Tandem A_N—A_N reactions in the synthesis of 1*H*-pyrrolo[3,2-*e*]-1,2,4-triazines and products of their oxidative transformations

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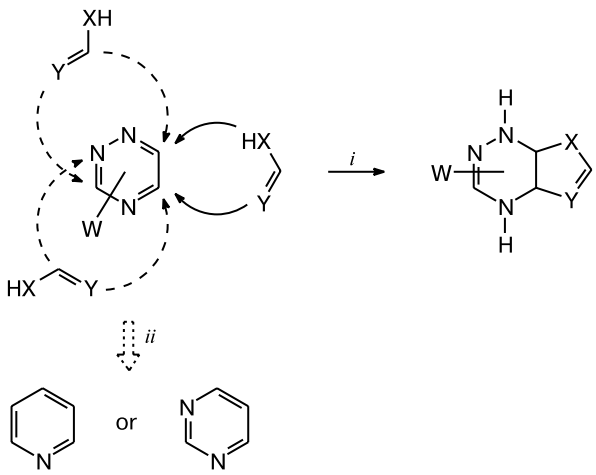
The reactions of 3-aryl-1,2,4-triazines with β-aminovinyl ketones or ethyl β-aminocrotonates in acetic anhydride at room temperature afforded cyclic products of the tandem nucleophilic addition, *viz.*, 3a,4,7,7a-tetrahydro-1*H*-pyrrolo[3,2-*e*]-1,2,4-triazines, in good yields. Under oxidative conditions, the latter compounds underwent the pyrrole-ring opening under the action of potassium permanganate to form the corresponding triazinones and were transformed into thriazolyl-substituted pyridines under the action of selenious acid.

Key words: 3-aryl-1,2,4-triazines, tandem nucleophilic addition, cyclizations, aminovinyl ketones, ethyl β-aminocrotonates, pyrrolo[3,2-*e*]-1,2,4-triazines, 5-hydroxy-2-(1*H*-1,2,4-triazol-1-yl)pyridines.

The tandem addition of bifunctional nucleophilic reagents to two *ortho*-arranged carbon atoms in π-deficient aromatic azaheterocycles (1,4-diazines and their aza and benzo analogs) continue to attract attention as an efficient route to the synthesis of fused heterocyclic systems.[1—8]

Earlier,[5—11] we have reported that the reactions of 1,2,4-triazines and their quaternary salts with 1,3-bifunctional reagents (CH-active amides, ketene *N,N*-aminals, or thioamides), which proceed according to the nucleophilic diaddition (A_N—A_N) or "addition—substitution" (A_N—S_N^{ipso}) schemes, provide an efficient approach to the synthesis of fused 1,2,4-triazines. Although 1,2,4-triazines have been extensively studied within the last several decades (the results of these studies were surveyed in reviews and monographs[5,6,12—15]), the behavior of this system with respect to 1,3-bifunctional reagents containing a double bond are difficult to predict *a priori*. On the one hand, 1,2,4-triazines are readily involved in 1,4-cycloaddition (1,4-CA) with enamines and other dienophiles containing an electron-rich double bond (inverse electron demands Diels—Alder reactions) and are transformed into pyridines or pyrimidines[15—18] (Scheme 1). On the other hand, enamines act as 1,3-*C,N*-bifunctional reagents. Taking into account the ability of charge-activated 1,2,4-triazines to be subjected to the tandem addition (A_N—A_N)[5—7,9—11] or addition—substitution

Scheme 1



i. 1,3-(A_N—A_N); *ii.* 1,4-CA.

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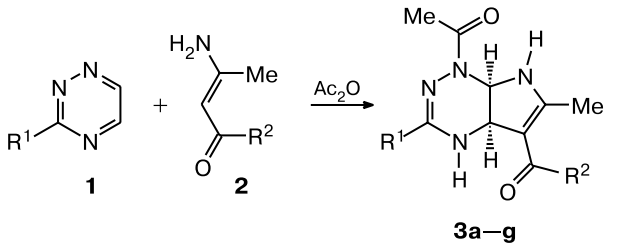
(A_N—S_N^{ipso})[8] reactions involving the adjacent C(5) and C(6) atoms of the triazine ring, one would expect the formation of fused 1,2,4-triazines (see Scheme 1).

In the present study, we report the results of investigation of the reactions of 1,2,4-triazines with enamino ketones and enamino esters in which the π-excessive character of the enamine C=C bond is decreased due to conjugation with the carbonyl or ester group.

Results and Discussion

It was found that cyclization of 3-aryl-1,2,4-triazines **1** with β-aminovinyl ketones and ethyl β-aminocrotonate **2** in acetic anhydride proceeded smoothly at room temperature and led to regioselective annelation of the pyrrole ring to form 3a,4,7,7a-tetrahydro-1*H*-pyrrolo[3,2-*e*]-1,2,4-triazines (**3a—g**) (Scheme 2).

Scheme 2



	a	b	c	d	e	f	g
R^1	Ph	*p*-MeO-C_6H_4	*p*-NO_2-C_6H_4	SCH_2Ph	Ph	Ph	SEt
R^2	OEt	OEt	OEt	OEt	Me	Ph	OEt

The structures of compounds **3a—g** were established based on ^{1}H and ^{13}C NMR spectroscopic data, including HETCOR and HMBC spectra. The presence of molecular ion peaks (M^+) in the mass spectra of compounds **3a—g** and elemental analysis of these compounds confirmed the formation of cyclic adducts of triazines with aminovinyl ketones and ethyl aminocrotonates with composition 1 : 1 (Table 1). The ^{1}H NMR spectra of compounds **3a—g**, in which signals for the bridgehead protons can readily be identified, are also indicative of annelation of the pyrrole ring but do not allow one to unambiguously establish its regio-orientation with respect to the 1,2,4-triazine moiety (Table 2). Thus, the ^{1}H NMR spectra of compounds **3a—g** have a signal for the H(3a) bridgehead proton at δ 4.36—4.85 as a doublet of doublets with the vicinal constants $^3J_{H(3a),H(7a)}$ = 8.2—8.8 and $^3J_{H(3a),N(4)H}$ = 1.0 Hz and the signal for the H(7a) bridgehead proton at δ 5.94—6.11 as a doublet of doublets with the vicinal constants $^3J_{H(7a),H(3a)}$ = 8.2—8.8 and $^3J_{H(7a),N(1)H}$ = 1.5 Hz. The vicinal constants $^3J_{H(7a),H(3a)}$ = 8.2—8.8 Hz are indicative of the *cis* orientation of the bridgehead hydrogen atoms upon annelation of the pyrrole ring and are in good agreement with the published data on tetrahydropyrazines and tetrahydro-1,2,4-triazines fused with five-membered heterocycles.[19] The ^{13}C NMR spectrum of compound **3c** has signals for the methine C(3a) and C(7a) atoms at δ 51.51 and 62.66, respectively, and signals for the quaternary C(2), C(3), and C(5) atoms at δ 143.06, 98.56, and 161.48, respectively. The spectra also show signals for the methyl, acyl, ester, and aryl groups in the corresponding regions, which is in good agreement with the structures of cycloadducts (Table 3). The conclusion about the regio-orientation of the pyrrole ring with respect to the 1,2,4-triazine ring was made based on the correlations observed in the 2D NOESY spectra. The N(4)H proton of the 1,2,4-triazine ring was reliably identified based on the cross-peaks with the *ortho*-protons of the aromatic substituent at the C(5) atom and the H(3a) bridgehead proton. The N(1)H proton of the pyrrole ring, in turn, gives cross-peaks with the bridgehead H(7a) proton and protons of the methyl group at the C(2) atom (Fig. 1).

