# Synthesis and X-Ray Crystal Structure of a 2,4,5-Trisubstituted 1,2,4-Triazolin-3-one



Gary D. Madding*

Department of Chemical Process Development

David W. Smith

Department of Preclinical CNS Research
Bristol-Meyers Company, Evansville, Indiana 47721

Robert I. Sheldon [1] and B. Lee [2]

Department of Chemistry, University of Kansas,
Lawrence, Kansas 60645

Received February 20, 1985

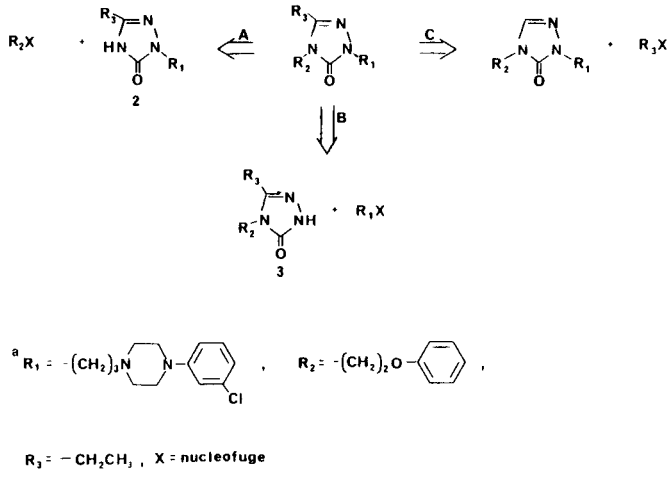
The synthesis and x-ray crystal structure of BMY 13754, a 1,2,4-triazolin-3-one under clinical evaluation as an antidepressant agent, is described. Several synthetic strategies are discussed.

*J. Heterocyclic Chem.*, **22**, 1121 (1985).

Recently, BMY 13754, known chemically as 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-3*H*-1,2,4-triazolin-3-one hydrochloride (**1**) [3], was identified [4] as a potential non-tricyclic antidepressant candidate. We have explored various synthetic approaches to this unique triazolinone [3] and herein report our findings. In addition, the x-ray crystal structure has been determined and will be presented.

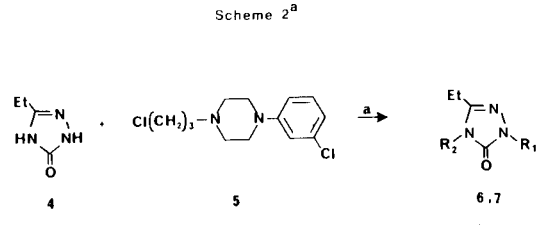
From the onset, we envisaged a convergent synthesis employing a suitably disubstituted triazolinone [5] synthon on which the third substituent could be appended, presumably *via* an appropriately functionalized alkylating agent (Scheme1). Paths A and B represented the most plausible manifolds and will be discussed further (*vide infra*). The anticipated ambident nature of the triazolin-3-one **4** anion necessarily precluded its utility as a synthon for BMY 13754. Indeed, alkylation of **4** with the 3-chloropropylpiperazine **5** resulted in a 4:6 mixture of 2- and 4-*N*-alkylated adducts, respectively (Scheme 2). No *O*-alkylated products were detected under the conditions employed.

Scheme 1[a]

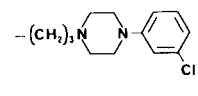


[a] $R_1$ = $-(CH_2)_3$-(4-(3-chlorophenyl)-1-piperazinyl), $R_2$ = $-(CH_2)_2O$-phenyl, $R_3$ = $-CH_2CH_3$, X = nucleofuge

Scheme 2[a]



[a] (a) $K_2CO_3$, $CH_3CN$, $\Delta$

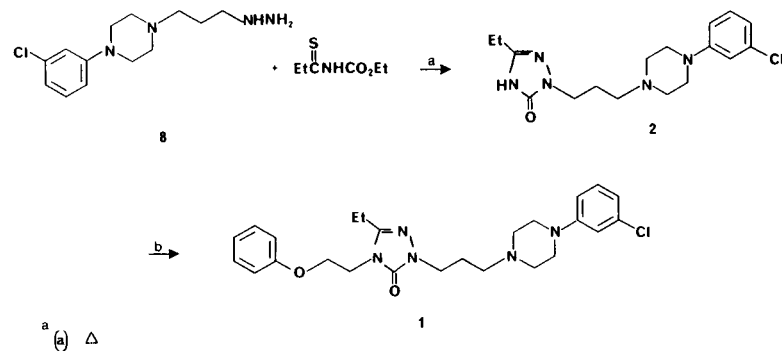


| | | |
|---|---|---|
| 6 | $R_1$ | $R_2$ |
| 7 | $R_2$ | $R_1$ |

Our initial efforts were directed toward the synthesis of the 5-ethyl-triazolin-3-one **2** (path A). Condensation of hydrazinopropylpiperazine **8** with *N*-ethoxycarboxythiopropionamide [6] resulted in triazolinone **2** (Scheme 3). Subsequent alkylation of **2** with 2-phenoxyethanyl bromide proceeded smoothly to afford the free base of BMY 13754. Although this route provided **1** in relatively few steps, other factors encouraged the development of other models of synthesis.

