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CYCLIZATION OF CEMBRANE DITERPENOIDS.

IV. STEREOSELECTIVE PHOTOCHEMICAL CYCLIZATION OF A NORCEMBRANE KETONE

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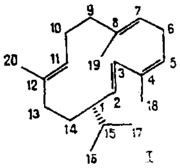
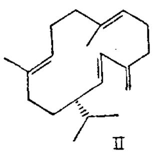
UDC 547.595.9+593.26

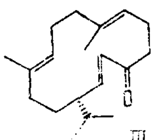
The possibility has been shown for the first time of the occurrence of an intramolecular [2 + 2]-cycloaddition for a derivative of a cembrane diterpenoid. The structure of the product, which was a higher isoprenolog of the bourbonane sesquiterpenoids, was established by the x-ray structural analysis of its epoxide.

The diterpene hydrocarbons cembrene (I) and isocembrene (II) are capable, under the action of electrophilic reagents, of undergoing intramolecular cyclization with the formation of tricyclic derivatives [1-3]. The first stage of the cyclizations, as is assumed, is the formation of a bond between the C_2 and C_{11} atoms. Such a process can take place if the C_2 and C_{11} double bonds in the reacting molecule or in an intermediate ion are sufficiently close in space. We have established that a cyclization similar in direction (the participation of a C_{11} double bond) can also be brought about photochemically. A suitable substrate for such cyclization has proved to be the ketone (III) [4] in which the C_2 double bond is activated by the neighboring keto group. This ketone has been obtained previously from isocembrene (II) by autooxidation or by its treatment with potassium permanganate in aqueous pyridine solution [4]. It has been found that a more convenient method for its synthesis is the oxidation of isocembrene with the Jones reagent by a procedure used previously [5] for cembrene. The ketone (III) was obtained in this way with a yield of 25%. When its pentane solution was irradiated with the light of a high-pressure mercury lamp, a mixture of products was formed that could be separated satisfactorily by chromatography on silica gel. A preliminary analysis of the PMR spectra of these products show that three of them had monocyclic carbon skeletons while one was a cyclization product. This compound (yield 14.0%, calculated on the ketone (III) that had reacted), which is the object of the present communication, was obtained in the form of colorless crystals with mp 35.5-36.5°C. According to its UV spectrum, its molecule did not contain an α-enonic system, while in the IR spectrum the band of an unconjugated carbonyl was observed (1710 cm^{-1}). The ^{13}C NMR spectrum showed the signals of three sp^2-hybridized carbon atoms (213.45 ppm, singlet, C=O; 122.07 ppm, doublet, $-CH=$, and 137.94 ppm, singlet, $-\overset{|}{C}=$). The signals of the other 16 carbon atoms were present in the 17-57 ppm region (see the Experimental part).



I


II


III

According to its mass spectrum, the substance obtained was an isomer of the initial ketone. In view of the ^{13}C NMR results, it was possible to conclude that it had a tricyclic carbon skeleton and was most probably a product of intramolecular [2 + 2]-cycloaddition with the participation of the C_2 double bond. On the basis of spectral characteristics alone it did not appear possible to draw an unambiguous conclusion concerning the structure of the product

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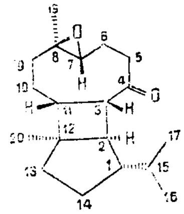
Novosibirsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 295-299, May-June, 1986. Original article submitted December 26, 1985.

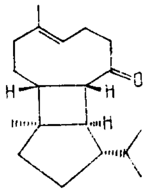
0009-3130/86/2203 0274$12.50

under investigation. In view of this, we used x-ray structural analysis. In order to obtain crystals suitable for this analysis, we performed the epoxidation of the substances under study with peracetic acid in chloroform. The epoxide obtained formed crystals with mp 90-91°C. The structure found for its molecule is shown in Fig. 1 and is expressed by formula (IV). For convenience, the numbering of the atoms in it has been kept as in the cembrane carbon skeleton. The lengths of the bonds and the valence angles in the molecule are the usual ones, with the exception of the C_3—C_{11} bond which is lengthened to 1.61 (1) Å).

