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PROPANAL IN THE SYNTHESES OF ALKYL-SUBSTITUTED 3-CYANO-2-PIPERIDONE, 3-CYANO-2,5,6,7-TETRAHYDROPYRINDIN-2(1H)-ONE, AND 3-CYANOPYRIDINE-2(1H)-THIONE

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Condensation of propanal with cyanothioacetamide and morpholine gave 3-cyano-4-ethyl-5-methyl-6-morpholino-2-piperidone, the structure of which was studied by X-ray analysis. Reaction of propanal with cyanothioacetamides and cycloalkanone enamines gave 3-cyano-4-ethyl-2,5,6,7-tetrahydropyrindin-2(1H)-one and 3-cyano-4-ethyl-5,6-hexamethylenepyridine-2(1H)-thione. The latter was used for the preparation of substituted 2-benzyloxycarbonylmethylthiopyridine and 3-amino-2-benzyloxycarbonylthieno[2,3-b]pyridine.

Keywords: Michael adduct, 3-cyano-4-ethyl-5,6-hexamethylenepyridine-2(1H)-thione, enamines, propanal, thieno[2,3-*b*]pyridine, cyanoacetamide, cyanothioacetamide, 3-cyano-4-ethyl-2,5,6,7-tetrahydropyrindin-2(1H)-one, condensation.

Alkyl-substituted pyridin-2(1H)-ones show promise in the search for compounds having biological activity [1, 2]. They represent a novel class of non-nucleosidic anti-AIDS substances [3, 4]. A convenient method for their synthesis is the formylation of methyl alkyl ketones [5, 6] and cycloalkanones [7] with subsequent condensation of the products formed with cyanoacetamide.

Continuing the search for potentially biologically active alkyl-substituted pyridine chalcogenones based on aliphatic aldehydes and cyanoacetic acid chalcogen amides [8, 9] we have studied the reaction of propanal (**1**) with cyanoacetamide (**2**) and morpholine. It was found that the condensation occurred at 20°C in ethanol to give 3-cyano-4-ethyl-5-methyl-6-morpholino-2-piperidone (**3**). The reaction route very likely includes the formation of enamine **4** and the substituted acrylamide **5**, reaction of which leads to the Michael adduct **6**. A regioselective intramolecular cyclization of the latter gives the substituted piperidone **3**. It should be noted that an equimolar ratio of reagents **1** and **2** gives a yield not exceeding 32% but the introduction of a two-fold excess of the propanal into this condensation led to an 84% yield of compound **3** and confirmed the proposed reaction mechanism (Scheme 1).

The structure of compound **3** was proved by X-ray analysis (Table 1 and Fig. 1). The central piperidone ring $N_{(1)}C_{(1\text{-}5)}$ has a *half-boat* conformation (the modified Cremer-Pople [10] parameters S, θ, and Ψ being 0.82, 30.3°, and 28.7° respectively) and the morpholine ring $N_{(3)}C_{(10\text{-}13)}O_{(2)}$ has a *chair* conformation (S = 1.20, θ = 0.7°, Ψ = 12.5°), the deviation of the torsional angles in the ring from the ideal value of 60.0° less than 2.8°.

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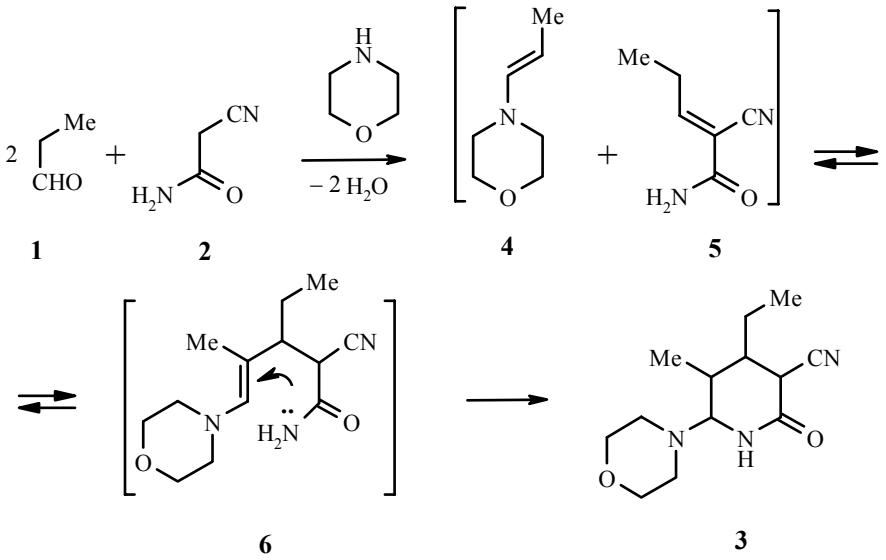
Scheme 1



