# REACTION OF ANHYDRIDES OF DICARBOXYLIC ACIDS OF SIX-MEMBERED NITROGEN HETEROCYCLES WITH CH-ACID COMPOUNDS

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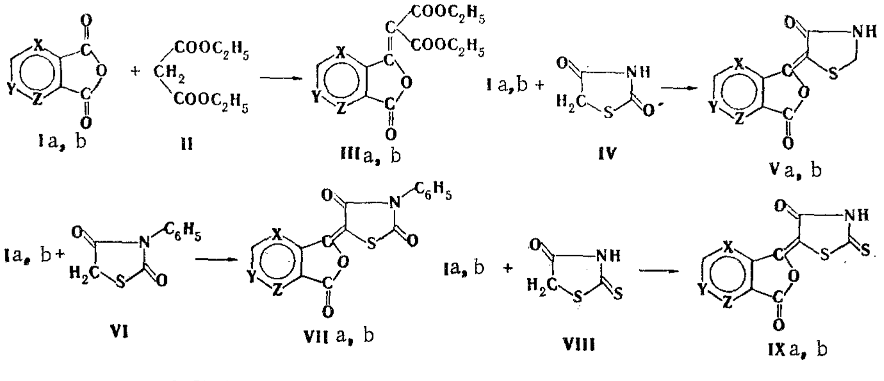
Condensation products with azaphthalidylidene structures were obtained by the reaction of anhydrides of cinchomeronic and pyrazine-2,3-dicarboxylic acids with malonic ester, thiazolidine-2,4-dione, N-phenylthiazolidine-2,4-dione, and rhodanine. Azaindan-1,3-dione derivatives were synthesized with cyanoacetic ester and malononitrile under the same conditions. The reaction of these anhydrides, as well as quinolinic acid anhydride, with α- and γ-methylquinolines, as well as 2,6-lutidine, gave compounds that have azaphthalidylidene structures, which were converted to azaquino- and pyrophthalones by the action of sodium methoxide.

It is known that phthalic anhydride and its derivatives readily undergo condensation with CH-acid methylene or methyl components [1] to give indan-1,3-dione derivatives or phthalidylidene derivatives. The latter in many cases can be isomerized to 2-substituted indan-1,3-diones, which are used as analytical reagents, blood anticoagulants, psychopharmacological and ganglion-blocking agents, rodent poisons, dyes, photoelectric semiconductors, etc. [2].

We attempted to extend these reactions to anhydrides of heterocyclic dicarboxylic acids and to ascertain peculiarities of these reactions in this case, since only individual examples of such reactions are described in the literature [3-8].

We used malonic ester (II), thiazolidine-2,4-dione (IV), N-phenylthiazolidine-2,4-dione (VI), rhodanine (VIII), cyanoacetic ester (Xa), and malononitrile (Xb) as the methylene components in reactions with anhydrides of cinchomeronic (Ia), pyrazine-2,3-dicarboxylic (Ib), and quinolinic (Ic) acids.

We established that anhydrides Ia, b react with II, IV, VI, and VIII in acetic anhydride in the presence of triethylamine or in pyridine with the addition of piperidine at room temperature to give the corresponding aza- and diazaphthalidylidene derivatives in good yields. The same compounds are formed by both methods; however, in some cases (Vb, VIIb, and IXa) it is better to carry out the reaction in pyridine, since in this case the yields of the reaction products are higher.



I, V, VII, IX a X=Z=CH, Y=N; b X=Z=N, Y=CH

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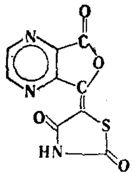
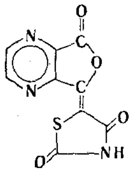
In the condensation of anhydrides Ia, b with the same methylene components under the same conditions anhydride Ib proved to be more active (the yields of the reaction products are higher in this case).

Resinous products from which we were unable to isolate analytically pure compounds were formed when the reactions with anhydride Ic were carried out by both methods.