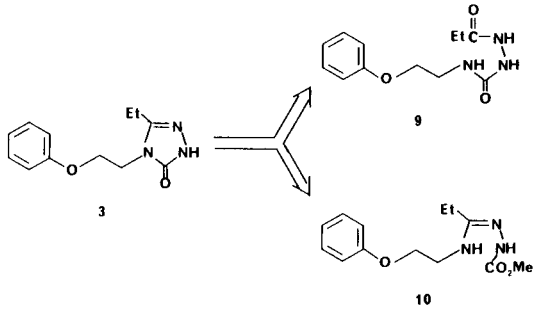
Alternatively, the synthesis of triazolinone **3** (path B) was investigated. Two approaches to **3** were identified (Scheme 4); one utilizing the semicarbazide **9** and the other requiring the *N*-carbomethoxyamidrazone **10**.

Scheme 3[a]



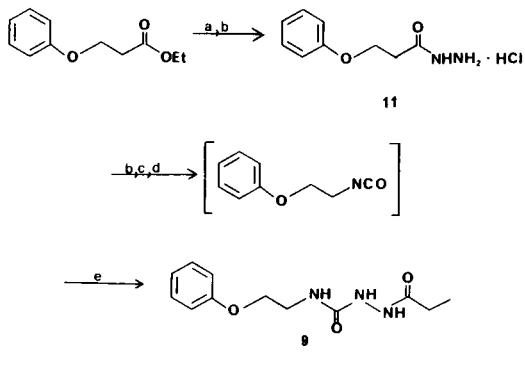
[a] (a) Δ
(b) $PhOCH_2CH_2Br$, $K_2CO_3$, Δ

Scheme 4



The semicarbazide **9** could best be prepared by reacting propionylhydrazide [7] with 2-phenoxyethylisocyanate (Scheme 5). Preparation of 2-phenoxyethylisocyanate, derived from the Curtius rearrangement of 3-phenoxypropionylazide, proceeded as follows. Hydrazine was combined with ethyl 3-phenoxypropionate [8] to provide 3-phenoxypropionyl hydrazide **11**, isolated as the hydrochloride salt.

Scheme 5[a]

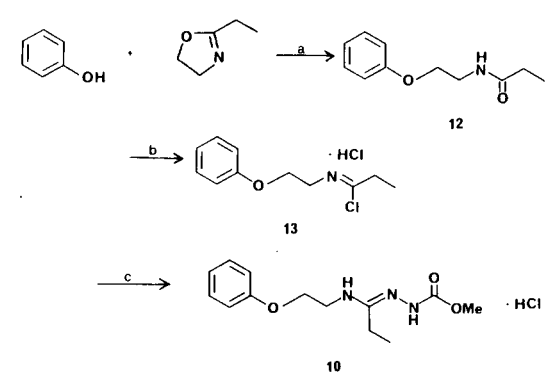


[a] (a) $NH_2NH_2$, (b) HCl, (c) $NaNO_2$, (d) Δ, (e) $EtCONHNH_2$

Careful thermolysis of 3-phenoxypropionyl azide, generated *in situ* via the treatment of hydrazide **11** with nitrous acid, yielded the penultimate 2-phenoxyethylisocyanate. Propionyl hydrazide when combined with this isocyanate afforded the semicarbazide **9**.

Synthesis of amidrazone **10** was achieved from the propionamide **12** [9] prepared from 2-ethyloxazoline and phenol (Scheme 6). A number of methods were explored to

Scheme 6[a]



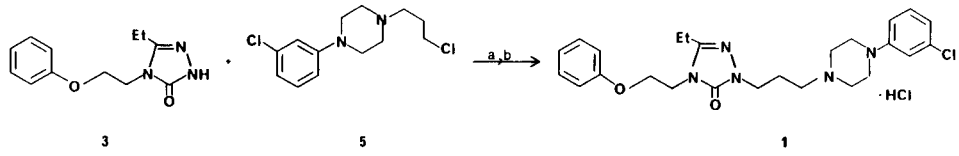
[a] (a) Δ, (b) $COCl_2$, (c) $NH_2NHCO_2Me$

activate the amide carbonyl of **12** toward nucleophilic attack. Of these methods, the imidoyl chloride **13** proved the most efficient. Thus, treatment of amide **12** with phosgene followed by methyl carbazate afforded the amidrazone **10**.