Therefore, cyclization of 1,2,4-triazines **1** with aminovinyl ketones and ethyl aminocrotonates **2** afforded 3a,4,7,7a-tetrahydro-1*H*-pyrrolo[3,2-*e*]-1,2,4-triazines **3**. Earlier, derivatives of the same system have been prepared by the reactions of protonic and quaternary 1,2,4-triazinium salts with acetoacetamides[7,10] and *N,N*-ketene aminals.[9] Aminovinyl ketones and ethyl aminocrotonate were first used as C-C-N-synthons for the synthesis of 3a,4,7,7a-tetrahydro-1*H*-pyrrolo[3,2-*e*]-1,2,4-triazines. It should be noted that this reaction follows the rule found earlier. Thus, the pyrrole ring in the cycloadducts formed by the addition of dinucleophiles to 1,2,4-triazines[6,7,10] has an opposite orientation with respect to the *N*-alkyl (acyl) group compared to that observed in the products of analogous reactions of 1,4-diazinium salts.[4] Apparently, the reactions of 1,2,4-triazines in acetic anhydride involve the formation of the N(1)-acyl salt as the first step. This conclusion is indirectly confirmed by an experiment on dissolution of 3-phenyl-1,2,4-triazine in acetic anhydride giving rise to the product of addition of two acetate anions at positions 5 and 6 of the N(1)-acetyl-1,2,4-triazinium salt (Scheme 3).

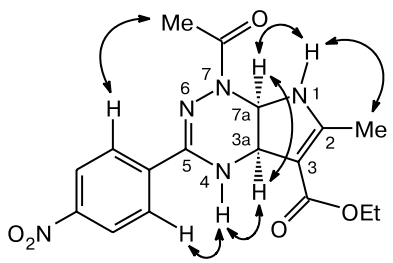


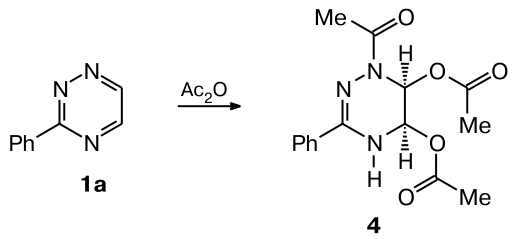
Fig. 1. Relationships in the ^{1}H—^{1}H NOESY spectra of compound **3c**.

Table 1. Reaction conditions, yields, melting points, elemental analysis data, and mass spectra of compounds **3a—g**, **4**, **5**, and **6a,e,f**

Compound	Reaction conditions		Yield (%)	M.p. /°C (solvent)*	Found / Calculated (%)			Molecular formula (mol. weight)	Mass spectrum, m/z (I_{rel} (%))
	Ac_2O /mL	τ/h			C	H	N		
3a	1	1	59	162—163	61.94 62.18	6.06 6.14	17.14 17.06	$C_{17}H_{20}N_4O_3$ (328.37)	329 $[M + 1]^+$ (20), 328 $[M]^+$ (100), 285 (29), 283 (24), 282 (74), 167 (28), 166 (25), 158 (20), 124 (31), 108 (43), 104 (72)
3b	2.5	6	58	190—192	60.28 60.32	6.10 6.19	15.63 15.63	$C_{18}H_{22}N_4O_4$ (358.40)	359 $[M + 1]^+$ (21), 358 $[M]^+$ (100), 315 (23), 312 (42), 166 (30), 134 (76), 124 (21), 108 (35)
3c	30	48	18	236—238	54.53 54.69	4.95 5.13	18.91 18.76	$C_{17}H_{19}N_5O_5$ (373.37)	373 $[M]^+$ (55), 330 (25), 327 (100), 167 (28), 166 (31), 153 (21), 124 (39), 108 (47), 103 (22)
3d	2.5	6	54	144—145	57.68 57.74	5.91 5.92	14.86 14.96	$C_{18}H_{22}N_4O_3S$ (374.47)	374 $[M]^+$ (51), 167 (31), 124 (21), 108 (27), 91 (100)
3e	1	1	49	215—217 (decomp.)	64.45 64.41	6.10 6.08	18.77 18.78	$C_{16}H_{18}N_4O_2$ (298.35)	298 $[M]^+$ (100), 255 (53), 152 (30), 137 (51), 124 (30), 123 (27), 108 (98), 104 (100), 82 (36), 77 (31)
3f	6	24	50	199—201 (decomp.)	69.93 69.98	5.64 5.59	15.54 15.54	$C_{21}H_{20}N_4O_2$ (360.42)	360 $[M]^+$ (86), 317 (34), 199 (36), 184 (44), 108 (44), 105 (100), 104 (62), 77 (54)
3g	2.5	1	13	142—143	49.92 49.98	6.40 6.45	17.93 17.93	$C_{13}H_{20}N_4O_3S$ (312.39)	313 $[M + 1]^+$ (100), 267 (45), 167 (64), 166 (33), 124 (43), 108 (52), 60 (29)
4	1	24	34	109—110	56.40 56.42	5.39 5.37	13.21 13.16	$C_{15}H_{17}N_3O_5$ (319.32)	319 $[M]^+$ (2), 259 (3), 158 (43), 129 (37), 103 (100), 76 (23), 60 (25)
5	—	—	17	242—243 (decomp.)	56.45 56.93	5.34 5.14	20.13 20.43	$C_{13}H_{14}N_4O_3$ (274.28)	274 $[M]^+$ (11), 231 (58), 190 (12), 189 (100), 174 (12), 146 (15), 104 (58), 77 (24)
6a	—	—	13	162—164 (propan-2-ol)	62.96 62.95	5.17 4.97	17.40 17.28	$C_{17}H_{16}N_4O_3$ (324.35)	325 $[M + 1]^+$ (20), 324 $[M]^+$ (100), 278 (20), 237 (80), 107 (17), 104 (16), 79 (27)
6e	—	—	13	172—173 (propan-2-ol)	65.31 65.30	4.77 4.79	19.19 19.04	$C_{16}H_{14}N_4O_2$ (294.32)	295 $[M + 1]^+$ (19), 294 $[M]^+$ (100), 253 (41), 123 (34), 104 (35), 95 (18), 52 (27)
6f	—	—	15	180—181 (ethanol)	70.75 70.78	4.50 4.53	15.81 15.72	$C_{21}H_{16}N_4O_2$ (356.39)	357 $[M + 1]^+$ (26), 356 $[M]^+$ (100), 315 (27), 157 (26), 105 (30), 102 (33), 77 (32)

* The solvent for crystallization.

