The First Authentic Synthesis of the Previously Reported 2-Phenyl-3,4-dihydro-5 *H*-1,3,4-benzotriazepin-5-one

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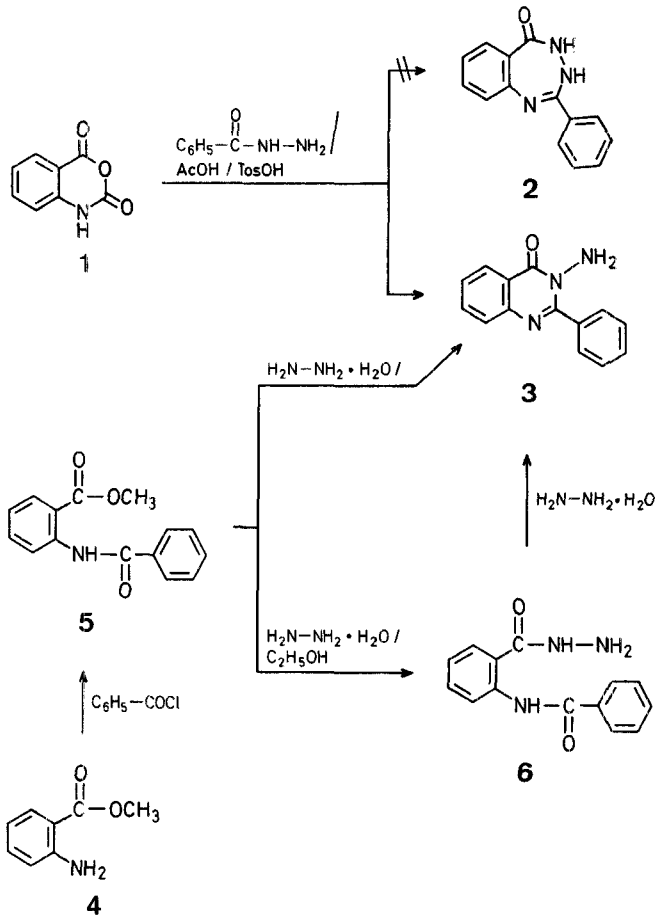
A recent communication describes the preparation of 2-phenyl-3,4-dihydro-5 *H*-1,3,4-benzotriazepin-5-one **(2)** by treatment of isatoic anhydride **(1)** with benzoylhydrazine in acetic acid containing *p*-toluenesulfonic acid. We have reinvestigated this work and found it to be in error. The product assigned as **2** by the authors of Ref.[1] is actually 3-amino-2-phenyl-4(3 *H*)-quinazolinone **(3)** (Scheme **A**).



Scheme **A**

Quinazolinone **3** has been prepared by several methods, which include: thermolysis of *o*-(benzoylamino)-benzoylhydrazine[2,3]; treatment of 2-phenyl-3,1-benzothiazine-4-one with hydrazine[4]; hydrazinolysis of 2-phenyl-4(3 *H*)-quinazolinone[5]; and the treatment of methyl 2-(benzoylamino)-benzoate with hydrazine hydrochloride, phosphorus pentoxide, and *N*,*N*-dimethylcyclohexanamine[6]. For our synthesis of an authentic sample of **5**, we used the same starting material as employed in the latter synthesis. Although it has been suggested[7] that product **3** is obtained from **5** and ethanolic hydrazine hydrate[8], we were only able to produce hydrazide **6** using these conditions. However, treatment of **5** or **6** with neat hydrazine hydrate did provide **3** efficiently.

Although benzotriazepinone **2** is not produced from **1** and benzoylhydrazine under the conditions of the reaction, an

