was warmed on a steam bath for 2 hr. The volatiles were removed under reduced pressure and the residue was taken up in 5% aqueous HCl and washed with Et_2O. Excess K_2CO_3 was added and the product extracted (Et_2O), dried (Na_2SO_4), and treated with Et_2O·HCl. The salt was recrystallized twice from Me_2CO to afford 4.3 g (73%) of product: mp 160–161°; ir (KBr) 1770 (ester C=O); nmr (D_2O) δ 2.40 (s 6, CH_3COOAr), 2.95 (s, 6, $N(CH_3)_2$), 3.25 (m, 4, CH_2CH_2), 7.30 (m, 3, Ar H). *Anal.* ($C_{14}H_{20}NO_4Cl$) C, H, N.

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Amidines. 5.[1] Synthesis of Pyrrolo[2,3-*b*]isoquinoline, Imidazo[1,2-*b*]isoquinoline, Pyrrolo[2,1-*b*]quinazoline, and 1,3-Thiazino[2,3-*b*]quinazoline Derivatives and Related Heterocycles as Potential Antihypertensive Agents

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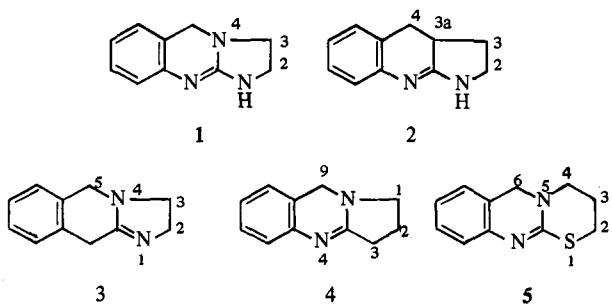
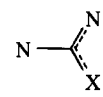
Further structural modifications of a new antihypertensive agent, 1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline (**1**), were investigated. Syntheses of 2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,3-*b*]quinoline (**2**), 2,3,5,10-tetrahydroimidazo[1,2-*b*]isoquinoline (**3**), 1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline (**4**), 3,4-dihydro-2*H*,6*H*-[1,3]thiazino[2,3-*b*]quinazoline (**5**), 2,3,3a,4-tetrahydrofuro[2,3-*b*]quinoline (**9**), and related heterocycles are described. Compounds **4** and **5** showed antihypertensive activity.

Our recent discovery of the potent antihypertensive agent **1**[2] prompted us to investigate further the chemistry and biological activity of related heterotricyclic systems **2**-**5** (Chart I). All of these modifications retain the "amidine" moiety which may be an essential structural feature for producing antihypertensive activity (the term "amidine" is used here for those compounds containing the moiety **A**).

Chart I

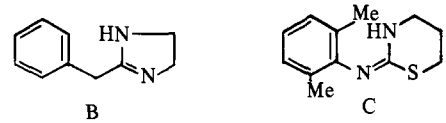


1 **2** **3** **4** **5**



A, X = C, N, O, or S

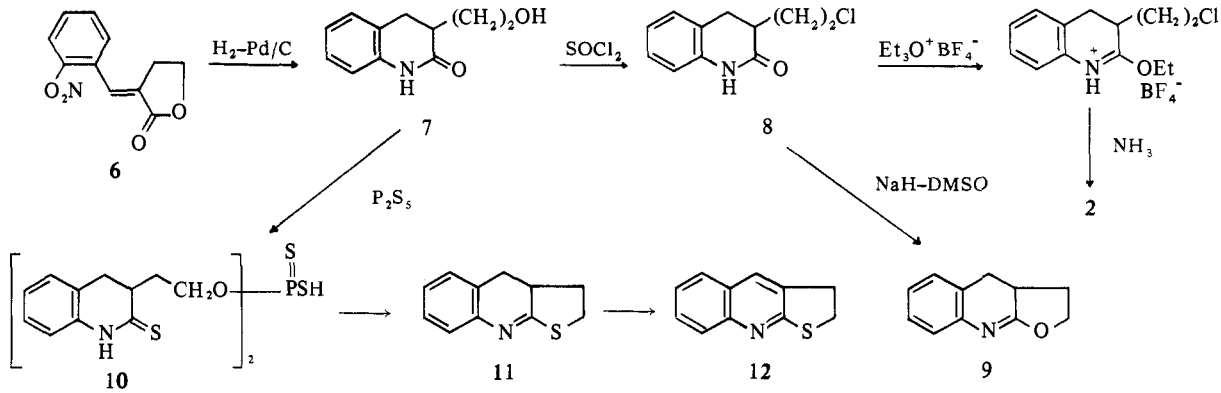
The imidazo[1,2-*b*]isoquinoline (**3**) and the 1,3-thiazino[2,3-*b*]quinazoline (**5**) may be considered "bridged" versions of tolazoline (**B**)[3] (an α-adrenergic blocking agent) and 2-(2,6-dimethylphenylimino)tetrahydro-2*H*-1,3-thiazine (**C**)[4] (an antihypertensive agent), respectively. Our previous application of this approach of structural modification on 2,6-dichlorophenylamino-2-imidazoline (clonidine) had led to the discovery of **1**.[2b]



