(s, 3 H), 6.21–6.68 (m, 1 H), 6.75–8.17 (m, 7 H); ^{1}H NMR (Me_2SO-d_6, 100 °C) δ 1.80 (s, 3 H), 3.09 (s, 6 H), 6.58–7.80 (m, 6 H), 7.97 (dd, 2 H, J = 7 Hz, J = 2 Hz).

Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.28; H, 5.80; N, 13.47.

6a-(Chloromethyl)-6a,7-dihydro-6,7-dimethyl-5*H*-quinazolino[1,2-*a*]quinazoline-5,8(6*H*)-dione (24). To an aqueous solution of **22** (1.5 g) was added aqueous $NaHCO_3$ to give a crystalline precipitate. Recrystallization from $CHCl_3$–diisopropyl ether gave **24** (1.0 g, 73.8%) as colorless prisms: mp 196–197 °C dec; IR (Nujol) 1675, 1660 cm^{-1}; ^{1}H NMR (Me_2SO-d_6, room temperature) δ 2.96 (s, 3 H), 3.46 (s, 3 H), 3.77, 4.59 (AB q, 2 H, J = 14.5 Hz), 6.36–6.70 (m, 1 H), 6.90–8.20 (m, 7 H); ^{1}H NMR (Me_2SO-d_6, 100 °C) δ 3.21 (s, 6 H), 4.11 (s, 2 H), 6.64–7.75 (m, 6 H), 7.98 (dd, 2 H, J = 8 Hz, J = 2 Hz).

Anal. Calcd for $C_{18}H_{16}ClN_3O_2$: C, 63.25; H, 4.72; Cl, 10.37; N, 12.29. Found: C, 63.21; H, 5.05; Cl, 10.40; N, 11.99.

Reduction of 21 with $NaBH_4$. $NaBH_4$ (0.277 g, 7.3 mmol) was added to a stirred solution of **21** (2.5 g, 7.3 mmol) in MeOH (20 mL) under ice cooling. The mixture was stirred at room temperature for 1 h. The solvent was evaporated in vacuo and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried ($MgSO_4$), and concentrated to dryness. The residual crystals were recrystallized from 2-PrOH–diisopropyl ether to give 2,3-dihydro-2,3-dimethyl-1-[2-(methylcarbamoyl)-phenyl]-4(1*H*)-quinazolinone (**25**; 1.55 g, 68.9%) as colorless prisms: mp 144–146 °C; IR 3300, 1650, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.49 (d, 3 H, J = 7 Hz), 2.85 (d, 3 H, J = 6 Hz), 3.03 (s, 3 H), 4.94 (q, 1 H, J = 7 Hz), 6.60–6.83 (m, 1 H), 6.85–7.70 (m, 6 H), 7.83–8.22 (m, 2 H).

Anal. Calcd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.67; H, 6.11; N, 13.55.

Pentacyclic Compound 28. A mixture of **5** (2.0 g, 7.8 mmol), 4-chlorobutyryl chloride (3.36 g, 23.4 mmol), and $CHCl_3$ (30 mL) was stirred under reflux for 9.5 h. The precipitate that had formed was collected by filtration, neutralized with aqueous $NaHCO_3$, and dissolved in $CHCl_3$. The $CHCl_3$ solution was allowed to stand for 5 h at room temperature. The solvent was removed in vacuo, and the residue was triturated with aqueous $NaHCO_3$ to give a crystalline product (1.4 g, 58.5%) which was recrystallized from DMF to give a pure sample of **28** (1.2 g, 50.5%) as colorless needles: mp >280 °C; IR (Nujol) 3240, 1678, 1642 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.70–2.35 (m, 4 H), 3.47–4.01 (m, 2 H), 6.39–6.62 (m, 1 H), 6.82–8.13 (m, 7 H), 9.37 (s, 1 H).

Anal. Calcd for $C_{18}H_{15}N_3O_2$: C, 70.80; H, 4.95; N, 13.76. Found: C, 70.55; H, 5.30, N, 13.54.

Acknowledgment. We thank Dr. I. Chibata (Director of this laboratory) and Dr. M. Miyoshi for their encouragement throughout the present study.

Registry No. **3**, 579-92-0; **4**, 76403-55-9; **5**, 32615-84-2; **6**, 76403-56-0; **7**, 76403-57-1; **8**, 66492-18-0; **11**, 76403-58-2; **14**, 70344-50-2; **15**, 76403-59-3; **16**, 76403-60-6; **17**, 76403-61-7; **18**, 76403-62-8; **19**, 76403-63-9; **20**, 76403-64-0; **21**, 76403-65-1; **22**, 76403-66-2; **23**, 76403-67-3; **24**, 76403-68-4; **25**, 76403-69-5; **28**, 76403-70-8; anthranilamide, 88-68-6; potassium *o*-chlorobenzoate, 16463-38-0; acetyl chloride, 75-36-7; isobutyryl chloride, 79-30-1; phenylacetyl chloride, 103-80-0; chloroacetyl chloride, 79-04-9; methoxyacetyl chloride, 38870-89-2; dichloroacetyl chloride, 79-36-7; 4-chlorobutyryl chloride, 141-75-3.

Synthesis of Aminoalkyl-Substituted Imidazo[1,2-*a*]- and Imidazo[1,5-*a*]benzodiazepines

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Aminoalkyl-substituted imidazo[1,2-*a*]benzodiazepines were prepared in good yields from benzodiazepine thione **1** and the novel amino ketals **2**. The 1-(hydroxymethyl)- and 1-unsubstituted-imidazo[1,2-*a*][1,4]benzodiazepines (i.e., **4a** and **9**) were easily transformed into 1-[(dimethylamino)methyl]imidazo[1,5-*a*][1,4]benzodiazepines (i.e., **7** and **16**) via a three-step procedure. This involved consecutive ring-opening, reductive methylation, and subsequent hydroxymethylation of the 1-unsubstituted starting material under Eschweiler–Clarke reaction conditions, followed by transformation of the hydroxyl group to a phthalimide and hydrazinolysis–cyclization to the imidazo[1,5-*a*] products. The preparations of the useful amino ketals **2** are also described.

Since Hester[1] and Meguro[2] reported that the fusion of a triazole ring to the a face of 1,4-benzodiazepines enhanced the potency and imparted novel biological activity to the parent molcule, there has been renewed[3] worldwide interest in the preparations and pharmaceutical properties of other, particularly five atom,[4] heterocyclic fused diazepine ring systems. Much of this interest has focused on the preparation of various imidazo[1,2-*a*][1,4]-,[5] -[1,2-*a*][1,5]-,[6] and -[1,5-*a*][1,4]benzodiazepines[7] and -diazepin-1-ones.[8] With the exception of one very novel approach,[7d] these methods were used to prepare only alkyl or unsubstituted imidazoles. Recently, Hester and co-workers[9] showed that 1-(aminoalkyl)triazole[1,4]benzodiazepines have activity in animal test models designed to find potential antidepressant activity. We now report the preparation of aminomethyl-substituted imidazo[1,2-*a*]- and

(1) (a) J. B. Hester, Jr., A. D. Rudzik, and B. V. Kamdar, *J. Med. Chem.*, **14**, 1078 (1971); (b) J. B. Hester, Jr., D. J. Duchamp, and C. G. Chidester, *Tetrahedron Lett.*, 1609 (1971).

(2) K. Meguro and Y. Kuwada, *Tetrahedron Lett.*, 4039 (1970).

(3) The preparation of 8-chloro-6-phenyl-4*H*-pyrrolo[1,2-*a*][1,4]-benzodiazepine was reported by scientists at Hoffmann-LaRoche in 1968: E. E. Garcia, J. B. Riley, and R. I. Fryer, *J. Org. Chem.*, **33**, 1359 (1968).

(4) For syntheses of pyrrolo- and pyrazolobenzodiazepines see: (a) T. Hara et al., *J. Med. Chem.*, **21**, 263 (1978); (b) N. W. Gilman and R. I. Fryer, *J. Heterocycl. Chem.*, **14**, 1171 (1977); (c) N. Gilman, R. I. Fryer, U.S. Patent 4 130 716 (1978).

(5) (a) J. B. Hester, Jr., and M. Gall, U.S. Patent 3 852 461 (1974); (b) A. R. Hanze and J. B. Hester, Jr., U.S. Patent 3 917 627 (1975); (c) J.-P. Maffrand, G. Ferrand, and F. Eloy, *Tetrahedron Lett.*, 3449 (1973); (d) J.-P. Maffrand, G. Ferrand, and F. Eloy, *Eur. J. Med. Chem.*, **9**, 539, (1974); (e) T. Hara, K, Itoh and N. Itoh, *J. Heterocycl. Chem.*, **13**, 1233 (1976).

(6) (a) T. Hara, H. Fujimori, Y. Kayama, T. Mori, K. Itoh, and Y. Hashimoto, *Chem. Pharm. Bull. Jpn.*, **25**, 2584 (1977); (b) A. W. Chow, R. J. Gyurik, and R. C. Parish, *J. Heterocycl. Chem.*, **13**, 163 (1976).

(7) (a) N. W. Gilman, B. C. Holland, and R. I. Fryer, *J. Heterocycl. Chem.*, **14**, 1163 (1977); (b) A. Walser, L. E. Benjamin, Sr., T. Flynn, C. Mason, R. Schwartz, and R. I. Fryer, *J. Org. Chem.*, **43**, 936 (1978); (c) A. Walser, R. F. Lauer and R. I. Fryer, *J. Heterocycl. Chem.*, **15**, 855 (1978); (d) A. Walser, T. F. Flynn and R. I. Fryer *ibid.*, **15**, 577 (1978); (e) A. Walser, U.S. Patents 4 118 386 (1978), 4 125 726 (1978), 4 146 722 (1979), 4 147 875 (1979).

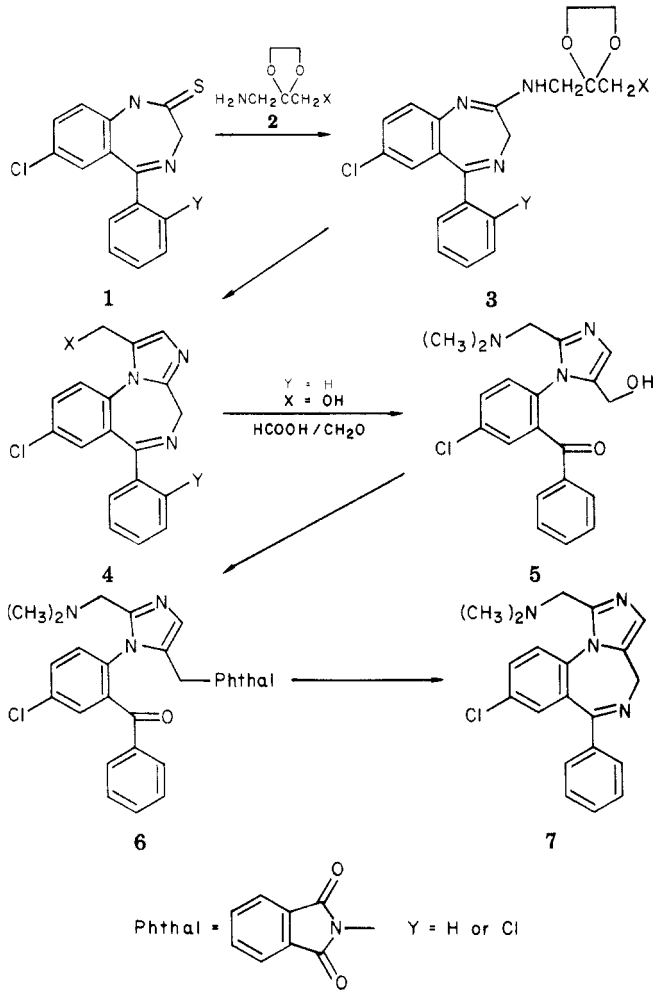
(8) I. R. Ager, G. W. Danswan, D. R. Harrison, D. P. Kay, P. D. Kennewell, and J. B. Taylor, *J. Med. Chem.*, **20**, 1035 (1977).

(9) (a) J. B. Hester, Jr., A. D. Rudzik and P. F. VonVoigtlander, *J. Med. Chem.*, **23**, 392 (1980). (b) See also Swiss Patents 567-023, 567-024, and 568-319 to Ciba-Geigy (1975). (c) K. Meguro and Y. Kuwada, South African Patent Application 718,044 (1971).

(10) G. A. Archer and L. H. Sternback, *J. Org. Chem.*, **29**, 231 (1964).

