ON PHTHALIDES AND INDANDIONES. XLIII.*

THE EFFECT OF SUBSTITUENTS ON THE RATE OF REARRANGEMENT OF 3-PHENYLMETHYLENE-6-AZAPHTHALIDES TO 2-PHENYL-5-AZA-1,3-INDANDIONES

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The rates of the rearrangement of 10 *m*- and *p*-substituted 3-phenylmethylene-6-azaphthalides to 2-phenyl-5-aza-1,3-indandiones induced by sodium methoxide in methanol have been measured spectrophotometrically. Logarithms of the rate constants obtained by extrapolation of concentration dependences to zero methoxide concentration, were correlated with σ and σ^0 substituent constants. The obtained correlations were compared with the corresponding dependences for the rearrangement of 15 *m*- and *p*-substituted benzylidenephthalides to 2-phenyl-1,3-indandiones. The effect of the nitrogen and transmission of substituent effects on the reaction center in the rate-determining step of the reaction are discussed.

The kinetics and mechanism of the rearrangement of *m*- and *p*-substituted benzylidenephthalides to 2-phenyl-1,3-indandiones induced by sodium methoxide in methanol was studied in detail by Creamer, Fischer and Vaughan[1]. The authors suggested a mechanism which can be depicted by Scheme 1 (after omitting the structures *II* and *IIIa* which are the result of considerations described in the present work). As *a*) after quenching by acidification, the reaction mixture contained the ester *VII* and the pseudo-ester of *o*-phenacetylbenzoic acid (*VIII*), but not the phthalide *I*, and *b*) the rates of formation of the indandione anion *VI* from the phthalide *I*, the ester *VII* and from the pseudo-ester *VIII* were the same, the authors concluded that after fast conversion of the phthalide *I* to the ester *VII*, an equilibrium between the ester *VII* and the pseudo-ester *VIII* is set up, which is continuously shifted through transformation of the ester *VII* via the anion *IIIb*, the intermediate *IV*, and the indandione *V* to the anion *VI*. The rate-determining step is thus either formation of the anion *IIIb*, by deprotonation of the ester *VII* (the reaction constant ϱ is high and positive), or, more likely, cyclization of *IIIb* to *IV*. The rate of setting-up of the equilibrium between the ester *VII* and the pseudo-ester *VIII* does not influence the rate of formation of the anion *VI* in the case of the reaction induced by sodium methoxide, contrary to the sodium ethoxide-induced rearrangement where the rate of formation of the anion *VI* was influenced, especially in the initial stage of the reaction. The authors found that except the *p*-nitro derivative the rate constants of other 10 derivatives examined can be well correlated with Taft σ^0 constants ($\log k = 1.91\sigma^0 - 2.35$). The rate constants used in the correlation were obtained by extrapolation of linear dependences of $\log k$ on ionic strength (methoxide concentration) to zero ionic strength. On the other hand, Escola[2] has assumed that the rearrangement of benzylidene-

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phthalides proceeds *via* formation of the anion of pseudo ester *VIII* which he isolated after acidification of the reaction mixture.

The present work is concerned with the effect of substituents X (in position 3' or 4') on the rate of rearrangement of 3-arylmethylene-6-azaphthalides (formula *I* in Scheme 1, Z = N) to 2-aryl-5-aza-1,3-indandiones (compounds *V* or *VI* in Scheme 1, Z = N) induced by sodium methoxide in methanol. For sake of comparison we studied also analogous rearrangement of 3-arylmethylenephthalides to 2-aryl-1,3-indandiones (Scheme 1, Z = CH).
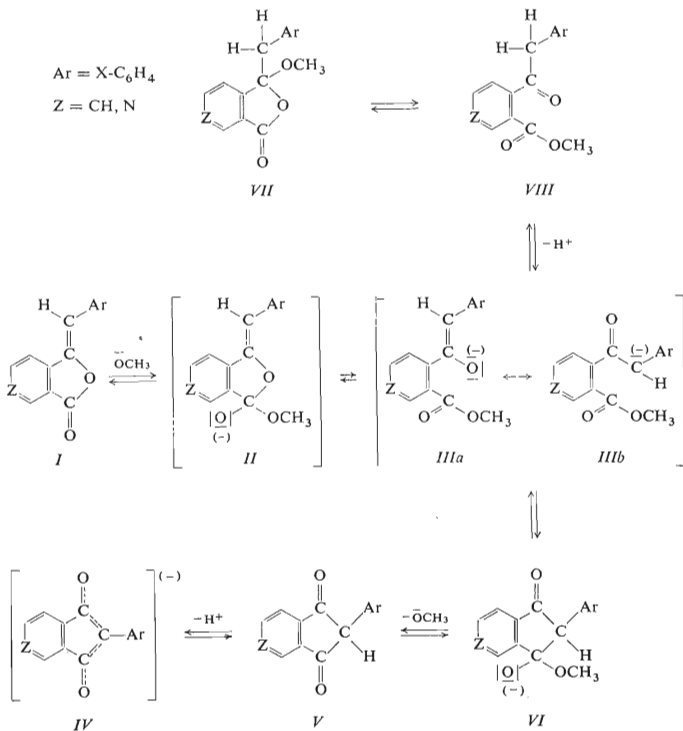
SCHEME 1

