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Cyclohexene-4-carbaldehyde in the Synthesis of 4-(Cyclohex-3-enyl)-Substituted 4*H*-Chromenes, 4*H*-Thiopyrans, 1,4,5,6,7,8-Hexahydroquinolines, 1,4-Dihydropyridines, Pyridines, and 6,7-Dihydro-5*H*-[1]pyrindines

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Abstract — Cyclocondensation of cyclohexene-4-carbaldehyde in the presence of morpholine with CH acids [malonodinitrile, dimedone, 1,3-cyclohexanedione, ethyl acetoacetate, cyanothioacetamide, β-aminophenol, resorcinol, and 4-(cyclopent-1-enyl)morpholine] yields the corresponding 4-(cyclohex-3-enyl)-substituted 4*H*-chromenes, 4*H*-thiopyrans, 1,4,5,6,7,8-hexahydroquinolines, 1,4-dihydropyridines, and 6,7-dihydro-5*H*-[1]pyrindines.

A promising strategy of the modern organic synthesis is performing a sequence of reactions without isolating intermediates (one-pot process). In this case, complex molecules can be "assembled" under mild conditions, often regio- and stereoselectively [1–6].

Proceeding with studies on the synthesis of heterocyclic compounds by multicomponent condensation [1–7], we studied the reaction of cyclohexene-4-carbaldehyde **I** with various CH acids under the conditions of the Knoevenagel reaction. Aliphatic aldehydes are used in the synthesis or carbo- and heterocycles to a lesser extent than their aromatic analogs, which may be associated with their higher toxicity, inflammability, and tendency to readily polymerize [12].

Here we report that aldehyde **I**, which was successfully used previously for preparing compounds with selective juvenile activity [13], enters into condensation with cyanothioacetamide **II** and 4-(cyclopent-1-enyl)morpholine **III** in the presence of a base B. The reaction occurs at 20°C in ethanol and yields 2-thioxo-4-(cyclohex-3-enyl)-2,5,6,7-tetrahydro-1*H*-[1]-pyrindine-3-carbonitrile **IV** as final product. The reaction apparently occurs via formation of Knoevenagel reaction product **V**, which subsequently undergoes regioselective Stork alkylation [14] with cyclopentanone enamine **III** to the corresponding derivative **VI**. This is followed by intramolecular amine interchange and dehydrogenation with the formation of **IV**. The composition and structure of **IV** were confirmed by elemental analysis (Table 1), spectroscopy (Table 2), and chemical transformations. In particular, alkylation of pyrindine-2-thione **IV** with **VIIa**–**VIIj** in DMF in a basic medium yields the corresponding organic sulfides **VIIIa**–**VIIIj**. The subsequent treatment of **VIIIa** with an aqueous alkali is accompanied by the intramolecular Thorpe reaction with the formation of imino derivative **IX** stabilized in the form of 3-amino-6,7-dihydro-4-(cyclohex-3-enyl)-8-aza-5*H*-thiaindacene-2-carbonitrile **X**, which is in agreement with the known chemical properties of 3-cyanopyridine-2-(1*H*)-thiones and their 2-alkylthio-substituted analogs [15, 16]. Note that compound **X** shows promise in synthesis of polycondensed heterocycles [17] and in development of substances with antibacterial [18–22] and antitumor [23] activity, telomerase inhibitors [24], and compounds with other kinds of biological activity [25].

With malonodinitrile **XI** taken instead of **III** in the condensation with aldehyde **I** and amide **II**, the reaction yields 2,6-diamino-4-(cyclohex-3-enyl)-4*H*-thiopyran-3,5-dicarbonitrile **XII** as a result of the Michael addition of CH acid **XI** to hypothetical alkene **V**. The adduct **XIII** arising in the process regioselectively cyclizes into compound **XII**. The latter, when refluxed in ethanol in the presence of an equimolar amount of morpholine, undergoes recyclization, similarly to 4-aryl-substituted analogs [26–29], into morpholinium 6-amino-3,5-dicyano-4-(cyclohex-3-enyl)pyridine-2-thiolate **XIV**. Treatment of an ethanol solution of **XIV** with a solution of hydrochloric acid in ethanol yields 6-amino-1,2-dihydro-2-thioxo-4-(cyclohex-3-enyl)py-

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Table 1. Yields, melting points, and elemental analyses of **IV, VIIIa**–**VIIIj, X, XII, XIV**–**XVI, XVIIIa**–**XVIIIc, XXII**, **XXIV, XXVIa, XXVIb**, and **XXIX**

