tern of distribution of total radioactivity was seen in the livers of rats which had received [^{3}H]-vitamin D_3 subcutaneously (Fig. 2). The total radioactivity of the liver was greatest in those animals which had been treated with vitamin D_3 in liposomes, so that at the saturation points, after 10 and 12 h, 55 and 20% of the [^{3}H]-cholecalciferol had been absorbed when given in liposomes and ethanol, respectively.

The above findings show that vitamin D_3 in liposomes is not only better absorbed in the intestine, but is also much more efficiently taken up by the liver, where it is hydrolyzed to 25-OH-D. To all appearances, these factors are those responsible for the high biological effectiveness of vitamin D_3 in liposomes.

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SYNTHESIS OF THE 21-ACETATE OF SUBSTANCE S FROM 17α-HYDROXYPROGESTERONE

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In the course of an investigation of the synthesis of corticosteroids from androst-4-ene-3,17-dione (AD), a product of the microbiological oxidation of sitosterol, we have studied a new variant of the synthesis of the 21-acetate of Reichstein's substance S (cortexolone acetate) (Vc), a key compound in the synthesis of antiinflammatory corticosteroids (hydrocortisone, prednisolone, 6-methylprednisolone, etc.).

As starting compound we used 17α-hydroxyprogesterone (I), the synthesis of which from AD has been sufficiently studied [3]. In this case, the problem came down to introducing a hydroxy or an acetoxy group at position 21 of the molecule.

In the literature there are several known methods for obtaining the 21-acetate of substance S from compound I [1, 2, 4, 5]. One of these, suggested by Ringold [8], was further developed in the work of Soviet investigators [2, 4]. This method consists of direct iodination of the steroid molecule at C(21) under conditions of cationic catalysis, with subsequent acetoxylation, with a yield of 68-70%.

Another possible way is to carry out selective bromination at C(21), and to prevent the competing reaction of substitution at positions 2 and 6 of the steroid molecule by building a conjugated system of double bonds in the Δ^4-iminium salt (the perchlorate), obtained by the reaction of compound I with pyrrolidine and subsequent treatment of the resulting enamine with 70% $HClO_4$ in alcohol, with the formation of a mixture of salts, which rearrange

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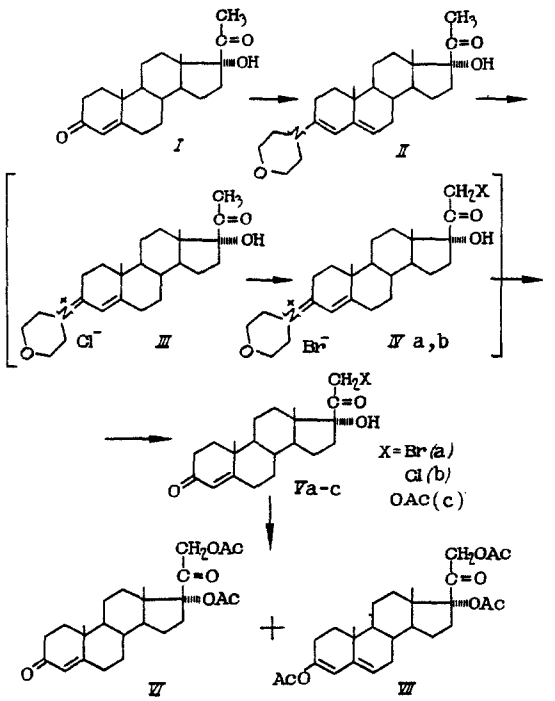
on heating to the Δ^4-iminium salt, with subsequent bromination and acetoxylation.

Another published variant of the synthesis of Vc is via the salt of the pyrrolidine enamine of hydroxyprogesterone with hydrogen chloride – the iminium chloride [5]. The yield of compound Vc by these two methods [1, 5] is 79%.

In the present article we study the possibility of using the morpholine enamine of hydroxyprogesterone and its salts for the synthesis of the acetate of substance S (Vc).



In the literature it is stated that, due to the lower reactivity of morpholine compared with pyrrolidine, harsher conditions are needed to obtain morpholine enamines [6]. However, the literature contains no account of a method for obtaining the morpholine enamine of hydroxyprogesterone and its physicochemical characteristics.

We successfully obtained compound II by refluxing 17α-hydroxyprogesterone with morpholine in benzene in the presence of an acid catalyst, with azeotropic distillation of water, for 5-7 h. The course of the reaction was monitored by IR spectroscopy from the disappearance of the absorption band corresponding to the double bond conjugated with the ketone. We obtained enamine II in quantitative yield.

