SYNTHESIS OF FURO[2,3-f]- AND FURO[3,2-e]INDOLE DERIVATIVES

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Two compounds — the diethylamides of 1,2-dimethyl-3-carbethoxy-6-carboxyfuro[2,3-f]- and 1,2-dimethyl-3-carbethoxy-5-carboxyfuro[3,2-e]indoles — are formed in the reaction of 1,2-dimethyl-3-carbethoxy-5-hydroxyacetic acid (I) with dimethylformamide and phosphorus oxychloride as a result of subsequent intramolecular cyclization of the intermediates. This constitutes evidence for formylation of the starting acid in the 6 and 4 positions. Formylation of the ethyl ester of acid I gives only the 6-formyl derivative, the intramolecular cyclization of which under the influence of sodium ethoxide gives 1,2-dimethyl-3,6-dicarbethoxyfuro[2,3-f]-indole. Hydrolysis of the latter with alcoholic alkali gives the corresponding dicarboxylic acid. The structures of the synthesized compounds were confirmed by the PMR, IR, and mass spectra.

In connection with the interest displayed in condensed heterocycles containing an indole fragment and in biologically active substances, we synthesized a number of furoindoles. The furoindoles were obtained by reaction of 5-indolyloxyacetic acids with dimethylformamide (DMF) under Vilsmeier formylation conditions. In this case initial formylation of the 5-indolyloxyacetic acids or their chlorides not only in the 6 position, as we have previously observed for 5-methoxy derivatives of 2-methyl-3-carbethoxyindoles [1], but also in the 4 position is possible. The chlorides of the formyl derivatives of 5-indolyloxyacetic acids are then converted by a known method [2] to dimethylamides by the action of DMF, and the dimethylamides are converted, after intramolecular cyclization, to furo[2,3-f]- and furo[3,2-e]indole derivatives. The dimethylamides (I and II, respectively) of 1,2-dimethyl-3-carboxyfuro[2,3-e]indole were obtained by this method from 1,2-dimethyl-3-carbethoxy-5-indolyloxyacetic acid (A) [3]. Three singlets at δ 7.45, 7.77, and 8.18 ppm, which are related, respectively, to the protons in the 8, 4, and 7 positions, are observed at weak field in the PMR spectrum of I, and this indicates the furo[2,3-f]indole structure. The PMR spectrum of II has doublets at δ 7.51 and 7.70 ppm with $J_{7,8}$ = 8.6 Hz, which are characteristic for the 7 and 8 ortho protons, and a singlet at δ 9.08 ppm (4-H); this is in agreement with the furo[3,2-e]indole structure. The IR spectra of I and II contain absorption bands relate to dimethylamido and carbethoxy groups. The most intense peak in the mass spectrum of I corresponds to the molecular ion (m/e 328). The principal fragmentation is due to stepwise disintegration of the carbethoxy and dimethylamido groups. Peaks of the following ions are observed in the high-mass number region in the mass spectrum: $[M-CH_3]^+$, $[M-C_2H_4]^+$, $[M-C_2H_5]^+$, $[M-N(CH_3)_2]^+$, $[M-OC_2H_5]^+$, $[M-CO_2, -C_2H_4]^{+\cdot}$, $[M-CO, -N(CH_3)_2]^+$, and $[M-CO, -N(CH_3)_2, -C_2H_4]^+$. The mass spectrum of II is similar to the mass spectrum of I (Table 2).

Ethyl 1,2-dimethyl-3-carbethoxy-5-indolyloxyacetate (III), which we obtained from the corresponding acid, undergoes formylation to give ethyl 1,2-dimethyl-3-carbethoxy-6-formyl-5-indolyloxyacetate (IV). 1,2-Dimethyl-3,6-dicarbethoxyfuro[2,3-f]indole (V) was synthesized by the Dieckmann reaction by intramolecular cyclization of IV with sodium ethoxide. 1,2-Dimethylfuro[2,3-f]indole-3,6-dicarboxylic acid (VI) was obtained by hydrolysis of V with alcoholic alkali.