Semicarbazide **9** and amidrazone **10** cleanly underwent base-induced intra-molecular condensation to the triazolone **3**. Alkylation of **3** with chloropropylpiperazine **5** [3] (Scheme 7) then completed the synthesis of BMY 13754.

In summary, we have identified three synthetic routes to BMY 13754 and have examined other potential avenues. Each route assembles a disubstituted triazolinone which is alkylated with an appropriately substituted electrophile to afford BMY 13754. Preparation of the triazolinone **3** *via*

Scheme 7[a]



3 5 1

[a](a) NaOH , (b) HCl

Table I

Fractional Atomic Coordinates (× $10^4$) with e.s.d.'s in Parentheses

| | x | y | z |
|---|---|---|---|
| N(1) | 2769(1) | 6187(2) | 5976(2) |
| N(2) | 2535(1) | 5102(2) | 5487(2) |
| C(3) | 1823(1) | 4910(2) | 5485(2) |
| N(4) | 1619(1) | 5896(2) | 6042(2) |
| C(5) | 2209(1) | 6637(2) | 6303(2) |
| C(6) | 2205(2) | 7791(3) | 6897(3) |
| C(7) | 2165(2) | 7676(4) | 8128(3) |
| C(8) | 876(1) | 6094(3) | 6189(2) |
| C(9) | 410(2) | 6609(3) | 5184(3) |
| O(10) | 712(1) | 7734(2) | 4990(2) |
| C(11) | 334(1) | 8488(3) | 4215(2) |
| C(12) | -294(2) | 8189(3) | 3516(3) |
| C(13) | -630(2) | 9067(5) | 2791(3) |
| C(14) | -346(2) | 10195(5) | 2785(3) |
| C(15) | 285(2) | 10464(4) | 3476(3) |
| C(16) | 627(2) | 9620(3) | 4183(3) |
| C(17) | 2982(2) | 4425(3) | 4864(2) |
| C(18) | 3632(1) | 3832(3) | 5557(2) |
| C(19) | 4019(1) | 3148(3) | 4769(2) |
| N(20) | 4775(1) | 2764(2) | 5241(2) |
| C(21) | 4815(1) | 1706(2) | 6000(2) |
| C(22) | 5581(1) | 1286(3) | 6390(2) |
| N(23) | 5915(1) | 1017(2) | 5431(2) |
| C(24) | 5925(1) | 2082(3) | 4745(2) |
| C(25) | 5174(1) | 2499(3) | 4312(2) |
| C(26) | 6524(1) | 262(2) | 5557(2) |
| C(27) | 6795(1) | -72(2) | 4612(2) |
| C(28) | 7366(1) | -849(2) | 4711(3) |
| C(29) | 7694(2) | -1320(3) | 5711(3) |
| C(30) | 7422(2) | -994(3) | 6640(3) |
| C(31) | 6846(2) | -220(3) | 6572(2) |
| O | 1442(1) | 4072(2) | 5089(2) |
| Cl | 7672.9(5) | -1270.8(9) | 3508.3(8) |
| Cl(32) | 5514.0(4) | 472.0(6) | 1975.5(6) |

cyclization of the *N*-carbomethoxyamidrazone **10** currently appears most amenable to large scale synthesis. The syntheses discussed herein as well as alternate methods have been utilized to prepare congenors of BMY 13754. The pharmacologic properties of these analogues [10] have been preliminarily disclosed and will be the subject of a forthcoming communication.

X-Ray Structure.

The space group of the irregularly shaped, colorless crystals which were obtained by evaporation of a saturated methanol solution of BMY 13754 hydrochloride was determined from precession photography. Accurate cell dimensions were determined by a least squares fit of the setting angles for 15 reflections on a Syntex $P2_1$ four circle diffractometer using graphite monochromatized MoK$\alpha$ radiation. These 15 reflections were widely distributed in reciprocal space with 2θ angles ranging from 15° to 32°. The density of the crystals was measured by flotation in chlorobenzene and bromobenzene. A summary of some crystal data follows: formula $C_{25}H_{32}ClN_5O_2 \cdot HCl$, crystal-system monoclinic, space group $P2_1/c$, a = 18.894(7)A, b = 11.202(4)A, c = 12.293(5)A, $\beta$ = 100.14(3)°, Z = 4 molecules/unit cell, $d_{obsd}$ = 1.32 g cm$^{-3}$, $d_{calcd}$ = 1.314g cm$^{-3}$, $\lambda$(MoK$\alpha$) = 0.71069A, $\mu$(MoK$\alpha$) = 2.89 cm$^{-1}$.

