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SYNTHESIS OF 5,7-DIHYDRO-6H-INDOLO[2,3-c]QUINOLIN-6-ONES

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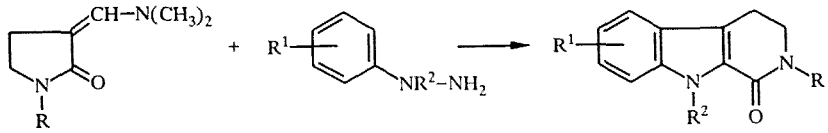
A new synthesis of derivatives of 5,7-dihydro-6H-indolo[2,3-c]quinolin-6-one was accomplished by the reaction of 1-methyl-3-formyloxindole with phenylhydrazines.

In previously published works [1, 2], we described the reaction of enamines of aliphatic α-formyllactams (I) with arylhydrazines, which is accomplished by the enlargement of the lactam ring leading to β-carboline derivatives (II).



I II

Interest was presented by the extension of this reaction to the aromatic lactam oxindole. In this case, we would manage to accomplish a principally new and simple synthesis of derivatives of indolo[2,3-c]quinoline, interest in which is determined by their high and varying biological activity. In particular, marked antitumor activity was found for 5,7-dihydro-6H-indolo[2,3-c]quinolin-6-ones [3-5]. However, known methods for their synthesis are fairly complex. Thus, key compounds utilized are the amides of 3-(2-fluorophenyl)indole-2-carboxylic acid [6, 7], which are not readily available, or 3-azido-4-phenyl-3,4-dihydroquinolin-2-one [4, 5].

In the given work, we investigated the reaction of 1-methyl-3-formyloxindole (III) with phenylhydrazines. It was found out that the formation of the expected indoloquinolines (VI) does not occur when the reaction is performed in the conditions of the synthesis of the carbolines (II) (the boiling in isopropyl alcohol in the presence of hydrochloric acid). The reaction stops at the stage of the formation of the hydrazones (IV). One of them [(IVc), R = Ph] was specially obtained as "marker" for the chromatographic monitoring of the course of the reaction. The indoloquinolines (VI) are formed, albeit with low yields of 5-10%, with the strong resinification of the reaction mixture under more drastic conditions — the prolonged boiling of solutions of the aldehyde (III) with hydrochlorides of hydrazines in formic or acetic acids and the fusion with toluenesulfonic acid. Their yield could be increased to 20-40% by the direct addition of the solution of the aldehyde (III) to the boiling solution of the phenylhydrazine in glacial acetic acid saturated with dry HCl. The cyclization of the hydrazone (IV) (R = Ph) under the same conditions did not lead to an increase in the yield of the corresponding indoloquinoline.

In all evidence, the mechanism of the formation of the compounds (VI) and the carbolines (II) [1] is one and the same, and is the combination of two acid-catalyzed rearrangements — the Fischer indolization for (IV) → (V), and the enlargement of the lactam ring for (V) → (VI). Strictly speaking, depending on the concrete conditions, these arrangements may proceed in a different sequence or in parallel (see top of the following page).

The necessity for more drastic conditions in the synthesis of the indoloquinolines (VI) and their lower yields by comparison with those in the synthesis of the carbolines (II) are probably associated with the fact that the enlargement of the oxindole ring, possessing a certain degree of aromaticity, is hampered in comparison with aliphatic lactams.

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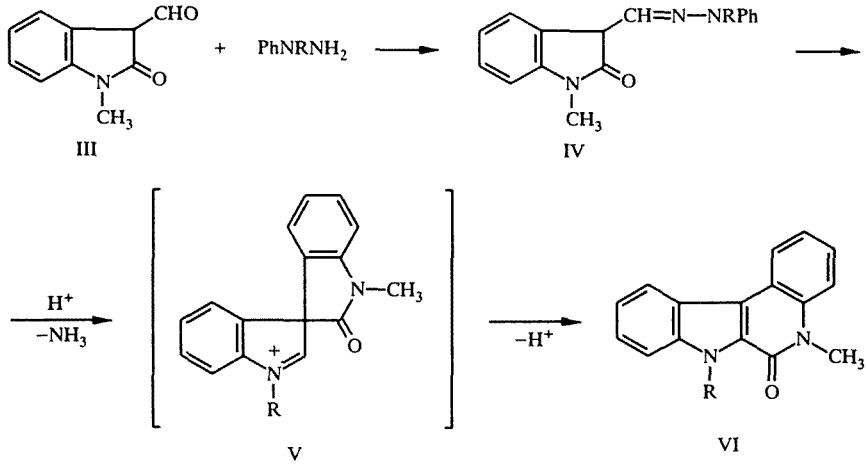
TABLE 1. Characteristics of the Compounds (VIa-d)

