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Synthesis of New 7-Alkylmethylene Derivatives of 2-(Thio)oxo-2,5,6,7-tetrahydro-1*H*-pyridine-3-carbonitriles

V. D. Dyachenko[a], E. N. Karpov[a], V. V. Dyakonenko[b], and O. V. Shishkin[b]

[a] *Taras Shevchenko Lugansk National University, ul. Oboronnaya 2, Lugansk, 91011 Ukraine fax: (0642)530008 e-mail: dvd_lug@online.lg.ua*

[b] *Scientific-Technological Concern "Institute of Monocrystals," National Academy of Sciences of Ukraine, Kharkov, Ukraine*

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Abstract—Alkylmethyleneamines of cyclic ketones were used for the synthesis of earlier unknown 7-alkylmethylene-2-(thio)oxo-2,5,6,7-tetrahydro-1*H*-pyridine-3-carbonitriles.

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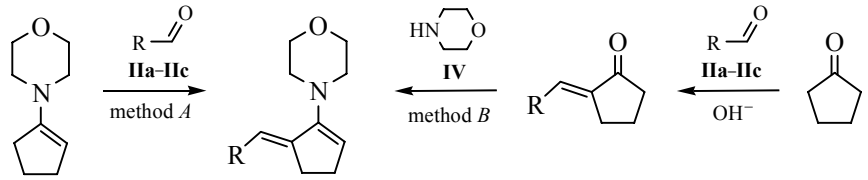
The cyclic ketone enamnes are convenient building blocks in organic chemistry. Earlier the behavior of these compounds have beeen studied in electrophile addition reactions [1] and their reactions with various reagents [2]. The analysis of published data showed that the accessible α-alkylmethylene substituted enamines have not been considered in these types reactions. Moreover, although the synthesis of the cyclic ketone alkyl-methyleneamines has been reported [2], such promising derivatives as enamines of aliphatic aldehydes were not isolated in pure state promising.

The activity of α-methylene substituted enamines was established to depend on the electronic nature of the methylene moiety [3]. The incorporation of an acceptor benzylidene substituent into the enamine system decreases the reactivity of the latter in addition reactions at the double bond. On the contrary, alkylmethylene substituents increase their efficiency. A number of previously not characterized alkylmethylene derivatives **Ia–Ic** was chosen for investigation of reactivity of this type enamines.

Main synthetic difficulty lies in the preparation of starting α-alkylmethyleneamines **Ia–Ic**. These compounds are oils, which are purified by distillation under reduced pressure. They are unstable in air and polymerize to lose the activity. α-Alkylmethyleneamines can be obtained by reaction of aliphatic aldehydes **IIa–IIc** with *N*-(cyclopent-1-enyl)morpholine **III** (method *A*) or by reaction of morpholine **IV** with alkylmethylenecycloketones **V**, which are in turn synthesized from cycloalkanone **VI** and aldehydes **IIa–IIc** in the presence of alkali aqueous solution (method *B*). As in the case of synthesis of arylmethylenecycloketone enamines [4], the use of method *A* leads to increase in the target products yield. It is probably connected with cross aldol condensations with formation of compound **V** by method *B*. Therefore all the alkylmethyleneamines **Ia–Ic** were obtained through enamine **III** by method *A*.