The IR spectra of IIIa, b, Va, b, VIIa, b, and IXa, b contain absorption bands at 1810-1820 cm$^{-1}$, which can be assigned to the stretching vibrations of the carbonyl group of the phthalide, and bands at 1640-1660 cm$^{-1}$, which we assigned to stretching vibrations of a double bond.

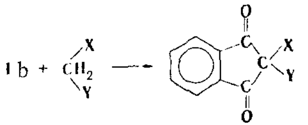
Compounds V, VII, and IX can theoretically exist in two stereoisomeric A and B forms.


A


B

Since we did not detect these isomers by chromatography, only one of them is evidently formed in the reaction. Configuration B is, in our opinion, preferable, although we did not specifically examine this problem.

When we carried out the reaction of anhydride Ib with cyanoacetic ester and malononitrile in pyridine with the addition of piperidine, we observed the formation of compounds that, on the basis of their IR spectra, should be classified as diazaindandione derivatives: The IR spectra of both compounds contain absorption bands at 1700 cm$^{-1}$, which are also characteristic for other cyclic diketones such as phthalones [2].

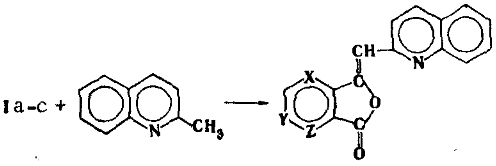

Xa, b XIa, b

Xa, XIa X=CN, Y=COOC$_2$H$_5$; Xb, XIb X=Y=CN

This result is in agreement with the data in [9], in which 2-cyanoindan-1,3-dione was obtained under similar conditions in the reaction of phthalic anhydride with malonic acid malonic acid.

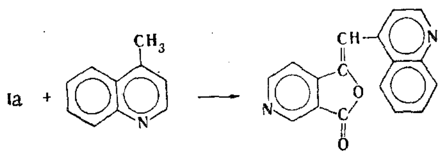
We investigated quinaldine (XII), lepidine (XIV), 2,6-lutidine (XVI), and α- and γ-picolines as the CH-acid methyl components. It is known that quino- and pyrophthalones are formed in the high-temperature condensation of these compounds with phthalic anhydride; however, when the reaction is carried out with quinaldine at up to 155°C, isoquinophthalone-3-(2-quinolylmethylene)phthalide is formed. The yields of isoquinophthalones do not exceed 25%, whereas phthalones are usually formed in good yields [1].

When we carried out the reaction under conditions for which phthalones are usually obtained (fusion and condensation in a high-boiling solvent), we observed resinification of the reaction mass and were unable to isolate the reaction products. Good results were obtained when the reaction was carried out in solution in acetic anhydride at no higher than 160°C. Thus heating a mixture of each of the three anhydrides with XVI in acetic anhydride at 100-160°C leads to the formation of XIII in 61-88% yields:


XII XIIIa-c

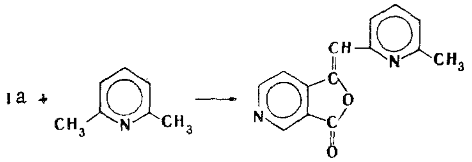
XIII a X=Z=CH, Y=N; b X=Z=N, Y=CH; c Y=Z=CH, X=N

The reaction also proceeds well with lepidine; however, in this case we obtained an analytically pure sample of only the product of the reaction of Ia with XIV:



XIV XV

The reactions with methylpyridines do not proceed nearly as well under these conditions. Resinification of the reaction mass occurs with α- and γ-picolines. The yield of the product of the reaction of Ia with XVI does not exceed 25%. The reaction in this case takes place at one methyl group, as was also observed in the case of phthalic anhydride [10]:

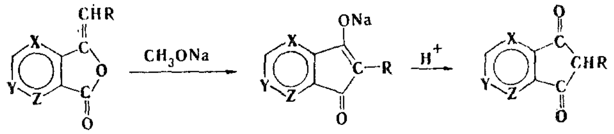


XVI XVII

All of the condensation products obtained under these conditions have isophthalone structures. Their IR spectra contain an absorption band at 1785-1790 $cm^{-1}$, which is characteristic for phthalide derivatives, and an absorption band at 1640-1660 $cm^{-1}$, which is characteristic for the stretching vibration of the double bond of phthalidylidene derivatives.

