7-Deazapurines II. Syntheses and Reactions of 5-Aminopyrrolo[2,3-*d*]pyrimidine-6-carbonitrile and Related Compounds

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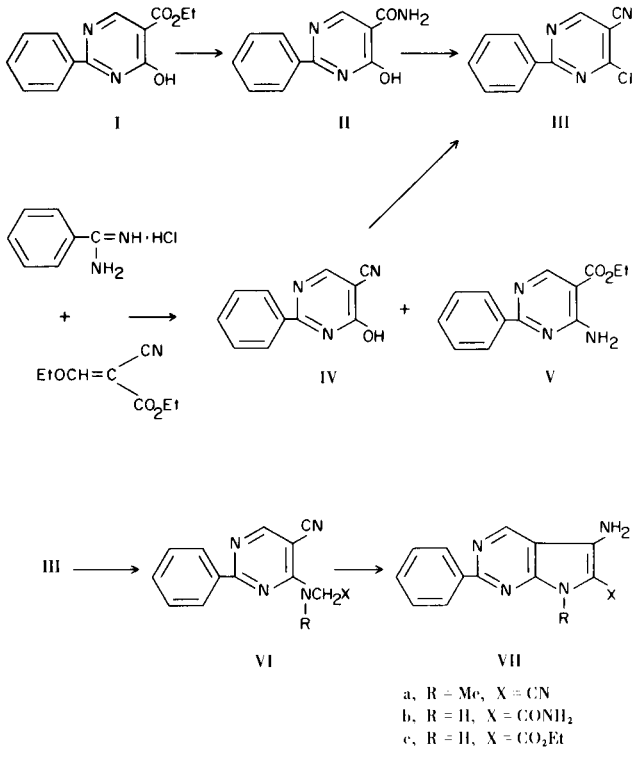
The reaction of 4-chloro-2-phenyl-5-pyrimidinecarbonitrile (III) with *N*-methylglycinonitrile gave 4-[(cyanomethyl)methylamino]-2-phenyl-5-pyrimidinecarbonitrile (VIa), which upon cyclization under Dieckmann conditions afforded 5-amino-7-methyl-2-phenyl-7*H*-pyrrolo[2,3-*d*]-pyrimidine-6-carbonitrile (VIIa). Other examples (VIIb and VIIc) were prepared similarly from the reactions of III with glycinamide and ethyl glycinate, respectively. The preparation of simple 5-amino derivatives of the pyrrolo[2,3-*d*]pyrimidines thus synthesized is described. The alkylation of VIIc with *N*-cycloheptylchloroacetamide took place at the ring nitrogen, giving XII. The reaction of VIIa with formamide gave 4-amino-5-methyl-7-phenyl-5*H*-pyrrolo[2,3-*d*:4,5-*d'*]-dipyrimidine (XIII), the first member of a new ring system. Treatment of VIIa with carbon disulfide and pyridine afforded another example of this new ring system, 1,5-dihydro-5-methyl-7-phenyl-2*H*-pyrrolo[2,3-*d*:4,5-*d'*]dipyrimidine-2,4-(3*H*)dithione (XIV).

A recent paper from this laboratory described a novel method for the preparation of pyrrolo[2,3-*d*]pyrimidines (7-deazapurines), *i.e.*, the reaction of 5-carbethoxy-4-chloropyrimidines with substituted amines which carry an active methylene group α to the amino nitrogen and the subsequent ring closure of the intermediates (1). We have extended this novel synthetic method to the preparation of several 5-aminopyrrolo[2,3-*d*]pyrimidine-6-carbonitriles and related compounds which were thought to be of potential biological interest.