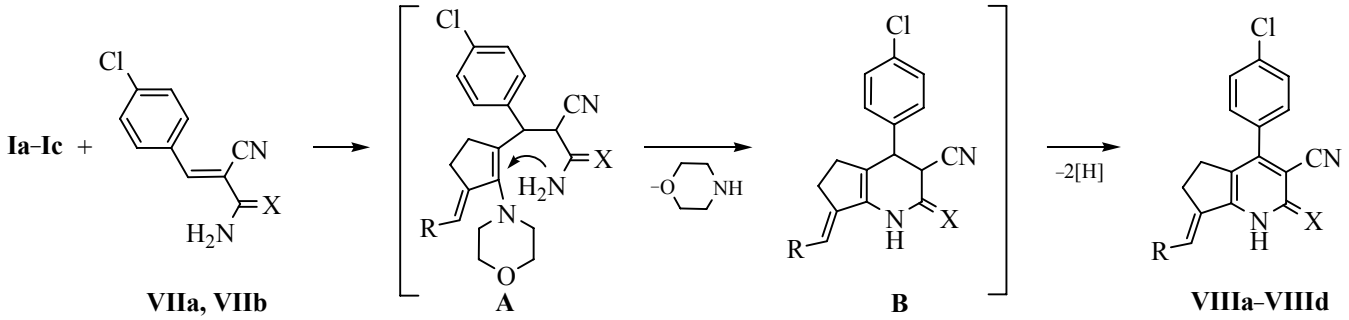
In the present work we use new compounds **Ia–Ic** to obtain partially hydrogenated functionalized pyridine-2-chalcogenones through their reaction with ac-



R = *i*-Pr (**a**), Et (**b**), *s*-Bu (**c**).

tivated alkenes **VIIa**, **VIIb**. Indeed, the use of α-alkylmethyleneamines in this reaction opens the way to obtain earlier unknown 7-alkylmethylene-2-(thio)oxo-2,5,6,7-tetrahydro-1*H*-pyridine-3-carbonitriles, and the latter are easily isolated single reaction product. The introduction of different alkyl substituents allows varying lipophilicity of molecule as a whole, and a double bond in C^8-position gives additional possibility for functionalization. Use of alkenes **VII** with the others aryl substituents does not lead to the target products formation.

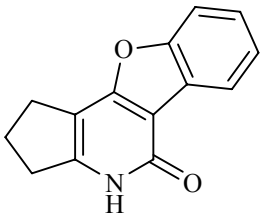
Probably, the mechanism of formation of compounds **IIa–IId** includes nucleophilic attack of enamines **Ia–Ic** on the activated double bond of alkenes **VIIa** and **VIIb** followed by intramolecular nucleophilic vinyl substitution in the intermediate **A** to form hydropyridine ring in compound **B,** which is oxidized to pyridine ring under the reaction conditions.

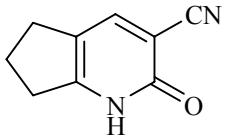


X = O, R = *i*-Pr (**a**), Et (**b**), *s*-Bu (**c**); X = S, R = *s*-Bu (**d**).

The structure of the products was established by means of ^{1}H NMR and mass spectrometry. We performed X-ray diffraction study of compound **VIIIa** to confirm the direction of the considered condensation (Figs. 1, 2, Tables 1, 2).

According to X-ray diffraction analysis data, in the molecule of **VIIIa** the bicyclic fragment is plane with in the accuracy of 0.02 Å. In the fragment C^4–C^8–C^7–C^6 of the pyridine ring a strong delocalization of electron density is observed. It leads to equalization of C–C bond lengths through shortening of the bond C^7–C^8 to 1.405(2) Å and lengthening of the bonds C^6–C^7 to 1.389(2) Å and C^4–C^8 to 1.370(2) Å in comparison with their average values 1.455 and 1.331 Å [5] respectively. Similar arrangement of bond length was earlier observed in compounds **IX** and **X** [6, 7].


