50 hr. The resulting dark solution was diluted with 100 ml of water and extracted with chloroform. The chloroform extract was dried over anhydrous potassium carbonate and evaporated to dryness to yield 3.58 g (73%) of crude **6a**: bp 205° (754 mm) (lit.[11a] bp 204–205°); mass spectrum mol wt, 82; 60 HMz pmr ($CDCl_3$), CH_3 (τ 7.69); ring protons H_A (2.94), H_B (2.49), J_{AB} = 2 cps.

3-Ethyl-5-methylpyrazole (6b).—A solution of 1 g (0.013 mol) of 2,4-hexadiyne and 1 g (0.03 mol) of hydrazine in 10 ml of ethanol was refluxed for 3 days. Water (50 ml) was added and the mixture was extracted with chloroform. The chloroform extract was dried over potassium carbonate and evaporated to dryness giving 1.12 g (78%) of **6b**: mass spectrum mol wt, 110; 60-MHz pmr ($CDCl_3$), methyl triplet (τ 8.78, J = 7.5 cps), methyl singlet (7.73, methylene quartet (7.34, J = 7.5 cps), one-proton singlet (4.27), picrate from benzene, mp 145–146° (lit.[11b] mp 139–140°).

3-Benzyl-5-phenylpyrazole (6c).—A mixture of 1 g (5 mmol) of 1,4-diphenyl-1,3-butadiyne and 2 g of hydrazine was refluxed for 1 hr. The mixture was diluted with water and extracted with benzene. Evaporation of the benzene extract afforded 1.16 g (99%) of **6c** as white crystals (mp 88–90°). An analytical sample was obtained by recrystallization from cyclohexane: mp 91.5–92.5° (lit.[11c] mp 90.5–91°); mass spectrum mol wt, 234; 60-MHz pmr ($CDCl_3$), two-proton singlet (τ 6.08), one-proton singlet (3.72), ten aromatic protons (2.1–2.8).

3-(β-Hydroxyethyl)-5-hydroxymethylpyrazole (6d).—A solution of 1.1 g (0.01 mol) of 1,6-dihydroxy-2,4-hexadiyne and 1 g of hydrazine in 10 ml of ethanol was refluxed overnight. The solution was decolorized with charcoal and the solvent and excess hydrazine was evaporated under vacuum affording 1.23 g (86%) of **6d** as a viscous, colorless oil: mass spectrum mol wt, 142; 60 MHz pmr (D_2O): two-proton triplet (τ 7.10); two-proton triplet (6.10), two-proton singlet (5.34), one-proton singlet (3.75).

Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71; Found: C, 50.48; H, 7.15; N, 19.82.

5-Benzyl-3-phenylisoxazole (7).—A mixture of 0.5 g (2.48 mmol) of 1,4-diphenyl-1,3-butadiyne and 2 g of hydroxylamine hydrochloride in 20 ml of pyridine was refluxed under nitrogen for 4 days. The reaction mixture was treated with 100 ml of water and the precipitated solid was collected and dissolved in 5 ml of ether which was then diluted with 30 ml of petroleum ether and cooled on ice. The resulting white crystals (0.29 g, 50%) were purified by sublimation at 80° (0.5 mm): mp 83–84°; 60-MHz pmr spectrum ($CDCl_3$), two-proton singlet (τ 5.92), one-proton singlet (3.83), ten aromatic protons (2.10–2.80); mass spectrum [*m/e* (%)] 235 (34), 144 (100), 116 (17), 103 (11), 101 (12), 91 (27), 77 (41), 65 (12), 63 (11), 51 (21), 44 (22).

Anal. Calcd for $C_{16}H_{13}NO$: C, 81.61; H, 5.56; N, 5.94. Found: C, 81.75; H, 5.70; N, 6.15.

