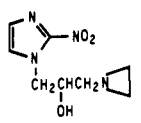
# Dual-Function Radiosensitizers. α-[[(2-Bromoethyl)amino]methyl]-2-nitro-1*H*-imidazole-1-ethanol and Related Compounds: Preparation via an Aziridine Equivalent

Mark J. Suto,* Michael A. Stier, and Leslie M. Werbel

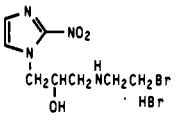
*Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, Michigan 48105.*
*Received August 31, 1990*

An improved synthesis of the dual-function radiosensitizer α-[[(2-bromoethyl)amino]methyl]-2-nitro-1*H*-imidazole-1-ethanol (2, RB 6145) has been developed. Previously, the synthetic difficulties associated with this compound limited its attractiveness as a clinical candidate, although its radiosensitizing activity in preclinical models warranted its further development. The synthesis described uses a 2-oxazolidinone as an aziridine equivalent and provides 2 in 47% yield.

The 2-nitroimidazole radiosensitizer α-[(1-aziridinyl)-methyl]-2-nitro-1*H*-imidazole-1-ethanol (1, RSU 1069) continues to receive considerable study both as a radiosensitizer and hypoxic cell cytotoxin.[1] It was the first "bifunctional" radiosensitizer discovered and is still one of the most potent radiosensitizers known in preclinical models. On the basis of its activity in animal models and novel mechanism of action,[2] 1 proceeded into Phase 1 clinical studies. It was dropped quickly due to uncontrollable gastric toxicity[3] that was attributed to the reactivity of the aziridine ring. This reactivity also contributed to the synthetic difficulty and lack of stability associated with 1.[4]



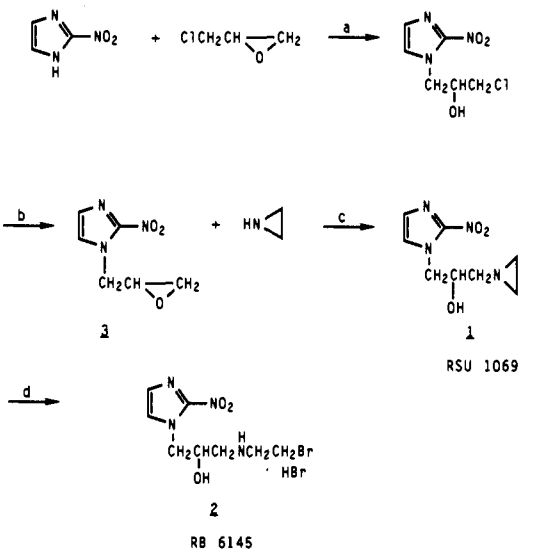
1
RSU 1069



2
RB 6145

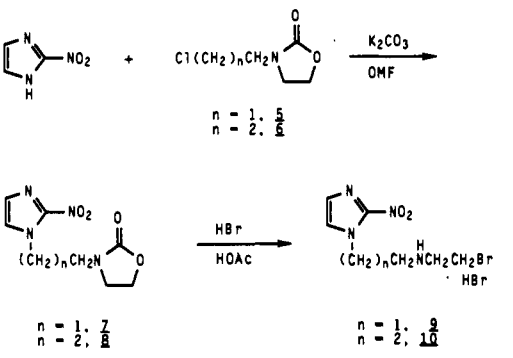
One additional drawback to this compound is its synthesis, which requires the use of the highly toxic ethylenimine. In a search for a less toxic analogue, Adams et al.[5] discovered a series of (β-haloethyl)amino analogues derived from 1. The most potent member of the series was α-[[(2-bromoethyl)amino]methyl]-2-nitro-1*H*-imidazole-1-ethanol (2, RB 6145). Preclinical data indicated that 2 was less toxic than 1, but equally active as a radiosensitizer,[6] thereby warranting its clinical evaluation. However, 2 was originally synthesized from 1 (Scheme I), and therefore it had the same synthetic difficulties as those described for 1. For 2 to be a viable clinical candidate, a new synthesis was needed that avoided the difficulties previously reported. Herein, we have described an alternative synthesis

**Scheme I**[a]



[a] (a) $K_2CO_3$/EtOH, (b) 10% NaOH, (c) 2.1 equiv of ethylenimine in methanol, (d) HBr/acetone.