IX


X

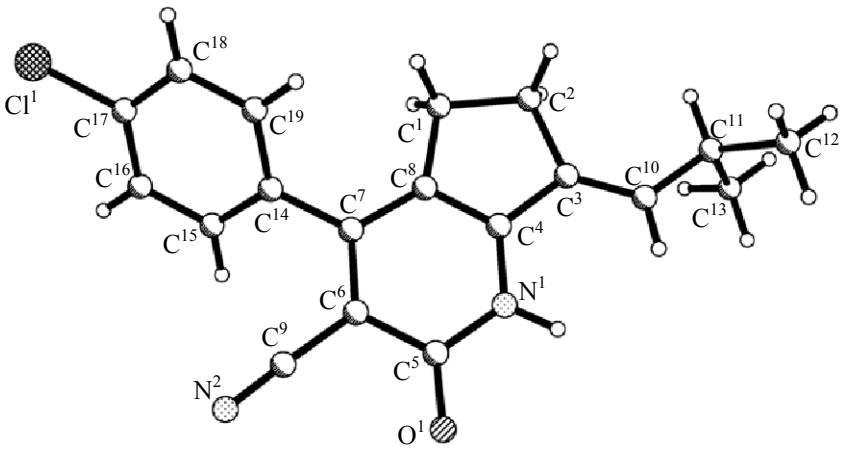


Fig. 1. Structure of compound **VIIIa** by X-ray diffraction data.

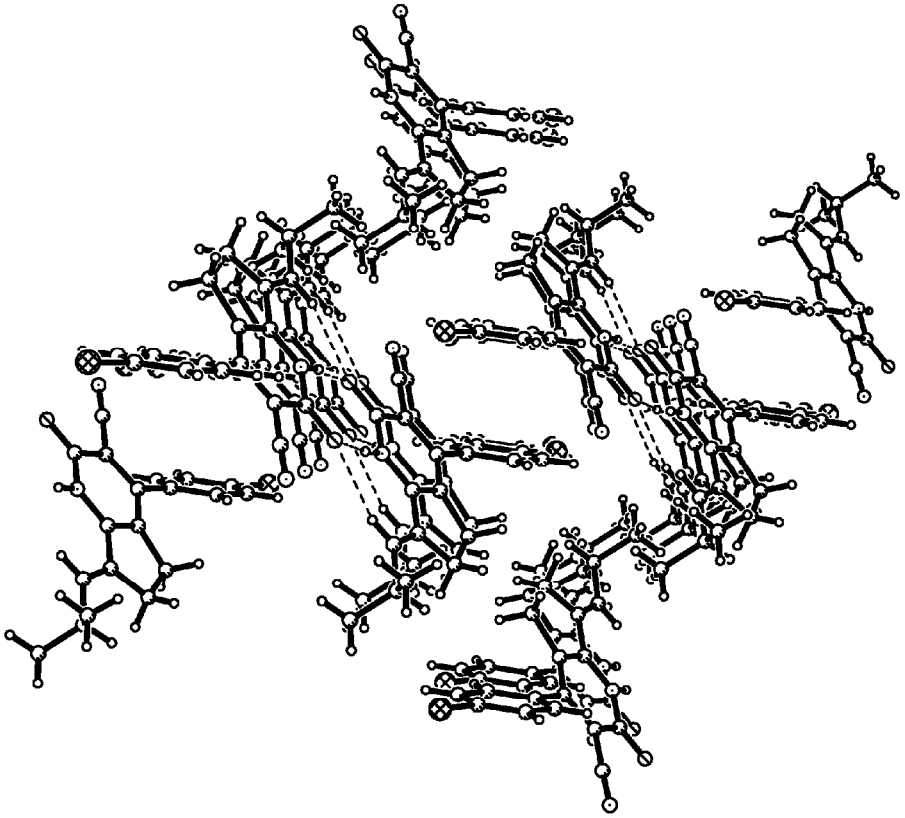


Fig. 2. Molecular packing of **VIIIa** in crystal.

The chlorophenyl substituent is appreciably turned relative to the bicycle plane [torsion angle C^{15}–C^{14}–C^7–C^6 –50.4(2)°] due to repulsion of these fragments as indicated by shortened intramolecular contacts $H^{1A}\cdots H^{19}$ [2.25 Å] (the sum of Van der Waals radii 2.32 Å [8]), $C^1\cdots C^{19}$ 3.20 Å (3.42 Å), $C^{19}\cdots C^{15}$ 3.02 Å (3.42 Å), $C^9\cdots H^{15}$ [2.70 Å (2.87 Å)]. The isopropyl substituent is in the *sp*-conformation relative to double bond C^{10}–C^3 [torsion angle C^3–C^{10}–C^{11}–H^{11} 10°] in spite of ap-pearance of short intramolecular contact $H^{10}\cdots H^1$ [2.24 Å (2.32 Å)].

