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CYCLIZATION OF ISOPRENOID COMPOUNDS

STEREOCHEMISTRY OF THE ADDITION TO THE TERMINAL (2,3) DOUBLE BOND

I. G. MURSAKULOV, A. V. SEMENOVSKY,* W. A. SMIT and V. F. KUCHEROV
Institute of Organic Chemistry,
U.S.S.R. Academy of Sciences, Moscow

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Abstract—A detailed stereochemical study of the initial step of acid-induced isoprenoid cyclization—the addition to the terminal (2,3) double bond—has been made using geranylacetone as the model compound. The process was shown to be non-stereospecific with regard to both the centers concerned, i.e. C_2 and C_3 of the acyclic isoprenoid molecule. Possible explanations of the observed stereochemical results and its biogenetical implications are discussed.

THE acid-catalysed formation of the decaline derivatives from the acyclic isoprenoid precursors proceeds stereospecifically, the stereochemistry of the ring-junction being determined by the configuration of the central (6,7) double bond in the starting compound.[1] Since the steric course of the enzyme-catalysed cyclization is supposed to be controlled by the same rule of *trans–anti*-planar addition[2] the close analogy between the acid- and enzyme-catalysed transformations of acyclic to cyclic terpenes is evident, at least as far as the steric course of the ring-formation is concerned. Whether this analogy could be extended to the initial step of the isoprenoid cyclization—the addition to the terminal double bond—requires clarification.

The biogenetic studies[3] have shown that the enzyme-catalysed formation of the cyclic terpenes is not accompanied by the randomization of the label in terminal methyl groups, i.e. the initiating attack takes a stereospecific course. At the outset of our work there were no data known on the steric course of this reaction for the acid-catalysed cyclization. Recently the cyclization of the simplest 1,5-diene–2,6-octadiene under the action of deuterated acids (D_2SO_4–HCOOD) showed that "the cyclization process is concerted with proton attack and follows the stereochemical predictions made for the terpene biosynthesis".[4] But the results cited have not so much bearing on the general problem of terpene cyclization since the stereochemistry of the addition at di- and trisubstituted double bonds may differ considerably and there is no obvious reason to suggest that the conclusions mentioned are valid for the case of isoprenoid compounds with trisubstituted double bonds.

The purpose of the present work was to investigate the stereochemistry of the addition to the terminal double bond in the course of acid-catalysed cyclization of

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* To whom any inquiries regarding this paper should be addressed.

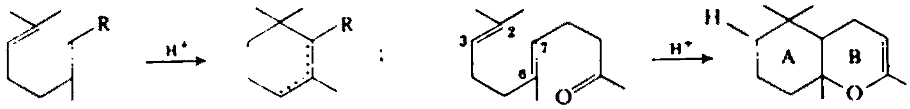
[1] W. A. Smit, A. V. Semenovsky and V. F. Kucherov, *Tetrahedron Letters*, No. 33, 2299 (1964); W. A. Smit, A. V. Semenovsky, I. I. Brunovlenskaya, S. L. Portnova, *Doklady Acad. Nauk SSSR* **160**(4), 849 (1965).

[2] L. Ruzicka, in *Perspectives in Organic Chemistry* p. 265. New York (1956).

[3] D. Arigoni, *Experientia* **14**, 153 (1958); J. J. Britt and D. Arigoni, *Proc. Chem. Soc.* 224 (1958); A. J. Birch, R. W. Richards and H. Smith, *Proc. Chem. Soc.* 192 (1958).

[4] H. E. Ulery and J. H. Richards, *J. Amer. Chem. Soc.* **86**, 3113 (1964).

isoprenoids, i.e. 1,5-dienic compounds with trisubstituted double bonds. In order to solve this problem it was necessary to examine the stereochemistry of the reaction at C_2 and/or C_3-centers of the starting diene



IA *trans*
B *cis*

IIA *trans* A/B
B *cis* A/B

The study of the process at C_2 requires the use of acyclic compounds with selectively labeled *cis*- or *trans*-terminal methyl groups. On the other hand deuterated acid may prove to be useful as a means to define the steric course of the proton addition at C_3. We took advantage of both approaches.

Geranylacetone (I) was chosen as a model isoprenoid compound since its cyclization had been studied.[5] Thus far there is no chemical method available to insert the isotope label selectively into one of the terminal methyl groups. On the other hand it is generally recognized that the ethyl group is stereochemically similar to the methyl group; for instance their conformational energy values (ΔG°) are almost equal (1·62–1·72 kcal/mole for methyl and 1·67–1·86 kcal/mole for ethyl groups).[6] Thus it was reasonable to suppose that the replacement of *cis*- or *trans*-terminal methyl group in I by ethyl group would not affect the steric course of the cyclization process. At the same time the presence of such a "label" would enable the steric course of this reaction at C_2 to be investigated.

