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Isobutyraldehyde in the Synthesis of Isopropyl-substituted 4*H*-Pyrans, 1,4-Dihydropyrano[2,3-*c*]pyrazole, 1,4-Dihydropyridines, and Cyclobutane

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Abstract — Condensation of isobutyraldehyde with CH acids, such as acetoacetanilide, dimedone, acetoacetamide, ethyl benzoylacetate, resorcinol, cyanoacetic acid, malononitrile, 3-methyl-1-ethyl-2-pyrazolin-5-one, benzoylacetone, and cyanoacetamide, in the presence of amines gave isopropyl-substituted 4*H*-pyrans, 1,4-dihydropyrano[2,3-*c*]pyrazole, 4*H*-benzo[*b*]pyranes, 1,4-dihydropyridines, and 1,1-dicyano-2-(1-cyano-1-ethoxycarbonyl)methyl-4-isopropyl-3,3-dimethylcyclobutane. The structure of the latter product was studied by X-ray diffraction analysis.

Aromatic aldehydes are widely used in the synthesis of 4-aryl-substituted pyridine-2-chalcogenones and pyrans [1–4] that are fairly thoroughly studied and used in practice [5, 6]. At the same time, alkyl-substituted analogs still remain poorly explored, on account of their enhanced reactivity and low selectivity of reactions with aliphatic aldehydes, as well as susceptibility of certain of them to polymerization [7].

Proceeding with the research into the synthesis of novel pyridin-2-chalcogenones and pyrans by multicomponent condensation involving aliphatic aldehydes [8–15], we turned to reactions of isobutyraldehyde (**I**) with CH acids, such as malononitrile (**II**), dimedone (**IV**), acetoacetanilide (**VIIIa**), acetoacetamide (**VIIIb**), ethyl benzoylacetate (**X**), resorcinol (**XII**), cyanoacetic acid (**XIII**), 2-ethyl-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (**XV**), and cyanothioacetamide (**XVII**), in the presence of amines. We showed that the three-component condensation of isobutyraldehyde (**I**) with malononitrile (**II**) and dimedone (**IV**) in ethanol in the presence of morpholine gives rise to 2-amino-4-isopropyl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**VI**). The reaction probably involves intermediate formation of substituted acrylonitrile **III** that takes up dimedone (**IV**) by the Michael reaction [16]. Adduct **V** undergoes cyclization into compound **VI** under reaction conditions.

The above condensation with acetoacetanilide (**VIIIa**), acetoacetamide (**VIIIb**), ethyl benzoylacetate (**X**), or 2-ethyl-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (**XV**), instead of dimedone (**IV**), gave 6-amino-5-cyano-4-isopropyl-2-methyl-4*H*-pyran-3-carboxamides **IXa** and **IXb**, ethyl 6-amino-5-cyano-4-isopropyl-2-phenyl-4*H*-pyran-3-carboxylate (**XI**), and 6-amino-1-ethyl-4-isopropyl-3-methyl-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitrile (**XVI**). The condensations of aldehyde **I** with such CH acids as resorcinol **XII** and cyanoacetic acid (**XIII**) provided ethyl 2-amino-7-hydroxy-4-isopropyl-4*H*-chromene-3-carboxylate (**XIV**). Compounds **IX**, **XI**, **XIV**, and **XVI** are probably formed by the same scheme as pyran **VI**.

The structures of compounds **VI**, **IX**, **XI**, **XIV**, and **XVI** were proved by their physicochemical and spectral characteristics (Tables 1 and 2). Thus, the IR spectra contain characteristic absorption bands of the conjugated cyano group at 2167–2210 cm^{-1}, as well as absorption bands due to stretching and bending vibrations of the amino group at 3088–3448 and 1642–1656 cm^{-1}, respectively. Furthermore, by treatment of compound **VI** with a solution of bromine in aqueous methanol at 20°C the cyano group was hydrolyzed into amide. Therewith, the pyran ring recyclized into pyridine and, as a result, 4-isopropyl-7,7-dimethyl-2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinoline-3-carboxamide (**VII**) was obtained.

With acetoacetanilide (**VIIIa**) and cyanothioacetamide (**XVII**) as CH-acid components in condensation with aldehyde **I** in the presence of *N*-methylmorpholine with subsequent introduction of ω-bromoacetyl-

