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REGIOSELECTIVITY OF THE REARRANGEMENT OF PROPIONIC ACID N,N-DIARYLHYDRAZIDES UNDER THE CONDITIONS OF THE KOST REACTION

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The transformation of propionic acid N,N-diarylhydrazides with electron-donor and electron-acceptor substituents in the aromatic rings under the conditions of the Kost reaction was studied. The ratios of the resulting isomeric N-aryl-2-aminoindoles were determined.

The question of the mechanism of the formation of the new C—C bond — the fundamental step in the scheme of the formation of indoles via the Fischer method — still remains open to discussion. The concept of Grandberg, who proposed that this step be regarded as a [3, 3]-sigmatropic rearrangement in all processes involving the formation of indole systems, viz., the Fischer and Brunner syntheses and the Kost reaction [1, 2], is finding increasing confirmation. As direct evidence that the indicated reactions proceed through a step involving [3, 3]-sigmatropic rearrangement the authors cite data on the slight, from their point of view, effect of the electronic nature of the substituents in the Fischer rearrangement of unsymmetrical N,N-diarylhydrazones of symmetrical carbonyl compounds on the ratios of the resulting arylindoles [3, 4]. The consideration of the conversion of arylacylhydrazines to 2-aminoindoles via the Kost reaction from these positions has not been experimentally confirmed.

The aim of the present research was to study the direction of the indolization of acid N,N-diarylhydrazides with different substituents in the aromatic rings and to investigate their relative orienting abilities with respect to this process. As the subjects of the investigation we selected propionic acid N,N-diarylhydrazides Ia-d, which contain, in the para

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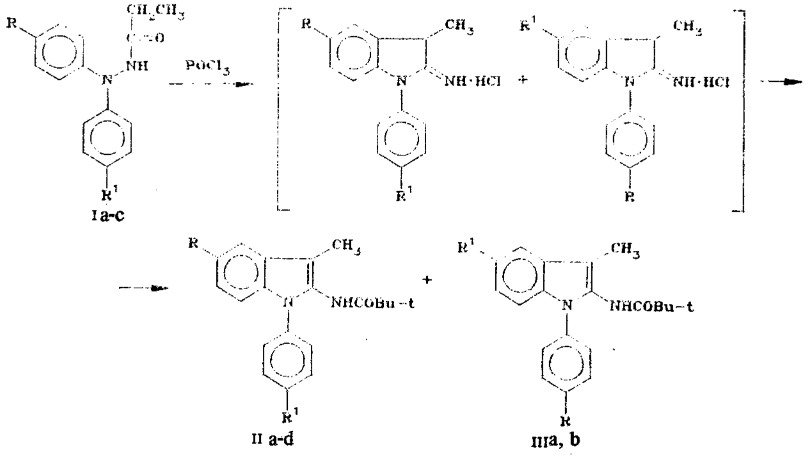

a,b $R=H$, c $R=CH_3$, d $R=OCH_3$; a $R^1=CH_3$, b–d $R^1=NO_2$

position, an electron-donor methyl group (Ia) or an electron-acceptor nitro group (Ib), as well as substituents of one or another type simultaneously in different aryl rings (Ic,d). We selected precisely these substances for our study due to the fact that unsymmetrical N,N-diarylhydrazones that contain substituents (CH_3, OCH_3, Cl) with rather similar, in our opinion, character of the mesomeric and inductive effects (or their overall effect under the given reaction conditions) were previously investigated in the Fischer rearrangement [3, 6] for the unambiguous interpretation of the results obtained.

Hydrazide Ia was obtained by the reaction of the corresponding hydrazine with a small excess of propionic anhydride in an inert solvent; hydrazides Ib, d were synthesized by the method in [7].

The reaction of N,N-diarylhydrazides Ia-d with excess phosphorus oxychloride in refluxing dioxane led to the formation of the hydrochlorides of the corresponding N-aryl-2-amino-3-methyl-indoles, which, without isolation, were then converted to stable N-acylamino derivatives IIa-d and IIIa,b by acylation. In view of the known ability of 2-aminoindoles to form N,N-diacyl derivatives [8], we used pivalyl chloride as the acylating agent; this makes it possible to obtain exclusively the monoacyl derivatives owing to the bulkiness of the acyl residue. The determination of the ratios of isomers IIa-d and IIIa, b in the reaction masses after acylation and subsequent chromatography on silica gel was made by means of the PMR spectra (Table 2).