In the crystal the **VIIIa** molecules form centrosymmetrical dimers due to intramolecular hydrogen bonds N^1–$H^1\cdots O^{1'}$ (x, 2 – y, 1 – z) H···O 1.88 Å N–H···O 172°. These dimers form stacks along crystallographic direction [100] (Fig. 2) and they are connected between themselves through intermolecular hydrogen bond C–H···π: C^{19}–$H^{19}\cdots C^{9'}$ (–1 – x, 3 – y, 1 – z) H···C 2.89 Å, C–H···C 115°. The formation of hydrogen bond N–H···O leads also to the bond O^1–C^5 lengthening to 1.242(2) Å (average value 1.210 Å).

EXPERIMENTAL

X-Ray diffraction analysis of compound **VIIIa** was performed on a Xcalibur-3 diffractometer (MoK_α irradiation, CCD-detector, graphite monochromator, ω-scanning, $2\theta_{max}$=50°). Crystals are triclinic, the unit cell parameters at 21°C are as follows: *a* 8.992(3) Å, *b* 9.092(3) Å, *c* 10.634(2) Å, α 81.73(3)°, β 83.60(2)°, γ 75.91(2)°, *V* 831.8(4) Å^3, *M* 324.8, *Z* 2, space group $P\overline{1}$, d_{calc} 1.297 g cm^{-3}, μ(MoK_α) 0.235 mm^{-1}, *F*(000) 340. Intensities of 6608 reflections were measured (2883 independent, R_{int} 0.013).

The structure was solved by the direct method by means of SHELXTL program package [9]. Hydrogen atoms position were revealed from differential synthesis of electron density and refined in a *rider*-model with $U_{iso} = nU_{equiv}$ (n = 1.5 for methyl groups and n = 1.2 for the remainder of hydrogen atoms) for non-hydrogen atom connected with this hydrogen atom. Hydrogen atom participating in the formation of hydrogen bond N–H···O was refined in the isotropic

Table 1. Bond lengths (*d,* Å) for structure **VIIIa**

Bond	*d*	Bond	*d*
Cl^1–C^{17}	1.741(2)	C^6–C^9	1.428(2)
O^1–C^5	1.244(2)	C^7–C^8	1.405(2)
N^1–C^4	1.355(2)	C^7–C^{14}	1.488(2)
N^1–C^5	1.365(2)	C^{10}–C^{11}	1.495(2)
N^2–C^9	1.144(2)	C^{11}–C^{12}	1.512(3)
C^1–C^8	1.506(2)	C^{11}–C^{13}	1.516(3)
C^1–C^2	1.527(3)	C^{14}–C^{15}	1.380(3)
C^2–C^3	1.515(2)	C^{14}–C^{19}	1.392(3)
C^3–C^{10}	1.330(2)	C^{15}–C^{16}	1.391(3)
C^3–C^4	1.453(2)	C^{16}–C^{17}	1.367(3)
C^4–C^8	1.370(2)	C^{17}–C^{18}	1.368(3)
C^5–C^6	1.444(2)	C^{18}–C^{19}	1.381(3)
C^6–C^7	1.389(2)		

approximation. The structure was refined by means of the full-matrix least-squares procedure on F^2 in anisotropic approximation for nonhydrogen atoms to wR_2 0.102 by 2856 reflexions [R_1 0.039 by 2181 reflexions with $F > 4\sigma(F)$, S 1.066]. The main crystallographic data were deposited into the Cambridge Crystallographic Data Center (CCDC 753380).