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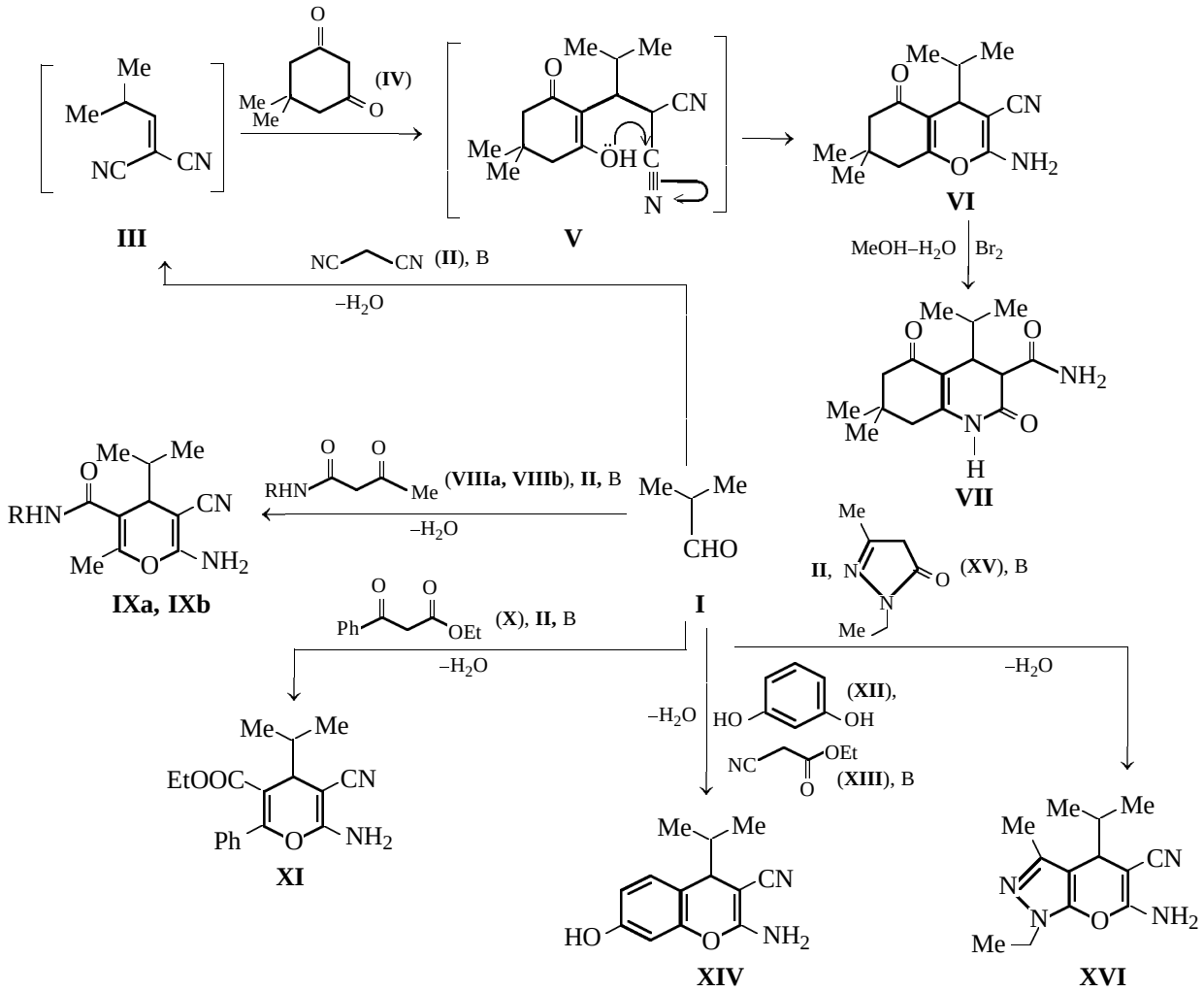
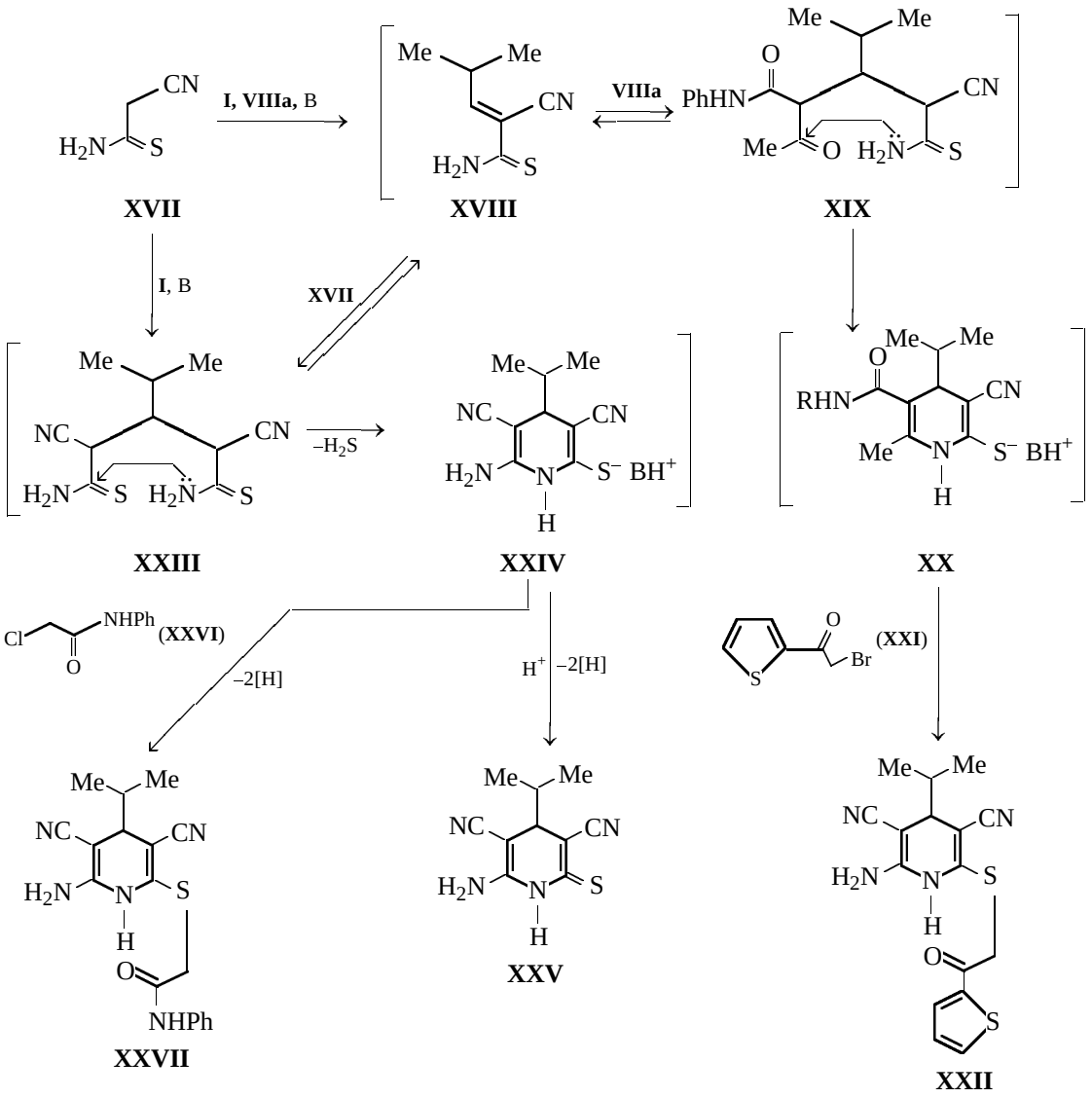


