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Synthesis of Substituted 1,3-Cyclohexadienes, Pyridine-2(1*H*)-thiones, and Thieno[2,3-*d*]pyrimidine-4(3*H*)-thiones by the Michael Reaction

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Abstract—Cyclopentylidene- and cyclohexylidene(cyano)acetamides reacted with malononitrile and cyano(thioacetamide) according to the Michael pattern with exchange of the methylene components to give substituted 1-amino-2,6,6-tricyano-1,3-cyclohexadienes and thieno[2,3-*d*]pyrimidine-4(3*H*)-thiones. Condensation of cyclopentylidene- and cyclohexylidene(cyano)acetamide with 1,3-dicarbonyl compounds afforded 4,6-dimethyl-3-cyanopyridine-2(1*H*)-thione and morpholinium 4-methyl-6-oxo-3-cyano-1,6-dihydropyridine-2-thiolate which were converted into substituted 2-alkylsulfanylpyridines, thieno[2,3-*b*]pyridines, thiazolo[3,2-*a*]pyridine, and 2*H*-[1,3]thiazino[3,2-*a*]pyridine.

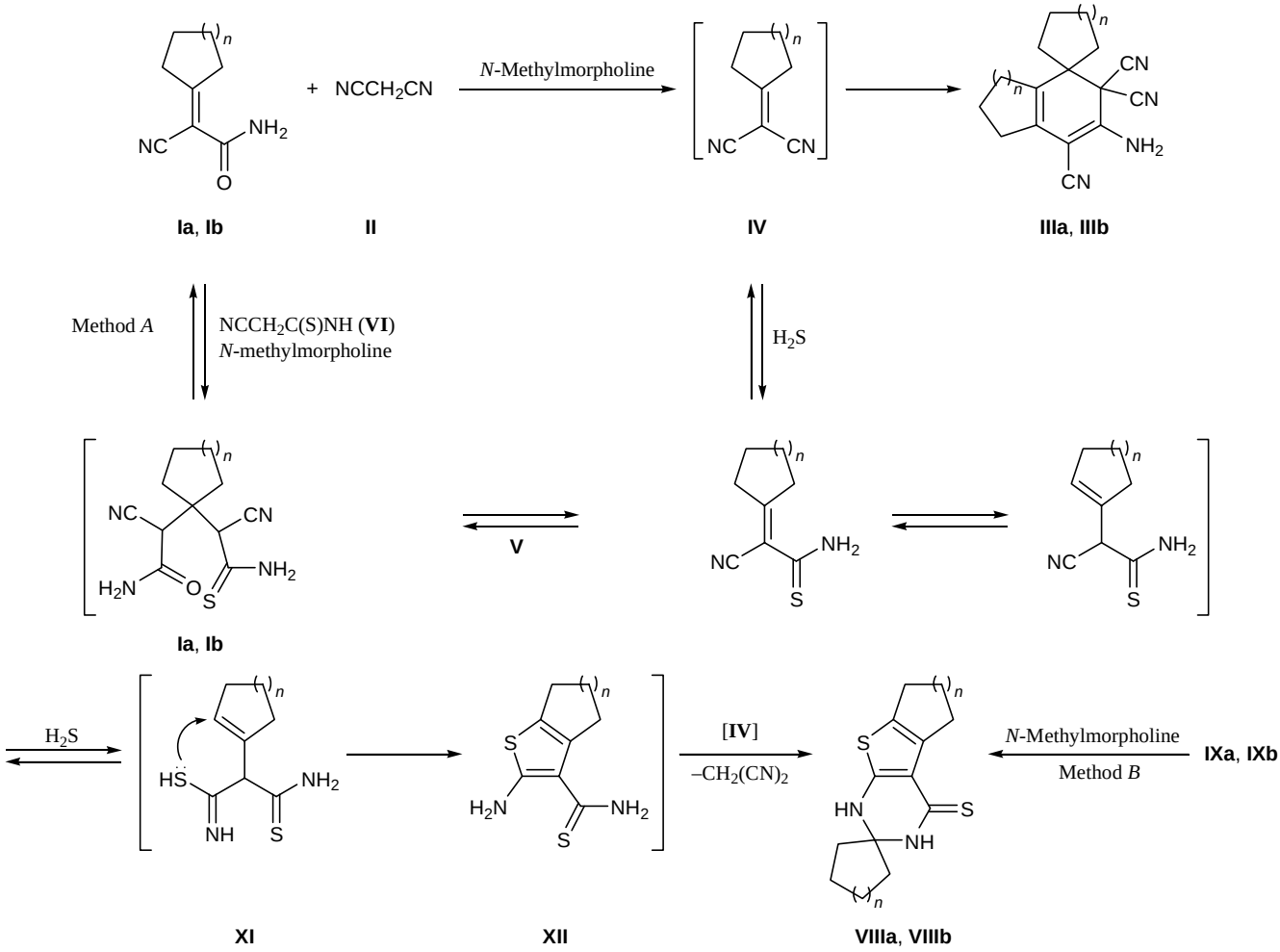
The importance of the Michael reaction for synthetic organic chemistry is well known [1]. It is successfully used in the synthesis of functionally substituted pyridine-2-chalcogenones [2], a number of which exhibit biological activity [3]. However, only a few examples have been reported on the synthesis of heterocyclic compounds by the Michael reaction involving exchange of the methylene components [4, 5].

The present work extends the scope of the Michael reaction with exchange of the methylene components to the synthesis of carbo- and heterocycles. We have found that cycloalkylidene(cyano)acetamides **I** react with malononitrile (**II**) at 20°C in ethanol in the presence of *N*-methylmorpholine to give spiro-cyclohexadienes **III** (Scheme 1). The reaction is likely to involve intermediate formation of cycloalkylidenemalononitriles **IV** as a result of exchange of the methylene components: the cyanoacetamide moiety is replaced by malononitrile fragment. As shown previously [6], compounds **IV** readily undergo cyclodimerization in the presence of a base.

