ISSN 1070-3632, Russian Journal of General Chemistry, 2013, Vol. 83, No. 9, pp. 1716–1723. © Pleiades Publishing, Ltd., 2013.
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4-Alkyl-6-amino-N^3,N^5-diaryl-2-thioxo-1,2,3,4-tetrahydropyridine-3,5-dicarboxamides: II.[1] Synthesis and Selected Reactions

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Received August 20, 2012

Abstract—New 4-alkyl-6-amino-N^3,N^5-diaryl-2-thioxo-1,2,3,4-tetrahydropyridine-3,5-dicarboxamides have been prepared via enantioselective reaction of 3-amino-*N*-aryl-3-thioxopropanamides with *N*-aryl-2-cyanoacetamide and aliphatic aldehydes. The prepared products can be regioselectively alkylated at sulfur atom.

DOI: 10.1134/S1070363213090156

The 5-carbamoyl-substituted nicotinic acid nitriles form a well-studied class of organic compounds [2–5]. Their preparation methods have been developed, and some of the chemical and biological properties have been explored [6–13]. The most striking of the properties are hepatoprotective activity [14], potential antiviral activity towards a group of arboviruses, and good antioxidant activity [4]. However, the attempts to replace the cyano group in the position 3 with a less toxic amide fragment are scarce [4, 15, 16], and 3,5-diarylcarbamoylpyridine-2(1*H*)-thiones have been considered in a few works only [4, 17, 18]. Carbamoyl substituent, in contrast to the nitrile one, reduces the compound toxicity; however, preparation of such derivatives from nitriles is problematic because under severe conditions the regioselectivity of the synthesis is poor, and the yield decreases due to the formation of side products [19, 20]. Replacement of the 4-aryl substituent of the pyridine ring with an alkyl should also reduce the toxicity, and increase the lipophilicity of the final product [9, 21]. However, of the corresponding examples, only 3-carbamoyl-6-methyl-2-thioxo-5-phenylcarbamoyl-1,2,3,4-tetrahydropyridine-4-*spiro*-cyclohexane [18] has been known; recently, we have prepared 4-alkyl-3,5-diarylcarbamoylpyridine-2-thiones [1].

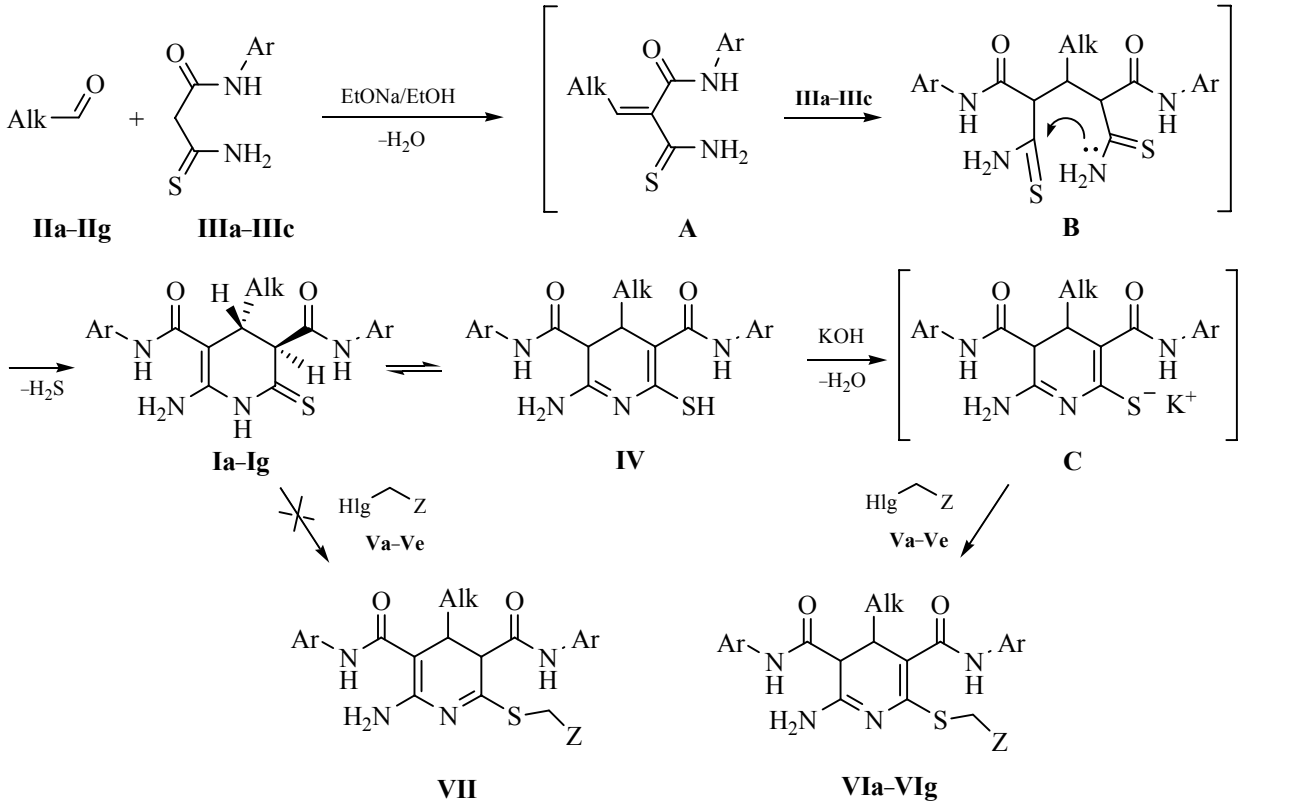
The aim of this study was to investigate the ways of the partially hydrogenated pyridines synthesis, the amide fragment of the initial CH-acid being retained in the pyridine nucleus.

The known methods for the preparation of 6-amino-3,5-dicarbamoyl-2-thioxodihydropyridines boil down to sequential reaction of three components: an aldehyde reacts with a cyanoacetanilide via the Knoevenagel reaction, and the alkene formed reacts with a thioxopropanamide [4]. However, in the case addressed in this work, the described approach was not applicable due to a number of reasons, such as the instability of the *in situ* formed alkene and its subsequent dimerization [22–24], the exchange of methylene components [25], the release of the Michael adduct [26], and the aldol condensation in the basic medium, leading to tarring of the reaction mixture [27].

