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DEHYDROGENATION OF METHYLTESTOSTERONE WITH SELENIOUS ACID

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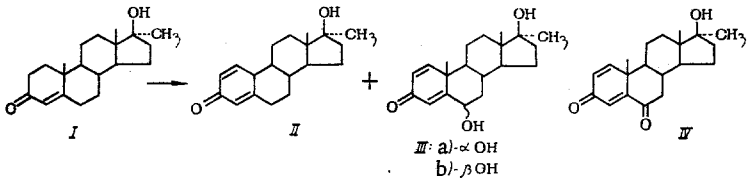
One of the effective methods for the preparation of Δ^1-dehydrosteroids is dehydrogenation with selenium oxide and selenious acid [1]. Under the conditions which we developed, the dehydrogenation of methyltestosterone (I) to metandrostenolone (II) by means of methyl selenate in butyl acetate gives a yield of 70% [2]. According to the literature data, the yield of this compound is considerably lower.

We were the first to observe that the Δ^1-dehydrogenation reaction is complicated by allylic oxidation at the C_6-carbon atom with the formation of 6-hydroxy compounds (III) with an α and β configuration of the hydroxyl. By thin-layer chromatography (silufol, 3:2 heptane—acetone system), it was found that besides the main compound (R_f 0.22), there are more polar admixtures in the reaction mixture with R_f 0.08 and 0.12, with a total content of about 5%.



During the chromatography of the mother liquors on aluminum oxide, an individual compound with R_f 0.12 was isolated. From the data of spectral and elemental analysis, the structure of 17α-methylandrosta-1,4-diene-6β,17β-diol-3-one (IIIb) was assigned to this compound. In the IR spectrum, besides the groupings characteristic of metandrostenolone (3500 (OH), 1660 (CO), 1620 (C=C) cm^{-1}), there is a band of yet another hydroxyl group at 3400 cm^{-1}. In the UV spectrum of compound IIIb, a 3 nm bathochromic shift is observed, compared with the spectrum of II, which corresponds to the presence of hydroxyl in the 6β position. The character of the splitting of the proton signal at C_6 in the PMR spectrum indicates an axial 6β orientation of the hydroxyl: the H-6 signal in the form of a triplet with a halfwidth of 5 Hz.

During the oxidation of (IIIb) with chromic acid according to Jones, ketone (IV) was obtained, with an absorption maximum at 254 nm in the UV region.

17α-Methylandrosta-1,4-diene-6β,17β-diol-3-one was isolated as a metabolite of metandrostenolone [4]. The authors believe that one of the possible courses of the metabolism of the $\Delta^{1,4}$-3-keto-17-alkylsteroids in humans is 6β hydroxylation.

Studies on the hormonal properties of compounds (IIIb) and (IV) showed that the two compounds have a weak androgenic activity, causing an increase in the weight of the ventral prostata of one and a half to two times [5], and are much inferior to testosterone propionate in their effectiveness. The compounds studied also had a weak antiinflammatory activity (20-30% of the effect of hydrocortisone), which was evaluated from the decrease in weight of the inflamed granuloma in andranalectomized rats [6]. Compound (IIIb) has an appreciable

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TABLE 1. Androgenic Activity of Compounds (IIIb) and (IV) in Comparison with the Action of Testosterone Propionate (TP)

Preparation*	Weight of animals		Weight of organs (mg per 100 g body weight)					
			seminal vesicles		ventral prostata		levator ani muscle	
	initial	final	$M \pm m$	P	$M \pm m$	P	$M \pm m$	P
—	55	67	10,7±0,9	—	14,5± 1,4	—	21,1±3,1	—
TP	55	82	160,1± 12,2	<0,001	141,7± 13,8	<0,001	59,9± 1,9	<0,001
IIIb	54	64	12,3±0,7	>0,25	21,4± 1,7	<0,01	18,2± 1,0	>0,25
IV	54	71	12,0±0,9	>0,25	23,2± 3,4	<0,05	17,4± 1,7	>0,25

*The preparations were introduced in a dose of 10 mg/kg/day for 7 days.
†Five animals in a group.

catatoxic activity: During its preliminary intragastric administration in a dose of 100 mg/kg for four days, the strong toxic action of meprobamate, introduced in an absolute lethal dose (1100 mg/kg) to mice, was reduced by nearly 60%.

Compounds (IIIb) and (IV) did not lead to gestagenic [8], thymolytic [9], mineralocorticoid [10] and antiandrogenic [11] effects.