B = morpholine; **VIII, IX**, R = Ph (**a**), H (**b**).

thiophene (**XXI**) into the reaction mixtures, 4-isopropyl-6-methyl-2-thenoylmethylsulfanyl-5-phenylcarbamoyl-3-cyano-1,4-dihydrolyridine (**XXII**) was isolated. The reaction is likely to involve formation of alkene **XVIII** (Knoevenagel condensation [16]), followed by the Michael addition of acetoacetanilide **VIIIa** to compound **XVIII**, leading to adduct **XIX**. The latter undergoes regioselective cyclocondensation into substituted *N*-methylmorpholinium 1,4-dihydropyridine-2-thiolate (**XX**) that is further alkylated with compound **XXI** into derivative **XXII**.

The above condensation without CH acid **VIIIa** and α-chloroacetanilide (**XXVI**) instead of alkylating agent **XXI** gave *N*-phenyl-2-[(6-amino-3,5-dicyano-4-isopropylidene-1,4-dihydropyridin-2-yl)sulfanyl]acetamide (**XXVII**). Note that this condensation involves oxidation, probably, with atmospheric oxygen, of structure **XXIV**, that results in formation of an isopropylidene fragment, rather than in aromatization of the dihydropyridine nucleus. This result can be explained in terms of hydrogen bonding between the anilide oxygen and N^1H hydrogen atoms. The same reason is likely to underlie the resistance of 1,4-dihydropyridine **XXII** to oxidation. The preservation of the *boat* conformation of the 1,4-dihydropyridine nucleus [17, 18] and the lack of conformational isomerism make compound **XXIV** fairly resistant to oxidants [19]. Thus, the two-component oxidation of aldehyde **I** with cyanothioacetamide (**XVII**) in the presence of *N*-methylmorpholine provides a dehydrogenation product, 6-amino-4-isopropyl-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitirile (**XXV**). It is reasonable to suggest that the reaction involves formation of alkene **XVII** that reacts with amide **XVII** to form adduct **XXIII** whose heterocyclocondensation affords *N*-methylmorpholinium dihydropyridinethiolate (**XXIV**). Treatment of the reaction mixture with dilute HCl gives substituted pyridine-2(1*H*)-thione **XXV** that



B = *N*-methylmorpholine.

was previously prepared via recyclization of 2,6-diamino-3,5-dicyano-4-isopropyl-4*H*-thiopyran [14].

The structure of compounds **XXII** and **XXVII** was proved by their physicochemical and spectral characteristics (Tables 1 and 2). Evidence for the presence of a hydrogen bond in **XXII** and **XXVII** comes from their ^{1}H NMR spectra. The ^{1}H NMR spectrum of dihydropyridine **XXII** contains, along with characteristic dihydropyridine and substituent signals in the expected δ ranges (Table 2), signals of nonequivalent protons of the SCH_2 group as doublets at δ 4.42 and 4.67 ppm (^2J 17.32 Hz). Such a splitting of the methylene proton signals suggests lack of free rotation of the thenoyl fragment.

The two-component condensation of aldehyde **I** with malononitrile (**II**) in ethanol in the presence of morpholine at 20°C formed substituted cyclobutane **XXXII**, rather than expected cyclohexene **XXX** [20–23]. Thus, isopropylmethylenemalononitrile (**III**) formed by the Knoevenagel condensation dimerizes by the Michael scheme to give adduct **XXVIII** that undergoes regioselective intramolecular cyclization into cyclobutane **XXIX**. The formation of the latter is a result of three reactions: Knoevenagel condensation and two Michael additions, inter- and intramolecular. Further on alcoholysis of one of the nitrile group in compound **XXIX** occurs, yielding imidoester **XXXI**. Note that malononitrile [24] and other aliphatic nitriles [25] readily form imidoesters like **XXXI** in

Table 1. Yields, melting points, and elemental analyses of octahydroquinolin-2-one **VII**, pyrans **IXa, XIb, XI, XIV, XXXVI**, and **XXXVII**, pyrano[2,3-*c*]pyrazole **XVI**, dihydropyridines **XXII** and **XXVII**, and cyclobutane **XXXII**

