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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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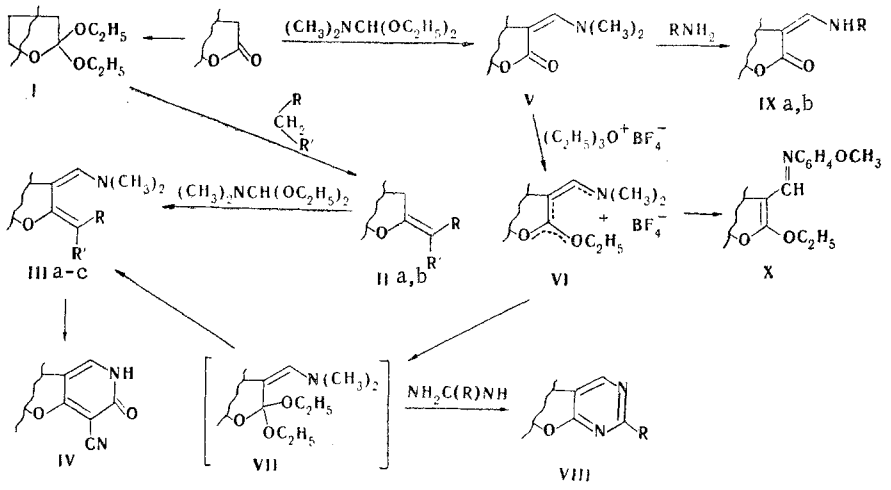
of its low stability. However, an alcohol solution of acetal VII reacts vigorously with cyanacetamide at room temperature to give dieneamine IIIb. When this compound is heated in water, it undergoes smooth cyclization to 6-oxo-7-cyano-2,3,5,6-(5H)-tetrahydrofuro[3,2-c]pyridine (IV). Acetal VII, which combines lactone acetal and vinylogous amide acetal functions in its structure, is an extremely reactive compound, for which one can easily conceive of an extremely energically favorable ambident cation that is formed via a dissociative process that is normal for amide acetals [1, 2]. This acetal (VII) therefore should react readily not only with CH acids but also with other nucleophilic reagents. In fact, we found that the reaction of VII with thiourea and dicyandiamide leads to hydrogenated furo[2,3-d]pyrimidine derivatives VIII.



II, III a R=$COOC_2H_5$, R′=CN; b R=$CONH_2$, R′=CN; c R=CON=CHN$(CH_3)_2$, R′=CN;
VIII a R=SH; b R=NHCN; IX a R=$CH_2CH_2C_6H_5$; b R=$CH_2C_6H_5$

The synthetic possibilities of the use of the compounds obtained are not limited to the transformations presented above. Enaminolactone V undergoes transamination with aliphatic aromatic amines. When V is heated with phenylethylamine and benzylamine at 150-160°C, it is converted to the corresponding enaminolactones IX. The reaction of complex VII with p-anisidine also proceeds similarly — the nucleophile does not attack the C_2 atom of the furan ring; instead one observes transamination of the enamine NMe_2 group to give N-anisyl(2-ethoxy-4,5-dihydro-3-furyl)aldimine (X).

The structures of all of the synthesized compounds were confirmed by the spectral data (see the experimental section).

EXPERIMENTAL

The IR spectra of mineral oil pastes of the compounds were obtained with a Perkin-Elmer 599 spectrometer. The UV spectra of solutions of the compounds in alcohol were obtained with EPS-3 and Perkin-Elmer 575 spectrophotometers. The PMR spectra were obtained with an XL-100 spectrometer with tetramethylsilane as the internal standard.

2-(2'-Ethoxycarbonyl-2'-cyanomethylene)tetrahydrofuran (IIa). A mixture of 4.8 g (30 mmole) of acetal I and 3.9 g (30 mmole) of cyanoacetic ester was refluxed for 1 h with removal of the liberated alcohol by distillation, after which it was distilled to give 4.3 g (79%) of IIa with bp 138-140°C (1.33 hPa). IR spectrum: 1570 (C=C), 1700 ($COOC_2H_5$), and 2200 cm^{-1} C≡C). UV spectrum, λ_{max} (log ε): 256 nm (4.26). Found: C 59.6; H 6.2; N 7.6%. $C_9H_{11}NO_3$. Calculated: C 59.7; H 6.1; N 7.7%.

2-(2'-Carbamido-2-cyanomethylene)tetrahydrofuran (IIb). A mixture of 4.2 g (50 mmole) of cyanacetamide and 11.2 g (70 mmole) of acetal I was refluxed for 1 h with removal of the alcohol by distillation. It was then cooled, treated with ether, and filtered to give 4.1 g (54%) of IIb with mp 179-181°C (from methanol). IR spectrum: 1560-1660 (C=C, CO); 2200 (C≡N); 3260, 3400 cm^{-1} (NH_2). UV spectrum, λ_{max} (log ε): 250 nm (4.20). Found: C 55.4; H 5.2; N 18.3%. $C_7H_8N_2O_2$. Calculated: C 55.3; H 5.3; N 18.4%.

