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NOVEL APPROACH TO THE SYNTHESIS OF 3-ACYL SUBSTITUTED INDOLIZINES. THE SYNTHESIS OF 3-(INDOLIZINYL-2)ALANINE AND 4-(INDOLIZINYL-3) HOMOALANINE DERIVATIVES*

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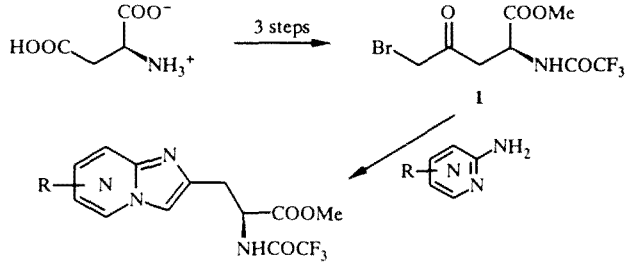
A novel approach to the synthesis of 3-acylindolizines and the transformations of some hetarylacetic acids into tryptophane analogues are described. Reaction of ethyl 2-pyridinylacetate and methyl 2-quinolinylacetate with N-trifluoroacetyl-5-bromo-4-oxonorvaline methyl ester led to N-trifluoroacetyl-3-(1-ethoxycarbonylindolizinyl-2) alanine methyl ester and N-trifluoroacetyl-3-(3-methoxycarbonylpyrrolo [1,2-a]quinolinyl-2) alanine methyl ester, respectively. Treatment of ethyl 2-pyridinylacetate and 2-pyridinylacetonitrile, first with N,N-dimethylformamide dimethyl acetal (DMFDMA), followed by reaction with phenacyl bromide, gave the corresponding 3-benzoylindolizines, while the reaction of ethyl 2-pyridinylacetate and 2-pyridinylacetonitrile with DMFDMA, followed by treatment with (S)-N-trifluoroacetyl-5-bromo-4-oxonorvaline methyl ester, gave the corresponding N-trifluoroacetyl-4-oxo-4-(indolizinyl-3)homoalanine methyl esters.

Our research in the field of heteroaryl substituted α-amino acids (for a review see [1]) has recently focused on the preparation of various azatryptophane analogues. In this connection, (*S*)-N-trifluoroacetyl-5-bromo-4-oxonorvaline methyl ester (**1**) and its (*R*)- and (*R,S*)-isomers are promising reagents for the preparation of imidazo[1,2-*x*]azin-2-yl-substituted α-amino acid derivatives [2].



The synthesis of 2-substituted indolizines from 2-methylsubstituted pyridines such as **2** and α-halo ketones is a well established reaction, which proceeds with great ease, when methyl group is activated by an electron-withdrawing group. Formation of indolizine system proceeds via formation of intermediate quarternary salt **3** followed by cyclodehydration and by elimination of hydrogen halide [3-5].

*Dedicated to Professor Édmund Lukevits, Latvian Institute of Organic Synthesis, Riga, on the occasion of his 60th birthday.

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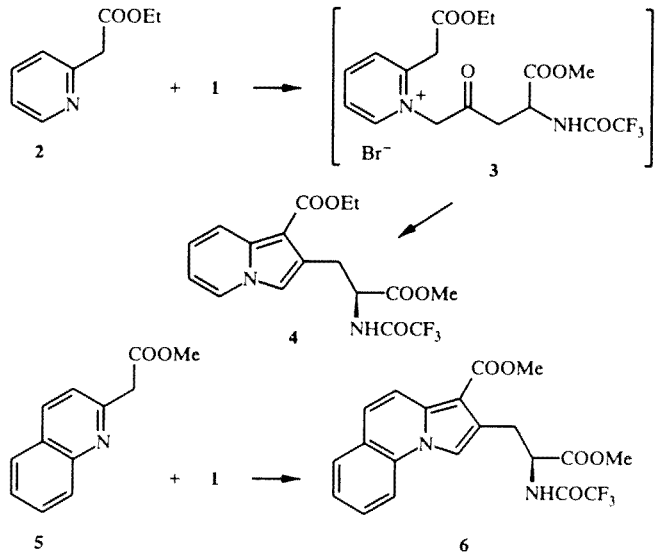
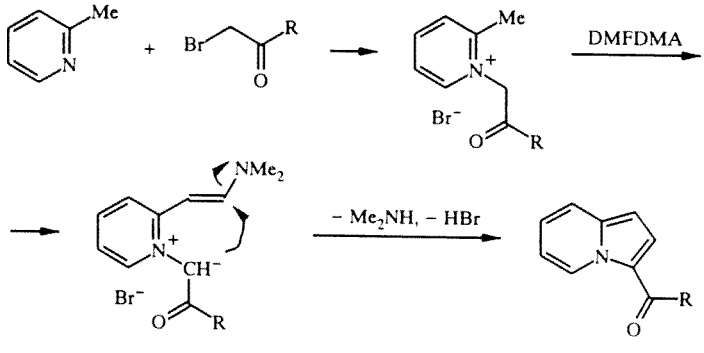
Scheme 1