Scheme 3



The structure of compound **4** was established based on ^1H and ^{13}C NMR spectroscopic data, including HETCOR, as well as on mass spectra. The ^1H NMR spectrum has a signal for the H(5) proton at δ 6.04 as a doublet of doublets with the vicinal constants $^3J_{H(5),NH}$ = 4.6 and $^3J_{H(5),H(6)}$ = 2.3 Hz and a signal for the H(6) proton at δ 7.15 as a doublet with the vicinal constant $^3J_{H(6),H(5)}$ = 2.3 Hz. The methyl groups of the acetate fragments as observed as a singlet at δ 2.07 and the *N*-acetyl group gives a signal at δ 2.47. The carbon atoms were reliably identified based on the HETCOR spectra; the signals for C(5) and C(6) are observed at δ 73.44 and 67.70, respectively.

With the aim of preparing aromatic fused systems, we studied oxidation of tetrahydropyrrolotriazines **3**. According to the published data, potassium permanganate is extremely efficient in dehydrogenation of dihydro- and tetrahydroazines.[20—22]

Table 2. Data from ^{1}H NMR spectroscopy (DMSO-d_6/CCl_4) of 3a,4,7,7a-tetrahydro-1*H*-pyrrolo[3,2-*e*]-1,2,4-triazines **3a—g**

Compound	δ (*J*/Hz)						
	COMe (s)	Me (s)	R^1	R^2	H(3a)	H(7a)	N(4)H N(1)H
3a*	2.27	2.07	7.11 (m, 3 H, Ph, *m*-H and *p*-H); 7.44 (m, 2 H, Ph, *o*-H)	1.23 (t, 3 H, $OCH_2C\underline{H}_3$, *J* = 7.1); 4.09 (q, 2 H, $OC\underline{H}_2CH_3$, *J* = 7.1)	4.61 (d, *J* = 8.6)	6.03 (dd, *J* = 8.6, *J* = 1.5)	6.69 (br.s); 7.59 (br.s)
3b	2.27	2.06	3.80 (s, 3 H, $C_6H_4OC\underline{H}_3$); 6.89 (d, 2 H, $C_6\underline{H}_4OCH_3$, *J* = 8.9);7.60 (d, 2 H, $C_6\underline{H}_4OCH_3$, *J* = 8.9)	1.27 (t, 3 H, $OCH_2C\underline{H}_3$, *J* = 7.0); 4.09 (q, 2 H, $OC\underline{H}_2CH_3$, *J* = 7.0)	4.57 (d, *J* = 8.6)	5.97 (d, *J* = 8.6)	6.31 (br.s); 7.52 (br.s)
3c*	2.30	2.08	7.99 (d, 2 H, $C_6H_4NO_2$, *J* = 9.1); 8.27 (d, 2 H, $C_6H_4NO_2$, *J* = 9.1)	1.24 (t, 3 H, $OCH_2C\underline{H}_3$, *J* = 7.1); 4.11, 4.07 (both dq, 2 H each, $OC\underline{H}_2CH_3$, AB system, J_{AB} = 10.7, *J* = 7.1)	4.55 (dd, *J* = 8.2, *J* = 1.0)	6.00 (dd, *J* = 8.2, *J* = 1.5)	7.07 (d, *J* = 1.0); 7.59 (d, *J* = 1.5)
3d	2.14	2.08	7.20—7.35 (m, 5 H, Ph); 4.14 (m, 2 H, SCH_2)	1.22 (t, 3 H, $OCH_2C\underline{H}_3$, *J* = 7.1); 4.05 (q, 2 H, $OC\underline{H}_2CH_3$, *J* = 7.1)	4.36 (d, *J* = 8.2)	5.94 (dd, *J* = 8.2, *J* = 1.5)	6.57 (br.s); 7.45 (br.s)
3e	2.29	2.14	7.36—7.39 (m, 3 H, Ph); 7.65—7.69 (m, 2 H, Ph)	2.14 (s, 3 H, CH_3)	4.65 (d, *J* = 8.6)	5.99 (dd, *J* = 8.6, *J* = 1.5)	6.57 (br.s); 7.91 (br.s)
3f	2.32	1.57	7.38—7.44 (m, 3 H, Ph); 7.66—7.70 (m, 2 H, Ph)	7.38—7.44 (m, 5 H, Ph)	4.85 (d, *J* = 8.5)	6.11 (d, *J* = 8.5)	6.63 (br.s); 8.26 (br.s)
3g	2.16	2.07	1.29 (t, 3 H, $SCH_2C\underline{H}_3$, *J* = 7.2); 2.78—3.00 (m, 2 H, $SC\underline{H}_2CH_3$, *J* = 7.2)	1.23 (t, 3 H, $OCH_2C\underline{H}_3$, *J* = 7.1); 3.99—4.11 (m, 2 H, $OC\underline{H}_2CH_3$, *J* = 7.1)	4.40 (d, *J* = 8.8)	5.95 (d, *J* = 8.8)	6.33 (br.s); 7.44 (br.s)

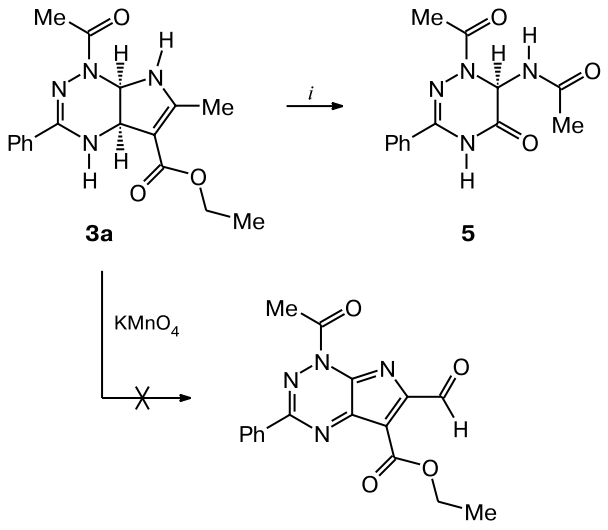
* The spectra were recorded in DMSO-d_6.