**Scheme II**



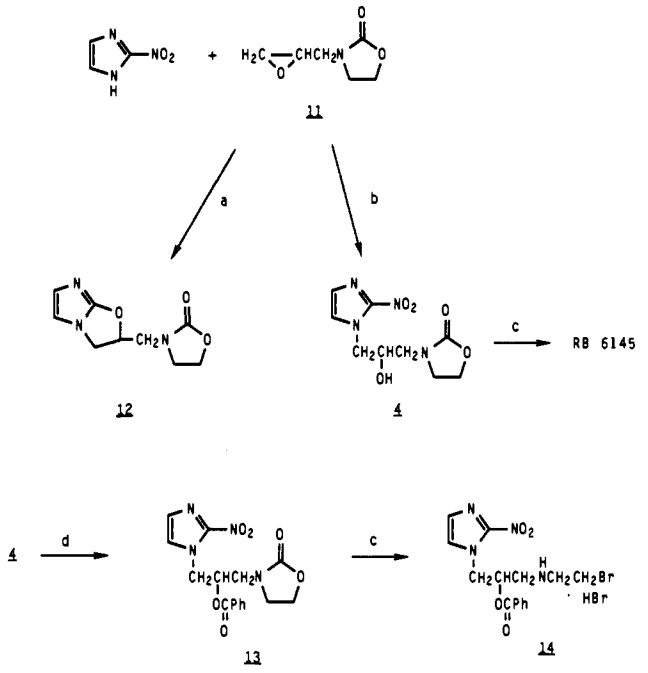
of 2 that does not proceed through 1 and avoids the use of ethylenimine. During the course of this work, we have also determined that 2 can be converted cleanly to 1 in situ.

Our approach centered on finding an "aziridine equivalent". A review of the literature indicated that 2-oxazolidinone had been used as a latent aziridine equivalent.[7] Also, Piper[8] described the reaction of 2-oxazolidinones with HBr in acetic acid to provide (β-bromoethyl)amino compounds. Therefore, if the 2-nitroimidazole

(1) Adams, G. E.; Ahmed, I.; Sheldon, P. W.; Stratford, I. J. *Br. J. Cancer* **1984**, *49*, 571.
(2) Stratford, I. J.; O'Neill, P.; Sheldon, P. W.; Silver, A. J.; Walling, J. M.; Adams, G. E. *Biochem. Pharmacol.* **1986**, *35*, 105, and references cited therein.
(3) Horwich, A.; Holiday, S. B.; Deacon, J. M.; Peckham, M. A. *Br. J. Radiology* **1986**, *59*, 1238.
(4) 1 decomposes rapidly upon storage at room temperature to an unidentified polymeric material. Samples have been stored at 0 °C over sodium hydroxide for short periods.
(5) Jenkins, T. C.; Stratford, I. J.; Adams, G. E.; Fielden, E. M.; Walling, J. M.; O'Neill, P.; Naylor, M.; Suto, M. J.; Chemical Modifiers of Cancer Treatment Meeting, 1988, Abstract #2-13, Paris, France.
(6) Jenkins, T. C.; Naylor, M. A.; O'Neill, P.; Threadgill, M. M.; Cole, S.; Stratford, I. J.; Adams, G. E.; Fielden, E. M.; Stier, M. A.; Suto, M. J. *J. Med. Chem.* **1990**, *33*, 2603.
(7) Poindexter, G. S. *J. Heterocycl. Chem.* **1983**, *20*, 1431.
(8) Piper, J. R.; Elliott, R. D.; Stringfellow, C. R.; Johnston, J. P. *Chem. Ind.* **1966**, 2010.