3-Benzyl-5-phenylisoxazole (9).—Compound **9** was prepared by the method of Bulow and Grotowsky:[11c] mp 91–92°; 60-MHz pmr spectrum ($CDCl_3$), two-proton singlet (τ 6.00), one-proton singlet (3.79), ten aromatic protons (2.18–2.80); mass spectrum [*m/e* (%)] 235 (100), 144 (46), 130 (15), 116 (15), 105 (23), 103 (10), 101 (10), 92 (24), 91 (75), 89 (15), 77 (50), 65 (35), 63 (49), 51 (28).

Registry No.—**3**, 18761-60-9; **3** picrate, 18753-54-3; **6d**, 18753-55-4; **7**, 18753-56-5.

Diazocine Chemistry. IV. Ring Contractions to Diazepines and Piperidines

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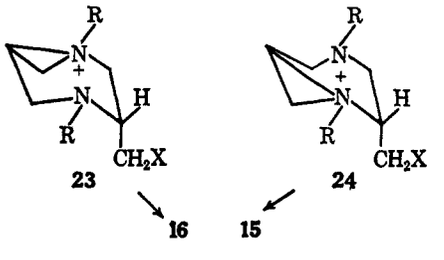
Treatment of *cis*- and *trans*-diazocine derivatives **1** and **2** with thionyl chloride afforded *cis*- and *trans*-diazepines **3** and **5**, respectively. *trans* compound **2** also yielded *trans*-piperazine **4**. Similar ring-contracted diazepines were obtained from *cis*- and *trans*-tetratosyl derivatives **7** and **8**. Free aminediols **11** and **12** were prepared by hydrolysis of N,N′-ditosyl compounds **1** and **2**. *cis*-Diol **13** rearranges, when passed over hot alumina, to 2-methyl- (**14**), 2,5-dimethyl- (**15**), 2,6-dimethyl- (**16**), and 2,3,5-trimethylpyrazine (**17**). The mode of formation of these compounds is described in terms of the involvement of intermediate aziridinium ions.

In connection with efforts directed toward the synthesis of 1,5-diazocine, we investigated the reaction of a mixture of *cis*- and *trans*-1,5-bis(*p*-toluenesulfonyl)-3,7-dihydroxyoctahydro-1,5-diazocine (**1** and **2**) with thionyl chloride and reported the isolation of the ring contracted products **3** and **4**.[1] In an attempt to elucidate the stereochemical consequences of this reaction, we have now studied it in some detail, utilizing the pure diols **1** and **2**.

