1-ETHYLTHIO-2,3,3-TRIARYLISOINDOLINIUM SALTS AND THEIR REACTIONS WITH NUCLEOPHILIC REAGENTS

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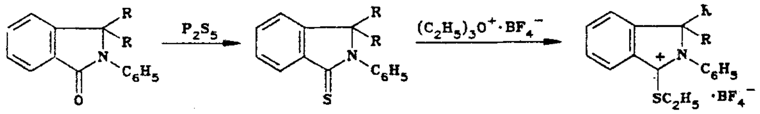
Stable 1-ethylthioisoindolinium salts were obtained by alkylation of 2-phenyl-3,3-diaryl-1-thiophthalimidines with triethyloxonium tetrafluoroborate. The reactions of these salts with O-, N-, and C-nucleophiles were studied.

Products of addition of the nucleophiles to the $C_{(1)}$ atom of the conjugated heterocarbonium ions are generally formed in the reaction of condensed five-membered heterocarbonium ions with one heteroatom (isoindolinium, phthalylium, and thiophthalylium ions). In the case of salts with aromatic substituents in the 1 position this reaction is reversible over a range of acidities that is determined for each compound [1-3]. At the same time, in the case of phthalylium [4, 5] and thiophthalylium [4, 6] salts it has been shown that the reaction proceeds irreversibly in most cases when the aromatic radical attached to the $C_{(1)}$ atom is replaced by an alkoxy or alkylthio group. The resulting products of nucleophilic addition are stabilized in the reaction itself or during purification by splitting out of an alcohol or a mercaptan to give (thio)phthalides or compounds that contain a thiophthalylidene grouping.

Isoindolinium salts with alkoxy and alkylthio groups attached to a positively charged carbon atom have not been described in the literature. In developing our research on five-membered heterocyclic conjugated carbonium ions with one heteroatom we synthesized 1-ethylthio-2,3,3-triarylisoindolinium salts containing two reaction centers – in the ring and in the side chain – and studied their reactions with nucleophiles, viz., hydroxide and methoxide ions, aniline, o,p-toluidines, ethyl cyanoacetate, and Meldrum's acid. The selection of 1-alkylthio-substituted isoindolinium salts was based on data [4] regarding the greater stabilities of thiophthalylium ions with alkylthio radicals as compared with the analogous ions with alkoxy groups.

1-Ethylthioisoindolinium salts IIIa-c were synthesized in high yields (>90%) by alkylation with triethyloxonium tetrafluoroborate of the corresponding 1-thiophthalimidines IIa-c, which were obtained, in turn, by thionation of phthalimidines Ia-c by means of P_2S_5.



Ia-c IIa-c IIIa-c

I-IIIa R=3-$CH_3C_6H_4$; b R=4-$CH_3C_6H_4$; c R=4-ClC_6H_4

Tetrafluoroborates IIIa-c are stable, colorless, crystalline substances that have one intense absorption band (λ_{max} 291-293 nm, log ε 4.24-4.32) in their UV spectra. The position of the maximum is located in the same region of the spectrum as the position of the short-wave maximum in the spectra of 1-arylisoindolinium ions [7], the appearance of which is associated [8] with the presence of an isoindolinium grouping in the cations. These data constitute evidence for the ionic character of salts IIIa-c. Let us note that 1-alkylthioisoindolinium ions absorb in a shorter-wave region of the spectrum as compared with the similarly constructed thiophthalylium ions [6] ($\Delta\lambda \cong 50$ nm); a similar principle is also observed in the case of cations with aromatic radicals attached to the $C_{(1)}$ atom [8].

A study of the electrophilic activity of the 1-alkyl-thioisoindolinium ions was made in the case of tetrafluoroborate IIIa.

