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THE POTENTIAL USE OF 6-AMINO-5-METHOXY(METHYL)-2,3-DIMETHYL- AND 6-AMINO-5-METHOXY(METHYL)-1,2,3-TRIMETHYL-INDOLES IN THE SYNTHESIS OF PYRROLO[2,3-*f*]QUINOLINES

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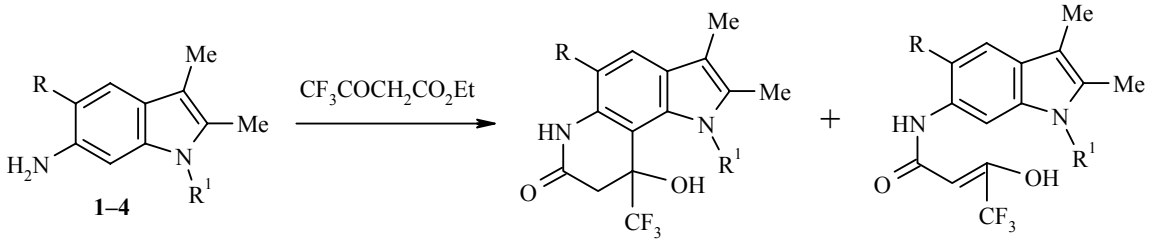
The reaction of 6-amino-2,3-dimethyl- and 6-amino-1,2,3-trimethyl-5-methoxy(methyl)indoles with 4,4,4-trifluoroacetoacetic ester and of 6-amino-5-methoxy-1,2,3-trimethylindole also with other β-dicarbonyl compounds has been studied. It was found that all of the amines investigated undergo condensation readily to form the corresponding enamines while the possible subsequent cyclization to give pyrrolo[2,3-f]quinolines was found only for the condensation product of 6-amino-2,3,5-trimethylindole with 4,4,4-trifluoroacetoacetic ester.

Keywords: 6-amino-5-methoxy-2,3-dimethylindole, 6-amino-5-methoxy-1,2,3-trimethylindole, 6-amino-1,2,3,5-tetramethylindole, 6-amino-2,3,5-trimethylindole, acetylacetone, acetoacetic ester, pyrrolo[2,3-*f*]quinoline, ethyl 4,4,4-trifluoroacetoacetate.

Continuing our investigation of the development of targeted methods for the synthesis of substituted (including trifluoromethyl-containing) pyrroloquinolines (potential biologically active compounds) with specific ring conjugation [1] we have studied the reactions of 6-amino-2,3,5-trimethylindole (**1**), 6-amino-1,2,3,5-tetramethylindole (**2**), 6-amino-5-methoxy-2,3-dimethylindole (**3**), and 6-amino-5-methoxy-1,2,3-trimethylindole (**4**) with 4,4,4-trifluoroacetoacetic ester and other dicarbonyl compounds.

Heating a mixture of the aminoindole **1** with trifluoroacetoacetic ester in benzene with a catalytic amount of glacial acetic acid gave a compound which had spectroscopic data corresponding to the structure **5**.



1,5 R = Me, R^1 = H, **2,6** R = R^1 = Me, **3,7** R = OMe, R^1 = H, **4,8** R = OMe, R^1 = Me

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The ^{1}H NMR spectrum of compound **5** (Table 1) shows signals for the protons of the 2-, 3-, 5-methyl groups, an unresolved signal for the H-4 and 9-OH protons (7.17 ppm), and also two singlets for H-1 and H-6. The methylene group protons appear as two doublets (2.85 and 3.07 ppm) with a spin-spin coupling of 15 Hz. The nonequivalence of the H-8 protons is explained by the effect of the differently placed CF_3 and OH groups on the asymmetric carbon $C_{(9)}$. The IR spectrum shows two signals at 1630 and 1650 cm^{-1} for nonequivalent amide carbonyl groups. The strongest peak in the mass spectrum of compound **5** is the signal for the fragment ion with *m/z* 243 which corresponds to loss of the CF_3 radical from molecular ion and leads to the stable pyrrolo[2,3-*f*]quinoline-7,9-dione system. The spectroscopic data quoted and the UV spectrum of amide **5** agree well with literature data for similar structures prepared from 7-amino-2,3-dimethyl- and 6-amino-7-methoxy-1,2,3-trimethylindoles [1, 2].

