FORMATION OF ISOINDOLE DERIVATIVES BY REACTION OF PHTHALONITRILE WITH SODIUM METHOXIDE

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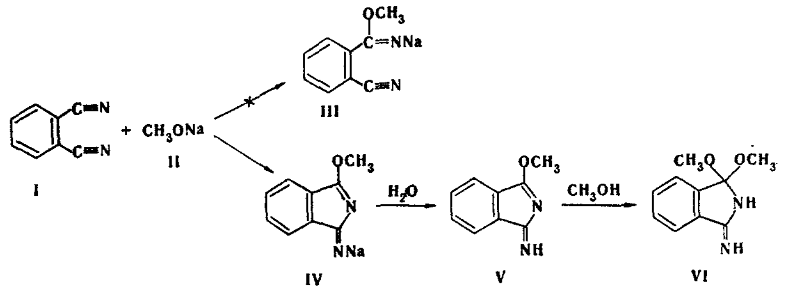
It is shown by means of IR spectra that the reaction of phthalonitrile with sodium methoxide in benzene in the presence of traces of water or methanol proceeds via a series-parallel mechanism in two steps to give cyclic products. The proposed structure of the intermediate is an oligomeric isoindolenine chain with terminal NNa and OCH_3 groups. The final product is the sodium salt of monomethoxyiminoisoindolenine. The analogous reaction in methanol proceeds at a higher rate that makes it impossible to isolate or detect the intermediate; the final product is 1,1-dimethoxy-3-iminoisoindoline.

It is known that phthalonitrile in polar solvents is capable of reacting with nucleophilic reagents to give various isoindole derivatives. The data relative to its reactivity in nonpolar solvents are extremely scanty and, in addition, are contradictory: Drew and Kelly [1] report the absence of any reaction, whereas Borodkin [2] indicates the formation of addition products with noncyclic structures.

We have established that the sodium salt of monomethoxyiminoindolenine (IV) rather than the Na salt of the methyl imino ester of o-cyanobenzoic acid (III), as asserted in [2], is formed in the reaction of phthalonitrile with sodium methoxide in benzene:



The absorption of a $C \equiv N$ bond of both the nitrile itself ($\nu_{C \equiv N} = 2235\ cm^{-1}$) and of the possible complexes or salts of the general formula $RCN \cdot X$, the spectra of which are usually characterized by a shift of 20-30 cm^{-1} in the absorption band to the low-frequency region or broadening of this band [3], is absent in the IR spectrum of the reaction product (Fig. 1, spectrum 4).

In analogy with the spectrum of sodium methoxide (Fig. 1, spectrum 1), the strong absorption at 1070 cm^{-1} can be assigned to the stretching vibrations of the $-OCH_3$ group, and the broad intense band at 1500 cm^{-1} can be assigned to the vibrations of the ionized $-C=N^-$ group bonded to sodium. The correctness of the assignment of the latter band is confirmed by the fact that it vanishes when the product is treated with water (Fig. 1, spectrum 5), and new intense bands characteristic for the stretching vibrations of an exocyclic $C=N$ bond in isoindole rings [4] appear at 1630-1670 cm^{-1}. Absorption with λ_{max} 385 nm characteristic for isoindolenine systems [5, 6] is observed in the UV spectrum of the reaction product in benzene.

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The percentage of sodium in the reaction products is close to the percentage calculated for structure IV, but the product is very unstable and is easily hydrolyzed. A compound, the results of elementary analysis and the IR, UV, and mass spectra of which confirmed the expected 1-methoxy-3-iminoisoindolenine structure V, was isolated in higher than 70% yield when it was treated with water. When the reaction product is treated with dilute hydrochloric acid, it is converted quantitatively to phthalimide, whereas either o-cyanobenzoic acid, o-cyanobenzamide, or phthalic acid should have formed in the case of structure III.

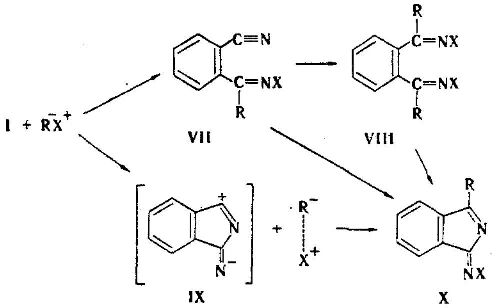
The structure of the reaction product was confirmed definitively by its conversion to the known 1,1-dimethoxy-3-iminoisoindolenine.