Comp. no.	Yield, %	mp, °C (solvent for crystallization)	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IV	86	262–265[a] (AcOH)	70.14	6.12	10.88	$C_{15}H_{16}N_2S$	70.28	6.29	10.93
VIIIa	85	133–134 (EtOH)	68.95	5.71	14.16	$C_{17}H_{17}N_3S$	69.12	5.80	14.22
VIIIb	79	130–131 (EtOH)	65.70	5.96	8.42	$C_{18}H_{20}N_2O_2S$	65.83	6.14	8.53
VIIIc	81	111–113 (PrOH)	76.14	6.31	7.95	$C_{22}H_{22}N_2S$	76.26	6.40	8.08
VIIId	88	105–106 (*i*-PrOH)	67.22	6.58	7.72	$C_{20}H_{24}N_2O_2S$	67.39	6.79	7.86
VIIIe	87	109–110 (EtOH)	66.50	6.37	7.99	$C_{19}H_{22}N_2O_2S$	66.64	6.48	8.18
VIIIf	92	92–93 (EtOH)	71.60	6.88	9.74	$C_{17}H_{20}N_2S$	71.79	7.09	9.85
VIIIg	73	121–122 (AcOH)	73.60	6.14	7.31	$C_{23}H_{22}N_2OS$	73.76	5.92	7.48
VIIIh	90	117–118 (AcOH)	67.44	4.99	6.72	$C_{23}H_{21}ClN_2OS$	67.55	5.18	6.85
VIIIi	85	85–86 (EtOH)	72.81	6.64	9.32	$C_{18}H_{20}N_2S$	72.93	6.80	9.45
VIIIj	94	188–190 (BuOH)	70.38	4.88	6.19	$C_{26}H_{22}N_2O_3S$	70.57	5.01	6.33
X	70	173–175 (AcOH)	68.91	5.72	14.03	$C_{17}H_{17}N_3S$	69.12	5.80	14.22
XII	81	199–201 (EtOH)	60.31	5.39	21.50	$C_{13}H_{14}N_4S$	60.44	5.46	21.69
XIV	80	174–176 (EtOH)	59.28	5.93	20.22	$C_{17}H_{21}N_5OS$	59.45	6.16	20.39
XVA	77	229–231 (AcOH)	60.82	4.58	21.70	$C_{13}H_{12}N_4S$	60.91	4.72	21.86
XVI	72	235–237 (EtOH)	67.28	4.70	15.11	$C_{21}H_{18}N_4OS$	67.36	4.85	14.96
XVIIIa	76	189–190 (BuOH)	62.88	6.04	12.32	$C_{18}H_{21}N_3O_2S$	62.95	6.16	12.24
XVIIIb	79	233–235 (AcOH)	59.26	5.41	8.14	$C_{26}H_{28}BrN_3O_2S$	59.31	5.36	7.98
XVIIIc	76	206–208 (AcOH)	69.34	7.14	8.42	$C_{19}H_{24}N_2OS$	69.48	7.37	8.53
XXII	68	228–230[b] (EtOH)	63.01	6.48	9.15	$C_{16}H_{20}N_2O_2S$	63.13	6.62	9.20
XXIV	70	184–186 (EtOH)	59.68	6.32	11.50	$C_{18}H_{23}N_3O_3S$	59.81	6.41	11.63
XXVIa	95	227–229 (EtOH)	71.51	5.88	10.33	$C_{16}H_{16}N_2O_2$	71.62	6.01	10.44
XXVIb	80	194–196 (EtOH)	71.72	6.29	15.64	$C_{16}H_{17}N_3O$	71.89	6.41	15.72
XXIX	76	177–179 (EtOH)	76.92	6.02	7.74	$C_{23}H_{22}N_2O_2$	77.07	6.19	7.82

Notes: Sublimation temperature, °C: [a] 220 and [b] 110.

Table 2. IR and ^{1}H NMR spectra of **IV, VIIIa**–**VIIIj, X, XII, XIV**–**XVI, XVIIIa**–**XVIIIc, XXII, XXIV, XXVIa, XXVIb**, and **XXIX**

Comp. no.	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
IV	1218 (C=S), 2219 (C≡N)	1.79 m (1H, CH), 2.04 m (6H, $3CH_2$), 2.41 m (1H, CH), 2.85 m (4H, CH), 3.10 m (1H, CH), 5.79 m (2H, CH=CH), 14.16 br.s (1H, NH)
VIIIa	2224, 2253 (C≡N)	1.78 m (1H, CH), 2.05–2.23 m (6H, $3CH_2$), 2.40 m (1H, CH), 3.02 m (4H, CH), 3.14 m (1H, CH), 4.32 s (2H, SCH_2), 5.77 m (2H, CH=CH)
VIIIb	1740 (C=O), 2223 (C≡N)	1.80 m (1H, CH), 2.06–2.19 m (6H, $3CH_2$), 2.42 m (1H, CH), 2.91–3.09 m (5H, CH), 3.66 s (3H, Me), 4.11 s (2H, SCH_2), 5.78 m (2H, CH=CH)
VIIIc	2218 (C≡N)	1.79 m (1H, CH), 2.01–2.18 m (6H, $3CH_2$), 2.37 m (1H, CH), 2.99 m (4H, CH), 3.14 m (1H, CH), 4.46 s (2H, SCH_2), 5.76 m (2H, CH=CH), 7.22 t (1H, Ph, *J* 7.14), 7.29 t (2H, Ph), 7.38 d (2H, Ph, *J* 7.54)
VIIId	1722 (C=O), 2215 (C≡N)	1.21 d (6H, 2Me, *J* 5.02), 1.78 m (1H, CH), 2.02–2.23 m (6H, $3CH_2$), 2.44 m (1H, CH), 3.91 t (2H, CH_2, *J* 6.15), 2.99 t (2H, CH_2, *J* 6.13), 3.07 m (1H, CH), 3.97 s (2H, SCH_2), 4.92 m (1H, OCH), 5.76 m (2H, CH=CH)

Table 2. (Contd.)