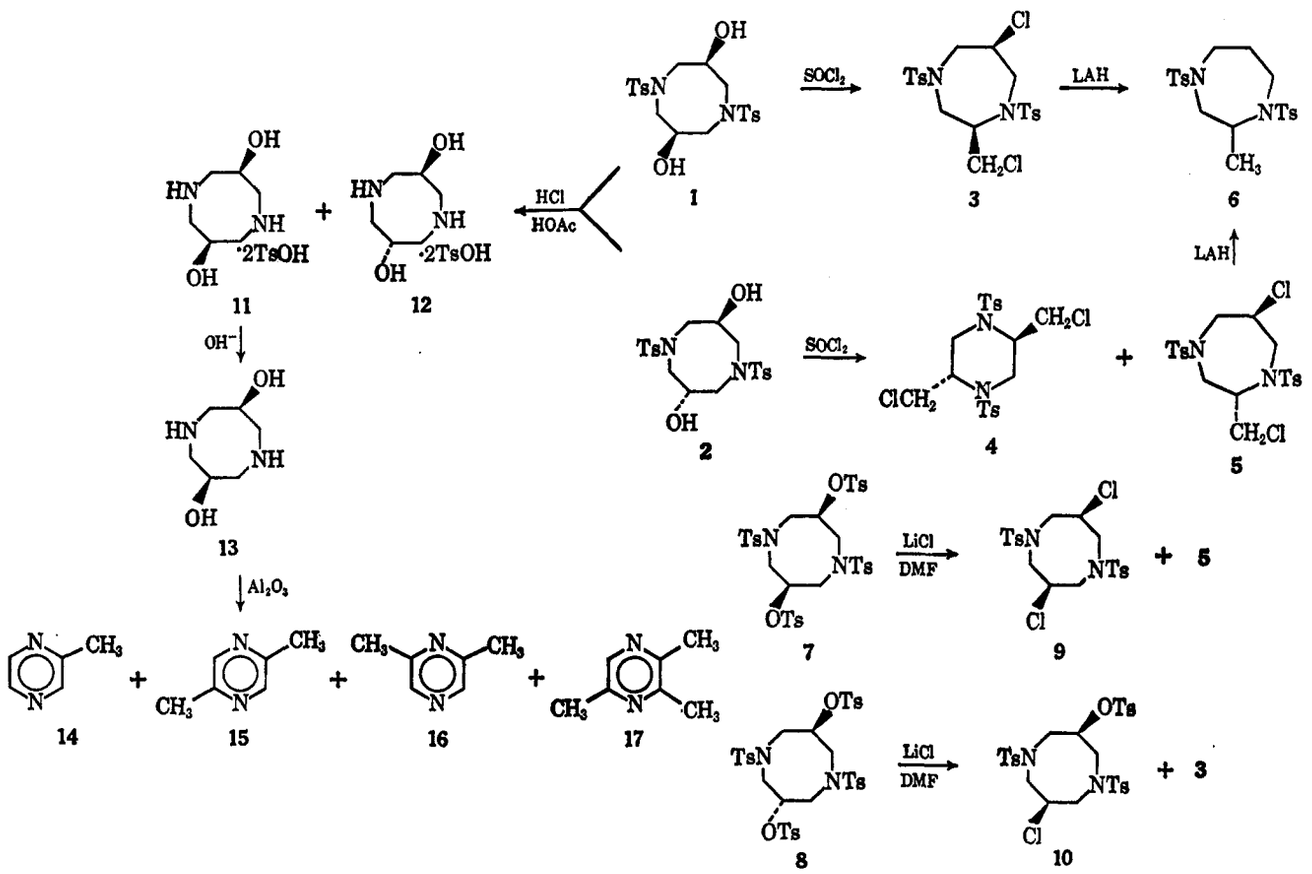
Treatment of the pure *cis*-diol **1** with thionyl chloride afforded the previously described, but stereochemically nondefined, perhydro-1,4-diazepine **3** as essentially the sole reaction product. Similar treatment of the *trans*-diol with thionyl chloride yielded the *trans*-2,5-di(chloromethyl)piperazine derivative **4** along with a compound (**5**) which is isomeric with the diazepine derivative **3**. That this material is, indeed, a stereoisomer of compound **3** was established by its conversion into perhydro-1,4-diazepine **6**, the same product as was obtained from the reduction of compound **3**. Since the substance resulting from the conversion of the *cis*-diol has a dipole moment of 6.05 D, while the isomer obtained from the transformation of the *trans*-diol has a dipole moment of 4.34 D, we can assign the *cis* configuration to compound **3** and the *trans* configuration to compound **5**.

SCHEME I



(1) W. W. Paudler and A. G. Zeiler, *J. Org. Chem.*, **32**, 2425 (1967).

SCHEME II



It now became of interest to investigate similar displacement reactions on the tetratosyl compounds **7** and **8**.[2] When *cis* isomer **7** is treated with lithium chloride in refluxing dimethylformamide, at least three different products are obtained, which, unfortunately, were not totally separable by solvent or chromatographic techniques. The two components that could be isolated were identified as the previously described, but stereochemically undefined, dichloro compound **9**, as well as diazepine **5**.

That the dichloro compound is the *cis* isomer is readily established by comparing its nmr spectrum with that of the *cis*-tetratosyl compound **7** (*cf.* Experimental Section).[3]

The reaction of *trans*-tetratosyl compound **8** with lithium chloride in refluxing dimethylformamide afforded a mixture of at least two compounds. These two major components were identified as diazepine **3** and the monochloromono-O-tosyl compound **10**. The *cis* relationship of the chloro and the O-tosyl groups is again established by nmr spectroscopy of compound **10** (*cf.* Experimental Section).

