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Synthesis of 3-Amino-1-benzyl-4-benzenesulfonyl-2-carbonitrilo-1*H*-pyrrole and Preparation of Related Pyrrolo[3,2-*d*]pyrimidines

R. N. Solomyannyi[a], S. R. Slivchuk[a], A. N. Vasilenko[a], E. B. Rusanov[b], and V. S. Brovarets[a]

[a] *Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, ul. Murmanskaya 1, Kiev, 02660 Ukraine*
e-mail: brovarets@bpci.kiev.ua

[b] *Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Kiev, Ukraine*

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Abstract—A method for the synthesis of a new 4-phenylsulfonyl-substituted 3-aminopyrrole was developed and related pyrrolo[3,2-*d*]pyrimidine derivatives were synthesized.

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The 3-aminopirrole derivatives are known to possess antibacterial, anticonvulsant, antiphlogistic, analgesic and antipyretic activity [1–4]. Therefore, the synthesis of new biologically active 3-aminopyrrole derivatives is a relevant task. In our work we succeeded to synthesize a new compound of this class which contains a phenylsulfonyl group in position *4* of the pyrrole fragment that is important for the creation of drugs with antiviral activity [5] belonging to this class of compounds. As the starting reagent we used enaminonitrile **I** (Scheme 1) that had been synthesized previously [6]. In its reaction with chloroacetonitrile in the presence of K_2CO_3, obviously, the alkylation product **II** is initially formed**.** The latter was not isolated in individual state, as the reaction proceeds with intramolecular cyclization involving the nitrile and active methylene groups and leading to the formation of tetrasubstituted pyrazole **III** in 43% yield (Table 1) [7–9]. Structure of **III** was proved reliably by the complex spectral study (Table 2).

Since compound **III** contains a nitrile and a primary amine groups at the neighboring carbon atoms of the ring, we used it for fusion of a pyrimidine fragment. Like in other studies [10, 11], we used dimethylformamide dimethylacetal as a one-carbon com-

Table 1. Yields, melting points, and elemental analysis data of compounds **III, IV,** and **VII**

Comp. no.	Yield, %	mp, °C (solvent)	Found, %		Formula	Calculated, %	
			N	S		N	S
III	43	169–171 (EtOH)	12.57	9.42	$C_{18}H_{15}N_3O_2S$	12.45	9.50
IV	75	185–187 (C_6H_6)	14.32	8.20	$C_{21}H_{20}N_4O_2S$	14.27	8.17
VIIa	60	176–178 (C_6H_6)	13.94	7.86	$C_{22}H_{20}N_4O_2S$	13.85	7.93
VIIb	81	180–182 (C_6H_6)	12.61	7.13	$C_{24}H_{24}N_4O_3S$	12.49	7.15
VIIc	93	218–220 ($C_6H_5CH_3$)	12.68	7.18	$C_{24}H_{20}N_4O_3S$	12.60	7.21
VIId	97	219–221 ($C_6H_5CH_3$)	12.45	7.01	$C_{26}H_{22}N_4O_2S$	12.33	7.05
VIIe	92	203–205 ($C_6H_5CH_3$)	12.03	6.77	$C_{27}H_{24}N_4O_2S$	11.96	6.84
VIIf	85	188–190 ($C_6H_5CH_3$)	12.84	7.25	$C_{25}H_{20}N_4O_2S$	12.72	7.28

Scheme 1.