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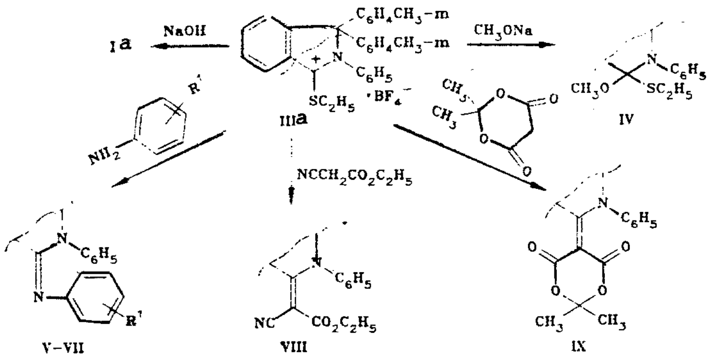

V $R^1=H$, VI $R^1=2\text{-}CH_3$, VII $R^1=4\text{-}CH_3$

In an analysis of the stabilities of isoindolinium, thiophthalylium, and phthalylium ions with aromatic radicals in the 1 position it was established [8] that their resistance to hydrolysis is determined primarily by the nature of the heteroatom. With respect to their degree of participation in delocalization of the positive charge on the $C_{(1)}$ atom these heteroatoms in similarly constructed groups of cations are arranged in the following order: $O < S < N$. A similar relationship is also observed for the cations investigated in the present paper. Thus, whereas air moisture is sufficient for the hydrolysis of 1-alkoxyphthalylium salts and 10% sodium bicarbonate solution is sufficient for the hydrolysis of 1-ethylthio-substituted thiophthalylium salts [4], the hydrolysis of tetrafluoroborate IIIa proceeds only under the influence of 10% sodium hydroxide solution. The hydrolysis of tetrafluoroborate IIIa, as well as phthalylium and thiophthalylium salts with alkoxy and alkylthio groups [4], also proceeds irreversibly with the formation of phthalimidine Ia.

The methoxide ion reacts unambiguously with the 1-ethylthioisoindolinium ion, adding to the carbon atom in the 1 position. The IR spectrum of methyl ester IV contains characteristic bands of stretching vibrations of OCH_3 (2832 cm^{-1}) and C—N (1313 cm^{-1}) groups, and the UV spectrum is represented by a typical (for hydroxyisoindolines [9]) broad absorption band with λ_{max} 261 (log ε 3.9).

The reaction of tetrafluoroborate IIIa with aniline, o,p-toluidines, ethyl cyanoacetate, and isopropylidene malonate in the presence of organic bases (pyridine or triethylamine) yielded the corresponding derivatives V-IX containing an isoindolylidene grouping, the structures of which were confirmed by spectral data.

The IR spectra of 1-aryliminoisoindolines V-VII contain intense absorption bands at 1642-1649 cm^{-1}, which are characteristic for the stretching vibrations of an exocyclic C═N group [10], and bands at 1344-1346 cm^{-1}, which correspond to the stretching vibrations of a ring C—N—C grouping. In addition to the typical (for isoindolines) absorption at 265-290 nm, a pronounced shoulder at 316-323 nm (log ε 3.5-3.7), which is probably due to the presence of an azomethine grouping, appears in the UV spectra of V-VII.

In the IR spectrum of VIII the carbonyl band of an ester grouping is found in the region that is characteristic for α-unsaturated esters (1702 cm^{-1}), and the C—O stretching vibrations show up in the form of two bands at 1243 [C(C═O)—O] and 1128 cm^{-1} (O—C—C). The low frequency of the cyano group (2200 cm^{-1}) and its high intensity also indicate the presence of an unsaturated conjugated Ph—$C_{(1)}$═C grouping [11] in the α position relative to the C≡N bond.

The asymmetrical and symmetrical stretching vibrations of the C═O bond are represented in the IR spectrum of IX by two absorption bands with maxima at, respectively, 1771 and 1672 cm^{-1} Of these bands, the low-frequency band is characterized by greater intensity and asymmetry; this is a consequence of superimposition of the band of stretching vibrations of the $C_{(1)}$═C bond. Thus the formation of an intermolecular hydrogen bond between the carbonyl group and a proton donor (p-nitrophenol) gives rise to a decrease in the intensity of the band at 1672 cm^{-1} and the appearance of a new band at 1640 cm^{-1} (C═O...H—$OC_6H_4NO_2$). The C—H deformation vibrations in the gem-CH_3 groups show up in the form of a characteristic doublet at 1386 and 1373 cm^{-1}.

