Steroids. XXXV. A Study of the Nucleophilic Exchange Reaction of the Iodine in Position 21 of 17α-Hydroxy-21-Iodoprogesterone

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Great attention is being devoted at the present time to the synthesis of analogs of the corticosteroid hormones. The preparation of compounds with various substituents in position 21 of the steroid molecule is of definite practical and theoretical interest. There is information on the synthesis of a number of 21-N- and 21-S-containing corticosteroids [1-3], among them depersolon - 21-deoxy-21-N-(N'-methylpiperazinyl)-prednisolone - a highly active soluble analog of prednisolone [4].

We have studied the exchange reaction of the halogen in position 21 of 17α-hydroxy-21-iodoprogesterone (I) under the action of various nucleophilic agents, as a result of which we have obtained a number of 21-substituted derivatives of 17α-hydroxyprogesterone. The replacement of a halogen in position 21 of 10-oxosteroids has been described previously for a number of cases [1, 5, 6]. Compound I, which we selected as the starting material, is an intermediate in the synthesis of cortisone by the method developed in our laboratory [7].

Like other α-halo ketones, 17α-hydroxy-21-iodoprogesterone readily reacts with amines. Its reaction with a number of secondary amines led to the formation of the corresponding 21-amino derivatives in the form of bases (II, IV-VI) or hydriodides (III, VIc).

From the bases were obtained the hydrochlorides (IIa-VIa) and the methiodide (IIc) of compound II.

The course of the reactions was followed, and the purity of the products isolated was checked, by means of thin-layer chromatography. It was found that the rates of formation of the various amino derivatives were not the same. Thus, the reaction with diethylamine takes place more slowly and at a higher tem-
temperature than with the other amines. In all cases, the technical product contained a small amount of 17α-hydroxyprogesterone (VII) as impurity; in the case of the reaction with a 25% aqueous solution of ammonia, the latter was the predominating product and it was isolated and identified. The reactions with aqueous ammonia and aqueous solutions of dimethylamine and diethylamine led to the formation of a small amount of Reinhold's substance "S" (17α,21-dihydroxy-4-pregnene-3,20-diol) (VIII), as was shown by the results of chromatographic analysis.

The IR spectra of the compounds obtained exhibited the absorption bands characteristic for a hydroxy group (3430–3150 cm⁻¹), a conjugated carbonyl group (1660–1680 cm⁻¹), an unconjugated carbonyl group (1719–1720 cm⁻¹) and a C= C-double bond (1619–1621 cm⁻¹).

The nuclear magnetic resonance spectra of all the compounds obtained exhibited the signals of the 19 and 18 angular methyl groups in the 0.5–1.5 ppm region and a singlet signal at 5.74–5.75 ppm corresponding to a proton on the double bond in position 4. The spectrum of compound II also exhibited signals of the methyl protons of a -N(CH₃)₂ group at 2.33 ppm. Signals of the methylene protons in the morpholine, piperidine, and piperazine rings in the spectra of compounds IV–VI, respectively, appear in the 2.5 ppm region for -CH₂–N⁻ and the 3.8 ppm region for -CH₂–O⁻. The protons of the CH₂-group in position 21 appear in the spectra of all the compounds in the form of a quartet, which shows the nonequivalence of the two protons of this group.

The hydrochlorides IIa–Va were subjected to pharmacological investigation. The hydrochloride IIa was studied in most detail: its toxicity, general action on the organism of experimental animals, influence on the arterial pressure and vegetative nervous system, the presence of antihistamine, anti spasmodic, analgesic, and spasmylytic activity, and its interaction with narcotics (hexenal) were determined. It was found that this material has a local anesthetic effect (the investigation was carried out on the rabbit eye by Renier's method). In respect of its capacity for causing superficial anaesthesia, the substance is approximately three times weaker than dicaine (and six times less toxic than dicaine) and in its capacity for causing conduction anaesthesia it is seven times weaker than dicaine and three times weaker than novocaine.

The other compounds studied exhibited no local anaesthetic activity. All the compounds studied had a low pharmacological activity in other respects.

**EXPERIMENTAL**

The IR spectra were obtained for substances in the crystalline state in paraffin oil using a UR-10 spectrophotometer, and the nuclear magnetic resonance spectra were taken for the substances in CDCl₃ solution on a FNM-4H-100 instrument (100 MHz).