3. H. Brederick, H. Herlinger, and I. Graudums, Chem. Ber., 95, 54-57 (1962).
4. M. Sekija, J. Suzuki, and Y. Terao, Chem. Pharm. Bull. (Tokyo), 24, 1331-1335 (1976).
5. U. Ya. Mikstais, A. A. Autse, and I. B. Apene, Inventor's Certificate No. 517594; Otkrytiya, No. 22, 75 (1976).
6. U. Ya. Mikstais, A. A. Autse, and I. B. Apene, Inventor's Certificate No. 523097; Otkrytiya, No. 28, 65 (1976).
7. E. S. Golovchinskaya, L. A. Gutorov, L. A. Nikolaeva, et al., Inventor's Certificate, No. 463672; Otkrytiya, No. 10, 58 (1975).
8. L. A. Gutorov, Inventor's Certificate No. 207918; Izobreteniya, No. 18, 37 (1967).

SYNTHESIS OF 16-DEHYDRO-16-ALKYL(ARYL) PREGNANES FROM O,N-DIACETATES OF 16-ALKYL(ARYL)PSEUDOSOLASODINES

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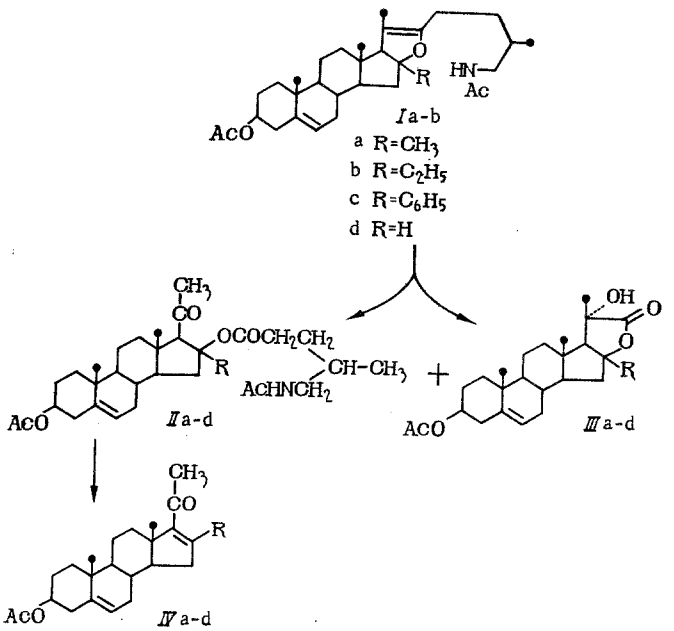
We have already reported [1] on the synthesis of O,N-diacetates of 16-alkyl(aryl)pseudosolasodines (I). In the present work, we report on the conversion of the latter into 16-dehydro-16-alkyl(aryl)pregnanes (IV), which are the starting compounds for the synthesis of several steroid preparations (betamethasone, melengestrol acetate, superlutin) with a β-methyl or methylene group in the 16-position of the molecule.



Compound I was converted into IV by a known method [2], consisting in the oxidation of the double bond of pseudosolasodine O,N-diacetate (Id) with sodium dichromate in acetic acid, followed by splitting of the ester side-chain of the oxidation product by boiling it in glacial acetic acid. This method is used on an industrial scale for the preparation of dehydropregnenolone acetate (IVd) in high yields at the oxidation stage (70-75%), and at the splitting stage (90-95%) [3, 4]. The total yield of IVd based on Id is 65-70%. In the case of 16-alkyl-(aryl)pseudosolasodines (Ia-c), under the above conditions, the end products IVa and c were obtained in lower yields (about 50 and 20%, respectively), while IVb was obtained in trace amounts only. During a chromatographic study of the mother liquors after the crystallization of IVa-c, 16-alkyl(aryl)-3β-acetoxy-20-hydroxy-5-bisnorcholene-22,16-lactones (IIIa-c) were obtained as the side products of the oxidation of Ia-c. We had already obtained similar hydroxylactone (IIId), which is unsubstituted in position 16, during the oxidation of

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TABLE 1. Physicochemical Characteristics of Lactones IIIa-c