The ^{1}H NMR spectra were registered on a Varian Mercury-500 (499.9601 MHz) (compounds **Ia**, **VIIIa**–**VIIId**) and Varian Mercury VX-200 instruments (200 MHz) (**Ib**, **Ic**) in DMSO-d_6 relative to internal TMS. Mass spectra were recorded on a Crommas GC/MS-Hewlett-Packard 5890/5972 device, column HP-5MS (70 eV). Melting points were measured on a Koffler apparatus. The reaction progress and the purity of the compounds obtained were monitored by TLC method on Silufol UV-254 plates in acetone-hexane system, 3:5 detecting with iodine vapors and UV irradiation.

General procedure of synthesis of compounds I. *Method A.* A mixture of 200 ml of anhydrous benzene, 0.15 mol of freshly distilled enamine, 0.10 mol of aldehyde and 5 mol % of *p*-toluenesulfonic acid was placed into a flask equipped with Dean-Stark trap and куадгч condenser. Dean-Stark trap was filled with benzene. This mixture was stirred for 5–10 min at room temperature and then refluxed to the end of water release (5–8 h). The solvent was removed under a reduced pressure and the product was distilled in high vacuum to give yellow oily liquid.

Table 2. Bond angles (ω, deg) for structure **VIIIa**

Angle	ω	Angle	ω
$C^4N^1C^5$	122.8(2)	$C^4C^8C^7$	119.8(2)
$C^8C^1C^2$	105.0(2)	$C^4C^8C^1$	109.6(2)
$C^3C^2C^1$	106.7(2)	$C^7C^8C^1$	130.5(2)
$C^{10}C^3C^4$	126.2(2)	$N^2C^9C^6$	177.8(2)
$C^{10}C^3C^2$	127.8(2)	$C^3C^{10}C^{11}$	126.9(2)
$C^4C^3C^2$	105.9(2)	$C^{10}C^{11}C^{12}$	111.3(3)
$N^1C^4C^8$	121.6(2)	$C^{10}C^{11}C^{13}$	109.3(2)
$N^1C^4C^3$	125.6(3)	$C^{12}C^{11}C^{13}$	111.2(2)
$C^8C^4C^3$	112.8(2)	$C^{15}C^{14}C^{19}$	118.8(3)
$O^1C^5N^1$	120.7(2)	$C^{15}C^{14}C^7$	122.1(2)
$O^1C^5C^6$	123.5(3)	$C^{19}C^{14}C^7$	119.1(2)
$N^1C^5C^6$	115.7(3)	$C^{14}C^{15}C^{16}$	120.2(2)
$C^7C^6C^9$	123.2(3)	$C^{17}C^{16}C^{15}$	119.5(2)
$C^7C^6C^5$	122.3(2)	$C^{16}C^{17}C^{18}$	121.5(2)
$C^9C^6C^5$	114.4(2)	$C^{16}C^{17}Cl^1$	119.2(2)
$C^6C^7C^8$	117.6(3)	$C^{18}C^{17}Cl^1$	119.3(3)
$C^6C^7C^{14}$	121.2(2)	$C^{17}C^{18}C^{19}$	118.9(2)
$C^8C^7C^{14}$	121.2(2)	$C^{18}C^{19}C^{14}$	121.1(2)

Method B. To 0.10 mol of cyclopentanone was added 0.05 mol of aldehyde in 50 ml of 0.5% KOH aqueous solution. The reaction mixture was stirred for 3 h and extracted with diethyl ether. The organic part was dried with sodium sulfate, the solvent was removed under a reduced pressure. Oily liquid was used without further purification. It was refluxed with morpholine in benzene in a flask equipped with the Dean-Stark trap and reflux condenser in the presence of catalytic amounts of *p*-toluenesolfonic acid (5 mol %). This mixture was boiled to the water of water release (6–8 h). Then benzene was distilled off under a reduced pressure. The product was isolated by a vacuum distillation to yield yellow oil.

