CHEMISTRY OF INDOLES

XLII.[†] SPECTROSCOPIC STUDY OF 3-INDOYLALKANOIC ACIDS

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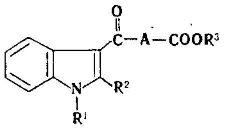
It is shown on the basis of data from the UV and IR spectra that keto acids of the indole series exist in the open acid form. The anomalies in the spectral behavior in alkaline media are determined by the formation of an anion involving the indole hydrogen atom.

Previously [2] in a study of the PMR spectra of indolylketocarboxylic acids of the I type it was concluded that the trans conformation of the keto group in these compounds with respect to the pyrrole portion of the molecule is preferred. However, in this case the possibility of ring–chain tautomerism, which is known for several 4-ketocarboxylic acids [3, 4], and the possibility of the realization of an indolenine structure remained open. In this connection, we made a systematic study of the electronic spectra of a number of keto acids I and of the necessary model compounds.



I–III

I $R^3 = H$; II $R^3 = CH_3$; III $R^3 = Na$

N-Methylated keto acids of the I type ($R^1 = CH_3$) were obtained by direct alkylation of acids I ($R^1 = H$) with dimethyl sulfate in an aqueous acetone solution of alkali; the alkylation is accompanied by esterification of the carboxyl group. Esterification of acids I in the presence of sulfuric acid gives satisfactory yields of the acid esters ($R^2 = CH_3$, C_6H_5), but the preparation of an ester from salt III and an alkyl halide proceeds somewhat better for models that do not have substituents in the 2 position of the pyrrole ring ($R^2 = H$). Completely satisfactory results were also obtained by direct synthesis from the appropriate organomagnesium compound of indole or its 2-substituted derivative and the half-ester of succinoyl chloride, but the value of the latter method is reduced by the necessity for the synthesis of this half-ester.

Primarily two absorption maxima at 240-250 and 298-305 nm are observed in the UV spectra of pyrrole nitrogen-unsubstituted 3-indolylketo acids I ($R^1 = H$) (a short-wave maximum at 210 nm can also be sometimes observed). In strongly alkaline solutions both bands undergo a bathochromic shift, which is particularly considerable for the long-wave $\pi-\pi^*$ band ($\Delta\lambda$ 28-40 nm, λ_{max} 330-340 nm, see Fig. 1).

In the case of N-methylated keto acids I ($R^1 = CH_3$) the UV spectra in alcohol and aqueous solutions are absolutely identical (Fig. 2). The electronic spectra of alcohol solutions of keto acid esters II and salts of these keto acids (III) (in water) are identical and very similar to the spectra of alcohol solutions of free keto acids I (Fig. 1), i.e., salt formation (involving the carboxyl group) or even replacement of the hydrogen atom of the carboxyl group have practically no effect on the character of the UV spectra.

[†] See [1] for communication XLI.

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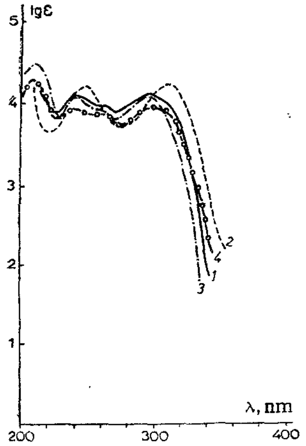


Fig. 1

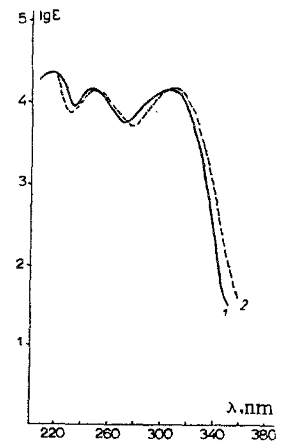
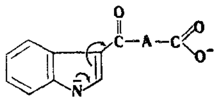


Fig. 2

Fig. 1. UV spectra of γ-(3-indoyl)propionic acid in alcohol (1) and in 2 N aqueous NaOH (2), of methyl γ-(3-indoyl)propionate in alcohol (3), and of sodium γ-(3-indoyl)propionate in water (4).

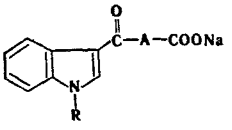
Fig. 2. UV spectra of (N-methyl-3-indoyl)propionic acid in alcohol (1) and in 2 N aqueous NaOH (2).

