Utility of Sulfones in Heterocyclic Synthesis: Synthesis of Some New Polysubstituted Pyran and Pyridine Derivatives

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Phenylsulfonylacetonitrile reacted with formaldehyde and activated nitriles to yield pyran, pyridine, and thiophene derivatives.

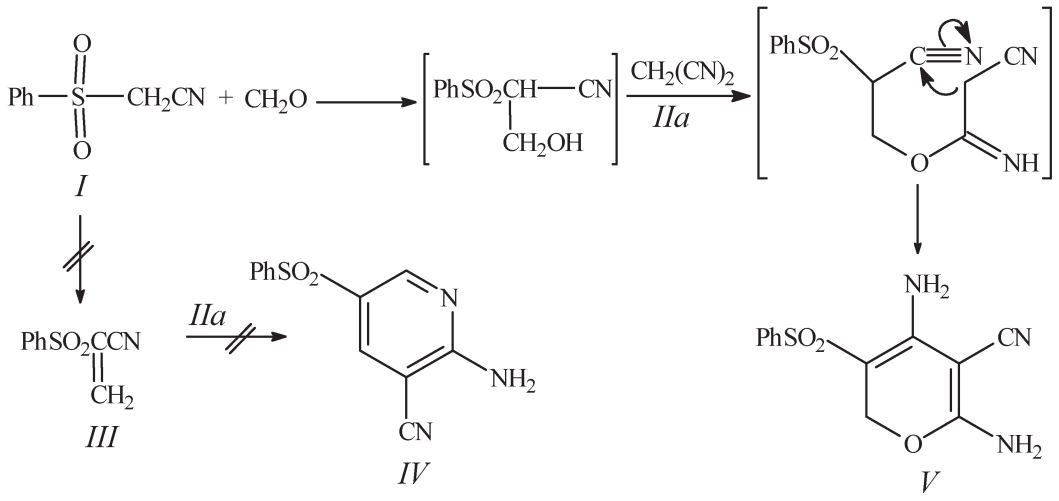
Synthesis of pyridine and pyran derivatives has recently received considerable attention due to their pharmaceutical importance [1—4]. Activated nitriles have become an important area of heterocyclic synthesis [5—8]. A variety of polyfunctionally substituted pyridines were prepared by reacting enaminonitriles with formaldehyde and active methylene reagents or cinnamonitrile derivatives [7]. Phenylsulfonylacetonitrile (*I*) when reacted with α,β-unsaturated nitriles and/or 2-hydroxynaphthaldehyde yields pyridine derivatives.

In the present work *I* reacted with formaldehyde and activated nitriles *IIa*—*IIg* to yield polysubstituted pyran and pyridines.

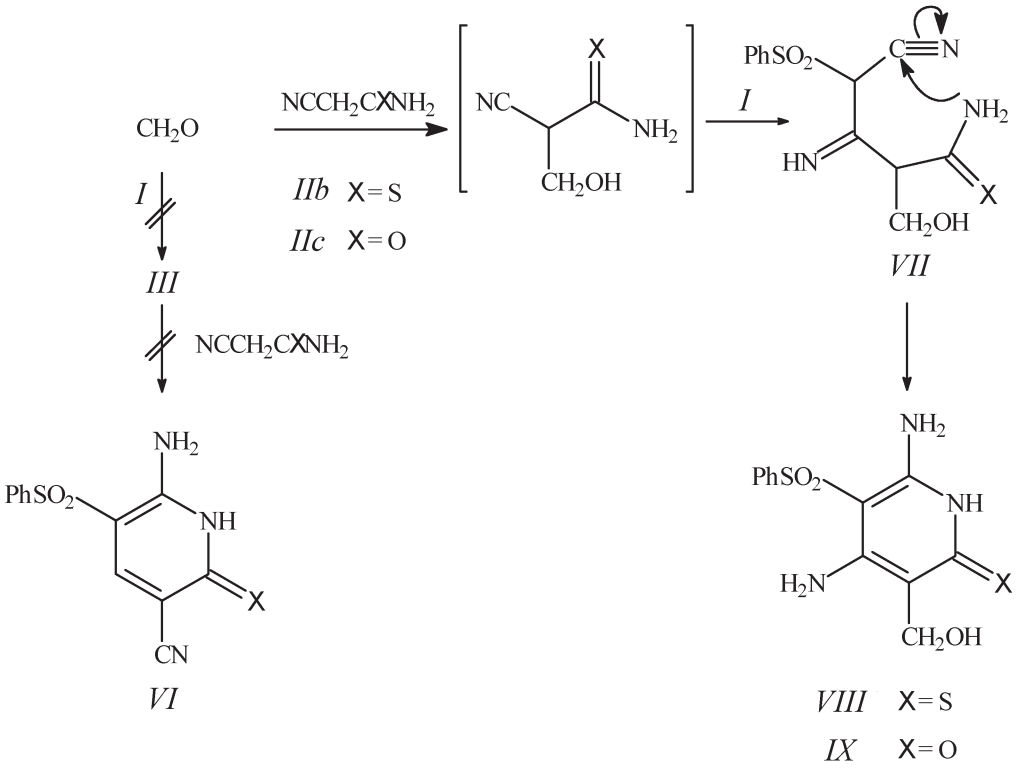
A mixture of equimolar amounts of malononitrile *IIa*, formaldehyde, and *I* reacts in refluxing ethanol solution in the presence of triethylamine to yield 6*H*-2,4-diamino-3-cyano-5-phenylsulfonylpyran *V* (Scheme 1).