In the course of the investigation, we studied the possibility of using different enamine salts (perchlorate, chloride) for the synthesis of cortexolone acetate. It is known [1] that upon reaction of steroidal 3-enamines with 70% $HClO_4$, except for salts that require subsequent bromination at C(21) of the conjugated enamine system, salts are formed with reactive double bonds in the B ring. However, in contrast to salts of pyrrolidine enamines, salts of morpholine enamines turned out to be unstable under the conditions of isomerization of the double bonds (heating to the boiling point); partial hydrolysis of the latter to hydroxyprogesterone occurred.

From the literature [5] it is also known that in obtaining chlorides of steroidal enamines by the action of dry alcoholic HCl, one isomeric salt with conjugated double bonds is formed. We confirmed that we obtained the salt of the morpholine enamine of hydroxyprogesterone (III) in this way by the IR spectrum, in which the absorption band in the region 1672-1667 cm^{-1}, corresponding to the isolated Δ^5-double bond, was absent.

The obtained eniminium salt (the chloride) III of the morpholine derivative was easily and selectively brominated at C(21) by a molecule of bromine at room temperature.

We determined the optimal conditions for carrying out the bromination, hydrolysis, and subsequent acetoxylation.

The bromination was carried out at room temperature because slight heating causes the formation of the 21,21-dibromo derivative as a by-product, which makes it difficult to introduce nucleophilic substituents in subsequent reactions. In addition, apart from the main reaction, the occurrence of an ion-exchange process was noted, namely, the displacement by a bromide anion of a chloride anion from the enamine salt [5], as well as the exchange of halogens at C(21), resulting in the formation of the 21-chloro (IVb) and 21-bromo (IVa) derivatives in a 1:1 ratio. This was confirmed by elemental analysis and mass spectroscopy of the reaction products following hydrolysis of the protecting groups.

The resulting mixture of 21-haloiminium salts IVa and IVb was subjected to hydrolysis, without separation, by an aqueous KOH solution at 45°C for 15 min, giving a mixture of the 21-bromo and 21-chloro derivatives of 17α-hydroxyprogesterone (Va and Vb), the mass spectrum of which contained peaks of two molecular ions with m/z = 408 (^{79}Br) and 364 (^{35}Cl) and the isotropic compositions of which are consistent with a content of one atom of bromine or chlorine per molecule.

The mixture of 21-halides Va and Vb was treated, without further purification, with potassium acetate in boiling acetone in the presence of a small amount of NaI (5% of the weight of the steroid), which was added following 3 h of refluxing to speed up the process of nucleophilic substitution of the 21-chloride Vb. We obtained the technical 21-acetate of substance S (Vc) with an overall yield of 95% of theoretical, based on hydroxyprogesterone. Yield of the purified product was 79%.

To shield position 14 of the steroid molecule and increase the yield of hydrocortisone in the subsequent microbiological hydroxylation, we acetylated the 17α-hydroxy group of cortexolone-21-acetate, Vc, with acetic anhydride in the presence of $HClO_4$ [7]. We thus obtained a mixture of two compounds, the diacetate of substance S (VI) and the triacetate (VII). The amount of the latter (20-25%) was determined from the relative areas of the peaks of the angular methyl groups at C(18) in the PMR spectrum of the acetylation products. The mixture obtained was suitable for microbiological hydroxylation to hydrocortisone [1].

We conducted an investigation to demonstrate the possibility of using morpholine in the synthesis indicated above. The nonuniqueness of the reaction scheme, namely the formation of a mixture of 21-chloro and 21-bromo derivatives, does not lower the high overall yield of the 21-acetate of substance S.

EXPERIMENTAL

IR spectra were taken on a Perkin–Elmer 599 instrument (Sweden), and PMR spectra on a Varian X-200 (Germany), using TMS as internal standard. Mass spectra were obtained on a Varian MAT-112 (Germany) at an ionization energy of 50 eV. TLC was carried out on Silufol UV-254 plates in a 9:1 CH_2Cl_2–acetone system.

17α-Hydroxy-3-(N-morpholinyl)pregna-3,5-dien-20-one (II). A solution of 5 g (0.015 mole) I, 70 mg p-toluenesulfonic acid, and 12 ml (0.13 mole) of morpholine in 100 ml benzene was refluxed with constant distillation of water for 7 h. The reaction mass was evaporated and dried under vacuum. Yield was 7.46 g, mp 201-203°C (decomp.) following recrystallization from acetone. IR spectrum, ν_{max}, cm^{-1}: 3280 (C–O), 1690 (C^{20}=O), 1635 and 1605 ($\Delta^{3,5}$). Mass spectrum, m/z: 399 (M^+), 384, 381, 288, 270. PMR spectrum ($CDCl_3$), δ, ppm: 0.72 s (3H, 18-CH_3), 0.98 s (3H, 19-CH_3), 2.28 s (3H, Ac), 2.92 q (4H, CH_2NCH_2, J ~ 5 Hz), 3.75 t (4H, CH_2OCH_2, J ~ 5 Hz), 5.14 s (1H, 4H), 5.24 m (1H, 6-H).

