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CYCLIZATION OF CEMBRANE DITERPENOIDS VII. EXPERIMENTAL CONFIRMATION OF THE SCHEME OF ACID-CATALYZED CYCLIZATION OF 5β-ACETOXYISO-CEMBROL

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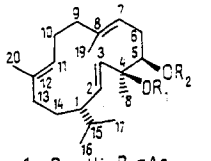
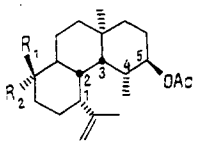
It has been established that during the cyclization of 5β-acetoxyisocembrol under the action of HCOOH + D_2O the D atom enters position 7α of the product molecules exclusively, which is in harmony with the proposed cyclization scheme. Using model compounds, an alternative scheme for the formation of one of the products has been disproved.

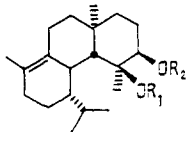
Under the action of 85% HCOOH in $CHCl_3$ at room temperature, β-acetoxyisocembrol (I) is converted into a mixture of products the main components of which are the formylacetates (2) and (3) and the hydroxyacetates (4) and (5) [1]. As is assumed, cyclization proceeds by a scheme analogous to that which has been proposed for cembrene [2] but with the primary formation of a carbonium center at C-4 through the heterolysis of the C(4)-O bond. Then intramolecular cyclization takes place through the intermediate cation (6), which is neutralized as the result of the addition at C-12 of a nucleophilic particle ($^-$OOCH, $^-$OH) or by the splitting out of the H-11 proton. Under the reaction conditions, the neutral bicyclic compounds formed undergo attack of the proton at C-7 with subsequent cyclization to the carbocations (7) and (8), respectively. In the first of them, a 1,5-hydride shift from C-15 to C-4 takes place, leading in the final account to products (2-4). In the case of cation (8), as we have shown [1], such a shift is impossible for steric reasons, and the neutralization of this cation takes place by the addition at C-4 of the relatively small nucleophilic particle $^-$OH from the medium. It must be mentioned that a precursor of the hydroxyacetate (5) may be the 11-epimer of cation (6), the formation of which is quite probable in view of the conformational mobility of the (1) molecule (Dreiding models).



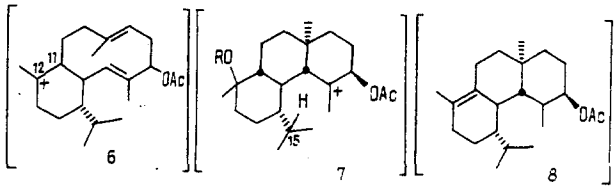
1. R_1 = H; R_2 = Ac
9. R_1 = R_2 = Me



2. R_1 = OCHO; R_2 = Me
3. R_1 = Me; R_2 = OCHO
4. R_1 = OH; R_2 = Me



5. R_1 = H; R_2 = Ac
10. R_1 = R_2 = Me



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The scheme illustrated for the formation of the products appears obvious, but other variants must also be considered. Thus, for the hydroxyacetate (5) it is possible to suggest a different scheme for its formation, without heterolysis of C(4)—O bond in the first stage. Initially, H^+ adds to C-7 of the (1) molecule, followed by the successive formation of the σ-bonds C(8)—C(3) and C(2)—C(11). The resulting carbocation with the charge on C-12 splits out the H-11 proton, leading to (5). The

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TABLE 1. Chemical Shifts and Multiplicities of the Signals in the ^{13}C NMR Spectra of Compounds (1), (9), and (10) (c = 40-50 mg/ml in each case).

Ci	1	9	10
1	45.78 d	45.88 d	39.52 d
2	131.72 d	133.38 d	38.39 d
3	134.74 d	134.69 d	51.55 d
4	74.04 s	79.41 s	78.10 s
5	80.96 d	89.59 d	79.08 d
6	29.74 t	27.45 t*	20.06 t
7	122.11 d	124.58 d	34.27 t
8	134.85 s	133.45 s	36.23 s
9	39.23 t	38.99 t	46.37 t
10	23.60 t	23.49 t	27.22 t
11	124.82 d	124.80 d	133.07 s
12	132.24 s	132.13 s	122.15 s
13	36.57 t	36.51 t	27.89 t
14	27.19 t	27.62 t*	20.41 t
15	32.74 d	33.36 d	27.62 d
16	19.24 q	19.08 q	21.58 q
17	20.20 q	20.38 q	22.16 q
18	24.63 q	18.11 q	15.35 q
19	14.83 q	15.03 q	20.32 q
20	14.40 q	14.72 q	18.80 q
$\underline{C}H_3CO$	21.01 q	-	-
$\underline{C}OO$	170.31 s	-	-
4-OCH_3	-	57.35 q	55.68 q
5-$O\underline{C}H_3$	-	50.38 q	46.04 q

*The signals may change places.

possibility of the realization of such a scheme is disproved, however, by the fact that, on the use of the model compound (9), its interaction with HCOOH under the same conditions is greatly retarded (conversion 20%), and among the reaction products there are not even traces of the diether (1), which should be formed if the cyclization process took place without the participation of the C(4)—OR group. The diether (10) is stable under the conditions of the interaction of (1) with HCOOH (checked in a model experiment).