Comp. no.	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)
VIIIe	1733 (C=O), 2217 (C≡N)	1.26 t (3H, Me, *J* 7.21), 1.81 m (1H, CH), 2.08–2.19 m (6H, $3CH_2$), 2.42 m (1H, CH), 2.93 t (2H, CH_2, *J* 8.01), 2.30 t (2H, CH_2, *J* 7.21), 3.10 m (1H, CH), 3.99 s (2H, SCH_2), 4.15 q (2H, OCH_2, *J* 7.21), 5.77 m (2H, CH=CH)
VIIIf	2220 (C≡N)	1.32 t (3H, Me, *J* 6.04), 1.76 m (1H, CH), 2.01–2.23 m (6H, $3CH_2$), 2.44 t (2H, CH_2, *J* 7.22), 2.95 m (3H, CH), 3.01 m (1H, CH), 3.23 t (2H, SCH_2, *J* 6.04), 5.77 m (2H, CH=CH)
VIIIg	1694 (C=O), 2219 (C≡N)	1.77 m (1H, CH), 1.95–2.24 m (6H, $3CH_2$), 2.42 m (1H, CH), 2.73 t (2H, CH_2, *J* 7.61), 2.95 t (2H, CH_2, *J* 8.41), 3.01 m (1H, CH), 4.74 s (2H, SCH_2), 5.77 m (2H, CH=CH), 7.54 t (2H, Ph, *J* 6.95), 7.63 t (1H, Ph, *J* 6.95), 8.02 d (2H, Ph, *J* 7.03)
VIIIh	1688 (C=O), 2215 (C≡N)	1.79 m (1H, CH), 1.94–2.22 m (6H, $3CH_2$), 2.39 m (1H, CH), 2.72 t (2H, CH_2, *J* 8.41), 2.95 t (2H, CH_2, *J* 7.61), 3.08 m (1H, CH), 4.70 s (2H, SCH_2), 5.77 m (2H, CH=CH), 7.57 d and 8.04 d (2H each, C_6H_4, *J* 8.41)
VIIIi	2226 (C≡N)	1.78 m (1H, CH), 2.03–2.19 m (6H, $3CH_2$), 2.37 m (1H, CH), 2.96 m (4H, $2CH_2$), 3.07 m (1H, CH), 3.92 d (2H, SCH_2, *J* 6.58), 5.12 d (1H, $=CH_2$, J_{cis} 9.54), 5.34 d (1H, $=CH_2$, J_{trans} 17.49), 5.79 m (2H, CH=CH), 5.96 m (1H, CH=)
VIIIj	1685, 1726 (C=O), 2218 (C≡N)	1.76 m (1H, CH), 1.93–2.18 m (6H, $3CH_2$), 2.37 m (1H, CH), 2.74 t (2H, CH_2, *J* 8.42), 2.99 t (2H, CH_2, *J* 8.38), 3.06 m (1H, CH), 4.74 s (2H, SCH_2), 5.76 m (2H, CH=CH), 7.44 t (1H, H arom., *J* 7.85), 7.51 d (1H, H arom.), 7.78 t (1H, H arom., *J* 7.94), 7.99 d (1H, H arom.), 8.71 s (1H, C^4H of coumarin)
X	1648 [δ(NH_2)], 2194 (C≡N), 3182, 3330, 3445 (NH_2)	1.84 m (1H, CH), 2.02–2.19 m (4H, $2CH_2$), 2.25 m (2H, CH_2), 2.36 m (1H, CH), 2.94 m (2H, CH_2), 3.11 t (2H, CH_2, *J* 7.54), 3.90 m (1H, CH), 5.79 m (2H, CH=CH), 5.97 br.s (2H, NH_2)
XII	1645 [δ(NH_2)], 2195 (C≡N), 3310, 3388, 3420 (NH_2)	1.24 m (1H, CH), 1.63–2.18 m (6H, $3CH_2$), 2.82 d (1H, C^4H, *J* 13.14), 5.64 m (2H, CH=CH), 6.86 br.s (4H, $2NH_2$)
XIV[a]	1648 [δ(NH_2)], 2208 (C≡N), 3211, 3340, 3442 (NH_2)	1.68 m (1H, CH), 2.03–2.38 m (6H, $3CH_2$), 3.13 t (4H, CH_2NCH_2, *J* 4.37), 3.72 t (4H, CH_2OCH_2), 5.75 m (2H, CH=CH), 7.48 br.s (2H, NH_2)
XVA	1213 (C=S), 1640 [δ(NH_2)], 2200 (C≡N), 3190, 3288, 3350 (NH_2)	1.73 m (1H, CH), 2.01–2.33 m (6H, $3CH_2$), 5.78 m (2H, CH=CH), 7.82 br.s (2H, NH_2), 12.91 br.s (1H, NH)
XVI	1642 [δ(NH_2)], 1686 (C=O), 2200 (C≡N), 3205, 3321, 3466 (NH_2)	1.80 m (1H, CH), 2.05–2.32 m (6H, $3CH_2$), 4.96 s (2H, SCH_2), 5.78 m (2H, CH=CH), 7.48–7.70 m (3H, Ph), 7.77 br.s (2H, NH_2), 8.06 d (2H, Ph, *J* 7.12)
XVIIIa	1668 (CONH), 1712 (C=O), 2196 (C≡N), 3310 (NH)	1.14 m (1H, CH), 1.33–2.34 m (12H, $6CH_2$), 3.61 d and 3.87 d (1H each, SCH_2, ^2J 14.76), 3.41 d (1H, C^4H, *J* 7.20), 5.58 m (2H, CH=CH), 7.53 br.s and 7.85 br.s (1H each, NH_2), 10.47 br.s (1H, NH)
XVIIIb	1674 (CONH), 1695 (C=O), 2202 (C≡N), 3337 (NH)	1.02 s (6H, 2Me), 1.18 m (1H, CH), 1.42–1.95 m (6H, $3CH_2$), 2.18 s (2H, CH_2), 2.38 s (2H, CH_2), 3.44 d (1H, C^4H, *J* 7.18), 3.99 s (2H, SCH_2), 5.56 m (2H, CH=CH), 7.49 d and 7.52 d (2H each, C_6H_4, *J* 7.52), 9.92 br.s (1H, NH), 10.46 br.s (1H, CONH)
XVIIIc	1688 (C=O), 2200 (C≡N), 3325 (NH)	0.95 s (3H, Me), 1.02 s (3H, Me), 1.48 m (1H, CH), 1.59–2.14 m (6H, $3CH_2$), 2.19 s (2H, CH_2), 2.40 s (2H, CH_2), 2.48 s (3H, SMe), 3.48 d (1H, C^4H, *J* 7.04), 5.60 m (2H, CH=CH), 9.61 br.s (1H, NH)
XXII	1720 (C=O), 2247 (C≡N)	1.30 t (3H, CH_2CH_3, *J* 6.19), 1.58 m (1H, CH), 1.64–1.99 m (6H, $3CH_2$), 2.27 s (3H, Me), 4.01 d (1H, C^3H, *J* 4.13), 4.15 m (3H, C^4H and OCH_2), 5.51 m (2H, CH=CH), 9.38 br.s (1H, NH)
XXIV	1668 (CONH), 1734 (C=O), 2205 (C≡N), 3302 (NH)	1.29 t (3H, CH_2CH_3, *J* 6.21), 1.52 m (1H, CH), 1.63–2.14 m (6H, $3CH_2$), 2.29 s (3H, Me), 3.42 d (1H, C^4H, *J* 4.18), 3.48 d and 3.59 d (1H each, SCH_2, ^2J 15.14), 4.12 q (2H, OCH_2), 5.58 m (2H, CH=CH), 7.41 br.s and 7.82 br.s (1H each, NH_2), 10.43 br.s (1H, NH)

