CYCLIZATION OF AZINIUM CATIONS WITH BIFUNCTIONAL NUCLEOPHILES.

27. ACETOACETAMIDES IN SYNTHESIS OF DERIVATIVES OF A NEW HETEROCYCLIC SYSTEM OF PYRROLO[3,2-e]-1,2,4-TRIAZINE‡

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Reactions of nucleophilic diaddition to 1,2,4-triazines have been reported in recent years [2-6], but attempts to obtain condensed 1,2,4-triazines by reactions with aromatic ortho-diamines were unsuccessful due to the low stability of the cyclic adducts formed [2, 7]. In the present work, we report the successful application of the diaddition reaction of bifunctional nucleophiles to the triazine ring resulting in the synthesis of a new condensed system.

It was found that 4,4a,5,6,7,7a-hexahydro-6-oxo-1H-pyrrolo-[3,2-e]-1,2,4-triazines (IIIa-h) (Table 1) are formed in good yields by reacting 3-morpholino-1-ethyl-1,2,4-triazinium borofluoride (I) with acetoacetamides (AAA) (IIa-h) in alcohol. The structure of compounds (IIIa-h) was established on the basis of spectral data. In the ^{1}H NMR spectra of compounds (IIIa-h), the signal of the H^{4a} proton is in the form of a doublet of doublets with vicinal constants of $^3J_{4a,5}$ = 2.6-4.4 and $^3J_{4a,7a}$ = 7.4-8.6 Hz (Table 2), the components of which are broadened due to spin–spin coupling between the H^{4a} and NH^4 protons. The latter is confirmed by double resonance and leads to the conclusion that the annelated pyrrole ring is regioorientated, indicating the formation of pyrrolo[3,2-e]-1,2,4-triazines (IIIa-h) and not their isomeric pyrrolo[2,3-e]-1,2,4-triazines. For compounds (IIIa, h), ^{13}C NMR spectra were also obtained in DMSO-d_6 (Table 3). In these spectra, signals are observed of methine C^6, C^{4a}, and C^{7a} carbon atoms in the 42-77 ppm region, of the C^3 and C^6 quaternary carbon atoms, and also of the Ac, morpholino and Et groups in the corresponding

TABLE 1. Properties of Compounds (III), (V), and (VI)

Compound	Mp, °C (dec.)	Found, %			Empirical formula	Calculation, %			Yield,* %
		C	H	N		C	H	N	
(IIIa)	181–185	49,8	5,7	15,0	$C_{19}H_{25}N_5O_3\cdot HBF_4$	49,7	5,7	15,3	92(53)
(IIIb)	189–190	50,5	6,0	14,6	$C_{20}H_{27}N_5O_3\cdot HBF_4$	50,8	6,0	14,8	95(74)
(IIIc)	173–175	42,4	4,8	13,0	$C_{19}H_{24}BrN_5O_3\cdot HBF_4$	42,4	4,7	13,0	86(49)
(IIId)	181–183	49,0	5,7	14,4	$C_{20}H_{27}N_5O_4\cdot HBF_4$	49,1	5,8	14,3	95(64)
(IIIe)	119–121	48,7	5,7	14,6	$C_{20}H_{27}N_5O_4\cdot HBF_4$	49,1	5,8	14,3	76(58)
(IIIf)	138–140	47,1	5,5	17,9	$C_{18}H_{24}N_6O_3\cdot HBF_4$	47,0	5,5	18,3	65(57)
(IIIg)	150–152	46,4	5,5	18,2	$C_{18}H_{24}N_6O_3\cdot HBF_4$	47,0	5,5	18,3	79(37)
(IIIh)	198–202	51,0	6,0	14,9	$C_{20}H_{28}N_5O_3\cdot HBF_4$	50,8	6,0	14,8	72(51)
(Va)	132–135	45,6	4,0	13,4	$C_{14}H_{16}N_4O_2\cdot CF_3COOH$	45,9	4,1	13,4	68(28)
(Vb)	132–135	47,6	4,2	12,9	$C_{15}H_{18}N_4O_2S\cdot CF_3COOH$	47,2	4,4	13,0	57(45)
(Vd)	117–118	45,6	4,3	12,6	$C_{15}H_{18}N_4O_3S\cdot CF_3COOH$	45,5	4,3	12,6	94(29)
(Vc)	163–168	46,0	4,5	12,6	$C_{15}H_{18}N_4O_3S\cdot CF_3COOH$	45,5	4,3	12,6	87(20)
(Vf)	124–125	43,2	3,8	16,8	$C_{13}H_{15}N_5O_2S\cdot CF_2COOH$	43,0	3,9	16,7	59(34)
(VIa)	159–162	50,4	4,5	21,3	$C_{14}H_{15}N_5O_3S$	50,4	4,5	21,0	85(59)
(VIb)	154–157	51,7	4,9	20,1	$C_{15}H_{17}N_5O_3S$	51,9	4,9	20,2	93(42)
(VIc)†	141–142	40,8	3,6	17,1	$C_{14}H_{14}BrN_5O_3S$	40,8	3,4	17,0	79(34)
(VId)†	152–154	48,1	4,5	19,7	$C_{14}H_{15}N_5O_4S$	48,1	4,3	20,0	77(56)