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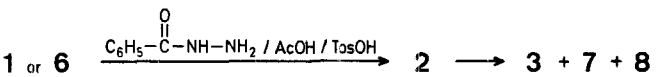
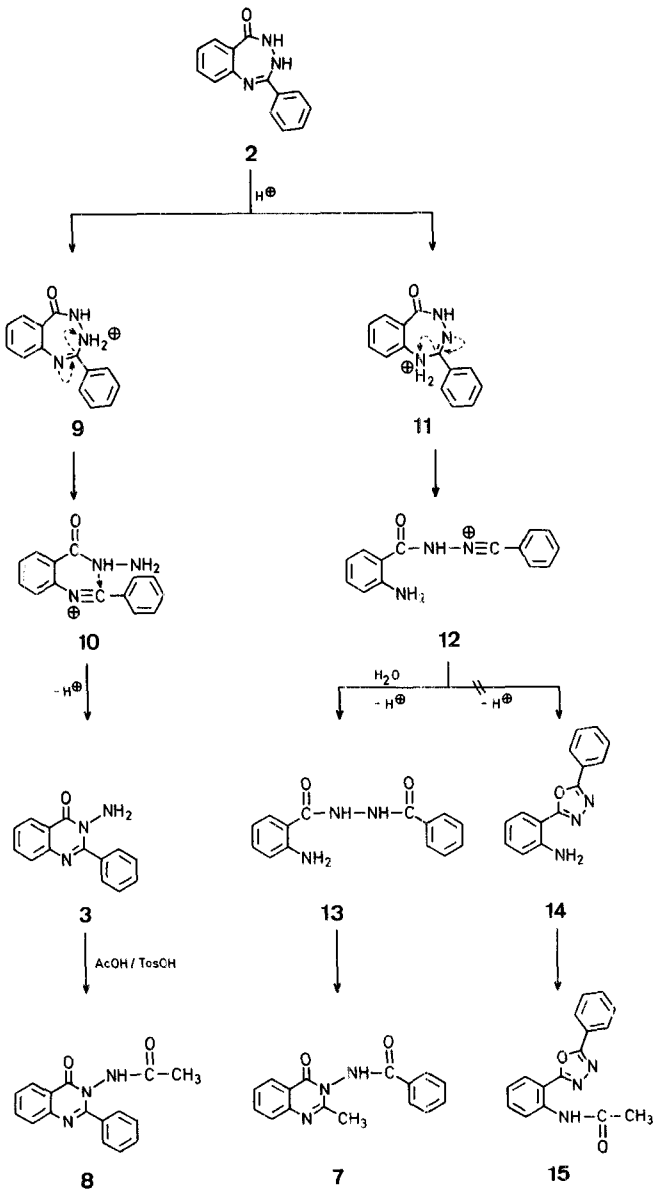
additional experiment showed that **2** was an intermediate. Treatment of **2** or **6** with acetic acid and *p*-toluenesulfonic acid gave reaction mixtures which were identical to that produced from **1** and benzoylhydrazine (Scheme **B**), as shown by T. L. C. profiles. Moreover, two additional products of these reactions were identified as 3-benzoylamino-2-methyl-4(3*H*)-quinazolinone (**7**) and 3-acetylamino-2-phenyl-4(3*H*)-quinazolinone (**8**). Compounds **3**, **7**, and **8** were isolated by flash chromatography. The isomeric compounds **7** and **8** were chromatographically inseparable in our hands and were thus isolated as a 1 : 1 mixture. The components of this mixture were identified by preparing authentic samples of each. Benzoylation of 3-amino-2-methyl-4(3*H*)-quinazolinone provided **7**, while acetylation of **3** produced **8**. A mixture of authentic samples of **7** and **8** was spectrally identical to the mixture of compounds which co-eluted.