The facts presented above make it possible to assume that the observed changes in the UV spectra of N-unsubstituted keto acids I ($R^1 = H$) are due to the formation in alkaline solutions of an anion involving the indole nitrogen atom. This sort of ease of formation of an anion is due to the well-known N—H acidity of indole systems and is facilitated in the case of keto acids by stabilization of this anion through conjugation with the carbonyl group.

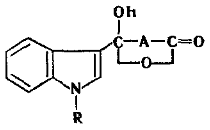


In the case of N-substitution [acids of the I type ($R^1 = CH_3$)] the formation of this sort of anion becomes impossible, and the electronic structure reflected in the UV spectra is retained on passing from alcohol to alkaline media. These conclusions are in agreement with the data on the behavior of 3-acylindoles [5].

However, there may be another alternative explanation for the anomalous spectral behavior of keto acids of the indole series. It is known that aliphatic and aromatic γ- and δ-keto acids may exist in solution and in the solid state in the cyclic lactol form [3, 4], which is converted to the open acid form in alkaline media. The possibility of this sort of ring—chain tautomerism might also be assumed for 3-indoylalkanoic acids.



C

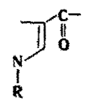


B

The transition from form B to open structure C should be accompanied by a change in the UV spectrum, inasmuch as conjugation of the indole ring with the carbonyl group shows up in this case. However, a study of the UV spectra makes it possible to suppose that cyclic form B is not realized in our case. In fact, as pointed out above, the spectra of alcohol solutions of free keto acids I, their esters II, and salts III in neutral aqueous solutions are identical. Thus keto acids of the indole series exist in the open form in solution, and the anomalies in the spectral behavior are due exclusively to the formation of an anion involving the indole hydrogen atom.

However, the question of the structure of such keto acids in the solid state remains open. It was found that an absorption band at 1700-1720 cm^{-1} (carboxyl C=O group) is observed in the IR spectra of

TABLE 1. Spectra of Keto Acids of the Indole Series and Their Derivatives

Compound	R¹	R²	A	UV spectra											IR spectra, cm⁻¹		
				Acids I in alcohol		Acids I in 2 N NaOH		Esters II in alcohol				Isolated salts III in water					
				λ_{max}	lg ε	λ_{max}	lg ε	Δλ	λ_{max}	lg ε	Δλ	λ_{max}	lg ε	Δλ		C=O OH	NH
Ia	H	H	$(CH_2)_2$	242 298	4,12 4,12	267 331	4,26 4,29	33	210 241 298	4,50 4,11 4,08	0				1640	1710	3290
Ib	H	CH_3	$(CH_2)_2$	242 265 302	4,13 4,03 4,08	270 330	4,17 4,23	28	215 242 266 300	4,49 4,12 4,01 4,04	2	211 242 266 303	4,42 4,04 3,99 4,00	1	1610	1710	3205
Ic	H	C_6H_5	$(CH_2)_2$	250 303	4,33 4,20	272 336	4,36 4,23	33				209 252 306	4,45 4,28 4,04	3	1610	1700	3090
Id	H	H	$(CH_2)_3$	210 242 299	4,63 4,18 4,13	275 340	4,34 4,39	41	210 242 298	4,49 4,13 4,12	1	209 242 260 300	4,10 3,80 3,72 3,79	1	1640	1720	3210
Ie	H	CH_3	$(CH_2)_3$	213 243 268 301	4,64 4,18 4,08 4,10	270 333	4,22 4,28	32	216 243 269 303	4,15 3,79 3,71 3,74	2				1610	1700	3210
If	H	C_6H_5	$(CH_2)_3$	207 245 301	4,45 4,32 4,16	272 336	4,45 4,30	35							1610	1700	3150
Ig	H	H	o-Phenylene	210 242 306	4,72 4,26 4,16	268 338	4,24 4,30	32	210 305	4,51 4,11	1	206 245 310	4,64 4,12 4,09	4	1615	1705	3160
Ih	H	CH_3	o-Phenylene	212 269 310	4,68 4,08 4,11	270 337	4,34 4,41	27	208 240 268 310	4,83 4,26 4,00 4,03	0				1600	1695	3150
Ii	H	C_6H_5	o-Phenylene	209 289 312	4,75 4,11 4,10	277 350	4,26 4,14	38	211 250 291	4,72 4,31 4,14					1600	1700	3160
Ij	CH_3	H	$(CH_2)_2$	213 245 304	4,38 4,18 4,18	247 306	4,15 4,17	2	213 245 307	4,72 4,31 4,14	3				1638	1705	
Ik	CH_3	CH_3	$(CH_2)_2$	213 245 268 306	4,64 4,08 3,89 4,03	247 265 310	4,11 4,00 4,09	4	218 247 268 308	4,48 4,18 4,00 4,13	2						
Il	CH_3	H	$(CH_2)_3$	213 245 304	4,38 4,08 4,20	247 306	4,15 4,13	2							1610	1730	
Im	CH_3	H	o-Phenylene	213 246 313	4,72 4,30 4,26	252 317	4,15 4,17	4	213 245 312	4,65 4,30 4,26	1						
3-Acetylindole				208 238 292	4,49 4,09 4,06	265 329	4,21 4,20	37									

