Phosphorus Pentoxide in Organic Synthesis. XIX [1]. Mixtures of Phosphorus Pentoxide and *ortho*-Substituted Arylamines as Reagents in the Synthesis of 9-Aryl-9*H*-purin-6-amines

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9-Aryl-9*H*-purin-6-amines **2** were readily obtained by heating 5-acetamido-4-amino-2-methylpyrimidin-6(1*H*)-one **1** in mixtures of phosphorus pentoxide, triethylamine hydrochloride and sterically hindered arylamines. Nonsterically hindered arylamines resulted in formation of 6-arylaminopurines **3**. The mechanism for rearrangement of **2** into **3** is discussed.

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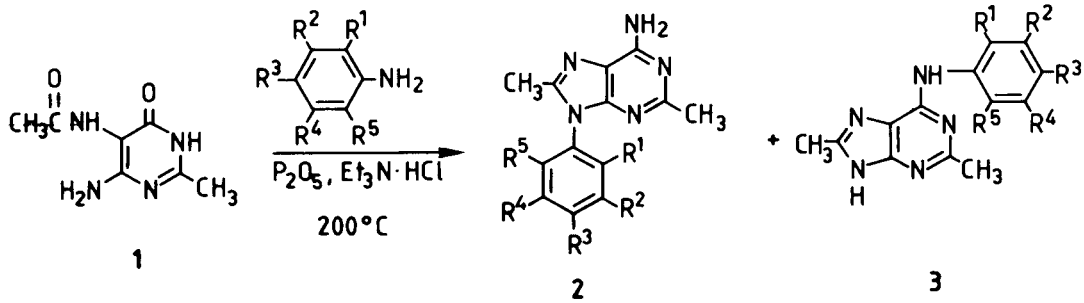
Because many purines have been claimed in the last decades to possess numerous useful biological activities [3], we have developed new syntheses of purin-6-amines based on mixtures of phosphorus pentoxide and amines as reagents [4]. Recently we have also reported that this reagent mixture can be used for a new one pot synthesis of N^6-alkyl and N^6-arylpurin-6-amines [1,5] from 5-acetamido-4-amino-2-methylpyrimidin-6(1*H*)-one (**1**) which was prepared from commercially available ethyl acetamidocyanoacetate [6]. In order to find the scope and limitations of the latter reaction we now investigate sterically hindered aromatic amines as components in the reaction mixtures with phosphorus pentoxide.

Accordingly, it was found in the present investigation that the unexpected 9-arylpurinamines **2** could be easily obtained when arylamines substituted in both *ortho* positions were used for our reagent mixtures. Furthermore, it was found that **2** could be obtained together with the expected 6-arylaminopurines **3** in the same reaction upon using selected examples of the arylamines which were either substituted in only one *ortho* position with a bulky group such as phenyl or substituted in both *ortho* positions with the relatively small flourine atoms.

Thus, in the present work we have prepared a series of new 9-aryl-2,8-dimethyl-9*H*-purin-6-amines **2a-h**, in a one pot reaction by heating one equivalent of 5-acetamido-4-

Table 1

Preparation of 2,8-dimethyl-9*H*-purin-6-amines **2** and **3**



1 **2** **3**

R¹	R²	R³	R⁴	R⁵	Reaction time (hours)	Product **2**	Yield %	Product **3**	Yield %
Di-*ortho* substituted:									
CH_3	H	H	H	CH_3	4	**2a**	35		
CH_2CH_3	H	H	H	CH_2CH_3	4	**2b**	29		
$CH(CH_3)_2$	H	H	H	$CH(CH_3)_2$	4	**2c**	19		
Cl	H	H	H	Cl	4	**2d**	55		
Cl	H	Cl	H	Cl	4	**2e**	29		
CH_3	H	CH_3	H	CH_3	4	**2f**	39		
F	F	F	F	F	3	**2g**	45	**3g**	19
Mono-*ortho* substituted:d									
C_6H_5	H	H	H	H	4	**2h**	32	**3h**	22
	-Benzo[2,3]-	H	H	H	4			**3i**	63
CH_3	H	H	H	H	4			**3j**	40 [5]
Cl	H	H	H	H	4			**3k**	16 [5]
F	H	F	H	H	1.5			**3l**	50 [5]
CH_3	H	Cl	H	H	4			**3m**	58 [5]

amino-2-methylpyrimidin-6(1*H*)-one (**1**) with four equivalents of each phosphorus pentoxide, triethylamine hydrochloride and an *ortho*-substituted aniline at 200° for 2-6 hours.