Intensity data were collected on an automated Syntex $P2_1$ diffractometer using a θ-2θ scan procedure. Graphite monochromatized MoK$\alpha$ radiation was employed for the data collection. The scan rate was varied between 2 and 24° min$^{-1}$ depending upon the scan intensity and the scan range was from 1° below the 2θ angle for the K$\alpha$1 component to 1° above that for the K$\alpha$2 component. Background intensity was measured for each reflection by counting for half the total scan time at each end of the scan range. Four "standard" reflections were measured after every 96 reflections. The 2θ values for the 4540 independent reflections collected ranged from 2 to 50° and of

Table II

Bond Lengths (Å)

| | | | |
|---|---|---|---|
| N(1)-N(2) | 1.393(3) | C(15)-C(16) | 1.368(5) |
| N(1)-C(5) | 1.298(3) | C(17)-C(18) | 1.520(4) |
| N(2)-C(3) | 1.362(3) | C(18)-C(19) | 1.519(4) |
| N(2)-C(17) | 1.450(3) | C(19)-N(20) | 1.506(3) |
| C(3)-N(4) | 1.389(3) | N(20)-C(21) | 1.502(3) |
| C(3)-O | 1.229(3) | N(20)-C(25) | 1.504(3) |
| N(4)-C(5) | 1.380(3) | C(21)-C(22) | 1.518(4) |
| N(4)-C(8) | 1.464(3) | C(22)-N(23) | 1.463(3) |
| C(5)-C(6) | 1.486(4) | N(23)-C(24) | 1.464(3) |
| C(6)-C(7) | 1.533(5) | N(23)-C(26) | 1.415(3) |
| C(8)-C(9) | 1.501(4) | C(24)-C(25) | 1.500(4) |
| C(9)-O(10) | 1.421(3) | C(26)-C(27) | 1.401(3) |
| O(10)-C(11) | 1.376(3) | C(26)-C(31) | 1.396(3) |
| C(11)-C(12) | 1.377(4) | C(27)-C(28) | 1.375(4) |
| C(11)-C(16) | 1.388(4) | C(28)-C(29) | 1.380(4) |
| C(12)-C(13) | 1.403(5) | C(28)-Cl | 1.746(3) |
| C(13)-C(14) | 1.373(6) | C(29)-C(30) | 1.383(4) |
| C(14)-C(15) | 1.370(5) | C(30)-C(31) | 1.382(4) |

Table III

Bond Angles (°)

| | | | |
|---|---|---|---|
| N(2)-N(1)-C(5) | 104.9(2) | C(11)-C(16)-C(15) | 120.2(3) |
| N(1)-N(2)-C(3) | 112.1(2) | N(2)-C(17)-C(18) | 114.9(2) |
| N(1)-N(2)-C(17) | 121.0(2) | C(17)-C(18)-C(19) | 107.2(2) |
| C(3)-N(2)-C(17) | 125.7(2) | C(18)-C(19)-N(20) | 115.4(2) |
| N(2)-C(3)-O | 129.0(2) | C(19)-N(20)-C(21) | 113.9(2) |
| N(2)-C(3)-N(4) | 103.4(2) | C(19)-N(20)-C(25) | 109.3(2) |
| N(4)-C(3)-O | 127.5(2) | C(21)-N(20)-C(25) | 109.8(2) |
| C(3)-N(4)-C(5) | 108.1(2) | N(20)-C(21)-C(22) | 112.4(2) |
| C(3)-N(4)-C(8) | 122.4(2) | C(21)-C(22)-N(23) | 109.3(2) |
| C(5)-N(4)-C(8) | 129.3(2) | C(22)-N(23)-C(24) | 110.4(2) |
| N(1)-C(5)-N(4) | 111.3(2) | C(22)-N(23)-C(26) | 119.5(2) |
| N(1)-C(5)-C(6) | 124.3(2) | C(24)-N(23)-C(26) | 117.2(2) |
| N(4)-C(5)-C(6) | 124.3(2) | N(23)-C(24)-C(25) | 110.5(2) |
| C(5)-C(6)-C(7) | 114.7(3) | C(24)-C(25)-N(20) | 111.2(2) |
| N(4)-C(8)-C(9) | 113.1(2) | N(23)-C(26)-C(27) | 118.5(2) |
| C(8)-C(9)-O(10) | 106.5(2) | N(23)-C(26)-C(31) | 123.2(2) |
| C(9)-O(10)-C(11) | 119.0(2) | C(27)-C(26)-C(31) | 118.2(2) |
| O(10)-C(11)-C(12) | 124.7(3) | C(26)-C(27)-C(28) | 119.4(3) |
| O(10)-C(11)-C(16) | 114.7(3) | C(27)-C(28)-C(29) | 123.0(3) |
| C(12)-C(11)-C(16) | 120.6(3) | C(27)-C(28)-Cl | 117.9(2) |
| C(11)-C(12)-C(13) | 118.0(4) | C(29)-C(28)-Cl | 119.1(2) |
| C(12)-C(13)-C(14) | 121.0(4) | C(28)-C(29)-C(30) | 117.4(3) |
| C(13)-C(14)-C(15) | 119.9(4) | C(29)-C(30)-C(31) | 121.3(3) |
| C(14)-C(15)-C(16) | 120.3(4) | C(30)-C(31)-C(26) | 120.7(3) |

