A NEW SYNTHESIS OF THE PHEROMONE OF THE CODLING MOTH – DODECA-8E,10E-DIEN-1-OL – VIA AN ENYNIC INTERMEDIATE

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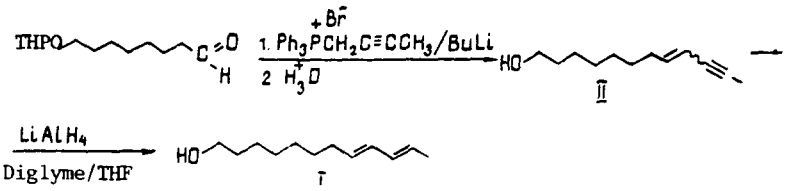
A new method has been developed for the synthesis of the main component of the pheromone of the codling moth – dodeca-8E,10E-dien-1-ol – using in the key stages Wittig reactions and the trans-hydride reduction of the triple bond of an intermediate enynol.

Dodeca-8E,10E-diene-1-ol (codlemone) (I), known as the main component of the pheromone of the codling moth Cydia pomonella L., is widely used in our country and abroad for the fight against this pest [1-4]. A number of methods for synthesizing codlemone based on all possible ways of constructing a conjugated dienic grouping have been described [3-5]. However, there is practically no information in the literature on the synthesis of codlemone through intermediate enynes. There is a report on a nonstereospecific synthesis of dodeca-8E,10E-dienol by the cis-hydrogenation of dodec-8E-en-10-yn-1-ol with the subsequent isomerization of the 8E,10Z-isomer into dodeca-8E,10E-dien-1-ol by heating with thiophenol [6]. Comparatively recently, a method for synthesizing dienes by the stereospecific trans-reduction of conjugated enynes by $LiAlH_4$ in the diglyme/THF system has been reported [7]. We have attempted to use this method for the direct trans-reduction of the triple bond of dodec-8-en-10-yn-1-ol (II), which was obtained in the form of a mixture of the 8E and 8Z isomers in a ratio of 70:30 by the Wittig reaction from 8-(tetrahydropyran-2-yloxy)octanal [8-THPO-octanal] with a yield of 37%.



The reduction of the enynol (II) with $LiAlH_4$ in the solvent system diglyme/THF at 140°C led, as was shown, to only a low yield (10-15%) of codlemone (I). In the PMR spectrum of the crude mixture, the integral intensity of the vinyl protons was far smaller than that expected, which permitted the assumption that under reaction conditions further reduction of the dienic grouping had taken place. This was also shown by the mass spectrum, which contained, together with a peak having m/z 182 (M^+ of codlemone) a peak of equal intensity with m/z 184. We have previously observed similar "overreduction" in the case of β-isopropenylacetylenic alcohols [8].

In order to improve the selectivity of the hydrogenation of the enynol (II), it appeared desirable to introduce into the molecule of the latter close to the triple bond a hydroxy group ensuring regio- and trans-stereoselective reduction [9] and then to carry out deoxygenation.

The total synthesis of codlemone with the use of such an approach is shown in Scheme 2. The enynation of 8-THPO-octanal with triphenyl(3-trimethylsilyprop-2-ynylidene)phosphorane led with 68% yield to the enyne (III) containing 87% of the E isomer. The ratio of E and Z isomers was determined by GLC methods on a capillary column with HP-5 and by a PMR comparison

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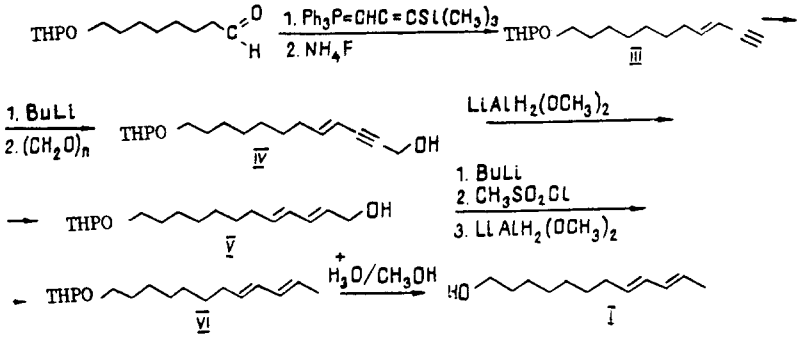
of the integral intensities of the acetylenic protons, which appeared in the E isomer in the form of a doublet of doublets at 2.75 ppm, and in the Z isomer as a broadened doublet at 3.08 ppm.



