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NEW METHOD FOR THE INITIATION OF THE CYCLISATION REACTION OF ISOPRENOID COMPOUNDS

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The mechanism of the acid cyclisation of isoprenoid compounds is rather obscure but it is well known that this reaction starts with the protonisation of the terminal 2,3-double bond accompanied by concerted (or non-concerted) interaction with other double bonds (6,7-, 10,11-, etc.). It seems reasonable to suggest that the same process may be induced by the addition of any electrophilic cation of the type X^+ to the terminal double bond. As a rule the interaction of conventional electrophiles such as Br_2, $Hg(OAc)_2$, NO_2Cl, etc. with open-chain 1,5-dienes proceeds by means of the addition of the elements X^+ and Y^- to the one double bond, the other double bonds taking no part in the process. One may anticipate that such participation would become possible in the case of electrophilic

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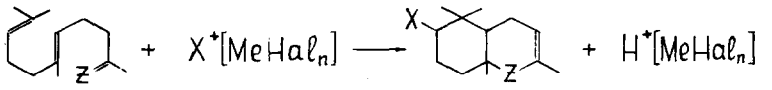
reagents with anions Y^- of decreased nucleophilicity.

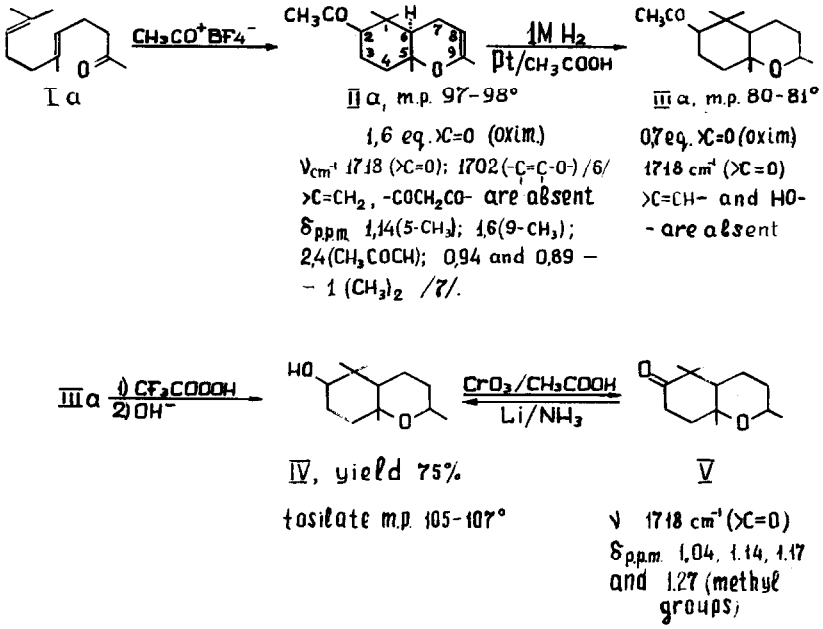
Olah and his coworkers have extensively studied reagents of the general formula $X^+/MeHal_n/$, where $X = J^+$, R^+, RCO^+, NO_2^+, etc., Me = Sb, B, As and Hal = F, Cl, and have showed that these were very powerful agents for aromatic electrophilic substitution /1/ and for the initiation of olefin polymerisation /2/. The purpose of the present investigation was to study the possibility of carrying out the cyclisation reaction of 1,5-dienes by the general scheme shown below



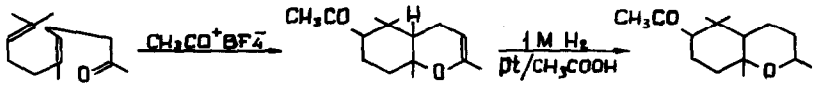
As a model compound we have chosen geranylacetone (I) since the steric and structural course of its cyclisation under different conditions, had been thoroughly investigated earlier /3/.

It was observed that under the action of CH_3CO^+ BF_4^- (3 moles; prepared by the reaction of CH_3COCl with $AgBF_4$ in nitromethane) in nitromethane solution trans-6,7-geranylacetone (Ia) is smoothly converted (-20°, 5 min.) into a mixture of the cycloproducts. According to g.l.c.-data there are three main products in this mixture in the ratio 4:2:1 which account for more than 85% of the total sum. The major product has been isolated by chromatography on silica with a yield up to 35%. Its empirical formula,

$C_{15}H_{24}O_2$/4/, is compatible with a structure formed by the addition of one acetyl group to geranylacetone. This structure, IIa, has been established by the chemical and spectral evidence shown in the following scheme /5/.



The cyclisation of the cis-isomer (Ib) proceeds in the same sense, but the resulting mixture is more complicated and the content of the desired product IIb doesn't exceeds 35%. It was isolated in the same way and its structure was substantiated by the data quoted in the scheme.



I β

II β, m.p. 35-37°

1.7 eq. >C=O (oxim.)

ν cm⁻¹ 1720 (>C=O); 1696 (-C=C-O-)

δ_{ppm} 1.16 (5-CH_3); 1.53 (9-CH_3); 2.1 (CH_3COCH); 0.88-1-$(CH_3)_2$

III β

0.7 eq. >C=O (oxim.)

