Chemistry of Heterocyclic Compounds, Vol. 40, No. 3, 2004

ACYLATION OF 3,4-DIHYDRO-PYRROLO[1,2-*a*]PYRAZINES*

V. I. Terenin, E. V. Kabanova, N. A. Tselishcheva, M. A. Kovalkina, A. P. Pleshkova, and N. V. Zyk

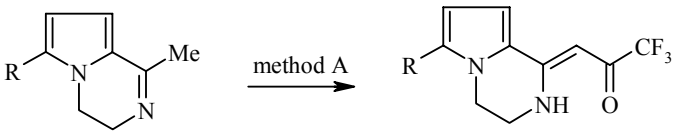
The direction of trifluoroacetylation with trifluoroacetic anhydride of 3,4-dihydropyrrolo[1,2-a]-pyrazines containing an alkyl or aralkyl substituent in position 1 depends on both the structure of the 3,4-dihydropyrrolo[1,2-a]pyrazine starting materials and on the ratio of reagent:substrate. It may lead to both mono- and disubstituted products. Trifluoroacetylation of 1-methyl-3,4-dihydropyrrolo[1,2-a]-pyrazines occurs at the methyl group. Acetylation of 3,4-dihydropyrrolo[1,2-a]pyrazines leads only to N-acetyl-substituted reaction products.

Keywords: 3,4-dihydropyrrolo[1,2-*a*]pyrazine, acetylation, trifluoroacetylation.

Organic compounds containing fluorine atoms are of considerable interest to the pharmaceutical, agrochemical, and polymer fields of chemistry [2]. In this paper a method for the preparation of new heteroaromatic trifluoromethyl ketones is described.

We have shown previously that formylation of 3,4-dihydropyrrolo[1,2-*a*]pyrazines, which are analogs of pyrrole with an imino group in the α-position of the pyrrole ring, occurs ambiguously and depends on the structure of the 3,4-dihydropyrrolo-[1,2-*a*]pyrazine starting materials [3]. Acylation of pyrroles with trifluoroacetic anhydride occurs rapidly at 0°C [4], but dipyrrolo[1,2-*a*;2',1'-*c*]pyrazines gave ditrifluoroacetyl derivatives as the principal reaction products at room temperature [5].

In a continuation of the behavior under electrophilic substitution conditions of pyrrolo[1,2-*a*]pyrazine [6] and its dihydroanalog, 3,4-dihydropyrrolo[1,2-*a*]pyrazine, we studied the reaction the 3,4-dihydropyrrolo-[1,2-*a*]pyrazines **1-8**, containing alkyl or aralkyl substituents at positions 1 and 6 of the heterocycle, with trifluoroacetic anhydride Reaction of 1-methyl- and 1,6-dimethyl-3,4-dihydropyrrolo[1,2-*a*]pyrazines **1** and **2** with a 2.5 fold excess of trifluoroacetic anhydride in benzene (method A) led respectively to the formation of trifluoroacetyl derivatives at the methyl group in position 1, 1,1.1-trifluoro-3-(1,2,3,4-tetrahydropyrrolo[1,2-*a*]-pyrazin-1-yliden)acetone (**9**) and its 6-methyl-substituted analog **10** with yields of 47-48%.



1, **2** **9**, **10**

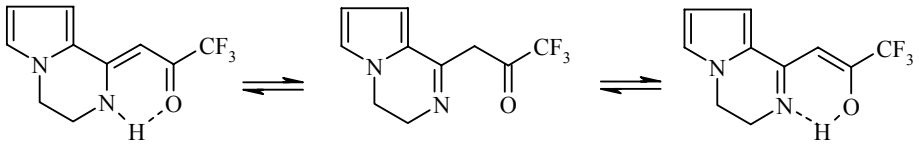
1, **9** R = H; **2**, **10** R = Me

* For previous Communication, see [1].

M. V. Lomonosov Moscow State University, Moscow 119899, Russia; e-mail: vter@org.chem.su.ru.
Translated from Khimia Geterotsiklicheskikh Soedinenii, pp. 431-442, March 2004. Original paper submitted August 27, 2001.

Analogous results of trifluoroacetylation – formation of trifluracetonyl-substituted derivatives – have been obtained with a number of methyl-substituted azines [7] such as pyridine, pyrimidine, quinoline, oxazole, benzoxazole, benzimidazole, and benzothiazole, on treatment with a three-fold excess of trifluoroacetic anhydride in the presence of pyridine at room temperature. Pyridine was shown to promote the reaction. It is interesting that the reaction of a 2:1 mixture of 2,6-, 2,4-, or 3,4-dimethylpyridines with acetic anhydride in benzene required refluxing for 6 h, and addition of pyridine reduced the yield of the reaction products.

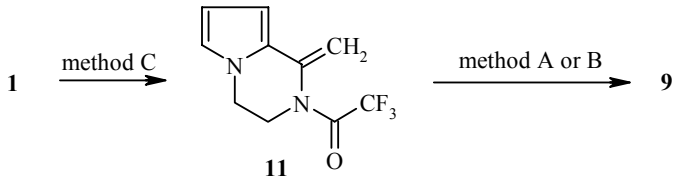
Compounds **9** and **10**, which are nitrogen-containing analogs of 1,3-diketones, can exist in three tautomeric forms, in the case of compound **9** as isomers **9a-c**:



9a **9b** **9c**

It was confirmed from the ^{1}H and ^{13}C NMR spectra that the imino ketone forms **9b** and **10b** do not exist in deuterochloroform solution (signals of the methylene group in position 1 were not observed). The differences between the tautomeric forms **9a** and **9c** are negligible because the transformation of one into the other consists of the small shift of the acid proton relative to the oxygen and nitrogen and the energy of the barrier between them is not large. Compounds similar to **9** and **10** exist in solution predominantly (to 95%) in the an amino ketone form, depending on the solvent [8]. In the ^{1}H NMR spectra of compound **9**, signal of only one form are observed, presumably the enamino ketone form **9a**, whereas in the spectra of compound **10** the signals of the two tautomeric forms **10a** and **10c**, are observed.