Comp. no.	Yield, %	mp, °C (solvent for crystallization)	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
VII	41	227–229 (EtOH)	64.60	8.11	9.88	$C_{15}H_{22}N_2O_3$	64.73	7.97	10.06
IXa	82	221–222 (*i*-PrOH)	68.51	6.32	14.00	$C_{17}H_{19}N_3O_2$	68.67	6.44	14.13
IXb	65	243–245 (BuOH)	59.62	6.71	19.08	$C_{11}H_{15}N_3O_2$	59.71	6.83	18.99
XI	89	168–169 (EtOH)	69.10	6.34	9.15	$C_{18}H_{20}N_2O_3$	69.21	6.45	8.97
XIV	83	171–172 (EtOH)	65.12	7.06	4.85	$C_{15}H_{19}NO_4$	64.97	6.91	5.05
XVI	71	177–178 (MeOH)	63.44	7.20	22.58	$C_{13}H_{18}N_4O$	63.39	7.37	22.75
XXII	72	158–160 (BuOH)	62.95	5.15	9.71	$C_{23}H_{23}N_3O_2S_2$	63.13	5.30	9.60
XXVII	66	191–193 (AcOH)	61.40	4.72	20.15	$C_{18}H_{17}N_5OS$	61.52	4.88	19.93
XXXII	77	118–119 (EtOH)	66.72	7.25	14.54	$C_{16}H_{21}N_3O_2$	66.88	7.37	14.62
XXXVI, XXXVII	65	177–179 (EtOH)	72.19	6.50	10.08	$C_{17}H_{18}N_2O_2$	72.32	6.43	9.92

Table 2. IR and ^{1}H NMR spectra of octahydroquinolin-2-one **VII**, pyrans **IXa, XIb, XI, XIV, XXXVI**, and **XXXVII**, pyrano[2,3-*c*]pyrazole **XVI**, dihydropyridines **XXII** and **XXVII**, and cyclobutane **XXXII**

Comp. no.	IR spectrum, cm^{-1}		^{1}H NMR spectrum, δ, ppm			
	ν(C≡N), ν(C=O),	ν(NH_2); δ(NH_2)	C^4H, d	NH_2, br.s; $CH(CH_3)_2$, m	$CH(CH_3)_2$, two d	other signals
VII	1710, 1678	3305, 3390; 1655	3.07 m	6.79 and 7.20; 1.65	0.78, 0.83 (*J* 6.92 Hz)	1.05 s (6H, $2CH_3$), 2.12 s (2H, C^8H_2), 2.11 d and 2.29 d (at 1H, C^6H_2, ^2J 18.4 Hz), 2.95 d (1H, C^3H, *J* 5.46 Hz), 9.91 br.s (1H, N^1H)
IXa	2167, 1680	3192, 3340, 3448; 1656	3.79 (*J* 4.0 Hz)	5.67; 1.28	0.98, 1.12, (*J* 6.87 Hz)	2.27 s (3H, CH_3), 7.14 m (2H, H_{arom}), 7.46 m (3H, H_{arom}), 8.85 br.s (1H, CONH)
IXb	2210, 1642	3214, 3356, 3444; 1653	3.42 (*J* 3.96 Hz)	6.06; 1.60	0.69, 0.93 (*J* 6.90 Hz)	2.13 s (3H, CH_3)
XI	2188, 1694	3091, 3213, 3298; 1642	3.23 (*J* 4.11 Hz)	6.69; 1.92	0.88, 1.01 (*J* 7.02 Hz)	0.99 t (3H, CH_3CH_2O), 3.94 q (2H, CH_2, *J* 6.20 Hz), 7.42 br.s (5H, H_{arom})
XIV	1714	3115, 3302, 3407; 1644	3.51 (*J* 3.86 Hz)	7.15; 1.76	0.62, 0.81 (*J* 6.18 Hz)	1.28 t (3H, CH_3CH_2O), 4.10 q (2H, CH_2, *J* 6.14 Hz), 6.39 s (1H, H_{arom}), 6.48 d (1H, H_{arom}), 8.83 d (1H, H_{arom}, *J* 7.98 Hz), 9.01 br.s (1H, OH)
XVI	2197	3088, 3241, 3415; 1649	3.19 (*J* 3.95 Hz)	6.61; 1.70	0.74, 0.80 (*J* 6.85 Hz)	1.25 t (3H, CH_3CH_2), 2.24 s (3H, CH_3), 4.15 q (2H, CH_2, *J* 6.21 Hz)
XXII	2190, 1713; 1668	3315	3.45 (*J* 4.1 Hz)	1.70	0.85, 0.92 (*J* 7.03 Hz)	2.18 s (3H, C^2CH_3), 4.42 d and 4.67 d (at 1H, SCH_2, ^2J 17.32 Hz), 7.26 m (3H, H_{arom}), 7.02 t (1H, thienyl C^4H), 7.68 d (2H, H_{arom}, *J* 5.16 Hz), 8.03 d (1H, thienyl C^3H, *J* 5.2 Hz), 8.09 d (1H, thienyl C^5H, *J* 3.8 Hz), 8.40 br.s (1H, NH), 9.15 br.s (1H, NHCO)