The ^{1}H NMR spectrum revealed a pattern that can be interpreted only for structure *V*. Thus, H-2$_{\text{pyran}}$ protons appeared at $\delta = 5.4$ in addition to the presence of two D_2O-exchangeable protons at $\delta = 4.6$ and 5.2 for two amino functions, also, the protons of phenyl group, which appeared as multiplet at $\delta = 7.43$—7.52 for H-3$_{\text{phenyl}}$ and 8.03—8.09 for H-2$_{\text{phenyl}}$.

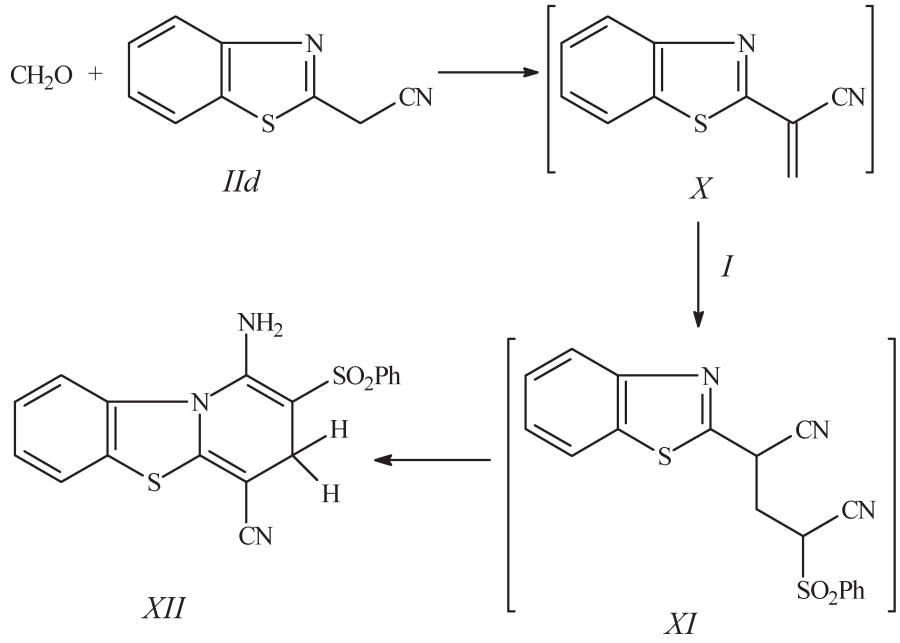
Cyanothioacetamide *IIb* reacts with formaldehyde and *I* in boiling ethanol in the presence of triethylamine to yield 2,4-diamino-3-phenylsulfonyl-5-hydroxymethylpyridine-6(1*H*)-thione *VIII* (Scheme 2). The structure *VIII* was inferred from its spectral data. Thus, the IR spectrum showed absorption bands at $\tilde{\nu}/\text{cm}^{-1}$: 3450—3500, 3300, 3250, 1550, 1270—1280, and 1050—1140 corresponding to NH_2, OH, NH, Ph, SO_2, and C=S functions. ^{1}H NMR spectrum showed singlet at $\delta = 4.3$ due to CH_2 protons, a broad singlet at $\delta = 4.6$—5.4 integrated for $2NH_2$ protons in addition to the presence of signals for the NH, hydroxyl, and phenyl groups.