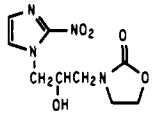
0022-2623/91/1834-1207$02.50/0 

**Scheme III**[a]




[a] (a) $K_2CO_3$/DMF, (b) $Cs_2CO_3$/EtOH, (c) 31% HBr/HOAc, (d) $(PhCO)_2O$/pyridine.

oxazolidinone **4** could be synthesized, it should function as a precursor to **2** and provide an alternative synthesis.



**4**

## Chemistry

We first determined if indeed a 2-oxazolidinone attached to a 2-nitroimidazole could serve as an aziridine precursor. The initial approach (Scheme II) involved the use of the readily available 1-(2-chloroethyl)-2-oxazolidinone[9] (**5**) and 1-(3-chloropropyl)-2-oxazolidinone[10] (**6**). Treatment of 2-nitroimidazole with either **5** or **6** in DMF containing $K_2CO_3$ gave the oxazolidinone derivatives **7** and **8** (35% and 42%). The oxazolidinone was then opened with 31% HBr in acetic acid to provide the desired 2-nitroimidazole ($\beta$-bromoethyl)amino analogues **9** and **10** (54% and 80%). Having established that indeed the 2-oxazolidinone could serve as an aziridine equivalent in the presence of the 2-nitroimidazole, we turned our attention to the synthesis of the desired oxazolidinone **4**.

Our first approach to **4** involved treatment of the 2-nitroimidazole epoxide **3**, with 2-oxazolidinone directly. This was unsuccessful due to decomposition of the 2-oxazolidinone prior to its reaction with the epoxide. Only the starting 1-glycidyl-2-nitroimidazole **3** was recovered.

Our second approach (Scheme III) utilizing the treatment of 2-nitroimidazole with 2 equiv of 1-glycidyl-2-oxazolidinone **11**[11] in ethanol containing $K_2CO_3$ gave compound **4** in a 56% yield. The use of cesium carbonate increased the yield to 85%. If nonprotic solvents such as DMF or toluene were used, the major product obtained was compound **12** (Scheme III) resulting from displacement of the nitro group by the alkoxide formed.[12] In protic solvents such as ethanol this displacement reaction does not occur. Also, use of less than 2 equiv of 1-glycidyl-2-oxazolidinone resulted in incomplete reaction under a variety of conditions. The synthesis of **2** was then completed by treating compound **4** with HBr in acetic acid.

We have also identified conditions for converting **2** to **1**. Treatment of a saline solution of **2** with 2.1 equiv of triethylamine cleanly provides **1** in situ which is biologically equivalent in radiosensitization studies to authentic samples of **1**.[13] The use of other bases as a means of effecting the desired transformation were also investigated. Treatment of **2** with either phosphate buffer or sodium hydroxide gave in addition to **1** a number of unidentified side products that were not observed when triethylamine was used.[14]

In addition to the aforementioned desoxy analogues **9** and **10**, this methodology has allowed us to prepare esters of **2** that were previously not accessible. Thus treatment of **4** with benzoic anhydride in pyridine gave the ester **13**. Ring opening of the oxazolidinone with HBr in acetic acid cleanly provided the ($\beta$-haloethyl)amino ester **14** (Scheme III).

## Conclusion

In conclusion, we have synthesized **2** in 47% yield overall, in two steps from 2-nitroimidazole. The synthesis does not use **1** as an intermediate nor does it use the highly toxic ethylenimine and thus eliminates the remaining hurdle preventing the further clinical development of **2**. We have also shown that **2** can be cleanly converted to **1** in situ. In addition, this work has resulted in the synthesis of a number of desoxy analogues of **2** (compounds **9** and **10**) and provides a means of synthesizing esters of **2**. These compounds have recently been shown to be potent radiosensitizers[15] and are currently undergoing more extensive in vivo evaluations.

