yield. The salt may be separated and purified at this stage or alternatively the crude reaction mixture can be treated with sodium carbonate and the free amine extracted with solvent. Results obtained with several benzaldehydes are shown in Table I. Our

TABLE I

AMINES FROM REDUCTIVE AMINATION OF BENZALDEHYDES

Aldehyde[a]	Amine product	% yield[b,c]	Bp, °C (mm)
Benzaldehyde	Benzylamine	59	182–184 (atm)[d]
p-Methoxybenzaldehyde	*p*-Methoxybenzylamine	64	121–123 (14)[e]
o-Chlorobenzaldehyde	*o*-Chlorobenzylamine	70	99.5–102 (11)[f]
p-Chlorobenzaldehyde	*p*-Chlorobenzylamine	77	106–108 (11–12)[g]

[a] Liquid aldehydes were freshly distilled before use; *p*-chlorobenzaldehyde was employed as a 50% solution in DMF. [b] Yields are based on weights of distilled amines. [c] Product infrared spectra were identical with spectra of known, commercially available amines. [d] Lit. bp 184° [J. L. E. Erickson, *Chem. Ber.*, **59**, 2665 (1926)]. [e] Lit. bp 122–124° (14 mm) [M. Tiffeneau, *Bull. Soc. Chim. Fr.*, **9**, 819 (1911)]. [f] Lit.[8] bp 103–104° (11 mm). [g] Lit. bp 106–107° (15 mm) [J. v. Braun, M. Kühn, and J. Weismantal, *Justus Liebigs Ann. Chem.*, **449**, 249 (1926)].

yields compared favorably with those obtained in other reductive aminations of aromatic aldehydes.[2]

When reactions were run without dropwise addition or when excess aldehyde was used as solvent, lower yields of benzylamines were obtained. The method was unsatisfactory for reductive amination of conjugated unsaturated aliphatic aldehydes.[6]

The reductive amination proceeded more slowly in diglyme. Thus, when 0.05-mol quantities of *p*-anisaldehyde and isovaline were refluxed in diglyme (30 ml), only 75% of the amino acid was consumed after 4 hr. Under these conditions the yield of *p*-methoxybenzylamine based on amino acid reacted was 62%. In this instance dropwise addition of aldehyde did not improve the yield of amine.

The reaction succeeded to a still lesser extent when isovaline was replaced with α-aminoisobutyric acid (α-methylalanine). When equimolar amounts of benzaldehyde and α-aminoisobutyric acid were refluxed in diglyme (40 ml) for 2.7 hr, 57% of the amino acid was consumed and the yield of benzylamine based on amino acid reacted was only 31%.

Experimental Section[7]

General Procedure for the Preparation of Benzylamines.—To a stirred, refluxing slurry of *dl*-2-amino-2-methylbutyric acid (5.81 g, 0.0493 mol) in 30 ml of reagent grade DMF was added dropwise 5.34 ml (0.0490 mol) of redistilled [bp 92° (13 mm)] *o*-chlorobenzaldehyde. The aldehyde was added over a period of 20 min. After the addition, the mixture was refluxed 1 hr, cooled to 25°, and filtered to remove 0.22 g of unchanged amino acid. The filtrate was concentrated to a viscous syrup under vacuum and the syrup was hydrolyzed by boiling it with 100 ml of 2 *N* aqueous HCl for 2 hr. The cooled acidic solution was extracted with benzene to remove traces of colored impurities and the aqueous phase was concentrated to yield crude *o*-chlorobenzylamine hydrochloride. The crystalline residue was treated with *ca.* 50 ml of 5% Na_2CO_3 solution and extracted with ether to remove the benzylamine. The ether solution was dried (Na_2SO_4) and concentrated on a rotatory film evaporator, and the residue was distilled to give 4.86 g of *o*-chlorobenzylamine, bp 99.5–102° (11 mm) [lit.[8] bp 103–104° (11 mm)]. The liquid film ir of the product was identical with the ir of commercially available *o*-chlorobenzylamine.

Registry No.—Benzaldehyde, 100-52-7; *p*-methoxybenzaldehyde, 123-11-5; *o*-chlorobenzaldehyde, 89-98-5 *p*-chlorobenzaldehyde, 104-88-1.

(6) In the case of citral, only 10–15% of citralamine was obtained; most of the aldehyde was converted to higher boiling products.