Scheme 1



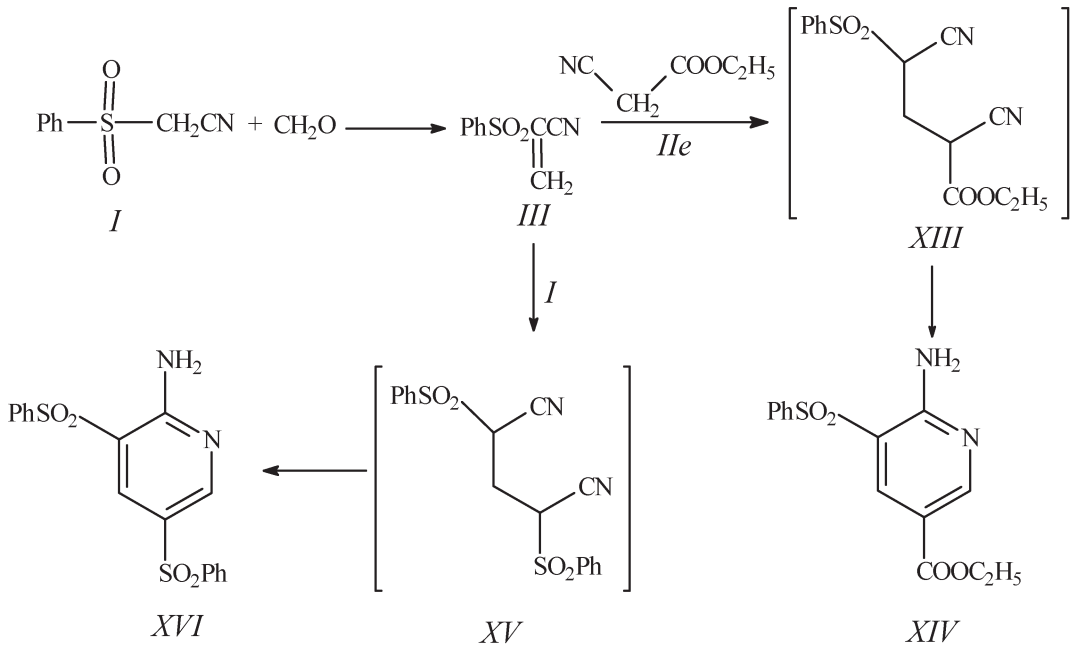
Scheme 2



Scheme 3

It is assumed that formaldehyde and cyanothioacetamide react to generate hydroxymethylcyanothioacetamide which then adds *I* to yield the intermediate *VII* which then spontaneously cyclizes into the final isolable product *VIII*. Similar to the above reported reaction, a mixture of *I*, formaldehyde, and cyanoacetamide *IIc* afforded 2,4-diamino-3-phenylsulfonyl-5-hydroxymethylpyridine-6(1*H*)-one *IX* when refluxed in ethanolic triethylamine.

Compound *I* reacted with formaldehyde and 2-benzothiazoleacetonitrile *IId* to yield 3,10-dihydro-1-amino-2-phenylsulfonyl-4-cyanopyridino[2,1-*b*]benzo-



Scheme 4

thiazole *XII* (Scheme 3). This compound is assumed to be formed *via* the reaction of formaldehyde and 2-benzothiazoleacetonitrile to form methylenebenzothiazoleacetonitrile *X* which then adds *I* to yield the intermediate *XI* that spontaneously cyclizes into pyridine [8, 9] derivative *XII*, the structure of which was established on the basis of analytical and spectral data. Molecular modelling suggests that compound *XII* is not planar and that methylene protons should appear as a pair of doublets. Rapid inversion would explain the appearance of the methylene protons as singlet, but the fused five-membered ring should slow it down a lot.