If the treatment of compound **1** with excess trifluoroacetic anhydride was carried out in the presence of pyridine (method B), the yield of compound increased to 75%. When the reaction of the substrate was with an equimolar amount of trifluoroacetic anhydride in the presence of pyridine (method C) the direction of the reaction changed to give a 62% yield of 1-methylene-2-trifluoroacetyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine (**11**), i.e., the product of acylation at the nitrogen atom of the pyrazine ring, $N_{(2)}$.



1 method C **11** method A or B **9**

Unlike the trifluoroacetonyl derivatives **9** and **10**, compound **11** is unstable and rapidly polymerizes in the air and in solution. On treatment with an excess of trifluoroacetic anhydride compound **11** is converted into the more stable compound **9**.

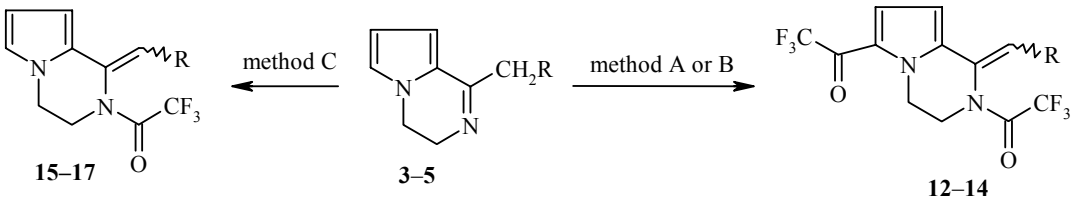
In the case of 1,6-dimethyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine (**2**) trifluoroacetylation in the presence gave only compound **10** (the yield of the reaction product dropped from 44 to 12% with an equimolar ratio of the reagents).

Reaction of the 3,4-dihydropyrrolo[1,2-*a*]pyrazines **3-7**, which have substituents other than methyl at position 1, with excess trifuoroacetic anhydride gave disubstitution at $N_{(2)}$ and in the pyrrole ring. For example, compounds **3-5,** in which the α-position of the pyrrole ring is free for electrophilic attach, gave ditrifluoroacetyl derivatives at $N_{(2)}$ and at $C_{(6)}$ – respectively 1-ethyliden-, 1-propyliden-, and 2,6-di(trifluoroacetyl)-1-(1-phenylmethyliden)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazines **12-14**. The presence of pyridine in the reaction led

TABLE 1. Yields of Trifluoroacetyl Derivatives of 3,4-Dihydropyrrolo-[1,2-*a*]pyrazines

Compound	Yield, %			Compound	Yield, %		
	Method A	Method B	Method C		Method A	Method B	Method C
9	47	75		**16**			72
10	48	45	12	**17**			49
11			62	**18**	28	43	
12	58	81		**19**	39	46	
13	64	73		**20**			41
14	62	83		**21**			46
15			76	**22**	52		

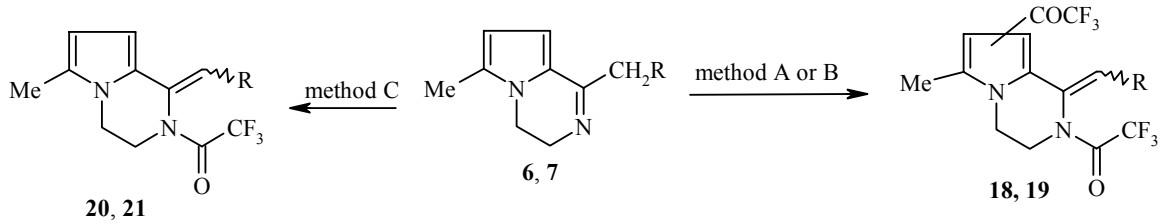
to a considerable increase (up to 70-80%) in the yields of the reaction products (see Table 1). Trifluoroacetylation with an equimolar ratio of substrate:reagent in the presence of pyridine led to formation of monosubstituted derivatives at $N_{(2)}$ of the pyrazine ring **15-17**:



3, **12**, **15** R = Me; **4**, **13**, **16** R = Et; **5**, **14**, **17** R = Ph

It should be noted attempts to obtain the N-monosubstituted trifluoroacetyl derivatives **15-17** by treatment of 3,4-dihydropyrrolo[1,2*a*]pyrazines with trifluoroacetic anhydride in the absence of pyridine were unsuccessful – the change to an equimolar ratio of substrate:reagent only led to a considerable decrease in the yields of theditrifluoroacetyl derivatives.

When the α-position of the 3,4-dihydropyrrolo[1,2-*a*]pyrazine starting materials was occupied by a methyl group, acylation in the presence of pyridine with an excess of reagent occurred at $N_{(2)}$ and at carbon atoms $C_{(7)}$ or $C_{(8)}$ of the pyrrole ring with the formation of compounds **18** and **19**, while with an equimolar ratio of substrate:reagent the $N_{(2)}$ monosubstituted products **20** and **21** were formed. In contrast to the analogous formylation products [4] the exact position of the trifluoroacetyl groups in the pyrrole rings of compounds **18** and **19** could not be established.



