Quinazolines and 1,4-Benzodiazepines. LXIII.[1] Preparation and Nucleophilic Reactions of 7-Chloro-5-phenyl-3H-1,4-benzodiazepine

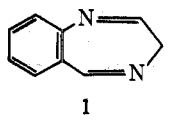
D. L. Coffen,* J. P. DeNoble, E. L. Evans, G. F. Field, R. Ian Fryer, D. A. Katonak, B. J. Mandel, L. H. Sternbach, and W. J. Zally

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

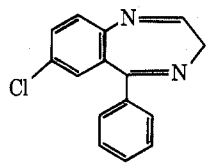
Received August 8, 1973

The title compound was obtained by manganese dioxide oxidation of the corresponding 1,2-dihydrobenzodiazepine. The 1,2-imine function exhibits greater reactivity toward nucleophiles than the 4,5-imino function and additions of methanol, piperidine, various mercaptans, and hydrogen cyanide proceeded selectively. Hydrogen sulfide adds to both imine functions to produce a 2,5-sulfur-bridged 1,4-benzodiazepine. Oxidation of the hydrogen cyanide adduct produced a 2-cyano-3H-1,4-benzodiazepine in which the α-iminonitrile function displayed a reactivity pattern qualitatively similar to that of acyl cyanides.

The many benzodiazepines synthesized for chemical and pharmacological investigation have generally been derivatives in the 2H-1,3-dihydro series.[2] Derivatives in the same oxidation state as the (yet unknown) parent heterocycle 1 which are unsubstituted in the 2 position are relatively rare and this prompted the study of some of the chemistry of compound 2 described in this paper.



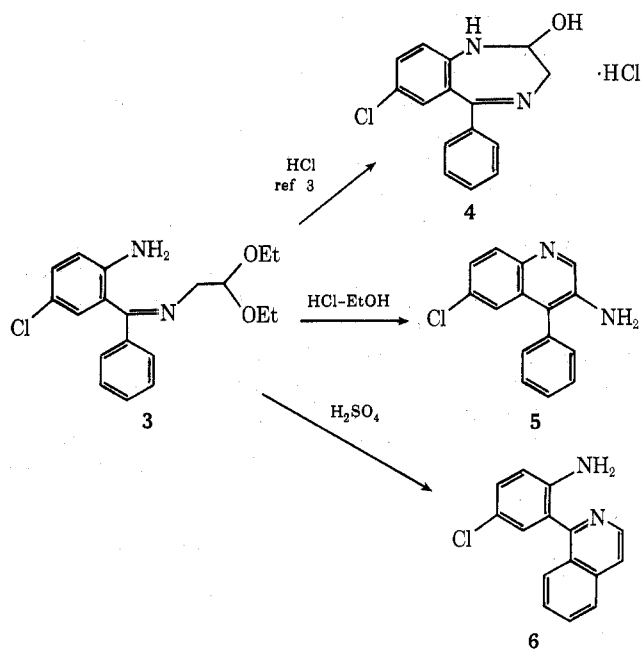
1



2

2-Amino-5-chlorobenzophenone can be condensed indirectly with aminoacetaldehyde diethyl acetal to give compound 3,[3] which was examined as a potential precursor to compound 2. The reactions of this substance with acid are remarkably dependent on the conditions employed (Scheme I). The reaction with HCl is reported[3] to give 4,

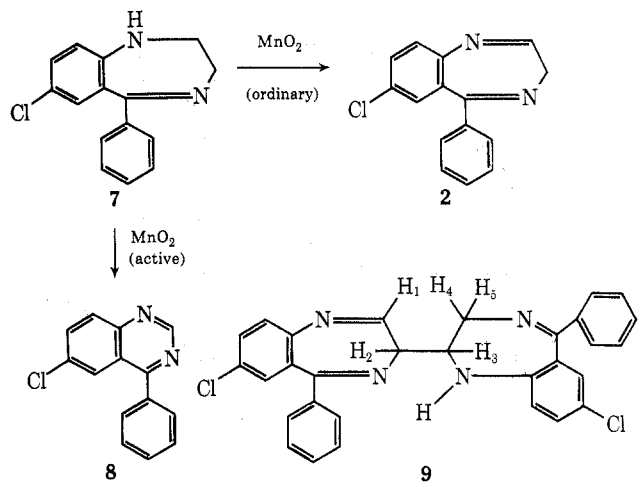
Scheme I



a hydrate of 2, as its hydrochloride. This did not provide a convenient route to compound 2, as in our hands the precursor 4 was not accessible by this method. Moreover, we found that cyclization with HCl in boiling ethanol produces the known quinoline 5[4] and cyclization with concentrated sulfuric acid produces the isoquinoline 6[5] (Scheme I).

An alternative route to compound 2 was suggested by instances of imine formation in the oxidation of N-alkylanilines with manganese dioxide,[6] and a convenient preparation of 2 by oxidation of 7 was thus realized[7] (Scheme II).

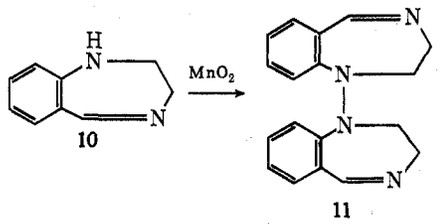
Scheme II



Initial attempts to oxidize the dihydrobenzodiazepine 7[8] with active manganese dioxide produced mixtures from which the quinazoline 8[9] was the only readily isolable substance. Ordinary manganese dioxide produced the desired product 2 but as a mixture with variable quantities of the dimer 9. High yields of 2 are contingent on preliminary removal of water from the manganese dioxide by azeotropic distillation with benzene; and if in addition a small quantity of acetic acid is added, the product is free of dimeric impurities. Crystallization of compound 2 is difficult but the crude product is sufficiently pure for subsequent transformations.

The structure (9) assigned to the dimer was based initially on analogy with that formed in the dimerization of Δ^1-piperideine.[10] This assignment was corroborated by the nmr spectrum, in which signals for the five numbered protons are clearly resolved. After washing with D_2O to remove the NH signal at 4.90 ppm, H_1 appears as a doublet at δ 7.69 ($J_{1,2}$ = 4 Hz), H_2 as a quartet at 3.09 ($J_{2,3}$ = 10 Hz), H_3 as a multiplet of seven lines at 4.83 ($J_{3,4}$ = 6, $J_{3,5}$ = 4 Hz), H_4 and H_5 as an AB quartet (J_{AB} = 11 Hz) with each line split again at 3.80 and 4.14 ppm.