With the aim to estimate the accuracy and reliability of experimental data obtained by automatic spectrophotometric system as well as the suitability of the chosen calculation procedures and programs, we have also determined rate constants of the rearrangement of 12 3-arylmethylnephthalides. Some of these derivatives were already studied by Creamer and coworkers[1]. We have thus obtained 22 experimental points for a total of 15 derivatives.

EXPERIMENTAL

Compounds Studied

Substituted benzylidenephthalides were prepared according to the work[3] and were recrystallized. Melting points agreed well with the literature data[3].

Substituted benzylideneazaphthalides were prepared according to the literature[4]. The melting points and analyses of some compounds not included in the work[4] are given in the communication[5]. As some of the benzylideneazaphthalides were brownish, in spite of satisfactory elemental analyses and narrow temperature range of their melting, all the compounds were purified by column chromatography to avoid difficulties in measuring, spectra of these compounds in visible region caused by their discolouration. We used silica gel CH 900 (Spolana). The eluent was tetrachloromethane containing $5-15\%$ chloroform. Zone of the main portion of the substance chromatographed was yellow or orange after purification and was distinctly separated from the intense brown to violet zone of admixtures which were thus perfectly removed.

Kinetic Measurements

Methanol (chemical purity) dried by magnesium and purified by distillation through a 30 TP column was used as solvent. Stock solution of c. $1\text{M-}CH_3ONa$ was prepared by dissolving the appropriate amount of sodium in dry methanol. Its molarity was determined by titration with $1\text{N-}H_2SO_4$.

Instrument and arrangement. The changes of absorbances of reaction mixture in dependence on time were measured on Perkin-Elmer spectrophotometer, Model 450. The instrument was equipped with the block for cylindrical cells (1 cm thick), whose constant temperature was kept by external temperature-controlled circuit. The temperature of the block near-by the cell was measured by thermocouple (connected with the recorder) with the accuracy of $\pm0.05°C$. In long-termed experiments the temperature was kept constant within $\pm0.1°C$. The spectrophotometer was further equipped with automatic repetitive scanning accessory, a digital data recording accessory enabling to record the chosen part of the spectrum in digital form on punched tape, and with a device recording the time of the beginning and the end of record. A detailed description of the system used will be given in a separate communication.

Procedure. At the beginning and at the end of each kinetic run the spectrum of the solvent in both cells and the spectrum of standard gray filter, which was used for automatic correction of small deviations in calibration of the linear absorbance scale during the run, were recorded. The concentration of studied compounds in the reaction mixture was chosen so that the absorbance in the region of absorption maximum of the anion *VI* was at the end of kinetic run around 1. All the derivatives of benzylidenephthalide and of benzylideneazaphthalide were used as $7.5 . 10^{-4}\text{M}$ solutions, except the *p*-nitro derivative of benzylidenephthalide whose concentration was $6 . 10^{-5}\text{M}$. The concentration range of sodium methoxide used in individual measurements

is given in Tables I and II. Before commencing the experiment, pipetted stock solutions of both reaction components in methanol (10 ml of each) were warmed up to the reaction temperature (generally 20.0°C, in studying the temperature dependence to 20—40°C). At the beginning of the reaction the reaction mixture was thoroughly mixed and then rapidly transferred into the cell.

TABLE I

Logarithms of Rate Constants of the Rearrangement of Benzylidenephthalides I ($Z = CH$), log k^a, and Spectral Data for Reaction Product VI

Initial concentrations: the phthalides 1—13 $7.5 \cdot 10^{-4}$M, the phthalide 15 $6.5 \cdot 10^{-5}$.