In this paper we propose a method of new 4-alkyl-6-amino-N^3,N^5-diaryl-2-thioxo-1,2,3,4-tetrahydropyridine-3,5-dicarboxamides (**Ia–Ig**) preparation consisting in the interaction of an aliphatic aldehyde **IIa–IIg** with a thiocarbamoylacetanilide **IIIa–IIIc**. The reaction proceeded, apparently, via the formation of the Knoevenagel condensation product **A**, which reacted with the second mole of a reagent **IIIa–IIIc** to form the Michael adduct **B**, giving finally the product **Ia–Ig** via intramolecular cyclocondensation.

The target products **I** were formed independently of the reagents ratio in the original mixture. For example, we studied the reaction at **IId**: **IIIa** ratio ranged from

[1] For communication I, see [1].



I, Alk = *i*-Bu, Ar = Ph (**a**); *i*-Pr, Ph (**b**); Et, Ph (**c**); $(CH_2)_5Me$, Ph (**d**); $(CH_2)_6Me$, 2-MeC_6H_4 (**e**); $CH_2CH(Ph)CH_3$, Ph (**f**); Et, 3-MeC_6H_4 (**g**); **II**, Alk = Et (**a**); *i*-Pr (**b**); *i*-Bu (**c**); $(CH_2)_5Me$ (**d**); $(CH_2)_6Me$ (**e**); $CH(Ph)CH_3$ (**f**); $CH_2CH(Ph)CH_3$ (**g**); **III**, Ar = Ph (**a**); 2-MeC_6H_4 (**b**); 3-MeC_6H_4 (**c**); **V**, Z = $CH{=}CH_2$, Hlg = Br (**a**); H, I (**b**); $(CH_2)_7Me$, I (**c**); Ph, Cl (**d**); 4-$MeOC_6H_4NHCO$, Cl (**e**); **VI**, Alk = *i*-Bu, Ar = Ph, Z = $CH{=}CH_2$ (**a**); $(CH_2)_5Me$, Ph, $CH{=}CH_2$ (**b**); *i*-Pr, Ph, $CH{=}CH_2$ (**c**); $(CH_2)_5Me$, Ph, $(CH_2)_7Me$ (**d**); $(CH_2)_5Me$, Ph, Ph (**e**); *i*-Pr, Ph, H (**f**); $(CH_2)_6Me$, 2-MeC_6H_4, 4-$MeOC_6H_4NHCO$ (**g**).

1:2 to 4:1. In all the cases, the major product was 4-alkyltetrahydropyridine-3,5-dicarboxanilide (**Id**), but not the expected alkene (**A**).

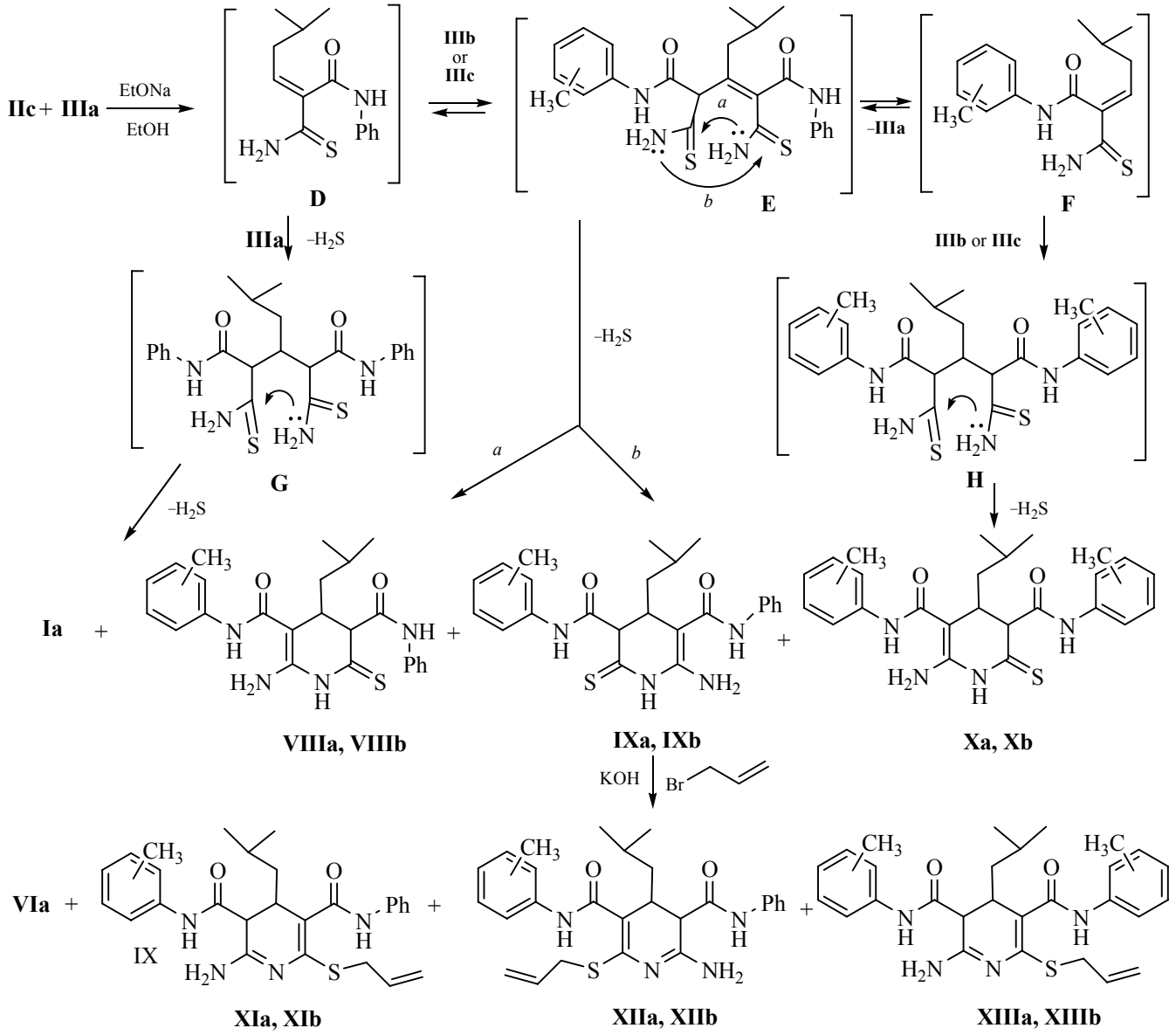
The Michael adduct (**B**) formation followed by cyclization proceeded enantioselectively. The only isomers isolated were σ-diastereomers with *trans*-location of arylcarbamoyl and alkyl substituents at C^3 and C^4 of the pyridine ring, respectively. That conclusion was based on ^{1}H NMR data taking into account results of the previous studies [1, 4]. In particular, in the ^{1}H NMR spectrum of compounds **Ia–Ig** the protons at C^3 and C^4 coupling constants were less than 1 Hz, and the signals were practically not split into multiplets. This could be due to several factors, including the C^3–C^4 bond elongation due to steric hindrance, increasing the C^3C^4H and C^4C^3H bond angles, and the implementation of the cycle conformation with the dihedral angle HC^3C^4H close to 90° as derived from the Karplus equation [28].

