subsequently *tert*-butyloxycarbonylated by the method of Schwyzer.[12] Arg(NO_2) was purchased from Schwarz Bioresearch and *tert*-butyloxycarbonylated.[12] All other Boc-protected amino acid derivatives were obtained from Miles Research Products Division. All *tert*-butyloxycarbonylamino acids were checked for purity by tlc before use. Paper chromatograms were run on Whatman No. 1 paper in the following solvent systems: A, *n*-BuOH–HOAc–H_2O (4:1:1); B, *i*-PrOH–H_2O (2:1); C, *n*-BuOH–HOAc–pyridine–H_2O (15:3:10:12). Chromatograms were developed by ninhydrin, Cl_2–starch–iodide,[13] and Sakaguchi reagents. DMF, Et_3N, and dioxane were distilled prior to use. All other solvents were reagent grade and were used as received.

Synthesis of Peptides. Peptides were synthesized by the solid-phase procedure essentially as described by Stewart and Young.[14] After coupling of the last amino acid on the resin, peptides were cleaved from the resin using liquid HF and subsequently purified by ion-exchange chromatography on IRC-50.[15] Purity of peptides was ascertained by paper chromatography in systems A, B, and C.

Pharmacology. The three peptides were tested for bradykinin-like activity using the cascade technique of Vane.[16] Assays were performed on three smooth muscle tissues (rat fundus strip, rat colon, and rat duodenum) which were superfused with oxygenated Krebs–Henselheit solution at 37°. The three peptides were tested for antagonism of bradykinin activity also using the cascade technique. In each experiment, a subthreshold dose of each peptide was added to a known reference dose of bradykinin.

Acknowledgments. The authors thank Dr. H. O. J. Collier and Mr. P. J. Gardiner of Miles Laboratories, Stoke Poges, Buckinghamshire, England, for the biological assays. We also thank Mr. Gary Studebaker for the amino acid analyses.

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Quinazolines and 1,4-Benzodiazepines. 69.[1] 1-Vinyl-1,4-benzodiazepin-2-ones and 1-Vinylquinazolin-2(1*H*)-ones

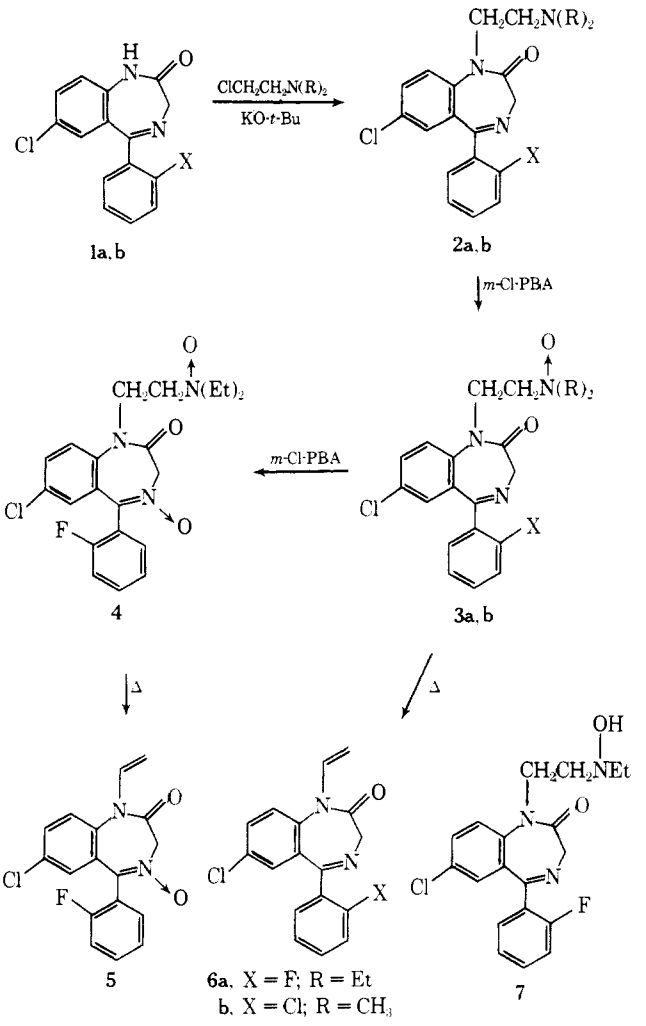
A. Walser* and R. I. Fryer

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110. *Received June 6, 1974*