In our previous work [5] we prepared our reaction mixtures from anilines without any or just one *ortho* substituent to the amino group and the 6-arylaminopurines **3** were formed without any formation of 9-arylpurinamines **2**. Apparently the preparation of the latter type of purines **2** mainly depends on using more sterically hindered arylamines in our reagent. Therefore highly sterically hindered arylamines were selected for this work for the synthesis of 9-aryl-9*H*-purin-6-amines **2**, and they could be divided into two main groups: the first group includes di-*ortho* substituted anilines; the second group mono-*ortho* substituted anilines.

Using the first group of anilines, the reaction proceeded smoothly in all examples investigated. Even for the extremely sterically hindered aniline with isopropyl groups in both *ortho* positions, a 19% yield of **2** was obtained. The best yield was obtained for 2,6-dichloroaniline which afforded **2d** in 55% yield. In the latter case it was attempted to increase the yield by raising the reaction temperature to 240°, but without success. On the contrary, the yield dropped dramatically to 16%, probably due to instability of the product at high reaction temperature.

Using anilines with methyl or chlorine in both *ortho* positions to the amino group, only the 9-arylpurinamines **2** could be isolated. When the size of the *ortho* substituents was diminished by replacement with flourine atoms, a mixture of **2g** and **3g** was obtained.

Regarding the second group of amines we have previously shown that a small *ortho* substituent like methyl, chlorine or flourine in the aniline molecule resulted in formation of the 6-arylaminopurines **3j-m**, without any **2** [5]. The size of the *ortho* substituent was now increased by using 1-naphthylamine as a component of the reaction mixture with phosphorus pentoxide, but **3i** only was isolated in 63% yield which was actually the highest yield obtained for this group of compounds. However, if the steric hindrance was further increased using 2-aminobiphenyl, a mixture of **2h** and **3h** was obtained.

Table 2

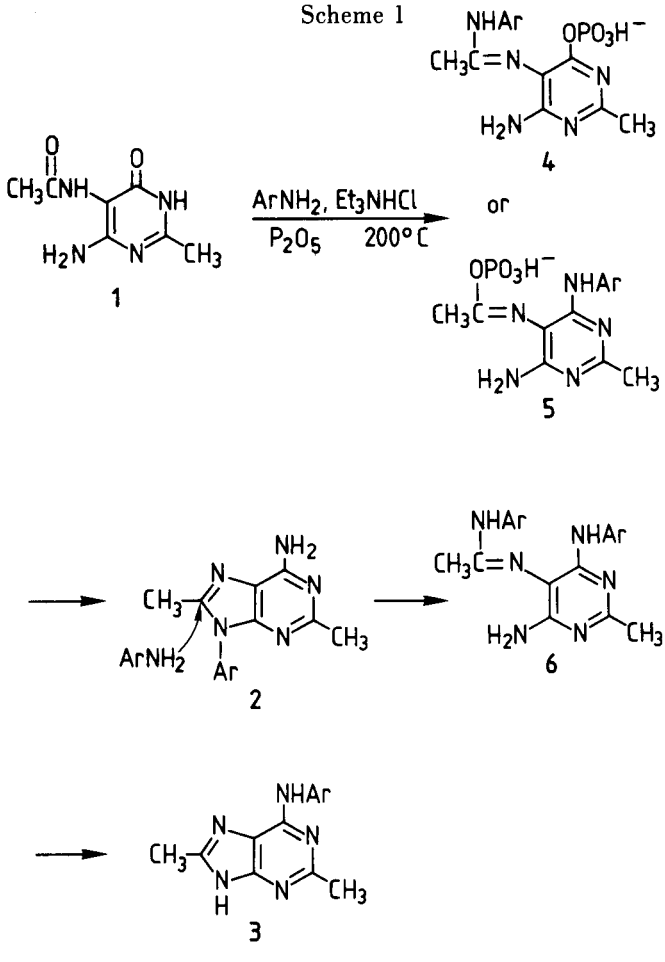
Reaction of **1** with 2-Aminobiphenyl, Triethylamine Hydrochloride, and Phosphorus Pentoxide at 200° for 2-6 hours.

Reaction time [hours]	**2h** [%]	**3h** [%]	Total yield [%]
2	28	2	30
4	22	32	54
6	6	42	48

In order to settle the question whether **2** and **3** were formed from a common intermediate or in successive reactions, we carried out some reactions with different reaction times selecting 2-aminobiphenyl for our reaction mixture.

