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meta-SUBSTITUTED ARYLHYDRAZIDES IN THE KOST REACTION

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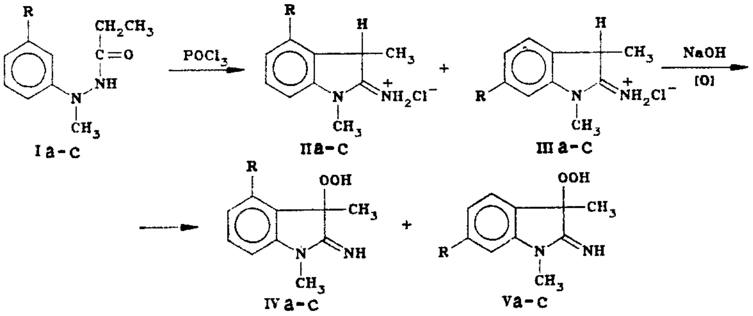
Kost cyclization of meta-substituted arylhydrazides results primarily in the formation of mixtures of 4- and 6-substituted 2-aminoindoles.

The Fischer cyclization of meta-substituted arylhydrazides invariably affords mixtures of 4- and 6-substituted indoles [1]. It would be expected that the use of meta-substituted arylhydrazides in the Kost reaction would give similar results, since the latter reaction proceeds by a mechanism very similar to that involved in the Fischer synthesis [2]. This report is concerned with a study of this problem. The principal compounds chosen as models were the meta-substituted hydrazides (Ia-c).

Rearrangement of the hydrazides (Ia-c) gave the chromatographically homogeneous hydrochlorides (II) and (III).



I—V a R=CH_3, b R=OCH_3, c R=Cl

Despite changes in the carriers used and the use of different systems, TLC failed to reveal the presence of isomeric compounds. In the PMR spectrum of (II) (Table 2), the $Ar{-}CH_3$ and OCH_3 signals appear as narrow singlets, and the aromatic proton signals were not susceptible to reliable interpretation. On the basis that there is no reason for such high stereoselectivity in this reaction, leading to the formation of only one isomer, we assumed that the physicochemical parameters and PMR spectral characteristics of the isomeric hydrochlorides (II) and (III) were similar. It was therefore necessary to modify these compounds in such a way as to change their physicochemical properties to a sufficient extent. For this purpose, we took advantage of such properties of the 2-aminoindoles as their oxidizability. It is well known that in the presence of atmospheric oxygen 2-aminoindoles as the free bases undergo ready autoxidation to give, depending on the substituents on the nitrogen, hydroxy or hydroperoxy-derivatives [3, 4].

In fact, following appropriate treatment and the isolation of bases both from mixtures of the pure hydrochlorides (II) and (III), and directly from the reaction mixture, compounds were obtained which according to TLC were mixtures of two isomers (IVa-c) and (Va-c). The free bases from the 2-aminoindoles (II) and (III), like other 1,3-disubstituted iminoindolines [3], form relatively stable peroxy-derivatives (IV) and (V). This was confirmed by elemental analyses and mass spectrometry. It is noteworthy that the molecular ion peaks for

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TABLE 1. meta-Substituted Propion-N-aryl-N-methylhydrazides (Ia-c)

Compound	mp, °C	IR spectrum, cm^{-1}	Found, %			Empirical formula	Calculated, %			Yield, %
			C	H	N		C	H	N	
Ia	41—42	1660, 3250	69,1	8,4	14,6	$C_{11}H_{16}N_2O$	68,8	8,3	14,6	42
Ib	Oil	1670, 3240	63,5	8,2	13,7	$C_{11}H_{16}N_2O_2$	63,5	7,7	13,5	62
Ic	46,5—47,5	1670, 3230	56,5	6,2	13,6	$C_{10}H_{13}ClN_2O$	56,1	6.1	13.2	71

(IV) and (V), which are of low intensity (up to 2%), could only be obtained at low ionizing electron energies (up to 15 eV) and at low temperatures. The main peak in the mass spectra at 15 and 70 eV is, however, that for $[M - O]^+$, corresponding to the approximate hydroximinoindolines. It did not appear to be possible to establish the positions of the substituents from the further fragmentation patterns of the pure compounds (IV) and (V).