The compound in question III—the ethyl analog of I—was synthesized[7] from methyl ethyl ketone (Experimental). The first pair of *cis–trans* isomers of 3-methyloct-3-en-7-one was separated by fractional rectification of their cyclic ketals.* The mixture of 7,8-*cis*- and *trans*-isomers of 3,7-dimethyldodeca-3,7-dien-11-one (III) was easily separated by efficient fractionation. All four geometric isomers of III (Aa, Ab, Ba and Bb) were stereochemically pure according to GLC. The configurations assigned to these compounds were based on their physical properties (b.p., GLC retention data) and are supported by well-known steric regularities of the reactions used for their preparation.[7]

Most of the cyclization experiments were carried out under essentially the same conditions (100% H_2SO_4 in nitropropane solution) which were shown earlier[5] to be optimum for the stereospecific (with regard to 6,7-double bond) conversion of I (A or B) to bicyclic II (yields up to 80%). In the case of III (Aa, Ab, Ba and Bb) the only reaction products obtained with yields of about 70–80% were also bicyclic

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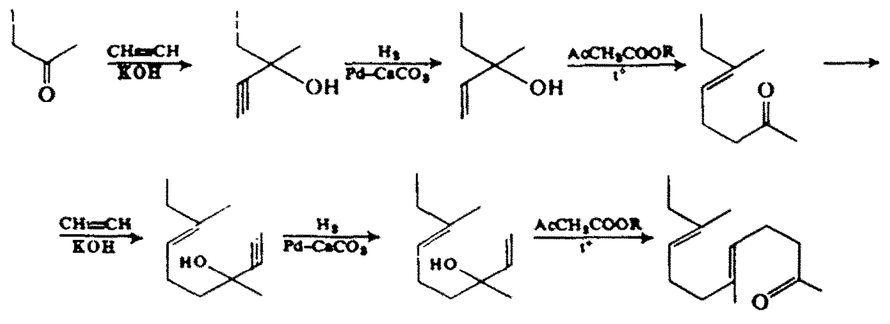
* The attempts to fractionate ketones were unsuccessful.

[5] W. A. Smit, A. V. Semenovsky, B. A. Rudenko and V. F. Kucherov, *Izv. Acad. Nauk SSSR, Ser. Khim.* 1782 (1963); W. A. Smit, A. V. Semenovsky and V. F. Kucherov, *ibid.* 1600 (1963).

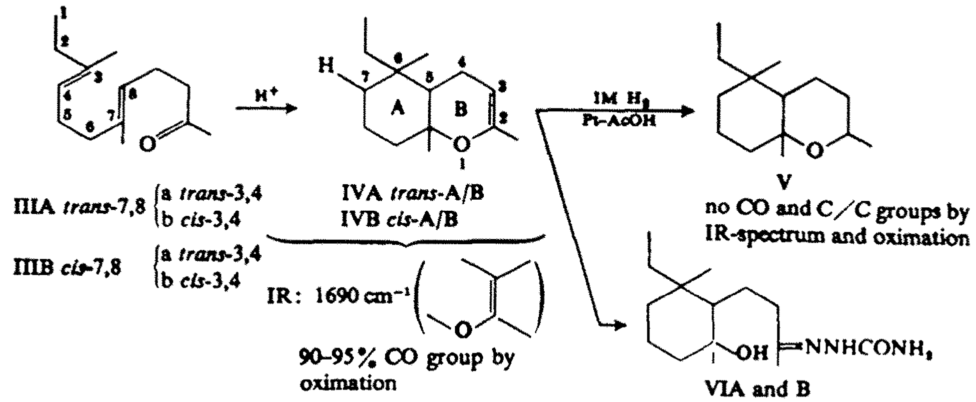
[6] E. Eliel and T. Brett, *J. Amer. Chem. Soc.* **87**, 5039 (1965); H. Feltkamp and N. Franklin, *Angew. Chem.* **77**, 806 (1965).

[7] I. N. Nazarov, B. P. Gusev, S. M. Makin, V. B. Mochalin, I. I. Nazarova, V. P. Vinogradov, B. K. Krupzov, O. A. Schavrigina and D. V. Nazarova, *Doklady Acad. Nauk SSSR* **114**(4), 796 (1957); O. Isler, R. Rüegg, L. Choparddit-Jean, A. Winterstein and O. Wiss, *Helv. chim. acta* **41**, 786 (1958).



III

derivatives—isomeric 2,6,10-trimethyl-6-ethylhexahydrochromans—the stereochemistry of the ring-junction being controlled completely by the stereochemistry of the central double bond in the starting compound, i.e. *trans*-fused derivatives (IVA) arose from *trans*-7,8 isomers (IIIAa or IIIAb) and *cis*-fused (IVB) from *cis*-7,8 isomers (IIIBa or IIIBb). The reaction is highly selective and the admixture of IVA in the product IVB (and *vice versa*) never exceeds 3–5%.*



The bicyclic structures of unsaturated oxides for IVA and IVB were proved by the above series of reactions. The stereochemistry of the ring-junction has been taken by analogy with the well-known case of IA or B cyclization[5] and was substantiated further by the close identity of NMR (Table 1) and MS of the corresponding cyclization products: IVA with IIa and IVB with IIb. The isomerization experiments (IVA → IVB and *vice versa*) also confirmed the stereochemistry of their ring-junction.

According to GLC (filled columns) IVA (formed from IIIAa or IIIAb) seemed to be an individual isomer. With the use of high-efficiency capillary column we were able to demonstrate that in fact IVA was not homogeneous but consisted of two closely related compounds (IVAa and IVAb). These compound could not be separated by chromatography due to the similarity of the corresponding retention data in TLC and GLC in the wide range of conditions used. This mixture gave a high yield of a crystalline semicarbazone of corresponding hydroxyketone (VIA), which could not be separated into individual components (the hydrolysis of VIA after recrystallization to a constant m.p. gave rise to the initial mixture IVAa and

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* Relative GLC retention data IVB:IVA = 1:1·53.