Thus, the ^{1}H NMR spectrum of the reaction product revealed a pair of doublets at δ = 3.5 and δ = 3.8 for CH_2 group, broad singlet at δ = 5.4 for NH_2 protons, in addition to a multiplet at δ = 7.48—8.00 for aromatic protons. On shaking the compound with D_2O, the broad signal at δ = 5.4 disappeared. The mass spectroscopic measurements gave M^+ = 367.

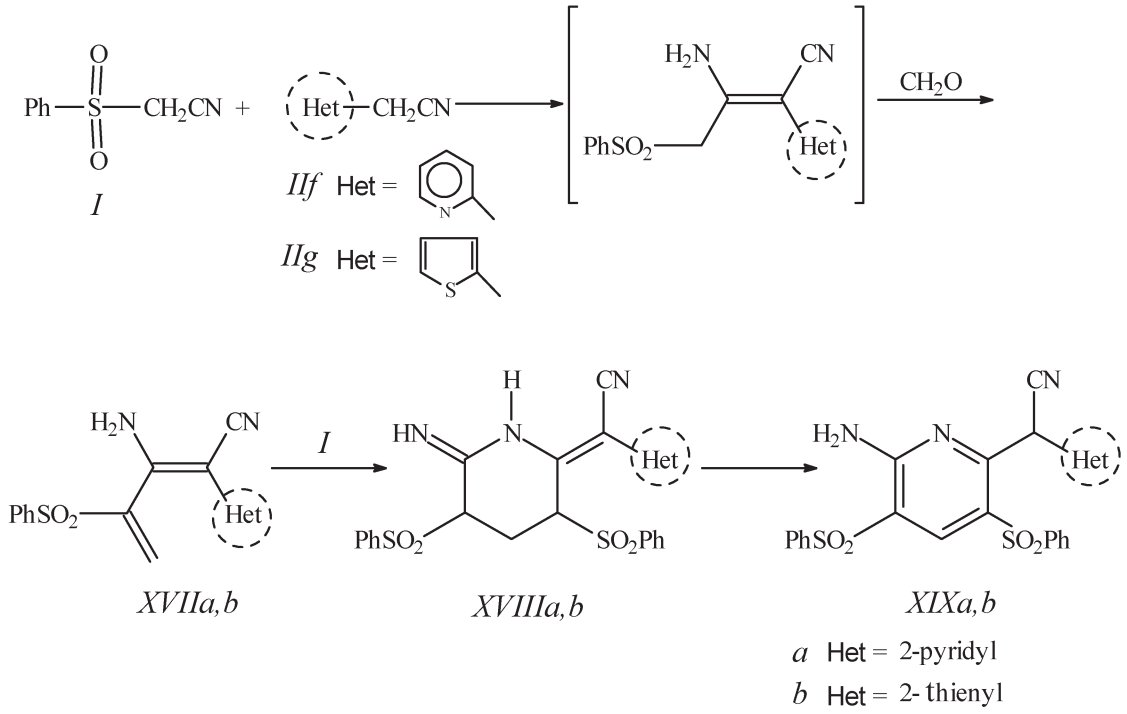
Compound *I* reacted with ethyl cyanoacetate *IIe* and formaldehyde to yield 2-amino-3-phenylsulfonyl-5-ethoxycarbonylpyridine *XIV* (Scheme 4). Compound *XIV* is assumed to be formed *via* the addition of methylenephenylsulfonylacetonitrile *III* to ethyl cyanoacetate to yield *XIII*, which then cyclizes and aromatizes under the reaction conditions to yield the final product *XIV*. In accordance with this structure, the ^{1}H NMR spectrum revealed one ester group (a triplet at δ = 1.3 for CH_3 and a quartet at δ = 4.4 for CH_2). In addition, the NH_2 protons appeared at δ = 3.8, H-$2_{pyridine}$ at δ = 8.3, and the phenyl aromatic protons at δ = 7.43—7.52 for H-3_{phenyl} and 8.03—8.09 for H-2_{phenyl} as multiplet.

