ELECTROCHEMICAL REDUCTION OF 16α,17α-EPOXYPREGN-5-EN-3β-OL-20-ONE

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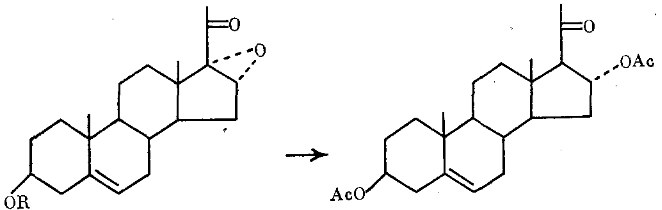
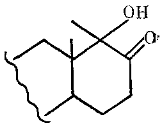
The previously described synthesis [1] of the natural phytosteroid shiogralactone employs the 3,16-diacetate of pregn-5-en-3β,16α-diol-20-one (I), which is usually obtained by the reduction of the corresponding 16α,17α-epoxide by Cr^{2+} salts [2]. This reduction involves certain difficulties and gives a yield of 50%.

Recently it was reported [3] that 16α,17α-epoxypregn-5-en-3β-ol-20-one (II) can be reduced electrochemically, but the yield of (I) amounted to only 30%. We studied a number of versions of this reaction in order to increase the yield of (I) with variation in the nature of the indifferent electrolyte and with the use of various additives. Simple reproduction of the procedure in [3] led to the production of (I) with yields of up to 40%. Replacement of the 3-hydroxy derivative (II) by the 3-acetate under the same conditions led to an increase in the yield of (I) to 60%. The use of tetramethylammonium bromide as indifferent electrolyte instead of tetramethylammonium iodide increased the yield of (I) to 83.5%, and the addition of a strong proton donor (HBr) to the electrolysis solution led to an almost quantitative yield. On the other hand, replacement of the solvent, e.g., ethanol by DMFA, greatly reduced the regioselectivity of the reduction, leading to a mixture of (I) and (III). An attempt to realize the indirect reduction with an electron transfer agent [4], for which purpose we used biphenyl, also led to the formation of this mixture. Compound (III) evidently represents a D-homosteroid, the structure of which was confirmed by reduction with sodium borohydride and subsequent oxidation with periodic acid. The structure of (I) was confirmed by comparison with an authentic sample, obtained by the method in [2]. The results from investigation of the dependence of the yield of the reaction products on the conditions are given in Tables 1 and 2.



(II) (I)



(III)

EXPERIMENTAL

The melting points were determined on a Kofler block. The IR spectrum was measured on a UR-20 spectrometer for solutions in chloroform. The mass spectra were recorded on a Varian MAT CH-6 mass spectrometer with direct injection of the samples into the ion source with an ionizing potential of 70 eV. The PMR spectra were recorded on an HA-100 spectrometer with TMS as internal standard. For TLC we used silica gel 5/40 μ (+13% gypsum). The mixtures were separated on columns with silica gel 40/100 μ in an atmosphere of nitrogen.

The electrolysis cell was a glass cylindrical vessel with a total volume of ~ 60 cm^3 with a flat bottom covered with mercury, which served as cathode (area ~ 30 cm^2). A narrower and shorter beaker, which served as cathode compartment, was inserted into the electrolysis cell at the top through a ground-glass joint; the porous glass plate at the bottom of the beaker served as diaphragm. The anode was a platinum gauze. The cathode and anode compartments were filled with the same electrolyte, and the substance being reduced was placed in the cathode compartment. The reference electrode was an external aqueous saturated calomel electrode. The electrolysis was realized at ~ 20°C in a three-electrode circuit with a P-5848 potentiostat at E = −2.1 V (s.c.e.) in an atmosphere of nitrogen. The process took 2-3 h, i.e., until the reduction current had

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TABLE 1. Dependence of the Yield of the Electrolysis Products on the Conditions

Structure of the initial steroid	Electrolysis conditions			Yield, %	
	solvent	indifferent salt	additions	(I)	(III)
3-Hydroxy-16α, 17α-epoxide	75% aq. EtOH	TBAI *	–	40	–
3-Acetoxy-16α,17α-epoxide	Same	TBAI	–	60	–
Same	»	TMABr	–	83,5	–
»	»	TMABr	HBr	96	–
»	DMFA 10% H_2O	TBAPC	0.1 g BP	–	53

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* TBAI = tetrabutylammonium iodide; TMABr = tetramethylammonium bromide; TBAPC = tetrabutylammonium perchlorate; BP = biphenyl.

TABLE 2. Dependence of the Ratio of the Final Electrolysis Products on the Solvent and on the Amount of Biphenyl (BP)

Structure of initial steroid	Electrolysis conditions			Ratio of reaction products according to mass spectra	
	solvent	indifferent salt	addition of BP, g	(I)	(III)
3-Acetoxy-16α, 17α-epoxide	DMFA+10% H_2O	TBAPC	0,1	1	6
Same	Same	Same	0,05	0,5	10
»	DMFA	»	0,1	1	1

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* According to the intensity ratio of the peaks, corresponding to $[M - 60]^+$.

decreased to the level of the background current, which was recorded before (II) was placed in the electrolysis cell. The volume of the catholyte was ~ 30 cm^3, and the amount of the substance being reduced was 0.3 to 0.5 g. After separation from the mercury the reaction mixture was treated in the following way. The solvents were evaporated. The residue was diluted with water and extracted with EA, and the extract was washed with water, dried with magnesium sulfate, and evaporated. The residue was acetylated with acetic anhydride in pyridine. After the standard treatment and chromatographic separation of the mixture on a column in a 3:1 mixture of heptane and ether we obtained compounds (I) and (III).