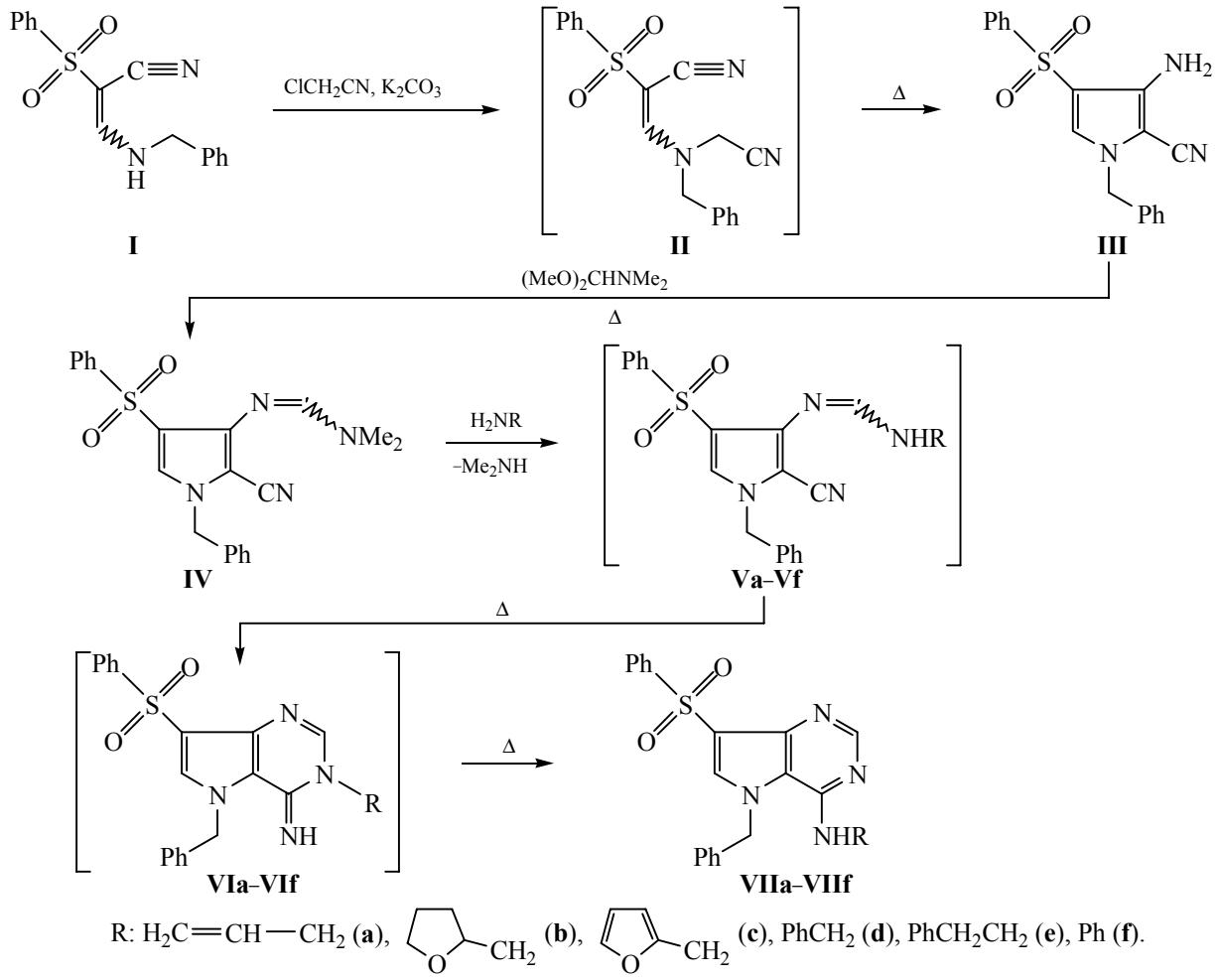
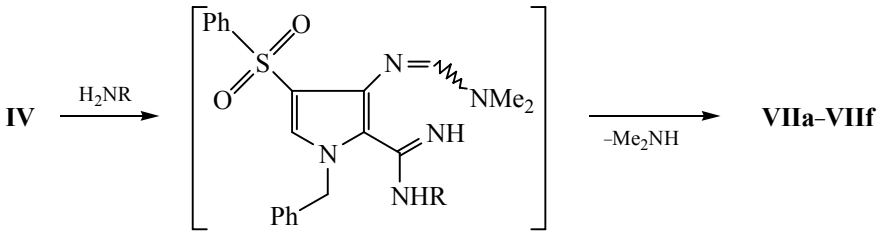