The starting material in the present synthesis, 4-chloro-5-cyano-2-phenylpyrimidine (III) was prepared from 5-carbethoxy-4-hydroxy-2-phenylpyrimidine (I) (2). Treatment of I with concentrated ammonium hydroxide in a sealed steel bomb at steam bath temperature afforded the corresponding amide (II) in 86% yield. The conversion of the latter compound into III was effected smoothly in high yield by treatment of II with a large excess of phosphorus oxychloride under refluxing conditions. An alternative synthesis of III, which involves the formation of 5-cyano-4-hydroxy-2-phenylpyrimidine (IV) from benzamidine and ethyl ethoxymethylenecyanoacetate, followed by replacement of the hydroxy with a chloro group by phosphorus oxychloride, proved to be less efficient. Thus, although the reaction of benzamidine with the ethoxymethylenecyanoacetate did yield the expected IV, it was formed admixed with 4-amino-5-carbethoxy-2-phenylpyrimidine (V) in low yield. Several attempts to improve the yield of IV were unsuccessful (3). The conversion of IV into III was effected by means of phosphorus oxychloride in high yield.

SCHEME I



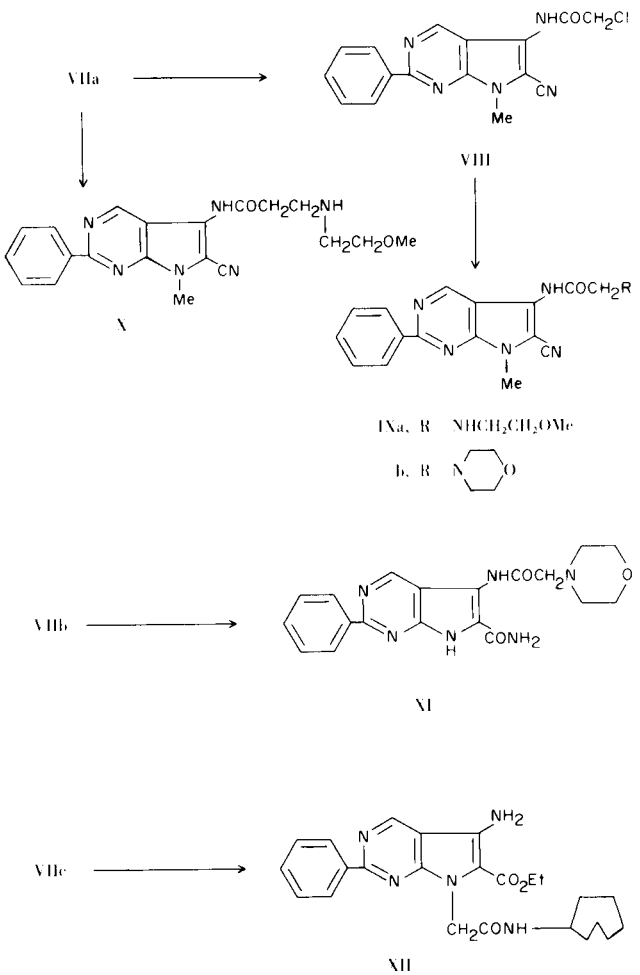
Treatment of III with *N*-methylglycinonitrile in ethanol under refluxing conditions afforded 4-[(cyanomethyl)-methylamino]-2-phenyl-5-pyrimidinecarbonitrile (VIa). Ring closure of the intermediate VIa to the 5-amino-pyrrolo[2,3-*d*]pyrimidine VIIa was effected by heating VIa in refluxing ethanol in the presence of sodium ethoxide. Undoubtedly, the process of cyclization involves an initial intramolecular Dieckmann type condensation of VIa to form a cyclic imine and the subsequent tautomerization of the cyclic imine to VIIa. Other examples of the pyrrolo[2,3-*d*]pyrimidines thus synthesized are shown in Scheme I. The pyrrolo[2,3-*d*]pyrimidines thus obtained showed their infrared -NH_2 absorption bands at 3.0 and 3.2 μ which were absent in the spectra of precursors VIa-c. There was also a sharp band at 4.59 μ (C≡N) in the case of VIIa.

It was thought to be of pharmacological interest to prepare some 5-amino derivatives of the pyrrolo[2,3-*d*]-pyrimidines under discussion. When VIIa was allowed to react with chloroacetyl chloride, 5-chloroacetamido-7-methyl-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carbonitrile (VIII) was formed. Subsequent treatment of the latter compound with methoxyethylamine and morpholine afforded IXa and IXb, respectively (Scheme II).