## Experimental Section

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Purity was determined by HPLC (Alltech, CN column, 0.1 M $KH_2PO_4$/MeOH, pH 3.4, 313 mm) and by TLC (silica gel 60f 254, Merck). $^1H$ NMR were obtained on a Varian Associates EM-390 (90 MHz), XL-200 (200 MHz), XL-300 (300 MHz) or an IBM WP 100SY (100 MHz) spectrometer using $CDCl_3$ or DMSO-$d_6$ as an internal reference standard. Mass spectra were recorded on a Finnigan 4500 (EI, CI) or a VG 7070 E/HF (EI, CI, FAB) mass spectrometer. Elemental analyses were determined on a CEC Model 440 analyzer. All compounds possessed analytical data consistent with the proposed structures.

**3-[2-(2-Nitro-1*H*-imidazol-1-yl)ethyl]-2-oxazolidinone (7).** A mixture of 2-nitroimidazole (5.0 g, 44.2 mmol) and potassium

(9) Available from Aldrich Chemical Co., Inc., 1001 West Saint Paul Avenue, Milwaukee, WI 53233.

(10) Delaby, R.; Damiens, R.; d'Huyteza, G. *Ann. Pharm. Fr.* **1955**, *13*, 565.

(11) This compound was prepared in a yield of 34% (bp 100–102 °C 0.05 mm) as described by Endo, T.; Numazawa, R.; Okawara, M. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 1101.

(12) The imidoxazole was obtained in anywhere from 19 to 36% yield depending upon conditions. Similar reactions were observed: Prisbe, E. J.; Verheyden, J. P.; Moffat, J. G. *J. Org. Chem.* **1978**, *43*, 4784. Sehgal, R. K.; Agrawal, K. C. *J. Heterocycl. Chem.* **1979**, *16*, 1499.

(13) Unpublished data of J. S. Sebolt-Leopold and Carla M. Arundel-Suto, Department of Biological Chemistry, Parke-Davis Pharmaceutical Research Division.

(14) This transformation was monitored by HPLC using an Alltech CN column, 0.1 M $KH_2PO_4$, (pH 3.4)/MEOH, 9/1, 313 nm, 1 mL/min.

(15) Sebolt-Leopold, J. S.; Arundel-Suto, C. M.; Elliott, W. E.; Leopold, W. R.; Werbel, L. M.; Suto, M. J.; Radiation Research Society, Annual Meeting, New Orleans, LA, 1990, Abstract #CV-14.

carbonate (6.1 g, 44.2 mmol) in DMF (50 mL) was heated at 60 °C for 0.5 h. Then 3-(2-chloroethyl)-2-oxazolidinone[9] (6.6 g, 44.2 mmol) was added and heating was continued for 18 h at 60 °C. The reaction was allowed to cool to room temperature and concentrated under reduced pressure and the resulting solid partitioned between $CHCl_3$ and $H_2O$. The organic layer was dried ($MgSO_4$), filtered, and concentrated to a solid which was recrystallized to provide compound **7** (3.5 g, 35%): mp 103–104 °C; $^1H$ NMR ($CDCl_3$) δ 3.43 (m, 2 H), 3.70 (m, 2 H), 4.14 (m, 2 H), 4.61 (t, 2 H), 7.20 (s, 2 H); MS (M + 1) 227. Anal. ($C_8H_{10}N_4O_4$) C, H, N.

**3-[3-(2-Nitro-1*H*-imidazol-1-yl)propyl]-2-oxazolidinone (8).** Compound **8** was prepared as described above starting with 2-nitroimidazole and 3-(3-chloropropyl)-2-oxazolidinone[10] in a yield of 42%: mp 89–91 °C (recrystallized from ethanol); $^1H$ NMR ($CDCl_3$) δ 2.13 (m, 2 H), 3.38 (m, 2 H), 3.60 (m, 2 H), 3.60 (m, 2 H), 4.41 (q, 4 H), 7.18 (d, 1 H), 7.39 (d, 1 H); MS (M + 1) 241. Anal. ($C_9H_{12}N_4O_4$) C, H, N.