6, **18**, **20** R = Me, **7**, **19**, **21** R = Et

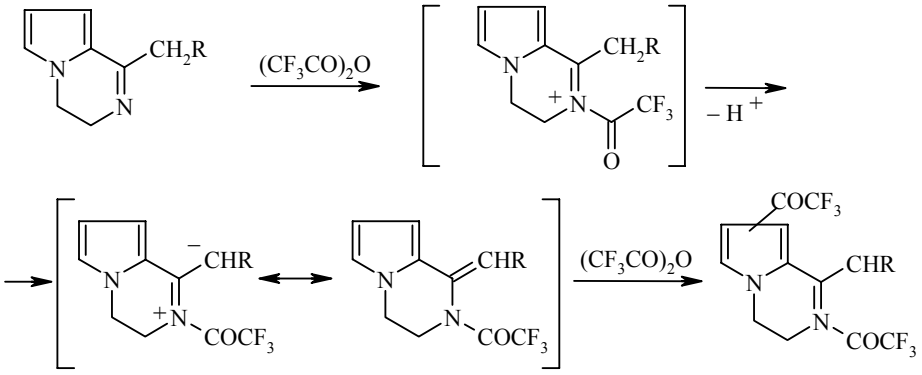
The ^{1}H NMR spectra of the trifluoroacetyl derivatives **12-21** present a complex picture because the compounds are mixtures of the *Z*- and *E*-isomers with respect to the double bond at position 1. Moreover each of them may exist as the two configurational isomers relative to the C-N amide bond. In the case of compounds

TABLE 2. Characteristics of the Compounds Synthesized

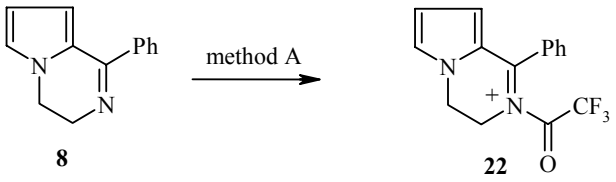
Compound	Empirical formula	Found, % / Calculated, %			Mass spectrum, *m/z* (I_{rel}, %)
		C	H	N	
9	$C_{10}H_9F_3N_2O$	52.40 / 52.18	4.08 / 3.94	11.89 / 12.17	230 (M^+, 67.6), 162 (12.35), 161 (100), 106 (8.86), 105 (4.86), 104 (6.92), 93 (7.93), 78 (6.52), 77 (4.71)
10	$C_{11}H_{11}F_3N_2O$	52.88 / 54.10	4.21 / 4.54	10.90 / 11.47	244 (M^+, 55), 176 (10.47), 175 (100), 147 (6.73), 118 (7.63), 107 (9.78), 87 (12.69), 69 (7.61), 44 (15.3)
11	$C_{10}H_9F_3N_2O$	51.93 / 52.18	4.02 / 3.94	11.86 / 12.17	230 (M^+,100), 161 (70.5), 134 (38.38), 133 (86.13), 106 (58.82), 104 (62.49), 93 (53.75), 92 (42.33), 69 (57.64), 51 (50.91)
12	$C_{13}H_{10}F_6N_2O_2$	45.91 / 45.89	2.76 / 2.96	8.37 / 8.23	340 (M^+, 55.35), 271 (100), 272 (14.75), 243 (15.98), 174 (10.66), 146 (13.08), 145 (9.87), 69 (24.23), 77 (7.76)
13	$C_{11}H_{11}F_3N_2O$				354 (M^+, 45.92), 339 (48.94), 285 (100), 257 (58.91), 161 (56.28), 148 (79), 118 (30.29), 69 (92.12), 45 (36.46), 44 (81.46)
14	$C_{18}H_{12}F_6N_2O_2$	51.91 / 53.74	2.82 / 3.01	7.01 / 6.96	402 (M^+, 100), 333 (53.20), 332 (17.35), 305 (42.43), 304 (25.24), 208 (35.54), 207 (27.58), 206 (19.09), 105 (25.99)
15	$C_{11}H_{11}F_3N_2O$				244 (M^+, 89.56), 175 (97.88), 149 (26.34), 148 (54.80), 147 (100), 120 (31.06), 106 (26.30), 92 (40.88), 69 (66.97), 51 (33.13)
16	$C_{12}H_{13}F_3N_2O$				258 (M^+, 56.84), 243 (100), 230 (21.74), 189 (53.42), 174 (23.81), 161 (62.14), 145 (22.90), 118 (21.73), 117 (17.70), 69 (34.76)
17	$C_{16}H_{13}F_3N_2O$	62.71 / 62.74	4.12 / 4.28	8.95 / 9.15	306 (M^+, 100), 238 (14.18), 237 (80.44), 209 (44.64), 208 (32.56), 207 (11.38), 180 (20.79), 167 (10.70), 104 (12.43)
18	$C_{14}H_{12}F_6N_2O_2$	47.78 / 47.47	3.17 / 3.41	8.02 / 7.91	354 (M^+, 39.06), 285 (100), 257 (58.45), 188 (23.26), 160 (23.20), 159 (15.42), 132 (14.10), 94 (18.57), 69 (40.93), 44 (15.70)
19	$C_{15}H_{14}F_6N_2O_2$	49.24 / 48.92	3.94 / 3.83	7.59 / 7.61	368 (M^+, 49.62), 366 (19.81), 353 (65.60), 339 (26.10), 299 (100), 284 (24.52), 273 (18.08), 69 (33.00)
20	$C_{12}H_{13}F_3N_2O$				258 (M^+, 98.96), 257 (21.25), 231 (27.60), 189 (100), 175 (17.13), 162 (26.43), 161 (78.82), 159 (20.06), 118 (18.26), 69 (22.97)
22	$C_{15}H_{12}F_3N_2O$				197 (M^+, 14.48), 196 (100), 195 (91.89), 194 (10.86), 193 (7.54), 169 (5.90), 168 (29.97), 167 (26.65), 69 (9.42)
23	$C_{11}H_{14}N_2O$				190 (M^+, 41.65), 178 (12.23), 175 (19.32), 163 (32.95), 148 (25.15), 147 (100), 136 (12.44), 121 (13.03), 120 (21.53), 119 (11.57)
24	$C_{12}H_{16}N_2O$				204 (M^+, 51.35), 189 (71.19), 175 (21.15), 161 (51.68), 147 (100), 137 (17.92), 134 (31.25), 121 (18.65), 94 (17.69), 44 (68.98)
25	$C_{16}H_{16}N_2O$				252 (M^+, 57.93), 211 (12.52), 210 (71.84), 209 (68.55), 208 (21.81), 207 (12.71), 205 (13.63), 180 (17.67), 137 (100)
26	$C_{12}H_{16}N_2O$				204 (M^+, 73.49), 189 (34.01), 162 (38.90), 161 (100), 147 (5.80), 135 (11.41), 134 (12.89), 133 (7.21), 120 (7.23), 118 (5.41)
27	$C_{13}H_{18}N_2O$				218 (M^+, 39.38), 203 (58.27), 175 (55.22), 162 (13.34), 161 (100), 159 (11.69), 149 (11.71), 148 (37.28), 135 (12.23), 44 (36.98)

