SUBSTITUTED HYDRAZIDES OF HYDROXY CARBOXYLIC ACIDS

LXVII*. REACTION OF ETHYL ESTERS OF ARYLHYDRAZIDES OF OXALIC ACID WITH INDOLYLMAGNESIUM BROMIDE

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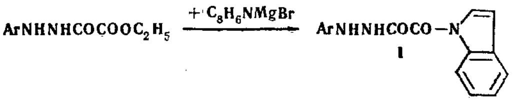
The reaction of ethyl esters of arylhydrazides of oxalic acid with indolylmagnesium bromide has given arylhydrazides of N-indolylglyoxilic acid which, by reaction with benzoyl chloride, have been converted into β-aryl-δ-benzoylhydrazides of N-indolylglyoxilic acid. The reaction of arylmagnesium halides with arylhydrazides of indolylglyoxilic acid has given arylhydrazides of diarylglycolic acids. The spectra of the arylhydrazides of N-indolyglyoxilic acid have been studied.

Indolylmagnesium halides react with esters to form N or C derivatives. Thus, depending on the reaction temperature, indolylmagnesium bromide reacts with ethyl formate [2] to form, in the cold, N-formylindole, and, in the hot, 3-formylindole. The reaction with ethyl oxalate gave N,N'-oxalyldiindole [3]. Lapkin and Dormidontov obtained esters of indol-1-yl and indol-2-ylglyoxilic acids by the reaction of indolylmagnesium bromide with oxalic acid esters. The formation of the products of the N or 2- or 3-C substitution in reactions of indolylmagnesium bromides can be explained by the structure of this Grignard reagent as a strongly ionic resonance hybrid [5]. The occurrence of the reaction at one nucleophilic center or another of this hybrid depends on the nature of the reagent and the reaction conditions.

The present investigation was carried out to determine the influence of the replacement of one ethoxy group in diethyl oxalate by an arylhydrazine residue on the course of the reaction with indolylmagnesium halides. We have shown that indolylmagnesium bromide reacts with ethyl esters of arylhydrazides of oxalic acid at a ratio of 3 : 1 to form good yields of arylhydrazides of N-indolylglyoxilic acid (when the amount of Grignard reagent is increased, resinification takes place).



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Even after the first crystallization, the substances melted in a narrow range, which shows the individuality of the compounds obtained and the absence of contaminating 2- or 3-C isomers.

The substances synthesized (Table 1) are light yellow crystals insoluble in water, sparingly soluble in ether, and readily soluble in benzene, toluene, ethanol, and glacial acetic acid. Their benzoyl derivatives (Table 1) are colorless. Benzoylation led only to monobenzoyl derivatives with the acyl residue attached to the hydrazine nitrogen, which confirms the structure of compounds I.

In the IR spectra (Fig. 1) taken in solution, for compound I in the 3000 cm^{-1} region there are bands with frequencies of 3426, 3330–3340 and 3175 cm^{-1}, and on passing to the crystals there is a lowering of the frequency of the first two bands connected with the inclusion of the NH groups of the hydrazine part

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*For Communication LXVI, see [1].

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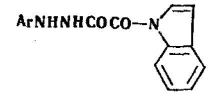
TABLE 1



Ar	mp, °C	Empirical formula	N, %	
			found	calculated
C_6H_5	160—161	$C_{16}H_{13}N_3O_2$	15,4	15,0
o-$CH_3C_6H_4$	158—159	$C_{17}H_{15}N_3O_2$	14,2	14,3
m-$CH_3C_6H_4$	152—153	$C_{17}H_{15}N_3O_2$	14,2	14,3
p-$CH_3C_6H_4$	164—165	$C_{17}H_{15}N_3O_2$	14,0	14,3
o-$CH_3OC_6H_4$	143—144	$C_{17}H_{15}N_3O_3$	13,3	13,6
3,4-$(CH_3)_2C_6H_3$	179—180	$C_{18}H_{17}N_3O_2$	13,9	13,7
o-ClC_6H_4	153—154	$C_{16}H_{12}ClN_3O_2$	13,7	13,4
m-ClC_6H_4	170—171	$C_{16}H_{12}ClN_3O_2$	13,6	13,4
p-ClC_6H_4	190—191	$C_{16}H_{12}ClN_3O_2$	13,7	13,4
o-BrC_6H_4	173—174	$C_{16}H_{12}BrN_3O_2$	11,5	11,7
m-BrC_6H_4	175—176	$C_{16}H_{12}BrN_3O_2$	11,4	11,7
p-BrC_6H_4	183—184	$C_{16}H_{12}BrN_3O_2$	11,9	11,7

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*Solvent for crystallization: toluene.