In this paper we report a novel approach to the synthesis of 3-acylindolizines (Scheme 1), and the transformations of ester **1** into 3-(indolizinyl-2)alanine, 3-(pyrrolo[1,2-*a*]quinolinyl-2)alanine, and 4-(indolizinyl-3)homoalanine derivatives. In order to prepare 3-(indolizinyl-2)alanine derivatives, the reactions of ethyl 2-pyridinylacetate (**2**) and methyl 2-quinolinylacetate (**5**) with bromonorvaline **1** were performed. Thus, treatment of (*S*)-N-trifluoroacetyl-5-bromo-4-oxonorvaline methyl ester (**1**) with ethyl 2-pyridinylacetate (**2**) gave (*S*)-N-trifluoroacetyl-3-(1-ethoxycarbonylindolizinyl-2)alanine methyl ester (**4**). (*R,S*)-isomer of **4** was also prepared by treatment of **2** with the (*R,S*)-isomer of **1**. Reaction of methyl 2-quinolinylacetate (**5**) with **1** afforded (*S*)-N-trifluoroacetyl-3-(3-methoxycarbonylpyrrolo[1,2-*a*]quinolinyl-2) alanine methyl ester **6** (Scheme 1).

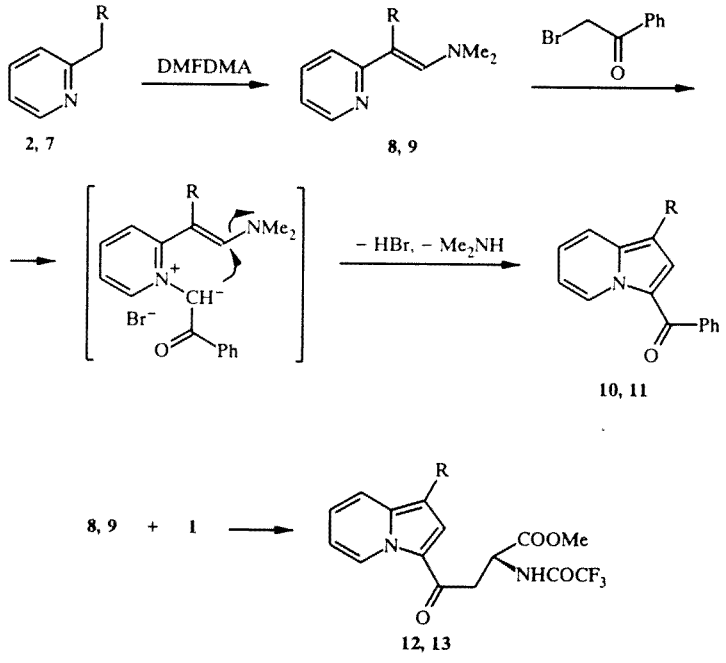
On the other hand, once α-bromo ketone is transformed into the corresponding quarternary salt **3** (Scheme 1), the methylene group attached to ring nitrogen atom can react also as a nucleophile, because of the combined electron-withdrawing effect of the carbonyl group and quarternary nitrogen atom. By suitable functionalization of the 2-methylene group, thus by the introduction of an electrophilic fragment possessing a good leaving group, e.g., by the reaction with N,N-dimethylformamide dimethyl acetal (DMFDMA), cyclization to 3-substituted indolizine system can be accomplished. Some reactions of this type have been performed recently [6].



