The Synthesis of Some 7- and 7,8-Substituted 2,3,4,5-Tetrahydro-1*H*-3-benzazepines

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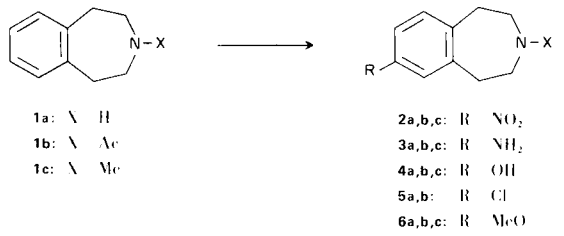
The nitration of 2,3,4,5-tetrahydro-1*H*-3-benzazepine and its 3-methyl and 3-acetyl derivatives yields the corresponding 7-nitro derivatives which can be further transformed by classical procedures. The preparation of the ether cleavage products of the known 2,3,4,5-tetrahydro-7,8-dimethoxy-1*H*-3-benzazepine is also reported.

The number of 7-substituted tetrahydro-3-benzazepines (1) which have been reported in the literature is relatively small since most of the known methods (2) for the preparation of benzazepines limit the nature of the substituents that may be present in the aromatic ring or require intermediates which are inaccessible. This paper describes various 7-substituted benzazepines which were prepared from 7-nitrobenzazepines. The latter were obtained by the direct nitration of compounds such as **1a**, **b**, or **c** (Scheme I). The sequences employed in this work are shown in Scheme I and the pertinent data for the compounds obtained are summarized in Table I.

SCHEME I



1a: X = H
1b: X = Ac
1c: X = Me

2a,b,c: R = NO_2
3a,b,c: R = NH_2
4a,b,c: R = OH
5a,b: R = Cl
6a,b,c: R = MeO

SCHEME II

7: X = H
8: X = Me

9: R_1 = H; R_2 = Me
10: R_1 = R_2 = H

Since 7,8-dimethoxytetrahydrobenzazepine was readily available by the procedure of Wood (3), the preparation of the monophenol **9** by partial ether cleavage with sodium in liquid ammonia, and the diphenol **10** by treatment with 48% hydrobromic acid was included in our program (Scheme II).

EXPERIMENTAL

For brevity detailed experimental procedures are given only for the sequence beginning with compound **1a**. In those cases where significant changes in the procedure were made when **1b** or **1c** were the starting materials the appropriate changes are noted.

2,3,4,5-Tetrahydro-1*H*-3-benzazepine (**1a**).

This compound was prepared by the method of Ruggli et al. (2c) in 42% yield; b.p. 109.5-110°/10 mm., n_D^{22} 1.5605. The hydrochloride melted at 255.5-256.5°.

2,2′-*o*-Phenylenebisethylamine Dihydrochloride.

The still pot residue from **1a** yielded a second base, b.p. 63.5-65.0°/0.5 mm. in about 10-12% yield, n_D^{24} 1.5545. This base gave a hydrochloride of m.p. 255-257° dec after recrystallization from ethanol-ethyl acetate (5).

Anal. Calcd. for $C_{10}H_{18}Cl_2N_2$: C, 50.64; H, 7.65; Cl, 29.90. Found: C, 50.94; H, 7.82; Cl, 29.59.

3-Acetyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**1b**).

This compound was obtained by refluxing **1a** with acetic anhydride (3.4 ml./g.) for 2.5 hours after which the acetic acid and acetic anhydride were distilled at atmospheric pressure up to 138°. From the residue, **1b** was distilled at 118-119°/0.3 mm. as a colorless rapidly crystallizing oil, yield 77%, m.p. 69-71°, lit. (2c), 70°; ir spectrum (chloroform): ν co 1630 cm^{-1}.

2,3,4,5-Tetrahydro-3-methyl-1*H*-3-benzazepine (**1c**)

A mixture of 13.7 g. (0.093 mole) of **1a**, 8.3 g. (0.102 mole) of 37% formaldehyde solution and 6 g. of ethanol-washed Raney nickel in 200 ml. of ethanol was shaken with hydrogen at 50 p.s.i. for 40 minutes. The catalyst was filtered, the solvent distilled, and the residual pale amber oil distilled at 101.5-102.5°/10 mm., yield 14 g., n_D^{24} 1.5432; homogeneous on tlc. The hydrochloride was prepared in 2-propanol and recrystallized from 2-propanol-ethyl acetate, m.p. 251-252° dec.