The $N_{(1)}$ atom has a planar trigonal bond configuration (the sum of valence angles being 357.8(2.9)°) and the $N_{(3)}$ atom is pyramidal (the sum of the valence angles is 340.0(5)°). As a result of $n(N_{(1)})$–$\pi(C_{(1)}=O_{(1)})$ conjugation the $N_{(1)}$–$C_{(1)}$ bond length (1.331(3) Å) is markedly shortened when compared with the length $d = 1.45$ Å which is typical of a pure $N(sp^2)$–$C(sp^2)$ single bond [11]. Thanks to moderately strong $N_{(1)}$–$H_{(1)}\cdots O_{(1)}$ intermolecular hydrogen bonding [12] compound **3** forms a centrosymmetric dimer in the crystal (Fig. 2). The basic geometric parameters for this H bond are: $N_{(1)}$–$H_{(1)}$ 0.91(2), $N_{(1)}\cdots O_{(1)}$ 2.917(3), $O_{(1)}\cdots H_{(1)}$ 2.02(2) Å with $N_{(1)}$–$H_{(1)}$–$O_{(1)}$ 168(1)°.

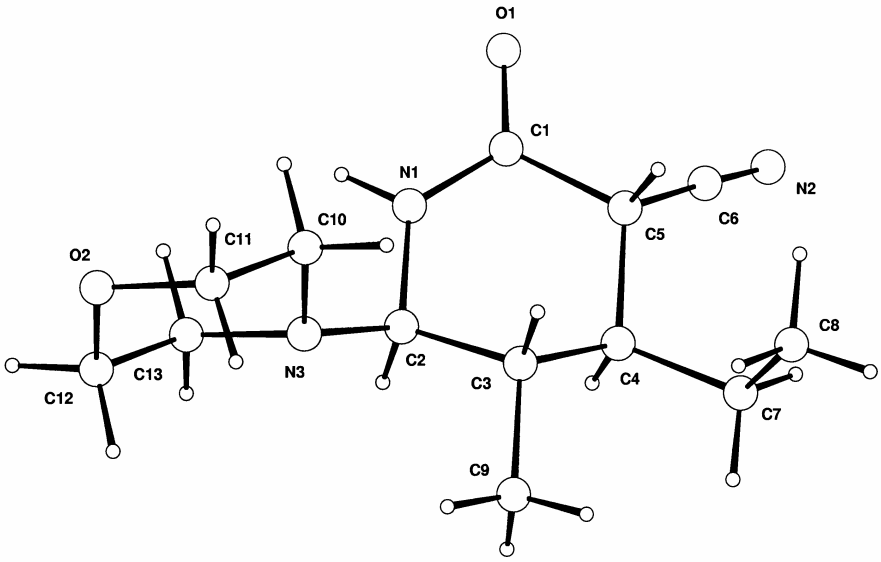
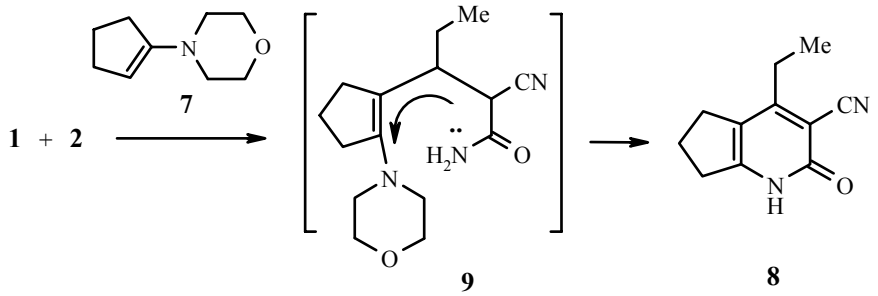
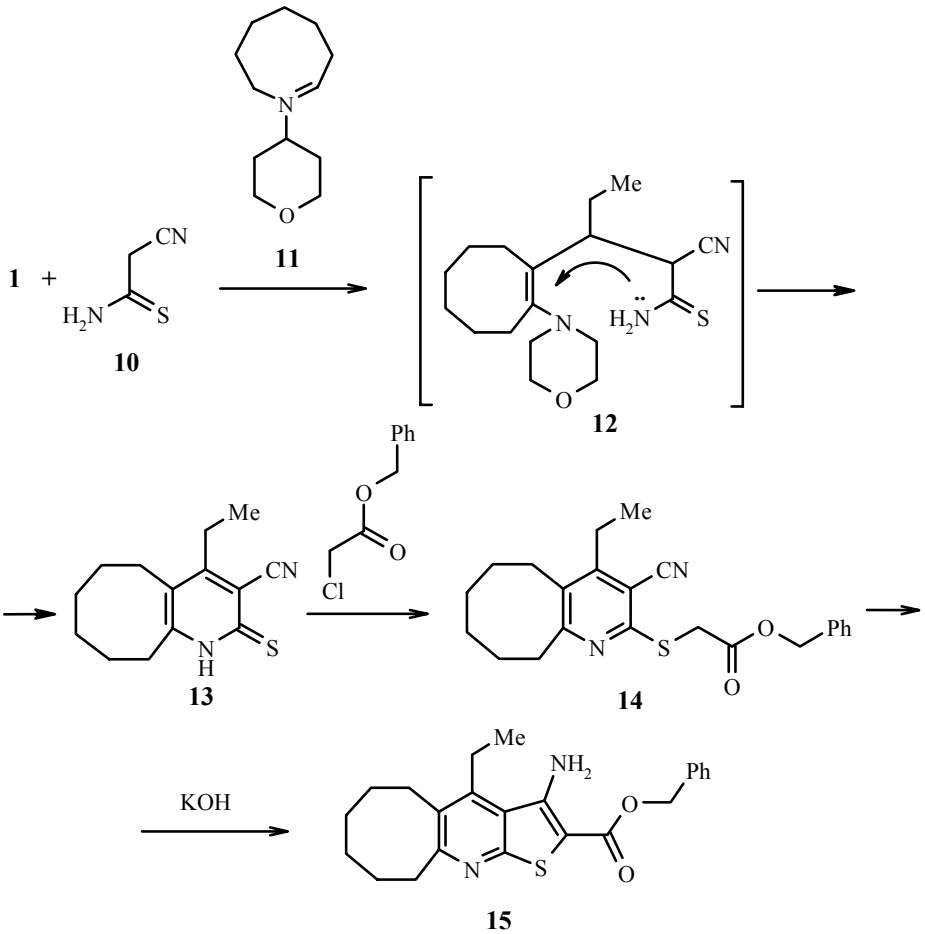


Fig. 1. General view of molecule **3** with atomic numbering.

The introduction of the 1-morpholinocyclopentene (**7**) into the condensation with propanal (**1**) and cyanoacetamide (**2**) gives 3-cyano-4-ethyl-2,5,6,7-tetrahydropyrindin-2(1H)-one (**8**). Evidently the reaction route includes the formation of alkene **5**, to which enamine **7** reacts by a Michael addition. The adduct **9** arising in this way undergoes an intramolecular cyclocondensation to give compound **8**.



The propanal (**1**) also readily takes part in a condensation with cyanothioacetamide (**10**) and 1-morpholinocyclooctene (**11**) to form the Michael adduct **12** *in situ*. Under these reaction conditions the latter regioselectively cyclizes to 3-cyano-4-ethyl-5,6-hexamethylenepyridine-2(1H)-thione (**13**).



Its structure was confirmed by spectroscopic investigational data and by chemical reactions. Hence the pyridinethione **13** is regioselectively alkylated by benzyl monochloroacetate in basic medium to the sulfide **14** which can be converted to the corresponding substituted thieno[2,3-*b*]pyridine **15** using KOH.