Pregn-5-en-3β,16α-diol-20-one 3,16-Diacetate (I). mp 174-177°C (from methanol) [2]. IR spectrum (ν, cm^{-1}): 1720, 1250. Mass spectrum (m/z): 356 $[M - 60]^+$, 296 $[M - 2 \times 60]^+$, 281 $(M - 2 \times 60-15)^+$, 253. PMR spectra (δ, ppm): 0.65 s (3H, 18-CH_3), 1.0 s (3H, 19-CH_3), 1.97, 2.0 (6H acetate), 2.13 s (3H, $COCH_3$), 4.6 m (1H, 3-H), 5.33 m (2H, 6-H, 16-H) in deuterochloroform.

D-Homo Derivative (III). mp 138-140°C (from methanol). IR spectrum (ν, cm^{-1}): 3615, 1725, 1700, 1250. Mass spectrum (m/z): 314 $[M - 60]^+$, 296 $[M - 60 - 18]^+$, 281 $[M - 60 - 18 - 15]^+$, 253. PMR spectrum (δ, ppm): 0.58 s (3H, 18-CH_3), 0.92 s (3H, 19-CH_3), 1.98 s (3H, acetate), 4.77-5.2 m (2H, 3-H, 6-H) in pyridine. To a solution of 30 mg of (III) in 6 ml of DMFA we added a solution of 30 mg of sodium borohydride in 1 ml of water. After 18 h the mixture was diluted with water, neutralized with 2% hydrochloric acid, and extracted with EA. The extract was washed with water, dried with magnesium sulfate, and evaporated. The product with R_f 0.25 (5:1 ether–hexane) was oxidized without further purification with an excess of periodic acid in ether (4 days, 20°C). After the usual treatment the isolated unoxidized product with R_f 0.25 was more polar than the acetate of dehydroepiandrosterone (R_f 0.78 in the same system).

CONCLUSIONS

A method was developed for the quantitative production of 3,16-diacetoxypregnenolone by the electrochemical reduction of 16,17α-epoxypregnenolone in aqueous ethanol in the presence of tetramethylammonium bromide and catalytic amounts of hydrobromic acid.

LITERATURE CITED

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REACTION OF BENZIMIDAZOLE-2-THIONE WITH CYANOACETYLENE ALCOHOLS

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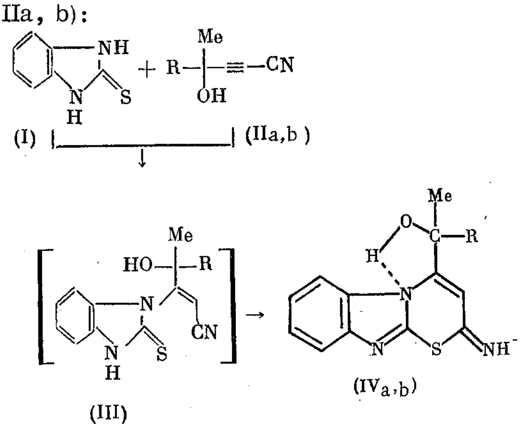
We have described the synthesis of 1,3-thiazines and acrylonitrile derivatives based on azolethiones and phenylcyanoacetylene before [1, 2]. It is also known [3] that in reaction with cyanoacetylene alcohols imidazole forms hydroxyl-containing acrylonitrile derivatives, which are easily converted into dihydrofuran compounds. In the present work we investigated for the first time the reaction of benzimidazole-2-thione (I) with tertiary cyanoacetylene alcohols (IIa, b):



where R = Me (a), Et (b).

The reactions of the thione (I) with the alcohols (IIa, b) in the presence of 5-10% potassium hydroxide in dioxane led to the formation of 2-imino-4-(1-hydroxy-1-methylethyl)benzimidazo[2,3-c]-1,3-thiazine (IVa) and 2-imino-4-(1-hydroxy-1-methylpropyl)benzimidazo[2,3-c]-1,3-thiazine (IVb); the products from heterocyclization with the dihydrofuran substituent were not found. Evidently, the acrylonitrile (III) formed at the first stage has the Z configuration, which assists the instantaneous intramolecular cyclization of the nitrile group at the S atom to form the 1,3-thiazine ring. The direction of cyclization is confirmed by the appearance in the IR spectra of compounds (IVa, b) of absorption bands in the region of 3596 cm^{-1}, which indicate the presence of a hydroxyl group.

The yields of the 1,3-thiazine imines (IVa, b) were not greater than 38-55%. (The remainder consisted of resinous products.) This is evidently due to the ability of the tertiary cyanoacetylene alcohols to be cleaved by the action of alkalis into the corresponding ketones and cyanoacetylene [4].

The obtained 1,3-thiazine imines (IVa, b) were white crystalline substances soluble in the majority of organic solvents. Unlike the 4-phenyl-substituted 1,3-thiazines which we described in [1], they exhibit increased stability toward alkalis and hardly undergo any changes even in the presence of 50% potassium hydroxide. Such stability may be explained by the formation of an intramolecular hydrogen bond between the hydroxyl group and the nitrogen of the imidazole ring in compounds (IVa, b). (The absorption band in the IR spectra at 3596 cm^{-1} does not depend on the degree of dilution.)

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