(7) All boiling points were not corrected. Reactions involving aldehydes were performed under an atmosphere of predried nitrogen. Substituted benzaldehydes, benzylamines, and *dl*-isovaline were purchased from Aldrich Chemical Co. Infrared spectra were obtained on liquid film samples on a Perkin-Elmer Model 137 instrument.

(8) H. Franzen, *Chem. Ber.*, **38**, 1415 (1905).

Preparation of 1,4-Bis(*p*-tolylsulfonyl)-hexahydro-6-hydroxy-1*H*-1,4-diazepine and 1,4-Bis(*p*-tolylsulfonyl)-2-hydroxymethylpiperazine

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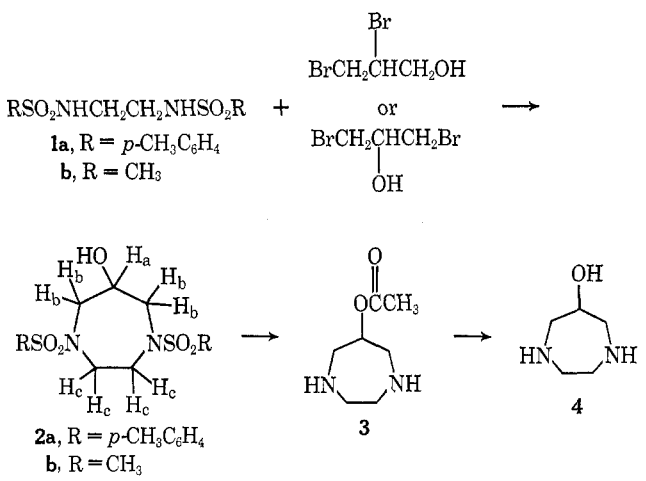
Synthesis of 1,4-bis(*p*-tolylsulfonyl)-2-hydroxymethylpiperazine (**6a**) by reaction of the disodium salt of *N*,*N*′-ethylenebis(*p*-toluenesulfonamide) (**1a**) with 2,3-dibromo-1-propanol and conversion of the ditosylamide to 2-substituted piperazine derivatives has been reported several times.[1] We have found that the reaction of **1a** with 2,3-dibromo-1-propanol under these conditions gives only a small amount of the piperazine **6a**, the major product being the hexahydro-1*H*-1,4-diazepine **2a**.



Reaction of the disodium salt of **1a** with either 2,3-dibromo-1-propanol or 1,3-dibromo-2-propanol in ethanol gave the same hexahydro-1*H*-1,4-diazepine **2a**, mp 175–177°, in 56–59% yield. Initially the hexahydrodiazepine structure was assigned to **2a** on the basis of its nmr spectrum in $CDCl_3$ which showed a one-proton multiplet at 4.0–4.4 ppm for the carbinol hydrogen, H_a. Addition of trichloroacetyl isocyanate to the solution shifted this one-proton multiplet down-

(1) (a) J. Gootjes, A. B. H. Funcke, H. M. Tersteege, and W. Th. Nauta, *Arzneim. Forsch.*, **16**, 1557 (1966); (b) J. R. Piper and T. P. Johnston, *J. Org. Chem.*, **28**, 981 (1963); (c) F. L. Bach, Jr., H. J. Brabander, and S. Kushner, *J. Amer. Chem. Soc.*, **79**, 2221 (1957); (d) F. L. Bach, Jr., S. Kushner, and J. H. Williams, *ibid.*, **77**, 6049 (1955).

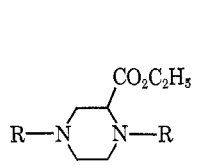
field 1.0 ppm[2] and formed a new one-proton signal at 8.96 ppm for the carbamate NH. Furthermore, conversion to the trichloroacetyl carbamate simplified the remainder of the spectrum. The four H_b protons now appeared as a doublet, J = 5 Hz, centered at 3.62 ppm, and the four H_c protons appeared as a singlet at 3.43 ppm. No change was observed in the methyl protons of the tosyl group or in the aromatic region. Additional evidence that the product contained a secondary alcohol and not a primary alcohol, as in **6**, was obtained by the appearance of the hydroxyl proton as a doublet, J = 3.5–4.0 Hz, at 5.20 ppm when the nmr was recorded in dimethyl sulfoxide.[3] That this doublet was the result of coupling of the hydroxyl proton with H_a was confirmed by its disappearance upon addition of D_2O.