*Yield of crude product, in brackets of analytical sample.
†Pyrrolotriazines (Vc, g) were converted without preliminary purification into nitroso compounds (VIc, d).

‡For previous communication, see [1].

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TABLE 2. ^1H NMR Spectroscopy Data for Compounds (III), (IV), and (VI) in DMSO-d_6 at 20°C

Compound	δ, ppm				SSCC, Hz		Tautomer B, %
	H^{4a}, br.d.d	H^5, d	H^{7a}, d	H^4, br.s	$^3J_{5,4a}$	$^3J_{4a,7a}$	
(IIIa)	4,75	4,26	5,80	8,98	2,9	8,3	80
(IIIb)	4,72	4,27	5,72	9,00	2,9	7,9	90
(IIIc)	4,74	4,26	5,78	8,97	2,9	8,0	80
(IIId)	4,74	4,21	5,64	8,95	2,8	8,1	80
(IIIe)	4,77	4,18	5,44	8,90	2,6	7,4	90
(IIIf)	5,00	4,46	6,16	9,12	2,4	8,6	80
(IIIg)	4,77	4,32	5,84	9,04	2,4	8,4	80
(IIIh)	4,76	4,10	4,52	8,93	2,9	7,6	95
(Va)	4,57	4,15	5,48	*	4,4	5,9	70
(Vb)	4,55	4,12	5,41	*	4,4	5,7	90
(Vc)	4,57	4,13	5,48	*	4,4	5,8	85
(Vd)	4,58	4,11	5,36	*	4,1	5,9	80
(Ve)	4,52	4,03	5,31	*	2,3	5,5	95
(Vf)	4,59	4,26	5,67	*	6,2	5,8	80
(Vg)	4,56	4,05	5,35	*	2,6	5,9	95
(VIa)	4,83 †	3,97 ‡	6,80	8,34	–	5,4	90
(VIb)	4,80 †	3,99 ‡	6,77	8,33	–	5,4	90
(VIc)	4,87	4,01	6,95	8,30	1,3	5,4	85
(VId)	4,84 †	3,96 ‡	**	8,23	–	5,4	90

*Because of exchange processes with the participation of CF_3-COOH and broadening, the intensity of the NH-proton signals is commensurable with the noise level.
†Broadened doublet.
‡Broadened singlet.
**The signal of the H^{7a} proton overlaps with the absorption of aromatic protons.