these 2922 observed reflections with $I > 3\sigma(I)$ were subsequently used in the structure analysis. The intensity data were converted to structure factors through the application of the Lorentz-polarization factor, but no absorption, decay or extinction corrections were made. The structure was solved using the symbolic addition technique [11] and refined by full matrix least squares which minimized the function $\Sigma w(F_o - F_c)^2$. The weight w was taken as $1/\sigma_F^2 = Lp I/\sigma_I^2$ where Lp is the Lorentz-polarization factor and I the intensity with estimated variance $\sigma_I^2$. All hydrogen atom positions could easily be found in a difference electron density map after several cycles of refinement of non-hydrogen atoms. In subsequent refinement, the isotropic temperature factor of a hydrogen atom was fixed equal to the equivalent isotropic temperature factor of the atom to which it was attached. The final discrepency factors after refinement of positional and anisotropic thermal parameters for non-hydrogen atoms and positional parameters for hydrogens are $R = [\Sigma w(F_o - F_c)^2/\Sigma w F_o^2]^{1/2} = 0.039$.

The structure and atom numbering for the molecule are shown in Figure 1. Table I contains the atomic, coordinates; Tables II and III contain bond lengths and angles. Some selected mean planes are given in Table IV. The triazole, phenoxy and chlorophenyl moieties are essentialy planar while the piperazine ring assumes a chair conformation. N(20) carries a hydrogen and the molecule is therefore positively charged.

Hydrogen positions, thermal parameters and structure factors are available upon request from the authors.

Table IV

Mean Planes

-0.0940X + 0.4698Y - 0.8777Z = -3.4688

| | | | |
|---|---|---|---|
| N(1) | 0.0066 [a] | N(4) | -0.0107 |
| N(2) | -0.0135 | C(5) | 0.0029 |
| C(3) | 0.0148 | O | 0.0532 [b] |

rms(d) = 0.0107 [c]

0.6538X - 0.2965Y - 0.6962Z = 6.5444

| | | | |
|---|---|---|---|
| C(11) | -0.0096 | C(15) | 0.0009 |
| C(12) | 0.0012 | C(16) | 0.0086 |
| C(13) | 0.0083 | O(10) | -0.0544 [b] |
| C(14) | -0.0094 | | |

rms(d) = 0.0074

-0.4069X - 0.7417Y - 0.5332Z = -8.6792

| | | | |
|---|---|---|---|
| N(20) | -0.2089 | N(23) | 0.2610 |
| C(21) | 0.2168 | C(24) | -0.2503 |
| C(22) | -0.2408 | C(25) | 0.2222 |

rms(d) = 0.2341

-0.6181X - 0.7739Y - 0.1379Z = -8.0257

| | | | |
|---|---|---|---|
| C(26) | -0.0043 | C(30) | 0.0003 |
| C(27) | 0.0003 | C(31) | 0.0039 |
| C(28) | 0.0040 | Cl | 0.0507 [b] |
| C(29) | -0.0042 | | |

rms(d) = 0.0034

[a] Displacement (Å) from the mean plane. [b] Atom not included in determination of mean plane parameters. [c] Root mean square displacement (Å) of atoms used to determine mean plane parameters.