The hexahydro-1*H*-1,4-diazepine **2b** was obtained by a similar reaction between the disodium salt of *N*,*N*′-ethylenebis(methanesulfonamide) (**1b**) and either 2,3-dibromo-1-propanol or 1,3-dibromo-2-propanol.

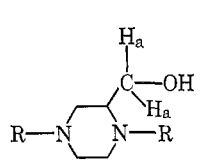
The *p*-toluenesulfonamide groups of **2a** were cleaved cleanly by phenol and hydrobromic acid[4] in acetic acid to give the acetoxy compound **3** as the dihydrobromide. Conversion of **2a** to the acetate prior to cleavage of the sulfonamide significantly increased the yield of **3**. The corresponding alcohol **4** was obtained by hydrolysis of **3** in hot water.

An authentic sample of 1,4-bis(*p*-tolylsulfonyl)-2-hydroxymethylpiperazine (**6a**), mp 170.7–173.7°, was obtained by lithium aluminum hydride reduction of the ditosyl ester **5c** which was prepared in turn from the known dibenzyl ester **5a**.[5] This piperazinyl alcohol **6a**, was distinctly different from the disulfonamide obtained in the dibromopropanol reactions as determined by mixture melting point, tlc, ir, mass spectrum, and nmr. In the nmr ($CDCl_3$) spectrum of **6a**, the shielded carbinol protons, H_a, were observed as a doublet, J = 3 Hz, at 2.25 ppm. Reaction with trichloroacetyl isocyanate shifted this doublet 2.1 ppm downfield, illustrating the value of carbamate formation for the detection of carbinol protons. The 70-eV mass spectrum of **6a** showed loss of CH_2OH from the molecular ion to be a major fragmentation path. Abundant M − tosyl[6] ions were observed in the mass spectra of both **2a** and **6a**.

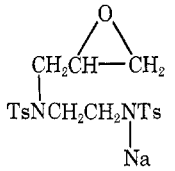
The piperazinyl alcohol **6c** was prepared by catalytic hydrogenation of **6b**[5] for comparison with the hexahydro-1*H*-1,4-diazepine alcohol **4**.



5a, R = $CH_2C_6H_5$
b, R = H
c, R = $SO_2C_6H_4CH_3$



6a, R = *p*-$CH_3C_6H_4SO_2$
b, R = $CH_2C_6H_5$
c, R = H



7

(2) A downfield shift of 1.0–1.5 ppm has been reported for secondary alcohol carbinol protons under these conditions: I. R. Trehan, C. Monder, and A. K. Bose, *Tetrahedron Lett.*, 67 (1968); V. W. Goodlett, *Anal. Chem.*, **37**, 431 (1965).

(3) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964); J. G. Traynham and G. A. Knesel, *ibid.*, **87**, 4220 (1965).

(4) D. I. Weisblat, B. J. Magerlein, and D. R. Myers, *ibid.*, **75**, 3630 (1953); H. R. Snyder and H. C. Geller, *ibid.*, **74**, 4864 (1952).

(5) E. Jucker and E. Rissi, *Helv. Chim. Acta*, **45**, 2383 (1962).

(6) *p*-Toluenesulfonyl, $C_7H_7O_2S$.

Examination of the crude products (80–85% yield) from reaction of the disodium salt of **1a** with the two isomeric dibromopropanols by tlc and nmr showed both products to be essentially identical, consisting of the hexahydrodiazepine **2a** as the major component contaminated by small amounts of the piperazine **6a** and **1a**. It was found that the crude product contained less than 10% of the piperazine **6a** by nmr comparison with an authentic mixture of **6a** and **2a**.

Formation of the same products, qualitatively, in both reactions suggests the presence of a common intermediate such as **7**. The epoxide **7** may be formed from reaction of the disodium salt of **1a** with either dibromopropanol or with epibromohydrin formed *in situ*. Ring opening of the epoxide function in **7** would occur at the preferred terminal methylene position to form the seven-membered hexahydro-1*H*-1,4-diazepine system.[7] The intermediacy of epibromohydrin in these reactions must be considered since reaction of the disodium salt of **1a** with epibromohydrin yielded the same crude product mixture as was obtained in the dibromopropanol reactions. In this experiment, the hexahydro-1*H*-1,4-diazepine **2a** was isolated in 29% yield.