Table 2. (Contd.)

Comp. no.	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)
XXVIa	1648 [δ(NH_2)], 2200 (C≡N), 3172, 3314, 3445 (NH_2), 3496 (OH)	1.21 m (1H, CH), 1.62–2.17 m (6H, $3CH_2$), 3.36 d (1H, C^4H, *J* 3.17), 5.61 m (2H, CH=CH), 6.39 s (1H, C^8H), 6.52 d (1H, C^6H, *J* 8.46), 6.61 br.s (2H, NH_2), 6.99 d (1H, C^5H), 9.47 br.s (1H, OH)
XXVIb	1647 [δ(NH_2)], 2195 (C≡N), 3336, 3390, 3471 (NH_2)	1.42 m (1H, CH), 1.64 m (4H, $2CH_2$), 1.96 m (2H, CH_2), 3.44 d (1H, C^4H, *J* 3.14), 5.16 br.s (2H, C^7NH_2), 5.18 m (2H, CH=CH), 6.19 s (1H, C^8H), 6.33 d (1H, C^6H, *J* 8.44), 6.65 br.s (2H, NH_2), 6.82 d (1H, C^5H)
XXIX	1649 [δ(NH_2)], 2193 (C≡N), 3330, 3372, 3484 (NH_2)	1.25 m (1H, CH), 1.72–2.15 m (6H, $3CH_2$), 3.36 d (1H, C^4H, *J* 3.01), 5.04 s (2H, OCH_2), 5.55 m (2H, CH=CH), 6.46 br.s (2H, NH_2), 6.57 s (1H, C^8H), 6.71 d (1H, C^6H, *J* 8.43), 6.99 d (1H, C^5H), 7.59 t (1H, Ph, *J* 6.91), 7.71 t (2H, Ph), 7.80 d (2H, Ph, *J* 6.95)

[a] The $^+NH_2$ signals are not manifested, probably besause of deuterium exshange.

ridine-3,5-dicarbonitrile **XVA**. The corresponding prototropic tautomer **XVB** is apparently unstable under the conditions of recording the ^1H NMR and IR spectra. In particular, the IR spectrum of **XV** contains, along with the characteristic absorption bands of the cyano and amino groups (Table 2), also an absorption band of the stretching vibrations of the C=S group at 2212 cm^{-1}, in agreement with [30, 31]. The ^1H NMR spectrum of **XV** contains, along with proton signals from the cyclohexenyl substituent and amino group (Table 2), also an NH signal of the pyridine core in the form of a broadened singlet at δ 12.91 ppm, typical of the related compounds [29]. The saltlike structure of **XIV** is readily confirmed by spectroscopic data (Table 2) and by the fact that this compound reacts with phenacyl bromide **VIIg** in DMF to form the expected organic sulfide **XVI**.

