184–184.5 °C.

2-(5-Isothiocyanato-1-methyl-1*H*-benzimidazol-2-yl)-1-methylpyridinium Iodide (1q). A mixture of 4 g (0.016 mol) of **1c** and 80 mL of MeI in a sealed tube was heated on the steam bath for 1 h. A solid separated on standing. The MeI was poured off and the solid was dissolved in the minimum amount of DMF. The solution was chilled to yield a solid. The above mixture was diluted with 3 mL of ice-cold MeCN, and the solid was filtered off. Recrystallization of the yellow-brown solid yielded 0.7 g of **1q**, mp 225–227 °C.

5-Isothiocyanato-2-(2-pyridyl)-1*H*-benzimidazole *N*-Oxide (1r). Route A. To a solution of 5.0 g of **1c** in $CHCl_3$ there was added 5.0 g of MCPBA, and the mixture was stirred at room temperature for 2 h. An additional 2.0 g of MCPBA was added, and the mixture was stirred for 2 h. The solvent was removed in vacuo and the residue was chromatographed. Elution with $CHCl_3$ furnished a solid, which was crystallized from $CHCl_3$ to give 0.4 g of **1r**, mp 241–244 °C.

Route B. To a solution of 4.2 g of 5-amino-2-(2-pyridinyl)-1*H*-benzimidazole in 40 mL of pyridine there was added 2.3 g of Ac_2O. After standing for 1 h, the precipitated product was filtered off to yield 4.7 g. Crystallization from MeCN yielded 5-(acetylamino)-2-(2-pyridinyl)-1*H*-benzimidazole, mp 250–252 °C. This compound was oxidized[9] to the pyridine *N*-oxide. A mixture of 1.4 g of 5-(acetylamino)-2-(2-pyridinyl)-1*H*-benzimidazole *N*-oxide and 14 mL of concentrated HCl was refluxed for 10 min. The precipitated product was filtered off and washed with a small amount of cold EtOH and then Et_2O to furnish 5-amino-2-(2-pyridinyl)-1*H*-benzimidazole *N*-oxide, which was immediately subjected to thiocarbonylation using $CHCl_3$–H_2O as the solvent system. After 1 h, the mixture was filtered and the organic layer was separated, dried, and evaporated to yield 1.0 g, identical (IR, mixed mixture melting point, microanalysis) with **1r**.

5-Isothiocyanato-2-(2-pyridinyl)-1*H*-benzimidazole–Zinc Chloride Complex (1:1; 1s). To a solution of 3 g of **1c** in 250 mL of MeCN there was added a saturated solution of methanolic $ZnCl_2$. The resulting precipitate was filtered off and washed with MeCN to yield 4 g of **1s**, mp 342–350 °C dec. **1t** and **1u** were prepared analogously.

Acknowledgment. We thank the Squibb Analytical Section under the direction of Dr. A. I. Cohen for microanalytical data and spectra.

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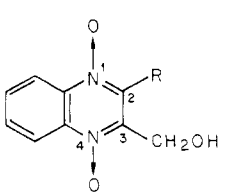
Synthesis and Antibacterial Activity of 1-Hydroxy-1-methyl-1,3-dihydrofuro[3,4-*b*]quinoxaline 4,9-Dioxide and Related Compounds

John P. Dirlam,* Leonard J. Czuba, Beryl W. Dominy, Richard B. James, Richard M. Pezzullo, Joseph E. Presslitz, and Wendell W. Windisch

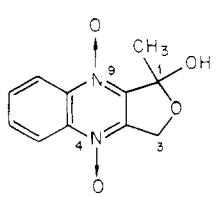
Pfizer Central Research, Groton, Connecticut 06340. *Received February 20, 1979*

A Free–Wilson analysis of the antibacterial activity found in a variety of quinoxaline 1,4-dioxides prepared and tested in these laboratories unexpectedly predicted that potent activity should be found in the case where the heterocyclic ring system was substituted with an acetyl group in the 2 position and a hydroxymethyl group in the 3 position (**2**). The synthesis and antibacterial activity of this compound, which was actually isolated in the hemiketal form (**3**), and of several of its derivatives are reported. 1-Hydroxy-1-methyl-1,3-dihydrofuro[3,4-*b*]quinoxaline 4,9-dioxide (**3**) possesses exceptional activity in vivo against *Escherichia coli*, *Salmonella choleraesuis*, and *Pasteurella multocida*.