Experimental Section

Nmr spectra were determined with a Varian A-60A spectrophotometer. Spectra were recorded in deuteriochloroform or trifluoracetic acid using TMS as an internal standard; those in D_2O were calibrated by the water band at 4.65 ppm. Infrared spectra were recorded with a Perkin-Elmer Model 21 spectrophotometer. Mass spectra were determined at 70 eV with a AEI-MS902 mass spectrometer. All melting points are corrected. Fluorescent silica gel G plates were used for tlc and the spots detected by uv or exposure to iodine vapor.

1,4-Bis(*p*-tolylsulfonyl)hexahydro-6-hydroxy-1*H*-1,4-diazepine (2a). Method A. From 1,3-Dibromo-2-propanol.—The sodium salt of *N*,*N*′-ethylenebis(*p*-toluenesulfonamide) was prepared by adding 50 g (0.136 mol) of the disulfonamide[8] to 600 ml of ethanol containing 0.27 mol of sodium methoxide. After being stirred at reflux for 20 min to ensure complete formation of the disodium salt, the solution was cooled to room temperature, 32.3 g (0.148 mol) of freshly distilled 1,3-dibromo-2-propanol[9] was added, and the reaction mixture was stirred at reflux for 24 hr. After cooling, 400 ml of water was added and the pH was adjusted to 10 with 10% sodium hydroxide solution. The crude product was removed by filtration, washed with water, and recrystallized from methanol to give 34 g (59%) of the title compound: mp 175.3–177.3°; homogeneous upon tlc (5% methanol–chloroform); nmr ($CDCl_3$) δ 2.45 (s, 6, CH_3), 3.0–3.9 (m, 9, OH, NCH_2), 4.0–4.4 (m, 1, CHO), 7.5 (q, 8, aromatic CH); mass spectrum, major fragments at *m/e* (rel intensity) 424 (3, M^+), 406 (3, M − H_2O), 393 (2, M − CH_2OH, possible impurity), 381 (10), 269 (100, M − tosyl[6]), 251 [10, M − (tosyl + H_2O)], 239 (10), 155 (36, tosyl), 114 (20, M − 2 tosyl).

Anal. Calcd for $C_{19}H_{24}N_2O_5S_2$: C, 53.75; H, 5.69; N, 6.60. Found: C, 53.97; H, 5.67; N, 6.59.

Method B. From 2,3-Dibromo-1-propanol. No. 1.—The disodium salt of *N*,*N*′-ethylenebis(*p*-toluenesulfonamide) was prepared from the bissulfonamide and sodium methoxide in methanol, isolated, and dried. The disodium salt, 45 g (0.109 mol), was added to a stirred solution of 25.5 g (0.117 mol) of 2,3-dibromo-1-propanol[9,10] and 6.12 g of potassium hydroxide in

(7) Rearrangement of 2,3-dibromo-1-propanol to 1,3-disubstituted 2-propanol derivatives *via* epoxide intermediates has been proposed by W. W. Paudler, G. R. Gapski, and J. M. Barton, *J. Org. Chem.*, **31**, 277 (1966); F. P. Doyle and J. H. C. Nayler, *Chem. Ind. (London)*, 714 (1955); and F. C. Whitmore, H. S. Mosher, D. P. Spalding, R. B. Taylor, G. W. Moersch, and W. H. Yanko, *J. Amer. Chem. Soc.*, **68**, 531 (1946).

(8) H. Stetter and E. E. Roos, *Chem. Ber.*, **87**, 566 (1954).

(9) The dibromopropanols used in these experiments were shown by nmr ($CDCl_3$) not to contain significant amounts of the isomeric dibromopropanol.

(10) M. L. Wolfrom, G. H. McFadden, and A. Chaney, *J. Org. Chem.*, **25**, 1079 (1960).

500 ml of ethanol at reflux. After stirring at reflux for an additional 4 hr, the reaction mixture was allowed to cool to room temperature overnight. The reaction mixture was then warmed to reflux, filtered, and cooled to give 25.4 g (56%) of the hexahydro-6-hydroxy-1,4-diazepine ditosylate, mp 175–177°. This product was identical with that prepared in method A from 1,3-dibromo-2-propanol as determined by mixture melting point, nmr ($CDCl_3$), and ir.