21-Halo-17α-hydroxypregn-4-ene-3,20-dione (Va, Vb). To a solution of 7.46 g (0.015 mole) technical II in 80 ml ethanol containing 16 ml (0.1 mole) of a 23% solution of HCl in alcohol at room temperature was slowly added a solution of 1.30 ml (0.024 mole) bromine in 20 ml ethanol, and the resulting solution was stirred for 1.5 h. Then a 30% aqueous solution of K_2CO_3 was added to pH 9.0 and 50% AcOH to pH 6.0, and the resulting solution mixed at 45°C for 15 min. The mixture was evaporated under vacuum and transferred to sodium bicarbonate. After filtration and washing with water, 5.85 g of a mixture of Va and Vb was obtained, mp 206-208°C. IR spectrum, ν_{max}, cm^{-1}: 3500 (C–O), 1711 (C^{20}=O), 1660 (C^3=O), 1620 (Δ^4). Mass spectrum, m/z: 408/410 (M_1^+), 364/366 (M_2^+), 329, 287, 269. Found, %: Br 12.94, Cl 5.74.

21-Acetoxy-17α-hydroxypregn-4-ene-3,20-dione (Vc). A suspension of 5.85 g of a mixture of Va and Vb and 3.27 g AcOK in 150 ml acetone was refluxed for 3 h. NaI (0.29 g) was added, and after refluxing 0.5 h more, the mixture was evaporated under vacuum. The residue was

resuspended in 60 ml water, washed, and dried. Compound Vc (5.57 g) was obtained in 95% yield based on compound I, mp 214-216°C. After recrystallization from acetone, 4.63 g (79%) was obtained, mp 223-226°C (225-227°C according to [5]). IR spectrum, ν_{max}, cm^{-1}: 3420 (OH), 1740 (COOR), 1716 (C^{20}=O), 1660 (C^3=O), 1610 (Δ^4), 1235. Mass spectrum, m/z: 388 (M^+), 328, 287, 269, 241.

17α,21-Diacetoxypregn-4-ene-3,20-dione (VI) and 3,17α,21-Triacetoxypregna-3,5-dien-20-one (VII). To a solution of 0.7 ml 30% $HClO_4$, 12 ml Ac_2O, and 28 ml CH_2Cl_2 at −8 to −7°C was added 2 g (0.005 mole) Vc. This was mixed for 20 min at −5 to −4°C. Aqueous ammonia was added to pH 7.0, and mixing was continued for 2 h more. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 ml). The combined organic layers were washed with water and dried. MeOH was added (15 ml), and the mixture was evaporated to a volume of 6 ml (temperature of distillate 64°C), cooled, and filtered. Yield 2.05 g. Mass spectrum, m/z: 472 (M_1^+), 430 (M_2^+), 357, 287, 269.

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SYNTHESIS, STRUCTURE, AND ANTIARRHYTHMIC ACTIVITY OF COORDINATION COMPOUNDS OF MAGNESIUM

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A promising route to the identification of highly active antiarrhythmic drugs is by the synthesis and examination of compounds capable of reducing the oxygen requirements of the heart, which is related to antagonism to calcium ions [7].

Magnesium is known to function as a calcium antagonist in the body. It may reduce the metabolic rate of energy-rich phosphates, thereby reducing the requirements of the myocardium for oxygen. On the other hand, it has been found that in 90% of cases myocardial infarction is accompanied by disturbances of cardiac rhythm [6], while in patients with myocardial infarction and ischemic cardiac disease the blood magnesium levels are considerably reduced [14].

Several workers have shown [1, 2, 5] that coordinately bonded metals are more biologically active and less toxic than their inorganic salts. Furthermore, the combination in a single complex of magnesium, potassium, and a bioactive organic compound could result in synergism between them.

With these considerations in view, we have attempted to carry out the goal-directed synthesis of some coordination compounds of magnesium with pyridoxine, pantothenic acid, and asparaginic acid. These ligands were chosen for the following reasons. Pyridoxine (L_I) is an active biocatalyst for many metabolic reactions involved in the normal functioning of the central and peripheral nervous systems. Complex formation increases the activity of L_I and decreases the toxicity of metal ions [11-13]; pantothenic acid (L_{II}) facilitates

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