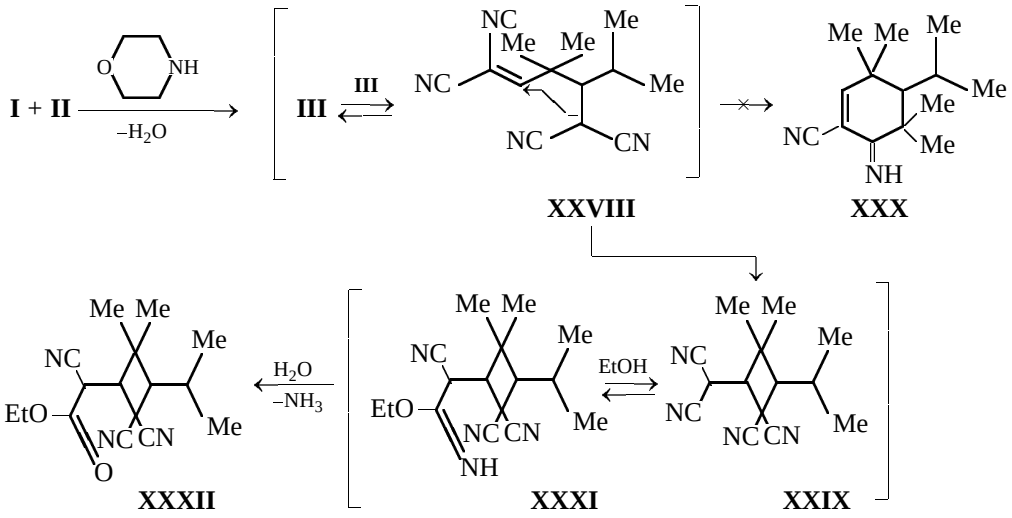
Table 2. (Contd.)

Comp. no.	IR spectrum, cm^{-1}		^1H NMR spectrum, δ, ppm			
	ν(C≡N), ν(C=O),	ν(NH_2); δ(NH_2)	C^4H, d	NH_2, br.s; $CH(CH_3)_2$, m	$CH(CH_3)_2$, two d	other signals
XXVII	2200 sh; 1673	3240, 3330, 3412; 1645	–	5.81	1.21 s	3.86 s (2H, SCH_2), 7.12 d.d (1H, H_{arom}, *J* 6.14 Hz), 7.35 d.d (2H, H_{arom}), 7.58 d (2H, H_{arom}, *J* 5.20 Hz), 9.41 br.s (1H, NH), 10.32 br.s (1H, NHCO)
XXVII	2255 sh; 1718	–	–	2.03 m	0.92, 1.03, (*J* 6.84 Hz)	1.06 s (3H, CH_3), 1.27 s (3H, CH_3), 1.39 t (3H, CH_3CH_2O), 2.43 d (1H, C^4H, *J* 6.80 Hz), 3.39 d (1H, C^2H, *J* 7.22 Hz), 4.30 m (3H, CH_2 and C^1H)
XXXVI, XXXVII	2196, 1715	3184, 3319, 3420; 1647	3.19 (*J* 4.0 Hz)	6.56[a] and 6.69; 1.65	0.80[a] and 0.92[a], 0.83 and 1.11 (*J* 6.92 Hz)	1.79 s and 1.83[a] s (3H, CH_3), 7.42–7.79 m (5H, H_{arom})

[a] Signals of isomer **XXXVI**.

basic media. Under reaction conditions, adduct **XXXI** is hydrolyzed to ester **XXXII** that is a promising candidate for medical applications [26, 27].

The structure of compound **XXXII** was proved by X-ray diffraction analysis. The molecular structure and its principal geometric parameters are given in Fig. 1. The central four-membered carbocycle $C^1C^2C^3C^4$ is appreciable nonplanar (the atomic deviations from the mean plane attain 0.13 Å) and has a "butterfly" shape: The fold along the $C^2\cdots C^4$ line is 26.5°. All bond lengths and bond angles in molecule **XXXII** are normal values [28].

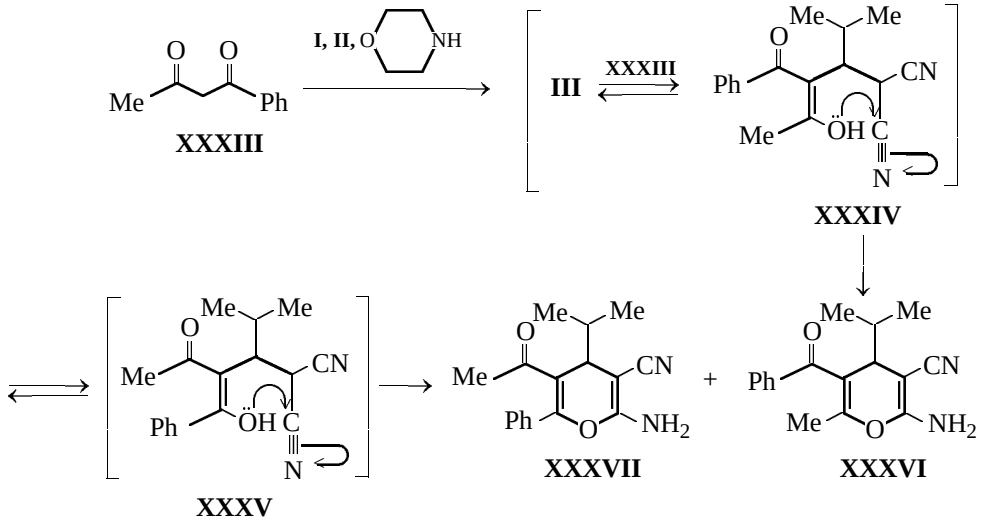


The crystal packing of compound **XXXII** is shown in Fig. 2.

The three-component condensation of aldehyde **I**, malononitrile (**II**), and unsymmetrical 1,3-diketone **XXXIII** provides a 2 : 1 mixture of structural isomers **XXXVI** and **XXXVII**. This conclusion follows from the ^1H NMR spectrum of this mixture (Table 2). The proton signals were assigned with account for data of Marchalin *et al.* [29] for analogs of pyrans **XXXVI**

and **XXXVII**, viz. 5-acetyl-2-amino-3-cyano-4-(2-furyl)-6-methyl-4*H*-pyran derivatives.

