tained a further 0.5 g for a total yield of 91% of 37. A sample recrystallized from MeOH-Et_2O melted at 139–140°. *Anal.* ($C_{17}H_{16}Br_2OS$).

Conversion of Sulfonium Salt 37 to the Corresponding Tetrahydrofurfuryl Bromide (38). The sulfonium salt **37**, 6.6 g (15 mmol), was heated at 160° (12 mm) for 30 min and then distilled at 158–162° (0.02 mm) to yield 4.35 g (81%) of the solid product **38**, mp 68–71°. *Anal.* ($C_{17}H_{15}BrOS$).

General Procedures for the Preparation of VI. Procedure A. To a stirred and cooled (0–5°) solution of 0.1 mol of γ,δ-unsaturated alcohol and 0.1 mol of pyridine in 100 ml of CCl_4 (or CH_2Cl_2) was added dropwise a solution of 0.1 mol of bromine in 100 ml of CCl_4 during 15 min. The mixture was then washed with water and dilute HCl, dried over Na_2SO_4, and concentrated *in vacuo* to yield **VI** (Table IV).

Procedure B. When procedure A failed to give tetrahydrofurfuryl bromide **VI**, which was easily detected by ir spectra and tlc, cyclization was accomplished by chromatography on alumina (activity 2–3 on the Brockman scale)[13] and slow elution with C_6H_6.

4-Acetoxymethyl-4-phenyltetrahydrofurfuryl Bromide (50). 4-Hydroxymethyl-4-phenyltetrahydrofurfuryl bromide (**49**), 4.34 g (16 mmol), was treated with 2.02 g (20 mmol) of Ac_2O and 1.6 g (20 mmol) of pyridine in 20 ml of C_6H_6. After standing at room temperature for 16 hr the mixture was treated with water, dried (Na_2SO_4), and concentrated *in vacuo* to yield 4.94 g (98%) of **50**. The product distills at 125–130° (0.02 mm). *Anal.* ($C_{14}H_{17}BrO_3$).

Substituted Tetrahydrofurfurylamines II. To a cooled (ice-salt) solution of 50 mmol of tetrahydrofurfuryl bromides **VI** in 50 ml of the solvent indicated in Table I was introduced 15–20 g of methylamine or dimethylamine, respectively, and the mixture was heated in a pressure bomb for 18 hr at 50–55° unless specified otherwise (see Table I). After cooling, it was poured into water and extracted with Et_2O. The ether extract was washed with water and extracted with 1 *N* HCl. The acidic extract was basified with NH_4OH and the free base taken up in C_6H_6. Drying and evaporation of C_6H_6 extracts afforded crude products which were purified by crystallization of suitable salts. Exceptions were compounds **5** and **18** where purification was done by distillation of free bases.

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Amidines. 4.[1] Synthesis of Tricyclic Guanidines Related to 1,2,3,5-Tetrahydroimidazo[2,1-*b*]quinazoline, a New Antihypertensive Agent

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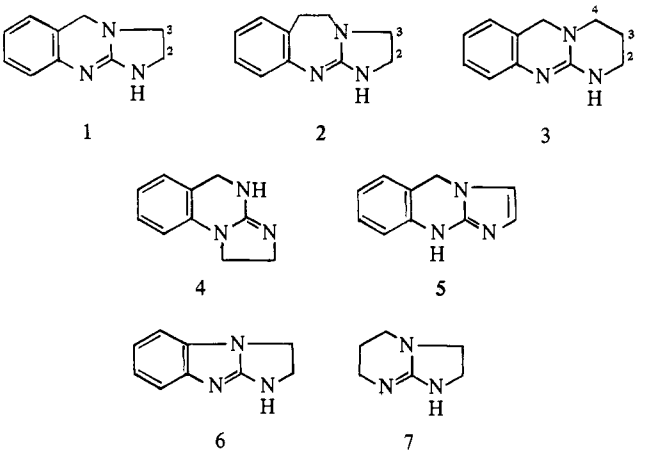
To study the influence of structural modification of 1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (**1**) on antihypertensive activity, a series of tricyclic compounds containing a guanidine moiety was synthesized and evaluated. This series included derivatives of imidazo[2,1-*b*]benzo-1,3-diazepine (**2**), pyrimido[2,1-*b*]quinazoline (**3**), imidazo[1,2-*a*]quinazoline (**4**), imidazo[2,1-*b*]quinazoline (**5**), and imidazo[1,2-*a*]-benzimidazole (**6**). The synthetic routes to the new compounds and assignment of tautomeric structures based on nmr spectral data are discussed. Compounds **3** and **6** showed antihypertensive activity at oral doses of 2 and 10 mg/kg, respectively, in unanesthetized neurogenic hypertensive dogs.