An attempt to prepare 3H-1,4-benzodiazepine itself (1) by the same oxidation procedure gave strikingly different results. The hydrazobenzene derivative 11 was the sole product obtained from the oxidation of 10, indicating

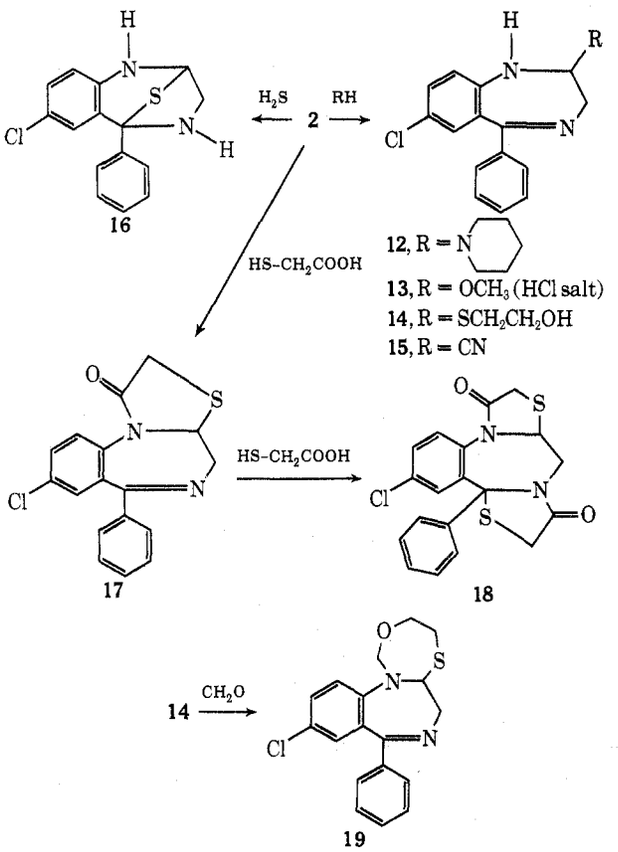


10 11

that, for reasons which are not at all clear, the reaction proceeds along the pathway that normally converts anilines to azobenzene derivatives[11] in the absence of the 5-phenyl and 7-chloro substituents.

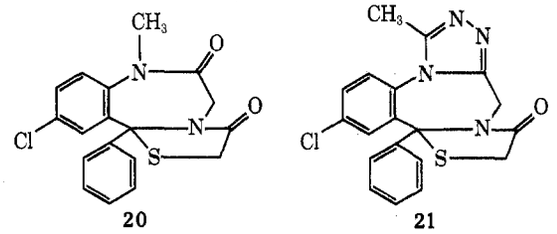
Treatment of compound 2 with excess piperidine in ether led to the formation of the piperidine adduct 12 (Scheme III). The crystalline product is stable with respect to reversal of this addition. Methanol adds to compound 2 in a similar fashion. The crystalline hydrochloride 13 was formed directly with methanolic HCl in ether. These and other nucleophilic additions[12] to compound 2 are presented in Scheme III.

Scheme III



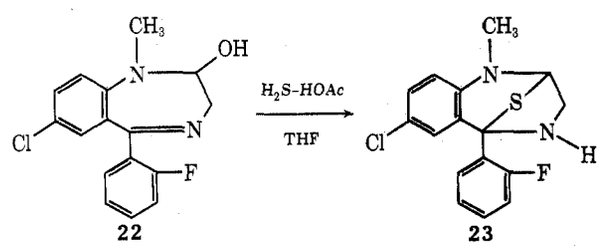
16 17 18 19

Mercaptans were also found to add readily to compound 2.[13] Mercaptoethanol yields adduct 14, reflecting the superior nucleophilicity of the mercaptan function. Cyclization of this material with formaldehyde gave the oxathiazepinobenzodiazepine 19. Mercaptoacetic acid in boiling benzene produced a mixture of the thiazolones 17 and 18. The spontaneous lactam ring formations leading to these compounds are not surprising, as a recent article[14] describes amide formation from mercaptoacetic acid and ethylamine under even milder conditions. This type of addition across the 4,5 C=N bond was demonstrated with two other representative members of the benzodiazepine series, namely, 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one[15] and 8-chloro-1-methyl-6-phenyl-4*H*-*s*-triazolo[4,3-*a*][1,4]benzodiazepine (34),[16] which are converted to thiazolone derivatives 20 and 21 in this manner.



20 21

The addition of hydrogen sulfide to compound 2 proceeds rapidly and exothermically in THF solution. The simple adduct with a 2-mercapto function has not been detected, as the addition occurs across both C=N bonds to produce the 2,5-epithiobenzodiazepine 16.[17] 16 is thermally converted to 2, demonstrating the reversibility of the hydrogen sulfide addition. 16 can thus be used in place of 2 for some of these preparations. A similar sulfur-bridged benzodiazepine was prepared from the known 1-methyl-2-hydroxy precursor 22[18] by acid-catalyzed reaction with hydrogen sulfide.



22 23

As expected, 23 exhibits greater thermal stability than 16.

Another series of novel benzodiazepines was derived from 2 *via* its HCN adduct 15 (Scheme IV). This compound is readily formed by treatment of a solution of 2 in tetrahydrofuran with aqueous KCN and methanolic HOAc.

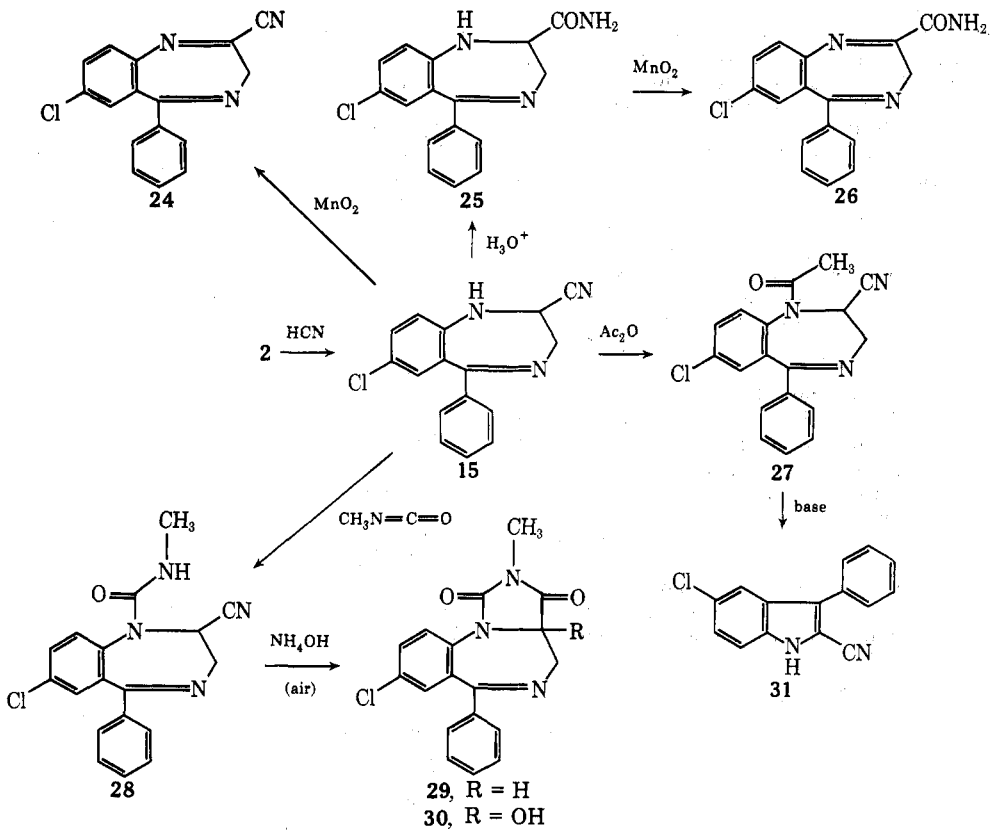
Reoxidation with manganese dioxide produces the 2-cyano-3*H*-1,4-benzodiazepine 24. The cyano group in this compound exhibits considerable reactivity toward nucleophilic substitution, presumably by the addition–elimination pathway, and is thus comparable to an acyl cyanide (Scheme V). If, however, the cyano group is first hydrolyzed to the amide 25 and this product oxidized, the resulting 3*H*-1,4-benzodiazepine 26 is one with greatly attenuated reactivity toward nucleophilic additions.

