Aromatic-substituted Derivatives of 2,3,4,5-Tetrahydro-7,8-methylenedioxy-1*H*-3-benzazepine. Syntheses *via* Chloromethylation

B. Pecherer, R. C. Sunbury, and A. Brossi

Chemical Research Department, Hoffman-La Roche Inc., Nutley, N. J. 07110

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Chloromethylation of *N*-acetyl-2,3,4,5-tetrahydro-7,8-methylenedioxy-1*H*-3-benzazepine (**4**) proceeded, depending on reaction conditions, at the 6- or 6,9- positions. Subsequent transformation of these intermediates provided a series of mono and bis aromatic-substituted derivatives of the parent benzazepine **3**.

Our continuing interest in the tetrahydro-3-benzazepine series (1,2,3) prompted the preparation of a variety of aromatic-substituted derivatives of one of our more active compounds (4), 2,3,4,5-tetrahydro-7,8-methylenedioxy-1*H*-3-benzazepine (**3**) (5). Large quantities of **3** and its acetyl derivative **4** were readily accessible from 1,2-bis-chloromethyl-4,5-methylenedioxybenzene (**1**) (6). Reaction with cyanide converted **1** to the crystalline dinitrile **2** which, on high pressure hydrogenation, was transformed to a mixture of amines from which the crystalline *N*-acetyl derivative **4** could be separated without difficulty. Alkaline hydrolysis of **4** afforded **3**.

1, R = Cl
2, R = CN

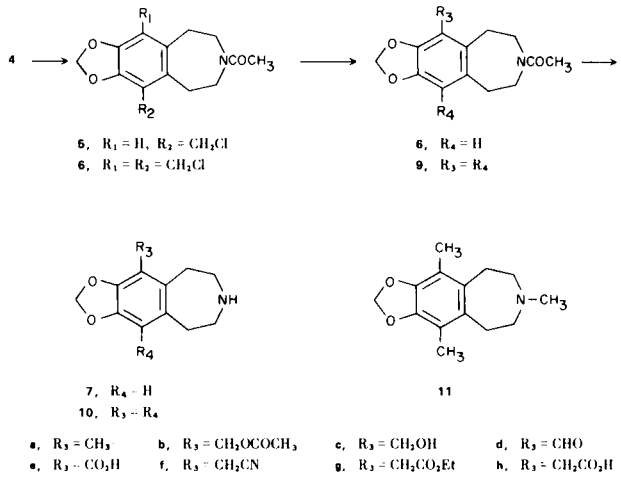
3, R = H
4, R = Ac

Chloromethylation of the *N*-acetylated benzazepine **4** readily provided, depending on the reaction conditions, either the benzyl chloride **5** or the bisbenzyl chloride **8**. This afforded a convenient route to the 6- and 6,9-substituted derivatives of **3**. The conversion of the monochloride **5** by means of well-established procedures into a variety of derivatives **6a-h** is outlined in Scheme I. Alkaline hydrolysis of the *N*-acetyl group which leaves the methylenedioxy grouping intact afforded the secondary benzazepines, **7a, c, e, h**.

By application of a similar series of reactions, the bis-chloromethylated benzazepine **8** was converted into derivatives **9a, b, c, f, g, h** from which benzazepines **10a, c, h** were prepared by alkaline hydrolysis. Reductive *N*-methylation of **10a** afforded 2,3,4,5-tetrahydro-3,6,9-trimethyl-7,8-methylenedioxy-1*H*-3-benzazepine (**11**) which was characterized as its crystalline hydrochloride.

None of the derived compounds showed any separation of the many biological activities associated with compound **3**.

SCHEME I



5, R_1 = H, R_2 = CH_2Cl
6, R_1 = R_2 = CH_2Cl

6, R_4 = H
9, R_3 = R_4

7, R_4 = H
10, R_3 = R_4

11

a, R_3 = CH_3 b, R_3 = CH_2OCOCH_3 c, R_3 = CH_2OH d, R_3 = CHO
e, R_3 = CO_2H f, R_3 = CH_2CN g, R_3 = CH_2CO_2Et h, R_3 = CH_2CO_2H

EXPERIMENTAL (7)

4,5-Methylenedioxy-1,2-benzenediacetonitrile (**2**).