We have recently reported a new antihypertensive agent 1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (**1**) and the effect of some basic structural modifications on its activity.[2,3] The present paper describes the synthesis of related heterocycles **2–7** (Chart I) containing a guanidine moiety and the influence of ring size and electron distribution on antihypertensive activity.

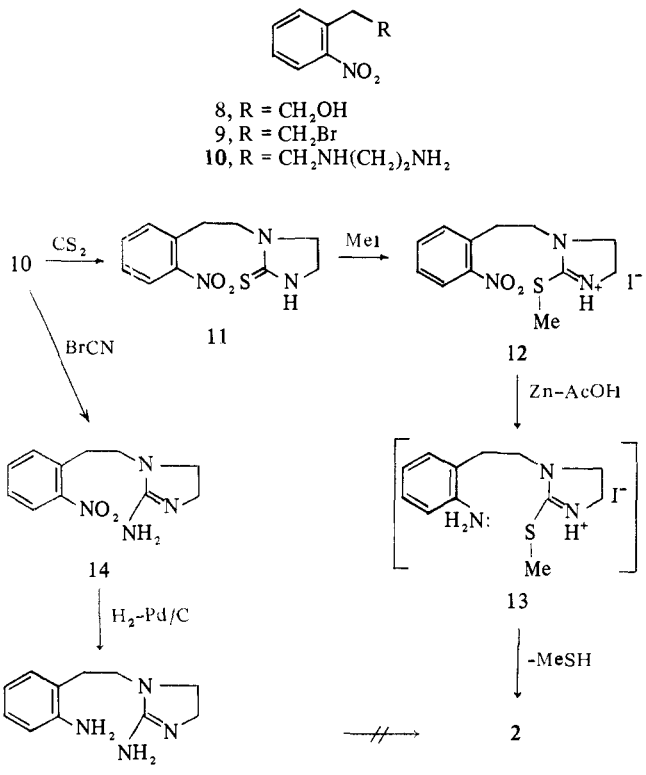
Chart I



Chemistry. The first synthetic approach (Scheme I) to **2** required linking a phenethyl moiety to an imidazoline followed by cyclization to the fused diazepine. The bromide **9**[4] was prepared efficiently *via* reduction of *o*-nitrophenylacetic acid to the alcohol **8**[5] followed by treatment with HBr. The diamine **10** was obtained when **9** was heated with a large excess of ethylenediamine. Treatment of **10** with CS_2 and MeI gave **11** and **12**, respectively. Reduction of the nitro group of **12** with Zn in AcOH solution afforded **2**, presumably *via* **13**. Treatment of the diamine **10** with BrCN gave the imidazoline **14** which was reduced to **15** by catalytic hydrogenation. Attempts to convert **15** to **2** were unsuccessful.

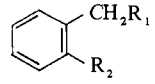
Alternative approaches for the synthesis of **2** were also explored. One involved preparation of the benzo-1,3-diazepine system **21** (Scheme II) capable of cyclization to **2**. The diamine **18**[6] was prepared by reduction of **16** to **17** with BH_3 followed by catalytic hydrogenation. Treatment of **18**

Scheme I



with *N,N'*-carbonyldiimidazole (CDI) gave **19**. Addition of $Et_3O^+BF_4^-$ to **19** followed by displacement with 2-aminoethanol furnished the diazepine **20** having the required side chain. Heating **20** with $SOCl_2$ gave the HCl salt of **21** instead of a cyclization product. Treatment of **21** with base gave a product tentatively assigned structure **22** on the basis of spectral data.†

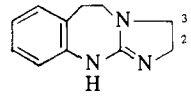
In another approach to **2**, cyclization of **25** prepared *via* **23** and **24** was investigated. However, treatment of **25**



23, $R_1 = CONH(CH_2)_2OH$; $R_2 = NO_2$
24, $R_1 = CONH(CH_2)_2OH$; $R_2 = NH_2$
25, $R_1 = CH_2NH(CH_2)_2OH$; $R_2 = NH_2$

with *N,N'*-carbonyldiimidazole, phosgene, or $ClCO_2Et$ failed to afford a benzodiazepine.

