CONTROLLING OF ISOMERIZATION OF 6-METHYLENE-4-PREGNEN-17α-OL-3,20-DIONE ACETATE INTO MEGESTROL ACETATE BY UV SPECTROSCOPY

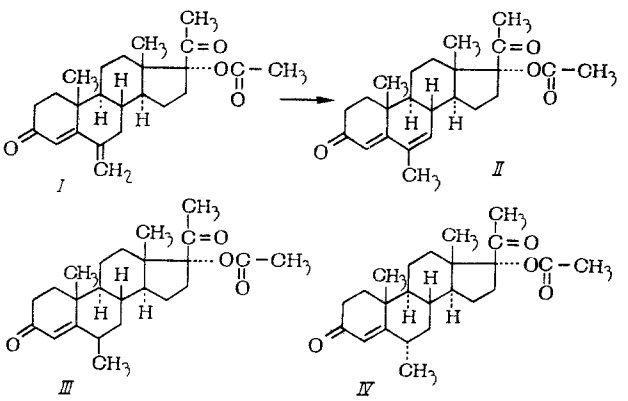
L. N. Mikhailova, G. M. Kadat-skii, and G. S. Grinenko

UDC 615.256.52.012.1.07

The proposed method is concerned with the spectrophotometric determination of the end of the reaction of isomerization of 6-methylene-4-pregnen-17α-diol-3,20 acetate (I) into 6-methyl-4,6-pregnadiene-3,20-dione acetate (II) and the spectral determination of the purity of the isolated product.

The isomerization was effected by boiling an alcoholic suspension of I in the presence of a catalyst — palladium on charcoal — and a hydrogen donor — cyclohexene and sodium acetate. This reaction is the last stage in a multistage synthesis of megestrol acetate (II), an important hestogen, which is widely applied for gynecological diseases, for contraception purposes, as well as in the veterinary and stock breeding practice [1].

Economic indices of the production of II, such as the product quality, depend on the accuracy of controlling the end of the isomerization reaction. If the reaction holding time is too short, the end product contains very slightly soluble derivatives of I. If the reaction holding time is too long, hydrogenation products of II, 6-β-methyl-4-pregen-17α-ol-3,20-dione acetate (III) and its 6α-isomer (IV), accumulate in the reaction mixture [2, 3]. The presence in reaction mixtures of both I and III, and IV hinders the isolation of II in a pure state, and requires repeated crystallizations, leading to a decrease in yield.



A method is known for controlling the course of the isomerization by running UV spectra of the reaction mixtures, isolated after complete treatment of samples [3]. However, this method is time consuming. The optimal moment of the completion of reaction could thus be missed, and the reaction mixture obtained could contain an increased amount of difficultly separable hydrogenation products.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 9, No. 10, pp. 58-59, October, 1975. Original article submitted June 13, 1974.

TABLE 1. Results of the Analysis of the Reaction Mixture at the Isomerization Stage

No of experiment	Time of withdrawing samples, measured from beginning of reaction	$\frac{D_{240}}{D_{288}}$	$\frac{D_{260}}{D_{288}}$
1	15 min	0,19	0,41
	30 min	0,17	0,38
	45 min	0,12	0,31
2	45 min	0,12	0,31
3	45 min	0,12	0,32
4	45 min	0,22	0,43
	1 hr 35 min	0,12	0,32
5	2 hr	0,12	0,33

The aim of the present work is the simplification, acceleration and increase in the reliability of the method for controlling the course of the isomerization. For this purpose, we withdrew samples of the reaction mixture after definite intervals of time, diluted them to the corresponding concentration with methanol or ethanol, and measured the optical density of the solution at three points, corresponding to the absorption maximum of the above compounds: 240 nm — the absorption maximum of the hydrogenation products III and IV, 260 nm — the absoption maximum of the starting compound I, and 288 nm — the absorption maximum of II.

As the indices of the reaction course and its completion, we propose to use two ratios of the optical densities D_{240}/D_{288} and D_{260}/D_{288} which at a correct course of the reaction should decrease to values of 0.15 and 0.35. The proposed method for the determination of the end of the isomerization reaction of I into II was verified during the development of a method for the preparation of II at the experimental plant of the All-Union Scientific-Research Institute of Pharmaceutical Chemistry, and at the chemical-pharmaceutical factory "Akrikhin," and it has been positively evaluated. The results obtained are shown in Table 1.

Method for the Determination of the End of the Isomerization Reaction

The volume of the reaction mass corresponding to 500 mg of the starting compound is measured (accurately) with a pipette into a 50 ml measuring flask, and brought to a mark with methanol or ethanol. The mixture is thoroughly mixed, and the optical density measured at three wavelengths, 240, 260, and 288 nm. Samples are withdrawn every 15 min. The reaction is considered to be completed if the D_{240}/D_{288} ratio does not exceed 0.15 and the $D_{260}/_{288}$ does not exceed 0.35.

LITERATURE CITED

1. V. I. Maksimov, Yu. D. Klinskii, G. M. Kadat-skii, et al., "Synchronization of sexual desire in animals," Auth. Cert. No. 258762 (1967); Izobreteniya, No. 1, 138 (1971).
2. D. Burn, G. Cooley, M. T. Davies, et al., "Modified steroid hormones. XXXIII. Steroidal 6-formyl-3-alkoxy-3,5-dienes and some of their transformations," Tetrahedron, 20, 597-609 (1964).
3. D. Burn, D. H. Kirk, and V. Petrow, "Modified steroid hormones. XXXVIII. Some transformations of steroidal 3-alkoxy-6-formyl-3,5-dienes and related compounds," Tetrahedron, 21, 1619-1624 (1965).