The reaction of cycloalkylidene(cyano)acetamides **I** with cyano(thioacetamide) (**VI**) gave spiro derivatives of thieno[2,3-*d*]pyrimidine-4(3*H*)-thiones **VII** (Method *A* in Scheme 1). Presumably, intermediate Michael adduct **VIII** decomposes to give new alkene **IX** and CH acid **V** as a result of exchange of the methylene components. Compound **IX** loses hydrogen sulfide molecule, yielding cycloalkylidenemalononitrile **IV**. The subsequent addition of hydrogen sulfide to proto-tropic tautomers **IX** and **X** leads to formation of dithioamides **XI**, and the latter undergo intramolecular cyclization to substituted thiophenes **XII**. The condensation of **XII** with alkenes **IV** gives products **VII**. The structure of **VII** was confirmed by elemental analysis, ^{1}H NMR and IR spectroscopy, and mass spectrometry (Tables 1–3). It should be noted that thienopyrimidine **VIIb** was synthesized previously by condensation of cyclohexanone with sulfur and cyano(thioacetamide); however, its structure was derived only from the elemental analysis data [7]. Also, compounds **VIIa** and **VIIb** are readily formed by cyclodimerization of thioamides **IXa** and **IXb** (Method *B* in Scheme 1). These findings confirm the above assumption concerning intermediate formation of structures **IX** during exchange of the methylene components.

The methylene component exchange pattern is also typical of reactions of cycloalkylidene(cyano)(thioacetamides) **IX** with CH acids **XIIIa**–**XIIIc** in the presence of an equimolar amount of morpholine. The condensation gave salts **XIV** (R = PhNH, Method *A*, or R = EtO, Method *B*) and pyridinethione **XV** (R = Me). Here, the primary intermediates are β-enamino-

Scheme 1.

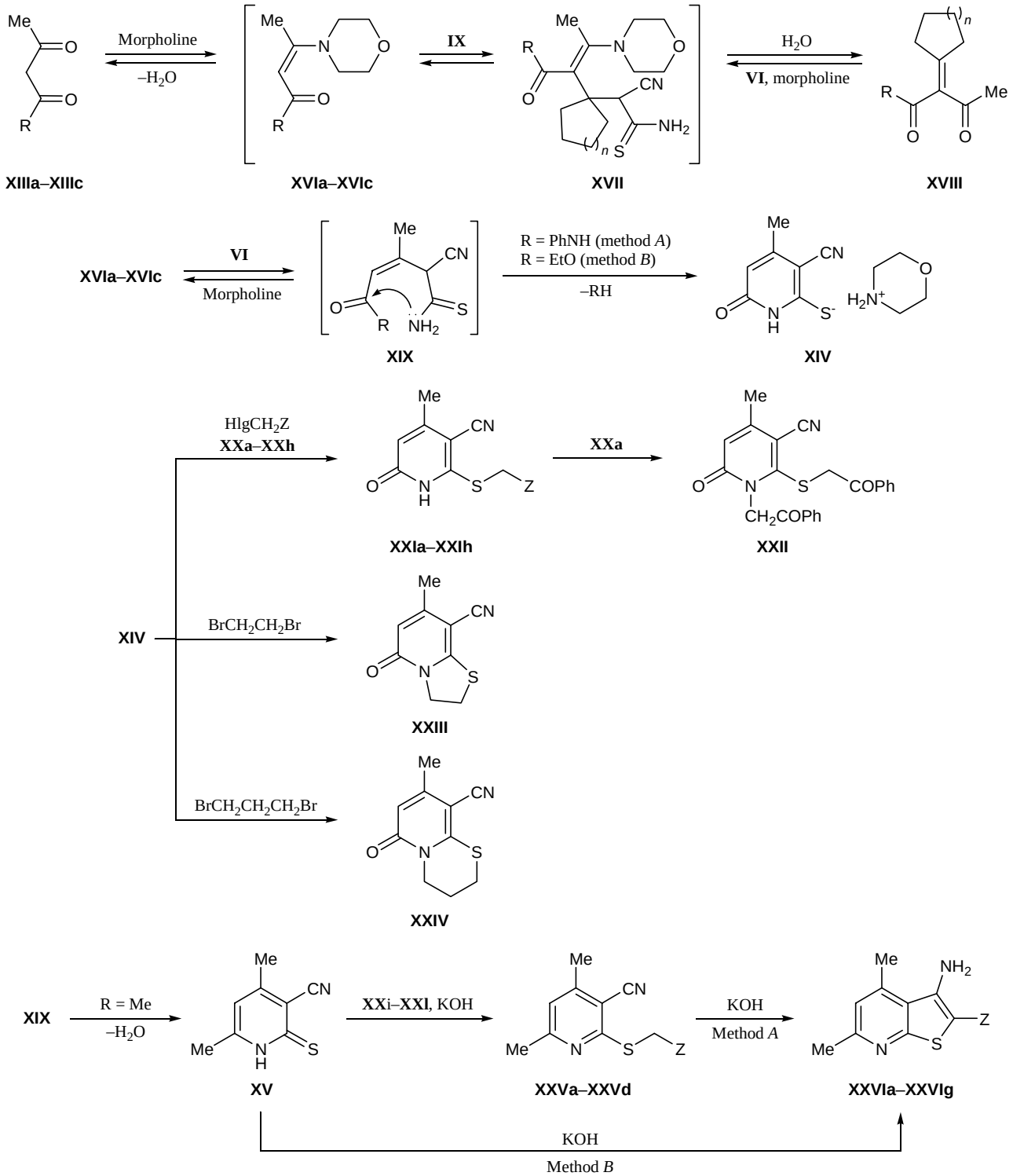


I, **III**, **VII**, **IX**, $n = 1$ (**a**), $n = 2$ (**b**).

carbonyl compounds **XVIa**–**XVIc** which react with alkenes **IX** to form adducts **XVII** (Scheme 2). Elimination of cyano(thioacetamide) (**VI**) from the latter gives alkenes **XVIII**. The presence of a CH acid (compound **VI**) in the mixture gives rise to its reaction with β-enaminoketones **XVI** through adducts **XIX** to afford the corresponding pyridines **XIV** and **XV**. The structure of compounds **XIV** and **XV** was proved by independent synthesis: salt **XIV** was obtained by condensation of 3-morpholinocrotonanilide (**XVIa**) with cyano(thioacetamide) (**VI**) [8], and thione **XV** was prepared by reaction of acetylacetone (**XIIIc**) with cyano(thioacetamide) (**VI**) [9]. Also, some characteristic chemical transformations of these products were studied. For example, salt **XIV** reacted with halogen derivatives **XX** to give sulfides **XXIa**–**XXIh**. Further alkylation of **XXIa** with phenacyl bromide **XXa** resulted in formation of *N*-phenacylpyridin-2-one **XXII**. By reaction of thiolate **XIV** with α,ω-dibromoalkanes we obtained thiazolo[3,2-*a*]pyridine **XXIII** and [1,3]thiazino[3,2-*a*]pyridine **XXIV**. Alkylation of thione **XV** with halogen derivatives **XX** led to sulfides **XXV** which were converted into the corresponding substituted thieno[3,2-*b*]pyridines **XXVI** by the action of a base (Method *A* in Scheme 2). Also, compounds **XXVI** can readily be obtained from thione **XV** and halides **XX** in the presence of 2 equiv of alkali (Method *B*).