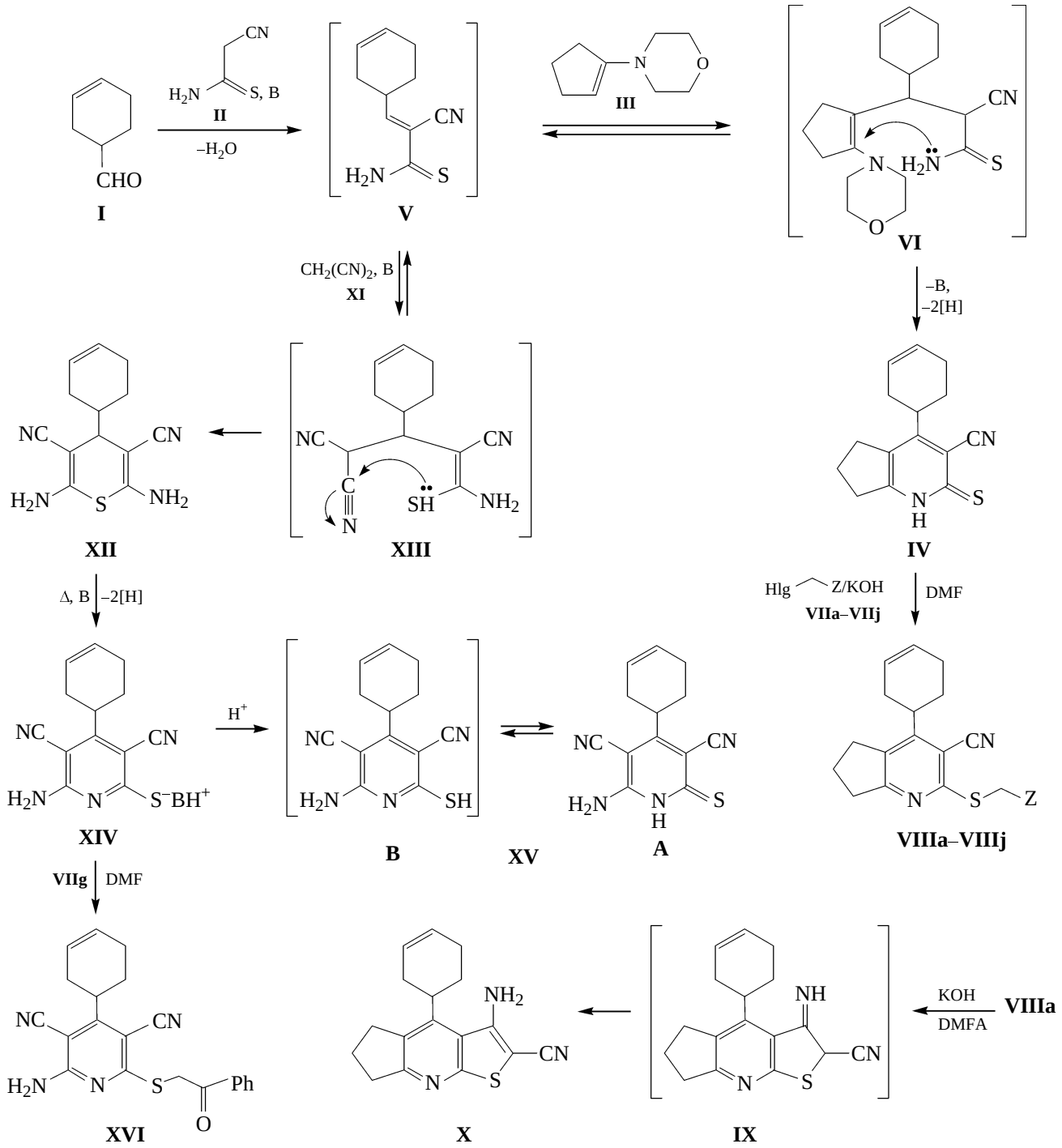
Multicomponent condensation involving aldehyde **I**, CH acid **II**, 1,3-dicarbonyl component **XVII**, morpholine, and alkyl halides **VIIk**–**VIIm** in ethanol at 20°C yields as final products substituted partially hydrogenated 2-alkylsulfanylquinoline-3-carbonitriles **XVIIIa**–**XVIIIc**. Taking into account the structure of **XVIIIa**–**XVIIIc**, we can suggest the following condensation scheme: initially alkene **V** is formed, which is followed by Michael addition of CH acid **XVII**. Adduct **XIX** arising in the process undergoes regioselective cyclocondensation to salt **XX**. The latter reacts with alkylating agents **VIIk**–**VIIm** to form the corresponding derivatives **XVIIIa**–**XVIIIc**. Replacement of diketones **XVIIa** and **XVIIb** in this reaction by ethyl acetoacetate **XXI** and exclusion of alkyl halides **VIIk**–**XIIm** result in formation of substituted ethyl 6-thioxo-5-cyano-1,4,5,6-tetrahydropyridine-3-carboxylate **XXII**. The pathway of its formation is similar to that of **XX**. The Michael adduct in this case will probably have structure **XXIII**. In alkylation of **XXII** with chloroacetamide **VIIk**, we obtained ethyl 6-carbamoylmethylsulfanyl-2-methyl-5-cyano-4-(cyclohex-3-enyl)-1,4-dihydropyridine-3-carboxylate **XXIV**, which, along with the spectroscopic data (Table 2), additionally confirms the thione structure of **XXII**.