IVAb). Since the *trans*-fused bicyclic structure for IVA (a + b) has been proved (see above) the only possibility left is that IVAa and IVAb differ only by a configuration at C_6. The same mixture of IVAa and IVAb in the ratio of about 1 : 1 results from the cyclization of both 3,4-double bond isomers of IIIA (a or b). The variation of the reaction conditions (time, temp, molecular proportion of H_2SO_4 and solvent) or even the change of initiating agent (BF_3 instead of H_2SO_4) does not affect the composition of this mixture (IVA).

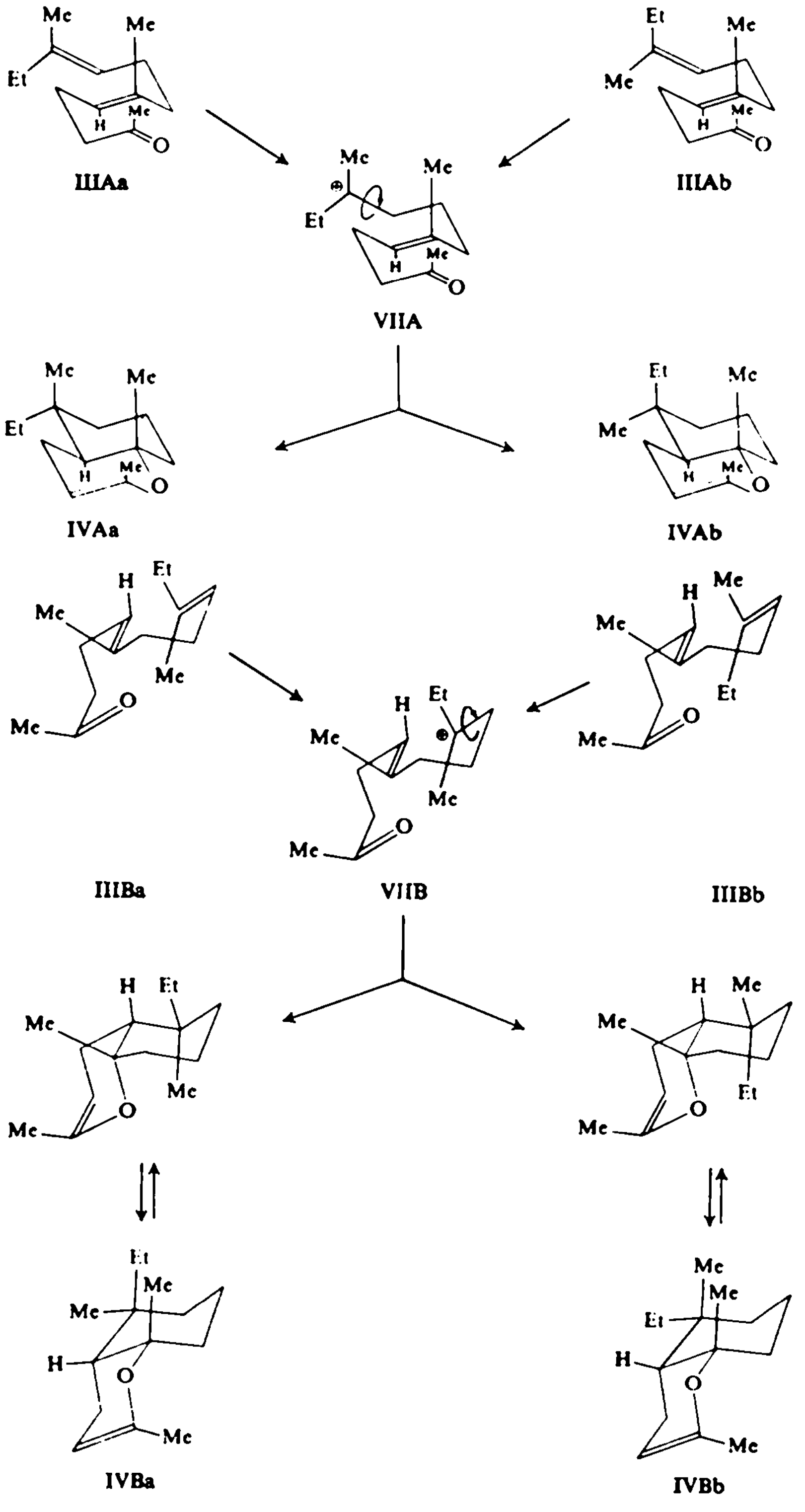
A similar picture was observed for the cyclization of *cis*-7,8-isomers (IIIBa and IIIBb). GLC showed that the reaction product IVB is a mixture of two closely related isomers, their ratio being independent either of the configuration of the 3,4-double bond in IIIB (a or b) or of the reaction conditions. Attempts to isolate pure IVBa and/or IVBb in this case also failed because the difference in the retention time in GLC was too small (1 : 1·05) to allow an efficient separation and because the corresponding derivative VIB could not be crystallized. The structure and stereochemistry of the ring-junction for this mixture IVB (a + b) has been proved (see above) and therefore one should assume that both IVBa and IVBb possess the same structure of *cis*-fused bicyclic oxides and differ only by the stereochemistry at C_6.