It is reasonable to suggest that the condensation gives rise to alkene **III** that enters the Michael reaction with benzoylacetone (**XXXIII**). Adduct **XXXIV** that forms can undergo prototropic isomerization into enol **XXXV**. Intramolecular cyclization of adducts **XXXIV** and **XXXV** under the action of morpholine gives corresponding structural isomers **XXXVI** and **XXXVII**.



Thus, isobutyraldehyde in mild conditions smoothly condenses with various CH acids to form unstable alkenes that further react with a new CH component or dimerize into corresponding isopropyl-substituted 4*H*-pyranes, 4*H*-benzo[*b*]pyranes, 1,4-dihydropyrano-[2,3-*c*]pyrazoles, 1,4-dihydropyridines, and cyclobutanes.

EXPERIMENTAL

The IR spectra were measured on an IKS-29 instrument in mineral oil. The ^{1}H NMR spectra were recorded on Bruker WP-100SY (100 MHz) (for **VI**, **IXa, IXb, XXV**, and **XXVII**), Gemini200 (199.975 MHz) (for **VII**), Bruker WM-250 (250.13 MHz) (for **XI**, **XXXVI**, and **XXXVII**), Varian Mercury-400 (400.397 MHz) (for **XXII** and **XXXII**), and Bruker DR-500 (500.13 MHz) (for **XIV** and **XVI**) instruments in DMSO-d_6, internal reference TMS. The mass spectra were obtained on a Kratos MS-890 instrument, ionizing energy 70 eV. The melting points were determined on a Kofler hot stage. Reaction progress was followed by TLC (Silufol UV-254, acetone–hexane, 3:5, developer iodine vapor).

X-ray diffraction analysis of a single crystal ($0.20 \times 0.25 \times 0.30$ mm) of compound **XXXII** was performed at room temperature on an Enraf–Nonius CAD-4 automated four-circle diffractometer (MoK_α radiation, $2\theta/\omega$ 1.2 scanning, θ_{max} 24°, sphere segment $0 \le h \le 8$, $-11 \le k \le 11$, $-12 \le l \le 12$). A total of 2466 reflections were measured, of which 2180 were symmetrically independent (averaging *R* factor 0.019). Crystals of compound **XXXII**, triclinic, *a* 7.738(2), *b* 10.421(2), *c* 11.127(2) Å; α 75.23(3), β 74.90(3), γ 83.65(3)°; *V* 840.96 Å^3, *M* 287.36, *Z* 2,

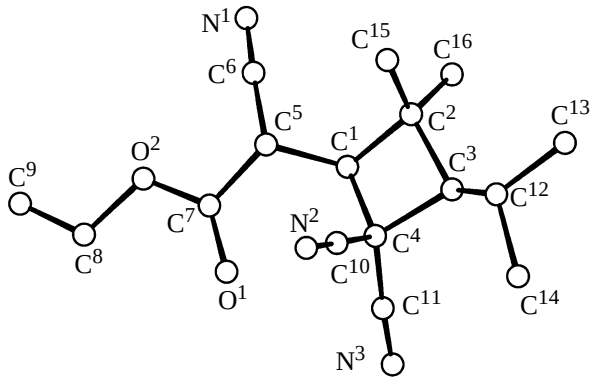


Fig. 1. Molecular structure of compound **XXXII** with atom numbering (hydrogen atoms are not shown). Principal geometric parameters: $l(C^1–C^2)$ 1.563(11), $l(C^1–C^4)$ 1.610(10), $l(C^1–C^5)$ 1.497(11), $l(C^2–C^3)$ 1.580(10), $l(C^3–C^4)$ 1.593(11) Å; $\angle C^1C^2C^3$ 87.2(6), $\angle C^2C^3C^4$ 90.8(6), $\angle C^1C^4C^3$ 85.2(6), and $\angle C^2C^1C^4$ 90.8(6)°.

