INDOLE DERIVATIVES

LIII*. α-OXO EPOXIDES OF THE INDOLE SERIES

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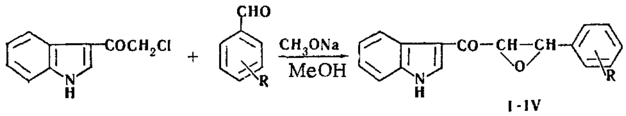
Reactions between 3-chloroacetylindole and aromatic aldehydes, leading to the formation of the α-oxo epoxides I-IV, have been performed. The reaction of the latter with piperidine and dimethylamine has given α-hydroxy-β-amino ketones of the indole series.

The Darzens reaction for aldehydes and ketones of the indole series has been considered previously [1]. It appeared of interest to investigate this reaction using an indole radical as the methylene component. With this object, in the present work we have studied the reaction of 3-chloroacetylindole with aromatic aldehydes.



I-IV

I R=H; II R=p-CH(CH$_3$)$_2$; III R=p-Br; IV R=m-NO$_2$

The aryl indol-3-yl oxo epoxides I-IV were obtained in quantitative yields. The presence in the aromatic ring of the aldehyde of strong electron-donating substituents hinders the reaction; thus, for example, it does not take place with vanillin, anisaldehyde, and p-dimethylaminobenzaldehyde. The structure of the oxo epoxides obtained was established by analysis and spectroscopy. The UV spectra of compounds I-IV are similar to those of 3-acetylindole. The IR spectra have characteristic absorption bands of a C=O group at 1630 cm^{-1}, of an aromatic system of bonds at 1610 cm^{-1}, and of an NH group at 3210 cm^{-1}. In the PMR spectrum of compound I there are two doublets at δ = 4.24 and 4.45 ppm interacting with one another with a spin-spin coupling constant J = 1.8 Hz. The magnitude of J permits the signals to be assigned to the protons of a three-membered oxide ring probably present in the trans position. The molecular weights of the oxo epoxides I-IV were determined mass-spectrometrically (Table 1).

TABLE 1. Characteristics of the α-Oxo Epoxides Synthesized

Compound	mp, °C	Empirical formula	Molecular weight		Found, %				Calculated %				Yield, %
			found	calc.	C	H	N	Br	C	H	N	Br	
I	198—199	$C_{17}H_{13}NO_2$	263	263	77,5	5,0	5,1	—	77,6	5,0	5,3	—	98
II	183—184	$C_{20}H_{19}NO_2$	305	305	78,5	6,3	4,6	—	78,7	6,3	4,6	—	91
III	204—205	$C_{17}H_{12}BrNO_2$	341—343	342	59,9	3,8	4,4	23,6	59,7	3,5	4,1	23,4	96
IV	223—224	$C_{17}H_{12}N_2O_4$	308	308	66,4	3,9	9,2	—	66,2	3,9	9,1	—	98

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*For Communication LII, see [5].

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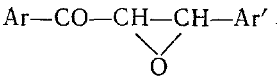
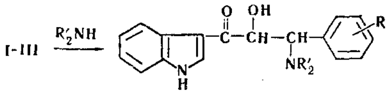
It is known [2] that diaryl oxo epoxides of the type of  $Ar{-}CO{-}\underbrace{CH{-}CH}_{O}{-}Ar'$ react with secondary amines with the opening of the epoxide ring and the formation of β-amino-α-hydroxy ketones. The oxo epoxides I-III that we obtained react similarly (Table 2). Under these conditions no reaction with compound IV takes place.



V-X

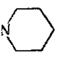
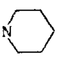
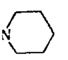
The structure of products V-X was established by elementary analyses and IR, UV, and PMR spectroscopy. Their UV spectra are similar to that of 3-acetylindole. The IR spectra of compounds V-X have the characteristic absorption bands of C=O groups at 1630-1650 cm^{-1}, NH at 3200-3280 cm^{-1}, and OH at 3440-3490 cm^{-1}.

In the mass spectra of the compounds studied, the peak of the ion with m/e 144 corresponding to the fragment β-Ind$-C\equiv O^{+}$ [3] has the maximum intensity. In the mass spectra of compounds I-IV, there are peaks of the molecular ions with m/e 263, 305, 308, and 342/344 (calculated for the isotopes Br^{79} and Br^{81}). In spite of the absence of the peak of the molecular ion in the spectrum of compound IX, the correctness of the proposed structure is confirmed by the existence of a strong peak with m/e 176 corresponding to the fragment $(CH_3)_2CH-Ph-CH=\overset{+}{N}(CH_3)_2$. The process for the formation of this ion is similar to that for the formation of the $CH_2=\overset{+}{N}H_2$ ion with m/e 30 [4].