Compounds (9) and (10) were synthesized by the methylation (MeI/NaH/THF) of the corresponding diols, which were formed when (1) and (5) were treated with lithium tetrahydroaluminate in diethyl ether. Details of the ^{13}C NMR spectra for (1), (9), and (10) are given in Table 1 (the interpretation of the spectra for (1) and (10) was made with the use of two-dimensional $^{1}H—^{1}H$ (COSY) and $^{13}C—^{1}H$ (COSY, COLOC) NMR spectra, and for (9) by comparison with the ^{13}C NMR spectrum of (1)).

In the formation of products (2-5) from (1) we cannot exclude the possibility of the occurrence of processes of deprotonation—protonation of the molecules of the intermediate cations (7) and (8) under the conditions of an acid medium,

TABLE 2. Chemical Shifts and Multiplicities of the Signals (SSCC shown in parentheses, Hz) in the ^{13}C and ^{1}H NMR Spectra of the Formylacetate (3)

i	δC_i	δH_i
1	52.53 d	1.71*
2	35.55 d	1.91 ddd (10.5; 10.0; 9.5)
3	48.54 d	1.34*
4	33.02 d	2.14 m ($W_{1/2}$=16 Hz)
5	75.10 d	4.71 m
6	21.26 t	1.53*; 1.88 dddd (14.0; 4.0; 2.5)
7	36.72 t	1.18 ddd (H-7α) (13.5; 4.5; 2.5); 1.36* (H-7β)
8	34.07 s	—
9	44.97 t	1.14 ddd (H-9β) (13; 13; 4); 1.32* (H-9α)
10	34.80 t	1.55*; 1.64*
11	49.36 d	1.06 ddd (dt) (11.5; 11.5; 3.5)
12	84.14 s	—
13	28.84 t	1.56*; 2.44 ddd (14.0; 6.0; 3.5)
14	20.85 t	1.36*; 1.50*
15	149.44 s	—
16	110.58 t	4.70 m; 4.71 m
17	22.76 q	1.72 br. s
18	15.96 q	0.79 d (7.2)
19	20.59 q	0.92 s
20	25.21 q	1.52 s
$CH_3\underline{C}O$	170.27 s	—
$\underline{C}H_3CO$	21.43 q	2.03 s
$H\underline{C}OO$	160.46 d	8.09 s

*From the two-dimensional ^{13}C—^{1}H NMR spectrum.

and then the stereochemical treatment of the reaction scheme will be different. In order to check this possibility, we performed the cyclization of the hydroxyacetate (1), using, instead of 85% HCOOH, a mixture of 99% HCOOH and 98% D_2O, equivalent to it, and isolated products (2-5) as described in [1]. The ^{1}H NMR spectrum of (5) has been interpreted completely previously [1]. For the sample of (5) obtained we recorded the ^{2}H NMR spectrum, in which there proved to be only one signal (apart from the $CDCl_3$ signal), coinciding in its CS with the H-7α signal in the PMR spectrum. Consequently, in the process of forming the hydroxyacetate (5), the D-atom enters the 7α position exclusively (in the stage of cyclization of the intermediate bicyclic compound) and the possibility of the occurrence of processes of deprotonation-protonation of the intermediate cation (8) is not confirmed.

Of the three other products (2-4), belonging to one structural scheme, we selected the formylacetate (3), in the PMR spectrum of which we observed the best separation of the signals.

The ^{13}C and ^{1}H NMR spectra obtained by the use of the two-dimensional ^{1}H—^{1}H and ^{13}C—^{1}H NMR spectra are given in Table 2. In the ^{2}H NMR spectrum of this product, likewise, only one signal was observed, the CS of which coincided with that for H-7α in the PMR spectrum.

In the PMR spectra of products (2) and (4), according to the two-dimensional NMR spectra, the CS of the H-7α signal coincided with that of the H-9β signal (and in the case of (4) also with the H-11 signal), while in the ^{2}H NMR spectra one signal was observed for each of them, corresponding to the CS of the H-7α (H-9β, H-11) signal in the PMR spectra.

On the basis of the ^{2}H NMR spectra obtained for products (2-4) it may be concluded that the formation of the isopropenyl fragment in their molecules is not connected with the deprotonation—protonation of the intermediate cation (7) (the deuterium atom does not enter positions 1 to 4 of the (2-4) molecules). The possibility of the formation of these compounnds and the occurrence of a series of successive intramolecular 1,2-shifts of a hydrogen atom (from C-3 to C-4, from C-2 to C-3, from C-1 to C-2, and from C-15 to C-1) must also be rejected, since in this case the 2β-epimers of compounds (2-4) should be formed through a 1,2-shift of the 1β-H atom.

The results of the present work, together with calculations of the conformational state of the hydroxyacetate (5) molecule [1] are in complete harmony with the hypothesis put forward previously [2] of the occurrence in the intermediate cation (7) of an unusual 1,5-hydride shift with the participation of the methine proton of the isopropyl group.