The mechanism of formation of salt **XIV** and pyridinethione **XV** was proved by the isolation from the reaction mixture at 20°C of pure enaminoketone **XVIa** whose structure was proved by X-ray analysis. Compound **XVIa** in crystal exists as two symmetrically independent molecules A and B. The principal geometric parameters of molecules A and B are given in Table 4, and their structure is shown in Fig. 1. The

Scheme 2.



XIII, **XVI**, R = PhNH (**a**), EtO (**b**), Me (**c**); **XX**, Hlg = Br, Z = PhCO (**a**), 3,4-$(HO)_2C_6H_3CO$ (**b**), HC≡C (**c**); Hlg = I, Z = Me (**d**); Hlg = Cl, Z = PrOCO (**e**), 2-MeC_6H_4NHCO (**f**), *i*-PrOCO (**g**), CH_2=C(Me) (**h**), 2-thiazolylcarbamoyl (**i**), 4-AcC_6H_4NHCO (**j**), 8-quinolinylcarbamoyl (**k**), 2-HOC_6H_4CO (**l**), $Me(CH_2)_7OCO$ (**m**); Hlg = Br, 4-$MeOC_6H_4CO$ (**n**), 4-ClC_6H_4CO (**o**), 4-HOC_6H_4CO (**p**); **XXI**, Z = PhCO (**a**), 3,4-$(HO)_2C_6H_3CO$ (**b**), HC≡C (**c**), Me (**d**), PrOCO (**e**), 2-MeC_6H_4NHCO (**f**), *i*-PrOCO (**g**), CH_2=C(Me) (**h**); **XXV**, Z = 2-thiazolylcarbamoyl (**a**), 4-AcC_6H_4NHCO (**b**), 8-quinolinylcarbamoyl (**c**), 2-HOC_6H_4CO (**d**); **XXVI**, Z = 4-AcC_6H_4NHCO (**a**), 8-quinolinylcarbamoyl (**b**), 2-HOC_6H_4CO (**c**), $Me(CH_2)_7OCO$ (**d**), 4-$MeOC_6H_4CO$ (**e**), 4-ClC_6H_4CO (**f**), 4-HOC_6H_4CO (**g**).

Table 1. Yields, melting points, and elemental analyses of compounds **VIIa**, **VIIb**, **XVIa**, **XXIb**–**XXIh**, **XXII**–**XXIV**, **XXVa**–**XXVd**, and **XXVIa**–**XXVIg**

Comp. no.	Yield, % (*A*/*B*)	mp, °C (solvent)	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
VIIa	69/71	227–229 (EtOH)	58.84	5.91	10.45	$C_{13}H_{16}N_2S_2$	59.05	6.10	10.60
VIIb	75/76	255–256 (DMF)[a]	61.48	6.72	9.67	$C_{15}H_{20}N_2S_2$	61.60	6.89	9.58
XVIa	68	145–147 (EtOH)	68.02	7.14	11.60	$C_{14}H_{18}N_2O_2$	68.27	7.37	11.37
XXIb	69	300–304 (AcOH)	57.13	4.02	8.67	$C_{15}H_{12}N_2O_4S$	56.95	3.82	8.85
XXIc	77	180–182 (AcOH)	58.96	4.12	13.59	$C_{10}H_8N_2OS$	58.81	3.95	13.71
XXId	85	178–180 (AcOH)	55.48	4.97	14.63	$C_9H_{10}N_2OS$	55.65	5.19	14.42
XXIe	73	98–100 (EtOH)	53.94	5.41	10.38	$C_{12}H_{14}N_2O_3S$	54.12	5.30	10.52
XXIf	68	202–203 (AcOH)	61.14	5.01	13.18	$C_{16}H_{15}N_3O_2S$	61.32	4.82	13.41
XXIg	70	110–112 (EtOH)	53.94	5.18	10.72	$C_{12}H_{14}N_2O_3S$	54.12	5.30	10.52
XXIh	69	147–148 (AcOH)	60.17	5.56	12.49	$C_{11}H_{12}N_2OS$	59.98	5.49	12.72
XXII	78	190–192 (DMF)	68.50	4.42	7.13	$C_{23}H_{18}N_2O_3S$	68.64	4.51	6.96
XXIII	69	201–203 (DMF)	56.34	3.98	14.50	$C_9H_8N_2OS$	56.23	4.19	14.57
XXIV	84	224–225 (AcOH)	58.11	4.95	13.42	$C_{10}H_{10}N_2OS$	58.23	4.89	13.58
XXVa	75	264–266 (AcOH)	51.14	4.12	18.19	$C_{13}H_{12}N_4OS_2$	51.30	3.97	18.41
XXVb	66	209–211 (AcOH)	63.59	4.87	12.41	$C_{18}H_{17}N_3O_2S$	63.70	5.05	12.38
XXVc	61	161–163 (AcOH)	65.39	4.50	15.91	$C_{19}H_{16}N_4OS$	65.50	4.63	16.08
XXVd	69	159–161 (EtOH)	64.28	4.85	9.18	$C_{16}H_{14}N_2O_2S$	64.41	4.73	9.39
XXVIa	84/72	225–226 (AcOH)	63.44	4.87	12.49	$C_{18}H_{17}N_3O_2S$	63.70	5.05	12.38
XXVIb	79/76	273–274 (AcOH)	65.31	4.72	15.84	$C_{19}H_{16}N_4OS$	65.50	4.63	16.08
XXVIc	70/63	209–210 (AcOH)	64.52	4.58	9.21	$C_{16}H_{14}N_2O_2S$	64.41	4.73	9.39
XXVId	59	98–99 (EtOH)	64.56	7.70	8.45	$C_{18}H_{26}N_2O_2S$	64.64	7.84	8.38
XXVIe	79	183–185 (AcOH)	65.12	5.30	9.08	$C_{17}H_{16}N_2O_2S$	65.36	5.16	8.97
XXVIf	81	187–189 (AcOH)	60.72	4.03	8.59	$C_{16}H_{13}ClN_2OS$	60.66	4.14	8.84
XXVIh	53	301–303 (AcOH)	64.28	4.64	9.48	$C_{16}H_{14}N_2O_2S$	64.41	4.73	9.39

[a] Published data [7]: mp 255–256°C (from formamide).