14 and **17**, which contain a benzylidene group at position 1, the ^{1}H NMR spectra show that compound **14** consists of a mixture of one *E*- and two *Z*-isomers relative to the double bonds at position 1, whereas compound **17** is a mixture of *E*- and *Z*-isomers. The signal of the proton at position 8 in the pyrrole ring of the *E*-isomers (5.84-5.89 ppm) is at considerably stronger field than that of the *Z*-isomers (6.53-6.69 ppm) because it falls into the field of screening by the phenyl substituent.

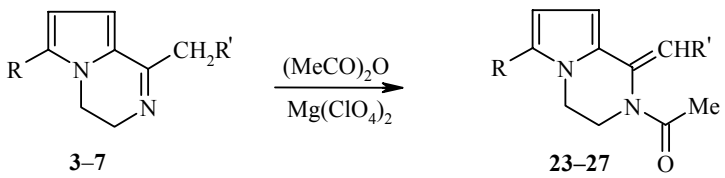
It may be proposed that the interaction of 3,4-dihydropyrrolo[1,2-*a*]pyrazines with trifluoroacetic anhydride begins with attack of the electrophile on the nitrogen atom of the imino group, $N_{(2)}$, of the 3,4-dihydropyrrolo[1,2-*a*]pyrazine starting material with formation of an iminium cation, which is stabilized by loss of a proton from a methyl or methylene group in position 1. Disappearance of the imino group deactivates the pyrrole ring and prevents the possibility of electrophilic substitution in the latter.



Confirmation of this mechanism is the fact that treatment of 1-phenyl-3,4-dihydripyrrolo[1,2-*a*]pyrazine (**8**), which does not have a methyl group in position 1, with an excess of trifluoroacetic anhydride gave a 1-phenyl-3,4-dihydropyrrolo[1,2-*a*]pyrazinium salt (probably a trifluoroacetate) (**22**) and not a product of acylation of the pyrrole ring:



Acylation of 3,4-dihydropyrrolo[1,2-*a*]hydrazines **3-7** with acetic anhydride, a weaker electrophile than trifluoroacetic anhydride, led to the formation of only the N-acetylated reaction product (in the presence of magnesium perchlorate as Lewis acid). Separation of the products of acetylation of 1-methyl and 1,6-dimethyl-3,4-dihydropyrrolo[1,2-*a*]pyrazines **1** and **2** was not successful.



3, **23** R = H, R' = Me (65%); **4**, **24** R = H, R' = Et (56%); **5**, **25** R = H, R' = Ph (25%);
6, **26** R = Me, R' = Me (87%); **7**, **27** R = Me, R' = Et (67%)