B **C**

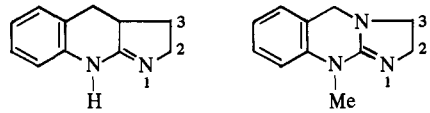
Despite the many publications dealing with the chemistry of the related pyrrolo[2,3-*b*]indole ring system which followed the discovery of physostigmine, only a few pyrrolo-

Scheme I



[2,3-*b*]quinolines have appeared in the literature. Neither of the literature methods for the synthesis of di-[5] or (isomeric) tetrahydro[6] analogs was suitable for the preparation of **2**. The synthesis of **2** is outlined in Scheme I. The alcohol **7**[7] was obtained by catalytic hydrogenation of **6**[8] with Pd/C in AcOH. Treatment of **7** with $SOCl_2$ afforded the chloride **8** without affecting the lactam group. Addition of triethyloxonium fluoroborate to **8** gave the corresponding imidate ester which smoothly underwent aminolysis and cyclization to furnish **2**.

Compound **2** is potentially tautomeric. The assignment of structure **2** instead of D as the predominant tautomer is based on nmr analysis. The chemical shift of the C-2 protons in **2** would be expected to be similar to that in **1** (δ 3.34),[2b] whereas the C-2 protons in D would resonate at lower field as do the C-2 protons in E (δ 3.78) due to the anisotropy of the imino bond.[2b] In fact, a multiplet centered at δ 3.37 corresponding to the C-2 protons of **2** was observed.



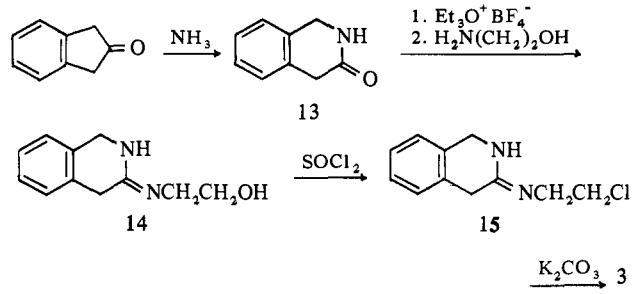
D E

The intermediate lactam **8** also permitted the synthesis of a related new heterocycle. Thus, treatment of **8** with NaH in DMSO led to the furo[2,3-*b*]quinoline (**9**). This ring system is found in some of the alkaloids of *Lunasia amara* Blanco.[9]

When the alcohol **7** was heated with P_2S_5 in pyridine, compound **12** rather than the expected **11** was isolated. This may have occurred *via* intermediates such as **10** and **11**. When the reaction was carried out in dioxane, a mixture of **11** and **12** was obtained. However, compound **11** was more efficiently prepared by employing THF as the solvent. Aromatization of **11** to **12** occurred simply by refluxing in pyridine. The assignment of structure **11** was supported by nmr and mass spectral data. The properties of **12** prepared in this way are identical with those previously described.[10]