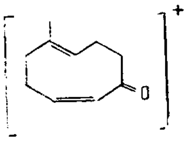
Thus, the initial compound has the structure (V). Its C_7 double bond has the E configuration, as follows from the stereochemistry of the epoxide (IV) and also from the chemical shift of the C_{19} carbon atom (17.45 ppm) [6] in the ^{13}C NMR spectrum. In the PMR spectra both of the ketone (V) and of its epoxide signals similar in form are observed (doublet of doublets at J = 9.0 and 5.0 Hz) at 3.11 and 3.18 ppm, respectively, which can be assigned quite unambiguously to the H_3 proton.



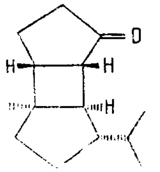
IV



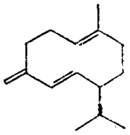
V

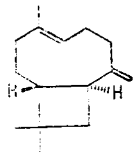


VI



VII


VIII



IX

The mass spectrum of the ketone (V) shows a considerable peak of ions with m/z 150.1037 ± 0.0027 (34% of the main peak), which is absent from the mass spectrum of the initial ketone (III). In view of its empirical formula ($C_{10}H_{14}O$), it is possible to suggest for this ion the structure expressed by formula (VI). Its formation corresponds to a typical pathway for the mass-spectrometric fragmentation of tetrasubstituted cyclobutanes [7].

Ketone (V) is the product of an intramolecular [2 + 2]-cycloaddition [8] and, judging from its stereochemistry, it is formed directly from ketone (III) and not from its geometric isomers. It was quite possible to assume this in view of the capacity of double bonds for undergoing cis-trans isomerization on irradiation [8].

It is interesting to note that the compound obtained is stereochemically analogous to β-bourbonene (VII) — a natural sesquiterpenoid isolated from essential oils [9] — which is likewise formed by the photocyclization of a monocyclic precursor — germacrene D (VIII) [10]. In view of this analogy, it may be assumed that natural cembranoids may also undergo a similar cyclization *in vivo* with the formation of compounds having the skeleton of tricyclo[7,5,0,$0^{10,14}$]tetradecane. So far, no such compounds have been found in plants. It is also impossible to observe a clear analogy of the structure of ketone (V) with the caryophyllane sesquiterpenoids and, in particular, with caryophyllene (IX).

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Bruker WP-200 SY instrument (200.13 MHz for ^1H and 50.327 MHz for ^{13}C) using solutions in deuterochloroform (TMS, δ scale). Type L silica gel (Czechoslovakia) with a grain size of 0.100-0.160 mm was used for chromatography, the ratio of substance and the sorbent being ~1:20 and the eluent being petroleum ether containing amounts of diethyl ether rising from 0 to 15%. The high-resolution mass spectra were obtained on an MS-902 instrument (70 eV, direct introduction).

Ketone (V) ((1R,4E,9S,10R,11S,14S)-11-Isopropyl-4,14-dimethyltricyclo[7,5,0,$0^{10,14}$]tetradec-4-en-8-one). A solution of 0.620 g of ketone (III) in 40 ml of n-pentane was irradiated in an argon atmosphere with the light of a DRSh-1000 mercury lamp for 4 h. Chromatography of