EXPERIMENTAL METHOD

Dehydrogenation of Methyltestosterone with Selenious Acid. A solution of 13 g of selenious acid in 30 ml of methanol and 250 ml of butyl acetate is added with boiling for 3-4 h to a solution of 25 g of methyltestosterone (I) in 900 ml of butyl acetate. At the end of the addition of the selenious acid solution, the reaction mixture is boiled for 2-3 h, then cooled to room temperature, and metallic selenium is filtered off. A 200 ml portion of 30% hydrogen peroxide is added to the filtrate with stirring, care being taken that the temperature does not rise above 20-22°, and the mixture is stirred for another 2 h. The butyl acetate layer is separated, and washed with 2 N sodium hydroxide, a 15% solution of sodium sulfate and water, to a neutral reaction. After evaporation of butyl acetate, the residue is stirred with ether, and 18.5 g of crude metandrostenolone (II) is obtained. This product is then dissolved in 260 ml of toluene, and passed through a column with 37 g of aluminum oxide, the height of the layer being not less than 10 cm. The product is eluted with a 25- to 30-fold amount of toluene, and 16.2 g of a pharmacopoea pure metandrostenolone is obtained (yield 64.5% of theoretical, calculated on methyltestosterone). During elution with ethyl acetate, 0.8 g of 17 α-methylandrosta-1,4-diene-6β,17β-diol-3-one (III), R_f 0.12, is obtained. After crystallization from methanol, the compound melted at 230-231°, $[\alpha]_D$ − 44° (1% in chloroform). According to the literature data [4], mp 228-229°.

17α-methylandrosta-1,4-diene-17β-ol-3,6-dione (IV). A 1 g portion of (III) is dissolved in 50 ml of acetone, the solution is cooled to 0°, and 2 ml of Jones reagent is added with stirring. The mixture is stirred for 10 min at 0°. The reaction mixture is poured into water, and extracted with methylene chloride, washed with water, dried over sodium sulfate, and evaporated. After crystallization from methanol, 17α-methylandrosta-1,4-diene-17β-ol-3,6-dione is obtained, mp 161-161.5°, $[\alpha]_D$ − 181° (1% in chloroform), $\varepsilon^{1\%}$ 420 at λ 254 nm.

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STUDY OF THE MODES OF CONVERSION OF p-NITRO-α-METHOXYSTYRENE INTO p-NITRO-α-BROMOACETOPHENONE

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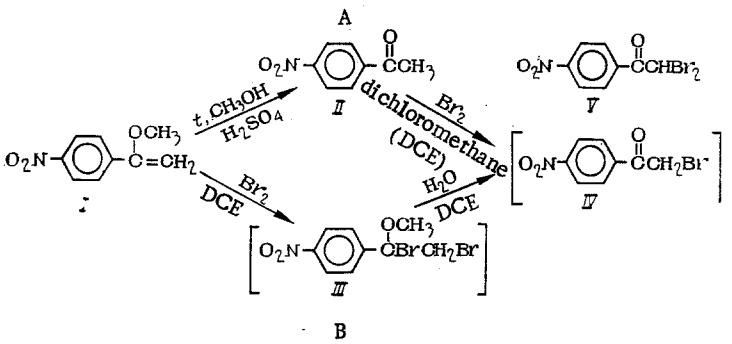
During the production of laevomycetin and syntomycetin, p-nitro-α-bromoacetophenone (IV) is prepared from p-nitro-α-methoxystyrene (I) by two methods.



According to method A, (I) is hydrolyzed in aqueous methanol in the presence of catalytic amounts of sulfic acid while the reaction mixture is boiled [1]. The solution of p-nitroacetophenone (II) purified by charcoal is cooled to 18-20°, and (II), which separates out, is filtered, dried, and used in dry dichloroethane for the preparation of (IV).

According to method B, (I) is brominated in dry dichloroethane [1, 2], and 1-(p-bromophenyl)-1-methoxy-1,2-dibromoethane (III) thus formed is hydrolyzed to (IV). Then the solution is dried by azeotropic distillation of water with dichloroethane, and used for the preparation of the urotropin complex.

A gas–liquid chromatographic (GLC) analysis of the solution of the bromoketone (IV) obtained by the above methods showed that in both cases the yield and the quality of the required product are practically the same. The product obtained after bromination contains not only the required compound (IV) but also up to 5-7% of p-nitro-α,α-dibromoacetophenone (V) and its equivalent amount of ketone (II). The formation of (V) can be explained by acid-catalyzed bromination of (IV) (method A) and the disproportionating action of hydrogen bromide (methods A and B).

If the above methods for the preparation of (IV) are compared, it is seen that method A is more labor and raw-material consuming, requires a more complex apparatus, and has a more prolonged production cycle. Therefore, in the present work, we studied the process of preparation of (IV) by method A, without isolation of ketone (II), and we also considered the problem of the possible preparation of the required bromoketone from compound (III) by its thermal dissociation.

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