Chromatography of the crude products showed in all cases that they contained, in addition to the principal product, which has an azaphthalidylidene structure, small amounts of admixed azaphthalones, which were identified by comparison of the $R_f$ values of the impurities with the $R_f$ values of genuine samples.

The compounds obtained (XIIIa-c, XV, and XVII) very readily undergo rearrangement to azaphthalones when they are treated with a methanol solution of sodium methoxide via the scheme



XIII a-c, XV XVIII a-e XIX a-e

XIII, XVIII, XIX a-c R=2-quinolyl; d R=4-quinolyl; e R=2-methyl-6-pyridyl, XVIII, XIXa, d, e X=Z=CH, Y=H; b X=Z=N, Y=CH; c Y=Z=CH, X=N.

Compounds XVIIIa-e are red high-melting substances. After treatment with a solution of acid (and sometimes with water), they are converted to yellow products. The IR spectra of these compounds contain an absorption band at 1670-1690 $cm^{-1}$, which corresponds to the stretching vibration of the carbonyl group of the phthalone [2].

In all of the reactions that we investigated we observed the formation of reaction products involving only one carbonyl group. Since Ia and Ic are unsymmetrical, the question as to which carbonyl group undergoes condensation arises.

A similar reaction of anhydride Ia with phenylacetic acid was carried out in [3], and it was demonstrated by a number of transformations of the compound obtained that the reaction takes place at the carbonyl group in the para position relative to the nitrogen heteroatom. Later Neiland and Vanag [4] confirmed the structure of this compound. Moreover, they assigned a 4-azaphthalide structure to the products of condensation of quinolinic acid anhydride with phenylacetic acid and its p-substituted analogs under the assumption that in this case the condensation takes place in the ortho position relative to the nitrogen heteroatom [5]. The same reaction pathway was also noted in the condensation of 3-nitrophthalic anhydride with malonic acid [11]. On the basis of these literature data we assigned 4-aza- and 5-azaphthalidylidene structures to the compounds that we obtained.

TABLE 1. Characteristics of the Azaphthalides and Azaindandiones

| Compound | mp, °C (solvent) | IR spectrum, cm$^{-1}$ |  | UV spectrum, $\lambda_{max}$ nm | N found, % | Empirical formula | N calc., % | $R_f$ | Reaction time, h | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|
|  |  | C=O | C=C |  |  |  |  |  |  |  |
| IIIb | 120 ($CCl_4$) | 1820 | 1660 | 225, 271 | 9,5 | $C_{13}H_{12}N_2O_6$ | 9,6 | 0,75 | 18 | 77 |
| Va | 281 (glac. $CH_3COOH$) | 1810 | 1650 | 224, 272, 368 | 11,1 | $C_{10}H_4N_2O_2S$ | 11,2 | 0,71 | 18 | 61 |
| VIIa | 187—188 (*n*-$C_4H_9OH$) | 1820 | 1650 | 220, 275 | 8,6 | $C_{16}H_8O_4S$ | 8,6 | 0,79 | 18 | 55 |
| VIIb | 174 ($CH_3OH$) | 1820 | 1650 | 223, 270, 321 | 13,0 | $C_{15}H_7N_3O_4S$ | 12,9 | 0,78 | 18 | 60 |
| IXa | 252 (glac. $CH_3COOH$) | 1820 | 1640 | 223, 275, 407 | 11,3 | $C_{10}H_4N_2O_3S_2$ | 11,3 | 0,90 | 1 | 93 |
| IXb | 148 (acetone) | 1820 | 1640 | 225, 270, 393 | 16,2 | $C_9H_3N_3O_4S_2$ | 15,9 | 0,87 | 1 | 94 |
| XIa | 181 | 1700 | — | 220, 266 | 17,1 | $C_{11}H_7N_3O_4$ | 17,1 | 0,21 | 0,5 | 31 |
| XIb | 105 | 1700 | — | 225, 275 | 28,0 | $C_9H_2N_4O_2$ | 28,3 | 0,60 | 1 | 76 |