Scheme **B**

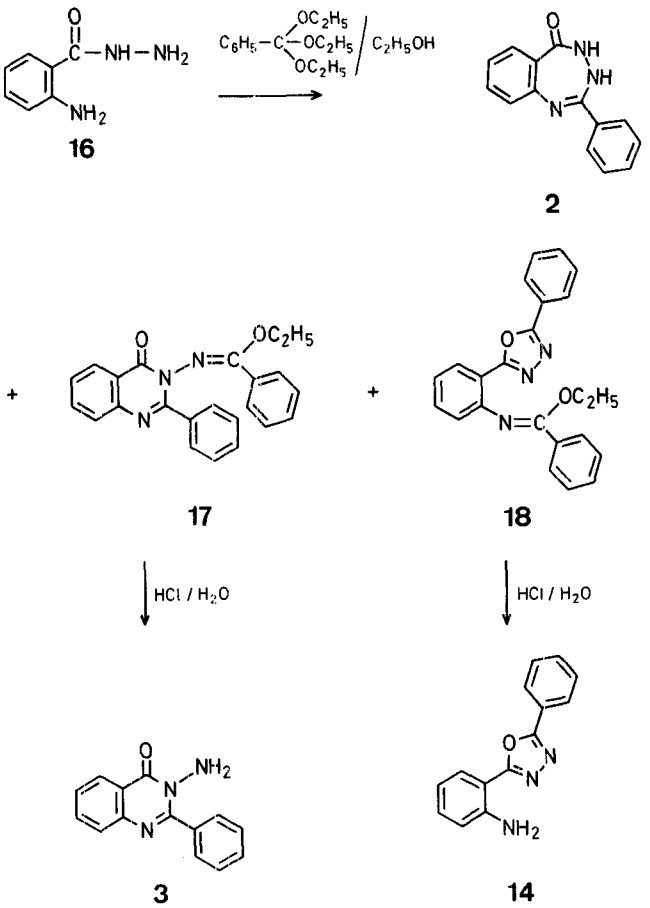
A proposed mechanistic pathway for the conversion of benzotriazepinone **2** to quinazolinones **7** and **8** is shown in Scheme **C**. Protonation of **2** would give ion **9**, which could fragment as shown to nitrilium ion **10**. Cyclization of **10** and deprotonation would produce aminoquinazolinone **3**, which could be acetylated under the reaction conditions to give **8**. Alternatively, protonation of **2** would produce ion **11**, which could fragment to nitrilium ion **12**. Quenching of ion **12** with water and deprotonation would give diacylhydrazine **13**, which could cyclize with acetic acid to produce **7**. Nitrilium ion **12**, in the presence of a protic medium, does not undergo internal trapping to give oxadiazole **14**, since neither **14** nor its *N*-acetyl derivative **15** were significantly present in the reaction mixtures which produced **3**, **7**, and **8**.



Scheme **C**

Our authentic synthesis of 2-phenyl-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-one (**2**) involved treatment of *o*-aminobenzoylhydrazine (**16**) with triethyl orthobenzoate (Scheme **D**). Benzotriazepinone **2**, produced in 20% yield by this procedure, displayed physical characteristics that were typical of this class of compound[9], i.e., the compound (which crystalized directly from the reaction mixture) was high-melting (256–257°C), and the needle-like crystals were bright yellow. The ^{1}H-N.M.R. spectrum (DMSO-d_6) of **2** showed two NH signals at $\delta = 10.00$ and 8.67 ppm.

Comprising the remainder of the mass balance in the reaction mixture which produced **2** were the imino ethers **17** and **18**, which were isolated by flash chromatography. All spectral data were in accord with these structures, and the products were hydrolyzed on treatment with dilute hydrochloric acid to give compounds **3** and **14**, respectively.



Scheme **D**

Since we have recently investigated the acid-catalyzed (TosOH) rearrangements of 2-methyl-3,4-dihydro-5*H*-1,3,4-benzotriazepine-5-one (**19**) and its 7-methyl analog (**20**)[10]

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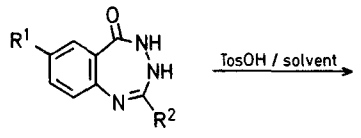
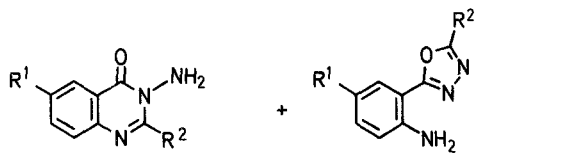
compounds described in Ref.[11], we subjected compound **2** to the same rearrangement conditions (Scheme **E**). In all three cases, the same rearrangements take place, to give aminoquinazolinones **21**, **22**, and **3** and oxadiazoles **23**, **24**, and **14**, respectively.