The pure isomers (IVa-c) and (Va-c) were obtained by TLC on alumina, and were characterized by physicochemical methods of analysis. The substitution pattern in the indole ring was established from the PMR spectra of the pure isomers. For example, in the PMR spectrum of (Vb) the signal at lowest field (7.20 ppm) is a doublet for the 4H proton ($^3J_{4,5}$ = 8 Hz), the signal for the 5-H proton being seen as a quadruplet at 6.52 ppm with $^3J_{5,4}$ = 8 and $^4J_{5,7}$ = 2 Hz. The 7-H proton occurs as a doublet with $^4J_{7,5}$ = 2 Hz, at 6.37 ppm. The shift of the 4-H proton to lower field as compared with that for 7-H is evidently due to descreening by the substituents (OOH, CH_3) in the 3-position of the indole ring. The 7-H proton, on the other hand, is screened by the OCH_3 and N—CH_3 groups, and appears at higher field. In addition, the spectrum contains signals for 3-CH_3 (1.5 ppm), N—CH_3 (3.07 ppm), OCH_3 (3.75 ppm), and a broadened signal for the OOH (or NH) group centered on 4.15 ppm.

The PMR spectrum of the isomeric compound (IVb) shows in the aromatic proton region doublets for the 5-H (6.40 ppm) and 7-H (6.57 ppm) protons, with $^3J_{5,6}$ = 7 and $^3J_{7,6}$ = 8 Hz. The multiplet for the protons in the 6-position lies at 7.0-7.2 ppm, this region also containing the signal for OOH (or NH). The shift of the proton signals to higher field is also evidently due to their being screened by the 4-OCH_3 and N—CH_3 groups. Slight differences in the analogous PMR spectra are shown by the methyl- and chloro-compounds (IVa, c) and (Va, c) (Table 4).

As a result of the presence of all the isomeric 2-iminoindolines (IV) and (V) in the pure state, and as a result of the clear differences in the positions of the signals for the 3-CH_3 groups in the 4- and 6-isomers in the PMR spectra (in the 4-substituted compounds the signal for the 3-CH_3 group is shifted to lower field), it was possible to determine quantitatively the proportions of the isomers formed, from the integral intensities of the 3-CH_3 groups. As expected (Table 3), rearrangement of the hydrazides (I) resulted in all cases in the preferential formation of the 6-isomers. The electronic character of the substituent R (from a strong donor, OCH_3, to a fairly weak acceptor, Cl) had no material effect on the isomer ratio. The hydrazide with a nitro-group in the meta-position did not undergo the Kost reaction, and was recovered unchanged from the reaction mixture, but under more severe conditions it gave the chlorohydrazone, i.e., it behaved similarly to p-nitro-substituted hydrazides [5].

EXPERIMENTAL

IR spectra were obtained on a Perkin-Elmer 577 in Vaseline oil. PMR spectra were obtained on a Tesla BS-467 (60 MHz) and a WP-200-SY (200 MHz) in deuteroacetone-D_6, $CDCl_3$, and CF_3COOH. The course of the reactions and the purities of the products were followed by TLC on Silufol UV-254 plates in the system benzene—propan-2-ol (10:1) and on alumina L 40/250 (with the addition of LSL 254 5/40 alumina) in the system chloroform—methanol (20:1).