Compound	X	σ	σ^0	log k	$S(\log k)$	CH_3ONa mol/l	VI λ_{max} nm	ε_{max} $mol^{-1}lcm^{-1}$
1	4'-NH$_2$	−0.66	−0.38	−2.909	0.000	0.05 −0.21	475	1 510
2	4'-OCH$_3$	−0.27	−0.16	−2.686 −2.672^b	0.011	0.02 −0.10	472	1 690
3	4'-CH$_3$	−0.17	−0.15	−2.586 −2.561^b	0.012	0.01 −0.10	465	1 810
4	3'-CH$_3$	−0.07	−0.07	−2.460^b				
5	H	0.00	0.00	−2.408 −2.400^b	0.08	0.01 −0.10	462	1 590
6	4'-F	0.06	0.17	−2.280	0.016	0.006−0.10	463	1 830
7	3'-OCH$_3$	0.12	0.06	−2.360 −2.297^b	0.006	0.01 −0.10	461	1 810
8	4'-J	0.18	0.27	−1.796	0.000	0.006−0.05	458	1 810
9	4'-Cl	0.23	0.27	−1.904 −1.818^b	0.017	0.006−0.03	460	1 830
10	4'-Br	0.23	0.26	−1.842	0.024	0.006−0.03	459	1 850
11	3'-F	0.34	0.35	−1.815 −1.738^b	0.038	0.006−0.03	457	1 870
12	3'-Cl	0.37	0.37	−1.636^b				
13	3'-Br	0.39	0.38	−1.659	0.049	0.006−0.03	454	1 810
14	3'-NO$_2$	0.71	0.70	−0.996^b				
15	4'-NO$_2$	0.78	0.82	−0.571 −0.368^b	0.048	0.002−0.006	439	23 300

^{a}For zero methoxide concentration; for calculation see Experimental. ^{b}Calculated from data taken from ref.[1].

The scanning of the spectrum, including the return to the initial position, took about 50 s, which was satisfactory even in the case of the reaction with the half-time of around 10 min. Limit values of absorbance of reaction mixture were either directly obtained in kinetic measurements, or, if not possible, they were measured separately after a longer period (always at least two times) after filling the cell with an excess of reaction mixture maintained at reaction temperature in a temperature-controlled bath.

Treatment of spectral and time data for calculating rate constants was performed on a Gier digital computer (Regnezentralen), using Gier-Algol 1V language. The treatment of spectral data recorded on punched tape consisted of the calculation of absorbance from the value read on the scale for each recorded datum, mathematical filtration according to Savitzky and Golay[6] which resulted in a substantial decrease of the noise, the selection of absorbance values for individual wavelengths chosen, the standardization of absorbance scale by means of gray filter, and the correction for absorbance of the solvent. The time for each wavelength chosen from the corresponding spectral record was calculated by linear interpolation of time data for the beginning and the end of the record by means of the respective wavelengths. The above treatment of time and spectral data yielded matrix of absorbances for individual records and chosen wavelengths, and the corresponding matrix of time data which was arranged in the same way. When studying the reaction described in the present work we recorded 60—100 values of absorbance in the vicinity of absorption maximum of the product *VI* in visible region (in the interval of 75 nm). Rate constants were calculated separately for each of the five wavelengths chosen. Data in absorbance matrix were accurate within $\pm$ 0·001 and those in time matrix within $\pm$0·5 s.

TABLE II

Logarithms of Rate Constants of the Rearrangement of Benzylideneazaphthalides *I* (Z = N), log k^a and Spectral Data for the Reaction Product

Initial concentration of benzylideneazaphthalides was $7·5 \cdot 10^{-4}$ M.

Com-pound	X	σ	σ^0	log k^b	S(log k)	CH_3ONa mol/l	Product λ_{max} nm	ε_{max} mol^{-1} lcm^{-1}
16	4'-OCH$_3$	−0·27	−0·16	−1·421	0·006	0·013 − 0·05	488	1 770
17	4'-CH$_3$	−0·17	−0·15	−1·388	0·009	0·006 − 0·05	480	1 730
18	3'-CH$_3$	−0·07	−0·07	−1·281	0·028	0·008 − 0·05	475	1 720
19	H	0·00	0·00	−1·189	0·032	0·008 − 0·05	474	1 690
20	3'-OCH$_3$	0·12	0·06	−1·247	0·016	0·008 − 0·05	474	1 830
21	4'-J	0·18	0·27	−0·840	0·044	0·009 − 0·05	473	1 970
22	4'-Cl	0·23	0·27	−0·822	0·023	0·008 − 0·05	472	1 770
23	3'-F	0·34	0·35	−0·774	0·023	0·006 − 0·03	466	1 340
24	3'-J	0·35	0·35	−0·830	0·030	0·002 − 0·05	465	1 920
25	3'-Br	0·39	0·38	−0·723	0·017	0·006 − 0·03	468	1 800