Similarly, the reaction of two moles of *I* with formaldehyde afforded 2-amino-3,5-diphenylsulfonylpyridine *XVI* directly, most likely *via* the intermediacy of *XV* which could not be isolated.

On the other hand, compound *I* reacted with formaldehyde and 2-cyanomethylpyridine *IIf* or 2-cyanomethylthiophene *IIg* in refluxing ethanol in the presence of triethylamine (Scheme 5) to afford products 2-amino-3,5-di(phenylsulfonyl)-6-(cyano-2-pyridylmethyl)pyridine *XIXa* and 2-amino-3,5-di(phenylsulfonyl)-6-(cyano-2-thiophenomethyl)pyridine *XIXb* of molecular formula $C_{24}H_{18}N_4O_4S_2$ (M^+ = 490) and $C_{23}H_{17}N_3O_4S_3$ (M^+ = 495), respectively. These two compounds are assumed to be formed *via* the addition of heterocyclic nitriles to *I* followed by reaction with formaldehyde which results in the formation of the methylene derivatives *XVIIa*, *XVIIb* which on their turn cyclize with another molecule of *I* to yield the hydropyridine derivatives *XVIIIa* and *XVIIIb*. Those readily oxidize under the reaction conditions to give the final isolable products *XIXa* and *XIXb*.

EXPERIMENTAL

Melting points were determined on a Gallenkamp electrothermal apparatus. The IR spectra were recorded on a Pye—Unicam SP 110 spectrophotometer as KBr disks. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini NMR spectrometer (200 MHz for ^{1}H, 75.5 MHz for ^{13}C) using Me_4Si as an internal



Scheme 5

reference. Mass spectra were measured on GC/MS-QP 1000 Ex mass spectrometer at 70 eV. Microanalyses were carried out at the Microanalytical Centre of the Cairo University.

Pyran *V*, Pyridine *VIII*, *IX*, *XII*, *XIV*, *XVIIa*, *XIXa*, *XIXb*, and Thiophene *XVIIb* Derivatives

A suspension of *I* (1.81g; 0.01 mol for *V*, *VIII*, *IX*, *XII*, *XIV*, *XVIIa*, and *XVIIb*, 3.62 g; 0.02 mol for *XIXa* and *XIXb*), formaldehyde (1.0 cm^3, 30 % solution), and activated nitrile *IIa*—*IIg* (0.01 mol) in ethanol (50 cm^3) was treated with a few drops of triethylamine. The reaction mixture was refluxed for 3 h, then poured on ice water. The resulting solid product was collected by filtration and crystallized from ethanol.

V: Yield = 2.495 g (90 %), m.p. = 230 °C (ethanol). For $C_{12}H_{11}N_3O_3S$ (M_r = 277.3029) w_i(calc.): 51.97 % C, 3.99 % H, 15.15 % N, 11.56 % S; w_i(found): 51.95 % C, 3.90 % H, 15.00 % N, 11.47 % S. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 3450—3500 (NH_2), 2220 (CN), 1550 (C_6H_5), 1270—1280 (SO_2). ^{1}H NMR spectrum (DMSO-d_6), δ: 7.43—7.52 (m, 3H, $3H_{phenyl}$), 8.03—8.09 (m, 2H, $2H_{phenyl}$), 5.4 (s, 2H, $2H_{pyran}$), 4.6, 5.2 (br, 4H, two NH_2 exchangeable with D_2O).^{13}C NMR spectrum (DMSO-d_6), δ: 63.2 (CH_2), 114.6 (CN), 132.2 (CH), 132.6 (CH), 133.4 (CH), 133.8 (CH), 134.5 (CH), 135.2 (C), 136.9 (C), 137.9 (C), 138.2 (C), 140.8 (C). Mass spectrum, m/z (I_r/%): 277 (83.7).