Compound	Empirical formula	mp, °C	R_f	IR spectrum, ν, cm^{-1}		PMR spectrum, δ, ppm			Yield, %
				C=O	N—H	5-CH_3 3H, S	7-R S	H_{arom}, m	
VIa	$C_{16}H_{12}N_2O$	292	0,20	1635	3170				20
VIb	$C_{17}H_{14}N_2O$	244	0,50	1640	—	3,68	4,21 (3H,CH_3)	7,0...7,4 (6H), 8,0...8,3 (2H)	19
VIc	$C_{22}H_{16}N_2O$	188	0,50	1650	—				23
VId	$C_{23}H_{18}N_2O$	179	0,65	1650	—	3,67	6,02 (2H, CH_2)	6,9...7,4 (11H), 8,1...8,4 (2H)	41



VI a R = H, b R = CH_3, c R = Ph, d R = CH_2Ph

The structure of the compounds (VI) was confirmed by the data of the elemental analysis and spectral characteristics (cf. the Tables). Thus, the IR spectra contain a strong absorption band of the amide carbonyl group in the region of 1635-1650 cm^{-1}. The UV spectra are the most characteristic for the identification of the compounds (VI). They contain up to 12 absorption maxima, the position of which shows little dependence on the substituent at the indole nitrogen atom. The UV spectra of the indoloquinolines (VI) synthesized by us are presented in Table 2, and are in agreement with the UV spectra of the compounds of this class described in the literature [6]. The compounds (VI) exhibit fairly intense fluorescence in the near UV region, allowing simple chromatographic monitoring to be achieved in both the thin layer and column alternatives. The fluorescence spectra were also registered for the compounds (VI), and the relative quantum yields were determined (cf. Table 2). The PMR spectra of the compounds (VI) are not highly informative due to a large number of aromatic protons, the signals of which are superimposed and appear in the form of multiplets. The accurate assignment of the signals can only be performed for the methyl groups and the methylene group of the benzyl radical at the nitrogen atoms. It should be noted that the signals of the methyl and methylene groups at the indole nitrogen atom in the compounds (VIb) and (IVd) are shifted to low field by 0.5 and 0.9 ppm less correspondingly by comparison with the analogous derivatives of indole not having the amide group at the position 2. That fact, which is also observed for the carbolines (II), indicates the close steric disposition of the amide carbonyl and the substituent at the indole nitrogen atom.

EXPERIMENTAL

The IR spectra were taken on the Specord IR-75 instrument using KBr tablets. The UV spectra were taken on the Hitachi EPS-3T spectrophotometer in isopropyl alcohol. The fluorescence spectra were taken on the same spectrophotometer in isopropyl

TABLE 2. UV Absorption Spectra and Fluorescence Characteristics of the Compounds (VIa-d)

Compound	UV spectrum, λ_{max}, nm (log ε)	Fluorescence	
		λ_{max}, nm	quantum yield
VIa	220 (4,33) 238 (4,46), 250 (4,51), 257* (4,51), 263 (4,49), 271 (4,33), 285 (3,82), 297 (3,38), 310 (4,01), 323 (3,91), 336 (4,10), 352 (4,11)	357, 374, 388*	0,44
VIb	221 (4,45), 241 (4,53), 252 (4,57), 257 (4,56), 266 (4,56), 288 (3,87), 298 (3,96), 314 (4,02), 331* (3,99), 345 (4,21), 363 (4,21)	369, 386, 404*	0,45
VIc	208 (4,48), 239 (4,57), 255 (4,62), 264* (4,51), 273 (4,32), 284* (3,91), 297 (3,96), 310 (4,02), 330* (4,07), 343 (4,24), 358 (4,22)	370*, 387, 407	0,30
VId	218 (4,50), 239 (4,55), 255 (4,57), 265 (4,55), 273 (4,38), 287 (3,88), 297 (3,96), 314 (4,03), 332* (4,06), 345 (4,25), 362 (4,24)	367, 384, 403	0,35