Quinoxaline 1,4-dioxides (QNO's) are a well-known class of synthetic antibacterial agents.[1] A series of QNO's of medicinal interest includes analogues substituted with a hydroxymethyl group in the 3 position (**1**).[2] In the present work, a Free–Wilson analysis[3] was carried out from the antibacterial activity found in a variety of QNO's prepared and tested in these laboratories. Unexpectedly, this analysis predicted that potent activity should be found in the case where the heterocyclic ring system was substituted with an acetyl group in the 2 position and a hydroxymethyl group in the 3 position (**2**). The synthesis and antibacterial activity of this compound, which was actually isolated in the hemiketal form (**3**), are reported in this paper. Several additional derivatives of this 1,3-dihydrofuro[3,4-*b*]-quinoxaline ring system were also prepared.[4]



1, R = H, CH_3, or CH_2OH
2, R = $COCH_3$



3

Rationale for Drug Design. A Free–Wilson analysis of 78 QNO's previously prepared in these laboratories

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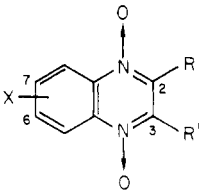
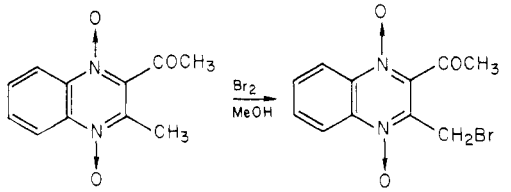


showed that the contributions by the substituents (R, R', and X) to the biological activity (based on an MIC vs. *E. coli*) were highly additive. Included in the analysis were 13 different substituents for R, 9 for R', and 12 for X, with at least two examples of each substituent. The coefficient of the multiple correlation was 0.84, and the *F* ratio for the overall evaluation of the terms in the model was significant at the 0.005% level. The substituent constant for the acetyl group at position 2 derived from the analysis was larger than expected, since the compounds with acetyl groups that were actually used for the analysis had only modest activity. It was desirable, therefore, to prepare compounds containing both the acetyl group and the hydroxymethyl moiety, which had been previously recognized[2] as imparting good activity to the QNO system. The fact that the parent compound (R = $COCH_3$, R' = CH_2OH, X = H) exists as the stable hemiketal **3** allowed us to synthesize several additional derivatives of this novel ring system.[5]

Synthesis. Several different preparations of the parent compound, 1-hydroxy-1-methyl-1,3-dihydrofuro[3,4-*b*]-quinoxaline 4,9-dioxide (**3**), are outlined in Scheme I. A key intermediate, 2-acetyl-3-(bromomethyl)quinoxaline 1,4-dioxide (**5**), was obtained by bromination of 2-