Table 3. Data from ^{13}C NMR spectroscopy (DMSO-d_6) of 3a,4,7,7a-tetrahydro-1*H*-pyrrolo[3,2-*e*]-1,2,4-triazines **3a,c**

Fragment	δ ($J_{C,H}$/Hz)	
	3a	**3c**
CH_3	13.50 (qd, *J* = 128.9, *J* = 1.2)	13.54 (qd, *J* = 129.2, *J* = 1.4)
$COOCH_2\underline{C}H_3$	14.58 (qt, *J* = 126.4, *J* = 2.5)	14.56 (qt, *J* = 126.4, *J* = 2.5)
$CO\underline{C}H_3$	21.21 (q, *J* = 128.9)	21.15 (q, *J* = 129.0)
C(3a)	51.51 (dd, *J* = 157.1, *J* = 5.2)	51.51 (dd, *J* = 157.1, *J* = 5.2)
$COO\underline{C}H_2CH_3$	58.04 (tq, *J* = 146.4, *J* = 4.5)	58.10 (tq, *J* = 146.4, *J* = 4.5)
C(7a)	62.80 (d, *J* = 160.9)	62.66 (d, *J* = 160.4)
C(3)	98.22 (m)	98.56 (m)
o-C	125.96 (ddd, *J* = 159.9, *J* = 8.3, *J* = 6.3)	127.38 (dd, *J* = 165.8, *J* = 7.0)
m-C	128.22 (dd, *J* = 159.2, *J* = 5.4)	123.30 (dd, *J* = 169.3, *J* = 4.8)
p-C	129.81 (dt, *J* = 162.2, *J* = 6.7)	147.98 (tt, *J* = 9.6, *J* = 3.3)
ipso-C	133.56 (t, *J* = 6.9)	139.52 (t, *J* = 7.8)
C(2)	145.44 (m)	143.06 (m)
C(5)	161.35 (dt, *J* = 6.7, *J* = 2.7)	161.48 (m)
$\underline{C}OOCH_2CH_3$	165.09 (t, *J* = 3.1)	164.94 (t, *J* = 2.7)
$\underline{C}OCH_3$	170.36 (qd, *J* = 6.4, *J* = 0.9)	170.57 (qd, *J* = 6.4, *J* = 0.8)

However, oxidation of tetrahydropyrrolo[3,2-*e*]-1,2,4-triazine **3a** by potassium permanganate led to destruction of the fused system to form trazinone **5** (Scheme 4). The ^{1}H NMR spectrum of trazinone **5** shows a resonance of the H(6) proton at δ 6.01, which is characteristic of hydrogenated structures, as a doublet with the constant of spin-spin coupling on the proton of the NH group *J* = 7.5 Hz.

Scheme 4



i. $KMnO_4$, Me_2CO, ~20 °C, 24 h.

An attempt to oxidize tetrahydropyrrolo[3,2-*e*]-1,2,4-triazines **3** to aromatic structures using a milder oxidizing agent, *viz.*, selenious acid, led to an unexpected result. Oxidation of 3-ethoxycarbonyl-2-methyl-5-phenyl-3a,4,7,7a-tetrahydro-1*H*-pyrrolo[3,2-*e*]-1,2,4-triazine (**3a**) by selenious acid in an aqueous—dioxane medium at 100 °C for 6 h afforded compound **6a** (Scheme 5), whose elemental composition and molecular weight ($M^+ = 324$) correspond to the molecular formula $C_{17}H_{16}N_4O_3$. The ^1H NMR spectrum of compound **6a** in deuteriochloroform revealed the presence of the ester and acetyl groups, the phenyl fragment, and a mobile proton, which disappears upon deuterium exchange. In the spectrum of this compound, signals for the bridgehead protons of the starting product **3a** are absent, but the spectrum has two doublets at δ 8.24 and 8.35 with the small constant J = 0.6 Hz (Tables 4 and 5).

Structurally similar products were prepared by oxidation of tetrahydropyrrolo[3,2-*e*]-1,2,4-triazines **3e,f** (see Table 4, Scheme 5). To establish the structures of oxi-

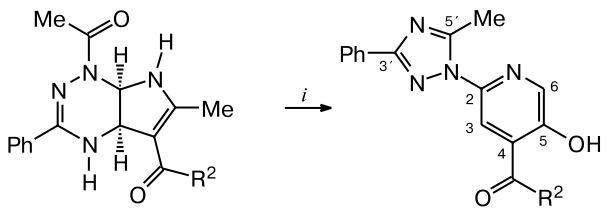
Table 4. Data from ^1H NMR spectroscopy ($CDCl_3$) of 5-hydroxy-2-(1*H*-1,2,4-triazol-1-yl)pyridines **6a,e,f**

Compound	R^2	δ ($J_{C,H}$/Hz)					
		Me (s)	Ph (m)	H(6), Py	H(3), Py	R^2	OH (s)
6a	OEt	2.84	7.41—7.48 (3 H); 8.16—8.18 (2 H)	8.35 (d, ^5J = 0.6)	8.24 (d, ^5J = 0.6)	1.48 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.2); 4.52 (q, 2 H, $C\underline{H}_2CH_3$, J = 7.2)	10.43
6e	Me	2.87	7.41—7.49 (3 H); 8.16—8.18 (2 H)	8.39 (s)	8.19 (s)	2.80 (s, 3 H, Me)	11.51
6f	Ph	2.87	7.39—7.44 (3 H); 8.07—8.09 (2 H)	8.47 (s)	8.09 (s)	7.59—7.63 (m, 2 H); 7.70—7.74 (m, 1 H); 7.83—7.85 (m, 2 H)	11.09

Table 5. Data from ^{13}C and ^1H NMR spectroscopy (400 and 100 MHz, $CDCl_3$, δ, $J_{C,H}$/Hz) of compound **6a**

Fragment	^{13}C ($J_{C,H}$)	^1H (HETCOR)	HMBC cross-peaks
$COCH_2\underline{C}H_3$	14.10 (qt, J = 127.7, J = 2.7)	1.48 (t, J = 7.2)	4.52 (OCH_2)
CH_3	15.14 (q, J = 130.8)	2.84 (s)	—
$CO\underline{C}H_2CH_3$	62.86 (td, J = 149.3, J = 4.4)	4.52 (q, J = 7.2)	1.48 (H(9))
C(3)	115.15 (dd, J = 172.4)	8.24 (d, J = 0.6)	—
C(4)	120.69 (ddd, J = 4.7, J = 3.9)	—	8.35 (H(6)), 10.43 (OH)
o-C	126.48 (dm, J = 160.9)	8.17 (m)	8.17 (*o*-H′), 7.41 (*p*-H)
m-C	128.54 (ddd, J = 160.1, J = 7.4)	7.45 (m)	7.45 (*m*-H′)
p-C	129.38 (dt, J = 160.5, J = 8.2)	7.41 (m)	8.17 (*o*-H)
ipso-C	130.64 (t, J = 7.5)	—	7.45 (*m*-H)
C(6)	139.29 (dd, J = 185.2, J = 8.6)	8.35 (d, J = 0.6)	10.43 (OH)
C(2)	143.50 (dd, J = 13.0, J = 1.9)	—	8.35 (H(6))
C(5′)	154.02 (q, J = 7.5)	—	2.84 (H(6′))
C(5)	154.75 (ddd, J = 6.5, J = 4.4, J = 4.4)	—	8.24 (H(3)), 10.43 (OH), 8.35 (H(6))
C(3′)	160.86 (t, J = 4.4)	—	8.17 (*o*-H)
$\underline{C}OCH_2CH_3$	168.24 (dtd, J = 4.8, J = 3.1, J = 1.8)	—	4.52 (OCH_2), 8.24 (H(3))
OH	—	10.43 (s)	