Table 2. Spectral data of synthesized compounds

Comp. no.	IR spectrum, ν, cm^{-1}	^1H NMR spectra (DMSO-d_6) δ, ppm
III	2207 (C≡N), 3357, 3444 (NH_2)	5.10 s (2H, CH_2), 5.69 s (2H, NH_2), 7.21–7.35 m (5H, C_6H_5), 7.61 m (3H, C_6H_3), 7.85 s (1H, C^5H), 7.95 d (2H, C_6H_2)
IV	2199 (C≡N)	2.90 s (3H, CH_3), 2.99 s (3H, CH_3), 5.23 s (2H, CH_2), 7.23–7.62 m (8H, C_6H_5, C_6H_3), 7.71 s (1H, C^5–H), 7.92 d (2H, C_6H_2), 7.97 s (1H, CH)
VIIa	3442 (NH)	4.05 m (2H, CH_2), 4.90 d, 4.92 d (2H, NCH_2), 5.78m (3H, CH_2, CH), 6.89 t (1H, NH), 7.08–7.35 m (5H, C_6H_5), 7.64 m (3H, CH_3), 8.12 d (2H, C_6H_2), 8.29 s (1H, C^6–H), 8.41 s (1H, C^2–H)
VIIb	3414 (NH)	1.26–1.57 m (4H, $2CH_2$), 3.42–3.90 m (5H, $2CH_2$, CH), 5.75 s (2H, CH_2), 6.57 br..m. (1H, NH), 7.10–7.40 m (5H, C_6H_5), 7.60 m (3H, C_6H_3), 8.10 d (2H, C_6H_2), 8.38 s (1H, C^6–H), 8.40 s (1H, C^2–H)
VIIc	3444 (NH)	4.64 d (2H, CH_2), 5.77 s (2H, CH_2), 5.63 m (1H, CH), 7.11–7.60 m (10H, C_6H_5, C_6H_3, CH, NH), 8.11 d (2H, C_6H_2), 8.32 s (1H, C^6–H), 8.44 s (1H, C^2–H)
VIId	3444 (NH)	4.64 d (2H, CH_2), 5.83 s (2H, CH_2), 7.16–7.60 m (14H, $2C_6H_5$, C_6H_3, NH), 8.12 d (2H, C_6H_2), 8.25 s (1H, C^6–H), 8.45 s (1H, C^2–H)
VIIe	3465 (NH)	2.74 t (2H, CH_2), 3.66 m (2H, CH_2), 5.72 s (2H, CH_2), 6.83 m (1H, NH), 7.07–7.34 m (10H, $2C_6H_5$), 7.64 m, 8.12 d (5H, C_6H_5), 8.33 s (1H, C^6–H), 8.37 s (1H, C^2–H)
VIIf	3463 (NH)	5.92 s (2H, CH_2), 7.08–7.40 m (10H, $2C_6H_5$), 7.63 m, 8.19 d (5H, C_6H_5), 8.35 s (1H, NH), 8.40 s (1H, C^6–H), 8.61 s (1H, C^2–H)

Scheme 2.



VIIIa–VIIIf

ponent. The condensation of the latter with substituted 3-aminopyrrole **III** afforded amidines **IV** in a good yield (75%). The **III** → **IV** transformation was well confirmed by the data of IR and ^{1}H NMR spectra. Thus, the IR spectra of compounds **IV** do not contain intense signals at ν 3357 cm^{-1} and ν 3444 cm^{-1} characteristic of the primary amino group. The absence of the primary amino group follows also from the data of ^{1}H NMR spectroscopy: the signal at δ 5.69 ppm disappears, while two singlet signals appear of methyl groups at δ 2.90 ppm and δ 2.99 ppm.

The pyrimidine cyclization was carried out in boiling toluene under the action of an excess of the corresponding amine and a catalytic amount of $TsOH·H_2O$. The first stage of the process probably includes transamination to the corresponding intermediate amidine **V** (Scheme 1), which under the reaction conditions undergoes intramolecular cyclization involving the nitrile and amino groups. As a result the intermediate imino compounds **VI** are apparently formed which are converted into the corresponding pyrrolo[3,2-*d*]pyrimidines **VII** by the process of the Dimroth rearrangement [10, 11]. We do not exclude that the formation of compounds **VII** may also occur by an alternative way (Scheme 2). The key stage in this process is adding amine to the nitrile group followed by **VIII** → **VII** cyclization [12]. The choice between these two directions is difficult, as we failed to isolate any intermediate.

For an unambiguous proof of the structure of final compounds **VII** we used two-dimensional NMR spectroscopy (COSY, NOESY, HMQC, HMBC), as well as XRD analysis of compound **VIId**. Such dual proof of the structure was carried out in order to avoid in future application for the pyrrolo[3,2-*d*]pyrimidine system of the X-ray diffraction method which was not always possible to be employed. We completely assigned all ^{1}H and ^{13}C NMR signals of compound **VIId** (Fig. 1) and found the correlations listed in Table 3.

