2-(3-DIOXINDOLYL)-SUBSTITUTED STEROIDS

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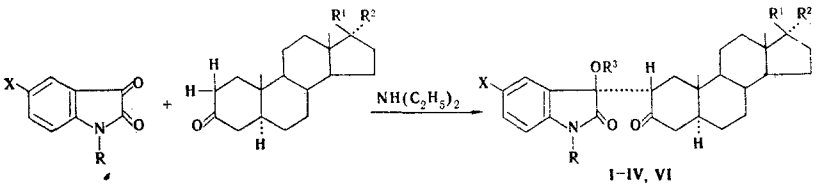
Condensation of isatins with 3-keto-substituted steroids gives 2-(3-dioxindolyl)steroids. A mixture of two epimeric 2α-(3-indolyl)cholestan-3-ols is obtained by reduction of 2-(3-dioxindolyl)-3-ketocholestane.

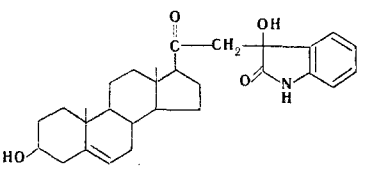
Studies devoted to the preparation of androstano-(2,3-b)-5'-hydroxyindole derivatives [1], the steroid analogs of 5-hydroxytryptamine, are known. Hexahydro-6H-indeno[5,4]indole derivatives, which are like steroid hormones in which the A and B rings are replaced by the indole ring [2], are generating a great deal of interest.

We have shown that steroid derivatives of dioxindole (I-V) are obtained by condensation of keto steroids with isatins at 20°C in the presence of diethylamine in alcohol. Products I-V were isolated in the reaction of cholestanone, pregnenolone, and 17 α-methyldihydrotestosterone with isatin and 1-methyl- and 5-bromoisatin. We suppose that the dioxindole residue in the course of this transformation apparently takes the more advantageous equatorial configuration at the C_2 atom of the 3-keto steroid as a result of attack of the steroid molecule by isatin "from the rear" (the upper side is shielded by the angular methyl groups).



I-IV, VI

I $R=R^2=R^3=X=H$, $R^1=C_8H_{17}$; II $R=R^2=R^3=H$, $X=Br$, $R^1=C_8H_{17}$; III $R=CH_3$, $R^2=R^3=X=H$, $R^1=C_8H_{17}$; IV $R=R^3=X=H$, $R^1=OH$, $R^2=CH_3$; VI $R=X=H$, $R^1=CH_3COO$, $R^2=CH_3$, $R^3=CH_3CO$



V

Absorption maxima of the dioxindolyl chromophore appear at 208-214 nm in the UV spectra of I-V; the IR spectra contain bands of carbonyl groups at 1715-1730 cm^{-1}, and the broad band at 3200-3600 cm^{-1} confirms the presence of a hydroxyl group included in an intermolecular hydrogen bond. The C–N stretching vibration appears at 1308-1345 cm^{-1}.

5α-Androstan-17-one does not react with isatin under these conditions; this should apparently be explained by steric factors introduced by isatin.

In a confirmation of the proposed structure we have shown that reduction of 2-(3-dioxindolyl)-3-keto steroids with lithium aluminum hydride in tetrahydrofuran (THF) gives a mixture of equal amounts of two

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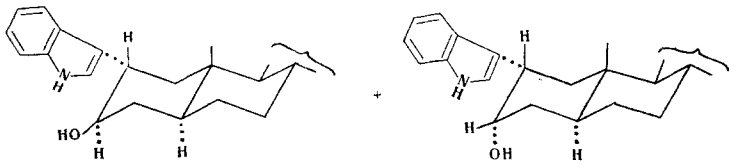
TABLE 1. Steroid Derivatives of Dioxindole

Compound	M.p. °C	$[\alpha]_D^{20}$ (pyridine)	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
I	191	+38° (C 1)	$C_{35}H_{51}NO_3 \cdot 1/2H_2O$	77,8 77,3	9,5 9,4	2,7 2,3	77,5	9,6	2,6	87
II	213	+25° (C 1,5)	$C_{35}H_{50}NO_3Br \cdot 2H_2O$	64,4	8,0	2,2	64,7	8,4	2,2	87
III	175	+45° (C 1,5)	$C_{36}H_{53}NO_3 \cdot 1/2H_2O$	77,9	9,8	2,6	77,7	9,7	2,5	98
IV	137	±0° (C 3)	$C_{28}H_{37}NO_4$	—	—	—	—	—	—	80
V	216	+120° (C 1,5)	$C_{29}H_{37}NO_4 \cdot 1/2H_2O$	72,4	8,1	2,9	72,3	8,1	2,9	80

epimeric tryptophols, which have opposite optical rotations. For example, a mixture of epimers VII and VIII is obtained by reduction of I:



VII VIII

The 3β-OH configuration (VII) was assigned to the higher-melting levorotatory stereoisomer, while the 3α-OH configuration (VIII) was assigned to the dextrorotatory epimer. In confirmation of this, one should note that the absorption band at 1057 cm^{-1} in the IR spectrum of epimer VII is more intense than the band at 1025 cm^{-1}, whereas for epimer VIII, on the other hand, the band at 1018 cm^{-1} is more intense than the band at 1043 cm^{-1} [3, 4].