1-(*N*-Morpholino)-5-(2-methylpropylidene)-cyclopent-1-ene (Ia). Yield 13 g (63%) by method *A*, bp 107–109°C (2 mm Hg). ^{1}H NMR spectrum, δ, ppm: 0.99 d (6H, $2CH_3$, J 6 Hz), 1.92 m (1H, CH), 2.34 m (2H, CH_2), 2.47 m (2H, CH_2), 2.85 m (4H, $2CH_2$), 3.78 m (4H, $2CH_2$), 5.05 m (1H, CH), 5.16 m (1H, CH). Mass spectrum, *m/z*, I_{rel}, %: 207 (50) $[M]^+$; 164 (100) $[M - C_3H_7]^+$. Found, C 75.37; H 10.27. $C_{13}H_{21}NO$. Calculated, %: C 75.32; H 10.21. M 207.16.

1-(*N*-Morpholino)-5-propylidenecyclopent-1-ene (Ib). Yield 11.6 (60%) by method *A*, 7.15 g (37%) by method *B*. bp 92–95°C (2 mm Hg). ^{1}H NMR spectrum, δ, ppm: 0.94 t (3H, CH_3, *J* 7.52 Hz), 2.02 m (2H, CH_2), 2.26 m (2H, CH_2), 2.37 m (2H, CH_2), 2.74 m (4H, $2CH_2$), 3.61 m (4H, $2CH_2$), 5.15 t (1H, CH, *J* 2.34 Hz), 5.24 m (1H, CH). Found, %: C 74.61; H 9.94. $C_{12}H_{19}NO$. Calculated, %: C 74.57; H 9.91. *M* 193.15.

1-(*N*-Morpholino)-5-(3-methylbutylidene)cyclopent-1-ene (Ic). Yield 9.74 g (44%) by method *A*, bp 118–120°C (2 mm Hg). ^{1}H NMR spectrum, δ, ppm: 0.85 d (6H, $2CH_3$, *J* 6.6 Hz), 1.62 m (1H, CH), 1.91 t (2H, CH_2, *J* 7.1 Hz), 2.27 m (2H, CH_2), 2.40 m (2H, CH_2), 2.72 m (4H, $2CH_2$), 3.63 m (4H, $2CH_2$), 5.16 m (1H, CH), 5.25 m (1H, CH). Found, %: C 75.93; H 10.27. $C_{14}H_{23}NO$. Calculated, %: C 75.97; H 10.47. *M* 221.18.

General procedure for the synthesis of compounds VIII. To a solution of alkene **VII** (10 mmol) in a mixture of 20 ml of anhydrous ethanol and 10 ml of DMF was added dropwise the corresponding alkylmethyleneamine **I** under stirring within 3 min. This mixture was kept for 1–3 days at room temperature. The precipitate was filtered off, washed with alcohol and hexane.

4-(*N*-Chlorophenyl)-7-*sec*-butylidene-2-oxo-2,5,6,7-tetrahydro-1*H*-pyridine-3-carbonitrile (VIIIa). Yield 1.06 g (26%), yellow powder, mp 310–311°C (EtOH). ^{1}H NMR spectrum, δ, ppm: 1.02 d (6H, $2CH_3$, *J* 6.45 Hz), 2.45 m (1H, CH), 2.55 m (2H, CH_2), 2.65 m (2H, CH_2), 6.46 d (1H, CH, *J* 9.15 Hz), 7.54 d (2H, CH_{Ar}, *J* 8.17 Hz), 7.62 d (2H, CH_{Ar}, *J* 8.15 Hz), 12.62 br.s (1H, NH). Mass spectrum, *m/z*, I_{rel}, %: 325 (100) $[M + 1]^+$; 323 (23) $[M - 1]^+$; 213 (11) $[M - 4\text{-}ClC_6H_4]^+$; 111 (11) $[4\text{-}ClC_6H_4]^+$. Found, %: C 70.22; H 5.21; N 8.64. $C_{19}H_{17}ClN_2O$. Calculated, %: C 70.26; H 5.28; N 8.62. *M* 324.8.