0022-3263/81/1946-1575$01.25/0

Scheme I



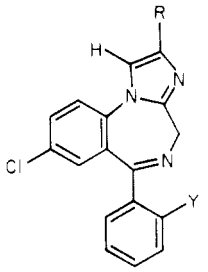
a, X = OH; b, X = Phthal; c, X = $N(CH_3)_2$; d, X = N_3; e, X = CH_2Phthal; f, X = Br; g, X = CH_2OH; h, X = $CH_2N(CH_3)_2$

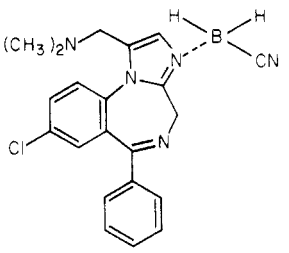
imidazo[1,5-*a*][1,4]benzodiazepines from common intermediates and show that several substituted aminoacetone ketals are useful for synthesizing functionalized heterocyclic fused imidazoles in good yields.

Results

[1,2-*a*] Derivatives. Condensation of 1 to 3 equiv of the hydroxy-, phthalimido-, dimethylamino-, or azido-substituted aminoacetone ketals, **2a–d** (see Scheme I), with the very useful benzodiazepine-2-thione, **1**,[10] provided amidines **3a–d** (Y = H) in 90, 53, 90, and 87% yields, respectively. With concentrated sulfuric acid,[5,11] cyclization of **3a** and **3b** produced a 32% yield of the (hydroxymethyl)imidazole **4a** (Y = H) and a 63% yield of the phthalimido derivative **4b** (Y = H), respectively. Since the yield of **4a** (Y = H) was raised to 64% by heating **3a** (Y = H) in methanesulfonic acid for 20 h and since **4a** could be converted to **4b** in 88% yield via Mitsunobu's procedure[12] using triphenylphosphine, phthalimide and diethylazodicarboxylate, the two-step synthesis of phthalimide **4b** from alcohol **3a** was practical. However, a quite satisfactory 74% of crystalline phthalimide **4b** (Y = Cl) was obtained from **3b** (Y = Cl) when care was taken to neutralize the reaction mixture with a slight excess of cold, dilute, aqueous sodium hydroxide solution.

Under the usual cyclization conditions, azido amidine **3d** (Y = H) decomposed to several unidentified products, and basic amidine **3c** (Y = H) was recovered unchanged. Their utilization as intermediates to **4c** was abandoned. The desired 1-[(dimethylamino)methyl]imidazo[1,2-*a*]-[1,4]benzodiazepine (**4c**, Y = H) was prepared in 47% yield by hydrazinolysis of phthalimide **4b** (Y = H) followed by Borch reductive methylation with $NaCNBH_3$ and formaldehyde in acetonitrile.[13,14] This (aminomethyl)imidazole, **4c** (mp 181–182 °C), was identical with the major product obtained by heating the unsubstituted imidazole **8**[5a–c] with $^-ClCH_2{=}N^+(CH_3)_2$[15] (Böhme's salt) in dimethylformamide at 55–80 °C.[16]





8, R = H; Y = H
9, R = CH_3; Y = Cl

4c′

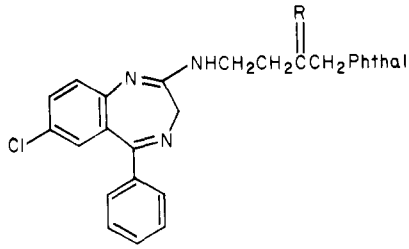
The scale-up of the reductive methylation yielded less **4c** (Y = H) with concomitant formation of the cyanoborane adduct **4c′** in 20% crystallized yield. The borane adduct could not be converted to **4c** even on refluxing it for 2 h in a 25% aqueous ethylenediamine solution in an equivalent volume of methanol.[15b] A comparison of the NMR spectra of **4c** and **4c′** (vide infra) suggested that the boron was bound to the imidazole nitrogen, rather than the diazepine C=N or $(CH_3)_2NCH_2$, and the structure was proven unambiguously by X-ray analysis.[17]

The use of the aminobutanone ketal derivative **2e** to prepare **4e** (Y = H) led to some unusual, if not entirely unexpected, results. Thus, while **3e** (Y = H) was the major crystalline product (58% yield) of the reaction of **2e** with thione **1** (Y = H), the isomeric amidine ketal **10a** crystallized directly from the crude reaction mixture in 36% yield based on recovered starting material.

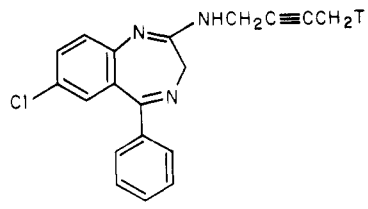
Structures were assigned to **3e** and **10a** on the basis of NMR and mass spectral data. The desired isomer **3e** (Y = H) had NMR signals at δ 3.80 (2 H, t, Phthal CH_2), 3.60 (2 H, br s, $NHCH_2$), and 2.10 (2 H, t, CCH_2) while **10a** had NMR signals at δ 3.80 (2 H, s, Phthal CH_2), 3.55 (br t, $NHCH_2C$), and 2.05 (2 H, t, CCH_2). Both isomers had molecular ion peaks at *m/e* 528 but **3e** had a fragment ion at *m/e* 282 (M^+ – Phthal – $CH_2CH_2\overline{COCH_2CH_2O}$) while **10a** had fragment ions at 368 (M^+ – Phthal – CH_2) and 296 (M^+ – Phthal – $CH_2\overline{COCH_2CH_2O}$).

10a reacted with concentrated sulfuric acid at room temperature to afford ketone **10b** [mp 178–179 °C; fragment ions at *m/e* 187 (Phthal – $CH_2C{=}O$) and 160 (Phthal – CH_2)]. Ketone **10b** was recovered unchanged when re-

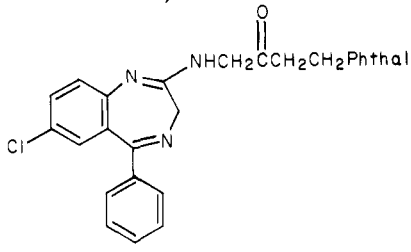
(11) (a) M. Gall, U.S. Patent 3763179 (1973). See also (b) Japan Patent 47-390-74 (unexamined).
(12) O. Mitsunobu, M. Wada, and T. Sano, *J. Am. Chem. Soc.*, **94**, 679 (1972).
(13) (a) The products were eluted with 90% chloroform/10% methanol mixtures on Analtech silica gel 250-μm GF TLC plates. (b) See the Experimental Section.
(14) (a) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971); (b) C. F. Lane, *Synthesis*, 135 (1975).
(15) (a) H. Böhme and K. Hartke, *Chem. Ber.*, **93**, 1305 (1960); (b) J. B. Hester, Jr., *J. Heterocycl. Chem.*, **17**, 575 (1980).
(16) (a) M. Gall, unpublished results. See also (b) M. Gall, U.S. Patent 4001261 (1977).
(17) Private communication from Dr. D. J. Duchamp, C. G. Waber, and C. G. Chidester of these laboratories.



10a, R = O O
b, R = O



11a, T = OH
b, T = Phthal

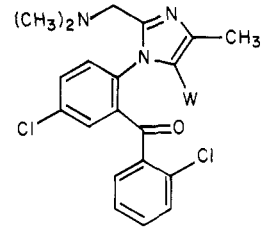


12

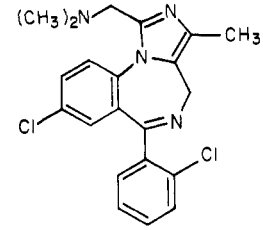
subjected to acid-catalyzed cyclization. Under similar conditions, isomer **3e** afforded a mixture of imidazole **4e** and ketone **12** as crude oils in 60 and 35% respective yields. Ketone **12** [mp 210–212 °C; fragment ions at *m/e* 282 (M^+ – Phthal – $CH_2CH_2C{=}O$)] was identical with the ketone isolated in 33% yield via mercuric sulfate catalyzed hydration of phthalimido acetylene **11b** (obtained via Mitsunobu's method[12] from alcohol **11a**).[13b] When the mercuric sulfate catalyzed acetylene hydration was scaled up and the products were chromatographed, crystalline imidazole **4e** (Y = H) was obtained in 32% yield along with crude ketones **12** (50% yield) and **10b** (<10% yield). The formation of ketone **10b** indicated that the hydrolysis of **11b** was regioselective rather than regiospecific.[18a]

Ketone **12** did not readily cyclize to imidazole **4e**. Even after 6 days in concentrated sulfuric acid only 30% conversion to **4e** had occurred. Better yields were obtained in P_2O_5–methanesulfonic acid mixtures[18b] (~60% crude yield) or in glyme–titanium tetrachloride mixtures (43% crystalline yield). These results suggest that the direct cyclization of ketal **3e** (Y = H) and acetylene **11b** occurred more readily than the cyclization of the corresponding ketone, **12**. Because of its ready availability, acetylene **11b** may be more useful than ketal **3e** for preparing imidazole **4e** (Y = H).

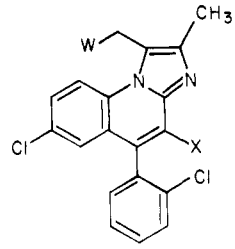
[1,5-*a*] Derivatives. The easy production of (hydroxymethyl)imidazo[1,2-a]benzodiazepines **4a** suggested the simple synthesis of the [1,5-*a*] derivatives outlined in Scheme I. The benzodiazepine ring was hydrolyzed and methylated in one pot under standard Eschweiler–Clarke reaction conditions to produce benzophenone **5** (Y = H).[19,20] Phthalimidation[12] (**5** → **6**) followed by hydrazinolysis, cyclization, and chromatography produced imidazo[1,5-*a*]benzodiazepine **7** (Y = H; mp 213–215 °C) in 39% yield.[13b] Since heating imidazoles under Eschweiler–Clarke reaction conditions resulted in hydroxymethylation of the imidazole ring,[11,19] we investigated the possibility that 1-unsubstituted imidazo[1,2-*a*]benzodiazepines, such as **9**, could be used to prepare [1,5-*a*] analogues directly. We had shown earlier that **14** was formed from **9** (via intermediate **13**) in 60% crystalline



13, W = H
14, W = CH_2OH
15, W = CH_2Phthal



16



17a, W = OH;
X = $N(CH_3)_2$
17b, W = $N(CH_3)_2$;
X = OH

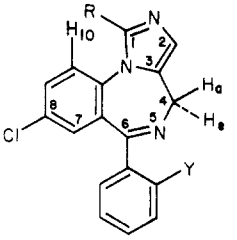
yield after heating for 24 h.[19] In an attempt to increase the yield of **14**, we increased the length of heating. We found that the quinoline derivative **17a** (λ_{max} 217, 239, 335, 345 nm; M^+ at *m/e* 399), presumably formed via base-catalyzed intramolecular condensation of amino ketone **14**, was obtained as a minor byproduct after heating for several days. Alcohol **14** was converted to phthalimide **15**[12] (44%) which underwent hydrazinolysis and cyclization to **16** (41%, mp 185–186.5 °C), thereby establishing the viability and simplicity of this route.

NMR Spectra. Table I lists the chemical shifts (δ, in $CDCl_3$) for the 4-H axial,[22] 4-H equatorial,[22] H_{10} imidazole CH, and $XCH_2C_1{=}$ methylene protons observed for the amino- and other 1-heteroalkyl-substituted imidazobenzodiazepines. Several points emerge from an analysis of these data. Comparisons of **4c** (δ 5.34), boron complex **4c′** (δ 5.75), **7** (δ 5.13) and **16** (δ 5.12) show that the 4-H equatorial proton in each is very sensitive to changes at position 3 of the imidazobenzodiazepine, with nitrogen or complexed nitrogen having a significant deshielding effect. The 4-H equatorial proton may also be sensitive to changes in the solvent [cf. **4a** (Y = H), **4a** (Y = Cl)] but very likely is not greatly influenced by the presence of a 2′-Cl [cf. **16** and **7**, and **4b** (Y = H) and **4b** (Y = Cl)].

In contrast these changes do not affect the 3-H axial proton although complexation of the imidazole nitrogen with boron changes its chemical shift slightly from δ 4.04

(18) (a) G. Stork and R. Borch, *J. Am. Chem. Soc.*, **86**, 935 (1964); (b) P. E. Eaton, G. R. Carlsen, and J. T. Lee, *J. Org. Chem.*, **38**, 4071 (1973).
(19) M. Gall, J. B. Hester, Jr., A. D. Rudzik, and R. A. Lahti, *J. Med. Chem.*, **19**, 1057 (1976).
(20) (a) S. H. Pine and B. L. Sanchez, *J. Org. Chem.*, **36**, 829 (1971); (b) R. N. Icke and B. B. Wisegarver, *Org. Synth.*, **3**, 723 (1955).
(21) An analogous inversion of functionality about a triazolobenzodiazepine based on this methodology has recently been reported; see ref 9a.
(22) (a) W. Bley, P. Nuhn, and G. Benndorf, *Arch. Pharm.*, **301**, 444 (1968); (b) A. Mannschreck, G. Rissmann, F. Vogtle, and D. Wild, *Chem. Ber.*, **100**, 335 (1967).