19 $R^1 = H$, $R^2 = CH_3$
20 $R^1 = R^2 = CH_3$
2 $R^1 = H$, $R^2 = C_6H_5$

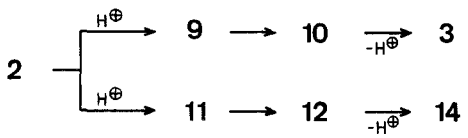


21 $R^1 = H$, $R^2 = CH_3$ (56%)
22 $R^1 = R^2 = CH_3$ (78%)
3 $R^1 = H$, $R^2 = C_6H_5$ (26%)

23 $R^1 = H$, $R^2 = CH_3$ (44%)
24 $R^1 = R^2 = CH_3$ (22%)
14 $R^1 = R^2 = C_6H_5$ (66%)

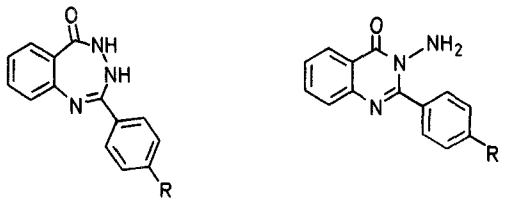
Scheme **E**

We assume that the same intermediates as shown in Scheme **D** are involved in this rearrangement, with one exception. Nitrilium ion **12**, in the absence of water, undergoes internal trapping via a favored 5-*endo*-digonal closure[12], to yield oxadiazole **14** (Scheme **F**). All three of the rearrangements are very clean, in that the two products shown are formed exclusively.



Scheme **F**

The preparation of the methyl **(25a)**, methoxy **(25b)**, and nitro **(25c)** derivatives of compound **2** is also claimed in Ref.[1]. These compounds are undoubtedly the respective aminoquinazolines **26a**, **26b**, and **26c**, instead. The latter compounds are known and their melting points are in reasonable agreement with those reported for the erroneus benzotriazepinones.



25a R = CH_3 (152°C)[1]
b R = OCH_3 (182°C)[1]
c R = NO_2 (242°C)[1]

26a R = CH_3 (164.5°C)[4]
b R = OCH_3 (185°C)[4]
c R = NO_2 (253°C)[13]

We have reinvestigated other literature reports describing syntheses of triazepine systems which have proven to be, instead, quinazolinediones[14], quinazolinones[15], benzimidazoles[16], an imidazoline[16], oxadiazoles[17], and other materials[19]. Other investigators have also reinvestigated reported triazepines and reassigned their structures as azetidinediones[20], oxadiazoles[21], pyrazolotriazoles[22], pyrazolonaphthotriazines[23], and oxadiazolones[24].

Treatment of Isatoic Anhydride (1) with Benzoylhydrazine in Acetic Acid containing *p*-Toluenesulfonic Acid:

Following the procedure of Ref.[11], a mixture of isatoic anhydride (**1**; 1.63 g, 10.0 mmol), benzoylhydrazine (1.36 g, 10.0 mmol), *p*-toluenesulfonic acid (20 mg), and acetic acid (20 ml) is heated at reflux for 9 h. The solution is diluted with water (250 ml), the suspension is extracted with chloroform (3 × 50 ml), and the dried (sodium sulfate) and concentrated extracts are flash-chromatographed on Baker Silica Gel 7024-R (ethyl acetate/hexane; 65/35) to initially give *3-amino-2-phenyl-4(3H)-quinazolinone* **(3)**, spectrally identical with an authentic sample; yield: 460 mg (19%); m.p. 178–179°C (Ref.[5], m.p. 178–179°C).

The second major fraction is an inseparable 1:1 mixture of *3-benzoylamino-2-methyl-4(3H)-quinazolinone* **(7)** and *3-acetylamino-2-phenyl-4-(3H)-quinazolinone* **(8)** as identified by adding, to a deuteriochloroform solution of the mixture, authentic samples of **7** and **8**, and monitoring, by ^{1}H-N.M.R., enhancement of signals due to each component.

2-Phenyl-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-one (2):

A solution of 2-aminobenzoic hydrazide (**16**; 1.51 g, 10.0 mmol) and triethyl orthobenzoate (8.97 g, 40.0 mmol) in ethanol (50 ml) is heated at reflux for 16 h. The yellow solution is concentrated and the resultant slurry is triturated with ether. The yellow solid is collected to give **2**; yield: 0,47 g (20%); m.p. 256–257°C (ethanol).

$C_{14}H_{11}N_3O$	calc.	C 70.87	H 4.67	N 17.71
(237.25)	found	70.49	4.52	17.36

M.S. (70 eV, electron impact): *m/e* = 237 (M^+).

