CYCLIZATION OF ISOPRENOID COMPOUNDS

31. STEREOCHEMISTRY OF THE REACTION AND CONFORMATIONAL STABILITY OF INTERMEDIATES*

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In developing a method for cyclizing isoprenoids under the influence of mercury salts [2], we investigated the cyclization of cis-6,7-farnesenate (Ia) and trans-6,7-farnesenate (Ib) esters. It is known that both isomers are converted under the influence of acids into mono- (III) and then into trans-A/B-bicyclofarnesenate (VIII) esters, i.e., the reaction is not stereospecific with respect to the central 6,7 double bond [3].

It has been found that treatment of trans-6,7-trans-10,11-farnesenate ester (Ib) with $Hg(CF_3COO)_2$ at 0°C in CH_3NO_2 leads (after treatment with $NaBH_4$) to the formation of trans-bicyclofarnesenate ester (VIII) in a yield of 60%; the corresponding acid has a mp of 131°C. Under analogous conditions, however, the cis-6,7-trans-10,11 ester (Ia) gives (according to GLC analysis of the crude product) 20-25% of the α- and β-monocyclofarnesenate esters (III), up to 25% of the trans-A/B-bicyclofarnesenate ester (VIII), and up to 50% of a product which corresponds to none of the previously known farnesenate esters and has a shorter retention time that the trans-type bicyclic esters. A cis-A/B ring structure was postulated for this product (reaction scheme 1).

It is impossible to obtain cis-A/B-bicyclofarnesenic acid (or ester) in pure form by preparative methods of separating the reaction products, including GLC. Consequently, the products were enriched in one or other isomer by chemical methods based on the difference in the saponification rates of monocyclic and bicyclic esters or based on reducing the number of isomers by isomerizing α-structures into β-bicyclo esters [3]. Comparison of the chemical behavior, GLC parameters, and PMR and other spectra of individual cis- and trans-A/B isomers makes it possible to form reliable conclusions about the cis-A/B structure of the products.

Treatment of the mixture of cyclization products derived from (Ia) with 10% methanolic KOH at 40°C resulted in saponification of the monocyclic esters (III); the neutral fraction contained (GLC) the ester (VIII) and an unknown product which was also difficult to saponify. The trans-A/B-bicyclofarnesenate esters can be saponified by heating at 150°C with 10% methanolic KOH in a closed vessel. In this case, the trans-cis ester (VIII) corresponding to the acid with a mp of 131°C is converted into the more stable trans-anti acid (IX) (mp 138°C) in which the COOH group is in the axial position [3]. We were able to select conditions close to those under which the unknown ester is largely saponified and ester (VIII) is only partially saponified (with epimerization). In this way we isolated from the acidic fraction an acid which, after repeated recrystallization, had an mp of 107°C; this was characterized, both in acid form and as its methyl ester, by a single peak, different from all of the known peaks, in chromatograms obtained under effective separation conditions (capillary column). However, the PMR spectrum of this acid contained twice the number of CH_3-group signals, and the spectrum of its methyl ester indicated unequivocally the presence of a mixture (in a ratio of ~1:1) of two bicyclofarnesenate esters. By comparing the PMR spectrum of this mixture, especially the signals from the CH_3 groups at C^{10} and C^8 and from the H atoms at C^9 (Table 1), with those of the known trans-A/B-bicyclofarnesenate esters (VIII), (IX), and (XI), we were able to show that these products are new α- and β-bicyclofarnesenate esters with a cis-A/B ring system, viz., (V) and (VI), respectively.

* See [1] for previous communication.