Compound **2** is potentially tautomeric. The assignment of structure **2** as the predominant tautomer rather than **2a** was



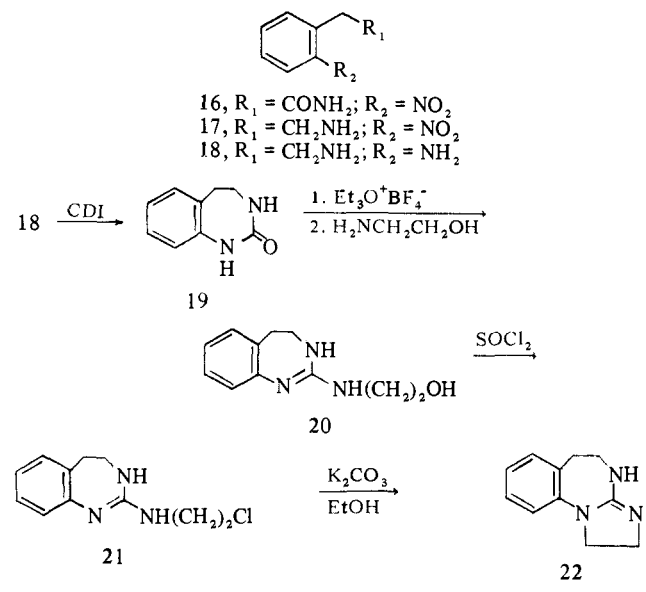
2a

based on nmr analysis analogous to that of **1**.[3] A four-proton singlet at δ 3.52 corresponding to the C-2 and C-3 protons of **2** indicates the absence of an anisotropic effect of the imino bond on the C-2 protons.

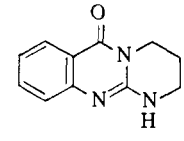
The pyrimido[2,1-*b*]quinazoline **3** was prepared by reduction of **26**[7] with $LiAlH_4$. Assignment of the location of the imino bond to the predominant tautomer **3** was based on nmr analysis. The C-2 and C-4 proton signals appeared

†Mass spectrum showed the correct molecular ion and major fragments similar to those of **2** with some differences in relative intensities; structure **2** was excluded by the nmr spectrum which lacked a four-proton singlet at δ 3.52 as observed for **2**; uv absorption is different from that of **2**.

Scheme II



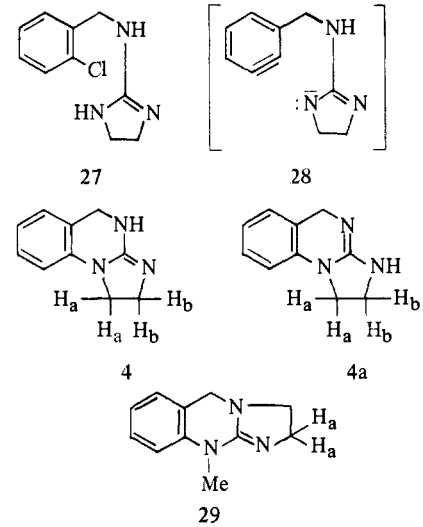
as a pair of triplets‡ with only a small difference in chemical shifts (Δδ = 0.13). If the imino bond were in the tautomeric position, the C-2 proton signal would appear at lower field than the observed signals and a larger Δδ would be expected.



26

The imidazo[1,2-*a*]quinazoline **4** was synthesized by a route involving intramolecular nucleophilic addition of an anion to a benzyne intermediate[8] (Chart II). Treatment of **27** with $NaNH_2$ in liquid NH_3 gave **4** presumably *via* **28**.

Chart II

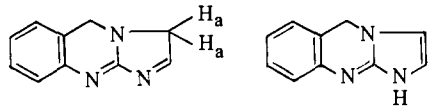


The nmr spectrum supported structure **4** rather than **4a** as the predominant tautomer. It showed a four-proton singlet at δ 3.67 corresponding to the accidentally equivalent H_a and H_b signals of **4**. In both **4** and **4a** the H_a protons (influenced by the deshielding effect of the aromatic ring) would be expected to have similar chemical shifts. The H_b

‡Chemical shifts of the triplets for the C-2 and C-4 protons could not be readily assigned.

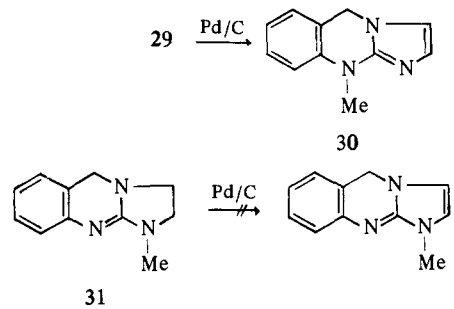
protons of **4** (deshielded by the anisotropy of the imino bond) should have a chemical shift similar to that of the H_b protons of **29**,[3] *i.e.*, δ 3.79. The chemical shift of the H_b protons (less influenced by the imino bond) of **4a**, however, would be similar to that of the C-2 protons of **1**, *i.e.*, δ 3.34. In addition, multiplicity of H_a and H_b signals would be expected for **4a** (for which accidental equivalence is unlikely).