Acylation of 15 with acetic anhydride yields 27, and reaction with methyl isocyanate yields the urea derivative 28. Upon treatment with a methanol solution of ammonium hydroxide in air, a mixture of two benzodiazepine hydantoins, 29 and 30, is produced from the latter. Compound 29 is not converted to 30, the major product, under these conditions, indicating that the aerial oxidation occurs at an earlier stage. If 28 is partly hydrolyzed with acid before treatment with ammonia, hydantoin 29 is the only product obtained, suggesting that 28 itself is the air-oxidizable species.

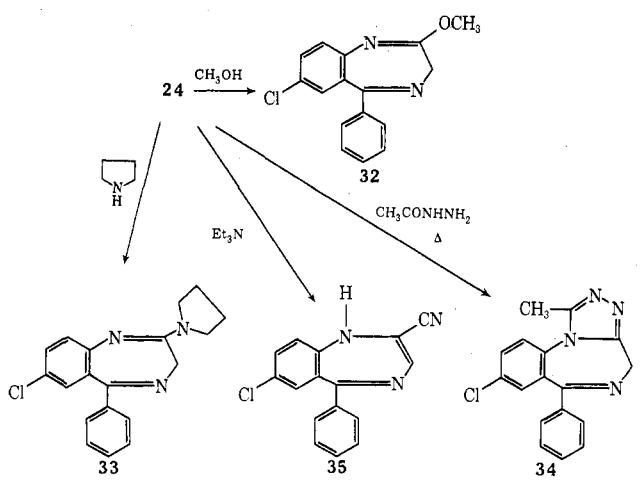
Attempts to effect analogous cyclization of 27 with base led to the known indole 31.[19] Ring contractions of this type have been encountered previously in the benzodiazepine series.[2a]

The substitution reactions in Scheme V illustrate how the acyl cyanide character of compound 24 makes it a convenient precursor to a variety of other 2-substituted 3*H*-1,4-benzodiazepines and also to the pharmacologically interesting[16] triazolobenzodiazepine 34. Treatment with triethylamine in THF at reflux effects isomerization to the dark red 1*H* isomer 35.

Scheme IV



Scheme V



Experimental Section[20]

3-Amino-6-chloro-4-phenylquinoline (5). A solution of the Schiff base 3[3] (2 g) in ethanol (40 ml) was saturated with dry hydrogen chloride, giving a red solution. Heating under reflux for 3.5 hr gave a yellow-orange solution, which was cooled, diluted with water, and gradually made basic by addition of aqueous sodium carbonate solution. The product was collected, washed, and dried to give 1.45 g (99%) of light yellow crystals, mp 155–160° (lit.[4] mp 161–162°), identified by ir and tlc comparison with an authentic sample.[4]

1-(2-Amino-5-chlorophenyl)isoquinoline (6). The Schiff base 3 (10 g) was added slowly to concentrated sulfuric acid (150 ml) and the resulting red solution was heated, first to 80° for 1 hr and then to 125° for 1 hr. This solution was cooled, poured over ice, made basic with aqueous sodium hydroxide and ammonia, and extracted with ether. The basic product was extracted from the ether with hydrochloric acid and then liberated by treatment with aqueous ammonia. Recrystallization of the crude product from ether–petroleum ether (bp 30–60°) gave 5.8 g (82%) of yellow crystals: mp 109–110°; ir (Nujol) 3400, 3300, 1625, 1585, and 1500 cm^{-1}; nmr ($CDCl_3$) δ 4.01 (s, broad, NH_2), 6.64–8.10 (m, 8 H, aromatic), and 8.58 (d, J = 5.5 Hz, N=CH); mass spectrum m/e 254 (100, M^+).

Anal. Calcd for $C_{15}H_{11}ClN_2$: C, 70.73; H, 4.35; N, 11.00; Cl, 13.92. Found: C, 70.61; H, 4.36; N, 11.40; Cl, 13.70.

Manganese Dioxide Oxidation of 7-Chloro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine (7). A. With Activated MnO_2. 7 (10 g) was added to a slurry of activated manganese dioxide (100 g) in benzene (1 l.) which had been dried by heating under reflux for 1 hr while collecting water in a Dean–Stark trap. The mixture was stirred and heated under reflux for 6 hr, then cooled and filtered through Celite. The solid was washed with benzene. Evaporation of the filtrate and washings left a red, syrupy mixture of several products which was taken up in ether. 6-Chloro-4-phenylquinazoline (0.9 g, 10%) crystallized out on chilling as tan crystals, mp 138–139° (lit.[9] mp 136–138°). Several subsequent crops were less pure but of the same material.

B. With Ordinary MnO_2. 7 (10 g) was added to a slurry of ordinary manganese dioxide[21] (100 g) in benzene (1 l.) which had been dried as in A. The reaction and work-up were also conducted as above. The oily residue crystallized (with difficulty) from ether–hexane to give 6.3 g (64%) of crude **2**, mp 97–100°. An analytical sample was prepared by two recrystallizations from ethyl acetate, giving off-white prisms: mp 101–104°; ir (Nujol) 1610 and 1575 cm^{-1}; nmr ($CDCl_3$) δ 3.92 (s, broad, 2 H), 7.44 (m, 8 H), and 7.92 (t, J = 4 Hz, 1 H).

Anal. Calcd for $C_{15}H_{11}N_2Cl$: C, 70.73; H, 4.35. Found: C, 70.76; H, 4.48.

In some preparations, the product crystallizing from ether was a high-melting (223–224°), pale yellow solid (yield up to 14%) which was identified as the dimer **9**, 7-chloro-3-(7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-5-phenyl-3*H*-1,4-benzodiazepine: ir (KBr) 3400, 1605, 1595, 1570, 1535 cm^{-1}; nmr ($CDCl_3$) δ 4.96 (s, broad, NH), 6.7–7.6 (m, 16 H, aromatic), and peaks listed in the text; mass spectrum m/e 255 (100) and 508 (M^+).