In contrast to imino derivatives V-VII, VIII and IX absorb in the visible region of the spectrum at, respectively, 363 nm (log ε 4.08) and 395 nm (log ε 3.82).

TABLE 1. Characteristics of the Compounds Obtained

Compound	mp, deg C	Found, %				Empirical formula	Calculated, %				Yield, %
		C	H	N	S (Cl)		C	H	N	S (Cl)	
Ia	150—152	86,1	6,1	3,5	—	$C_{28}H_{23}NO$	86,3	6,0	3,6	—	63
Ic	212—215	72,5	4,1	3,2	(16,3)	$C_{26}H_{17}Cl_2NO$	72,6	4,0	3,3	(16,5)	79
IIa	167—168	83,0	5,8	3,4	7,9	$C_{28}H_{23}NS$	82,9	5,7	3,5	7,9	59
IIb	197—199	83,0	6,0	3,3	7,8	$C_{28}H_{23}NS$	82,9	5,7	3,5	7,9	69
IIc	196—197	70,2	4,1	3,0	7,1 (15,6)	$C_{26}H_{17}Cl_2NS$	70,0	3,8	3,1	7,2 (15,9)	67
IIIa	145—147	68,8	5,6	—	5,9	$C_{30}H_{28}BF_4NS$	69,1	5,4	—	6,1	92
IIIb	187—189	68,9	5,5	—	6,0	$C_{30}H_{28}BF_4NS$	69,1	5,4	—	6,1	93
IIIc	204—207	59,6	4,2	—	5,5	$C_{28}H_{22}BCl_2F_4NS$	59,8	4,0	—	5,7	95
IV	106—109	79,6	6,9	2,8	6,7	$C_{31}H_{31}NOS$	79,9	6,7	3,0	6,9	76
V	178—180	87,8	6,2	5,8	—	$C_{34}H_{28}N_2$	87,9	6,1	6,0	—	94
VI	166—168	87,9	6,5	5,8	—	$C_{35}H_{30}N_2$	87,8	6,3	5,9	—	89
VII	106—108	88,0	6,4	5,9	—	$C_{35}H_{30}N_2$	87,8	6,3	5,9	—	91
VIII	139—141	81,7	5,9	5,7	—	$C_{33}H_{28}N_2O_2$	81,8	5,8	5,8	—	58
IX	211—214	79,0	5,8	2,5	—	$C_{34}H_{29}NO_4$	79,2	5,7	2,7	—	51

The formation of phthalimidine Ia in the hydrolysis of tetrafluoroborate IIIa, as well as isoindolylidene derivatives V-IX in reactions with N- and C-nucleophiles, constitutes evidence that nucleophilic reagents react, as in the case of ions with aromatic substituents attached to the $C_{(1)}$ atom, unambiguously with 1-ethylthioisoindolinium ions at the α-carbon atom of the heteroring with the formation of unstable addition products. However, the latter, in contrast to stable isoindoline derivatives with aromatic radicals, in most cases spontaneously split out ethyl mercaptan during the reaction to give stable Ia and V-IX.

EXPERIMENTAL*

The IR spectra of the compounds in CCl_4 were recorded with a Specord 75-IR spectrometer. The UV spectra of IIIa-c in CH_2Cl_2 and of the remaining compounds in C_2H_5OH were recorded with a Specord UV-vis spectrophotometer. The purity and individuality of the compounds were monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates. Starting phthalimidine Ib was synthesized by the method in [9]. The characteristics of the compounds obtained are presented in Table 1.

2-Phenyl-3,3-di-m-tolyl(p-chlorophenyl)-phthalimidines Ia, c. These compounds were obtained via the Fischer reaction [12] by refluxing a mixture of 16 mmole of the 3,3-di-m-tolyl (p-chlorophenyl)-phthalide [13, 14], 20 g (215 mmole) of aniline, and 10 g (77 mmole) of aniline hydrochloride for 12 h. For isolation of the desired products, the reaction mixtures were treated with a solution of 4.4 g of KOH in 50 ml of water, the aniline was removed by steam distillation, and the residues were crystallized from benzene or ethanol with charcoal. IR spectra: Ia; 1340 (C—N), 1704 cm^{-1} (C=O); Ic; 1338 (C—N), 1710 cm^{-1} (C=O). UV spectra, λ_{max} (log ε): Ia: 262 (3.85), 268 (3.83) sh, 276 (3.78) sh; Ic: 364 nm (3.89) sh.

