REARRANGEMENT OF 1-[2-OXOALKYL(ARYL)]INDOLE-2,3-DIONE TO FORM 2-ACYLINDOLYL-3-CARBOXYLIC ACID

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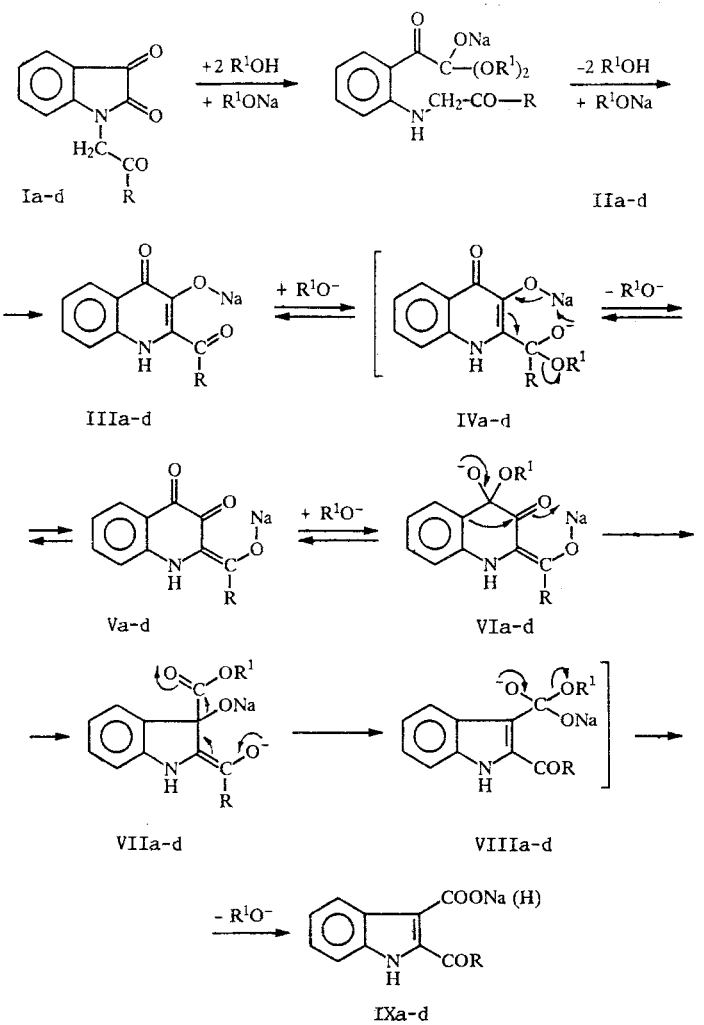
It has been shown that 1-[2-oxoalkyl(aryl)]indole-2,3-diones are recyclized under the influence of sodium alcoholate to form 2-acylindolyl-3-carboxylic acids. A reaction scheme is proposed for this rearrangement.

It was shown previously [1] that the ethyl ester of isatin-1-acetic acid (I) is recyclized under the influence of sodium methylate in boiling methanol to form the ethyl ester of 3,4-dihydroxyquinaldinic acid (III, R = OC_2H_5). An intermediate in this reaction is the partial orthoester II ($R^1 = CH_3$), which was isolated successfully.

We have shown that when the ester group is replaced by a keto group in compound I, the reaction proceeds with a further contraction of the pyridine ring of the quinoline III to a pyrrole ring. The final product is the sodium salt of the acid



I—IXa R = C_2H_5, R = P-C_3H_7, R = —CH(CH₃)—CH_2CH_3, R = $CH_2CH(CH_3)_2$, R = 4-Cl—C_6H_4, R = 4-Br—C_6H_4

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TABLE 1. Characteristics of Compounds I and IX