It must be mentioned that the stereoselectivity of the Wittig reaction in the case of 8-THPO-octanol was somewhat lower than in a number of examples described in the literature [10-13]. However, the possibility of isolating pure codlemone in the last stage of recrystallization from pentane [4] makes the use of the enyne (III) with 87% isomeric purity in the final stage of the synthesis by Scheme 2 acceptable. The hydroxymethylation of enyne (III) was performed with 73% yield by the action of paraformaldehyde on the intermediate lithium acetylenide.

For the trans-reduction of the enynol (IV) we used lithium dihydrodimethoxyaluminate, obtained in situ from $LiAlH_4$ and CH_3OH in THF. The yield of the dienol (V), purified by column chromatography, was 90%. The employment of $LiAlH_4$, which has found use in the synthesis of some pheromones by analogous schemes [14-16], is less desirable in this case in view of the formation of by-products and a fall in the yield of the desired dienol (V).

In the ^1H NMR spectrum of the dienol (V), the vinyl protons of the main isomer interacted with vicinal constants $^3J_{2,3}$ and $^3J_{4,5}$ of 14.8 Hz, showing the E configuration of both double bonds. It is characteristic that the H-3 signal of the 2E,4E-dienol (V) appeared in a stronger field (6.19 ppm) than the analogous signal of the minor 2E,4Z-isomer (6.60 ppm) [17]. Analysis of the mixture with the aid of GLC in a capillary column showed that the ratio of the 2E,4E- and 2E,4Z-dienols was 87:13.

It must be mentioned that the synthesis of the 2E,4E-dienol (V) by the reduction of the corresponding ester and the production of codlemone through an intermediate mesylate has been described in the literature [18]. In view of the instability of the mesylate, we carried out its reduction without isolation – by the action of lithium dihydrodimethoxyaluminate. In this case, together with the cleavage of the C–O bond, the partial (15%) reductive saponification of the mesylate [19] took place with regeneration of the initial dienol (V). The yield of the deoxygenation product (VI) calculated to the dienol that had reacted was 60%. The ratio of the 2E,4E and 2E,4Z isomers of the diene (VI) was approximately the same (86:14) as in the dienol (V), as was shown by GLC results and ^1H NMR spectra (signals of H-6 at 2.07 ppm in the 2E,4E-diene and 2.20 cm in the 2E,4Z-diene). Acid hydrolysis of these dienes led to dodeca-8,10-diene-1-ol containing 86% of the 8E,10E-isomer (I) with a yield of 90%. The overall yield of codlemone was 23%, calculated on the initial aldehyde. Pure codlemone (mp 28-29°C) was obtained by low-temperature crystallization from pentane.

EXPERIMENTAL

The ^1H NMR spectra of compounds (II-IV) were measured on a Tesla BS-497 instrument with a working frequency of 100 MHz. The ^1H and ^{13}C NMR spectra of the other compounds were measured on a Varian VXR-300 instrument with a working frequency of 300 MHz at 28°C in CCl_4, $CDCl_3$, and C_6D_6. The chemical shifts are expressed on the δ scale relative to TMS. The accuracy of the measurement was ±1.5 Hz for ^{13}C and ±0.15 Hz for ^1H. Mass spectra were obtained on a MKh-1320 instrument with the direct introduction of the sample into the ionization region at a temperature of 70°C. The GLC of compounds (II) and (VI) was conducted on a LKhM-80 instrument with a 3 mm × 2 m column containing as support Chromaton N-Super (0.125-0.160 mm) PMCS, impregnated with 5% of XE-60, the carrier gas being helium at a rate

of flow of 40 ml/min. The GLC of compounds (I), (III), (V), and (VI was carried out on a Hewlett-Packard HP-5890 instrument using a 0.3 mm × 25 m glass capillary column with the liquid phase HP-5, and the carrier gas nitrogen at a rate of 3 ml/min. Column chromatography was conducted on silica gel L 40/100 μm (Czechoslovakia), and TLC on Silufol UV-254 plates (Czechoslovakia) with detection of the spots by iodine vapor or a solution of $KMnO_4$. The melting point of the codlemone was determined on a Boëtius stage.