N^1 atom in both molecules has planar–trigonal bond configuration (the sum of the bond angles at N^1 is 360° within the experimental error). The N^2 atom has a flattened pyramidal configuration: the sum of the bond angles at N^2 in molecules A and B is 350.6(6) and 350.5(6)°, respectively. The bond system $N^1C^{7-10}O^1N^2$ is almost planar: deviations of atoms from the mean-square plane in molecules A and B do not exceed 0.21 and 0.22 Å, respectively, and the torsion angles $N^2C^9C^8C^7$ and $C^9C^8C^7N^1$ are –173.6(2) and –167.4(2)° in molecule A and 173.8(2) and 167.2(2)° in molecule B. Such conformation is favorable for electron density delocalization in the central fragment via $n(N^1)$–$\pi(O^1{=}C^7)$, $\pi(O^1{=}C^7)$–$\pi(C^9{=}C^{10})$, and $n(N^2)$–$\pi(C^8{=}C^9)$ conjugation. In fact, the N^1–C^7 and N^2–C^9 bonds [1.359(3) and 1.377(3) Å in molecule A; 1.361(3) and 1.378(3) Å in molecule B] are considerably shorter than the standard $N(sp^2)$–$C(sp^2)$ bond (1.43–1.45 Å) [10]. The benzene ring is almost coplanar to the $N^2C^{7-10}O^1N^1$ plane (the corresponding dihedral angles in molecules A and B are as small as 2.9 and 5.7°, respectively), which implies the possibility for the π system of the C^1–C^6 benzene ring to participate in conjugation with the central fragment. An additional argument indicating efficiency of such interaction is shortening of the N^1–C^1 bond in molecule A to 1.402(3) Å, and in molecule B, to 1.398(3) Å.

Molecules **XVIa** in crystal are linked through N^1–$H(N^1)\cdots O^1$ hydrogen bonds, giving rise to infinite chains (Fig. 2). The hydrogen bonds are characterized by the following parameters: $N^1(A)\cdots O^1(B)$ 2.853(2) Å, $N^1(A)H(N^1A)O^1(B)$ 165(2)°, $N^1(B)\cdots O^1(A)$ 2.893(2) Å,

Table 2. IR and ^{1}H NMR spectra of compounds **VIIa**, **VIIb**, **XVIa**, **XXIb**–**XXIh**, **XXII**–**XXIV**, **XXVa**–**XXVd**, and **XXVIa**–**XXVIg**

Comp. no.	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum, δ, ppm, ^3J, Hz
	NH, OH	C=N, C=O	
VIIa	3340	–	1.10–1.82 m [10H, $(CH_2)_5$], 2.34 q (2H, CH_2, 7.09), 2.93 t (2H, CH_2, 8.01), 7.91 br.s and 8.90 br.s (1H each, NH)
VIIb	3335	–	1.11–1.84 m [14H, $(CH_2)_7$], 1.94 m (2H, CH_2), 2.90 m (2H, CH_2), 7.83 br.s and 8.62 br.s (1H each, NH)
XVIa	3300	1723	2.40 s (3H, Me), 3.12 t (4H, CH_2NCH_2, 4.75), 3.65 t (4H, CH_2OCH_2, 4.80), 5.04 s (1H, CH=), 6.92 d.d (1H, Ph, 7.50), 7.31 d.d (2H, Ph, 7.96), 7.54 d (2H, Ph), 9.21 br.s (1H, NH)
XXIb	3290, 3475	2218, 1714	2.36 s (3H, Me), 4.76 s (2H, CH_2), 6.28 s (1H, 5-H), 6.81 d (1H, Ar, 8.10), 7.38 s (1H, Ar), 7.45 d (1H, Ar), 9.09 br.s and 9.64 br.s (1H each, OH), 11.64 br.s (1H, NH)
XXIc	3214	2215, 1710	2.38 s (3H, Me), 2.89 s (1H, ≡CH), 4.03 s (2H, CH_2), 6.32 s (1H, 5-H), 11.80 br.s (1H, NH)
XXId	3319	2214, 1683	1.35 t (3H, Me, 9.90), 2.33 s (3H, Me), 3.20 q (2H, CH_2, 9.90), 6.29 s (1H, 5-H), 11.56 br.s (1H, NH)
XXIe	3342	2216, 1695	0.82 t (3H, Me, 8.40), 1.56 m (2H, CH_2), 2.32 s (3H, Me), 4.01 t (2H, OCH_2, 6.39), 4.13 s (2H, SCH_2), 6.40 s (1H, 5-H), 11.90 br.s (1H, NH)
XXIf	3330	2215, 1700	2.14 s (3H, Me), 2.37 s (3H, Me), 4.06 s (2H, CH_2), 6.36 s (1H, 5-H), 7.13 m (3H, Ar), 7.44 d (1H, Ar, 7.56), 9.25 br.s (1H, NHAr), 11.94 br.s (1H, NH)
XXIg	3325	2214, 1715	1.14 d (6H, Me, 8.47), 2.31 s (3H, Me), 4.02 q (1H, OCH, 9.42), 4.87 s (2H, SCH_2), 6.42 s (1H, 5-H), 12.01 br.s (1H, NH)
XXIh	3321	2213, 1687	1.81 s (3H, Me), 2.33 s (3H, Me), 3.90 s (2H, SCH_2), 5.08 s and 4.82 s (1H each, CH_2=), 6.30 s (1H, 5-H), 11.62 br.s (1H, NH)
XXII	–	2195, 1682, 1710	2.45 s (3H, Me), 4.62 s (2H, SCH_2), 5.62 s (2H, NCH_2), 6.69 s (1H, 5-H), 7.30–7.82 m (10H, Ph)
XXIII	–	2200, 1677	2.22 s (3H, Me), 3.64 t (2H, SCH_2, 3.65), 4.43 t (2H, NCH_2, 7.50), 6.02 s (1H, 6-H)
XXIV	–	2214, 1675	2.20 m (5H, Me and CH_2), 3.25 t (2H, SCH_2, 6.34), 3.98 t (2H, NCH_2, 5.54), 6.03 s (1H, 7-H)
XXVa	3380	2218, 1695	2.35 s and 2.43 s (3H each, Me), 4.18 s (2H, CH_2), 6.99 s (1H, 5-H, pyridine), 7.02 d (1H, 5-H, thiazole, 4.05), 7.38 d (1H, 4-H, thiazole), 12.30 br.s (1H, NH)
XXVb	3342	2215, 1684	2.43 s (6H, Me), 2.51 s (3H, MeCO), 4.12 s (2H, CH_2), 6.97 s (1H, 5-H), 7.69 d and 7.85 d (2H each, H_{arom}, 8.60), 10.46 br.s (1H, NH)
XXVc	3312	2223, 1680	2.44 s and 2.63 s (3H, Me), 4.23 s (2H, CH_2), 7.08 s (1H, 5-H, pyridine), 7.53 m (3H, 3-H, 6-H, 7-H, quinoline), 8.26 d (1H, 5-H, quinoline, 8.29), 8.63 d (1H, 4-H, quinoline, 7.12), 8.73 d (1H, 2-H, quinoline, 4.20), 10.54 br.s (1H, NH)
XXVd	3340	2218, 1702	2.25 s and 2.42 s (3H, Me), 4.76 s (2H, CH_2), 6.97 m (3H, 5-H, H_{arom}), 7.47 m (1H, H_{arom}), 7.94 d (1H, H_{arom}, 8.34), 11.38 s (1H, OH)
XXVIa	3300	1674	2.43 s and 2.51 s (3H each, Me), 2.76 s (3H, MeCO), 6.91 br.s (3H, 5-H, NH_2), 7.84 d and 7.87 d (2H each, H_{arom}, 8.55), 9.46 br.s (1H, NHCO)
XXVIb	3328, 3450	1685	2.49 s and 2.75 s (3H each, Me), 7.05 br.s (3H, 5-H in pyridine, NH_2), 7.63 m (3H, 3-H, 6-H, 7-H, quinoline), 8.40 d (1H, 5-H, quinoline, 8.24), 8.68 d (1H, 4-H, quinoline, 7.04), 8.95 d (1H, 2-H, quinoline, 4.26), 9.98 br.s (1H, NH)
XXVIc	3345, 3428, 3496	1700	2.51 s and 2.75 s (3H each, Me), 6.86 m (3H, H_{arom}, 5-H), 7.28 d.d (1H, H_{arom}, 8.34), 7.66 d (1H, H_{arom}, 6.86), 7.93 br.s (2H, NH_2), 11.25 s (1H, OH)