VIII: Yield = 2.522 g (81 %), m.p. = 290 °C (ethanol). For $C_{12}H_{13}N_3O_3S_2$ (M_r = 311.3847) w_i (calc.): 46.28 % C, 4.20 % H, 13.49 % N, 20.59 % S; w_i(found): 46.26 % C, 4.15 % H, 13.45 % N, 20.55 % S. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 3450—3500 (NH_2), 2330 (OH), 3250 (NH), 1550 (C_6H_5), 1270—1280 (SO_2), 1065—1140 (CS). ^{1}H NMR spectrum (DMSO-d_6), δ: 8.7 (s, 1H, NH), 8.4 (s, 1H, OH), 7.43—7.52 (m, 3H, $3H_{phenyl}$), 8.03—8.09 (m, 2H, $2H_{phenyl}$), 4.6, 5.3 (br, 4H, two NH_2 exchangeable with D_2O), 4.3 (s, 2H, CH_2). ^{13}C NMR spectrum (DMSO-d_6), δ: 70.8 (CH_2), 132.2 (CH), 132.6 (CH), 133.4 (CH), 133.8 (CH), 134.5 (CH), 135.2 (C), 137.8 (C), 138.3 (C), 141.2 (C), 144.6 (C), 181.6 (CS). Mass spectrum, m/z (I_r/%): 311 (45.4).

IX: Yield = 2.510 g (85 %), m.p. = 310 °C (ethanol). For $C_{12}H_{13}N_3O_4S$ (M_r = 295.3177) w_i (calc.): 48.81 % C, 4.43 % H, 14.22 % N, 10.85 % S; w_i(found): 48.76 % C, 4.38 % H, 14.20 % N, 10.80 % S. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 3450—3500 (NH_2), 3300 (OH), 3250 (NH), 1670 (CO), 1270—1280 (SO_2), 1550 (C_6H_5). ^{1}H NMR spectrum (DMSO-d_6), δ: 8.6 (s, 1H, NH), 8.4 (s, 1H, OH), 4.3 (s, 2H, CH_2), 7.43—7.52 (m, 3H, $3H_{phenyl}$), 8.03—8.09 (m, 2H, $2H_{phenyl}$), 4.6, 5.3 (br, 4H, two NH_2 exchangeable with D_2O). ^{13}C NMR spectrum (DMSO-d_6), δ: 70.6 (CH_2), 132.2 (CH), 132.6 (CH), 133.4 (CH), 133.8 (CH), 134.5 (CH), 135.2 (C), 135.3 (C), 137.8 (C), 138.3 (C), 144.6 (C), 181.6 (CO). Mass spectrum, m/z (I_r/%): 295 (48.6).

XII: Yield = 2.939 g (80 %), m.p. = 170 °C (ethanol). For $C_{18}H_{13}N_3O_2S_2$ (M_r = 367.4517) w_i(calc.): 58.83 % C, 3.56 % H, 11.43 % N, 17.41 %

S; w_i(found): 58.79 % C, 3.48 % H, 11.39 % N, 17.38 % S. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 3450—3500 (NH_2), 2220 (CN), 1550 (C_6H_5), 1270—1280 (SO_2). ^{1}H NMR spectrum (DMSO-d_6), δ: 7.48—8.00 (m, 9H_{arom}), 5.4 (br, 2H, NH_2 exchangeable with D_2O), 3.5, 3.8 (pair of doublets, 2H, CH_2). ^{13}C NMR spectrum (DMSO-d_6), δ: 50.6 (CH_2), 113.2 (CN), 122.4 (CH), 123.8 (CH), 124.6 (CH), 130.5 (CH), 131.4 (CH), 131.9 (CH), 132.5 (CH), 132.6 (CH), 132.8 (CH), 133.4 (C), 133.7 (C), 135.1 (C), 137.8 (C), 138.0 (C), 141.9 (C), 144.5 (C). Mass spectrum, m/z (I_r/%): 367 (35.8).