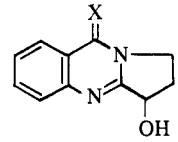
The synthesis of the tetrahydroimidazo[1,2-*b*]isoquinoline (**3**) is outlined in Scheme II. In the course of this work, a one-step synthesis of the lactam **13** was developed employing the Schmidt reaction on 2-indanone; previous synthesis required a lengthy route.[11] Addition of triethyloxonium fluoroborate to **13** gave the corresponding imidate ester which, on treatment with 2-aminoethanol, gave **14**. The

Scheme II



alcohol **14** was converted, without cyclization, to the corresponding chloride **15**. Cyclization to **3** was accomplished by treating **15** with base. Nmr analysis indicates that structure **14** (base) is the predominant tautomer. The methylene protons adjacent to the imino nitrogen atom in the side chain of **14** resonate at δ 3.40 while the signal of the methylene protons adjacent to the amino group in 2-aminoethanol appears at δ 2.80. The downfield shift (Δδ 0.6) is largely due to the anisotropic effect of the exocyclic imino bond.

The tetrahydropyrrolo[2,1-*b*]quinazoline (**4**) is a desoxy analog of the alkaloid vasicine[12] (peganine, **16a**) and synthe-

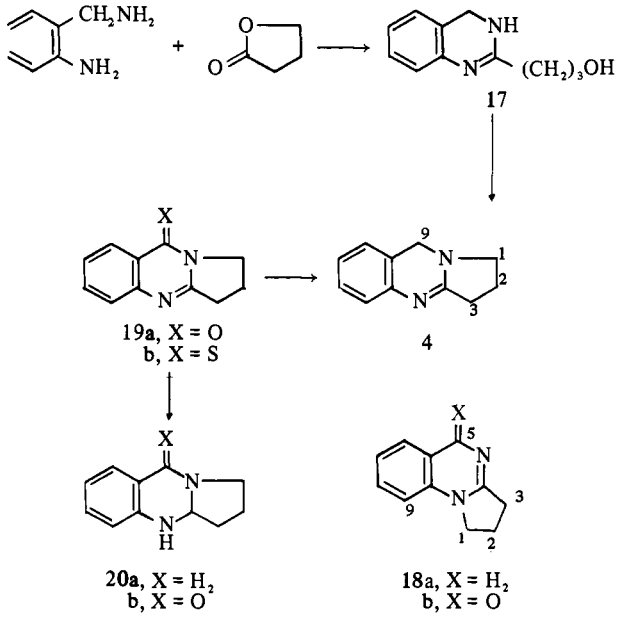


16a, X = H_2
b, X = O

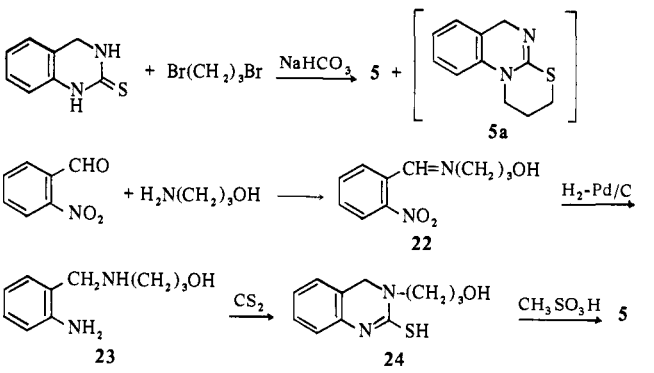
ses have previously been reported.[13] We encountered difficulties in attempting to duplicate Späth's route[13a] (Scheme III). The condensation product of 2-aminobenzylamine and γ-butyrolactone (not characterized by Späth) was identified as **17**. Treatment of **17** with $POCl_3$ under a nitrogen atmosphere gave a mixture of **4** and its angular isomer **18a** in a 1:2 ratio as shown by nmr and glc analyses.

Although **18a** was not isolated, its structure was deduced by relating the nmr spectrum of the mixture to that of authentic **4** (synthesized by a different route described later) and by isolation of the oxidation product **18b**.[14] The nmr spectrum of the mixture shows characteristic signals corresponding to pure **4**: δ 3.30 (t, C-1 H) and 4.54 (s, C-9 H). The signals at δ 3.58 (t) and 4.65 (s) are assigned to the C-1 and C-5 protons in **18a**, respectively. The relative downfield shift (Δδ 0.28) for the C-1 proton signal of **18a** from that of **4** is due to the adjacent aromatic ring current in

Scheme III



Scheme IV

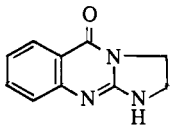


18a. An aromatic proton signal at rather high field (δ 6.61, d, J = 7 Hz) corresponding to the C-9 proton of **18a** characterizes the partial aniline system.

