SYNTHESES OF 1-(3-OXOALKYL)INDOLE-2-3-DIONES

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Hydration of the triple bond in 1-(alkyn-2-yl)indole-2, 3-diones under Kucherov reaction conditions takes place under the orienting influence of the nitrogen atom with formation of an oxo group exclusively at the γ -carbon atoms.

1-[2-Oxoalkyl(aryl,hetaryl)]indole-2,3-diones are used as the starting compounds in the indoledione – indole rearrangement. Two methods of preparing them – one general and one specific – have been described. The general method is based on condensation of β -ethylene acetals of indole-2,3-diones with bromomethyl ketones, followed by a splitting of the dioxolane ring in an acid medium [1]. The possibilities of this method are considerably expanded by the use of chloromethyl ketones. In the present study, β -ethylene acetal (III) was obtained from the water-soluble lithium or sodium salt of isatin β -etylene acetal (I) and 1-chloro-3-ethyl-2-pentanone (II), synthesized from diethylacetyl chloride and diazomethane. (When lithium hydride or sodium hydride is replaced by K₂CO₃ [2] as the condensing agent, the reaction product III must be separated by chromatographic methods.) The ketone (IVa) obtained after removal of the protective group is recyclized in an alkaline medium, apparently via the keto acid (V), to 2-(2-ethyl-1-oxobutyl)indole-3-carboxylic acid (VI). Note that the Na salt of the latter decarboxylates in aqueous solution at 100°C for 1.5 h to form the corresponding 2-acylindole (VII).

As we know, dialkylacetic acids with identical or different groups can readily be prepared by malonic synthesis; this makes it possible to vary the acyl part of acids VI.



In a study of the indoledione – indole rearrangement of N-diacylisatin (IVb), the error made in [1], which for the acid VIb gave mp 173°C (dec.), was corrected. A repeated synthesis showed that in such media as aqueous solution of NaOH (medium A), powdered NaOH in anhydrous methanol (B), NaOH in 80% aqueous methanol (C), in 50% aqueous DMFA (D) and sodium methoxide in methanol (E), the same acid VIb is formed, the purest sample of which has mp 218-219°C.

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An attempt to obtain 2-tosylindole-3-carboxylic acid (VI, R = Ts) from 1-(p-tosylmethyl)-2,3-indoledione (IV, R = Ts) was unsuccessful [3]. The latter compound, however, under the conditions of an indoledione – indole rearrangement in aqueous alkali and an alcohol solution of sodium alcoholate [3], undergoes a splitting off of the substituent at the nitrogen atom even before the acid is formed.

A drawback of the synthesis of diketone IVa is the necessity of protecting the β -oxo group in the position of 3-indole-2,3-dione (VIII) prior to alkylating with chloromethyl ketone II. Attempts to use it in a direct alkylation of indoledione VIII proved unsuccessful and gave only apoxides, which apparently form in accordance with the Darzens reaction:



A direct method of synthesizing the acids VIa,b could be alkylation of *o*-aminophenylglyoxylic acid with halomethyl ketones II. However, the nitrogen atom of this acid remains inert even in highly basic media [4], and only ketones undergo chemical changes.

A special and previous thoroughly described [5] method of obtaining diketones IV is the transformation of the propargyl group of N-propargylindoledione (IX, R = H) into a 2-oxopropyl group under Kucherov reaction conditions. Formation of a diketone (X) could be expected in this case, the triple bond being hydrated according to the Markownikoff rule, and of a diketoaldehyde (XI, R = H), under the orienting influence of the nitrogen atom. However, the diketoaldehyde was not separated from the reaction mixture.

The direction of hydration of the disubstituted triple bond in diketones IXa-d has not been studied thus far. We obtained these compounds by condensation of indole-2,3-dione VIII with 1-bromo-2-alkynes (XIIa-c) and with 1,4-dichloro-2-butyne (IId). Diketones IXd was isolated in low yield, since the main product of the reaction is a tetraketone (XIII). It is sparingly soluble in organic solvents and can be recrystallized from DMSO. When the Kucherov reaction is carried out with diketones IXa-d, one can expect formation of a mixture of 1-(2-oxoalkyl)- (IV) and 1-(3-oxoalkyl)indole-2,3-diones (XIa-d), or only the latter (see [6]).

The reaction products were analyzed by means of ESR spectra of samples periodically taken from the reaction mixtures.