[a] See footnote[a] in Table I. [b] The slopes of the dependence of log k on methoxide concentration had the following values: −0·917 for 1, −1·391 for 2, −3·453 for 4, −9·429 for 6, −14·605 for 8, and −15·624 for 10.

Calculation of rate constant. From matrices of absorbance, A_{ig}, and time, T_{ig}, for individual records i there were chosen vectors A_i and T_i (at constant wavelength g) which were used in calculating the rate constant of the reaction defined by Eq. (*1*)

$$k = \frac{2,303}{(a-b)\,T_i}\,\log\frac{A_{\lim} - A_i\cdot(b/a) - A_p(1-b/a)}{A_{\lim} - A_i}\,, \qquad (1)$$

where k is the rate constant (in l mol^{-1} s^{-1}), a and b is the initial methoxide and the initial phthalide (azaphthalide) concentration (in mol l^{-1}), respectively, $A_{\lim}$ is the absorbance at corresponding wavenumber g for time $T \to \infty$ (*i.e.* limit absorbance), and A_p is the absorbance at the same wavenumber in time $T = 0$, obtained by extrapolation of the dependence of A_i on T_i. This relation was derived from the known expression for the rate constant of the second order reaction under assumption that absorbance of the reaction product is proportional to its concentration and that the initial absorbance A_p is either constant or decreases with concentration throughout experiment. The rate constant k is then determined from the slope of the regression line obtained by linear correlation of the second term of Eq. (*1*) with T_i. The calculation is first performed for all experimental points and for each kinetic run, and then only for points at which

TABLE III

Parameters of Hammett Correlations for the Rearrangement of Benzylidenephthalides I (Z = CH)
Meaning of symbols see text.

Source	Points omitted	ϱ	$S(\varrho)$	$\log k_0$	$S(\log k_0)$	r
			Correlation with σ			
This work	—	1·603	0·189	−2·232	0·067	0·937
	1	1·994	0·178	−2·334	0·102	0·965
Ref.[1]	—	2·057	0·173	−2·314	0·111	0·973
	15	1·767	0·120	−2·312	0·050	0·984
Together	—	1·800	0·132	−2·256	0·092	0·950
	1[a]	2·033	0·118	−2·326	0·101	0·970
	1[a], 15[b]	1·886	0·109	−2·321	0·076	0·971
			Correlation with σ^0			
This work	—	1·936	0·129	−2·373	0·070	0·978
Ref.[1]	—	2·139	0·118	−2·363	0·082	0·988
	15	1·898	0·059	−2·353	0·027	0·997
Together	—	2·044	0·088	−2·368	0·076	0·982
	15[a]	1·921	0·077	−2·365	0·055	0·985
	15[b], 1[a]	1·993	0·077	−2·387	0·063	0·987

[a] From this work, [b] from the work[1].

the conversion subsequently reached only 80 and 90%. The differences of values of k obtained for individual cases then indicate an anomalous course of the reaction at the end of each experiment. The values of k for individual wavenumbers were averaged and expressed as $\log k$. The standard deviation $S(\log k)$ was usually less than 1.5% of the value of $\log k$. The correlation coefficient of regression lines was usually 0.999.

Calculation of $\log k$ *vs* a *and* $\log k$ *vs* $\sigma(\sigma^0)$ *plots.* As the rate constant of the rearrangement of both series studied was dependent on ionic strength (methoxide concentration) we calculated for each derivative the value of $\log k$ extrapolated to zero ionic strength. With benzylidenephthalides the value of the slope of the dependence of $\log k$ on a was positive and increased with the substituent constant (from 0.5 to 2.2). In the case of benzylideneazaphthalides the slope was negative (Table II). The slopes as well as parameters of Hammett correlation were computed using the program written in Gier-Algol IV language according to relations given in the work[8]. Constants σ and σ^0 used were those given by McDaniel and Brown[8] and Taft[9], respectively. The program for calculation of the linear correlation enables to subsequently eliminate from the set of data individual experimental points in the order of decreasing deviations from the regression line. The results of measurements and of the treatment of experimental data are presented in Tables I—IV.