Scheme 5



3a,e,f **6a,e,f**

R^2 = OEt (**a**), Me (**e**), Ph (**f**)

i. H_2SeO_3, dioxane, 100 °C, 6 h.

dized products **6**, we carried out X-ray diffraction study of compound **6a** and found that both heterocycles in 3-ethoxycarbonyl-2-methyl-5-phenyl-3a,4,7,7a-tetrahydro-1*H*-pyrrolo[3,2-*e*]-1,2,4-triazine (**3a**) underwent ring transformations upon oxidation of this compound by selenious acid, the 1,2,4-triazine ring being contracted to the triazole ring, while the pyrrole ring being expanded to the pyridine ring (Fig. 2, Tables 6 and 7). The triazole and pyridine rings are planar within 0.007(4) and 0.009(3) Å, respectively. The dihedral angles between the planes of the triazole, pyridine, and benzene rings are 13.7(2), 6.2(2), and 8.9(2)°, respectively. Therefore, molecule **6a** is approximately planar. In this molecule, a conjugated system can occur involving three aromatic rings and the carbonyl group at the C(4) atom, which also lies in the plane of the pyridine ring. The distribution of the bond lengths in the molecule is indicative of the presence of a long conjugation chain. In the crystal, molecules **6a** are linked in centrosymmetrical dimers through the O(5)—H(5)...O(12)′ hydrogen bonds ($-1-x$, $1-y$, $-z$).

Table 6. Selected bond lengths (*d*) in the structure of **6a**

Bond	*d*/Å	Bond	*d*/Å
O(5)—C(5)	1.358(4)	C(14)—C(15)	1.471(6)
O(12)—C(12)	1.218(4)	C(14)—H(141)	0.93(3)
O(13)—O(12)	1.316(4)	C(14)—H(142)	0.91(3)
O(13)—C(14)	1.453(5)	C(15)—H(151)	0.94(2)
N(1)—C(2)	1.319(4)	C(15)—H(152)	1.07(4)
N(1)—C(6)	1.333(4)	C(15)—H(153)	0.97(4)
N(7)—N(8)	1.368(4)	C(16)—C(17)	1.372(5)
N(7)—N(2)	1.433(4)	C(16)—C(21)	1.379(5)
N(7)—N(11)	1.353(4)	C(17)—C(18)	1.385(5)
N(8)—N(9)	1.320(4)	C(17)—H(17)	0.98(2)
N(10)—C(9)	1.357(4)	C(18)—C(19)	1.372(5)
N(10)—C(11)	1.315(4)	C(18)—H(18)	0.95(3)
C(2)—C(3)	1.356(4)	C(19)—C(20)	1.353(6)
C(3)—C(4)	1.389(4)	C(19)—H(19)	0.99(3)
C(3)—H(3)	0.92(2)	C(20)—C(21)	1.377(5)
C(4)—C(5)	1.388(5)	C(20)—H(20)	0.90(3)
C(4)—C(12)	1.463(5)	C(21)—H(21)	0.86(2)
C(5)—C(6)	1.375(5)	C(22)—H(221)	1.01(4)
C(6)—H(6)	0.94(3)	C(22)—H(222)	0.92(3)
C(9)—C(16)	1.456(5)	C(22)—H(223)	0.88(3)
C(11)—C(22)	1.487(5)		

The parameters of this bond are as follows: O(5)—H(5), 0.84(2) Å; H(5)...O(12)′, 2.48(2) Å; O(5)...O(12)′, 3.079(3) Å; O(5)—H(5)...O(12)′, 129(2)°. In molecule **6a**, there is the intramolecular O(5)—H(5)...O(12) hydrogen bond with the following parameters: H(5)...O(12), 1.92(2) Å; O(5)...O(12), 2.671(3) Å; O(5)—H(5)...O(12), 149(2)°. The hydrogen bonds in the crystal are shown in Fig. 3.

In addition to the hydrogen bonds observed in the crystal of **6a**, there are also numerous short contacts be-

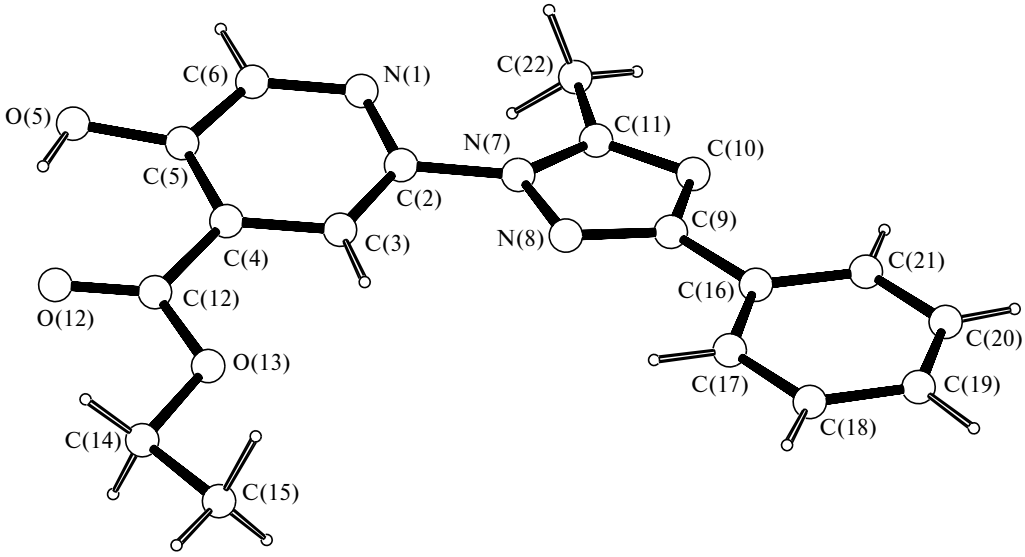


Fig. 2. Overall view of molecule **6a** in the crystal.