Catalytic dehydrogenation of **1** with Pd/C gave a dehydro compound **5** which could also exist in two other possible tautomeric forms such as **5a** and **5b**. The absence of an H_a



5a 5b

signal in the nmr spectrum excludes structure **5a**. To provide a model system to distinguish structure **5** from **5b**, compounds **29** and **31**[3] were treated with Pd/C under similar conditions. Only **29** gave a dehydro product **30**. The striking similarity between **30** and the dehydrogenation product of **1** in their respective uv and nmr spectral properties supports structure **5** as the predominant tautomer.



Compounds **6**[9] and **7**[10] were prepared by known procedures.

Antihypertensive Activity. The antihypertensive activity of compounds **2–7** was evaluated in unanesthetized neurogenic hypertensive dogs.[11] The systolic and diastolic blood pressures were measured before and after (3 hr) oral administration of the compounds; the mean arterial blood pressures were calculated and evaluated. The minimum effective doses§ for **1** (HCl), **3** (HBr), and **6** (HCl) are 2.5, 2, and 10 mg/kg, respectively. Compounds **2** (picrate), **4** (furmarate), **5** (HCl), and **7** (picrate) did not show significant activity at doses up to 20, 18, 10, and 30 mg/kg, respectively. Testing in metacorticoid hypertensive rats[13] indicated that **3** was less potent than **1** (80 *vs.* 5 mg/kg) in lowering systolic pressure.

Structure–Activity Discussion. A correlation between molecular conformation of **1** and antihypertensive activity was described in our previous paper.[3] The present ring-size modifications of **1** not only altered the molecular conformation but also affected the basicity of the resulting compounds: **3** (pK_a = 10.51) > **2** (pK_a = 9.46) > **1** (pK_a = 8.29) > **6** (pK_a = 5.68).# Since only **2** in this group of compounds of widely differing basicities failed to show antihypertensive activity, perhaps marked conformational differences between **2** and **1** influence the ability of the molecule to interact with the receptor site.

The lack of activity of the angular isomer **4** and the bicyclic compound **7** suggests that a linearly fused tricyclic system is required for activity. In view of the similarities of stereochemistry and basicity (pK_a = 8.29) of **5** and **1**, the lack of activity of **5** may be due to its inability to interact with the receptor site by hydrogen bonding as suggested in our previous paper.[3]

Experimental Section**

N-(*o*-**Nitrophenethyl**)**ethylenediamine** (**10**). **(a) 2-(*o*-Nitrophenyl)ethanol** (**8**). A solution of 40.0 g (0.22 mol) of *o*-nitrophenylacetic acid in 250 ml of anhydrous THF was added to a solution of BH_3 in 400 ml of THF (0.4 mol) at 0–5°. The mixture was stirred at 25° for 18 hr. The excess BH_3 was decomposed with H_2O and the mixture evaporated to dryness. The residue was extracted with Et_2O. Evaporation of the Et_2O gave 35.2 g of **8** (oil). It was shown by tlc to be homogeneous. The ir and nmr spectra were consistent with the structure.

(b) *o*-**Nitrophenethyl Bromide** (**9**). A vigorously stirred suspension of 35.0 g of **8** in 350 ml of 48% aqueous HBr was heated to 105–110° for 3 hr. After cooling, the mixture was extracted with C_6H_6 and the extract washed with H_2O until the washings became neutral. Evaporation of the solvent gave 45.0 g of an orange liquid. Distillation at 100–105° (0.1 mm) gave **10** as a yellow semisolid [lit.[4] bp 127–130° (1.0 mm)].

(c) *N*-(*o*-**Nitrophenethyl**)**ethylenediamine** (**10**). A solution of 5.0 g (0.022 mol) of **9** in 10 ml of C_6H_6 was added dropwise to 13.1 g (0.22 mol) of ethylenediamine refluxing under N_2. After 3 hr of reflux, the solvent and excess ethylenediamine were evaporated and the residue was dissolved in H_2O. The aqueous solution was basified with NaOH solution and extracted with $CHCl_3$. Evaporation of the solvent gave 2.0 g of a red oil which on treatment with fumaric acid in EtOH gave the fumarate of **10**, mp 207–209° (recrystallized from H_2O). *Anal.* ($C_{10}H_{15}N_3O \cdot C_4H_4O_4$) C, H, N.

1-(*o*-**Nitrophenethyl**)-**2-imidazolidinethione** (**11**). To a stirred solution of 3.0 g (0.014 mol) of **10** in 10 ml of EtOH and 5 ml of H_2O was added dropwise 1.37 g (0.018 mol) of CS_2. The mixture was refluxed for 48 hr, cooled, and filtered to give a brown solid. Recrystallization from $CHCl_3$–hexane gave 2.0 g of **11**, mp 177–180°. *Anal.* ($C_{11}H_{13}N_3O_2S$) C, H, N.