Taking into account the above-mentioned facts, the possible structure of the compounds **I** could be represented as pair of prototropic thione-thiol tautomers **I** and **IV**. The ^{1}H NMR patterns of those forms should be nearly identical. In the crystalline state, the thione form should exist exclusively, as evidenced by the valence vibration bands of C=S at 1166–1193 cm^{-1} in the IR spectrum [29]. Likely, the same form was present in DMSO-d_6 solution (at the conditions of ^{1}H NMR spectra recording). However, in the GS–MS spectra several molecular ion peaks with the same molecular mass were observed, thus indicating possible tautomerization in CH_2Cl_2 solution (at the conditions of GS–MS experiment).

The regioselective alkylation of the prepared dihydropyridines with alkyl halides **V** occurred at sulfur atom to give thioesters **VI**, being in agreement with the previously reported results on the alkylation of 4-aryl analogues of **VI** [3]. The set of the spectral data did not

allow discrimination the real structure of the compounds between the two possible tautomers, **VI** and **VII**. In [1], the tautomer **VI** was shown and its structure was proved by X-ray diffraction with Alk = *i*-Bu, Ar = 3-MeC_6H_4, Z = CH=CH_2. The reaction was carried out in ethanol in the presence of 10% aqueous KOH solution. Apparently, under those conditions the thiol tautomer **IV** readily formed salt **B**, further reacting with alkyl halide in basic medium.

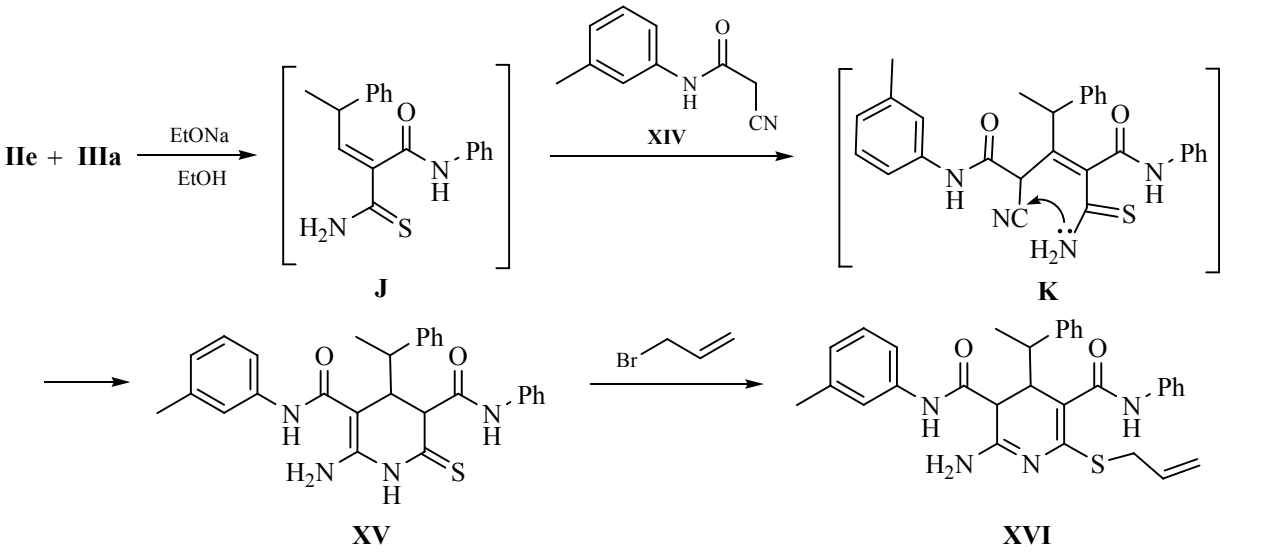
In the further part of the study, we focused at preparation of tetrahydropyridines **I** analogs containing various arylcarbamoyl substituents at positions 3 and 5. First, the Knoevenagel condensation product, alkene (**D**), was formed *in situ*, and then the second equivalent of another CH-acid (**IIIb** or **IIIc**) was added to it. However, according to the GS–MS results, a complex mixture of the products was formed, including **Ia, VIII, IX**, and the product of methylenes exchange **X** likely formed via the reversible reactions through the intermediates **E**–**H**. In the intermediate **E,** two ways the nucleophilic attack were possible (paths *a* and *b*), resulting in the formation of isomeric products **VIII** and **IX**. The alkylation of the so obtained mixture of **Ia, VIII, IX,** and **X** with allyl bromide occurred at S atom and led to the mixture of **VIa**, **XI**, **XII**, and **XIII**. The latter mixture was reflected in the GC-MS spectra by three molecular ions peaks with the masses differing



2-MeC_6H_4 (**a**), 3-MeC_6H_4 (**b**).

by one CH_2 group as a result of presence or absence of the tolyl fragment; thus, the initial mixture composition was confirmed. In the ^{1}H NMR spectrum of the **VIa** + **XI** + **XII** + **XIII** mixture**,** the following signals were identified: δ of 0.75–1.74 ppm (aliphatic substituent protons), 2.16–2.27 ppm (methyl substituent in aromatic ring), 3.36–3.40 (characteristic multiplets of allyl fragment), 3.71–3.74 ppm (methylene protons), 4.85, 5.07–5.09, and 5.8–5.82 ppm (vinyl group protons), 6.81–7.61 ppm (aromatic protons and protons of the amino group), and 8.76–9.61 ppm (several broad singlet of amide protons). We failed to isolate the mixture components by fractional crystallization.