The autoxidation of vasicine (**16a**) to vasicinone (**16b**) was reported to be catalyzed by sunlight.[15] We found that bubbling air into a boiling solution of $POCl_3$ containing a mixture of **4** and **18a** converted these into a mixture of **18b** and **19a**. These results thus support **18a** as the precursor of **18b** and also suggest that **19a** is an artifact rather than a natural constituent of the plant alkaloids.[16] This suggestion supports the implication that vasicinone could be an artifact.[15]

A more practical preparation of **4** was carried out by reduction of the lactam **19a**[17] with Zn in AcOH.[18] Compound **4** was also obtained by desulfurization of **19b** with Raney nickel.

The dihydro derivative **20a** can be prepared by reduction of **19a** with $LiAlH_4$,[14b] and selective reduction of the imino bond in **19a** by $NaBH_4$ gives **20b**.[14b] The unusual chemical reactivity of the imino linkage in this amidine system toward reducing agents is comparable to that in an isolated imine. One possible explanation is that the lone pair of electrons in the *amino* nitrogen atom overlaps the carbonyl π electrons and therefore is not freely available to stabilize the imino bond. The fact that the imino bond in **21** remains



21

intact during $LiAlH_4$ reduction to **1**[2b] suggests that, for stability, the amidine system requires the free electrons from the N-1 nitrogen atom.

The 1,3-thiazino[2,3-*b*]quinozoline **5** was prepared by alkylation of 3,4-dihydro-2(1*H*)-quinazolinethione[19] (Scheme IV) under conditions similar to those described for the synthesis of 3,4-dihydro-2*H*-[1,3]thiazino[3,2-*a*]-benzimidazole.[20] Since this reaction could lead to two possible products (**5** and its angular isomer **5a**), an unequivocal synthesis of **5** was undertaken to verify the structure. *o*-Nitrobenzaldehyde was condensed with 3-aminopropanol to give the imine **22** which was hydrogenated with Pd/C to **23**. Treatment with carbon disulfide gave **24**. Cyclization of **24** to **5** was catalyzed by methanesulfonic acid. The products from both syntheses were identical.

Antihypertensive Activity. The antihypertensive activity of the compounds was evaluated in unanesthetized neurogenic hypertensive dogs.[21] 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), **4** (fumarate), and **5** (base) are 2.5, 5, and 10 mg/kg, respectively. Compounds **2** (HCl), **3** (fumarate), **9**, **19a**, and **20a** (fumarate) did not show significant antihypertensive activity† at doses up to 10 mg/kg.

The biological testing results suggest that the guanidine moiety in **1** is an essential structural feature for eliciting antihypertensive activity. Replacing this with an amidine moiety greatly diminishes the activity. The requirement of an NH group for **1** to produce antihypertensive activity has been described.[2a] The lack of activity of **2** and the activity of **4** are rather surprising in view of the presence of an NH group in **2** and the absence of an NH group in **4**. It is speculated that the mode of action of **4** and **5** is different from that of **1**. Since these compounds are less potent than **1**, further pharmacological studies have not been carried out. As of this point, various major and minor structural modifications[1,2a] have failed to produce a more active compound than **1**.

Experimental Section‡

3-(2-Hydroxyethyl)-3,4-dihydrocarbostyril (7). A solution of 21.3 g (0.097 mol) of **6** in 200 ml of AcOH was hydrogenated with 4.0 g of 5% Pd/C. After the theoretical amount of H_2 was taken up,

†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, and 10 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 MBP's. The MBP'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.[22]

‡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.

the catalyst was filtered and the solvent was evaporated. Recrystallization of the residue from H_2O gave 12.2 g (65%) of 7, mp 100–104° (lit.[7] 103–104°).