The presence of a formyl group in the 6 position of the indole ring in IV was confirmed by the PMR spectrum, in which two 4-H and 7-H singlets at 7.61 and 7.79 ppm and one singlet

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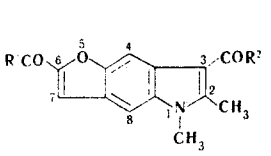
TABLE 1. Characteristics of the Synthesized Compounds (I-VI)

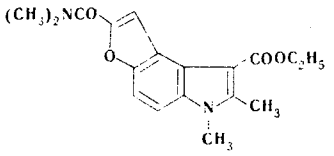
Compound	mp, °C	Found, %			Empirical formula	Calc., %			IR spectrum, cm^{-1}	Yield,
		C	H	N		C	H	N		
I	157—158	65,4	6,4	8,8	$C_{18}H_{20}N_2O_4$	65,8	6,1	8,5	$(CH_3)_2NCO$—1620, C_2H_5OCO—1675	16
II	243,5—244,5	66,0	6,2	8,5	$C_{18}H_{20}N_2O_4$	65,8	6,1	8,5	$(CH_3)_2NCO$—1618, C_2H_5OCO—1677	11
III	95,1—95,8	63,8	6,5	4,6	$C_{17}H_{21}NO_5$	63,9	6,6	4,4	C_2H_5OCO—1680, $C_2H_5OCOCH_2O$—1755	74
IV	124—124,6	62,3	6,2	4,1	$C_{18}H_{21}NO_6$	62,2	6,1	4,0	HCO—1667, C_2H_5OCO—1687, $C_2H_5OCOCH_2O$—1756	23
V	152—153	65,8	5,9	4,3	$C_{18}H_{19}NO_5$	65,6	5,8	4,3	C_2H_5OCO—(3)—1690, C_2H_5OCO—(6)—1765	34
VI	>320	59,6	4,2	4,9	$C_{14}H_{11}NO_5 \cdot {}^1/_2H_2O$	59,6	4,3	5,0	CO— br, 1660, HO—3100, 3530	79

TABLE 2. Mass Spectra of I, II, and V

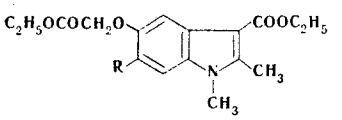
Compound	m/e values (relative intensities of the ion peaks in percent of the maximum peak)
I	328 (100), 313 (1), 300 (8), 299 (15), 284 (25), 283 (17), 256 (11), 228 (10)
II	328 (100), 313 (1), 300 (7), 299 (14), 284 (67), 283 (20), 256 (29), 228 (19)
V	329 (38), 300 (1), 284 (2), 257 (100), 228 (5), 212 (5), 185 (4)



I, V, VI



II



III, IV

I $R^1 = N(CH_3)_2$, $R^2 = OC_2H_5$;
V $R^1 = R^2 = OC_2H_5$; VI $R^1 = R^2 = OH$;
III R = H; IV R = —CHO

of the proton of an aldehyde group at δ 10.54 ppm are observed. The PMR spectrum of V, obtained from IV, is characterized by the presence of three singlets at δ 7.71, 7.79, and 8.08 ppm, which are related to the 8-H, 4-H, and 7-H protons; this confirms the furo[2,3-f]indole structure. A molecular ion peak with m/e 329 is observed in the mass spectrum of V. The most intense peak (m/e 257) is due to fragmentation of the molecular ion with splitting out of a carbethoxy group, which is accompanied by migration of a hydrogen atom. Peaks of $[M-C_2H_5]^+$, $[M-OC_2H_5]^+$, and $[M-2C_2H_4, -2CO_2]^+$ ions, which develop because of stepwise detachment of two carbethoxy groups, are also present in the spectrum.

EXPERIMENTAL*

The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. 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 30 eV; the temperature of the ionizing chamber was 125°. The IR spectra were recorded with Perkin—Elmer and UR-10 spectrometers.

The physical constants, results of elementary analysis, IR and mass spectral data, and yields of the synthesized compounds are presented in Tables 1 and 2.

*The experimental portion of this research was carried out with the participation of R. A. Zinov'ev.

