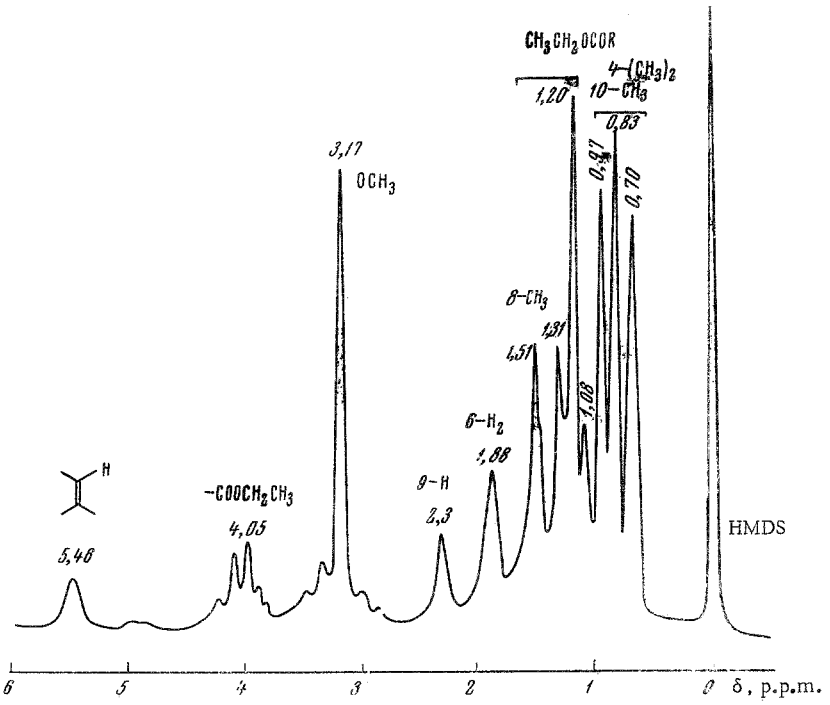


Fig. 1. NMR spectrum of (III).

cases (Expts. 2 and 8), apart from the products described unidentified substances with long retention times were formed in considerable amounts. With the object of diminishing their amount we attempted to use other agents for the generation of the same carbonium ion $CH_3OCH_2^+$ on the view that the observed complications may be associated with the possibility of the transformation of the initiator in accordance with the scheme $R^+BF_4^- \rightarrow RF \rightarrow BF_3$. It was in fact found that on change from BF_4^- to the 1,3,5-trinitrobenzenesulfonate (TNBS) anion, which is not capable of dissociation, the situation was greatly improved, and under the action of the agent $CH_3OCH_2Cl + Ag$ TNBS the formation of monocyclic products went very much more smoothly with yields of up to 60-70% (cf. Expts. 2 and 9; 8 and 10). Also, with the use of Ag TNBS the content of the α-monocyclofarnesylic esters (IV) and (VI) in the mixture of cyclization products is greater than that of the β-monocyclofarnesylic esters (II) and (V). This is a further indication that the primary product of the cyclization of (Id) [or (Ic)] is the α-ester (IV) [or (VI)] and that the formation of β-esters in these cases is due to the occurrence of the isomerization (IV) $\rightarrow$ (II) [or (VI) $\rightarrow$ (V)] under the action of acidic reagents. It should be noted that Ag TNBS has been used previously only for the preparation of episulfonium salts [10] and has not been used for the generation of carbonium ions, although it has a number of advantages over the usually used $AgBF_4$ and $AgSbF_6$, particularly in that it is nonhygroscopic.

The results presented, in conjunction with those published by us earlier [6], show that the main patterns of behavior in the formation of both mono- and bicyclic systems are preserved for isoprenoids of very varied types regardless of the nature of the electrophilic initiator (H^+ or $CH_3OCH_2^+$). Our results suggest, in particular, that the stereochemistry of the formation of bicyclic systems must be the same for both proton and nonproton initiation and that it is possible to effect the stereospecific synthesis of polycyclic isoprenoids with simultaneous introduction of a substituent at C-3 by the nonproton cyclization of isoprenoids with isolated double bonds. The preparation of trans-bicyclofarnesylic esters with a substituent at C-3 may also be of interest for its own sake, since substances of such structure (with a substituent in ring A) are important intermediate products in the synthesis of various terpenoids

EXPERIMENTAL

NMR spectra were determined with a PC-60 instrument in CCl_4 solution. Chemical shifts δ are expressed in p.p.m. relative to hexamethyldisiloxane as internal standard. IR spectra were determined with a UR-10 instrument. Progress in the separation of the original farnesylic esters was followed by means of GLC (10% of 2,2-dimethyltrimethylene succinate on Celite 545, 190°, 110 ml/min of helium, detection by

katharometer). Analysis of the cyclization products was also conducted by the GLC method (2% of 2,2-dimethyltrimethylene succinate on Chromosorb W in a glass column [11] 2 m in length and 4 mm in diameter, 180°, 50 ml/min of helium, flame-ionization detection). A solution of $AgBF_4$ in nitromethane was prepared by a known method [12].

