UNSATURATED KETONES AND MACROCYCLIC LACTONES

COMMUNICATION 12. SYNTHESIS OF MACROCYCLIC β-HYDROXY LACTONES

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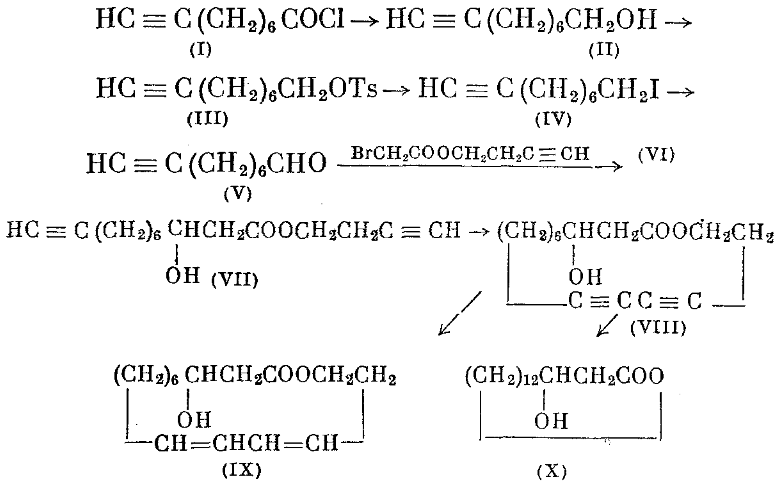
Most of the macrolidic antibiotics that have been studied contain a glycosidically substituted hydroxy group in the β-position to the lactone grouping [1], which is evidently determined by the mechanism of the biosynthesis of these substances, which goes in accordance with the acetate and propionate rules. The synthesis of polyunsaturated β-hydroxy lactones is therefore an important stage in the synthesis of macrolidic antibiotics. On the other hand, microbiological tests on the unsaturated macrocyclic lactones that we have synthesized [2-4] showed that their activity falls sharply with reduction of the solubility in water. In view of this it seemed desirable to increase the polarity of the macrolidic molecule by the introduction of hydroxy groups. For this purpose we synthesized the unsaturated hydroxy lactones (VIII) and (IX) as follows:



8-Nonynoyl chloride (I) [2] was reduced with lithium aluminum hydride to 8-nonyn-1-ol (II), whose tosylate (III) gave 9-iodo-1-nonyne (IV) when boiled with sodium iodide in butanone. By treating the latter with trimethylamine oxide [5] and hydrolyzing the product we obtained 8-nonynal (V). The condensation of this aldehyde with 3-butynyl bromoacetate (VI) led to 3-butynyl 3-hydroxy-10-undecynoate (VII), which on oxidative condensation under high-dilution conditions by the procedure which we developed earlier [2, 3] gave 3-hydroxy-10,12-pentadecadiynolide [3,15-dihydroxy-10,12-pentadecadiynoic acid ξ-lactone] (VIII). By the hydrogenation of the diacetylenic hydroxy lactone (VIII) over Lindlar's catalyst [6] we obtained 3-hydroxy-10,12-pentadecadienolide (IX), and the hydrogenation of (VIII) over platinum black led to 3-hydroxypentadecanolide (X). The structure of the diacetylenic hydroxy lactone (VIII), was confirmed by the presence of a triplet in the ultraviolet spectrum characteristic for 1,3-diynes (cf. [7]), and the structure of the dienic hydroxy lactone (IX) – by the presence of an intense maximum at 234 mμ.

EXPERIMENTAL

8-Nonyn-1-ol (II). A solution of 15.2 g of 8-nonynoyl chloride (I) in 10 ml of ether was added over a period of 20 min at 5-10° to a solution of 3.4 g of lithium aluminum hydride in 200 ml of ether, the mixture was stirred further for 30 min without cooling, and 100 ml of 2 N sulfuric acid was added dropwise. The upper layer was separated, and the lower was extracted with three 50-ml portions of ether. The combined extracts were washed with sodium carbonate solution and with water, and they were dried with magnesium sulfate. Solvent was driven off, and the residue was vacuum-distilled. We obtained 11.3 g (92%) of 8-nonyn-1-ol (II); b.p. 68-69° (0.5 mm); n_D^{25} 1.4531; d_4^{25} 0.8791. Found: C 77.08; H 11.46%; MR 43.12. $C_9H_{16}O$. Calculated: C 77.09; H 11.50%; MR 43.22. The 3,5-dinitrobenzoate of 8-nonyn-1-ol had m.p. 45-46° (from alcohol). Found: N 8.53%. $C_{16}H_{18}O_6N_2$. Calculated: N 8.38%.

