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Reaction of 2,3-Dimethyl- and 1,2,3-Trimethyl-6-aminoindoles with Ethyl 4,4,4-Trifluoroacetoacetate

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Abstract—The comparative reactivity of 2,3-dimethyl- and 1,2,3-trimethyl-6-aminoindoles in the reaction with ethyl trifluoroacetoacetate has been studied with the aim of developing the synthesis of corresponding trifluoromethylpyrroloquinolines. Depending on the amine used, the reaction proceeds differently both at the initial stage of the formation of amides and during their transformation into trifluoropyrroloquinolines.

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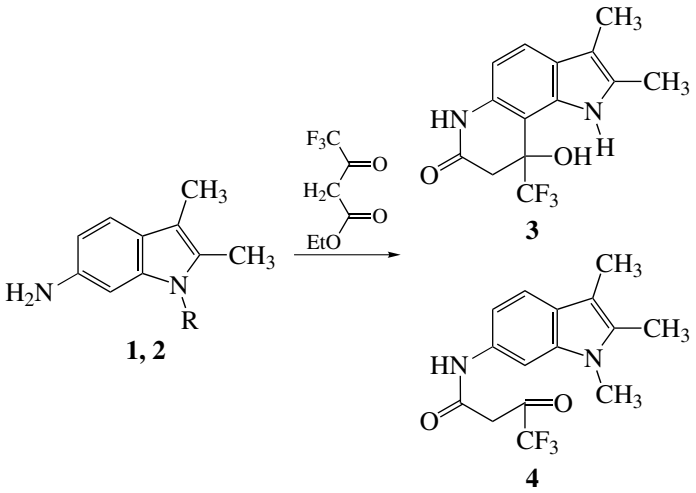
In the framework of the search for convenient methods of synthesis of pharmacologically interesting trifluoromethylpyrroloquinolines [1, 2], we have studied the behavior of aminoindoles **1** and **2** in the reaction with ethyl 4,4,4-trifluoroacetoacetate. On heating in absolute benzene, the latter reacts with **1** mainly through the ester group to form the corresponding amide, which, under the reaction conditions (traces of acetic acid), is likely cyclized to compound **3** through the most reactive 7-position of the indole moiety (Scheme 1).



1 R = H, **2** R = CH_3

Scheme 1.

The structure of compound **3** is confirmed by the ^1H NMR spectrum, which shows signals of the protons of two methyl groups, two doublets due to nonequivalent methylene protons, doublets of two *ortho*-coupled protons of the benzene ring (H-4, H-5), and singlets of OH, H-1, and H-6 (Table 1).

The strongest peak in the mass spectrum of amide **3** is the peak of the fragment ion with m/z = 229, which corresponds to the removal of the CF_3 radical from the molecular ion leading to the formation of the stable pyrrolo[2,3-*f*]quinoline-7,9-dione system. The IR spectrum of solid compound **3** shows two bands at 1696 and 1683 cm^{-1} due to stretching vibrations of the amide group, which are presumably caused by the existence of the amide in two forms. The spectral characteristics of amide **3**, including its UV spectrum, are in agreement with the literature data on similar structures described previously in [3].

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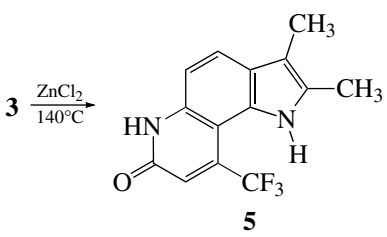
Table 1. Spectral parameters of compounds **3–6**