1-(*o*-**Nitrophenethyl**)-**2-methylmercapto-2-imidazoline** (**12**). A stirred mixture of 1.0 g (4.45 mmol) of **11** and 0.92 g (6.8 mmol) of MeI in 10 ml of MeOH was refluxed for 12 hr. Evaporation of the solvent gave a solid. Recrystallization from EtOH afforded 0.9 g of **12**·HI, mp 157–159°. *Anal.* ($C_{12}H_{15}N_3O_2S \cdot HI$) C, H, N.

2,3,5,6-Tetrahydro-1*H*-imidazo[2,1-*b*]benzo-1,3-diazepine (**2**). A stirred mixture of 9.0 g (0.023 mol) of **12** and 13.5 g of Zn dust in 340 ml of 50% aqueous AcOH solution was heated to 90° for 3.5 hr. The hot mixture was filtered and the filtrate concentrated. The residue was taken into H_2O, basified (40% NaOH solution), and shaken with CH_2Cl_2. The inorganic precipitate was removed by filtration of the mixture. The CH_2Cl_2 layer was washed with H_2O, dried, and evaporated to a solid. Recrystallization from C_6H_6–hexane gave 2.1 g (40%) of **2**: mp 200–202°; nmr ($CDCl_3$) δ 2.98 (m, 2 H), 3.45 (m, 2 H), 3.52 (s, 4 H); uv $\lambda_{max}^{EtOH\ (NaOH)}$ (log ε) 294 mμ (4.97); mass spectrum *m/e* 187 (M^+), 186, 172, 159, 145, 132, 117, 104, 89. *Anal.* ($C_{11}H_{13}N_3$) C, H, N. The picrate salt had mp 210–212°.

§ The control mean blood pressure (MBP) and its 95% confidence limits of *each* trained dog were determined from six readings over a period of several weeks prior to dosing. The test compounds were generally dosed at 1, 2.5, 5, 10, 20, and 30 mg/kg to two or three dogs in 2 consecutive days. The systolic and diastolic blood pressures were determined after dosing and were converted to MPB's. The MPB's thus obtained were compared with the control MBP's of the same dog. The lowest dose of a compound for which there was a statistically significant difference ($P \leq 0.05$) between control MBP and MBP after dosing was referred to as the minimum effective dose. The statistical method for calculation of the confidence limits is based on a modification of the t test.[12]

#pK_a determinations were performed by Mr. W. Hamill of our laboratories on a Sargent Titrimeter Model-D. Potentiometric titration of the compounds was carried out in methylcellosolve–H_2O (4:1) solution.

**Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by the Analytical Department of Smith Kline and French Laboratories. Mass spectra were obtained on a Hitachi Perkin-Elmer RMN-6E spectrometer. Nmr spectra were obtained on a Varian T-60 instrument (Me_4Si). Uv spectra were obtained on a Cary-II instrument. Where analyses are indicated only by symbols of the elements, analytical results for those elements were within ±0.4% of the theoretical values.

1-(*o*-Nitrophenethyl)-2-amino-2-imidazoline (14). A solution of 1.0 g (4.8 mmol) of **10** in 20 ml of anhydrous C_6H_6 at 15–25° was treated dropwise with a solution of 0.55 g (4.8 mmol) of BrCN in 10 ml of C_6H_6. The mixture was stirred at 25° for 30 min and refluxed for 30 min. On cooling, a solid precipitated. Recrystallization from 2-PrOH gave 1.3 g of **14**·HBr, mp 156–158°. *Anal.* ($C_{11}H_{14}N_4O_2$·HBr) C, H, N.

1-(*o*-Aminophenethyl)-2-amino-2-imidazoline (15). A solution of 1.0 g of **14** in 80 ml of EtOH was hydrogenated over 10% Pd/C at 52 psi. When the uptake of H_2 ceased, the catalyst was removed by filtration and the solvent evaporated to give an oil, which solidified upon trituration with 2-PrOH. Recrystallization from EtOH–Et_2O gave 0.7 g of **15**·HBr, mp 168–171°. *Anal.* ($C_{11}H_{16}N_4$·HBr) C, H, N.

o-Aminophenethylamine (18). (a) *o*-Nitrophenethylamine (17).[14] A suspension of 30.0 g (0.167 mol) of **16**[6] in 300 ml of anhydrous dioxane was added to a stirred solution of BH_3 in 500 ml of THF (0.5 mol) at 0–5° under N_2. The mixture was refluxed for 72 hr. The excess BH_3 was decomposed with MeOH and the solvent evaporated. The residual oil was refluxed in MeOH for 1 hr, and the insoluble material was filtered. Evaporation of the solvent gave 17 as an oil with no amide carbonyl absorption in the ir spectrum.