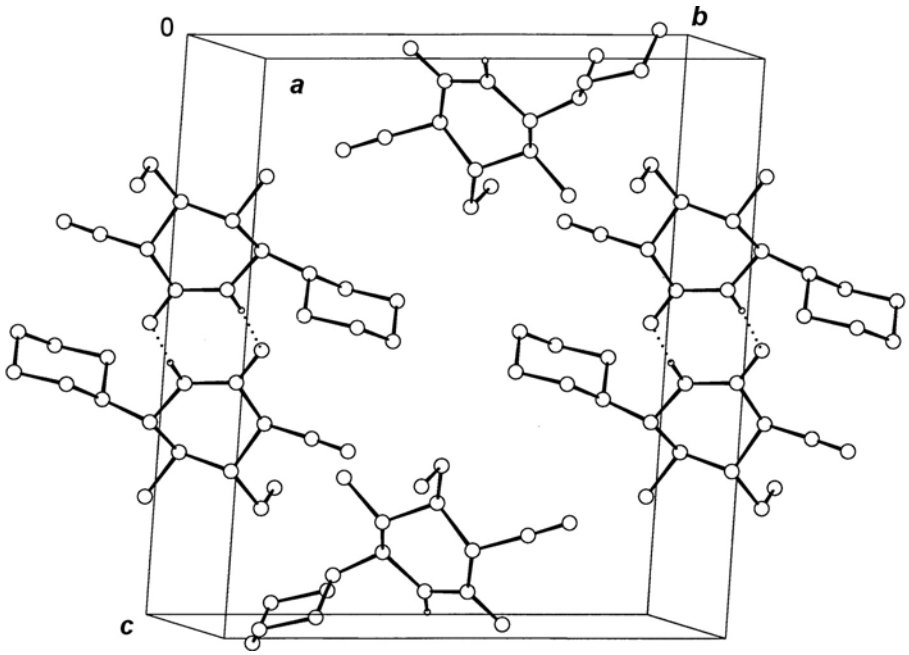


Fig. 2. Crystal packing of compound **3** (dotted lines indicate the intermolecular hydrogen bonds).

TABLE 1. Basic Bond Lengths (*d*) and Valence Angles (ω) in the Compound **3** Molecule

Bond	*d*, Å	Angle	ω, deg.
$O_{(1)}$–$C_{(1)}$	1.230(2)	$C_{(1)}$–$N_{(1)}$–$C_{(2)}$	127.72(17)
$N_{(1)}$–$C_{(1)}$	1.331(3)	$N_{(1)}$–$C_{(1)}$–$C_{(5)}$	117.24(18)
$N_{(1)}$–$C_{(2)}$	1.490(3)	$N_{(1)}$–$C_{(2)}$–$C_{(3)}$	110.82(17)
$N_{(2)}$–$C_{(6)}$	1.136(3)	$C_{(3)}$–$C_{(4)}$–$C_{(5)}$	108.22(16)
$C_{(1)}$–$C_{(5)}$	1.524(3)	$C_{(1)}$–$C_{(5)}$–$C_{(4)}$	114.83(16)
$C_{(2)}$–$C_{(3)}$	1.526(3)	$N_{(2)}$–$C_{(6)}$–$C_{(5)}$	178.2(2)
$C_{(3)}$–$C_{(4)}$	1.534(3)	$C_{(1)}$–$N_{(1)}$–$C_{(2)}$	127.72(17)
$C_{(4)}$–$C_{(5)}$	1.542(3)	$C_{(1)}$–$N_{(1)}$–$H_{(1)}$	112.6(14)
$C_{(5)}$–$C_{(6)}$	1.479(3)	$C_{(2)}$–$N_{(1)}$–$H_{(1)}$	117.5(13)
$N_{(1)}$–$H_{(1)}$	0.91(2)		

EXPERIMENTAL

X-ray Analysis of the Compound 3 Single Crystal with the linear size 0.31 x 0.31 x 0.31 mm was carried out at room temperature on an Enraf-Nonius CAD-4, four circle, automatic diffractometer (MoKα irradiation, relative scanning rate $2\theta/\omega = 1.2$, $\theta_{max} = 25°$, spherical segment $0 \le h \le 7$, $0 \le k \le 16$, $-18 \le l \le 18$). In all, 2772 reflections were collected of which 2421 are symmetrically independent ($R_{int} = 0.02$). Crystals of **3** are monoclinic with $a = 6.653(2)$, $b = 13.558(1)$, $c = 15.444(2)$ Å; $\beta = 75.15(1)°$; $V = 1381.6(5)$ Å^3; M = 251.33; $Z = 4$; $d_{calc} = 1.21$ g/cm^3; $\mu = 0.78$ cm^{-1}, $F(000) = 544.1$, and space group $P2_1/n$ (N 14). The structure was solved by a direct method and refined by least squares analysis using the full matrix anisotropic approximation and the CRYSTALS program package [13]. 1540 Reflections with $I > 3(I)$ were used in the refinement (247 refined