Anal. Calcd for $C_{30}H_{22}Cl_2N_4$: C, 70.73; H, 4.35. Found: C, 71.18; H, 4.30.

1,1-Bi(2,3-dihydro-1*H*-1,4-benzodiazepinyl) (11). Ordinary manganese dioxide (5 g) and acetic acid (5 drops) in benzene (50 ml) were heated and stirred under reflux for 1 hr while water was collected in a Dean–Stark trap. Compound **10**[22] (500 mg) was

added and stirring with reflux was continued for 16 hr. Tlc analysis of the reaction mixture showed only starting material and the dimer in approximately 1:1 ratio. After filtration and evaporation, the residue was separated by preparative layer silica gel chromatography, giving 60 mg of dimer **11** and 110 mg of starting material **10**. Sublimation of the dimer [120° (0.03 mm)] afforded pale yellow crystals: mp 178–180°; ir (Nujol) 1630, 1590, and 1550 cm^{-1}; nmr ($CDCl_3$) δ 3.67 (t, J = 5 Hz, 4 H), 4.20 (t, 4 H), 6.8–7.6 (m, 8 H), and 8.30 (s, 2 H); mass spectrum m/e 117 (100), 145, 290 (M^+).

7-Chloro-2,3-dihydro-5-phenyl-2-piperidino-1*H*-1,4-benzodiazepine (12). A solution of **2** (1.2 g) in ether (20 ml) was treated with piperidine (1 ml) and kept overnight, during which 1.5 g (94%) of **12** separated out. Recrystallization from ethyl acetate gave pale yellow spars, mp 130–135° dec, ir ($CHCl_3$) 1610 cm^{-1}.

Anal. Calcd for $C_{20}H_{22}ClN_3$: C, 70.68; H, 6.53. Found: C, 70.72; H, 6.50.

7-Chloro-2,3-dihydro-2-methoxy-5-phenyl-1*H*-1,4-benzodiazepine Hydrochloride (13). A solution of compound **2** (4 g) in methanol (5 ml) was added to a solution of 6 *N* methanolic hydrogen chloride (8 ml) in ether (25 ml). Compound **13** (4.3 g, 85%) crystallized out. Recrystallization from methanol–ether gave yellow needles, mp 185–193° dec.

Anal. Calcd for $C_{16}H_{16}Cl_2N_2O$: C, 59.45; H, 4.99. Found: C, 59.52; H, 5.17.

7-Chloro-2,3-dihydro-2-(2-hydroxyethylthio)-5-phenyl-1*H*-1,4-benzodiazepine (14). Compound **7** (10 g) was oxidized to compound **2** as described above with the addition of 0.1 ml of acetic acid to inhibit dimerization. The crude oxidation product was taken up in THF (60 ml), treated with 2-mercaptoethanol (10 ml), and heated under reflux overnight. The resulting solution was concentrated under reduced pressure until the product began to crystallize and then diluted with 100 ml of ether. The product was collected and washed with ether to give 10.13 g (78%) of colorless crystals, mp 135–140° dec, ir (Nujol) 3260, 3200, 1610, and 1570 cm^{-1}.

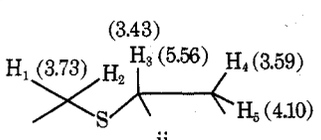
Anal. Calcd for $C_{17}H_{17}ClN_2OS$: C, 60.98; H, 5.72; Cl, 10.59; N, 8.37; S, 9.58. Found: C, 60.86; H, 5.49; Cl, 10.66; N, 8.40; S, 9.65.

10-Chloro-3,4,5a,6-tetrahydro-8-phenyl-1*H*-1,5,3-oxathiazepino[3,4-*a*][1,4]benzodiazepine (19). Compound **14** (500 mg) in THF (10 ml) was treated with 37% aqueous formaldehyde solution (2 ml) and kept for 5 hr. Dilution with water while scratching induced crystallization of 400 mg (78%) of yellow solid. Recrystallization from methylene chloride–ether gave pale yellow prisms: mp 160–164°; ir ($CHCl_3$) 1615 cm^{-1}; nmr ($CDCl_3$) δ 3.08 (t, J = 6 Hz, SCH_2), 3.26, 4.25, and 5.19 (ABX, J_{AB} = 11.5, J_{AX} = 12, J_{BX} = 4 Hz, NCH_2CHN), 4.12 (t, J = 6 Hz, OCH_2), 4.87 (q, J_{AB} = 12.5 Hz, NCH_2O), 7.05 (d, 1 H), 7.5 (m, 6 H), and 7.80 (d, 1 H); mass spectrum m/e 253 (100) and 344 (M^+).

Anal. Calcd for $C_{18}H_{17}ClN_2OS$: C, 62.69; H, 4.97; Cl, 10.28; N, 8.12; S, 9.30. Found: C, 62.59; H, 5.02; Cl, 10.55; N, 8.14; S, 9.49.

3a,4-Dihydro-8-chloro-6-phenylthiazolo[3,2-*a*][1,4]benzodiazepin-1(2*H*)-one (17) and 2-Chloro-8a,9-dihydro-13a-phenyl-13a*H*-bisthiazolo[3,2-*a*:3′,2′-*d*][1,4]benzodiazepin-6,11(7*H*,12*H*)-dione (18). Crude **2** from the oxidation of **7** (15 g) in benzene (1 l.) was treated slowly with excess mercaptoacetic acid (15 ml) and then stirred and heated under reflux for 23 hr. The cooled solution was washed with aqueous sodium carbonate, dried, and evaporated, and the oily residue was taken up in ether. A mixture of **17** and **18** (15 g) crystallized out on standing. Chromatography of 8.4 g of this mixture on 500 g of silica gel with hexane–ethyl acetate mixtures as eluent provided, after a recrystalization from methylene chloride–methanol, 1.9 g of **17**, which is the more polar substance, and 3.3 g of **18**.

17 was obtained as pale yellow crystals: mp 228–230°; ir (Nujol) 1680, 1605, and 1560 cm^{-1}; nmr ($CDCl_3$) δ 7.15–7.60 (m, 8 H, aromatic) and a multiplet for the aliphatic H with long-range couplings shown in partial structure ii, $J_{1,2}$ = 16; $J_{1,3}$ = 1.5; $J_{2,3}$ = 1.5; $J_{3,4}$ = 4; $J_{3,5}$ = 0; $J_{4,5}$ = 13 Hz; mass spectrum m/e 327 (100), 328 (M^+).



ii

Anal. Calcd for $C_{17}H_{13}N_2OSCl$: C, 62.10; H, 3.99; N, 8.52; S, 9.75; Cl, 10.78. Found: C, 62.24; H, 3.97; N, 8.41; S, 9.60; Cl, 10.90.

Compound **18** was obtained as colorless crystals: mp 256–257°; ir (Nujol) 1675 and 1585 cm^{-1}; nmr ($CDCl_3$) δ 2.8–3.5 (m, 3 H), 3.60 (s, 2 H), 4.30 (m, 1 H), 4.50 (m, 1 H), 6.9–7.6 (m, 7 H), and 8.52 (d, J = 2 Hz, 1 H); mass spectrum m/e 402 (100, M^+).