Table 2. (Contd.)

Comp. no.	IR spectrum, ν, cm^{-1}		^1H NMR spectrum, δ, ppm, ^3J, Hz
	NH, OH	C=N, C=O	
XXVId	3320	1698	0.92 t (3H, Me, 7.35), 1.60 m [10H, $(CH_2)_2$], 1.72 m (2H, CH_2), 2.48 s and 2.73 s (3H each, Me), 4.20 t (2H, OCH_2, 8.40), 6.58 br.s (2H, NH_2), 6.80 s (1H, 5-H)
XXVIe	3475	1702	2.54 s and 2.78 s (3H each, Me), 3.88 s (3H, OMe), 7.05 s (1H, 5-H), 6.95 d and 7.78 d (2H each, H_{arom}, 8.74), 7.85 br.s (2H, NH_2)
XXVIf	3387	1684	2.52 s and 2.76 s (3H each, Me), 6.93 s (1H, 5-H), 7.46 d and 7.75 d (2H each, H_{arom}, 8.01), 7.96 br.s (2H, NH_2)
XXVIg	3289, 3457	1708	2.53 s and 2.77 s (3H each, Me), 7.02 s (1H, 5-H), 6.87 d and 7.68 d (2H each, H_{arom}, 8.60), 7.88 br.s (2H, NH_2), 10.06 s (1H, OH)

Table 3. Mass spectra of compounds **VIIb**, **XIV**, **XV**, **XVIa**, **XXIc**, **XXId**, **XXIf**, **XXIh**, **XXII**–**XXIV**, **XXVb**, **XXVc**, **XXVIa**, **XXVIb**, and **XXVId**

Comp. no.	*m*/*z* (I_{rel}, %)	
	M^+	other ions
VIIb	292 (84)	259 (36), 249 (100), 236 (41), 167 (19), 81 (45), 53 (38), 41 (62)
XIV	166 (77),[a] 87 (32)[b]	138 (48), 133 (22), 105 (29), 83 (12), 78 (60), 57 (10), 51 (32)
XV	164 (100)	149 (34), 131 (10), 120 (75), 104 (14), 77 (20), 51 (22), 39 (44), 33 (6)
XVIa	246 (13)	203 (24), 154 (100), 126 (19), 108 (27), 93 (29), 69 (47), 58 (40), 55 (31)
XXIc	204 (68)	203 (29), 176 (100), 175 (73), 143 (22), 78 (59), 71 (37), 69 (26), 63 (16)
XXId	194 (98)	179 (32), 166 (27), 161 (100), 138 (29), 105 (14), 78 (43), 51 (22), 39 (14)
XXIf	313 (4)	207 (15), 179 (30), 107 (100), 91 (12), 78 (18)
XXIh	220 (51)	205 (100), 187 (91), 172 (17), 78 (51)
XXII	402 (12)	297 (9), 105 (100), 91 (14), 77 (38)
XXIII	192 (100)	164 (50), 136 (22), 78 (18), 59 (20), 45 (17)
XXIV	206 (100)	205 (17), 191 (48), 178 (24), 173 (20), 150 (23)
XXVb	339 (3)	205 (100), 177 (68), 131 (20), 120 (19), 73 (12)
XXVc	348 (4)	204 (29), 177 (16), 171 (100), 144 (32), 116 (15)
XXVIa	339 (39)	205 (100), 177 (13), 150 (10), 133 (7), 120 (5)
XXVIb	348 (30)	205 (34), 78 (19), 144 (100), 116 (11)
XXVId	334 (95)	222 (56), 204 (100), 176 (13), 149 (11), 132 (14), 55 (6), 41 (19)

[a] Anion.
[b] Cation.

$N^1(B)H(N^1B)O^1(A)$ 165(2)°. The standard N···O distance for hydrogen bonds like N–H···O is 2.89 Å [11].