2-(2'-Ethoxycarbonyl-2'-cyanomethylene)-3-dimethylaminomethylenetetrahydrofuran (IIIa). A mixture of 4.3 g (23.6 mmole) of IIa and 4.5 g (30 mmole) of dimethylformamide acetal was refluxed for 1.5 h with removal of the liberated alcohol by distillation through a fractionating column. The mixture was then evaporated, and the residue was triturated with ether, removed by filtration, and dried to give 4.4 g (78.5%) of IIIa with mp 188-190°C (from alcohol). IR spectrum: 1550, 1610 (C=C); 1665 (COOEt); 2180 cm^{-1} (C≡N). UV spectrum, λ_{max} (log ε): 230 (4.09), 250 (3.88), and 380 nm (4.54). PMR spectrum ($CDCl_3$): 1.27 and 4.18 (3H, t, 2H, q, OC_2H_5), 3.09 (2H, t, 4-CH_2), 3.16 [6H, s, $N(CH_3)_2$], and 4.26 ppm (2H, t, 5-CH_2). Found: C 61.0; H 6.9; N 11.8%. $C_{12}H_{16}N_2O_3$. Calculated: C 61.0; H 6.8; N 11.9%.

2-(2'-Dimethylaminomethyleneiminocarbonyl-2'-cyanomethylene)-3-dimethylaminomethylenetetrahydrofuran (IIIc). A mixture of 3 g (19.7 mmole) of IIb, 8 g of dimethylformamide acetal, and 20 ml of anhydrous toluene was refluxed for 2 h, after which it was cooled, and the precipitate was removed by filtration to give 4.7 g (91%) of IIIc with mp 213-215°C (from DMF). IR spectrum: 1560, 1600 (C=C, C=N, C=O); 2185 cm^{-1} (C≡N). UV spectrum, λ_{max} (log ε): 280 (4.33), 403 nm (4.59). Found: C 59.7; H 7.1; N 21.8%. $C_{13}H_{18}N_4O_2$. Calculated: C 59.5; H 6.9; N 21.4%.

6-Oxo-7-cyano-1,2,5,6-tetrahydrofuro[3,2-c]pyridine (IV). A 1-g (3.8 mmole) sample of IIIb was refluxed in 20 ml of water, the mixture was cooled and filtered, and the solid product was dried to give 0.57 g (92%) of IV with mp >320°C (dec., from DMF). UV spectrum, λ_{max} (log ε): 224 (4.36), 258 (3.63), and 314 nm (3.82). PMR spectrum (in deuterated DMF): 3.11 (2H, t, 4-CH_2), 4.88 (2H, t, 5-CH_2), and 7.62 ppm (1H, s, =CH). Found: C 59.0; H 3.7; N 17.1%. $C_8H_6N_2O_2$. Calculated: C 59.3; H 3.7; N 17.3%.

2-Oxo-3-dimethylaminomethylenetetrahydrofuran (V). A 100-ml sample of dimethylformamide acetal was added slowly dropwise to 4.3 g (0.05 mole) of refluxing butyrolactone with simultaneous removal of the liberated alcohol by distillation through a fractionating column. The reaction mixture was refluxed for 2 h, after which it was evaporated, and the residue was cooled. The semicrystalline mass was triturated with ether and filtered to give 30.8 g of V. The filtrate was evaporated, and the residue was distilled *in vacuo* to give 4.9 g of V for an overall yield of 36.7 g (52%) of a product with mp 105-108°C (from ethyl acetate) and bp 143-155°C (2.66 hPa) (mp 96°C [8]).

2-Ethoxy-3-dimethylaminomethylenetetrahydrofuran Tetrafluoroborate (VI). A mixture of 22.6 g (0.16 mole) of V, 30.5 g (0.16 mole) of triethyloxonium tetrafluoroborate, and 80 ml of anhydrous chloroform was allowed to stand for 20 h, after which the precipitated crystals were removed by filtration and dried to give 29 g of VI. Workup of the filtrate gave another 8.4 g of VI for an overall yield of 37.4 g (90%) of a product with mp 112-114°C (from alcohol). UV spectrum, λ_{max} (log ε): 310 nm (4.52). PMR spectrum (in $CDCl_3$): 1.45 and 4.53 (3H, t, 2H, q, OC_2H_5); 3.33 and 3.37 [3H, s, 3H, s, $N(CH_3)_2$]; 3.37 (2H, t, 4-CH_2); 4.83 (2H, t, 5-CH_2); 7.74 ppm (1H, s, =CH). Found: C 41.8; H 6.8; N 5.2%. $C_9H_{16}BF_4NO_2$. Calculated: C 42.0; H 6.2; N 5.5%.