3-(2-Chloroethyl)-3,4-dihydrocarbostyril (8). To a stirred suspension (chilled) of 0.382 g (2 mmol) of 7 in 5 ml of $CHCl_3$ was added 0.25 g (2.1 mmol) of $SOCl_2$ in 3 ml of $CHCl_3$. The mixture was kept at 25° for 72 hr and then refluxed for 1 hr. Evaporation of the solvent gave 0.42 g (100%) of **8**, mp 113–115°. Recrystallization from Me_2CO–hexane furnished the analytical sample, mp 114–115°. *Anal.* ($C_{11}H_{12}ClNO$) C, H, N.

2,3,3a,4-Tetrahydro-1*H*-pyrrolo[2,3-*b*]quinoline (2). To a solution of $Et_3O^+BF_4^-$ (0.055 mol) in 150 ml of CH_2Cl_2 was added 10.0 g (0.048 mol) of **8**. The mixture was kept free from moisture at 25° for 18 hr and the solvent was evaporated to give the corresponding imidate ester with no definite melting point. Without further purification a solution of the adduct in 200 ml of EtOH saturated with NH_3 was kept at 25° for 18 hr during which time a portion of the product precipitated. The solvent was evaporated and the residue stirred in H_2O. An insoluble oil was removed by extraction with Et_2O. The precipitated solid (8.0 g) obtained from basifying (10% NaOH) the aqueous solution was recrystallized from EtOH to give 5.62 g (68%) of 2 (base): mp 214–217°; nmr (DMSO-*d*) δ 3.37 (m, 2 H, C-2 H); nmr (TFA-*d*) δ 4.0 (2 t, 2 H, C-2 H). The HCl salt (recrystallized from $CHCl_3$–hexane) had mp 248–249°. *Anal.* ($C_{11}H_{12}N_2 \cdot HCl$) C, H, N.

2,3,3a,4-Tetrahydrofuro[2,3-*b*]quinoline (9). To a chilled mixture of 0.213 g (8.9 mmol) of NaH (the oil was removed by washing with hexane) in 100 ml of DMSO under N_2 was added 1.86 g (8.9 mmol) of **8**. The mixture was stirred at 25° for 30 min and diluted with ice–H_2O. The precipitate was filtered and additional product was recovered by extracting the filtrate with C_6H_6 to give 1.4 g (90%) of crude **9**. The analytical sample recrystallized from C_6H_6–hexane had mp 104–106°, mass spectrum *m/e* 173 (M^+). *Anal.* ($C_{11}H_{11}NO$) C, H, N.

2,3,3a,4-Tetrahydrothieno[2,3-*b*]quinoline (11) and 2,3-Dihydrothieno[2,3-*b*]quinoline (12). (a) Reaction of 7 in Pyridine. A mixture of 0.3 g (1.57 mmol) of **7** in 25 ml of pyridine was refluxed for 1 hr. The solution was concentrated and the residue was taken into dilute HCl solution. The aqueous mixture was washed with C_6H_6, basified with 40% NaOH, and extracted with CH_2Cl_2. Evaporation of the solvent gave 0.15 g (51%) of **12**, mp 95–100° (lit.[10] 104–106°). The picrate had mp 193–196° (lit.[10] 197–199°); mass spectrum *m/e* 187 (M^+); λ_{max}^{EtOH} mμ (log ε) 262 (4.36), 334 (3.96), 346 (3.98) [lit.[10] 262 (4.83),§ 337 (3.96), 349 (3.99)]; nmr ($CDCl_3$) δ 3.40 (s, 4 H, C-2 and C-3 H); nmr (DMSO-*d*) δ 7.95 (s, 1 H, C-4 H).

(b) Reaction of 7 in Dioxane. A mixture of 1.7 g of 7 and 5.0 g of P_2S_5 in 100 ml of dioxane was refluxed for 17 hr. Following the work-up procedure given in (a), a mixture of **11** and **12** was isolated (1.37 g, mmp 90–95°). Nmr analysis of this mixture with reference to pure **11** (obtained from procedure c) and **12** indicated that it consisted of 63% **11** and 37% **12**. Glc analysis# showed that **11** had a shorter retention time than **12**.