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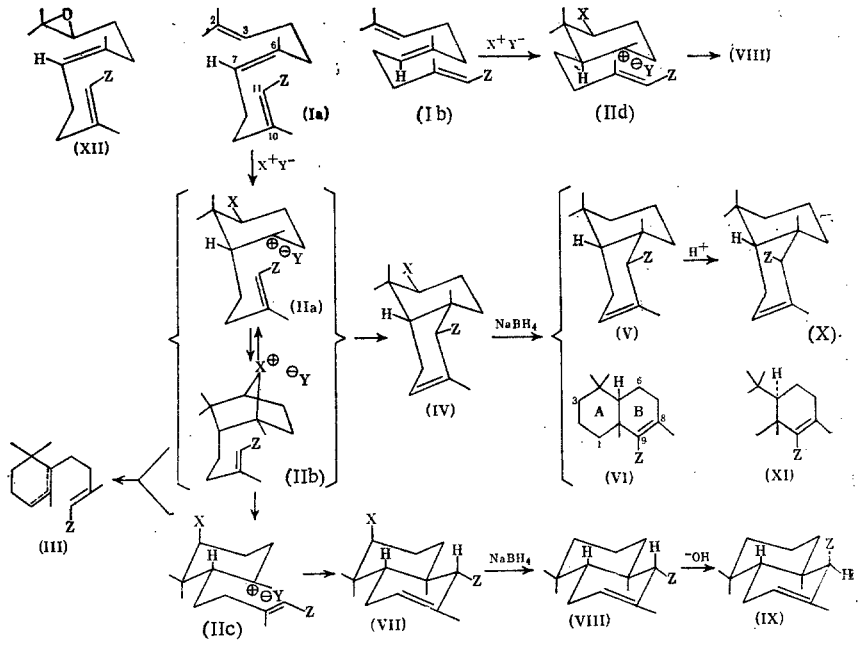
Reaction Scheme 1



$X^+Y^- = Hg(CF_3COO)_2$; Z=COOR, R = C_2H_5, CH_3 or H (see text).

TABLE 1. Characteristic Signals in the PMR Spectra of Methyl Bicyclofarnesenate Esters (in CCl_4, δ, ppm, relative to TMS)

Compound R=CH_3	α-CH_3* at C^4	e-CH_3* at C^4	CH_3 at C^{10}	CH_3 at C^8	2H at C^6 or C^7	H at C^9	$COOCH_3$	=CH
(VIII)	0,87	0,92	0,92	1,56	1,95 †	2,82	3,59	5,43
(IX)	0,90	0,93	0,93	1,57	1,95 †	2,37	3,60	5,50
(XI)	0,85	0,88	1,05	1,53	2,03	–	3,60	–
(V)	0,88	0,92	0,92	1,58	1,97 †	3,26	3,60	5,40
(X)	0,92	0,92	0,92	1,57	1,97 †	2,50	3,61	5,50
(VI)	0,92	0,92	1,15	1,54	1,98	–	3,65	–

*The axial or equatorial position of the CH_3 groups was assigned on the basis of the general principle that α-CH_3 groups are more strongly shielded by the rigid ring system [4].
† Center of multiplet.