Thus phthalonitrile is also capable of forming isoindole derivatives in nonpolar solvents.

In particular, the use of nonpolar solvents may shed light on the mechanism of the cyclization of phthalonitrile to isoindole derivatives, since the reaction rate in this case is markedly slowed down, and this makes it possible to monitor the process.

There is currently no unified point of view regarding the mechanism of formation of isoindole derivatives in the reaction of phthalonitrile with nucleophilic reagents.

In the opinion of some authors [1, 2, 7, 8], phthalonitrile reacts like mononitriles, i.e., through successive opening of the triple bonds and addition of a nucleophilic reagent to the nitrile groups with subsequent intramolecular rearrangement leading to ring closing. In the opinion of others [9, 10], phthalonitrile is converted to a polar isoindolenine form (IX) under the influence of a strongly polarizing medium, and, in the form of a dipolar ion, reacts with various nucleophilic reagents:



However, neither point of view is supported practically by experimental data.

We attempted to study the mechanism of the reaction of phthalonitrile with sodium methoxide by means of IR spectroscopy. The reaction was carried out in dry benzene and methanol at room temperature.

The reaction was monitored from the absorption bands that change during the reaction and have sufficient intensity and the least overlapping by other bands.

The reaction rate in methanol is so high that no intermediate whatsoever can be detected by means of the IR spectra even when the reaction is carried out directly in the spectrophotometer cuvette. Only the spectrum of the final product was obtained (Fig. 1, spectrum 6).

Various authors have assigned 1,1-dimethoxy-3-iminoisoindoline [9], 1-methoxy-3-iminoisoindolenine [11], 1-methoxy-3-iminoisoindolenine sodium salt, and 1-methoxy-3-iminoisoindolenine solvate structures to the product of the reaction of phthalonitrile with methanol in the presence of sodium methoxide.* By reproducing the indicated methods we established that compounds having identical IR and UV spectra and close results of elementary analysis in good agreement with the values calculated for 1,1-dimethoxy-3-iminoisoindoline and monomethoxyiminoisoindolenine solvate are formed in all cases. Because of the extreme instability of the reaction product, we were unable to directly determine the solvate methanol. The choice between the two possible structures was made on the basis of the IR and UV spectra.

Intense bands of stretching vibrations of an exocyclic $C = N$ bond (ν 1690 cm^{-1}) and a band of stretching vibrations of OCH_3 (ν 1080 cm^{-1}) and NH (ν 3440 cm^{-1}) groups are observed in the IR spectrum of the reaction product (Fig. 1, spectrum 6), whereas the absorption characteristic for the stretching vibrations of the OH group at 3600 cm^{-1} is absent. The position of the longest-wave absorption maxima in the electronic spectrum with λ_{max} 220 and 243 nm also corresponds to the isoindoline structure rather than to the isoindolenine struc-

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* Private communication by B. D. Vidkina and L. G. Krolik (Scientific-Research Institute of Organic Intermediates and Dyes, Moscow).

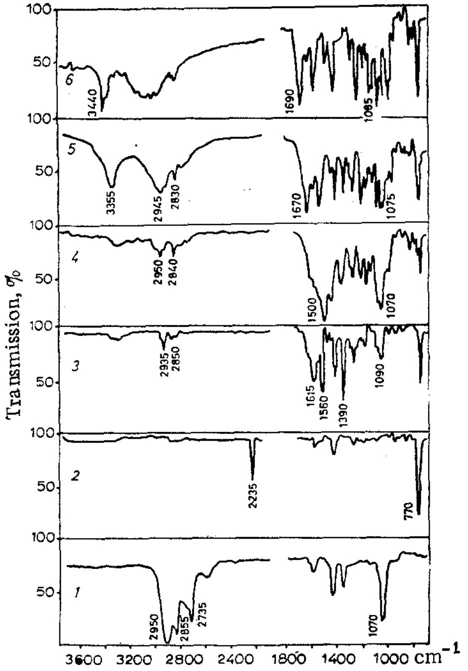


Fig. 1. IR spectra: 1) CH_3ONa in mineral oil; 2) phthalonitrile in benzene (0.16 mm); 3) product A in benzene (0.123 mm); 4) product IV in benzene (0.15 mm); 5) 1-methoxy-3-iminoisoindolenine (V) (KBr pellets); 6) 1,1-dimethoxy-3-iminoisoindoline (KBr pellets).