Table 7. Selected bond angles (ω) in the structure of **6a**

Angle	ω/deg	Angle	ω/deg	Angle	ω/deg
C(12)—O(13)—C(14)	116.9(3)	C(17)—C(160—C(21)	117.1(3)	O(13)—C(14)—H(142)	106(2)
C(2)—N(1)—C(6)	115.8(3)	C(16)—C(17)—C(18)	121.8(3)	C(15)—C(14)—H(141)	104(2)
N(8)—N(7)—C(2)	118.2(2)	C(16)—C(17)—H(17)	122(1)	C(15)—C(14)—H(142)	123(2)
N(8)—N(7)—C(11)	109.6(2)	C(18)—C(17)—H(17)	116(1)	H(141)—C(14)—H(142)	108(3)
C(2)—N(7)—C(11)	132.1(3)	C(17)—C(18)—C(19)	119.8(3)	C(14)—C(15)—H(151)	107(1)
N(7)—N(8)—C(9)	102.2(2)	C(17)—C(18)—H(18)	118(2)	C(14)—C(15)—H(152)	102(2)
C(9)—N(10)—C(11)	103.6(3)	C(19)—C(18)—H(18)	122(2)	C(14)—C(15)—H(153)	105(2)
N(1)—C(2)—N(7)	115.2(3)	C(18)—C(19)—C(20)	119.1(3)	H(151)—C(15)—H(152)	109(3)
N(1)—C(2)—C(3)	125.2(3)	C(18)—C(19)—H(19)	118(2)	H(151)—C(15)—H(153)	116(3)
N(7)—C(2)—C(3)	119.6(3)	C(20)—C(19)—H(19)	123(2)	H(152)—C(15)—H(153)	116(3)
C(2)—C(3)—C(4)	119.0(3)	C(19)—C(20)—C(21)	121.0(3)	C(9)—C(16)—C(17)	121.0(3)
C(2)—C(3)—H(3)	128(1)	N(8)—C(9)—N(10)	114.8(3)	C(19)—C(20)—H(20)	124(2)
C(4)—C(3)—H(3)	113(1)	N(8)—C(9)—C(16)	122.6(3)	C(21)—C(20)—H(20)	115(2)
C(3)—C(4)—C(5)	117.3(3)	N(10)—C(9)—C(16)	122.6(3)	C(16)—C(21)—C(20)	121.2(3)
C(3)—C(4)—C(12)	122.1(3)	N(7)—C(11)—N(10)	109.7(3)	C(16)—C(21)—H(21)	119(1)
C(5)—C(4)—C(12)	120.6(3)	N(7)—C(11)—C(22)	125.4(3)	C(20)—C(21)—H(21)	120(1)
O(5)—C(5)—C(4)	124.7(3)	N(10)—C(11)—C(22)	124.9(3)	C(11)—C(22)—H(221)	108(2)
O(5)—C(5)—C(6)	116.8(3)	O(12)—C(12)—O(13)	123.0(3)	C(11)—C(22)—H(222)	105(2)
C(4)—C(5)—C(6)	118.5(3)	O(12)—C(12)—C(4)	123.2(3)	C(11)—C(22)—H(223)	109(2)
N(1)—C(6)—C(5)	124.3(3)	O(13)—C(12)—C(4)	113.9(3)	H(221)—C(22)—H(222)	106(3)
N(1)—C(6)—H(6)	119(2)	O(13)—C(14)—C(15)	106.7(3)	H(221)—C(22)—H(223)	115(3)
C(5)—C(6)—H(6)	117(2)	O(13)—C(14)—H(141)	109(2)	H(222)—C(22)—H(223)	113(3)
C(9)—C(16)—C(21)	121.8(3)				

tween the π-systems of the aromatic rings (π—π interactions). The latter contacts are, apparently, responsible for a layered type of the molecular packing in the crystal (Fig. 4).

The formation of 4-carbonyl-substituted 5-hydroxy-2-triazolylpyridines accounts for the appearance of two signals in the ^{1}H NMR spectra, which correspond to the H(3) and H(6) protons of the pyridine ring with $J_{H(3),H(6)}$ = 0.6 Hz. The spectroscopic characteristics of compounds **6a,e,f** are given in Tables 4 and 5.

Apparently, oxidative recyclization of tetrahydropyrrolotriazines **3a,e,f** involves oxidation of the methyl group to the aldehyde moiety under the action of selenious acid followed by hydration and acid-catalyzed dehydration giving rise to the carbocation. Then the pyrrole ring is expanded through the 1,2-sigmatropic shift to this electron-deficient carbon atom, which is typical of many rearrangements. Opening of the 1,2,4-triazine ring and its recyclization to form the triazole ring as well as aromatization of the pyridine ring complete the formation of 5-hydroxy-2-triazolylpyridines **6a,e,f** (Scheme 6). In the triazine ring, analogous recyclizations were observed in the reactions of 3-aryl-1,2,4-triazin-5(2*H*)-ones with *N*-alkylureas in acetic anhydride upon heating.[23]

To summarize, the reactions of 3-aryl-1,2,4-triazines with aminovinyl ketones or ethyl aminocrotonates in

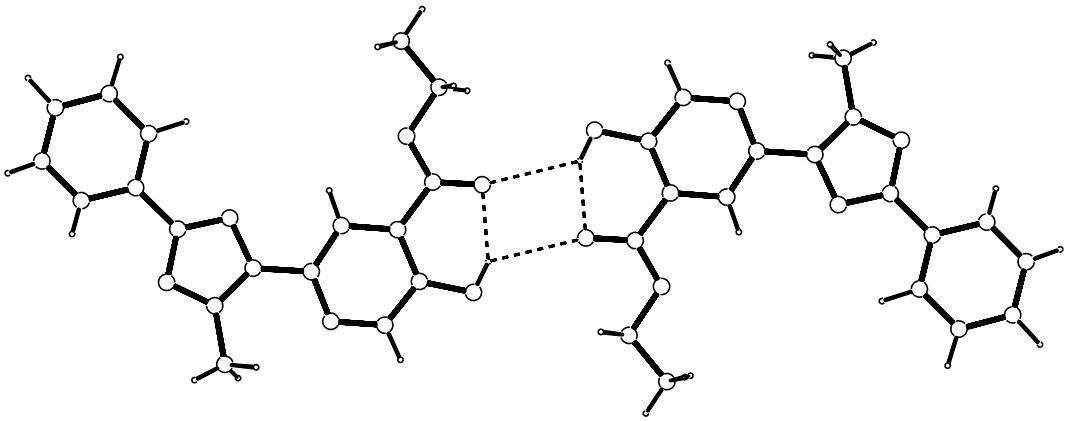


Fig. 3. System of hydrogen bonds in the crystal of **6a**. Hydrogen bonds are indicated by dashed lines.