The original isomeric farnesylic esters were prepared by the reactions of the individual cis- and trans-geranylacetones with ethyl ethynyl ether in presence of BF_3 ether complex [4]. The mixture of isomers with respect to the 10,11-bond then formed was separated by rectification through an efficient column (length 130 cm, diameter 1.4 cm, ca. 120 theoretical plates) with a copper filling at 120-125° (2 mm). In this way we obtained: (Ia), n_D^{20} 1.4822, emergence time 10.7 min; (Ib), n_D^{20} 1.4800, emergence time 9 min; (Ic), n_D^{20} 1.4820, emergence time 8.8 min; (Id), n_D^{20} 1.4808, emergence time 6.5 min.

1. Cyclization of the Ester (Ia). Solutions of 0.68 g of (Ia) in 4 ml of nitromethane and 1 g of $AgBF_4$ in 5 ml of nitromethane were added with stirring in the course of 30 sec to a solution of 0.48 g of chloromethyl methyl ether in 5 ml of nitromethane cooled to between −28 to −30°. The temperature then rose to −20°. The mixture was stirred for 5 min at between −28 and −30° and then decomposed by a 1:1 mixture of 10% $NaHCO_3$ solution and methanol cooled to −30°. After the usual treatment we obtained a mixture of products containing up to 59% of the ester (V)* (emergence time 13.5 min), which was isolated by means of preparative TLC on alumina in benzene. We isolated 0.23 g (29%) of homogeneous (V), n_D^{20} 1.4934. Found %: C 74.05, 73.80; H 10.50, 10.25. $C_{19}H_{32}O_3$. Calculated %: C 73.98; H 10.46. IR spectrum (ν, cm^{-1}): 1718 and 1648 (ester CO and C=C in α,β-unsaturated ester). The NMR spectrum is given in Table 1.

2. Cyclization of the Ester (Ic). Cyclization was conducted analogously, but at −60° in nitropropane solution. From 0.68 g of (Ic) we obtained 0.80 g of a mixture containing 23% of (VI) (emergence time 11.5 min) and 30% of (V). We did not succeed in separating these substances, and they were isolated as a mixture by means of TLC on alumina in a 1:1.5 mixture of hexane and benzene. We obtained 0.28 g (35.5%) of a mixture of (V) and (VI), n_D^{25} 1.4918. Found %: C 74.13, 73.85; H 10.30, 10.41. $C_{19}H_{32}O_3$. Calculated %: C 73.98; H 10.46.

IR spectrum (ν, cm^{-1}): 1720 and 1650 (ester CO and C=C in α,β-unsaturated esters). The ester (V) was identified by TLC by comparison with a known sample (see Expt. 1). The α-isomer (VI): in the NMR spectrum the signal at 5.25 p.p.m. corresponds to the proton at C-4. The presence of the γ-isomer follows from the IR spectrum (898 and 3080 cm^{-1}) and NMR spectrum (4.65 p.p.m.).

3. Cyclization of the Ester (Ic) at −30°. The cyclization was conducted under the conditions of Expt. 1. According to GLC the product contained 57% of (V) and 3% of (VI). In this case the isolation of (V) and (VI) was not carried out.

4. Cyclization of the Ester (Ib) at −60°. The cyclization of 0.34 g of (Ib) under the conditions of Expt. 2 gave a mixture containing 60% of (II) and 6% of (III) (emergence times 9.1 and 7.9 min respectively). By means of TLC on alumina in benzene we isolated 0.18 g (46%) of homogeneous (II), n_D^{20} 1.4910. Found %: C 73.97, 73.75; H 10.20, 10.21. $C_{13}H_{32}O_3$. Calculated %: C 73.98; H 10.46. IR spectrum (ν, cm^{-1}): 1720 and 1660 (ester CO and C=C in α,β-unsaturated ester). For NMR spectrum see Table 1.

5. Cyclization of the Ester (Ib) at −30°. The cyclization of (Ib) under the conditions of Expt. 1 gave a mixture containing 43% of (II) and 20% of (III), identified by means of GLC.