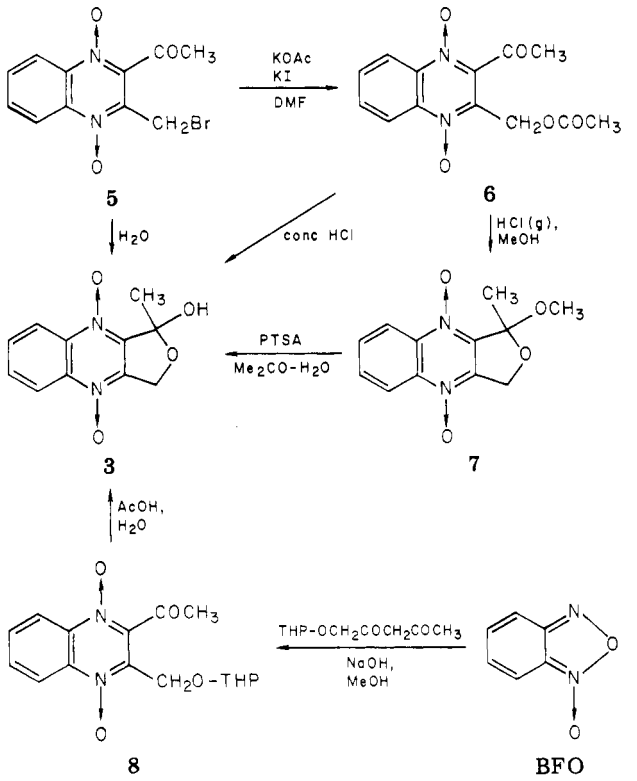
4 **5**

acetyl-3-methylquinoxaline 1,4-dioxide (**4**). Solvolysis of **5** in boiling water was the most direct route leading to **3**. Displacement of bromide with potassium acetate–potassium iodide took place as expected, and the acetoxymethyl derivative **6** was isolated in good yield. Compound **6** could be converted to **3** directly but in rather low yield by treatment with concentrated hydrochloric acid or via a two-step sequence. The latter involved the preparation of 1-methoxy-1-methyl-1,3-dihydrofuro[3,4-*b*]quinoxaline 4,9-dioxide (**7**) from **6** using methanol saturated with HCl gas. When **7** was heated in aqueous acetone containing a trace amount of *p*-toluenesulfonic acid (PTSA), **3** was obtained in quantitative yield.[6]

In order to study the metabolism of **3** we later sought a convenient synthesis for ^{14}C-labeled **3** starting from available [^{14}C]benzofuran 1-oxide (BFO). An alternative two-step route was developed. BFO was allowed to react with 1-[(2-tetrahydropyranyl)oxy]-2,4-pentanedione, and 2-acetyl-3-[[(2-tetrahydropyranyl)oxy]methyl]quinoxaline 1,4-dioxide (**8**) was obtained from this "Beirut reaction".[7] The removal of the THP-protecting group of **8** with acetic acid–water afforded **3** in 43% overall yield (Scheme I).

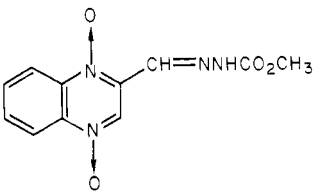
A series of derivatives of **3** was prepared that included the aforementioned 1-methoxy analogue **7** and the 1-ethoxy and 1-(benzyloxy) compounds, **9** and **10**, respectively. Both **9** and **10** were prepared by treatment of **3** with the appropriate alcohol solvent, i.e., ethanol or benzyl alcohol, respectively, in the presence of a small amount of PTSA.

Scheme I



Biological Results and Discussion. Compounds **3**, **7**, **9**, and **10** were evaluated in vitro and in vivo for antibacterial activity against Gram-negative and Gram-positive bacteria. The in vitro data are summarized in Table I. In general, slightly lower MIC's were obtained with **3** and **7** than those found with **9** and **10**. In vivo, compound **3** was superior to compounds **7**, **9**, and **10** when evaluated against *S. choleraesuis*, either by the oral or subcutaneous route of treatment at a dose of 25 mg/kg in mice (Table II).

Additional testing revealed that compound **3** possesses potent in vivo antibacterial activity against two other important veterinary pathogens. The PD_{50} values in mice are shown in Table III. Carbadox, a QNO of commercial

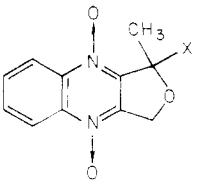


carbadox

importance, was used as a reference antibacterial agent.[8] Compound **3** and carbadox were comparable in activity against *E. coli* and *P. multocida*, and **3** was superior to carbadox against *S. choleraesuis* regardless of the route of treatment. Identical MIC's were obtained with **3** and carbadox (i.e., 0.09 μg/mL) when evaluated in vitro against *T. hyodysenteriae*, a causative agent in swine dysentery.[9] In another comparative study, **3** was greater than twofold more active than a previously prepared 2-Ac-QNO, 2-acetyl-3-methylquinoxaline 1,4-dioxide,[10] against a *S. choleraesuis* infection in mice.

In conclusion, an analysis of a number of QNO's by the Free–Wilson method led to the synthesis of a series of 1,3-dihydrofuro[3,4-*b*]quinoxaline 4,9-dioxides. One of these compounds, **3**, was found to have outstanding antibacterial activity, comparable to that observed for a

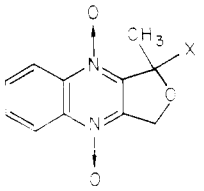
Table I. In Vitro Antibacterial Activity



compd	X	MIC,[a] μg/mL *Strep. pyogenes*	*E. coli*	*S. choleraesuis*	*P. multocida*
3	OH	0.78	1.56	1.56	12.5
7	OCH_3	0.78	3.12	1.56	3.12
9	OCH_2CH_3	3.12	12.5	12.5	12.5
10	OCH_2Ph	6.25	12.5	12.5	3.12
carbadox		0.19	0.39	0.19	0.78

[a] Minimum inhibitory concentration; determined under anaerobic conditions as described under the Experimental Section.