Compound	Empirical formula	mp, °C	PMR spectra, δ, ppm,	J, Hz
Ia	$C_{12}H_{11}NO_3$	159...161	1,13 (3H, t, J=7,3, CH_3), 2,60 (2H, q, J=7,3, CH_2), 4,55 (2H, s, CH_2N), 6,63...7,66 (4H, m, H_{arom})	77
Ib	$C_{13}H_{13}NO_3$	108...109	0,97 (3H, t, J=6,4, CH_3), 1,64 (2H, m, CH_2), 2,53 (2H, t, J=7,1, CH_2CO), 4,52 (2H, s., CH_2N), 6,59...7,68 (4H, m, H_{arom})	75
Ic	$C_{14}H_{15}NO_3$	95...96	0,95 (3H, t, J=7,2, $CH_2C\underline{H_3}$), 1,19 (3H, d, J=6,9, $CHC\underline{H_3}$), 1,78 (2H, m, $C\underline{H_2}CH_3$), 2,66 (1H, m, CH), 4,59 (2H, s, CH_2N), 6,57...7,65 (4H, m, H_{arom})	75
Id	$C_{14}H_{15}NO_3$	141...142	0,97 (6H, d, J=6,4, $2CH_3$), 2,30 (2H, m, CH), 2,43 (2H, d, J=5,5 CH_2), 4,50 (2H, s, CH_2N), 6,57...7,66 (4H, m, H_{arom})	79
IXa	$C_{12}H_{11}NO_3$	215...222*	1,13 (3H, t, J=7,2, CH_3), 3,19 (2H, q, J=7,2, CH_2), 7,16...8,11 (4H, m, H_{arom})	100
IXb	$C_{13}H_{13}NO_3$	210...220*	0,93 (3H, t, J=7,3, CH_3), 1,62 (2H, m, CH_2), 3,13 (2H, , J=7,3, $COCH_2$), 7,19...8,12 (4H, m, H_{arom})	100
IXc	$C_{14}H_{15}NO_3$	204...210*	0,86, (3H, t, J=7,3, $CH_2C\underline{H_3}$), 1,06 (3H, d, J=7,3, $CHC\underline{H_3}$), 1,78 (2H, m, $C\underline{H_2}CH_3$), 3,60 (1H, m CH), 7,09...8,10 (4H, m. H_{arom})	84
IXd	$C_{14}H_{15}NO_3$	204...205	0,94 (6H, d, J=6,6, $2CH_3$), 2,17 (1H, m, CH), 3,06 (2H, d, J=6,8, CH_2), 7,12...8,11 (4H, m, H_{arom})	79

*Decarboxylation temperature.

**Owing to a typographical error in the Russian original, no heading is given for this column; the numbers in this column probably represent percentage yields — Translator.

IX. The rearrangement goes forward at 20°C, but under these conditions requires a large quantity of sodium alcoholate. With an equimolar ratio of the ketone I and R^1ONa, the conversion of the original ketone is very low; but with a ratio of 2.5/1 to 3/1, the reaction proceeds with a high yield.

The role of the sodium alcoholate apparently comes down to conversion of the intermediate quinoline III to its tautomeric form V, which has the structure of a cyclic 1,2-diketone and, like other compounds of this type, can undergo ring contraction — a benzyl type rearrangement to an ester of benzylic acid. Subsequent aromatization of the indole ring proceeds via migration of the ONa from the C_3 atom to the carbon atom of the ester group in the intermediate VII, leading to the formation of the structure VIII with subsequent detachment of the alkoxide ion.

It is obvious that the acid IX could also be formed by intramolecular crotonaldehyde condensation of compound II, followed by cleavage of the orthoester group by acid treatment of the reaction mixture. However, this possibility can be eliminated on the basis of the evidence that has been obtained. After completing the rearrangement of 1-phenacylindole-2,3-dione in CD_3OD-CD_3ONa, we obtained the ^{13}C NMR spectrum of the reaction mixture before it had been treated and acidified. In addition to the signals of the carbon atoms of the benzene and pyrrole rings, we observed two more signals at 176 and 197 ppm, indicating the presence of two carbonyl groups. If, after completing the reaction in a methanol solution of sodium methylate, the reaction mixture is treated with the calculated quantity of water, and the methanol is replaced by a 9:1 mixture of DMF and water, and then an excess of methyl iodide is added, the main product of the conversion is the methyl ester of 2-benzoylindolyl-3-carboxylic acid, along with a small admixture of its 1-methyl derivative. From this we conclude that in the reaction mixture before acidification, there was no orthoester of the acid IX, and the signal in the ^{13}C NMR spectrum are assigned to two CO groups of its sodium salt.