In the PMR spectrum of compound VI in the strong field region at δ = 1.08 ppm there is a doublet due to the methyl protons of an isopropyl group. The signal of the protons of the methyl groups in the β and γ positions of the piperidine ring partially overlaps this signal. In the 2.10-2.70 ppm region there are the signals of the protons of the methylene groups in the α position of the piperidine ring. The signals of the protons of the methine groups are located at δ = 4.41 $\left(>CH{-}N\right)$ and 5.76 ppm $\left(>CH{-}OH\right)$. Their spin-spin coupling constant is 6.4 Hz.

In the PMR spectrum of compound VII, in the 0.90-1.40 ppm region there are the signals of the protons of methylene groups in the β and γ positions of the piperidine nucleus. In the weaker field, in the 2.15-2.60 ppm region, there are the signals of the protons of the methylene groups in the α positions of the piperidine ring. The signals of the protons of the methine groups are located at δ = 4.42 $\left(>CH{-}N\right)$ and 5.66 ppm $\left(>CH{-}OH\right)$; J = 6.4 Hz.

TABLE 2. Characteristics of the β-Amino-α-hydroxy Ketones Synthesized.

Compound	R	NR'₂	mp, °C	Empirical formula	Found, %				Calculated, %				Yield, %
					C	H	N	Br	C	H	N	Br	
V	H		102— —103	$C_{22}H_{24}N_2O_2$	75,7	7,1	8,2	—	75,8	6,9	8,0	—	50
VI	p-CH(CH₃)₂		165— —166	$C_{25}H_{30}N_2O_2$	76,9	7,9	7,4	—	76,9	7,7	7,2	—	52
VII	p-Br		161— —162	$C_{22}H_{23}BrN_2O_2$	61,9	5,7	6,3	18,3	61,8	5,4	6,6	18,7	40
VIII	H	—N(CH₃)₂	94— —95	$C_{19}H_{20}N_2O_2$	73,9	6,7	8,6	—	74,0	6,5	9,1	—	60
IX	p-CH(CH₃)₂	—N(CH₃)₂	159— —160	$C_{22}H_{26}N_2O_2$	75,5	7,5	8,0	—	75,4	7,5	8,0	—	90
X	p-Br	—N(CH₃)₂	156— —157	$C_{19}H_{19}BrN_2O_2$	58,9	5,0	7,3	20,4	58,9	4,9	7,2	20,6	50

The PMR spectrum of IX has the signal of the protons of an isopropyl group: a doublet belonging to the protons of the methyl groups at $\delta = 1.05$ ppm and a septet of the proton of the methine group at $\delta = 2.68$ ppm. The protons of the methyl groups $-N(CH_3)_2$ give a singlet at $\delta = 2.25$ ppm. In the weaker field region there are two doublets due to the protons of the methine groups $>$CH—N ($\delta = 4.31$ ppm) and $>$CH—O ($\delta = 5.70$ ppm). Their spin-spin coupling constant is 7 Hz.

EXPERIMENTAL

Preparation of the Aryl Indol-3-yl Oxo Epoxides. With ice-water cooling and vigorous stirring, a solution of 0.065 mole of sodium methoxide in 20 ml of methanol was added dropwise to a suspension of 0.089 mole of 3-chloroacetylindole and 0.076 mole of the appropriate aromatic aldehyde in 50 ml of methanol. The reaction mixture was poured into ice water acidified with acetic acid. The precipitate that deposited was filtered off, washed with water and ether, and dried. Yield 91-98 %. The compound was purified by recrystallization from ethanol.

Reaction of the Aryl Indol-3-yl Oxo Epoxides with Piperidine and Dimethylamine. To a suspension of 0.002 mole of the appropriate oxo epoxide in 200 ml of methanol was added 0.004 mole of the appropriate secondary amine. The mixture was heated until dissolution was complete and was left overnight at room temperature. The crystals of unchanged oxo epoxides that had deposited were filtered off, and the solvent was distilled off in vacuum. The residue was crystallized from ethanol.

The UV spectra were measured on an SF-4A spectrophotometer in ethanol. The IR spectra were measured on a UR-10 instrument in the form of mulls in paraffin oil. The mass spectra were obtained on a MKh-1303 instrument with a system for the introduction of the sample directly into the ion source (30 eV, 100-160°C). The PMR spectra were taken on a JNM-4H-100 instrument with pyridine (VI, VII, IX) and deuterated dimethylformamide (I) as solvents and tetramethylsilane as internal standard.

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LITERATURE CITED

1. V. E. Zhigachev and N. N. Suvorov, Trudy MKhTI im. D. I. Mendeleeva, 61, 159 (1969).
2. N. G. Barker and N. H. Cromwell, J. Am Chem. Soc., 72, 4110 (1950).
3. N. S. Vul'fson, V. I. Zaretskii, A. V. Kisin, N. N. Suvorov and Zh. D. Ovchinnikova, KhGS [Chemistry of Heterocyclic Compounds], 3, 502 (1967).
4. K. Biemann, Mass Spectrometry, N. Y., 87 (1962).
5. V. G. Avramenko, V. D. Nazina, and N. N. Suvorov, KhGS [Chemistry of Heterocyclic Compounds], 6, 1071 (1970).