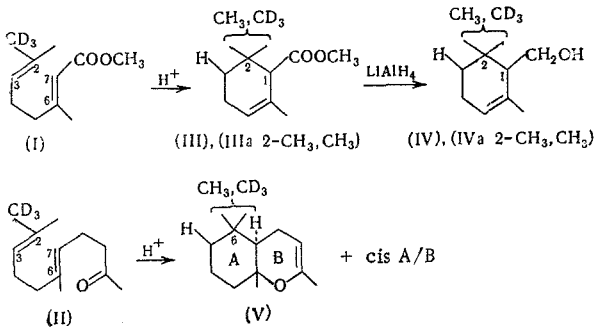
STEREOCHEMISTRY OF PROTONATION AND MERCURATION OF TRISUBSTITUTED DOUBLE BOND DURING CYCLIZATION OF ISOPRENOIDS

M. T. Mustafaeva, V. A. Smit, A. V. Semenovskii, and V. F. Kucherov

UDC 541.63:66.095.252:541.571.3

The problem of the stereochemistry of the addition of an "external" electrophile to the 2, 3 double bond of the isoprenoid molecule is of interest not only in connection with a study of electrophilic cyclization, but also as a part of the general problem regarding the stereochemical rules of the reaction for electrophilic addition to the trisubstituted double bond. Previously we had obtained some data on the nonspecific nature of this reaction under the influence of acids for the case of the isoprenoid analogs that contain an ethyl group (as a label) in place of one of the methyl groups at C_2 [1]. However, these data have not permitted making as yet any unequivocal conclusions regarding the "ordinary" isoprenoids. A method was described recently for the synthesis of isoprenoids that contain the completely deuterated trans-methyl group at C_2 as the label [2]. In the present paper we studied the stereochemistry of the cyclization of the D_3-analog of geranic ester (I) and geranylacetone (II) under the influence of acids and mercury salts.

The method used to cyclize (I) and (II) under the influence of acids and the identification of the formed products were described previously [3]. In the case of (I) the pure trans-6, 7-isomer (trans-CD_3 at C_2) was used in the reaction. In the case of (II) the reaction was run with a mixture of the cis–trans isomers at the 6, 7 bond (both with a trans-CD_3 group at C_2), each of which was stereospecifically converted [3] under the experimental conditions respectively to the bicyclic product with either a cis- or a trans-coupling of the A/B rings. The pure trans-A/B isomer (V) was isolated from the mixture by preparative GLC.



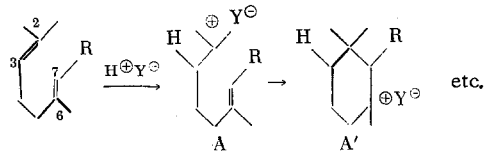
(II) trans-6,7 (+ cis-6,7) (V) trans-A/B (Va, CH_3, CH_3).

The stereochemistry of the reaction for addition to the 2, 3 bond was determined from the data on the relative intensity of the signals of the geminal CH_3 groups in the NMR spectra of the cyclization products of the duetero analogs, since it is known that the corresponding signals for the undeuterated products appear as two separate 3H singlets in the 0.7–0.9 ppm region. Thus, the undeuterated (Va) has two 3H singlets at 0.74 and 0.85 ppm. In the NMR spectrum of (IIIa) the signals of these groups merge, but two 3H singlets again appear in its reduction product (IVa) at 0.8 and 0.93 ppm.

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 5, pp. 1151–1153, May, 1973. Original article submitted July 19, 1972.

We found that the NMR spectra of the deuterated products of the proton cyclization of (IV) and (V) coincide completely with the spectra of (IVa) and (Va), but the intensity of each of the signals of the geminal CH_3 groups in (IV) and (V) is half of the intensity of these signals in (IVa) and (Va). From this it unequivocally follows that both (IV), and consequently also (III), and (V) are an equimolar mixture of two epimers, which differ in the configuration of the CD_3 group at C_2 in (IV) or C_6 in (V). Consequently, the protonation of the 2, 3 double bond and its subsequent reaction with the 6, 7 double bond proceed as a nonstereospecific process.

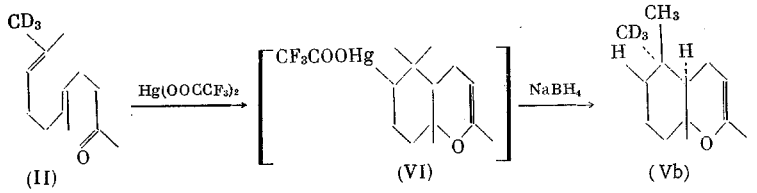
The obtained result is in agreement with the electrophilic cyclization mechanism that was proposed by us earlier [4], which predicates the intermediate formation of carbonium ions of the A type (as intimate ion pairs).



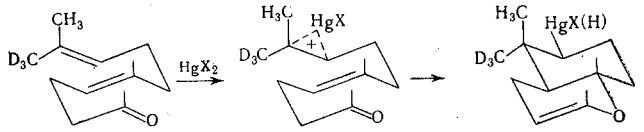
It is characteristic that the same completely nonstereospecific nature of the reaction is observed for the cyclization of (I) and (II), although in the first case the 6, 7 double bond, which is substantially less nucleophilic (due to conjugation with the carbomethoxy group) than the 6, 7 double bond in (II), takes part in the reaction of addition to the 2, 3 bond.

It is also interesting that the use of various acids as cyclization initiators (100% H_2SO_4, FSO_3H, or SbF_5–FSO_3H) in nitromethane or in SO_2 is without effect on the steric directivity of the studied step of the cyclization reaction.

