N-DEALKYLATION OF 2-(tert-BUTYL)-3-HYDROXY-3-(4-CHLOROPHENYL)ISOINDOLINONE AND N-(tert-ALKYL)-2-AROYLBENZAMIDES IN CONCENTRATED SULFURIC ACID

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It has been established that 2-(tert-butyl)-3-hydroxy-3-(4-chlorophenyl)isoindolinone and N-(tert-Alkyl)-2-aroylbenzamides are dealkylated in concentrated sulfuric acid to give 3-hydroxy-3-arylisoindolinones. The reaction is realizable only when there is a tert-alkyl group attached to the nitrogen atom. The reaction mechanism is discussed on the basis of data on the change with time in the electronic spectra of the investigated compounds in concentrated sulfuric acid and a comparison with the spectra of model structures.

Nitrogen-unsubstituted and N-monosubstituted 2-acylbenzamides exist in the stable chain form of 3-hydroxyindolinones. Cases in which closing of the hydroxyindolinone ring is impossible because of the large volume of the substituent attached to the nitrogen atom or the keto group and in which the substituent attached to -he nitrogen atom has a strong —I effect constitute exceptions to this rule [1]. We have recently shown [2] that N-tert-butyl)-2-aroylbenzamides in both the amide (I) and chain (II) form of 2-(tert-butyl)-3-aryl-3-hydroxyisoindolinones can be obtained when electron-acceptors (NO_2 and CL) are introduced in the benzoyl group.

The aim of the present research was to study the possibility of realizing I → II isomerization in solutions in concentrated sulfuric acid.

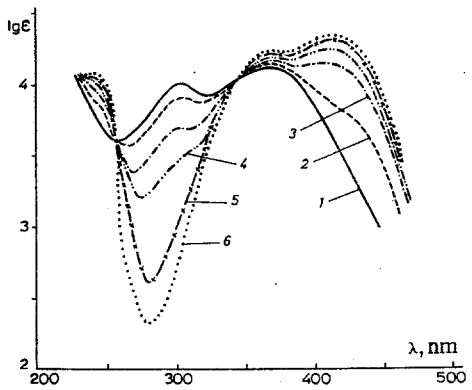

Fig. 1

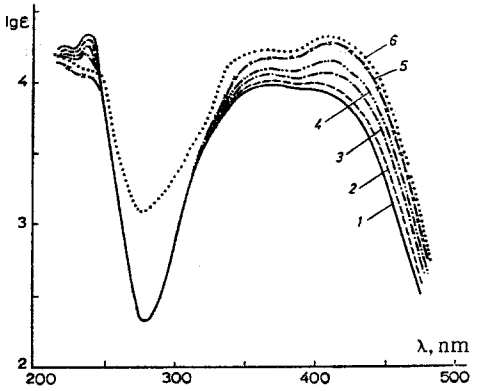

Fig. 2

Fig. 1. Electronic spectrum of a solution of N-(tert-butyl)-2-(4-chlorobenzoyl)benzamide (Ia) in concentrated H_2SO_4: 1) 5 min from the time of dissolving; 2) after 10 min; 3) after 20 min; 4) after 30 min; 5) after 90 min; 6) after 24 h.

Fig. 2. Electronic spectrum of a solution of 2-(tert-butyl)-3-hydroxy-3-(4-chlorophenyl)isoindolinone (IIa) in concentrated H_2SO_4: 1) 5 min from the time of dissolving; 2) after 10 min; 3) after 20 min; 4) after 30 min; 5) after 90 min 6) after 24 h.