EXPERIMENTAL

^2H NMR spectra were recorded on a Bruker AM-400 (61.4 MHz) instrument for solutions in $CDCl_3$ (the internal standard was $CDCl_3$, the signal of which was taken as 7.24 ppm, δ scale). The other instruments used and also the conditions for recording the spectra and performing chromatography have been described in [1].

Interaction of 5β-Acetoxyisocembrol (1) with HCOOH and D_2O. At room temperature, a mixture of 57 ml of 99% HCOOH and 10 ml of 98% D_2O was added to a solution of 1.02 g of compound (1) in 30 ml of $CHCl_3$. The subsequent reaction, the working up of the mixture, and the separation of the products were carried out as described in [1] for the reaction of (1) with 85% HCOOH in $CHCl_3$. Chromatography led to the successive isolation of 0.13 g of an acetate fraction, 0.16 g of the diester (3), 0.44 g of the diester (2), 0.05 g of the hydroxyester (4), 0.08 g of a mixture of unidentified products, and 0.011 g of the hydroxyester (5).

The ^2H NMR spectra for compounds (5), (3), (2), and (4) each showed one signal (broadened singlets with CSs of 1.12, 1.18, 1.17, and 1.15 ppm, respectively, the signal:noise ratio being ~40).

Synthesis of the Diester (9). A solution of 0.12 g of (1) in 5 ml of diethyl ether (DE) was treated with 0.1 g of $LiAlH_4$, and the mixture was stirred at 20°C for 1 h. After the usual working up, the product obtained (0.11 g) was treated with 5 ml of THF, 0.2 g of NaH, and 2 ml of MeI. The resulting mixture was stirred and was left for a day at 20°C. After this, it was poured into water and extracted with DE. Chromatography of the product led to 0.07 g of the diester (9).

(1S,4S,5R)-4,5-Dimethoxycembra-2E,7E,11E-triene (9). Colorless oil with $[\alpha]_{580}^{20}$ + 73° (c 0.41). PMR spectrum: 0.81 and 0.84 (each 3H, doublets, J = 7.0 Hz each, 2Me-15), 1.32 (3H, s, Me-4), 2.49 (3H, s Me-12), 1.59 (3H, br.s. Me-8), 1.70 (1H, m, H-1), 1.89 (1H, ddd, J = 13.0, 13.0, and 3.0 Hz, H-13a), 2.82 (2H, m, H-5 and H-6a), 3.14 and 3.39 (each 3H, singlets, 4-OMe and 5-OMe), 4.93 (1H, br.s. J = 7 Hz, H-11), 5.17 (1H, br.t, J ≈ 5 Hz, H-7). For the ^{13}C NMR spectrum, see Table 1.

Synthesis of the Diester (10). A solution of 0.025 g of the hydroxyacetate (5) in 5 ml of DE was treated with 0.02 g of $LiAlH_4$, and the mixture was stirred at 20°C for 1 h. After the usual working up, the product (0.02 g) was dissolved in 5 ml of THF, and 0.05 g of NaH and 1 ml of MeI were added to the resulting solution. The mixture was stirred and was left for a day at 20°C. After the usual working up and chromatography, 0.02 g of the diester (10) was isolated.

(1S,2R,3S,4R,7S,14S)-14-Isopropyl-3,4-dimethoxy-3,7,11-trimethyltricyclo[8.4.0.0^{2,7}]tetradec-10-ene (10). Colorless oil with $[\alpha]_{580}^{20}$ −72° (c 1.59). IR spectrum: 1200 (C−O) cm^{-1}. For the ^{13}C NMR spectrum, see Table 1. ^1H NMR spectrum: 0.86 and 0.90 (each, 3H, doublets, J = 7.0 Hz each, 2Me-15), 1.07 (3H, s, Me-4), 1.09 (3H, s, Me-8), 1.19 (1H, ddd, J = 13.0, 13.0 and 3.0 Hz, H-9β), 1.30 (1H, ddd, J = 13.0, 4.5 and 3.0 Hz, H-9α), 1.52 (3H, br.s, Me-12), 1.78 (1H, J = 11, H-2), 3.15 (1H, J = 4.5, H-5), 3.02 and 3.25 (singlets, each, 3H, 4-OMe, 5-OMe) ppm. CS values for the other signals (from the ^{13}C-^1H NMR spectrum): 1.81 (H-1), 1.80 (H-6a), 1.49 (H-6b), 1.48 (H-7a), 0.98 (H-7b), 2.43 (H-10a), 1.79 (H-10b), 1.84 (H-13a), 1.64 (H-13b), 1.45 (H-15) ppm.

Interaction of the Diester (9) with HCOOH. A solution of 0.020 g of the diester (9) in 2 ml of $CHCl_3$ was treated with 2 ml of 85% HCOOH. The reaction and the subsequent working up of the reaction mixture were carried out as in [1] for the acetate (1). After chromatography, 0.015 g of the initial diester (9) was obtained together with 0.004 g of a mixture of unidentified products among which, according to PMR and TLC, compound (10) was absent.

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