8-Nonyn-1-ol Tosylate (III). 11.3 g of 8-nonyn-1-ol was added with stirring to a cooled mixture of 19 g of p-toluenesulfonyl chloride and 9.5 ml of pyridine in such a way that the temperature did not rise above 25°. The mixture was stirred further with cooling for 15 min and then left at room temperature for 20 h; 10 ml of water was then added dropwise. 100 ml of ether was added to the mixture, and the ethereal solution was washed with 5% sulfuric acid, with water, and with sodium bicarbonate solution; it was dried with magnesium sulfate. Solvent was driven off, and the residue was dried at 100° (0.3 mm). We obtained 22.3 g (94%) of 8-nonyn-1-ol tosylate as a thick colorless oil, which slowly crystallized on standing. After two crystallizations from methanol we obtained 8-nonyn-1-ol tosylate, m.p. 26-27°. Found: C 65.37; H 7.63 S; 10.76%. $C_{16}H_{22}O_3S$. Calculated: C 65.27; H 7.53; S 10.89.

8-Nonynal (V). A mixture of 25.9 g of 8-nonyn-1-ol tosylate (III), 40 g of sodium iodide, and 500 ml of dry butanone was boiled for 17 h. The precipitated sodium tosylate (15.2 g; 97%) was filtered off, and solvent was driven off. 250 ml of petroleum ether was added to the residue, and the solution was washed with 5% sodium thiosulfate solution and with water, and it was dried with magnesium sulfate. Solvent was driven off, and we obtained 21.2 g of 9-iodo-1-nonyne, which was used in the next synthesis without purification.

Anhydrous trimethylamine oxide prepared from 27 g of the dihydrate by the azeotropic distillation of water with m-xylene was dissolved in 70 ml of chloroform and 30 ml of dimethylformamide. The solution was warmed to 70°, and in the course of 30 min a solution of the 9-iodo-1-nonyne (IV) in 20 ml of dimethylformamide was added dropwise. The mixture was stirred further for 30 min at 70°, and cooled; 150 ml of petroleum ether and 100 ml of 5% HCl were added. The upper layer was separated, washed with water and sodium bicarbonate solution, and dried with magnesium sulfate. Solvent was driven off, and the residue was vacuum-distilled. We isolated 5.73 g (49%, based on 8-nonyn-1-ol tosylate) of 8-nonynal (V); b.p. 101-102° (20 mm); n_D^{20} 1.4499; d_4^{20} 0.8951; found MR 41.48; calculated MR 41.61. Its 2,4-dinitrophenylhydrazone had m.p. 82-83° (from alcohol). Found: C 56.54; H 5.58%. $C_{15}H_{18}O_4N_4$. Calculated: C 56.59; H 5.70%.

3-Butynyl Bromoacetate (VI). 24.5 g of bromoacetyl bromide was added with cooling to a solution of 8.4 g of 3-butyn-1-ol [8] and 9.5 ml of pyridine in 200 ml of ether at such a rate that the temperature did not rise above 20°. The mixture was stirred further for 1 h, washed with 5% hydrochloric acid, water, and sodium bicarbonate solution, and dried with magnesium sulfate. Solvent was driven off, and vacuum distillation of the residue gave 18.5 g (81%) of 3-butynyl bromoacetate (VI); b.p. 111° (28 mm); n_D^{20} 1.4863; d_4^{20} 1.4795. Found: C 37.82; H 3.74; Br 42.10%; MR 37.09. $C_6H_7O_2Br$. Calculated: C 37.72; H 3.70; Br 41.83%; MR 37.26.

3-Butynyl 3-Hydroxy-10-undecynoate (VII). 3.25 g of zinc in 10 ml of benzene was heated to 80°, and a solution of 5.65 g of 8-nonynal (V) and 9.5 g of 3-butynyl bromoacetate (VI) in 20 ml of benzene was added in the course of 20 min; the mixture boiled gently. The mixture was then boiled further for 2 h and cooled. 120 ml of iced 5% hydrochloric acid and 50 ml of ether were added, and the mixture was stirred until all the solid present had dissolved. The upper layer was separated, and the lower was extracted with two 50-ml portions of ether; the combined extracts were washed with water, with sodium bicarbonate solution, and again with water; they were dried with magnesium sulfate. The residue remaining after the removal of solvent was mixed with 20 g of alumina of activity IV and transferred to the upper part of a column (38 · 280 mm) of alumina (activity IV). Elution was with 1500 ml of petroleum ether (b.p. 40-60°) and then 800 ml of a 1 : 1 mixture of petroleum ether and diethyl ether. This gave 4.6 g (45%) of 3-butynyl 3-hydroxy-10-undecynoate (VII) as a thick colorless oil; b.p. 130° (0.3 mm); n_D^{20} 1.4718; d_4^{20} 0.9926. Found: C 71.84; H 8.85%; MR 70.59. $C_{15}H_{22}O_3$. Calculated: C 71.97; H 8.86%; MR 70.52. The substance did not form a 3,5-dinitrobenzoate or naphthylurethan.