IX, XI, XII a R = Et, b R = C6H13, c R = C9H19, d R = CH2Cl; XIIa-cHal = Br, d Hal = Cl

Formation of 1-(2-oxoalkyl)indole-2,3-diones IV was accompanied by the appearance, in the spectra, of the singlet signal of the methylene group at the nitrogen atom, and formation of their 1-(3-oxo) isomers XI, by two triplets of the methylene groups. In the ESR spectra, only the triplet signals of compounds XI were recorded, irrespective of the nature of the substituents at the triple bond.

Thus, hydration of the monosubstituted triple bond in compound IX (R = H) takes place largely in accordance with the Markownikoff rule, and to a lesser extent under the orienting influence of the nitrogen atom, and hydration of the disubstituted triple bond in compounds IXa-d takes place exclusively under the influence of the latter factor. These compounds cannot be used to synthesize diketones IV. The described simple synthesis of 1-(3-oxoalkyl)indole-2,3-diones XIa-d is applicable to the preparation of antioxidants — 1,4-dihydro-3-acylquinoline-4-carboxylic acids [7].

Further development of the indoledione – indole rearrangement necessitates a method of direct N-alkylation of indole-2,3-diones with halomethyl ketones or compounds in which the halogen atom has been replaced by a different departing group, and calls for a search for basic-type reactants capable of causing the opening of the 5-membered ring of diketones IV without splitting off the substituent at the nitrogen atom, as well as alternative syntheses of acids V for their subsequent intramolecular cyclization under basic catalysis conditions (for example, under action of alkali metal hydrides).

EXPERIMENTAL

1-Bromo-2-alkynes (XIIa-c) were obtained by condensation of bromoalkanes with propargyl alcohol, followed by substitution of a bromine atom for the hydroxyl group by reaction with PBr_3 [8]. 1,4-Dichloro-2-butyne (XIId) was synthesized as described in [8]. The ESR spectra were taken with a Bruker-80 instrument, and the IR spectra, with an IR-71 spectrometer. The purity of the substances obtained was monitored by TLC on Silufol plates in benzene and 4(5):1 benzene – acetone systems. The spots were developed in iodine vapor, and in the case of compounds XIa-d, in aqueous KMnO₄ solution.

The data of ultimate analyses for C, H, N, and Cl were consistent with the calculated data.

β-Ethylene Acetyl of 1-(3-Ethyl-2-oxopentyl)indole-2,3-dione (III). To 100 ml anhydrous DMFA are added 9.55 g (50 mmole) of β-ethylene acetal of indole-2,3-dione and, while the flask is cooled with ice water, 0.8 g (101 mmole) of powdered lithium hydride in portions, the mixture is agitated, and after 30 min, 10.4 g (69 mmole) of 1-chloro-2-oxo-3ethylpentane is added. After 3 h, the reaction mixture is diluted with water (900 ml), the precipitate is separated, washed with water and dried in air, then over P₂O₅, and crystallized from 1:2 benzene – hexane mixture. The yield is 9.7 g (63%) of a substance with mp 126-128°C. The product was pure according to TLS in a 5:1 benzene – acetone system (R_f 0.33). Found, %: C 66.7, H 7.0, N 4.6. C₁₇H₂₁NO₄. Calculated, %: C 67.3, H 7.0, N 4.6.

1-(3-Ethyl-2-oxopentyl)indole-2,3-dione (IVa). To 200 ml of isopropanol are added 20 ml of conc. HCl and 4 g of β -ethylene acetal III, the mixture is boiled for 20 min, the solvent is evaporated down to about one-half, water is added (400 ml), and the precipitate is separated, washed with water and dried over P₂O₅. Crystallization is carried out from a 1:2 benzene-hexane mixture. Yield, 3.14 g (93%) of a substance with mp 96-98°C. Found, %: C 69.7, H 6.4, N 5.5. C₁₅H₁₇NO₃. Calculated, %: C 69.5, H 6.6, N 5.4.

2-(2-Ethyl-1-oxobutyl)indolyl-3-carboxylic Acid (IVa). To 100 ml of a 1% aqueous NaOH solution (medium A) is added 0.7 g of ketone IV, and the mixture is agitated for several minutes. The homogeneous mass is allowed to stand for 2 h at 20°C, then poured into a solution of 97 ml of water and 3 ml of conc. HCl. The residue is separated, washed with water to a neutral reaction, and crystallized from a 2:1 methanol-water mixture. Yield, 90%, mp 204-205.5°C. ESR spectrum (DMSO-D₆): 0.90 (6H, t, J = 7.3, 2CH₃), 1.46-1.87 (4H, m, J = 6.8, 2CH₂), 3.57-3.73 (1H, m, J = 7.6, CH), 7.25-8.19 (4H, m, H_{arom}), 12.40 ppm (1H, s, COOH). Found, %: C 70.1, H 6.9, N 5.3. $C_{15}H_{17}NO_3$. Calculated, %: C 69.5, H 6.6, N 5.4.