TABLE 3. Data of ^{13}C NMR Spectra for Pyrrolotriazines (III), (V), and (VI) in DMSO-d_6

Compound	δ, ppm ($^1J_{(C,H)}$, Hz)						
	C^3	C^{4a}	C^5	C^6	C^{7a}	$COCH_3$	$\underline{C}OCH_3$
(IIIa)	154,25	44,95 (153,1)	63,67 (137,5)	166,30	76,09 (155,0)	29,81	101,08
(IIIh)	154,00	45,80 (153,8)	63,49 (140,4)	166,60	73,79 (158,7)	29,93	201,80
(Va)	161,67	49,60 (159,5)	62,30 (140,4)	166,89	68,07 (164,8)	30,33	201,30
(Vb)	162,15	49,67 (158,3)	62,24 (138,8)	166,86	68,28 (165,1)	30,32	201,45
(Vf)	162,92	49,41 (~152)	62,88 (~140)	167,63	65,63 (~172)	30,55	201,47
(VIa)	154,35	50,44 (161,1)	63,47 (141,6)	166,76	70,74 (168,5)	29,96	200,87
(VIb)	154,35	50,47 (162,8)	63,47 (141,4)	166,83	70,95 (168,0)	29,96	201,16
(VIc)	154,41	59,32 (160,5)	63,35 (140,4)	166,70	70,43 (167,2)	29,85	200,45

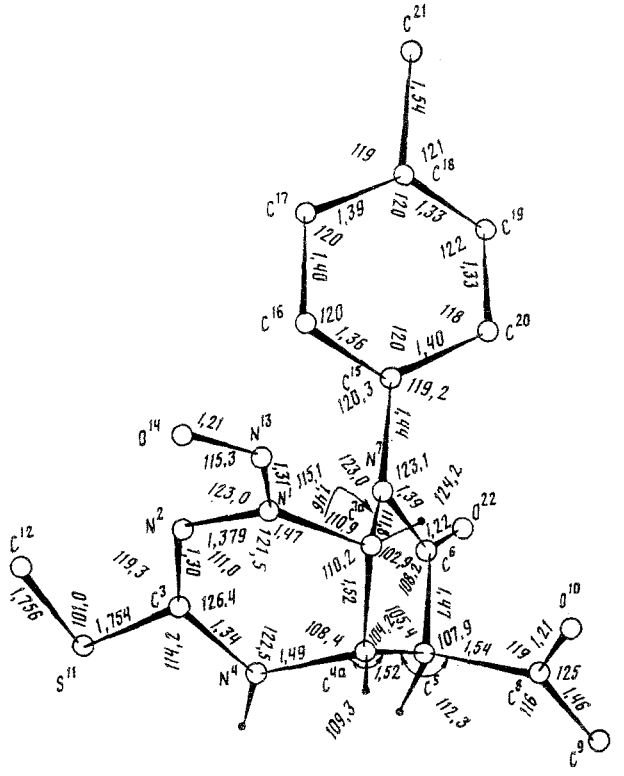
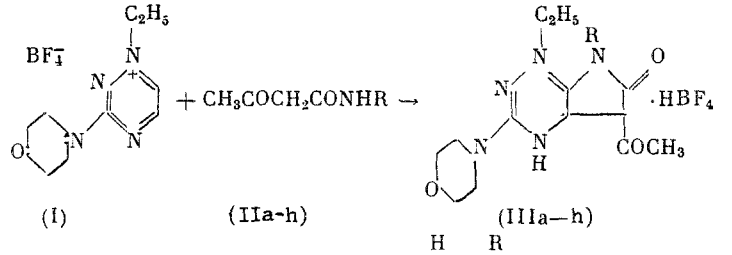
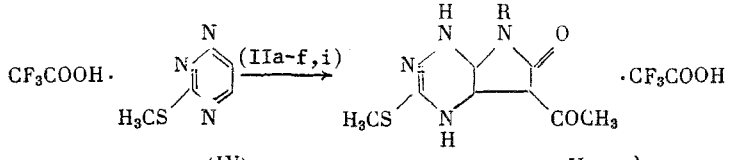