The cyclization of isoprenoids under the influence of mercury salts [5] was developed as an alternate route for the synthesis of the same cyclic products as are obtained when the cyclization is run under the influence of acids. We studied the stereochemistry of this reaction at the 2, 3 bond on the example of the cyclization of CD_3–eranylacetone (II). In this case the starting material



was a mixture of the isomers at the 6, 7 double bond and the pure trans-isomer (Vb) was isolated by preparative GLC. An analysis of the NMR spectrum disclosed the complete disappearance of the signal of the CH_3 group at 0.95 ppm, with a retention of the 3H singlet at 0.74 ppm. Consequently, stereospecific addition at the 2, 3 bond occurs when the cyclization is initiated by a mercury salt. Since mercuration is usually accomplished as a trans-stereospecific reaction, with the probable formation of the mercurinium ion [6], it is possible to assume that the stereospecific formation of (Vb) proceeds by an analogous scheme:



According to this scheme, the CH_3 group at C_6 in (Vb) should have an axial configuration. This is apparently corroborated by the data of the NMR spectrum, for of the two signals of the gem-dimethyl group the signal of the axial group is found, as a rule, further upfield [7].

The obtained data show that the use of mercury salts makes it possible to assure a stereospecific progress of the initial step of the cyclization and obtain cyclic isoprenoids with a strictly definite configuration of the geminal substituents.

METHOD

The NMR spectra (on the δ scale) were taken on a Varian DA-60IL instrument relative to HMDS. The mass spectra were recorded on a Varian CH-6 instrument.

Cyclization of (I). a) The treatment of 0.1 g of (I) with 0.054 g of FSO_3H in CH_3NO_2 at −20°C [3] gave 0.072 g of (III), which was reduced ($LiAlH_4$, ether) to (IV). NMR spectrum: 0.8 and 0.93 ppm (two identical singlets with a total intensity of 3H, $CH_3-\underset{|}{\overset{|}{C}}-CD_3)_5$ 1.67 (3H, broad singlet, $CH_3C=C-$), 3.57 (2H, doublet, J = 3.5 Hz, CH_2OH), and 5.45 (1H, broad, $CH=C-$). Mol. wt. (by mass spectrometry) 157; $C_{10}H_{15}D_3O$.

b) The treatment of 0.1 g of (I) with 0.054 g of FSO_3H in CH_3NO_2 at −20°C [3] gave 0.072 g of (III), which was reduced ($LiAlH_4$, ether) to (IV) with an identical NMR spectrum.

Cyclization of (II). a) The treatment of 0.3 g of (II) with 0.13 ml of FSO_3H and 0.17 ml of SbF_3 in SO_2 solution at −65° gave 0.18 g of (V) (mixture of cis–trans isomers). The pure trans isomer was isolated by preparative GLC; NMR spectrum: 0.74 and 0.85 ppm (two identical singlets with a total intensity of 3H, $CH_3-\underset{|}{\overset{|}{C}}-CD_3$), 1.05 ($\diagdown\!\!-C-(CH_3)-O-$, 3H, singlet), 1.54 (3H, broad singlet, $CH_3-C=C-$), and 4.28 (1H, broad, $-CH=C-O$). Mol. wt. (by mass spectrometry 197; $C_{13}H_{19}D_3O$.

b) The treatment of 0.3 g of (II) with 0.75 ml of 100% H_2SO_4 in $C_2H_5NO_2$ at −70° [5] gave (after reduction) product (V) with an identical NMR spectrum.

c) The treatment of 0.2 g of (II) with 0.51 g of $Hg(OOCCF_3)_2$ in CH_3NO_2 at −20° [5] gave (after reduction with $NaBH_4$ and separation of the cis–trans isomers) 0.05 g of (Vb), which, based on the data of GLC and the mass spectrum, is identical with the above described (V) samples. NMR spectrum: absence of a singlet at 0.74 ppm, and a 3H singlet at 0.85 ppm; the remaining signals coincide with the signals of the described (V) samples.

CONCLUSIONS

Initiation of the reaction for the cyclization of isoprenoids by acids proceeds as a nonstereospecific process at the 2, 3 bond, while when this reaction is initiated by mercury salts it proceeds as a stereospecific reaction.

LITERATURE CITED

1. A. V. Semenovsky, W. A. Smit, V. F. Kucherov, and I. G. Mursakulov, Tetrahedron, 23, 1621 (1967).
2. M. T. Mustafaeva, V. A. Smit, V. A. Kuzovkin, and V. F. Kucherov, Izv. Akad. Nauk SSSR, Ser. Khim., 384 (1972).
3. M. Kurbanov, A. V. Semenovskii, and V. A. Smit, Izv. Akad. Nauk SSSR, Ser. Khim., 390 (1972); V. A. Smit, A. V. Semenovskii, and V. F. Kucherov, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 312 (1962); V. A. Smit, A. V. Semenovskii, and F. F. Kucherov, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 2193 (1960).
4. M. Kurbanov, A. V. Semenovskii, V. A. Smit, and V. F. Kucherov, Izv. Akad. Nauk SSSR, Ser. Khim., 2541 (1971).
5. M. Kurbanov, A. V. Semenovsky, W. A. Smit, L. V. Shmelev, and V. F. Kucherov, Tetrahedron Letters, 2175 (1972).
6. N. S. Zefirov, Usp. Khim., 34, 1272 (1965).
7. W. Wechfer, G. Slomp, F. McKellar, R. Wiechert, and N. Kerb, Tetrahedron, 21, 1625 (1965).