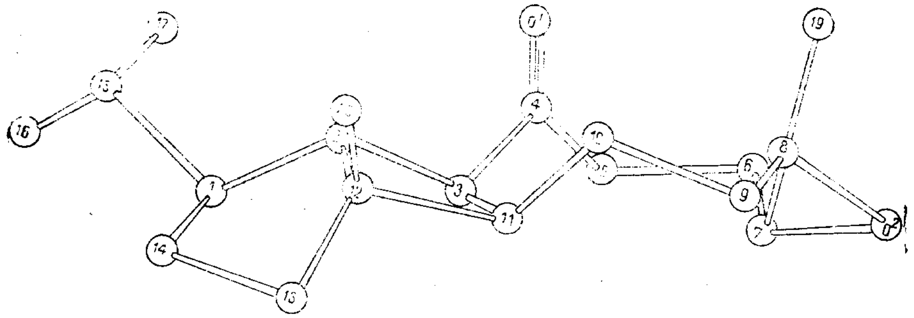


Fig. 1. Crystal structure of the epoxyketone (IV).

TABLE 1. Coordinates (in fractions of the cell) of the Nonhydrogen Atoms of the Molecule of the Epoxyketone (IV)

Atom	$-X\times10^4$	$-Y\times10^3$	$-Z\times10^4$	Atom	$-X\times10^4$	$-Y\times10^3$	$-Z\times10^4$
C_1	2359 (6)	145 (2)	6461 (4)	C_{11}	3826 (6)	243 (2)	7939 (4)
C_2	2859 (6)	308 (1)	6985 (4)	C_{12}	3942 (6)	225 (2)	7216 (4)
C_3	2658 (5)	272 (1)	7684 (4)	C_{13}	3909 (7)	−014 (2)	6978 (4)
C_4	2096 (6)	453 (2)	7943 (4)	C_{14}	3204 (8)	−003 (2)	6344 (5)
C_5	1334 (5)	392 (2)	8359 (4)	C_{15}	1877 (7)	261 (2)	5837 (4)
C_6	1670 (6)	452 (2)	9080 (4)	C_{16}	1445 (8)	101 (3)	5302 (5)
C_7	2724 (6)	368 (2)	9253 (4)	C_{17}	1060 (8)	416 (3)	5960 (5)
C_8	3571 (6)	514 (2)	9261 (4)	C_{19}	3461 (8)	758 (2)	9202 (5)
C_9	4461 (6)	417 (2)	9059 (4)	C_{20}	4761 (7)	353 (2)	6985 (4)
C_{10}	4424 (6)	428 (2)	8323 (4)	O_1	2190 (4)	644 (1)	7802 (3)
				O_2	3317 (4)	429	9860 (3)

the mixture of products on silica gel yielded 0.056 g of ketone (V) (eluent: petroleum ether containing 1% of diethyl ether) in the form of colorless crystals with mp 35.5-36.5°C (from acetonitrile), $[\alpha]^{22}_D$ +64° (c 3.90; chloroform). PMR spectrum (ppm): 0.75 and 0.79 (3 H each, doublets, J = 6.5 Hz, each $-CH(CH_3)_2$); 1.03 (3 H, singlet, Me_{12}); 1.52 (3 H, doublet, J = 1.3 Hz, Me_8); 3.11 (1 H, doublet of doublets, H_3, $J_{3,2}$ = 9.0 Hz, $J_{3,11}$ = 5.0 Hz); 5.36 (1 H, doublets of doublets with broadened components, J = 10 and 4 Hz, H_7). ^{13}C spectrum (ppm): singlets at 213.45 (C_4), 137.94 (C_8), and 44.92 (C_{12}); doublets at 122.07 (C_7), 56.66, 55.05, 51.72, and 48.28; triplets at 43.69, 41.87, 40.77, 31.05, 24.66, and 22.17; and quartets at 21.48, 21.32 (C_{16} and C_{17}), 20.54 (C_{20}) and 17.45 (C_{19}). The assignment of the quartets was made on the basis of the observed values of their residual splitting. Mass spectrum m/z 274, 2298 ± 0.0027 (M^+, 22%, $C_{19}H_{30}O$).

In addition to the ketone (V), we isolated from the mixture of photolysis products three other substances (totaling 0.210 g), which will be described in a separate communication, together with 0.220 g of the initial ketone (III) and 0.140 g of a mixture of highly polar compounds.