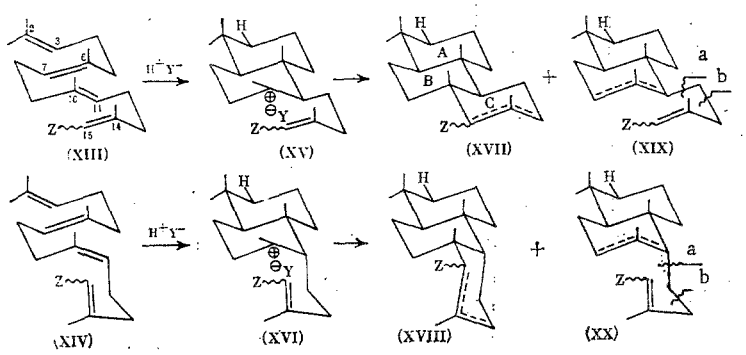
In view of the difficulty involved in separating the mixture of (V) and (VI), it seemed expedient to convert it entirely into the β-isomer (VI) by treatment with a 4:1 mixture of HCOOH and H_2SO_4 [3] in order to characterize (VI) in more detail. This treatment did indeed increase the proportion of the β-acid in the mixture to a β:α ratio of 4:1 (according to the PMR spectra of the methyl esters), but the α-acid proved to be a new α-bicyclofarnesenic acid; we also isolated a neutral fraction (up to 50% of the acidic fraction) consisting of the methyl ester of this acid, i.e., the (V) → (VI) isomerization is evidently accompanied by (V) → (X) epimerization. According to GLC analysis (in a capillary column with an efficiency of ~15,000 theoretical plates), (X) differs from all known bicyclofarnesenate esters, including (V) and (VI), and has the shortest retention time. The structure of (X) is in accord with its PMR data (see Table 1). On the basis of a comparison of the chemical shifts of the H atoms at C^9 in (VIII) and (IX) and in (V) and (X), we can assume that the α-cis-bicyclofarnesenate ester obtained by cyclization has structure (V), while the isomer formed by acid treatment has structure (X). These data do not provide rigorous proof of the configuration at C^9 in (V) and (X), and do not reveal the reason why the β-ester (VI) is formed together with the α-ester in the (Ia) → (V) route (this is not observed during protonic cyclization of the trans-6,7-farnesenate ester*). However, there is no doubt that up to 50% of cis-A/B-bicyclofarnesenate esters are formed by cyclization of (Ia) with $(CF_3COO)_2Hg$. Proceeding from [6,7], this fact may be explained by an increase in the conformational stability of the intermediate of

* A small amount of β-bicyclic ester is formed when the farnesenate ester is cyclized with $CH_3OCH_2^+ \cdot BF_4^-$ [5].

type (II). Unlike even CH_3 [6], the HgY group has no effect on the conformational stability of the ring system ($\Delta G \cong 0$). This has recently been conclusively established for simple cases [8] and has been demonstrated by us in the case of related isoprenoid structures [9]. Consequently, the conformational stability of intermediate (IIa) may be due to the formation of an unstable onium structure (IIb), which cannot occur during protonic cyclization. When 2,3-epoxy-cis-6,7-trans-10,11-farnesenate ester (XII) was cyclized with H_3PO_4, 3% of the corresponding cis-A/B hydroxy ester was isolated [10]. In the light of the results of the present investigation, this can be explained by the stabilizing influence of the OH group at C^3 in a monocyclic intermediate of type (II).*

The conformational stabilization of the intermediate during cyclization of the cis-farnesenate ester (Ia) with $Hg(CF_3COO)_2$ results

Reaction Scheme 2



$Z = COOC_2H_5$; $H^+Y^- = H_2SO_4$

in the formation of 50% of the cis-A/B-bicyclic product. We can assume that the formation of the B/C system by cyclization of cis-10,11-geranylgeranate (XIV) and trans-10,11-geranylgeranate (XIII) esters will be completely stereospecific, even in the presence of acids. In this case, the rigid trans-decalin structure of the A/B ring system must be the factor which stabilizes the conformation of intermediates (XVI) and (XV). The correctness of this hypothesis has been verified experimentally (reaction Scheme 2).