To a stirred suspension of 98 g. (2.0 moles) of sodium cyanide in 1.71 l. of dimethylsulfoxide, cooled to 18-20°, 175 g. (0.8 mole) of the dichloride **1** was added in one portion. The temperature rose rapidly, but was arrested and maintained at 40° by intermittent cooling until it fell spontaneously after about 20-30 minutes. The reaction mixture was poured into 3 l. of ice-water and 1 l. of chloroform. When the ice had melted, the organic layer was separated and the aqueous layer was extracted with two 500-ml. portions of chloroform. The combined extracts were washed with five 500-ml. portions of saturated salt solution, once with water, and dried over magnesium sulfate. Distillation of the solvent at reduced pressure in a rotary evaporator gave a pale yellow crystalline residue; wt. 138 g. This solid was recrystallized from approximately 2 l. of 2-propanol to yield 119 g. of cream colored

nitrile **2**, m.p. 105-107°. While the material (90-93% pure by VPC) was satisfactory for conversion to **3**, an analytical sample, m.p. 116-117°, was obtained by recrystallization from ethanol-water.

Anal. Calcd. for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 13.99. Found: C, 65.66; H, 4.18; N, 13.97.

2,3,4,5-Tetrahydro-7,8-methylenedioxy-1*H*-3-benzazepine (**3**).

The dinitrile **2** (90-93%, 119 g., 0.595 mole) was hydrogenated in 2.4 l. of saturated ammoniacal ethanol at an initial pressure of 1000 PSI and 100° in the presence of 24 g. of Raney nickel for 4-5 hours. The catalyst was filtered, washed with 500 ml. of hot ethanol and the filtrate was distilled under vacuum to leave 120 g. of dark gray oily residue. Distillation from a Claisen flask gave 69.6 g. of product, b.p. 100-130° (0.3 mm.) (8).

2,3,4,5-Tetrahydro-7,8-methylenedioxy-1*H*-3-benzazepine Hydrochloride (**3**·HCl).

Purified *N*-acetyl-2,3,4,5-tetrahydro-7,8-methylenedioxy-1*H*-3-benzazepine (**4**) (58.4 g., 0.25 mole) was refluxed for 18 hours with a solution of 40 g. (1.0 mole) of sodium hydroxide in 200 ml. of ethanol and 200 ml. of water. The mixture was poured into 1 l. of ice-water and the base was extracted with four 250-ml. portions of benzene. The combined benzene solution was washed with 250 ml. of water and then the base was extracted with three 200-ml. portions of 1*N* hydrochloric acid. The combined aqueous extract was evaporated to dryness in a rotary evaporator, the residue was suspended in 200 ml. of 2-propanol and the evaporation was repeated. The dry hydrochloride was transferred to a funnel with ethyl acetate, washed with the same solvent, and dried to constant weight; yield, 45.8 g. (80%), m.p. 282-284° dec.

Anal. Calcd. for $C_{11}H_{13}NO_2$·HCl: C, 58.22; H, 6.05; N, 5.89; Cl, 15.49. Found: C, 58.02; H, 6.20; N, 6.15, Cl, 15.57.

N-Acetyl-2,3,4,5-tetrahydro-7,8-methylenedioxy-1*H*-3-benzazepine (**4**).

A solution of 69.6 g. of distilled **3** (8) in 150 ml. of toluene was treated with 16.1 g. of anhydrous sodium acetate and, with a reflux condenser in place, 140 ml. of acetic anhydride was added *very cautiously* to the suspension. The mixture was stirred and refluxed for 1.5 hours and after cooling, the mixture was evaporated completely on a rotary evaporator. Water (500 ml.) was added to the residual white solid, the suspension was stirred for 20 minutes, the solid filtered, washed thoroughly with water and dried at 100° to constant weight. The crude product (89 g.) was dissolved in 1.65 l. of hot ethanol and the solution allowed to stand at room temperature for 18 hours. The crystals of **4** were filtered, washed with a small amount of cold ethanol and dried; yield, 63 g., m.p. 178-180°.

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.86; H, 6.66; N, 6.00.

3-Acetyl-6-chloromethyl-2,3,4,5-tetrahydro-7,8-methylenedioxy-1*H*-3-benzazepine (**5**).