TABLE 3. NMR Spectra of the Compounds Synthesized

Compound	mp, °C	^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz)	^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz)
1	2	3	4
9	142-143	3.76 (2H, m, H-3(4)); 4.17 (2H, m, H-4(3)); 5.77 (1H, s, =C<u>H</u>COCF$_3$); 6.30 (1H, dd, J_{76} = 2.53, J_{78} = 3.99, H-7); 6.86 (1H, dd, J_{87} = 3.96, J_{86} = 1.47, H-8); 6.91 (1H, dd, J_{68} = 1.39, J_{67} = 2.46, H-6); 11.05 (1H, br. s, NH)	39.74, 43.35 (C-3,4); 83.11 (=<u>C</u>HCOCF$_3$); 110.85, 113.80 (C-7,8); 118.01 (J_{C-F}=288, CF$_3$); 122.53 (C-8a); 126.15 (C-6); 155.92 (C-1); 175.09 (J_{C-F}=32, C=O)
10	171	2.30 (3H, s, CH$_3$-6); 3.75 (2H, m, H-3(4)); 4.03 (2H, m, H-4(3)); 5.73 (1H, s, =C<u>H</u>COCF$_3$); 6.08 (1H, d, *J* = 3.79, H-7(8)); 6.82 (1H, d, *J* = 4.2, H-8(7)); 11.05 (1H, s, NH)	11.50 (CH$_3$); 39.54, 40.30 (C-3,4); 82.68 (=<u>C</u>HCOCF$_3$); 110.37, 113.98 (C-7, 8); 118.00 (q, J_{C-F}=288, CF$_3$); 121.76, 135.62 (C-6, 8a); 155.87 (C-1), 174.31 (q, J_{C-F}=32, C=O)
11	142	4.00-4.13 (4H, 2m, H-3,4); 5.01-5.60 (2H, 2m, =CH$_2$); 6.17 (1H, dd, J_{78} = 3.80, J_{76} = 2.77, H-7); 6.44 (1H, dd, J_{87} = 3.65, J_{86} = 1.41, H-8); 6.60 (1H, dd, J_{68} = 1.35, J_{67} = 2.75, H-6) **Acetone-d$_6$:** 4.15 (4H, m, H-3,4); 5.1–5.6 (2H, 2m, = CH$_2$); 6.10 (1H, dd, J_{78} = 3.82, J_{76} = 2.41, H-7); 6.48 (1H, dd, J_{87} = 3.88, J_{86} = 1.76, H-8); 6.72 (1H, dd, J_{68} = 1.50, J_{67} = 2.67, H-6)	44.00-44.22 (m, C-3,4); 103.01, 105.44, 109.63, 120.84 (C-6,7,8,=CH$_2$), 116.21 (q, J_{C-F} = 288.2, CF$_3$); 124.93, 128.17 (C-1,8a); 156-156.2 (C=O)
12	*	Isomer 1: 2.08 (3H, d, *J* = 7.10, =CHC<u>H</u>$_3$); 4.05-4.30, 4.48-4.70 (4H, 2m, H-3,4); 6.08-6.16 (1H, m, =C<u>H</u>CH$_3$); 6.58 (1H, m, H-8); 7.30 (1H, dq, J_{CF_3} = 2.18, H-7) Isomer 2: 1.74 (3H, d, *J* = 7.27, =CHC<u>H</u>$_3$); 4.05-4.3, 4.48-4.7 (4H, 2m, H-3,4); 6.42 (1H, q, *J* = 7.34, =C<u>H</u>CH$_3$); 6.52 (1H, d, *J* = 4.64, H-8); 7.22 (1H, dq, J_{CF_3} = 2.17, H-7)	
13	*	Isomer 1: 1.20 (3H, t, *J* = 7.49, =CHCH$_2$C<u>H</u>$_3$); 2.48 (2H, m, *J* = 7.28, =CHC<u>H</u>$_2$CH$_3$); 4.10-4.28 (2H, m, H-3(4)); 4.50-4.61 (2H, m, H-4(3)); 6.00 (1H, t, *J* = 7.29, =C<u>H</u>CH$_2$CH$_3$); 6.53 (1H, m, H-8); 7.28 (1H, dq, J_{CF_3} = 2.19, H-7) Isomer 2: 1.13 (3H, t, *J* = 7.57, =CHCH$_2$C<u>H</u>$_3$); 2.09 (2H, m, *J* = 7.39, =CHC<u>H</u>$_2$CH$_3$); 4.10-4.28 (2H, m, H-3(4)); 4.50-4.61 (2H, m, H-4(3)); 6.27 (1H, t, *J* = 7.28, =C<u>H</u>CH$_2$CH$_3$); 6.53 (1H, m, H-8); 7.23 (1H, dq, J_{CF_3} = 2.14, H-7)	

TABLE 3 (continued)

