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A Convenient Synthesis of Retinal Derivatives with Modified Trimethylcyclohexene Ring

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Abstract—A method of simultaneous one-stage synthesis of three retinal derivatives (5,6-dioxo-5,6-seco-, 5,6-dihydro-5,6-epoxy-, and 4-oxoretinal) was proposed, with the yield of the first derivative being ~50%. These compounds are useful tools for studying the antitumor activity of retinoids, the reconstituted bacteriorhodopsin analogues with changed parameters of photocycle, and the reactivity of retinal derivatives in the processes of oxidation by molecular oxygen.

Key words: *pyridinium chlorochromate, retinoids, ring oxidation*

INTRODUCTION

The modification of trimethylcyclohexene ring of retinoids affects their A-vitamin activity, antitumor action, toxicity of retinoic acid derivatives [1–4], photochemical properties and transport of proton by the corresponding bacteriorhodopsin analogues [5, 6], and the functional activity of analogues of visual rhodopsin [7].[2] The modified retinal analogues have been intensively studied to understand the functional role of this important moiety in retinoid molecules.

In parallel, the reactivity of retinoids and carotenoids toward various oxidative agents have been investigated in detail, in order to get a deep insight into the mechanism of antioxidative action of retinoids. The methods of oxidative degradation of carotenoids isolated from various natural sources were already described in the first studies for confirmation of their structures [1, 2]. The processes of oxidation [8, 9, 11–13], photooxidation [14], and epoxidation [15, 16] of the retinoid molecule were shown to be of the main practical importance.

All the known synthetic methods for preparation of the retinoids with various ring modifications can be divided into two strategically different groups: total synthesis that applies a combination of two or more fragments with the formation of retinoid molecule [17–23] and the modification of the cyclic part in the ready C_{20}-carbon skeleton of a suitable precursor [8–12, 24–27].

All the known methods of preparation of the retinal analogues were presented in our previous reviews [5, 6, 28], whereas those for the derivatives of retinoic acid, in the books [1–3, 17]. In this study, we would briefly describe only the variants of oxidative modification of trimethylcyclohexene ring of retinal (**I**) (see scheme 1).

At first, the retinoids with oxidized ring were proposed to obtain by the elongation of polyenic chain of the corresponding derivative of β-ionone [17–23]. However, all the described syntheses were multistage. Later, the structure of the commercially available retinal (**I**) was suggested to modify by introducing functional groups into the trimethylcyclohexene ring by its oxidation in position 4 [8–11], by allylic bromination with *N*-bromosuccinimide [9, 10], by epoxidation of 5,6-double bond [15, 16], or by more complex modifications with the introduction of several substituents [27].

4-Oxoderivatives now outrank among the retinoid derivatives with the oxidized ring, because they are the analogues of metabolites of retinoic acid and retinal [8–11] and important starting compounds for synthesis of 4-hydroxyderivatives [24], 4,4-difluoroderivatives, and 3-substituted analogues of retinoids [27, 29].

As a rule, the previously studied oxidative agents exhibited no pronounced regioselectivity and caused the isomerization of double bonds in the polyenic chain, which resulted in complex mixtures of products [11, 13, 14, 30]. Only the preparations of active manganese(IV) oxide obtained by various procedures [8–12] were of practical importance.

Previously, the process of directed allyl oxidation of methylene group position 4 of the ring in *all-E*- and 13*Z*-isomers of retinal by the acidic form of manganese dioxide with the formation of the corresponding derivatives of 4-oxoretinal was studied in our laboratory. We

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[2] Abbreviations: PCC, pyridinium chlorochromate.