An alternative solution to the stated problem could be a three-component interaction of aldehyde **II**, tiocarbamoylacetanilide **III**, and cyanoacetanilide **XIV**. That approach was successfully applied in the case of aromatic aldehydes [4, 30]. In our case, it was not applicable due to the methylene components exchange and *in situ* formation of alkylmethylene-cyanoacetanilide, further dimerizing as described in [22]. However, in the case of 2-phenylpropanal **IIe**, the alkene **J** was stabilized by the phenyl substituent and gave the target **XV** through the adduct (**K**). The alkylation of **XV** resulted in thioester **XVI**.



EXPERIMENTAL

^{1}H NMR spectra were recorded with Bruker AVANCE DRX-500 (500 MHz) (compounds **Id, Ie, Ig; VId, VIf,** and **VIg**; mixture **Ia** + **VIIIb** + **IXb** + **Xb**) and Bruker AVANCE II-400 (400 MHz) (compounds **Ia**–**Ic, If; VIa**–**VIc, VIe; XV,** and **XVI**; mixtures **Ia** + **VIIIa** + **IXa** + **Xa**, **VIa** + **XIa** + **XIIa** + **XIIIa**, and **VIa** + **XIb** + **XIIb** + **XIIIb)** instruments**,** in DMSO-d_6 (with TMS as internal standard). Mass spectra were recorded with Chrommas GC/MS-Hewlett-Packard 5890/5972 instrument with HP-5MS column (CI, 70 eV). IR spectra were recorded with FIR Spectrum One (Perkin-Elmer) instrument in KBr pellets. Melting points were measured with Kofler bench. Reaction monitoring and the compounds purity check were performed by TLC (Silufol UV-254 plates, in acetone–hexane 3:5 mixture, developers were iodine vapor and UV irradiation).

Synthesis of compounds I *(general procedure).* 5 mmol (0.115 g) of sodium was dissolved in 20 ml of anhydrous ethanol, then 5 mmol of the corresponding 3-amino-*N*-aryl-3-thioxopropanamide **IIIa–IIIc** and 5 mmol of aldehyde **IIa–IIg** were added upon stirring. After 10 min, another 5 mmol of **IIIa–IIIc** was added, and the mixture was left for 48 h at room temperature. The precipitate was filtered off, washed with water, cold ethanol, and hexane.

Compound Ia. Yield 1.46 g (69%). Yellow powder, mp 178–180°C (EtOH). IR spectrum, ν, cm^{-1}: 3143–3527 (NH, NH_2), 1688, 1658 (CONH), 1623 [δ(NH_2)], 1180 (C=S). ^{1}H NMR spectrum, δ, ppm: 0.89 d (3H, CH_3, *J* 6.4 Hz), 0.97 d (3H, CH_3, *J* 6.4 Hz), 1.02–1.29 m (2H, CH_2), 1.46–1.66 m (1H, CHMe$_2$), 3.78 d (1H, C^{4}H, *J* 4.4 Hz), 3.81 s (1H, C^{3}H), 6.91 t (1H, H_{arom}, *J* 6.9 Hz), 7.06 t (1H, H_{arom}, *J* 6.9 Hz), 7.22 t (2H, H_{arom}, *J* 6.8 Hz), 7.30 t (2H, H_{arom}, *J* 6.8 Hz), 7.49–7.57

m (4H, H_{arom}), 7.60 br.s (2H, NH_2), 10.27 br.s (2H, 2NHCO), 13.22 br.s (1H, N^1H). Mass spectrum, *m*/*z* (I_{rel}, %): 423.2 (100) $[M + 1]^+$. Found, %: C 65.22; H 6.14; N 13.19. $C_{23}H_{26}N_4O_2S$. Calculated, %: C 65.38; H 6.20; N 13.26. *M* 422.54.

Compound Ib. Yield 0.85 g (42%). Yellow powder, mp 184–186°C (EtOH). IR spectrum, ν, cm^{-1}: 3155–3540 (NH, NH_2), 1685, 1662 (CONH), 1619 [δ(NH_2)], 1166 (C=S). ^1H NMR spectrum, δ, ppm: 0.72–1.02 m (6H, $2CH_3$), 1.52–1.73 m (1H, $\underline{CH}Me_2$), 3.53 d (1H, C^4H, *J* 6.0 Hz), 4.08 s (1H, C^3H), 6.90 t (1H, H_{arom}, *J* 6.8 Hz), 7.05 t (1H, H_{arom}, *J* 6.8 Hz), 7.15–7.35 m (4H, H_{arom}), 7.52–7.65 m (4H, H_{arom}), 8.42 br.s (1H, NH_2), 9.86 br.s (1H, NH_2), 10.26 br.s (1H, NHCO), 10.40 br.s (1H, NHCO), 13.34 br.s (1H, N^1H). Mass spectrum, t/*z* (I_{rel}, %): 409.2 (100) $[M + 1]^+$. Found, %: C 64.55; H 5.76; N 13.64. $C_{22}H_{24}N_4O_2S$. Calculated, %: C 64.68; H 5.92; N 13.71. *M* 408.517.

Compound Ic. Yield 0.30 g (15%). White powder, mp 202–204°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 3120–3490 (NH, NH_2), 1690, 1670 (CONH), 1621 [δ(NH_2)], 1193 (C=S). ^1H NMR spectrum, δ, ppm: 0.82 t (3H, CH_3, *J* 6.9 Hz), 1.22–1.43 m (2H, CH_2), 3.53–3.65 m (1H, C^4H), 4.01–4.07 m (1H, C^3H), 6.82–6.93 m (2H, H_{arom}), 6.97–7.12 m (1H, H_{arom}), 7.14–7.32 m (3H, H_{arom}), 7.46 br.s (1H, NH_2), 7.52–7.67 m (4H, H_{arom}), 7.90 br.s (1H, NH_2), 10.11 br.s (1H, NHCO), 10.62 br.s (1H, NHCO), 13.56 br.s (1H, N^1H). Mass spectrum, t/*z* (I_{rel}, %): 395.2 (100) $[M + 1]^+$. Found, %: C 63.85; H 5.47; N 14.12. $C_{21}H_{22}N_4O_2S$.