In a 1 l. creased flask provided with a stirrer, thermometer, reflux condenser, and a gas inlet tube was placed 41.5 g. (0.178 mole) of **4**, 21.6 ml. (0.267 mole) of 37% formaldehyde solution and 356 ml. of 1,2-dichloroethane. A stream of hydrogen chloride gas was passed into the stirred mixture at 25-27° (strong initial exotherm, cooling required) for 10-12 hours until TLC showed that all of the starting material had disappeared. The mixture was diluted with 250 ml. of water, the organic layer was separated, and the aqueous phase was extracted with three 100-ml. portions of chloroform. The combined organic extracts were washed first with water, then with saturated sodium bicarbonate solution, and finally dried. Removal of the solvent in a rotary evaporator gave 52 g. of a colorless oil, which crystallized after solution in 100 ml. of ethyl acetate. A first crop of 27.4 g., m.p. 131-133°, was collected and by concentrating and chilling the mother liquor, a second crop of 12.9 g., m.p. 126-129°, was obtained. Both crops were suitable for further work.

Two recrystallizations from 2-propanol gave an analytical sample, m.p. 133-135°. The nmr spectrum (deuteriochloroform), δ = 2.12 (3 H, s, CH_3CO), 3.03, 3.08, (4 H, m, CH_2-1 and CH_2-5), 3.67 (4 H, m, CH_2-2 and CH_2-4), 4.63 (2 H, s, CH_2Cl), 5.98 (2 H, s, CH_2O_2), and 6.65 (1 H, s, CH-9).

Anal. Calcd. for $C_{14}H_{16}ClNO_3$: C, 59.70; H, 5.72; Cl, 12.59; N, 4.97. Found: C, 59.76; H, 5.94; Cl, 12.64; N, 5.29.

3-Acetyl-2,3,4,5-tetrahydro-6-methyl-7,8-methylenedioxy-1*H*-3-benzazepine (**6a**).

Two g. of **5** was shaken under hydrogen (50 PSI) together with 0.5 g. of 10% Pd/C and 0.82 g. of anhydrous sodium acetate in 125 ml. of glacial acetic acid. Hydrogen uptake was complete after 20 minutes, after which the catalyst was filtered and the solvent removed in the rotary evaporator leaving a solid residue. This residue was suspended in 60-90° petroleum ether and recovered by filtration. The filter cake, 1.2 g., m.p. 101-103°, was recrystallized from ethyl acetate-petroleum ether to give white crystals, m.p. 103-104°. The nmr spectrum (deuteriochloroform), δ = 2.12 (3 H, s, CH_3CO), 2.17 (3 H, s, CH_3-6), 2.83 (4 H, t, CH_2-1 and CH_2-5), 3.62 (4 H, m, CH_2-2 and CH_2-4), 5.88 (2 H, s, CH_2O_2), and 6.50 (1 H, s, CH-9).

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.07; H, 7.00; N, 5.67.

6-Acetoxymethyl-3-acetyl-2,3,4,5-tetrahydro-7,8-methylenedioxy-1*H*-3-benzazepine (**6b**).

A mixture of 16.3 g. (0.058 mole) of **5**, 22.8 g. of anhydrous potassium acetate (0.232 mole), and 70 ml. of acetic acid was refluxed for one hour and then the solvent was removed in a rotary evaporator. On rubbing the residual oil under water, it crystallized. After 30 minutes at 0° the solid was filtered and dried; yield 14.4 g. of crystals, m.p. 167-169°, unchanged after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 63.04; H, 6.36; N, 4.81.

3-Acetyl-2,3,4,5-tetrahydro-6-hydroxymethyl-7,8-methylenedioxy-1*H*-3-benzazepine (**6c**).

Compound **6b** (27 g., 0.0885 mole) was refluxed for 3 hours with 7.1 g. of sodium hydroxide (0.177 mole) in 177 ml. of 50% ethanol. After distilling the ethanol, the *p*H of the aqueous residue was adjusted to 5 with hydrochloric acid, and the solution was extracted with five 100-ml. portions of chloroform. The combined extracts were washed once with water and dried. Removal of the solvent yielded 19.0 g. of oil which crystallized after being covered with 50 ml. of ethyl acetate. The solid was filtered and dried; yield 16.7 g. (72%), m.p. 145-147°. An analytical sample, m.p. 146-148°, was obtained by recrystallization from ethyl acetate.

