CHEMISTRY OF INDOLE

XLV.* NEW SYNTHESIS AND SOME TRANSFORMATIONS OF KETO ACIDS OF THE INDOLE SERIES

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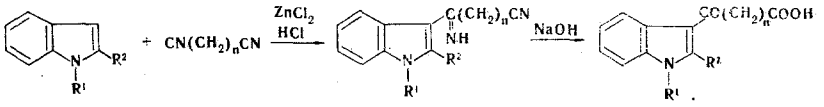
UDC 547.757

Indolyl keto acids were synthesized by the action of dinitriles on substituted indoles under the conditions of the Hoesch reaction. The reaction of these keto acids with isatin in alkali leads to quinoline derivatives, whereas pyridazinones of the indole series are obtained with hydrazine hydrate.

A method for the synthesis of keto acids of the indole series by reaction of indolylmagnesium halides with dicarboxylic acid anhydrides and also the reaction of 2-methylindole with phthalic anhydride in acetic acid was previously developed in [2]. In an attempt to find methods for the preparation of indolyl keto acids without utilization of the Grignard reaction we turned to the Hoesch reaction.

It is known that 2-methyl-3-indolyl chloromethyl ketone, which was converted to β-(2-methyl-3-indolyl)-β-ketopropionitrile (I – acid) by the action of potassium cyanide [3], was obtained by reaction of chloroacetonitrile with 2-methylindole under the conditions of the Hoesch reaction. Ethyl 2-methyl-3-indolylglyoxylate was also synthesized under similar conditions from 2-methylindole and ethyl cyanoformate [4]. However, only the intermediate ketimine, the hydrolysis of which led to complete resinification of the reaction mixture, could be isolated under the same conditions in an attempt to synthesize the ester of homologous acid I with ethyl cyanoacetate [5].

In the present research we used the Hoesch reaction with dinitriles in order to obtain keto acids of the indole series



II

II a R^1=H, R^2=CH_3, n=2; b R^1=CH_3, R^2=H, n=2; c R^1=H, R^2=CH_3, n=4; d R^1=H, R^2=C_6H_5, n=4; e R^1=CH_3, R^2=H, n=4

The yields of the products of the Hoesch reaction depend to a considerable degree on steric factors and also on the nature of the nitriles and substituents in the pyrrole ring of the indoles [6, 7]. In our case the nitrile group is also hydrolyzed simultaneously during hydrolysis of the ketimine. The yields of keto acids do not exceed 50%, but the yield of keto acid IId is only 5% in the reaction of 2-phenylindole (in which the nucleophilicity of the pyrrole ring is reduced) with adiponitrile. The reaction of 2-methylindole with adiponitrile leads to the simultaneous formation of keto acid IIc and a diketone, even in the case of an equimolecular reagent ratio. In the remaining cases the diketones were not isolated, and only a resin was obtained after hydrolysis for separation of the keto acid, or the starting indole was recovered unchanged

* See [1] for communication XLIV.

M. V. Lomonosov Moscow State University. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1512-1517, November, 1975. Original article submitted February 4, 1975.

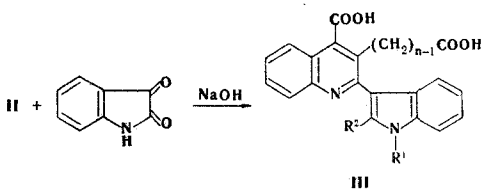
TABLE 1. [2-(3-Indolyl)-4-carboxy-3-quinolinyl]alkanoic Acids (III)