TABLE I

7- and 7,8-Substituted 2,3,4,5-Tetrahydro-1*H*-3-Benzazepines

Compound No.	Formula	M.p., °C (Crystallization solvent)	Analyses (Calcd.) (Found) C	H	N or (Cl)
1a	$C_{10}H_{13}N$	109.5-110/10 mm (a)	81.58 81.75	8.90 9.20	9.52 9.65
1b	$C_{12}H_{15}NO$	69-71		Not analyzed	
1c·HCl	$C_{11}H_{15}N$·HCl	251-252 dec.	66.82 67.08	8.16 8.19	17.93 (Cl) 17.89 (Cl)
2a	$C_{10}H_{12}N_2O_2$	76.5-77.5 (b)	62.48 62.46	6.29 6.57	14.58 14.33
2b	$C_{12}H_{14}N_2O_3$	126-127 (c)	61.53 61.41	6.02 5.95	11.96 11.75
2c·HCl	$C_{11}H_{14}N_2O_2$·HCl	235-236 (d)	54.43 54.09	6.23 6.45	11.54 11.29
3a·HCl	$C_{10}H_{14}N_2$·2HCl	283-286 (e)	51.07 51.07	6.85 6.91	30.15 (Cl) 30.24 (Cl)
3b	$C_{12}H_{16}N_2O$	180-183 (f)	70.56 70.53	7.90 8.06	13.72 13.65
3c·H_2SO_4	$C_{11}H_{16}N_2$·H_2SO_4	261 dec. (g)	48.16 48.49	6.61 6.78	10.21 10.21
4a·½H_2SO_4	$C_{10}H_{13}NO$·½H_2SO_4	317-318d (h)	56.59 56.24	6.65 6.60	6.60 6.58
4b	$C_{12}H_{15}NO_2$	181-181.5 (b)	70.22 70.41	7.37 7.60	6.82 6.57
4c·HCl	$C_{11}H_{15}NO$·HCl	232-235d (i)	61.82 61.64	7.55 7.63	16.52 (Cl) 16.42 (Cl)
5a·HCl	$C_{10}H_{12}ClN$·HCl	177-178.5 (j)	55.06 54.82	6.01 6.17	32.51 (Cl) 32.56 (Cl)
5b	$C_{12}H_{14}ClNO$	85-87 (k)	64.43 64.35	6.31 6.27	15.87 (Cl) 15.81 (Cl)
6a·HCl	$C_{11}H_{15}NO$·HCl	231-234 (h)	61.82 61.64	7.55 7.48	16.59 (Cl) 16.57 (Cl)
6b	$C_{13}H_{17}NO_2$	94-96 (l)	71.20 71.41	7.82 8.12	6.39 6.41
6c·HCl	$C_{12}H_{17}NO$·HCl	194-195 (m)	63.29 63.67	7.97 7.89	15.57 (Cl) 15.57 (Cl)
7·HCl	$C_{12}H_{20}N_2O_2$·2HCl	280 dec. (f)	48.49 48.11	7.46 7.75	23.86 (Cl) 23.60 (Cl)
8·HCl	$C_{13}H_{19}NO_2$·HCl	262-263 dec. (d)	60.58 60.38	7.82 8.00	13.75 (Cl) 13.78 (Cl)
9·HCl	$C_{11}H_{15}NO_2$·HCl	240-242 dec. (h)	57.52 57.40	7.02 7.02	15.43 (Cl) 15.30 (Cl)
10·HCl	$C_{10}H_{13}NO_2$·HCl	263-270 dec. (n)	55.69 55.85	6.54 6.64	16.44 (Cl) 16.64 (Cl)

(a) B.p. (b) Water. (c) Benzene-cyclohexane. (d) 2-Propanol. (e) Ethanol-ether. (f) Ethanol. (g) Aq. ethanol. (h) Aq. 2-propanol. (i) 1-Butanol. (j) 2-Propanol-ether. (k) 60-90° Petroleum ether. (l) Ethyl acetate-60-90° petroleum ether. (m) 1-Butanol-butyl acetate. (n) Methanol.