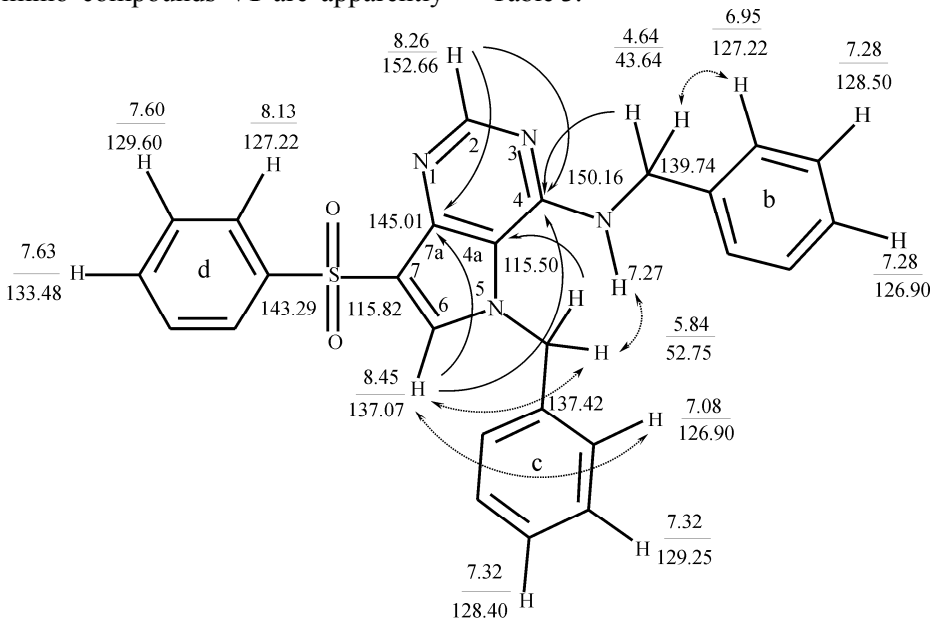


Fig. 1. The main correlations (indicated by arrows) and the assignment of signals (ppm) in ^{1}H and ^{13}C NMR spectra of compound **VIId**.

Table 3. Correlations in compound **VIId**[a] revealed using the COSY, NOESY, HMQC, and HMBC spectra

^{1}H, δ, ppm	^{1}H, δ, ppm		^{13}C, δ, ppm	
	COSY	NOESY	HMQC	HMBC
7.63 ($C^{4d}H$)	7.60	7.60	133.48	127.22 (C^{2d}, C^{6d})
7.60 ($C^{3d}H$, $C^{5d}H$)	7.63, 8.13	7.63, 8.13	129.60	143.29 (C^{1d}), 129.60 (C^{3d}, C^{5d})
8.13 ($C^{2d}H$, $C^{6d}H$)	7.60	7.60	127.22	133.48 (C^{4d}), 127.22 (C^{2d}, C^{6d})
8.26 ($C^{2}H$)	–	–	152.66	145.01 (C^{7a}), 150.16 (C^{4})
8.45 ($C^{6}H$)	–	7.08, 5.84	137.07	115.82 (C^{7}), 145.01 (C^{7a}), 150.16 (C^{4}), 52.75 (CH_2)
6.95 ($C^{2b}H$, $C^{6b}H$)	7.28	7.28, 4.64	127.22	126.90 (C^{4b}), 127.22 (C^{2b}, C^{6b})
7.28 ($C^{3b}H$, $C^{5b}H$)	6.95	6.95	128.50	139.74 (C^{1b}), 128.50 (C^{3b}, C^{5b})
7.28 ($C^{4b}H$)	–	–	126.90	127.22 (C^{2c}, C^{6c})
7.08 ($C^{2c}H$, $C^{6c}H$)	7.32	7.32	126.90	128.40 (C^{4c}), 126.90 (C^{2c}, C^{6c})
7.32 ($C^{3c}H$, $C^{5c}H$)	7.08	7.08	129.25	137.42 (C^{1c}), 129.25 (C^{2c}, C^{6c})
7.32 ($C^{4c}H$)	–	–	128.40	126.90 (C^{2c}, C^{6c})
5.84 (CH_2)	–	7.27, 8.45	52.75	115.50 (C^{4a}), 137.42 (C^{1c}), 137.07 (C^{6})
4.64 ($NHCH_2$)	7.27	6.95	43.64	139.74 (C^{1b}), 150.16 (C^{4})

[a] For the assignment of the signals in compound **VIId**, see Fig. 1.