Table I. ^{1}H NMR Chemical Shift Data

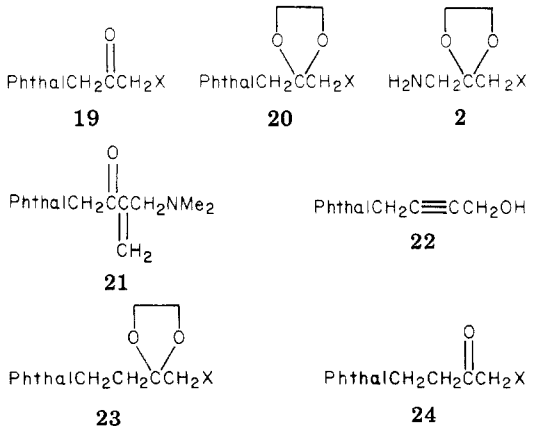


compd	Y	R	W	Z	δ[a] (multiplicity) H_a	H_e	H_{10}	$=C_1CH_2X$	CH_3N	imidazole CH
4c	H	$CH_2N(CH_3)_3$	CH	N	4.04 (d, J = 13.0 Hz)	5.34 (d, J = 13.0 Hz)	8.39 (d, J = 8.5 Hz)	3.39 (AB)	2.22	7.00 (s)
4c′	H	$CH_2N(CH_3)_2$	CH	N·$\cdot BH_2CN$	3.93 (d, J = 13.0 Hz)	5.75 (d, J = 13.0 Hz)	8.57 (d, J = 8.5 Hz)	3.38 (s)	2.24	7.16 (s)
7	H	$CH_2N(CH_3)_2$	N	CH	4.05 (d′ J = 13.0 Hz)	5.13 (d, J = 13.0 Hz)	8.34 (d, J = 8.5 Hz)	3.51 (s)	2.30	6.99 (s)
4a	H	CH_2OH	CH	N	4.03 (d,[b] J = 12.5 Hz)	5.12 (d,[b] J = 12.5 Hz)	8.15 (d,[b] J = 8.5 Hz)	4.59 (ABX)[b]		7.00 (s)[b]
4a	Cl	CH_2OH	CH	N	4.08 (d, J = 13.0 Hz)	5.31 (d, J = 13.0 Hz)	8.10 (d, J = 9.0 Hz)	4.59 (ABX)		7.00 (s)
4b	H	CH_2Phthal	CH	N	3.99 (d, J = 13.0 Hz)	5.27 (d, J = 13.0 Hz)	<7.8	4.99 (s)		7.16 (s)
4b	Cl	CH_2Phthal	CH	N	4.08 (d, J = 12.5 Hz)	5.37 (d, J = 12.5)	<7.8	5.01 (s)		7.20 (s)
18	H	CH_2NH_2	CH	N	4.00 (d, J = 12.5 Hz)	5.30 (d, J = 12.5 Hz)	8.01 (d, J = 8.5 Hz)	3.95 (AB)		6.96 (s)
4e	H	CH_2CH_2Phthal	CH	N	4.01 (d, J = 12.5 Hz)	5.29 (d, J = 12.5 Hz)	<7.8	3.19 (m)		6.98 (s)
4h	H	$CH_2CH_2N(CH_3)_2$	CH	N	4.00 (d, J = 13.0 Hz)	5.30 (d, J = 1.30 Hz)	<7.7	2.2-2.7 (m)	2.20	6.92 (s)
16	Cl	$CH_2N(CH_3)_2$	N	CCH_3	4.04 (d, J = 13.0 Hz)	5.12 (d, J = 13.0 Hz)	8.33 (d, J = 8.5 Hz)	3.41 (s)	2.33	

[a] Chemical shifts, obtained at 60 MHz, were determined from spectra run in $CDCl_3$. [b] The spectrum was run in a mixture of $CDCl_3$-Me_2SO-d_6.

to 3.93. A C_1CH_2 heteroatom having a *localized* lone pair of electrons significantly deshields the aromatic proton H_{10}. C_1 alkyl substituents (data not provided), aminoethyl derivatives (**4c**), and phthalimidomethyl substituents (**4b**) do not deshield this proton. Finally the position of the imidazole CH remains nearly constant at ~ δ 7.0 although the boron complex **4c′** and phthalimido derivatives **4a** (Y = H, Cl) reveal a slight deshielding effect.

Substituted Amino Ketals 2. The variously substituted aminoacetone derivatives **2** were prepared in several steps by classical methods.[23] Phthalimidoacetone **19j** was converted to the bromo ketal **20f** via the ketal **20j** (50% yield) or directly in one step (55% yield) with bromine in ethylene glycol.[24] Although the bromo ketal **20f** was unreactive toward most nucleophiles [no reaction occurred with NaCN or $(CH_3)_2NH$], heating for 3 to 4 days at 100 °C in dimethyl sulfoxide (Me_2SO) with 2 to 3 equiv of sodium azide cleanly transformed it into azido ketal **20d** in 95% yield. In contrast, bromo ketone **19f** reacted completely with sodium azide in Me_2SO within 15 min at room temperature. However, the isolated yield of **19f** was only 40% and because of its sensitivity to the reaction conditions the synthesis could not be scaled up. Moreover, conversion to the ketal required 5 days and proceeded in only 52% yield. Catalytic reduction of **20d** afforded **2b** which was used immediately in reactions with thione 1 or was reductively methylated with sodium cyanoborohydride and formaldehyde to afford **20c** (mp 123–125 °C) in 86% yield. Bromo ketone **19f** was converted[25] to acetate **19i** in 67% yield. The same acetate was more conveniently prepared directly from **19j** in 51% yield by adaptation of the remarkably selective acetoxylation of methyl ketones with lead tetraacetate/boron trifluoride etherate.[26] Ketal formation was accomplished with simultaneous hydrolysis of the ester to afford **20a** in 70% yield. Each of the phthalimides **20f**, **20d**, **20c** and **20a** was treated with hydrazine hydrate in ethanol to afford the corresponding amines **2f**, **2d**, **2c** and **2a**, respectively, in good yields.



19 20 2

21 22

23 24

a, X = OH; b, X = Phthal; c, X = $N(CH_3)_2$; d, X = N_3; e, X = CH_2Phthal; f, X = Br; g, X = CH_2OH; h, X = $CH_2N(CH_3)_2$; i, X = $OCOCH_3$; j, X = H

The preparation of useful butanone derivatives related to **2e** or **2g** proved to be less straightforward. We first

(23) M. Gall, U.S. Patent 3 992 408 (1976).

(24) E. W. Garbisch, Jr., *J. Org. Chem.*, **30**, 2109 (1965).
(25) A. O. Jackson and C. S. Marvel, *J. Biol. Chem.*, **103**, 191 (1933).
(26) J. P. Guthrie and Y. Ueda, *Can. J. Chem.*, **51**, 3936 (1973).

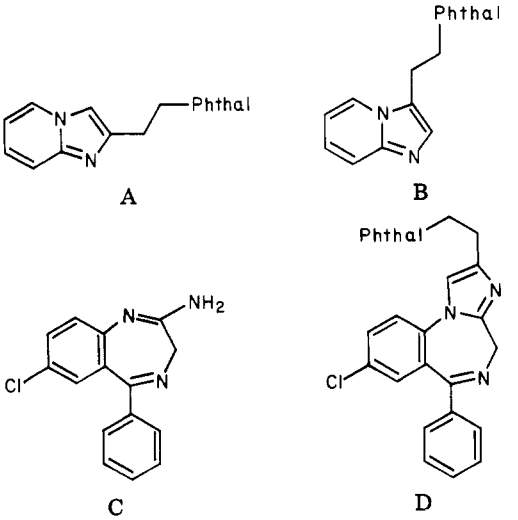
made use of the Mannich reaction of phthalimido ketone **19j** with Böhme's salt.[15,16] In 1,2-dimethoxyethane the desired product **19h** was formed in 70% yield; it was contaminated with a small amount of vinyl compound **21** when dimethylformamide (DMF) was used as a solvent. All attempts to convert **19h** to the ketal **20h** failed, as did a reaction designed to convert ketal **20j** to dimethylamino ketal **20h** directly.

Next, we attempted to prepare hydroxybutanone derivatives **19g** and **20g** starting with acetylene **22**,[27] readily prepared in 70% yield from potassium phthalimide and $ClCH_2C{\equiv}CCH_2OH$[28] in DMF. However, mercuric sulfate catalyzed hydration led to the formation of only **24a** (mp 107–109 °C) in 55% yield.[18a] Isomer **19g** was never detected. Structure **24a** was based on the NMR spectrum which revealed a two-proton doublet at 4.31 ppm which collapsed to a singlet, following D_2O exchange. The ketal **23a** (mp 137–140 °C) was prepared from the ketone **24a** in 37% yield. Alternatively, **23a** was prepared in 71% crystallized yield directly from acetylene **22** by the procedure of Hennion and Nieuwland[29] using $BF_3{\cdot}(Et_2O)_2$ and red HgO in ethylene glycol. Alcohol **23a** was converted to the mesylate which was treated with excess sodium azide and potassium iodide and heated to 130 °C in Me_2SO for 72 h. Azide **23d** [mp 83.5–85 °C; IR (Nujol) 2110 cm^{-1}] was isolated in 29% yield, following chromatography to separate two partially characterized byproducts.[13b] The crystalline azide could also be prepared in 64% yield without chromatography by heating the corresponding bromide **23f** (mp 121–122 °C, obtained from the known bromo ketone **24f** [mp 117–118 °C (lit.[30] mp 119–120 °C)] in 74% yield, with sodium azide in Me_2SO at 120 °C for 18 h. Catalytic reduction of azide **23d** over 10% Pd/C in ethyl acetate in a Parr bomb produced an 80% yield of crude aminophthalimide **2e**. This crude amine was treated immediately with thione 1 (Y = H) to generate **3c** and **10a**.

Discussion and Conclusion

When we began our studies we were not aware of any direct procedure for preparing 1-amino- or 1-hydroxyalkyl-substituted imidazo-fused [1,2-*a*] heterocycles.[30c] Furthermore, we were uncertain how an unsubstituted imidazobenzodiazepine ring system would behave under the conditions of electrophilic substitution reactions, particularly with regard to regioreactivity. Classically, heterocyclic fused imidazoles substituted with alkyl or heteroalkyl groups have been prepared from amidines and bromo ketones, a reaction first reported by Tschitschibabin.[31] For example, Durant and co-workers,[30b] using 1-bromo-4-phthalimido-2-butanone, **24f**, obtained 2-(phthalimidoethyl)imidazo[1,2-*a*]pyridine (A) in 64% yield from 2-aminopyridine. There was no evidence for the formation of the 1-substituted product, B, which would correspond to **4e** in the present work.

Although the mechanism of this Tschitschibabin reaction is not entirely understood, and while there does exist some confusion in the literature as to the assignment of



the position of the alkyl or aryl substituent on the fused imidazo[1,2-*a*]pyridines[32] which results from the reaction, the work of Adams and Dix[33] strongly supports the original notion[31] that 2-substituted products (i.e., A) are formed from the reaction of amidines and bromo ketones.[34] Thus the Tschitschibabin reaction of benzodiazepine C and bromo ketone **24f** would have been expected to give rise, in our case, to the undesired 2-substituted product D. Actually we failed to find evidence for the formation of this or any other imidazole product.[16a] Hara[5e] recently reported that benzodiazepine amidine C did react with simple halo ketones, such as bromoacetone, 1-bromo-2-butanone, and 1-bromo-2-pentanone, to form 2-methyl-, 2-ethyl- and 2-propylimidazo[1,2-*a*]benzodiazepine, but the yields were moderate to low (22, 35 and 14%, respectively). (For an example of the use of amino acetals or ketals to prepare, in excellent yield, the 2-methyl compound, where Y = Cl, see the Experimental Section.) Moreover, the reaction of 3-bromo-2-butanone afforded, unexpectedly, the 2-ethyl compound (12%) along with a low yield (5%) of the expected 1,2-dimethylimidazo[1,2-*a*]benzodiazepine. It thus seems unlikely that the reaction reported by Tschitschibabin could be utilized with the required appropriately substituted aldehydes to afford *good yields* of products of structure **4**.

We have shown that heterosubstituted aminoacetone and -butanone ketals **2**[35] are readily prepared in moderate to good yields and, along with acetylenes, such as $H_2NCH_2C{\equiv}CCH_2OH$, may be used to prepare, regiospecifically, 1-(heteroalkyl)-substituted imidazo[1,2-*a*]benzodiazepines. Because of its ease of preparation, stability, and good reactivity with benzodiazepine-2-thiones, hydroxy derivative **2a** may be the most useful of these new reagents, particularly since, for our purposes, the resulting 1-(hydroxymethyl)imidazo[1,2-*a*]benzodiazepine (**4a**) had the added versatility of serving as an intermediate for the preparation of 1-[(dimethylamino)methyl]imidazo[1,2-*a*]-(**4c**) or -[1,5-*a*][1,4]benzodiazepine (**7**).