(c) Reaction of 8 in THF. A mixture of 0.5 g of 7 and 2.0 g of P_2S_5 in 50 ml of anhydrous THF was refluxed for 17 hr. Following the work-up procedure given in (a), 0.25 g (50%) of crude **11** (mp 100–104°) was isolated containing a trace of **12** (glc analysis).# Recrystallization from EtOH–H_2O gave pure **11**: mp 103–106°; nmr ($CDCl_3$) 96–206 (m, 7 H), 420–442 Hz (m, 4 H); mass spectrum *m/e* 189 (M^+). *Anal.* ($C_{11}H_{11}NS$) C, H, N.

(d) Conversion of **11** to **12**. A 50-mg sample of **11** was refluxed in pyridine for 17 hr. Glc analysis# of the recovered product showed that it was a mixture of **11** and **12**.

1,4-Dihydro-3(2*H*)-isoquinolinone (13). To a vigorously stirred solution of 33.0 g (0.25 mol) of 2-indanone (commercial, recrystallized from *i*-Pr_2O) in 200 ml of $CHCl_3$ at 10° was added 173 ml of a solution of HN_3 in $CHCl_3$[23] (containing 0.28 mol of HN_3 as determined by titration against a standardized NaOH solution). A solution of 40 ml of concentrated H_2SO_4 was added dropwise in 45 min keeping the temperature of the mixture at 10–15° by efficient cooling. The mixture was stirred for another 15 min before addition of an ice–H_2O mixture. It was extracted wtih $CHCl_3$ and washed with $NaHCO_3$ solution, and the solvent was evaporated to dryness. Recrystallization of the residue from H_2O (some polymeric material was removed by charcoal in the process) gave 16.5 g (45%) of **13**, mp 148–150° (lit.[11] 150°).

3-(2-Hydroxyethylimino)-1,4-dihydro-2*H*-isoquinoline (14). To a solution of 60 ml of CH_2Cl_2 containing 12.9 g (0.068 mol) of $Et_3O^+BF_4^-$ was added 8.0 g (0.054 mol) of **13**. The mixture was kept at 25° for 18 hr. It was concentrated by evaporation *in vacuo* and the adduct (imidate ester) was precipitated by addition of Et_2O. Without further purification the above adduct (11.7 g) was added in portions to a stirred solution of 25 ml of 2-aminoethanol at 0° under N_2. The mixture was kept at 25° for 1 hr and warmed on a steam bath for 10 min, during which time the color of the solution changed from green to tan. It was diluted with H_2O and extracted with $CHCl_3$. The aqueous solution A was retained for further isolation of the product. The $CHCl_3$ solution was washed with base and H_2O. After drying (molecular sieves), the solvent was evaporated to leave a viscous oil which solidified in Et_2O to give 3.4 g of **14**, mp 104–109°. Solution A was basified (10% NaOH) and extracted with $CHCl_3$. Following the usual work-up, an additional amount (1.5 g) of **14** was obtained (48% total yield) having mp 110–111°; nmr ($CDCl_3$–D_2O) δ 3.40 (m, 2 H), 3.71 (m, 2 H), 4 57 (s, 4 H). Recrystallization of the base did not raise the melting point but developed coloration. The HCl salt recrystallized from $CHCl_3$–Et_2O had mp 144–145° *Anal.* ($C_{11}H_{14}N_2O \cdot HCl$) H; C: calcd, 58.28; found, 57.84. N: calcd, 12.36; found, 11.44.

3-(2-Chloroethylimino)-1,4-dihydro-2*H*-isoquinoline (15). To a solution of 3.3 g (0.017 mol) of **14** (base) in 70 ml of $CHCl_3$ at 0° under N_2 was added 5 ml of $SOCl_2$. It was kept at 25° for 18 hr and heated to a reflux for 30 min. After evaporating the solvent and $SOCl_2$, the residue was recrystallized (after treatment with charcoal) from 2-PrOH to give 2.4 g (57%) of **15** (HCl), mp 204–205°. *Anal.* ($C_{11}H_{13}ClN_2 \cdot HCl$) C, H, N.