When the reaction of thioamides **IX** with 1,3-diketones **XIII** was carried out in the presence of a tertiary amine, *N*-methylmorpholine, as catalyst, the products were compounds **VII**, i.e., the CH acids were not involved in the Michael reaction. On the other hand, the use as a base of morpholine (which is a secondary amine) makes it possible to obtain enamines **XVI** which are stronger nucleophiles than ketones **XIII** [12]; the result is that the Michael reaction does occur.

EXPERIMENTAL

X-Ray diffraction study of a single crystal of **XVIa** was performed at room temperature on an Enraf–Nonius CAD-4 automatic four-circle diffractometer

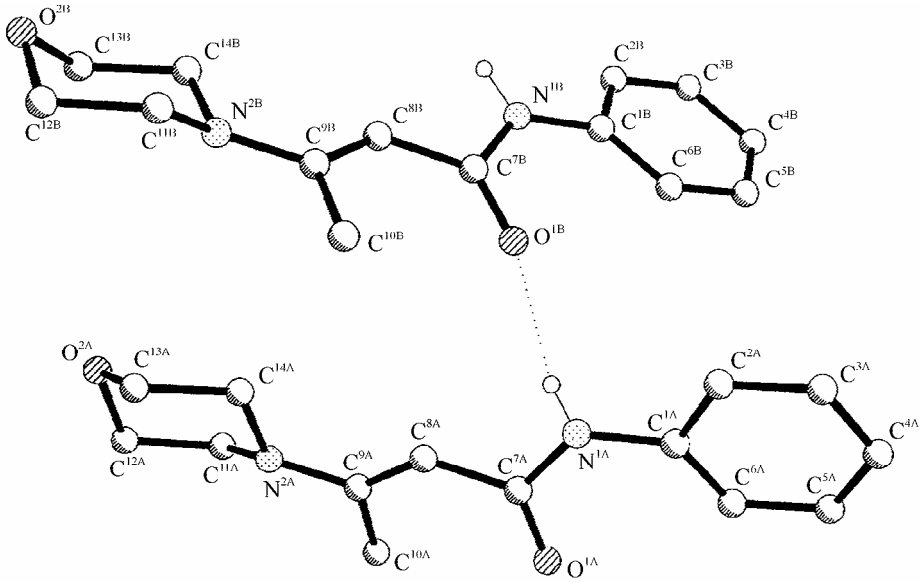


Fig. 1. Structure of two independent molecules of compound **XVIa** with atom numbering.

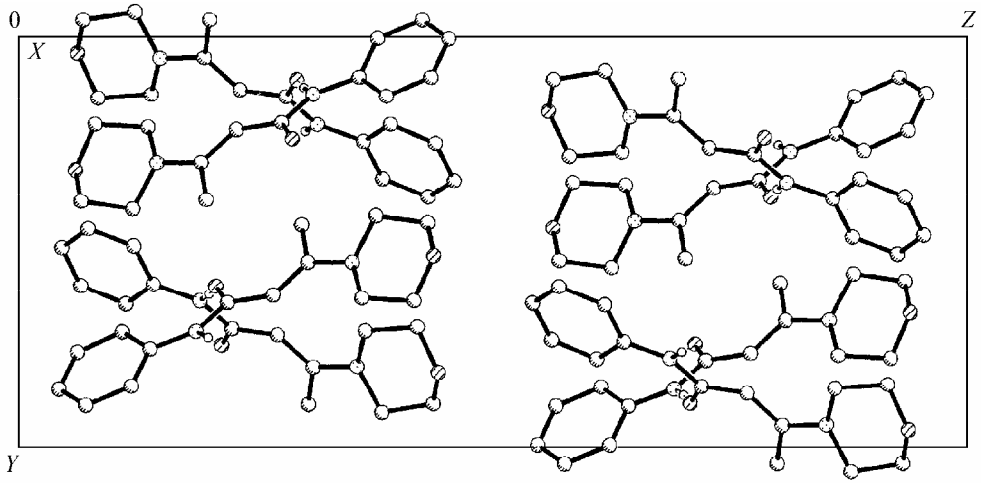


Fig. 2. Packing of molecules **XVIa** in crystal.

(λCuK_α radiation, graphite monochromator, scan rate ratio $\omega/2\theta = 1.2$, $\theta_{max} = 60°$, spherical segment $-9 \le h \le 10$, $-11 \le k \le 12$, $-29 \le l \le 29$). Total of 4335 reflections were measured, 4049 of which were independent (averaging R factor 0.023). Monoclinic crystals; unit cell parameters: $a = 9.195(2)$, $b = 11.300(1)$, $c = 26.207(4)$ Å; $\beta = 90.22(1)°$; $V = 2723.0(8)$ Å^3; $Z = 8$, $d_{calc} = 1.20$ g/cm^3, m = 0.65 mm^{-1}; $F(000) = 1056$; space group $P2_1/n$ (no. 14). The structure was solved by the direct method and was refined by the least-squares procedure in full-matrix anisotropic approximation using SHELXS and SHELXL-93 programs [13]; 3612 reflections with $I > 2\sigma(I)$ were used in the refinement {333 refined parameters, 10.9 reflections per parameters; weight scheme $\omega = 1/[\sigma^2(Fo^2) + (0.0978P)^2 + 0.6018P]$, where $P = (Fo^2 + 2Fc^2)/3$}. A correction for anomalous scattering was introduced; absorption by the sample was not taken into account. All hydrogen atoms were visualized objectively and were included in the refinement with fixed thermal and positional parameters. Exceptions were the H(N^{1A}) and H(N^{1B}) atoms involved in hydrogen bonding; their positions were refined in isotropic approximation. The final divergence factors were $R_1(F) = 0.055$ and $R_W(F^2) = 0.148$, GOF = 1.020; the residual electron density from the Fourier difference synthesis after the last iteration procedure was 0.21 and –0.24 e/Å^3. The coordinates of atoms and their equivalent isotropic (isotropic for hydrogen atoms) thermal parameters are listed in Table 5.