(27) I. A. Shikhiev et al., *Zh. Obshch. Khim.*, **40**, 2629 (1970).
(28) W. J. Bailey and R. E. Fujiwara, *J. Am. Chem. Soc.*, **77**, 165 (1955).
(29) G. F. Hennion, D. B. Killian, T. H. Vaughn, and J. A. Nieuwland, *J. Am. Chem. Soc.*, **56**, 1130 (1934).
(30) (a) R. G. Jones, E. C. Kornfeld, and K. C. McLaughlin, *J. Am. Chem. Soc.*, **72**, 4526 (1950); (b) G. J. Durant, J. M. Loynes, and S. H. B. Wright, *J. Med. Chem.*, **16**, 1272 (1973); (c) M. R. Grimmett, *Adv. Heterocycl. Chem.*, **12**, 103–183 (1970).
(31) (a) A. E. Tschitschibabin, *Chem. Ber.*, **57**, 2092 (1924); **58**, 1704 (1925); (b) N. Campbell and E. B. McCall, *J. Chem. Soc.*, 2411 (1951); (c) F. Kröhnke, B. Rickhofen and C. Thoma, *Chem. Ber.*, **88**, 1117 (1955).
(32) C. Djerassi and G. R. Pettit, *J. Am. Chem. Soc.*, **76**, 4470 (1954).
(33) R. Adams and J. S. Dix, *J. Am. Chem. Soc.*, **80**, 4618 (1958).
(34) (a) Nevertheless, Rapoport[34b] concluded, prior to his own elegant contributions in this area, that "methods of synthesis or of structural elucidation of unsymmetrical imidazoles are inadequate or ambiguous, except for the procedure of Jones"[34c] to prepare 1,5-disubstituted (and nonfused) imidazoles, a procedure not applicable to our synthetic problem. (b) P. K. Martin, H. R. Matthews, H. Rapoport, and G. Thyagarajan, *J. Org. Chem.*, **33**, 3758 (1968); (c) R. G. Jones, *J. Am. Chem. Soc.*, **71** 644 (1949).
(35) For another potentially useful intermediate, see H. Newman, *J. Org. Chem.*, **39**, 100 (1974).
(36) T. Mukaiyama and K. Saigo, *Chem. Lett.*, 479 (1973).

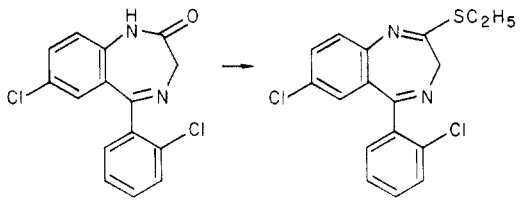
Experimental Section

Methods and Reagents. Melting points were determined with a Thomas-Hoover capillary melting-point apparatus and were corrected. Infrared (IR) spectra were determined in Nujol on a Perkin-Elmer Model 421 recording spectrophotometer. Ultraviolet (UV) spectra were determined in 95% EtOH on a Cary Model 14 spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Model A-60D; chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (Me_4Si, δ 0.0) as an internal standard. Mass spectra were determined with a Varian MAT CH7 or LKB.

Unless otherwise stated analytical thin-layer chromatography (TLC) was conducted by eluting the products with 10% methanol–90% chloroform mixtures on 2.5 × 10 cm precoated silica gel GF plates, layer thickness 0.25 mm, manufactured by Analtech. Columns for chromatography were packed with E. Merck (Darmstadt) silica gel 60, 70–230 mesh ASTM.

Chloroform ($CHCl_3$) suitable for chromatography and preserved with 1% (v/v) ethanol, dimethyl sulfoxide (Me_2SO), and dimethylformamide (DMF) were used as received ("distilled in glass") from Burdick and Jackson, Inc., unless otherwise stated. Tetrahydrofuran (THF) and 1,2-dimethoxyethane, also obtained from Burdick and Jackson, Inc., were distilled from lithium aluminum hydride prior to use.

Benzodiazepine-2-thiones 1 (Y = H and Cl) were prepared according to the published procedure.[10] The ethyl thioether **28** was prepared from amide **27** via a modification of Mukaiyama's



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thiolenol ether synthesis.[36] A solution of ethanethiol (17 g, 0.275 mol) and triethylamine (Et_3N, 50.5 g, 0.50 mol) in 0.5 L of freshly distilled tetrahydrofuran (THF) was added dropwise to a vigorously stirred suspension of benzodiazepine amide **27** (77.8 g, 0.255 mol) and titanium tetrachloride ($TiCl_4$, 47.5 g, 0.25 mol) in 1 L of distilled THF. The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 0.75 h and then it was concentrated in vacuo to a dark oil. Following chromatography, the product **28** was obtained in 59% yield (52 g). The analytical sample, recrystallized from ethyl acetate–hexane mixtures had the following: mp 118–119 °C; IR (Nujol) 1605, 1580 cm^{-1} (C=C/C=N); UV (95% EtOH) λ_{max} 210 nm (ϵ 32 050), 246 (23 800), 288 (16 550); ^{1}H NMR ($CDCl_3$) δ 6.97–7.70 (m, 7 H, aromatic), 4.22 (s, 2 H, ring CH_2), 3.14 (q, J = 7.5 Hz, 2 H, SCH_2), 1.35 (t, J = 7.5 Hz, 3 H, CH_3); mass specectrum, molecular ion peak at m/e 349 with fragment ions at m/e 319, 313, 288, 182, 125.

Anal. Calcd for $C_{17}H_{14}ClN_2S$: C, 58.47; H, 4.04; N, 8.02; Cl, 20.30; S, 9.16. Found: C, 58.94; H, 4.10; N, 8.38; Cl, 20.45; S, 9.42.

Unless otherwise stated, all reactions were carried out under a positive nitrogen atmosphere.

***N*-[[2-[[7-Chloro-5-phenyl- and -5-(*o*-chlorophenyl)-3*H*-1,4-benzodiazepin-2-yl]amino]methyl]-1,3-dioxolan-2-yl]methylphthalimide, 3b (Y = H, Cl).** A suspension of 37.0 g (0.140 mol) of aminophthalimidoacetone ketal, **2b**, and 20.16 g (0.70 mol) of benzodiazepine-2-thione (1, Y = H) in 560 mL of absolute EtOH was heated at 60 °C for 18 h while bubbling a small stream of nitrogen through the reaction mixture. The reaction was cooled and the white solid was filtered, washed with ethanol, and dried to afford 1.9 g of powder. The analytical sample had the following: mp 226–229 °C; IR (Nujol) 3600, 3540 (OH), 1780, 1770, 1710 (C=O), 1625, 1610 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$) δ 7.58–8.01 (m, 8 H, aromatic CH), 4.0 (s, 4 H, OCH_2), 3.94 (s, 4 H, NCH_2); mass spectrum, no molecular ion peak (M^+, 392), strong fragment ion at m/e 160 (·Phthal–CH_2^+).

Anal. Calcd for $C_{21}H_{16}N_2O_6$·0.5CH_3OH: C, 63.23; H, 4.43; N, 6.86. Found: C, 63.11; H, 4.34; N, 7.05.

The data support a structure of (Phthal–$CH_2)_2\overline{COCH_2CH_2O}$·0.5$CH_3OH$ (**20b**) for this minor byproduct.

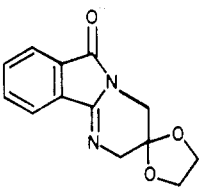
The mother liquor from **20b** was concentrated in vacuo to a brown oil which was chromatographed over silica gel by eluting with 10 L of 1% oMeOH/99% $CHCl_3$ mixtures to afford 3.0 g (15%) of starting material 1 (Y = H) and 16 g (52.8% based on recovered starting material) of phthalimido amidine **3b** (Y = H), mp 115–125 °C (from acetone). The dried analytical sample had the following: mp 143–145 °C; IR (Nujol) 3260 (NH), 1775, 1720 (C=O), 1615 cm^{-1} (C=C); UV (95% EtOH) λ_{max} 219 nm (ϵ 79 350); ^{1}H NMR ($CDCl_3$) δ 6.90–7.90 (m, 12 H, aromatic), 5.55 (br s, 1 H, NH), 3.98 (s, 4 H, OCH_2), 3.80–4.00 (1 br s, overlapping a sharp s, 4 H, $C(O)NCH_2$ + ring CH_2), 3.55 (br d, 2 H, $NHCH_2$); mass spectrum, weak molecular ion at m/e 514 with fragment ions at m/e 283 (M^+ – Phthal – $CH{=}\overline{COCH_2CH_2O}$), 232 (Phthal-$CH_2\overline{C^+OCH_2CH_2O}$), 160 (Phthal – CH_2^+).

Anal. Calcd for $C_{28}H_{23}ClN_4O_4$: C, 65.30; H, 4.50; N, 10.85; Cl, 6.88. Found: C, 65.10; H, 4.55; N, 10.85; Cl, 6.79.

In an analogous way, 18 g (0.056 mol) of 1 (Y = Cl) was treated with 28.9 g (0.112 mol) of **2b** in 800 mL of absolute EtOH to provide 27 g (84%) of **3b** (Y = Cl), mp 180–190 °C. The analytical sample, crystallized from methanol–ethyl acetate mixtures, had the following: mp 200–202 °C; IR (Nujol) 3420 (NH), 1775, 1710 (C=O); ^{1}H NMR ($CDCl_3$) δ 6.82–7.95 (m, 11 H, aromatic), 5.61 (br s, 1 H, NH), 3.80–4.28 (m, 8 H, OCH_2, $C(O)NCH_2$), 3.66 (br s, 2 H, $NHCH_2$); mass spectrum, molecular ion peak at m/e 548 with fragment ions at m/e 317, 232, 160.

Anal. Calcd for $C_{28}H_{22}Cl_2N_4O_4$: C, 61.21; H, 4.04; N, 10.20; Cl, 12.90. Found: C, 61.42; H, 4.11; N, 9.93; Cl, 12.57.

When 42.0 g (0.120 mol) of imino thioether **28** was treated with slightly more than 1 equiv of **2b** (34 g, 0.132 mol) and refluxed for 18 h in 300 mL of *n*-butanol, only 0.25 g (0.4%) of **3b** (Y = Cl) was isolated after extensive chromatography over silica gel. The major compounds isolated were starting material **28** (~80%), bisphthalimide **20b** (5%), and acyl amidine **29** (~10%) which



29

crystallized from ethyl acetate–hexane mixtures as prisms: mp 175–177 °C; IR (Nujol) 1735 (C=O) 1670 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$) δ 4.05 (s, 4 H, CH_2O), 3.82 (AB, 2 H, CH_2N), 3.73 (AB, 2 H, CH_2N); mass spectrum, molecular ion peak at m/e 224, with a fragment ion at m/e 172 (M^+ – $C{=}\overline{OCH_2CH_2O^+}$).

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.95; H, 4.97; N, 11.46.

***N*-[[8-Chloro-6-phenyl- and -6-(*o*-chlorophenyl)-4*H*-imidazo[1,2-*a*][1,4]benzodiazepin-1-yl]methyl]phthalimide 4b (Y = H, Cl).** After a suspension of 31 g (0.060 mol) of **3b** (Y = H) in 100 mL of concentrated H_2SO_4 was stirred at room temperature for 18 h the resulting solution was quenched, by pouring onto ice-cold water, and carefully neutralized with a 10% aqueous sodium hydroxide solution. After chloroform extraction and concentration[37] the resulting yellow oil was crystallized from methanol–ethyl acetate mixtures to afford 15.5 g (65%) of imidazole **4b** (Y = H), mp 236–240 °C. The analytical sample had the following: mp 240–242 °C; IR (Nujol) 1770, 1715 (C=O), 1605, 1595, 1550, 1510, 1480 cm^{-1} (C=C/C=N); UV (95% EtOH) λ_{max} 220 nm (ϵ 76 200); ^{1}H NMR ($CDCl_3$), see Table I; mass spectrum, molecular ion peak at m/e 452 with a base peak at m/e 292 (M^+ – Phthal CH_2).

Anal. Calcd for $C_{26}H_{17}ClN_4O_2$: C, 68.95; H, 3.78; N, 12.37; Cl,

(37) In cases where reaction intermediates or products were isolated "following extraction and concentration", the procedure carried out was to dilute the reaction mixture with the indicated solvent or to extract an aqueous sodium hydroxide solution with several portions of the indicated solvent. If the aqueous layer contained sodium bicarbonate, then the products were isolated "following bicarbonate extraction". The combined organic extracts were dried over sodium sulfate unless otherwise specified.

7.83. Found: C, 68.87; H, 4.22; N, 12.35; Cl, 7.63.

In the same way 16.0 g (0.029 mol) of **3b** (Y = Cl) afforded 10.5 g (74%) of **4b** (Y = Cl) as a fluffy orange powder. The analytical sample, recrystallized from ethyl acetate–hexane mixtures, had the following: mp 218–220 °C; ^{1}H NMR ($CDCl_3$), see Table I; mass spectrum, molecular ion peak at m/e 486.