Compound	Melting point, °C	IR spectrum, cm⁻¹	Found, %		Empirical formula	Calculated, %	
			C	H		C	H
IIIa	222—4	3400, 1750, 1720	72,25	8,69	$C_{25}H_{36}O_5$	72,08	8,71
IIIb	214—7	3520, 1750, 1720	71,85	8,80	$C_{26}H_{38}O_5$	72,52	8,89
IIIc	252—5	3400, 1770, 1740	74,83	8,11	$C_{30}H_{38}O_5$	75,28	8,00

TABLE 2. Values of Chemical Proton Shifts of Lactones IIIa-c

Compound	Angular CH_3		CH_3 at C_{20}	OAc	H		R at C_{16}
	C_{19}	C_{18}			at C_3	at C_6	
IIIa	0,77	0,95	1,52 s	1,97 s	4,53 m	5,29 m	1,59 s
IIIb	0,79	0,96	1,53 s	1,97 s	4,56 m	5,33 m	0,96 tr
IIIm	0,91	1,00	1,49 s	1,97 s	4,54 m	5,30 m	7,3 m

Note. s — singlet; tr — triplet; m — multiplet.

pseudosolasodine O,N-diacetate (Id) [3]. However, the oxidation of Ia-c leads to the formation of the corresponding lactones in a higher yield than in the case of Id. The shift of the oxidation reaction for Ia-c containing substituents in the 16-position in the direction of formation of the hydroxylactones IIIa-c is apparently due to steric hindrances occurring in the course of the main reaction with the formation of IIa-c. In the latter, the bulky substituents of the cyclopentane ring are present in a screened conformation. We obtained the hydroxylactones IIIa-c for the first time, and their characteristics are given in Tables 1 and 2.

During the oxidation of Ib, followed by boiling in acetic acid, we isolated, after the chromatography, 16-ethyl-16β - δ-acetylamino-γ-methylvaleryloxy-3β-acetoxy-5-pregnen-20-one (II) instead of the expected IVb. The latter had an exceptional stability, compared with II (R=H), not only during boiling in acetic acid, but also during thermal treatment: when heated in dimethylformamide, the product remained unchanged.

The ester chain in IIb could be split by boiling the compound in acetic acid containing a small amount (10%) of concentrated hydrochloric acid. Under these conditions, we obtained IVb in a yield of 40%. The splitting of the ester group in IIc in a mixture of acetic and hydrochloric acids also increased the yield of IVc to 40%.

EXPERIMENTAL

The IR spectra were run on a UR-10 apparatus in mineral oil, the PMR spectra on the JNM-4H-100 apparatus in deuterochloroform with tetramethylsilane as the internal standard. The chemical shifts are given on the δ-scale. Preparative chromatography was carried out on silica gel, brand L40/100 (Chemapol).

3β-Acetoxy-16-methyl-5,16-pregnadien-20-one (IVa). A solution of 2 g of sodium dichromate in 10 ml of acetic acid is added in one portion at 20°C, with stirring, to a solution of 4.26 g of Ia in 40 ml of glacial acetic acid. The temperature in the mixture increases to 43-45°C. The mixture is stirred for 10 min, and after the addition of 0.3 g of sodium sulfite, it is boiled for 3 h. When cool, 55 ml of water is added, the precipitate is filtered, washed with water, dried, and recrystallized from ethanol. Yield of IVa 1.4 g, mp 172-174°C [5]. The alcoholic mother liquor is evaporated to dryness, and the residue chromatographed on silica gel. Elution with a benzene — chloroform mixture (8 : 2) yields another 0.3 g of IVa. Total yield 1.7 g (55%). Elution with a benzene—chloroform mixture (6 : 4) yields 0.32 g of IIIa.

3β-Acetoxy-16-ethyl-5,16-pregnadien-20-one (IVb). A) A solution of 1.2 g of sodium dichromate in 5 ml of acetic acid is added to a solution of 2.7 g of Ib in 30 ml of acetic acid, and the reaction is carried out as described for Ia. When cool, the mixture is diluted by 40 ml of water, and the oily product is extracted by methylene chloride. The extract is then washed with a sodium bicarbonate solution and water, the solvent is distilled in vacuo, and the residue chromatographed on silica gel. Elution with benzene yields 0.04 g of IVb, mp 139-143°C [6]. Elution with a benzene—chloroform mixture (3 : 7) yields 0.54 g of IIIb, and with chloroform, 0.8 g of II (R = C_2H_5), mp 96-98°C (from ether). Found, %: C 71.03; H 9.3; N 2.55. $C_{33}H_{51}O_6$. Calculated, %: C 71.06; H 9.22; N 2.51. IR spectrum, cm⁻¹: 3290, 1730, 1675, 1635. PMR spectrum, ppm: 0.97 s (angular CH_3), 0.84 m (CH_3 at C_{25}, C_2H_5), 1.96 s (CH_3CO), 2.18 s (CH_3CO), 3.07 tr (CH_2 at C_{26}), 4.51 m (H at C_3), 5.30 (H at C_6), 6.0 (NH).