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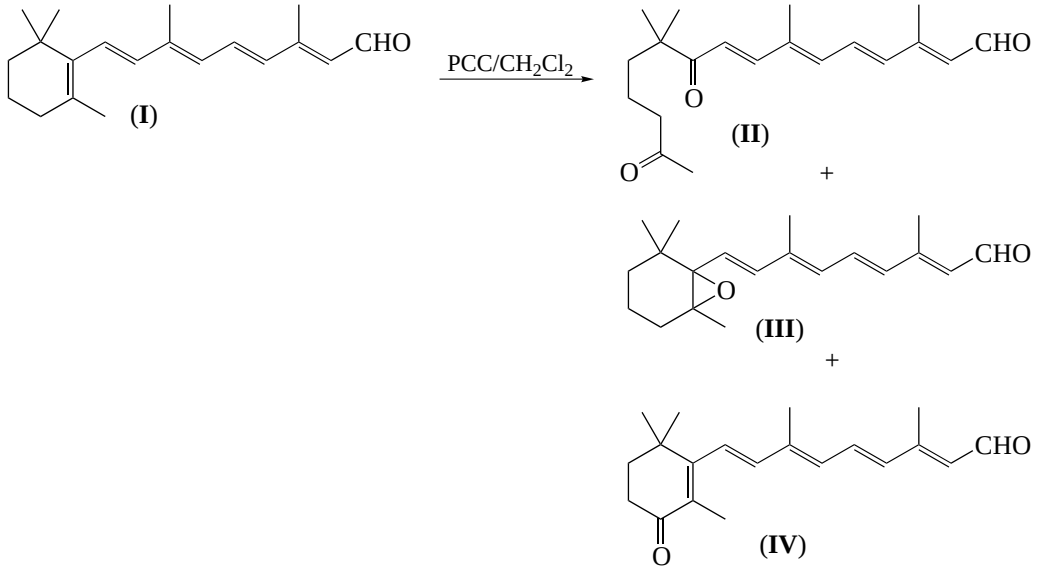


Scheme 1. Oxidation of retinal by pyridinium chlorochromate.

widely varied the procedure of the reagent preparation and the conditions of process (temperature, solvent, and the ratio of oxidative reagent and substrate), but could not achieve the degree of retinal conversion higher than 30–40%. Manganese dioxide caused no remarkable isomerization, however, the main difficulty was the preparation of the oxidative agent with a standard oxidative capacity. Additional experiments were therefore necessary for testing every portion of the oxidative agent [9, 10]. Recent studies [11, 12, 30] significantly extended the synthetic potential of manganese dioxide as an oxidative agent. The paper [12] is of especial interest, because a selective cleavage of the polyenic retinal chain with formation of isomers of C_{19} aldehyde with the *retro*-arrangement of double bond system was described in this article. Unfortunately, we failed to reproduce these results.

We examined the following oxidative agents for the optimal oxidation of the trimethylcyclohexene ring of retinal:

(a) samples of manganese dioxide prepared according to various procedures in hexane and dichloromethane;

(b) pyridinium chlorochromate in dichloromethane (PCC/CH_2Cl_2);

(c) cerium(IV) ammonium nitrate in dichloromethane;

(d) cerium(IV) sulfate in the methanol–water mixture; and

(e) potassium permanganate in benzene in the presence of 18-crown-6.

The goal of this study was the search for the method of oxidation that allowed the synthesis of a number of retinal derivatives with modified trimethylcyclohexene ring in a sufficiently high yield. We planned to use these derivatives for the preparation of bacteriorhodopsin analogues and for studying the reactivity of retinal and the corresponding retinoic acid derivatives in the oxidative processes with molecular oxygen. The oxidation experiments were necessary to choose the stabilization methods for retinoids used as individual substances or in complex preparations [31, 32], since fat-soluble polyenic vitamins, are, as a rule, easily oxidized by molecular oxygen, with the kinetics of these processes being scarcely studied.