Table 4. Principal bond lengths and bond angles in molecules A and B of compound **XVIa**

Parameter	Molecule A	Molecule B
Bond lengths *d*, Å		
O^1–C^7	1.237(2)	1.238(2)
N^1–C^7	1.359(3)	1.361(3)
N^1–C^1	1.402(3)	1.398(3)
N^1–H(N^1)	0.80(2)	0.86(2)
N^2–C^9	1.377(3)	1.378(3)
C^7–C^8	1.449(3)	1.452(3)
C^8–C^9	1.355(3)	1.357(3)
C^9–C^{10}	1.500(3)	1.498(3)
Bond angles ω, deg		
$C^7N^1C^1$	129.8(2)	129.7(2)
$C^7N^1H(N^1)$	113(2)	110(2)
$C^1N^1H(N^1)$	117(2)	120(2)
$C^9N^2C^{14}$	119.5(2)	119.2(2)
$C^9N^2C^{11}$	119.5(2)	119.4(2)
$C^{14}N^2C^{11}$	111.6(2)	111.9(2)
$O^1C^7N^1$	121.1(2)	121.2(2)
$O^1C^7C^8$	126.0(2)	125.8(2)
$N^1C^7C^8$	112.9(2)	113.1(2)
$C^9C^8C^7$	127.5(2)	127.6(2)
$C^8C^9N^2$	121.8(2)	121.6(2)
$C^8C^9C^{10}$	122.7(2)	122.9(2)
$N^2C^9C^{10}$	115.5(2)	115.5(2)

The IR spectra were measured on an IKS-29 spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra were recorded on Bruker WP-100SY (100 MHz) (compounds **IIIa**, **IIIb**, **VIIa**, **XIV**, **XV**, **XXIe**, **XXIg**), Bruker WM-250 (250.13 MHz) (**VIIb**, **XVIa**, **XXIc**, **XXId**, **XXIh**, **XXII**, **XXIII**), Gemini-200 (199.975 MHz) (**XXIb**, **XXIf**, **XXIV**, **XXVa**–**XXVd**, **XXVIa**–**XXVIc**, **XXVIe**–**XXVIg**), and Bruker DR-500 (500.13 MHz) instruments (**XXVId**) from solutions in DMSO-d_6 using tetramethylsilane as internal reference. The mass spectra were obtained on a Kratos MS-890 spectrometer (electron impact, 70 eV). The melting points were determined on a Koefler device. The progress of reactions was monitored, and the purity of products was checked, by TLC on Silufol UV-254 plates using acetone–hexane (3:5) as eluent; development with iodine vapor.

2-Amino-4,5:6,6-bis(trimethylene)-2,4-cyclohexadiene-1,1,3-tricarbonitrile (IIIa). *N*-Methylmorpholine, 1.1 ml (10 mmol), was added at 20°C to a suspension of 1.5 g (10 mmol) of cyano(cyclopentylidene)acetamide (**Ia**) and 0.66 g (10 mmol) of malononitrile (**II**) in 15 ml of ethanol. The mixture was stirred for 30 min and was left to stand for 24 h. The precipitate was filtered off and washed with ethanol and hexane. Yield 1.95 g (74%), mp 181–182°C. The melting point and ^{1}H NMR spectrum of the product coincided with those reported in [6].

2-Amino-4,5:6,6-bis(tetramethylene)-2,4-cyclohexadiene-1,1,3-tricarbonitrile (IIIb) was synthesized as described above for compound **IIIa**, using cyano(cyclohexylidene)acetamide (**Ib**) as starting compound. Yield 2.36 g (81%), mp 181–183°C. The melting point and ^{1}H NMR spectrum of the product coincided with those reported in [6].

2,2:5,6-Bis(trimethylene)-1,2-dihydrothieno-[2,3-*d*]pyrimidine-4(3*H*)-thione (VIIa). *Method A.* *N*-Methylmorpholine, 1.1 ml (10 mmol), was added at 20°C to a suspension of 1.5 g (10 mmol) of cyano-(cyclopentylidene)acetamide (**Ia**) and 1.0 g (10 mmol) of cyano(thioacetamide) (**VI**) in 15 ml of ethanol. The mixture was stirred for 30 min and was left to stand for 24 h. The precipitate was filtered off and washed with ethanol and hexane. The yield, melting point, and analytical and spectral data of the product are given in Tables 1 and 2.

2,2:5,6-Bis(tetramethylene)-1,2-dihydrothieno-[2,3-*d*]pyrimidine-4(3*H*)-thione (VIIb) was synthesized as described above for compound **VIIa**, using cyano(cyclohexylidene)acetamide (**Ib**) as starting compound (Tables 1–3).

Method B. A mixture of 10 mmol of cyano(cycloalkylidene)(thioacetamide) **IX** and 1.1 ml (10 mmol) of *N*-methylmorpholine in 15 ml of ethanol was stirred for 30 min at 20°C and was left to stand for 24 h. The precipitate was filtered and washed with ethanol and hexane. Compounds **VIIa** and **VIIb** obtained in such a way were identical to those synthesized according to method *A* in the melting points and ^{1}H NMR spectra.

Morpholinium 3-cyano-4-methyl-6-oxo-1,6-dihydropyridine-2-thiolate (XIV). *Method A.* A mixture of 1.66 g (10 mmol) of cyano(cyclopentylidene)-

(thioacetamide) (**IXa**), 1.77 g (10 mmol) of acetoacetanilide (**XIIIa**), and 0.87 ml (10 mmol) of morpholine in 15 ml of ethanol was heated to the boiling point, filtered, and left to stand for 24 h. The precipitate was filtered off and washed with ethanol and hexane. Yield 2.02 g (80%), mp 226– 228°C. The melting point and ^{1}H NMR spectrum of the product coincided with those reported in [8]. The yield of salt **XIV** from thioamide **IXb** was 1.92 g (76%).

Method B. The procedure was the same as in method *A*, but ethyl acetoacetate was used instead of acetoacetanilide. Yield 2.00 g (79%); from thioamide **IXb**, 2.05 g (81%).

4,6-Dimethyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (XV) was synthesized as described above for salt **XIV** (method *A*) from compounds **IXa** and **XIIIc**. Yield 1.29 g (79%), mp 263–265°C (from AcOH); published data [9]: mp 264°C. The yield of **XV** from **IXb** and **XIIIc** was 1.38 g (84%).

3-Morpholino-2-butenanilide (XVIa). A mixture of 1.66 g (10 mmol) of cyano(cyclopentylidene)-(thioacetamide) (**IXa**), 1.77 g (10 mmol) of acetoacetanilide (**XIIIa**), and 0.87 ml (10 mmol) of morpholine in 15 ml of ethanol was stirred for 30 min at 20°C and was left to stand for 48 h. The precipitate was filtered off and washed with ethanol and hexane. Compound **XVIa** was isolated as yellow crystals (Tables 1–5).

2-Substituted 4-methyl-6-oxo-1,6-dihydropyridine-3-carbonitriles XXIa–XXIh were synthesized by the procedure described in [8] (Tables 1–3). The properties of compound **XXIa** were reported in [8].