No. 2.—In another experiment, 2.2 g (0.010 mol) of 2,3-dibromo-1-propanol[9,10] in 20 ml of ethanol was added over 40 min to a stirred solution of 4.1 g (0.010 mol) of the dried disodium salt of *N,N'*-ethylenebis(*p*-toluenesulfonamide) in 80 ml of ethanol and 10 ml of water at reflux. After addition was complete, the mixture was stirred at reflux for 6 hr more and then overnight at room temperature. Water (500 ml) was added. The precipitated solid was removed, washed with water, and dried to give 3.4 g (80%) of crude product, mp 122–165°. The nmr of this crude product was essentially identical with the crude product (85% yield, mp 122–157°) obtained from an identical reaction of the disodium salt with 1,3-dibromo-2-propanol. Both products were shown by tlc (5% methanol–chloroform) to contain 1,4-bis(*p*-tolylsulfonyl)hexahydro-6-hydroxy-1*H*-1,4-diazepine as the major component and *N,N'*-ethylenebis(*p*-toluenesulfonamide) and 1,4-bis(*p*-tolylsulfonyl)-2-hydroxymethylpiperazine as minor components. Recrystallization of the crude product from methanol gave 2.1 g (50%) of *N,N'*-ditosylhexahydro-6-hydroxy-1*H*-1,4-diazepine (**2a**), mp 173.7–176.7°, softens at 170°, identical with the product obtained in method A by mixture melting point and tlc.

Method C. From Epibromohydrin.—When epibromohydrin, 1.5 g (0.011 mol), was substituted for 2,3-dibromo-1-propanol in method B, No. 2, 3.35 g (79%) of crude product, mp 108–158°, was obtained which was essentially identical, tlc and nmr, with the crude product of method B, No. 2.

Recrystallization from methanol afforded 1.25 g (29%) of **2a**, mp 172.7–176.7°, identical with the product obtained in method A by mixture melting point and tlc.

1,4-Bis(methylsulfonyl)hexahydro-6-hydroxy-1*H*-1,4-diazepine (2b). Method A. From 2,3-Dibromo-1-propanol.—To a solution of 2.7 g (0.050 mol) of sodium methoxide in 50 ml of methanol was added 5.0 g (0.0232 mol) of *N,N'*-ethylenebis(methanesulfonamide).[11] After the solution was stirred at reflux for 30 min, it was cooled, 1.3 g of potassium hydroxide was added, and the solution returned to reflux. A solution of 5.45 g (0.025 mol) of 2,3-dibromo-1-propanol[9,10] in 10 ml of methanol was added slowly to the hot reaction mixture. After addition was complete, the reaction mixture was stirred at reflux for 4 hr and then allowed to stand at room temperature for 3 days. The precipitated product was removed and recrystallized from methanol to give 1.5 g (24%) of product, mp 155.3–156.8°. An analytical sample, mp 156.8–158.8°, was obtained by further recrystallization from methanol: nmr (CF_3CO_2H) δ 3.14 (s, 6, CH_3), 3.6–3.9 (m, 8, NCH_2), 4.2–4.7 (m, 1, CHO).

Anal. Calcd for $C_7H_{16}N_2O_5S_2$: C, 30.86; H, 5.92; N, 10.28. Found: C, 30.81; H, 5.72; N, 10.26.

Method B. From 1,3-Dibromo-2-propanol.—The product, 21% yield, mp 157.0–162.0°, obtained from reaction of the disodium salt of *N,N'*-ethylenebis(methanesulfonamide) with 1,3-dibromo-2-propanol[9] by the above procedure was found to be identical with that obtained in method A from 2,3-dibromo-1-propanol by mixture melting point, nmr (CF_3CO_2H), and ir (KBr).

