REACTIONS OF HALOGENOMETALALKOXIDES

XIX. Esters of α-Keto Acids Containing the Indolyl Radical*

I. I. Lapkin and Yu. P. Dormidontov

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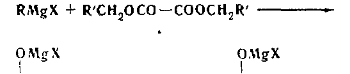
Investigation of the thermal stability of halogenometalalkoxides obtained by reacting Grignard compounds with esters of oxalic acid and containing an indolyl group, is continued. Despite the aromatic nature of the indolyl radical, the ordinary decomposition of the halogenomagnesiumalkoxides with splitting off of aldehyde (ketone) does not take place at 40°–110° C. This is due to hydrogen bonding between hydrogen on the nitrogen and the alkoxy group. The IR spectra of the esters of N-indolyl- and α-indolylglyoxylic acids synthesized are investigated. The latter are shown to contain a hydrogen bond between the NH group hydrogen and the carbonyl group.

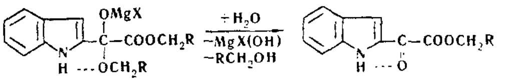
Continuing a study of the thermal stability of halogenometalalkoxides [1] formed by treating oxalic acid esters with Grignard reagents, it has been shown that these compounds, where an indolyl group enters into their composition, differ from similar compounds containing alkyl, aryl, alicyclic [2], and alkylethynyl [3] radicals.

If at 40°–110° C the latter are readily decomposed according to the equation



$$RMgX + R'CH_2OCO{-}COOCH_2R' \longrightarrow R{-}\overset{OMgX}{\underset{OCH_2R'}{C}}{-}COOCH_2R' \longrightarrow R{-}\overset{OMgX}{\underset{H}{C}}{-}COOCH_2R' + R'CHO,$$

complexes containing the α- or N-indolyl radical are unchanged over the same temperature range, despite the aromatic character of the indolyl group. This is explained by the stabilizing action of a hydrogen bond arising in the resultant complex.



For clear reasons, when the complex contains an N-indolyl radical, it does not lose the aldehyde. Hydrogen bonding is observed in the esters of α-indolylglyoxylic acid which are the products of this reaction, their IR spectra showing this (see figure).

With esters of α-indolylglyoxylic acid, the frequency of the NH group valence vibrations (3200–3160 cm^{-1}) is considerably less than that of the vibrations of a free NH group [4], because of hydrogen bonding between the hydrogen atom of the NH group and the oxygen atom of the ketone carbonyl group. Naturally there is an absence of absorption in this region with esters of N-indolylglyoxylic acid.

The occurrence of hydrogen bonding in the first group of compounds is indicated by the fact that the frequency of the ketone carbonyl vibrations (1625–1617 cm^{-1}) is less than in compounds not containing a hydrogen bond [4], and on the other hand close to the frequency data for the absorption of the compounds not containing a hydrogen bond [5].

The IR spectra of esters of α-indolylglyoxylic acid have a strong peak near 1730 cm^{-1}, to be assigned to valence vibrations of ester carbonyl. With the esters of N-indolylglyoxylic acid the value is a little higher (1725–1748 cm^{-1}). Esters of α-indolylglyoxylic acid also give a strong peak in the 1585 cm^{-1} region, due to deformation vibrations of the N—H bond, but these lines are lacking with esters of N-indolylglyoxylic acid.

Under ordinary conditions the reaction between α-indolylmagnesium bromide and esters of oxalic acid (heating for 2 hr in ether solution) gives a mixture of esters of N-indolyl- and α-indolylglyoxylic acids in almost equimolecular amounts (see table).

Raising the reaction temperature (2 hr refluxing in toluene) gives almost solely esters of α-indolylglyoxylic acid (64%), the second product being formed in 6% yield. On the other hand with 30 minutes heating in ether the main reaction products are esters of N-indolylglyoxylic acid (49%), esters of α-indolylglyoxlic acid being formed to the extent of 8%.