Compound Id. Yield 1.28 g (29%). Yellow powder, mp 191–193°C (EtOH). IR spectrum, ν, cm^{-1}: 3137–3510 (NH, NH_2), 1672, 1658 (CONH), 1620 [δ(NH_2)], 1174 (C=S). ^1H NMR spectrum, δ, ppm: 0.86 t (3H, CH_3, *J* 6.14 Hz), 1.07–1.46 m (10H, $5CH_2$), 3.72 br.s (1H, C^4H), 3.91 s (1H, C^3H), 6.92 t (1H, H_{arom}, *J* 6.8 Hz), 7.05 t (1H, H_{arom}, *J* 6.8 Hz), 7.22 t (2H, H_{arom}, *J* 7.6 Hz), 7.29 t (2H, CH_{arom}, *J* 7.6 Hz), 7.51–7.70 m (4H, CH_{arom}), 8.58 br.s (1H, NH_2), 9.57 br.s (1H, NH_2), 10.37 br.s (2H, 2NHCO), 13.28 br.s (1H, N^1H). Mass spectrum, *m*/*z* (I_{rel}, %): 451.2 (100) $[M + 1]^+$. Found, %: C 66.47; H 6.67; N 12.37. $C_{25}H_{30}N_4O_2S$. Calculated, %: C 66.64; H 6.71; N 12.43. *M* 450.596.

Compound Ie. Yield 0.60 g (24%). Yellow powder, mp 169–171°C (EtOH). IR spectrum, ν, cm^{-1}: 3135–3527 (NH, NH_2), 1680, 1655 (CONH), 1612 [δ(NH_2)], 1182 (C=S). ^1H NMR spectrum, δ, ppm: 0.87 t (3H, CH_3, *J* 6.15 Hz), 1.11–1.45 m (12H, $6CH_2$), 2.12 s (3H, CH_3), 2.33 s (3H, CH_3), 3.88 br.s (2H, C^3H, C^4H), 6.77–7.51 m (9H, $7H_{arom}$ and NH_2), 8.19 d (1H, H_{arom}, *J* 7.5 Hz), 9.76 br.s (1H, NHCO), 10.28 br.s (1H, NHCO), 12.47 br.s (1H, N^1H). Mass spectrum, *m*/*z* (I_{rel}, %): 493.2 (100) $[M + 1]^+$. Found, %: C 68.20; H 7.29; N 11.20. $C_{28}H_{36}N_4O_2S$. Calculated, %: C 68.26; H 7.37; N 11.37. *M* 492.676.

Compound If. Yield 0.18 g (7%). Yellow powder, mp 225–227°C (EtOH). IR spectrum, ν, cm^{-1}: 3120–3480 (NH, NH_2), 1668, 1656 (CONH), 1616 [δ(NH_2)], 1192 (C=S). ^1H NMR spectrum, δ, ppm: 1.31 d (3H, CH_3, *J* 6.4 Hz), 1.39–1.49 m (1H, CH_2), 1.50–1.61 m (1H, CH_2), 2.84–2.96 m (1H, $\underline{CH}Me_2$), 3.84 t (1H, C^4H, *J* 6.8 Hz), 3.89 s (1H, C^3H), 6.93 t (1H, H_{arom}, *J* 6.9 Hz), 7.07 t (1H, H_{arom}, *J* 6.8 Hz), 7.11–7.40 m (9H, H_{arom}), 7.44–7.63 m (4H, H_{arom}), 8.22 br.s (1H, NH_2), 9.51 br.s (1H, NH_2), 10.18 br.s (1H, NHCO), 10.39 br.s (1H, NHCO), 13.22 s (1H, N^1H). Mass spectrum, *m*/*z* (I_{rel}, %): 485.2 (100) $[M + 1]^+$. Found, %: C 69.23; H 5.76; N 11.38. $C_{28}H_{28}N_4O_2S$. Calculated, %: C 69.40; H 5.82; N 11.56. *M* 484.613.

Compound Ig. Yield 0.40 g (19%). White powder, mp 218–220°C (EtOH). IR spectrum, ν, cm^{-1}: 3146–3512 (NH, NH_2), 1684, 1667 (CONH), 1628 [δ(NH_2)], 1188 (C=S). ^1H NMR spectrum, δ, ppm: 0.88 t (3H, CH_3, *J* 7.4 Hz), 1.29–1.35 m (1H, CH_2), 1.39–1.47 m (1H, CH_2), 2.24 s (3H, CH_3), 2.26 s (3H, CH_3), 3.70 t (1H, C^4H, *J* 6.2 Hz), 3.78 s (1H, C^3H), 6.74 d (1H, H_{arom}, *J* 7.6 Hz), 6.88 d (1H, H_{arom}, *J* 7.8 Hz), 7.10 t (1H, H_{arom}, *J* 7.6 Hz), 7.18 t (1H, H_{arom}, *J* 7.8 Hz), 7.32 d (1H, H_{arom}, *J* 8.5 Hz), 7.36 d (1H, H_{arom}, *J* 8.5 Hz), 7.40 s (1H, CH_{arom}), 7.42 s (1H, CH_{arom}), 8.23 br.s (1H, NH_2), 9.48 br.s (1H, NH_2), 10.16 br.s (1H, NHCO), 10.36 br.s (1H, NHCO), 13.10 br.s (1H, N^1H). Mass spectrum, t/*z* (I_{rel}, %): 423.2 (100) $[M + 1]^+$. Found, %: C 65.25; H 6.12; N 13.12. $C_{23}H_{26}N_4O_2S$. Calculated, %: C 65.38; H 6.20; N 13.26. *M* 422.543.

Synthesis of compounds VIa–VIg and XVI *(general procedure).* 0.5 mmol (0.26 ml) of 10% aqueous KOH solution was added upon stirring to a suspension of 0.5 mmol of the compound **Ia–Ig** or **XV** in 15 ml of ethanol; after 10 min, 0.5 mmol of the appropriate alkyl halide was added. The mixture was left for 24 h, the precipitate was filtered off, washed with water, cold methanol, and ethanol. The product was dried under vacuum.