The 8-THPO-octanal [20], but-2-ynyltriphenylphosphonium bromide [21], and the triphenyl(3-trimethylsilylprop-2-ynyl)phosphonium bromide [10] were obtained by known methods.

Dodec-8-en-10-yn-1-ol (II). In an atmosphere of N_2 at −78°C, 1.54 ml of a 2.02 M solution of C_4H_9Li (3.4 mmole) in pentane was added to a suspension of 1224 mg (3.1 mmole) of but-2-ynyltriphenylphosphonium bromide in 13 ml of absolute THF. The resulting mixture was stirred at −78°C for 0.5 h, and then 700 mg (3.07 mole) of 8-THPO-octanal in 3.2 ml of absolute THF was added at the same temperature. The mixture was stirred at −70°C for 0.5 h and at −40°C for 0.5 h. After this, it was poured into ice water and extracted with ether–hexane (1:1), and the extract was dried with Na_2SO_4. After column chromatography [with hexane–ether (15:1) as eluent], 300 mg of the THPO derivative of the enynol (II) was isolated in the form of a mixture of the E and Z isomers in a ratio of 70:30 (according to GLC and PMR), R_f 0.15 [hexane–ether (15:1)]. The substance obtained was dissolved in 3.5 ml of CH_3OH, and 15 mg (0.087 mmole) of p-toluenesulfonic acid, 0.35 ml of H_2O, and 4 ml of ether were added. The mixture was boiled for 2 h, and after the addition of 14 mg of K_2CO_3, it was stirred for 10 min, the bulk of the solvent was eliminated, 5 ml of H_2O was added, and extraction was carried out with ether.

After the extract had been dried with Na_2SO_4 and the ether had been driven off, 205 mg (37%) of a mixture of the 2E- and 2Z-enynols (II) in a ratio of 70:30 (according to GLC and ^1H PMR was isolated, R_f 0.21 (hexane–ether (10:3)). ^1H PMR (CCl_4): 1.2-1.5 (10H, m, H-2-H-6), 1.85 [3H, d, $J_{12,9}$ = 2.0 Hz, H-12 (11E)], 1.95 [3H, d, $J_{12,9}$ = 2.0 Hz, H-12 (11Z)], 2.0-2.3 (2H, m, H-7), 3.5 (3H, t, $J_{1,2}$ = 6.5 Hz, H-1), 5.27 (1H, dm, $J_{9,8}$ = 16.0 Hz, H-9), 5.83 (1H, dt, $J_{8,9}$ = 16.0 Hz, $J_{8,7}$ = 7.0 Hz, H-8, 11E), 5.67 (1H, dt, $J_{8,9}$ = 11.0 Hz, $J_{8,7}$ = 7.0 Hz, H-8, 11Z). Found, %: C 79.72, H 11.02. $C_{12}H_{20}O$. Calculated, %: C 80.00, H 11.11.

Reduction of the Enynol (II). A mixture of 98.8 mg (2.6 mmole) of $LiAlH_4$, 0.64 ml of THF, and 3.6 ml of diglyme was heated in an atmosphere of argon, and the fraction boiling up to 140°C was distilled off. Then a solution of 205.2 mg (1.14 mmole) of the enynol (II) in 1 ml of diglyme was added dropwise at 0 to −10°C, and the mixture was heated at 140°C for 2 h (the end of the reaction was determined by GLC). The mixture was cooled to 0°C and, after the addition of 0.1 ml of H_2O, 0.1 ml of 15% NaOH solution, and 0.3 ml of H_2O, it was stirred for 20 min and was filtered. The filtrate was extracted with ether, the extract was dried with Na_2SO_4, and after the solvent had been driven off the crude product was chromatographed on a column. This led to the isolation of 200 mg of a substance with R_f 0.44 [ether–petroleum ether (1:1)] in the PMR spectrum (CCl_4) of which the ratio of the integral intensities of the vinyl protons in the 5.0-6.3 ppm and of the $C\underline{H}_2$-OH group at 3.5 ppm was 1:1. The mass spectrum of the product contained in addition to a peak with m/z 182 (M^+ of codlemone) a peak with m/z 184. Recrystallization from pentane at −50°C led to the isolation of 20.7 mg (10%) of codlemone with mp 29°C.