Anal. Calcd for $C_{26}H_{16}Cl_2N_4O_2$: C, 64.08; H, 3.31; N, 11.50; Cl, 14.35. Found: C, 63.90; H, 3.35; N, 11.26; Cl, 14.06.

8-Chloro-1-[(dimethylamino)methyl]-6-phenyl- and -6-(*o*-chlorophenyl)-4*H*-imidazo[1,2-*a*][1,4]benzodiazepine, 3c (Y = H, Cl). A suspension of 1.0 g of **4b** (Y = H; 2.0 mmol) and 0.5 g of hydrazine hydrate (10.0 mmol) in 25 mL of absolute EtOH was stirred for 18 h at room temperature. After the white phthalazide precipitate was filtered, the filtrate was concentrated in vacuo, dissolved in chloroform, washed with a saturated sodium chloride solution, dried over sodium sulfate, and concentrated in vacuo to an oil. The oil was taken up in dry methanolic HCl and crystallized from MeOH–EtOAc mixtures to afford 830 mg (95%) of **18** (i.e., 4, X = NH_2; Y = H). The analytical sample had the following: mp 275–280 °C dec; IR (Nujol) 2790, 2620, 2600 (NH^+-alkyl), 1605, 1590, 1545, 1510, 1495 cm^{-1} (C=C/C=N); ^{1}H NMR ($CDCl_3$ for the free base), see Table I.

Anal. Calcd for $C_{18}H_{15}ClN_4 \cdot 2HCl \cdot 0.5H_2O$: C, 53.42; H, 4.48; N, 13.85; Cl, 26.27. Found: C, 53.53; H, 4.34; N, 14.05; Cl, 26.17.

A stirred solution of **18** (free base; 1.42 g, 4.30 mmol) in 20 mL of acetonitrile was treated successively with 2.2 mL of a 37% formalin solution and 550 mg of sodium cyanoborohydride (8.91 mmol). The pH of the solution was maintained between 6.4–6.8 by periodically adding, dropwise, a solution of 0.2 mL of acetic acid dissolved in 2.0 mL of acetonitrile. The total reaction time was 2 h. After concentration, chloroform extraction,[37] and reconcentration, the resulting yellow oil was chromatographed over silica gel by eluting with 2% MeOH/98% $CHCl_3$ mixtures to afford 700 mg (47% yield) of the desired [(dimethylamino)-methyl]imidazole **4c** (Y = H), mp 170–175 °C. The analytical sample, crystallized from ethyl acetate–hexane mixtures, had the following: mp 181–182 °C; IR (Nujol) 2770 (*N*-alkyl), 1610, 1595, 1555, 1515, 1490 cm^{-1} (C=C/C=N); UV (95% EtOH) λ_{max} 222 nm (ϵ 38 350); ^{1}H NMR ($CDCl_3$), see Table I; mass spectrum, molecular ion peak at m/e 350 with a strong fragment ion at m/e 306 ($M^+ - Me_2N$).

Anal. Calcd for $C_{20}H_{19}ClN_4$: C, 68.46; H, 5.46; N, 15.97; Cl, 10.10. Found: C, 68.50; H, 5.50; N, 15.90; Cl, 10.37.

When the reductive methylation was scaled up (11.5 g, 0.035 mol of **18**), **4c** (Y = H; R_f 0.45)[13a] was isolated in only 18% yield. The cyano boron adduct **4c'** (R_f 0.73)[13a] was isolated in 20% crystallized yield. The analytical sample crystallized from ethyl acetate–hexane mixtures had the following: mp 211–213 °C; IR (Nujol) 3120 (=CH), 2410 (BH), 2190 cm^{-1} (C≡N); UV (95% EtOH) λ_{max} 223 nm (ϵ 37 371); ^{1}H NMR ($CDCl_3$), see Table I; mass spectrum, no molecular ion. Stong fragment ions were observed at m/e 350 and 306.

Anal. Calcd for $C_{20}H_{19}ClN_4 \cdot BH_2CN$: C, 64.72; H, 5.43; N, 17.98; Cl, 9.10; B, 2.77. Found: C, 64.95; H, 5.64; N, 18.34; Cl, 9.16; B, 3.30.

Dichloroimidazole **4c** (Y = Cl) was prepared in 30% yield from **4b** (Y = Cl) by an analogous two-step procedure. It crystallized in two forms, an $HBr \cdot 0.5MeOH \cdot H_2O$ solvate (mp 168–171 °C, bubbles) and a 1.5HBr salt (mp 199–201 °C, from methanol–ether): ^{1}H NMR ($CDCl_3$, free base), see Table I; mass spectrum, molecular ion peak at m/e 384 with a strong fragment ion at m/e 340 ($M^+ - Me_2N$).

Anal. Calcd for $C_{20}H_{18}Cl_2N_4 \cdot 1.5HBr$: C, 47.41; H, 3.88; N, 11.06. Found: C, 47.51; H, 3.98; N, 11.31.

Preparation and Attempted Cyclization of Amidines 3c and 3d. Crude amidine **3c** (Y = H) was isolated as a yellow oil in 90% yield from 0.90 g (3.3 mmol) of **1** (Y = H) and 1 g (10 mmol) of **2c** in 40 mL of *n*-butanol at 60 °C for 30 min; ^{1}H NMR ($CDCl_3$) δ 3.95 (s, OCH_2CH_2O), 3.65–4.2 (m, NCH_2, $NHCH_2$ ring CH_2), 2.28 (s, NMe_2). All attempts to affect its cyclization to **4c** (Y = H) failed.

Azido amidine **3d** (Y = H) was obtained in 87% yield as a brown solid from the reaction of 0.143 g (0.5 mmol) of **1** (Y = H) and 0.240 g (1.5 mmol) of **2d** in 10 mL of absolute EtOH. The analytical sample had the following: mp 181.5–182.5 °C; IR (Nujol) 3250 (NH) 2100 cm^{-1} (N_3); ^{1}H NMR ($CDCl_3$) δ 7.06–7.82 (m, 8 H, aromatic), 5.35 (br s, 1 H, NH), 4.00 (s, 4 H, OCH_2), 3.82–4.80 (br s, 2 H, ring CH_2), 3.60 (br s, 2 H, $NHCH_2$), 3.30 (s, 2 H, CH_2N_3); mass spectrum, weak molecular ion at m/e 410 with fragment ion peaks at m/e 354 ($M^+ - CH_2N_3$), 282 ($M^+ - N_3CH_2COCH_2CH_2O$), 269 ($M^+ - N_3CH_2COCH_2CH_2OCH$).

Anal. Calcd for $C_{20}H_{19}ClN_2O_4$: C, 58.46; H, 4.66; N, 20.46; Cl, 8.63. Found: C, 58.41; H, 4.69; N, 20.38; Cl, 9.00.

Attempts to cyclize the azido amidine **3d** (Y = H) in acid led to extensive decomposition of the starting material with the formation of unrecognizable products.

8-Chloro-1-(hydroxymethyl)-6-phenyl- and -6-(*o*-chlorophenyl)-4*H*-imidazo[1,2-*a*][1,4]benzodiazepine, 4a (Y = H, Cl). After a suspension of **1** (Y = H; 34.32 g, 0.12 mol) and **2a** (31 g, 0.24 mol) in 1 L of *n*-butanol was heated for 18 h at 100 °C, the solvent was removed in vacuo, and the residue, dissolved in chloroform, was washed with water and a saturated brine solution. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to a dark red oil which was chromatographed over silica gel by eluting with 1–3% methanol/97–99% chloroform mixtures to afford 36 g (78%) of crystalline product **3a** (Y = H), mp 165–168 °C. When the same reaction was run with 50 g of **1** (Y = H) and 40 g (1.5 equiv) of **2a** in 1 L of ethanol for 3 h, **3a** (Y = H) was isolated in 90% yield without chromatography. The analytical sample recrystallized from ethyl acetate had the following: mp 169–171 °C; IR (Nujol) 3240 cm^{-1} (NH/OH); UV (95% EtOH) λ_{max} 231 nm (ϵ 20 800); NMR ($CDCl_3$) δ 6.40 (br s, 1 H, NH), 5.80 (br s, 1 H, OH), 3.90 (s, 4 H, OCH_2CH_2O), 3.40 (m, 4 H, NCH_2, CH_2O); mass spectrum, molecular ion peak at m/e 385.

Anal. Calcd for $C_{20}H_{20}ClN_3O_3$: C, 62.25; H, 5.22; N, 10.89; Cl, 9.19. Found: C, 62.39; H, 5.44; N, 11.09; Cl, 9.26.

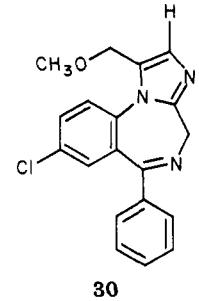
Similarly, 3.85 g (12.0 mmol) of **1** (Y = Cl) and 3.3 g (24.0 mmol) of **2a** in 150 mL of *n*-butanol afforded 4.1 g (82% yield) of **3a** (Y = Cl), mp 195–199 °C. The analytical sample, crystallized from ethyl acetate, had the following: mp 198–200 °C; UV (95% EtOH) λ_{max} 219 nm (ϵ 28 600); ^{1}H NMR ($CDCl_3$) δ 6.15 (br s, 1 H, NH), 5.42 (br s, 1 H, OH), 3.96 (s, 4 H, OCH_2CH_2O), 3.33–3.72 (m, 4 H, collapses to 2 single lines on D_2O exchange, NCH_2 and OCH_2).

Anal. Calcd for $C_{20}H_{19}Cl_2N_3O_3$: C, 57.15; H, 4.56; N, 10.00; Cl, 16.87. Found: C, 57.17; H, 4.58; N, 10.15; Cl, 16.90.

After solid **3a** (Y = H; 35 g, 0.090 mol) was stirred in 75 mL of concentrated H_2SO_4 the solution was treated as described for the preparation of **4b** to provide, after silica gel chromatography, 9 g (32% yield) of **4a** (Y = H), mp 210–213 °C (R_f 0.57). The analytical sample crystallized from methanol–ethyl acetate mixtures had the following: mp 213–215 °C; IR (Nujol) 3100 (br, OH), 1605 cm^{-1} (C=C); ^{1}H NMR (Me_2SO-d_6), see Table I; mass spectrum, molecular ion peak at m/e 323 with a strong fragment ion at m/e 292 ($M^+ - CH_2O$).

Anal. Calcd for $C_{18}H_{14}ClN_3O$: C, 66.77; H, 4.36; N, 12.98; Cl, 10.95. Found: C, 66.66; H, 4.35; N, 12.96; Cl, 11.00.

Early fractions from the column were pooled to yield 3.5 g of crude oil (R_f 0.57) from which crystallized 0.50 g of yellow crystalline ether **30**, mp 195–200 °C. The analytical sample had the



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following: mp 202–203 °C; IR (Nujol) 3100, 3040 (sharp, =CH), 1605 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$) δ 8.01 (d, J = 4.5 Hz, 1 H, aromatic CH_{10}), 7.17 (s, 1 H, imidazole CH), 5.35 (d, J = 12.5 Hz, 1 H, CH_A), 4.42 (m, 2 H, CH_2O), 4.04 (d, J = 12.5 Hz, 2 H, CH_B), 3.41 (s, 3 H, OCH_3); mass spectrum, molecular ion peak at m/e 336 with a strong fragment ion at m/e 291 ($M^+ - CH_2OCH_3$).

Anal. Calcd for $C_{19}H_{16}ClN_3O$: C, 67.55; H, 4.78; N, 12.44. Found: C, 67.68; H, 4.77; N, 12.39.

Heating **3a** (Y = H; 7.72 g, 0.02 mol) in 30 mL of reagent methanesulfonic acid to 58 °C for 20 h, followed by the usual workup procedure, afforded 4.13 g (64%) of **4a** (Y = H) without chromatography.

Dichloro analogue **4a** (Y = Cl) was obtained in 50% yield on a 5.0-mmol reaction scale via cyclization of **3a** (Y = Cl) in sulfuric acid. The analytical sample, crystallized from ethyl acetate–hexane, had the following: mp 193–195 °C; ^{1}H NMR ($CDCl_3$), see Table I; mass spectrum, molecular ion peak at m/e 357 with a base peak at m/e 326 ($M^+ - CH_2O$).

Anal. Calcd for $C_{18}C_{13}Cl_2N_3O$: C, 60.35; H, 3.66; N, 11.73; Cl, 19.79. Found: C, 60.39; H, 3.66; N, 11.64; Cl, 19.78.