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.58; H, 6.35; N, 5.10.

3-Acetyl-2,3,4,5-tetrahydro-7,8-methylenedioxy-1*H*-3-benzazepine-6-carboxaldehyde (**6d**).

Compound **6c** (16.7 g.) was refluxed for 6 hours with 83.5 g. of activated manganese dioxide (9) in 835 ml. of chloroform under a trap for the removal of water. The manganese dioxide was fil-

tered on a bed of filter aid, then slurried with two 600-ml. portions of chloroform. From the combined chloroform filtrates, 12 g. (72%) of aldehyde **6d**, m.p. 177-179°, was obtained after removal of the solvent. Recrystallization of a sample from 2-propanol gave creamy crystals, m.p. 178-179°. The ir spectrum (chloroform) showed bands at 3025, 2825, 2526, 1695, and 1635 cm^{-1}. The nmr spectrum (deuteriochloroform): δ = 2.07 (3 H, s, CH_3CO), 2.75-3.25 (2 H, broad s, CH_2-1), 3.25-4.00 (6 H, m, CH_2-2, CH_2-4, and CH_2-5), 6.08 (2 H, s, CH_2O_2), 6.90 (1 H, s, CH-9), and 10.37 (1 H, s, 6-CHO).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.39; H, 5.84; N, 5.18.

3-Acetyl-2,3,4,5-tetrahydro-7,8-methylenedioxy-1*H*-3-benzazepine-6-carboxylic Acid (**6e**).

Aldehyde **6d** (7.7 g., 0.03 mole) was oxidized with 0.03 mole of silver oxide prepared from 5.1 g. of silver nitrate and 1.32 g. of sodium hydroxide (10) in the presence of 4.8 g. (0.12 mole) of sodium hydroxide in methanol at 60°. The solid material was removed by filtration and the filtrate distilled in a rotary evaporator. The resulting semi-solid residue was dissolved in 75 ml. of warm water, the pale amber solution was acidified with hydrochloric acid to *p*H 3 and cooled, whereupon a cream-colored solid separated. After cooling in an ice bath for 1 hour the solid was filtered and dried; yield 6.3 g., m.p. 184-190°. After two recrystallizations from aqueous ethanol the product, 5.0 g., melted at 204-206°. The nmr spectrum (DMSO-d_6): δ = 2.0 (3 H, s, CH_3CO); 2.67-3.20 (4 H, m, CH_2-1 and CH_2-5), 3.4 to 3.6 (4 H, m, CH_2-2 and CH_2-4), 6.05 (2 H, s, CH_2O_2), and 6.92 (1 H, s, CH-9).

Anal. Calcd. for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.96; H, 5.57; N, 5.09.

3-Acetyl-6-cyanomethyl-2,3,4,5-tetrahydro-7,8-methylenedioxy-1*H*-3-benzazepine (**6f**).

To a stirred solution of 11.3 g. (0.04 mole) of **5** in 113 ml. of dimethyl sulfoxide was added 2.5 g. (0.05 mole) of sodium cyanide. The temperature rose to 35° from 20° over a period of 15 minutes and then fell. After 45 minutes the mixture was poured into 300 ml. of water and the suspension was extracted with five 100-ml. portions of chloroform. The combined extracts were washed five times with saturated brine, once with water, dried, and the solvent was finally distilled in a rotary evaporator. The white crystalline residue was slurried in 30-60° petroleum ether and collected by filtration; yield 10.5 g., m.p. 179-182°. Recrystallization from ethanol raised the m.p. to 184-185°.

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.32; H, 6.01; N, 10.35.

2,3,4,5-Tetrahydro-6-methyl-7,8-methylenedioxy-1*H*-3-benzazepine Hydrochloride (**7a**·HCl).