11-THPO-Undec-3-en-1-yne (III). In an atmosphere of nitrogen at −78°C, 2.66 ml of a 2.02 M solution of C_4H_9Li in pentane (5.37 mmole) was added to a suspension of 2400 mg (5.3 mmole) of triphenyl(3-trimethylsilylprop-2-ynyl)phosphonium bromide in 27 ml of THF. The resulting mixture was stirred at −78°C for 0.5 h, and 1200 mg (5.26 mmole) of 8-THPO-octanal in 10.3 ml THF was added at the same temperature. The mixture was kept at −70°C for 1 h and was stirred at 0°C for 20 min and then at room temperature for 0.5 h. Then it was poured into 100 ml of glacial H_2O and extracted with petroleum–ether (1:1), and the extract was dried with Na_2SO_4. After partial elimination of the solvent, a precipitate of triphenylphosphine oxide deposited, which was filtered off through a short layer of SiO_2. After a second evaporation of the solvent, the residue was dissolved in 10 ml of THF; 20 ml of a saturated solution of NH_4F in DMFA and 2400 mg of NH_4F were added and the mixture was stirred for 16 h (the course of the reaction being followed by TLC). Then it was poured into 40 ml of glacial H_2O and extracted with petroleum ether–diethyl ether (1:1), and the extract was dried with Na_2SO_4. After the elimination of the solvent, the residue (2200 mg) was chromatographed on a column [with ether–hexane (1:20) as eluent].

This led to the isolation of 900 mg (68.34%) of a mixture of the enynes (IIIE) and (IIIZ) in a ratio of 87:13 (according to GLC and PMR), R_f 0.30 [ether–petroleum ether (1:10)]. PMR ($CDCl_3$): 1.05-1.95 (16H, m, H-6-H10, $(CH_2)_3$ in a ring, 2.09 [2H, dt, $J_{5,4} \simeq J_{5,6}$ = 6.3 Hz, H-5, III (E)], 2.30 [2H, dt, $J_{5,4} \simeq J_{5,6}$ = 7.0 Hz, H-5, III(Z)], 2.75 [1H, dd, $J_{1,3}$ = 2.2 Hz, $J_{1,4}$ = 0.8 Hz, H-1, III(E)], 3.08 [1H, d, br., $J_{1,3}$ = 2.2 Hz, H-1, III(Z)], 3.2-4.0 (4H, m, OCH_2 in a ring, H-11), 4.56 (1H, m, OCHO), 5.45 (1H, ddt, $J_{3,4}$ = 16.0 Hz, $J_{3,1}$ = 2.2 Hz, $J_{3,5}$ = 1.6 Hz, H-3), 6.0 [1H, dtd, $J_{4,3}$ = 10.5 Hz, $J_{4,5}$ = 7.6 Hz, $J_{4,1}$ = 0.8 Hz, H-4, III(Z)], 6.23 [1H, dt, $J_{4,3}$ = 16.0 Hz, $J_{4,5}$ = 7.0 Hz, H-4, III(E)]. Found, %: C 76.43, H 13.39. $C_{16}H_{26}O_2$. Calculated, %: C 76.80, H 13.54.

12-THPO-Dodec-4-en-2-yn-1-ol (IV). At −10 to −15°C, 1.9 ml (3.44 mole) of a 2.02 M pentane solution of C_4C_9Li was added to a solution of 860 mg (3.44 mmole) of the enyne (III) in 3.4 ml of absolute ether. The resulting white suspension was stirred at the same temperature for 0.5 h, and then 1.8 ml of absolute THF (200 mg) (4.13 mmole) of paraformaldehyde were added. The reaction mixture was stirred at 20°C for 45 min and then at the boil for 2.5 h. The mixture was poured into ice water and extracted with ether, and the extract was washed with saturated NH_4Cl solution and was dried with $MgSO_4$. After the solvent had been driven off, the residue (900 mg) was chromatographed on a column (with ether–hexane (1:5)-(1:3) as eluent).