parameters, number of reflections per parameter 6.2). All of the hydrogen atoms were revealed in electron density difference synthesis and included in the refinement with fixed positions and thermal parameters. Calculation of the absorption in the crystal was carried out using the azimuthal scanning method [14]. The refinement used the Chebyshev weighting scheme with the five parameters: 0.76, -0.07, 0.53, -0.15, and 0.14. The final values of the difference factors were $R = 0.039$ and $R_W = 0.040$, $GOF = 1.191$. The residual electron density from Fourier difference synthesis was 0.16 and -0.15 e/Å^3. The coordinates of the non-hydrogen atoms can be obtained from one of the authors (A. N. Chernega).

The IR spectra of the synthesized compounds were recorded on an IRS-29 instrument using vaseline oil. ^{1}H NMR spectra were recorded on Gemini-200 (200 MHz) (compounds **3, 8, 14, 15**) and Bruker WP-100 SY (100 MHz) (compound **13**) instruments using DMSO-d_6 and TMS internal standard. Mass spectra were taken on a Kratos MS-890 (70 eV) spectrometer. Melting points were determined on a Koffler block. Monitoring of the reaction course was carried out by TLC using Silufol UV-254 plates with acetone–hexane (3:5) and revealed using iodine vapor.

3-Cyano-4-ethyl-5-methyl-6-morpholino-2-piperidone (3). A mixture of propanal **1** (1.46 ml, 20 mmol), cyanoacetamide **2** (0.84 g, 10 mmol), and morpholine (0.87 ml, 10 mmol) was stirred in ethanol (15 ml) at 20°C for 2 h and left for 1 day. The precipitate formed was filtered off and washed with ethanol and hexane to give compound **3** (2.11 g, 84%) as colorless crystals; mp 179-180°C (EtOH). IR spectrum, ν, cm^{-1}: 3200 (NH), 2247 (C≡N), 1648 (CONH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.93 (3H, t, $J = 7.26$, CH_3); 1.02 (3H, d, $J = 6.20$, CH_3); 1.69 (4H, m, $C\underline{H}_2CH_3$, $C_{(4)}H$ and $C_{(5)}H$); 2.36 (2H, m, CH_2); 2.77 (2H, m, CH_2); 3.09 (1H, m, $C_{(6)}H$); 3.57 (4H, m, CH_2OCH_2); 3.80 (1H, d, $J = 11.80$, $C_{(3)}H$); 8.23 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 251 $[M]^+$ (3), 181 (70), 135 (17), 86 (67), 57 (100), 41 (27). Found, %: C 61.92; H 8.30; N 16.89. $C_{13}H_{21}N_3O_2$. Calculated, %: C 62.13; H 8.42; N 16.72.

3-Cyano-4-ethyl-2,5,6,7-tetrahydropyrindin-2(1H)-one (8). A mixture of propanal **1** (0.73 ml, 10 mmol), cyanoacetamide **2** (0.84 g, 10 mmol), and 1-morpholinocyclopentene **7** (1.53 g, 10 mmol) was stirred in ethanol (15 ml) at 20°C for 1 h and left for 1 day. The precipitate formed was filtered off and washed with ethanol and hexane to give compound **8** (1.39 g, 74%) as colorless flakes with mp 185-187°C (EtOH) and fluorescing with a blue light upon UV irradiation. IR spectrum, ν, cm^{-1}: 2214 (C≡N), 1644 (CONH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.20 (3H, t, $J = 7.62$, CH_3); 2.10 (2H, m, CH_2); 2.59 (2H, t, $J = 7.78$, CH_2); 2.71 (2H, t, $J = 7.62$, CH_2); 2.79 (2H, t, $J = 7.88$, $C\underline{H}_2CH_3$); 12.47 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 188 $[M]^+$ (100), 187 (90), 159 (36), 77 (10). Found, %: C 70.04; H 6.52; N 15.03. $C_{11}H_{12}N_2O$. Calculated, %: C 70.19; H 6.43; N 14.88.