The reactions of VIIb and VIIc with acylating and alkylating agents proved to be somewhat complex. Thus, acylation of VIIb with chloroacetyl chloride proceeded in analogous fashion to VIIa, reacting preferentially with the 5-amino group, as shown by the formation of XI on treatment of the acetylation product with morpholine. The uv spectrum of XI [(95% EtOH) 271 (ϵ, 34,700), 305 (ϵ, 11,300), and 340 mμ (ϵ, 10,400)] resembles closely those of 5-acetamidopyrrolopyrimidines IXa, b and X, and differs considerably from that of VIIb (see Experimental section). In contrast, however, alkylation of VIIc with *N*-cycloheptylchloroacetamide took place at the ring nitrogen giving XII. The structural assignment of XII was supported by the nmr spectral data: the ring N-H proton signal present at δ 11.50 ppm in the nmr spectrum of VIIc is absent in the spectrum of XII. The singlet at δ 6.27 ppm resulting from the 5-amino proton resonance of VIIc is still found in the spectrum of XII, but slightly shifted to δ 6.35 ppm.

o-Aminonitriles or *o*-aminocarboxamides have been frequently utilized for the formation of heterocycles, especially pyrimidines (5). Since VIIa appears to be a novel type of *o*-aminonitrile, an attempt was made to construct a second pyrimidine nucleus fused to the pyrrole site of the deazapurine. Thus, when VIIa was treated with formamide under refluxing conditions for 45 minutes the first example of the heretofore unreported ring system of pyrrolo[2,3-*d*:4,5-*d*']dipyrimidine, XIII was obtained in good yield. Another example of this new class of compounds was obtained in nearly quantitative yield by treatment of VIIa with a mixture of carbon disulfide and pyridine according to a general method described by Tay-

SCHEME II



SCHEME III

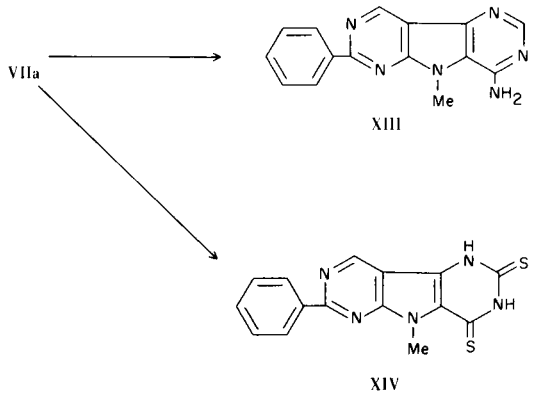
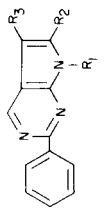


TABLE I



Compd.	R_1	R_2	R_3	Recryst'd. from	M.p., °C	Yield, %	Formula	Calcd., % C	H	N	Found, % C	H	N
IXa	Me	CN	$NHCOCH_2NHCH_2CH_2OMe$	EtOH	158-160	41	$C_{19}H_{20}N_6O_2$	62.62	5.53	23.06	62.32	5.19	22.77
IXb	Me	CN	$NHCOCH_2N$(O)	DMF	275-277 dec.	69	$C_{20}H_{20}N_6O_2$	63.82	5.36	22.33	63.47	5.39	22.35
X	Me	CN	$NHCOCH_2CH_2NH$-CH_2CH_2OMe	DMF	245-248	35	$C_{20}H_{23}ClN_6O_2$ (a)	57.90	5.59	20.26	57.78	5.58	20.48
XII	CH_2CONH-cycloC_7H_{13}	CO_2Et	NH_2	EtOH	223-225.5	30	$C_{24}H_{29}N_5O_3$	66.18	6.71	16.08	66.16	6.80	16.22
XI	H	$CONH_2$	$NHCOCH_2N$(O)	DMF	304-306 dec.	40	$C_{19}H_{20}N_6O_3$	59.99	5.30	22.09	60.07	5.37	21.87

(a) Isolated and characterized as the hydrochloride.

lor, McKillop, and Warrener (6). The product thus obtained was 1,5-dihydro-5-methyl-7-phenyl-2*H*-pyrrolo-[2,3-*d*:4,5-*d'*]dipyrimidine-2,4(3*H*)-dithione (XIV). This transformation of VIIa into XIV was accompanied by the appearance of new infrared absorption bands at 6.50, 8.55 and 8.70 μ (7) at the expense of the characteristic NH_2 and nitrile absorption bands which were present in the spectrum of VIIa.