All of the transformations of the various 3,7-disubstituted octahydro-1,5-diazocines so far described have dealt with the N,N′-ditosyl derivatives. The investigation of the free amines becomes especially attractive if one considers that these amines are potentially highly reactive since they are β-substituted amines reminiscent of the mustard gas like compounds.[4] The most successful procedure thus far developed for the removal of the N-tosyl groups involves treatment of diols **1** and **2** with a mixture of acetic acid and 6 N hydrochloric acid for a period of 4 weeks. That this drastic procedure did not alter the ring skeleton was established by conversion of pure *cis* and *trans* amine salts **11** and **12** to the respective starting materials **1** and **2**.

Free *cis*-diamine **13** was obtained from its salt by ion-exchange chromatography. When this compound is vaporized and passed over hot (360°) alumina, there is obtained a complex mixture. Vapor phase chromatography indicates that the mixture is composed of four major and several minor components. Preparative vpc afforded three major fractions, two of which were pure compounds, while the third fraction contained a 50:50 mixture of two components which were nonseparable by preparative vpc.

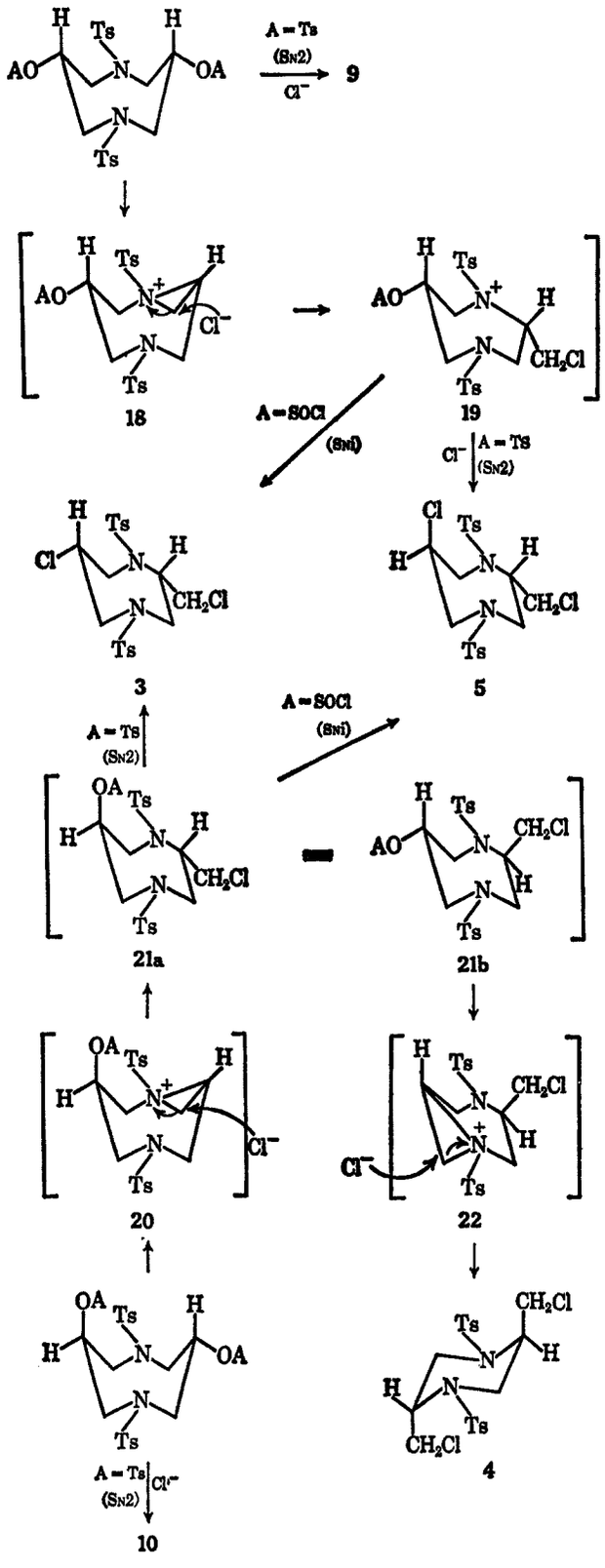
A comparison with authentic materials identified the various compounds as 2-methyl- (**14**), 2,5- (**15**), and 2,6-dimethyl- (**16**), as well as 2,3,5-trimethylpyrazine (**17**).