1720 (>C=O)

The products IIa and IIb are formed exclusively, or at least mainly by a stereospecific process since the admixture of IIb in IIa is never more than 5% and that of IIa in IIb - about 30% /8/.

The stereochemistry of ring-junction in II (a and b) has not been unambiguously proved thus far, but on the basis of our previous study on the steric course of the acid cyclisation of geranylacetone /3/ we may assuredly suggest trans ring-junction for IIa and cis- for IIb. In order to establish the configuration of the substituent at C-2 in IIa we have investigated the steric course of the reduction of ketone V. It is well known, that the reduction of ketones with lithium in liquid ammonia gives rise to the more stable equatorial isomer. In the case of V this method led to the exclusive formation of the starting alcohol IV, identified by g.l.c.comparison on polar and apolar phases. It follows that the hydroxyl group in IV is equatorial /9/. This result also established the equatorial configuration of the acetyl group in IIa since

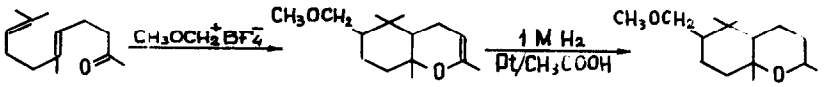
the formation of IV from IIa proceeds with the retention of configuration at C-2.

The products of type II (a and b) could also be formed by the analogous treatment of I with other acyl cations of general formula $RCO^+BF_4^-$ (R = C_2H_5, i-C_3H_7, etc.).

We also found that alkyl cations from reagents of the type $R^+BF_4^-$ also may serve as the initiators of the cyclisation reaction. The compound $CH_3OCH_2^+BF_4^-$, readily prepared by the interaction of CH_3OCH_2Cl and $AgBF_4$ in nitromethane, proved to be especially active. It was shown that the reaction of Ia with two equivalents of such a complex proceeded smoothly (-25°, 5 min.) yielding a cyclic product VIa. It was almost homogeneous according g.l.c-data (about 85% of the major peak) and could be purified by distillation over sodium (to remove traces of ketone impurities) with a total yield up to 55%. The cyclisation of Ib may be carried out under the same conditions but the resulting mixture is more complicated and the content of the desirable product VIb doesn't exceed 50%. VIb was also isolated by distillation with a yield about 30% /5/.

The structure VI (a and b) for these ciclisation products was confirmed by the evidence illustrated below.

By analogy the stereochemistry of the ring junction was taken to be the same as with II (a and b) /3/.



I a) trans
β) cis

VI a) trans ; β) cis

m.p. 120-125°/2 mm; 117-122°/2 mm

>C=O eq. (orim)	0.95	0.95
ν cm⁻¹ (-C=C-O-)	1696	1693
δ ppm CH3OCH2	3.22	3.1
δ ppm 9-CH3	1.64	1.54
δ ppm 5-CH3	1.12	1.05

VII

a) trans
β) cis
} < 0.1 eq. >C=O

HO⁻, >C=CH- — — are absent

The formation of almost pure VIa from Ia and of predominantly VIb from Ib (admixture of VIa in the VIb is not more than 25% /8/) points to the same degree of stereospecificity of the cyclisation process in this case as in the aforesaid case.

To our knowledge the described reactions are the first examples of the initiation of stereospecific isoprenoid cyclisation by aprotic heterolytic agents with simultaneous incorporation of the substituent at C-2. The preliminary observations demonstrate that this reaction has rather interesting peculiarities concerning the stereochemistry of the addition at the 2,3-double bond. The use of the different cationic initiators may permit the cyclisation of complex acyclic terpenoids in a selective way. Moreover this reaction may provide a convenient route to the cyclic terpenoids bearing different substituents at C-2, which are difficult to obtain by conventional methods. Further studies are in progress in order to delineate the scope and mechanism of this reaction.

REFERENCES

1. G.Olah, H.Quinn, S.Kuhn, J.Am.Chem.Soc., 82, 426 (1960).
2. G.Olah, S.Kuhn, S.Flood, B.Hardie, J.Am.Chem.Soc., 86, 2203 (1964).
3. W.A.Smit, A.V.Semenovsky, V.F.Kucherov, Izvestia Acad. Nauk SSSR, Otd.chim.Nauk, 1963, 1782.
4. All the compounds reported gave satisfactory elementary analysis.
5. Other components of the reaction mixture haven't been identified thus far.
6. IR-Spectra were taken in CCl_4 on UR-10 spectrophotometr in the Optical Laboratory of the Institute of Organic Chemistry.
7. N.m.r.-spectra were taken in CCl_4 with tetramethylsilane as internal standard on a JEOL-60 spectrometer in the Laboratory of Physico-chemical Methods of the Institute of the Chemistry of Natural Products.
8. The formation of trans-bicycloproducts (IIa and VIa), as by products in the cyclisation of Ib may be accounted for by the isomerisation process (IIb ⟶ IIa or VIb ⟶ VIa respectively)under the reaction conditions (c.f.such an isomerisation under the action of BF_3 /3/).
9. The axial isomer (with an admixture of 20% of IV) may be obtained by Meerwein-Ponndorf reduction of V.