The initial trans-6,7-cis-10,11- (XIV) and trans-6,7-trans-10,11-geranylgeranate (XIII) esters were prepared from the individual farnesylacetones [11] by reaction with ethoxyacetylene [12]. Cyclization under the influence of H_2SO_4 was carried out under the farnesenate conversion conditions described in [3] using a mixture of isomers in which the conjugated 14,15 double bond was cis and trans. In this case, (XIII) and (XIV) each formed two products with nonoverlapping GLC peaks; these were separated by preparative GLC. The products with the shorter retention time, judging from their PMR spectrum (four CH_3 signals in the 0.85-1.0 ppm range and one at 1.58 ppm) and mass spectrum (M^+, $M^+ - CH_3$, $M^+ - CH_3 - EtOH$, $M^+ - EtOH - CO$), are the tricyclogeranylgeranate esters (XVII) and (XVIII), respectively. The PMR spectra of the products with the longer retention times contain three CH_3 signals in the 0.85-0.90 ppm range and two CH_3 signals at 1.55 and 1.90 ppm. The mass spectra of this pair of products, besides containing the fragments listed above, have intense peaks with m/e values of 205 and 191, corresponding to the two types of allylic cleavage (*a* and b) indicated in formulas (XIX) and (XX). On the basis of these data, we can assume that the products with the longer retention times are bicyclogeranylgeranate esters (XIX) and (XX). In the PMR spectra of all four products, the doubling up of the signals from the protons in the $COOC_2H_5$ group indicates the presence of a mixture of isomers connected with the isomerism of the 14,15 double bonds in the initial esters (XIII) and (XIV). We have specially not discussed the question of the position of the double bond (α or β) in ring C for (XVII) and (XVIII) and in ring B for (XIX) and (XX), but type-*a* cleavage in the mass spectrum of (XIX) is substantially more intense than the corresponding cleavage for (XX), which rules out the predominance of a structure with a β double bond in the ring in (XIX) (cf. [13]). At the same time, this may indicate a difference in the stability of the configurations of (XIX) and (XX). By analogy with the bicyclofarnesenate esters [3], we can assume that (XX) is more stable than (XIX). Then, in accordance with the ideas expressed in [14], the mass-spectral data confirm that the side chain and angular CH_3 group have a syn configuration in (XIX) and an anti configuration in (XX).

* When treated with electrophilic reagents, isoprenoids do not tend to cyclize in their prereaction conformation with ring A in the boat form [7].

Because of the lack of sufficient quantities of the substances and the complexity of separating the individual isomers, we did not obtain chemical evidence for their structures. However, on the basis of the fact that cyclization of (XIII) and (XIV), which differ only in the configuration of the 10, 11 double bond, results in the formation of different tricyclic products (XVII) and (XVIII), we can assume that this difference lies in the geometry of the B/C ring system, and we can assign a trans-anti-trans structure to isomer (XVII) and a trans-syn-cis structure to isomer (XVIII),* i.e., the cyclization of (XIII) and (XIV) under the influence of acids proceeds as a stereospecific process involving the formation of intermediates (XV) and (XVI) with fixed configurations.

EXPERIMENTAL

The GLC analysis was performed with an instrument with a glass flame-ionization detector, using a column (3 m × 4 mm) packed with 8% Apiezon M on silanized Chromosorb W at 180°C for (I)-(XX) and using a glass capillary (50 m × 0.5 mm) packed with 5% PEG 2000 at 160°C for (V)-(XX). The preparative GLC separation of (XVII)-(XX) was carried out with a glass column (3 m × 8 mm) containing 5% XE 60 on silanized Chromaton AW at 200°C, with an evaporator temperature of 270°C and a catherometer detector. The PMR spectra were recorded with an IL-DA-60 instrument using solutions in CCl_4 with TMS as internal standard. The mass spectra were obtained with an MKh-1303 instrument at an ionizing voltage of 70 eV.

The initial isomeric farnesenic esters were prepared by reacting the individual cis- and trans-geranylacetones with ethoxyacetylene in the presence of BF_3 etherate [12]. The resulting mixture of 10,11 double bond isomers, with a cis:trans ratio of 2:3, was separated by fractional rectification in vacuo on a column with an efficiency of ~120 theoretical plates (130 cm × 1.4 cm, copper packing, reflux ratio ~90) at 120-125°C/2 mm. The separation was monitored by GLC.

The individual cis-6,7- and trans-10,11-farnesylacetones were prepared from the individual geranylacetones via the corresponding dihydronerolidols, followed by reaction with acetoacetic ester [11] and separation by fractional rectification in vacuo on the aforementioned column at 100-115°C/1 mm. The mercury trifluoroacetate was prepared as in [15].