The data obtained suggest that a sufficiently characteristic criterion of the formation of the pyrrolo-[3,2-*d*]pyrimidine system is the disappearance of the ^{13}C signal of CN at ~114 ppm in the spectrum of compound **IV** and a downfield shift of the $\underline{C}CN$ ^{13}C signal corresponding to compound **VIId** from ~90 ppm to ~115 ppm. Note a fairly strong downfield shift of the ^{1}H signal of the H^6 atom to 8.45 ppm instead of the expected ~7.5 ppm and of the ^{13}C signal of C^6 to 137.07 ppm instead of ~128 ppm, obviously due to the magnetic anisotropy of the SO_2 group.

The X-ray diffraction analysis of compound **VIId** indicates that the distribution of bond lengths and angles in the central bicyclic fragment N^1–N^3C^1–C^6 is common for such delocalized systems (Fig. 2). The bicyclic fragment is almost planar, the average deviation of atoms from the mean-square plane is 0.014 Å.

Phenyl groups C^8–C^{13}, C^{15}, C^{20} and C^{21}–C^{26} are turned relative to the central heterocyclic system by 99°, 101°, and 84°, respectively. The bonds C^2N^4 1.344(3) and C^7N^4 1.457(3) Å are not equivalent. The length of the first is in the typical range of delocalized CN bonds in the nitrogen heterocycles, while the length of the second bond is typical for a standard single C–N (average 1.45 Å). The reason for such non-equivalence is the conjugation of the lone pair of the N^4 nitrogen atom with the aromatic system of the heterocycle as indicates also the spatial orientation of the NH group (the dihedral angle formed between the plane of $H^1NC^2C^7$ atoms and the $N^1N^3C^1C^6$ mean-square plane is only 7°.

Thus, starting with enaminonitrile **I** we succeeded to prepare a new 3-aminopyrrole **III**, which proved to be a convenient reagent for the synthesis of cyclic pyrrolo[3,2-*d*] pyrimidines **VIIa–VIIf**. This approach allows us to introduce regioselectively an alkylamino or arylamino group in position *4*, as well as aryl-sulfonyl group in position *7* of the pyrrolo[3,2-*d*]pyri-midine system, which provides a possibility of the syn-thesis of a large number of compounds for the develop-ment of new biologically active substances [13–18].

EXPERIMENTAL

IR spectra of compounds were recorded on a Vertex 70 spectrophotometer from tablets with KBr.

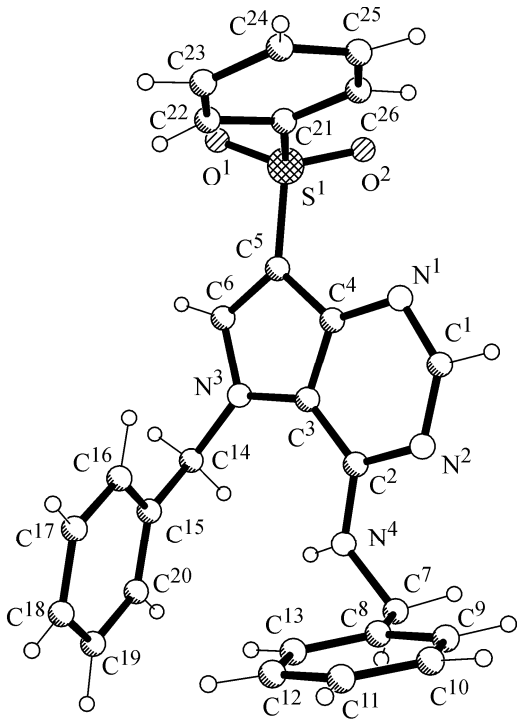


Fig. 2. The general view of the molecule **VIId** and the main bond lengths and angles: N^1C^1 1.315(3), N^1C^4 1.359(3), N^2C^1 1.339(3), N^2C^2 1.338(3), C^2C^3 1.405(3), C^3C^4 1.387(3), N^3C^3 1.398(2), N^3C^6 1.361(3), C^5C^6 1.368(3), C^4C^5 1.424(3), N^4C^2 1.344(3), N^4C^7 1.457(3) Å; $N^1C^1N^2$ 129.8(2)°, $C^1N^2C^2$ 118.0(2)°, $N^2C^2C^3$ 118.08(19)°, $C^2C^3C^4$ 117.96(18)°, $C^3C^4N^1$ 124.22(19)°, $C^1N^1C^4$ 111.8(2)°, $C^3C^4C^5$ 107.51(18)°, $C^6C^5C^4$ 106.57(19)°, $C^4C^3N^3$ 107.67(18)°, $N^3C^3C^2$ 134.33(19)°, $N^4C^2C^3$ 125.49(19)°, $C^6N^3C^3$ 107.97(17)°, $N^2C^2N^4$ 116.4(2)°.