***N*-[[8-Chloro-6-phenyl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepin-1-yl]methyl]phthalimide, 4b (Y = H). From 4a.** To 900 mg (3.00 mL) of **4a** (Y = H), 780 mg (3.00 mmol) of triphenylphosphine, and 450 mg (3.00 mol) of phthalimide suspended in 15 mL of THF cooled to 0 °C was added, dropwise, 550 mg (3.00 mmol) of diethyl azodicarboxylate.[12] After being stirred for 1 h at room temperature, the resulting solution was quenched in cold water and extracted with three 50-mL portions of chloroform. After being washed with brine, the chloroform solution was dried (Na_2SO_4) and concentrated in vacuo to an orange oil which was chromatographed over silica gel to afford 1.20 g (88% yield) of phthalimide **4b** (Y = H), mp 240–242 °C, identical with the material described above.

8-Chloro-1-[2-(dimethylamino)ethyl]-6-phenyl-4*H*-imidazo[1,2-*a*][1,4]benzodiazepine, 4h (Y = H). Via 2e. After a suspension of 10 g (0.035 mol) of **1** (Y = H) and 12.7 g (0.046 mol) of **2e** in 150 mL of absolute EtOH was heated at 60 °C overnight, the resulting white solid was filtered, washed with EtOH, and dried to afford 5 g of solid **10a** (36% yield based on recovered starting material). The analytical sample, recrystallized from methanol–chloroform mixtures, had the following: mp 210–212 °C; IR (Nujol) 3280 (NH), 3070 (C=CH), 1770, 1720 cm^{-1} (C=O); UV (95% EtOH) λ_{max} 220 nm (ϵ 60 700), 240 (34 800); ^{1}H NMR ($CDCl_3$) δ 7.10–7.95 (m, 12 H, aromatic), 6.10 (br s, 1 H, NH), 4.10 (m, 4 H, OCH_2CH_2O), 3.80 (s, 2 H, $PhthalCH_2C$), 4.0 (br s, 2 H, ring CH_2), 3.55 (br t, J = 6.5 Hz, 2 H, $NHCH_2$), 2.05 (t, J = 6.5 Hz, 2 H, CCH_2); mass spectrum, molecular ion peak at m/e 528 with fragment ions at m/e 368 ($M^+ - PhthalCH_2$), 296 ($M^+ - PhthalCH_2COCH_2CH_2O$), 160 ($PhthalCH_2^+$).

Anal. Calcd for $C_{29}H_{25}ClN_4O_4$: C, 65.84; H, 4.76; N, 10.59; Cl, 6.70. Found: C, 65.66; H, 4.58; N, 10.68; Cl, 7.08.

The filtrate from **10a** was concentrated in vacuo to a gum, which was chromatographed over silica gel (vide supra) to provide 2.5 g (25% yield) of starting material and 9.0 g (65% yield based on recovered starting material) of a white gum. After trituration with ethyl acetate, 300 mg of this gum afforded 200 mg of a crystalline solid, which, when recrystallized from ethyl acetate–hexane mixtures, afforded **3e** as white needles: mp 216–218 °C; IR (Nujol) 3220 (NH), 3050 (C=CH), 1765, 1710 cm^{-1} (C=O); UV (95% EtOH), λ_{max} 220 nm (ϵ 61 450), 240 (36 650); ^{1}H NMR ($CDCl_3$) δ 7.10–7.95 (m, 12 H, aromatic), 6.40 (br s, 1 H, NH), 4.10 (br s, 2 H, ring CH_2), 4.00 (s, 4 H, OCH_2CH_2O), 3.80 (m, 2 H, Phthal CH_2), 3.60 (br s, 2 H, $NHCH_2$), 2.10 (t, J = 7.0 Hz, 2 H, CCH_2); mass spectrum, molecular ion peak at m/e 528 with fragment ions at m/e 282 ($M^+ - PhthalCH_2CH_2COCH_2CH_2O$), 246 ($PhthalCH_2CH_2COCH_2CH_2O^+$), 160 ($PhthalCH_2^+$).

Anal. Calcd for $C_{29}H_{25}ClN_4O_4$: C, 65.84; H, 4.76; N, 10.59; Cl, 6.70. Found: C, 65.96; H, 4.74; N, 10.51; Cl, 6.68.

A solution of 8.0 g (0.015 mol) of a 4:1 mixture of **3e** (Y = H)/**10a** in 25 mL of 97% H_2SO_4 was stirred at room temperature overnight. After chloroform extraction and concentration[37] the resulting oil was chromatographed over silica gel (vide supra) to afford 2.5 g (35% yield) of a 4:1 mixture of **12**/**10b** (vide infra) and 4.2 g (60% yield) of an oil which crystallized as a methanol solvate from methanol–chloroform mixtures to give **4e** (Y = H): mp 228–231 °C; IR (Nujol) 3620, 3330 (OH), 1770, 1720 cm^{-1} (C=O); UV (95% EtOH) λ_{max} 220 nm (ϵ 67 150), 238 (26 650); ^{1}H NMR ($CDCl_3$), see Table I; mass spectrum, molecular ion peak at m/e 466 with fragment ions at m/e 319 ($M^+ - PhthalH$), 292 ($M^+ - PhthalCH_2CH_2$), 160 ($PhthalCH_2^+$).

Anal. Calcd for $C_{27}H_{19}ClN_4O_4 \cdot CH_3OH$: C, 67.39; H, 4.65; N, 11.23; Cl, 7.10. Found: C, 67.03; H, 4.67; N, 11.24; Cl, 7.41.

When a 2-g sample of crude ketone **12** was subjected to the sulfuric acid cyclization reaction for 6 days, TLC (vide supra) and ^{1}H NMR analysis of the 1.5 g of product indicated that 70% of the starting material remained. Apparently cyclization of the ketone is very slow (cf. titanium tetrachloride procedure).

When a solution of 260 mg (0.50 mmol) of ketal **10a** was subjected to the sulfuric acid cyclization reaction for 1 h or longer, 60 mg (25% yield) of ketone **10b** was obtained as white needles, following workup and extraction from aqueous sodium carbonate solution. The analytical sample had the following: mp 178–179 °C; IR (Nujol) 3260 (NH), 3070 (C=CH), 1780, 1725 cm^{-1} (C=O); UV (95% EtOH), λ_{max} 219 nm (ϵ 65 150), 235 (37 500); ^{1}H NMR ($CDCl_3$) δ 7.10–8.00 (m, 12 H, aromatic), 5.90 (br s, 1 H, NH), 4.50 (s, 2 H, $PhthalCH_2C{=}O$), 4.15 (br s, 2 H, ring CH_2), 3.60 (br m, becomes t on D_2O exchange, J = 6.0 Hz, 2 H, $NHCH_2$), 2.80 (m, J = 6.0 Hz, 2 H, $CH_2C{=}O$); mass spectrum, weak molecular ion at m/e 484 with strong fragment ions at m/e 268 ($M^+ - PhthalCH_2C(O)CH_2CH_2$), 187 ($PhthalCH{=}C{=}O^+$), 160 ($PhthalCH_2^+$) (cf. **12**, vide infra).

Anal. Calcd for $C_{21}H_{21}ClN_4O_3$: C, 66.87; H, 4.37; N, 11.56; Cl, 7.31. Found: C, 66.64; H, 4.31; N, 11.45; Cl, 7.39.

By the procedure described above to prepare **18**, 466 mg (1.00 mmol) of phthalimide **4e** was converted to 306 mg (84%) of 8-chloro-1-(2-aminoethyl)-6-phenyl-4*H*-imidazo[1,2-*a*][1,4]-benzodiazepine, **32** (i.e., **4**, X = CH_2NH_2; Y = H), isolated as a foam: IR (Nujol) 3360, 3280 (NH), 3060 cm^{-1} (C=CH); UV (95% EtOH) λ_{max} 221 nm (ϵ 35 150); ^{1}H NMR ($CDCl_3$) δ 7.30–7.70 (m, 8 H, aromatic), 6.89 (s, 1 H, imidazole CH), 5.28 (d, J = 12.5 Hz, 1 H, equatorial CH), 3.99 (d, J = 12.5 Hz, 1 H, axial CH), 2.89 (s, 4 H, CH_2CH_2N), 1.40 (br m, 2 H, NH_2); mass spectrum, no molecular ion peak, but a large fragment ion at m/e 307 ($M^+ - CH_2{=}NH$), found m/e 307.0866, (calcd for $C_{18}H_{14}ClN_3$ m/e 307.0876).

A solution of 5.4 g (0.016 mol) of **32** and 16 mL (0.186 mol) of a 37% formalin solution in 55 mL of methanol was stirred at room temperature for 1 h, at which time imine formation was complete. After being cooled to 0 °C in an ice bath the reaction mixture was treated cautiously with 2.13 g (0.056 mol) of sodium borohydride, then warmed to room temperature, and stirred for 42 h. Since both TLC (vide supra) and NMR evidence indicated the presence of unreduced imine, the reaction was quenched in water, extracted with chloroform, dried over sodium sulfate, and concentrated in vacuo to an oil, which was resubjected to the above reduction methylation reaction conditions. Repeating the workup afforded the product as 6.3 g of a gum. This gum was subjected to medium-pressure liquid chromatography on a Merck prepacked (size C) silica gel 60 column by eluting with 4 L of 2–15% methanol/98–85% chloroform mixtures at a flow rate of 5 mL/min. The amine **4h** was obtained as 2.9 g (43%) of oil which was converted to a semicrystalline foam after concentration from ether: IR (Nujol) 3380 (OH), 3060 (C=CH), 2740 cm^{-1} (*N*-alkyl); ^{1}H NMR 7.32–7.74 (m, 8 H, aromatic), 6.92 (s, 1 H, imidazole CH), 5.31 (d, J = 12.5 Hz, 1 H, CH equatorial), 4.00 (d, J = 12.5 Hz, 1 H, CH axial), ~2.2–3.1 (m, 4 H, NCH_2CH_2), 2.20 (s, 6 H, $N(CH_3)_2$); mass spectrum, strong molecular ion peak at m/e 364 with weak fragment ions at m/e 320 ($M^+ - NMe_2$), 306 ($M^+ - Me_2NCH_2$), 58 ($Me_2NCH_2^+$).

Anal. Calcd for $C_{21}H_{21}ClN_4 \cdot H_2O$: C, 65.87; H, 6.06; N, 14.64. Found: C, 65.43; H, 5.59; N, 14.52.

When sodium cyanoborohydride was used for the reductive methylation, boron complexes of the product were formed according to NMR evidence. These complexes could not be converted to the free base.

4b. From Acetylene 11a. Acetylene **11a** was prepared from thione **1** (Y = H) and $H_2NCH_2C{\equiv}CCH_2OH$ in THF at room temperature in 57% crystalline yield. The analytical sample recrystallized from ethyl acetate–hexane mixtures had the following: mp 174–175 °C; IR (Nujol) 3260 cm^{-1} (NH/OH); ^{1}H NMR ($CDCl_3$) δ 7.20–7.70 (m, 8 H, aromatic), 6.80 (br s, 1 H, NH), 4.00 (br s, 4 H, ring CH_2 and OCH_2), 3.85 (br s, 2 H, $NHCH_2$); mass spectrum, molecular ion peak at m/e 337 with fragment ions at m/e 306 ($M^+ - CH_2OH$) and 292 ($M^+ - CH_2CH_2OH$, i.e., from the imidazole).

Anal. Calcd for $C_{19}H_{16}ClN_3O$: C, 67.55; H, 4.78; N, 12.49; Cl, 10.49. Found: C, 67.53; H, 4.92; N, 12.78; Cl, 10.63.

By the Mitsunobu procedure[12] 6.74 g (0.020 mol) of alcohol **11a** was converted to 8.3 g (89% yield) of phthalimide **11b**. The analytical sample was crystallized from methanol–ethyl acetate mixtures: mp 203–205 °C; IR (Nujol) 3240 (NH), 1775, 1725 cm^{-1} (C=O); ^1H NMR 4.45 (br s, 2 H, CH_2Phthal), 4.10 (br m, 4 H, $NHCH_2$, ring CH_2); mass spectrum, molecular ion peak at m/e 466 with weak fragment ions at m/e 319 (M^+ - PhthalH) and 292 (M^+ – PhthalCH_2CH_2, i.e., from the imidazole).

Anal. Calcd for $C_{27}H_{19}ClN_4O_2$: C, 69.45; H, 4.10; N, 12.00; Cl, 7.59. Found: C, 69.33; H, 4.11; N, 12.02; Cl, 7.80.