2-(2-Ethyl-1-oxobutyl)indole (VII). In 50 ml of a 1% aqueous NaOH solution is dissolved 0.5 g of ketone IVa, the mixture is kept for 1 h 10 min at 20°C, and the Na salt of acid VI, obtained *in situ*, is heated in this solution on a boiling water bath for 1.5 h. The solution is cooled to 20°C, and the finely crystalline precipitate is separated, washed with water to a neutral reaction, and dried over P_2O_5 . Yield, 63%, mp 137°C. Found, %: C 78.5, H 8.1, N 6.7. $C_{14}H_{17}NO$. Calculated, %: C 78.1, H 8.0, N 6.5.

2-Benzoylindole-3-carboxylic Acid (VIb). Medium B. To 40 ml of absolute methanol are added 0.53 g (2 mmole) of N-phenacylindole-2,3-dione VIb and 0.4 g (10 mmole) of powdered NaOH, and the mixture; is agitated for 3-4 h and poured into a solution of 245 ml of water and 5 ml of conc. HCl. The precipitate is separated, washed with water, and dispersed in 100 ml of a 1% NaOH solution. After extraction of the impurities with ether (2 \times 50 ml), the aqueous layer is acidified to pH 1, and the precipitate is separated and dried over P₂O₅. Yield, 0.3 g, mp 214-215°C.

Medium C. To 32 ml of methanol is added a solution prepared from 8 ml of water and 0.4 g (0.01 mmole) of NaOH, followed by 0.53 g of ketone IVb, then the procedure is similar to that with medium A. Yield, 0.4 g, mp 217-218°C.

Medium D. To 40 ml of a 1:1 DMFA-water mixture containing 0.4 g (10 mmole) of NaOH is added 0.53 g of IVb, then the procedure is similar to that with medium A. Yield, 0.45 g, mp 210-212°C.

Medium E. To sodium methoxide prepared from 0.4 g of sodium in 40 ml of absolute methanol is added 0.53 g of ketone IVb, then the procedure is the same as with medium A. Yield, 0.3 g, mp 218-219°C.

1-(Pentyn-2-yl)indole-2,3-dione (IXa). Method A. In 35 ml of DMFA are dissolved 2.94 g (20 mmole) of indole-2,3dione. 3.23 g (22 mmole) of 1-bromo-2-pentyne, and 5.52 g (40 mmole) of finely ground anhydrous K_2CO_3 . The reaction mixture is agitated for 4 h at 20°C and 1 h and 60°C, cooled, and diluted with water (350 ml), the reaction product IXa is extracted with benzene (4 × 100 ml), the combined benzene extract is washed with water (4 × 100 ml) to remove the dissolved DMFA, benzene is evaporated to dryness, and the residue is chromatographed on silica gel L 160/100 μ (eluent, benzene). Yield 85-90%.

Method B. Using the same method, but replacing K_2CO_3 with 0.32 g (40 mmole) of lithium hydride, we obtained diketone IXa in 96-98% yield, mp 96-97°C (from hexane). ESR spectrum (CDCl₃): 1.10 (3H, t, J = 7.3, CH₃), 2.18 (2H, m, J = 2.0, J = 7.3, CH₂), 4.49 (2H, t, J = 2.0, CH₂-N), 7.06-7.74 ppm (4H, m, H_{arom}). IR spectrum (cm⁻¹): 1746 (2-CO and 3-CO). Found, %: C 73.3, H 5.3, N 6.3. $C_{13}H_{11}NO_2$. Calculated: %: 73.2, H 5.2, N 6.6.

The indoles listed below were similarly obtained.

1-(Nonyn-2-yl)indole-2,3-dione (IXb) from indole-2,3-dione and 1-bromo-2-nonyne (85%), mp 47-48°C (from hexane). ESR spectrum (CDCl₃): 0.88 (3H, t, J = 5.5, CH₃), 1.24 [8H, m, (CH₂)₄], 2.14 (2H, m, J = 2.2, J = 5.5, CH₂-C \equiv C), 4.50 (2H, t, J = 2.2, CH₂-N), 7.03-7.66 ppm (4H, m, H_{arom}). IR spectrum (cm⁻¹): 1744 (2-CO), 1732 (3-CO). Found, %: C 75.6, H 6.9, N 5.0. C₁₇H₁₉NO₂. Calculated, %: C 75.8, H 7.1, N 5.2.