our keto acids. The presence of this band and the absence of absorption at 1790-1795 cm^{-1}, which is characteristic for the carbonyl group of a lactol ring [6], make it possible to assume that open acid form A is also realized in the solid state. The vibrations of the carbonyl group conjugated with the aromatic ring fall in the region of vibration of C=C and C=N bonds (1600-1640 cm^{-1}). In the case of 2-unsubstituted keto acids I ($R^2 = H$) this band lies at 1640 cm^{-1}. The introduction of substituents ($R^2 = CH_3$, C_6H_5) into acid molecule I [$A = (CH_2)_n$] in the 2 position leads to a shift of this band to 1600-1610 cm^{-1}. Inasmuch as the retention of the trans conformation of the keto group relative to the pyrrole portion of the molecule when substituents were introduced into the 2 position was shown previously [2] by the results of PMR spectroscopy, it might be assumed that this shift is due to electronic rather than to conformational factors. In the case of keto acids I (A = o-phenylene) the donor effect of the 2-CH_3 and 2-C_6H_5 groups on the vibrations of the conjugated ring–carbonyl system is practically liquidated due to extension of the chain of conjugation with the o-carboxyphenyl residue. The absorption band for acids I ($R^2 = H$) lies at 1615 cm^{-1}, as compared with 1600 cm^{-1} when $R^2 = CH_3$ or $R^2 = C_6H_5$. All of this information corresponds to the existence of our substances in the open form.

EXPERIMENTAL METHOD

The UV spectra of solutions of the compounds in alcohol and 2 N aqueous NaOH were recorded with Cary, Specord, and SF-4 spectrophotometers. The IR spectra of mineral oil suspensions of the compounds

TABLE 2. Methyl Esters of Keto Acids of the Indole Series

Compound	R^1	R^2	A	mp, °C (benzene–petroleum ether)	Empirical formula	Found, %		Calc., %		IR spectrum, cm^{-1}			R_f*	Yield, %	
						C	H	C	H		COOR	NH		method A	method B
IIa	H	H	$(CH_2)_2$	115–116						1620	1745	3185	0,3		42
IIb	H	CH_3	$(CH_2)_2$	151–152	$C_{14}H_{15}NO_3$	68,4	6,2	68,6	6,1	1640	1730	3345	0,3		42
IId	H	H	$(CH_2)_3$	179–180	$C_{14}H_{15}NO_3$	68,3	6,4	68,6	6,1	1630	1725	3160	0,3	35	37
IIe	H	CH_3	$(CH_2)_3$	135–136†	$C_{15}H_{17}NO_3$	69,7	6,8	69,5	6,6	1615	1710	3285	0,4	34	
IIg	H	H	o-Phenylene	202–203†	$C_{17}H_{13}NO_3$	73,0	4,8	73,1	4,7	1615	1732	3210	0,4	64	33
IIh	H	CH_3	o-Phenylene	232–233†	$C_{18}H_{13}NO_3$	73,4	5,3	73,7	5,1	1595	1720	3285	0,4	57	
IIi	H	C_6H_5	o-Phenylene	187–188†	$C_{23}H_{17}NO_3$	77,6	5,0	77,8	4,8	1610	1735	3190	0,5	31	27

* Thin-layer chromatography on Al_2O_3 (activity II) with benzene–methanol (9:1).

† Recrystallized from methanol.

were recorded with IKS-22 and UR-20 spectrometers. The PMR spectra of trifluoroacetic acid solutions were recorded with a T-60 spectrometer with hexamethyldisiloxane as the external standard. Keto acids I ($R^1 = H$) were obtained by the method in [2], and 2-(1-methyl-3-indoyl)benzoic acid (Im, $R^1 = CH_3$, $R^2 = H$, and A = o-phenylene) and its methyl ester (IIm) were obtained by the method in [7]. Methyl 3-(3-indoyl)-propionate (IIa, $R^1 = R^2 = H$) was obtained from indolylmagnesium bromide and the methyl half-ester of succinoyl chloride by the method in [8] in 30% yield and had mp 116-117° (benzene–petroleum ether). Methyl 3-(2-methyl-3-indoyl)propionate (IIb, $R^1 = H$, $R^2 = CH_3$) was similarly obtained in 21% yield and had mp 151-152° (benzene–petroleum ether).