A study of molecular models suggests satisfactory explanations for the stereospecificity encountered in these ring contractions. The formation of *cis*-diazepine derivative **3** from *cis*-diol **1** can be satisfactorily accounted for by considering the intermediacy of the aziridinium ion **18**,[5] which, by the indicated bond

(2) W. W. Paudler, G. R. Gapski, and J. M. Barton, *J. Org. Chem.*, **31**, 227 (1966).

(3) We have described the details of the nmr approach to the establishment of the *cis* and *trans* configuration of these 3,7-disubstituted octahydro-1,5-diazocines in previous publications.[1,2]

(4) B. Cohen, E. R. Van Artsdalen, and J. Harris, *J. Amer. Chem. Soc.*, **74**, 1878 (1952), and earlier papers.



cleavage (see Scheme II), is converted into intermediate **19**.[6] Finally, this intermediate, where A = SOCl, is converted by an SN*i* process to *cis*-dichlorodiazepine **3**. On the other hand, when A = Ts, and under the reaction conditions used for this transformation, the O-tosyl group is displaced *via* the expected SN2 process to afford *trans*-diazepine **5**. Similarly, the *cis*-dichloro compound **9** is formed by SN2 displacement of both O-tosyl groups of the *cis*-tetratosyl derivative **7**.

The reaction products resulting from the *trans* isomer can also be explained by the intermediacy of an aziridinium ion. Scheme II outlines those transformations in adequate detail to preclude further discussion. The only comment that appears to be called for is to mention that intermediates **21a** and **21b** are identical and that the latter is drawn only for ease of representing the transformation leading to the piperazine **4**, which is clearly formed *via* two successive ring contractions.

The formation of the pyrazine derivatives can be envisioned to occur by similar paths, followed by facile aromatization. However, the intermediacy of aziridinium ions **23** (R = H) and **24** (R = H), where X may be OH or an alumina complex of some type, are of almost equal likelihood. In the N,N′-ditosyl compounds the aziridinium ion of type **24** (R = Ts) is apparently not involved. An alternate explanation might be that the species **24** (R = H) is also not formed in this thermal rearrangement process and that the 2,6-dimethylpyrazine results, in fact, from a "methyl migration."

The formation of the monomethyl and of the trimethylpyrazine (**14** and **17**) is still somewhat of a mystery. However, migration of methyl groups under severe thermal conditions in the N-methylpyridinium derivatives has been described[7] and we might suggest that a similar process, involving a species such as **25**, might account for the formation of these products, along with the 2,6-dimethylpyrazine.

Experimental Section[8]

***cis*-1,4-Bis(*p*-toluenesulfonyl)-6-chloro-2-chloromethylhexahydro-1,4-diazepine (3).**—To 3 g (6.7 mmol) of **1** in a Carius tube was added 10 ml of thionyl chloride and the mixture was warmed until reaction had ceased and all of the solid had dissolved. The tube was then sealed and heated at 130° for 3 hr. The reaction mixture was transferred to a beaker and 30 ml of methanol was added slowly. Water (10 ml) was added and the resulting white solid was filtered and washed with methanol. The dried product (2.1 g, 64%; mp 202–204°) was identical

(5) We have suggested this intermediate in a prior publication.[1] Since submission of that paper, D. A. Nelson and J. A. Worman (153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967) have described, *via* a similar intermediate, the ring contraction upon lithium aluminum hydride reduction of the *cis*- and *trans*-1,4-diphenyl-2,6-dimethylpiperazine. Unfortunately they utilized the observation that one of the octahydrodiazocines affords the *cis*-piperazine derivatives, while the other diazocine derivative yields a mixture of *cis*- and *trans*-piperazines to determine the stereochemistry of the starting materials. A more convincing proof of this assignment would be afforded by a study of the pmr spectra of the starting materials.