The following were isolated: fraction I (248 mg of the initial enyne (III); fraction (II)) 500 mg (73% calculated on the enyne (III) that had reacted) of the enynol (IV) with a ratio of the E and Z isomers of 87:13, R_f 0.41 [ether–hexane (1:2)]. PMR spectrum (CCl_4): 1.1-1.7 (16H, m, $(CH_2)_3$ in a ring, H-7-H-11), 2.01 (2H, m, H-6), 3.2-3.8 (5H, m, OCH_2 in a ring, H-12, OH), 4.22 (2H, m, H-1), 4.5 (1H, m, OCHO), 5.45 (1H, dm, $J_{4,5}$ = 16.0 Hz, H-4), 6.05 (1H, dt, $J_{5,4}$ = 16.0 Hz, $J_{5,6}$ = 6.5 Hz, H-5). Mass spectrum, m/z (%): 280 (M^+, 3), 262(2), 249(5), 101(8), 85(100).

12-THPO-Dodeca-2E,4-dien-1-ol (V). At −10°C, in an atmosphere of nitrogen, 2.4 ml of a 1.25 N ethereal solution of $LiAlH_4$ (3 mmole) was added to a solution of 192 mg (6 mmole) of absolute CH_3OH in 4 ml of absolute THF. The resulting solution was treated with 400 mg (1.43 mmole) of the enynol (IV) and was stirred at room temperature for 2 h (the end of the reaction was detected by TLC). Then the mixture was cooled to −10°C, and 0.12 ml of H_2O, 0.12 ml of a 15% solution of NaOH, and another 0.36 ml of H_2O were added. The precipitate that had deposited was filtered off and was washed with ether (3 × 30 ml), and the ethereal extract was dried with Na_2SO_4. After the ether had been driven off, the residue was chromatographed on a column [with ether–hexane (2:5) as eluent].

This led to the isolation of 363 mg (90%) of a mixture of the 2E,4E- and 2E,4Z-dienols (V) in a ratio of 87:13 (according to GLC and PMR), R_f 0.25 [ether–hexane (2:5)]. PMR of the 2E,4E-dienol (V) (C_6D_6): 1.20-1.60 (16H, m, $(CH_2)_3$ in a ring, H-7-H-11), 1.89 (1H, s, br., OH), 1.98 (2H, dtd, $J_{6,5}$ = 6.9 Hz, $J_{6,7}$ = 6.9 Hz, $J_{6,4}$ = 1.2 Hz, H-6), 3.35-3.8 (4H, m, CH_2O in a ring, H-12), 3.98 (2H, dd, $J_{1,2}$ = 5.7 Hz, $J_{1,3}$ = 1.5 Hz, 1-H), 4.60 (1H, m, OCHO), 5.58 (1H, dtd, $J_{5,4}$ = 14.8 Hz, $J_{5,6}$ = 6.9 Hz, $J_{5,3}$ = 1.0 Hz, H-5), 5.64 (1H, dtd, $J_{2,3}$ = 14.8 Hz, $J_{2,1}$ = 5.7 Hz, $J_{2,4}$ = 1.0 Hz, H-2), 6.03 (1H, ddtd, $J_{4,5}$ = 14.8 Hz, $J_{4,3}$ = 10.4 Hz, $J_{4,6}$ = 1.2 Hz, $J_{4,2}$ = 1.0 Hz, H-4), 6.19 (1H, ddtd, $J_{3,2}$ = 14.8 Hz, $J_{3,4}$ = 10.4 Hz, $J_{3,1}$ = 1.5 Hz, $J_{3,5}$ = 1.0 Hz, H-3).

In addition to those mentioned, there was a characteristic signal at 6.60 ppm (1H, dddt, $J_{3,2}$ = 15.3 Hz, $J_{3,4}$ = 11.1 Hz, $J_{3,1} = J_{3,6}$ = 1.4 Hz) relating to the 2E,4Z-dienol (V). Mass spectrum, m/z (%): 282 (M^+, 2), 264 (2.5), 198 (12), 180 (6), 85 (100).