TABLE 1. CHEMICAL SHIFTS (δ) OF METHYL PROTONS SIGNALS (60 MHz, CCl_4, TMS)

Compound	6,6-Me$_2$ or 6′,6-Me*		10-Me	2-Me
IIA (*trans*-fusion)	0·80	0·89	1·09	1·57
IVA (a + b) (*trans*-fusion)	0·82	0·90	1·20	1·69
IIB (*cis*-fusion)	0·835		1·09	1·57
IVB (a + b) (*cis*-fusion)	0·825		1·13	1·63

* The replacement of one C_6-methyl group in IIA for ethyl group in IVA should have led to the splitting of one or another C_6-methyl protons bands (δ 0·8 or 0·89). The similarity of NMR spectra of IIA and IVA, i.e. the apparent absence of such splitting may be explained by the overlap of the splitted bands of both C_6-epimers present (IVAa and IVAb).

The evidence listed indicates clearly that in the course of the reaction studied *the attack of proton at the terminal double bond led to the loss of stereochemical identity of the terminal substituents, whereas the subsequent addition to the central double bond proceeds stereospecifically in agreement with the data published earlier.*[1,5] *In other words, the first step of the acid-induced isoprenoid cyclization—the protonation of the terminal double bond—is a non-stereospecific process.* The reported results may be best described in terms of non-concerted addition to the terminal 3,4-double bond via the possible intermediate carbonium ion (VIIA or VIIB in the scheme below). The formation of both possible C_6-isomers of the cyclic products (for IVA as well as for IVB) in the ratio close to 1 : 1 suggests the low value of the barrier for the rotation at C_3–C_4 bond in VII (A or B) and confirms the supposed steric equivalence of methyl and ethyl groups.


IIIAa
IIIAb
VIIA
IVAa
IVAb
IIIBa
VIIB
IIIBb
IVBa
IVBb
Me
Et
H
O

The mechanism presented in the scheme implies that the proton added to the terminal double bond may occupy equatorial as well as axial positions in the cyclic product. In order to prove this we studied the steric outcome of the proton addition at C_3 in I (A or B) or respectively at C_4 in III (A) with the use of D_2SO_4 as described for H_2SO_4-induced cyclizations. The deuterium content of the compounds formed [II (A or B) or IVA] was determined mass spectrometrically (Table 2). The data show that the main reaction products at −70° are monodeutero derivatives (see Nos. 1 and 2). The position of deuterium at C_7 follows from the consideration of generally assumed reaction scheme[2] and was confirmed by the detailed analysis of mass spectra.[8]

TABLE 2. RELATIVE CONTENT OF DEUTERO DERIVATIVES IN CYCLIZATION PRODUCTS (%)

No.	Reaction conditions	Number of D atoms incorporated per molecule					
		0	1	2	3	4	5
1	$\mathrm{IA} \xrightarrow[-70^\circ]{D_2SO_4} \mathrm{IIA}^*$	36	56	8	—	—	—
2	$\mathrm{IIIA} \xrightarrow[-70^\circ]{D_2SO_4} \mathrm{IVA}\ (a + b)$	31	61	8	—	—	—
3	$\mathrm{IA} \xrightarrow[+10^\circ]{D_2SO_4} \mathrm{IIA}$	16	59	22	3	—	—
4	$\mathrm{VIII} \xrightarrow[+10^\circ]{D_2SO_4} \mathrm{IX} \rightarrow \mathrm{X} \xrightarrow[-70^\circ]{H_2SO_4} \mathrm{IIA}$	5	20	27	25	13	10
5	$\mathrm{VIII} \xrightarrow[-10^\circ]{D_2SO_4} \mathrm{IX}$[9]†	4	11	18	21	19	14

* For IIB the distribution of deuterium incorporation was qualitatively the same but exact figures are difficult to calculate due to the presence of M-1 peaks.

† In this case a large amount of incorporation (about 13% of the total) of more than 5 D-atoms per molecule was observed.[9]

From the data reported previously in some cases it is possible to deduce the orientation of deuterium atom in the cyclic monodeuterated compounds from their IR spectra. For example, the IR spectra of monocyclic compounds with equatorial position of deuterium clearly show C–D stretching absorption at 2171 cm^{-1}, whereas the spectrum of axial isomer shows absorption at 2158 cm^{-1}.[10] Similar data were used to identify the deuterium position in 2,3-dimethylcyclohexanol formate.[4] For more complicated compounds the occurrence of two instead of one C–D stretching absorption band was reported.[10,11] But as was shown clearly for cholestane derivatives

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[8] N. S. Vulfson, V. I. Zaretsky, V. A. Sadovskaya, A. V. Semenovsky, W. A. Smit and V. F. Kucherov, *Tetrahedron* **22**, 603 (1966).

[9] Th. J. De Boer, H. A. Van'tHof and J. U. Veenland, *Rec. trav. chim.* **83**, 689 (1964).

[10] E. J. Corey, M. G. Howell, A. Boston, R. Young and R. Sneen, *J. Amer. Chem. Soc.* **78**, 5036 (1956).

[11] G. Frejaville, Y. Gounell, J. Julien and A. Paillons, *Bull. Soc. chim. France* 2171 (1963).