Table II. In Vivo Activity against *Salmonella choleraesuis*



compd	X	% protection at 25 mg/kg[a] oral	sc
3	OH	100	100
7	OCH_3	70	70
9	OCH_2CH_3	70	50
10	OCH_2Ph	40	60
carbadox		80	40

[a] Determined as described under the Experimental Section.

Table III. In Vivo Antibacterial Activity of 3 and Carbadox

microorganism	PD_{50},[a] mg/kg 3	carbadox
E. coli		
oral	14 ± 4.1	8.2 ± 2.9
sc	13 ± 4.7	7.0 ± 2.3
S. choleraesuis		
oral	6.0 ± 1.4	20 ± 5.5
sc	4.4 ± 0.9	44 ± 6.8
P. multocida		
oral	11 ± 2.7	16 ± 4.1
sc	8.1 ± 1.0	18 ± 4.7

[a] Determined as described under the Experimental Section; 95% confidence limits.

commercially available QNO.

Experimental Section

Experimental Infections in Mice. Male and female mice weighing 11–13 g obtained from Blue Spruce Farms, Alamont, N.Y., were used in all experiments. Acute systemic infections were produced by intraperitoneal inoculation of one to ten times the number of organisms necessary to kill 100% of the nonmedicated mice in 4 days. Standardized bacterial cultures of *Escherichia coli* and *Salmonella choleraesuis* were suspended in 5% hog gastric mucin, and *Pasteurella multocida* was suspended in brain–heart infusion broth. Treatment was initiated 0.5 h after infection. A second treatment was administered at 4.0 h and a third at 24 h. A 50% protective dose value (PD_{50}) was calculated by the probit method.[11]

Antimicrobial Susceptibility Tests. Minimum inhibitory concentrations were determined as previously described,[1c] except for *Treponema hyodysenteriae*. *T. hyodysenteriae* was maintained by weekly subculturing on tryptose agar containing 5% citrated bovine blood (Flow Laboratories, Inc., Rockville, Md.). Streaked plates were incubated anaerobically for 72 h at 37 °C in a Gas Pak and stored at 4 °C between subculturing.

Minimal inhibitory concentrations (MIC) vs. *T. hyodysenteriae* were determined by inoculation of 5% bovine blood–tryptose agar plates containing the compound under evaluation with a replicating device. The inoculum was prepared by scraping the surface of a fresh 3-day growth of *T. hyodysenteriae* into 3 mL of 0.95% sterile saline. The cell suspension was removed from the surface of the plate and diluted 1:10 with 0.95% sterile saline. This served as the inoculum for MIC determination. The MIC was taken to be the lowest concentration of compound which prevents the formation of a hemolytic zone after 72 h of incubation at 37 °C in a Gas Pak.

Chemistry. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. NMR spectra were recorded on Varian A-60 and T-60 spectrometers with Me_4Si as internal standard. IR spectra were determined with a Perkin-Elmer Model 21 spectrophotometer. UV spectra were recorded on a Cary Model 14 spectrophotometer. Mass spectra were obtained with a Perkin-Elmer RMU-6E mass spectrometer. All compounds gave spectra data consistent with the proposed structure. Microanalyses were performed by the Pfizer Analytical Department.

2-Acetyl-3-(bromomethyl)quinoxaline 1,4-Dioxide (5). To a stirred suspension of 343 g (1.57 mol) of 2-acetyl-3-methylquinoxaline 1,4-dioxide[10] in 3 L of methanol was added bromine (278 g, 1.74 mol) over a period of 2 h. The reaction mixture was then stirred for 5 days at room temperature. The resulting yellow solid was collected by suction filtration, washed with methanol and ether, and dried to give 331 g (71%) of **5**, mp 164–166 °C. Anal. ($C_{11}H_9N_2O_3Br$) C, H, N.