From Table 2 it is seen that the 9-arylpurinamine **2h** was almost exclusively formed in the first two hours; after 4 hours **2h** and the 6-arylaminopurine **3h** were formed in nearly equal amounts; after 6 hours the highest yield of **3h** was isolated and **2h** was nearly consumed. Therefore we conclude that 9-arylpurinamines **2** are first formed and then rearranged into the 6-arylaminopurines **3** as outlined in Scheme 1. An arylamine attacks **2** or its protonated form in the 8-position causing a ring opening reaction of the imidazole ring. The ring opened intermediate **6** rapidly undergoes a new ring closure reaction in which the free amino group of the pyrimidine ring attacks the acetamidine moiety and **3** is formed. Alternatively, it could be suggested that **3** was formed from **2** during the alkaline work up of the products because action of alkali on some 9-alkyladenines has been reported to open the imidazole ring [7]. This possibility was easily turned down by boiling **2h** in 2*N* sodium hydroxide for 5 hours without any formation of **3h**.

Scheme 1



With regard to the formation of **2**, the oxo groups of the starting material **1** are phosphorylated by the reagent mixture and the thus formed phosphate groups are good leaving groups and they are easily replaced by amino groups. With two oxo groups in **1** many combinations of phosphorylated and aminated derivatives can be proposed, but we think that the two intermediates **4** and **5** are representative. On further reactions with the reagent mixture they can lead to both products **2** and **3**. This is an important quality although **2** is formed first in the reactions of this investigation. However, we have shown in a preceeding paper that the reagent mixtures prepared from dialkylamines by reaction with **1** can produce 6-dialkylaminopurines similar to **3** even though intermediates similar to **2** cannot be formed [1]. The 6-dialkylaminopurines are supposed to be formed directly *via* an intermediate like **5**.

The mechanism given in Scheme 1 also explains why sterically hindered anilines produce 9-arylpurinamines **2** and not **3**. Substituents in both *ortho* positions of the 9-aryl group of **2** cause steric hindrance against an attacking nucleophile at the 8-position. Furthermore, the nucleophile assumed to be the aniline molecule will be sterically hindered itself due to the *ortho* substituents and attack at the 8-position and subsequent ring opening of the imidazole ring is not possible.

As far as we are aware, this is the first report where evidence has been given for rearrangements of 9-aryl-9*H*-purin-6-amines into 6-arylaminopurines while rearrangement of 7,9-dialkyladeninium salts into N^6,7-dialkyladenines in boiling 1*N* sodium hydroxide has been previously reported [8]. Also, numerous examples are available of N^1-alkyl-6-iminopurines rearranging into 6-alkylaminopurines, the simplest case being the conversion of 1-methyladenine to 6-methylaminopurine [9].

EXPERIMENTAL

Infrared spectra were obtained on a Perkin-Elmer 580 spectrophotometer using potassium bromide disks. The ^{1}H-nmr spectra were determined on a JEOL JNM-PMX 60 spectrometer and the chemical shifts are given in ppm relative to TMS as the internal standard. The uv absorption spectra were recorded on a Varian Cary 219 spectrophotometer using absolute ethanol as solvent. Mass spectra were obtained on a Varian MAT 311 A and a Varian MAT CH 7 A mass spectrometer. Microanalyses were carried out by Novo Microanalytical Laboratory A/S, NOVO Alle, DK-2880 Bagsvaerd, supervised by Dr. R. E. Amsler. Thin layer chromatography (tlc) was performed on aluminium plates precoated with Merck's silica gel 60 F_{254}.

9-Aryl-2,8-dimethyl-9*H*-purin-6-amines **2a-f**. General procedure.