Taking into account our experience with the synthesis of 3-acyl-azaindolizines [7], we decided to examine an alternative route to 3-acyl-indolizines. Ethyl 2-pyridinylacetate **2** and 2-pyridinylacetonitrile (**7**), both possessing an activated methylene group, were chosen as starting materials. Reaction with DMFDMA gave ethyl 3-dimethylamino-2-(pyridinyl-2)propenoate (**8**) and 3-dimethylamino-2-(pyridinyl-2)propenonitrile (**9**), respectively. Ethyl 3-dimethylamino-2-(pyridinyl-2)propenoate (**8**) proved to be moisture-sensitive and was used for further transformations without isolation and purification, while 3-dimethylamino-2-(pyridinyl-2)propenonitrile (**9**) is a stable crystalline compound. Reaction of ethyl 3-dimethylamino-2-(pyridinyl-2)propenoate (**8**) and 3-dimethylamino-2-(pyridinyl-2)propenonitrile (**9**) with phenacyl bromide afforded 1-ethoxycarbonyl-3-benzoylindolizine (**10**) and 3-benzoyl-1-cyanoindolizine (**11**) (Scheme 2).

Encouraged by successful preparations of 3-benzoyl indolizines **10**, **11**, we extended the reaction to ethyl 3-dimethylamino-2-(pyridinyl-2)propenoate (**8**) and 3-dimethylamino-2-(pyridinyl-2)propenonitrile (**9**) with (*S*)-N-trifluoroacetyl-5-bromo-4-oxonorvaline methyl ester (**1**) to give (*S*)-N-trifluoroacetyl-4-oxo-4-(1-ethoxycarbonylindolizinyl-3)homoalanine methyl ester (**12**) and (*S*)-N-trifluoroacetyl-4-oxo-4-(1-cyanoindolizinyl-3)homoalanine methyl ester (**13**), respectively (Scheme 2).

Scheme 2



2, 8, 10, 12 R = COOEt; **7, 9, 11, 13** R = CN

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage and on a Büchi 535 melting point apparatus. The ^{1}H NMR spectra were obtained on a Varian E-360 (60 MHz) and on a Bruker Avance DPX 300 (300 MHz) spectrometer with DMSO-D_6 as solvent and TMS as internal standard. The microanalyses for C, H, and N were obtained on a Perkin-Elmer CHN Analyzer 2400. The optical rotations were measured on a Perkin-Elmer 241 MC Polarimeter.

(*S*)-N-Trifluoroacetyl-5-bromo-4-oxonorvaline methyl ester (**1**) and its (*R,S*)-isomer were prepared according to the procedures described in [2].

N-Trifluoroacetyl-3-(1-ethoxycarbonylindolizinyl-2)alanine Methyl Ester (4).

***S*-Isomer**. A mixture of (*S*)-N-trifluoroacetyl-5-bromo-4-oxonorvaline methyl ester **1** (0.320 g, 0.001 mole), ethyl 2-pyridinylacetate **2** (0.165 g, 0.001 mole) and anhydrous ethanol (2 ml) was stirred at room temperature for 20 h, and then refluxed for 4 h. Then water (10 ml) was added and the reaction mixture warmed up in order to obtain a clear solution. The product, which precipitated upon cooling, was collected by filtration to give the (*S*)-isomer of **4** in 39% yield, mp 104-107°C (from ethanol/water 1:3), $[\alpha]_D^{25} = -9.8°$ (c = 0.715, methanol), ^{1}H NMR (DMSO-D_6, 300 MHz): δ 1.33 (3H, t, $\underline{CH_3}CH_2$), 3.21 (1H, dd, $\underline{CH_2}CH$), 3.56 (1H, dd, $\underline{CH_2}CH$), 3.68 (3H, s, OMe), 4.28 (2H, q, $\underline{CH_2}CH_3$), 4.74 (1H, m, $\underline{CH}COOMe$), 6.82 (1H, t, $H_{6'}$), 7.15 (1H, t, $H_{7'}$), 7.43 (1H, s, $H_{3'}$), 8.02 (1H, d, $H_{8'}$), 8.44 (1H, d, $H_{5'}$), 9.85 (1H, d, NH), J_{CH2CH} = 7.1, J_{NHCH} = 7.6, $J_{H5'H6'}$ = 6.7, $J_{H7'H8'}$ = 9 Hz. Found, %: C 52.52; H 4.27; N 7.12. $C_{17}H_{17}F_3N_2O_5$. Calculated, %: C 52.83; H 4.44; N 7.25.