Compound VIa. Yield 0.11 g (49%). White powder, mp 152–154°C (EtOH). IR spectrum, ν, cm^{-1}: 3180–3430 (NH, NH_2), 1670, 1652 (CONH), 1614 [δ(NH_2)]. ^1H NMR spectrum, δ, ppm: 0.88 d (6H,

2CH_3, *J* 4.0 Hz), 1.00–1.14 m (1H, CH_2), 1.26–1.38 m (1H, CH_2), 1.69 s (1H, CHMe$_2$), 3.31 s (1H, C^3H), 3.35–3.43 m (2H, C^4H and SCH_2), 3.73 d.d (1H, SCH_2, ^2J 13.2, ^3J 6.4 Hz), 4.84 d (1H, =CH_2, J_{cis} 9.8 Hz), 5.06 d (1H, =CH_2, J_{trans} 17.0 Hz), 5.73–5.88 m (1H, CH=), 7.00 t (1H, H_{arom}, *J* 7.2 Hz), 7.06 t (1H, H_{arom}, *J* 7.2 Hz), 7.27 t (2H, H_{arom}, *J* 7.6 Hz), 7.32 t (2H, H_{arom}, *J* 7.6 Hz), 7.40 br.s (1H, NH_2), 7.49 br.s (1H, NH_2), 7.54–7.68 m (4H, 4H_{arom}), 9.32 br.s (1H, NHCO), 9.78 br.s (1H, NHCO). Mass spectrum, *m*/*z* (I_{rel}, %): 463.2 (100) $[M + 1]^+$. Found, %: C 67.43; H 6.39; N 12.06. $C_{26}H_{30}N_4O_2S$. Calculated, %: C 67.50; H 6.54; N 12.11. *M* 462.607.

Compound VIb. Yield 0.047 g (19%). White powder, mp 151–153°C (EtOH). IR spectrum, ν, cm^{-1}: 3164–3412 (NH, NH_2), 1668, 1650 (CONH), 1612 [δ(NH_2)]. ^1H NMR spectrum, δ, ppm: 0.75–0.90 m (3H, CH_3), 1.05–1.47 m (10H, 5CH_2), 3.28–3.32 m (1H, C^4H), 3.34 s (1H, C^3H), 3.44 d.d (1H, SCH_2, ^2J 13.1, ^3J 7.6 Hz), 3.74 d.d (1H, SCH_2, ^2J 13.1, ^3J 6.5 Hz), 4.89 d (1H, =CH_2, J_{cis} 9.9 Hz), 5.10 d (1H, =CH_2, J_{trans} 17.1 Hz), 5.78–5.93 m (1H, CH=), 7.00 t (1H, H_{arom}, *J* 7.1 Hz), 7.06 t (1H, H_{arom}, *J* 7.1 Hz), 7.27 t (2H, H_{arom}, *J* 7.6 Hz), 7.32 t (2H, H_{arom}, *J* 7.6 Hz), 7.41 br.s (2H, NH_2), 7.52–7.63 m (4H, 4H_{arom}), 9.18 br.s (1H, NHCO), 9.63 br.s (1H, NHCO). Mass spectrum, *m*/*z* (I_{rel}, %): 491.2 (100) $[M + 1]^+$. Found, %: C 68.40; H 6.82; N 11.25. $C_{28}H_{34}N_4O_2S$. Calculated, %: C 68.54; H 6.98; N 11.42. *M* 490.66.

Compound VIc. Yield 0.014 g (6%). White powder, mp 183–185°C (EtOH). IR spectrum, ν, cm^{-1}: 3176–3422 (NH, NH_2), 1656, 1648 (CONH), 1615 [δ(NH_2)]. ^1H NMR spectrum, δ, ppm: 0.91 d (6H, 2CH_3, *J* 6.3 Hz), 1.55–1.69 m (1H, CHMe$_2$), 3.08 d (1H, C^4H, *J* 7.3 Hz), 3.38 d.d (1H, SCH_2, ^2J 13.3, ^3J 7.8 Hz), 3.45 s (1H, C^3H), 3.73 d.d (1H, SCH_2, ^2J 13.3, ^3J 6.4 Hz), 4.84 d (1H, =CH_2, J_{cis} 9.9 Hz), 5.06 d (1H, =CH_2, J_{trans} 17.1 Hz), 5.72–5.88 m (1H, CH=), 7.00 t (1H, H_{arom}, *J* 7.2 Hz), 7.07 t (1H, H_{arom}, *J* 7.2 Hz), 7.27 t (2H, H_{arom}, *J* 7.6 Hz), 7.32 t (2H, H_{arom}, *J* 7.6 Hz), 7.45 br.s (2H, NH_2), 7.51–7.72 m (4H, H_{arom}), 9.29 br.s (1H, NHCO), 9.58 br.s (1H, NHCO). Mass spectrum, *m*/*z* (I_{rel}, %): 449.2 (100) $[M + 1]^+$. Found, %: C 66.80; H 6.39; N 12.32. $C_{25}H_{28}N_4O_2S$. Calculated, %: C 66.94; H 6.29; N 12.49. *M* 448.58.

Compound VId. Yield 0.098 g (34%). White powder, mp 152–154°C (EtOH). IR spectrum, ν, cm^{-1}: 3138–3415 (NH, NH_2), 1668, 1643 (CONH), 1608 [δ(NH_2)]. ^1H NMR spectrum, δ, ppm: 0.74–0.92 m (6H, 2CH_3), 1.03–1.55 m (24H, 12CH_2), 2.64–2.74 (1H, SCH_2), 3.00–3.09 m (1H, SCH_2), 3.27 t (1H, C^4H, *J* 6.5 Hz), 3.32 s (1H, C^3H), 7.00 t (1H, H_{arom}, *J* 7.2 Hz), 7.05 t (1H, H_{arom}, *J* 7.2 Hz), 7.19–7.46 m (6H, 4H_{arom} and NH_2), 7.60 t (4H, H_{arom}, *J* 8.2 Hz), 9.39 br.s (1H, NHCO), 9.71 br.s (1H, NHCO). Mass spectrum, *m*/*z* (I_{rel}, %): 577.4 (100) $[M + 1]^+$. Found, %: C 70.90; H 8.49; N 9.82. $C_{34}H_{48}N_4O_2S$. Calculated, %: C 70.79; H 8.39; N 9.71. *M* 576.836.