We have found that *N*-vinylamides are easily accessible from dialkylaminoethylamido *N*-oxides by a Cope elimination[2] and we have utilized this reaction in the preparation of the title compounds.

Oxidation of the benzodiazepine derivatives **2** (Scheme I) with 1 equiv of *m*-chloroperbenzoic acid occurred quite selectively at the more basic nitrogen in the side chain and led to the *N*-oxides **3**. Treatment of **3a** with an additional equivalent of peracid yielded in a much slower reaction the di-*N*-oxide **4**. These amine oxides were very water soluble and had to be extracted from the aqueous phase with a mixture of ethanol and methylene chloride after saturation with sodium chloride. Both **3a** and **3b** crystallized with incorporation of water and were analyzed as hydrates. Because of the thermal lability of these *N*-oxides, high-temperature drying had to be avoided.

Scheme I

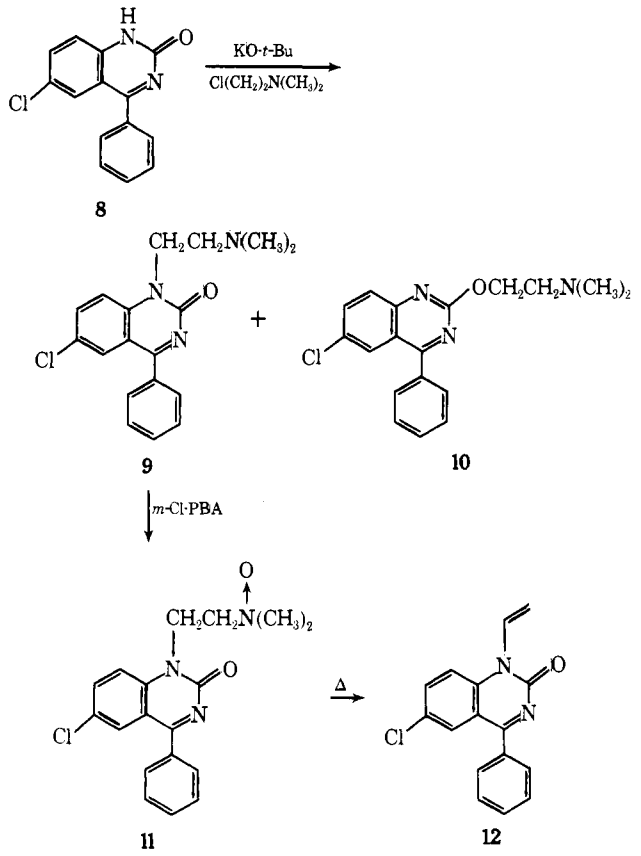


Thermolysis of **3a** in boiling toluene gave a mixture of the 1-vinylbenzodiazepine **6a** and the hydroxylamine **7**. Due to the considerable differences in polarity, these compounds were readily separated by chromatography on silica gel. A similar mixture of vinyl derivative and hydroxylamine was obtained by thermolysis of the di-*N*-oxide **4**. In this case only the vinylbenzodiazepine **5** which crystallized from the mixture was isolated. Treatment of the oxide of the dimethylaminoethyl derivative **3b** under the same reaction conditions gave exclusively the vinyl compound **6b**. The benzodiazepine **2b** was prepared in an analogous manner to that used for the synthesis of **2a**[3] by the alkylation of the 1-potassium salt of **1b**[4] with 2-dimethylaminoethyl chloride in dimethylformamide.