4-Methyl-2-oxo-1-phenacyl-2-phenacylsulfanyl-1,2-dihydropyridine-3-carbonitrile (XXII). To a solution of 2.84 g (10 mmol) of compound **XXIa** in 10 ml of DMF we added 5.6 ml (10 mmol) of a 10% aqueous solution of potassium hydroxide and 1.99 g (10 mmol) of phenacyl bromide (**XXa**). The mixture was stirred for 3 h, diluted with 15 ml of water, and left to stand for 24 h. The precipitate was filtered off and washed with ethanol and hexane. Compound **XXII** was isolated as a white powder (Tables 1–3).

7-Methyl-5-oxo-2,3-dihydrothiazolo[3,2-*a*]pyridine-8-carbonitrile (XXIII). To a solution of 2.53 g (10 mmol) of salt **XIV** in 10 ml of DMF we added 5.6 ml (10 mmol) of a 10% aqueous solution of potassium hydroxide and 0.86 ml (10 mmol) of 1,2-dibromoethane. The mixture was stirred for 3 h, an additional portion (5.6 ml, 10 mmol) of 10% aqueous KOH was added, and the mixture was left to

Table 5. Coordinates of atoms ($\times10^4$) and their equivalent anisotropic (isotropic for hydrogen atoms) thermal parameters (U_{eq}, Å$^2\times10^3$) in structure **XVIa**

Atom	*x*	*y*	*z*	U_{eq}
O^1(A)	2623(2)	7458(2)	2117(1)	64(1)
O^2(A)	6900(3)	8163(2)	4399(1)	102(1)
N^1(A)	4586(2)	6374(2)	1893(1)	54(1)
N^2(A)	5007(2)	8006(2)	3542(1)	58(1)
C^1(A)	4183(2)	5965(2)	1407(1)	48(1)
C^2(A)	4983(3)	5028(2)	1206(1)	57(1)
C^3(A)	4648(3)	4595(2)	730(1)	72(1)
C^4(A)	3531(3)	5053(3)	450(1)	81(1)
C^5(A)	2740(3)	5983(3)	646(1)	73(1)
C^6(A)	3063(3)	6437(2)	1119(1)	59(1)
C^7(A)	3837(2)	7060(2)	2227(1)	49(1)
C^8(A)	4596(2)	7223(2)	2708(1)	55(1)
C^9(A)	4283(2)	8012(2)	3081(1)	51(1)
C^{10}(A)	3102(3)	8921(2)	3029(1)	67(1)
C^{11}(A)	5309(3)	9128(2)	3801(1)	74(1)
C^{12}(A)	5714(4)	8931(3)	4345(1)	95(1)
C^{13}(A)	6520(4)	7057(3)	4186(1)	93(1)
C^{14}(A)	6154(3)	7143(3)	3632(1)	81(1)
H(N^{1}A)	5393(27)	6213(21)	1989(9)	53(7)
O^1(B)	7623(2)	6021(2)	2060(1)	65(1)
O^2(B)	11796(2)	5322(2)	4366(1)	95(1)
N^1(B)	9596(2)	7115(2)	1850(1)	54(1)
N^2(B)	9926(2)	5470(2)	3502(1)	56(1)
C^1(B)	9212(2)	7535(2)	1366(1)	49(1)
C^2(B)	10073(3)	8438(2)	1167(1)	60(1)
C^3(B)	9777(3)	8895(3)	689(1)	75(1)
C^4(B)	8624(3)	8497(3)	410(1)	80(1)
C^5(B)	7767(3)	7599(3)	606(1)	72(1)
C^6(B)	8060(3)	7118(2)	1078(1)	59(1)
C^7(B)	8828(2)	6426(2)	2179(1)	49(1)
C^8(B)	9561(2)	6253(2)	2665(1)	54(1)
C^9(B)	9226(2)	5463(2)	3036(1)	49(1)
C^{10}(B)	8054(3)	4552(2)	2976(1)	65(1)
C^{11}(B)	10240(3)	4345(2)	3758(1)	71(1)
C^{12}(B)	10628(4)	4528(3)	4304(1)	86(1)
C^{13}(B)	11403(4)	6422(3)	4153(1)	97(1)
C^{14}(B)	11052(3)	6344(3)	3597(1)	83(1)
H(N^{1}B)	10439(28)	7276(21)	1977(9)	59(7)

stand for 24 h. It was then diluted with 15 ml of water and kept for 5 h, and the precipitate was filtered off and washed in succession with water, ethanol, and hexane. Compound **XXIII** was isolated as a white cottonlike material (Tables 1–3).

8-Methyl-6-oxo-3,4-dihydro-2*H*-[1,3]thiazino-[3,2-*a*]pyridine-9-carbonitrile (XXIV) was synthesized as described above for compound **XXIII**, using 1.01 ml (10 mmol) of 1,3-dibromopropane (Tables 1–3).

2-Substituted 4,6-dimethylpyridine-3-carbonitriles XXVa–XXVd (*general procedure***).** To a solution of 1.64 g (10 mmol) of compound **XV** in 10 ml of DMF we added under stirring 5.6 ml (10 mmol) of a 10% aqueous solution of potassium hydroxide and 10 mmol of the corresponding halogen derivative **XXi**–**XXl**. The mixture was stirred for 30 min and diluted with 15 ml of water, and the precipitate was filtered off and washed in succession with water, ethanol, and hexane (Tables 1–3).

2-Substituted 3-amino-4,6-dimethylthieno-[2,3-*b*]pyridines XXVIa–XXVIg (*general procedure***).** *Method A*. To a solution of 10 mmol of the corresponding sulfide **XXV** in 15 ml of DMF we added 5.6 ml (10 mmol) of a 10% aqueous solution of potassium hydroxide, and the mixture was stirred for 2 h. The precipitate was filtered off and washed in succession with water, ethanol, and hexane (Tables 1–3).

Method B. To a solution of 1.64 g (10 mmol) of pyridinethione **XV** in 10 ml of DMF we added with stirring 5.6 ml (10 mmol) of a 10% aqueous solution of potassium hydroxide and then 10 mmol of the corresponding halogen derivative **XXj**–**XXp**. The mixture was stirred for 30 min, an additional 5.6 ml (10 mmol) of 10% aqueous KOH was added, and the mixture was stirred for 2 h. The precipitate was filtered off and washed in succession with water, ethanol, and hexane (Tables 1–3).

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