In contrast to amine **1**, compound **2** reacts with trifluoroacetoacetic ester under the same conditions to form the noncyclic amide **6** which exists in $CDCl_3$ as a mixture of the *Z*,*E*-enol forms (*Z*:*E* = 1:1 according to the integrated intensities of the vinyl proton signal in the ^{1}H NMR spectra).

The ^{1}H NMR spectrum of compound **6** shows singlet signals for the protons of four methyl groups, the NH, H-4 and H-7, *Z*-H_{vinyl} (5.39) and *E*-H_{vinyl} (5.70 ppm) and a broadened signal for the OH group proton at 13.90 ppm. The mass spectrum of amide **6** shows a low intensity molecular ion peak and a strongest peak with *m/z* 188 ($[M\text{-}138]^{+)}$) which corresponds to M^+ for the aminoindole **2**. The ion is formed by loss of trifluorodiketene from the molecular ion of **6** ($[M\text{-}138]^+$).

Hence the N–CH_3 group in the aminoindole **2** blocks position 7 for formation of the cyclic amide system. The latter is also not formed in the case of an N–H indole, e.g. the methoxyindole **3**.

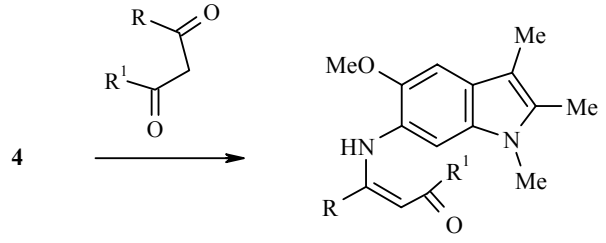
Compound **3**, as amine **2**, forms amide **7** with trifluoroacetoacetic ester and on the basis of the δ value of the vinyl proton (5.68 ppm) in the ^{1}H NMR spectrum ($CDCl_3$) has a trifluoroacetoacetylamide structure in the *Z*-enol form. In addition there are singlet signals for the H-1, H-4, and H-7 protons and the 2-, 3-CH_3, 5-OCH_3, amide N–H groups, and a broadened singlet for the OH group proton at 13.90 ppm.

The first step in the fragmentation of the amide **7** molecular ion under electron impact conditions is similar to the decomposition of amide **6** and, in fact, shows a low intensity peak for the molecular ion and a maximum for $[M\text{-}138]^+$ with *m/z* 190 due to loss of trifluorodiketene from the molecular ion. The formed molecular ion of the aminoindole **3** (with *m/z* 190) subsequently eliminates a Me radical and CO molecule which is typical of 5-methoxy-substituted indoles [3].

The impossibility of forming a cyclic amide for the aminoindole **3** is evidently connected with deactivation of position 7 of the indole towards electrophilic attack by the *meta*-related 5-OMe group, as has been reported previously [4]

As might be expected, although not disregarding the possible increase in the electron density at the $C_{(7)}$ atom *via* the effect of the NMe group, the aminoindole **4** and trifluoroacetoacetic ester form the amide **8**, the spectroscopic parameters of which (including the UV spectra) are fully in agreement with that of compound **7** and confirm their common structure.

By contrast with the trifluoroacetoacetate ester its nonfluorinated analog reacts with the aminoindole **4** at the acetyl group to give the enaminocrotonate **9**.