6-Acetoxyhexahydro-1*H*-1,4-diazepine Dihydrobromide (3).—A solution of 10 g (0.0236 mol) of 1,4-bis(*p*-tolylsulfonyl)hexahydro-6-hydroxy-1*H*-1,4-diazepine and 2.4 g (0.0236 mol) of acetic anhydride in 150 ml of a 30% anhydrous hydrogen bromide acetic acid solution was allowed to stir at room temperature for 30 min. An 8.9-g (0.094 mol) portion of phenol was added, and the reaction mixture was stirred at 60° for 6 hr and allowed to cool to room temperature overnight. Solvents were removed at 70° and 15–25-mm pressure to give an oil which, after trituration with ethyl ether and stirring with 100 ml of absolute ethanol, yielded 6.1 g (81%) of product, mp 222–223° dec. The decomposition point of this product has varied from 210 to 228° and is dependent upon the rate of heating and the temperature at which the sample is introduced. An analytical sample was obtained by recrystallization from methanol–ethyl acetate: nmr (CF_3CO_2H) δ 2.44 (s, 3, $CH_3C{=}O$), 4.0–4.4 (br m, 8, NCH_2), 5.8–6.0 (br m, 1, CHO), 8.0–8.9 (br m, 4, NH_2^+); nmr (D_2O) δ 2.24 (s, 3, $CH_3C{=}O$), 3.2–3.5 (m, 4, NCH_2), 3.5–3.9 (m, 4, NCH_2), 4.0–4.5 (m, 1, CHO); ir (KBr) 1735 cm^{-1} (ester C=O).

Anal. Calcd for $C_7H_{16}Br_2N_2O_2$: C, 26.27; H, 5.04; Br, 49.94; N, 8.75. Found: C, 25.96; H, 4.99; Br, 49.56; N, 8.71.

Hexahydro-6-hydroxy-1*H*-1,4-diazepine Dihydrobromide (4).—A solution of 200 mg (6.25 mmol) of 6-acetoxyhexahydro-1*H*-1,4-diazepine dihydrobromide in 10 ml of water was heated at reflux for 24 hr. After removing water under reduced pressure, the residue was recrystallized from methanol–ethyl acetate to give 150 mg (86%) of the alcohol, mp 257–261° dec, darkened at 247°. Further recrystallization from methanol–ethyl acetate gave an analytical sample, mp 259–262° dec, darkened at 252°.

Anal. Calcd for $C_5H_{12}N_2O \cdot 2HBr$: C, 21.60; H, 5.08; N, 10.08. Found: C, 21.70; H, 5.08; N, 10.11.

1,4-Bis(*p*-tolylsulfonyl)-2-carbethoxypiperazine (5c).—A mixture of 3.4 g (0.010 mol) of 2-carbethoxy-1,4-dibenzylpiperazine[5] and 1.5 g of a 5% palladium-on-carbon catalyst in 50 ml of glacial acetic acid was hydrogenated at an initial pressure of 50 psi until uptake of hydrogen was complete. After removal of catalyst by filtration through Supercel, the solution was concentrated under reduced pressure. The residue was stirred with 150 ml of ethyl ether, 75 ml of water, 3 g of potassium carbonate, and 3.8 g of *p*-toluenesulfonyl chloride at room temperature overnight. Addition of more potassium carbonate was necessary to keep the pH of the water solution above 8.0. After separating the ether layer and washing with a saturated sodium carbonate solution and water, it was dried (Na_2SO_4), filtered, and concentrated to an oil. Recrystallization from ethanol–water gave 1.2 g (26%) of product, mp 150.9–154.9°.[12]

Anal. Calcd for $C_{21}H_{26}N_2O_6S_2$: C, 54.06; H, 5.62; N, 6.01. Found: C, 53.98; H, 5.65; N, 6.11.

1,4-Bis(*p*-tolylsulfonyl)-2-hydroxymethylpiperazine (6a).—A solution of 0.5 g (1.07 mmol) of 1,4-bis(*p*-tolylsulfonyl)-2-carbethoxypiperazine in 10 ml of dry tetrahydrofuran was added over 5 min to a stirred slurry of 0.15 g of lithium aluminum hydride in 5 ml of tetrahydrofuran under an atmosphere of nitrogen. The mixture was stirred at reflux for 2 hr and then at room temperature for another 2 hr. After decomposing unreacted lithium aluminum hydride with a saturated sodium potassium tartrate solution, the tetrahydrofuran solution was decanted and combined with fresh tetrahydrofuran washings of the gel. After drying (Na_2SO_4), the combined tetrahydrofuran extracts were concentrated and the residue was recrystallized from ethanol–water to give 0.3 g (66%) of the alcohol, mp 168.7–171.7°. Another recrystallization from ethanol–water gave an analytical sample: mp 170.7–173.7°; nmr ($CDCl_3$) δ 2.25 (d, 2, CH_2O, J = 3 Hz), 2.37 (s, 3, CH_3), 2.44 (s, 3, CH_3), 3.2–4.0 (m, 7, NCH), 7.1–7.7 (m, 8, aromatic CH); mass spectrum, major fragments at *m/e* (rel intensity) 424.1186 (3, M^+ calcd 424.1127), 393.0951 (76, M − CH_2OH), 269.0948 (10, M − tosyl[6]), 238.0768 [100, M − (CH_2OH + tosyl)], 155.0162 (43, tosyl). A mixture melting point with 1,4-bis(*p*-tolylsulfonyl)-hexahydro-6-hydroxy-1*H*-1,4-diazepine prepared from 2,3-dibromo-1-propanol was depressed to 144–152°. The ditosyl-2-hydroxymethylpiperazine, R_f 0.45–0.55, and the ditosylhexahydro-6-hydroxydiazepine, R_f 0.62–0.71, separated cleanly on tlc (5% methanol–chloroform).