12-THPO Dodeca-2E,4-diene (VI). In an atmosphere of nitrogen at −40°C, 0.94 ml (1.5 mole) of a 1.6 M ethereal solution of C_4H_9Li was added to a solution of 400 mg (1.42 mmole) of the dienol (V) in 6 ml of absolute ether. The mixture was stirred at the same temperature for 15 min, and then a solution of 250 mg (2.18 mmole) of methanesulfonyl chloride in 4 ml of ether was added. The resulting mixture was kept for 1 h, and then, at −10°C, 3 mmole of a solution of $LiAlH_2(OCH_3)_2$ (2.4 ml of a 1.25 M solution of $LiAlH_4$ in ether, 0.23 ml of CH_3OH, and 4 ml of THF) was added. The reaction mixture was stirred at −10°C for 1 h and was left overnight at 0°C. It was then treated at −10°C with 0.12 ml of H_2O, 0.12 ml of 15% NaOH solution, and another 0.36 ml of H_2O. The resulting precipitate was filtered off and washed with ether, and the ethereal extracts were dried with Na_2SO_4. After the solvent had been driven off, the residue (400 mg) was chromatographed on a column [with hexane–ether (40:1) as eluent].

This led to the isolation of 188.2 mg (60%) of the diene (VI) [calculated on the dienol (V) that had reacted], R_f 0.30 [hexane–ether (20:1)], PMR (C_6D_6): 1.2-1.9 (16H, m, $(CH_2)_3$ in a ring, H-7-H-11), 1.68 (3H, dm, $J_{1,2}$ = 6.6 Hz, H-1), 2.07 [1H, dt, $J_{6,5} = J_{6,7}$ = 6.7 Hz, H-6, 2(E), 4(E)-VI], 2.20 [1H, dt, $J_{6,5} = J_{6,7}$ = 6.7 Hz, H-6, 2(E), 4(Z)-VI], 3.35-3.53 (2H, m, CH_2O in a ring), 3.9 (2H, m, H-12), 4.67 (1H, t, J = 3.5 Hz, OCHO), 5.5-5.7 (2H, m, H-2, H-5), 6.13 (2H, m, H-3, H-4), 6.48 [1H, ddq, $J_{3,2}$ = 15.1 Hz, $J_{3,4}$ = 10.8 Hz, $J_{3,1}$ = 1.3 Hz, H-3 2(E), 4(Z)-VI]. ^{13}C NMR (C_6D_6): 18.1, 19.7, 26.0, 26.7, 29.5, 29.7, 30.2, 30.3, 31.1, 32.9, 61.6, 67.5, 98.6, 126.5, 131.1, 132.1, 132.5. In addition, 60 mg of the initial dienol (V) was isolated.

Dodeca-8E,10E-dien-1-ol (I). A mixture of 90 mg (0.34 mmole) of (VI), 4.5 mg of p-toluenesulfonic acid, 1 ml of CH_3OH, 0.1 ml of H_2O and 1.2 ml of ether was boiled for 2 h, and then the solvent was driven off and, after the usual working up, the mixture was purified on a column [with hexane–ether (10:1) as eluent]. This led to the isolation of 81.9 mg (90%) of the dienol (I) the ratio of E,E- and E,Z-(I) being 86:14. PMR (C_6D_6): 1.2-1.5 (m, H-2-H-6), 1.65 [d, $J_{12,11}$ = 6.0 Hz, H-12 8(E), 10(E)-I], 1.68 [dm, $J_{12,11}$ = 6.0 Hz, H-12 8(Z), 10(E)-I], 2.06 [dt, $J_{7,6} = J_{7,8}$ = 6.6 Hz, H-7 8(E), 10(E)-I], 2.20 [dt, $J_{7,6} = J_{7,8}$ = 7.0 Hz, H-7 8(Z), 10(E)-1], 3.42 (t, $J_{1,2}$ = 6.4 Hz, H-1), 5.5-5.7 (m, H-8, H-11), 6.12 (m, H-9, H-10), 6.50 (ddq, $J_{10,11}$ = 15.0 Hz, $J_{10,9}$ = 10.8 Hz, $J_{10,12}$ = 1.3 Hz, H-10). ^{13}C NMR (C_6D_6): 18.1 (C-12), 26.1, 29.5, 29.7, 29.8, 32.9, 33.2 (C-2-C-7), 62.7 (C-1), 126.5, 131.1, 132.0, 132.5, (C-8-C-11). Mass spectrum, m/z: 182.