***R,S*-Isomer**. A mixture of (*R,S*)-N-trifluoroacetyl-5 bromo-4-oxonorvaline methyl ester **1** (0.320 g, 0.001 mole), ethyl 2-pyridinylacetate **2** (0.165 g, 0.001 mole), and anhydrous ethanol (2 ml) was stirred at room temperature for 20 h, and then refluxed for 7 h. Then water (10 ml) was added, and the reaction mixture was stirred. Upon cooling, the precipitate was collected by filtration to give the *R,S*-isomer of **4** in 36% yield, mp 101.5-103°C (from ethanol/water 1:3), ^{1}H NMR (DMSO-

D_6, 300 MHz): δ 1.33 (3H, t, $\underline{CH_3}CH_2$), 3.21 (1H, dd, $\underline{CH_2}CH$), 3.56 (1H, dd, $\underline{CH_2}CH$), 3.68 (3H, s, OMe), 4.28 (2H, q, $\underline{CH_2}CH_3$), 4.74 (1H, m, $\underline{CH}COOMe$), 6.82 (1H, t, $H_{6'}$), 7.15 (1H, t, $H_{7'}$), 7.43 (1H, s, $H_{3'}$), 8.02 (1H, d, $H_{8'}$), 8.44 (1H, d, $H_{5'}$), 9.85 (1H, d, NH), J_{CH2CH} = 7.1, J_{NHCH} = 7.6, $J_{H5'H6'}$ = 6.7, $J_{H7'H8'}$ = 9 Hz. Found, %: C 52.36; H 4.22; N 7.19. $C_{17}H_{17}F_3N_2O_5$. Calculated, %: C 52.83; H 4.44; N 7.25.

(*S*)-N-Trifluoroacetyl-3-(3-methoxycarbonylpyrrolo[1,2-*a*]quinolinyl-2) alanine methyl ester (6). A mixture of methyl 2-quinolinylacetate **5** (1.000 g, 0.005 mole), (*S*)-N-trifluoroacetyl-5-bromo-4-oxonorvaline methyl ester **1** (1.600 g, 0.005 mole) and anhydrous ethanol (10 ml) was stirred at room temperature for 24 h and then refluxed for another 20 h. Volatile components were evaporated *in vacuo*, and water (10 ml) was added to the residue. The precipitate was collected by filtration to give **6** in 5% yield, mp 144-146°C (from ethyl acetate/*n*-heptane 1:6), $[\alpha]_D^{23}$ = +452° (c = 0.000928, methanol), ^{1}H NMR (DMSO-D_6, 300 MHz): δ 3.27 (1H, dd, $\underline{CH_2}CH$), 3.60 (1H, dd, $\underline{CH_2}CH$), 3.68 (3H, s, COOMe), 3.86 (3H, s, Het-COOMe), 4.79 (1H, dd, $\underline{CH}CH_2$), 7.51 (1H, dt, $H_{7'}$), 7.57 (1H, d, $H_{5'}$), 7.72 (1H, ddd, $H_{8'}$), 7.92 (1H, dd, $H_{6'}$), 8.04 (1H, d, $H_{4'}$), 8.13 (1H, s, $H_{1'}$), 8.22 (1H, d, $H_{9'}$), 9.98 (1H, d, NH), J_{CH2CH} = 5.0 and 9.9, J_{NHCH} = 7.2, $J_{H4'H5'}$ = 9.5, $J_{H6'H7'}$ = $J_{H7'H8'}$ = 7.8, $J_{H6'H8'}$ = 1.1, $J_{H7'H9'}$ = 0.6, $J_{H8'H9'}$ = 8.4 Hz. Found, %: C 56.66; H 4.03; N 6.58. $C_{20}H_{17}F_3N_2O_5$. Calculated, %: C 56.88; H 4.06; N 6.63.

