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STEREOSPECIFIC CYCLIZATION OF ISOPRENOIDS. THE CYCLIZATION OF FARNESYLACETONE STEREOISOMERES AND THEIR MONOCYCLIC ANALOGS

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The acid-catalyzed cyclization of 1,5-dienes may serve as a model for the chemical study of the biogenetic pathways leading to the formation of polycyclic terpenes from their acyclic precursors. Considerable work has been done on the scope of this reaction /1/, but the systematical study of its stereochemistry is lacking.

Eschenmoser et al /2/ reported that the acid-catalyzed cyclization of cis-6.7- and trans-6.7-isomeres of apofarnesylic acid proceeds non-stereospecifically and gives derivatives of the trans-decaline series only. This result prompted these authors to suggest that the stereospecific cyclization of isoprenoids is possible only with the participation of enzymes /3/. But as we had shown earlier it is possible to carry out the stereospecific acid-catalyzed transformation of stereoisomeric geranylacetones /4/ and geranylacetic acids /5/ into the derivatives of hexahydrochromane, stereochemistry of ring junction in the latter

being determined by the cis- or trans-configuration of the 6.7-double bond in the initial molecule. Hence we supposed /4/ that in general the stereospecific course of the non-enzymatic cyclisation can be achieved provided an effective nucleophylic centre is present in the molecule (oxygen of C=O group in cited examples). From this point of view the afore mentioned results of Eschenmoser may find reasonable explanation in the reduced nucleophilicity of the 10.11-double bond owing to the conjugation with carboxy group.

This study was undertaken to determine whether the removal of the electron-accepting group from the conjugation with 10.11-double bond would result in the change in the stereochemistry of the cyclization. Pure cis-6.7-trans--10.11 (Ia) and trans-6.7-trans-10.11 (Ib) isomeres of farnesylacetone were taken as the models. The reaction was carried out with the sulphuric acid (100%) in the solution of nitropropane at -70% (the procedure previously used for the stereospecific cyclization of geranylacetone /4/).

We have found that Ia as well as Ib could be smoothly converted into the mixture of cyclic products. It was shown that the ratio of the components* in this mixture depends

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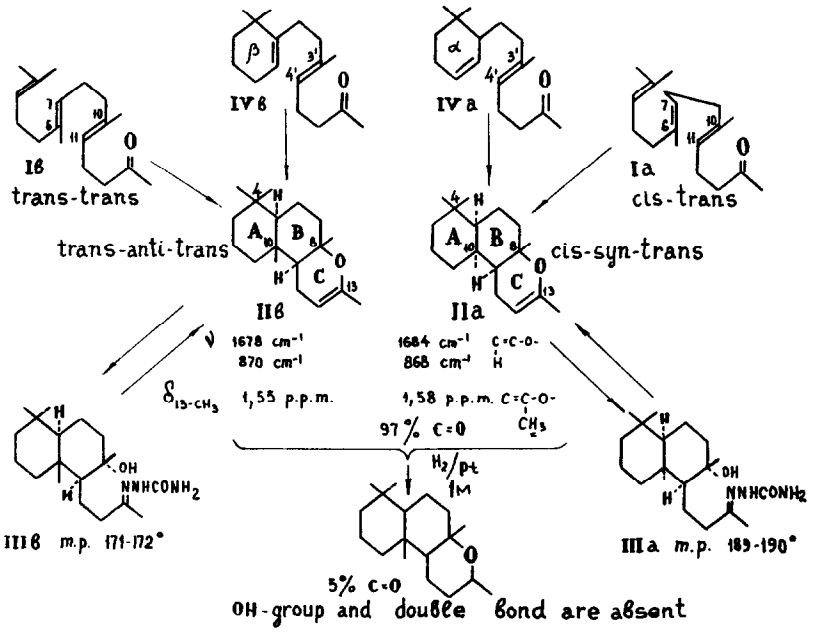
* Determined by g.l.c.with G.-L.-Chromatograph SKB-IOCH, USSR, Stationary phazes: 10% Apiezon M (A) or 10% neopenthylglycolsuccinate (B) on chromosorb W (60-80 mesh size, alkali washed); gas-carrier- He, 60 ml/min., t°C 210°, column l=2,3 m., ∅ = 3 mm; detector - catharometer).

entirely on the reaction conditions. When a large excess of sulphuric acid is used it is possible to get as a main product the tricyclic oxide II (up to 60% in the mixture by g.l.c.-data). This substance may be isolated in the pure form with a yield up to 30% by preparative scale thin-layer chromatography on neutral silica gel with subsequent purification via the semicarbazone of hydroxyketone. The oxides prepared from Ia and Ib are quite different by their g.l.c.-characteristics. Semicarbazones of the corresponding hydroxyketones have different melting points. The reactions summarized in the scheme, as well as I.R.- and N.M.R.-data show that both IIa and IIb are tricyclic unsaturated oxides.



I.R.- and N.M.R.-spectra of IIb are completely superimposable with those of (-) sclareoloxide, prepared by the oxidation of natural sclareol /6/. They are also identical by g.l.c.-data. Hence it follows that the acid cyclization of trans-6.7-trans-10.11-farnesylacetone (Ib) results in the formation of racemic sclareoloxide with trans-anti--trans-configuration as shown in the structure IIb.