***N*-(2-Bromoethyl)-2-nitro-1*H*-imidazole-1-ethanamine Monohydrobromide (9).** A mixture of **7** (3.5 g, 15.5 mmol) and 31% hydrogen bromide/acetic acid[9] (30 mL) was stirred at 25 °C for 18 h. The dark solution was diluted with ether and methanol and provided compound **9** (3.0 g, 54%): mp 103–104 °C; $^1H$ NMR (DMSO-$d_6$) δ 3.45 (m, 4 H), 3.70 (m, 2 H), 4.66 (t, 2 H), 7.28 (s, 1 H), 7.71 (s, 1 H), 8.90 (bs, 2 H); MS $m/e$ = 263, (M + 2) 265. Anal. ($C_7H_{11}N_4Br_2O_2 \cdot H_2O \cdot HBr$) C, H, N, Br.

***N*-(2-Bromoethyl)-2-nitro-1*H*-imidazole-1-propanamine Monohydrobromide (10).** Compound **10** was prepared as described above for compound **9**, starting with **8**, in a yield of 80%: mp 164–168 °C dec (recrystallized from ethanol); $^1H$ NMR (DMSO-$d_6$) δ 2.24 (m, 2 H), 3.00 (m, 2 H), 3.41 (m, 2 H), 3.70 (t, 2 H), 4.48 (t, 2 H), 7.23 (d, 1 H), 7.75 (d, 1 H), 8.70 (bs, 2 H); MS $m/e$ = 277, (M + 2) 279. Anal. ($C_8H_{13}N_4BrO_2 \cdot HBr \cdot 0.5H_2O$) C, H, N, Br.

**3-[2-Hydroxy-3-(2-nitro-1*H*-imidazol-1-yl)propyl]-2-oxazolidinone (4).** A suspension of 2-nitroimidazole (8.8 g, 78 mmol) and cesium carbonate (0.9 g, 2.8 mmol) in absolute ethanol (180 mL) was heated under reflux for 20 min. Then 1-glycidyl-2-oxazolidinone (21.2 g, 160 mmol) was added and the suspension was heated at reflux for 6 h. The mixture was cooled and filtered, and the residue was washed with ethanol to provide compound **4** (16.3 g, 85%): mp 216–218 °C; $^1H$ NMR (DMSO-$d_6$) δ 3.22 (t, 2 H), 3.63 (t, 2 H), 3.99 (m, 1 H), 4.27 (m, 3 H), 4.55 (dd, 1 H), 5.43 (d, 1 H), 7.17 (s, 1 H), 7.62 (s, 1 H); MS $m/e$ = 256. Anal. ($C_9H_{12}N_4O_5$) C, H, N.

**α-[[(2-Bromoethyl)amino]methyl]-2-nitro-1*H*-imidazole-1-ethanol Monohydrobromide (2, RB 6145).** A mixture of **4** (0.5 g, 1.9 mmol) and 31% hydrogen bromide/acetic acid (5 mL) was stirred at room temperature. After 20 min a solution resulted and stirring was continued for 20 h. The reaction was concentrated under reduced pressure and the resulting dark solid was recrystallized from methanol (2×) to provide compound **2** (0.40 g, 54%): mp 159–160 °C dec; $^1H$ NMR (DMSO-$d_6$) δ 3.00 (m, 1 H), 3.29 (m, 1 H), 3.42 (m, 2 H), 3.69 (t, 2 H), 4.25 (m, 1 H), 4.39 (m, 1 H), 4.53 (m, 1 H), 5.97 (bs, 1 H), 7.22 (s, 1 H), 7.66 (s, 1 H), 8.83 (bs, 2 H); MS $m/e$ = 293, (M + 2) 295. Anal. ($C_8H_{13}N_4BrO_3$) C, H, N, Br.