Compound	^{1}H NMR (δ, ppm; *J*, Hz)	Mass spectrum, *m/z* (I_{rel}, %)	UV	
			λ_{max}, nm	log ε
3	2.11 (s, 3H, 3-CH_3), 2.32 (s, 3H, 2-CH_3), 2.82 (d, 1H, *J* = 15 Hz, H-8), 3.07 (d, 1H, *J* = 15 Hz, H'-8'), 6.61 (d, 1H, *J* = 8 Hz, H-5), 7.27 (s, 1H, 9-OH), 7.29 (d, 1H, *J* = 8 Hz, H-4), 10.00 (s, 1H, H-6), 10.17 (s, 1H, H-1)	298 (86), 280 (6), 259 (6), 229 (100), 228 (10), 214 (13), 211 (19), 187 (10), 183 (12), 159 (38), 158 (10), 149 (11), 115 (12), 114 (10), 93 (16), 92 (10), 91 (16), 80 (22), 78 (24), 77 (14), 44 (10), 43 (24), 42 (10)	215 253 317	4.27 4.37 3.97
4	2.17 (s, 3H, 3-CH_3), 2.31 (s, 3H, 2-CH_3), 2.79 (s, 2H, CH_2CO), 3.58 (s, 3H, 1-CH_3), 7.04 (1H, d br, *J* = 8 Hz, H-5), 7.33 (d, 1H, *J* = 8 Hz, H-4), 7.36 (s br, 1H, H-7), 10.25 (s, 1H, N–H)	312 (29), 175 (14), 174 (100), 173 (42), 159 (13), 78 (10), 69 (11)	233 249 306	4.25 4.30 4.09
5	2.17 (s, 3H, 3-CH_3), 2.39 (s, 3H, 2-CH_3), 6.93 (s, 1H, H-8), 7.15 (d, 1H, *J* = 8 Hz, H-5), 7.73 (d, 1H, *J* = 8 Hz, H-4), 9.64 (s, 1H, H-6), 12.32 (s, 1H, H-1)	280 (100), 279 (30), 265 (9), 260 (23), 259 (45), 245 (30), 231 (35), 217 (16), 140 (31), 121 (18), 116 (27), 115 (24), 109 (14), 113 (30), 106 (16), 102 (44), 95 (16), 78 (60), 77 (31), 63 (28), 53 (22), 52 (31), 50 (20), 42 (21), 39 (28)	240 284 350	4.37 4.32 3.68
6	2.23 (s, 3H, 3-CH_3), 2.35 (s, 3H, 2-CH_3), 3.69 (s, 3H, 1-CH_3), 6.74 (s, 1H, H-6), 7.25 (s, 1H, H-9), 7.64 (s, 1H, H-4), 12.07 (s, 1H, H-8)	294 (100), 293 (51), 279 (29), 265 (5), 147 (10), 123 (8), 44 (8)	242 282 357	4.53 4.44 4.14

Under the same conditions, reaction with aminoindole **2** yields acyclic amide **4**, which exists in the keto form in DMSO-d_6 (Scheme 1). The ^{1}H NMR spectrum of compound **4** differs from the spectrum of cyclic amide **3**: it shows the signal of the H-7 proton, and the signal of the CH_2–CO protons is a singlet. The mass spectrum of amide **4** shows the weak peak of the molecular ion and the strongest peak with *m/z* = 174, which corresponds to M^+ of aminoindole **2**. The latter ($[M-138]^+$) is formed when the molecular ion of **4** loses 4,4,4-trifluorodiketene, which also confirms an acyclic structure of **4**. As distinct from the IR spectrum of **3**, the spectrum of **4** shows the stretching vibration band of one carbonyl group at 1651 cm^{-1}, which is likely evidence of the enol form of this compound in the solid state.

The behavior of amides **3** and **4** in the reaction of the formation of pyrroloquinolines was studied. We found that, under acid cyclization conditions, the aromatization of amide **3** proceeds with difficulty even upon prolonged heating with CF_3COOH so that the reaction mixture contains, in addition to pyrroloquinoline **5**, the initial compound (according to ^{1}H NMR). The latter is completely transformed into pyrroloquinoline **5** (which has an angular structure) under more severe conditions ($ZnCl_2$, 140°C) (Scheme 2).



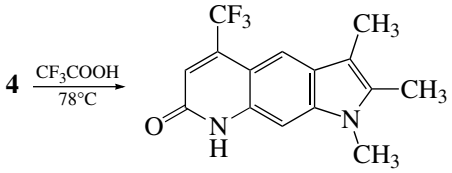
5

Scheme 2.

The ^{1}H NMR spectrum of compound **5**, as distinct from that of amide **3**, lacks two doublets of the methylene protons and the singlet of the hydroxyl group and shows the signal of the aromatic proton H-8, whereas the doublets of the H-4 and H-5 protons are shifted downfield. The mass spectrum of pyrroloquinoline **5** shows, in addition to the peaks of the molecular ion with *m/z* = 280 (100%) and $[M-H]^+$ (30%), rather strong peaks with *m/z* = 259 (45%) and 260 (23%), which are likely caused by the elimination of HF from the interacting *peri* substituents (CF_3, N–H) to form a polycyclic structure.

The UV spectrum of compound **5** supports the transformation of the cyclic amide system into the quinoline system: it shows a strong band at about 284 nm corresponding to *n*–π transitions in the pyridine ring.