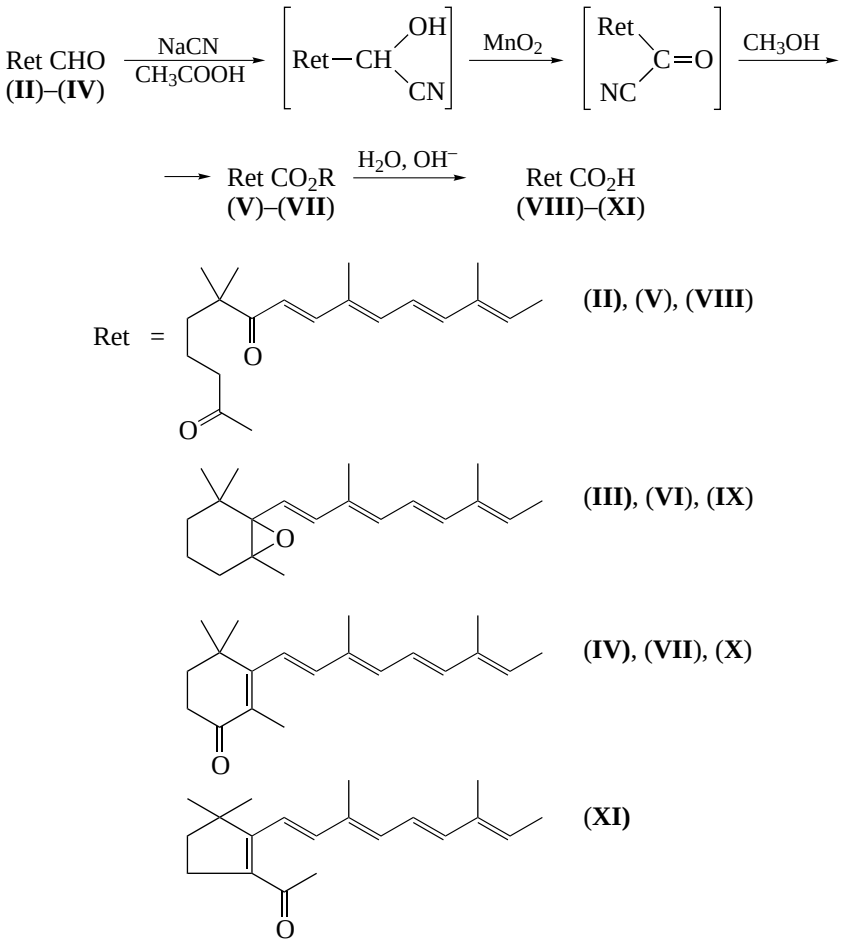
RESULTS AND DISCUSSION

In this paper, we propose an approach to the simultaneous one-step preparation of three retinal derivatives (Scheme 1): 5,6-dioxo-5,6-secoretinal (**II**), 5,6-dihydro-5,6-epoxyretinal (**III**), and 4-oxoretinal (**IV**). We also describe synthesis of the corresponding acids (**VIII**)–(**X**) and their methyl esters (**V**)–(**VII**) (Scheme 2).

Retinal (**I**) was stable under the conditions of oxidation with potassium permanganate in benzene: it was not modified for two weeks. Its oxidation with cerium compounds resulted in a number of products with truncated polyenic chains. The most interesting results that were obtained with the PCC/CH_2Cl_2 system will be described below.

Modified retinals (**II**)–(**IV**) were obtained by the treatment of retinal (**I**) with PCC in dichloromethane; aldehyde (**II**) was the main product of this reaction, and its yield was approximately 50%.

Retinal derivatives (**II**)–(**IV**) were converted into the corresponding analogues of retinoic acid methyl esters (**V**)–(**VII**) according to the Corey method [33] (Scheme 2). The corresponding analogues of retinoic



Scheme 2. Method of synthesis of the analogues of retinoic acid and their methyl esters.

acid (**V**)–(**VII**) were obtained by the saponification of the methyl esters (**VIII**)–(**X**).

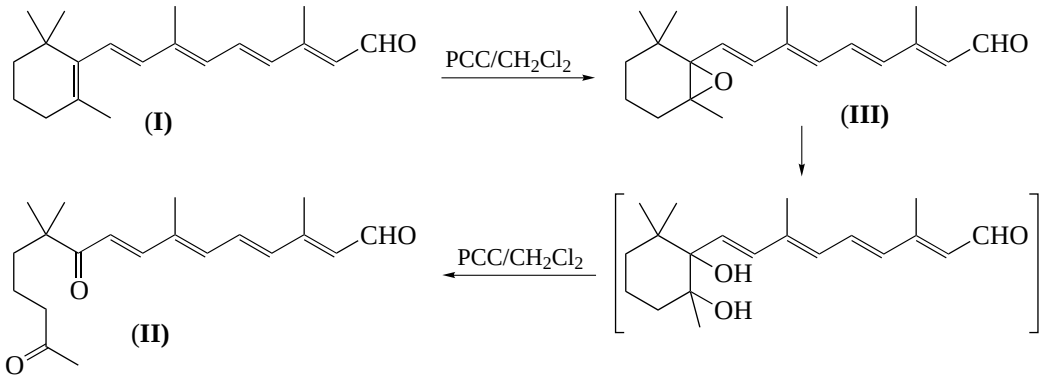
Chromium compounds have already been used for oxidative modification of retinoids. Schwieter *et al.* oxidized retinoic acid and its ethyl ester by the Jones reagent (solution of H_2CrO_4 in acetone) [13]. In this case, the oxidation process in strongly acidic medium proceeds through the rearrangement of 5,6-epoxide into 5,8-furanoid derivative with the subsequent cleavage of 7,8-bond, which leads to low yields of products in a complex mixture; for example, the yield of 5,6-dioxo-5,6-secoretinoic acid (**VIII**) and its ethyl ester (**V**) were obtained in 0.8 and 12.6% yields, respectively.