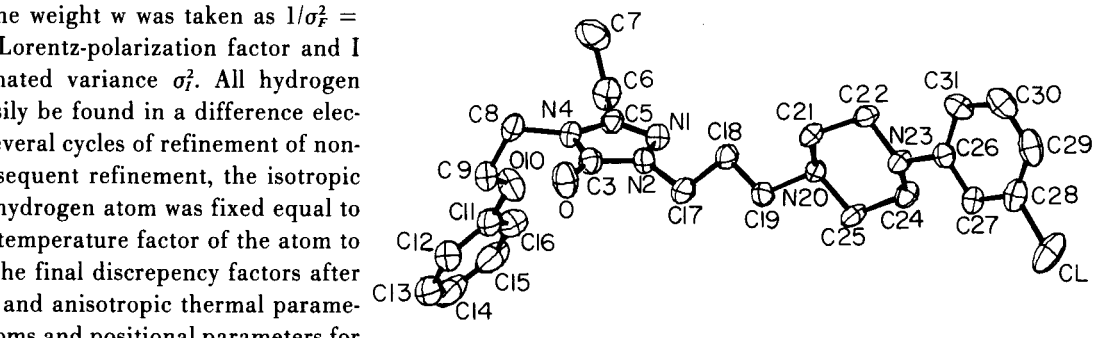



Figure 1. ORTEP [12] view of the molecule. Thermal ellipsoids enclose 50% probability.

## EXPERIMENTAL

Melting points were determined by using a Büchi 510 capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet MX1 spectrophotometer. Proton nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R32 instrument. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.0) as an internal standard. Data are reported as follows: (solvent) chemical shift (multiplicity, assignment, integrated intensity). Elemental analyses were performed on a Perkin-Elmer 240B analyzer.

3-Phenoxypropionyl Hydrazide Hydrochloride (**11**).

Ethyl 3-phenoxypropionate [8] (1481.0 g, 7.62 moles) was stirred at 10° as 95% hydrazine (308.3 g, 9.14 moles) was added. After 0.5 hours, a precipitate formed. The mixture was allowed to stand at 25° for 5 hours, and then cooled to 10° for 16 hours. The precipitate was collected by filtration and allowed to air-dry, yielding 1128.0 g of white solid which was subsequently converted to the hydrochloride salt. The crude 3-phenoxypropionyl hydrazide (2000.6 g, 11.0 mole) was dissolved in 5 liters of methylene chloride. The solution was stirred at 10° as anhydrous hydrogen chloride was delivered into the mixture until moistened indicator paper showed *p*H 3. The solid was collected on a filter, rinsed with methylene chloride (2 × 200 ml) and air-dried to give 2100.0 g (87% of theory) product, mp 145-156°. An analytical sample was obtained by crystallization from 95% ethanol, mp 155-157.5°; nmr (deuteriodimethylsulfoxide): δ 2.80 (t, $CH_2CO$, 2H), 4.25 (t, $ArOCH_2$, 2H), 6.96 (m, aromatic, 3H), 7.20 (m, aromatic, 2H), 10.62 (broadsinglet, $NH_3^+$, 3H), 11.35 (broad singlet, NHCO, 1H).

*Anal.* Calcd. for $C_9H_{13}ClN_2O_2$: C, 49.89; H, 6.05; Cl, 16.36; N, 12.93. Found: C, 49.70; H, 6.07; Cl, 16.29; N, 12.61.

1-Propionyl-4-(2-phenoxyethyl)semicarbazide (**9**).

A slurry of 705.0 g (3.25 moles) of **11**, 271.3 ml (3.26 moles) of 37% aqueous hydrochloric acid, 2.9 liters of ice/water and 1.7 liters of toluene was stirred in an ice bath as a solution of 247.0 g (3.58 moles) of sodium nitrite in 1.0 liter of water was added over 20 minutes. The reaction temperature was not allowed to exceed 18°. After 20 minutes, the mixture was filtered and the organic phase was separated. The aqueous layer was extracted with 500 ml toluene. The combined layers were dried over anhydrous magnesium sulfate. The dried toluene solution was slowly added over 1 hour with stirring to a 5.0 liter flask which was pre-heated and kept hot on a steam-bath. When the addition was completed and nitrogen evolution had stopped, the solution was cooled in an ice-bath, and 286.8 g (3.26 moles) of propionyl hydrazide [7] was added dropwise over 1.5 hours. After the addition was complete, the mixture was stirred an additional 15 minutes. The product was collected by filtration, rinsed with toluene, and allowed to air-dry. The solid weighed 717.0 g (88% of theory), mp 180.0-183.0°; nmr (hexadeuterodimethylsulfoxide): δ 1.04 (t, $CH_3$, 3H), 2.15 (q, $CH_2CO$, 2H), 3.45 (m, $CH_2N$, 2H), 3.99 (t, $CH_2O$, 2H), 6.52 (t, CNHCO, 1H), 6.97 (m, aromatic, 3H), 7.29 (m, aromatic, 2H), 7.80 (broad, NHCO, 1H), 9.41 (broad, NHCO, 1H).