Amide **4** is readily cyclized through the 5-position in boiling CF_3COOH to form compound **6** (Scheme 3). The product of the alternative closing of the ring has not been detected.

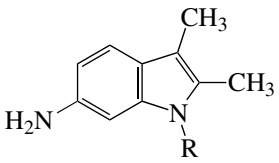


6

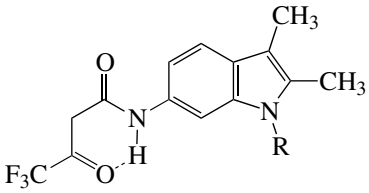
Scheme 3.

The linear structure of pyrroloquinoline **6** is confirmed by singlet signals of the aromatic protons in the ^{1}H NMR spectrum. The EI mass spectrum of **6** shows the strongest M^+ peak and the $[M-H]^+$ (51%) and

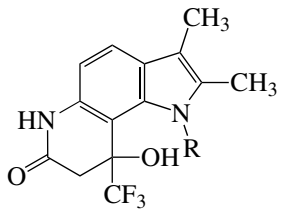
Table 2. Quantum-chemical semiempirical calculation of molecules of compounds **1**, **2**, **3**, **3a**–**3c**, **4**, and **4a**



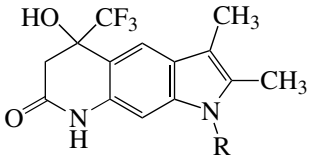
1, 2



4, 4a



3, 3a



3b, 3c

Compound	Charge			Compound	E_f, kcal/mol
	N amine	C-5	C-7		
1	0.067			**3**	–216.36
2	0.066			**3a***	–211.57
4		–0.108	–0.128	**3b***	–218.99
4a*		–0.108	–0.128	**3c***	–219.84

Note: R = H in **1**, **3**, **3b**, and **4a**; R = CH_3 in **3a**, **3c**, and **4**; * hypothetical structures.

$[M–CH_3]^+$ peaks, which points to the lack of interaction between the *peri* substituents (as distinct from **5**) and, hence, to the linear arrangement of the fused rings in the molecule. The UV spectrum of compound **6** shows three absorption bands (242, 282, and 357 nm) caused by n–π transitions in the pyrrole and pyridine rings, which is characteristic of the pyrroloquinoline system [1–3].

Thus, aminoindoles **1** and **2** react with ethyl trifluoroacetoacetate under the same conditions to produce trifluoromethylpyrrolo[2,3-*f*]quinoline **5** and trifluoromethylpyrrolo[3,2-*g*]quinoline **6**, respectively. These different paths of the reaction can be explained by the effect of the N-methyl group. It is likely that, at the first stage of interaction involving the ethoxycarbonyl group of the keto ether, amine **1** forms intermediate acyclic amide **4a** (hypothetical structure) (Table 2). Under the reaction conditions (CH_3COOH traces), this amide undergoes electrophilic cyclization at the more reactive (of the two alternative positions) C-7 atom to form compound **3**. In amide **4**, the N–CH_3 group sterically blocks, to some extent, the 7-position of the benzene ring, thus preventing the formation of the cyclic amide, whereas the electron density at the C-5 atom is low for ring formation under these conditions. These speculations are supported by quantum-chemical calculations. According to these calculations, the N–CH_3 group has no noticeable effect on the electron density distribution in both amine and amide molecules (Table 2). The charges on the amine nitrogen in aminoindoles **1** and **2** are virtually the same (0.067 and 0.066). In amides **4** and **4a**, the analogous carbon atoms *ortho* to the NH group (calculations for the structures with a hydrogen bond in the side chain) carry the same charges. The reactivity of the C-7 position is confirmed by its larger negative charge (–0.128) as compared with the charge on the C-5 atom (–0.108). Therefore, from the standpoint of charge control, structure **3** and hypothetical angular amide **3a** are equally probable. Hence, in this case, the energy of formation of a given structure is decisive for the direction of cyclization. An insignificant difference (2.6 kcal/mol) between the energies of formation of cyclic amides **3** and **3b** allows us to conclude that cyclization is a charge-controlled process. For the formation of hypothetical methylated analogues **3a** and **3c** (the difference between the formation energies is 8.27 kcal/mol), the energy factor is decisive: the formation of linear cyclic system **3c** is energetically more favorable since it readily transforms into an aromatic system due to the lack of steric hindrances in the resulting pyrrolo[3,2-*g*]quinoline **6** as distinct from pyrrolo[2,3-*f*]quinoline **5**, whose formation depends to an extent on the steric requirements of *peri* substituents and takes place under more severe conditions.