Fig. 1. Projection of molecule of compound (VIb) on a plane.

regions of the spectrum (Table 3)



(I) (IIa-h) (IIIa—h)



(IV) (Va—g)

R = Ph (IIa), (IIIa), (Va); $C_6H_4CH_3$-4 (IIb), (IIIb), (Vb); C_6H_4Br-4 (IIb), (IIIc), (Vc); $C_6H_4OCH_3$-4 (IId), (IIId), (Vd); $C_6H_4OCH_3$-2 (IIe), (IIIe), (Ve); Py-2 (IIf), (IIIf), (Vf); Py-3 (IIg), (IIIg); $C_6H_5CH_2$ (IIh), (IIIh); C_6H_4OH-2 (IIi), (Vg).

3-Methylthio-1,2,4-triazine (IV) also reacts with the AAA (IIa-f, i), if the reaction is carried out in $CHCl_3$ in the presence of CF_3COOH. In the preceding investigations [2, 8] it was shown that under these conditions (IV) is protonated preferentially at the N^1 atom, and thus the protonic salt (IV) can be regarded as an analog of the quaternary salt (I). In fact, the AAA (IIa-f, i) form with (IV) products (Va-g) having a similar structure as those in the reaction with 1-ethyltriazinium (I). Pyrrolotriazines (Va-g) were obtained in the form of crystalline trifluoroacetates (Table 1). In DMSO and CH_3OH solutions they partially dissociate to the corresponding bases and CF_3COOH, whereby, because of the exchange processes, the signal of the NH^4 proton cannot be detected in the PMR spectra. Thus, it is impossible to establish the regioorientation of the pyrrole ring in compounds (Va-g) from the PMR spectroscopy data. To determine their structure, we studied the ^{13}C NMR spectra of compounds (Va, b, f) (Table 3). The assignment of the C^{4a}, C^5, and C^{7a} signals was made on the basis of experiments on the selective uncoupling of the HFI of carbons with corresponding protons. In the ^{13}C NMR spectra of monocyclic 1,2,4-triazines, the $^3J_{C^3,H^5}$ con-

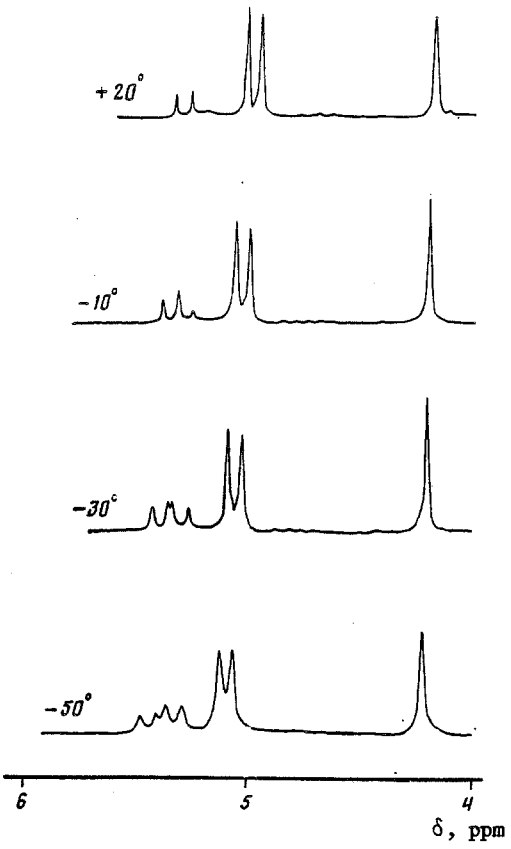
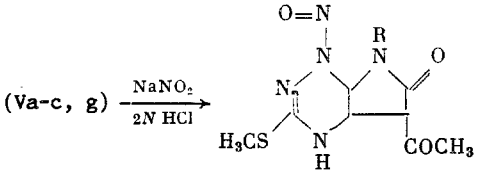