The target products were also synthesized in rather low yields by oxidation of retinyldenedimedone by pyridinium dichromate [25]. In this case, the yield of 2-(5,6-dioxo-5,6-secoretinyliden)dimedone was 34%, and the corresponding aldehyde (**II**) was obtained from this compound in 12.6% yield (from retinyldenedimedone).

It is interesting to note that the PCC/CH_2Cl_2 system has already been used as an oxidative agent for the synthesis of oxidized retinoids in [26]. However, 4-hydroxyretinal was the starting substance and 4-oxoretinal (**IV**) was formed in yield of 50%. In this case, trymethylcyclohexene ring was not cleaved probably due to the fact that an oxidized (in position 4) retinal derivative was the starting compound.

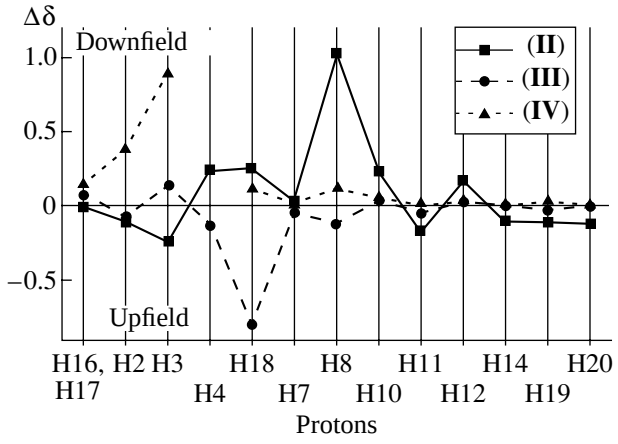
In our case, we oxidized the unmodified retinal by the PCC/CH_2Cl_2 system and obtained predominantly 5,6-dioxo-5,6-secoretinal (**II**) in yield of 47% after the selective cleavage of 5,6-double bond in trimethylcyclohexene ring. In addition, 4-oxoretinal (**IV**) (7%) and 5,6-dihidro-5,6-epoxyretinal (**III**) (19%) were isolated from the reaction mixture. Note that, at this instant, the process of cleavage of the trimethylcyclohexene ring proceeded under comparatively mild conditions through the intermediate 5,6-epoxide and glycol (Scheme 3). The presence of 5,6-dihydro-5,6-epoxyretinal (**III**) confirms our conclusions on the reaction pathway.

The structure of (**II**) was proved by spectral methods. Two additional signals from carbonyl groups (203.6 and 208.2 ppm) were observed in the ^{13}C NMR spectrum along with the signal from aldehyde group



Scheme 3. Possible mechanism of the retinal oxidation by pyridinium chlorochromate.

(190.6 ppm), and the signals from protons of all the fragments of molecular structure (**II**) were found in the ^{1}H NMR spectrum (see table). Electronic spectra (taken in methanol) additionally confirmed the structure of diketone (**II**). The absorption maximum of analogue (**II**) observed at 364 nm and shifted to the short-wave area by 16 nm relative to unmodified retinal (**I**) indicated that the conjugated chain length decreased by one bond. We compared ^{1}H NMR spectra of the main reaction products (**II**)–(**IV**) with that of the starting retinal (**I**) (see figure) and should point out the following tendencies: the H3 and H11 signals of 5,6-dioxo-5,6-secoretinal (**II**) were shifted to the upfield area (Δδ –0.24 and –0.18 ppm, respectively), the resonances from H4, H18, H8, and H12 were shifted to the low field area (Δδ 0.24, 0.25, 1.03, and 0.16 ppm, respectively), and the downfield shifts for H3 (Δδ 0.14 ppm) and upfield shifts for H4, H18, and H8 (Δδ –0.13, –0.78, and –0.13 ppm) were characteristic of the spectrum of 5,6-dihydro-5,6-epoxyretinal (**III**). It was also noticed that methyl (H16 and H17) groups (δ 1.16 and 1.11 ppm) displayed not equivalent signals, which was not observed for the most of retinal analogues. The downfield shifts of the H2 and H3 multiplets (Δδ 0.37 and 0.89 ppm) were found for 4-oxoretinal (**IV**).