The reaction could give two isomers, α and β, but only α isomers are obtained. This was shown as follows. When all the esters of indolylglyoxylic acid synthesized were saponified (with the exception of the N-indolylglyoxylic acid one), one and the same indolylglyoxylic acid, (mp 223°–224° C) was obtained. By fusing with KOH at 220° C it was converted to α-indolylcarboxylic acid, whose structure is proved by the Fischer synthesis from pyrotartaric acid phenylhydrazone [6], as well as by syntheses of Reissert [7] and Gränacher [8]. The esters of α-indolylglyoxylic acid synthesized are also converted to indolyl carboxylic acid by oxidation with aqueous $KMnO_4$.

Majima and coworkers [9] investigated the reaction of α-indolylmagnesium bromide with esters of oxalic acid, and obtained N, N-oxalylindole, N, β-(indolylglyoxyl)indole, and in very small amount the ester of α-indolylglyoxylic acid, which he mistook for the β isomer.

EXPERIMENTAL

General method. An ether solution of indole (0.1 mole) was added to an ether solution of EtMgBr (0.1 mole) and the mixture heated for 30 min. The resultant solution of MgBr indole was added to a solution of the ester of oxalic acid dissolved in the same volume of solvent and the whole heated for 2 hr. The products were then hydrolyzed with 10%

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*For Part XVIII see [12].

Esters of N-indolyl- and α-Indolylglyoxylic Acids

Name of ester reacted with indolylmagnesium bromide (mole ratio 1:1)	Esters of N-indolylglyoxylic acid (I) and α-indolylglyoxylic acid (II)	MP, °C (pressure mm)	Mp, °C	d_4	n_D	MR_D		Formula	Found, %				Calculated, %				Yield, %
						Found	Calculated		C	H	N	Active hydrogen	C	H	N	Active hydrogen	
Dimethyl oxate	Methyl ester I	147—148 (4)	49					$C_{11}H_9NO_3$	64.80	4.31	6.89		65.02	4.45	6.89		22
	Methyl ester II		220					$C_{11}H_9NO_3$	65.22	4.62	6.78	0.47	65.02	4.45	6.89	0.49	31
Diethyl oxalate	Ethyl ester I	152—153 (4)		1.1817 (18°)	1.5380 (18°)	57.44	56.96	$C_{12}H_{11}NO_3$			6.62				6.45		25
	Ethyl ester II		184					$C_{12}H_{11}NO_3$	66.58	5.39	6.79	0.44	66.35	5.10	6.45	0.46	33
Di-n-propyl oxalate	n-Propyl ester I	168—169 (5)		1.1807 (16°)	1.5461 (16°)	61.95	61.58	$C_{13}H_{13}NO_3$	67.32	5.53	5.85		67.52	5.66	6.06		28
	n-Propyl ester II		164					$C_{13}H_{13}NO_3$*	67.71	5.83	5.75	0.42	67.52	5.66	6.06	0.43	33
Diisopropyl oxalate	Isopropyl ester I	150—151 (3)		1.1738 (17°)	1.5430 (17°)	62.03	61.58	$C_{13}H_{13}NO_3$			6.05				6.06		29
	Isopropyl ester II		172					$C_{13}H_{13}NO_3$	67.54	5.89	6.00	0.41	67.52	5.66	6.06	0.43	32
Di-n-butyl oxalate	n-Butyl ester I	173—174 (3)		1.1784 (15°)	1.5551 (15°)	66.73	66.20	$C_{14}H_{15}NO_3$	68.72	6.10	5.57		68.55	6.15	5.71		30
	n-Butyl ester II		153					$C_{14}H_{15}NO_3$**	68.78	6.07	5.44	0.38	68.55	6.15	5.71	0.40	35
Diisobutyl oxalate	Isobutyl ester I	176—177 (5)		1.1726 (16°)	1.5532 (16°)	66.86	66.20	$C_{14}H_{15}NO_3$			5.41				5.71		30
	Isobutyl ester II		168					$C_{14}H_{15}NO_3$	68.62	6.38	5.45	0 39	68.55	6.15	5.71	0.40	35