3-Cyano-4-ethyl-5,6-hexamethylenepyridine-2(1H)-thione (13). A mixture of propanal **1** (0.73 ml, 10 mmol), cyanothioacetamide (1.0 g, 10 mmol), and 1-morpholinocyclooctene **11** (1.95 g, 10 mmol) was stirred in ethanol (15 mol) for 1 h at 20°C and left for one day. The precipitate was separated and washed with ethanol and hexane to give compound **13** (1.85 g, 75%) as bright-yellow crystals; mp 234°C (EtOH, sublimation occurs at 150°C). IR spectrum, ν, cm^{-1}: 2224 (C≡N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.16 (3H, t, $J = 7.60$, CH_3); 1.36-1.61 (6H, m, $(CH_2)_3$); 2.43-2.98 (8H, m, $(CH_2)_4$); 13.77 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 246 $[M]^+$ (100), 245 (9), 230(27), 217 (50), 203 (46), 178 (14), 91 (15), 77 (13), 41 (25). Found, %: C 68.12; H 7.20; N 11.42. $C_{14}H_{18}N_2S$. Calculated, %: C 68.25; H 7.36; N 11.37.

2-Benzyloxycarbonylmethylthio-3-cyano-4-ethyl-5,6-hexamethylenepyridine (14). Aqueous KOH solution (10%, 5.6 ml, 10 mmol) and benzyl monochloroacetate (1.85 g, 10 mmol) were added successively with stirring to a solution of the pyridinethione **13** (2.46 g, 10 mmol) in DMF (10 ml) and the product was stirred for 4 h. The reaction mixture was diluted with water (15 ml) and filtered to give a precipitate which was washed with water, ethanol, and hexane to give compound **14** (2.96 g, 72%) as yellow crystals; mp 97-98°C (EtOH). IR spectrum, ν, cm^{-1}: 2220 (C≡N), 1694 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.23 (3H, t, $J = 7.12$, CH_3); 1.33 (4H, m, $(CH_2)_2$); 1.64 (4H, m, $(CH_2)_2$); 2.81 (6H, m, $(CH_2)_3$); 4.03 (2H, s, SCH_2); 5.09 (2H, s, OCH_2); 7.28 (5H, m, C_6H_5). Mass spectrum, *m/z* (I_{rel}, %): 394 $[M]^+$ (18), 259 (100), 246 (11), 91 (58), 77 (4), 65 (10). Found, %: C 69.84; H 6.72; N 6.95. $C_{23}H_{26}N_2O_2S$. Calculated, %: C 70.02; H 6.64; N 7.10.

3-Amino-2-benzyloxycarbonyl-4-ethyl-5,6-hexamethylenethieno[2,3-b]pyridine (15). Aqueous KOH solution (10%, 5.6 ml, 10 mmol) was added to a solution of compound **14** (3.94 g, 10 mmol) in DMF (10 ml) with stirring and then stirred for 5 h. The reaction mixture was treated with ethanol (10 ml) and filtered to give a precipitate which was washed with ethanol and hexane to give compound **15** (3.51 g, 89%) as opaque flakes; mp 184-185°C (EtOH). IR spectrum, ν, cm^{-1}: 3240, 3318, 3492 (NH_2), 1718 (C=O), 1646 (δ NH_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.28 (3H, t, *J* = 7.11, CH_3); 1.50 (4H, m, $(CH_2)_2$); 1.73 (4H, m, $(CH_2)_2$); 2.97 (6H, m, $(CH_2)_3$); 5.30 (2H, s, OCH_2); 6.76 (2H, br. s, NH_2); 7.35 (5H, m, C_6H_5). Mass spectrum, *m/z* (I_{rel}, %): 394 $[M]^+$ (70), 285 (33), 260 (12), 91 $[PhCH_2]^+$ (100), 77 (3), 65 (9). Found, %: C 70.14; H 6.51; H 7.19. $C_{23}H_{26}N_2O_2S$. Calculated, %: C 70.02; H 6.64; N 7.10.

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