1	2	3	4
14	*	Isomer 1: 3.5–5.2 (4H, 4m: 3.55, 4.35, 4.70, 5.09, H-3,4); 6.69 (1H, d, *J* = 4.70, H-8); 7.09 (1H, s, =CHPh); 7.26-7.28 (1H, m, H-7); 7.28-7.45 (5H, m, Ph) Isomer 2: 4.25, 4.52 (4H, 2m, H-3,4); 5.89 (1H, d, *J* = 4.92, H-8); 6.98–7.00 (1H, m, H-7); 7.28-7.45 (6H, m, =CHPh) Isomer 3: 4.00-4.75 (4H, m, H-3,4); 6.64 (1H, d, *J* = 4.84, H-8); 7.00 (1H, s, =CHPh); 7.28-7.45 (6H, m, H-7, Ph)	
15	*	Isomer 1: 1.95 (3H, d, *J* = 7.31, =CHCH_3); 4.09 (4H, m, H-3, 4); 5.68 (1H, q, *J* = 7.16, =CHCH_3); 6.26 (1H, dd, J_{76} = 2.76, J_{78} = 3.71, H-7); 6.34 (1H, d, *J* = 2.61, H-8); 6.66 (1H, m, H-6) Isomer 2: 1.63 (3H, d, *J* = 7.17, =CHCH_3); 4.09 (4H, 4m, H-3, 4); 6.01 (1H, q, *J* = 7.35, =CHCH_3); 6.16 (1H, dd, J_{76} = 2.75, J_{78} = 3.65, H-7); 6.31 (1H, dd, J_{86} = 1.46, J_{87} = 3.85, H-8); 6.57 (1H, dd, J_{68} = 1.72, J_{67} = 2.07, H-6)	
16	*	Isomer 1: 1.14 (3H, t, *J* = 7.53, CH_2CH_3); 2.38 (2H, m, *J* = 7.29, CH_2CH_3); 4.09-4.15 (4H, m, H-3, 4); 5.57 (1H, t, *J* = 7.01, =CHCH_2CH_3); 6.24 (1H, dd, J_{78} = 3.77, J_{76} = 2.81, H-7); 6.32 (1H, d, J_{67} = 2.76, H-6); 6.65 (1H, dd, J_{87} = 2.46, J_{86} = 1.60, H-8) Isomer 2: 1.06 (3H, t, *J* = 7.56, CH_2CH_3); 1.98 (2H, m, *J* = 7.66, CH_2CH_3); 3.9-4.3 (4H, 4m, H-3,4); 5.86 (1H, t, *J* = 7.28, =CHCH_2CH_3); 6.13 (1H, dd, J_{78} = 3.70, J_{76} = 2.95, H-7); 6.30 (1H, m, H-8); 6.54 (1H, dd, J_{67} = 2.64, J_{68} = 1.58, H-6)	Isomer 1: 13.32(CH_3); 21.47 (CH_2); 43.65, 44.11 (C-3,4); 108.49, 109.47, 120.70, 126.38 (C-6,7,8, =CHCH_2CH_3); 124.24, 126.93 (C-1,8a); 116.36 (q, $J_{C–F}$ = 287, CF_3); 156.20 ($J_{C–O}$ = 35, C=O)
17	*	Isomer 1: 3.97-4.27 (4H, m, H-3,4); 5.84 (1H, dd, J_{86} = 1.36, J_{87} = 3.82, H-8); 5.98 (1H, dd, J_{76} = 2.69, J_{78} = 3.93, H-7); 6.57 (1H, m, H-6); 7.20–7.40 (6H, m, =CH–Ph) Isomer 2: 3.00-5.10 (4H, 4m, H-3,4); 6.24 (1H, dd, J_{76} = 2.92, J_{78} = 3.50, H-7); 6.53 (1H, dd, J_{86} = 1.43, J_{87} = 3.90, H-8); 6.65 (1H, m, H-6); 6.83 (1H, s, =CHPh), 7.20–7.40 (5H, m, Ph)	
18	*	Isomer 1: 2.00 (3H, d, *J* = 7.12, =CHCH_3); 2.59 (3H, s, CH_3-6); 4.01, 4.20 (4H, 2m, H-3,4); 5.85 (1H, m, =CHCH_3); 6.75 (1H, s, H-7(8)) Isomer 2: 1.91 (3H, d, *J* = 7.31, =CHCH_3); 2.22 (3H, s, CH_3-6); 3.42-5.02 (4H, 4m, H-3,4); 6.47 (1H, s, H-7(8)); 7.31 (1H, q, *J* = 7.21, =CHCH_3) Isomer 3: 1.75 (3H, d, *J* = 6.94, =CHCH_3); 2.24 (3H, s, CH_3-6); 3.42-5.02 (4H, 4m, H-3,4); 6.52 (1H, s, H-7(8)); 7.78 (1H, q, *J* = 7.04, =CHCH_3)	

TABLE 3 (continued)