Anal. Calcd for $C_{19}H_{15}N_2O_2S_2Cl$: C, 56.64; H, 3.72; N, 6.95; S, 15.92. Found: C, 56.72; H, 3.72; N, 6.97; S, 15.51.

10-Chloro-7,11b-dihydro-7-methyl-11b-phenylthiazolo[3,2-*d*][1,4]benzodiazepin-3,6(2*H*,5*H*)-dione (20). A solution of 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one[15] (5 g) in benzene (200 ml) was treated with mercaptoacetic acid (2.9 ml) and heated under reflux for 5 days. The benzene was then evaporated from the solution, and the residue was taken up in methylene chloride, washed with aqueous sodium bicarbonate, dried, evaporated, and the oily residue allowed to crystallize from a small volume of methylene chloride. Two recrystallizations from methylene chloride–methanol gave colorless crystals (2.4 g, 38%): mp 212–214°; ir (Nujol) 1680, 1600, and 1570 cm^{-1}; nmr ($CDCl_3$) δ 2.43 (s, 3 H), 3.69 (q, J_{AB} = 16 Hz, 2 H), 3.43 and 4.73 (q, J_{AB} = 14 Hz, 2 H), 6.90–7.7 (m, 7 H), and 8.26 (d, J = 2 Hz, 1 H); mass spectrum m/e 285 (100) and 358 (M^+).

Anal. Calcd for $C_{18}H_{15}N_2O_2SCl$: C, 60.25; H, 4.21; N, 7.81; S, 8.93; Cl, 9.87. Found: C, 59.98; H, 4.19; N, 7.70; S, 8.73; Cl, 10.06.

10-Chloro-7,8a-dihydro-1-methyl-8a-phenyl-4*H*-*s*-triazolo[4,3-*a*]thiazolo[3,2-*d*][1,4]benzodiazepin-6-one (21). A solution of **34** (280 mg) in benzene (125 ml) was treated with mercaptoacetic acid (2 ml) and heated under reflux for 24 hr. Following the work-up procedure for compound **20**, the crude product was recrystallized from ethanol to give 200 mg (58%) of colorless crystals: mp 278–280°; ir (Nujol) 1680 and 1530 cm^{-1}; nmr ($CDCl_3$) δ 1.97 (s, 3 H), 3.70 (s, 2 H), 3.98 and 5.53 (q, J_{AB} = 14 Hz, 2 H), 6.90–7.8 (m, 7 H), and 8.45 (d, J = 2 Hz, 1 H); mass spectrum m/e 382 (M^+).

Anal. Calcd for $C_{19}H_{15}N_4OSCl$: C, 59.60; H, 3.95; N, 14.63; S, 8.37; Cl, 9.26. Found: C, 59.38; H, 3.87; N, 14.51; S, 7.98; Cl, 9.17.

7-Chloro-2,3,4,5-tetrahydro-5-phenyl-2,5-epithio-1*H*-1,4-benzodiazepine (16). A stirred solution of crude compound **2** from the oxidation of compound **7** (120 g) in THF (1 l.) was saturated with hydrogen sulfide gas during 1.5 hr. The solvent was evaporated and the solid residue was triturated with ether, filtered, and washed with ether to give 77.3 g (57%) of pure **16** as a colorless powder. Crystals from methylene chloride–ether had mp 142–144° dec; ir (KBr) 3250 and 1600 cm^{-1}; nmr (DMSO-d_6) δ 3.27 (d, J_{AB} = 11.5 Hz, 1 H), 3.58 (q, J_{AB} = 11.5, J_{vic} = 4.5 Hz, 1 H), 3.88 (s, NH), 5.67 (t, $J_{vic} \cong J_{NH}$ = 5 Hz, 1 H), 6.10 (d, J = 2 Hz, 1 H), and 6.6–7.7 (m, 8 H incl NH); mass spectrum m/e 254 (100, $M^+ - H_2S$).

Anal. Calcd for $C_{15}H_{13}N_2SCl$: C, 62.38; H, 4.54; N, 9.70; S, 11.10; Cl, 12.28. Found: C, 62.66; H, 4.54; N, 9.80; S, 10.91; Cl, 12.04.

7-Chloro-5-(2-fluorophenyl)-2,3,4,5-tetrahydro-1-methyl-2,5-epithio-1*H*-1,4-benzodiazepine (23). A solution of compound **22**[18] (5.0 g) in glacial acetic acid (25 ml) was stirred overnight while bubbling in a slow stream of hydrogen sulfide gas. The solution was then poured slowly into excess aqueous sodium carbonate and the crude solid product (5 g) was filtered and washed. Two recrystallizations from methylene chloride–ether gave 3.3 g (63%) of pale yellow prisms: mp 177° dec; ir (Nujol) 3260 cm^{-1}; nmr ($CDCl_3$–DMSO–TFA) δ 3.18 (s, 3 H), 3.85 (m, 2 H), 5.76 (d, J_{vic} = 5 Hz, 1 H), 6.4–8.0 (m, 7 H); mass spectrum m/e 259 (100), 287, and 320 (M^+).

Anal. Calcd for $C_{16}H_{14}FN_2SCl$: C, 59.90; H, 4.40; N, 8.73; S, 9.99; Cl, 11.05. Found: C, 60.08; H, 4.25; N, 8.82; S, 9.84; Cl, 10.92.

7-Chloro-2-cyano-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (15). A stirred solution of crude **2** from the oxidation of **7** (128 g) in THF (500 ml) was cooled in a water bath with simultaneous addition of the following solutions: (a) potassium cyanide (88 g) in water (180 ml) and (b) glacial acetic acid (100 ml) in methanol (300 ml). The resulting mixture was stirred for 30 min after completion of the additions and then concentrated to *ca.* 400 ml under reduced pressure, during which the product began to separate. Crystallization of the crude product was completed by dilution with 2 l. of water and chilling. The solid was collected and dissolved in methylene chloride. This solution was dried and then boiled down with gradual addition of cyclohexane. Three crops of material were thus obtained of which the second and third crops were combined and recrystallized to give a total of 85.15 g (60%) of pale yellow crystals: mp 181–183° dec; ir[23] (Nujol) 3330, 1620, and 1580 cm^{-1}; nmr ($CDCl_3$) δ 3.73 (t, J_{AB} = 12, J_{vic} = 10.5 Hz, 1 H), 4.10 (s, NH), 4.18 (q, J_{AB} = 12, J_{vic} = 4 Hz, 1 H), 4.89 (m, 1 H), 6.92–7.65 (m, 8 H); mass spectrum m/e 253 (100) and 281 (M^+).

Anal. Calcd for $C_{16}H_{12}N_3Cl$; C, 68.21; H, 4.29; N, 14.91; Cl, 12.58. Found: C, 67.78; H, 4.19; N, 14.95; Cl, 12.57.