It is apparent from Table 2 that the indolization of hydrazide Ia, which contains an electron-donor methyl group, leads, according to the PMR spectral data and the results of thin-layer chromatography (TLC), to a mixture of equal amounts of isomers IIa and IIIa; this is probably associated with the weak orienting effect of the CH_3 group, which is in the meta position with respect to the carbon atom that participates in the formation of the new C–C bond. The composition of the mixture of isomers was also confirmed by the mass spectrum and the results of elementary analysis (Table 1).

The introduction of a nitro group into the aromatic ring of the diarylhydrazide (Ib) does not affect the reaction rate but does have a significant effect on the direction of indolization, leading to a mixture of isomers IIb and IIIb in a ratio of 80:20 (Table 2). For their identification and assignment the mixture of substances, after chromatography, was subjected to additional separation by means of preparative TLC on silica gel. The accurate assignment of the isolated substances was made from data from their PMR spectra. Thus two doublets (J = 8 Hz) with intensities of two proton units in each case, which were assigned to the N-4-nitrophenyl substituent, are present in the PMR spectrum of the more labile (with respect to TLC) substance IIb, which constitutes 80% of the total reaction mass after acylation, at 7.58 and 8.4 ppm. In addition to signals of protons of methyl groups at

TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, deg C	IR spectrum, cm^{-1}	PMR spectrum, δ, ppm	Found, %			Empirical formula	Calculated, %			Yield, %
				C	H	N		C	H	N	
I a	151—152	3260 (NH), 1668 (C=O), 1590 (C=C)	0,98 (3H, t, CH_2CH_3); 2,12 (2H, q, CH_2CH_3); 2,21 (3H, s, $CH_3C_6H_4$); 6,6—7,4 (9H, aromatic protons); 10,4 (NH, br.)	75,8	7,2	11,0	$C_{16}H_{18}N_2O$	75,6	7,1	11,0	49
I b	178—179	3260—3200 (NH), 1670 (C=O), 1590 (C=C), 1500 (NO_2)	1,13 (3H, t, CH_2CH_3); 2,33 (2H, q, CH_2CH_3); 7,0, 8,2 (2×2H, 2d, J=8 Hz, $C_6H_4NO_2$); 7,27—7,8 (5H, m, phenyl); 10,9 (NH, br.)	63,8	5,1	14,8	$C_{15}H_{15}N_3O_3$	63,1	5,3	14,7	72
I c	203,5—204,5	3240 (NH), 1680 (C=O), 1590 (C=C), 1500 (NO_2)	1,13 (3H, t, CH_2CH_3); 2,3 (2H, q, $-CH_2CH_3$); 2,4 (3H, s, $CH_3C_6H_4$); 6,91, 8,17 (2×2H, 2d, J=8 Hz $C_6H_4NO_2$); 7,37 (4H, br. $C_6H_4CH_3$); 10,87 (NH, br.)	64,5	5,5	14,2	$C_{16}H_{17}N_3O_3$	64,2	5,7	14,0	71
I d	198—199	3240 (NH), 1670 (C=O), 1590 (C=C)	1,02 (3H, t, CH_2CH_3); 2,14 (2H, q, CH_2CH_3); 3,8 (3H, s, $CH_3OC_6H_4$); 6,78, 8,08 (2×2H, 2d, J=9,6 Hz, $C_6H_4NO_2$); 7,03, 7,35 (2×2H, 2d, J=8,8 Hz, $C_6H_4OCH_3$); 10,75 (NH, br.)	60,9	5,5	13,4	$C_{16}H_{17}N_3O_4$	60,9	5,4	13,3	96
II a + III a	196,5—197,5	3280 (NH), 1665 (C=O), 1610 (C=C), 1600 (C=C)	—	78,9	7,3	8,9	$C_{21}H_{24}N_2O$	78,7	7,5	8,7	65
II b	260—261	3260 (NH), 1665 (C=O), 1505 (NO_2)	—	67,8	5,9	11,7	$C_{20}H_{21}N_3O_3$	68,4	6,0	11,9	65
III b	203—204	3280—3240 (NH), 1665 (C=O), 1625, 1600—1580 (C=C), 1500 (NO_2)	—	68,4	6,1	11,6	$C_{20}H_{21}N_3O_3$	68,4	6,0	11,9	
II c	291—292	3260 (NH), 1660 (C=O), 1630, 1600 (C=C), 1520 (NO_2)	—	69,3	6,2	11,5	$C_{21}H_{23}N_3O_3$	69,0	6,3	11,5	72
II d	264—265	3260 (NH), 1663 (C=O), 1600 (C=C)	—	66,0	6,2	11,0	$C_{21}H_{23}N_3O_4$	66,1	6,1	11,0	78