2-Acetyl-3-(acetoxymethyl)quinoxaline 1,4-Dioxide (6). To a stirred slurry of **5** (50.0 g, 0.168 mol) in *N,N*-dimethylformamide (200 mL) was added potassium acetate (18.2 g, 0.185 mol), followed by finely ground potassium iodide (4.15 g, 25 mmol). Stirring was continued for 20 min at ambient temperature, and then the reaction mixture was filtered. The dark filtrate was added dropwise to 4 L of ether, and the solid which precipitated was removed by filtration and discarded. Evaporation of the ether in vacuo afforded a yellow solid, which was recrystallized from methanol. This gave 31.6 g (76%) of **6** having mp 124–125 °C. Anal. ($C_{13}H_{12}N_2O_5$) C, H, N.

1-Methoxy-1-methyl-1,3-dihydrofuro[3,4-*b*]quinoxaline 4,9-Dioxide (7). A suspension of **6** (30.0 g, 0.11 mol) in methanol (300 mL), which was saturated with dry hydrogen chloride gas, was stirred at ambient temperature for 2 days. The tan solid was collected by filtration and then was recrystallized from methanol to give 17.0 g (63%) of **7**, mp 201–202 °C. Anal. ($C_{12}H_{12}N_2O_4$) C, H, N.

1-[(2-Tetrahydropyranyl)oxy]-2,4-pentanedione. This compound was prepared in a manner similar to that previously described[12] for the synthesis of 5-[(2-tetrahydropyranyl)oxy]-2,4-hexanedione. To a stirred solution of ethyl glycolate (15.5 g, 0.15 mol) in methylene chloride (60 mL), cooled to 5 °C, was

added dihydropyran (12.6 g, 0.15 mol), followed by *p*-toluenesulfonic acid monohydrate (50 mg). After the immediate exothermic reaction which ensued had subsided, the methylene chloride solution was washed successively with water, 5% sodium bicarbonate, and water. The dried solution was then evaporated to give ethyl 2-[(2-tetrahydropyranyl)oxy]acetate (23.8 g, 85%) as a clear oil, which was not purified. The NMR spectrum ($CDCl_3$) had characteristic absorptions at δ 1.20 (t, J = 8 Hz, 3 H, CH_3), 1.60 [m, 6 H, $-(CH_2)_3-$], 4.15 (s, 2 H, $-OCH_2CO-$), 4.75 (m, 1 H, -OCHO-). Under an atmosphere of dry nitrogen, 2.35 g of a 50% dispersion of sodium hydride in mineral oil was washed several times with hexane. To the oil-free sodium hydride was added ether (25 mL), followed by ethyl 2-[(2-tetrahydropyranyl)oxy]-acetate (9.18 g, 49 mmol), and then acetone (3.11 g, 49 mmol) dissolved in ether (10 mL). The reaction mixture was stirred at ambient temperature for 1.5 h, at which point a vigorous, exothermic reaction took place. After the exothermic reaction had subsided, the reaction mixture was stirred for an additional 30 min and then was quenched by pouring it into an ice-cold mixture prepared from 49 mL of 11 N hydrochloric acid and 100 mL of water. After 5 min, the organic phase was separated, washed with water, dried, and evaporated to give 7.8 g of an oil. This oil was distilled to give 1-[(2-tetrahydropyranyl)oxy]-2,4-pentanedione (4.5 g, 46%) as a clear liquid, bp ca. 60 °C (0.4 mm), which was not purified further prior to use in the preparation of compound 8. The NMR spectrum ($CDCl_3$) had characteristic absorptions at δ 1.60 [m, 6 H, $-(CH_2)_3-$], 2.10 (s, CH_3, enol form), 2.25 (s, CH_3, keto form), 5.80 (s, =CH-, enol form).

2-Acetyl-3-[[(2-tetrahydropyranyl)oxy]methyl]quinoxaline 1,4-Dioxide (8). To a solution of benzofuran 1-oxide (0.50 g, 3.67 mmol) and 1-[(2-tetrahydropyranyl)oxy]-2,4-pentanedione (1.10 g, 5.49 mmol) in dry ethanol (10 mL) was added powdered sodium hydroxide (16 mg). The reaction mixture was stirred at ambient temperature for 18 h, and the product was collected by suction filtration and washed with ether to give 0.60 g (51%) of 8, mp 133–134 °C. Anal. ($C_{16}H_{18}N_2O_5$) C, H; N: calcd, 8.80; found, 8.18.