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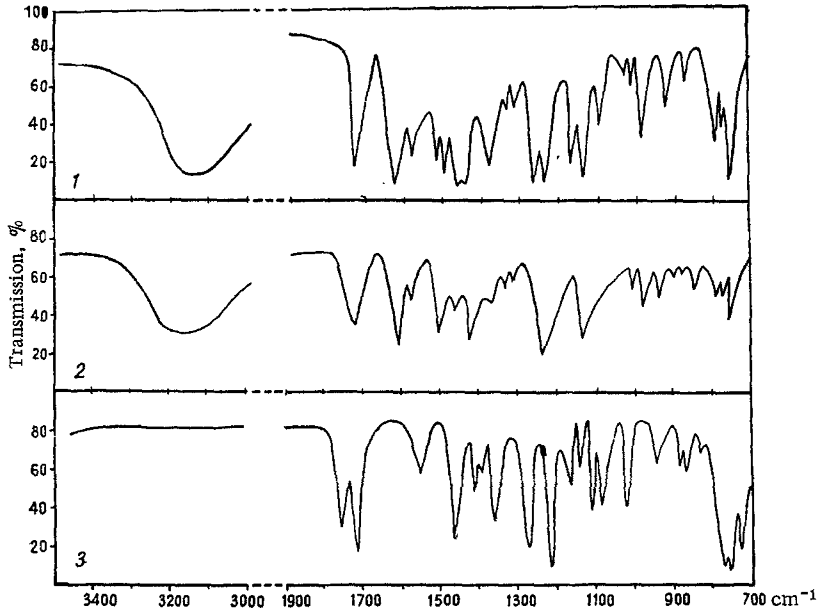
*Rast molecular weight 234; calculated 231.

**Molecular weight, found: 250, calculated 245.



IR spectra: 1) n-Propyl α-indolylglyoxylate (in vaseline); 2) n-propyl α-indolylglyoxylate (in CCl_4); 3) ethyl N-indolylglyoxylate.

HCl, and the ether layer containing the solid ester of α-indolylglyoxylic acid separated off from the water layer. The solid was filtered off and purified by recrystallization from toluene. The filtrate was washed with 10% $NaHCO_3$ solution, then with water, and dried over anhydrous Na_2SO_4. After distilling off the ether, the ester of N-indolylglyoxylic acid was purified by vacuum distillation. When dimethyl oxalate was reacted, a second precipitate formed after the bicarbonate and water washings; it was N, N-diindolyldiketone, mp 156° C. The literature gives [10] mp 154°-156° C. Found: N 9.58%, calculated for $C_{18}H_{12}N_2O_2$: N 9.71%.

As was already stated, with 30 min heating the main reaction product is the ester of N-indolylglyoxylic acid.

The MgBr indole prepared by mixing ether solutions of EtMgBr and indole (30 min heating), is usually a mixture of N-indolyl and α-indolyl MgBr.

The ether was replaced by toluene and refluxing was then continued for 30 min more. The first isomer was almost completely converted to the second. If the ester of oxalic acid is added to this, and the toluene solution refluxed for 2 hr, esters of α-indolylglyoxylic acid are formed along with a trace of esters of N-indolylglyoxylic acid.

Saponification of the esters of N-indolylglyoxylic acid with 10% KOH gives indole, mp 52° C, and oxalic acid mp 189° C. Oxidation of the esters with $KMnO_4$ solution gives α-indolyl carboxylic acid, mp 203°-204° C (ex aqueous MeOH [6]). Undepressed mixed mp with the α-indolyl carboxlic acid obtained by Fischer's method. Saponification of esters of α-indolylglyoxylic acid gives α-indolylglyoxylic acid mp 224°-225° C (ex benzene), agreeing with the literature value [11]. Found: N 7.31%, calculated for $C_{10}H_7NO_3$: N 7.40%.

Fusion of α-indolylglyoxylic acid with KOH at 200° C gave α-indolyl carboxylic acid mp 203°-204° C.

The IR spectrum were observed with a twin-beam UR-10 recording instrument, over the range 3800-700 cm^{-1}. The spectra of the esters of N-indolylglyoxylic acid were determined using the liquids, those of α-indolylglyoxylic acid as a vaseline mull, and CCl_4 solution (concentration 0.05%, layer thickness 10 mm).

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Gor'kii Perm State University