The dependence of changes in chemical shifts of proton resonances in ^{1}H NMR spectra of retinal derivatives (**II**), (**III**), and (**IV**) on the type of modification of trimethylcyclohexene ring relative to unmodified retinal (**I**).

Thus, the synthesized 5,6-dioxo-5,6-secoretinal (**II**) is a promising starting compound for introduction of various labels and reporter groups into retinoid molecules. Derivatives (**III**) and (**IV**) are interesting tools for studying the retinoid–protein complexes and the kinetics of the retinoid autooxidation.

The structures of minor oxidation products (**III**) and (**IV**) were established on the basis of spectral data (see table and the Experimental section) and by the comparison of their physicochemical properties (mps and R_f) with those of similar compounds previously synthesized in our laboratory by other methods.

It was found during the synthesis of 5,6-dioxo-5,6-secoretinoic acid (**VIII**) that the derivatives with such a modification of the ring [(**II**), (**V**), and (**VIII**)] are prone to aldol and crotonic condensations at elevated temperature under acidic or basic conditions. For example, the recyclization of the cleaved trimethylcyclohexene ring with the formation of five-membered cyclic structure (**VI**) proceeded when obtaining 5,6-dioxo-5,6-secoretinoic acid (**VIII**) from its methyl ester (**V**). The data of ^{1}H NMR of (**XI**) are given in the table. The reaction should be carried out under more mild conditions (room temperature and neutralization with a highly diluted hydrochloric acid) in order to increase the yield and avoid the recyclization process.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker MSL-200 spectrometer (Germany) in chloroform-d^3 at working frequencies 200 and 50.32 MHz, respectively. The chemical shifts are given in ppm relative to hexamethyldisiloxane as internal standard

Parameters of ^{1}H NMR spectra (δ, ppm, multiplicity of signal, *J*, Hz) of retinoids (**I**)–(**XI**)

Number	H16, H17 (6H)	H2 (2H)	H3 (2H)	H4 (2H)	H18 (3H)	H7 (1H)	H8 (1H)	H10 (1H)	H11 (1H)	H12 (1H)	H14 (1H)	H15 (1H)	H19 (3H)	H20 (3H)	OCH_3 (3H)
(**I**)	1.03, s	1.48, m	1.61, m	2.03, t, 6.5	1.72, s	6.36, d, 16.5	6.18, d, 16.5	6.20, d, 12.0	7.15, dd, 12.0/15.4	6.37, d, 15.4	5.98, d, 8.0	10.12, d, 8.0	2.03, s	2.33, s	–
(**II**)	1.02, s	1.37, m	1.37, m	2.27, t, 6.0	1.97, s	6.39, d, 15.0	7.21, d, 15.0	6.42, d, 11.0	6.97, dd, 11.0/15.0	6.53, d, 15.0	5.87, d, 8.0	9.97, d, 8.0	1.91, s	2.20, c	–
(**III**)	1.16; 1.11, c	1.40, m	1.75, m	1.90, m	0.94, c	6.32, d, 15.5	6.05, d, 15.5	6.23, d, 11.2	7.10, dd, 11.2/15.0	6.39, d, 15.0	5.98, d, 8.0	10.11, d, 8.0	2.00, d, 1.2	2.32, d, 1.5	–
(**IV**)	1.17, c	1.85, t, 6.5	2.50, t, 6.5	–	1.83, c	6.37, d, 16.0	6.30, d, 16.0	6.25, d, 11.5	7.15, dd, 11.5/15.0	6.40, d, 15.0	5.98, d, 8.0	10.12, d, 8.0	2.05, c	2.33, c	–
(**V**)	1.12, s	1.48, m	1.48, m	2.36, t, 6.5	2.07, s	6.58, d, 15.0	7.32, d, 15.0	6.49, d, 11.5	6.92, dd, 11.5/15.0	6.58, d, 15.0	5.82, s	–	1.97, s	2.31, d, 0.8	3.68, c
(**VI**)	1.13; 1.09, c	1.45, m	1.78, m	1.90, m	0.93, c	6.29, d, 15.5	5.97, d, 15.5	6.17, d, 11.5	6.95, dd, 11.5/15.0	6.27, d, 15.0	5.78, c	–	1.95, c	2.34, d, 1.5	3.70, c
(**VII**)	1.19, c	1.86, t, 6.5	2.52, t, 6.5	–	1.86, c	6.35, m, 16.0	6.35, m, 16.0	6.25, d, 11.5	6.97, dd, 11.5/15.0	6.35, d, 15.0	5.81, c	–	2.03, c	2.36, c	3.73, c
(**VIII**)	1.11, s	1.48, m	1.48, m	2.38, t, 6.5	2.08, s	6.42, d, 15.0	7.32, d, 15.0	6.51, d, 15.0	6.94, dd, 11.0/15.0	6.56, d, 15.0	5.83, s	–	1.96, s	2.30, d, 0.8	–
(**IX**)	1.12; 1.08, s	1.42, m	1.75, m	1.85, m	0.91, s	6.29, d, 15.5	5.97, d, 15.5	6.16, d, 11.5	6.95, dd, 11.5/15.0	6.29, d, 15.0	5.79, s	–	1.93, s	2.31, s	–
(**X**)	1.16, s	1.82, t, 7.0	2.49, t, 7.0	–	1.83, s	6.31, m	6.31, m	6.25, d, 11.5	6.99, dd, 11.5/15.0	6.35, d, 15.0	5.81, s	–	2.01, s	2.33, s	–
(**XI**)	1.26, s	1.73, t, 7.0	2.63, t, 7.0	–	2.24, s	7.22, d, 16.5	6.74, d, 16.5	6.29, d, 11.5	7.02, dd, 11.5/15.0	6.35, d, 15.0	5.81, s	–	2.01, s	2.34, s	–