(b) *o*-Aminophenethylamine (18). Crude 17 from above was dissolved in EtOH and hydrogenated over 10% Pd/C at 45 psi for 4 hr. The catalyst was filtered and evaporation of the solvent gave a brown oil, which was converted to a fumarate salt in EtOH. Recrystallization from MeOH gave 20 g of 18 (fumarate), mp 219–220°. *Anal.* ($C_8H_{12}N_2$·$C_4H_4O_4$) C, H, N.

1,3,4,5-Tetrahydro-2*H*-benzo-1,3-diazepin-2-one (19). A mixture of 0.3 g (2.2 mmol) of 18 and 0.36 g (2.2 mmol) of *N,N'*-carbonyldiimidazole in 10 ml of anhydrous THF was stirred for 12 hr at 25° and refluxed for 2 hr. The insoluble material was filtered and the filtrate evaporated to an oil which was dissolved in $CHCl_3$ and washed with dilute HCl. Evaporation of the solvent gave 0.14 g of a solid. Recrystallization from $CHCl_3$–hexane gave 19, mp 169–171°. *Anal.* ($C_9H_{10}N_2O$) C, H, N.

4,5-Dihydro-2-[(2-hydroxyethyl)amino]-3*H*-benzo-1,3-diazepine (20). (a) 2-Ethoxy-4,5-dihydro-3*H*-benzo-1,3-diazepine. A mixture of 3.5 g (0.022 mol) of 19 and 5.6 g (0.028 mol) of $Et_3O^+BF_4^-$ in 150 ml of anhydrous CH_2Cl_2 was stirred at 25° for 12 hr. The solvent was evaporated and the gummy residue digested in boiling Et_2O. The solid material (6.0 g) was filtered and recrystallized from CH_2Cl_2–Et_2O to give the titled product, mp 118–121°. *Anal.* ($C_{11}H_{15}N_2O$·BF_4) C, H, N.

(b) A mixture of 3.0 g (0.011 mol) of the above adduct and 5 ml (0.082 mol) of 2-aminoethanol was stirred at 25° for 3 hr and heated to 80° for 45 min. The mixture was poured into H_2O and basified with NaOH solution. Extraction with $CHCl_3$ and evaporation of the solvent gave 0.9 g of **20**. The HCl salt (2-PrOH–Et_2O) had mp 199–200°. *Anal.* ($C_{11}H_{15}N_3O$·HCl) C, H.

2-[(2-Chloroethyl)amino]-4,5-dihydro-3*H*-benzo-1,3-diazepine (21). A mixture of 0.8 g (0.004 mol) of **20** and 1.39 g (0.012 mol) of $SOCl_2$ in 15 ml of $CHCl_3$ was stirred for 12 hr and then refluxed for 90 min. The solvent was evaporated to give 0.6 g of a solid. Recrystallization from 2-PrOH gave **21**·HCl, mp 178–180°. *Anal.* ($C_{11}H_{14}ClN_3$·HCl) C, H, N.

Cyclization of 21 to 22. A solution of 0.10 g (0.38 mmol) of **21** in 15 ml of absolute EtOH was treated with 0.105 g (0.76 mmol) of K_2CO_3. After stirring at 25° for 1 hr the mixture was refluxed for 3 hr. It was filtered and the solvent evaporated. The residue was chromatographed by preparative tlc on a cellulose plate (MeOH). A product (tentatively assigned structure **22**†) was isolated, having an R_f value similar to **2**: mass spectrum *m/e* 187 (M^+), 186, 185, 172, 159, 132, 118, 91; uv λ_{max}^{EtOH} 246 mμ.

N-(2-Hydroxyethyl)-*o*-nitrophenylacetamide (23). A solution of 3.0 g (0.015 mol) of *o*-nitrophenylacetyl chloride[14] in 25 ml of MeCN was added dropwise to a stirred solution of 2.3 g (0.037 mol) of 2-aminoethanol in 20 ml of MeCN at 5°. The mixture was stirred for 18 hr. Evaporation of the solvent gave a red oil which was triturated with H_2O to yield 2.0 g of crude **23**, mp 95–97°. Recrystallization from $CHCl_3$–Et_2O raised the melting point to 104–107°. *Anal.* ($C_{10}H_{12}N_2O_4$) C, H, N.