Compound	mp, °C	Empirical formula	Found, %		Calc., %		PMR spectrum, δ, ppm					R_f	Yield, %	pK_{a_1}	pK_{a_2}
			C	H	C	H	R¹	R²	$(CH_2)_{n-1}$	Ar=H (indole)	Ar=H (quinoline)				
IIIa	286—287	$C_{20}H_{14}N_2O_4$	68,9	4,0	69,4	4,0	9,90	7,78	4,30	7,40	8,10	0,32	57	5,5	8,1
IIIb	321—322* (dec.)	$C_{21}H_{16}N_2O_4$	69,6	4,7	70,0	4,4	10,43	2,56	4,33	7,13	8,10	0,36	53	5,5	8,1
IIIc	283—284 (dec.)	$C_{21}H_{16}N_2O_4$	69,7	4,6	70,0	4,4	3,85	7,77	4,33	7,37	8,10	0,36	55	5,4	7,9
IIId	289—290	$C_{22}H_{18}N_2O_4$	70,2	4,9	70,6	4,8	3,67	2,35	4,23	7,13	8,10	0,37	53	5,6	8,2
IIIe	310—311	$C_{21}H_{16}N_2O_4$	69,5	4,6	70,0	4,4	9,83	7,83	2,53	7,33	8,00	0,31	45	5,8	7,9
IIIf	301—302	$C_{22}H_{18}N_2O_4$	70,2	5,2	70,6	4,8	3,73	7,60	3,53 2,50 3,50	7,17	7,77	0,31	53	5,7	8,2
IIIg	319—320	$C_{22}H_{18}N_2O_4$	70,3	5,1	70,6	4,8						0,45	40		
IIIh	326—327 (dec.)	$C_{23}H_{20}N_2O_4$	70,8	5,4	71,1	5,1						0,44	41		

* PMR spectrum in pyridine: 2.10 ($2\text{-}CH_3$), 4.23 (CH_2), 9.76 (NH), and 11.76 (COOH).

(as in the case of 2-phenylindole). The spectral characteristics of the keto acids of the indole series [II, also including those with a longer aliphatic chain (n=4)] newly synthesized by this method are similar to those observed for keto acids that we have previously described [2-8].

The methods developed in this study made it possible to obtain the most diverse 3-indolylalkanoic acids. However, the presence of a carbonyl–carboxyl bifunctional system in them makes it possible to synthesize 3-hetarylindoles by means of various heterocyclization reactions. Thus, in analogy with the conversion of keto acids of the aliphatic series to quinoline derivatives [9], we obtained a number of [2-(3-indolyl)-4-carboxy-3-quinolinyl]alkanoic acids (III) in satisfactory yields by reaction of 3-indolylalkanoic acids with isatin in alkali (Table 1):



III a $R^1=R^2=H$, $n-1=1$; b $R^1=H$, $R^2=CH_3$, $n-1=1$; c $R^1=CH_3$, $R^2=H$, $n-1=1$; d $R^1=R^2=CH_3$, $n-1=1$; e $R^1=R^2=H$, $n-1=2$; f $R^1=CH_3$, $R^2=H$, $n-1=2$; g $R^1=H$, $R^2=CH_3$, $n-1=2$; h $R^1=H$, $R^2=CH_3$, $n-1=3$.

It might have been expected that the formation of the stable 3-indolyl keto acid anion in alkaline media would substantially change the trend of the reaction. However, our results showed that keto acids of the indole series can be successfully used in the Pfitzinger reaction. In particular, condensation of the carbonyl group with the α position of the pyrrole ring was not observed.

The UV spectra of III are similar to the spectra of 2-(3-indolyl)-quinoline systems [10] and contain two intense maxima at 268-275 and 330-347 nm.

The singlets of the protons of the methylene group in the PMR spectra of IIIa-d lie at rather weak field (~4.3 ppm); this is due to the proximity of two strong acceptor groupings (the carboxyl and 4-carboxyquinoline groupings). In the case of the corresponding propionic acids (IIIe-g), each methylene group experiences the effect of only one adjacent acceptor grouping, and their triplets therefore lie at stronger field (~3.5 and 2.5 ppm). A considerable weak-field shift of the signals of the protons of the $N\text{-}CH_3$ group (3.85 ppm) as compared with the 3-unsubstituted N-methylindole (3.37 ppm) due to conjugation of the nitrogen atom of the indole ring with the acceptor groupings in the 3 position (4-carboxyquinoline or keto acid, respectively) is observed for N-methylated (at the indole nitrogen atom) IIIc, d, f, just as in a number of starting keto acids II.