Recrystallization from pentane at 0 to −5°C yielded 40.5 mg of dodeca-8E,10E-dien-1-ol (I) with mp 29-30°C [4]. PMR ($CDCl_3$): 1.25-1.40 (8H, m, H-3, H-4, H-5, H-6), 1.475 (1H, m, OH), 1.49-1.60 (2H, m, H-2), 1.71 (3H, d, $J_{12,11}$ = 6.75 Hz, H-12), 1.98-2.07 (2H, dt, $J_{7,6} = J_{7,8}$ = 6.55 Hz, H-7), 3.61 (2H, t, $J_{1,2}$ = 6.5 Hz, H-1), 5.92-6.04 (2H, m, H-9, H-10), 5.54 (1H, dtm, $J_{8,9}$ = 14.4 Hz, $J_{8,7}$ = 6.8 Hz, H-8), 5.57 (1H, dqm, $J_{11,10}$ = 14.3 Hz, $J_{11,12}$ = 6.7 Hz, H-11), 5.98 (1H, m, H-9), 6.01 (1H, m, H-10). ^{13}C NMR ($CDCl_3$): 18.92 (C-12), 26.60, 30.04, 30.19, 30.27, 33.43, 33.69 (C-7-C-2), 63.89 (C-1), 127.49, 131.06, 132.49, 132.85, (C-8-C-11) [23].

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^{13}C NMR SPECTRA OF BIOLOGICALLY ACTIVE COMPOUNDS

IX. * DIASTEREOMERS OF (±)-16-ARYLOXY-11-DEOXYPROSTAGLANDINS OF THE E_1 AND F_1 SERIES

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The diastereomeric effects on the ^{13}C NMR chemical shifts of thirteen epimeric pairs of 16-aryloxy-11-deoxyprostaglandins of the E_1 and F_1 series caused by the change in the configuration of the 15-hydroxy group, which are differential parameters for assigning epimers to the 15α- and 15β-stereochemical series, have been determined.

We have previously published details of the ^{13}C NMR spectroscopy of α-homo and ω-aryloxy analogs of the 11-deoxyprostaglandins E_1 [2, 3]. As differential parameters for determining the epimeric prostaglandins (PGs) and other compounds having two and more chiral centers, we have proposed the diastereomeric effects on the ^{13}C NMR chemical shifts (CSs) determined by the difference in the screening of the characteristic carbon atoms:

$$\Delta_{diasCi} = \delta_{CiA} - \delta_{CiB}.$$

In the present paper we consider the ^{13}C NMR spectra of ten new 16-aryloxy-11-deoxy-PGE_1's (I-X) and three pairs of 16-aryloxy-11-deoxy-PGF_1's (XI-XIII) epimeric at the C-15 hydroxy group and the observed values of the diastereomeric effects in the chemical series discussed (see scheme on following page).

The racemic compounds (I-XIII) each have three chiral centers (at C-8, C-12, and C-15), which makes the existence of four diastereomers probable. Thanks to the fact that in the course of chemical synthesis [4] the precursors of the prostanoids had the correct stereochemistry at C-8 and C-12 and only the oxo function at C-15 was subjected to transformation, only pairs of epimers at the C-15 alcohol groups were obtained, each of which was isolated in the individual form with the aid of column chromatography on silica gel and was characterized spectrally (Table 1). In the spectra of the individual compounds, all the characteristic signals corresponding to the prostanoid structure were detected. In the weakest field there were the signals of the 9-keto and the carboxy groups. The carbon atoms of the double bond and of the aromatic ring resonated in the 114-158 ppm region. In contrast to the values given in]5], we found that for compound (I) the doublet signal at 70.7 ppm corresponded to C-15, and the triplet signal at 71.8 ppm to C-16. Two doublets at 54.5 and 45.6 ppm characterized the C-8 and C-12 atoms. The other triplet signals in the strong-field region related to the methylene groups of the α-chain and of the cyclopentane ring.

The differences in the spectra of the two stereoisomers were very slight and exceeded the error of the measurements (±0.03 ppm) only for a few of the carbon atoms – C-3–C-6, C-8, and C-12–C-15. These diastereomeric effects were not connected with the change in

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