† Solvent: glacial acetic acid.

of the molecule in hydrogen bonds. In these circumstances the frequency of the third does not change, and this band is also present in the benzoyl derivative. It may be assigned to the stretching vibrations of the CH bonds of the pyrrole part of the indole ring. In the 1600 cm^{-1} region for compound I there are two bands of carbonyl groups the frequencies of which rise in solution in view of the liberation of the carbonyls from hydrogen bonds. The benzoyl derivative has yet another carbonyl band. Because of the absence of substituents in positions 2 and 3 of the indole ring, in the compound studied there is a band at 720–730 cm^{-1} corresponding to the cis CH=CH group in the indole ring [6].

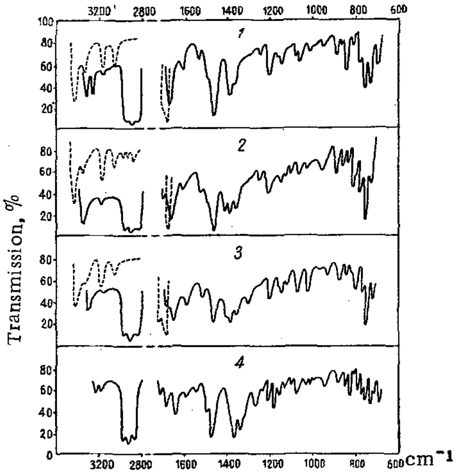

Fig. 1. IR spectra (the dashed line shows the spectra of 0.2 % solutions in CCl_4, l 5 mm): 1) phenyl-, 2) o-tolyl-, 3) o-bromophenylhydrazides of N-indolylglyoxilic acid; 4) β-phenylhydrazide of N-indolylglyoxilic acid.

To confirm the structure of the compounds I synthesized, the NMR spectrum of the phenylhydrazide of N-indolylglyoxilic acid was obtained (it was recorded and interpreted by L. M. Alekseeva, to whom the authors express their deep gratitude). In the NMR spectrum (Fig. 2), the signals of the protons of the benzene and indole rings are found in the region from 6.5 to 8.5 ppm. From the general pattern it proved possible to isolate two doublets at 6.7 and 7.94 ppm with a spin-spin coupling constant of 3.5 Hz. This value of the constant agrees with the value of $J_{\alpha,\beta}$ of the pyrrole ring of indole [7]. This permits the doublet at 7.94 ppm to be assigned to the α-proton and the doublet at 6.7 ppm to the β-proton of the pyrrole ring of indole and to deduce that compounds I are N-substituted indoles.

In the UV region (Table 1) for compounds I two maxima are observed which differ somewhat in wavelength and extinction according to the nature of the aryl residue attached to the nitrogen, which is analogous to the UV spectra of N-acetylskatole [8] and N-acetyl-2,3-dimethylindole [9].

On reaction with arylmagnesium halides, compounds I are converted into arylhydrazides of diarylglycolic acids, like tertiary amides of carboxylic acids, which on reaction with organomagnesium compounds give ketones [10]. In our case, the arylhydrazide of an α-oxo acid formed initially reacts with an excess of the Grignard reagent to form a tertiary alcohol group:

UV spectrum (in ethanol)				Yield, %	Benzoyl derivatives			
K band		B band			mp, °C*	empirical formula	N, %	
λ_{max}, nm	log ε	λ_{max}, nm	log ε				found	calculated
244	4,40	288	3,85	88	224—225†	$C_{23}H_{17}N_3O_3$	11,2	10,9
240	4,41	290	3,84	60	178—179	$C_{24}H_{19}N_3O_3$	10,3	10,6
244	4,34	290	3,84	85	148—149	$C_{24}H_{19}N_3O_3$	10,3	10,6
242	4,39	292	3,84	98	196—197	$C_{24}H_{19}N_3O_3$	10,5	10,6
—	—	—	—	82	—	—	—	—
—	—	—	—	97	159—160	$C_{25}H_{21}N_3O_3$	10,2	10,2
—	—	—	—	72	—	—	—	—
—	—	—	—	45	—	—	—	—
244	4,50	290	3,90	52	—	—	—	—
246	4,32	292	3,87	84	—	—	—	—
244	4,42	288	3,94	97	—	—	—	—
246	4,43	294	3,88	82	208—209†	$C_{23}H_{16}BrN_3O_3$	9,1	9,1

TABLE 2.

X	R	mp, °C	Yield, %
H	C_6H_5	143—144	75
H	p-$CH_3C_6H_4$	168—169	60
H	p-ClC_6H_4	168—169	90
H	$C_6H_5CH_2$	210—212	58
o-CH_3	p-$CH_3C_6H_4$	174—176	99
o-CH_3	$C_6H_5CH_2$	198—200	62
p-CH_3	C_6H_5	161—163	46
p-CH_3	p-$CH_3C_6H_4$	150—152	89
o-CH_3O	C_6H_5	206—207	80

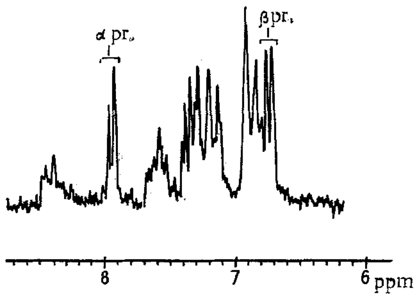

Fig. 2. NMR spectrum of the phenylhydrazide of N-indolylglyoxilic acid.

$$ArNHNHCOCONC_8H_6 \xrightarrow[-BrMgNC_8H_6]{+RMgBr} ArNHNHCOCOR \xrightarrow[+H_2O]{+RMgBr} ArNHNHCOC(OH)R_2$$

The compounds obtained are shown in Table 2 and are identical with the compounds obtained by the reaction of ethyl esters of arylhydrazides of oxalic acid with arylmagnesium halides [11-15]. Their identity was shown by mixed melting point tests and UV spectra. Arylhydrazides of N-indolylglyoxilic acid do not react with alkylmagnesium halides and with α-thienylmagnesium bromides.

EXPERIMENTAL

Phenylhydrazide of N-Indolylglyoxilic Acid. An ethereal solution of 7.0 g (0.06 mole) of indole was added to the ethylmagnesium bromide obtained from 2.9 g (0.12 g-at.) of magnesium and 13.1 g (0.12 mole) of ethyl bromide, and the mixture was heated on the water bath for 1 hr. Then 4.2 g (0.02 mole) of the ethyl ester of the phenylhydrazide of oxalic acid [11] was added, and the reaction mixture was heated for 1 hr and decomposed with dilute acetic acid. The reaction product precipitated. Yield 4.9 g. Found, %: C 68.7; H 5.0. Calculated for $C_{16}H_{13}N_3O_2$, %: C 68.8; H 4.6. Found: 2 active hydrogen atoms.

The other compounds I were obtained similarly from the appropriate esters (Table 1).

The β-aryl-β-benzoyl hydrazides of N-indolylglyoxilic acid were obtained by heating a benzene solution of one of the arylhydrazides with benzoyl chloride (see Table 1).

Phenylhydrazide of Benzilic Acid. 2.8 g (0.01 mole) of the phenylhydrazide of N-indolylglyoxilic acid was added to the Grignard reagent obtained from 1.2 g (0.05 g-at) of magnesium and 7.9 g (0.05 mole) of bromobenzene. The reaction mixture was heated for 40 min and was decomposed with dilute hydrochloric acid. Yield 2.4 g. A mixture with the substance obtained as described previously [11] gave no depression of the melting point (see Table 2). The IR spectra were measured on an IKS-14 spectrophotometer for mulls in paraffin oil and solutions in CCl_4. The NMR spectra were taken on a 4H-100 spectrometer in a mixture of dimethyl sulfoxide and CCl_4 and with the addition of CD_3OD. The UV spectra were obtained on an SF-4 spectrophotometer.

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