(6) N. J. Leonard and J. V. Paukstelis [*J. Org. Chem.*, **30**, 821 (1965), and earlier papers] have considered the substitution products of various aziridinium perchlorates when they are treated with chloride or bromide ions and have pointed out that a cleavage at the less substituted carbon should occur *via* an SN2 process while in their examples, in the absence of severe steric effects, substitution at the most highly substituted carbon occurs. This is assumed to occur *via* ionization and collapse of the ion pair to form the appropriate product. A referee has suggested that *cis*-dichloro **9** might also be formed through the aziridinium intermediate **18**, by chloride ion attack at the most substituted carbon of aziridinium species **18**. In view of the absence of any *trans*-dichloro compound isomeric with **9**, it appears that this path does not obtain.

(7) L. E. Tenebaum, "The Chemistry of Heterocyclic Compounds," Vol. 14, Part 2, Interscience Publishers, New York, N. Y., 1961, pp 163–164.

(8) Nmr spectra were obtained with a Varian A-60 or HA-100 spectrometer. Mass spectra were obtained with a Hitachi-Perkin Elmer RMU-6E instrument equipped with a solid sample injector. The ion-izing voltage employed was 80 V. Elemental analyses were done by Mrs. K. Decker of this department. The dipole moments were measured with a Heterodyne–Beat dipole moment apparatus as described by A. C. Vandenbrouke, Jr., R. W. King, and J. G. Verkade, *Rev. Sci. Instr.*, **39**, 558 (1968).

(tlc, nmr) with the previously described material,[1] dipole moment (C_6H_6) 6.05 D.

trans-**N,N'-Di(*p*-toluenesulfonyl)-2,5-di(chloromethyl)piperazine (4) and *trans*-1,4-Bis(*p*-toluenesulfonyl)-6-chloro-2-chloromethylhexahydro-1,4-diazepine (5).**—The reaction of 1.2 g (2.7 mmol) of **2** with 5 ml of thionyl chloride was carried out as in the preparation of **3**. The resulting white solid (780 mg) was recrystallized from 10 ml of dioxane affording 280 mg (15%) of compound **4** which was identical with the previously prepared material.[1] The mother liquor was evaporated to dryness and the resulting white solid was recrystallized from methanol to yield 320 mg (24%) of pure **5**: mp 185–186°; mol wt (mass spectrum), 490; 100-MHz nmr (CF_3COOH) δ 7.82 (H_A), 7.71 ($H_{A'}$), 7.40 ($H_{B,B'}$) (AA'B, 8, $J_{A'B} = J_{AB} = 8$ Hz), 4.48–2.98 (m, 10), 2.24 (s, 6); dipole moment (C_6H_6) 4.34 D.

Anal. Calcd for $C_{20}H_{24}S_2O_4Cl_2$: C, 48.87; H, 4.92; N, 5.70. Found: C, 48.95; H, 5.03; N, 5.91.

Reduction of 5 with Lithium Aluminum Hydride.—A solution of 0.5 g of **5** in 25 ml of tetrahydrofuran was treated with an excess of lithium aluminum hydride and refluxed for 6 hr. Excess reagent was decomposed with water, 100 ml of 10% NaOH solution was added, and the solution was extracted with chloroform. Removal of the solvent gave a colorless oil which was treated with a solution of 1 g of *p*-toluenesulfonyl chloride in 10 ml of pyridine. After 12 hr the reaction mixture was diluted with 20 ml of water and 30 ml of concentrated HCl. The resulting solid was filtered and recrystallized from ethanol to yield 93 mg of pure **6** (mp 149–150°).