Compound **6a** (9.9 g., 0.04 mole) was refluxed with 6.4 g. (0.16 mole) of sodium hydroxide in 80 ml. of 50% aqueous ethanol for 48 hours. After distilling the ethanol in a rotary evaporator, 40 ml. of water was added followed by sufficient hydrochloric acid to bring the *p*H to 3. The cooled solution was extracted several times with ether to remove any unhydrolyzed **6a**. The solution was then brought to *p*H 10 and the liberated base extracted with ether. After drying the ethereal extract (potassium carbonate), the solvent was distilled to yield 6.0 g. of a colorless oil. This oil was dissolved in 50 ml. of ethanol and a slight excess of ethanolic hydrochloric acid was added. Distillation of the solvent gave a white crystalline solid which was recrystallized from ethanol; yield 4.5 g., m.p. 264.5-266° dec. A second crop weighing 0.95 g. had the same m.p.

Anal. Calcd. for $C_{12}H_{15}NO_2$·HCl: C, 59.63; H, 6.67; Cl, 14.67; N, 5.80. Found: C, 59.52; H, 6.67; Cl, 14.76; N, 5.71.

2,3,4,5-Tetrahydro-6-hydroxymethyl-7,8-methylenedioxy-1*H*-3-benzazepine Hydrochloride (**7c**·HCl).

Compound **6c** (5.3 g., 0.02 mole) was refluxed for 18 hours in a solution of 1.6 g. (0.04 mole) of sodium hydroxide in 20 ml. of 50% aqueous ethanol. The ethanol was distilled and 20 ml. of water added to the suspension followed by sufficient hydrochloric acid to bring the *p*H to 2. After extracting twice with 25-ml. portions of chloroform, the solution was made alkaline with sodium hydroxide and the liberated base extracted with eight 50-ml. portions of 1:1 ether-benzene. The combined extracts were dried (potassium carbonate) and the solvent was distilled in a rotary evaporator to leave a crystalline solid, m.p. 136-137°. This solid was dissolved in 100 ml. of ethanol and the solution acidified with ethanolic hydrogen chloride. Distillation of the solvent left a crystalline residue which was slurried in ethyl acetate and filtered; yield 4.6 g. Recrystallization from 2-propanol containing a small amount of water yielded 3.3 g. of product, m.p. 250-251° dec.

Anal. Calcd. for $C_{12}H_{15}NO_3$·HCl: C, 55.92; H, 6.26; Cl, 13.76; N, 5.44. Found: C, 55.83; H, 6.40; Cl, 13.92; N, 5.49.

2,3,4,5-Tetrahydro-7,8-methylenedioxy-1*H*-3-benzazepine-6-carboxylic Acid Hydrochloride (**7e**·HCl).

Compound **6e** (5.0 g., 0.18 mole) was refluxed in a solution of 3.6 g. (0.09 mole) of sodium hydroxide in 50 ml. of 50% aqueous ethanol for 28 hours. A trace of insoluble material was removed by filtration and after distilling the alcohol, the *p*H of the solution was adjusted to 7.5. On cooling, 3.8 g. of the zwitterion (m.p. 235-240° dec.) crystallized. The crystals were suspended in 20 ml. of water and dissolved by the addition of hydrochloric acid to *p*H 2-3. Distillation of the solvent left a crystalline residue which was recrystallized from aqueous 2-propanol; yield 2.2 g., m.p. 272-273° dec. After another recrystallization from the same solvent the m.p. was 273-275° (11).

Anal. Calcd. for $C_{12}H_{13}NO_4$·HCl: C, 53.05; H, 5.19; Cl, 13.05; N, 5.16. Found: C, 53.56; H, 5.12; Cl, 12.90; N, 5.23.

2,3,4,5-Tetrahydro-7,8-methylenedioxy-1*H*-3-benzazepine-6-acetic Acid Hydrochloride (**7h**·HCl).

Nitrile **6f** (10.5 g.) was stirred at room temperature with 105 ml. of saturated ethanolic hydrogen chloride. The mixture was warmed gradually, refluxed for 2.5 hours and then it was cooled to room temperature and allowed to stand overnight. The ammonium chloride was removed by filtration and the filtrate evaporated in a rotary evaporator. Chloroform (50 ml.) was added and the resulting solution was washed free of acid with water. Distillation of the chloroform left 12.0 g. of pale amber oil, 3-acetyl-6-carbethoxymethyl-2,3,4,5-tetrahydro-7,8-methylenedioxy-1*H*-3-benzazepine (**6g**), which was refluxed for 24 hours with 7.6 g. (0.19 mole) of sodium hydroxide and 76 ml. of 50% aqueous ethanol. Most of the solvent was removed in a rotary evaporator and the residue was redissolved in 50 ml. of water. Hydrochloric acid was added to *p*H 2 and the solution evaporated completely to leave a white, crystalline residue. This residue was recrystallized from 126 ml. of 2-propanol containing 10% of water to give 5.2 g. of crystalline **7h**·HCl, m.p. 265-266° dec.