To a solution of 4.66 g (0.010 mol) of **11b** in 20 mL of 97% sulfuric acid was added, in portions, 100 mg (0.3 mmol) of mercuric sulfate. The resulting mixture was stirred at room temperature for 18 h. After the usual chloroform extraction and concentration,[37] the resulting yellow oil was chromatographed over silica gel to afford 2.5 g (46% yield) of crude ketones consisting primarily of **12** and 2.5 g (54% yield) of crude imidazole **4e**, mp 227–229 °C. After crystallization from ethyl acetate the crude ketone **12** [contaminated with 10–20% of ketone **10b** (^1H NMR evidence)] afforded white crystals: mp 210–212 °C; IR (Nujol) 3350 (NH), 1750, 1710 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 6.30 (br s, 1 H, NH), ~4.0–5.0 (br s, 2 H, ring CH_2), 4.06 (br s, 2 H, $NHCH_2C$=O), 3.97 (t, J = 7.0 Hz, PhthalCH_2), 2.84 (t, J = 7.0 Hz, 2 H, CH_2C=O); mass spectrum, molecular ion peak at m/e 484 with fragment ions at m/e 466 ($M^+ - H_2O$, i.e., the imidazole derivative), 338 (weak, M^+ - Phthal), 337 (weak, M^+ - PhthalH), 320 ($M^+ - H_2O$ - Phthal), 319 ($M^+ - H_2O$ - PhthalH), 306 ($M^+ - H_2O$ - PhthalCH_2), 292 ($M^+ - H_2O$ - PhthalCH_2CH_2), 268 (M^+ - $CH_2C(O)CH_2CH_2$Phthal).

Anal. Calcd for $C_{27}H_{21}ClN_4O_3$: C, 66.87; H, 4.37; N, 11.56; Cl, 7.31. Found: C, 66.83; H, 4.51; N, 11.59; Cl, 6.78.

A suspension of 2.33 g of crude **12** (0.005 mol) in 30 mL of 1,2-dimethoxyethane (DME) at 0 °C was treated, dropwise, with 0.75 mL of titanium tetrachloride (0.0068 mol). The resulting yellow suspension was warmed to room temperature and then refluxed for 18 h. After the usual extraction and concentration,[37] the crude yellow semisolid was chromatographed over silica gel (vide supra) to provide 0.50 g (22%) of starting material and 1.2 g of crude imidazole **4e**, which crystallized from ethyl acetate to afford 1.0 g of product **4e**, mp 227–228 °C. This solid was not solvated.

8-Chloro-6-phenyl-1-[(dimethylamino)methyl]-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine, 7. A solution of 6.54 g (0.02 mol) of **4a** (Y = H) and 26.2 g (0.5 mol) of 88% formic acid in 13.5 mL of a 37% aqueous formalin solution was heated to 100 °C for 3 h. After the usual base extraction and concentration,[37] the resulting oil was chromatographed over silica gel (vide supra). The purified amino alcohol **5** (4.0 g) had the following: ^1H NMR ($CDCl_3$) δ 7.20–8.00 (m, 8 H, aromatic), 6.90 (s, 1 H, imidazole CH), 4.40 (s, 2 H, OCH_2), 4.08 (br s, exchanged in D_2O, 1 H, OH), 3.18 (br s, not sharpened in D_2O, 2 H, CH_2N), 1.71 (s, 6 H, $N(CH_3)_2$). By Mitsunobu's procedure[12] and the usual extraction, concentration,[37] and silica gel chromatography, the oil **5** was converted to 3.2 g of phthalimide **6**.

Treating **6** with 1.2 g (0.025 mol) of hydrazine hydrate in 20 mL of absolute EtOH for 18 h afforded, after filtration and chromatography, 1.3 g of **7**, mp 209–211 °C. The analytical sample, recrystallized from ethyl acetate, had the following: mp 213–215 °C; IR (Nujol) 2780 (*N*-alkyl); ^1H NMR ($CDCl_3$), see Table I; mass spectrum, weak molecular ion at m/e 350 with strong fragment ions at m/e 307 ($M^+ - CH_3N{=}CH_2$), 306 [M^+ - N-$(CH_3)_2$], 58 [$(CH_3)_2N^+{=}CH_2$].

Anal. Calcd for $C_{20}H_{19}ClN_4$: C, 68.46; H, 5.46; H, 5.46; N, 15.97; Cl, 10.10. Found: C, 68.15; H, 5.47; N, 16.22; Cl, 10.38.

8-Chloro-6-(*o*-chlorophenyl)-1-[(dimethylamino)-methyl]-3-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine, 16. 2-Bromo-1,1-dimethoxypropane (35 g, prepared in 51% yield from 29 g of propionaldehyde and 81 g of bromine in 400 mL of methanol)[24] dissolved in 150 mL of DMF was heated with 32.5 g (2.5 equiv) of sodium azide at 90 °C for 3 days. The cooled reaction mixture was quenched in an aqueous sodium bicarbonate solution and extracted with benzene. The dried ($MgSO_4$) benzene layer was concentrated on a steam bath under a Vigreaux column and the resulting oil distilled [67–70 °C (300 mmHg)] to afford 27.5 g of colorless azide containing a small amount of bromide starting material; IR (Nujol) 2100 cm^{-1} (N_3). The azide was reduced in 50 mL of absolute EtOH with 0.50 g of 10% Pd/C catalyst in a Parr bomb at room temperature and 50 psi. After the catalyst was filtered and the EtOH was removed on a steam bath, the crude product was poured into cold water made basic to pH ~10 with sodium hydroxide and extracted with hexane to remove any unreacted bromo acetal. The aqueous layer was made basic to pH >13 (solid NaOH) and extracted with chloroform. After the solution was dried ($MgSO_4$) the oil was distilled at 78 °C (67 mmHg) [lit.[38] bp 56–58 °C (40 mmHg)] to afford 11.8 g (52%) of 2-amino-1,1-dimethoxypropane: IR (Nujol) 3360 cm^{-1} (NH); ^1H NMR ($CDCl_3$) δ 3.99 (d, J = 6.0 Hz, 1 H, CHO), 3.41 [2 s, 6 H, $(OCH_3)_2$], 3.01 (m, 1 H, CHN), 1.36 (s, 2 H, NH_2), 1.08 (d, J = 6.0 Hz, 3 H, CH_3); mass spectrum, weak molecular ion peak at m/e 119.

1 (Y = Cl; 80 g) and 80 g of 2-amino-1,1-dimethoxypropane afforded 85 g (84% yield) of the corresponding amidine (mp 155.5–157 °C; mass spectrum, molecular ion at m/e 405) which cyclized in concentrated sulfuric acid to afford imidazole **9**[5e] in 86% yield: ^1H NMR ($CDCl_3$) δ 4.74 (br s, 2 H, ring CH_3), 2.28 (d, J = 1.0 Hz, 3 H, CH_3), mass spectrum, molecular ion peak at m/e 341 with fragment ions at m/e 306 (M^+ - Cl) and 301 (M^+ - $CH_3C{\equiv}CH$).

Anal. Calcd for $C_{18}H_{13}Cl_2N_3$: C, 63.17; H, 3.83; N, 12.28; Cl, 20.72. Found: C 63.18; H, 3.88; N, 12.35; Cl, 20.75.

Heating 6.84 g (0.02 mol) of benzodiazepine **9** in 13.5 mL of 37% formalin (0.180 mol) and 26.2 g (0.30 mol) of 88% formic acid for 18 h afforded benzophenone **14** in 55% yield via intermediate **13**, as reported earlier.[19] However, when the heating period was extended for an additional 18 h, several less polar products were observed by TLC (vide supra). After silica gel chromatography the least polar of the products, quinoline **17a**, was crystallized in 3.4% yield: mp 237–240 °C (foaming); 3260 (OH), 2800 cm^{-1} (*N*-alkyl); UV (95% EtOH) λ_{max} 217 nm (ϵ 33000), 239 (28100), 246 (29200), 345 (12050); ^1H NMR ($CDCl_3$) δ 8.56 (d, J = 9 Hz, 1 H, aromatic H_9), 7.16–7.66 (m, 5 H, aromatic), 7.05 (d, $J \simeq$ 2 Hz, 1 H, aromatic), 5.07 (s, 2 H, CH_2O), 2.78 (s, 6 H, $N(CH_3)_2$), 2.46 (br s, 1 H, OH), 2.33 (s, 3 H, CH_3); mass spectrum, molecular ion peak at m/e 399 with fragment ions at m/e 384 (M^+ - CH_3), 364 (M^+ - Cl), 355 [M^+ - $N(CH_3)_2$]. The NMR and mass spectra rule out isomeric structure **17b**.

Anal. Calcd for $C_{21}H_{19}Cl_2N_3O$: C, 63.01; H, 4.78; N, 10.50; Cl, 17.71. Found: C, 62.86; H, 4.95; N, 10.68; Cl, 17.63.

By Mitsunobu's procedure, 8.37 g (0.020 mol) of alcohol **14** was converted to 4.84 g (44.2%) of crystalline phthalimide **15**: mp 162–165 °C (from ethyl acetate); IR (Nujol) 1770, 1715, 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 4.77 (d, J = 16 Hz, 1 H, CH_APhthal), 4.29 (d, J = 16 Hz, 1 H, CH_BPhthal), 3.10 (s, 2 H, CH_2N), 2.24 (s, 3 H, CH_3); mass spectrum, weak molecular ion at m/e 547 with a fragment ion at m/e 468 ($M^+ - CH_3N{=}CH_2$ - Cl).

Anal. Calcd for $C_{29}H_{24}Cl_2N_4O_3$: C, 63.62; H, 4.42; N, 10.24; Cl, 12.95. Found: C, 63.43; H, 4.48; N, 10.03; Cl, 13.10.

Treatment of **15** (1.09 g, 2.00 mmol) in 12 mL of absolute EtOH with 0.20 mL (~4.2 mmol) of hydrazine hydrate at 73 °C for 90 min afforded, after filtration, chromatography, and recrystallization from ethyl acetate, 330 mg (41%) of imidazo[1,5-*a*][1,4]-benzodiazepine (**16**): mp 185–186.5 °C; ^1H NMR, see Table I; mass spectrum, very weak molecular ion at m/e 398 with strong fragment ions at m/e 355 ($M^+ - CH_3N{=}CH_2$) and 354 [M^+ - $(CH_3)_2N$].

Anal. Calcd for $C_{21}H_{20}Cl_2N_4$: C, 63.16; H, 5.05; N, 14.03; Cl, 17.75. Found: C, 62.97; H, 5.03; N, 14.29; Cl, 17.67.

***N*-[[2-(Aminomethyl)-1,3-dioxolan-2-yl]methyl]methyl]-phthalimide, 2b.** Phthalimidoacetone[39] (**19j**) was converted to the corresponding ketal **20j** in 90% yield, mp 92–94 °C (lit.[40] 51%, mp 92–93 °C), and to the bromo ketone **19f** in 43% yield, mp 146–148 °C (lit.[41] mp 145–146 °C), with Br_2 in diethylene glycol. Bromo ketal **20f** was obtained in 55% yield by the slow addition

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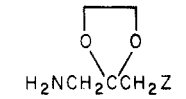
Table II. Physical Properties for Amino Ketals 2



Z	compd	mp, °C	bp, °C (mmHg)	NMR, δ (multiplicity) NCH$_2$	CH$_2$Z	OCH$_2$CH$_2$O	properties
OH	2a	>55		2.87 (s)	3.56 (s)	4.00 (s)	stable amorphous solid
Phthal	2b			2.90 (s)	3.87 (s)	4.17 (s)	stable for several hours
N(CH$_3$)$_2$	2c			2.81 (s)	2.40 (s)	3.98 (s)	stable oil
N$_3$	2d		60-62 (0.03-0.10)	2.80 (s)	3.30 (s)	4.08 (s)	n^{27}D 1.481
CH$_2$Phthal	2e				broad signals		unstable
Br	2f		56-58 (0.05)	3.00 (s)	3.49 (s)	4.10 (s)	n^{28}D 1.499

of 1.6 g (0.010 mol) of Br_2 to a hot solution of 2.47 g (0.010 mol) of ketal **20j** in 10 mL of diethylene glycol: mp 140–141 °C; IR (Nujol) 1775, 1715 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) 4.15 (s, 4 H, OCH_2CH_2O), 3.95 (s, 2 H, CH_2Phthal), 3.60 (s, 2 H, CH_2Br). The same bromo ketal **20f** was obtained directly from **19j** in 55% yield by heating with Br_2 in ethylene glycol. A suspension of 70 g (0.21 mol) of **20f** and 33 g (0.504 mol) of sodium azide (NaN_3) in 250 mL of Me_2SO was heated on a steam bath for 100 h, then cooled, and quenched in ice water. The product was extracted with chloroform, dried (Na_2SO_4), and concentrated in vacuo to a solid, 59 g (95%), mp 92.5–93.5 °C. The analytical sample of **20d** had the following: mp 92.5–93.5 °C; IR (Nujol) 2180, 2140, 2100 (N_3), 1770, 1715 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 4.12 (s, 4 H, OCH_2CH_2O), 3.88 (s, 2 H, CH_2Phthal), 3.40 (s, 2 H, CH_2N_3).

Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 54.16; H, 4.20; N, 19.44. Found: C, 53.95; H, 4.23; N, 19.15.