2-Phenyl-3,3-diaryl-1-thiophthalimidines IIa-c. A mixture of 4.75 mmole of the phthalimidine and 1.2 g (5.4 mmole) of P_2S_5 in 25 ml of anhydrous o-xylene was refluxed for 30 min, and the hot solution was filtered. The solvent was removed, and the residue was recrystallized from ethanol to give thiophthalimidines IIa-c. IR spectra: IIa: 1360 (C—N), 1304 cm^{-1} (C=S); IIb: 1362 (C—N), 1302 cm^{-1} (C=S); IIc: 1355 (C—N), 1302 cm^{-1} (C=S). UV spectra, λ_{max} (log ε): IIa: 266 (4.11), 313 nm (3.98); IIb: 265 (4.14), 313 nm (4.02); IIc: 267 (4.20), 310 (4.04) sh, 320 nm (4.05).

1-Ethylthio-2-phenyl-3,3-diarylisoindolinium Tetrafluoroborates IIIa-c. Solutions containing 2.6 mmole of the corresponding thiophthalimidine IIa-c and 0.49 g (2.6 mmole) of triethyloxonium tetrafluoroborate in 10 ml of anhydrous methylene chloride were maintained at 20°C for 24 h, after which they were diluted with a five-fold volume of absolute ether. The resulting crystalline products IIIa-c were removed by filtration, washed with ether, and purified by reprecipitation from CH_2Cl_2 by means of ether.

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*With the participation of V. A. Shalygina and D. R. Kotskaya.

Hydrolysis of Tetrafluoroborate IIIa. A suspension of 0.26 g (0.5 mmole) of salt IIIa in 30 ml of ether was treated with 10 ml of 10% NaOH solution until the salt had dissolved completely, after which the ether layer was separated, washed with water (three 10-ml portions), and dried with Na_2SO_4. Removal of the solvent and crystallization of the residue from ethanol gave colorless crystals (89% yield) that did not depress the melting point of phthalimidine Ia and were identical to the latter with respect to their chromatographic mobility and spectral characteristics.

1-Methoxy-1-ethylthio-2-phenyl-3,3-di(m-tolyl)isoindoline (IV). A 0.4-g (0.77 mmole) of salt IIIa was added in portions with stirring to 5 ml of a cooled (to 5°C) solution of sodium methoxide (0.3 mole/liter) in CH_3OH. After 30 min, the resulting colorless crystalline precipitation was removed by filtration and recrystallized from hexane to give ether IV.

1-Arylimino-2-phenyl-3,3-di(m-tolyl)isoindolines V-VII. A 0.2-g (0.38 mmole) sample of tetrafluoroborate IIIa was added with stirring to a solution of 0.38 mmole of the corresponding aromatic amine in 1 ml of anhydrous pyridine. After 1 h, the reaction mixture was diluted with 25 ml of cold water, and the precipitate was removed by filtration, washed with water, dried, and recrystallized from ether–hexane (1:2).

Ethyl [2-Phenyl-3,3-di(m-tolyl)isoindolin-1-ylidene)-cyanoacetate (VIII). A solution of 0.3 ml (2.13 mmole) of triethylamine in 1 ml of CH_2Cl_2 was added to a solution of 0.5 g (0.96 mmole) of salt IIIa and 0.22 g (1.94 mmole) of ethyl cyanoacetate in 5 ml of anhydrous methylene chloride. After 24 h, the solvent was removed, and the residue was recrystallized from ether–pentane to give VIII.

1-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-2-phenyl-3,3-di(m-tolyl)isoindole (IX). This compound was obtained from 0.5 g (0.96 mmole) of tetrafluoroborate IIIa and 0.28 g (1.94 mmole) of Meldrum's acid by a procedure similar to that in the preceding experiment.

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