A number of the deazapurines described in the present report showed depressant activity when tested by a standard pharmacological screening procedure (8).

EXPERIMENTAL

Melting points were taken in capillary tubes (Thomas-Hoover melting point apparatus) and are uncorrected. Infrared spectra were obtained in potassium bromide pellets using a Perkin-Elmer 21 spectrophotometer, and nmr spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as the internal reference. Ultraviolet absorption spectra were obtained with a Perkin-Elmer 450 spectrophotometer. The reported yields are the results of single experiments.

4-Hydroxy-2-phenyl-5-pyrimidinecarboxamide (II).

A mixture of 5-carbethoxy-4-hydroxy-2-phenylpyrimidine (2) (5.8 g.) and 90 ml. of concentrated ammonium hydroxide was charged in a steel bomb, and heated in a steam bath for 4.5 hours. The bomb was opened after being chilled, and the excess ammonia was evaporated on a steam bath to give *ca.* 60 ml. of the concentrated solution. Acidification of the solution with dilute hydrochloric acid caused separation of a precipitate which was collected on a filter and washed with water several times, affording 4.4 g. of product, m.p. 286° dec. Recrystallization from DMF improved the m.p. to 292-295° dec.; ir 3.00 (OH) and 6.00 μ (C=O).

Anal. Calcd. for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.10; H, 4.26; N, 19.21.

4-Chloro-2-phenyl-5-pyrimidinecarbonitrile (III).

A mixture of II (1.1 g.) and phosphorus oxychloride (30 ml.) was refluxed for 3.5 hours. The excess phosphorus oxychloride was removed under reduced pressure to give a solid residue. The remaining trace of phosphorus oxychloride in the residue was destroyed by adding crushed ice. The product was collected on a filter and washed with water several times: m.p. 190°; yield, 1.0 g. Recrystallization from absolute ethanol increased the m.p. to 193-194°; ir 4.50 μ (C≡N).

Anal. Calcd. for $C_{11}H_6ClN_3$: C, 61.27; H, 2.80; N, 19.49; Cl, 16.44. Found: C, 61.56; H, 2.80; N, 19.70; Cl, 16.36.

4-[(Cyanomethyl)methylamino]-2-phenyl-5-pyrimidinecarbonitrile (VIa).

A mixture of III (2.5 g.), *N*-methylglycinonitrile hydrochloride (5.3 g.), and sodium bicarbonate (5 g.) in 45 ml. of ethanol was heated under reflux and vigorous stirring for 3 hours. The inorganic salt was removed by filtration after the reaction mixture was cooled to room temperature. Concentration of the filtrate under reduced pressure, and subsequent chilling in ice caused separation of a precipitate which was collected on a filter, affording 0.7 g. of product, m.p. 179-182°. Recrystallization from absolute ethanol afforded an analytical sample, m.p. 182-184°; ir 4.55 μ (C≡N); uv max (95% ethanol) 263 (ϵ, 27,800), and 315 mμ

(ϵ, 7,280); nmr (DMSO-d_6), δ 8.90 (s, 1H, pyrimidine), 8.50 (m, 2H, aromatic), 7.59 (m, 3H, aromatic), 4.88 (s, 2H, CH_2), and 3.57 ppm (s, 3H, CH_3).

Anal. Calcd. for $C_{14}H_{11}N_5$: C, 67.45; H, 4.45; N, 28.10. Found: C, 67.40; H, 4.40; N, 28.20.

4-[(Carbamoylmethyl)amino]-2-phenyl-5-pyrimidinecarbonitrile (VIb).

Ten g. of III was added to a mixture of glycinamide hydrochloride (22 g.), sodium bicarbonate (16 g.) and 95% ethanol (100 ml.) which had been under reflux for 45 minutes. The heating was continued for an additional 2 hours. After the reaction mixture was cooled to room temperature, *ca.* 100 ml. of cold water was added, whereby precipitation of a solid material occurred. The precipitate was collected on a filter and washed with water several times. Recrystallization from DMF afforded 10 g. of product, m.p. 275-277°; ir 3.04, 3.20 (NH_2), 4.53 (C≡N), and 5.95 μ (CO).