Alkylation of the quinazolinone 8[5] (Scheme II) under comparable conditions led to a mixture of both the N-alkylated and the known[6] O-alkylated derivatives, compounds

9 and 10, respectively. These compounds were separated by fractional crystallization. Oxidation of 9 with *m*-chloroperbenzoic acid again produced the hydrophilic *N*-oxide, compound 11, which on heating in toluene yielded the 1-vinylquinazolinone 12.

Scheme II



8 9 10 11 12

Biological Activity. All of the compounds described were screened for the usual CNS effects of benzodiazepines according to previously described procedures.[3,7] The 24-hr preliminary toxicity and the results of the antipentylenetetrazole test are given in Table I. The vinyl derivatives **6a** and **6b** showed greater activity than diazepam. The 4-oxides **4** and **5** were considerably less active than their corresponding 4-desoxy derivatives (**3a** and **6a**, respectively). The hydroxylamine **7** and the *N*-oxide **3a** were comparable to flurazepam while the dimethylaminoethyl compounds **2b** and **3b** had an activity in the range of chlordiazepoxide. The quinazolines **9–12** were found to be inactive at the dose tested (up to 400 mg/kg po).

Experimental Section

Melting points were determined in a capillary melting point apparatus. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer. Nmr spectra were recorded with a Varian T-60 instrument with TMS as internal standard. Ir spectra were determined on a Beckman IR-9 spectrometer. Silica gel Merck (70–325 mesh) was used for chromatography and anhydrous sodium sulfate for drying.

7-Chloro-5-(2-chlorophenyl)-1-(2-dimethylaminoethyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (2b). Potassium *tert*-butoxide, 8.2 g (0.072 mol), was added to a solution of 15 g (0.05 mol) of 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**1b**)[4] in 100 ml of DMF. After stirring for 30 min at 0° a solution of 2-dimethylaminoethyl chloride in 25 ml of C_6H_6 [liberated with concentrated NaOH from 14.3 g (0.1 mol) of hydrochloride] was added. The mixture was stirred for 30 min at room temperature, then heated to reflux for another 30 min, and poured into ice–H_2O. The precipitated material was collected, washed with H_2O, and dissolved in CH_2Cl_2. The solution was dried and evaporated. Crystallization of the residue from Et_2O yielded 14 g (76%) of product with mp 175–177°. For analysis it was recrystallized from CH_2Cl_2–Et_2O–hexane: mp 178–180°. *Anal.* ($C_{19}H_{19}Cl_2N_3O$) C, H, N.

Table I

Compd	24-hr toxicity (mice), LD_{50}, mg/kg po	Antipentylenetetrazole (mice), ED_{50}, mg/kg po
Diazepam		1.4
Chlordiazepoxide		8
Flurazepam		1.6
2b	>1000	7
3a	>1000	1.1
3b	>1000	10.6
4	>1000	28
5	>1000	7.7
6a	>1000	0.36
6b	>1000	0.67
7	>1000	1.4

7-Chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one ω-Oxide Hydrate (3a). *m*-Chloroperbenzoic acid, 8.6 g (0.05 mol), was added at 10° to a solution of 7-chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**2a**)[3] [liberated from 23 g (0.05 mol) of dihydrochloride] in 200 ml of CH_2Cl_2. The mixture was stirred for 10 min while the temperature was allowed to reach 18°. The solution was extracted with two 50-ml portions of 3 *N* HCl. The extracts were washed with Et_2O and were made alkaline by addition of solid Na_2CO_3. After extraction with Et_2O to remove unreacted starting material, the solution was saturated with NaCl and the product was extracted with five 100-ml portions of CH_2Cl_2 containing 10% (v/v) of EtOH. The combined extracts were dried and evaporated. Crystallization of the residue from EtOAc yielded 13.5 g of product with mp 90–95°. A second crop of 2 g [total yield 15.5 g (71%)] was obtained from the mother liquor. For analysis it was recrystallized from EtOAc and dried under high vacuum at room temperature: mp 90–95°; nmr ($CDCl_3$) δ 1.22 (t, 3, J = 6.5 Hz, CH_2CH_3), 1.3 (t, 3, J = 6.5 Hz, CH_2CH_3), 2.9–3.5 (m, 8.5, NCH_2 + H_2O), 3.76 (d, 1) and 4.81 (d, 1) (AB system, J = 11 Hz, C_3-**H**), 4.51 (m, 2, NCH_2), 6.8–7.8 ppm (m, 7, arom H). *Anal.* ($C_{21}H_{23}ClFN_3O_2 \cdot 1.75H_2O$) C, H, N, H_2O.