Azido ketal **20d** was also prepared by first treating bromo ketone **19f** with sodium azide in Me_2SO at room temperature for 20 min to form, after water extraction and chromatography, azido ketone **19d**: mp 124–126 °C; 40% yield; IR (Nujol) 2190, 2100 (N_3), 1775, 1740, 1715 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 4.60 (s, 2 H, CH_2Phthal), 4.15 (s, 2 H, CH_2N_3). The ketal **20d** was prepared in 52% yield by refluxing a 0.1 M solution of ketone **19d** with 2 equiv of ethylene glycol in benzene containing 1 drop of concentrated sulfuric acid and 1 mg of *p*-toluenesulfonic acid for 100 h. (The yields were not maximized.) A solution of 11.52 g (0.040 mL) of **20d** in 250 mL of ethyl acetate was hydrogenated over 1 g of 10% Pd/C at room temperature and 50 psi for 2.5 h. After the catalyst was filtered and the solution was concentrated in vacuo, 10 g of **2b** as a white oil was obtained (^{1}H NMR, see Table II). Attempts to purify the amino phthalimide led to extensive decomposition so the crude oil was used for subsequent reactions.

***N*-[[2-[(Dimethylamino)methyl]-1,3-dioxalan-2-yl]methyl]phthalimide, 20c.** A mixture of 5.2 g (0.020 mol) of **2b** and 6.4 g (0.08 mol) of 37% formalin solution in 250 mL of 4:1 methanol–ethyl acetate was hydrogenated over 5 g of 10% Pd/C at room temperature at 50 psi for 18 h. The catalyst was filtered and the filtrate was concentrated in vacuo to 5 g (86%) of white oil **20c** which crystallized on standing: mp 123–125 °C; IR (Nujol) 2760 (*N*-alkyl), 1770, 1720 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 4 H, aromatic), 3.98 (s, 2 H, CH_2Phthal), 3.90 (s, 4 H, OCH_2CH_2O), 2.95 (s, 2 H, CH_2N), 2.3 [s, 6 H, $N(CH_3)_2$]; mass spectrum, weak molecular ion at *m/e* 290 with fragment ions at *m/e* 232 [$M^+ - CH_2N(CH_3)_2$] and 160 (PhthalCH$_2^+$).

Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25; N, 9.65. Found: C, 61.62; H, 6.45; N, 9.54.

***N*-[[2-(Hydroxymethyl)-1,3-dioxolan-2-yl]methyl]phthalimide, 20a.** Phthalimidoacetate **19i**, mp 140–142 °C, was prepared in 67% yield from bromo ketone **19f** according to the literature procedure.[25] More conveniently, a mixture of 3.04 g (0.015 mol) of **19j** and 9.3 g (0.021 mol) of lead tetraacetate in 210 mL of a 95:5 mixture of benzene–methanol was treated, dropwise, with 27.9 mL of boron trifluoride etherate at 0.5 °C. After being stirred at room temperature for 4 h the reaction mixture was poured on ice and extracted with ethyl acetate. After a brine wash, the organic layer was dried (Na_2SO_4) and concentrated in vacuo to afford, from EtOH, 2.0 g (51% yield) of **19i**, mp 140–142 °C (lit.[25] mp 140–142 °C). The hydroxy ketal **20a** was formed in 70% yield by refluxing a 0.3 M benzene solution of **19i** and 4 equiv of ethylene glycol (catalytic *p*-TsOH and H_2SO_4 present) for 5 h: mp 114–117 °C; IR (Nujol) 3520, 3480 (OH), 1770, 1710 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.80 (s, 4 H, aromatic), 4.09 (m, 4 H, OCH_2CH_2O), 3.89 (s 2 H, CH_2Phthal), 3.58 (d, $J \simeq 7$ Hz, collapses to s in D_2O, CH_2O), 3.05 (t, $J \simeq 7$ Hz, exchanged in D_2O, OH); mass spectrum, very weak $M^+ + 1$ peak at *m/e* 264 with fragment ions at *m/e* 232 ($M^+ - CH_2OH$) and 160 (PhthalCH$_2^+$).

Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.55; H, 5.05; N, 5.15.

1-Phthalimido-4-(dimethylamino)butan-2-one, 19h. Phthalimido ketone **19j** (20.3 g, 0.100 mol) was added to the salt generated from 15.3 g (0.150 mol) of bis(dimethylamino)methane (Aldrich) and 10.5 mL (0.100 mol) of acetyl chloride in 200 mL of DME. Gaseous HCl was bubbled in, causing a vigorous exothermic reaction accompanied by dissolution of all solids. The solution was heated on a steam bath for 2 h and then permitted to cool over 3 days. The reaction mixture was concentrated in vacuo to a yellow green oil which crystallized from methanol–ethyl acetate mixtures to afford 20.5 g (70% **24**) of white needles: mp 193–196 °C; IR (Nujol) 2610, 2510 (NH$^+$), 1775, 1725 cm^{-1} (C=O); mass spectrum, molecular ion at *m/e* 260 with fragment ions at *m/e* 187 (PhthalCH$^+$=C=O) and 160 (PhthalCH$_2^+$).

Anal. Calcd for $C_{14}H_{16}N_2O_3$·HCl: C, 56.66; H, 5.77; N, 9.44; Cl, 11.95. Found: C, 56.39; H, 5.88; N, 9.38; Cl, 11.87.

When the same reaction was carried out in DMF adduct **21** was isolated in 4% yield (HCl salt): mp >215 °C dec; IR (Nujol) 2540, 2500 (NH$^+$), 1770, 1720, 1695 cm^{-1} (C=O); mass spectrum, very weak molecular ion peak at *m/e* 272 with fragment ions at *m/e* 160 (PhthalCH$_2^+$) and 112 [O=CC(=CH$_2$)CH$_2$N(CH$_3$)$_2$].

Anal. Calcd for $C_{15}H_{16}N_2O_3$·HCl: C, 58.35; H, 5.55; N, 9.08; Cl, 11.48. Found: C, 58.57; H, 5.69; N, 8.90; Cl, 11.58.

***N*-[2-[2-(Hydroxymethyl)-1,3-dioxolan-2-yl]ethyl]phthalimide, 23a.** Phthalimido-2-butyn-1-ol, **22** (mp 171–173 °C),[27] was prepared in 70% yield from 292 g (1.58 mol) of potassium phthalimide and 164 g (1.58 mol) of 4-chloro-2-butyn-1-ol[28] in 1.5 1 of DMF. To a mixture of 0.45 g (2.06 mmol) of red mercuric oxide and boron trifluoride etherate (0.6 mL) in 1.5 mL of ethylene glycol was added 6.45 g (0.03 mol) of **22** suspended in 33.5 mL of ethylene glycol. After the initial exotherm, the reaction mixture was first heated on a steam bath for 1 h and then stirred at room temperature overnight. After sodium bicarbonate extraction and concentration[37] the product was crystallized from ethyl acetate–hexane mixtures to afford 5.94 g (71%) of ketal alcohol **23a**: mp 137–140 °C; IR (Nujol) 3480, 3420 (OH), 1765, 1710 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.65–7.90 (m, 4 H, aromatic), 4.00 (s, 4 H, OCH_2CH_2O), 3.85 (t, 2 H, CH_2Phthal), 3.55 (br s, 2 H, OCH_2), 2.25 (br s, 1 H, OH), 2.20 (t, 2 H, CCH_2); mass spectrum, no molecular ion, but fragment ions at *m/e* 246 ($M^+ - CH_2OH$) and 160 (PhthalCH$_2^+$).

Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.66; H, 5.67; N, 5.35.

***N*-[2-[2-(Azidomethyl)-1,3-dioxolan-2-yl]ethyl]phthalimide, 23d.** Hydroxy ketal **23a** (2.77 g, 0.010 mol) was converted to the corresponding mesylate in the usual way.[42] After bicarbonate extraction and concentration[37] the crude mesylate was taken up in 25 mL of Me_2SO, treated with 3.12 g (0.048 mol) of

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sodium azide, and heated to 130 °C for 18 h. After bicarbonate extraction, concentration,[37] and chromatography over silica gel (vide supra), azido ketal **23d** was crystallized from ethyl acetate–hexane mixtures to afford 980 mg of prisms (29%): mp 83.5–85 °C; IR (Nujol) 2110 (N_3), 1770, 1710 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.50–8.00 (m, 4 H, aromatic), 4.05 (s, 4 H, OCH_2CH_2O), 3.83 (t, 2 H, $CH_2Phthal$), 3.30 (s, 2 H, CH_2N_3), 2.17 (t, 2 H, CCH_2); mass spectrum, no molecular ion, but fragment ions at m/e 246 ($M^+ - CH_2N_3$) and 160 ($PhthalCH_2^+$).

Anal. Calcd for $C_{14}H_{14}N_4O_4$: C, 55.62; H, 4.67; N, 18.54. Found: C, 56.00; H, 4.90; N, 18.39.

On scaleup two unidentified more polar compounds were isolated in low yield from the chromatography. The less polar compound, crystallized as prisms from methanol–ethyl acetate mixtures, had the following: mp 154–160 °C; IR (Nujol) 1770, 1715 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 8.50 (s, 1 H), 7.60–7.90 (m, 4 H, aromatic), 4.80 (s, 2 H, CH_2), 4.10 (t, 2 H, $CH_2Phthal$), 3.80–4.10 (m, 4 H, OCH_2CH_2O), 2.20 (t, 2 H, CCH_2).

Anal. Found: C, 54.57; H, 4.68; N, 20.47.

The more polar compound, crystallized from chloroform–methanol mixtures, had the following: mp 225–227.5 °C; ^1H NMR ($CDCl_3$) δ 8.9 (s, 1 H), 7.70–7.90 (m, 4 H, aromatic), 4.60 (s, 2 H, CH_2), 3.85 (t, 2 H, $CH_2Phthal$), 3.60–4.00 (m, 4 H, OCH_2CH_2O), 2.05 (t, 2 H, CCH_2).

Anal. Found: C, 54.16; H, 4.85; N, 21.28.

Azido ketal **23d** was prepared in 64% isolated yield without chromatography by heating bromo ketal **23f** with 5 equiv of sodium azide in Me_2SO at 120 °C for only 18 h. Bromo ketal **23f** (mp 121–122 °C) was prepared in quantitative yield from the known bromo ketone **24f**[41] by refluxing for 5 h with 10 equiv of ethylene glycol in benzene containing several drops of concentrated H_2SO_4.

Amino Ketal Derivatives 2a,c-h. Azido ketal **23d** (14 g, 0.047 mol) in 250 mL of ethyl acetate was hydrogenated over 1.5 g of 10% Pd/C catalyst for 2 h in a Parr bomb. The resulting 12.7 g of oil was treated immediately with thione 1.

Phthalimido ketals **20a-d,f** (10–50 mmol) were dissolved in 100–250 mL of absolute EtOH and treated with 4 equiv of hydrazine hydrate at room temperature for 18 h. After the resulting white solid was filtered, the amines **2a,c,d,f** were obtained by concentration in vacuo and where appropriate distillation. Pertinent physical properties are reported in Table II.

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Intramolecular Aminolysis of Esters. *O*-Acetylserine and γ-Esters of Glutamic Acid

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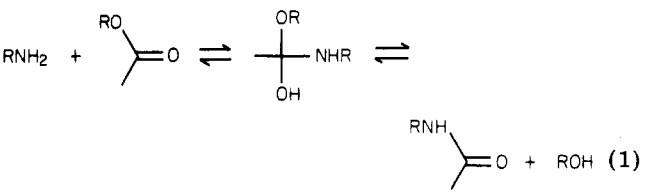
The kinetics of the concurrent hydrolysis and intramolecular aminolysis of γ-ethyl glutamate have been studied in aqueous solution (40 °C) in the range of pH 7.6–10.4. While hydrolysis contributes only 3% to the overall rate of reaction of γ-ethyl glutamate at pH 10.4, its importance relative to aminolysis increases with decreasing pH; at pH 8, the hydrolysis pathway accounts for 32% of the rate of disappearance of the ester. The pH–rate profile for the aminolysis pathway indicates the presence of a water and a hydroxide-catalyzed reaction and provides no evidence for intermediates. The conversion of diethyl glutamate to pyrrolidone-5-carboxylate may occur through either of two competing pathways: (a) rate-determining aminolysis to ethyl pyrrolidone-5-carboxylate, followed by rapid hydrolysis of the ester; (b) rate-determining hydrolysis to γ-ethyl glutamate, followed by rapid cyclization. The pH–rate profile for the intramolecular aminolysis of *O*-acetylserine, determined at zero buffer concentration (30 °C), has the complex appearance characteristic for acyl-transfer reactions involving neutral and anionic tetrahedral intermediates. Quantitative support for the interpretation of the pH–rate profile comes from the analysis of the nonlinear increases in the rate of aminolysis observed in the presence of increasing concentrations of phosphate buffers. The results of this and earlier studies suggest that there may not be major differences in the mechanisms of the intra- and intermolecular aminolysis of weakly acidic alcohols.

Considerable evidence exists that the aminolysis of esters[1-7] (and its reverse, the alcoholysis of amides)[8-12] in aqueous solution involves the participation of unstable tetrahedral addition intermediates (eq 1). Since these



(1)

intermediates do not usually accumulate, their presence has of necessity been demonstrated by indirect means,

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