TABLE 2. PMR Spectra and Ratios of Arylindoles II and III

Hydrazide	Indolization product	Ratio, %	PMR spectrum, δ, ppm
Ia	IIa + IIIb	50:50	1,0 (9H, s, Bu-*t*); 2,03 (3H, s, 3-CH_3); 2,28, 2,32 (2×1,5H, 2s, 5-CH_3, $-C_6H_4CH_3$); 6,8—7,6 (8H, m, aromatic H), 9,07 (NH, br.)
Ib	IIb	80	1,08 (9H, s, Bu-*t*); 2,07 (3H, s, 3-CH_3); 6,9—8,7 (4H, m, arom. H); 7,58, 8,4 (2×2H, 2d, *J*=8 Hz, $-C_6H_4NO_2$); 9,3 (NH, br.)
	IIIb	20	1,03 (9H, s, Bu-*t*); 2,18 (3H, s, 3-CH_3); 7,2—7,5 (6H, m 7-H, NC_6H_5); 7,9 (1H, q, 6-H, J_{46}=2,4 Hz, J_{67}=8 Hz); 8,46 (1H, d, 4-H, J_{46}=2,4 Hz); 9,3 (NH, br.)
Ic	IIc	100	1,08 (9H, s, Bu-*t*); 2,08 (3H, s, 3-CH_3); 2,37 (3H, s, 5-CH_3), 6,7—8,5 (3H, m, arom. H); 7,53, 8,33 (2×2H, 2d, *J*=8 Hz, $-C_6H_4NO_2$)
Id	IId	100	1,08 (9H, s, Bu-*t*); 2,07 (3H, s, 3-CH_3); 3,78 (3H, s, $CH_3OC_6H_4$); 6,78 (1H, q, 6-H, J_{67}=9 Hz, J_{64}= 2 Hz); 7,05 (1H, d, 4-H, J_{46}=2 Hz); 7,24 (1H, d, 7-H, J_{76}=9Hz); 7,55, 8,35 (2×2H, 2d, *J*=9 Hz, $-C_6H_4NO_2$); 9,3 (NH, br.)

7.9 ppm, a quartet of a 6-H proton (J_{46} = 2.4 Hz, J_{67} = 8 Hz) and a doublet (J_{46} = 2.4 Hz) of a 4-H proton at ~8.46 ppm are present in the PMR spectrum of isomer IIIb.

The effect of substituents on the direction of the rearrangement is most significant when two orienting groups of different types (hydrazides Ic, d) are present in the aromatic residues. In this case only individual isomers IIc, d were obtained in ~70% yields after acylation and purification. In addition to other signals, doublets (J = 8 Hz) at ~7.5 and 8.3 ppm, which are related to the protons of the N-nitrophenyl residue, are present in their PMR spectra (Table 2).