The isomeric oxide, prepared from cis-6.7-trans-10.11-farnesylacetone (Ia), has larger retention time in g.l.c. (t_{IIa} : t_{IIb} = 1,05 (phaze A) or 1,12 (phaze B) and its I.R.- and especially N.M.R.spectra show remarkable distinction from those of IIb. Since the initial ketones Ia and Ib differ only by the configuration of the 6.7-double bond, their cyclisation products IIa and IIb should differ only by the stereochemistry of A/B-ring junction*. Trans-junction of A/B-rings in IIb has been already proved; consequently IIa should have cis-junction of A/B rings, as shown in its formula. The comparison of N.M.R.-spectra of IIa and IIb also substantiates the stereochemistry as assigned above.

Proceeding from the N.M.R.-spectral data on di- and triterpenes /7,8/, we suppose that the chemical shift for angular methyl group at C_{10} is in the highest field in comparison with the other methyl group signals i.e. $\delta_{10\text{-}CH_3}$ = 0.875 p.p.m. in IIa and $\delta_{10\text{-}CH_3}$ = 0.76 p.p.m.

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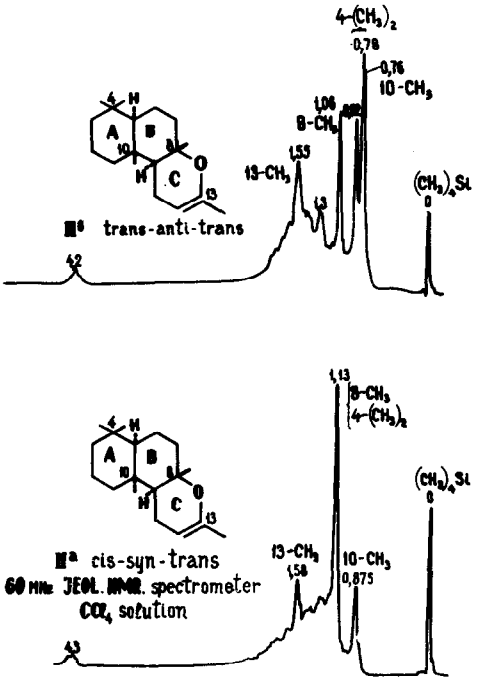
* Oxide IIa as well as IIb should have trans-fusion of B/C rings in accordance with the data on the stereochemistry of the cyclization of geranylacetone to the derivatives of hexahydrochromane /4/.



in IIb. From the study on sterols /9/ and simple decaline derivatives /10/ it is known that the angular 10-methyl peak for the trans-decaline system lies 0.1-0.13 p.p.m. to high field from the position for the corresponding cis-decaline isomer. The difference observed for IIa and IIb ($\delta_{IIa} - \delta_{IIb}$ = 0.115 p.p.m. to low field) is quite consistent with supposed cis- A/B ring junction in IIa*. The choice between cis-syn-trans and cis-anti-trans-configuration in IIa in favour of the former has been made on the basis of the consideration of the stereospecific

* The comparison of mass-spectra of IIa and IIb also confirmed the assigned stereochemistry (preliminary data).

cyclization as trans-antiplanar addition in the most favourable all-chair conformation of acyclic molecule /2/.

The stereospecific formation of the trans-decaline system from trans-6.7-farnesylacetone and the cis-decaline system from its cis-6.7-isomer is the first example of non-enzymatic stereospecific cyclization of isoprenoids. This result shows the chemical validity of the main postulates of the Biogenetic isoprene rule.

We also found out, that under the conditions mentioned above it is possible to carry out the cyclization of α- and β-monocyclofarnesylacetones (IVa and IVb; trans-configuration of the 3',4'-double bond). Strikingly enough tricyclic oxide products from IVa and IVb were different. They were isolated from the reaction mixture (content up to 70% by g.l.c.) by the conventional procedure with the yields about 40%. By use of I.R.- and N.M.R.-spectra, and g.l.c.-data we identified the product formed by the cyclisation of IVa with tricyclic oxide IIa and that derived from IVb with oxide IIb. Thus we have shown that the difference in the position of the double bond in the ring of monocyclofarnesylacetone (α- or β-) determines the difference in the stereochemistry of A/B ring junction in the tricyclic product formed (cis- or trans-resp.). It is the first example of a new pathway for the stereospecific synthesis of polycyclic compounds and it may be also useful when considering the biogenetic problems. Similar regularity had been observed by us earlier for the cyclisation of α- or β-dihydroionones /11/.

All these results demonstrate that the nucleophilicity of the isolated 10.11-double bond is quite sufficient to warrant the stereospecificity of the decaline system formation. Hence we suppose that in general, stereospecificity of the acid-catalyzed cyclization should be observed for all cases, where only isolated double-bonds with similar nucleophilicity are involved. But such equivalence of the double bonds would be the main reason for the structural non-selectivity of the process. Therefore special attention should be paid to the study of the factors affecting the structural trend of the reaction.

A detailed paper on the whole subject will be published shortly.

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