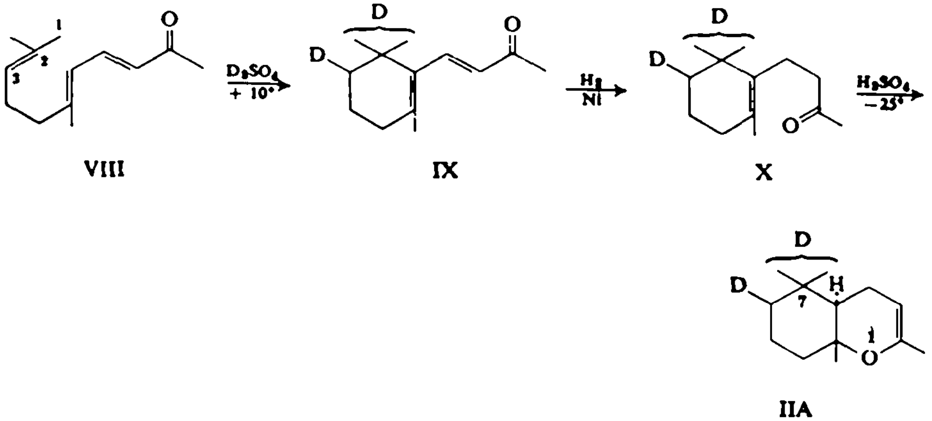
these absorption bands for the isomer with equatorial deuterium occur as a rule at a frequency higher than that of corresponding axial isomer ($\Delta\nu \cong$ 20–30 cm^{-1}).

From the data published (some examples are listed in Table 3) one may suppose that these conclusions are valid also for other six-membered cyclic compounds.

Corresponding IR data for the monodeutero derivatives of IIA and IVA are also shown in Table 3. The most striking result is the appearance of several (3–4) C–D stretching bands of comparable intensity, their position covering the whole range of absorption bands for (a) and (e) deuterium positions. We consider this fact as an evidence that these monodeutero derivatives are mixtures of isomers with (e) and (a) deuterium configuration. This interpretation is substantiated by the corresponding data for *cis*-fused isomer, IIB, where the presence of both (e) and (a) deuterium configurations is ensured by the conformational flexibility of the *cis* ring-junction.

Thus we have shown that *proton addition at the terminal double bond leads to the formation of the mixture of epimers at* C_7, *i.e. the reaction proceeds non-stereospecifically* most probably via cationic intermediate of type VII (A or B) with unfixed configuration and conformation (see scheme on p. 1625).

The intermediate formation of carbonium ions may be ascertained by the deuterium incorporation at α-carbon atom (in respect to cationic center).[12] The cyclization of ψ-ionone (VIII) on treatment with D_2SO_4 in nitromethane solution at 10° is accompanied by the significant amount of deuterium incorporation in the molecule of β-ionone (IX) formed, especially in *gem*-dimethyl group (~0·8 D-atoms per molecule).[9] This result was advanced as an argument in favour of the formation of carbonium ion intermediate.[9] Since our results presented above indicate clearly that the intermediate involved in the initiating step of the cyclization of I is of the carbonium ion nature it seems interesting to compare the extent of deuterium incorporation in the latter case with that of ψ-ionone cyclization. To this end we carried out the cyclization of VIII and IA under the same conditions (D_2SO_4, $C_3H_7NO_2$, +10°) and compared the MS of IIA formed from IA with that of another sample of IIA, prepared from VIII by the reaction sequence shown below



VIII IX X

IIA

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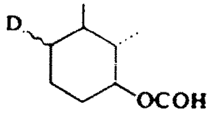
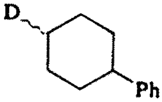
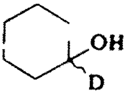
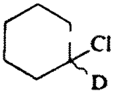
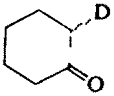
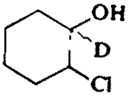
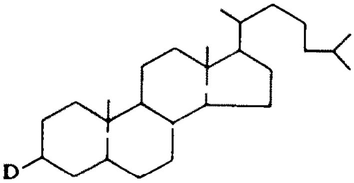
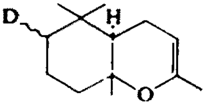
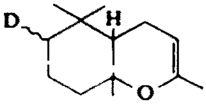
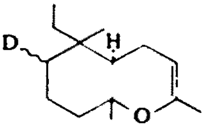
[12] D. N. Kursanov, E. V. Bikova and V. N. Setkina, *Izv. Acad. Nauk SSSR, Otd. Khim. Nauk* 809 (1958); D. N. Kursanov and S. N. Parnes, *Zh. Obshch. Khim.* 27, 668 (1958).