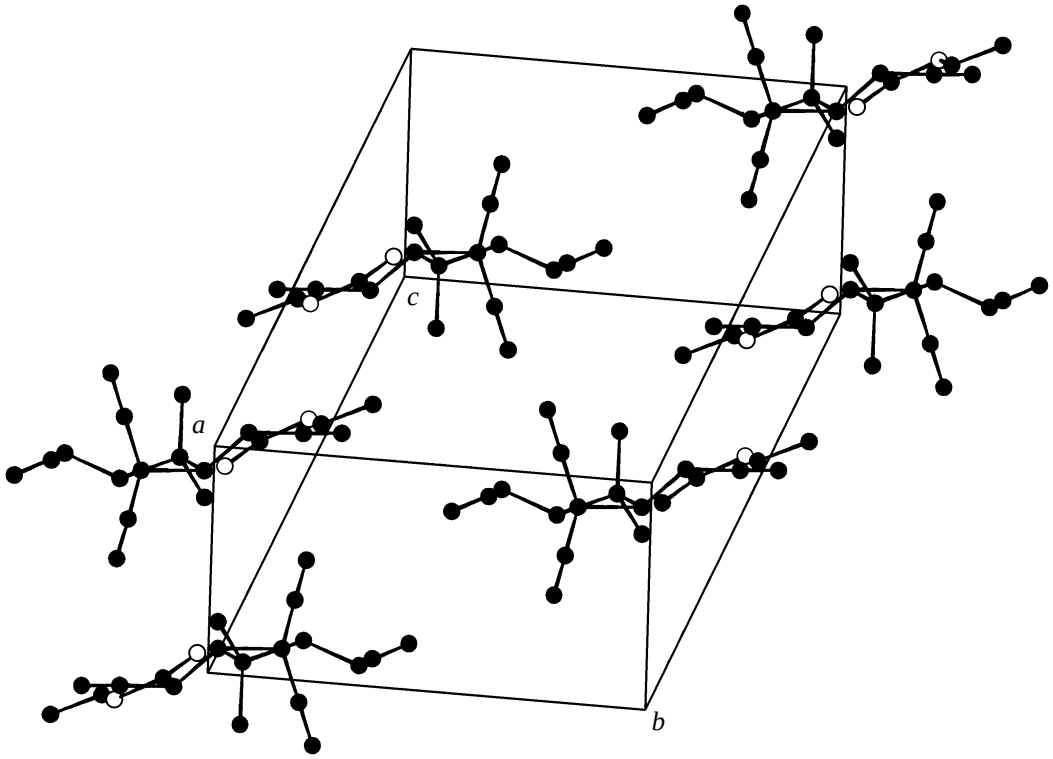


Fig. 2. Crystal packing of compound **XXXII**.

Table 3. Atomic coordinates and equivalent isotropic thermal parameters U_{eq} in structure **XXXIIa**[a]

Atom	*x*	*y*	*z*	U_{eq}, Å^2
O^1	0.240(1)	1.0108(7)	0.9143(8)	0.1202
O^2	0.2379(8)	0.8783(6)	0.7855(6)	0.0826
N^1	0.6593(11)	0.8875(8)	0.5806(7)	0.0778
N^2	0.1815(14)	1.3508(9)	0.744(1)	0.1007
N^3	0.4130(13)	1.1890(8)	1.0650(9)	0.0926
C^1	0.5594(12)	1.1253(8)	0.7531(9)	0.0674
C^2	0.6924(11)	1.2252(8)	0.6521(8)	0.0524
C^3	0.6368(12)	1.3210(8)	0.7467(8)	0.0652
C^4	0.4600(12)	1.2422(8)	0.8201(9)	0.0538
C^5	0.4464(11)	1.0429(8)	0.7141(8)	0.0590
C^6	0.5669(12)	0.9507(9)	0.6395(8)	0.0593
C^7	0.2957(12)	0.9751(9)	0.8162(9)	0.0648
C^8	0.0868(15)	0.8106(12)	0.8777(14)	0.1394
C^9	0.0426(19)	0.7093(15)	0.8440(18)	0.2002
C^{10}	0.3048(15)	1.3019(9)	0.7787(9)	0.0597
C^{11}	0.4297(12)	1.2107(8)	0.957(1)	0.0587
C^{12}	0.6233(12)	1.4668(8)	0.7042(8)	0.0616
C^{13}	0.7984(13)	1.5287(9)	0.627(1)	0.0835
C^{14}	0.5374(14)	1.5324(9)	0.815(1)	0.0862
C^{15}	0.6465(15)	1.2768(9)	0.525(1)	0.0874
C^{16}	0.8833(14)	1.170(1)	0.6395(12)	0.1023

[a] For atom numbering, see the legend to Fig. 1.

ρ_{calc} 1.13 g cm^{-3}, μ 0.713 cm^{-1}, space group $P\bar{1}$ (*N* 2). The structure was solved by the direct method and refined by full-matrix least squares in the anisotropic approximation using the CRYSTALS program package [30]. The refinement included 1004 reflections with $I > 4\sigma(I)$ (170 refined parameters, reflections per parameter 5.9, singular weight scheme). All hydrogen atoms were refined geometrically and included in the calculation with fixed positional and thermal parameters. Final divergence factors: *R* 0.073 and R_W 0.074, and residual electron density from the Fourier difference series 0.32 and –0.19 $\bar{e}$ Å^{-3}. The atomic coordinates are given in Table 3.

2-Amino-4-isopropyl-7,7-dimethyldimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (VI). To a solution of 0.91 ml of isobutyraldehyde (**I**) in 20 ml of ethanol at 20°C, malononitrile (**II**), 0.66 g, and 1 drop of morpholine were added, and the resulting mixture was stirred for 15 min. Dimedone (**IV**), was then added, and the mixture was stirred for 1 h and left to stand for 1 day. A precipitate formed and was filtered off, washed with ethanol and hexane, and recrystallized from ethanol to obtain 2.34 g (90%) of compound **VI** whose melting point, ^{1}H NMR spectrum, and chromatographic parameters were similar to those reported in [15].

4-Isopropyl-7,7-dimethyl-2,5-dioxo-1,2,3,4,5,6,-

7,8-octahydroquinolin-3-carboxamide (VII). To a solution of 5 ml of water in 20 ml of methanol, pyran **VI**, 2.6 g, was added, and a solution of 0.51 ml of bromine in 5 ml of methanol was added to the resulting suspension dropwise over the course of 10 min. The mixture was allowed to stand for 1 day and then diluted with equal volume of water. The precipitate was filtered off and washed with water, ethanol, and hexane to obtain compound **VII** whose characteristics are given in Tables 1 and 2. Mass spectrum, *m/z* (I_{rel}, %): 278 (4) $[M]^+$; 234 (100), 192 (79), 178 (10), 135 (14), 118 (10), 108 (7), 55 (9).

6-Amino-5-cyano-4-isopropyl-2-methyl-4*H*-pyran-3-carboxamides IXa and IXb were prepared similarly to **VI**, replacing dimedone (**IV**) by 10 mmol of CH acid **VIIIa** or **VIIIb** (Tables 1 and 2).