***Z*-9, *Z*-10**

9 R = Me, R^1 = OEt; **10** R = R^1 = Me

TABLE 1. Spectroscopic Characteristics of Compounds **5-11**

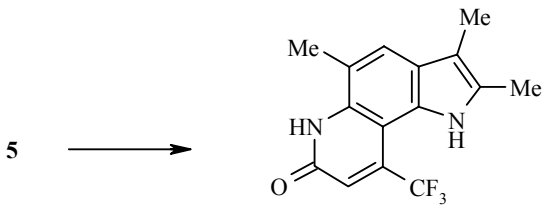
Compound	UV spectrum		^{1}H NMR spectrum, δ, ppm (*J*,Hz)	Mass spectrum, *m/z* ($I_{rel.}$, %)
	λ_{max}, nm	log ε		
5	222 260 322	4.35 4.33 4.12	2.10 (3H, s, 3-CH_3); 2.30 (6H, s, 2-, 5-CH_3); 2.85 (1H, d, *J* = 15, H-8); 3.07 (1H, d, *J* = 15, H-8); 7.17 (2H, s, H-4, 9-OH); 9.20 (1H, s, H-6); 9.72 (1H, s, H-1)	312 $[M]^+$ (44), 311 (64), 243 (100), 241 (10), 228 (14), 225 (14), 173 (17), 156 (10), 69 (8)
6	208 241 303	4.32 4.48 4.03	2.20–2.30 (9H, m, 2-, 3-, 5-CH_3); 3.64 (3H, s, 1-CH_3); 5.39 (0.5H, s, H vin. (*E*)); 5.70 (0.5H, s, H vin. (*Z*)); 7.00-7.70 (3H, m, H-4,7, NH); 13.90 (1H, br. s, OH)	326 $[M]^+$ (29), 188 (100), 69 (34)
7	208 227 263 (sh.) 323	4.39 4.38 4.23 4.26	2.20 (3H, s, 3-CH_3); 2.35 (3H, s, 2-CH_3); 3.96 (3H, s, 5-OCH_3); 5.68 (1H, s, H vin.); 6.90 (1H, s, H-4); 7.63 (1H, s, NH); 7.95 (1H, s, H-1); 8.31 (1H, s, H-7); 13.85 (1H, br. s, OH)	328 $[M]^+$ (23), 190 (100), 189 (22), 175 (68), 147 (28), 146 (24), 69 (45)
8	208 227 256 (sh.) 323	4.37 4.35 4.27 4.21	2.21 (3H, s, 3-CH_3); 2.33 (3H, s, 2-CH_3); 3.65 (3H, s, 1-CH_3); 3.96 (3H, s, 5-OCH_3); 5.68 (1H, s, H vin.); 6.92 (1H, s, H-4); 8.00 (1-H, s, NH); 8.30 (1H, s, H-7); 13.87 (1H, br. s, OH)	342 $[M]^+$ (19), 204 (100), 203 (17), 189 (73), 161 (24), 160 (22), 146 (13), 69 (34)
9	208 227 317	4.35 4.30 4.23	1.20 (3H, t, *J* = 7, $OCH_2C\underline{H}_3$); 1.92 (3H, s, C=C–CH_3); 2.17 (3H, s, 3-CH_3); 2.30 (3H, s, 2-CH_3); 3.59 (3H, s, 1-CH_3); 3.80 (3H, s, 5-OCH_3); 4.05 (2H, q, *J* = 7, $OC\underline{H}_2$–CH_3); 4.62 (1H, s, H vin.); 6.99 (1H, s, H-4); 7.18 (1H, s, H-7); 10.13 (1H, s, NH)	316 $[M]^+$ (53), 270 (100), 255 (17), 227 (35), 212 (14), 135 (23)
10	211 222 323	4.49 4.48 4.41	1.94 (3H, s, C=C–CH_3); 1.97 (3H, s, 3-CH_3); 2.18 (3H, s, 2-CH_3); 2.31 (3H, s, O=C–CH_3); 3.60 (3H, s, 1-CH_3); 3.80 (3H, s, 5-OCH_3); 5.20 (1H, s, H vin.); 7.00 (1H, s, H-4); 7.23 (1H, s, H-7); 12.20 (1H, s, NH)	286 $[M]^+$ (100), 271 (9), 256 (13), 243 (19), 229 (29), 228 (55), 214 (40), 213 (41), 212 (40), 202 (44), 189 (23), 160 (12), 143 (30), 135 (18), 127 (14), 115 (16), 114 (20), 107 (22), 43 (91)
11	225 (sh.) 240 280 357	4.06 4.19 4.28 3.65	2.16 (3H, s, 3-CH_3); 2.40 (3H, s, 2-CH_3); 2.54 (3H, s, 5-CH_3); 6.99 (1H, s, H-8); 7.61 (1H, s, H-4); 9.39 (1H, s, H-6); 10.98 (1H, s, H-1)	294 $[M]^+$ (100), 273 (23), 259 (10)

Formation of this enaminocrotonate **9** is confirmed by the ^{1}H NMR spectrum which shows a triplet and quadruplet for the protons of the OCH_2CH_3 group and singlet signals for the protons of five methyl groups, the vinyl proton, and H-4, H-7, and N–H. The chemical shifts of the protons of the ethoxy group, the C=C–CH_3, and N–H group point to a *Z*-structure for the aminocrotonate [5].

The mass spectrum of compound **9** shows a low intensity peak for the molecular ion and an ion $[M-46]^+$ (100%) which is typical of the mass spectroscopic decomposition of indolylaminocrotonates [6]. Subsequent fragmentation, as for compounds **7, 8**, is due to the presence of the 5-methoxy group in the molecule.