Phosphorus pentoxide (17.0 g, 0.12 mole), triethylamine hydrochloride (16.5 g, 0.12 mole) and the appropriate arylamine (0.12 mole) were carefully mixed in a flask fitted with a mechanical stirrer and a condenser with drying tube. The flask was immersed into an oil bath preheated to 200°. The mixture was stirred until a homogeneous melt was achieved (0.5-0.75 hour). The 5-acetamido-4-amino-2-methylpyrimidin-6(1*H*)-one (**1**) (5.5 g, 0.03 mole) was added and stirring was continued at 200° for the reaction time given in Table 1. The reaction was followed by taking out small samples (~ 100 mg) which were treated with 2*N* sodium hydroxide followed by 4*N* hydrochloric acid until *p*H 6-7 and extracted with dichloromethane for silica gel tlc with dichloromethane-methanol (98:2). When the starting material **1** had dissappeared according to tlc, the reaction mixture was allowed to cool to about 100° and 2*N* sodium hydroxide (*ca.* 250 ml) was added until alkaline reaction (*p*H 12-14). The mixture was stirred at room temperature until the reaction cake was completely digested (~ 0.5 hour). Then 4*N* hydrochloric acid was added until neutral reaction (*p*H 6-7). If a precipitate was formed (**2a,b,d** and **e**), it was collected by filtration, washed with water, dried, and recrystallized from a suitable solvent. **2c** and **2f** were instead isolated by extraction with dichloromethane (3 × 100 ml). The extract was washed with water, dried with sodium sulphate, and evaporated. The residue was purified by crystallization.

2,8-Dimethyl-9-(2,6-dimethylphenyl)-9*H*-purin-6-amine (**2a**).

This compound had mp 299-301° [benzene-methanol (3:1)]; ir: 3290, 3140, 1660, 1625, and 1600 cm^{-1}; uv: λ max 264 (log ε = 4.24) nm; ^{1}H-nmr (DMSO-d_6): δ 1.91 (s, 6H, 2C*H*$_3$), 2.21 (s, 3H, C*H*$_3$), 2.33 (s, 3H, C*H*$_3$), 7.17 (broad s, 2H, NH$_2$), 7.3-7.5 (m, 3H, ArH); ms: m/e (relative intensity) 268 (11), 267 (M$^+$, 60), 253 (20), 252 (100), 77 (12), 42 (16).

Anal. Calcd. for $C_{15}H_{17}N_5$ (267.33): C, 67.39; H, 6.41; N, 26.20. Found: C, 67.48; H, 6.44; N, 26.31.

9-(2,6-Diethylphenyl)-2,8-dimethyl-9*H*-purin-6-amine (**2b**).

This compound had mp 250-252° (benzene); ir: 3290, 3130, 1655, 1630, 1595 cm^{-1}; uv: λ max 264 (log ε = 4.26) nm; ^{1}H-nmr (DMSO-d_6): δ 0.97 (t, J = 7 Hz, 6H, 2CH$_2$C*H*$_3$), 2.18 (q, J = 7 Hz, 4H, 2C*H*$_2$CH$_3$), 2.20 (s, 3H, C*H*$_3$), 2.33 (s, 3H, C*H*$_3$), 7.17 (broad s, 2H, NH$_2$), 7.3-7.6 (m, 3H, ArH); ms: m/e (relative intensity) 296 (19), 295 (M$^+$, 100), 294 (37), 281 (17), 280 (89).

Anal. Calcd. for $C_{17}H_{21}N_5$ (295.39): C, 69.13; H, 7.16; N, 23.71. Found: C, 69.56; H, 7.22; N, 23.45.

9-(2,6-Diisopropylphenyl)-2,8-dimethyl-9*H*-purin-6-amine (**2c**).

This compound had mp 188-190° (ligroin 80-100°); ir: 3300, 3170, 1625, 1590 cm^{-1}; uv: λ max 264 (log ε = 4.21) nm; ^{1}H-nmr (DMSO-d_6): δ 1.00 (d, J = 7 Hz, 6H, 2CHC*H*$_3$), 1.12 (d, J = 7 Hz, 6H, 2CHC*H*$_3$), 2.21 (s, 3H, C*H*$_3$), 2.33 (s, 3H, C*H*$_3$), 7.22 (broad s, 2H, NH$_2$), 7.5-7.8 (m, 3H, ArH), the signal for C*H*(CH$_3$)$_2$ was superimposed by other signals; ms: m/e (relative intensity) 324 (19), 323 (M$^+$, 19), 322 (35), 309 (21), 308 (100), 266 (11), 147 (10).

Anal. Calcd. for $C_{19}H_{25}N_5$ (323.44): C, 70.56; H, 7.79; N, 21.65. Found: C, 70.08; H, 7.84; N, 21.44.

9-(2,6-Dichlorophenyl)-2,8-dimethyl-9*H*-purin-6-amine (**2d**).