Cyclization of trans-6,7-trans-10,11-Farnesenic Ester (Ib). A solution of 2.13 g (5 mmoles) of $Hg(CF_3COO)_2$ in 10 ml CH_3NO_2 was added in 1 min at 0°C to a stirred solution of 1.2 g (4.6 mmoles) of trans-6,7-trans-10,11-farnesenic ester in 10 ml of abs. CH_3NO_2. The mixture was stirred for 0.5 h at 0°C and treated successively with 3 ml of 3 M NaOH solution and 0.1 g of $NaBH_4$ in 5 ml of 3 M NaOH. Stirring was continued at 0°C for 0.5 h, metallic mercury being precipitated. The suspension was diluted with water and the organic layer extracted with hexane. The hexane solution was dried with Na_2SO_4, the hexane removed, and the residue distilled in vacuo to give .73 g (60%) of a product with a bp of 120-125°C/0.6 mm, $n_D^{20} = 1.4900$, which was identified as trans-α-bicyclofarnesic ester (VIII) by GLC.

Cyclization of cis-6,7-trans-10,11-Farnesenic Ester (Ia). A solution of 3.28 g (7.6 mmole) of $Hg(CF_3COO)_2$ in 5 ml CH_3NO_2 was added in 1 min at 10°C to a stirred solution of 1.7 g (6.5 mmole) of cis-6,7-trans-10,11-farnesenic ester in 10 ml of abs. CH_3NO_2. The mixture was stirred for a further 10 min, after which it was reduced as above and worked up in the normal way to give 1.6 g of product. Analysis by GLC indicated the presence of 20-25% of a mixture of α- and β-monocyclofarnesenic esters (III), up to 25% of trans-A/B-bicyclofarnesenic ester (VIII), and up to 50% of a product which did not correspond to any known farnesenic ester and had a shorter retention time than the transbicyclic esters. A portion (1.6 g) of this mixture was treated with 40 ml of 10% methanolic KOH at 40°C for 10 h (conditions for saponifying acyclic and monocyclic esters). Conventional working up gave 0.8 g of a neutral fraction containing (GLC) the ester (VIII) and an unknown difficultly saponifiable ester.

A metal bomb containing 0.7 g of the neutral fraction and 5 ml of 10% methanolic KOH was heated at 150-160°C for 6 days. The methanol was distilled off and the residue treated with water and extracted with ether. The aqueous layer was acidified with 2 N H_2SO_4 to liberate an oil which crystallized on standing. Repeated recrystallization gave an individual (GLC) acid with a mp of 107°C (from hexane—acetone). Treatment of this acid with CH_2N_2 gave a pure (GLC) methyl ester (PMR spectrum discussed in text). This was treated with a 4:1 mixture of HCOOH and H_2SO_4 at ~20°C for 4 days. The mixture was then diluted with water, extracted with hexane, and the extract washed with 20% KOH. According to GLC data, the hexane solution contained (X). Acidification of the alkaline solution with 2 N H_2SO_4 gave a mixture of (V) and (VI) in a ratio of 1:4 (GLC of methyl esters).

* The stereospecificity of the formation of the A/B ring system is indicated by data on the cyclization of farnesylacetone isomers [1], etc.

trans-6,7-cis-10,11-(cis,trans)-14,15-Geranylgeranic Ester (XIV). A solution of 5.25 g (20 mmoles) of trans-6,7-cis-10,11-farnesylacetone in 35 ml of abs. ether was treated at 5°C with 2.4 g of BF_3 etherate, stirred for 15 min, and treated at −10°C with 2.1 g (30 mmoles) of freshly distilled ethoxyacetylene. The reaction mixture was stirred at ~20°C for 4 h, poured into saturated $NaHCO_3$ solution, extracted with ether, and the extract dried with $NaSO_4$. The ether was removed and the residue distilled to give 4.1 g (62%) of a product with a bp of 165-170°C/1 mm. This, according to GLC data, was a mixture of cis-14,15- and trans-14,15-trans-6,7-cis-10,11-geranylgeranic ester in a ratio of 2:3.