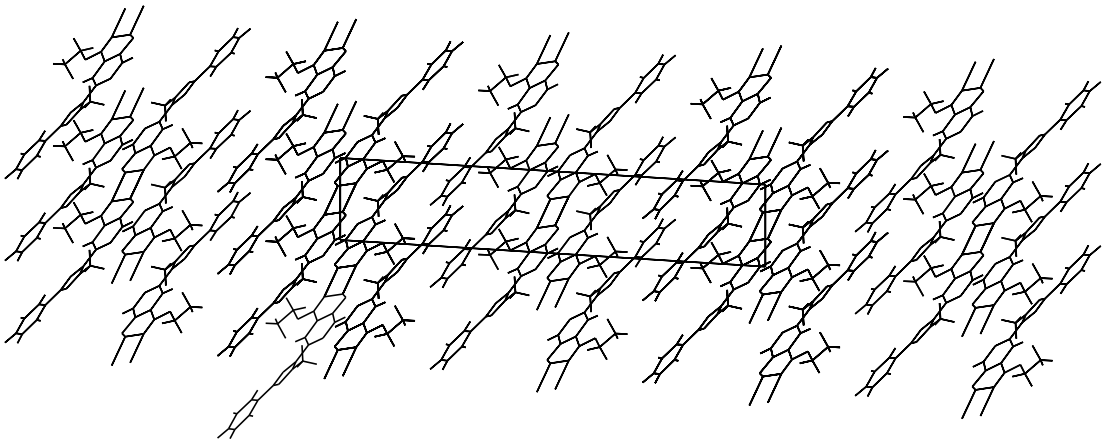
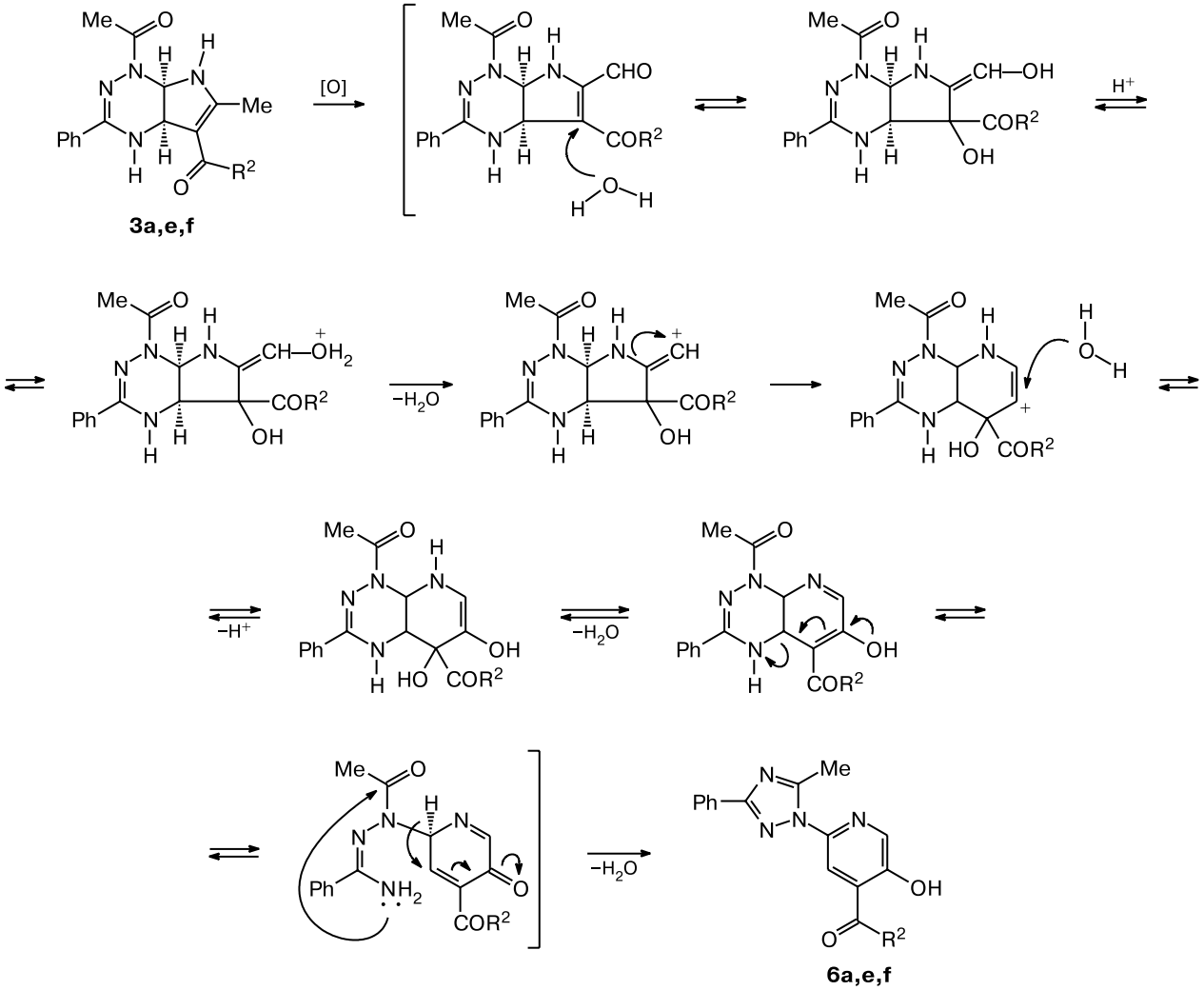


Fig. 4. Molecular packing in the crystal of **6a** projected along the axis *b*.

Scheme 6



acetic anhydride at room temperature serve as a convenient procedure for the preparation of 3a,4,7,7a-tetrahydro-1*H*-pyrrolo[3,2-*e*]-1,2,4-triazines, which are transformed into 4-carbonyl-substituted 5-hydroxy-2-triazolylpyridines under the action of selenious acid. The above-described transformations belong to an unusual type of simultaneous transformations of two heterocycles of the bicyclic system, the six-membered triazine ring being contracted to the triazole ring, while the five-membered pyrrole ring being expanded to the pyridine ring.

Experimental

The ^{1}H and ^{13}C NMR spectra in DMSO-d_6 and $CDCl_3$ were recorded on Bruker DRX-400 (400.13 and 100.61 MHz for ^{1}H and ^{13}C, respectively) and Bruker WP-250 (250.13 MHz for ^{1}H) spectrometers with Me_4Si as the internal standard. The mass spectra were obtained on a Varian MAT-311A spectrometer with direct inlet of the sample into the ion source; the accelerating voltage was 3 kV; the energy of ionizing electrons was 70 eV. The course of the reactions and purities of the products were monitored by TLC on Silufol UV-254 plates.

The yields, melting points, elemental analysis data, and spectroscopic characteristics of the compounds synthesized are given in Tables 1—5.

3-Aryl-1,2,4-triazines **1** were prepared according to a known procedure.[24] Aminovinyl ketones and ethyl β-aminocrotonate **2** were synthesized according to a procedure described earlier.[25]

3a,4,7,7a-Tetrahydro-1*H*-pyrrolo[3,2-*e*]-1,2,4-triazines (3a—g) (general procedure). β-Aminovinyl ketone or ethyl β-aminocrotonate **2** (3.2 mmol) was added to a solution or suspension of 3-substituted 1,2,4-triazine **1** (3.2 mmol) in acetic anhydride depending on the substrate. The reaction mixture was stirred at ~20 °C for 1 h—2 days. The precipitate that formed was filtered off, washed with a small amount of acetic anhydride and diethyl ether, and dried in air.