7-Chloro-2-cyano-5-phenyl-3H-1,4-benzodiazepine (24). Manganese dioxide[21] (25 g) slurried in benzene (150 ml) was stirred and heated under reflux for 1 hr while water was collected in a Dean–Stark trap. **15** (5 g) was added and stirring with reflux was continued for 16 hr. The solid was filtered and washed with methylene chloride. The filtrate and washings were evaporated to a yellow oil which was taken up in ether, giving 1.7 g of pure **24** as pale yellow crystals, mp 151–154°. A second crop of less pure material, 2.3 g (80% total yield), was obtained. Pure **24** has ir (Nujol) 1605, 1580, 1565, and 1540 cm^{-1}; Raman (neat powder, 4880 Å) band at 2225 cm^{-1}; nmr ($CDCl_3$) δ 4.20 (s, 2 H) and 7.5 (m, 8 H); mass spectrum *m/e* 279 (100, M^+).

Anal. Calcd for $C_{16}H_{10}N_3Cl$: C, 68.70; H, 3.60; N, 15.02; Cl, 12.67. Found: C, 69.06; H, 3.55; N, 15.20; Cl, 12.44.

2-Carboxamide-7-chloro-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepine (25). **15** (10 g) was dissolved in concentrated hydrochloric acid (40 ml) and warmed in a 40° water bath for 45 min. The resulting solution was poured over ice, made basic with aqueous sodium carbonate, and extracted with methylene chloride. After drying and evaporation, the residue was recrystallized from methylene chloride–ether to give 6.3 g (60%) of the amide in four crops. Pure crystals of **25** are colorless: mp 210–213°; ir (KBr) 3460, 3260, 1695, 1620, and 1580 cm^{-1}; nmr ($CDCl_3$) δ 3.05 (s, NH_2), 3.96–4.28 (m, 3 H), 5.5 (s, broad, NH), 6.8–7.5 (m, 8 H); mass spectrum *m/e* 255 (100) and 299 (M^+).

Anal. Calcd for $C_{16}H_{14}N_3OCl$: C, 64.11; H, 4.71; N, 14.02. Found: C, 64.20; H, 4.74; N, 14.25.

2-Carboxamido-7-chloro-5-phenyl-3H-1,4-benzodiazepine (26). A slurry of manganese dioxide[21] (50 g) in benzene (250 ml) containing acetic acid (0.2 ml) was heated under reflux for 2 hr while water was collected in a Dean–Stark trap. The amide **25** (5 g) was added and stirring with reflux was continued for 17 hr. The mixture was cooled, filtered with washing of solid, and evaporated to give 4.45 g (85%) of tan solid. Recrystallization from chloroform–ether gave 3.35 g of colorless needles: mp 219–221° dec; ir (Nujol) 3200, 3100, 1680, 1600, and 1535 cm^{-1}; nmr ($CDCl_3$–DMSO) δ 3.40 (s, NH_2), 4.25 (s, broad, 2 H), and 7.5 (m, 8 H); mass spectrum *m/e* 297 (100, M^+).

Anal. Calcd for $C_{16}H_{12}N_3OCl$: C, 64.54; H, 4.06; N, 14.11; Cl, 11.91. Found: C, 63.84; H, 4.05; N, 14.09; Cl, 11.76.

1-Acetyl-7-chloro-2-cyano-2,3-dihydro-5-phenyl-1H-1,4-benzodiazepine (27). A solution of aminonitrile **15** (1.41 g) in toluene (10 ml) was treated with acetic anhydride (3 ml) and potassium carbonate (2 g) and stirred with reflux for 16 hr. The mixture was cooled, washed with water and then with 0.1 *N* hydrochloric acid, dried, and evaporated. The residue crystallized from isopropyl alcohol and was recrystallized from ethyl acetate–ether to give 730 mg (45%) of pale yellow crystals: mp 208–210°; ir (KBr) 1670, 1600, 1590, 1565, and 1550 cm^{-1}; Raman (neat powder, 5145 Å) band at 2240 cm^{-1}; nmr ($CDCl_3$) δ 1.92 (s, 3 H), 3.37 (q, J_{AB} = 11.5, J_{vic} = 13 Hz, 1 H), 4.37 (q, J_{vic} = 5 Hz, 1 H), 5.90 (q, 1 H), and 7.6 (m, 8 H); mass spectrum *m/e* 323 (M^+).

Anal. Calcd for $C_{18}H_{14}N_3OCl$: C, 66.77; H, 4.36; N, 12.98; Cl, 10.95. Found: C, 66.69; H, 4.25; N, 12.98; Cl, 11.07.

7-Chloro-2-cyano-2,3-dihydro-1-methylaminocarbonyl-5-phenyl-1H-1,4-benzodiazepine (28). A mixture of the aminonitrile **15** (7.1 g) and methyl isocyanate (25 ml) in a sealed flask was heated in a 90–100° oil bath for 18 hr. The flask was cooled, excess methyl isocyanate was evaporated, and the residue was triturated with ether. After dilution with petroleum ether and chilling, the product was collected and washed to give 6.05 g (71%) of crude urea, mp 227–231°. An analytical sample from methylene chloride–ether crystallized as pale yellow prisms: mp 229–230°; ir (KBr) 3410, 1670, and 1595 cm^{-1}; Raman (neat powder, 5145 Å) band at 2240 cm^{-1}; nmr ($CDCl_3$) δ 2.71 (d, 3 H, $NHCH_3$), 3.33 (t, $J_{AB} \cong J_{vic} \cong$ 12 Hz, 1 H), 4.32 (q, 1 H), 4.42 (broad, NH), 5.76 (q, J'_{vic} = 5 Hz, 1 H), 7.2–7.8 (m, 8 H); mass spectrum *m/e* 253 (100) and 338 (M^+).

Anal. Calcd for $C_{18}H_{15}N_4OCl$: C, 63.81; H, 4.46; N, 16.58; Cl, 10.46. Found: C, 63.56; H, 4.40; N, 16.52; Cl, 10.37.

8-Chloro-3a,4-dihydro-2-methyl-6-phenyl-2H-imidazo[1,5-a][1,4]benzodiazepine-1,3-dione (29). The urea **28** (6.05 g) was added to ice-cold concentrated hydrochloric acid (26 ml) and the resulting solution was then warmed to 40° and stirred for 25 min. It was then cooled and diluted by adding ice and poured into a stirred slush of ice in aqueous ammonia. The resulting mixture was kept for 6 hr. The product was collected, dissolved in methylene chloride, dried, concentrated, and crystallized by adding ether to give 4.05 g (67%) of colorless crystals: mp 164–165°; ir (Nujol) 1770, 1700, 1600, and 1550 cm^{-1}; nmr ($CDCl_3$) δ 2.95 (s, 3 H), 3.50 (q, J = 5, 12 Hz, 1 H), 4.52 (d, 1 H), 4.67 (d, 1 H), and 7.2–7.6 (m, 8 H); mass spectrum *m/e* 339 (M^+).

