SYNTHESIS AND SOME PROPERTIES OF 2,3-DIHYDROFURO[2,3-b]QUINOL-4-ONE

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The reaction of O-ethylbutyrolactonium tetrafluoroborate with ethyl anthranilate gave the corresponding imido ester, which undergoes cyclization to a furo[2,3-b]-quinol-4-one derivative when it is heated in a solution of sodium butoxide. When the latter product is heated in diphenyl oxide, it is converted to a furo[3,2-c]-quinol-2-one derivative.

This paper is devoted to the synthesis of furo[2,3-b]quinoline derivatives on the basis of the reaction of O-ethylbutyrolactonium tetrafluoroborate (I) with ethyl anthranilate (II). A number of alkaloids that are furo[2,3-b]quinoline derivatives have been described [1]; compounds with pharmacological activity have been detected among them [2], but their preparation from activated lactones has not been realized [3-6]. In general, in contrast to activated lactams, O-alkyl derivatives of lactones have not been previously used in the synthesis of heterocycles, and information with respect to this is limited, to the best of our knowledge, to our research on the synthesis of furo[3,2-c]pyridines and furo[2,3-d]pyridines [7].

Taking into account the fact that complex I [8], like butyrolactone diethylacetal (III), reacts with aromatic amines [9], we made an attempt to obtain the corresponding cyclic imido ester by the reaction of O-alkyl derivatives of butyrolactone with ester II. However, we were unable to obtain the desired product from acetal III. At the same time, tetrafluoroborate I reacts readily under mild conditions with ethyl anthranilate to give imido ester tetrafluoroborate IV.

It is known that an aza analog of IV (in the base form), viz., 1-methyl-2-(o-ethoxycarbonylphenyl)iminopyrrolidine, readily undergoes cyclization to a pyrrolo[2,3-b]quinoline derivative when it is heated to 200°C in the presence of an acidic catalyst [10]. It is also known that as the basicity of amidines of this type decreases (due to an increase in the electron-acceptor character of the substituent attached to the exocyclic nitrogen atom), the cyclization takes place better when basic catalysts are used [11]. Proceeding from this fact, as well as from previously obtained data on the relatively low basicities of 2-aryliminotetrahydrofurans [9], we used basic catalysis to obtain 2,3-dihydrofuro[2,3-b]quinol-4-one (V). Treatment of salt IV with triethylamine and subsequent refluxing of the imido ester base in a solution of sodium butoxide lead to three-ring quinolone V. In order to shed some light on the question as to whether cyclization is accompanied by simultaneous rearrangement, we accomplished the conversion of V to an isomeric three-ring 2-quinolone (VI) by heating it in diphenyl oxide and compared the spectral characteristics of isomers V and VI. It is known [12] that in the case of 2-quinolones, in contrast to 4-quinolones, absorption bands above 1625 cm^{-1} are observed, in agreement with the spectral data for V and VI (ν_{CO} 1620 and 1650 cm^{-1}, respectively). Data from the UV spectra for quinolones V and VI (see the experimental section) are also in good agreement with the results of a comparative study of their electronic spectra. The absence of an absorption maximum at 270-285 nm in the spectrum of V and the presence of a maximum at 286 nm in the spectrum of VI constitute evidence in favor of linear and angular structures for furoquinolones V and VI, respectively [12].

Compound VII was obtained by alkylation of the sodium salt of furoquinolone V with methyl iodide in DMF. The difference in the melting points of VII (199-201°C) and the known 4-methoxy-2,3-dihydrofuro[2,3-b]quinoline (103-104°C) [4] and the similarity in the UV spectra of VII and V confirm the N-alkylation of V.

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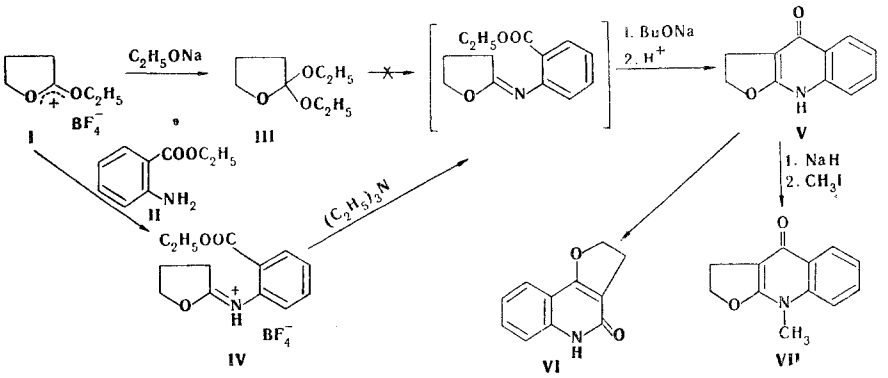

EXPERIMENTAL

The UV spectra of solutions of the compounds in alcohol were obtained with a Perkin-Elmer 575 spectrophotometer. The IR spectra of mineral oil pastes of the compounds were obtained with a Perkin-Elmer 599 spectrometer. The mass spectra were obtained with an MAT-112 spectrometer.

2-(2-Ethoxycarbonylphenyl)iminotetrahydrofuran Tetrafluoroborate (IV). A mixture of 5 g (30 mmole) of ethyl anthranilate (II) and 6.1 g (30 mmole) of complex I in 50 ml of anhydrous methylene chloride was stirred at room temperature for 1 h, after which the solvent was evaporated, and the residue was triturated with anhydrous ether. The solid material was removed by filtration and dried to give 8.9 g (92%) of IV with mp 103-106°C (from ethyl acetate). Found: N 4.4%. $C_{13}H_{16}BF_4NO_3$. Calculated: N 4.5%.