^{1}H NMR spectra were obtained on a Varian VXR-300 NMR spectrometer, heteronuclear ^{1}H–^{13}C correlation spectra, on a Mercury-400 spectrometer (400 and 100 MHz respectively) from solutions in DMSO-d_6, with TMS as internal reference. Melting points were measured on a Fisher–Johns instrument.

The X-ray diffraction study of a single crystal of compound **VIId** with linear dimensions of 0.14× 0.26×0.38 mm was performed at 173K on a Bruker Smart Apex II diffractometer (λMoK_α radiation, graphite monochromator, θ_{max} 26.55°, spherical segment range $-10 \le h \le 10$, $-27 \le k \le 28$, $-14 \le l \le 14$). In total, 15021 reflections were collected, of which 4737 were independent (the averaging *R*-factor 0.0486). The crystals of compound **VIId,** $C_{26}H_{22}N_4O_2S$, M = 454.54, are monoclinic, space group P2/c, a = 8.5497(5), b = 22.8987(13), c = 11.7020(7) Å, β = 95.432(2)°, V = 2280.7(2) Å^3, Z = 4, d_c = 1.324, μ = 0.173 mm^{-1}, F(000) = 952. The structure was solved by thevdirect method and refined by the full-matrix least-squares method in anisotropic approximation using the SHELXS97 and SHELXL97 software packages [19, 20]. The correction for extinction was introduced using the SADABS program by the multiscan method (the minimum to maximum correction ratio T_{min}/T_{max} = 0.646871). The hydrogen atoms were found in differential electron density syntheses and were refined isotropically. In the refinement 4737 reflections were used with $I > 2\sigma(I)$, {386 refined parameters, number of reflections per parameter 12.3, a weight scheme was used, $\omega = 1/[\sigma^2(F_0^2) + (0.0523P)^2 + 0.2209P]$, where $P = (F_0^2 + 2F_c^2)/3$, the ratio of maximum (average) shift to the error in the final cycle was 0.028(0.005)}. The final divergence factors $R_1(F)$ = 0.0473, $wR_2(F^2)$ = 0.1010 for the reflections with $I > 2\sigma(I)$, $R_1(F)$ = 0.0894, wR_2 (F^2) = 0.1202, *GOF* = 0.999 over all independent reflections. Residual electron density from the difference Fourier series after the final refinement cycle was 0.20 and –0.28 e Å^{-3}.

A complete set of X-ray data for compound **VIId** is deposited in the Cambridge Crystallographic Database (CCDC 797022).

3-Amino-1-benzyl-4-benzenesulfonyl-2-carbonitrilo-1*H*-pyrrole (III). To a suspension of 0.02 mol of K_2CO_3 in 30 ml of acetonitrile was added 0.01 mol of 2-benzenesulfonyl-3-benzylaminoacrylonitrile (**I**) and 0.02 mol of chloroacetonitrile. The mixture was refluxed at stirring for 8 h, then cooled, and 100 ml of water was added. The precipitate formed was filtered off, washed with water, and compound **III** was isolated and purified by recrystallization.

***N*'-(1-Benzyl-4-benzenesulfonyl-2-carbonitrilo-1*H*-pyrrol-3-yl)-*N*,*N*-dimethylformamidine (IV)**. To a solution of 0.01 mol of compound **III** in 25 ml of DMF was added 0.02 mol of dimethylformamide dimethylacetal, and the mixture was stirred for 4 h at 100°C. The solvent was removed in a vacuum and compound **IV** was isolated and purified by crystallization.

4-[*N*-alkyl(aryl)amino]-5-benzyl-7-benzenesulfonyl-5*H*-pyrrolo[3,2-*d*]-pyrimidines (VIIa–VIIf). A mixture of 0.001 mol of the compound **IV**, 0.002 mol of corresponding amine and 0.005 g of *p*-toluenesulfonic acid in 5 ml of toluene was refluxed at stirring for 8 h. The mixture was then cooled, the solvent was removed in a vacuum and a compound **VIIa–VIIf** was isolated and purified by crystallization.

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