Anal. Calcd. for $C_{13}H_{15}NO_3$·HCl: C, 54.65; H, 5.65; Cl, 12.41; N, 4.90. Found: C, 54.46; H, 5.62; Cl, 12.45; N, 4.59.

3-Acetyl-6,9-bis(chloromethyl)-2,3,4,5-tetrahydro-7,8-methylenedioxy-1*H*-3-benzazepine (**8**).

In a 2 l. creased flask provided with a stirrer, thermometer, reflux condenser, and a gas inlet tube were placed 93.3 g. (0.4 mole) of **4**, 180 g. (6.0 moles) of paraformaldehyde, 365 ml. of concentrated hydrochloric acid and 800 ml. of 1,2-dichloroethane. Hydrogen chloride gas was slowly passed into the stirred mixture as the temperature was raised to 50-55°, where it was maintained for 17 hours. At the end of this time, the yet warm two-phase system was poured into a separatory funnel and the lower organic layer was removed. The remaining aqueous layer was extracted with three 250-ml. portions of chloroform.

The combined extracts were washed successively with water, saturated sodium bicarbonate solution, water, then dried and the solvent removed in a rotary evaporator. This residue, 131 g., m.p. 201-202.5°, was suspended in 1 l. of 60-90° petroleum ether and the mixture was agitated until all the lumps were broken up. Filtration, followed by air drying of the filter cake gave 127.5 g. (96%) of white solid, m.p. 201-202.5°. An analytical sample was obtained by recrystallization from ethyl acetate; m.p. 202-202.5°. The nmr spectrum (DMSO-d_6): δ = 2.20 (3 H, s, CH_3CO), 2.83-3.25 (4 H, m, CH_2-1 and CH_2-5), 3.50-3.83 (4 H, m, CH_2-2 and CH_2-4), 3.80 (4 H, s, CH_2-6 and CH_2-9), and 6.25 (2 H, s, CH_2O_2).

Anal. Calcd. for $C_{15}H_{17}Cl_2NO_3$: C, 54.56; H, 5.19; N, 4.24. Found: C, 54.59; H, 4.89; N, 4.20.

3-Acetyl-2,3,4,5-tetrahydro-6,9-dimethyl-7,8-methylenedioxy-1*H*-3-benzazepine (**9a**).

Compound **8** (33 g., 0.1 mole) and 18.1 g. (0.22 mole) of anhydrous sodium acetate, together with 2 g. of 10% palladium on charcoal, were shaken under 50 PSI of hydrogen pressure in 220 ml. of glacial acetic acid until no more hydrogen was abosrbed. The catalyst was removed by filtration, washed with acetic acid, and the acetic acid was distilled from the filtrate in a rotary evaporator leaving a colorless oil. The oil was covered with water (250 ml.) and the mixture stirred vigorously until the organic phase solidified. The solid was then recovered by filtration, washed free of chloride, and dried; yield, 23-24 g. (88-92%), m.p. 172-175°. This material is generally suitable for further use, but, if necessary, it may be recrystallized from a boiling mixture of 185 ml. of acetic acid and 180 ml. of water; m.p. 177-178°. The nmr spectrum (deuteriochloroform); δ = 2.07 (3 H, s, CH_3CO), 2.15 (6 H, s, CH_3-6 and CH_3-9), 2.80-3.08 (4 H, m, CH_2-1 and CH_2-5), 3.50-3.96 (4 H, m, CH_2-2 and CH_2-4), and 5.88 (2 H, s, CH_2O_2).

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.53. Found: C, 68.70; H, 7.19; N, 5.38.

The following compounds were obtained by procedures which were analogous to those used in preparing their 6-substituted analogs:

6,9-bis(Acetoxymethyl)-3-acetyl-2,3,4,5-tetrahydro-7,8-methylenedioxy-1*H*-3-benzazepine (**9b**).