cis- **and** *trans*-**1,5-bis(*p*-toluenesulfonyl)-3,7-bis(*p*-toluenesolfonoxy)octahydro-1,5-diazocine**[1] **(7 and 8)** had the following 100-MHz nmr spectra (*cis* isomer **7**): (CF_3COOH) δ 7.95 (H_A), 7.52 (H_B) (AB, 8, $J = 8$ Hz), 7.52 (H_A), 7.38 (H_B) (AB, 8, $J = 8$ Hz), 5.00 (m, 2, H_C), 3.86 (H_A), 3.16 (H_B) (AB, 8, $J_{AB} = 16$ Hz, $J_{AC} = 3$ Hz, $J_{BC} = 10$ Hz), 2.57 (s, 6), 2.48 (s, 6), (*trans* isomer **8**) (CF_3COOH) δ 7.81 (H_A), 7.40 (H_B) (AB, 8, $J = 8$ Hz), 7.50 (H_A), 7.32 (H_B) (AB, 8, $J = 8$ Hz), 5.00 (m, 2), 3.45 (d, 8), 2.45 (s, 6), 2.41 (s, 6).

Reaction of *cis*-Tetratosyl Compound 7 with Lithium Chloride.—A solution of 3 g (3.9 mmol) of **7** and 5 g of LiCl in 25 ml of dimethylformamide was refluxed for 0.5 hr. Water (25 ml) was added and the reaction mixture was cooled to room temperature, filtered, and the resulting white solid was washed with ethanol. Recrystallization from acetone afforded 1.2 g (63%) of **9** which was identical with a sample prepared by a different route:[1] 100-MHz nmr (CF_3COOH) δ 7.84 (H_A), 7.44 (H_B) (AB, 8, $J = 8$ Hz), 3.99 (m, 2, H_c), 4.26 (H_A), 3.02 (H_B) (AB, 8, $J_{AB} = 16$ Hz, $J_{AC} = 2$ Hz, $J_{BC} = 11$ Hz), 2.47 (s, 6). The mother liquor from the separation of **9** was evaporated to dryness and the residue was recrystallized from 100 ml of methanol.

The first crop (210 mg, mp 173–179°) was a mixture (determined by nmr) of compounds **5**, **9** and an unidentified substance that could not be isolated. A second crop of crystals was obtained by evaporating the mother liquor to about one-half of its original volume and cooling in an ice bath. This material (140 mg, 7.3%, mp 185–186°) was identical with **5**.

Reaction of *trans*-Tetratosyl Compound 8 with Lithium Chloride.—A solution of 1 g (1.3 mmol) of **8** and 2 g of LiCl in 15 ml of dimethylformamide was refluxed for 20 min. Water (20 ml) was added and the mixture was cooled to room temperature. The resulting white precipitate was filtered, dried, and chromatographed on 100 g of grade II neutral alumina. Elution with a mixture of benzene and carbon tetrachloride (v/v 3:1) afforded two compounds. The first compound was recrystallized from methanol to afford 217 mg (31%) of **3**. The second substance was recrystallized from ethanol to yield 185 mg (21%) of *cis*-1,5-bis(*p*-toluenesulfonyl)-3-chloro-5-*p*-toluenesulfonoxyoctahydro-1,5-diazocine (**10**): mp 215–216°; 100-MHz nmr (CF_3COOH) δ 7.82 (H_A), 7.37 (H_B) (AB, 4, $J = 8$ Hz), 7.52 (H_A), 7.23 (H_B) (AB, 8, $J = 8$ Hz), 4.69 (m, 1, H_C), 4.26 (m, 1, $H_{C'}$), 4.06 (H_A), 3.74 ($H_{A'}$), 2.72 ($H_{B,B'}$) (AA'B, 8, $J_{AB} = J_{AB'} = 16$ Hz, $J_{AC'} = 4$ Hz, $J_{A'C} = 3$ Hz, $J_{BC} = J_{BC'} = 14$ Hz), 2.43 (s, 3), 2.36 (s, 6).

Anal. Calcd for $C_{27}H_{31}N_2S_3O_7Cl$: C, 50.89; H, 4.90; N, 4.39. Found: C, 50.73; H, 5.00; N, 4.07.