Anal. Calcd for $C_{18}H_{14}ClN_3O_2$: C, 63.62; H, 4.15; Cl, 10.43; N, 12.36. Found: C, 63.59; H, 4.09; Cl, 10.21; N, 12.46.

8-Chloro-3a,4-dihydro-3a-hydroxy-2-methyl-6-phenyl-2H-imidazo[1,5-a][1,4]benzodiazepine-1,3-dione (30). Cyclization of the urea **28** (3.43 g) by heating under reflux with concentrated aqueous ammonia (17 ml) in methanol (60 ml) for 6 hr gave, after work-up with water and methylene chloride extraction, a mixture of **29** and **30**. Separation was accomplished by silica gel preparative layer chromatography (five plates) giving 400 mg (11.5%) of **29** and 1.2 g (33%) of **30**. The latter crystallized from ether as colorless crystals: mp 193–196°; ir (KBr) 3400, 1790, 1720, 1610, 1600, and 1565 cm^{-1}; nmr (DMSO-d_6) δ 2.86 (s, 3 H), 3.24 (d, J_{AB} = 11 Hz, 1 H), 3.42 (s, NCOH),[24] 4.37 (d, 1 H), and 7.2–7.9 (m, 8 H); mass spectrum *m/e* 355 (M^+).

Anal. Calcd for $C_{18}H_{14}ClN_3O_3$: C, 60.77; H, 3.97; Cl, 9.96; N, 11.81. Found: C, 60.21; H, 3.93; Cl, 10.01; N, 11.51.

7-Chloro-2-methoxy-5-phenyl-3H-1,4-benzodiazepine (32). **24** (200 mg) in methanol (5 ml) was heated under reflux for 3 hr and then evaporated down and the residue was crystallized from a small volume of ether. The crude product consisted of 193 mg (95%) of brownish-white crystals, mp 87–94° (lit.[25] mp 88–92°), identical by ir and tlc comparison with an authentic sample.[25]

7-Chloro-5-phenyl-2-pyrrolidino-3H-1,4-benzodiazepine (33). **24** (200 mg) was treated with excess pyrrolidine (0.5 ml), causing an exothermic reaction. Crystallization from ether–cyclohexane gave 150 mg (65%) of crude product. Recrystallization from ethanol gave pale yellow prisms, mp 140–143° (lit.[24] mp 139–141°). This material was identical by ir and tlc comparison with an authentic sample.[26]

8-Chloro-1-methyl-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (34). Compound **15** (25 g) was oxidized to compound **24** with 250 g of manganese dioxide as described above. The benzene solution containing crude **24** was treated with acetylhydrazide (10 g) and concentrated by boiling to *ca.* 300 ml during 2 hr. The remaining solvent was removed under reduced pressure and replaced by 1-butanol (250 ml). This solution was heated under reflux for 16 hr and then concentrated under reduced pressure, causing the product to crystallize in a brown paste. Trituration with ether, filtering, and washing with water and then more ether gave 16.4 g (60%) of light tan, crystalline solid, mp 227–230° (lit.[16] mp 228°). This material was identical by ir and tlc with an authentic sample.[16]

7-Chloro-2-cyano-5-phenyl-1H-1,4-benzodiazepine (35). A solution of compound **24** (1.5 g) in THF (50 ml) was treated with triethylamine (1 ml) and heated under reflux for 1 hr. Evaporation under reduced pressure left a dark red oil which was taken up in hot cyclohexane. Gradual cooling with scratching induced crystallization and 1.0 g (66%) of brownish-red needles was thus obtained. A further recrystallization from cyclohexane afforded an analytical sample: mp 148–150°; ir (Nujol) 3300, 2220, 1625, 1590, and 1575 cm^{-1}; nmr ($CDCl_3$) δ 4.6 (s, broad, 1 H, NH), 6.70 (d, J = 8 Hz, 1 H, aromatic), 6.97 (d, J = 2 Hz, 1 H, aromatic), 7.10 (d, J = 1.5 Hz, 1 H, vinyl H), and 7.5 (m, 6 H, aromatic) (upon washing with D_2O the signal at δ 4.6 vanishes and the doublet at δ 7.10 becomes a singlet); mass spectrum *m/e* 252 (100) and 279 (M^+).

Anal. Calcd for $C_{16}H_{10}ClN_3$: C, 68.70; H, 3.60; N, 15.02; Cl, 12.67. Found: C, 68.67; H, 3.55; N, 14.95; Cl, 12.73.

Registry No. 2, 16398-00-8; **3,** 26418-94-2; **6,** 42915-30-0; **7,** 1694-78-6; **9,** 42915-32-2; **10,** 5945-91-5; **11,** 42915-34-4; **12,** 16398-01-9; **13,** 42915-36-6; **14,** 43000-57-3; **15,** 42915-37-7; **16,** 42915-38-8; **17,** 43000-58-4; **18,** 42915-39-9; **19,** 42915-40-2; **20,** 42915-41-3; **21,** 42915-42-4; **22,** 41218-65-9; **23,** 42915-44-6; **24,** 42915-45-7; **25,** 42915-46-8; **26,** 42915-47-9; **27,** 42915-48-0; **28,** 42915-49-1; **29,** 42915-50-4; **30,** 42915-51-5; **34,** 28981-97-7; **35,** 42915-53-7; 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one, 439-14-5.

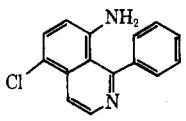
References and Notes

(1) Paper LXII: R. Y. Ning, W. Y. Chen, and L. H. Sternbach, *J. Org. Chem.*, **38**, 4206 (1973).

(2) Recent reviews: (a) R. Ian Fryer, *J. Heterocycl. Chem.*, **9**, 747 (1972); (b) G. A. Archer and L. H. Sternbach, *Chem. Rev.*, **68**, 747 (1968); L. H. Sternbach, *Angew. Chem., Int. Ed. Engl.*, **10**, 34 (1971).

(3) The Schiff base with ethanolamine is used as an intermediate: Takeda Chemical Industries, Japanese Patent 7,237,190; *Chem. Abstr.*, **77**, 164778 (1972); U. S. Patent 3,692,772 (1972).