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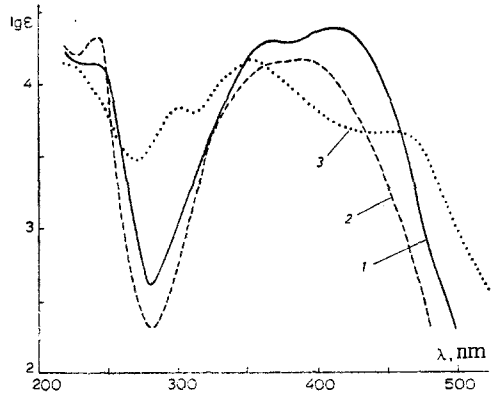
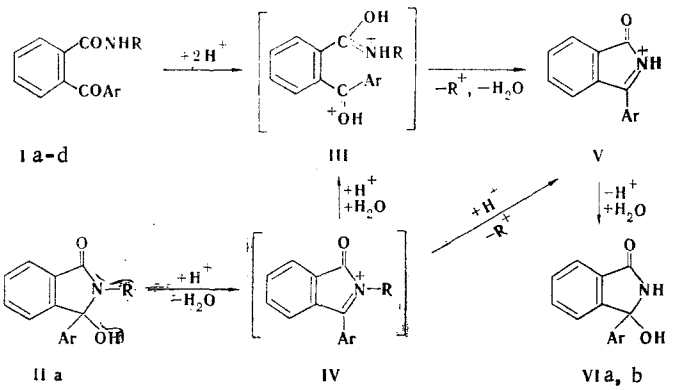


Fig. 3. Electronic spectra of solutions in concentrated H_2SO_4: 1) VIa; 2) IIb; 3) Ie.

During an attempt to accomplish the cyclization of Ia we found that in concentrated sulfuric acid at room temperature the tert-butyl group is split out to give the chain isomer of the nitrogen-unsubstituted amide — 3-hydroxy-3-(4-chlorophenyl)isoindolinone (VIa). A similar dealkylation reaction has been described [3, 4] for some N-tert-alkyl)amides. Cleavage of the C-N bond to give VIa is also realized when the isomer of amide Ia — 2-(tert-butyl)-3-(4- chlorophenyl)-3-hydroxyisoindolinone (IIa) — is dissolved in concentrated sulfuric acid. The dealkylation reaction takes place only when a tert-alkyl group that is most capable of forming a carbonium ion is attached to the nitrogen atom. The starting compounds were recovered when 2-phenyl-, 2-propyl-, or 2-isopropyl-3-phenyl-3-hydroxyisoindolinones were dissolved in concentrated sulfuric acid.

Other N-(tert-alkyl)-2-aroylbenzamides that are incapable of cyclization under alkaline catalysis conditions were also subjected to dealkylation. The corresponding 3-hydroxy-3-arylisoindolinones (VIa, b) were obtained from N-(1-adamantyl)- and N-(1,1,3,3-tetramethylbutyl)-2-(4-chlorobenzoyl)benzamides (Ib, c) and N-(tert-butyl)-2-benzoylbenzamide (Id).

In order to study the reaction mechanism we recorded the electronic spectra of Ia and IIa in concentrated sulfuric acid (Figs. 1 and 2). The spectra change with time in both cases, and the absorption curves of these solutions after 24-48 h are extremely similar to the absorption curve of a solution of 3-hydroxy-3-(4-chlorophenyl)isoindolinone (VIa) in concentrated sulfuric acid (Fig. 3). We used N-isopropyl-2-(2,4-dimethylbenzoyl)benzamide (Ie) and 2-isopropyl-3-hydroxy-3-(4-chlorophenyl)isoindolinone (IIb) as model compounds. The spectra of solutions of these compounds in concentrated sulfuric acid do not change in the course of 48 h and, in our opinion, correspond to immonium structures III and IV (Fig. 3). The formation of 1-oxo-1H-isoindolium cations (IV) in solutions of 2-substituted 3-hydroxy-3-arylisoindolinones in concentrated sulfuric acid was confirmed in [5, 6]. Compounds Ie and IIb were recovered unchanged after dilution of the solutions with water.