RESULTS AND DISCUSSION

The spectra of reaction products *VI* of the rearrangement of benzylidenephthalides and benzylideneazaphthalides differ from each other in position of the long-wavelength absorption band in visible region. This band shows in the series of azaphthalides a bathochromic shift by 15 nm, relative to the respective members of the phtha-

TABLE IV

Parameters of Hammett Correlation for the Rearrangement of Benzylideneazaphthalides *I* (Z = N)

Meaning of symbols see text.

Points omitted	ϱ	$S(\varrho)$	$\log k_0$	$S(\log k_0)$	r
		Correlation with σ			
—	1·136	0·14	−1·176	0·049	0·943
20	1·141	0·094	−1·154	0·031	0·977
20, 31	1·123	0·075	−1·166	0·021	0·987
20—22	1·094	0·056	−1·176	0·012	0·994
		Correlation with σ^0			
—	1·260	0·078	−1·215	0·032	0·985
20	1·239	0·050	−1·200	0·021	0·994
20, 21	1·281	0·032	−1·197	0·010	0·998
20—22	1·265	0·027	−1·200	0·006	0·999

lide series. We were not able to determine accurately the magnitude of the slope of the dependence of λ_{max} on σ because the determination of the position of a relatively wide absorption band was ladden with great error. A graphical treatment of the data given in Tables I and II showed that slopes of both dependences are nearly equal.

Small variations of the absorptivity of the band of reaction product *VI* indicate that substituents do not seriously affect the moment of the corresponding transition and further that the equilibrium concentration of the reaction product is comparable with the concentration of the anion of 2-aryl-1,3-indandione or of 2-aryl-5-aza-1,3-indandione corresponding to quantitative reaction. The value of ε_{max} was markedly lower in the case of the *m*-fluoro derivative of azaphthalide and exceptionally high in the case of the *p*-nitro derivative of phthalide. The high value observed for the *p*-nitro derivative is not surprising and may be due to the strong —M effect of the nitro group. For four phthalides we compared the spectra of reaction products with those of corresponding indandiones, using the same medium, and found them to be identical. This provides evidence that during spectrophotometric following of the course of the reaction the measured absorbance is proportional to the concentration of the reaction product, the anion *VI*.

When comparing results of our kinetic measurements of the rearrangement of benzylidenephthalides with those obtained by Creamer and coworkers[1] (Table III) we have found that log k's are better correlated with σ° than with σ constants. When the points 1^a (*p*-NH$_2$, this work) and 15^b (*p*-NO$_2$, ref.[1]) are omitted, the correlations of the other results of both studies with σ and σ° are practically equivalent, as indicated by nearly the same slopes and intercepts. In this way we obtained reliable data for comparison of kinetics of the studied rearrangement in both series. Although the parameters of the correlations of log k of the rearrangement of benzylideneazaphthalides with σ and with σ^0 somewhat differ (Table IV), they are independent of the number of experimental points cho-sen. The standard deviations are comparable with those obtained in the preceding case.
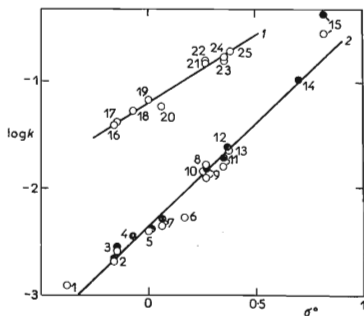

FIG. 1

Dependence of Rate Constants of the Rearrangement on σ^0

1 3-Arylmethylene-6-azaphthalides, *2* 3-arylmethylenephthalides (the constants taken from ref.[1] are designated by solid circles). Numbering of compound ssee Tables I and II.

Mutual position of the regression lines for both series of the phthalides is seen on Fig. 1. The ratio of the slopes $\varrho_{\text{phthalide}}/\varrho_{\text{azaphthalide}}$ amounts to 0·60 for the correlation of log k with σ and to 0·63 for the correlation with σ^0.

The results of kinetic study of the rearrangement of benzylidenephthalides and benzylideneazaphthalides lead to the following conclusions: *1*. The slopes ϱ of both correlations of log k with $\sigma(\sigma^0)$ are highly positive. *2*. The presence of the nitrogen in position 6 of the phthalide ring markedly facilitates the reaction. *3*. The slope ϱ for the reaction of azaphthalides has much lower value.