Ethyl 6-amino-5-cyano-4-isopropyl-2-phenyl-4*H*-pyran-3-carboxamide (XI) was prepared similarly to compound **VI**, replacing dimedone **IV** by 1.73 ml of ethyl benzoylacetate (**X**) (Tables 1 and 2). Mass spectrum, *m/z* (I_{rel}, %): 312 (4) $[M]^+$; 269 (100), 241 (13), 197 (10), 168 (11), 115 (7), 105 (12), 77 (9), 43 (8).

Ethyl 2-amino-7-hydroxy-4-isopropyl-4*H*-chromene-3-carboxamide (XIV). To a solution of 0.91 ml of isobutyraldehyde (**I**) in 20 ml of ethanol at 20°C, cyanoacetic ester (**XIII**), 1.06 ml, and 1 drop of morpholine were added, and the resulting mixture was stirred for 30 min. Resorcinol (**XII**), 1.1 g, was then added, and the mixture was stirred for 3 h, and then allowed to stand for 2 days at room temperature. A precipitate formed and was washed with ethanol and hexane (Tables 1 and 2). Mass spectrum, *m/z* (I_{rel}, %): 277 (3) $[M]^+$; 235 (13), 234 (100), 206 (8), 189 (7), 188 (67), 161 (6), 134 (8), 43 (6).

6-Amino-1-ethyl-4-isopropyl-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazol-5-carbonitrile (XVI) was prepared similarly to compound **VI**, replacing dimedone (**IV**) by 1.26 g of CH acid **XV** (Tables 1 and 2). Mass spectrum, *m/z* (I_{rel}, %): 246 (4) $[M]^+$; 235 (11), 221 (15), 209 (26), 208 (50), 207 (100), 180 (29), 179 (68), 163 (25), 162 (47), 161 (55), 134 (48), 119 (21), 106 (22), 105 (36), 67 (41), 58 (30).

***N*-Phenyl-5-cyano-4-isopropyl-2-methyl-6-[[2-oxo-2-(2-thienyl)ethyl]sulfanyl]-1,4-dihydropyridine-3-carboxamide (XXII).** To a solution of 0.91 ml of isobutyraldehyde (**I**) in 20 ml of ethanol at 20°C, cyanothioacetamide (**XVII**), 1.0 g, and 1 drop of *N*-methylmorpholine were added, and the mixture was stirred for 25 min. Acetoacetanilide (**VIIIa**), 1.77 g, and 1.1 ml of *N*-methylmorpholine were then added, the mixture was stirred for 2 h, after which 2.05 g of ω-bromoacetophenone (**XXI**) was added, and stirring was continued for an additional 3 h. The mixture was then diluted with equal volume of water, and the precipitate that formed was separated and washed in succession with water, ethanol, and hexane to obtain compound **XXII** (Tables 1 and 2.)

6-Amino-4-isopropyl-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile (XXV). To a mixture of 0.91 ml of isobutyraldehyde (**I**) and 1.0 g of cyanothioacetamide (**XVII**) at 20°C, *N*-methylmorpholine, 1 drop, was added, and the mixture was stirred for 1 h. Cyanothioacetamide (**XVII**), 1.0 g, and 1.1 ml of *N*-methylmorpholine were then added, and stirring was continued for an additional 5 h. The mixture was diluted with 10% hydrochloric acid to pH 7 and allowed to stand for 3 day. The precipitate that formed was separated and washed in succession with water, ethanol, and hexane to obtain 1.72 g (79%) of compound **XXV**, whose melting point and ^{1}H NMR spectra were the same as those reported in [14, 31].

***N*-Phenyl-2-[(6-amino-3,5-dicyano-4-isopropylidene-1,4-dihydropyridin-2-yl)sulfanyl]acetamide (XXVII).** To a solution of 0.91 ml of isobutyraldehyde (**I**) in 20 ml of ethanol at 20°C, cyanothioacetamide (**XVII**), 1.0 g, and 1 drop of *N*-methylmorpholine were added, and the mixture was stirred for 25 min, after which 1.0 g of CH acid **XVII** and 1.1 ml of *N*- methylmorpholine were added, and stirring was continued for 2 h. ω-Chloroacetanilide (**XXVI**) was then added, and the mixture was stirred for 4 h, diluted with equal volume of water, and allowed to stand for 1 day. The precipitate that formed was separated and washed in succession with water, ethanol, and hexane to obtain compound **XXVII** (Tables 1 and 2).

Ethyl (4,4-dicyano-3-isopropyl-2,2-dimethylcyclobutyl)cyanoacetate (XXXII). To a solution of 0.91 ml of isobutyraldehyde (**I**) in 10 ml of ethanol at 20°C, malononitrile (**II**), 0.66 g, and 0.87 ml of morpholine were added. The mixture was stirred for 2 h and allowed to stand for 4 days. The precipitate that formed was filtered off and washed with ethanol and hexane to obtain compound **XXXII** (Tables 1 and 2).

2-Amino-5-benzoyl-4-isopropyl-6-methyl-4*H*-pyran-3-carbonitrile (XXXIV) and 5-acetyl-2-amino-4-isopropyl-6-phenyl-4*H*-pyran-3-carbonitrile (XXXVII) were obtained as a 2 : 1 mixture by the procedure for compound **VI**, replacing dimedone (**IV**) by 1.62 g of benzoylacetone (**XXXIII**) (Tables 1 and 2).

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