One of the signals under discussion in the PMR spectra of both compounds is repeated in both spectra – at 3.78 ppm for the 3β-OH epimer and at 3.73 ppm for the 3α-OH epimer – and these signals are identical with respect to their half-widths and the character of their splitting, which confirms the axial character of the proton attached to the C_2 atom of the cholestane skeleton. Consequently, the indole residue in both compounds takes on an equatorial configuration.

The signal of the C_3 protons adjacent to the hydroxyl group differ appreciably in character and position – it is found at 3.00 ppm for the 3β-OH epimer (VII) and at 3.26 ppm for the 3α-OH epimer (VIII) – and this makes it possible to suppose that the proton attached to C_3 in epimer VII is axially oriented, while the hydroxyl group is equatorially oriented, respectively; the C_3 proton in epimer VIII is equatorially oriented.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-10 spectrometer. The PMR spectra of deuterochloroform solutions of the compounds were recorded with a JNM 4H-100 spectrometer with hexamethyldisiloxane as the internal standard. The UV spectra of methanol solutions were recorded with a Specord spectrophotometer.

2-(3-Dioxindolyl)keto Steroids (I-V). A 1.8-ml sample of diethylamine was added to a mixture of solutions of 0.01 mole of isatin or its homolog in 0.01 mole of the keto steroid in 50 ml of absolute alcohol, and the mixture was stirred at 20° for 24 h. The products either precipitated from the reaction mixture spontaneously or were precipitated by the addition of water. Their characteristics are presented in Table 1.

2-(3-Dioxindolyl)-17α-methyldihydrotestosterone Diacetate (VI). A solution of 0.45 g of IV in 2 ml of pyridine was treated with 5 ml of acetic anhydride, and the mixture was allowed to stand overnight. The product was isolated in the usual manner to give colorless crystals (20%) with mp 212° (from methanol). Found, %: C 69.6; H 7.9; N 2.5. $C_{32}H_{41}NO_6 \cdot H_2O$. Calculated, %: C 69.4; H 7.8; N 2.5. IR spectrum (mineral oil), cm^{-1}: 3530, 1770, 1760, 1720, 1700, 1615, 1380, 1235, and 1180. UV spectrum, λ_{max}, nm (log ε): 203 (4.66), 232 (4.28).

Reduction of 2-(3-Dioxindolyl)-3-ketocholestane (I). A 1-g sample of lithium aluminum hydride was added to 1 g of I in absolute THF, and the mixture was refluxed for 12 h. After the usual workup of the reaction mixture, the product was extracted with dichloroethane, and the extract was washed with water and dried with sodium sulfate. The dichloroethane was evaporated to dryness, and the residue was dissolved

in alcohol. A total of 0.2 g (20%) of VII with mp 243° precipitated. Found, %: C 83.5; H 10.8; N 2.9. $C_{35}H_{52}NO$. Calculated, %: C 83.8; H 10.4; N 2.8. $[\alpha]_D^{20}$ −24° (c 2.7, pyridine). IR spectrum, cm^{-1}: 3200-3600, 2950, 1630, 1467, 1388, 1345, 1057, and 1025. UV spectrum λ_{max}, nm (log ε): 223 (4.50), 283 (3.61), and 289 (3.54). PMR spectrum, δ, ppm: 0.58 (s,* CH_3 attached to C_{18}), 0.84 (s, CH_3 attached to C_{19}), 3.00 (split t, 3-α-proton), 3.78 (m, 2-α-proton), 7.00-7.55 (m, protons attached to C_5, C_6, and C_7 of the benzene ring of indole), 7.66 (q, C_4 proton of benzene), and 8.18 (d, NH).

Concentration of the filtrate gave 0.2 g (20%) of VIII with mp 180°. Found, %: C 83.4; H 10.6; N 2.9. $C_{35}H_{52}NO$. Calculated, %: C 83.8; H 10.4; N 2.8. $[\alpha]_D^{20}$ + 64° (c 2.5, pyridine). IR spectrum, cm^{-1}: 3200-3600, 2950, 1630, 1465, 1388, 1343, 1043, and 1018. UV spectrum, λ_{max}, nm (log ε): 223 (4.53), 283 (3.78), 2.89 (3.72). PMR spectrum, δ, ppm: 0.60 (s, CH_3 attached to C_{18}), 0.86 (s, CH_3 attached to C_{19}), 3.26 (split t, 3-e-proton), 3.73 (m, 2-α-proton), 6.90-7.40 (m, protons attached to C_5, C_6, and C_7), 7.54 (q, benzene C_4 proton), and 8.13 (broad s, NH).

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* The following abbreviations are used here and subsequently: s is singlet, d is doublet, t is triplet, q is quartet, and m is multiplet.