XIV: Yield = 2.297 g (75 %), m.p. = 145 °C (ethanol). For $C_{14}H_{14}N_2O_4S$ (M_r = 306.3406) w_i(calc.): 54.89 % C, 4.60 % H, 9.14 % N, 10.46 % S; w_i(found): 54.87 % C, 4.50 % H, 9.09 % N, 17.38 % S. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 3450—3500 (NH_2), 1720 (CO), 1550 (C_6H_5), 1270—1280 (SO_2). ^{1}H NMR spectrum (DMSO-d_6), δ: 8.3 (s, 2H, 2$H_{pyridyl}$), 7.43—7.52 (m, 3H, 3H_{phenyl}), 8.03—8.09 (m, 2H, 2H_{phenyl}), 1.3 (t, 3H, CH_3), 4.4 (q, 2H, CH_2), 3.8 (br, 2H, NH_2 exchangeable with D_2O). ^{13}C NMR spectrum (DMSO-d_6), δ: 22.5 (CH_3), 60.3 (OCH_2), 125.3 (CH), 125.4 (CH), 129.7 (C), 132.2 (CH), 132.6 (CH), 133.4 (CH), 133.8 (CH), 134.5 (CH), 135.2 (C), 137.4 (C), 137.7 (C), 166.7 (CO). Mass spectrum, m/z (I_r/%): 306 (27.7).

XVIIa: Yield = 2.086 g (67 %), m.p. = 280 °C (ethanol). For $C_{16}H_{13}N_3O_2S$ (M_r = 311.3637) w_i(calc.): 61.72 % C, 4.20 % H, 13.49 % N, 10.29 % S; w_i(found): 61.69 % C, 4.15 % H, 13.47 % N, 10.25 % S. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 3450—3500 (NH_2), 2220 (CN), 1550 (C_6H_5), 1270—1280 (SO_2), 1590—1620 (pyridyl), 1625 (C=C, conjugated). ^{1}H NMR spectrum (DMSO-d_6), δ: 7.43—7.52 (m, 3H, 3H_{phenyl}), 5.38 (s, 2H, CH_2), 8.03—8.09 (m, 2H, 2H_{phenyl}), 5.2 (br, 2H, NH_2 exchangeable with D_2O), 7.06—7.09, 8.4—8.5 (m, 4H, 4$H_{pyridyl}$). ^{13}C NMR spectrum (DMSO-d_6), δ: 105.4 (C), 116.7 (CN), 123.8 (CH), 125.8 (CH), 126.8 (CH), 129.7 (CH), 130.2 (C), 132.2 (CH), 132.6 (CH), 133.4 (CH), 133.8 (CH), 134.5 (CH), 135.2 (C), 133.9 (CH_2), 137.2 (C), 143.6 (C). Mass spectrum, m/z (I_r/%): 311 (46.2).

XVIIb: Yield = 1.771 g (56 %), m.p. = 264 °C (ethanol). For $C_{15}H_{12}N_2O_2S_2$ (M_r = 316.4038) w_i(calc.): 56.94 % C, 3.82 % H, 8.85 % N, 20.26 % S; w_i(found): 56.91 % C, 3.74 % H, 8.81 % N, 20.22 % S. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 3450—3500 (NH_2), 2220 (CN), 1550 (C_6H_5), 1270—1280 (SO_2), 1625 (C=C, conjugated), 1520—1530 (thienyl). ^{1}H NMR spectrum (DMSO-d_6), δ: 7.43—7.52 (m, 3H, 3H_{phenyl}), 8.03—8.09 (m, 2H, 2H_{phenyl}), 5.2 (br, 2H, NH_2 exchangeable with D_2O), 5.38 (s, 2H, CH_2), 7.06—7.09, 7.05—7.18 (m, 3H, 3$H_{thienyl}$). ^{13}C NMR spectrum (DMSO-d_6), δ: 105.7 (C), 115.8 (CN), 132.2 (CH), 132.6 (CH), 133.4 (CH), 133.8 (CH), 134.5 (CH), 135.2 (C), 133.7 (CH_2), 136.3 (C), 140.8 (CH), 141.4 (CH), 142.9 (CH), 143.8 (C), 144.4 (C). Mass spectrum, m/z (I_r/%): 316 (52.7).