4-(4-Chlorophenyl)-7-propylidene-2-oxo-2,5,6,7-tetrahydro-1*H*-pyridine-3-carbonitrile (VIIIb). Yield 0.87 g (43%), yellow powder, mp 290–291°C (EtOH). ^{1}H NMR spectrum, δ, ppm: 1.13 t (3H, CH_3, *J* 7.45 Hz), 2.54–2.65 m (6H, $3CH_2$), 6.50 m (1H, CH), 7.57 d (2H, CH_{Ar}, *J* 8.15 Hz), 7.65 d (2H, CH_{Ar}, *J* 8.10 Hz), 12.72 br.s (1H, NH). Mass spectrum, *m/z*, I_{rel}, %: 310 (100) $[M]^+$; 309 (33) $[M - 1]^+$; 311 (22) $[M + 1]^+$; 312 (27) $[M + 2]^+$; 199 (7) $[M - 4\text{-}ClC_6H_4]^+$; 111 (6) $[4\text{-}ClC_6H_4]^+$. Found, %: C 69.52; H 4.85; N 4.89. $C_{18}H_{15}ClN_2O$. Calculated, %: C 69.57; H 4.86; N 9.01. *M* 310.78.

4-(4-Chlorophenyl)-7-(3-methylbutylidene)-2-oxo-2,5,6,7-tetrahydro-1*H*-pyrimidine-3-carbonitrile (VIIIc). Yield 2.04 g (47%), white powder, mp 263–265°C (EtOH). ^{1}H NMR spectrum, δ, ppm: 0.93 m (6H, $2CH_3$), 2.06 m (1H, CH), 2.43–.61 m (6H, $3CH_2$), 6.44 d (1H, CH, *J* 10 Hz), 7.54 d (2H, CH_{Ar}, *J* 8.5 Hz), 7.62 d (2H, CH_{Ar}, *J* 8.5 Hz), 12.67 br.s (1H, NH). Mass spectrum, *m/z*, I_{rel}, %: 339 (100) $[M + 1]^+$; 340 (17) $[M + 2]^+$; 227 (8) $[M - 4\text{-}ClC_6H_4]^+$; 111 (11) $[4\text{-}ClC_6H_4]^+$. Found, %: C 70.82; H 5.61; N 8.24. $C_{20}H_{19}ClN_2O$. Calculated, %: C 70.90; H 5.65; N 8.27. *M* 338.83.

4-(4-Chlorophenyl)-7-(3-methylbutylidene)-2-thioxo-2,5,6,7-tetrahydro-1*H*-pyridine-3-carbonitrile (VIIId). Yield 1.6 g (36%), dark green powder, mp 225-226°C (C_6H_6). ^{1}H NMR spectrum, δ, ppm: 0.9 d (6H, $2CH_3$, *J* 6 Hz), 1.02 m (1H, CH), 1.64–1.81 m (4H, $2CH_2$), 2.07 t (2H, CH_2, *J* 6.36 Hz), 4.72 br.s (1H, NH), 6.66 s (1H, CH), 7.36 d (2H, CH_{Ar}, *J* 6.98 Hz), 7.51 d (2H, CH_{Ar}, *J* 7.02 Hz). Mass spectrum, *m/z*, I_{rel}, %: 354 (62) $[M]^+$; 356 (20) $[M + 2]^+$; 311 (80) $[M - C_3H_7]^+$; 242 (25) $[M - 4\text{-}ClC_6H_4]^+$; 41 (100) $[C_3H_5]^+$. Found, %: C 67.70; H 5.43; N 7.83. $C_{20}H_{19}ClN_2S$. Calculated, %: C 67.69; H 5.40; N 7.89. *M* 354.9.

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