4-Oxo-2,3,4,9-tetrahydrofuro[2,3-b]quinoline (V). A 7-g (22 mmole) sample of imido ester tetrafluoroborate IV was triturated thoroughly with 3 g of triethylamine in 80 ml of anhydrous ether, the resulting triethylamine tetrafluoroborate was removed by filtration and washed with 20 ml of anhydrous ether, and the filtrate was evaporated. The residue was added to a refluxing solution of sodium butoxide (from 1 g of sodium and 30 ml of freshly distilled n-butanol), 30 min after which, a yellow precipitate of the sodium salt of V formed. The mixture was refluxed for 2 h, after which it was evaporated to dryness. Water (50 ml) was added to the residue, and the mixture was acidified to pH 5 with 1 N HCl solution. The precipitate was removed by filtration and dried to give 2.3 g (56%) of V with mp 273-275°C (from DMF). UV spectrum, λ_{max} (log ε): 218 (4.47); 233 (4.51); 295 (3.96); 304 (4.0); 316 nm (3.95). Found: C 70.5; H 5.0; N 7.6%; M 187 (by mass spectrometry). $C_{11}H_9NO_2$. Calculated: C 70.6; H 4.8; N 7.5%; M 187.

4-Oxo-2,3,4,5-tetrahydrofuro[3,2-c]quinoline (VI). A 1-g (5.3 mmole) sample of V was refluxed in 20 ml of diphenyl oxide for 2 h, after which the mixture was filtered, and the filtrate was diluted with 150 ml of petroleum ether. The resulting precipitate was removed by filtration, washed with ether, and dried to give 0.86 g (86%) of VI with mp 283-285°C (from DMF) (mp 286-287°C [13]). UV spectrum, λ_{max} (log ε): 224 (4.20); 286 (3.49); 298 (3.46); 318 nm (3.48). Found: C 70.8; H 4.9; N 7.5%; M 187 (by mass spectrometry). $C_{11}H_9NO_2$. Calculated: C 70.6; H 4.8; N 7.5%; M 187.

4-Oxo-9-methyl-2,3,4,9-tetrahydrofuro[2,3-b]quinoline (VII). A mixture of 1.7 g (9.1 mmole) of V and 0.43 g of sodium hydride in 30 ml of distilled DMF was allowed to stand for 1 h, after which 2.6 g of methyl iodide was added, and the mixture was allowed to stand for 24 h. It was then filtered, and the filtrate was evaproated. The residue was triturated with water, and the solid material was removed by filtration and dried to give 1.1 g (60%) of VII with mp 199-201°C (from DMF). UV spectrum λ_{max} (log ε): 216 (4.38); 237 (4.32); 298 shoulder (3.86); 310 (3.98); 320 nm (3.94). Found: C 71.4; H 5.4; N 7.0%. $C_{12}H_{11}NO_2$. Calculated: C 71.6; H 5.5; N 7.0%.

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SYNTHESIS OF FURO[3,2-c]PYRIDINE AND FURO[2,3-d]PYRIMIDINE DERIVATIVES FROM BUTYROLACTONE DIETHYLACETAL

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The reaction of butyrolactone acetal with CH acids was used to synthesize 2-methylenetetrahydrofuran derivatives. The latter react with dimethylformimide acetal to give a dieneamine that is capable of undergoing cyclization to furo[3,2-c]pyrimidine derivatives. This two-ring system was also synthesized by the reaction of cyanacetamide with 3-dimethylaminomethylenebutyrolactone acetal. The indicated acetal can also react with amidine components to give furo[2,3-d]pyrimidine derivatives.

In contrast to acetals of amides and lactams, to the study of the properties and transformations of which extensive research has been devoted [1, 2], little study has been devoted to the activation of the lactone carbonyl group and to the chemistry of O-alkyl derivatives of lactones in general [3]. We have recently shown [4] that butyrolactone diethylacetal (I) is capable of reaction under relatively severe conditions with aromatic amines to give the corresponding 2-arylaminotetrahydrofurans.

In the present research we studied the reactions of acetal I with compounds that have active methylene groups such as cyanoacetic ester and cyanacetamide, which, under rather severe conditions (150-180°C), lead to the corresponding 2-methylenetetrahydrofuran derivatives (II), which can undergo heterocyclization. It should be noted that N-methylbutyrolactam acetal reacts with these CH acids even at room temperature [5]. This difference in the reactivities of these acetals can be explained by the fact that acetal I is capable to a considerably lesser extent of undergoing dissociation to give an ambident cation and an alkoxide anion as compared with lactam acetals. In the case of acetal I we were unable to detect the corresponding ambident cation, in contrast to what has been demonstrated for lactam acetals [6].

It is known that enamines obtained from N-methylpyrrolidone acetal do not react with dimethylformamide acetal at the C_3 atom of the pyrrolidine ring [7]. In contrast to the nitrogen analogs, methylenefuran derivatives II undergo condensation with dimethylformamide acetal to give enamines III. In the case of IIb dimethylformamide acetal reacts not only at the α-methylene link but also at the amide NH_2 group. When enaminoacylamidine IIIc is heated in water, it undergoes smooth cyclization to give hydrogenated furo[3,2-c]pyridine derivative IV.

In order to obtain an enamino amide with a free amide NH_2 group we studied another method for the synthesis of compounds of the III type. The reaction of butyrolactone with dimethylformamide acetal gave enaminolactone V [8], which is alkylated by triethyloxonium tetrafluoroborate to give complex VI. When complex VI is treated with an alcohol solution of sodium ethoxide, it gives acetal VII. The latter was not isolated in the individual state in view

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