Propion-N-aryl-N-methylhydrazides (Ia-c). A mixture of 0.05 mole of the m-substituted arylhydrazine and 0.052 mole of propionic anhydride was boiled for 2 h, cooled, the solid filtered off, washed with hexane, and recrystallized from ethanol. To the resulting N-aryl-N'-propionylhydrazine (0.05 mole) in 70 ml of xylene was added 0.2 mole of anhydrous sodium carbonate, followed by the dropwise addition with vigorous stirring and heating of 5.5 ml (0.06 mole) of dimethyl sulfate, and the mixture was boiled for 2 h. The organic layer was then

TABLE 2. Properties of Mixtures of Hydrochlorides of 4- and 6-Substituted 2-Iminoindolines (II) and (III)

Compound	mp, °C	IR spectrum, cm^{-1}	PMR spectrum, ppm (in CF_3COOH)	Found, %		Empirical formula	Calculated, %		Yield, %
				C	H		C	H	
II, IIIa	273—273,5	1690, 2560—3300	1,26 (3H, d, 3-CH_3); 2,06 (3H, s, CH_3); 3,20 (3H, s, N—CH_3); 3,80 (1H, q, 3-H); 7,06—7,43 (3H, m, arom); 7,43 (1H, s, NH); 7,66 (1H, s, NH)	62,8	7,2	$C_{11}H_{15}ClN_2$	62,7	7,1	90
II, IIIb	268—269	1680, 2680—3250	1,23 (3H, d, CH_3); 3,17 (3H, s, N—CH_3); 3,6 (3H, s, OCH_3); 3,73 (1H, q, 3H); 6,4—7,2 (3H, m, arom.); 7,6 (1H, s, NH), 7,76 (H, s, NH)	58,5	6,5	$C_{11}H_{15}ClN_2O$	58,3	6,6	65
II, IIIc	250,5—252	1690, 2500—3250	1,23 (3H, d, CH_3); 3,17 (3H, s, N—CH_3); 3,83 (q, 1H); 6,7—7,13 (3H, m, C_6H_3—Cl); 7,57 (1H, s, NH); 7,83 (1H, s, NH)	52,4	5,2	$C_{10}H_{12}Cl_2N_2$	52,0	5,2	78

TABLE 3. Properties of Mixtures of 4- and 6-Substituted 2-Imino-3-peroxyindolines

Compound	mp, °C	IR spectrum, cm^{-1}	PMR spectrum, ppm (in $CDCl_3$)	Found, %			Empirical formula	Calculated, %			Yield, %	Ratio of 4- and 6-isomers
				C	H	N		C	H	N		
IV, Va	130—132	3290, 3100, 1660	1,55 (3H, s, 3-CH_3); 1,65 (3H, s, 3-CH_3); 2,35 (3H, s, CH_3); 2,45 (3H, s, CH_3); 3,15 (6H, s, N—CH_3), 3,33 (2H, s, OH); 5,55—7,35 (6H, m, Ar)	65,2	7,1		$C_{11}H_{14}N_2O_2$	64,1	6,8		77	1 : 1,7
IV, Vb	100	3300, 3080, 1650	1,50 (3H, s, 3-CH_3); 1,63, (3H, s, 3-CH_3); 3,12 (6H, s, N—CH_3); 3,35 (2H, s, OH); 3,76 (3H, s, OCH_3); 3,86 (3H, s, OCH_3); 6,32—7,35 (6H, m, Ar)	59,4	6,8	12,4	$C_{11}H_{14}N_2O_3$	59,5	6,3	12,6	59	1 : 2,7
IV, Vc	115	3300, 3060, 1660	1,50 (3H, s, 3-CH_3); 1,68 (3H, s, 3-CH_3); 3,10 (6H, s, N—CH_3); 3,85 (2H, s, OH); 6,65—7,33 (6H, m, Ar)	52,9	5,1	12,5	$C_{10}H_{11}ClN_2O_2$	53,0	4,9	12,4	71	1 : 2,6

TABLE 4. Spectral and Physicochemical Data for Pure Isomers of 2-Imino-3-peroxyindolines (IV) and (V)