7-Chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4,ω-Dioxide (4). A mixture of 25 g (0.14 mol) of *m*-chloroperbenzoic acid, 200 ml of CH_2Cl_2, and 7-chloro-1-(2-diethylaminoethyl)-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**2a**),[3] liberated from 23 g (0.05 mol) of its dihydrochloride, was stirred at room temperature for 16 hr. The product was isolated as described in the previous example. Crystallization of the extracted material from CH_2Cl_2–EtOAc yielded 11 g (50%) of product with mp 129–135°. The analytical sample was recrystallized from CH_2Cl_2–EtOAc–Et_2O and had mp 141–142°: nmr ($CDCl_3$) δ 1.23 (t, 3, J = 7 Hz, $-CH_3$), 1.33 (t, 3, J = 7 Hz, $-CH_3$), 2.8–3.6 (m, 6, NCH_2–), 4.66 (s, 2, C_3-H), 4.63 (m, 2, NCH_2), 6.9–8.0 ppm (m, 7, arom H). *Anal.* ($C_{21}H_{23}ClFN_3O_3$) C, **H**, N.

7-Chloro-5-(2-chlorophenyl)-1-(2-dimethylaminoethyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one ω-Oxide Hydrate (3b). *m*-Chloroperbenzoic acid, 6.8 g (0.04 mol), was added to a solution of 13.2 g (0.035 mol) of **2b** in 200 ml of CH_2Cl_2 cooled to 10°. After stirring for 15 min without cooling the reaction mixture was worked up as described above. Crystallization of the extracted product from CH_2Cl_2–Et_2O yielded 9 g (63%) with mp 131–133°. The analytical sample was recrystallized from the same solvents and had the same melting point: nmr ($CDCl_3$) δ 2.96 (s, 2, H_2O), 3.24 (s, 3, NCH_3), 3.30 (s, 3, NCH_3), 3.85 (d, 1) and 4.86 (d, 1) (AB system, J = 10.5 Hz, C_3-H), 4.6 (m, 2, NCH_2), 7.05 (d, 1, J = 2.5 Hz, C_6-**H**), 7.3–8.0 ppm (m, 6, arom H). *Anal.* ($C_{19}H_{19}Cl_2N_3O_2 \cdot H_2O$) C, H, N, H_2O.

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-1-vinyl-2*H*-1,4-benzodiazepin-2-one (6a) and 7-Chloro-5-(2-fluorophenyl)-1,3-di-

hydro-1-[2-(*N*-ethyl-*N*-hydroxy)aminoethyl]-2*H*-1,4-benzodiazepin-2-one (7). A mixture of 30 g of **3a** in 150 ml of toluene was heated to reflux for 15 min. The solvent was evaporated under reduced pressure and the residue was chromatographed over 600 g of silica gel. Elution with a 1:1 mixture of EtOAc and CH_2Cl_2 yielded 12.5 g (57.5%) of the vinyl derivative **6a**, which crystallized from hexane–Et_2O: mp 89–90°; nmr ($CDCl_3$) δ 3.94 (d, 1) and 4.89 (d, 1) (AB system, J = 11 Hz, C_3-H), 4.7 (m, 2, $=CH_2$), 6.8–8.0 ppm (m, 8, –CH= and arom H). *Anal.* ($C_{17}H_{12}ClFN_2O$) C, H, N.