EXPERIMENTAL

The ^1H NMR spectra in DMSO-d_6 were recorded on a Bruker DRX-500 spectrometer and referenced to

Table 3. Physicochemical characteristics of compounds

Compound	Empirical formula	Found, %/Calculated, %			R_f (system)*	T_m, °C (solvent for crystallization)	Yield, %
		C	H	M			
3	$C_{14}H_{13}N_2F_3O_2$	56.29/56.38	4.51/4.39	298/298	0.39 (A)	>300 (benzene)	63
4	$C_{15}H_{15}N_2F_3O_2$	57.47/57.69	5.19/4.84	312/312	0.69 (B)	174–175 (petroleum ether–benzene)	73
5	$C_{14}H_{11}N_2F_3O$	59.82/60.00	4.09/3.96	280/280	0.28 (A)	>300 (benzene)	85
6	$C_{15}H_{13}N_2F_3O$	61.20/61.22	4.46/4.45	294/294	0.33 (C)	>300 (ethanol)	82

* The (A) 1 : 1, (B) 3 : 1, and (C) 1 : 4 benzene–ethyl acetate systems.

TMS. The mass spectra were recorded on a Finnigan MAT INCOS-50 mass spectrometer with direct injection of a sample into the ion source at the ionization energy 70 eV. The UV spectra were recorded as ethanol solutions on a Specord spectrophotometer. The IR spectra were recorded as KBr pellets on an IKS Infra LYuM FT-02 spectrophotometer. Reaction products were purified by column chromatography. Aluminum oxide (neutral Brockmann I and II) was used as a sorbent. The reaction course and the purity of the resulting compounds were monitored and R_f was determined by TLC on Silufol UV-254 plates in benzene–ethyl acetate systems 1 : 1 (A), 3 : 1 (B), and 1 : 4 (C). The quantum-chemical calculation of the molecules of **1**, **2**, **3**, **3a**–**3c**, **4**, and **4a** was performed by the PM3 semiempirical method using the Hyper Chem 7.0 program package. Spectral, physicochemical, and quantum-chemical characteristics of the compounds are presented in Tables 1–3.

9-Hydroxy-2,3-dimethyl-9-(trifluoromethyl)-1,6,8,9-tetrahydro-7*H*-pyrrolo[2,3-*f*]quinolin-7-one (3). A mixture of 0.5 g (3.12 mmol) of 2,3-dimethyl-6-aminoindole (**1**) and 0.60 g (3.26 mmol) of ethyl 4,4,4-trifluoroacetoacetate in 300 mL of absolute benzene in the presence of catalytic amounts of glacial acetic acid was refluxed with a Dean–Stark trap. After all aminoindole reacted (heating for ~20 h, chromatographic monitoring), the volume of the reaction mixture was reduced to 20 mL by distilling off benzene. The amide was precipitated by adding petroleum ether and filtered off. The product was purified by recrystallization from benzene. Yield, 0.58 g.

4,4,4-Trifluoro-3-oxobutanoic acid N1-(1,2,3-trimethyl-1*H*-6-indolyl)amide (4) was obtained analogously from 0.45 g (2.59 mmol) of 1,2,3-trimethyl-6-aminoindole (**2**) and 0.5 g (2.72 mmol) of ethyl 4,4,4-trifluoroacetoacetate,but the reaction mixture was heated for 15 h. The product was purified by recrystallization from a petroleum ether–benzene mixture. Yield, 0.59 g.

2,3-Dimethyl-9-trifluoromethyl-6,7-dihydro-1*H*-pyrrolo[2,3-*f*]quinolin-7-one (5). A mixture of 0.2 g (0.67 mmol) of amide **3** and 2 g of $ZnCl_2$ was heated for 2 h at 140–145°C. After the reaction was complete, the reaction mixture was treated with dilute (10–12%) aqueous ammonia. The resulting precipitate was filtered off, repeatedly washed with warm water, and dried in air. The product was purified by recrystallization from benzene. Yield, 0.16 g.

1,2,3-Trimethyl-5-trifluoromethyl-7,8-dihydro-1*H*-pyrrolo[3,2-*g*]quinolin-7-one (6). A solution of 0.168 g (0.54 mmol) of amide **4** in 3 mL of trifluoroacetic acid was refluxed for 4 h. After cooling, the reaction mixture was poured into dilute (10–12%) aqueous ammonia with ice. The resulting precipitate was filtered off and purified by recrystallization from ethanol. Yield, 0.13 g.

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