*Shoulder

alcohol with the utilization of the G-3 fluorescence attachment. The wavelength of the excitation of the fluorescence was 340 nm. The relative quantum yields of the fluorescence were determined using 3-aminophthalimide as the standard. The PMR spectra were recorded on the Bruker CXP-200 instrument in CDCl, using TMS as the internal standard. The mass spectra were obtained on the Varian MAT-311-A instrument with the direct introduction of the sample at the ion source and the energy of the ionizing electrons of 70 eV. The melting temperatures were measured on the Mettler FP-5 instrument. The monitoring of the course of the reaction and the purity of the products was accomplished using TLC on plates of Silufol UV-254, with the development in UV light or iodine vapor. The R_f values were determined for the 3:1 system of benzene–ether.

The data of the elemental analysis of the compounds synthesized for C and H correspond with the calculated data.

The 1-methyl-3-formyloxindole (III) was obtained by the Claisen condensation of 1-methyloxindole with ethyl formate by the action of sodium ethoxide [8]; the yield was 88%.

1-Methyl-3-formyloxindole Diphenylhydrazone (IV) (R = Ph) ($C_{22}H_{19}N_3O$). The solution of 350 mg (2 mmoles) of the aldehyde (III) and 370 mg (2 mmoles) of 1,1-diphenylhydrazine in 25 ml of benzene is boiled with the distillation of water in the presence of catalytic amounts of p-toluenesulfonic acid in the course of 8 h. The benzene is evaporated, and the residue is recrystallized from ethyl alcohol. The yield of 450 mg (66%) of the hydrazone (IV) is obtained; it has the mp 174-176°C and the R_f 0.73. The IR spectrum ($CHCl_3$) was as follows: 3260 cm^{-1} (N–H of the enhydrazine form), 1675 cm^{-1} (C=O), and 1600-1630 cm^{-1} (C=C of the enhydrazine form and C=N of the hydrazone form). The UV spectrum, given as the λ_{max} (log ε), was as follows: 274 nm (4.39), 312 nm (4.10), and 344 nm (4.04). Found: M^+ 341. Calculated: M 341.41.

General Method for the Isolation of 5-Methyl-7-R-5,7-dihydro-6H-indolo[2,3-c]quinolin-6-ones (VIa-d). To 2 mmoles of the hydrochloride or sulfate of the corresponding phenylhydrazine are added 15 ml of glacial acetic acid. The mixture is saturated with dry HCl and heated to boiling prior to the dropwise addition of the solution of 2 mmoles of the aldehyde (III) in 10 ml of glacial acetic acid. The reaction mixture is boiled for 1 h, and the acetic acid is evaporated in vacuo. The residue is dissolved in 30 ml of chloroform. The solution is washed with water (2 × 15 ml) and dried with $MgSO_4$; the solvent is evaporated in vacuo. The compounds (VIa-d) are separated chromatographically on a column 15 × 1 cm with silica gel 40-100 μm, with the elution by the 3:1 system of benzene–ether. Recrystallization is performed as follows: (VIa) from the 1:1 mixture of dioxane–ethyl acetate, (VIb) from ethyl acetate, (VIc) from ethyl alcohol, and (VId) from the 1:1 mixture of ethyl acetate–methyl alcohol. The characteristics of the compounds (VIa-d) are presented in the Tables. The mass spectrum of compound (VIc), given as the *m/z* (%), was as follows: 324 (100, M^+), 308 (10), 295 (11), 165 (12), 162 (19), 77 (12), 71 (11), 57 (19), and 55 (12).

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