The above facts, together with the results of the works of Creamer and coworkers[1] and Perjéssy and Hrnčiar[5], can be utilized in discussing the probable rate determining step of the reaction. This can be (see Scheme 1) either the formation of anion *IIIa*, *IIIb* by the reaction *I → II → IIIa ↔ IIIb* or its cyclization to the anion of indandione (5-azaindandione) *VI* through steps *IIIa ↔ IIIb, IV, IV → V, V → VI*. According to the work[1] the deprotonization of the ester *VII → IIIb* rather then the reaction *I → IIIb* should be considered as possible rate determining step of the reaction.

The steps *I → IIIa ↔ IIIb* and *IIIb → IV* are nucleophilic intermediate stages of the reaction. In the step *I → II*, the substituents *X* by their properties increase or decrease electron deficiency on the carbonyl carbon of the phthalide(azaphthalide) and thus facilitate or render difficult the nucleophilic attack of the carbon by methoxide ion. The positive value of ϱ is thus in harmony with the assumption that the formation of the anion *IIIa, IIIb* could be rate determining step of the reaction. The nitrogen, acting as electron acceptor (it is *meta* to the carbonyl carbon), increases electron deficiency on the carbonyl carbon, which comports with the fact that the rearrangement of azaphthalides proceeds at a faster rate than that of phthalides. However, step *I ↔ II* can hardly account for a decreased value of ϱ in the case of azaphthalides. The assumption that electronic effects of substituents in azaphthalides are transmitted due to the presence of nitrogen in the phthalide ring less effectively can hardly be accepted. When studying $\nu(C{=}O)$ of phthalides and azaphthalides, Perjéssy and Hrnčiar[5] have found that substituent effects on this bond are transmitted predominantly through oxygen (the slopes of the dependences of $\nu(C{=}O)$ on σ were found to be nearly the same for both series studied). Transmission of electronic effects through a heteroatom have also been observed to take place in other types of phthalides[10]. It can be expected that if step *I → II, i.e.* prior to phthalide ring cleavage, were rate determining then ϱ for both series would be closely comparable. In such a case, the decreased value of ϱ observed in case of azaphthalides can be accounted for only under assumption that the nitrogen increases electron deficiency on the carbonyl carbon to such an extent that further changes of its electron density due to substituent effects are relatively small. Such an explanation is however not probable.

Cyclization of the anion *IIIb → IV* is intramolecular step of the reaction. It is to be expected that here substituents and the nitrogen of the heterocycle affect electron

density on the carbonyl carbon in the same way as they do in the step $I \rightarrow II$. Transmission of substituent effects on the carbonyl carbon in azaphthalides could, of course, be weaker than in phthalides, since in the former they are transmitted through pyridine ring while in the latter through benzene ring. However, it is above all unshaired electron pair which plays an important role in cyclization. The structure of the anion III very similar to the resonance structure $IIIb$ is prerequisite for cyclization reaction. In formation of $IIIb$ from $IIIa$, the effect of electron-attracting substituents and the opposite effect of nitrogen atom can be easily accounted for. On polarizing the double bond of $IIIa$ towards the structure $IIIb$ these effects will be oppositely operating, the net result being their partial compensation. On the other hand, when the C=O bond of the neighbouring carbonyl group is polarized by going from $IIIa$ to $IIIb$ they operate in the same direction, which, along with the effect of nitrogen on the carbon of the ester C=O group, might account for the higher reactivity of azaphthalides, compared to analogous phthalides. As a structure similar to $IIIb$ may operate also in transition state of the cyclization $IIIb \rightarrow IV$, it cannot be decided whether the rate determining step is the formation of $IIIb$ or the cyclization of $IIIb$ to IV. It seems likely that during cyclization the nitrogen exerts constant electron-acceptor effect rather on the carbonyl carbon of the ester group of anion $IIIb$, and at the same time, but in the opposite way, it affects the formation of the negative charge on the carbon of the carbanion $IIIb$, which is favourably influenced by the substituents X with electron-acceptor properties (a relatively high value of ϱ indicates the proximity of the reaction center). In this way the results of experimental study of the rearrangement of both series of compounds can be interpreted by one reaction step.

It seems to us that in the given medium a fast conversion of $IIIb$ to VII, suggested in the work[1], is not likely from thermodynamic reasons. We therefore do not consider the reverse reaction $VII \rightarrow IIIb$ as a possible rate determining step in the reactions of phthalides or azaphthalides.

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