Anal. Calcd. for $C_{13}H_{11}N_5O$: C, 61.65; H, 4.38; N, 27.66. Found: C, 61.44; H, 4.35; N, 27.52.

4-[(Carbethoxymethyl)amino]-2-phenyl-5-pyrimidinecarbonitrile (VIc) was prepared in the same fashion as VIb in 60% yield. An analytical sample was obtained by recrystallization from ethanol, m.p. 154-157°; ir 3.06 (NH), 4.57 (C≡N), and 5.80 μ (CO).

Anal. Calcd. for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.62; H, 5.18; N, 19.80.

5-Amino-7-methyl-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carbonitrile (VIIa).

To a solution prepared by dissolving 0.69 g. of sodium in 100 ml. of absolute ethanol was added 7.5 g. of VIa. The resulting mixture was heated under reflux for 1.5 hours, and allowed to set overnight, which caused deposition of yellow crystals. The precipitate was collected on a filter, and washed with ethanol several times to give 7.3 g. of product, m.p. 287-289° dec.; uv max (95% ethanol) 243 (ϵ, 13,600), 284 (ϵ, 37,600), 380 (ϵ, 3,460) and 315 mμ (ϵ, 9,700) shoulder; nmr (DMSO-d_6), δ 9.32 (s, 1H, pyrimidine), 8.59 (m, 2H, aromatic), 7.57 (m, 3H, aromatic), 6.48 (broad s, 2H, NH_2), and 3.75 ppm (s, 3H, CH_3).

Anal. Calcd. for $C_{14}H_{11}N_5$: C, 67.45; H, 4.40; N, 28.10. Found: C, 67.11; H, 4.47; N, 28.19.

5-Amino-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxamide (VIIb).

This compound was prepared in the same fashion as VIIa from VIb, and purified by recrystallization from DMF + water, m.p. > 360°; yield, 32%; ir 5.97 (CO); uv max (95% ethanol) 282 (ϵ, 37,600), and 375 mμ (ϵ, 5,070); nmr (DMSO-d_6), δ 11.30 (broad s, 1H, NH), 9.32 (s, 1H, pyrimidine), 8.50 (m, 2H, aromatic), 7.50 (m, 3H, aromatic), 7.24 (broad s, 2H, amide NH_2), and 6.24 ppm (s, 2H, NH_2 at C_5).

Anal. Calcd. for $C_{13}H_{11}N_5O$: C, 61.65; H, 4.38; N, 27.66. Found: C, 61.79; H, 4.31; N, 27.32.

5-Amino-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylic Acid Ethyl Ester (VIIc).

This compound was prepared similarly from VIc in 34% yield and purified by recrystallization from ethanol, m.p. 202-204.5°; ir 2.96, 3.10 (NH), 5.94 μ (CO), uv max (95% ethanol) 281 (ϵ, 41,100), 380 (ϵ, 5,230) and 312 mμ (ϵ, 10,800) shoulder; nmr (DMSO-d_6), δ 11.50 (broad s, 1H, NH), 9.36 (s, 1H, pyrimidine), 8.50 (m, 2H, aromatic), 7.54 (m, 2H, aromatic), 6.27 (broad s, 2H, NH_2), 4.40 (q, 2H, CH_2), and 1.38 ppm (t, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{14}N_4O_2$: C, 63.82; H, 5.00; N, 19.85. Found: C, 63.62; H, 5.18; N, 19.80.

5-[2-(2-Methoxyethylamino)acetamido]-7-methyl-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carbonitrile (IXa) Exemplifies the Preparation of IXb, X, and XI.