B) A 2.85 g portion of IB in 25 ml of glacial acetic acid is oxidized by a solution of 1.2 g of sodium dichromate in 5 ml of acetic acid, as described under A. After oxidation and addition of sodium sulfate, 3 ml of concentrated hydrochloric acid is added, and the mixture is boiled for 2 h. The solution is poured into water and extracted with methylene chloride. The extract is distilled in vacuo, and the residue chromatographed on silica gel. Elution with a benzene–chloroform mixture (1:1) yields 0.8 g of IVb (40%).

3β-Acetoxy-16-phenyl-5,16-pregnadien-20-one (IVc). A) A 1.68 g portion of Ic is cleaved, as described for Ia. Yield of IVc 0.2 g, mp 220-222°C (from ethanol). Found, %: C 80.67; H 8.30. $C_{29}H_{36}O_3$. Calculated, %: C 80.51; H 8.33. IR spectrum, cm^{-1}: 1728, 1670, 1610. PMR spectrum, ppm: 1.07, 1.14 s (angular CH_3), 1.88 s (CH_3CO), 2.04 s (CH_3CO), 4.61 m (H at C_3), 5.42 m (H at C_6), 7.31 m (C_6H_5).

After recrystallization of IVc, the mother liquor is chromatographed on silica gel. Elution with a benzene–chloroform mixture (3:7) yields 0.15 g of IIIc.

B) A 1.1 g portion of Ic in 12 ml of acetic acid is oxidized by a solution of 0.46 g of sodium dichromate in 4 ml of acetic acid. The mixture is reduced with sodium bisulfite, 1.5 ml of concentrated hydrochloric acid is added, and the mixture is boiled for 1 h. The solution is poured into water, and the precipitate is filtered, dried, and chromatographed on silica gel. Yield of IVc 0.3 g (39.5%).

LITERATURE CITED

1. L. M. Morozovskaya, É. S. Belen'kaya, L. I. Klimova, et al., Khim.-Farm. Zh., No. 11, 64-67 (1976).
2. N. N. Suvorov and L. M. Morozovskaya, Inventor's Certificate No. 118499; Byull. Izobret., No. 6, 10 (1959).
3. L. I. Klimova, L. S. Krasavina, G. G. Malanina, et al., Khim.-Farm. Zh., No. 9, 12-17 (1970).
4. L. I. Klimova, L. M. Morozovskaya, and N. N. Suvorov, Khim.-Farm. Zh., No. 6, 24 (1968).
5. P. de Ruggieri, US Pat. No. 3070614; Chem. Abst., 58, 11447d (1963).
6. Brit. Pat. No. 910118; Chem. Abstr., 58, 6900a (1963).

HALOGENATION OF 8-HYDROXYQUINOLINE WITH IODINE TRICHLORIDE IN HYDROCHLORIC ACID

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The synthesis of 5-chloro-7-iodo-8-hydroxyquinoline (I), the principal compound in the series of chemotherapeutic and antiseptic preparations [1], can be carried by several methods [2-8].

The present paper describes the study of the mechanisms of halogenation of 8-hydroxyquinoline (II) by iodine trichloride (III) in hydrochloric acid. These mechanisms have not yet been investigated.

$$HICl_4 \rightleftharpoons HCl + \underset{III}{ICl_3} \rightleftharpoons ICl + Cl_2$$

Quantitative and qualitative analyses by gas–liquid chromatography and mass-spectrometric methods of the intermediate and end products under different conditions of carrying out the reaction showed that the halogenation of compound II by III proceeds in successive parallel reactions (scheme top of next page).

This reaction is characterized by the fact that in hydrochloric acid, compound II and its halogen derivatives are able to form intermolecular complexes VII-X with iodine chloride and hydrogen chloride, which are removed from the reaction mixture in the form of a precipitate (an intermediate product). After separation and treatment with water, the complexes decompose with the formation of mono- and dihalo derivatives of II (the end product).

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