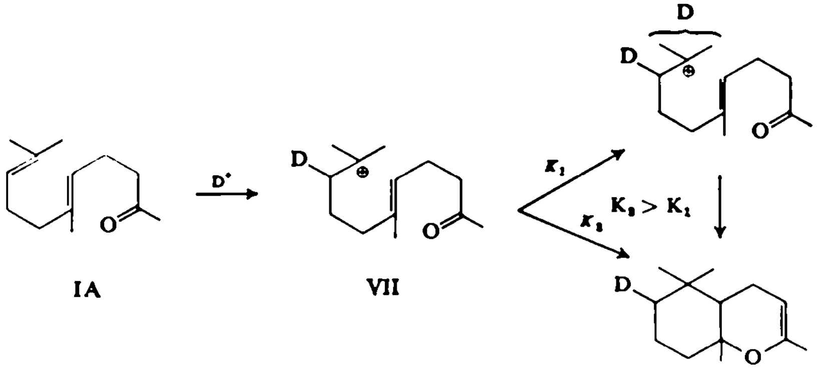
TABLE 3. C–D ABSORPTION BANDS

No.	Compound	ν cm^{-1}		Ref.
		C–D (e)	C–D (a)	
1		2171	2142	4
2		2171	2158	10
3		2155	2100	11
4		2198	2174	11
5		2202	2159	11
6		2136	2119	11
7		2171(m) 2155(s)	2154(s) 2129(m)	10
8	 IIA (*trans*)	2157(s) 2145(s) 2130(m) 2108(w)		this work
9	 IIB (*cis*)	2166(m) 2148(s) 2140(s) 2128(m)		this work
10	 IVA (a + b)	2173(s) 2153(s) 2140(m) 2110(w)		this work

The corresponding data, together with the earlier published data for IX[*] are included in Table 2 (Nos. 3–5).

As one may see, the extent of deuterium incorporation into the cyclization product IIA depends on the reaction temperature (compare Nos. 1 and 3), and at +10° a considerable deuterum incorporation is observed (up to 20–25% of IIA contains two deuterium atoms per molecule). The position of the second deuterium atom in that sample of IIA was deduced from the analysis of its MS. The MS of non-deuterated IIA shows an intensive peak with m/e 109 identified as a fragment containing ring A with two methyl groups.[8] The MS of the deuterated IIA (+10° sample) shows two intensive peaks with m/e 110 and 111, i.e. the second deuterium atom is incorporated in the above-mentioned fragment. Since the addition to the 6,7-double bond proceeds stereospecifically and the addition to the 2,3-double bond non-stereospecifically, one can reasonably assume that the second deuterium atom is incorporated at the α-position to C_7 center. *This is another independent evidence in favor of an intermediate cation of type* VII.

The comparison of the deuterium content of the two samples of IIA of different origin (Nos. 4 and 3 in Table 2) suggests that the observed differences of deuterium incorporation may be due to the life-time difference of the intermediate cations VII formed in the cyclization of IA and VIII. The longer life-time in the latter case and correspondingly greater degree of deuterium exchange reflects the decreased nucleophilicity of the conjugated 6,7-double bond in VIII in comparison with that of isolated double bond in IA. This suggestion is in good agreement with previously reported data about the dependence of steric and structural course of isoprenoid cyclization on the nucleophilicity of the double bonds involved.[1,5,13] The formation of a cation of type VII is thus a step common to the cyclization of both compounds (see scheme below) IA and VIII, but its further fate depends on the rate of the cation interaction with 6,7-double bond.



IA

VII

IIA

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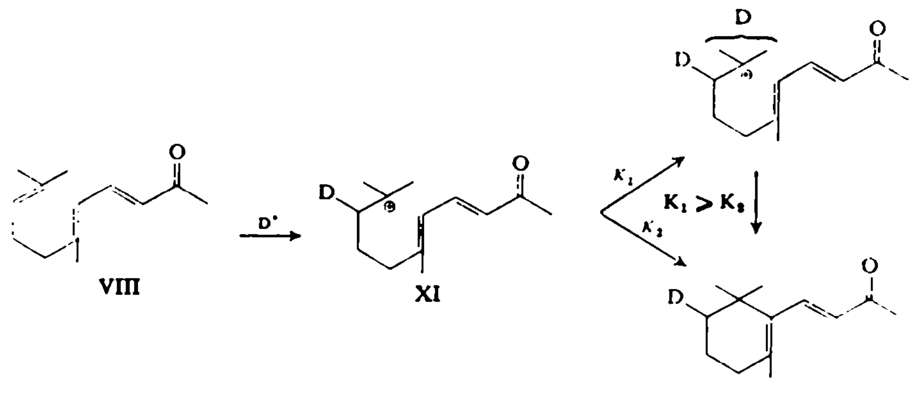
[*] The extent of deuterium incorporation in this work is a little less than in Ref. 9; it may be due to the different solvents used—nitromethane in Ref. 9 and nitropropane in the present work.

[13] W. A. Smit, A. V. Semenovsky, P. F. Vlad and V. F. Kucherov, *Izv. Acad. Nauk SSSR, Otd. Khim. Nauk* 312 (1962); A. V. Semenovsky, W. A. Smit and V. F. Kucherov, *Doklady Acad. Nauk SSSR* 132, 1107 (1960); W. A. Smit, A. V. Semenovsky, T. N. Chernova and V. F. Kucherov, *Izv. Acad. Nauk SSSR, Ser. Khim.* 1229 (1965); A. V. Semenovsky, W. A. Smit and V. F. Kucherov, *ibid.*, 1424 (1965).