2,3,5,10-Tetrahydroimidazo[1,2-*b*]isoquinoline (3). A suspension of 1.7 g (6.93 mmol) of **15** (HCl) and 2.01 g (2.1 equiv) of K_2CO_3 (finely ground) in 80 ml of MeOH was stirred at 25° under N_2 for 1 hr and heated to a reflux for 2 hr. After cooling, the mixture was filtered and the solvent was evaporated. The residue was dissolved in hot $CHCl_3$ solution and was treated with charcoal to remove some colored impurities (coloration of the free base developed rapidly in exposure to air; the work-up was therefore performed rapidly). The mixture was filtered into a solution of ethereal HCl to precipitate 0.8 g (55%) of **3** (HCl): mp 268–271°; nmr (TFA-*d*) δ 4.11 (s, 2 H), 4.22 (s, 4 H). Recrystallization of this material from various solvents failed to give satisfactory elemental analysis results.

To a stirred suspension of 0.6 g of **3** (HCl) in Et_2O was added dropwise a 10% NaOH solution until all the insoluble salt was converted to the soluble base. The Et_2O solution was dried (Na_2SO_4) and filtered into a solution of fumaric acid in Et_2O to precipitate 0.5 g of **3** (fumarate), mp 164–166° (recrystallized from MeOH–Et_2O). *Anal.* ($C_{11}H_{12}N_2 \cdot C_4H_4O_4$) C, H, N.

2-(3-Hydroxypropyl)-3,4-dihydroquinazoline (17). A stirred mixture of 9.0 g (0.074 mol) of *o*-aminobenzylamine and 6.66 g (0.074 mol) of γ-butyrolactone was heated to 200° for 2 hr under N_2. The unreacted starting material and impurities were removed from the reaction mixture by distillation at 95–135° (0.15 mm). The residue was recrystallized from $CHCl_3$ to give 2.4 g (17%) of **17**: mp 133–135°; mass spectrum *m/e* 190 (M^+); satisfactory ir and nmr spectra. *Anal.* ($C_{11}H_{14}N_2O$) H, N; C: calcd, 69.44; found, 68.74.

Conversion of **17** to **4** and **1,2,3,5-Tetrahydropyrrolo[1,2-*a*]quinazoline (18a).** A solution of 0.3 g of **17** in 5.5 ml of $POCl_3$ was refluxed under N_2 for 2 hr. It was poured into ice–H_2O, basified with 40% NaOH solution, and stirred with $CHCl_3$. The mixture was filtered and the solid was washed with $CHCl_3$. The $CHCl_3$ layer of the filtrate was washed with brine, dried, and evaporated to an oil which was analyzed by glc** to be a mixture of two major components in a 1:2 ratio. The nmr spectrum ($CDCl_3$) suggested that it was a mixture of **4** and **18a** (see discussion in text) in approximately 1:2 ratio.

Oxidation of 4 and 18a to 19a and 18b. A mixture of **4** and **18a** obtained from the previous experiment was refluxed in $POCl_3$ for 2 hr while air was bubbled through the solution. Following the same work-up procedure described in the previous experiment, an oily product was obtained. The nmr spectrum ($CDCl_3$) of this material showed the characteristic absorption peaks corresponding to those of authentic **19a** and **18b**.[14a] Trituration of this oil with Et_2O–

§The reported log ε is apparently an error.

Glc was performed on a F & M Model 240 instrument: column 2 ft × 0.25 in., SE-30 (10%) on Gas Chrom Z (100–120 mesh); temperature 170°; He.

**Glc was performed on a Hewlett-Packard 5750 instrument: column 8 ft × 0.125 in., 10% UCW 98 on Gas Chrom Q (60–80 mesh); temperature 215°; He 30 ml/min. Peaks were integrated automatically by an Infotronics CRS-100 instrument. Found retention time (min): 4, 20.8; 18a, 18.2.

petroleum ether gave a yellow solid which was recrystallized from $CHCl_3$–hexane to give **18b**: mp 208–213° (lit.[14a] 217–219°); mass spectrum *m/e* 186 (M^+); uv and nmr spectral data were in agreement with that reported.[14]

1,2,3,9-Tetrahydropyrrolo[2,1-*b*]quinazoline (4). Method A. Treatment of 5.0 g of **19a**[17] in AcOH with Zn dust under N_2 according to the procedure[18] for conversion of **16b** to **4** gave 2.3 g (55%) of **4**: nmr ($CDCl_3$) δ 2.50 (m, 2 H), 2.64 (t, 2 H), 3.30 (t, 2 H), 4.56 (s, 2 H). The fumarate salt recrystallized from MeOH–Et_2O had mp 250–251°. *Anal.* ($C_{11}H_{12}N_2 \cdot 0.5C_4H_4O_4$) C, H, N.