γ-(1-Methyl-3-indoyl)butyric Acid (I*l*, $R^1 = CH_3$, $R^2 = H$). An 8-ml sample of freshly distilled dimethyl sulfate was added dropwise to a refluxing solution of 1.15 g (0.005 mole) of acid Id ($R^1 = R^2 = H$) in 100 ml of acetone containing 5 g of potassium hydroxide and 25 ml of water, after which the mixture was heated on a water bath for 15 min. The solvent was then removed by vacuum distillation, 50 ml of 2 N NaOH was added to the residue, and the mixture was refluxed for 2 h. It was then filtered, and the filtrate was acidified with dilute acetic acid. The resulting precipitate of acid I*l* was removed by filtration to give 1.1 g (90%) of a product with mp 153-154°. PMR spectrum: δ 3.30 ppm (s,* 3H, $N-CH_3$); 2.17, 2.57, and 3.10 ppm (m, 2H each, CH_2 group); 7.93 ppm (m, 1H, 4-H); 8.43 ppm (s, 1H, 2-H); 7.30 ppm (m, 3H, aromatic protons). Found: C 68.8; H 6.4%. $C_{14}H_{15}NO_3$. Calculated: C 68.6; H 6.1%.

γ-(1,2-Dimethyl-3-indoyl)propionic Acid (Ik, $R^1 = R^2 = CH_3$) and Its Methyl Ester (IIk). A 15-ml sample of freshly distilled dimethyl sulfate was added dropwise to a refluxing mixture of 2.3 g (0.01 mole) of acid Ib ($R^1 = H$, $R^2 = CH_3$), 200 ml of acetone, 10 g of KOH, and 50 ml of water, after which the mixture was heated on a water bath for 15 min. The solvent was then removed by vacuum distillation, 50 ml of 2 N NaOH was added to the residue, and the mixture was stirred for 1 min. The resulting crystals of ester IIk were removed by filtration to give 1.1 g (42.5%) of a product with mp 118-119° (from methanol). IR spectrum: 1630 and 1735 cm^{-1}. Found: C 69.3; H 6.5%. $C_{15}H_{17}NO_3$. Calculated: C 69.5; H 6.6%.

The filtrate remaining after separation of the crystals of ester IIk was acidified with dilute acetic acid, and the resulting crystals of acid Ik were removed by filtration to give 0.8 g (30%) of a product with mp 194-195°. PMR spectrum: δ 2.87 ppm (s, 3H, $2-CH_3$); 3.85 ppm (s, 3H, $1-CH_3$); 3.03 and 3.53 ppm (m, each 2H, methylene protons); 7.70 ppm (m, 1H, 4-H); 7.50 ppm (m, 3H, aromatic protons). Found: C 68.5; H 6.5%. $C_{14}H_{15}NO_3$. Calculated: C 68.6; H 6.1%.

γ-(1-Methyl-3-indoyl)propionic Acid (Ij, $R^1 = CH_3$, $R^2 = H$) and Its Methyl Ester (IIj). As in the preceding experiment, ester IIj, with mp 115-116° (from methanol), was obtained in 49% yield. IR spectrum: 1640 and 1725 cm^{-1}. According to [9], this compound has mp 115-116°. Acid Ij, with mp 176° (mp 176° [8]), was simultaneously isolated in 39% yield.

Esterification of Keto Acids of the Indole Series with Alcohol in the Presence of Sulfuric Acid (Method A). A 0.005-mole sample of the keto acid was refluxed for 5 h with 1 ml of concentrated H_2SO_4 in 50 ml

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* Here and subsequently, s is singlet, d is doublet, and m is multiplet.

of methanol, after which the mixture was cooled to room temperature. The resulting precipitate of the ester was removed by filtration, washed with methanol, and recrystallized from methanol. The physical constants and yields of the esters are presented in Table 2.

Preparation of Esters of Keto Acids of the Indole Series from Sodium Salts (Method B). A mixture of the sodium salt of the corresponding keto acid (0.005 mole) with 5 ml of methyl iodide was refluxed in 50 ml of alcohol for 5 h, after which the solvent was removed by vacuum evaporation. The residue was treated with water, and the resulting precipitate was removed by filtration, air-dried, and recrystallized from benzene–petroleum ether (1 : 1) or methanol. The data on the esters obtained in this manner are presented in Table 2.

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