Ethyl 3-Dimethylamino-2-(pyridinyl-2)propenoate (8). A mixture of ethyl 2-pyridinylacetate **2** (0.031 mole), DMFDMA (13.3 ml, 0.1 mole), and anhydrous toluene (30 ml) was heated under reflux with exclusion of moisture for 2 h, cooled and volatile components evaporated *in vacuo* to give a crude **8** as an oily residue, which was subsequently used for further transformations. ^{1}H NMR (DMSO-D_6, 60 MHz): δ 1.10 (3H, t, $\underline{CH_3}CH_2$), 2.73 (6H, s, NMe_2), 3.98 (2H, q, $\underline{CH_2}CH_3$), 7.00-7.32 (2H, m, $H_{4'}$ and $H_{5'}$), 7.52 (1H, s, $\underline{CH}NMe_2$), 7.72 (1H, dd, $H_{3'}$), 8.50 (1H, dd, $H_{6'}$), J_{CH2CH3} = 7, $J_{H3'H4'}$ = 8, $J_{H3'H5'}$ = 2, $J_{H4'H6'}$ = 1, $J_{H5'H6'}$ = 5 Hz.

3-Dimethylamino-2-(pyridinyl-2)propenonitrile (9). A mixture of ethyl 2-pyridinylacetonitrile **7** (0.03 mole), DMFDMA (13.3 ml, 0.1 mole) and anhydrous toluene (30 ml) was heated under reflux with exclusion of moisture for 2 h, cooled and volatile components evaporated *in vacuo* to give a crude **9** as an oily residue, which was purified by flash chromatography (Silica gel 60 — Fluka, chloroform as eluent). Fractions containing **9** were combined and solvent evaporated *in vacuo*. Water was added to the residue and the precipitate collected by filtration to give **9** in 92% yield, mp 67-68°C (washed with water); IR 2160 cm^{-1} (CN); ^{1}H NMR (DMSO-D_6, 300 MHz): δ 3.31 (6H, s, NMe_2), 7.00 (1H, ddd, $H_{5'}$), 7.23 (1H, br dd, $H_{3'}$), 7.66 (1H, ddd, $H_{4'}$), 8.08 (1H, s, $\underline{CH}NMe_2$), 8.34 (1H, ddd, $H_{6'}$), $J_{H3'H4'}$ = 7.6, $J_{H3'H5'}$ = 1.0, $J_{H3'H6'}$ = 0.9, $J_{H4'H5'}$ = 7.6, $J_{H4'H6'}$ = 1.8, $J_{H5'H6'}$ = 4.8 Hz. Found, %: C 68.99; H 6.50; N 24.04. $C_{10}H_{11}N_3$. Calculated, %: C 69.33; H 6.40; N 24.27.

Ethyl 3-Benzoylindolizine-1-carboxylate (10) [8]. A mixture of ethyl 2-pyridinylacetate **2** (0.335 g, 0.002 mole), DMFDMA (0.97 ml, 0.0073 mole) and anhydrous toluene (3 ml) was refluxed for 2 h. Volatile components were evaporated *in vacuo*, anhydrous DMF (3 ml) and phenacyl bromide (0.279 g, 0.0014 mole) were added to the residue, and the mixture was stirred at room temperature for 72 h and then at 40°C for 3 h. Chloroform (10 ml) was added and the solution was washed with water (10 ml, 3 times). Organic phase was dried over anhydrous sodium sulphate, filtered, and volatile components evaporated *in vacuo* to give **10** in 18% yield, mp 93-95°C, lit. [8] mp 81-82°C.

3-Benzoyl-1-cyanoindolizine (11). A mixture of 3-dimethylamino-2-(pyridinyl-2)propenonitrile **9** (0.348 g, 0.002 mole), phenacyl bromide (0.398 g, 0.002 mole) and anhydrous ethanol (3 ml) was stirred at room temperature for 48 h, and then at the reflux temperature for 2 h. Volatile components were evaporated *in vacuo*, water (5 ml) was added to the residue and the mixture was left at room temperature for several days. The precipitate was collected by filtration to give **11** in 9% yield, mp 132-133°C (from ethyl acetate/*n*-heptane), IR 2200 cm^{-1} (CN),^{1}H NMR (DMSO-D_6, 300 MHz): δ 7.38 (ddd, 1H, H_6), 7.58 (ddd, 1H, H_7), 7.64-7.71 (m, 3H, 3H-Ph), 7.81-7.85 (m, 2H, 2H-Ph), 7.90 (s, 1H, H_2), 7.95 (ddd, 1H, H_8), 9.85 (ddd, 1H, H_5), J_{H5H6} = 7.0, J_{H5H7} = 1.2, J_{H5H8} = 1.1, J_{H6H7} = 6.8, J_{H6H8} = 1.2, J_{H7H8} = 8.4 Hz. Found, %: C 77.87; H 3.98; N 11.29. $C_{16}H_{10}N_2O$. Calculated, %: C 78.02; H 4.10; N 11.38.