TABLE 2. Characteristics of the Azaisophthalones and Azaphthalones

| Compound | mp, °C (solvent) | IR spectrum, cm$^{-1}$ |  | UV spectrum, $\lambda_{max}$, nm | Found, % |  |  | Empirical formula | Calc., % |  |  | $R_f$ | Reaction time, h | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  | C=O | C=C |  | C | H | N |  | C | H | N |  |  |  |
| XIIIb | 282 (acetone) | 1790 | 1665 | 291, 316, 346, 352 | 70,0 | 3,5 | 15,1 | $C_{16}H_9N_3O_2$ | 69,8 | 3,6 | 15,3 | 0,63 | 1,5 | 88 |
| XIIIc | 256 (acetone) | 1790 | 1665 | 289, 345 | 74,7 | 3,8 | 10,3 | $C_{17}H_{10}N_2O_2$ | 74,5 | 3,6 | 10,2 | 0,61 | 1,5 | 61 |
| XV | 258 (acetone) | 1795 | 1660 | 274, 348 | 74,2 | 4,0 | 10,4 | $C_{17}H_{10}N_2O_2$ | 74,5 | 3,6 | 10,2 | 0,49 | 1 | 76 |
| XVII | 232 (acetone) | 1785 | 1665 | 269, 342 | — | — | 12,4 | $C_{14}H_{10}N_2O_2$ | — | — | 11,8 | 0,59 | 1,5 | 25 |
| XIXb | 348 (glac. $CH_3COOH$) | 1685 | — | 278, 324, 426, 448 | 69,9 | 3,7 | 15,3 | $C_{16}H_9N_3O_2$ | 69,8 | 3,6 | 15,3 | 0,54 | 0,5 | 82 |
| XIXc | 262,5 (benzene) | 1690 | — | 275, 310, 325, 421, 444 | 74,6 | 3,9 | 10,4 | $C_{17}H_{10}N_2O_2$ | 74,5 | 3,6 | 10,2 | 0,56 | 0,5 | 65 |
| XIXd | 360 (water) | 1670 | — | 274, 471 | — | — | 9,8 | $C_{17}H_{10}N_2O_2$ | — | — | 10,2 | 0,11 | 0,5 | 34 |
| XIXe | 245 (benzene) | 1680 | — | 289, 318, 391 | — | — | 12,4 | $C_{14}H_{10}N_2O_2$ | — | — | 11,8 | 0,62 | 0,5 | 82 |

## EXPERIMENTAL

Thin-layer chromatography (TLC) of the compounds presented in Table 1 was carried out on Silufol plates in a methanol—chloroform—dioxane system (12:1:1), while TLC of the compounds presented in Table 2 was carried out in a chloroform—methanol—hexane system (13:1:1). The chromatograms were developed with iodine vapors. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The UV spectra of solutions of the compounds in ethanol were recorded with a Specord UV-vis spectrophotometer.

Anhydrides Ia-c were obtained by known methods [4, 12, 13].

6-Azaphthalidylidenemalonic Ester (IIIa). A 0.9-ml sample of triethylamine was added with stirring to a mixture of 1 g (6.7 mmole) of Ia, 4 ml of acetic anhydride, and 1 ml (6.7 mmole) of malonic ester, and the mixture was allowed to stand at room temperature for 18 h. The solution was then poured into a mixture of 20 g of ice with 2 ml of concentrated HCl. After decomposition of the acetic anhydride, the precipitate was separated to give 1.1 g (56%) of white needles of IIIa with mp 121°C (from butanol) and $R_f$ 0.73. UV spectrum, $\lambda_{max}$: 225 and 272 nm. IR spectrum: 1820 (C=O) and 1660 cm$^{-1}$ (C=C). Found: N 4.4%. $C_{14}H_{13}NO_6$. Calculated: N 4.8%. Compounds IIIb, Va, VIIa, and IXb were similarly obtained (Table 1).