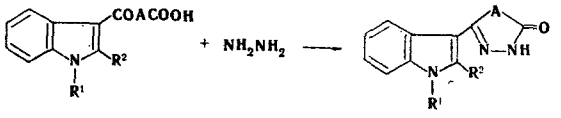
The acidities of the two carboxyl groups in III should differ substantially, inasmuch as one of them is bonded to an aliphatic grouping, and the other is bonded to a donor grouping [2-(3-indolyl)quinoline]. In fact, the presence of two acid groups with pK_a 5.5-5.8 (aliphatic carboxyl) and 7.9-8.2 (aromatic carboxyl)

TABLE 2. Indolylpyridazinones (IV)

Compound	mp, °C	Empirical formula	Found, %		Calc., %		IR spectrum, cm^{-1}		R_f	Yield, %	Literature
			C	H	C	H	CO	NH			
IVa	266—267	$C_{12}H_{11}N_3O$	—	—	—	—	1650	3150 3300	0,88	78	4,11
IVb	249—250	$C_{13}H_{13}N_3O$	68,5	5,7	68,7	5,7	1654	3210 3300 3340	0,88	75	12
IVc	248—249	$C_{18}H_{15}N_3O$	74,3	5,4	74,7	5,2	1670	3265	0,89	69	12
IVd	209—210	$C_{13}H_{13}N_3O$	—	—	—	—	1670	3220	0,87	70	4
IVe	250—251	$C_{14}H_{15}N_3O$	69,5	6,5	69,7	6,2	1630	3420	0,86	77	
IVf	314—315	$C_{16}H_{11}N_3O$	—	—	—	—	1650	3095 3145 3300	0,84	85	11
IVg	330—331	$C_{17}H_{13}N_3O$	74,1	5,0	74,2	4,7	1630	3230	0,88	86	
IVh	365—366	$C_{22}H_{15}N_3O$	78,2	4,8	78,3	4,5	1635	3150 3290	0,84	74	
IVi	236—237	$C_{13}H_{11}N_3O$	68,9	5,0	69,3	4,9	1625	3185 3270 3290	0,87	67	

was detected during potentiometric titration of solutions of acids III in water; this also confirms the proposed structure.

A number of 3-indolyltetrahydropyridazin-6-ones and 3-indolyl-phthalazones [11] with general formula IV (Table 2) were obtained by condensation of keto acids of the indole series with hydrazine hydrates:



IV

IV a $R^1=R^2=H$, $A=(CH_2)_2$; b $R^1=H$, $R^2=CH_3$, $A=(CH_2)_2$; c $R^1=H$, $R^2=C_6H_5$, $A=(CH_2)_2$; d $R^1=CH_3$, $R^2=H$, $A=(CH_2)_2$; e $R^1=R^2=CH_3$, $A=(CH_2)_2$; f $R^1=R^2=H$, $A=o\text{-}C_6H_4$; g $R^1=H$, $R^2=CH_3$, $A=o\text{-}C_6H_4$; h $R^1=H$, $R^2=C_6H_5$, $A=o\text{-}C_6H_4$; i $R^1=CH_3$, $R^2=CH_3$, $A=CH=CH$

One intense band at 1630-1670 cm^{-1}, which characterizes the stretching vibrations of the keto group in the pyridazinone system [13], appears in the IR spectra of IV. In addition, a broad band at 3100-3420 cm^{-1}, which is related to the stretching vibrations of free and bonded NH groups, is observed. Signals of the protons of two different NH groups at 10.9 and 11.7 ppm are observed in the PMR spectrum of indolylpyridazinone IVa in dimethyl sulfoxide (IV are insoluble in alcohol, chloroform, acetone, and trifluoroacetic acid).

The molecular ion peak corresponding to the empirical formula is the maximum peak in the mass spectrum of pyridazinone IVa; in addition, there is a low-intensity ion peak with m/e 117 (indole) and also peaks of fragment ions with m/e 142, 156, 170, and 184, which are formed by loss of NH—CH_2—CO—CH_2, and CHO and N_2, NHCO, and CHO, respectively, by the molecular ion. Similar processes are also observed in the mass spectra of other pyridazinones (Table 3).

EXPERIMENTAL

The UV spectra of alcohol and 2 N NaOH solutions of the compounds were recorded with a Cary-15 spectrophotometer. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in trifluoroacetic acid (unless stipulated otherwise) were recorded with a T-60 spectrometer with hexamethyldisiloxane as the external standard. Potentiometric titration was carried out with a pH-262 potentiometer (10^{-4} M solutions of acids III in water). The individuality of the compounds was monitored by chromatography on Silufol in an isopropyl alcohol—ammonia—water system (8 : 1 : 1). The mass spectra were recorded with an MKh-1303 spectrometer with direct introduction of the samples into the ion source at an ionizing electron energy of 50 eV and 170-220°.