6. Cyclization of the Ester (Ib) at −60° and Then at 0°. Solutions of 0.68 g of (Ib) in 5 ml of nitropropane and of 1 g of $AgBF_4$ in 5 ml of nitromethane were added to a solution of 0.48 g of chloromethyl methyl ether in 5 ml of nitropropane at −60°. The mixture was stirred for 2 min at −60°, and then the temperature was raised rapidly to 0°, at which temperature stirring was continued further for 15 min. The mixture obtained after the usual treatment contained, according to GLC, about 3% of cis-β-monocyclofarnesylic ester (II), 56% of α-bicyclofarnesylic ester (III), and 20% of β-bicyclofarnesylic ester (IIIa) (emergence time 5.1 min). By means of column chromatography on alumina we isolated 0.15 g of α- + β-bicyclofarnesylic esters (III) + (IIIa) (8:1 hexane-benzene) and 0.20 g of α-bicyclofarnesylic ester

*In all cases of the cyclization of (Ia)-(Id) (apart from the reactions with Ag THBS), apart from the desired products, the cyclization products contained also substances with considerably longer emergence times (30-45% content according to GLC results) and also some (up to 5%) of α- and β-monocyclofarnesylic esters (without the introduction of CH_3OCH_2 groups).

(III) (6:1 hexane-benzene). Total yield 0.35 g (44%); n_D^{20} 1.4900 for (III) + (IIIa) and 1.4910 for (III). For α-bicyclofarnesylic ester (III): Found %: C 74.27, 73.97; H 10.50, 10.41. $C_{19}H_{32}O_3$. Calculated %: C 73.98; H 10.46. IR spectrum (ν, cm^{-1}): 1735 (ester CO). For NMR spectrum see Fig. 1. For α-+β-bicyclofarnesylic esters (III) + (IIIa): Found %: C 73.77, 74.02; H 10.50, 10.70. $C_{19}H_{32}O_3$. Calculated %: C 73.98; H 10.46. IR spectrum (ν, cm^{-1}): 1735 (ester CO).

7. Cyclization of the Ester (Id) at −30°. The cyclization of 0.34 g of (Id) at −30° under the conditions of Expt. 1 gave 0.40 g of a mixture containing 31.5% of (II) and 36.5% of (III). The hydrolysis of this mixture with 5% methanolic KOH with heating for 2 h gave 0.16 g of neutral part [mainly the bicyclic ester (III) according to GLC] and 0.17 g of acidic part [after esterification gave the monocyclic ester (II), according to GLC].

8. Cyclization of the Ester (Id) at −60°. The cyclization of (Id) under the conditions of Expt. 2 gave a mixture containing 21% of (IV) (emergence time 7 min) and 32.5% of (II). The hydrolysis of this mixture under the conditions described went to completion, which indicates the absence of bicyclic products.

9. Cyclization of (Ic) under the Action of $CH_3OCH_2^+(NO_2)_3C_6H_2SO_3^-$. A solution of 0.68 g of (Ic) in 4 ml of nitropropane was added with stirring in the course of 40 sec to a solution of 0.64 g of chloromethyl methyl ether and 2.84 g of Ag TNBS in 20 ml of nitropropane and 2 ml of acetonitrile at −60°. The mixture was stirred for 5 min at −60° and then decomposed with 10% $NaHCO_3$ solution. After the usual treatment we obtained a mixture containing, according to GLC, 57% of (VI) and 26% of (V). By means of TLC on alumina (see Expt. 2) we isolated 0.48 g (60%) of a mixture of (V) and (VI). The NMR and IR spectra were similar to the spectra obtained in Expt. 2.

10. Cyclization of (Id) (0.68 g) under the Action of $CH_3OCH_2^+(NO_2)_3C_6H_2 \cdot SO_3^-$. The cyclization was conducted under the conditions of Expt. 3. We obtained a mixture containing 55% of (IV) and 18% of (II). By means of TLC on alumina in 2:1 benzene-heptane we isolated 0.41 g (52%) of a mixture of (II) and (IV). Found %: C 74.08; 74.09; H 10.80; H 10.63. $C_{19}H_{32}O_3$. Calculated %: C 73.98; H 10.48. IR spectrum (ν, cm^{-1}): 1720 and 1650 (ester CO and C=C in α,β-unsaturated ester); also 896 w and 3080 w (>C=CH_2). The NMR spectrum of the mixture contains signals of olefinic protons at 5.16 p.p.m. (>C=C<H) and 4.61 p.p.m. (>C=CH_2).

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CONCLUSIONS

1. The nonproton initiation of the cyclization of isoprenoids containing a conjugated double bond goes in accordance with the previously established relations holding for proton-initiated cyclization.

2. Silver 1,3,5-trinitrobenzenesulfonate was used for the first time for the generation of carbonium ions, which improved the yields of the desired products substantially.

3. It was shown that the method of nonproton initiation is applicable in principle for the synthesis of derivatives of the bicyclofarnesylic series with a functional substituent in the 3-position of the A ring.

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