(4) D. W. Ockenden and K. Schofield, *J. Chem. Soc.*, 3914 (1953). Acid-catalyzed Friedländer reactions have been reported in prior instances: E. H. Fehnel, J. A. Deyrup, and M. B. Davidson, *J. Org. Chem.*, **23**, 1996 (1958).
(5) Results obtained by Dr. W. Metlesics in these laboratories. Pomeranz–Fritsch isoquinoline syntheses are reviewed by W. J. Gensler, *Org. React.*, **6**, 191 (1951). While the less likely isoquinoline (i) could not be excluded on the basis of the usual spectral data, positive evidence for structure **6** was provided by its chelating ability with copper sulfate. The stoichiometry of the complex was established as L_2M using the absorption method of continuous variations of P. Job, *Ann. Chim. (Paris)*, **6**, 97 (1936). We are grateful to Dr. V. Toome for this determination.



i

(6) Review: O. Meth-Cohn and H. Suschitzky, *Chem. Ind. (London)*, 443 (1969).
(7) A similar oxidation had been used to prepare a 2-methyl analog of **2**: G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Amer. Chem. Soc.*, **89**, 332 (1967).
(8) L. H. Sternbach, E. Reeder, and G. A. Archer, *J. Org. Chem.*, **28**, 2456 (1963).
(9) S. C. Bell and P. H. Wei, *J. Org. Chem.*, **30**, 3576 (1965). The lactam corresponding to **7** does not yield **8** when exposed to the same conditions and is therefore probably not an intermediate in the reaction.
(10) C. Schöpf, A. Komzak, F. Braun, and E. Jacobi, *Justus Liebigs Ann. Chem.*, **559**, 1 (1947).
(11) M. Z. Barakat, M. F. Abdel-Wahab, and M. M. El-Sadr, *J. Chem. Soc.*, 4685 (1956); O. H. Wheeler and D. Gonzalez, *Tetrahedron*, **20**, 189 (1964).
(12) Additions of ethanol and various other amines to the N_4 oxide of **2** are described by G. F. Field and L. H. Sternbach in U. S. Patent 3,481, 921 (1969).
(13) For a recent study of reaction of thiols with Schiff bases see T. R. Oakes and G. W. Stacy, *J. Amer. Chem. Soc.*, **94**, 1594 (1972).
(14) C. S. Bhandari, U. S. Mahnot, and N. C. Sogani, *J. Prakt. Chem.*, **313**, 849 (1971).
(15) L. H. Sternbach, R. Ian Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).
(16) J. B. Hester, A. D. Rudzik, and B. V. Kamdar, *J. Med. Chem.*, **14**, 1078 (1971).
(17) A substance with this ring system was reported as the metal hydride reduction product of a 2-thione: M. Steinman, R. Alekel, Y.-S. Wong, E. F. York, and J. E. Topliss, Abstracts, 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971, No. FLUO 21. A 1,4-sulfone bridged 1,4-benzodiazepine was recently reported by K. Knollmüller, *Monatsh. Chem.*, **102**, 1055 (1971).
(18) R. I. Fryer, D. L. Coffen, J. V. Earley, and A. Walser, *J. Heterocycl. Chem.*, **10**, 474 (1973).
(19) H. Yamamoto, S. Inaba, T. Hirohashi, K. Ishizumi, I. Maruyama, and K. Mori, German Patent 1,817,757 (1970); *Chem. Abstr.*, **74**, 53528 (1971).
(20) Melting points are uncorrected. Nmr spectra were recorded on Varian T-60 and HA-100 instruments and are reported in parts per million from internal tetramethylsilane. Infrared and mass spectra were recorded on Perkin-Elmer 137 and CEC-110B instruments, respectively. Elemental analyses were conducted under the supervision of Dr. F. Scheidl of our microanalytical laboratory.
(21) General Metallic Oxides, type no. 37.
(22) M. Uskokovič, J. Iacobelli, and W. Wenner, *J. Org. Chem.*, **27**, 3606 (1962). The material used in this experiment was obtained from the condensation of ethylenediamine with o-fluorobenzaldehyde and had mp 134–136°.
(23) The ir spectra of **15** and the derived substances **24**, **27**, and **28** do not show C≡N bands. The presence of this group was verified by laser Raman spectroscopy in **24**, **27**, and **28** but this was not possible with **15**, as the laser beam destroyed the sample.
(24) *Cf.* O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964).
(25) J. V. Earley and R. I. Fryer, Belgium Patent 772,818 (1970).
(26) L. H. Sternbach, J. V. Earley, and R. I. Fryer, South African Patent 6,801,075 (1968); *Chem. Abstr.*, **70**, 68441 (1969).

1,3-Bridged Aromatic Systems. IX. Reactions of Syn and Anti Derivatives of 1-Substituted 12,13-Benzo-16-chloro[10](2,4)pyridinophanes[1]

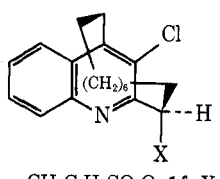
William E. Parham,*[2] Paul E. Olson, K. Ratnammal Reddy, and Kenneth B. Sloan

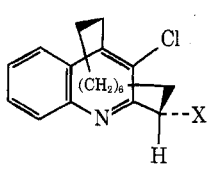
Paul M. Gross Laboratory of Chemistry, Duke University, Durham, North Carolina 27706, and the School of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

Received July 31, 1973

The reactions of 2,4-bridged meta cyclophanes of type **1** and **2**, containing *syn*- and *anti*-*p*-toluenesulfonyloxy groups (**1a** and **2a**) and *syn*- and *anti*-bromine atoms (**1b** and **2b**) at a benzylic carbon atom in the highly constrained methylene bridge, with a variety of reagents normally employed to effect substitution or elimination reactions are described. The behavior of these compounds is atypical of aliphatic benzyl substituents, which is a consequence of the steric constraint of the fused methylene bridge. The derivatives are highly resistant to bimolecular substitution and elimination reactions and also to ionization reactions. Under forcing conditions ionization reactions can be effected which are highly stereospecific in the syn series with retention of configuration. With silver acetate solvolyses of both **1b** and **2b** are stereospecific (SNi).

The availability of the meta cyclophanes (pyridinophanes) **1a,b** and **2a,b**, of known stereochemistry,[3] has prompted us to investigate in more detail the reactivity of side-chain substituents in these rigid systems. Models show that the back sides of the bridge methine carbon atoms in **1** and **2** are severely shielded to SN2 reactions; furthermore, change in hybridization of these carbon





1a, X = *p*-$CH_3C_6H_4SO_2O$ **1f**, X = $OCOCH_3$
b, X = Br **g**, X = OCH
c, X = H ‖
d, X = OH O
e, X = OC_2H_5 **h**, X = OCH_3

2

atoms from sp^3 to sp^2, which might be expected for SN1 type reactions, would not be favorable since such change in geometry would introduce additional strain into the tightly compacted and rather rigid methylene bridge. Lack of reactivity of such substituents was previously noted by the recovery of **1d** and **2d** unchanged from hot hydrobromic acid.[4]

Reactions of *syn*- and *anti*-1-*p*-Toluenesulfonyloxy-12,13-benzo-16-chloro[10](2,4)pyridinophane (1a and 2a). A. With Formic Acid–Water. Reaction of the anti tosylate **2a** in the highly ionizing solvent 90% formic acid–water was slow, but was complete after 48 hr at the reflux temperature. The crude product, which contained only anti alcohol **2d** contaminated with anti formate **2g** (tlc and nmr), was hydrolyzed with potassium hydroxide in methanol to remove formate, and the product thus obtained was analyzed by tlc and by isolation of products. The only product formed (~100% by tlc, 79% by isola-