Fig. 2. Fragments of PMR spectrum of pyrrolotriazine (VIa) in DMF-d_7 at various temperatures.

stants are usually evident [4, 9, 10]. In condensed pyrrolotriazines (Va, b, f) the HFI constants of the H^{4a} protons with the C^3 carbons were found to be small and were manifested only in broadening of the quartet components of the C^3 signal, characteristic for hydrogenated systems. To obtain additional data to confirm the structure of pyrrolotriazines (V), these were nitrosated with $NaNO_2$ in 2N HCl; 1-nitroso derivatives (VIa-d) were obtained in good yields (Table 1)



(VIa–d)

R =Ph (Va), (VIa); $C_6H_4CH_3$-4 (Vb), (VIb); C_6H_4Br-4 (Vc), (VIc); C_6H_4OH-2 (Vg), (VId).

For an unequivocal determination of the regioorientation of the pyrrole ring and the position of N=O group, and also to obtain information on the steric structure of the derivatives of the new heterocyclic system, an x-ray diffraction analysis (XRDA) of compound VIb was carried out (Fig. 1). The molecule of 5-acetyl-4,4a,5,6,7,7a-hexahydro-3-methylthio-1-nitroso-6-oxo-7-(tolyl-4)-1H-pyrrolo[3,2-e]-1,2,4-triazine (VIb) consists of cis-condensed pyrrole and triazine rings (Fig. 1, the $H^{4a}C^{4a}C^{7a}H^{7a}$ torsional angle is equal to 40°). The pyrrole ring has a conformation of a convert, with the C^{4a} atom at a distance of 0.45 Å from the plane of the remaining four atoms (Fig. 1), while the triazine ring has a distorted half-chair conformation – the C^{4a} and C^{7a} atoms are displaced from the plane of the remaining four atoms by 0.41 and 0.79 Å, respectively. The nitroso group is almost coplanar with the $N^2N^1C^{7a}$ fragment (the corresponding $C^{7a}N^1N^{13}O^{14}$ and $N^2N^1N^{13}O^{14}$ torsional angles are equal to 180.0 and 7.0°). The geometrical parameters of NO, CH_3S, $C_6H_4CH_3$-4 and Ac groups are close to the standard values. The analysis of the bond lengths distribution in the triazine ring for the $N^1N^2C^3N^4$ fragment indicates an appreciable delocalization of the π-electrons,

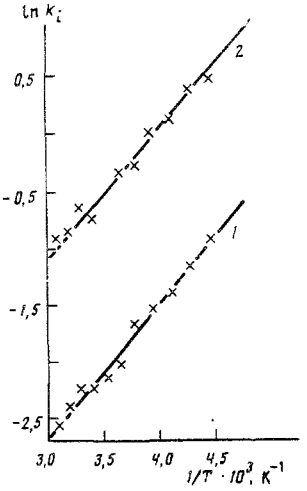
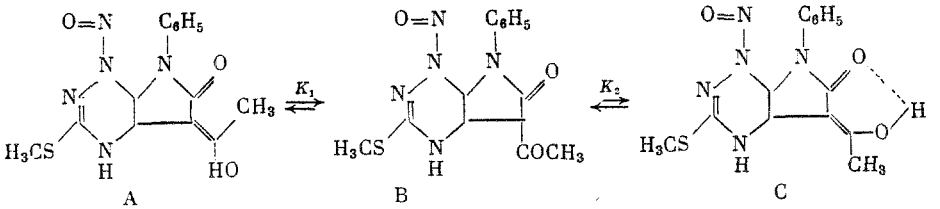


Fig. 3. Dependence of $\ln K_2$ (1) and $\ln K_3$ (2) on 1/T.

where formally, the ordinary N^4-C^3 (1.34 Å) and N^1-N^2 (1.379 Å) bonds exceed the length of the $N^2=C^3$ double bond (1.30 Å) by an inappreciable amount.