We had previously worked out in detail the recyclization of the ketone I in 1-5% aqueous caustic solution at 20°C. This reaction proceeds through a stage of formation of n-2-oxoalkyl(aryl)-ortho-aminophenylglyoxylic acid (X), which, through an intermolecular crotonaldehyde condensation, is converted to the acid IX [2, 3]. Thus, when the acid IX is obtained from the ketone I, we observe two different mechanisms of formation of its pyrrole ring. In an aqueous caustic solution, the blockage of the carboxyl group of the acid X in the form of the salt presupposes the crotonaldehyde mechanism of its cyclization and direct closure of this ring. Activation of the carboxyl group in the form of the partial orthoester II leads to

inclusion of its carbon atom in the new pyridine ring through an ester condensation mechanism. Here the pyrrole ring is formed as a result of a second process: contraction of the pyridine ring of the quinoline III under the influence of sodium alcoholate.

The structure of the compounds IXa-d that we obtained was proven by countersynthesis from the corresponding ketones I in an aqueous caustic solution. The acids IXe,f are identical to those described above; dissociative ionization is characteristic for 2-benzoylindolyl-3-carboxylic acid [3]. Unambiguous proof of the structure of the acid IX was also obtained by means of ^{13}C NMR data, which we will publish subsequently. The indicated contraction of the pyridine ring of the quinoline is described here for the first time; and this sort of recyclization is known [4] only for previously quaternized 4-nitro-3-hydroxyquinoline; other examples are concerned with the formation of the oxidized form of the pyrrole ring — indole-2,3-diones [5].

An extremely promising method for obtaining the halomethylketones that are required for the synthesis of the compounds I is a method described in [6], which gives a mixture of bromomethyl- and methylbromoalkylketones with a predominance of the former. Upon bromination of 2-butanone, 2-pentanone, or 3- or 4-methyl-2-pentanone, a mixture of bromoketones containing 75% of the bromomethylketone was obtained. Without separating the isomers, this was used for the N-alkylation of the 3-ethyleneacetal of indole-2,3-dione in a K_2CO_3/DMF system [7]. Under the conditions that were described, only the bromomethylketone reacts, while its isomer is apparently dehydrobrominated. An attempt to replace potassium carbonate by the weaker base $KHCO_3$ resulted only in a twofold reduction of the reaction yield. In the 3-ethyleneacetal of the ketone I, the dioxolane ring is readily cleaved in an alcoholic solution of of hydrochloric acid. The resulting ketone I is readily cyclized under mild conditions to the acid IX.

In conclusion, let us note that the rearrangement of the ketone I to the acid IX is an intramolecular variant of the intermolecular condensation of ortho-aminophenylglyoxylic acid with a halomethylketone. The accomplishment of this condensation under mild conditions could be a simple, general method for obtaining the acid IX. However, such a synthesis has not yet been accomplished, owing to the inertness of the nitrogen atom with respect to alkylation of the halomethylketone, even in an aprotic solvent at elevated temperatures [8] under conditions of interfacial catalysis [9], and also owing to the difficulty of performing the Darzens reaction with subsequent recyclization of the resulting epoxy compound to form an indole system [10]. The preliminary introduction of the 2-oxoalkyl group at the nitrogen atom of the ortho-aminophenylglyoxalic acid by N-alkylation of the indole-2,3-dione, with subsequent opening of the five-membered ring, has made it possible to work out the rearrangement of the ketone I that has been described previously [2, 3] and in the foregoing material; this is still the sole method for obtaining the acid IX.

EXPERIMENTAL

The 1-phenylacylindole-2,3-dione, its 4-chloro(bromo) derivatives, and the 3-ethyleneacetal of indole-2,3-dione were obtained by methods described in [3]. The bromoketones were analyzed by means of GLC in a Chrom-5 instrument (katharometer) in a 1.2-m glass column packed with 5% SE-30 on Inerton AW, with oven temperatures of 70° and 95°, vaporizer and detector temperature 270°, carrier gas helium at 60 ml/min; ratio of bromomethylketone to methylbromoalkylketone in the products 3:1. The PMR spectra were taken in a Bruker AC-80 instrument, TMS internal standard. The melting points were determing in a Boetius instrument and were not corrected. The individuality of the compounds that were obtained was monitored by TLC on Silufol plates in 5:1 toluene–acetone and 4:1 benzene–acetone systems, development by iodine vapor.