VIII XI IX

All these results taken together clearly show that in the acid-catalysed cyclization of geranylacetone and its analogs *proton attack at the terminal* (2,3) *double bond proceeds non-stereospecifically as regards to both centers concerned* (C_2 *and* C_3 *for* I). At the same time the addition to the central 6,7-double bond with the formation of bicyclic structures proceeds stereospecifically, thus demonstrating the difference of the mechanisms operating for the addition of proton to 2,3-double bond and for the addition of the carbonium ion to 6,7-double bond. In the former case the reaction involves the formation of carbonium ion of type VII with unhindered rotation, and in the latter the reaction should pass via intermediates with a fixed configuration like bridged cations or conformationally stabilized carbonium ions. The use of different cationic initiators[14] instead of proton may lead to the change of the stereochemistry of the initiating step of the cyclization process. Corresponding studies are in progress. Since geranylacetone is quite an ordinary isoprenoid compound we consider the results presented to be of general validity for the acid-catalysed isoprenoid cyclization. The remarkable difference in the stereochemistry of the proton attack observed for tri- and disubstituted double bonds indicates the different mechanism of the proton addition in these two cases.

We believe that the stereospecificity observed for the initiating step of the enzyme-catalysed isoprenoid cyclizations may be due to the rigid fixation of the substrate on the enzyme surface or/and to the non-protonic type of initiating species.

EXPERIMENTAL

All GLC analyses (unless otherwise stated) were with LChM-5 SKB-IOCh chromatograph (detector-catharometer, carrier gas He; apiezon M (10%) on chromosorb W (base-washed), copper columns (250 cm long, 4 mm i.d.).

IR (UR-10 spectrophotometer). NMR (60 MHz on J.E.O.L. instrument. MS (MCh-1303 mass-spectrometer). All m.ps are uncorrected.

A. *Preparation of isomeric* 3,7-*dimethyldodeca*-3,7-*diene*-11-*one* (III)

The title compds were prepared from methyl ethyl ketone by well known methods,[7] which include repeating the cycle of ethynylation, selective hydrogenation and reaction with acetoacetic ester (via intermediate allylic bromide formation or via pyrolysis of acetoacetic esters of allylic alcohols).

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[14] W. A. Smit and A. V. Semenovsky, *Tetrahedron Letters* No. 41, 3651 (1965).

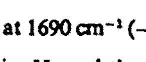
After each cycle the mixtures of *cis–trans* ketones formed were separated by a fractional rectification with the use of 130-cm glass column (i.e. 14 mm) packed with standard copper helices.

Separation of isomeric 3-methyloct-3-en-7-ones. Since the mixture of *cis-trans* isomeric 3-methyloct-3-en-7-ones could not be separated by fractionation, we transformed the ketones into the cyclic ketal derivative by the following procedure.*[14] A mixture of isomeric 3-methyloct-3-en-7-ones (100 g), ethylene glycol (500 ml), BF_3-etherate (150 ml) and ether (500 ml) was stirred at 20° for 7 hr. After usual treatment ethyleneketal was obtained (106 g, 80% yield, b.p. 70–77°/4 mm) and rectified b.p. 95–100° at 10 mm, reflux ratio 100:1). The course of fractionation was controlled by GLC (130°, 70 ml/min, relative retention time *cis*:*trans* = 1:1·1). The following fractions were collected: low boiling—*cis*-isomer, 25%; intermediate—mixture *cis* + *trans* (~1:1); and high boiling—*trans*-isomer, 60%. The pure ketals thus obtained were dissolved in hexane and then stirred with 5N H_2SO_4 for several hr. Ketones formed were isolated in the usual manner and were shown† to be chromatographically pure (less than 5% of other isomer). Semicarbazones (yields ~80%): *cis*-ketone, m.p. 124–125° (MeOH–H_2O); *trans*-ketone, m.p. 114° (MeOH–H_2O). Found: *cis*-C, 60·85; H, 9·74; *trans*-C, 60·86; H, 9·75. Calc. for $C_{10}H_{19}N_3O$: C, 60·88; H, 9·71.)

Separation of isomeric 3,7-dimethyldodeca-3,7-diene-11-ones (III). By the above-mentioned cycle of reactions each isomeric 3-methyl-3-octen-7-one (*cis* or *trans*) was transformed into the pair of 7,8-isomeric 3,7-dimethyldodeca-3,7-diene-11-one. Careful fractionation (b.p. 136–141°/10 mm, reflux ratio 100:1) gave pure *cis*-7,8-isomer—IIIBa or IIIBb—(25% of the total) as low boiling product and pure *trans*-7,8-isomer—IIIAa or IIIAb (55% of the total)—as high-boiling product. GLC (170°, 110 ml/min) showed that all four isomeric ketones are stereochemically pure (~95%). Respective retention data IIIAa:IIIBa = 1:1·14; IIIAb:IIIBb = 1:1·1. Their refractive indexes are very similar—1·4675–1·4679 at 20°. All four isomeric ketones show correct analysis for $C_{14}H_{24}O$. Semicarbazones (yields about 80%): IIIAa, m.p. 91–92°, IIIAb, m.p. 105–106°, IIIBa, m.p. 90–91°, IIIBb m.p. 100–101°. All four semicarbazones show correct analysis for $C_{15}H_{27}N_3O$.