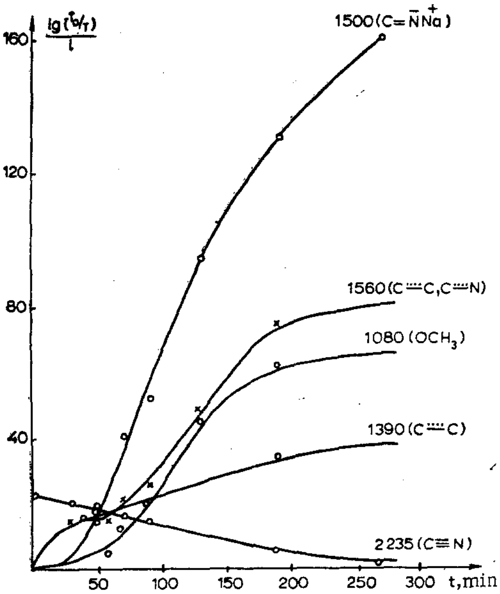


Fig. 2. Time dependence of the intensities of the bands in the IR spectrum of the phthalonitrile–sodium methoxide reaction system in benzene.

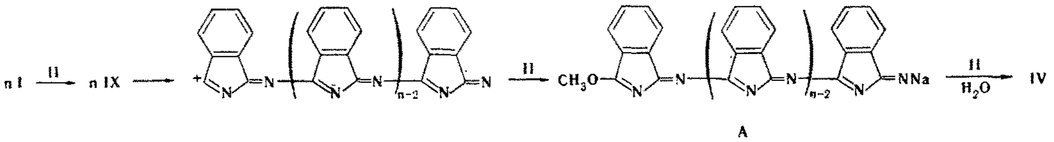
ture, for which, as noted above, maximum absorption at 320-380 nm is characteristic. All this makes it possible to assume that the product of the reaction of phthalonitrile with methanol in the presence of sodium methoxide is 1,1-dimethoxy-3-iminoisoindoline.

Two steps were detected when the reaction was carried out in benzene. Product A, with characteristic absorption bands at 1390 and 1560 cm^{-1}, appears initially as the phthalonitrile concentration decreases ($\nu_{C \equiv N}$ = 2235 cm^{-1}), a certain time after which final product IV, with characteristic bands at 1070 and 1500 cm^{-1} (Fig. 1, spectra 3 and 4), appears.

The overall character of the change in the intensities of the absorption bands in the IR spectrum of the reaction mixture (Fig. 2) corresponds to series-parallel reactions: Intermediate A appears as phthalontrile is consumed; as the concentration of intermediate A increases, the intensity of the absorption band of final product IV increases.

Intermediate A, isolated from the reaction mixture, reacts with sodium methoxide to give final product IV. Intermediate A is an extremely unstable compound, as a consequence of which we were unable to obtain it in analytically pure form. It contains ~2% sodium and is converted quantitatively to phthalimide on treatment with dilute hydrochloric acid. The IR spectrum of intermediate A (Fig. 1, spectrum 3) does not contain a $\nu_{C \equiv N}$ band at 2235 cm^{-1}. These data constitute evidence that product A cannot have structure VII or VIII. The intense bands at 1390 and 1560 cm^{-1} can be assigned only to the skeletal vibrations of conjugated C=C and C=N bonds, and the bands at 1615 cm^{-1} possibly characterize an oligomeric conjugated chain (−C=N−C=N−), since the spectra of the products of polymerization of acetonitrile contain absorption of similar intensity in similar positions [12, 13]. The less intense bands (2935, 2853, and 1090 cm^{-1}) constitute evidence for the presence of an $-OCH_3$ group in the molecule. The electronic spectrum of product A contains intense absorption in the long-wave region (λ_{max} 450 nm in benzene) characteristic for a multimembered conjugated chain. It should be noted that various isoindoline derivatives, including those containing polynuclear aromatic substituents, absorb in the shorter-wave region (370-380 nm) [5]. These data make it possible to assume that product A has the structure of an oligomeric isoindolenine chain with terminal OCH_3 and NNa groups; the tendency of isoindolenines to form oligomeric compounds has also been noted previously [9].

Thus compounds with the VII or VIII structure are not detected in either the reaction products or their transformation products. Moreover, the formation of A is most easily represented as being the result of stabilization of a chain of dipolar ions by sodium methoxide:



The relative ease of destruction of the oligomeric alkoxyiminoisoindolenines to monomers under the influence of bases has been described in [9]. The proposed reaction scheme also explains the experimental fact that product A is practically always obtained at the same rate, whereas the yields of final products after identical times are different. In some cases the reaction of A does not proceed further. The addition of small amounts of water or alcohol to the reaction mixture markedly accelerates the second step of the reaction.