(δ 0.055) and the spin–spin coupling constants in Hz. The UV-VIS spectra were recorded on a Hitachi 3400 spectrometer (Japan) in methanolic solution of compounds in quartz cells with the length of optical way of 1 cm. The qualitative composition of the reaction mixtures and homogeneity of the compounds were determined by TLC on Kieselgel 60 F_{254} plates (Merck, Germany) or on Silufol UV-254 plates (Kavalier, Czech Republic) in 1 : 1 hexane–ether mixture. Spots were detected by spraying with concentrated sulfuric acid. The adsorption column chromatography was performed on a Kieselgel 60 (0.063 μm, Merck, Germany). Solvents were removed on a rotary evaporator in a vacuum at a temperature no higher than 35°C. Pyridinium chlorochromate (Aldrich, United States), active manganese dioxide (*zur Synthese*, Merck, Germany), salts, and solvents of *kh. ch.* quality (reagent grade, Russia) are used in this study.

Modified retinals (II)–(IV). A solution of *all-E*-retinal (**I**) (1 g, 3.51 mmol) in dichloromethane (20 ml) was added to a suspension of PCC (3 g, 13.92 mmol) in 5 ml of dichloromethane, the reaction mixture was stirred for 1 h, the oxidative agent was removed by filtration through a layer of Celite, and the precipitate was washed with dichloromethane (10 ml). The filtrate was evaporated and dissolved in ether (30 ml). The solution was washed with water (3 × 15 ml), dried with anhydrous sodium sulfate, and evaporated. The residue was fractionated on a silica gel column eluted with a gradient of ether in hexane (from 0 to 100%). The fractions containing the corresponding retinal derivatives were collected, evaporated, and the residue was dried for 1 h at 0.1 mmHg.

5,6-Dioxo-5,6-secoretinal (II); yield 525 mg (47%); R_f 0.09; mp 76–78°C (lit. mp 77–79°C [24]); UV-spectrum, λ_{max}, nm (ε): 364 (58000); ^{1}H NMR spectrum: see the table; ^{13}C NMR: 13.0 (C19, C20), 19.0 (C3), 24.2 (C16, C17), 29.8 (C18), 39.1 (C2), 43.7 (C4), 46.4 (C1), 121.5 (C14), 130.4 (C7), 131.0 (C11), 137.7 (C12), 138.7 (C10), 138.4 (C9), 146.1 (C8), 153.4 (C13), 190.6 (C15), 203.6, and 208.2 (C6, C5).

5,6-Dihydro-5,6-epoxyretinal (III); yield 204 mg (19%); R_f 0.48; mp 104–106°C; UV-spectrum, λ_{max}, nm (ε): 362 (53500); ^{1}H NMR: see the table.

4-Oxoretinal (IV); yield 73 mg (7%); R_f 0.39; mp 113–115°C (lit. mp 113–114.5 [16, 18, 19]; UV-spectrum, λ_{max}, nm (ε): 374 (50 500); ^{1}H NMR spectrum: see the table.