From analysis of the ^1H and ^{13}C NMR spectra of pyrrolotriazines (III), (V), and (VI), it was found that in DMSO, CH_3OH and DMF solutions they exist in several tautomeric forms, whereby the diketo form B makes the main contribution to the tautomeric equilibrium. Its content in DMSO solutions at ~20°C is 70-95% (Table 2). The tautomeric equilibrium of pyrrolotriazines (III), (V), and (VI) was studied in DMF-d_7 over a wide range of temperatures from −50 to 120°C, using the nitroso compound (VIa) as a model (Fig. 2). In the PMR spectra of compound (VIa) in DMF-d_7, signals of three tautomers A, B, and C are recorded, the relative content of which (Table 4, Fig. 2) depends on the temperature, which indicates the existence of a dynamic equilibrium



Since the H^5 hydrogen atoms are absent in the keto-enol forms A and C, while the signals of the H^{7a} protons of these forms are overlapped by a multiplet of aromatic protons, the 4.9-5.5 ppm region, in which the signals of the H^{4a} protons appear, is the most informative for study of the tautomeric equilibrium using the PMR spectra. The assignment of the latter signals to the predominating diketo form B in the PMR spectra of the nitroso compound (VIa) does not present any difficulties. Of the two H^{4a} proton signals of the minor tautomers, the stronger-field signal at δ 5.34 ppm was preferentially assigned to the keto-enol tautomer C, while the signals at δ 5.45 ppm was assigned to the keto-enol form A (see PMR spectrum at −50°C, Fig. 2). Slow tautomeric transformations on the NMR time scale are characterized by equilibrium constants $K_1 = B/A$, $K_2 = C/B$, and $K_3 = C/A = K_1K_2$, which were measured according to the ratios of the integral intensities of the H^{4a} signals in the range of temperatures studied* (Fig. 2, Table 4). The measurements (Table 4) show that constant K_1 is practically independent of temperature, i.e., tautomers A and B are thermodynamically equivalent. The thermal effects of the B ⇄ C and A ⇄ C equilibria calculated from the slopes of the graphs in the $\ln K \sim 1/T$ coordinates (Fig. 3) are small and similar to one another: $\Delta H_2^0 = -2.3$ kcal/mole and $\Delta H_3^0 = -2.1$ kcal/mole, and the correlation coefficients are equal to 0.992 and 0.986, respectively. The inappreciable thermodynamic preference of tautomer C is clearly manifested in the increase in its thermodynamic content, compared with tautomer A on decrease of temperature (Table 4, Fig. 2). The thermodynamic preference of tautomer C compared with tautomer A can be attributed to the formation of an intramolecular hydrogen bond O...H.†

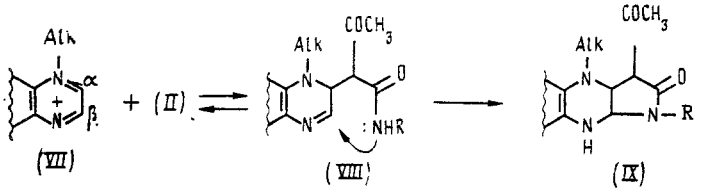
*At temperatures higher than 50°C, the intensity of the H^{4a} signal of tautomer C is low and commensurable with the noise level.

†The intermolecular hydrogen bonds are not evident in dilute solutions of a concentration of less than 5%.