**3-[(2,3-Dihydroimidazol[2,1-*b*]oxazol-2-yl)methyl]-2-oxazolidinone (12).** A mixture of 2-nitroimidazole (3.0 g, 26.5 mmol), potassium carbonate (7.3 g, 52.8 mmol), and 18-crown-6 (0.6 g, 2.7 mmol) in DMF (30 mL) was heated at 60 °C for 3 h. To the resulting solution was added 1-glycidyl-2-oxazolidinone (4.0 g, 27 mmol) and heating was continued at 60 °C for 28 h. TLC indicated that no 2-nitroimidazole remained. The mixture was concentrated under reduced pressure and the residue was dissolved in $CHCl_3$. The solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated to provide 3.8 g of an oil. Chromatography ($SiO_2$, $CHCl_3$/methanol, 98:2) provided **12** (1.8 g, 32%) which was recrystallized from ethyl acetate: mp 140–141.5 °C; $^1H$ NMR ($CDCl_3$) δ 3.63 (m, 4 H), 4.00 (m, 1 H), 4.27 (m, 3 H), 5.30 (m, 1 H), 6.55 (dd, 2 H); MS (M + 1) 210. Anal. ($C_9H_{11}N_3O_3$) C, H, N.

**Conversion of 2 to 1.** To a solution of **2** (3.74 mg, $1 \times 10^{-5}$ mol) in saline (2 mL) was added $Et_3N$ (3 μL, $2.1 \times 10^{-5}$ mol). The solution was stirred at 25 °C and monitored by HPLC (Alltech CN column, 0.1 M $KH_2PO_4$/methanol, 9/1, 313 mm). After 30 min complete conversion to **1** had occurred (identified by co-injection with an authentic sample of **1**). This provided a 5-mmol stock solution of **1**.[13]

**Acknowledgment.** The authors thank Dr. F. MacKellar and Dr. G. McClusky for their analytical support and Mr. W. Turner for his technical assistance and helpful discussions. We would also like to acknowledge our continued collaboration with the Medical Research Council of Great Britain and the British Technology Group.

# Triazolobenzo- and Triazolothienodiazepines as Potent Antagonists of Platelet Activating Factor

Armin Walser,* Thomas Flynn, Carl Mason, Herman Crowley,† Catherine Maresca,† Bob Yaremko,† and Margaret O'Donnell*,†

*Chemistry Research Department and Department of Pharmacology, Roche Research Center, Hoffmann-La Roche, Incorporated, Nutley, New Jersey 07110.* *Received July 25, 1990*

A series of [1,2,4]triazolo[4,3-*a*][1,4]benzodiazepines bearing an ethynyl functionality at the 8-position and the isosteric thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepines were prepared and evaluated as antagonists of platelet activating factor. The effects of substitution were explored in in vitro and in vivo test systems designed to measured PAF-antagonistic activity. Results are discussed and compared with previously published data. Many of the compounds had activity superior to WEB 2086, compound **1**. In general, the thieno analogues exhibited better oral activity than the corresponding benzodiazepines. The duration of activity upon oral administration was modulated by the substitution on the acetylenic side chain. Compounds **71** and **81** were selected for further pharmacological evaluation as a result of their good oral potency and exceptionally long duration of action.

Antagonists of platelet activating factor (PAF) have been discovered by several laboratories among classes of compounds with quite different structures.[1] The triazolothienodiazepines[2] have emerged as one of the more important series of PAF-antagonists, because of their selectivity, potency, and bioavailability, three properties which are essential to assess the clinical utility of a PAF antagonist in allergic and inflammatory diseases.

When we were confronted with the task of preparing compound **1** (WEB 2086)[3] for pharmacological comparison

† Department of Pharmacology.

(1) Cooper, K.; Parry, M. J. In *Annual Report in Medical Chemistry*; Allen, R. C., Ed.; Academic Press, Inc.: New York, 1989, p 81.
(2) Weber, K. H.; Heuer, H. O. *Med. Res. Rev.* **1989**, *9*, 181.

0022-2623/91/1834-1209$02.50/0 