I a R=t-C_4H_9, Ar=4-ClC_6H_4; b R=1-adamantyl Ar=4-ClC_6H_4; c R=$C(CH_3)_2CH_2C(CH_3)_3$, Ar=4-ClC_6H_4; d R=t-C_4H_9, Ar=C_6H_5; e R=i-C_3H_7, Ar=2,4-$(CH_3)_2C_6H_3$; II a R=t-C_4H_9, Ar=4-ClC_6H_4; b R=i-C_3H_7, Ar=4-ClC_6H_4; VI a Ar=4-ClC_6H_4, b Ar=C_6H_5

The initial absorption curves of solutions of Ia and IIa in concentrated sulfuric acid (Figs. 1 and 2) are extremely similar to the absorption curves of solutions of the model compounds — Ie and IIb, respectively (Fig. 3). This observation makes it possible to assume that two different cations (III and IV) are initially formed from Ia and IIa, respectively. In the case of amides I the tert-alkyl group is evidently split out from the protonated amide

group (see [3, 4]), and this is followed by cyclization (III → V → VI). Splitting out of a tert-alkyl group from 2-acylbenzamides that are not capable of cyclization and also from N-(tert-butyl)benzamide [3] constitutes indirect proof of this scheme. Two cleavage pathways (IV → V and IV → III → V) are possible in the case of isoindolinone IIa. The latter scheme, according to which the tert-butyl group is split out from the protonated amide group rather than from the 1-oxo-1H-isoindolium cation (IV), is confirmed by the fact that hydroxyisoindolinone VIa contaminated with the open isomer of amide Ia is isolated from the reaction mixture when a solution of IIa in concentrated sulfuric acid is allowed to stand for a shorter time (10 min).

During a study of the behavior of isomers Ia and IIa in trifluoroacetic acid (99%) solution it was found that amide Ia is recovered unchanged after dilution, whereas amide Ia is isolated in quantitative yield from a solution of hydroxyisoindolinone IIa. Dealkylation does not occur in the less protogenic solvent trifluoroacetic acid. However, the observed isomerization IIa → Ia, in our opinion, constitutes evidence in favor of the II → IV → III → V dealkylation mechanism.

EXPERIMENTAL

The electronic spectra in concentrated sulfuric acid (c $5 \cdot 10^{-5}$ M, l = 1 cm) were recorded with a Specord UV-vis spectrophotometer.

General Method for the Dealkylation of N-(tert-Alkyl)-2-aroylbenzamides (Ia-d) and 2-(tert-Butyl)-3-hydroxy-3-(p-chlorophenyl)isoindolinone (IIa). A 0.5-1.0 g sample of Ia-d or IIa was dissolved with stirring in 5 ml of concentrated H_2SO_4, and the mixture was stirred at this temperature for 1 h. The solutions turned intensely yellow. The mixture was poured over 50-100 g of finely crushed ice, and the resulting precipitate was removed by filtration, washed with water, and dried to give, respectively, VIa or VIb. Compound VIa, with mp 206-208° (from ethanol) (mp 214-217° [7]), was obtained in 96-100% yield. Compound VIb was dissolved in the minimum amount of ether, and the solution was washed successively with 5% sodium carbonate solution and water and dried over magnesium sulfate. The solution was vacuum evaporated, and the residue was recrystallized from ether to give a product with mp 164-165° (mp 167.5-169" [8]) in 30% yield. The IR spectra of the 3-hydroxy-3-arylisoindolinones (VIa, b) were in agreement with the literature data.

Isomerization IIa → Ia in Trifluoroacetic Acid. A solution of 0.5 g (1.5 mmole) of IIa in 3 ml of trifluoroacetic acid (99%) was allowed to stand at room temperature for 30 min, after which it was poured over 50 g of finely crushed ice. The resulting precipitate was removed by filtration and washed with water to give 0.43 g (86%) of a product with mp 144-148°. Recrystallization from benzene gave a product with mp 154-155° (mp 156-157° [2]). Its identity was proved by a mixed-melting-point determination and comparison of the IR spectra.

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