*Anal.* Calcd. for $C_{12}H_{17}N_3O_3$: C, 57.36; H, 6.82; N, 16.72. Found: C, 57.26; H, 6.98; N, 16.45.

Methyl [1-[(2-Phenoxyethyl)amino]propylidene]hydrazinecarboxylate Hydrochloride (**10**).

Phosgene (57.4 g, 0.58 mole) was added to a solution of 112.0 g (0.58 mole) of *N*-(2-phenoxyethyl)propionamide [9] and 0.4 g (0.006 mole) of imidazole in 450 ml of methylene chloride over 1 hour. During the course of the addition the reaction temperature was not allowed to exceed 25°. The solution was stirred at 25° for 2.5 hours. A solution of 52.2 g (0.58 mole) of methyl carbazate in 600 ml of methylene chloride was prepared and stirred over 25 g of 4A molecular sieves for 15 minutes; the solution was filtered. The filtrate was added under nitrogen over 0.5 hours to the amide/phosgene solution at 15-20°. The mixture was allowed to warm to 25° and stir 16 hours. The solid precipitate was collected, washed with 750 ml of methylene chloride, and dried *in vacuo* at 65° for 2 hours. The white solid weighed 135.2 g (77% of theory), mp 150-154°. An analytical sample was obtained by crystallization from 2-propanol, mp 157-159°. This material was found (nmr) to be a 60:40 mixture of *E*/*Z* isomers; nmr (hexadeuterodimethylsulfoxide): δ 1.15 and 1.28 (2 triplets, $CH_3$, 3H), 2.74 (m, $CH_2CO$, 2H), 3.66 and 3.70 (2 singlets, $OCH_3$, 3H), 3.81 (m, $CH_2N$, 2H), 4.19 (m, $OCH_2$, 2H), 6.98 (m, aromatic, 3H), 7.31 (m, aromatic, 2H), 9.67, 10.04, 10.40, 10.90, and 11.72 (broad triplet and 4 broad singlets, 3 NH, 3H).

*Anal.* Calcd. for $C_{13}H_{19}N_3O_3 \cdot HCl$: C, 51.74; H, 6.68; Cl, 11.75; N, 13.92. Found: C, 51.57; H, 6.71; Cl, 11.65; N, 13.59.

5-Ethyl-4-(2-phenoxyethyl)-2*H*-1,2-4-triazol-3(4*H*)-one (**3**). Method A.

To a solution of 88.4 g (1.58 mole) of potassium hydroxide in 10.0 liters of water heated to 95° was added with stirring 396.1 g (1.58 mole) of **9**. The mixture was stirred at 95-96° for 40 minutes and filtered while hot. The filtrate was then cooled in an ice-bath (the potassium salt of the title compounds began to precipitate) as 145 ml (1.75 mole) of 37% hydrochloric acid was added. The mixture was stirred at 10° for 1 hour. The solid was collected, rinsed with water and air-dried, yielding **3** (233.5 g, 64% of theory), mp 136-139°.

Method B.

Methyl [1-[(2-phenoxyethyl)amino]propylidene]hydrazinecarboxylate hydrochloride (655.3 g, 2.17 moles) was stirred vigorously with 4.0 liters of methylene chloride, 2.4 liters of water and 179.4 g of 50% aqueous sodium hydroxide (2.24 moles). The layers were separated, and the organic layer was dried over anhydrous potassium carbonate. The solution was concentrated *in vacuo*, and the residue was stirred in 1.2 liters of boiling xylene for 2.5 hours. The solid obtained by chilling the solution was collected, rinsed with toluene and air-dried to give 389.6 g (77% of theory) of product, mp 134.5-138°.

The crude **3** was purified by dissolving 171.2 g (0.72 mole) in a boiling solution of 41.0 g (0.73 mole) of potassium hydroxide in 3.0 liters of water. The solution was treated with Celite filter-aid and activated charcoal, and filtered. The filtrate was stirred in an ice-bath as 61.0 ml of 37% hydrochloric acid (0.73 mole) was added. The solid was collected on a filter, rinsed with water and air-dried to give 166.0 g (97% recovery) of **3**, mp 137.5-138°; nmr (hexadeuterodimethylsulfoxide): δ 1.19 (t, $CH_3$, 3H), 2.61 (q, $CH_2C$, 2H), 3.90 (t, $CH_2N$, 2H), 4.14 (t, $CH_2O$, 2H), 6.92 (m, aromatic, 3H), 7.28 (m, aromatic, 2H), 11.40 (broad singlet, NH, 1H).