The second more polar product was eluted with EtOAc. Crystallization of the combined clean fractions from Et_2O yielded 4 g (15.5%) of the hydroxylamine **7** with mp 132–133°: nmr ($CDCl_3$) δ 0.83 (t, 3, J = 7 Hz, CH_3), 2.52 (q, 2, J = 7 Hz, $-CH_2CH_3$), 2.66 [m, 2, $-N(OH)CH_2-$], 3.76 (d, 1) and 4.83 (d, 1) (AB system, J = 10.5 Hz, C_3-H), *ca.* 3.7 (m, 1) and *ca.* 4.67 (m, 1) (ABX_2 system, $-NCH_2CH_2-$), 5.5 (br s, 1, OH), 6.8–7.8 ppm (m, 7, arom H). *Anal.* ($C_{19}H_{19}ClFN_3O_2$) C, H, N.

7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-1-vinyl-2*H*-1,4-benzodiazepin-2-one (6b). A mixture of 8 g of **3b** and 150 ml of toluene was heated to reflux for 15 min. The solvent was evaporated under reduced pressure and the residue was crystallized from ether to yield 6 g (92%) of product with mp 106–108°. The analytical sample was purified by chromatography over silica gel using 10% EtOAc in CH_2Cl_2 and was crystallized from hexane: mp 114–115°; nmr ($CDCl_3$) δ 3.83 (d, 1) and 4.86 (d, 1) (AB system, J = 10.5 Hz, C_3-H), 4.73 (m, 2, $=CH_2$), 7.0–7.8 ppm (m, 8, –CH=, arom H). *Anal.* ($C_{17}H_{12}Cl_2N_2O$) C, H, N.

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-1-vinyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (5). A mixture of 10 g of 4 and 100 ml of toluene was heated to reflux for 15 min. The residue obtained after evaporation was chromatographed over 200 g of silica gel. Compound **5** was eluted with EtOAc and was crystallized from CH_2Cl_2–Et_2O: mp 183–184°; yield 4 g (50%). *Anal.* ($C_{17}H_{13}ClFN_2O_2$) C, H, N.

6-Chloro-1-(2-dimethylaminoethyl)-4-phenylquinazolin-2(1*H*)-one (9) and 6-Chloro-2-(2-dimethylaminoethoxy)-4-phenylquinazoline (10). Potassium *tert*-butoxide, 13 g (0.115 mol), was added to a solution of 25.6 g (0.1 mol) of 6-chloro-4-phenylquinazolin-2(1*H*)-one[5] in 150 ml of DMF. After stirring in an ice bath for 1 hr, a solution of 2-dimethylaminoethyl chloride, liberated from 21 g (0.145 mol) of hydrochloride, in 50 ml of C_6H_6 was added. The reaction mixture was stirred and refluxed for 2 hr, diluted with H_2O, and extracted with C_6H_6. The extracts were washed with H_2O, dried, and evaporated. Crystallization of the residue from CH_2Cl_2–petroleum ether and recrystallization from the same solvents yielded 10 g (30.5%) of compound **9** with mp 165–166°. *Anal.* ($C_{18}H_{18}ClN_3O$) C, H, N. Fractional crystallization of the mother liquor yielded 8 g (24.5%) of the known 6-chloro-2-(2-dimethylaminoethoxy)-4-phenylquinazoline[6] with mp 98–100°.