By using dinitrile **XI** and phenols **XXVa** and **XXVb** as CH-acid components in the reaction with **I** under mild conditions (20°C) in ethanol in the presence of morpholine, it is possible to prepare 4*H*-chromene-3-carbonitriles **XXVIa** and **XXVIb** showing promise in a search for new drugs [32–34]. Apparently, the reaction occurs via formation of cyclohex-3-enylmethylenemalonodinitrile **XXVII** acting subsequently as substrate in the Michael addition of phenols **XXVa** and **XXVb**. The subsequent intramolecular cyclization of adducts **XXVIIIa** and **XXVIIIb** thus formed gives as final products compounds **XXVIa** and **XXVIb** in quantitative yield. In the presence of an ethanol solution of sodium ethylate, product **XXVIa** is smoothly alkylated with benzyl chloride **VIIc** to 2-amino-7-benzyloxy-4-(cyclohex-3-enyl)-4*H*-chromene-3-carbonitrile **XXIX**. The ^1H NMR and IR spectra of the product (Table 2) are well consistent with the suggested structure.

Thus, condensation of cyclohexene-4-carbaldehyde with various CH acids under mild conditions is a promising route to potentially bioactive substances.

EXPERIMENTAL

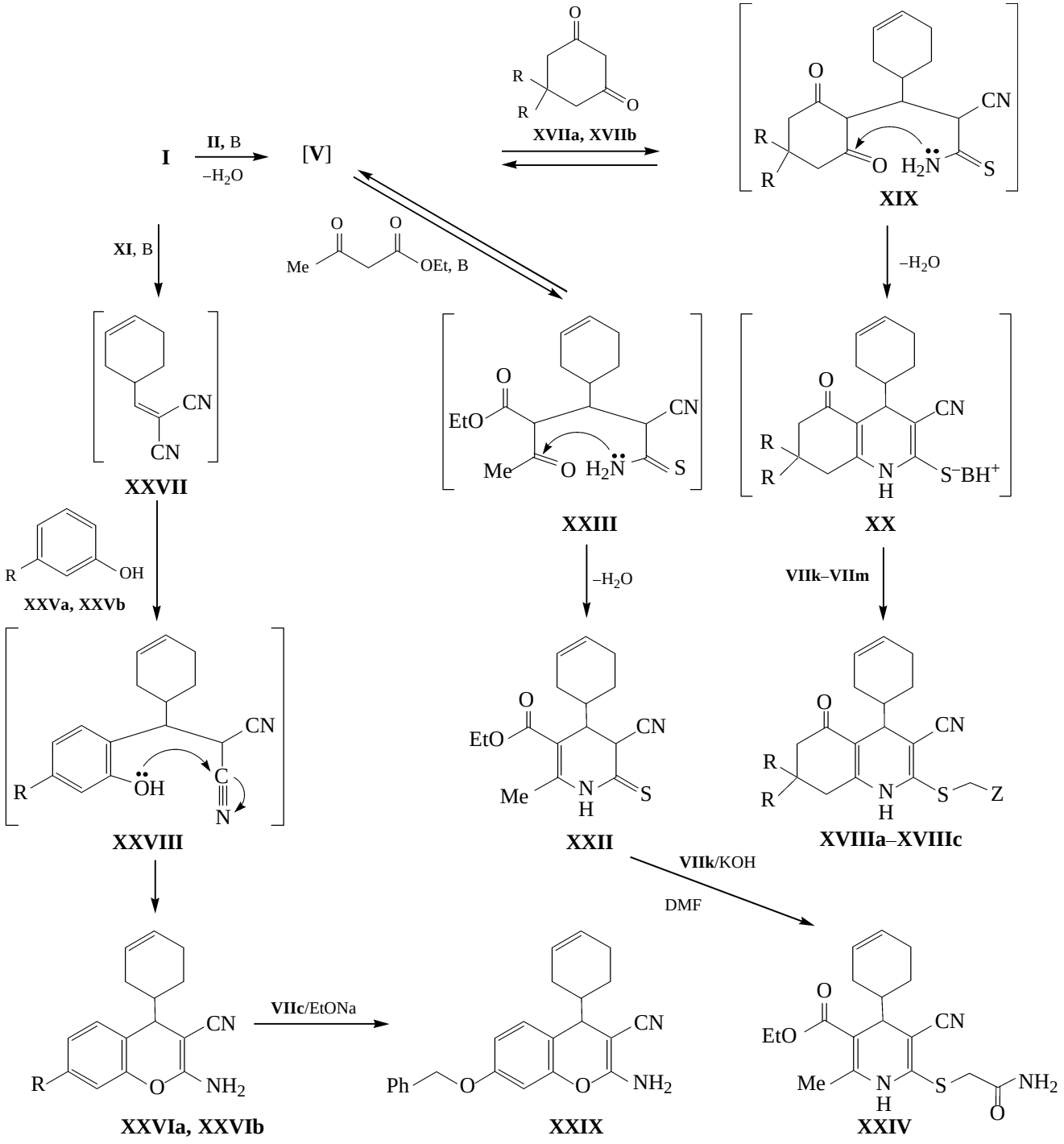
The IR spectra were recorded on an IKS-29 spectrometer from mulls in mineral oil and $CHCl_3$ solutions (compounds **IV**, **XV**). The ^1H NMR spectra