trans-6,7-trans-10,11-(cis,trans)-14,15-Geranylgeranic Ester (XIII). A solution of 6 g (22 mmoles) of trans-6,7-trans-10,11-farnesylacetone in 40 ml of abs. ether was treated at 5°C with 2.8 g of BF_3 etherate, stirred for 15 min, and treated at −7°C with 2.4 g (34 mmole) of freshly distilled ethoxyacetylene in 2 min. The reaction mixture was stirred at ~20°C for 3 h, poured into saturated $NaHCO_3$ solution, extracted with ether, and the extract washed with water and dried with Na_2SO_4. The ether was distilled off and the residue distilled in vacuo to give 6 g (79%) of a product with a bp of 170-180°C/1 mm. According to GLC data, this was a 2:3 mixture of cis-14,15- and trans-14,16-isomers of trans-6,7-trans-10,11-geranylgeranic ester.

Cyclization of (XIV) with H_2SO_4. A solution of 2 g (6 mmoles) of (XIV) in 5 ml of abs. nitropropane was added in 5 min at −70°C to a stirred solution of 3.2 ml of 100% H_2SO_4 in 10 ml of abs. nitropropane. Stirring was continued at −70°C for 20 min, at −40°C for 15 min, and at 0°C for 20 min. The solution was then treated with a mixture of hexane and saturated $NaHCO_3$ solution, stirred for 0.5 h, extracted with hexane, and the extract washed with water and dried with Na_2SO_4. The solvent was distilled off to give 1.6 g (80%) of a product which, according to GLC data, was a mixture of two substances in a ratio of 1:2. This mixture was separated by preparative GLC. The PMR and mass spectra of the isolated isomers are discussed in the general section.

Cyclization of (XIII) with H_2SO_4. Analogous treatment of 1.9 g (5.7 mmoles) of (XIII) in 10 ml of abs. nitropropane with 3.2 ml of 100% H_2SO_4 in 10 ml of abs. nitropropane gave 1.75 g (92%) of a product comprising according to GLC data, a mixture of two substances in a ratio of 1:2. This mixture was separated by preparative GLC. The PMR and mass spectra of the isolated isomers are discussed in the general section.

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CONCLUSIONS

1. In contrast to the nonstereospecific protonic cyclization of isomeric trans-6,7- and cis-6,7-farnesenate esters, which gives the trans-bicyclic ester in both cases, cyclization of the cis-6,7 isomer with $Hg(CF_3COO)_2$ results in a mixture (~1:1) of cis- and trans-A/B products.

2. Protonic cyclization of the trans-10,11 and cis-10,11 isomers of geranylgeranate esters results in the formation of different tricyclic products.

3. An interpretation of the stereochemistry of these reactions is proposed on the basis of the formation of corresponding mono- and bicyclic intermediates with fixed conformations.

LITERATURE CITED

1. A. V. Semenovskii, V. A. Smit, and A. I. Dyadchenko, Izv. Akad. Nauk SSSR, Ser. Khim., 743 (1974).
2. M. Kurbanov, A. V. Semenovskii (Semenovsky), W. A. Smit, L. V. Shmelev, and V. F. Kucherov, Tetrahedron Lett., 2175 (1972).
3. A. V. Semenovskii, V. A. Smit, and V. F. Kucherov, Izv. Akad. Nauk SSSR, Ser. Khim., 1424 (1965).
4. N. S. Bhacca and D. H. Williams, Applications of NMR Spectroscopy in Organic Chemistry: Illustrations from the Steroid Field, Holden-Day (1966), 69.
5. M. Z. Krimer, V. A. Smit, A. V. Semenovskii, and V. F. Kucherov, Izv. Akad. Nauk SSSR, Ser. Khim., 1352 (1968).
6. I. G. Mursakulov, A. V. Semenovskii, and V. A. Smit, Izv. Akad. Nauk SSSR, Ser. Khim., 384 (1967).
7. A. I. Dyadchenko, A. V. Semenovskii, and V. A. Smit, Izv. Akad. Nauk SSSR, Ser. Khim., 2276 (1976).
8. F. A. L. Anet, J. Krane, W. Kitching, D. Dodderel, and D. Praeger, Tetrahedron Lett., 3255 (1974).
9. A. I. Diadchenko, A. V. Semenovskii, and V. A. Smit, Izv. Akad. Nauk SSSR, Ser. Khim., 2281 (1976).
10. E. E. van Tamelen and J. P. McCormick, J. Am. Chem. Soc., 91, 1847 (1969).
11. O. Isler, R. Ruegg, L. H. Chopard-dit-Jean, A. Winterstein, and O. Wiss, Helv. Chim. Acta, 41, 786 (1958).
12. Zh. A. Krasnaya and V. F. Kucherov, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 1057 (1962).