3-(2-Methyl-3-indoyl)propionic Acid (IIa). Succinic acid dinitrile [2 g (0.025 mole)] and 1 g of anhydrous zinc chloride were added to a solution of 3.3 g (0.025 mole) of 2-methylindole in 10 ml of absolute

TABLE 3. Mass Spectra of Some 3-Indolyltetrahydropyridazin-6-ones

Compound	m/e (% of the maximum ion*)
IVb	227(100), 226(18,7), 198(5,0), 184(2,0), 183 (4,0), 170(5,0), 168(2,2), 157(2,5), 156(20,6), 155(13,7), 131(2,5), 130(4,6), 129(6,2), 128(4,4), 127(2,7), 115(2,5), 111(3,7), 97(9,3), 83(12,5), 77(7,5), 73(5,0), 71(13,4). W_M=18,4%
IVc	289 (100,0), 288 (87,0), 218 (14,1), 217 (11,4), 129 (3,2), 123 (2,3), 115 (5,0), 111(6,0), 110(2,7), 109(4,1), 98(9,7), 97(16,3), 96(8,1), 95(8,7), 85(8,7), 84(9,7), 83(22,3), 82(8,7), 81(12,0), 77(4,9), 73(9,7), 70(6,0), 68(5,0), 67(9,7), 60(8,1), 54 (3,4), 51 (2,2), 39 (8,7). W_M=13,5%
IVe	241(100,0), 240(20,0), 212(2,0), 197(2,6), 184(2,9), 170(12,5), 169(7,5), 168(2,2), 145(2,7), 144(2,5), 115(2,1), 97(4,1), 85(3,8), 84(2,0), 83(6,0), 81(2,6), 73(4,2), 72 (2,2), 70 (2,1), 60 (3,9), 56 (5,0), 42 (3,6). W_M=29,1%

*Ions with intensities higher than 2% are presented.

ether, after which a stream of dry hydrogen chloride was bubbled through the reaction mixture at room temperature for 15 h. The mixture was then allowed to stand overnight, and the precipitated solid was removed by filtration, washed with ether, and dissolved in 100 ml of 2 N NaOH. The solution was then refluxed for 2 h, after which it was cooled and filtered. The filtrate was acidified with 20% acetic acid, and precipitated acid IIa was removed by filtration, washed with water, and recrystallized from aqueous methanol to give 2.8 g (49%) of a product with mp 222-223° (mp 222-223° [2]) and R_f 0.57 (its chromatographic mobility was identical to that of a genuine sample).

3-(1-Methyl-3-indoyl)propionic Acid (IIb). As in the preceding experiment, 0.6 g (27%) of acid IIb, with mp 175-176° (from alcohol) (mp 176° [4, 8]) and R_f 0.54, was obtained from 1.3 g (0.01 mole) of 1-methylindole and 0.8 g (0.01 mole) of succinic acid dinitrile.

5-(1-Methyl-3-indoyl)valeric Acid (IIe). As in the preceding experiments, 1.5 g of acid IIa, with mp 131-132° (from alcohol) and R_f 0.58, was obtained in 26% yield from 3.3 g (0.025 mole) of 1-methylindole and 2.7 g (0.025 mole) of adiponitrile. IR spectrum: 1620 (CO) and 1738 cm^{-1} (COOH). UV spectrum, λ_{max} (log ε), in alcohol: 215 (4.28), 243 (4.08), and 301 nm (4.08); in 10% NaOH: 246 (4.10) and 308 nm (4.13). PMR spectrum: 1.80, 2.40, and 3.03 (methylene protons); 3.83 (1-CH_3); 7.90 (4-H), 8.43 (2-H), and 7.27 ppm (the remaining aromatic protons). Found: C 69.2; H 6.7%. $C_{15}H_{17}NO_3$. Calculated: C 69.5; H 6.6%.