Compound	R_f*	mp, °C	PMR spectrum, ppm (J, Hz) in $CDCl_3$	M^+ (mass spectrometry
IVa**	0,49	144—145	1,5 (3H, s, 3-CH_3); 2,4 (3H, s, CH_3); 3,07 (3H, s, N—CH_3); 4.65 (1H, s, OH); 6,56—6,8 (2H, m, Ar); 7,05 (1H, d, 7-H)	206
Va**	0,43	166—167	1,37 (3H, s., 3-CH_3); 2,26 (3H, s, CH_3); 3,0 (3H, s, N—CH_3); 3,76 (1H, s, OH); 6,73 (1H, s, 7-H); 6.8 (1H, d, 5-H); 7,2 (1H, d, 4-H)	206
IVb	0,53	118	1,57 (3H, s, 3-CH_3); 2,55 (1H, s, OH); 3,07 (3H, s, N—CH_3); 3,82 (3H, s, OCH_3); 6,4 (1H, d., Ar); 6,57 (1H, d, Ar); 7,2 (1H, m, 6-H)	222
Vb	0,50	125—128	1,50 (3H, s, 3-CH_3); 3,07 (3H, s, N—CH_3); 3,75 (3H, s, OCH_3); 4,15 (1H, s, OH); 6,37 (1H, d 7-H, $J_{7,5}=2$), 6,52 (1H, d.d, 5H, $J_{4,5}=8$, $J_{5,7}=2$); 7,2 (1H, d, 4-H, $J_{4,5}=8$)	222
IVc	0,54	128—130	1,68 (3H, s, 3-CH_3); 3,1 (3H, s, N—CH_3); 3,36 (1H, s., OH); 6,4—7,2 (3H, m, Ar)	228, 226
Vc	0,50	165—166	1,5 (3H, s, 3-CH_3); 3,1 (3H, s, N—CH_3); 3,16 (1H, s., OH); 6,76 (1H, d, 7-H, $J_{5,7}=$ =1,8); 7,05 (1H, d.d, 5-H, $J_{4,5}=8{,}0$; $J_{5,7}=$ =1,8); 7,23 (1H, d, 4-H, $J_{4,5}=8{,}0$)	228, 226

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*In the system chloroform—methanol, 20:1.

**The PMR spectra of (IVa) and (Va) were obtained in deuteroacetone-D_6.

separated, the solid washed with hot xylene, the combined organic fractions evaporated, the residue transferred to a column of silica gel (μ 100/250), and eluted with chloroform. The constants and yields of the compounds obtained are given in Table 1.

4- and 6-Substituted 2-Amino-1,3-dimethylindole Hydrochlorides (II, III). A mixture of 0.01 mole of (I) and 0.02 mole of phosphoryl chloride in 30 ml of dry benzene was boiled for 1.5-3 h (monitored by TLC). The solid was filtered off and recrystallized from absolute ethanol to give a mixture of the hydrochlorides of the 4- and 6-substituted 2-aminoindoles (II, III), the constants for which are given in Table 2.

1,3,4-Trimethyl- and 1,3,6-Trimethyl-2-imino-3-peroxyindolines (IVa-c, Va-c). A mixture of 1.92 g (0.01 mole) of (Ia) and 1.8 ml (0.02 mole) of $POCl_3$ in 30 ml of dry benzene was boiled for 2 h, and the benzene and excess $POCl_3$ was evaporated under reduced pressure. The residue was dissolved in water, basified with 1 N NaOH to pH 8, extracted with chloroform, the chloroform extract dried over Na_2SO_4, the chloroform removed, and the oily residue dissolved in ether and kept for one day. The resulting mixture of isomeric bases (IVa) and (Va) was purified on an alumina column, eluent chloroform.

Obtained similarly were mixtures of 4-methoxy- and 6-methoxy-, and 4-chloro and 6-chloro-2-imino-3-peroxyindolines (IVb, Vb and IVc, Vc) (Table 3).

The pure 4- and 6-substituted isomers of 2-imino-3-peroxyindolines (IV) and (V) were obtained by separating the isomer mixtures by TLC. The spectral and physicochemical properties of the isomers obtained are given in Table 4.

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