The results of elemental analyses for C, H, and N matched the calculated values.

3-Ethyleneketal of 1-(4-methyl-2-oxopentyl)indole-2,3-dione ($C_{16}H_{19}NO_4$) (3-Ethyleneketal of Compound Id). In 75 ml of methanol, with heating, 15 g of urea and 25 g (0.25 mole) of 4-methyl-2-pentanone were dissolved with heating; the solution was cooled to 20°C, and 4.5 ml (0.087 mole) of bromine was added dropwise over a period of 2.5 h; after decolorization of the solution, 75 ml of methanol and 16 ml of water were added, after which the solution was allowed to stand overnight and then diluted with 800 ml of water and extracted with chloroform (4 × 100 ml). The combined chloroform extracts were washed with a 5% $NaHCO_3$ solution and then with water (3 × 50 ml) and dried with Na_2SO_4, after which the chloroform was driven off. Obtained 29.2 g of a mixture of bromides. Into 85 ml of DMF, the following were introduced successively: 18.5 g (0.097 mole) of the 3-ethyleneketal of indole-2,3-dione, 16.5 g (0.12 mole) of K_2CO_3, and 29.2 g of the mixture of bromides. This mixture was then heated for 4 h at 50-60°C. After diluting the reaction mixture with 800 ml of water, obtained 15.1 g of a substance that was purified by column chromatography on silica gel 100/400 μm (225 g), eluent

9.5:5 benzene–acetone. Yield of pure substance 14.4 g (51%), mp 111-112°C. PMR spectrum ($CDCl_3$): 0.92 (6H, d, J = 6.4 Hz, $2CH_3$); 2.16 (1H, m, J = 6.7 Hz, CH); 2.34 (2H, d, J = 7.2 Hz, $CHCH_2CO$); 4.20-4.66 (4H, m, $2CH_2O$); 4.37 (2H, s, CH_2N); 6.51-7.44 m.d. (4H, m, H_{arom}).

3-Ethyleneketal of 1-(3-Methylpentyl)indole-2,3-dione (3-Ethyleneketal of Compound Ic, $C_{16}H_{19}NO_4$). This compound was obtained analogously from the 3-ethyleneketal of indole-2,3-dione and a mixture of the bromides of 3-methyl-2-pentanol, but with replacement of the potassium carbonate by $KHCO_3$; obtained 6.65 g (24%) of this compound, mp 99-101°C. PMR spectrum ($CDCl_3$): 0.89 (3H, t, J = 7.3 Hz, CH_3); 1.11 (3H, d, J = 6.9 Hz, CH_3); CH_2 see table for compound Ic; 2.58 (1H, m, J = 6.8 Hz, CH); 4.38 (2H, s, CH_2N); 6.52-7.44 m.d. (4H, m, H_{arom}).

3-Ethyleneketal of 1-(2-Oxopentyl)indole-2,3-dione (3-Ethyleneketal of Compound Ib, $C_{15}H_{17}NO_4$). To a mixture of 100 ml of absolute DMF, 40 ml of absolute methanol, and 43 g (0.5 mole) of 2-pentanone, 10 ml (~0.2 mole) of bromine was added dropwise over a period of 45 min. The solution began to be decolorized in 25 min. To the colorless solution, 55.2 g (0.4 mole) of finely ground K_2CO_3 was added in portions, then 19.1 g (0.1 mole) of the 3-ethyleneketal of indole-2,3-dione was added; the mixture was heated for 3.5 h at 45-50°C and then treated as described above. Obtained 13.1 g (50%) of the pure substance with mp 105-106°C. PMR spectrum ($CDCl_3$): 0.9 (3H, t, J = 7.2 Hz, CH_3); 1.57 (2H, m, J = 6.9 Hz, CH_2); 2.43 (2H, t, J = 7.0 Hz, CH_2CO); 4.20-4.65 (4H, m, $2CH_2O$); 4.32 (2H, s, CH_2N); 6.52-7.44 m.d. (4H, m, H_{arom}).