5-(4,7-Diazaphthalidylidene)thiazolidine-2,4-dione (Vb). Two drops of piperidine were added to a mixture of 1 g (6.7 mmole) of anhydride Ib, 0.78 g (6.7 mmole) of diazolidinedione IV, and 1.4 ml of pyridine, and the mixture was allowed to stand at room temperature for 18 h. The resulting precipitate was treated with acetone, and the mixture was filtered to give 1.2 g (72%) of Vb with mp 113°C [from propanol—ethyl acetate (1:1)]. The product was yellow and had $R_f$ 0.51. UV spectrum, $\lambda_{max}$: 233 and 268 nm. IR spectrum: 1810 (C=O) and 1660 cm$^{-1}$ (C=C). Found: N 17.3%. $C_9H_3N_3O_4$. Calculated: N 16.9%. Compounds VIIb, IXa, and XIa, b (Table 1) were similarly obtained.

3-(α-Quinolylmethylene)-6-azaphthalide (XIIIa). A mixture of 1.25 g (8.4 mmole) of anhydride Ia, 15 ml of acetic anhydride, and 2.5 ml (18.5 mmole) of quinaldine XII was heated at 150-160°C for 30 min in a flask equipped with a reflux condenser, after which it was allowed to stand overnight. The precipitate was washed with ether to give 1.72 g (75%) of azaphthalide XIIIa with mp 262°C (from acetone). The product was white and had $R_f$ 0.58.

UV spectrum, $\lambda_{max}$: 283 and 342 nm. IR spectrum: 1790 (C=O) and 1660 cm$^{-1}$. Found: C 74.8; H 3.9; N 10.4%. $C_{17}H_{10}N_2O_2$. Calculated: C 74.5; H 3.6; N 10.2%. Compounds XIIIb, c, XV, and XVII (Table 2) were similarly obtained.

5-Azaquinophthalone [2-(2-Quinolyl)-5-azaindan-1,3-dione] (XIXa). A mixture of 1.15 g (4.2 mmole) of XIIIa, 46 ml of methanol, and a solution of sodium methoxide (0.1 g of Na was dissolved in 12 ml of methanol) was heated at 50-60°C for 1 h, after which the precipitate was removed by filtration to give 0.68 g of salt XVIIIa, which was a red infusible substance. The salt was refluxed with 120 ml of water to give 0.62 g (54%) of azaindandione XIXa. Successive recrystallization of the latter from water and benzene gave a bright-yellow product with mp 268°C and $R_f$ 0.68. UV spectrum, $\lambda_{max}$: 291, 316, 454, and 478 nm. IR spectrum: 1685 cm$^{-1}$ (C=O). Found: C 74.3; H 3.7; N 10.6%. $C_{17}H_{10}N_2O_2$. Calculated: C 74.5; H 3.6; N 10.2%. Compounds XIXb-e (Table 2) were similarly obtained.

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# MACROHETEROCYCLES.
## 12.* SYNTHESIS AND PROPERTIES OF MACROCYCLIC TETRAAMIDES

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The N,N'-bis(methoxycarbonylmethyl)diamides of the corresponding acids were obtained by the reaction of glycine methyl ester hydrochloride with oxalic, succinic, adipic, diglycolic, and triglycolic acid dichlorides. Fourteen new macrocyclic tetraamides were obtained by the reaction of these diamides with various diamines. The structures of the synthesized compounds were proved by means of their IR, PMR, and mass spectra.

Polyfunctional macroheterocycles display interesting complexing properties and biological activity [2]. The least amount of study in this respect has been devoted to macrocyclic polyamides.

The synthesis of these compounds is generally accomplished by acylation of diamines (or polyamines with partially protected amino groups) by the corresponding dicarboxylic acid

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*See [1] for Communication 11.

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