I.R. (Nujol): ν = 3310, 3200 (NH); 1665 (C=O); 1610 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6/TMS_{int}): δ = 10.0 (s, 1H, NH); 8.67 (s, 1H, NH); 7.88–6.80 ppm (m, 9H_{arom}).

The filtrate is concentrated and flash-chromatographed on Baker Silica Gel 7024-R (ethyl acetate/hexane; 4/6) to initially give ethyl N-[*2-(5-phenyl-1,3,4-oxadiazol-2-yl)-phenyl*]-*benzenecarboximidate* **(18)**; yield: 480 mg (13%); m.p. 102–112°C (hexane).

M.S. (chemical ionization, CH_4): *m/e* = 370 ($M^+ - 1$), 398 ($M^+ + 29$), 410 ($M^+ + 41$).

I.R. ($CHCl_3$): ν = 1665 (C=N) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 8.2–7.8 (m, 3H_{arom}); 7.64–6.65 (m, 11H_{arom}); 4.45 (q, J = 7Hz, 2H, CH_2); 1.45 ppm (t, J = 7Hz, 3H, CH_3).

The structure of **18** was further verified by hydrolysis to **14** with 1 normal hydrochloric acid.

The major component of the filtrate eluted next is *ethyl* N-*(4-oxo-2-phenyl-3,4-dihydroquinazolin-3-yl)-benzenecarboximidate* **(17)**; yield: 1.40 g (38%); m.p. 102–107°C.

M.S. (chemical ionization, CH_4): *m/e* = 370 ($M^+ + 1$), 398 ($M^+ + 29$), 410 ($M^+ + 41$).

I.R. ($CHCl_3$): ν = 1675 (C=N) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 8.35–8.04 (m, 1H_{arom}); 7.87–6.90 (m, 13H_{arom}); 4.74–4.17 (m, 2H, CH_2); 1.32 ppm (t, J = 7Hz, 3H, CH_3).

The structure of **17** was further verified by hydrolysis to **3** with 1 normal hydrochloric acid.

Rearrangement of 2-Phenyl-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-one (2):

A mixture of compound **2** (500 mg, 2.11 mmol), *p*-toluenesulfonic acid (20 mg), and xylene (25 ml) is heated at reflux for 16 h. Solution never results and T.L.C. indicates mainly **2**. 2-Methoxyethanol (5 ml) is added to effect solution, and after 3 h, T.L.C. indicates the absence of **2** and the presence of two new materials. The solvents are removed by Kugelrohr distillation and the residue is triturated with aqueous sodium carbonate. The resulting solid (500 mg) is flash-chromatographed on Baker Silica Gel 7024-R (ethyl acetate/hexane; 4/6) to initially give 2-(2-aminophenyl)-5-phenyl-1,3,4-oxadiazole **(14)**; yield: 330 mg (66%); m.p. 167–168°C (hexane).

$C_{14}H_{11}N_3O$	calc.	C 70.87	H 4.67	N 17.71
(237.25)	found	70.90	4.72	17.75

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M.S. (70 eV, electron impact): $m/e = 237$ (M^+).

I.R. (Nujol): $\nu = 3420, 3330$ (NH_2); 1640 (C=N) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 8.35–7.87 (m, 2H); 7.87–7.68 (m, 1H); 7.68–7.35 (m, 3H); 7.31–7.08 (m, 1H); 6.95–6.58 (m, 2H); 5.88 ppm (s, 2H, NH_2).

The second component to elute is **3**, spectrally identical to the authentic sample; yield: 130 mg (26%); m.p. 179–180°C.

3-Amino-2-phenyl-4-(3*H*)-quinazolinone (3):

Methyl 2-Benzoylaminobenzoate **(5)**: This compound is prepared using a procedure described[8] for the corresponding *N*-acetyl compound: yield: 98%; m.p. 99–101°C (Ref.[35], m.p. 100°C).

2-Benzoylaminobenzoic Hydrazide **(6)**: A solution of compound **5** (25.0 g, 97.9 mmol) and hydrazine hydrate (10 ml) in ethanol (100 ml) is heated at reflux temperature for 15 h. The resultant mixture is cooled and the colorless solid product **6** isolated by suction; yield: 23.0 g (92%); m.p. 185–186°C (Ref.[26], m.p. 183–185°C).