Despite the fact that the data that we obtained in this study are still inadequate for a definitive conclusion regarding the mechanism of the cyclization of phthalonitrile, they nevertheless make it possible to assume that reaction through the initial formation of a dipolar ion is more likely.

EXPERIMENTAL

The IR spectra of the compounds were recorded with a UR-10 spectrometer. The UV spectra were recorded with an SF-4A spectrophotometer.

The reaction in benzene was carried out at room temperature in a stream of dry nitrogen with constant stirring. A solution of phthalonitrile and a suspension of sodium methoxide were used. The samples for the spectra were selected from the reaction flask after 15-30 min in the form of the residual solution. Prior to the start of the reactions, the absence of water, alkali, and sodium carbonate in the reagents was established from their spectra; the spectrum of sodium methoxide was in agreement with the reported spectrum [14]. Control reactions of phthalonitrile in benzene with the possible CH_3ONa impurities (water, sodium carbonate, and alkali) did not give products. No changes in the spectra of the selected samples in the spectral cuvettes (NaCl, 0.12-0.16 mm) were observed during the time required to record the spectra (20-25 min).

Reaction Product A. A solution of 1.28 g (0.01 mole) of phthalonitrile in 50 ml of benzene (distilled over sodium metal) was placed in a flask thoroughly protected from H_2O and CO_2 from the air, and 1.35 g (0.025 mole) of sodium methoxide was added with vigorous stirring. After 15-20 min, a yellow coloration appeared. The mixture was then filtered, and the unchanged sodium methoxide was washed with a small amount of benzene. The filtrate was vacuum evaporated without heating, and the resulting precipitate was found to be a mixture of the starting phthalonitrile and reaction product A. The mixture was separated by treatment with a small amount of cooled (to 5°) CCl_4, in which phthalonitrile is only slightly soluble, and the filtrate was vacuum evaporated without heating. The resulting precipitate was again treated with cooled CCl_4. This operation was repeated until the phthalonitrile vanished (monitored from the IR spectrum). The product was a brownish-yellow compound that changed to green at 100° and did not melt at 300°. The sodium content was ~2%; λ_{max} 450 nm (benzene).

Reaction Product IV. A mixture of 1.28 g (0.01 mole) of phthalonitrile, 1.35 g (0.025 mole) of sodium methoxide, 0.2115 g (0.0117 mole) of water, and 50 ml of benzene was stirred in a flask in a stream of dry nitrogen until the phthalonitrile vanished. The reaction was complete after 1.5-2 h. The brownish-yellow suspension was removed from the unchanged sodium methoxide by filtration and washed with a small amount of benzene. The benzene solution was diluted with an equal volume of dry petroleum ether, and the resulting precipitate was removed by filtration, washed with petroleum ether, and vacuum dried to give 1 g of a brownish-yellow substance that turned blue-green when it was heated above 100° and did not melt at 300°. Found: Na 10.4%. $C_7H_7N_2ONa$. Calculated: Na 12.6%. UV spectrum: λ_{max} 385 nm (in benzene).

1-Methoxy-3-iminoisoindolenine (V). A 0.64-g sample of IV was suspended in 20 ml of cold (5°) distilled water, after which the solid material was removed by filtration and washed to neutrality to give 0.42 g (74.2%) of slightly greenish V with mp 140-142° (from benzene). Found: C 67.17; H 5.18; N 17.77%. $C_9H_8N_2O$. Calculated: C 67.5; H 5.0; N 17.9%. The mass spectrum contained an intense molecular ion peak with m/e 160, corresponding to the theoretical value for empirical formula $C_9H_8N_2O$, and peaks at m/e 129 and 128, which characterize splitting out of CH_3OH and CH_3O fragments. UV spectrum: λ_{max} 300 nm (in benzene).

1,1-Dimethoxy-3-iminoisoindoline. A 0.3-g sample of indolenine V and 0.01 g of sodium methoxide were dissolved in 3 ml of absolute methanol, and the solution was allowed to evaporate in a vacuum desiccator to one-third of its original volume. The resulting white precipitate was removed by filtration, washed with cold methanol, and air dried to give 0.28 g of a white product with mp 126-130°, which, according to the IR and UV spectra, was identical to 1,1-dimethoxy-3-iminoisoindoline.

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