3-Ethyleneketal of 1-(2-oxobutyl)indole-2,3-dione (3-ethyleneketal of Compound Ia, $C_{14}H_{15}NO_4$). From the 3-kethyleneketal of indole-2,3-dione and a mixture of the bromides of 2-butanone, this compound was obtained with a yield of 50%, mp 66-67°C. PMR spectrum ($CDCl_3$): 1.06 (3H, t, J = 7.2 Hz, CH_3); 2.48 (2H, q, J = 7.3 Hz, CH_2); 4.20-4.65 (4H, m, $2CH_2O$); 4.54 (2H, s, CH_2N); 6.54-7.43 m.d. (4H, m, H_{arom}).

1-[2-Oxoalkyl(aryl)]indole-2,3-diones (I) (General Method). In a mixture of 40 ml of alcohol and 8.5 ml of concentrated HCl, 0.15 mole of the 3-ethyleneketal of compound Ia-d was dissolved, and the mixture was refluxed for 20-30 min and then cooled to 5°C. The precipitate was filtered out, washed with water to neutral reaction, and dried in air and then over P_2O_5. After driving off the alcohol, the precipitate was separated from the mother solution and treated as described above. For further purification, the combined precipitate was dissolved in a minimum quantity of boiling ethanol and then frozen for 24-48 h at −18°C. A different procedure was also used: After the end of the hydrolysis, the reaction mixture was diluted with 120 ml of water, and the precipitate was removed and recrystallized. The substance was vacuum-dried over P_2O_5. The constants of the substances that were obtained (compounds Ia-d) are listed in Table 1.

Recylization of Ketones I to Acids IX in Aqueous Caustic Solution. A 0.7-0.8 g quantity of the compound I was dissolved in 30 ml of 1% NaOH solution and stirred for 2.5 h at ~20°C, after which it was poured into a mixture of 22 ml of water and 3 ml of concentrated HCl. The precipitate was separated by centrifuging (3000-6000 rpm) and washed with water (3 × 5 ml), each time repeating the centrifuging operation; the product was then dried over P_2O_5 at 20°C. Yield about 90%. Compounds IXa,b were crystallized from a large volume of alcohol, IXc,d from 60-70% aqueous alcohol. In both cases it was necessary to use a funnel for hot filtration.

Rearrangement of Ketones I to Acids IX in Alcohol Solution of Sodium Alcoholate.

4-Bromobenzoylindolyl-3-carboxylic Acid (IXf). To a chilled solution of sodium butylate, prepared from 0.69 g (0.03 mole) of metallic sodium and 50 ml of butanol, 3.44 g (0.01 mole) of 4-bromophenacylindole-2,3-dione was added. The intensity of the red color of the solution decreased after 10-15 min; at 1 h, a curdlike precipitate began to form. The mixture was held for 3 h at 20°C and then poured into a mixture of 500 ml of water and 5 ml of concentrated HCl. The yellow precipitate was filtered off, washed with water to neutral reaction, dissolved in 150 ml of boiling alcohol, cooled, and left overnight at −18°C. Obtained 2.8 g (81%) of 4-bromobenzoylindolyl-3-carboxylic acid, mp 222-223°C (decomp.). According to [3], mp 221-224°C. When the quantity of sodium butylate was doubled, the yield was quantitative. Mass spectrum* m/z (and I_{rel}, %): 345 (14), 343 (14), 327 (10), 325 (10), 302 (14), 301 (89), 300 (22), 299 (100), 298 (10), 256 (8), 247 (8), 246 (20), 221 (24), 220 (78), 219 (16), 191 (20), 190 (24), 185 (24), 183 (24), 165 (16), 164 (10), 168 (8), 157 (32), 155 (32), 148 (8), 145 (8), 144 (86), 129 (14), 116 (30), 115 (27), 114 (20), 111 (10), 110 (14), 97 (20), 96 (14), 95 (14), 89 (86), 85 (20), 83 (27), 81 (24).