VII, Hlg = Cl (**a**–**e**), I (**f**), Br (**g**–**j**); **VII, VIII**, Z = CN (**a**), CO_2Me (**b**), Ph (**c**), $CO_2CH(Me)_2$ (**d**), CO_2Et (**e**), Me (**f**), PhCO (**g**), 4-ClC_6H_4CO (**h**), $CH{=}CH_2$ (**i**), coumarin-1-ylcarbonyl (**j**); B = morpholine.

were taken on Bruker WP-100SY (100 MHz, compounds **XII**, **XV**, **XVI**, **XVIIIa**, **XVIIIc**), Bruker WM-250 (250.13 MHz, compounds **XIV**, **XVIa**), Bruker AM-300 (300.13 MHz, compounds **VIIIb**, **XVIb**), and Bruker DR-500 (500.13 MHz, compounds **IV**, **VIIIa**–**VIIIj, X, XIX, XXII, XXIV**) spectrometers in DMSO-d_6, internal reference TMS. The mass spectra were recorded on a Kratos MS-890 mass spectrometer (70 eV) with direct sample inlet.

The melting points were determined with a Koefler device.



VII, Hlg = I, Z = $CONH_2$ (**k**); Hlg = Cl, 4-BrC_6H_4NHCO (**l**); Hlg = I, H (**m**). **XVII**, R = H (**a**), Me (**b**). **XVIII**, R = H, Z = $CONH_2$ (**a**); R = Me, Z = 4-BrC_6H_4NHCO (**b**); R = Me, Z = H (**c**). **XXV, XXVI**, R = OH (**a**), NH_2 (**b**).

The reaction progress was monitored by TLC (Silufol UV-254, acetone–hexane, 3 : 5; development with iodine vapor).

2-Thioxo-4-(cyclohex-3-enyl)-2,5,6,7-tetrahydro-1*H*-[1]pyrindine-3-carbonitrile IV. To a mixture of 10 mmol of aldehyde **I** and 10 mmol of amide **II** in 15 ml of absolute ethanol, we added three drops of morpholine, and the mixture was stirred for 5 min at 20°C. Then 10 mmol of substituted morpholine **III** was added, and the mixture was stirred for 40 min and kept for 24 h at room temperature, after which it was

acidified with 10% HCl to pH 5 and allowed to stand for 2 days. The precipitate thus formed was filtered off and washed with water, ethanol, and hexane (in the subsequent experiments the precipitates were worked up similarly, unless otherwise indicated).

2-*Z*-Methylsulfanyl-4-(cyclohex-3-enyl)pyridine-3-carbonitriles VIIIa–VIIIj. To a solution of 10 mmol of **IV** in 12 ml of DMF we added successively 5.6 ml of 10% aqueous KOH (10 mmol) and 10 mmol of appropriate halide **VIIa**–**VIIj**. The mixture was stirred for 1 h and diluted with an equal volume of water.

3-Amino-6,7-dihydro-4-(cyclohex-3-enyl)-8-aza-5*H*-thiaindacene-2-carbonitrile X. To a solution of 10 mmol of **VIIIa** in 15 ml of DMF, we added with stirring 5.6 ml of 10% aqueous KOH (10 mmol). The stirring was continued for an additional 2 h, after which the mixture was gradually diluted with an equal volume of water. Mass spectrum, *m/z* (I_{rel}, %): 297 (6) $[M + 2]^+$, 296 (20) $[M + 1]^+$, 295 (100) $[M]^+$, 294 (14) $[M - 1]^+$, 278 (9), 266 (9), 254 (8), 253 (15), 252 (55), 241 (39), 240 (50), 226 (19), 213 (14), 186 (10), 140 (8), 115 (5), 77 (6), 54 (7), 39 (16).

2,6-Diamino-4-(cyclohex-3-enyl)-4*H*-thiopyran-3,5-dicarbonitrile XII. To a mixture of 10 mmol of **I** and 10 mmol of **II** in 15 ml of absolute ethanol, we added three drops of morpholine, and the mixture was stirred for 5 min. Then 10 mmol of dinitrile **XI** was added, and the mixture was stirred for 10 min and allowed to stand for 1 h at room temperature.