Epoxyketone (IV). A solution of 0.054 g (0.2 mmole) of ketone (V) in 1.2 ml of chloroform was treated with 0.068 g of sodium bicarbonate, the mixture was cooled to 0°C, and, with stirring, a solution of 0.126 g (1.6 mmole) of peracetic acid in 2 ml of chloroform was added dropwise. After this, the solution was left with stirring to warm up to room temperature and was then kept for another 4 h. It was then diluted with diethyl ether and was washed with a saturated aqueous solution of sodium bicarbonate. Chromatography of the product yielded 0.008 g of the initial ketone (V) and 0.030 g of the epoxyketone (IV) in the form of colorless crystals with mp 90-91°C (from acetonitrile). PMR spectrum (ppm): 0.78 and 0.82 (3 H each, doublets, J = 6.0 Hz, each, $-CH(CH_3)_2$); 1.07 (3 H, singlet, Me_{12}); 1.13 (3 H, singlet, Me_8), 2.82 (1 H, doublet of doublets, J = 11.5 and 2.0 Hz, H_7); 3.18 (1 H, doublet of doublets, H_3, $J_{3,2}$ = 9.0 Hz, $J_{3,11}$ = 5.0 Hz).

The x-ray structural experiment (λ Mo K_α, ω-scanning, $2\theta < 50°$, 937 reflections with $I > 2\sigma$) was carried out on a SYNTEX-$P2_1$ diffractometer. The crystals of the epoxyketone (IV) were of the monoclinic system, a = 13.731(12), b = 6.116(6), c = 20.925(20) Å, β = 100.26(7)°, z = 4, space group C_2. The structure was deciphered by the direct method using the MULTAN-XTL program and was refined in the usual way [11] to R = 0.087 and R_w = 0.065. The coordinates of the nonhydrogen atoms are given in Table 1.

SUMMARY

The photochemical intramolecular cyclization of an α-enol of the cembrene series, leading to a higher isoprenolog of the bourbonane sesquiterpenes has been performed for the first time.

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DITERPENOIDS OF *Pulicaria salviifolia*.

II. STRUCTURE OF SALVICIN

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UDC 547.595.9

A new diterpenoid acid of the clerodane series, $C_{20}H_{32}O_4$, $[\alpha]_D^{20}$ −75.4° (c 0.26; methanol), which has been called salvicin, and the known flavonoid rutin have been isolated from a chloroform extract of the epigeal part of *Pulicaria salviifolia*. The structure of salvicin has been established on the basis of spectral characteristics and chemical transformations.

Continuing a study of the components of *Pulicaria salviifolia* Bunge (family Asteraceae) [1], we have isolated a new diterpenoid acid of the clerodane series which we have called salvicin (I). No diterpenoid acids of this series have previously been found in plants of the USSR flora.

Salvicin (I) has the elementary composition $C_{20}H_{32}O_4$ (M^+ 336) and is readily soluble in aqueous solutions of sodium bicarbonate. The acid nature of salvicin is shown by the presence in its IR spectrum of a broad band corresponding to the hydroxyl of a carboxy group at 2380-2680 and a strong absorption band at 1680 cm^{-1} which is assigned to an acid carbonyl, and also by the presence in the mass spectrum of a peak with m/z 291 which characterizes the splitting out of a carboxy group from the molecular ion (M^+ − COOH) [2]. In addition, in the PMR spectrum of (I) (C_5D_5N, 0 is TMS), a broadened one-proton singlet is observed at 8.76 ppm corresponding to the proton of a carboxy group. In analogy with compounds isolated previously [1], the PMR spectrum of salvicin has the signals of the protons of three methyl groups — two singlets at 1.57 and 0.74 ppm and a doublet at 0.79 ppm with ^3J = 6.7 Hz — and the broadened

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*Deceased.

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 299-301, May-June, 1986. Original article submitted March 27, 1985; revision submitted January 24, 1986.

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