3-Amino-2-phenyl-4(3H)-quinazolinone **(3)**: A mixture of compound **6** (10.0 g, 37.4 mmol) and hydrazine hydrate (100 ml) is heated at reflux. Solution results after 15 min, but a colorless solid begins to separate thereafter. After 30 min, the mixture is cooled and the colorless needles are collected to give **3**; yield: 6.30 g (71%); m.p. 179–180°C (Ref.[5], m.p. 178–179°C).

Alternatively, compound **3** can be prepared directly from **5** and hydrazine hydrate; yield: 64%.

3-Benzoylamino-2-methyl-4(3*H*)-quinazolinone (7):

A solution of 3-amino-2-methyl-4(3*H*)-quinazolinone[5] (3.50 g, 20.0 mmol), benzoyl chloride (3.09 g, 22.0 mmol), and triethylamine (2.23 g, 22.0 mmol) in dichloromethane (100 ml) is heated at reflux for 2 h. The solution is washed with water (100 ml) dried with sodium sulfate, and concentrated. The resultant oil (6.07 g) is flash-chromatographed on Baker Silica Gel 7024-R (ethyl acetate/hexane; 1/1 increasing to 3/1) to provide two pure materials.

3-Dibenzoylamino-2-methyl-4(3H)-quinazolinone (*N*-Benzoyl-**7**) is obtained from the early fractions; yield: 160 mg (2%); m.p. 204–205°C (toluene).

$C_{23}H_{17}N_3O_3$	calc.	C 72.05	H 4.47	N 10.96
(383.4)	found	72.13	4.46	10.99

M.S. (70 eV, electron impact): m/e = 383 (M^+).

I.R. (Nujol): ν = 1690 (C=O) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 8.33–8.23 (m, 1H); 7.90–6.97 (m, 13H); 2.67 ppm (s, 3H, CH_3).

3-Benzoylamino-2-methyl-4(3H)-quinazolinone **(7)** is obtained from the later fractions; yield: 2.51 g (45%); m.p. 185–186.5°C (toluene) (Ref.[27], m.p. 182–184°C).

3-Acetylamino-2-phenyl-4-(3*H*)-quinazolinone (8):

A solution of compound **3** (2.00 g, 8.43 mmol) and acetic anhydride (10 ml) in acetic acid (20 ml) is heated at reflux for 2 h. The clear solution is diluted while hot with water (100 ml) to effect crystallization. The resultant colorless solid (2.23 g), after recrystallization (1.90 g from ethanol/water) is still a mixture of two components according to T.L.C. analysis. The material is flash-chromatographed on Baker Silica Gel 7024-R (ethyl acetate/hexane; 1/1 increasing to 2/1) to provide the individual compounds.

3-Diacetylamino-2-phenyl-4-(3H)-quinazolinone (*N*-Acetyl-**8**) is obtained from the early fractions; yield: 320 mg (12%); m.p. 149–150°C (Ref.[28], m.p. 153°C).

3-Acetylamino-2-phenyl-4(3H)-quinazolinone **(8)** is obtained from the later fractions; yield: 1.44 g (66%); m.p. 118–121°C (ethanol/water) (Ref.[2], m.p. 122°C).

2-(2-Acetylaminophenyl)-5-phenyl-1,3,4-oxadiazole (15):

A solution of 2-(2-aminophenyl)-5-phenyl-1,3,4-oxadiazole (**14**; 100 mg, 0.421 mmol) and acetic anhydride (2 ml) in acetic acid (4 ml) is heated at reflux for 30 min and diluted while hot with water (20 ml). The colorless needles which result are collected to afford pure **15**; yield: 70.0 mg (59%); m.p. 166–167°C.

$C_{16}H_{13}N_3O_2$	calc.	C 68.80	H 4.69	N 15.05
(279.3)	found	68.76	4.72	15.08

M.S. (70 eV, electron impact): m/e = 279 (M^+).

I.R. (Nujol): ν = 1690 (C=O); 1615, 1595 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ = 10.9 (s, 1H, NH); 8.87–8.63 (m, 1H); 8.20–7.83 (m, 3H); 7.67–6.96 (m, 5H); 2.28 ppm (s, 3H, CH_3).

Received: January 31, 1984

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