Two g. of VIIa was added in small portions to 10 ml. of chloroacetyl chloride. The resulting mixture was stirred at room temperature for 0.5 hour, then warmed gently on a steam bath for 15 minutes. After the reaction mixture was chilled, 5-chloroacetamido-7-methyl-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carbonitrile (VIII) was collected by filtration, and added in small portions to 15 ml. of 2-methoxyethylamine. The resulting mixture was stirred at room temperature for 20 minutes, then heated on a steam bath for 5 minutes. Addition of water to the reaction mixture and chilling caused separation of a precipitate which was collected on a filter and recrystallized from ethanol, affording 1.2 g. of product, m.p. 158-160°; ir 3.12 (NH), 4.56 (CN), and 5.99 μ (CO); uv max (95% ethanol) 271 (ϵ, 33,000), and 308 mμ (ϵ, 16,100).

5-Amino-7-cycloheptylcarbamoylmethyl-2-phenyl-7*H*-pyrrolo-[2,3-*d*]pyrimidine-6-carboxylic Acid Ethyl Ester (XII).

To a mixture of VIIc (2.8 g.), sodium bicarbonate (0.8 g.), and DMF (30 ml.) was added 2.0 g. of *N*-cycloheptylchloroacetamide in small portions. The resulting mixture was stirred at room temerature for 1.5 hours, then heated under reflux for 0.5 hour. After being cooled to room temperature, the reaction mixture was poured into a large amount of cold water. The precipitate thus separated was collected on a filter, washed with water, and recrystallized from ethanol, giving XII, m.p. 223-225.5°; ir 2.98, 308 (NH), 6.00 (CO), and 6.06 μ (CO); uv max (95% ethanol) 285 (ϵ, 42,800), 385 (ϵ, 5,100) and 315 mμ (ϵ, 11,700) shoulder.

5-[3-(2-Methoxyethylamino)propionamido]-7-methyl-2-phenyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-6-carbonitrile (X).

Two g. of VIIa was added in small portions to 10 ml. of β-chloropyropionyl chloride. The reaction mixture was stirred for additional 0.5 hour at room temperature, and the excess acid chloride was removed under reduced pressure, giving a solid product. This product was added in small portions to 15 ml. of 2-methoxyethylamine with stirring. Stirring was continued for 1 hour. Removal of the excess amine under reduced pressure afforded a solid residue which was triturated with water, then recrystallized first from ethanol, then from DMF, giving 1.2 g. of product, m.p. 245-248°.

4-Amino-5-methyl-7-phenyl-5*H*-pyrrolo[2,3-*d*:4,5-*d'*]dipyrimidine (XIII).

A mixture of VIIa (2.6 g.) and formamide (60 ml.) was heated under reflux for 45 minutes. Chilling of the reaction mixture in a freezer overnight caused separation of a precipitate which was collected on a filter and washed with water several times, affording 2.4 g. of product, m.p. 342-345°. Recrystallization from DMF afforded an analytical sample, m.p. 352-354° dec.; uv max (95% ethanol) 274 (ϵ, 40,800), 310 (ϵ, 21,200), and 355 mμ (ϵ, 4,250); nmr (DMSO-d_6), δ 9.50 (s, 1H, H at C_2), 8.47 (s, 1H, H at C_9), 8.59 (m, 2H, phenyl), 7.59 (m, 3H, phenyl), 7.09 (broad s, 2H, NH_2), and 4.28 ppm (s, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{12}N_6$: C, 65.20; H, 4.38; N, 30.42. Found: C, 64.99; H, 4.42; N, 30.59.

1,5-Dihydro-5-methyl-7-phenyl-2*H*-pyrrolo[2,3-*d*:4,5-*d'*]dipyrimidine-2,4(3*H*)dithione (XIV).

A mixture of VIIa (2.5 g.), carbon disulfide (20 ml.), and pyridine (20 ml.) was heated under reflux for 4.5 hours, allowed to set overnight at room temperature, and chilled in ice. The precipitate thus separated was collected on a filter and washed with ethanol several times to give 4.7 g. of yellow solid, m.p. 355° dec. Recrystallization from DMF afforded an analytical sample, m.p. 353° dec.; uv max (0.1 *N* sodium hydroxide) 216 (ϵ, 26,800) shoulder, and 305 mμ (ϵ, 44,200).

Anal. Calcd. for $C_{15}H_{11}N_5S_2$: C, 55.38; H, 3.41; N, 19.68; S, 21.53. Found: C, 55.07; H, 3.87; N, 19.66; S, 21.34.

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