This compound had mp 285-287° (ethanol); ir: 3310, 3150, 1660, 1630, 1600 cm^{-1}; uv: λ max 263 (log ε = 4.22) nm: ^{1}H-nmr (DMSO-d_6): δ 2.28 (s, 3H, C*H*$_3$), 2.35 (s, 3H, C*H*$_3$), 7.31 (broad s, 2H, NH$_2$), 7.7-8.1 (m, 3H, ArH); ms: m/e (relative intensity) 311 (12), 310 (12), 309 (67), 308 (22), 307 (M$^+$, 100), 274 (29), 273 (17), 272 (85), 266 (17), 254 (38), 252 (46), 231 (19), 190 (21), 145 (12), 109 (10), 42 (44).

Anal. Calcd. for $C_{13}H_{11}Cl_2N_5$ (308.17): C, 50.67; H, 3.60; N, 22.73; Cl, 23.01. Found: C, 50.73; H, 3.55; N, 22.63; Cl, 22.93.

2,8-Dimethyl-9-(2,4,6-trichlorophenyl)-9*H*-purin-6-amine (**2e**).

This compound had mp 244-246° (ethanol); ir: 3310, 3160, 1630, 1595 cm^{-1}; uv; λ max 262 (log ε = 4.24) nm; ^{1}H-nmr (DMSO-d_6): δ 2.30 (s, 3H, C*H*$_3$), 2.34 (s, 3H, C*H*$_3$), 7.20 (broad s, 2H, NH$_2$), 8.05 (s, 2H, ArH); ms: m/e (relative intensity) 345 (31), 344 (15), 343 (99), 342 (17), 341 (M$^+$, 100), 308 (36), 306 (54), 302 (13), 300 (13), 265 (11), 224 (16), 42 (45).

Anal. Calcd. for $C_{13}H_{10}Cl_3N_5$ (342.61): C, 45.58; H, 2.94; N, 20.44; Cl, 31.04. Found: C, 45.68; H, 2.90; N, 20.77; Cl, 30.97.

2,8-Dimethyl-9-(2,4,6-trimethylphenyl)-9*H*-purin-6-amine (**2f**).

This compound had mp 245-247° (butanone); ir: 3320, 3180, 1640, 1605, 1580 cm^{-1}; uv: λ max 264 (log ε = 4.16) nm; ^{1}H-nmr (DMSO-d_6): δ 1.90 (s, 6H, 2C*H*$_3$), 2.15 (s, 3H, C*H*$_3$), 2.25 (s, 3H, C*H*$_3$), 2.40 (s, 3H, C*H*$_3$), 7.27 (broad s, 2H, NH$_2$), 7.38 (s, 2H, ArH); ms: m/e (relative intensity) 282 (15), 281 (M$^+$, 65), 267 (20), 266 (100), 42 (15).

Anal. Calcd. for $C_{16}H_{19}N_5$ (281.35): C, 68.31; H, 6.81; N, 24.89. Found: C, 68.05; H, 6.82; N, 24.64.

Synthesis of 2,8-Dimethyl-9-(2,3,4,5,6-pentafluorophenyl)-9*H*-purin-6-amine (**2g**) and 2,8-Dimethyl-*N*^{6}-(2,3,4,5,6-pentafluorophenyl)-9*H*-purin-6-amine (**3g**).

The general procedure for the preparation of **2** was followed. The crude solid mixture was extracted with hot benzene (4 × 25 ml) and the organic extract was partly evaporated and allowed to cool affording almost colourless crystals of **2g**. The solid residue not dissolved in hot benzene was recrystallized from toluene to give the rearranged product **3g**.

Compound **2g**.

This compound had mp 245-247° (benzene); ir: 3310, 3170, 1675 sh, 1640, 1605 cm^{-1}; uv: λ max 262 (log ε = 4.21) nm; ^{1}H-nmr (deuteriochloroform): δ 2.46 (s, 3H, C*H*$_3$), 2.53 (s, 3H, C*H*$_3$), 6.31 (broad s, 2H, NH$_2$); ms: m/e (relative intensity) 330 (19), 329 (M$^+$, 100), 310 (12), 289 (14), 288 (66), 287 (12), 208 (15), 194 (22), 193 (11), 167 (11), 117 (12), 78 (11), 54 (13), 43 (13), 42 (87).

Anal. Calcd. for $C_{13}H_8F_5N_5$: (329.23): C, 47.43; H, 2.45; N, 21.27. Found: C, 47.49; H, 2.37; N, 20.96.

Compound **3g**.