1,2-Dimethyl-3-carbethoxy-6-carbethoxy-6-dimethylaminocarbonylfuro[2,3-f]indole (I). A 5.7-ml [9.5 g (62.3 mmole)] sample of freshly distilled phosphorus oxychloride was added dropwise with stirring at 11° in the course of 40 min to 22.0 ml [20.9 g (286.0 mmole)] of dry dimethylformamide (DMF), after which a solution of 8.76 g (30.1 mmole) of 1,2-dimethyl-3-carbethoxy-5-indolyloxyacetic acid in 23.4 ml [22.2 g (304.3 mmole)] of DMF was added at 11°, and the mixture was stirred at 20° for 2 h. The temperature was then raised to 100°, and the mixture was stirred at this temperature for 7 h, after which it was cooled to 20° and poured into a mixture of 90 g of crushed ice and 55 ml of water. A total of 95.4 ml (190.8 meq) of 2 N aqueous sodium hydroxide solution was added to the mixture, and the resulting mixture was heated to 100° and allowed to cool with stirring of 20°. The precipitate was removed by filtration and washed on the filter with water. The yield of a mixture of isomers I and II was 5.47 g. A solution of 2.00 g of the mixture of isomers in 80 ml of chloroform was passed twice through a column (50-mm long and 10 mm in diameter) filled with a layer of activity II (brockmann classification) aluminum oxide at a rate of one drop per second. After the first pass, the residual substance was eluted from the adsorbent with 40 ml of chloroform, the eluate was added to the passed solution, and the operation was repeated with a fresh column. The chloroform was removed by vacuum distillation to give 1.75 g of dry substance, which was recrystallized from acetone–water (1:4) in a ratio of one part by weight of the substance in 183 parts by volume of aqueous acetone. The yield of pure I, which is quite soluble in acetone and chloroform, was 0.59 g. PMR spectrum (dueterodimethyl sulfoxide–deuteroacetone), δ: 1.38 (t, CH_3CH_2), 2.78 ,s, 2 CH_3), 3.17 [s, broad, N-$(CH_3)_2$], 4.35 (q, CH_3CH_2), 7.45 (s, 8-H), 7.77 (s, 4-H), and 8.08 ppm (s, 7-H).

1,2-Dimethyl-3-carbethoxy-5-dimethylaminocarboxylfuro[3,2-e]indole (II). A mixture of isomers I and II (see above) (1.0 g) was recrystallized from acetone–water (1:4) to give 0.20 g of yellowish crystals of II, which were only slightly soluble in chloroform. PMR spectrum (CF_3COOH), δ: 1.61 (t, CH_3CH_2), 2.93 (s, 2-CH_3), 3.82 [s, broad, N-$(CH_3)_2$], 3.97 (s, NCH_3), 4.56 (q, CH_3CH_2), 7.51 (d, 7-H), 7.70 (d, 8-H), and 9.08 ppm (s, 4-H).

Ethyl 1,2-Dimethyl-3-carbethoxy-5-indolyloxyacetate (III). A total of 11.6 ml [21.3 g (217.4 mmole)] of sulfuric acid with d_4^{15} 1,838 was added to a mixture of 8.85 g (30.4 mmole) of acid A and 83.4 ml [66.2 g (1435.5 mmole)] of absolute ethanol, and the mixture was refluxed in a flask equipped with a calcium chloride tube for 5 h, after which it was cooled to room temperature and poured into 95 ml of water. The precipitated III was removed by filtration, washed on the filter with water, dried, and recrystallized from the minimum amount of ethanol. The yield was 7.15 g.

Ethyl 1,2-Dimethyl-3-carbethoxy-6-formyl-5-indolyloxyacetate (IV). A 1.9-ml [3.2 g (20.8 mmole)] sample of freshly distilled phosphorus oxychloride was added dropwise with stirring at 11° to 7.3 ml [6.9 g (94.9 mmole)] of dry DMF, and the mixture was stirred at 11° for 30 min. A solution of 3.0 g (9.4 mmole) of ethyl 1,2-dimethyl-3-carbethoxy-5-indolyloxyacetate (III) in 7.3 ml [6.9 g (94.9 mmole)] of dry DMF was added dropwise with stirring at 20° to the resulting solution, and the mixture was stirred at 20° for 2 h and at 100° for 7 h. It was then cooled and poured into a mixture of crushed ice and water (60 g). A solution of 3.22 g (80.5 mmole) of sodium hydroxide in 18 ml of water was added (two-thirds dropwise and the last third all at once) with stirring to the resulting solution, and the mixture was diluted with 20 ml of water, heated rapidly to 100°, and cooled. The product was removed by filtration, washed on the filter with water, dried, and recrystallized from 25 ml of absolute ethanol to give 0.76 g (2.2 mmole) of yellowish crystals of IV, which were only slightly soluble in water but quite soluble in acetone. PMR spectrum (deuteroacetone), δ: 1.26 and 1.41 (t, CH_3CH_2), 2.76 (s, 2-CH_3), 3.81 (s, NCH_3), 4.20 and 4.31 (q, CH_3CH_2), 4.89 (s, O-CH_2), 7.61 (s, 7-H), 7.79 (s, 5-H), and 10.54 ppm (s, CHO).