13. A. V. Semenovskii, V. A. Smit, and V. F. Kucherov, Dokl. Akad. Nauk SSSR, 160, 1097 (1965).
14. S. Meyerson and A. W. Weitkamp, Org. Mass Spectrom., 1, 659 (1968).
15. H. C. Brown and Min-Hon Rei, J. Am. Chem. Soc., 91, 5646 (1969).

ALCOHOLYSIS OF 4-PROPENYL-1,3-DIOXANE

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The methanolysis of 4-substituted 1,3-dioxanes proceeds via the formation of mixed acetals, 1,3-diols, and products of the intra- and intermolecular dehydration of the latter [1-4]. The composition of the reaction products depends on the nature of the dioxane: monoalkyl-substituted dioxanes give mainly the corresponding diols [1, 3, 5, 6], while dialkyl-substituted dioxanes give both diols and also their monomethyl ethers [2, 3, 7, 8], unsubstituted alcohols, dienic hydrocarbons with conjugated double bonds [2, 3, 9], and compounds with a tetrahydrofuran structure [10].

The alcoholysis of 4-alkenyl-substituted dioxanes has never been studied. Their involvement in the reaction in question may provide information about the connection between the nature of the dioxane and the routes by which it is converted during alcoholysis. We have studied the reaction scheme of 4-propenyl-1,3-dioxane (I) with methanol, ethanol and propanol, and the products formed.

It might be expected that 4-hexen-1,3-diol (II) would be the major product or one of the products of the methanolysis of (I), but the reaction goes in the direction leading to the formation of 2-methyl-5,6-dihydropyran (III) and two isomeric hydroxy ethers, viz., 3-methoxy-4-hexen-1-ol (IVa) and 5-methoxy-3-hexen-1-ol (Va), while (II) and its intramolecular-dehydration products could not be detected.

The yield of the products varies over a quite narrow range (Table 1) when the methanolysis of (I) is carried out under different conditions. The total yield of the hydroxy ethers is 60-70% and that of the pyran is 30-40%.

The kinetic curves for the accumulation of the reaction products formed by methanolysis of (I) (Fig. 1) give us reason to suppose that (III), (IVa), and (Va) are formed directly from the dioxane, by-passing the formation of the hexenediol. Nevertheless, we tested experimentally the possibility of (IVa) being formed by reaction of (II) with methanol. The experiments showed that solvolysis of (II) with methanol does indeed give the

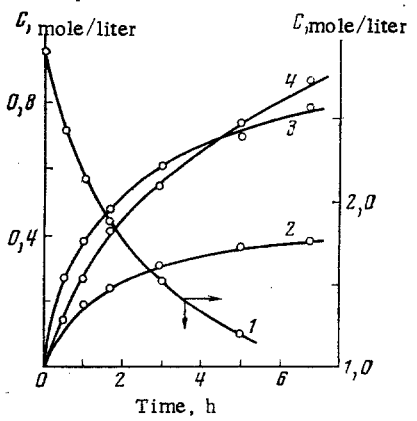

Fig. 1. Kinetic curves for the accumulation of products of the reaction of 4-propenyl-1,3-dioxane with methanol: 1) (I); 2) (IVa); 3) (Va); 4) (III). Temperature 70°C, $[(I)]_0 = 3.0$, $[CH_3OH]_0 = 14.6$ moles/liter, $[H_2SO_4] = 2.9\%$.

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