XIXa: Yield = 3.679 g (75 %), m.p. = 120 °C (ethanol). For $C_{24}H_{18}N_4O_4S_2$ (M_r = 490.5622) w_i(calc.): 58.76 % C, 3.69 % H, 11.42 % N, 13.07 % S; w_i(found): 58.70 % C, 3.61 % H, 11.40 % N, 13.01 % S. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 3450—3500 (NH_2), 2220 (CN), 1550 (C_6H_5), 1270—1280 (SO_2), 1590—1620 (pyridyl). ^{1}H NMR spectrum (DMSO-d_6), δ: 7.43—7.52 (m, 3H, 3H_{phenyl}), 8.03—8.09 (m, 2H, 2H_{phenyl}), 7.3 (s, 1H, $H_{pyridyl}$), 3.5 (s, 1H, CHCN), 4.2 (br, 2H, NH_2 exchangeable with D_2O), 7.06—7.09, 8.4—8.5 (m, 4H, 4$H_{pyridyl}$). ^{13}C NMR spectrum (DMSO-d_6), δ: 32.2 (CHCN), 114.7 (CN), 123.3 (CH), 125.7 (CH), 126.2 (CH), 128.6 (CH), 129.8 (CH), 130.0 (CH), 130.3 (CH), 132.6 (2CH), 133.4 (2CH), 133.8 (2CH), 134.5 (2CH), 135.2 (C), 136.7 (C), 137.4 (C), 139.6 (C), 140.7 (C), 141.6 (C), 142.8 (C). Mass spectrum, m/z (I_r/%): 490 (27.3).

XIXb: Yield = 3.617 g (73 %), m.p. = 230 °C (ethanol). For $C_{23}H_{17}N_3O_4S_3$ (M_r = 495.6023) w_i(calc.): 55.74 % C, 3.45 % H, 8.47 % N, 19.41 % S; w_i(found): 55.71 % C, 3.40 % H, 8.44 % N, 19.33 % S. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 3450—3500 (NH_2), 2220 (CN), 1550 (C_6H_5), 1270—1280 (SO_2), 1520—1530 (thienyl). ^{1}H NMR spectrum (DMSO-d_6), δ: 7.43—7.52 (m, 3H, 3H_{phenyl}), 8.03—8.09 (m, 2H, 2H_{phenyl}), 7.3 (s, 1H, $H_{pyridyl}$), 3.5 (s, 1H, CHCN), 7.05—7.18 (m, 3H, 3$H_{thienyl}$), 4.2 (br, 2H, NH_2 exchangeable with D_2O). ^{13}C NMR spectrum (DMSO-d_6), δ: 32.5 (CHCN), 115.4 (CN), 125.3 (CH), 125.9 (CH), 126.6 (CH), 128.1 (CH), 128.8 (CH), 132.2 (CH), 132.6 (CH), 133.4 (CH), 133.8 (CH), 134.5 (CH), 135.2 (2C), 137.7 (2C), 139.7 (C), 140.6 (C), 141.8 (C), 142.0 (C), 142.3 (CH), 143.6 (CH), 144.1 (CH). Mass spectrum, m/z (I_r/%): 495 (34.6).

Pyridine Derivative *XVI*

A suspension of *I* (3.62 g; 0.02 mol) in ethanol (50 cm^3) and formaldehyde (1.0 cm^3, 30 % solution) was treated with a few drops of triethylamine. The reaction mixture was refluxed for 3 h, then poured on ice water. The resulting solid product was collected by filtration and crystallized from ethanol.

XVI: Yield = 2.958 g (79 %), m.p. = 235 °C (ethanol). For $C_{17}H_{14}N_2O_4S_2$ (M_r = 374.4396) w_i(calc.): 54.53 % C, 3.76 % H, 7.48 % N, 17.12 % S; w_i(found): 54.49 % C, 3.70 % H, 7.48 % N, 17.10 % S. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 3450—3500 (NH_2), 1550 (C_6H_5), 1270—1280 (SO_2). ^{1}H NMR spectrum (DMSO-d_6), δ: 8.3 (s, 2H, 2$H_{pyridyl}$), 7.43—7.52 (m, 3H, 3H_{phenyl}), 8.03—8.09 (m, 2H, 2H_{phenyl}), 3.9 (br, 2H, NH_2 exchangeable with D_2O). ^{13}C NMR spectrum (DMSO-d_6), δ: 125.3 (CH), 125.6 (CH), 126.6 (CH), 127.3 (CH), 132.2 (2CH), 132.6 (2CH), 133.4 (2CH), 133.8 (CH), 134.5 (CH), 135.2 (C), 136.9 (C), 137.3 (C), 139.6 (2C). Mass spectrum, m/z (I_r/%): 374 (54.2).

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