Thus the results of the indolization of the series of substituted propionic acid N,N-diarylhydrazides that we studied provide evidence for the existence of a pronounced electronic effect of the substituents in the aromatic ring on the regioselectivity of their rearrangement under the conditions of the Kost reaction. This constitutes evidence that the formation of the C—C bond in the Kost reaction occurs primarily through intramolecular electrophilic substitution; this corresponds to the data [5] on the Fischer rearrangement of N-aryl-N-pyridyl-substituted hydrazones, which give only one isomer with the participation of the N-aryl ring.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were obtained with a Perkin-Elmer 577 spectrometer. The PMR spectra of solutions in d_6-DMSO were obtained with a Bruker WM-250 spectrometer with tetramethylsilane (TMS) as the internal standard. The mass spectra of the substances were recorded with an MKh-1303 spectrometer at an ionizing voltage of 70 eV. The course of the reactions and the purity of the compounds obtained were monitored by means of thin-layer chromatography (TLC) on Silufol UV-254 plates in a benzene—acetone system (4:1) and on Al_2O_3 (L 40/250 μm) in a benzene—2-propanol system (10:1). Silica gel (L 40/100 μm) was used for preparative chromatography.

The characteristics of I-III are presented in Table 1.

N-(4-Tolyl)-N-phenyl-N'-propionylhydrazine (Ia). A 7.8-mmole sample of propionic anhydride was added dropwise at 20-25°C to a vigorously stirred mixture of 7 mmole of N-(4-tolyl)-N-phenyl-hydrazine [6] and 60 ml of benzene, after which the mixture was stirred until the starting diarylhydrazine had vanished according to TLC [benzene—hexane (2:1)]. At the end of the reaction the precipitate was removed by filtration, washed with petroleum ether, and recrystallized from aqueous alcohol with charcoal.

Substituted 1-Aryl-2-N-acylamino-3-methylindoles IIa-d and IIIa,b (General Method). A mixture of 8 mmole of the corresponding diarylhydrazide, 12 mmole of phosphorus oxychloride, and 15 ml of dry dioxane was refluxed for 2-3 h until the starting diarylhydrazide had vanished according to TLC on Silufol. After this, the reaction mass was evaporated, and the excess phosphorus oxychloride was removed by distillation. Benzene (25 ml), 24 mmole of triethylamine, and 12 mmole of pivalyl chloride were added to the resulting oily residue, and the mixture was stirred at room temperature until the aminoindole hydrochloride had vanished according to TLC [benzene–2-propanol (10:1)]. The reaction mass was evaporated, and the oily residue was chromatographed with a column (25 by 300 mm) packed with silica gel by elution with chloroform–acetone (10:1). The fraction containing the N-acylaminoindoles was evaporated, and the residue was triturated in hexane. The solid material was removed by filtration and dried. The mixture of N-acylindoles IIb and IIIb obtained after chromatography was recrystallized from benzene, and the precipitated isomer IIb was separated. The filtrate, which, according to TLC, contained approximately equal amounts of isomers IIb and IIIb, was chromatographed on plates with silica gel in a benzene–ethyl acetate system (10:1). The fraction containing isomer IIIb was eluted with chloroform, the chloroform was evaporated, and the residue was recrystallized from alcohol to give N-acylaminoindole IIIb.

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SYNTHESIS OF BENZO(AMINOMETHYL)INDOLES

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The benzene ring in indoles has been aminomethylated in high yield by reaction with methylolphthalimide followed by hydrazinolysis of the phthalimidomethyl derivatives. In the hydrazinolysis of one of the phthalimidomethyl compounds, an intermediate product (the amino-methylindole phthalazine) was isolated and characterized.

It has been shown previously [1, 2] that 1,2,3-trialkylindoles, on reaction with powerful amidomethylating agents such as N-hydroxy-methylphthalimide and N-hydroxymethyltrichloroacetamide in acidic solution afford 5- or 6-aminomethylindoles. These model compounds have also been chloroacetamidomethylated [3] by activating the reagent with a mixture of concentrated sulfuric acid and phosphorus pentoxide. However, the amido-methylation of indoles with N-hydroxymethylphthalimide followed by hydrazinolysis has been examined to only a limited extent, and the yields of aminomethylindoles obtained were poor.

We have studied the amidomethylation of substituted indoles, varying the molar ratios of the reactants, temperature, and the concentrations of the condensing agent and acids. To avoid resinification and di-, tri-, and polymerization on dissolution in strong acids, we reduced the temperature to 0-5°C, and used freshly purified starting materials.

The amidomethylation of indoles which did not contain electron-donor substituents in the benzene ring occurred smoothly in the 5-position (Ia-d) when N-hydroxymethylphthalimide was used as the amidomethylating agent.

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