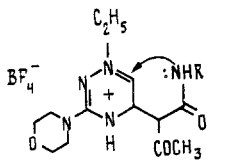
TABLE 4. Ratio of A-C Tautomers and Equilibrium Constants K_1-K_3 in a Solution of Nitroso Compound (VIa) in DMF-d_7 at Various Temperatures

T, °C	Fraction of tautomers, %			K_1=B/A	K_2=C/B	K_3=C/A
	A	B	C			
50	15	79	6	5,27	0,076	0,40
40	15	78	7	5,20	0,090	0,47
30	15	77	8	5,13	0,103	0,53
20	17	75	8	4,41	0,107	0,47
10	15	76	9	5,07	0,118	0,60
0	14	76	10	5,43	0,132	0,71
−10	17	70	13	4,12	0,186	0,77
−20	15	70	15	4,67	0,214	1,00
−30	15	68	17	4,53	0,250	1,13
−40	14	66	20	4,71	0,303	1,43
−50	15	61	24	4,07	0,393	1,60

Besides the keto-enol equilibrium, another important aspect of the chemical behavior of the β-keto-acid amides in the reactions with aromatic substrates is worth mentioning. Because of their polydentate nature, they can potentially be C,C-, C,N-, and C,O-dinucleophiles. In most of the reactions of polynitro aromatic compounds with β-keto acid amides, the latter display properties of 1,3-dicarbonyl reagents, while the N,C-diaddition is in general excluded from consideration as being only slightly probable [11]. Thus, in the reaction of trinitrobenzene with AAA, only C,C-diaddition was observed, which results in meta-bridging products [11]. The absence of cycloadducts of another type is explained by the fact that products of N- and O-addition of β-dicarbonyl derivatives are unstable [11-13]. At the same time it is known that the transformations of pyrimidines, 1,3,5-triazines and other azaaromatic compounds by the action of β-keto-acid amides proceed via the C,N-bicyclic intermediates [14]. In investigations carried out in our laboratory, it was shown that in reactions with azaaromatic substrates, the AAA behave also as bifunctional C,N-nucleophiles, forming as the result of cyclization with quinoxalinium, pteridinium, and pyrazinium salts, the corresponding pyrrolo-annelated 1,4-diazines (IX) [14]. The cyclization of the 1,2,4-triazinium salt (I) with AAA (II) is similar to the reaction of other 1,4-diazinium salts (VII), but the regioorientation of the pyrrole ring relative to the N-alkyl group is the reverse of that in the earlier obtained pyrrolodiazines (IX) [14]. This is probably due to to the differences in the stabilities of the intermediate dihydro compounds. While in reactions of the quaternary salts (VII), the primary attack of the AAA is directed to the most electrophilic α-carbon atom with the formation of C-adducts (VIII), the characteristic feature of 1,2,4-triazines is their tendency to form adducts with nucleophilic reagents, preferentially at the C^5 position. Transition to N^1 quaternary 1,2,4-triazinium salts creates a new electrophilic C^6 center in addition to the existing C^5 center. Therefore, these two carbon atoms are subjected to nucleophilic attack by AAA, but the role of the thermodynamic factor in the formation of cyclic adducts (III) via intermediates (X) is apparently more substantial.



(VII) (VIII) (IX)



(X)

EXPERIMENTAL

The ^1H NMR spectra of the compounds studied were run in DMSO-d_6 and DMF-d_7 on Perkin-Elmer R-12-B (60 MHz), Bruker WH-90 (90 MHz), and Bruker WP-80 (80.13 MHz) spectrometers, relative to TMS (δ 0.00 ppm). The ^{13}C NMR spectra were recorded in DMSO-d_6 on Bruker WP-80 (20.13 MHz) and Bruker WH-90 (22.62 MHz) spectrometers. The ^{13}C chemical shifts were measured relative to the solvent signal (δ 39.60 ppm). The XRDA was carried out on a Sinteks-R1 diffractometer. The crystals of compound (VIb) are monoclinic, a = 12.281(7), b = 11.071(7), c = 12.971(7) Å, β = 103.57(4)°, V = 1714(2) Å^3, Z = 4, space group $P2_1/c$. The structure was identified by a direct method, and was refined by the method of least squares in a full-matrix approximation R = 0.083, R_w = 0.095 for 1350 reflections with $F^2 \geq 2\sigma$.*

The properties of the compounds synthesized are given in Tables 1-3.