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

This compound was obtained by the method of Wood (3).

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

This material was prepared by the method used for **1c** except that the solvent for reduction was methanol. The hydrochloride melted at 262-263° dec. after two recrystallizations from 2-propanol; lit. 359-361° (3). This may be a misprint in the first digit since the structure of the product described here had the expected nmr spectrum in deuteriodimethylsulfoxide: δ = 2.77 (3H, s, CH_3-N), 3.22 (8H, s, CH_2CH_2-N-CH_2CH_2), 3.92 (6H, s, $2CH_3O$), and 6.88 (2H, s, CH-6 and -9).

2,3,4,5-Tetrahydro-7-nitro-1*H*-3-benzazepine (**2a**).

Two-tenths of a mole of the base **1a** (29.4 g.) (f.p. 2°) was cooled to 0° in a 500 ml. round bottomed flask equipped with a stirrer, dropping funnel, and a thermometer. To the cooled solid (ice-bath), 125 ml. of concentrated sulfuric acid precooled to 0°, was added in a single portion and the stirrer started whereupon the temperature rose to 35° and rapidly fell to 10°. Stirring was continued for 1 hour until a clear pale yellow solution was obtained. During this period a solution of 16.8 g. (0.21 mole) of ammonium nitrate in 125 ml. of sulfuric acid was prepared with the exclusion of moisture. This mixture was added dropwise to the sulfuric acid solution of the base at $< 5°$. After all the nitrating solution had been added, the mixture was kept at 0-5° for 1 hour, then allowed to warm to room temperature where it remained for 18 hours. The sulfuric acid solution was poured onto 1 kg. of crushed ice, and then with external cooling, sufficient ammonium hydroxide added to bring the *p*H to approximately 9. A yellow orange precipitate formed which soon became granular. This was collected by filtration, washed well with water, and dried *in vacuo* first at 65° and finally at 100°, yield, 22.2 g., uniform on tlc, m.p. 80-81°.

A sample, recrystallized from a large volume of water, was obtained as reddish yellow needles, m.p. 76.5-77.5°.

The ir spectrum (chloroform) showed bands at 3350 (NH), 1510 and 1350 (NO_2) cm^{-1}; the nmr spectrum (deuteriochloroform) showed δ = 2.23 (1H, s, NH), 3.00 (8H, s, CH_2-CH_2-N-CH_2-CH_2), and 7.25, 7.97, 7.99 (3H, ABX Jortho = 9, Jmeta = 2.5 Hz, CH-6, -8, and -9).

A hydrochloride was prepared from 5 g. of the above **2a**. After recrystallization from ethanol-ether, the m.p. was 287-289° dec., yield 5.6 g.

2,3,4,5-Tetrahydro-3-methyl-7-nitro-1*H*-3-benzazepine Hydrochloride (**2c**·HCl)

This compound was prepared by the method used to prepare **2a**, except that the free base, an oil, was collected by extraction with benzene. The base was converted to the hydrochloride, yield 23%, m.p. 235-236°.

7-Amino-2,3,4,5-tetrahydro-1*H*-3-benzazepine Hydrochloride (**3a**·HCl)

Seventeen and four-tenths g. (0.091 mole) of base **2a** in 220 ml. of ethanol was shaken under 50 p.s.i. of hydrogen with 6 g. of ethanol-washed Raney nickel. Removal of the catalyst and distillation of the solvent left 14.2 g. of a tan solid, m.p. 115-117°. The hydrochloride was prepared in 2-propanol with an excess of ethereal hydrogen chloride, m.p. 283-286°, unchanged after recrystallization from ethanol-ether, yield 16.8 g.

7-Amino-2,3,4,5-tetrahydro-3-methyl-1*H*-3-benzazepine Sulfate (**3c**·H_2SO_4).

This material was prepared by the method used for **3a**. From the hydrogenation liquor the free base was isolated and converted to the neutral sulfate in 2-propanol; yield 90%.

2,3,4,5-Tetrahydro-1*H*-3-benzazepin-7-ol Sulfate (**4a**·½H_2SO_4).