N-(2-Hydroxyethyl)-*o*-aminophenylacetamide (24). A solution of 15.0 g (0.067 mol) of **23** in absolute EtOH was hydrogenated over 10% Pd/C. The catalyst was removed by filtration and evaporation of the solvent yielded an oil which crystallized in EtOH–petroleum ether to give 12.2 g of **24**, mp 102–104°. *Anal.* ($C_{10}H_{14}N_2O_2$) H; C: calcd, 61.84; found, 61.40. N: calcd, 14.42; found, 13.95.

N-(2-Hydroxyethyl)-*o*-aminophenethylamine (25). A solution of 12.2 g (0.063 mol) of **24** in 0.8 l. of anhydrous THF was added dropwise to a solution of BH_3 in 186 ml of THF (0.168 mol) at 0–5° under N_2. The mixture was refluxed for 48 hr. The excess BH_3 was decomposed by MeOH, and the solvent was evaporated to leave a gummy residue. This material was triturated in a small amount of MeOH, and the insoluble material was filtered. Treatment of the filtrate with ethereal HCl afforded 14.5 g of crude **25** (HCl), mp 189–196°. Recrystallization from MeOH–Et_2O raised the melting point to 198–200°. *Anal.* ($C_{10}H_{16}N_2O$·2HCl) C, H, N.

1,2,3,4-Tetrahydro-6*H*-pyrimido[2,1-*b*]quinazoline (3). To a stirred suspension of 3.16 g of $LiAlH_4$ in 400 ml of anhydrous Et_2O was added 6.35 g (0.033 mol) of **26** and the mixture refluxed for 24 hr. After decomposition of the excess $LiAlH_4$, the mixture was filtered and the filter cake was extracted with boiling $CHCl_3$. Filtration and evaporation of the hot extract gave 3.7 g of **3**: mp 230–232°; nmr (DMSO-*d*) δ 1.91 (m, 2 H), 3.08 (t, 2 H), 3.21 (t, 2 H), 4.23 (s, 2 H). The HBr salt (recrystallized from EtOH–Et_2O) had mp 185–187°. *Anal.* ($C_{11}H_{13}N_3$·HBr) C, H, N.

1,2,4,5-Tetrahydroimidazo[1,2-*a*]quinazoline (4). To a suspension of 7.5 g (0.19 mol) of $NaNH_2$ in 650 ml of liquid NH_3 was added 8.1 g (0.039 mol) of **27**.†† After stirring for 7 hr, the mixture was quenched with 10.5 g (0.19 mol) of NH_4Cl and 5 ml of EtOH. The NH_3 was evaporated and H_2O was added to the residue. The aqueous solution was basified to pH 9 and extracted with CH_2Cl_2. Evaporation of the solvent and recrystallization of the residue from EtOAc–EtOH gave 1.6 g (24%) of **4**: mp 175–177°; nmr ($CDCl_3$) δ 3.67 (s, 4 H), 4.44 (s, 2 H). The fumarate salt (recrystallized from EtOH) had mp 214° dec. *Anal.* ($C_{10}H_{11}N_3$·0.5$C_4H_4O_4$) C, H, N.

5,10-Dihydroimidazo[2,1-*b*]quinazoline (5). A suspension of 4.0 g (0.023 mol) of 1 in 100 ml of anhydrous *p*-cymene was refluxed with 10% Pd/C for 2 hr. The cooled mixture was filtered; the filter cake was washed with petroleum ether and extracted with hot MeOH. Evaporation of the MeOH gave a solid which was recrystallized from 2-PrOH to give 1.6 g (41%) of 5: mp 233–235° dec; nmr ($CDCl_3$) δ 5.12 (s, 2 H); uv λ_{max}^{EtOH} (log ε) 230 (3.70), 237 (3.61), 274 mμ (4.10). The HCl salt (recrystallized from EtOH–Et_2O) had mp 210–213° dec. *Anal.* ($C_{10}H_9N_3$·HCl) C, H, N.

5,10-Dihydro-10-methylimidazo[2,1-*b*]quinazoline (30). A mixture of 0.39 g (1.8 mmol) of **29**[3] (fumarate) and 0.14 g of 10% Pd/C in 25 ml of *p*-cymene was refluxed under N_2 for 3 hr. The suspension was cooled and filtered. Treatment of the filtrate with HCl gas precipitated an oil. The supernatant solvent was decanted and the oil was rinsed with petroleum ether. The aqueous solution of the oil was basified and extracted with $CHCl_3$. Evaporation of the $CHCl_3$ and chromatography of the residue (on neutral alumina column, eluted with $CHCl_3$) gave 36 mg of **30** as an oily solid: nmr ($CDCl_3$) δ 3.50 (s, 3 H), 5.10 (s, 2 H); uv λ_{max}^{EtOH} (log ε) 230 (3.81), 239 (3.72), 278 mμ (4.06); mass spectrum *m/e* 185 (M^+).