1,2-Dimethyl-3,6-dicarbethoxyfuro[2,3-f]indole (V). A2.12-g (6.1 mmole) sample of IV was added to a solution of sodium ethoxide obtained from 0.12 g (5.2 mg-at) of sodium and 3.2 ml [2.5 g (55.1 mmole)] of absolute ethanol, and the mixture was heated at 80° for 1 h, after which it was cooled and mixed with 60 ml of water,and the mixture was allowed to stand for 1.5 h. The precipitate was removed by filtration, washed with water until the wash waters were neutral, and vacuum dried in a desiccator over calcium chloride to give 0.68 g (2.1 mmole) of orange crystals of V, which were only slightly soluble in water but soluble in alcohol, acetone, acetic acid, and DMF. The product showed up as an individual substance in UV light when it was chromatographed on Silufol (ascending chromatography) in a benzene–methanol system (9:1). PMR spectrum, δ: 1.38 and 1.42 (t, CH_3CH_2), 2.78 (s, 2-CH_3), 3.78 (s, NCH_3), 4.34 and 4.36 (q, CH_3CH_2), 7.71 (s, 4-H), 7.79 (s, 7-H), and 8.08 (s, 8-H).

1,2-Dimethylfuro[2,3-f]indole-3,6-dicarboxylic Acid (VI). A mixture of 0.5 g (1.5 mmole) of V and 16 ml of a 23.5% solution of potassium hydroxide in 95% ethanol was refluxed at 80° for 40 min, after which it was cooled to room temperature (20°), and the resulting precipitate was removed by filtration. The precipitate was dissolved in the minimum amount of water, and the solution was treated with activated charcoal and filtered. The filtrate was acidified with respect to Congo red (pH ≈ 3) with 2 N hydrochloric acid solution, and the precipitated VI was removed by filtration, washed on the filter with water, and dried in a vacuum desiccator over phosphorus pentoxide. The yield of VI was 0.34 g (1.2 mmole). The yellowish crystals were only slightly soluble in water, alcohol, acetone, and benzene and moderately soluble in DMF and DMSO. The product showed up as an individual substance in UV light when it was chromatographed on Silufol with a benzene–methanol system (9:1).

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SYNTHESIS OF ISOMERIC PYRROLOQUINOLINES FROM 5- AND 6-AMINOINDOLES

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In the case of 2,3-dimethyl-, 2-methyl-, and 2,3,6-trimethyl-5-aminoindoles, as well as 2,3-dimethyl- and 1,2,3-trimethyl-6-aminoindoles, it was shown that the enamino ketones formed in the reaction of 5- or 6-aminoindoles with 1,3-diketones undergo cyclization under the influence of acidic agents to substituted pyrroloquinolines with linear or angular ring fusion. The formation of the latter is limited by steric factors. Thus, the pronounced ortho effect of a substituent attached to the C_4 atom (in the pyrrole ring) or 5-indolylaminovinyl ketones substantially hinders cyclization in the 4 position of the indole and promotes primary or exclusive formation of the linear isomer. Similarly, in the case of enamino ketones obtained from 6-aminoindoles, the substituent attached to the pyrrole nitrogen atom sterically hinders electrophilic attack at C_7, i.e., formation of the angular isomer.

The condensation of aromatic amines with 1,3-diketones is well known as the Combes–Beyer synthesis of 2,4-disubstituted quinolines [1, 2]. The direction of cyclization depends on the presence of a second substituent in the benzene ring and is subject to the general principles of orientation during electrophilic attack [3]. The situation is more complex in the case of condensed systems. Thus, a mixture (21:1) of the linear and angular benzoquinolines is obtained in the condensation of 2-naphthylamine with acetylacetone under the influence of sulfuric acid [4]. However, it has been reported that the reaction gives only the angular isomer when zinc chloride is used as the cyclizing agent and that exclusively the linear benzoquinoline is obtained in hydrogen fluoride [4, 5]. 5-Aminocarbazole is converted to linear pyridocarbazoles in 15-20% yields when it is heated with 1,3-diketones in the presence of polyphosphoric acid (PPA) [6]. Thus, up until now the data on the

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