3-Hydroxy-10,12-pentadecadiynolide (VIII). A solution of 4.2 g of 3-butynyl 3-hydroxy-10-undecynoate (VII) in 50 ml of ether was added through a high-dilution head [9] over a period of 3 h with stirring to a boiling solution (57-58°) of 10 g of anhydrous copper acetate in 2 liters of a 3 : 2 mixture of pyridine and ether. The reaction mixture was cooled and filtered through 500 g of alumina of activity II, which was then washed with 1 liter of ether. The filtrate was vacuum-evaporated down to 60-70 ml, diluted with 300 ml of ether, and poured into 1 liter of iced

1 N HCl. The ether layer was separated, and the aqueous layer was extracted with four 150-ml portions of ether. The combined extracts were washed with water and dried with magnesium sulfate. Solvent was driven off; the residue was dissolved in ether, and the solution was mixed with 20 g of alumina (activity IV); ether was vacuum-distilled off, and the residue was placed in the upper part of a column (35 · 400 mm) of alumina of activity IV. The column was developed with 500 ml of petroleum ether (b.p. 40-60°), and then gradient elution was carried out with the system petroleum ether-diethyl ether (1.5 liters + 1.5 liters) with collection of the eluate in 100-ml fractions. The compositions of the fractions were checked with the aid of thin-layer chromatography on alumina of activity II in the system benzene—dioxane (9 : 1). To detect the spots on the plates we used a 1% solution of potassium permanganate in 2 N H_2SO_4. Fractions 18-21 contained 2.36 g (56%) of 3-hydroxy-10, 12-pentadecadiynolide, which was obtained as colorless crystals, which, after four crystallizations from a 4 : 1 mixture of hexane and ether, melted at 66-67°. Infrared spectrum (in mineral oil): ν_{max} 1734 (s), 2266 (w), 3410 (m) cm^{-1}. Ultraviolet spectrum: λ_{max} 226, 240, 254 mμ (ε 365, 334, 235). Found: C 72.45; H 8.01%. $C_{15}H_{20}O_3$. Calculated: C 72.55; H 8.12%.

3-Hydroxy-10,12-pentadecadienolide (IX). 0.237 g of 3-hydroxy-10,12-pentadecadiynolide (VIII) was hydrogenated in 10 ml of ethyl acetate over 20 mg of Lindlar's catalyst [6] poisoned with 10 mg of quinoline. In the course of 90 min 48.8 ml of hydrogen at 745 mm and 19° was absorbed (105% of the theoretical amount), and the rate of absorption had then fallen to one-eighth of its original value. The catalyst was filtered off and washed with ether, and the filtrate was washed with three 10-ml portions of 1% hydrochloric acid and water; it was dried with magnesium sulfate. Solvent was driven off, and we obtained 0.230 g of a thick colorless oil, which slowly crystallized on standing; m.p. 58-59° (from a 4 : 1 mixture of hexane and ether). Infrared spectrum (without solvent): ν_{max} 719 (m), 1732 (s), 3405 (m) cm^{-1}. Ultraviolet spectrum: λ_{max} 234 mμ (ε 18,400). Found: C 71.49; H 9.62%. $C_{15}H_{24}O_3$. Calculated: C 71.39; H 9.59%.

3-Hydroxypentadecanolide (X). In the hydrogenation of 0.23 g of 3-hydroxy-10,12-pentadecadiynolide (VIII) in ethanol over a platinum catalyst,89 ml of hydrogen (19°, 750 mm) was absorbed. The catalyst was filtered off and washed with alcohol. Solvent was driven off, and vacuum distillation of the residue gave 3-hydroxypentadecanolide (X) as a colorless oil, which crystallized on standing; m.p. 86-87.5° (from a 4 : 1 mixture of hexane and ether). Infrared spectrum(in mineral oil): ν_{max} 1738 (s), 3460(s) cm^{-1}. Found: C 70.20; H 11.16%; mol. wt. 266 (Rast method). $C_{15}H_{28}O_3$. Calculated: C 70.27; H 11.01%; mol. wt. 256.4.

SUMMARY

A sixteen-membered diacetylenic β-hydroxy lactone was synthesized by the oxidative intramolecular condensation of acetylenes, and by its reduction the corresponding dienic and saturated β-hydroxy lactones were prepared.

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