Morpholinium 6-amino-3,5-dicyano-4-(cyclohex-3-enyl)pyridine-2-thiolate XIV. To a suspension of 10 mmol of thiopyran **XII** in 15 ml of absolute ethanol, we added 10 mmol of morpholine; the resulting solution was refluxed for 2 h. After cooling, the precipitate was separated and washed with ethanol and acetone. Salt **XIV** thus obtained was used in the subsequent transformations without additional purification. Mass spectrum, *m/z* (I_{rel}, %): 258 (12) $[M_{anion} + 3]^+$, 257 (26) $[M_{anion} + 2]^+$, 256 (92) $[M_{anion} + 1]^+$, 255 (100) $[M_{anion}]^+$, 254 (19) $[M_{anion} - 1]^+$, 241 (20), 227 (15), 203 (31), 177 (14), 169 (12), 158 (14), 115 (20), 88 (9) $[M_{cation}]^+$, 87 (72) $[M_{cation} - 1]^+$, 81 (8) $[M_{cyclohex\text{-}3\text{-}enyl}]^+$, 79 (17), 67 (20), 58 (50), 57 (84).

6-Amino-2-thioxo-4-(cyclohex-3-enyl)pyridine-3,5-dicarbonitrile XV. A suspension of 10 mmol of salt **XIV** in 15 ml of ethanol was acidified under stirring with 10% HCl to pH 5. The solution was filtered and allowed to stand for 24 h at room temperature.

6-Amino-4-benzoylmethylsulfanyl-4-(cyclohex-3-enyl)pyridine-3,5-dicarbonitrile XVI. A mixture of 10 mmol of salt **XIV** and 10 mmol of phenacyl bromide **VIIg** in 15 ml of DMF was stirred for 3 h and diluted with an equal volume of water.

8-R-8-R-2-*Z*-Methylsulfanyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitriles XVIIIa–XVIIIc. To a mixture of 10 mmol of **I** and 10 mmol of **II** in 15 ml of ethanol, we added three drops of morpholine. After stirring for 5 min, we added 10 mmol of diketone **XVII**, stirred for 1 h, added 10 mmol of alkylating agent **VIIk**–**VIIm**, and stirred for 3 h. Then the mixture was diluted with an equal volume of water and allowed to stand for 24 h at room temperature.

Ethyl 2-methyl-6-thioxo-5-cyano-4-(cyclohex-3-enyl)-1,4,5,6-tetrahydropyridine-3-carboxylate XXII. To a mixture of 10 mmol of **I** and 10 mmol of **II** in 15 ml of ethanol, we added three drops of morpholine. After stirring for 5 min, we added 10 mmol of ester **XXI**, stirred for 30 min, and left for 24 h at room temperature. Mass spectrum, *m/z* (I_{rel}, %): $[M]^+$ absent, 277 (9) $[M - HCN]^+$, 262 (100), 234 (48), 216 (10), 188 (14), 161 (9), 149 (8), 79 (11), 65 (5), 53 (6), 44 (9).

Ethyl 6-carbamoylmethylsulfanyl-2-methyl-5-cyano-4-(cyclohex-3-enyl)-1,4-dihydropyridine-3-carboxylate XXIV. To a solution of 10 mmol of **XXII** in 15 ml of DMF, we added successively with stirring 5.6 ml of 10% aqueous KOH (10 mmol) and 10 mmol of amide **VIIk**, stirred for 1 h, diluted with an equal volume of water, and left for 24 h at room temperature. Mass spectrum, *m/z* (I_{rel}, %): 361 (5) $[M]^+$, 316 (19) $[M - HCONH_2]^+$, 299 (10), 280 (100) $[M$ – cyclohex-3-enyl$]^+$, 263 (92), 235 (68), 223 (10), 207 (43), 177 (9), 163 (15), 79 (22) $[M_{cyclohex\text{-}3\text{-}enyl}]^+$, 53 (18), 41 (17).

2-Amino-4-(cyclohex-3-enyl)-7-R-4*H*-chromene-3-carbonitriles XXVIa and XXVIb. To a solution of 10 mmol of **I** in 15 ml of ethanol, we added 10 mmol of dinitrile **XI** and three drops of morpholine; the mixture was stirred for 15 min. Then 10 mmol of substituted phenol **XXVa** or **XXVb** was added, and the mixture was stirred for 1 h and allowed to stand at room temperature for 3 days.

2-Amino-7-benzyloxy-4-(cyclohex-3-enyl)-4*H*-chromene-3-carbonitrile XXIX. To a suspension of 10 mmol of benzo[*b*]pyran **XXVIa** in 20 ml of absolute ethanol, we successively added with stirring a solution of 10 mmol of Na in 10 ml of absolute ethanol and then 10 mmol of benzyl chloride **VIIc**. The mixture was stirred for 4 h and allowed to stand for 24 h at room temperature. Mass spectrum, *m/z* (I_{rel}, %): 358 (4) $[M]^+$, 278 (19) $[M$ – cyclohex-3-

enyl]$^+$, 277 (100), 187 (6), 186 (5), 158 (5), 92 (6), 91 (92) $[PhCH_2]^+$, 65 (7).

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