Compound VIe. Yield 0.17 g (64%). White powder, mp 181–183°C (EtOH). IR spectrum, ν, cm^{-1}: 3157–3458 (NH, NH_2), 1666, 1656 (CONH), 1621 [δ(NH_2)]. ^1H NMR spectrum, δ, ppm: 0.83 t (3H, CH_3, *J* 6.18 Hz), 1.00–1.51 m (10H, 5CH_2), 3.38–3.50 m (2H, C^3H, C^4H), 4.10 d (1H, SCH_2, ^2J 13.0 Hz), 4.32 d (1H, SCH_2, ^2J 13.0 Hz), 6.97 t (1H, H_{arom}, *J* 7.0 Hz), 7.06 t (1H, H_{arom}, *J* 7.2 Hz), 7.11–7.71 m (15H, 13H_{arom} and NH_2), 9.06 br.s (1H, NHCO), 9.81 br.s (1H, NHCO). Mass spectrum, *m*/*z* (I_{rel}, %): 541.2 (100) $[M + 1]^+$. Found, %: C 71.23; H 6.64; N 10.18. $C_{32}H_{36}N_4O_2S$. Calculated, %: C 71.08; H 6.71; N 10.36. *M* 540.72.

Compound VIf. Yield 0.07 g (32%). White powder, mp 214–216°C (EtOH). IR spectrum, ν, cm^{-1}: 3189–3432 (NH, NH_2), 1672, 1662 (CONH), 1627 [δ (NH_2)]. ^1H NMR spectrum, δ, ppm: 0.91 d (6H, 2CH_3, *J* 6.0 Hz), 1.54–1.69 m (1H, CHMe$_2$), 2.24 s (3H, SCH_3), 3.11 d (1H, C^4H, *J* 6.8 Hz), 3.47 s (1H, C^3H), 6.99 t (1H, H_{arom}, *J* 7.6 Hz), 7.06 t (1H, H_{arom}, *J* 7.4 Hz), 7.26 t (2H, H_{arom}, *J* 7.8 Hz), 7.31 t (2H, H_{arom}, *J* 7.8 Hz), 7.37 br.s (2H, NH_2), 7.59 d (2H, H_{arom}, *J* 8.0 Hz), 7.62 d (2H, H_{arom}, *J* 8.0 Hz), 9.21 br.s (1H, NHCO), 9.66 br.s (1H, NHCO). Mass spectrum, *m*/*z* (I_{rel}, %): 423.1 (100) $[M + 1]^+$. Found, %: C 65.25; H 6.03; N 13.11. $C_{23}H_{26}N_4O_2S$. Calculated, %: C 65.38; H 6.20; N 13.26. *M* 422.543.

Compound VIg. Yield 0.13 g (40%). White powder, mp 186–188°C (EtOH). IR spectrum, ν, cm^{-1}: 3132–3421 (NH, NH_2), 1678, 1650 (CONH), 1618 [δ(NH_2)]. ^1H NMR spectrum, δ, ppm: 0.85 t (3H, CH_3, *J* 6.28 Hz), 1.19–1.53 m (12H, 6CH_2), 2.13 s (3H, CH_3), 2.19 s (3H, CH_3), 3.37–3.40 m (1H, C^4H), 3.48 s (1H, C^3H), 3.66 d (1H, SCH_2, ^2J 14.0 Hz), 3.69 s (3H, OCH_3), 3.87 d (1H, SCH_2, ^2J 14.2 Hz), 6.74 d (2H, H_{arom}, *J* 8.9 Hz), 7.01–7.25 m (7H, H_{arom}), 7.33 d (2H, H_{arom}, *J* 8.9 Hz), 7.37 d (2H, H_{arom}, *J* 7.7 Hz), 7.74 d (2H, NH_2, *J* 21.3 Hz), 8.81 br.s (1H, NHCO), 9.06 br.s (1H, NHCO), 9.91 br.s (1H, NHCO). Mass spectrum, *m*/*z* (I_{rel}, %): 656.4 (100) $[M + 1]^+$. Found, %: C 67.60; H 6.76; N 10.51. $C_{37}H_{45}N_5O_4S$. Calculated, %: C 67.76; H 6.92; N 10.68. *M* 655.849.

Compound XVI. Yield 0.08 g (31%). White powder, mp 193–195°C (EtOH). IR spectrum, ν, cm^{-1}: 3124–3446 (NH, NH_2), 1669, 1658 (CONH), 1626 [δ(NH_2)]. ^{1}H NMR spectrum, δ, ppm: 1.27 d (3H, CH_3, *J* 6.6 Hz), 2.26 s (3H, CH_3), 2.68–2.81 m (1H, CHMe), 3.45 d.d (1H, SCH_2, ^2J 13.0, ^3J 7.5 Hz), 3.47 br.s (1H, C^4H), 3.52 s (1H, C^3H), 3.69 d.d (1H, SCH_2, ^2J 13.0, ^3J 6.6 Hz), 4.88 d (1H, $=CH_2$, J_{cis} 9.8 Hz), 5.10 d (1H, $=CH_2$, J_{trans} 16.9 Hz), 5.68–5.81 m (1H, CH=), 6.82–7.48 m (16H, $14H_{arom}$ and NH_2), 8.43 br.s (1H, NHCO), 9.28 br.s (1H, NHCO). Mass spectrum, *m*/*z* (I_{rel}, %): 525.2 (100) $[M + 1]^+$. Found, %: C 71.13; H 6.10; N 10.52. $C_{31}H_{32}N_4O_2S$. Calculated, %: C 70.96; H 6.15; N 10.68. *M* 524.676.