Heating the aminoindole **4** in acetylacetone gives the *Z*-enamino ketone **10**, the ^{1}H NMR spectrum of which differs from the spectrum of compound **9** by the additional singlet for the protons of the methyl group (instead of the quadruplet and triplet for the protons of the OCH_2CH_3 group) and also the low field shifts of the signals for the vinyl and N–H group protons. The basic route of mass spectroscopic decomposition is elimination of an acetyl radical from the molecular ion to form the $[M-43]^+$ fragment ion which is typical of the majority of enamines formed by acetylacetone [7]. The electronic absorption spectra of compounds **9, 10** agree well with the spectra of the previously reported nonmethylated analogs [8].

The amides **5-8** and enamines **9, 10** were studied in the formation of pyrroloquinolines. It was found that the cyclic amide **5** is readily converted to the pyrroloquinoline **11** in trifluoroacetic acid or by heating above 100°C.



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This is indicated by the ^{1}H NMR spectrum which shows singlet signals for the protons of the three methyl groups (2-, 3-, 5-CH_3) and the H-1, H-4, H-6, and H-8 protons.

We have also shown that compounds **6-10** do not form the corresponding pyrroloquinolines thermally or in the presence of acids. Tarring occurs and the reaction mixtures shows only starting materials or their decomposition products.

Hence the aminoindoles **1-4** readily take part in an initial reaction with trifluoroacetoacetic ester to give the corresponding amides, with acetoacetic ester to form enaminocrotonates, and with acetylacetone to give an enamino ketone. Comparison of the reactivity of the amines shows that the aminoindoles **1, 2** react more readily than the methoxy-substituted analogs **3, 4**, as judged by the reaction time and the yields of products formed. The experimental data is indirectly confirmed by the results of quantum chemical calculations which show that the

TABLE 2. Physicochemical Characteristics of Compounds **5-11**

Compound	Empirical formula	Found, % / Calculated, %			R_f*	mp, °C*[2]	Yield, %
		C	H	N			
5*[3]	$C_{15}H_{15}F_3N_2O_2$	57.79 / 57.69	4.74 / 4.84	3.12 / 3.12	0.44		83
6	$C_{16}H_{17}F_3N_2O_2$	58.98 / 58.89	5.05 / 5.25	3.26 / 3.26	0.50	201-203	76
7	$C_{15}H_{15}F_3N_2O_3$	54.79 / 54.88	4.73 / 4.61	3.28 / 3.28	0.44	169-170	42
8	$C_{16}H_{17}F_3N_2O_3$	56.03 / 56.14	5.16 / 5.01	3.42 / 3.42	0.57	152-153	77
9	$C_{18}H_{24}N_2O_3$	68.22 / 68.33	7.79 / 7.65	3.16 / 3.16	0.81	122-123	73
10	$C_{17}H_{22}N_2O_2$	71.17 / 71.30	7.92 / 7.74	2.86 / 2.86	0.47	92-93	81
11	$C_{15}H_{13}F_3N_2O$	61.18 / 61.22	4.49 / 4.45	2.94 / 2.94	0.44	>300	77

* Systems: benzene–ethyl acetate, 3:1 (compounds **5, 11**) and 1:1 (compounds **6-10**).

*2 Crystallized from ethanol (compounds **5, 11**) and petroleum ether (compounds **6-10**).

*[3] Converted to the pyrroloquinoline upon heating.

charge on the amino nitrogen of compounds **3, 4** is higher (0.078, 0.079) than for the 5-methyl-substituted analogs **1, 2** (0.063, 0.064). The calculated data also agrees with the results of the experiment relating to the absence of an effect of the 1-Me group on the activity of the amines **2, 4** in the reactions discussed.

In the process of ring formation the deactivating effect of the methoxy group (the calculated charges on the $C_{(7)}$ atom for compounds **1, 2** being -0.154 and -0.157 and for compounds **3, 4** -0.130 and -0.138) occurs so that the amide **7** is unable to cyclize, even under rigid conditions. The methyl group on the pyrrole ring atom also generates steric hindrance to closing the ring and this evidently dictates the impossibility of cyclic amide formation in the case of the amine **2**. Hence, for all of the studied amines it only appeared possible to use the aminoindole **1** for preparation of the pyrrolo[2,3-*f*]quinoline system.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker DRX-500 (500 MHz) instrument for compounds **5, 9-11** using DMSO-d_6 and for compounds **6-8** using $CDCl_3$ with TMS as internal standard. Mass spectra were obtained on a Finnigan MAT INCOS-50 mass spectrometer with direct introduction of the sample into the ion source at an ionization energy of 70 eV. Electron absorption spectra were recorded on a Specord UV-vis spectrophotometer using ethanol. Purification of the reaction products was carried out by column chromatography. Al_2O_3 was used as sorbent (neutral, Brockmann I or II activity grade). Monitoring of the reaction course and the purity of the compounds prepared was performed using TLC on Silufol UV-254 plates and the solvent systems benzene–ethyl acetate 3:1 (A) or 1:1 (B). Semi-empirical quantum-chemical calculations were carried out for the aminoindoles **1-4** using the PM3 method and the Hyper Chem 5.0 program package.