In some experiments a third compound was formed that could not be separated from **3** and was not identified.

cis- **and** *trans*-**3,7-Dihydroxyoctahydro-1,5-diazocine Bis(*p*-toluenesulfonate) (11 and 12).**—A solution of 200 g (0.44 mol) of a mixture of **1** and **2** in 500 ml of 6 *N* HCl and 800 ml of glacial acetic acid was refluxed for 30 days. Evaporation of the solvents gave a brown solid which was recrystallized from 1 l. of water to afford 106 g (48%) of pure compound **11**: mp 279° dec; 60-MHz nmr (D_2O) δ 7.72 (H_A), 7.30 (H_B) (AB, 8, $J = 8$ Hz), 4.45 (m, 2), 3.98–3.14 (m, 8), 2.36 (s, 6). The N,N'-ditosyl derivative is identical with **1**.

Anal. Calcd for $C_{20}H_{30}N_2O_8S_2$: C, 48.96; H, 6.16; N, 5.71. Found: C, 48.93; H, 6.21; N, 5.87.

The mother liquor from the separation of **11** was concentrated to 300 ml and a second crop of crystals (**11** and **12**) weighing 35 g was obtained. The mother liquor was then evaporated to 150 ml and 100 ml of ethanol was added. This solution was then cooled overnight at 0° affording 16.1 g (7.5%) of pure **12**: mp 253°, 60-MHz nmr (D_2O) δ 7.69 (H_A), 7.31 (H_B) (AB, 8, $J = 8$ Hz), 4.48 (m, 2), 3.60–3.37 (m, 8), 2.37 (s, 6). The N,N'-ditosyl derivative is identical with **2**.

Anal. Calcd for $C_{20}H_{30}N_2O_8S_2$: C, 48.96; H, 6.16; N, 5.71. Found: C, 48.98; H, 6.08; N, 5.83.

cis-**3,7-Dihydroxyoctahydro-1,5-diazocine (13).**—A solution of 16 g (0.033 mol) of **11** in 200 ml of water was washed through a column containing 500 g of hydroxide-charged Amberlite CG-400 ion exchange resin. The column was eluted with water until the eluate was neutral to litmus paper. Removal of the water afforded a white solid which was recrystallized from absolute ethanol to yield 4.1 g (86%) of pure **13**: mp 181.5–182.5°; 60-MHz nmr (D_2O)δ 3.68 (m, 2), 2.88 (m, 8).

Anal. Calcd for $C_6H_{14}N_2O_2$: C, 49.29; H, 9.65; N, 19.17. Found: C, 49.25; H, 9.49; N, 19.05.

Dehydration of 13 over Alumina.—A 1.66 g (0.011 mol) sample of **13** was placed in a 5-ml flask which was attached to a 10-cm alumina (12 g) packed column. The top of the column was equipped with a Dry Ice cooled trap. The column was then heated to 360° and the sample was sublimed into the column by heating to 180° at a pressure of 0.004 mm. After the reaction was complete, the trap contained 1.04 g of material which was dissolved in 20 ml of ether and dried over anhydrous sodium sulfate. Removal of the ether gave 590 mg of a yellow oil. Analysis by vpc on a 5% silicone column at 105° indicated the presence of four major products and several minor components. The material was separated by preparative vpc into three fractions. The first fraction was shown to be 2-methylpyrazine (**14**) by comparison (ir, nmr, vpc) with an authentic sample. The second fraction contained a 50:50 mixture of 2,5- and 2,6-dimethylpyrazine (**15** and **16**) which was identical in every respect with a mixture prepared from commercial reagents. The last fraction was identified as 2,3,5-trimethylpyrazine (**17**) by comparison with an authentic sample prepared by the method of Klein and Spoerri.[9]

Registry No.—**5**, 19029-72-2; **6**, 13117-06-1; **7**, 13199-99-0; **8**, 13143-65-2; **10**, 19029-75-5; **11**, 19029-77-7; **12**, 19029-76-6; **13**, 19029-78-8.

Acknowledgment.—This investigation was supported in part by a research grant (CA-07917-1) from the National Cancer Institute, U. S. Public Health Service.

(9) B. Klein and P. E. Spoerri, *J. Amer. Chem. Soc.*, **72**, 1844 (1950).