General Method for the Preparation of Compounds (IIIa-h). A solution of 500 mg (1.77 mmoles) of 3-morpholino-1-ethyl-1,2,4-triazinium borofluoride (I) and 1.77 mmoles of the corresponding AAA in 3 ml of C_2H_5OH was heated and allowed to stand for 1-2 days at ~20°C. The precipitate that formed was washed with cold C_2H_5OH and ether. Analytical samples were obtained by recrystallization from 50-80% aqueous C_2H_5OH.

Preparation of Trifluoroacetates (Va-g). A 7.86 mmole portion of the corresponding AAA was added to a solution of 1 g (7.86 mmoles) of 3-methylthio-1,2,4-triazine in a mixture of 4 ml of $CHCl_3$ and 1 ml of CF_3COOH. The suspension obtained was heated to a complete dissolution and was allowed to stand for 24 h at ~20°C. The oily residue remaining after evaporation of the solvent was ground with hexane up to crystallization. The analytical samples were obtained after recrystallization from C_2H_5OH.

Nitrosation. A solution of $NaNO_2$ (330 mg, 4.78 mmoles) in 2.4 ml of H_2O was added dropwise to a solution of compound (V) (2.40 mmoles) in 5 ml of 2N HCl, cooled to 5°C. The mixture was stirred for 15 min at 5°C, the precipitate was filtered off, washed with copious amounts of H_2O to pH 7, and then with cold C_2H_5OH and ether. The nitrosopyrrolotriazine obtained was recrystallized from C_2H_5OH.

CONCLUSIONS

A new approach to the synthesis of condensed pyrrolo-1,2,4-triazines was carried out, based on the nucleophilic diaddition of acetoacetoamides to 1,2,4-triazine derivatives.

LITERATURE CITED

1. S. G. Alekseev (Alexeev), V. N. Charushin, O. N. Chupakhin, and G. G. Alexandrov, Tetrahedron Lett., 29, 1431 (1988).
2. O. N. Chupakhin, S. G. Alekseev (Alexeev), and V. N. Charushin, Proc. 11th Int. Congr. of Heterocyclic Chemistry, Ruprecht-Karls Universitat, Heidelberg (1987), p. 443.
3. S. G. Alekseev, V. N. Charushin, N. A. Klyuev, and O. N. Chupakhin, Chemistry, Biochemistry, and Pharmacology of Indole Derivatives [in Russian], Izd. Tbilis. Univ., Tbilisi (1986), p. 27.
4. S. G. Alekseev, V. N. Charushin, O. N. Chupakhin, et al., Khim. Geterotsikl. Soedin., 1535 (1986).
5. N. Vinot and J.-P. M'Packo, Bull. Soc. Chim. France, 1201 (1972).
6. G. Seitz, S. Dietrich, R. Dhar, et al., Arch. Pharm., 319, 798 (1986).
7. S. G. Alekseev, V. N. Charushin, and O. N. Chupakhin, Khim. Geterotsikl. Soedin., 280 (1987).
8. S. G. Alekseev, P. A. Torgashev, M. A. Fedotov, et al., Khim. Geterotsikl. Soedin., 525 (1988).
9. S. Braun and G. Frey, Org. Magn. Reson., 7, 194 (1975).
10. A. Yu. Denisov, V. I. Mamatyuk, and O. P. Shkurko, Khim. Geterotsikl. Soedin., 986 (1985).
11. L. Granadoss and N. Radha, J. Org. Chem., 48, 570 (1983).
12. L. Granadoss and D. Kalaivani, J. Org. Chem., 50, 1174 (1985).
13. L. Granadoss and D. Kalaivani, J. Org. Chem., 50, 1178 (1985).
14. V. N. Charushin, O. N. Chupakhin, and H. C. van der Plas, Adv. Heterocycl. Chem., 43, 301 (1988).

*The data on the x-ray structural analysis in a full volume are obtainable from the authors.