This compound had m.p. 126-127°.

Anal. Calcd. for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.36; H, 6.15; N, 3.97.

3-Acetyl-2,3,4,5-tetrahydro-6,9-bis(hydroxymethyl)-7,8-methylenedioxy-1*H*-3-benzazepine (**9c**).

This compound had m.p. 190.5-191.5°.

Anal. Calcd. for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.11; H, 6.78; N, 4.59.

3-Acetyl-6,9-bis(cyanomethyl)-2,3,4,5-tetrahydro-7,8-methylenedioxy-1*H*-3-benzazepine (**9f**).

This compound had m.p. 188.5-190°.

Anal. Calcd. for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.36; H, 5.67; N, 13.73.

3-Acetyl-2,3,4,5-tetrahydro-7,8-methylenedioxy-1*H*-3-benzazepine-6,9-diacetic acid (**9h**).

This compound had m.p. 263-263.5° dec.

Anal. Calcd. for $C_{17}H_{19}NO_7$: C, 58.45; H, 5.48; N, 4.01. Found: C, 58.14; H, 5.73; N, 4.30.

2,3,4,5-Tetrahydro-6,9-dimethyl-7,8-methylenedioxy-1*H*-3-benzazepine Hydrochloride (**10a**·HCl).

Compound **9a** (78.8 g., 0.286 mole) was dissolved in 695 ml. of hot ethanol and 500 ml. of water containing 45 g. (1.125 moles) of sodium hydroxide was added to the solution. This mixture was refluxed for 48 hours, cooled, and poured into a separatory funnel containing 500 ml. of benzene and 2 l. of cold water. After equlibrating, the benzene layer was removed and the aqueous layer was extracted with three 300-ml. portions of benzene. The base was then extracted into aqueous solution by shaking with a warm solution (45-50°) of 30 ml. of concentrated hydrochloric acid in 1 l. of water. The benzene solution was extracted once more with 100 ml. of water and the combined aqueous layers were concentrated in a rotary evaporator to a thick sludge of crystals. The crystals were filtered, and a second crop was taken by concentration of the filtrate. In this manner, a first crop of 55.8 g. (75%), m.p. 290-292° and a second crop of 14.7 g. (20%), m.p. 282-286° were obtained. For analysis, the material was recrystallized from aqueous 2-propanol; m.p. 292-293° dec. The nmr spectrum (deuterium oxide): δ = 2.45 (6 H, s, CH_3-6 and CH_3-9), 3.3-3.8 (8 H, m, CH_2-1, CH_2-2, CH_2-4, CH_2-5), 5.16 (2 H, s, $\overset{+}{N}H_2$), 6.22 (2 H, s, CH_2O_2).

Anal. Calcd. for $C_{13}H_{17}NO_2$·HCl: C, 61.05; H, 7.09; N, 5.48. Found: C, 61.03; H, 7.22; N, 5.59.

2,3,4,5-Tetrahydro-6,9-bis(hydroxymethyl)-7,8-methylenedioxy-1*H*-3-benzazepine (**10c**).

Compound **9c** (2.93 g., 0.01 mole) was refluxed with 1.6 g. (0.04 mole) of sodium hydroxide in 30 ml. of 50% aqueous ethanol for 18 hours. Distillation of the solvents in a rotary evaporator yielded a voluminous white solid which was dissolved in 100 ml. of 3*N* hydrochloric acid and extracted with three 50-ml. portions of a 1:1 mixture of chloroform and ether. The aqueous solution was filtered through a bed of filter aid to remove some finely divided solid, and the filtrate was made alkaline with 20% sodium hydroxide solution whereupon a crystalline precipitate formed. This was filtered, washed with water, and dried; yield 1.6 g., m.p. 214-216° dec. After one recrystallization from water the m.p. was 221-222° dec.

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.58; H, 6.70; N, 5.64.

2,3,4,5-Tetrahydro-7,8-methylenedioxy-1*H*-3-benzazepine-6,9-diacetic Acid (**10h**).