5,6-Diacetoxy-1-acetyl-3-phenyl-1,2,4-triazine (4). 1,2,4-Triazine **1a** (2 mmol) was dissolved in acetic anhydride (1 mL). The resulting solution was stirred at ~20 °C for one day. The precipitate that formed was filtered off and washed with diethyl ether. ^{1}H NMR, δ: 2.07 (s, 6 H, 2 $OCOCH_3$); 2.47 (s, 3 H, $COCH_3$); 6.04 (dd, 1 H, H(5), J = 4.6 Hz, J = 2.3 Hz); 6.27 (d, 1 H, NH, J = 4.6 Hz); 7.15 (d, 1 H, H(6), J = 2.3 Hz); 7.40—7.50 (m, 3 H, Ph, *m*-H and *p*-H); 7.50—7.70 (m, 2 H, Ph, *o*-H). ^{13}C NMR, δ: 20.80 (q, $OCOCH_3$, J = 130.4 Hz); 21.05 (q, $OCOCH_3$, J = 130.4 Hz); 21.16 (q, $COCH_3$, J = 129.9 Hz); 67.70 (d, C(6), J = 172.2 Hz); 73.44 (d, C(5), J = 171.6 Hz); 125.56 (d, Ph, *o*-C, J = 159.3 Hz); 128.76 (d, Ph, *m*-C, J = 162.4 Hz); 130.60 (dt, Ph, *p*-C, J = 161.7 Hz, J = 8.0 Hz); 132.16 (t, Ph, *ipso*-C, J = 7.4 Hz); 140.66 (m, C(3)); 169.42 (qd, $COCH_3$, J = 7.4 Hz, J = 2.9 Hz); 171.03 (qd, $OCOCH_3$, J = 7.2 Hz, J = 2.7 Hz); 172.11 (q, $OCOCH_3$, J = 7.0 Hz).

1-Acetyl-6-acetylamino-3-phenyl-1,4-dihydro-1,2,4-triazin-5-one (5). 1*H*-Pyrrolo[3,2-*e*]-1,2,4-triazine **3a** (560 mg, 1.71 mmol) was added to a solution of potassium permanganate (540 mg, 3.42 mmol) in acetone (100 mL). The reaction mixture was stirred at ~20 °C for 24 h and then filtered off from MnO_2. The mother liquor was evaporated on a rotary evaporator. The product was purified by gravitational column chromatography (silica gel, $CHCl_3$—acetone, 3 : 1). The starting compound **3a** (R_f = 0.48) and trazinone **5** (R_f = 0.17) were isolated in yields of 63 and 81 mg, respectively. ^{1}H NMR, δ: 1.79 (s, 3 H, $COCH_3$); 2.31 (s, 3 H, $COCH_3$); 6.01 (d, 1 H, H(6), J = 7.5 Hz); 7.40—7.50 (m, 3 H, Ph, *m*-H and *p*-H); 7.80—7.90 (m, 2 H, Ph, *o*-H); 9.01 (d, 1 H, NH, J = 7.5 Hz); 11.41 (s, 1 H, NH).

Oxidation of 1*H*-pyrrolo[3,2-*e*]-1,2,4-triazines 3a,e,f H_2SeO_3 (general procedure). Selenious acid (10.35 mmol) was dissolved in 95% aqueous dioxane (100 mL) at 50 °C and then a solution of 1*H*-pyrrolo[3,2-*e*]-1,2,4-triazine **3a,e,f** (5.18 mmol) in 95% aqueous dioxane was added. The resulting solution was brought to reflux and kept for 6 h. After 12 h, the reaction mixture was filtered off from a precipitate of selenium.

4-Ethoxycarbonyl-5-hydroxy-2-(5′-methyl-3′-phenyl-1*H*-1,2,4-triazol-1-yl)pyridine (6a). The resulting mother liquor was evaporated on a rotary evaporator and the oil was suspended in propan-2-ol. The precipitate was filtered off and purified by flash chromatography on a dry column. The product was eluted with three portions (3×20 mL) of a 3 : 1 $CHCl_3$—acetone mixture. The fractions were combined, the solvent was evaporated, and the residue was recrystallized from propan-2-ol.

4-Acetyl-5-hydroxy-2-(5′-methyl-3′-phenyl-1*H*-1,2,4-triazol-1-yl)pyridine (6e). The mother liquor was concentrated with silica gel on a rotary evaporator. The product was isolated by gravitational column chromatography (silica gel; $CHCl_3$—ethyl acetate, 10 : 1; R_f = 0.38) and recrystallized from propan-2-ol.

4-Benzoyl-5-hydroxy-2-(5′-methyl-3′-phenyl-1*H*-1,2,4-triazol-1-yl)pyridine (6f). The mother liquor was concentrated on a rotary evaporator. The product was isolated by flash chromatography on a dry column by eluting with five portions (5×20 mL) of a 3 : 1 $CHCl_3$—acetone mixture, R_f = 0.48. The fractions were combined, the solvent was evaporated, and the precipitate was recrystallized from ethanol.

X-ray diffraction study of compound 6a was carried out at the Department of X-ray Diffraction Studies of the Spectral and Analytical Center of the Collaborative Use of the Russian Foundation for Basic Research based on the A. E. Arbuzov Institute of Organic and Physical Chemistry of the Kazan Research Center of the Russian Academy of Sciences (Project No. 00-03-40133).

The crystals of **6a**, $C_{17}H_{16}N_4O_3$, m.p. 162—164 °C, belong to the monoclinic system. At 20 °C, a = 5.245(5) Å, b = 11.261(3) Å, c = 27.22(1) Å, β = 93.58(7)°, V = 1604(2) Å^3, Z = 4, d_{calc} = 1.34 g cm^{-3}, space group $P2_1/c$. The unit cell parameters and intensities of 4954 reflections, of which 1777 reflections were with $I \geq 3\sigma$, were measured on an automated four-circle Enraf-Nonius CAD-4 diffractometer (λ(Mo-Kα), graphite monochromator, ω/2θ scanning technique, θ ≤ 26.9°). The intensities of three check reflections showed no decrease in the course of X-ray data collection. Absorption was ignored (μ(Mo-Kα) = 0.89 cm^{-1}). The structure was solved by direct methods using the SIR program[26] and refined first isotropically and then anisotropically. The H atoms were revealed from difference electron density syntheses and refined isotropically at the final stage. The final reliability factors were as follows: R = 0.045, R_w = 0.047 using 1766 independent reflections with $F^2 \geq 3\sigma$. All calculations were carried out using the MOLEN program package[27] on an Alpha Station 200 computer. The molecules were drawn and the intermolecular interactions were analyzed using the PLATON program.[28]

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