2-(2-Carbamido-2'-cyanomethylene)-3-dimethylaminomethylenetetrahydrofuran (IIIb). A 2.6-g (10 mmole) sample of VI was added to a solution of sodium ethoxide (from 0.3 g of Na and 20 ml of absolute alcohol), and the mixture was allowed to stand for 20 min. It was then cooled to 15°C and filtered. The filtrate was treated with 0.84 g of cyanacetamide, and the mixture was allowed to stand for 30 min. The precipitate was removed by filtration and dried to give 1.45 g (70%) of IIIb with mp 189-191°C (from methanol). Found: C 58.6; H 6.3; N 20.5%. $C_{10}H_{13}N_3O_2$. Calculated: C 58.0; H 6.3; N 20.3%.

When IIIb was heated in water, it underwent cyclization to furopyridine IV with mp > 320°C (from DMF).

6-Mercapto-2,3-dihydrofuro[2,3-d]pyrimidine (VIIIa). A 0.3-g (11.8 mmole) sample of thiourea and a solution of 3 g (11.7 mmole) of VI in 20 ml of absolute alcohol were added to a solution of sodium ethoxide (from 0.65 g of Na and 20 ml of absolute alcohol), and the mixture was refluxed with stirring for 2 h. It was then cooled and filtered, and the filtrate was evaporated. Water (50 ml) was added to the residue, and the mixture was acidified to pH 5 with HCl to give 0.7 g (43%) of VIIIa with mp 255-257°C (dec., from water). UV spectrum, λ_{max} (log ε): 290 nm (4.1). Found: C 46.3; H 3.8; N 18.4; S 20.5%. $C_6H_6N_2OS$. Calculated: C 46.8; H 3.9; N 18.2; S 20.8%.

6-Cyanoamino-2,3-dihydrofuro[2,3-d]pyrimidine (VIIIb). This compound, with mp > 300°C (from DMF), was similarly synthesized in 30% yield. UV spectrum, λ_{max} (log ε); 260 nm (4.06). Found: C 51.8; H 4.0; N 34.7%. $C_7H_6N_4O$. Calculated: C 51.9; H 3.7; N 34.6%.

2-Oxo-3-(N-phenylethylamino)methylenetetrahydrofuran (IXa). A mixture of 1.8 g (12.8 mmole) of enaminolactone V and 1.65 g of β-phenylethylamine was heated at 150-160°C until the liberation of dimethylamine ceased (15 min). The reaction mixture was cooled, triturated with ether, and filtered to give 2.1 g (71%) of enaminolactone IXa with mp 106-108°C (from ethyl acetate). IR spectrum: 1700 (CO) and 3250 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 290 nm (4.45). Found: C 71.9; H 6.8; N 6.6%. $C_{13}H_{15}NO_2$. Calculated: C 71.9; H 6.9; N 6.5%.

2-Oxo-3-(N-benzylamino)methylenetetrahydrofuran (IXb). This compound, with mp 99-100°C (from ethyl acetate), was similarly synthesized. IR spectrum: 1710 (CO) and 3270 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 290 nm (4.48). Found: C 70.9; H 6.3; N 7.1%. $C_{12}H_{13}NO_2$. Calculated: C 70.9; H 6.4; N 6.9%.

N-Anisyl(2-ethoxy-4,5-dihydro-3-furyl)aldimine (X). A mixture of 4.7 g (18.4 mmole) of VI, 2.26 g (18.4 mmole) of p-anisidine, and 50 ml of anhydrous chloroform was refluxed for 3 h, after which it was cooled and filtered, and the filtrate was evaporated to give 4.5 g (99%) of X with mp 98-100°C (from ethyl acetate). IR spectrum: 1670 (C=N) and 1600 cm^{-1} (C=C). UV spectrum, λ_{max} (log ε): 195 (4.16), 240 (3.79) shoulder, 320 (4.23) shoulder, and 355 nm (4.43). PMR spectrum (in $CDCl_3$): 1.29 and 4.19 (3H, t, 2H, q, OC_2H_5); 2.93 (2H, t, 4-CH_2); 3.87 (2H, t, 5-CH_2); 3.77 (3H, s, OCH_3); 6.83 (4H, m, C_6H_4); 7.62 ppm (1H, s, =CH). Found: C 67.9; H 6.9; N 6.1%. $C_{14}H_{17}NO_3$. Calculated: C 68.0; H 6.9; N 5.7%.

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