Compound XV was prepared similarly to **I** using 5 mmol (0.97 g) of 3-amino-*N*-phenyl-3-thioxopropanamide (**III**), 5 mmol (0.67 g) of 2-phenylpropanal (**IIf**), and 5 mmol (0.87 g)of *N*-(*m*-tolyl)-2-cyanoacetamide (**XIV**). Yield 0.14 g (6%). Yellow powder, mp 167–169°C (Me 2 SO). IR spectrum, ν, cm^{-1}: 3186–3390 (NH, NH_2), 1668 (CONH), 1615 [δ(NH_2)], 1208 (C=S). ^{1}H NMR spectrum, δ, ppm: 1.25 d (3H, CH_3, *J* 6.3 Hz), 2.25 s (3H, CH_3), 2.86–2.98 m (1H, CH), 3.90 s (1H, C^3H), 4.06 d (1H, C^4H, *J* 4.6 Hz), 6.84–7.00 m (2H, H_{arom}), 7.09–7.58 m (12H, H_{arom}), 7.90 br.s (1H, NH_2), 9.32 br.s (1H, NH_2), 9.80 br.s (1H, NHCO), 10.07 br.s (1H, NHCO), 13.18 br.s (1H, N^1H). Mass spectrum, *m*/*z* (I_{rel}, %): 485.2 (100) $[M + 1]^+$. Found, %: C 69.24; H 5.68; N 11.49. $C_{28}H_{28}N_4O_2S$. Calculated, %: C 69.40; H 5.82; N 11.56. *M* 484.613.

The mixtures Ia + VIIIa + IXa + Xa, and **Ia + VIIIb + IXb + Xb** were prepared similarly to **I**, using 5 mmol of 3-amino-*N*-aryl-3-thioxopropanamides (**IIIa–IIIc**) and 5 mmol (0.535 ml) of 3-methylbutanal (**IIb**).

The mixture of compounds Ia, VIIIa, IXa, and Xa. ^{1}H NMR spectrum, δ, ppm: 0.84–1.04 m (6H, $2CH_3$), 1.09–1.34 m (2H, CH_2), 1.52–1.67 m (1H, $CHMe_2$), 2.06–2.15 m (3H, CH_3), 3.68–3.94 m (2H, C^3H, C^4H), 6.76–8.26 m (11H, NH_2, H_{arom}), 9.52 br.s, 9.67 br.s, 10.19 br.s, 10.35 br.s (2H, 2NHCO), 12.41 br.s, 13.20 br.s (1H, N^1H). Mass spectrum, *m*/*z* (I_{rel}, %): 423.2 (55) $[M + 1]^+$ (**Ia**), 437.2 (100) $[M + 1]^+$ (**VIIIa, IXa**), 451.2 (51) $[M + 1]^+$ (**Xa**).

The mixture of compounds Ia, VIIIb, IXb, and Xb. ^{1}H NMR spectrum, δ, ppm: 0.90 d, 0.98 d, 1.05 d (6H, $2CH_3$, *J* 6.0 Hz), 1.09–1.27 m (2H, CH_2), 1.53–1.68 m (1H, $CHMe_2$), 2.24 s, 2.26 s (3H, CH_3), 3.71 d, 3.74–3.86 m, 4.30 d (2H, C^3H, C^4H, *J* 4.0 Hz), 6.74 d, 6.88 d, 6.91 t, 7.03–7.12 m, 7.15–7.25 m, 7.28–7.42 m, 7.50–7.58 m (9H, H_{arom}), 8.25 br.s, 9.51 br.s (2H, NH_2), 10.07 br.s, 10.15 br.s, 10.31 br.s (2H, 2NHCO), 13.14 br.s, 13.19 br.s (1H, N^1H). Mass spectrum, *m*/*z* (I_{rel}, %): 423.2 (43) $[M + 1]^+$ (**Ia**), 437.2 (100) $[M + 1]^+$ (**VIIIb, IXb**), 451.2 (49) $[M + 1]^+$ (**Xb**).

The mixtures **VIa + XIa + XIIa + XIIIa** and **VIa + XIb + XIIb + XIIIb** were prepared similarly to **VI**.

The mixture of compounds VIa, XIa, XIIa, and XIIIa. ^{1}H NMR spectrum, δ, ppm: 0.77–1.02 m (6H, $2CH_3$), 1.05–1.19 m (1H, CH_2), 1.25–1.37 m (1H, CH_2), 1.62–1.76 m (1H, $CHMe_2$), 2.16 s and 2.23 s (3H, CH_3), 3.34–3.51 m (3H, C^3H, C^4H, SCH_2), 3.68–3.79 m (1H, SCH_2), 4.78–4.91 m (1H, $=CH_2$), 4.99–5.18 m (1H, $=CH_2$), 5.75–5.87 m (1H, CH=), 6.88–7.75 m (11H, $9H_{arom}$ and NH_2), 8.76 br.s, 8.87 br.s, 8.91 br.s, 9.17 br.s, 9.30 br.s, 9.57 br.s, 9.61 br.s (2H, 2NHCO). Mass spectrum, *m*/*z* (I_{rel}, %): 463.2 (20) $[M + 1]^+$ (**VIa**), 477.2 (100) $[M + 1]^+$ (**XIa, XIIa**), 491.2 (70) $[M + 1]^+$ (**XIIIa**).

The mixture of compounds VIa, XIb, XIIb, and XIIIb. ^{1}H NMR spectrum, δ, ppm: 0.76–0.96 m (6H, $2CH_3$), 1.00–1.16 m (1H, CH_2), 1.22–1.35 m (1H, CH_2), 1.59–1.75 m (1H, $CHMe_2$), 2.27 s (3H, CH_3), 3.25–3.46 m (3H, C^3H, C^4H, SCH_2), 3.67–3.80 m (1H, SCH_2), 4.81–4.89 m (1H, $=CH_2$), 5.07 d (1H, $=CH_2$, J_{trans} 16.8 Hz), 5.72–5.82 m (1H, CH=), 6.76–7.65 m (11H, $9H_{arom}$ and NH_2), 9.19 br.s, 9.22 br.s, 9.28 br.s, 9.32 br.s, 9.71 br.s, 9.80 br.s (2H, 2NHCO). Mass spectrum, *m*/*z* (I_{rel}, %): 463.2 (100) $[M + 1]^+$ (**VIa**), 477.2 (100) $[M + 1]^+$ (**XIb, XIIb**), 491.2 (100) $[M + 1]^+$ (**XIIIb**).

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