1	2	3	4
19	*	Major isomer : 1.17 (3H, t, J = 7.58, =CHCH$_2$C<u>H</u>$_3$); 2.38 (2H, m, =CHC<u>H</u>$_2$CH$_3$); 2.59 (3H, s, CH$_3$-6); 4.00, 4.20 (4H, 2m, H-3,4); 5.73 (1H, t, J = 6.88, =C<u>H</u>CH$_2$CH$_3$); 6.71 (1H, s, H-7(8))	
20	*	Major isomer: 1.93 (3H, d, J = 7.45, =CHC<u>H</u>$_3$); 2.21 (3H, s, CH$_3$-6); 3.90, 4.16 (4H, 2m, H-3, 4); 5.59 (1H, q, J = 7.19, =C<u>H</u>CH$_3$); 5.99 (1H, d, J_{78} = 3.43, H-7(8)); 6.27 (1H, d, J_{87} = 3.34, H-8(7))	
21	*	Major isomer: 1.13 (3H, t, J = 7.38, =CHCH$_2$C<u>H</u>$_3$); 2.21 (3H, s, CH$_3$-6); 2.37 (2H, m, J = 7.38, =CHC<u>H</u>$_2$CH$_3$); 3.91, 4.21 (4H, 2m, H-3,4); 5.49 (1H, t, J = 7.00, =C<u>H</u>CH$_2$CH$_3$); 5.98 (1H, d, J_{78} = 3.48, H-7(8)); 6.24 (1H, d, J_{87} = 3.33, H-8(7))	
22	165-167 (decomp.)	4.26 (2H, m, H-3(4)); 4.38 (2H, m, H-4(3)); 6.53 (1H, dd, J_{76} = 2.49, J_{78} = 4.35, H-7); 6.99 (1H, dd, J_{87} = 3.98, J_{86} = 1.35, H-8); 7.30 (1H, dd, J_{68} = 1.37, J_{67} = 2.43, H-6); 7.59 (2H, t, J = 7.61, *m*-Ph); 7.70 (1H, t. m, J = 7.45, *p*-Ph); 7.87 (2H, d. m, J = 8.45, *o*-Ph) **DMSO-d$_6$**: 4.09 (2H, m, H-3(4)); 4.46 (2H, m, H-4(3)); 6.57 (1H, dd, J_{76} = 2.33, J_{78} = 4.26, H-7); 7.02 (1H, dd, J_{87} = 4.13, J_{86} = 1.26, H-8); 7.65 (2H, t, J = 7.7, *m*-Ph); 7.76-7.83 (4H, m, H-6, *o*-Ph, *p*-Ph)	**DMSO-d$_6$**: 41.76, 42.31 (C-3,4); 117.30 ($J_{C–F}$ = 299, CF$_3$); 113.66, 125.09, 133.79, 134.33 (C-6,7,8, *p*-Ph); 129.24, 130.18 (*o*-Ph, *m*-Ph); 121.87, 129.77 (C-8a, *i*-Ph); 158.57 ($J_{C–O}$ = 31, C=O);161.01 (C-1)
23	*	Isomer 1: 1.77 (3H, d, J = 7.54, =CHC<u>H</u>$_3$); 2.06 (3H, s, COCH$_3$); 3.0-5.0 (4H, 4m: 3.15, 3.85, 4.11, 4.97, H-3, 4); 5.84 (1H, q, J = 7.24, =C<u>H</u>CH$_3$); 6.13 (1H, dd, J_{78} = 3.47, J_{76} = 2.71, H-7); 6.27 (1H, dd, J_{87} = 3.74, J_{86} = 1.38, H-8); 6.56 (1H, d, J_{68} = 1.22, H-6) Isomer 2: 1.97 (3H, d, J = 7.46, =CHC<u>H</u>$_3$); 2.15 (3H, s, COCH$_3$); 3.98 (2H, m, H-3(4)); 4.08 (2H, m, H-4(3)); 5.46 (1H, q, J = 7.39, =C<u>H</u>CH$_3$); 6.24 (1H, dd, J_{78} = 3.68, J_{76} = 2.74, H-7); 6.35 (1H, dd, J_{87} = 3.70, J_{86} = 1.44, H-8); 6.65 (1H, d, J_{68} = 1.2, H-6)	
24	*	Isomer 1: 1.16 (3H, t, J = 7.56, CH$_2$C<u>H</u>$_3$); 2.17 (3H, s, COCH$_3$); 2.41 (2H, m, J = 7.53, =CHC<u>H</u>$_2$CH$_3$); 4.00 (2H, m, H-3(4)); 4.10 (2H, m, H-4(3)); 5.35 (1H, t, J = 7.20, =C<u>H</u>CH$_2$CH$_3$); 6.24 (1H, dd, J_{78} = 3.96, J_{76} = 2.73, H-7); 6.33 (1H, dd, J_{87} = 3.66, J_{86} = 1.57, H-8); 6.66 (1H, dd, J_{67} = 2.50, J_{68} = 1.71, H-6)	

TABLE 3 (continued)

1	2	3	4
25	*	Isomer 1: 1.80 (3H, s, $COCH_3$); 3.25-5.2 (4H, 4m: 3.32, d. t, 3.90, dd, 4.12, d. t, 5.08, dd, H-3, 4); 6.21 (1H, dd, J_{78} = 3.55, J_{76} = 2.59, H-7); 6.49 (1H, dd, J_{87} = 3.86, J_{86} = 1.69, H-8); 6.64 (1H, m, H-6); 6.64 (1H, s, C<u>H</u>Ph); 7.19 (1H, t, *J* = 7.37, *p*-Ph); 7.31 (2H, t, *J* = 7.69, *m*-Ph); 7.39 (2H, d, *J* = 7.37, *o*-Ph) Isomer 1: 2.36 (3H, s, $COCH_3$); 4.00 (2H, m, H-3(4)); 4.18 (2H, m, H-4(3)); 5.87 (1H, dd, J_{87} = 3.82, J_{86} = 1.57, H-8); 5.97 (1H, dd, J_{78} = 3.92, J_{76} = 2.44, H-7); 6.28 (1H, s, C<u>H</u>Ph); 6.57 (1H, m, H-6); 7.29-7.43 (5H, m, Ph)	Isomer 1: 21.59($CO\underline{C}H_3$); 41.38, 44.04 (C-3, 4); 104.06, 109.40, 116.19 (C-6,7,8); 121.26 (<u>C</u>HPh); 126.80, 130.73, 135.45 (C-1,8a, *i*-Ph); 127.18 (*p*-Ph); 127.84, 128.76 (*m,o*-Ph); 170.46 (C=O)
26	*	Isomer 1: 1.95 (3H, d, *J* = 7.41, =CHC<u>H</u>$_3$); 2.15 (3H, s, CH_3-6); 2.21 (3H, s, $COCH_3$); 3.81 (2H, m, H-3(4)); 4.10 (2H, m, H-4(3)); 5.39 (1H, q, *J* = 7.43, =C<u>H</u>CH_3); 5.99 (1H, dd, *J* = 3.54, *J'* = 0.52, H-7(8)); 6.28 (1H, d, *J* = 3.80, H-8(7)) Isomer 2: 1.76 (3H, d, *J* = 7.54, =CHC<u>H</u>$_3$); 2.07 (3H, s, CH_3-6); 2.17 (3H, s, $COCH_3$); 3.1-5.1 (4H, 4m: 3.14, 3.75, 3.86, 5.02, H-3, 4); 5.77 (1H, q, *J* = 7.23, =C<u>H</u>CH_3); 5.87 (1H, dd, *J* = 3.57, *J'* = 0.79, H-7(8)); 6.35 (1H, d, *J* = 3.63, H-8(7))	
27	*	Isomer 1: 1.14 (3H, t, *J* = 7.63, $CH_2C\underline{H}_3$); 2.16 (3H, s, CH_3-6); 2.20 (3H, s, $COCH_3$); 2.39 (2H, m, *J* = 7.40, =CHC<u>H</u>$_2CH_3$); 3.81 (2H, m, H-3(4)); 4.10 (2H, m, H-4(3)); 5.27 (1H, t, *J* = 7.21, =C<u>H</u>CH_2CH_3); 5.97 (1H, d, *J* = 3.39, H-7(8)); 6.26 (1H, d, *J* = 3.83, H-8(7)) Isomer 2: 1.05 (3H, t, *J* = 7.60, $CH_2C\underline{H}_3$); 2.06 (3H, s, CH_3-6); 2.18 (3H, s, $COCH_3$); 2.20-2.25 (2H, m, =CHC<u>H</u>$_2CH_3$); 3.1-5.1 (4H, 4m: 3.15, 3.76, 3.85, 5.02, H-3, 4); 5.66 (1H, m, =C<u>H</u>CH_2CH_3); 5.87 (1H, d, *J* = 3.00, H-7(8)); 6.26 (1H, d, *J* = 3.54, H-8(7))	