Compound **9g** (12) (3.5 g., 0.01 mole) was refluxed with 70 ml. of 3*N* hydrochloric acid for 12 hours. When cool, the amber solution was stirred with 0.25 g. of decolorizing charcoal for 30 minutes, filtered, and the solvent was distilled in a rotary evaporator to leave 3.0 g. of a buff solid, m.p. 268-270° dec. The solid was suspended in 25 ml. of water and the stirred suspension was brought to *p*H 4 by the dropwise addition of 4% sodium hydroxide solution. The solid which was recovered by filtration was purified by resuspension in 20 ml. of water, and raising the *p*H to 7. The resulting solution was treated with 0.25 g. of decolorizing charcoal, filtered, and the *p*H was adjusted to 4. The creamy white

solid which separated was removed, washed with water, and dried overnight at 100° *in vacuo*; yield 2.8 g., m.p. <330°. The MW from the low resultion mass spectrum was 307, calcd. 307.

Anal. Calcd. for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.30; H, 5.56; N, 4.42.

2,3,4,5-Tetrahydro-3,6,9-trimethyl-7,8-methylenedioxy-1*H*-3-benzazepine Hydrochloride (**11**·HCl).

Compound **10a**·HCl (25.6 g., 0.1 mole) was suspended in 200 ml. of methanol, and to this suspension was added 15 ml. of 37% formaldehyde solution (0.18 mole), 4.1 g. (0.105 mole) of sodium hydroxide in 5 ml. of water, and 8-10 g. of methanol--washed Raney nickel. The mixture was shaken under 50 PSI of hydrogen pressure at room temperature; uptake ceased after 2.5 hours. The catalyst was removed by filtration and the filtrate distilled in a rotary evaporator leaving a colorless oil which crystallized readily. The solid was taken up in 200 ml. of benzene and 100 ml. of water, the benzene layer was washed several times with water, dried, and distilled in a rotary evaporator. The residual oil was dissolved in 50 ml. of benzene and this solution passed over a column of 100 g. of Woelm alumina (I) using 750 ml. of benzene to wash the column. From the effluent, 21 g. of colorless oil was obtained after distillation of the solvent. This base was dissolved in 200 ml. of 2-propanol and hydrochloric acid was added to *p*H 4. After chilling overnight, the resulting crystals were filtered, washed with 2-propanol, and dried; yield 20.1 g., m.p. 284.5-286° dec. with some previous discoloration.

Anal. Calcd. for $C_{14}H_{19}NO_2$·HCl: C, 62.33; H, 7.47; N, 5.19; Cl, 13.14. Found: C, 62.29; H, 7.49; N, 5.10; Cl, 13.20.

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(4) When screened by classical methods, **3** exhibited considerable analgetic, anoretic and anti-inflammatory activity, however, with substantial animal toxicity.

(5) The correct Chemical Abstracts nomenclature for **3** is 6,7,8,9-tetrahydro-5*H*-1,3-dioxolo[4,5-*h*][3]benzazepine. For simplicity, we classify this compound and its analogs as methylenedioxy derivatives and hereafter in the text these will be referred to simply as benzazepine.

(6) F. Dallacker, K. W. Glombitza and M. Lipp, *Ann. Chem.*, **643**, 67 (1961).

(7) Melting points were determined on a Thomas-Hoover apparatus and are corrected. Boiling points are uncorrected. Infrared spectra were determined on a Beckman IR-5 recording spectrophotometer. Nmr spectra were determined on a Varian A-60 spectrometer (TMS) and are reported in ppm (δ). Vapor phase chromatography was performed with 4% polyethylene glycol (molecular weight 4000) monostearate on Chromosorb W columns, unless otherwise stated. The instruments used were either the Beckman GC2A with Thermotrac or the F & M-810, Ri3N.

(8) Compound 3 solidifies at 88-89° and precautions must be taken to prevent blockage of the distillation delivery tube. The receiver should be cooled to minimize sublimation. Material prepared as described was somewhat impure and could not be purified by recrystallization of its free base or its nitrate, sulfate or hydrochloride. Pure **3** was obtained *via* its *N*-acetyl derivative **4**.

(9) Purchased from Beacon Chemical Company.

(10) I. A. Pearl, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, New York, N. Y., 1963, p. 972.

(11) The m.p. is greatly dependent on the rate of heating.

(12) Compound **9g**, obtained by a procedure analagous to that and for its 6-substituted analog, was a noncrystallizing oil.