1-(Dodecyn-2-yl)indole-2,3-dione (IXc) from indole-2,3-dione and 1-bromo-2-dodecyne (87%), mp 47.5-49°C (from hexane). ESR spectrum (CDCl₃): 0.88 (3H, t, J = 5.5, CH₃), 1.24 [14H, m, (CH₂)₇], 2.14 (2H, m, J = 2.2, J = 5.5, CH₂-C \equiv C), 4.50 (2H, t, J = 2.2, CH₂-N), 7.05-7.68 ppm (4H, m, H_{arom}). IR spectrum (cm⁻¹): 1742 (2-CO), 1722 (3-CO). Found, %: C 76.8, H 8.0, N 4.2. C₂₀H₂₅NO₂. Calculated, %: C 77.1, H 8.1, N 4.5.

1-(3-Oxopentyl)indole-2,3-dione (XIa). To 30 ml of water are added 0.22 g (0.69 mmole) of mercury (II) acetate, and dropwise with vigorous stirring, 0.56 ml of conc. H_2SO_4 . Then, 1.07 g (5 mmole) of diketone IXa in 55 ml of acetone is added at one time, and the reaction mixture is heated for 2 h at such a rate that the acetone boils vigorously. According to TLC data (4:1 benzene – acetone), the initial compound disappears after only 1 h 20 min. From the homogeneous red-colored solution, the acetone is driven off under vacuum, then the reaction product is extracted with benzene (3 × 25 ml) until the solution turns colorless. The product obtained, XIa, contains traces of indole-2,3-dione. The yield is practically quantitative, mp 115-116°C (from hexane). If in the course of hydration a small amount of indole-2,3-dione impurity is formed, it is removed by chromatographic methods (yield 85-90%). ESR spectrum (CDCl₃): 1.06 (3H, t, J = 7.3, CH₃), 2.48 (2H, q, J = 7.3, COCH₂), 2.90 (2H, t, J = 6.8, CH₂-CO), 3.98 (2H, t, J = 6.8, CH₂-N), 7.05-7.72 ppm (4H, m, H_{arom}. IR spectrum (cm⁻¹): 1745 (2-CO), 1731 (3-CO), 1700 (CO). Found, %: C 67.6, H 5.7, N 6.2. C₁₃H₁₃NO₃. Calculated, %: C 67.5, H 5.7, N 6.1.

The indolediones listed below were similarly obtained.

1-(3-Oxononyl)indole-2,3-dione (XIb). The yield is quantitative, mp 83-84°C (from hexane). ESR spectrum (CDCl₃): 0.87 (3H, t, J = 5.3, CH₃), 1.21 [8H, m, (CH₂)₄], 2.45 (2H, t, J = 7.0, COCH₂), 2.90 (2H, t, J = 6.8, CH₂-CO), 3.97 (2H, t, J = 7.0, CH₂-N), 7.64-7.69 ppm (4H, m, H_{arom}). IR spectrum (cm⁻¹): 1750 (2-CO), 1740 (3-C), 1714 (CO). Found, %: C 70.9, H 7.2, N 4.6. C₁₇H₂₁NO₃. Calculated, %: C 71.1, H 7.4, N 4.9.

1-(3-Oxododecyl)indole-2,3-dione (XIc). The yield is quantitative, mp 83-84°C (from hexane). ESR spectrum (CDCl₃): 0.87 (3H, t, J = 5.3, CH₃), 1.21 [14H, m, (CH₂)₇], 2.45 (2H, t, J = 7.0, COCH₂), 3.97 (2H, t, J = 7.0, CH₂-N), 7.05-7.67 ppm (4H, m, H_{arom}). Found, %: C 73.0, H 8.4, N 4.2. $C_{20}H_{27}NO_3$. Calculated, %: C 72.9, H 8.3, N 4.3.