Method B. **(a) 2,3-Dihydropyrrolo[2,1-*b*]quinazoline-9(1*H*)-thione (19b).** To a stirred solution of 1.0 g (5.4 mmol) of **19a** in 40 ml of pyridine was added 4.53 g (20 mmol) of P_2S_5 in portions. The mixture was refluxed for 5 hr and the solvent was evaporated. The residue was triturated in hot H_2O to give a yellow solid which was suspended in NaOH solution and extracted with $CHCl_3$. Evaporation of the $CHCl_3$ solution gave 0.88 g (80%) of **19b**, mp 138–140°. The analytical sample recrystallized from 2-PrOH had mp 140–142°. *Anal.* ($C_{11}H_{10}N_2S$) C, H, N.

(b) A mixture of 0.25 g of **19b** and 1.0 g of Raney nickel (commercial grade) in 40 ml of MeOH was refluxed for 1 hr. The insoluble material was removed by filtration of the hot solution and washed with MeOH. Evaporation of the filtrate gave 40 mg of **4**, mp 94–97° (lit.[18] 99–100°). The nmr spectrum of this material is identical with that of the sample prepared by method A.

3,4-Dihydro-2*H*,6*H*-[1,3]thiazino[2,3-*b*]quinazoline (5). Method **A.** To a boiling mixture of 2.0 g (10 mmol) of 1,3-dibromopropane and 2.0 g (23 mmol) of $NaHCO_3$ in 80 ml of 2-PrOH was added 1.0 g (6.1 mmol) of 3,4-dihydro-2(1*H*)-quinazolinethione. The mixture was refluxed for 18 hr, concentrated, and stirred with H_2O. After filtration the solid material was stirred with dilute HCl and the insoluble material discarded. Basifying the acid solution gave a precipitate which was recrystallized from EtOAc to afford 0.35 g (17%) of **5**: mp 185–187°; nmr ($CDCl_3$) δ 2.24 (m, 2 H, C-3 H), 2.99 (t, 2 H, C-4 H), 3.19 (t, 2 H, C-2 H), 4.39 (s, 2 H, C-6 H). *Anal.* ($C_{11}H_{12}N_2S$) C, H, N.

Method **B.** A solution of 37.8 g (0.25 mol) of *o*-nitrobenzaldehyde, 22.5 g (0.3 mol) of 3-aminopropanol, and 0.5 ml of AcOH in 150 ml of toluene was refluxed for 30 min (H_2O was removed from the reaction mixture by a Dean-Stark trap). The solvent was evaporated to give 50 g of crude imine **22** as an oil.

Catalytic hydrogenation of a solution of 40 g of crude **23** in EtOH with Pd/C was carried out in the usual manner. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was dissolved in CH_2Cl_2. The solution was washed with H_2O, dried ($MgSO_4$), and evaporated to give 23 g of crude **23**.

To a stirred solution of 23 g of crude **23** in 200 ml of C_6H_6 was added dropwise a solution of 10 g of CS_2 in 75 ml of C_6H_6. The mixture was refluxed for 1 hr, and the solvent was evaporated to give crude **24** as an orange gum. A solid isolated (EtOAc) from a sample of crude **24** had mp 95–98°.

Without further purification, crude **24** in a solution of methanesulfonic acid was heated on steam bath for 15 min. The solution was poured into ice and basified with 40% NaOH solution. After filtration, the precipitate was recrystallized from MeOH to give 12 g of **5** with melting point and nmr spectrum identical with those of the product obtained from method A. The HCl salt (recrystallized from $MeNO_2$) had mp 280°.

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