5-(2-Phenyl-3-indoyl)valeric Acid (IId). As in the preceding experiment, 0.16 g (5%) of acid IId, with mp 128-129° (from alcohol) and R_f 0.76, was obtained from 2 g (0.01 mole) of 2-phenylindole and 1 g (0.01 mole) of adiponitrile. IR spectrum: 1610 (CO), 1700 (COOH), and 3170 cm^{-1} (NH). UV spectrum, λ_{max} (log ε), in alcohol: 209 (4.56), 251 (4.32), and 303 nm (4.13); in 10% NaOH: 271 (4.33) and 335 nm (4.20). PMR spectrum: 1.47, 2.20, and 2.67 (methylene protons), 8.10 (4H), and 7.47 ppm (the remaining aromatic protons). Found: C 74.9; H 5.9%. $C_{20}H_{19}NO_3$. Calculated: C 74.7; H 5.9%.

5-(2-Methyl-3-indoyl)valeric Acid (IIc) and 1,6-Dioxo-1,6-di(2-methyl-3-indolyl)hexane. As in the preceding experiments, 3 g (47%) of acid IIc, with mp 192-193° (from alcohol) and R_f 0.57, was obtained from 3.3 g (0.025 mole) of 2-methylindole and 2.7 g (0.025 mole) of adiponitrile. IR spectrum: 1608 (CO), 1685 (COOH), and 3320 and 3490 cm^{-1} (NH). UV spectrum, λ_{max} (log ε), in alcohol: 214 (4.46), 242 (4.10), 267 (4.02), and 301 nm (4.04); in 10% NaOH: 270 (4.21) and 331 nm (4.28). PMR spectrum: 1.80, 2.43, and 3.10 (methylene protons), 2.70 (2-CH_3), 7.60 (4-H), and 7.23 (the remaining aromatic protons). Found: C 69.5; H 6.7%. $C_{15}H_{17}NO_3$. Calculated: C 69.5; H 6.6%.

The alkali-insoluble crystalline substance was removed from the alkaline hydrolyzate of the reaction mixture by filtration and recrystallized from a large volume of alcohol to give 1 g (21%) of a diketone with mp 275-276° and R_f 0.91. IR spectrum: 1620 (CO) and 3230 and 3490 cm^{-1} (NH). Found: C 77.1; H 6.5%. $C_{24}H_{24}N_2O_2$. Calculated: C 77.4; H 6.5%.

5-(1,2-Dimethyl-3-indoyl)valeric Acid. Freshly distilled dimethyl sulfate (4 ml) was added dropwise to a refluxing solution of 0.65 g (0.0025 mole) of acid IIc in 50 ml of acetone containing 2.5 g of potassium hydroxide in 13 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 cooled and filtered, and the filtrate was acidified with 20% acetic acid. The precipitated acid was removed by filtration, washed with water, dried, and recrystallized from

alcohol to give 0.5 g (74%) of a product with mp 163-164° and R_f 0.60. IR spectrum: 1600 (CO) and 1720 cm^{-1} (COOH). UV spectrum, λ_{max} (log ε), in 10% NaOH: 215 (4.64), 248 (4.13), 265 (4.02), and 311 nm (4.13). PMR spectrum: 1.95, 2.56, and 3.27 (methylene protons); 2.90 (2-CH_3), 3.83 (1-CH_3), 7.67 (4-H), and 7.46 (remaining aromatic protons). Found: C 70.0; H 7.2%. $C_{16}H_{19}NO_3$. Calculated: C 70.3; H 7.0%.

General Method for the Preparation of [2-(3-Indolyl)-4-carboxy-3-quinolinyl]alkanoic Acids (III). A mixture of 0.0025 mole of 3-indoyl-alkanoic acid and 0.0025 mole of isatin in 15 ml of 33% aqueous sodium hydroxide was refluxed for 50 h, after which it was cooled, diluted with water, and filtered. The filtrate was acidified with 25% acetic acid, and the yellow precipitate that formed in a few hours was removed by filtration and washed with alcohol or acetone. The product was recrystallized from a large amount of alcohol. The physical constants, spectral characteristics, and yields of III are presented in Table 1.

General Method for the Preparation of Indolylpyridazinones (IV). A mixture of 0.0025 mole of the corresponding indolyl keto acid in 10 ml of hydrazine hydrate was refluxed for 2 h, after which the resulting precipitate was treated with alcohol and removed by filtration. The physical constants and yields of IV are presented in Table 2.

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