1-(Chlorobutyn-2-yl)indole-2,3-dione (IXd). To 11.76 g (0.08 mmole) of isatin in 120 ml of anhydrous DMFA is added in small portions, with water cooling of the flask (0°C), 0.9 g (0.11 mmole) of powdered lithium hydride. After the liberation of hydrogen has stopped, 0.6 g of KI and 12 ml of 1,4-dichloro-2-butyne are added. After stirring for 2 h at 20°C and 2 h at 50-60°C, the reaction mixture is poured into 1 liter and water acidified with 20 ml of conc. HCl, and extracted with benzene (3 × 200 ml). The reaction product is separated on a column packed with L 160/100 μ silica gel (100 g) in an 8:1 benzene – acetone system. Yield, 5.2 g (27%), mp, 118°C. ESR spectrum (CDCl₃): 4.12 (2H, t, J = 2 CH-Cl), 4.59 (2H, t, J = 2.2, CH₂-N), 7.07-7.68 ppm (4H, m, H_{arom}). Mass spectrum: 235(5), 233(14), 198(15), 171(15), 170(100), 146(33), 142(17), 140(9), 130(9), 116(10), 115(50), 114(8), 90(76), 89(25), 77(11), 76(13), 64(16), 63(17), 52(14), 51(33), 50(16). Found, %: C 61.6, H 3.3, N 6.0, Cl 15.8. C₁₂H₈CINO₂. Calculated, %: C 61.7, H 3.5, N 6.0, Cl 15.2.

1,1'-Diisatinyl-2-butyne (XIII). Method A. In 50 ml of anhydrous DMFA is dissolved 2.94 g (20 mmole) of dried indole-1,3-dione, and, while the flask is cooled with ice water, 152 mg (24 mmole) of powdered lithium hydride is added. The mixture is agitated for 15-20 min, then 1.48 g (12 mmole) of 1,4-dichloro-2-butyne is added. The reaction mixture is agitated for 1 h at 20°C and 1 h at 50-60°C and poured into 500 ml of water, the precipitate is separated, washed with water (3×50 ml) and acetone (3×25 ml), and crystallized from DMSO, while the solution is heated at 100°C then cooled to room temperature.

Method B. The experiment is carried out as in Method A lithium hydride being replaced with 6.62 g (48 mmole) of potassium carbonate, and the reaction time being simultaneously increased (2-3 h at 20° C and 2 h at 50° C).

Method C. To 1.48 g of 1,4-dichloro-2-butyne in 20-30 ml of anhydrous DMFA at $+5^{\circ}$ C is added 3.98 g (24 mmole) of KI, the mixture is allowed to stand for 1-2 h at this temperature, them the 1,4-diiode-2-butyne solution obtained is poured into a solution of sodium salt of indole-2,3-dione, previously prepared from 2.94 g of indole-2,3-dione and 152 mg of lithium hydride. Subsequent procedure is the same as in A, but the reaction is carried out for 1-2 h without heating. Yield, 60-70%, mp 276-278°C. Found, %: C 69.9, H 3.4, N 6.2. $C_{20}H_{12}N_2O_4$. Calculated, %: C 71.2, H 3.6, N 6.2. Product XIII is characterized as the 5,5'-dibromo derivative. Yield, 70%, mp 280-281°C. Found, %: C 47.6, H 1.9, N 5.4, Br 30.9. $C_{20}H_{10}Br_2N_2O_4$. Calculated, %: C 47, H 20, N 5.6, Br 31.8.

1-(1-Chloro-3-oxobutyl)indole-2,3-dione (XId). To a solution of 2.5 g (10 mmole) of ketone IXd and 0.5 g (1.1 mmole) of $Hg(OAc)_2$ in 100 ml of water is added with vigorous stirring 1.5 ml of conc. H_2SO_4 followed by 200 ml of acetone. The mixture is heated for 4 h at the boiling point of acetone, 0.1 g of mercury (II) acetate is added, and the boiling is continued for another 6 h. The acetone is evaporated under vacuum. The yield of unpurified preparation in the form of precipitate is 1.9 g. It is crystallized from a 1:3 benzene – hexane mixture (0.82 g). Another 0.35 g was separated from the mother liquor. The total yield of substance XId was 1.17 g (44%), mp 132-135°C. ESR spectrum (CDCl₃): 3.12 (2H, t, J = 6.7, CH₂-CO), 4.02 (2H, t, J = 6.8, CH₂-N), 4.15 (2H, s, CH₂-Cl), 7.02-7.71 ppm (4H, m, H_{arom}). Mass spectrum: 253(15), 252(6), 251(49), 175(13), 160(13), 146(66), 132(63), 90(10), 78(100), 77(39), 76(8), 52(15), 51(15), 50(13). Found, %: C 61.6, H 3.3, N 6.0, Cl 15.8. Cl₁₂H₈ClNO₂. Calculated, %: C 61.7, H 3.5, N 6.0, Cl 15.2.

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