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††Compound 27 was prepared by the method of Aspinal and Bianco,[15a] with the melting point identical with that reported.[15b]

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Notes

Radioprotective Thiazolidines from β-Keto Esters†

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Antiradiation activity has been reported for a variety of thiazolidines,[1-7] although the absence of significant protection in certain other derivatives led Sweetman, *et al.*,[8] to conclude that a thiazolidine "ordinarily is likely to lock an aminothiol too firmly into a stable structure to afford a promising means of latentiating biologically active aminothiols."

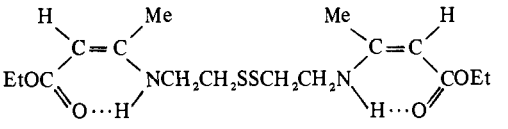
We have latentiated the well-known radioprotective 2-mercaptoethylamine (MEA) in the form of 2,2-disubstituted thiazolidine derivatives of some β-keto esters. The results of preliminary screening of these compounds for antiradiation activity in mice have been presented elsewhere.[9]

Results and Discussion

Data for the compounds prepared are shown in Table I. The synthesis of the thiazolidine bases **1-4** from MEA by a procedure similar to that used by Tondeur, *et al.*,[10] was straightforward. With the exception of **5**, the corresponding hydrochloride salts could not be obtained in an analogous manner from MEA hydrochloride. They were instead prepared from the parent bases and hydrogen chloride in anhydrous ether.

The carbamates **9-12** were prepared from equimolar quantities of ethyl chloroformate and the thiazolidine bases. In each instance, about half of the base was converted into its hydrochloride which was isolated and purified with little loss. The theoretic yield of carbamate, calculated from the thiazolidine, was thus reduced by *ca.* 50%, making the obtained yields (Table I) virtually quantitative. The use of tertiary bases to trap the hydrogen chloride generated by the condensation of the chloroformate and thiazolidine did not produce satisfactory yields of the carbamates.

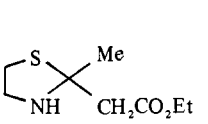
Neither the free bases nor the hydrochloride salts of these disubstituted heterocycles proved to be particularly stable. The thiazolidine bases decomposed on standing over a period of a few weeks. The acetoacetate condensation product **1** apparently underwent aerial oxidation to the disulfide **13** of ethyl 3-(2-mercaptoethylamino)crotonate. The ir spectrum (in KBr) of this substance shows weak N-H absorption at 3250 cm^{-1} and strong bands at 1645 and 1600 cm^{-1} for the intramolecularly hydrogen bonded carbonyl and the C=C stretching mode of the 3-aminocrotonate moiety.[11,12] Similarly, the pmr spectrum (in $CDCl_3$) supports structure **13**.



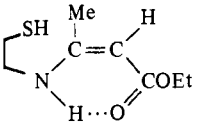
13

The low-field position (8.75 ppm) of the enamine NH proton is apparently due to the paramagnetic effect produced by intramolecular hydrogen bonding; the corresponding signal in related *trans*-enamines is near 5.5 ppm.[13]

Both the ir and pmr spectral data suggest that the four bases **1-4** themselves exist in tautomeric equilibria with the corresponding β-aminocrotonates (*e.g.*, **14**). These proto-



1

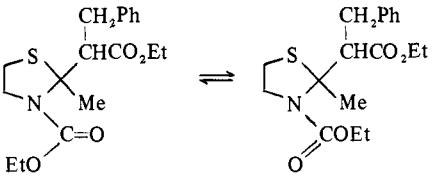


14

tropic reactions are interesting since they illustrate the lability of the C(2)-S(1) bond and therefore the reversibility of this form of latentiation. It seems that, while 2,2 disubstitution reportedly decreases the stability of thiazolidines,[10] further destabilization may occur in the β-keto ester derivatives, due to *stabilization* of the open chain tautomers (**14**) by the ester carbonyl, both through conjugation with the double bond and through hydrogen bonding with the amine proton.

Although the hydrochlorides were reasonably stable in the dry crystalline state, their hygroscopicity led to eventual acid hydrolysis of the thio-aminal linkage, so rapidly in the case of **5** that it was unsuited for biological evaluation.[9] The carbamates were much more stable.

Restricted rotation about the amide C-N bond of **12**, resulting in the presence of pseudo-geometric isomers **12a** and



12a 12b

12b, was evidenced in the pmr spectrum by the marked splitting of the singlet for the 2-methyl group and, to a lesser extent, of the triplet and quartet for the carbamate

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