B. *Cyclization of isomeric* 3,7-*dimethyldodeca* -3,7-*diene-one*-11

trans-7,8-*Series.* A cooled soln of H_2SO_4 (2·5–7 ml, 100%) in nitropropane‡ (10 ml) was added at −70° to a well-stirred soln of IIIAa or IIIAb (2·0 g) in nitropropane (10 ml). The resulting yellow soln was kept at −70° for 20 min and then poured into a mixture of pet. ether (40 ml) and ice-cooled water (50 ml). The aq layer was extracted with pet. ether (×3) and the extract washed with $NaHCO_3$aq and dried ($MgSO_4$). After removal of the solvent the residue (1·8 g) was distilled over Na giving 1·45 g of IVA, b.p. 103–104°/4 mm, n_D^{20} 1·4900. (Found: C, 80·50; H, 11·75. Calc. for $C_{14}H_{24}O$: C, 80·71; H, 11·61%.) GLC (180°, 95 ml/min) showed the absence of *cis*-isomers, IVB (relative retention data IVB:IVA = 1:1·53) and other impurities. The compd gave one spot on TLC on SiO_2 or Al_2O_3 in different systems.

Oximation of IVA gave 95–97% of carbonyl content. IR spectrum shows a strong absorption band at 1690 cm^{-1}  $(-CH=C\overset{O-}{<}$ group). Hydrogenation (Pt, AcOH, 20°) leads to the uptake of 1 equiv. H_2 and the dihydro product shows no absorption at 1650–1750 cm^{-1} and does not contain carbonyl group (by oximation). GLC using high-efficiency capillary column§ showed that IVA consists of a mixture of two compds in a ratio of about 1:1 (IVAa and IVAb). The mixture formed from IIIAa and IIIAb show completely identical IR and NMR spectra.

The semicarbazone obtained from mixture IVA (a + b) (yield about 85%) has m.p. 175–177°,

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* The conventional method (refluxing of benzene soln in the presence of *p*-TsOH) was found to induce double bond migration.

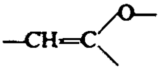
† The separation of ketones by GLC is rathes poor and we found it better to transform them into corresponding cyclic ketals for GLC analysis.

‡ A commercial mixture of 1- and 2-nitropropanes dried over $CaCl_2$ and distilled over P_2O_5 was used.

§ Copper capillary, 50 m × 0·25 mm, coated with the mixture of di-n-octyl sebacinate and Tween 40 (1:20), 140°, nitrogen 1 ml/min, flame ionization detector.

[14] D. N. Kirk, D. K. Patel and V. Petrow, *J. Chem. Soc.* 1046 (1957).

after two crystallizations from MeOH–H_2O 176·5–177·5°. (Found: C, 63·82; H, 10·42; N, 14·76. Calc. for $C_{15}H_{29}N_3O_2$: C, 63·57; H, 10·31; N, 14·83%.)

cis-7,8-*Series.* The cyclization of 2·0 g IIIB (a or b) under the conditions used for IIIA gave 1·2 g IVB, b.p. 73–75°/2 mm. (Found: C, 80·50; H, 11·80. Calc. for $C_{14}H_{24}O$: C, 80·71; H, 11·61%.) GLC analysis (180°, 95 ml/min) indicated the presence of two closely related compds (relative retention time 1·05:1). According to GLC, IR and NMR data the mixtures of IVB (a + b) derived from IIIBa and IIIBb are identical. Oximation shows the presence of 95% carbonyl equiv. There is a strong absorption band at 1690 cm^{-1}. Hydrogenation (Pt–AcOH, 1 M H_2, 20°) led to complete disappearance of  $—CH{=}C{\lt}^{O—}_{\diagdown}$ group as judged by IR data or oximation. No hydroxy compds were present in dihydro product according IR or TLC data.

Attempts to obtain crystalline semicarbazone from IVB (a + b) were unsuccessful.

Isomerization of IVB *into* IVA. The soln of IVB (a + b) (0·2 g) in nitropropane (2 ml) was added to a saturated solution of BF_3 (0·44 g) in nitropropane (8 ml) at −20°. The mixture was kept at −20° for 90 min. After working up as usual 0·1 g product was obtained, which according to GLC contained about 61% of IVB (a + b) and 39% of IVA (a + b). TLC data confirmed the absence of other impurities. Under the same conditions the isomerization of IVA gave a mixture of 80% IVA (a + b) and 20% IVB (a + b)[*].

C. D_2SO_4-*induced cyclizations*

At −70°. The cyclizations under the action of D_2SO_4 (95% deuterium) were carried out under the same conditions as described above. The products formed—IIA from IA, IIB from IB, IVA (a + b) from IIIAa—were pure according to GLC and TLC data. For MS and IR spectra, see Tables 2 and 3 respectively.

At +10°. (a) Geranylacetone (IA). A soln of D_2SO_4 (0·75 m,) in nitropropane (1 ml) was added at +10° to a soln of Ia (0·5 g) in nitropropane (3 ml). After stirring for another 5 min, the mixture was decomposed in the usual way. The product IIA (0·3 g, 80–82°/2 mm) was obtained, its identity being proved by TLC, GLC and IR comparison with the authentic sample of IIA. For MS, see Table 2.

(b) ψ-Ionone (VIII). A similar treatment of ψ-ionone (VIII, 6 g) gave β-ionone (IX, 2·3 g). which was hydrogenated into X (Ni Raney, MeOH, 20°). The cyclization of X into IIa under the action of H_2SO_4 had been already described.[4] Pure IIA (0·3 g) was isolated by preparative GLC. For MS, see Table 2.

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[*] Under comparable conditions the reversible isomerization of IIA into IIB gave similar results.[5]