(*S*)-N-Trifluoroacetyl-4-(1-ethoxycarbonylindolizinyl-3)-4-oxohomoalanine Methyl Ester (12). A mixture of ethyl 2-pyridinylacetate **2** (0.165 g, 0.001 mole), DMFDMA (0.4 ml) and anhydrous toluene (2 ml) was heated at reflux temperature for 1 h. Volatile components were evaporated *in vacuo*, anhydrous ethanol (2 ml) and (*S*)-N-trifluoroacetyl-5-bromo-4-oxonorvaline methyl ester **1** (0.320 g, 0.001 mole) were added to the residue, and the mixture was refluxed for 4 h. Volatile components were evaporated *in vacuo* to give **12** in 18% yield, mp 140-141°C (from ethanol), $[\alpha]_D^{25}$ = +151.3 (*c* = 0.00080, chloroform), ^{1}H NMR (DMSO-D_6): δ 1.34 (3H, t, $\underline{CH_3}CH_2$), 3.60 (2H, d, $\underline{CH_2}CH$), 3.72 (3H, s, COOMe), 4.32 (2H, q, CH_2CH_3), 4.88-5.12 (1H, m, $\underline{CH}CH_2$), 7.25 (1H, ddd, $H_{6'}$), 7.59 (1H, ddd, $H_{7'}$), 8.17 (1H, s, $H_{2'}$), 8.30 (1H, dd, $H_{8'}$), 9.70-

9.95 (2H, m, $H_{5'}$ and NH), J_{CH2CH3} = 7, J_{CH2CH} = 7, $J_{H5'H6'}$ = 6, $J_{H5'H7'}$ = 1.5, $J_{H6'H7'}$ = 7, $J_{H6'H8'}$ = 1.5, $J_{H7'H8'}$ = 9 Hz. Found, %: C 52.25; H 3.94; N 7.09. $C_{18}H_{17}F_3N_2O_6$. Calculated, %: C 52.16; H 4.14; N 6.76.

(*S*)-N-Trifluoroacetyl-4-(1-cyanoindolizinyl-3)-4-oxohomoalanine methyl ester hemihydrate (13). A mixture of 3-dimethylamino-2-(2-pyridinyl)propenonitrile **9** (0.373 g, 0.0022 mole), (*S*)-N-trifluoroacetyl-5-bromo-4-oxonorvaline methyl ester **1** (0.704 g, 0.0022 mole), and DMF (4 ml) was stirred, first at room temperature for 24 h and then at 40-50°C for 7 h. Volatile components were evaporated *in vacuo* to give a residue which was dissolved in chloroform (10 ml) and washed with water (3 × 10 ml). Organic phase was dried over anhydrous Na_2SO_4, filtered and the filtrate evaporated *in vacuo*. Small amount of water was added to the residue and the precipitate collected by filtration to give **13** in 7% yield, mp 176-180°C (from ethyl acetate/*n*-heptane 1:6), $[\alpha]_D^{22}$ +133.8° (*c* = 0.00080, chloroform), IR 2230 cm^{-1} (CN), ^1H NMR (DMSO-D_6, 300 MHz): δ 3.58 (2H, d, $\underline{CH_2}CH$), 3.70 (3H, s, COOMe), 4.95 (1 H, dt, $\underline{CH}CH_2$), 7.33 (1H, ddd, $H_{6'}$), 7.64 (1H, ddd, $H_{7'}$), 7.93 (1H, d, $H_{8'}$), 8.41 (1H, s, H_2), 9.76 (1H, d, $H_{5'}$), 9.91 (1H, d, NH), J_{CH2CH} = 7.1, J_{CHNH} = 7.0, $J_{H5'H6'}$ = 7.0, $J_{H5'H7'}$ = 1.0, $J_{H6'H7'}$ = 7.4, $J_{H6'H8'}$ = 1.2, $J_{H7'H8'}$ = 8.8 Hz. Found, %: C 51.00; H 3.27; N 10.98. $C_{16}H_{12}F_3N_3O_4$ = 0.5 H_2O: Calculated, %: C 51.05; H 3.48; N 11.17.

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