Anal. Calcd for $C_{19}H_{24}N_2O_5S_2$: C, 53.75; H, 5.69; N, 6.60. Found: C, 53.59; H, 5.70; N, 6.58.

2-Hydroxymethylpiperazine Dihydrobromide (6c).—A mixture of 1.43 g (4.8 mmol) of 1,4-dibenzyl-2-hydroxymethylpiperazine[5] and 0.4 g of a 5% palladium-on-carbon catalyst in 25 ml of glacial acetic acid was hydrogenated at atmospheric pressure and 60° until uptake of hydrogen was complete. Catalyst was removed by filtration and the solution was concentrated under reduced pressure. The residue was treated with a 30% hydrobromic acid–acetic acid solution to precipitate the hydrobromide salt. Two recrystallizations from methanol–ethanol–ethyl ether gave an analytical sample, 0.97 g (73%), mp 189–191°, softens at 181°.

Anal. Calcd for $C_5H_{12}H_2O \cdot 2HBr$: C, 21.60; H, 5.08; N, 10.08. Found: C, 21.79; H, 5.19; N, 9.87.

Registry No.—**2a**, 28860-33-5; **2b**, 28795-79-1; **3**, 28795-80-4; **4**, 28795-81-5; **5c**, 2758-80-7; **6a**, 14675-43-5; **6c**, 28795-50-8.

(11) M. Cohen, *Ind. Eng. Chem.*, **47**, 2095 (1955).

(12) Reported mp 140–141° by a different route (see ref 1d).

Acknowledgment.—We wish to thank K. B. Streeter, Y. C. Lee, and their staff for elemental analyses, W. R. McGaughran and Donna Kessler for the infrared and nmr spectra, and R. E. Rhodes for the mass spectra.

Reaction of Trichloromethyl Keto Acids and Lactols in Sulfuric Acid[1]

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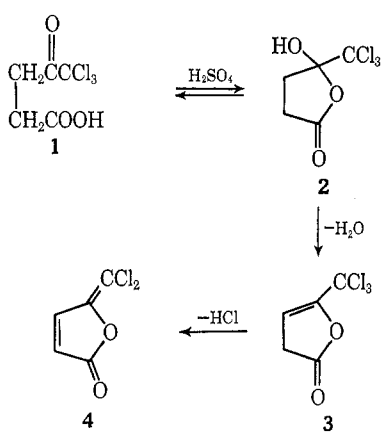
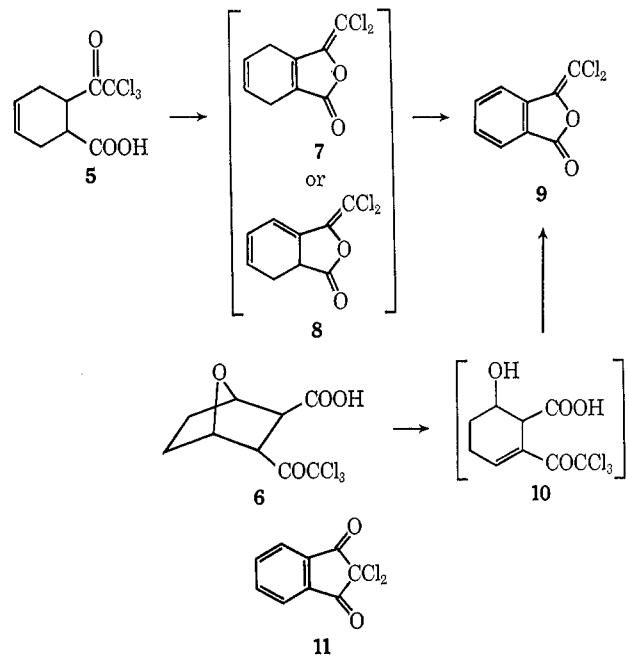
Earlier we suggested that the conversion of 5,5,5-trichlorolevulinic acid (**1**) to 5,5-dichloro-4-hydroxy-2,4-pentadienoic acid lactone (5,5-dichloroprotoanemonin) (**4**) in concentrated sulfuric acid proceeded by way of an initial cyclization to the lactol tautomer **2** followed in turn by a dehydration to **3** and a 1,4-conjugate elimination of hydrogen chloride to give **4** (Scheme I).[3]