This compound had mp 282-284° dec (toluene); ir: 3200-2400, 1620, 1590 cm^{-1}; uv: λ max 267 (log ε = 4.29) nm; ^{1}H-nmr (DMSO-d$_6$): δ 2.38 (s, 3H, C*H*$_3$), 2.47 (s, 3H, C*H*$_3$), *ca.* 9.7 (very broad s, 1H, *N*^{6}-H), *ca.* 12.7 (very broad s, 1H, N9-H); ms: m/e (relative intensity) 330 (11), 329 (M$^+$, 75), 311 (15), 310 (100), 42 (30).

Anal. Calcd. for $C_{13}H_8F_5N_5$ (329.23): C, 47.43; H, 2.45; N, 21.27. Found: C, 47.37; H, 2.44; N, 21.29.

Synthesis of 9-(2-Biphenylyl)-2,8-dimethyl-9*H*-purin-6-amine (**2h**) and *N*^{6}-(2-Biphenylyl)-2,8-dimethyl-9*H*-purin-6-amine (**3h**).

The general procedure for the preparation of **2** was followed, except that the precipitate formed upon addition of 2*N* sodium hydroxide to the reaction mixture was isolated, washed with water, and dried. The precipitate was extracted with hot benzene (4 × 25 ml). The organic extract was partly evaporated and allowed to cool to give almost colourless crystals of **2h**. Compound **3g** was obtained by crystallization from toluene of the solid residue which did not dissolve in the benzene. The change of the ratio between **2g** and **3g** at different reaction times is seen in Table 2.

Compound **2h**.

This compound had mp 229-231° (benzene); ir: 3300, 3160, 1625, 1590 cm^{-1}; uv: λ max 255 (log ε = 4.32) nm; ^{1}H-nmr (DMSO-d$_6$): δ 1.93 (s, 3H, C*H*$_3$), 2.33 (s, 3H, C*H*$_3$), 6.8-7.8 (m, 9H, ArH), 7.00 (broad s, 2H, NH$_2$); ms: m/e (relative intensity) 316 (19), 315 (M$^+$, 88), 314 (21), 301 (20), 300 (100), 274 (14), 273 (49), 272 (10), 258 (22), 257 (16), 205 (14), 190 (11), 179 (14), 178 (20), 152 (30), 151 (16), 42 (29).

Anal. Calcd. for $C_{19}H_{17}N_5$ (315.38): C, 72.36; H, 5.43; N, 22.21. Found: C, 72.34; H, 5.42; N, 22.37.

Compound **3h**.

This compound had mp 298-300° (toluene); ir: 3370, 3200-2400, 1620, 1600, 1575 cm^{-1}; uv: λ max 252 sh, 299 (log ε = 4.32) nm; ^{1}H-nmr (DMSO-d$_6$): δ 2.40 (s, 6H, 2C*H*$_3$), 7.2-8.3 (m, 9H, ArH), 8.38 (broad s, 1H, *N*^{6}-H), 12.8 (broad s, 1H, N9-H); ms: m/e (relative intensity) 316 (22), 315 (M$^+$, 100), 314 (41), 274 (20), 273 (84), 238 (24), 179 (11), 158 (12), 152 (13), 106 (11), 42 (21).

Anal. Calcd. for $C_{19}H_{17}N_5$ (315.38): C, 72.36; H, 5.43; N, 22.21. Found: C, 72.73; H, 5.43; N, 22.37.

2,8-Dimethyl-*N*^{6}-(1-naphthyl)-9*H*-purin-6-amine (**3i**).

The general procedure for the preparation of **2** was followed except that the precipitate, which separated in the alkaline water phase after the addition of 2*N* sodium hydroxide (200 ml) to the reaction mixture, was collected by filtration. The crude product was washed with water and recrystallized from dioxane affording pure **3i** with mp 276-278°; ir; 3200-2400, 1615, 1590 cm^{-1}; uv: λ max 273 sh, 327 (log ε = 4.18) nm; ^{1}H-nmr (DMSO-d$_6$): δ 2.38 (s, 3H, C*H*$_3$), 2.53 (s, 3H, C*H*$_3$), 7.3-8.3 (m, 7H, ArH), 9.4 (broad s, 1H, *N*^{6}-H), 12.6 (broad s, 1H, N9-H); ms: m/e (relative intensity) 290 (19), 289 (M$^+$, 100), 288 (46), 273 (10), 247 (11), 145 (15), 42 (10).

Anal. Calcd. for $C_{17}H_{15}N_5$ (289.34): C, 70.57; H, 5.23; N, 24.20. Found: C, 70.16; H, 5.20; N, 24.13.

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