The spectroscopic and physicochemical characteristics for the compounds obtained are given in Tables 1 and 2.

Preparation of the Amides and Aminocrotonates (General Method). An equimolar mixture of the aminoindole with ethyl 4,4,4-trifluoroacetoacetate or acetoacetate in absolute benzene (300 ml) was refluxed in the presence of a catalytic amount of glacial acetic acid in a Dean–Stark apparatus. After all of the aminoindole had reacted (chromatographic monitoring) the reaction mixture was evaporated to 20 ml. The amide or aminocrotonate was precipitated with petroleum ether and filtered off.

9-Hydroxy-2,3,5-trimethyl-9-trifluoromethyl-6,7,8,9-tetrahydro-1H-pyrrolo[2,3-*f*]quinolin-7-one (5) was prepared from the aminoindole **1** (1.00 g, 5.70 mmol) and ethyl 4,4,4-trifluoroacetoacetate (1.03 g, 5.70 mmol). Heating was carried out for 20 h. It was purified by recrystallization from alcohol. Yield 1.5 g.

N-(1,2,3,5-Tetramethyl-1H-indol-6-yl)-4,4,4-trifluoro-3-oxobutanamide (6) was prepared similarly from the aminoindole **2** (0.20 g, 1.06 mmol) and trifluoroacetoacetic ester (0.20 g, 1.08 mmol) by heating for 18 h. It was purified by recrystallization from petroleum ether. Yield 0.26 g.

N-(5-Methoxy-2,3-dimethyl-1H-indol-6-yl)-4,4,4-trifluoro-3-oxobutanamide (7) was prepared similarly from the aminoindole **3** (0.65 g, 3.42 mmol) and ethyl 4,4,4-trifluoroacetoacetate (0.63 g, 3.42 mmol) by heating for 30 h. It was purified by recrystallization from petroleum ether. Yield 0.4 g.

N-(5-Methoxy-1,2,3-trimethyl-1H-indol-6-yl)-4,4,4-trifluoro-3-oxobutanamide (8) was prepared similarly from the aminoindole **4** (0.67 g, 3.28 mmol) and ethyl 4,4,4-trifluoroacetoacetate (0.61 g, 3.30 mmol) by heating for 26 h. It was purified by repeated crystallization from petroleum ether. Yield 0.87 g.

Ethyl (*Z*)-3-(6-Amino-5-methoxy-1,2,3-trimethyl-1H-indolyl)-2-butenoate (9) was prepared similarly from the aminoindole **4** (1.00 g, 4.90 mmol) and acetoacetic ester (0.64 g, 4.90 mmol) by heating for 35 h. It was purified by recrystallization from petroleum ether. Yield 1.12 g.

(*Z*)-4-(6-Amino-5-methoxy-1,2,3-trimethyl-1H-indolyl)-3-penten-2-one (10). A mixture of the aminoindole **4** (0.40 g, 1.96 mmol) and acetylacetone (3 ml) was refluxed for 2.5 h. At the end of the reaction (chromatographic monitoring) the excess acetylacetone was distilled off in vacuo. The precipitate was purified

by passage through a layer (2 cm) of aluminium oxide in petroleum ether and recrystallized from petroleum ether. Yield 0.34 g.

2,3,5-Trimethyl-9-trifluoromethyl-6,7-dihydro-1H-pyrrolo[2,3-*f*]quinolin-7-one (11). A mixture of the amide **5** (0.10 g, 0.58 mmol) and a ten-fold excess of trifluoroacetic acid was heated for 30 min. The cooled mixture was poured into a dilute (10-12%) aqueous solution of ammonia with ice. The precipitate was filtered off, washed repeatedly with water, and dried in air. It was purified by recrystallization from alcohol. Yield 0.073 g.

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