Methyl esters of retinoic acid derivatives (V)–(VII). The corresponding retinal derivative (0.35 mmol), active manganese dioxide (1.0 g), and glacial acetic acid (0.06 ml) were successively added to a suspension of sodium cyanide (200 mg) in methanol (25 ml) under stirring at 4°C in argon atmosphere. The reaction mixture was stirred for 1 h at 4°C and 24–26 h at 20°C and filtered through a layer of Celite. The precipitate was washed with methanol (10 ml), and the combined filtrate was evaporated. The residue was stirred with water (15 ml), the substance was extracted with ether [3 × 15 ml; chloroform was used for methyl ester of 5,6-dioxo-5,6-secoretinoic acid (**V**)]. The combined extract was washed to pH 7, dried by sodium sulfate, and evaporated. The residue was fractionated on a silica gel column eluted with a gradient of ether in hexane (from 0 to 50%). The fractions containing methyl ester of the corresponding acid were combined, evaporated, and the residues were dried for 1 h at 0.1 mmHg.

Methyl 5,6-dioxo-5,6-secoretinoate (V) was prepared by a standard procedure from 5,6-dioxo-5,6-secoretinal (**II**) (82 mg, 0.26 mmol); yield 66 mg (73%); light-yellow crystals; R_f 0.33; mp 112–115°C; UV-spectrum λ_{max}, nm (ε): 263 (8000) and 353 (31700); ^{1}H NMR see in the table.

Methyl 5,6-dihydro-5,6-epoxyretinoate (VI) was prepared by a standard procedure from 5,6-dihydro-5,6-epoxyretinal (**III**) (100 mg, 0.33 mmol); yield 86 mg (72%); light-yellow crystals; R_f 0.78; mp 88–89°C (lit. mp 86–87°C [21]); UV-spectrum λ_{max}, nm (ε): 236 and 326 (28600); ^{1}H NMR see in the table.

Methyl 4-oxoretinoate (VII) was prepared by a standard procedure from 4-oxoretinal (**IV**) (100 mg, 0.34 mmol); yield 80 mg (70%), yellow crystals; R_f 0.56; mp 90–91°C (lit. mp 90–94°C [12, 21]); UV-spectrum λ_{max}, nm (ε): 362 (53000); ^{1}H NMR see in the table.

Retinoic acids (IX), (X). Water (1 ml) and 5 N KOH (2 ml) were added to a solution of the corresponding ester (0.15 mmol) in methanol (10 ml). The reaction mixture was heated in argon atmosphere for 1.5 h, cooled to 0°C, and neutralized with 1 N HCl. The substance was extracted with ether (3 × 15 ml) and the combined extract was dried by sodium sulfate and evaporated. The residue was fractionated on a silica gel column eluted with a gradient of ether in hexane (from 0 to 50%). The fractions containing the corresponding acid were combined and evaporated. The residue was dried 1 h at 0.1 mmHg.

5,6-Dihydro-5,6-epoxyretinoic acid (IX) was obtained by a standard procedure from (**VI**) (144 mg, 0.44 mmol); yield 100 mg (72%); light-yellow crystals; R_f 0.37; mp 160–165°C (lit. mp 163–164°C [21]); UV-spectrum λ_{max}, nm (ε): 237 (1200) and 326 (28600); ^{1}H NMR see in the table.

4-Oxoretinoic acid (X) was obtained by a standard procedure from (**VII**) (100 mg, 0.3 mmol); yield 82 mg (87%); yellow crystals; R_f 0.17; mp 175–179°C (lit. 186–189°C [12]); UV-spectrum λ_{max}, nm (ε): 354 (42000); ^{1}H NMR see in the table.

5,6-Dioxo-5,6-secoretinoic acid (VIII). A 5 N KOH solution in methanol (4 ml) and water (1 ml) were added to a solution of (**V**) (50 mg, 0.14 mmol) in methanol (10 ml). The reaction mixture was kept at room temperature for 14 h, cooled to 0°C, neutralized with

0.05 M HCl, and further, treated as described for acids (**IX**) and (**X**). Yield 86 mg (72%); R_f 0.12; mp 145–146°C (lit. mp 145–146°C [23]); UV-spectrum λ_{max}, nm (ε): 256 (3000) and 356 (25200); ^{1}H NMR see in the table.

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