6-Chloro-1-(2-dimethylaminoethyl)-4-phenylquinazolin-2(1*H*)-one *N*-ω-Oxide Hydrate (11). A solution of 9.8 g (0.03 mol) of **9** and 5.5 g (0.032 mol) of *m*-chloroperbenzoic acid in 200 ml of CH_2Cl_2 was stirred at room temperature for 20 min. The reaction mixture was worked up as described in previous examples, and the product was crystallized from CH_2Cl_2–Et_2O to yield 8 g (75%) of *N*-oxide hydrate with mp 170–171° dec: nmr ($CDCl_3$) δ 3.33 [s, 6, $N(CH_3)_2$], 3.68 [t, 2, J = 6.5 Hz, $-N(\rightarrow O)CH_2-$], 3.03 (t, 2, J = 6.5 Hz, NCH_2-), 7.5–8.5 ppm (m, 8, arom H). *Anal.* ($C_{18}H_{18}ClN_3O_2$) C, H, N, H_2O.

6-Chloro-4-phenyl-1-vinylquinazolin-2(1*H*)-one (12). A mixture of 6 g of 11 and 200 ml of toluene was refluxed for 1.5 hr. The solvent was removed under reduced pressure and the residue was crystallized from CH_2Cl_2–petroleum ether to yield 3.7 g (78%) of product with mp 186–187°. The analytical sample was recrystallized from Et_2O: nmr ($CDCl_3$) δ 5.8 (m, 2, $=CH_2$), 6.86 (q, 1, J_{AX} = 16 Hz, J_{BX} = 8 Hz, –CH=), 7.4–8.0 ppm (m, 8, arom H); ir ($CHCl_3$) 1670 cm^{-1} (CO). *Anal.* ($C_{16}H_{11}ClN_2O$) C, H, N.

Acknowledgment. The authors wish to thank the following members of our Physical Chemistry Department under the direction of Dr. R. Scott: Dr. F. Scheidl for the microanalyes, Mr. S. Traiman for the ir spectra, and Dr. V. Toome for the uv spectra. We thank Mr. C. Mason for technical assistance and we are obliged to Dr. L. O. Randall and Dr. W. Pool and their respective staff for the pharmacological data.

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α-(Ureidomethylene)lactones and Derived 5-(Hydroxyalkyl)uracils

George H. Denny* and Malcolm A. Ryder

Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, New Jersey 07065. *Received May 28, 1974*

Antitumor activity has been observed for a number of α,β-unsaturated lactone derivatives.[1] Lactones bearing an α-(ureidomethylene) substituent are readily converted to 5-substituted uracils, a class of compounds that includes several important antitumor agents.[2]

We now wish to report the preparation and testing of the α-(ureidomethylene)lactones Ia–d and the derived 5-(hydroxyalkyl)uracils IIa–d. The compounds were prepared from the appropriate simple lactones *via* the sodio-α-(hydroxymethylene) derivatives, which were then combined with urea under acidic conditions to give compounds Ia–d. Isomerization with aqueous alkali, followed by acidification, gave the corresponding 5-substituted uracil derivatives IIa–d. The procedures were modifications of those previously described[3,4] for the preparation of 5-(2-hydroxyethyl)uracil.

Spectral data (uv, ir, and nmr) were generally consistent with the proposed structures, with the exception that integration of the nmr spectrum of compound IIa did not show the presence of the aliphatic hydroxyl proton. As a structural probe the DMSO-d_6 solution of this compound was treated with trifluoroacetic anhydride. This resulted in the appearance of a new methine sextet centered at δ 4.85 ppm, in addition to the original sextet which was still visible in the spectrum at its original position (δ 3.78 ppm). This demonstrated that partial esterification had taken place causing a downfield shift of the methine protons adjacent to the ester function, thereby substantiating structure IIa. Molecular weight determination by mass spectrometry provided further confirmation in this instance.

The compounds were screened by the Drug Research and Development Branch, National Cancer Institute, against L1210 lymphoid leukemia in mice at dose levels between 100 and 400 mg/kg. Each compound was found to be inactive in this test system.

Experimental Section

Melting points were obtained on a Thomas-Hoover Unimelt using open capillary tubes and are uncorrected. Elemental analyses (C, H, and N) obtained for the compounds described in Tables I and II were within ±0.3% of the theoretical values. The ir spectra were obtained on a Perkin-Elmer Model 137 recording