SCHEME I



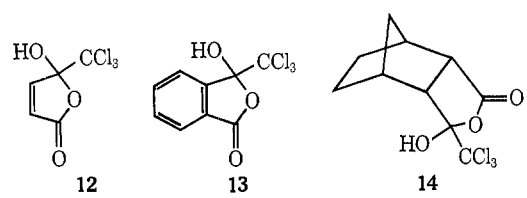
Although under normal conditions the open chain structure **1** is favored over the cyclic structure **2**,[4] protonation of the trichloroacetyl carbonyl group in the acid media would promote cyclization. To provide additional insight as to the course of this reaction and, at the same time, to explore the possibility of using this means as a general method for synthesizing halogen derivatives of protoanemonin, reactions of a variety of trichloromethyl keto acids or their cyclic lactol tautomers with concentrated sulfuric acid were examined.

Reaction of keto acid **5** was expected to give lactone **7** or **8**, but the evidence is clear that the aromatic structure **9** is formed. The analytical data reveal only four protons. The complex unsymmetrical multiplet centered at τ 2.2 in the nmr spectrum is consistent with an ABCD pattern of a unsymmetrical ortho disubstituted benzene. Infrared bands at 1795 (lactone C=O) and 1650 cm^{-1} (C=CCl$_2$) commonly occur in the spectra of protoanemonin derivatives.[3,5] As an alternate possibility, 2,2-dichloro-1,3-indandione (**11**), first reported by Zincke[6] in 1888, not only has a melting point of 124–125°, some 18° higher than ours, but is clearly inconsistent with the spectral data.



Reaction of *trans*-keto acid **6** also gave the aromatic dichloroprotoanemonin analog **9**, probably through an initial ring opening to keto acid **10**. Dehydration of **10** would bring the carbonyl and trichloroacetyl groups into coplanarity, which would favor cyclization to the lactol tautomer. A second dehydration and a dehydrohalogenation would lead to product **9**.

Lactols **12**, **13**, and **14** failed to react with concentrated sulfuric acid at room temperature even after prolonged reaction times and only starting materials were isolated. In accordance with the suggested mechanism (Scheme I), the failure of lactols **12** and **13** to react is consistent with the lack of appropriately placed hydrogens to provide for the dehydration and dehydrohalogenation steps. However, the stability of lactol **14** under these conditions must be due to other causes, since the required hydrogens are indeed present. We suggest that this stability is a direct result of the considerable strain energy involved in the ring distortion which would accompany a dehydration.



Unsaturated bicyclic lactol **15** failed to react normally with sulfuric acid to give an analog of dichloroprotoanemonin. However, a reaction did occur to give tetracyclic lactone **16**, the structure of which was consistent with the analytical data, spectral data, and

(1) From the Ph.D. dissertations of J. C. Sharp (1966) and R. F. Bargiband (1970).
(2) NASA Trainee, 1967–1970.
(3) A. Winston and J. C. Sharp, *J. Amer. Chem. Soc.*, **88**, 4196 (1966).
(4) A. Winston, J. P. M. Bederka, W. G. Isner, P. C. Juliano, and J. C. Sharp, *J. Org. Chem.*, **30**, 2784 (1965).
(5) A. Winston and R. N. Kemper, *Tetrahedron*, **27**, 543 (1971).
(6) T. Zincke, *Ber.*, **21**, 491 (1888).