1-Hydroxy-1-methyl-1,3-dihydrofuro[3,4-*b*]quinoxaline 4,9-Dioxide (3). A. Compound 5 (72.0 g, 0.24 mol) was added in three separated portions to boiling water (1.75 L) over a 1-h period. Hydrogen bromide was evolved as the solvolysis proceeded, and upon continued refluxing for 3–4 h all the starting material went into solution. The reaction mixture was cooled to room temperature, and the resulting black precipitate was removed by suction filtration and discarded. The filtrate was neutralized to pH 6 with 25% sodium hydroxide solution, causing a dark brown precipitate to form. The precipitate was removed by suction filtration and discarded. The filtrate was then extracted with hot ethyl acetate (ten 150-mL portions), and the combined extracts were dried over anhydrous magnesium sulfate and evaporated in vacuo. This afforded 24.9 g of 3 as tan crystals, mp 164–166 °C. The aqueous filtrate was then continuously extracted with methylene chloride, which gave an additional 13.1 g of product. The total product was, therefore, 40.0 g (66%). Anal. ($C_{11}H_{10}N_2O_4$) C, H, N.

B. Compound 6 (2.0 g, 7.24 mmol) was dissolved in ice-cold concentrated hydrochloric acid (9 mL). The reaction mixture was allowed to warm to room temperature and was stirred for 3 h. Methylene chloride (20 mL) was added, and the two-phase system was cooled in an ice bath and made slightly basic (pH 8) with 50% sodium hydroxide solution. The methylene chloride layer was separated and the aqueous layer was extracted with more methylene chloride (two 20-mL portions). The combined methylene chloride extracts were treated with activated carbon and evaporated under reduced pressure, leaving a yellow solid. Recrystallization from methanol gave 310 mg (18%) of 3, mp 163–165 °C.

C. To a mixture of acetone (1.5 L) and water (75 mL), containing *p*-toluenesulfonic acid monohydrate (3.78 g, 20 mmol), was added 7 (63.6 g, 0.26 mol). The reaction mixture was heated under reflux for 4.5 h and then allowed to cool to ambient temperature. The solvent was removed by evaporation in vacuo, and the residue was washed with ether. This afforded 58.7 g (98%) of crude product. The crude product was recrystallized from water with the aid of activated carbon, to give a 68% yield of 3, mp 159–160 °C. Anal. ($C_{11}H_{10}N_2O_4$) C, H, N.

D. A mixture of 8 (0.58 g, 1.8 mmol) and 5.7 mL of 40% aqueous acetic acid (prepared by mixing 40 parts of glacial acetic acid and 60 parts of water) was maintained at 40 °C for 3 h. The solvents were removed by evaporation in vacuo. To the residue was added a small quantity of ethyl acetate, which was then removed by evaporation in vacuo. This procedure of adding ethyl acetate and then removing it by evaporation in vacuo was repeated several times. The residue was then washed with methyl isobutyl ketone, which finally afforded 0.354 g (84%) of 3, mp 160–162 °C.

1-Ethoxy-1-methyl-1,3-dihydrofuro[3,4-*b*]quinoxaline 4,9-Dioxide (9). A suspension of 3 (0.50 g, 2.13 mmol) in ethanol (10 mL) containing *p*-toluenesulfonic acid monohydrate (16 mg) was stirred at 25 °C for 3 days. The tan solid was collected by filtration and dried to yield 0.37 g (65%) of 9, 157–159 °C. Anal. ($C_{13}H_{14}N_2O_4$) C, H, N.

1-(Benzyloxy)-1-methyl-1,3-dihydrofuro[3,4-*b*]quinoxaline 4,9-Dioxide (10). A suspension of 3 (1.00 g, 4.26 mmol) in benzyl alcohol (10 mL) containing *p*-toluenesulfonic acid monohydrate (32 mg) was stirred at ambient temperature overnight. The solvent was then removed by evaporation in vacuo, leaving the crude product as an oil which solidified on trituration using ethyl acetate–hexane. Recrystallization from ethyl acetate–hexane then afforded 0.28 g (21%) of 10, mp 112–116 °C. Anal. ($C_{18}H_{16}N_2O_4$) C, H, N.

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