*Anal.* Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.90; H, 6.45; N, 17.94.

BMY 13754, 2-[3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-4-(2-phenoxyethyl)-2*H*-1,2,4-triazol-3(4*H*)-one Hydrochloride (**6**).

A mixture of 258.8 g (1.11 moles) of **3**, 419.9 g (90 wt%, 337.9 g, 1.22 moles) of 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine hydrochloride [13], 195.2 g of 50% aqueous sodium hydroxide (2.44 moles) and 1650 ml of 2-propanol was stirred and heated at reflux for 7 hours. The mixture was filtered hot. The filtrate was treated with activated charcoal, filtered, and concentrated *in vacuo* to afford a viscous oil. Crystallization of this oil from 2-propanol/heptane gave nefazodone as the free base (438.5 g, 84% of theory), mp 83-84°.

A 414.3 g (0.88 mole) sample of the free base was dissolved in 1.0 liter of 2-propanol and 75.0 ml (0.9 mole) of 12 normal hydrochloric acid was added with stirring. The resulting solution was concentrated *in vacuo* to afford **1** as a solid mass. Subsequent recrystallization from 2-propanol gave 420.8 g (94% of theory) of BMY 13754 hydrochloride (**1**). If the product **1** is contaminated by 1,1′-trimethylene-bis-[4-(3-chlorophenyl)piperazine] hydrochloride, the impurity may be removed by dissolving the product in methylene chloride and removing the insoluble impurity by filtration. Purified **1** may be crystallized from 2-propanol by slow cooling to give a polymorph mp 186.0-187.0°, or by rapid cooling to give a polymorph mp 181.0-182.0°; nmr (hexadeuterodimethylsulfoxide): δ 1.20 (t, $CH_3$, 3H), 2.15 (m, $CH_2$, 2H), 2.66 (q, methyl-$CH_2$, 2H), 3.26 (m, $(CH_2)_4$, 8H), 3.73 (m, $(CH_2)_2$, 4H), 3.96 (t, $CH_2$, 2H), 4.17 (t, $CH_2$, 2H), 6.94 (m, aromatic, 6H0), 7.27 (m, aromatic, 3H), 11.70 (broad singlet, $NH^+$, 1H); ir (potassium bromide): 755, 945, 1240, 1495, 1570, 1595, 1705, 2580 $cm^{-1}$.

*Anal.* Calcd. for $C_{25}H_{32}ClN_5O_2 \cdot HCl$: C, 59.29; H, 6.57; Cl, 14.00; N, 13.83. Found: C, 59.27; H, 6.50; Cl, 14.04; N, 13.81.

## REFERENCES AND NOTES

[1] Present address: Los Alamos National Laboratory, Materials Science and Technology Div., Los Alamos, NM 87545.

[2] Present address: National Institutes of Health, PSL/DCRT, Bethesda, MD 20205.

[3] D. L. Temple, Jr., and W. G. Lobeck, U. S. Patent 4,338,317; *Chem. Abstr.*, **97**, 148432a (1982).

[4] D. P. Taylor, M. S. Eison, L. A. Riblet, D. L. Temple, J. P. Yevich and D. W. Smith, *Soc. Neurosci. Abstr.*, **8**, 465 (1982).

[5] C. Temple, Jr., in "The Chemistry of Heterocyclic Compounds", Vol 37, J. A. Montgomery, ed, John Wiley and Sons, Inc., New York, NY, 1981.

[6] E. P. Papadopoulous and B. George, *J. Org. Chem.*, **41**, 3233 (1976).

[7] T. Rabini and G. Vita, *J. Org. Chem.*, **30**, 2486 (1965).

[8] R. Hall and E. Stern, *J. Chem. Soc.*, 2035 (1949).

[9] Dow Technical Data, "Developmental 2-Ethyl-2-oxazoline XAS-1454", Dow Chemical Company, 1981.

[10] D. W. Smith, D. L. Temple, J. P. Yevich, W. G. Lobeck, M. E. Weber, D. P. Taylor and M. S. Eison, Abstr. 66, 186th National ACS Meeting, Division of Medicinal Chemistry.

[11] J. Karle and I. L. Karle, *Acta Cryst.*, **21**, 849 (1966).

[12] C. K. Johnson, ORTEP Report ORNL-3794 (1965); Oak Ridge National Laboratory, Tennessee.

[13] C. B. Pollard, W. M. Lauter and N. O. Nuessle, *J. Org. Chem.*, **24**, 745 (1959).