* Mixture of isomers.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-400 instrument with TMS as internal standard. Mass spectra were recorded with an MS Kratos instrument (ionization energy 70 eV). The course of reactions was monitored by TLC on Silufol UV-254 strips.

The 3,4-dihydropyrrolo[1,2-*a*]pyrazine starting materials were synthesized by a known method [9]. Elemental analyses and mass spectra are cited in Table 2, NMR spectra in Table 3.

Trifluoroacetylation of 3,4-Dihydropyrrolo[1,2-*a*]pyrazines (General Method). A. A solution 3,4-dihydropyrrolo[1,2-*a*]pyrazine (3 mmol) in benzene (10 ml) was cooled in ice and then a solution of trifluoroacetic acid (7.5 mmol) in dry benzene (5 ml) was added dropwise with stirring. The reaction mixture was stirred for 3-5 h at room temperature, after which the solvent and excess trifluoroacetic anhydride were removed in a rotary evaporator. The reaction mixture was chromatographed on a silica gel (100/160) column with benzene as eluent. The product was recrystallized from heptane.

B. Trifluoroacetic anhydride (3 mmol) in ether (10 ml) was added dropwise to a mixture of 3,4-dihydropyrrolo[1,2-*a*]pyrazine (3 mmol) and pyridine (3 mmol) in dry ether (10 ml) at room temperature. The reaction mixture was stirred for 3-5 h, poured into cold water, extracted three times with ether, and dried over 4 A molecular sieves. The ether was evaporated in a rotary evaporator and the residue was chormatographed on a silica gel (100/160) column with benzene as eluant. The product was recrystallized from heptane.

C. Trifluoroacetic anhydride (7.5 mmol) in dry ether (10 ml) was added dropwise at room temperature to a mixture of 3,4-dihydropyrrol0[1,2-*a*]pyrazine (3 mmol) and pyridine (7.5 mmol) in dry ether (10 ml). (Further work up was according to method B).

Acetylation of 3,4-Dihydropyrrol[1,2-*a*]pyrazines. $Mg(ClO_4)_2$ (30 mg) was added to a solution of 3,4-dihydropyrrolo[1,2-*a*]pyrazine (5 mmol) and acetic anhydride (120 mmol) in toluene (30 ml). The reaction mixture was kept for a day at room temperature. The solvent and the excess acetic anhydride were evaporated and the residue was chromatographed on a silica gel (100/160 column) with 1:1 heptane–ethyl acetate as eluent.

REFERENCES

1. V. I. Terenin, E. V. Kabanova, M. A. Kovalkina, and A. V. Borisov, *Khim. Geterotsikl. Soed.,* 1272 (1998).
2. J.-P. Begue and D. Bonnet-Delpon, *Tetrahedron*, **47**, 3207 (1991).
3. V. I. Terenin, N. A. Tselishcheva, E. V. Kabanova, A. P. Pleshkova, and N. V. Zyk, *Khim. Geterotsikl. Soed.,* 1395 (2000).
4. W. Cooper, *J. Org. Chem.,* **23**, 1382 (1958).
5. V. I. Terenin, E. L. Ruchkina, K. V. Karapetyan, V. I. Mamaev, and Yu. G. Bundel', *Khim. Geterotsikl. Soed*., 1566 (1995).
6. J. Minguez, M. Castellote, J. Vaquero, J. Garsia-Navio, J. Alvares-Builla, and O. Castano, *J. Org. Chem.,* **61**, 4655 (1996).
7. M. Kawase, M. Teshima, S. Saito, and S. Tani, *Heterocycles*, **48**, 2103 (1998).
8. G. O. Dudek and R. H. Holm, *J. Am. Chem. Soc.,* **84**, 2691 (1962).
9. V. I. Terenin, E. V. Kabanova, and Yu. G. Bundel', *Khim. Geterotsikl. Soed*., 763 (1991).
10. S. E. Korostova, A. I. Mikhaev, L. N. Sobenina, S. G. Shevchenko, M. G. Sigalov, I. M. Karataeva, and B. A. Trofimov, *Khim. Geterotsikl. Soed*., 48 (1989).