4-Chlorobenzoylindolyl-3-carboxylic Acid (IXe). This compound was obtained in 72% yield by the same procedure; mp 199-200°C. According to [3], mp 195°C. Mass spectrum: 301 (22), 300 (12), 299 (75), 283 (22), 282 (16), 281 (75), 257 (17), 255 (70), 254 (14), 253 (39), 220 (33), 191 (13), 191 (13), 190 (25), 175 (8), 143 (19), 141 (22), 116 (14), 115 (19), 114 (33), 113 (31), 111 (100), 89 (53), 88 (12), 83 (13), 81 (13).

*Here and subsequently, values are given for m/z (and relative intensity in %).

The same procedure was used in obtaining the acids XIa-d (Table 1).

Methyl Ester of 2-benzoylindolyl-3-carboxylic Acid. A. To a solution of sodium alcoholate (prepared from 0.4 g of metallic sodium and 30 ml of absolute methanol), 1.33 g (0.005 mole) of 1-phenacylindole-2,3-dione was added, and the mixture was held for 3 h at 20°C. Then 0.3 ml of water was added, the mixture was stirred for 10 min, the methanol was removed under vacuum, and 15 ml of a 9:1 mixture of DMF and water was added to the residue, after which carbon dioxide was passed through the liquid until a neutral reaction was obtained. To the resulting slurry, 3.5 g (0.025 mole) of methyl iodide was added; the mixture was stirred overnight and then diluted with 120 ml of water and acidified to pH 1; the precipitate was removed rapidly, washed with water to neutral reaction, and dried over P_2O_5. Obtained 1.2 g of a mixture of substances, which, according to the results of TLC in a 5:1 toluene–acetone system, consisted mainly of the methyl ester of 2-benzoylindolyl-3-carboxylic acid (R_f 0.74), the corresponding free acid (R_f 0.43), and traces of an unidentified substance with R_f 0.92. The precipitate was chromatographed in a column (220 × 30 mm) with silica gel L 160/100 μm in a 5:1 toluene–acetone system, recovering 1.1 g of the pure methyl ester of 2-benzoylindolyl-3-carboxylic acid with mp 177-178°C. PMR spectrum ($CDCl_3$): 3.39 (3H, s, CH_3); 7.20-8.23 (9H, m, H_{arom}); 9.64 ppm (1H, s, NH). The aqueous solution that remained after removing the precipitate was immediately neutralized with NaOH and extracted with benzene (5 × 60 ml); the benzene extract was washed with water (5 × 40 ml) and evaporated down. Recovered 0.15 g of a mixture of substances, which, according to TLC, consisted of the methyl ester of 2-benzoylindolyl-3-carboxylic acid with small amounts of its 1-methyl derivative (R_f 0.86). This fraction was not subjected to preparative separation, in view of the closeness of values of R_f of these substances.

B. To a methanol solution of sodium methylate (from 0.2 g of sodium and 20 ml of methanol), 0.5 g of the methyl ester of 2-benzoylindolyl-3-carboxylic acid was added; the mixture was held for 3 h at 20°C, diluted with 100 ml of water, and acidified to pH 1; the precipitate was removed, and the aqueous solution was treated as described above. According to TLC data, neither fraction contained even a trace of the acid IX.

1-(p-Toluenesulfonylmethyl)indole-2,3-dione ($C_{16}H_{13}NO_4S$). A mixture of 100 ml of anhydrous DMSO, 29 g (0.15 mole) of 1-chloromethylindole-2,3-dione, and 40 g (0.22 mole) of sodium sulfamate was stirred for 5 h at 20°C and then 3 h at 60-70°C, after which it was cooled and poured into a solution of 100 g of KCl in 600 ml of water. The precipitate, which had an intense yellow color, was removed and washed with water (5 × 200 ml) and then with methanol (3 × 50 ml). The product, which was difficultly soluble in organic solvents, was crystallized from a large volume of acetone. Yield 10 g (21%), mp 262-263°C. Mass spectrum m/z (I_{rel}, %): 315 (4), 162 (2), 161 (4), 160 (25), 155 (2), 147 (6), 146 (7), 132 (100).

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