To a solution of 2.4 g. (0.0125 mole) of **3a** in 25 ml. of 3*N* sulfuric acid, at 0-3°, a solution of sodium nitrite (1 g. in 5 ml. of water) was added dropwise until a positive test for nitrous acid was obtained. Excess nitrous acid was decomposed by adding 0.2-0.3 g. of urea and stirring for 10 minutes. The diazonium solution was added dropwise with stirring to 200 ml. of 50% sulfuric acid at 70° and maintained at 70° until all of the diazonium salt had been decomposed. On cooling the warm solution in an ice bath, a crystalline precipitate formed. After chilling for 30 minutes in an ice bath, the solid was recovered by filtration and washed with a little ice water. Recrystallization from 80% aqueous 2-propanol gave 2.1 g., 76%, of colorless salt, m.p. 317-318.5° dec. Analysis showed this to be the neutral sulfate.

2,3,4,5-Tetrahydro-3-methyl-1*H*-3-benzazepin-7-ol Hydrochloride (**4c**·HCl).

This compound was prepared by the method used for **4a**, but the free base was isolated by extraction with 1:1 ether-benzene from the solution of the decomposed diazonium salt after alkalizing with ammonia, and converted to the hydrochloride. The yield of **4c**·HCl was 82%.

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

This material was prepared by refluxing 6.6 g. (0.03 mole) of **6b** with 80 ml. of 3*N* hydrochloric acid for 5 hours. Distillation of the solvent in the rotary evaporator left a crystalline residue of m.p. 233-236° dec. This solid was recrystallized from 100 ml. of 2-propanol containing 2-3 ml. of water. White crystals separated on standing overnight, m.p. 231-234°. A second crop of the same m.p. was obtained by distilling the mother liquor to about one-half volume, total yield 5.3 g.

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

This compound was obtained by treatment of 4.3 g. of **4c** with excess diazomethane in methanol solution for 65 hours. After removal of the excess diazomethane and methanol, the residual base was dissolved in 25 ml. of 10% hydrochloric acid. The solution was washed several times with ether to remove polymeric material; the base was liberated and extracted into 1:1 ether-benzene. Removal of the solvent gave 4.0 g. of a pale amber oil that was converted to the hydrochloride with ethereal hydrogen chloride; yield 3.7 g. of m.p. 190-192°. This solid was recrystallized from 1-butanol-butyl acetate to yield 2.3 g. of crystals, m.p. 193-194°. An analytical sample was obtained by one more recrystallization from the same solvent, m.p. 194-195°.

3-Acetyl-2,3,4,5-tetrahydro-7-nitro-1*H*-3-benzazepine (**2b**).

Two-tenths of a mole of compound **1b** (37.8 g.) was nitrated as described above for **1a** except that the reaction was completed in 5 hours at 5° after the nitrating mixture had been added. After pouring onto ice, the crude nitro compound was collected in 1 liter of benzene and the extract washed free of acid with successive washes of water, saturated bicarbonate solution and water. Distillation of the solvent from the dried solution (magnesium sulfate) gave 44.1 g., 94% of a cream-colored solid, m.p. 92-110° (6). After drying and recrystallization from benzene-cyclohexane the m.p. was 126-127°.

The ir spectrum (chloroform) showed bands at 1710 (CO), and 1510 and 1330 (NO_2) cm^{-1}.

3-Acetyl-2,3,4,5-tetrahydro-7-methoxy-1*H*-3-benzazepine (**6b**).

Ten and three-tenths g. (0.05 mole) of **4b** was dissolved in 100 ml. of methanol containing 13 g. (0.1 mole) of dimethylsulfate and to the stirred solution, 100 ml. of methanol, in which 2.3 g. (0.1 mole) of sodium had been previously dissolved, was added. The temperature rose from 22° to 29°. After standing overnight, the apparent *p*H was 5-6. Ten ml. of 15% potassium hydroxide solution was added and the methanol distilled in the rotary evaporator. The residual solid was dissolved in 50 ml. of water and the solution extracted three times with 60 ml. portions of ether. The combined extracts were washed with two small portions of water, dried and the solvent distilled leaving 11.5 g. of a pale amber oil that rapidly formed a cream-colored mass of crystals. The solid was dissolved in 50 ml. of benzene and the solution passed over 50 g. of aluminum oxide (grade I) washing the column with another 150 ml. of benzene. Distillation of the solvent gave 9.3 g. of a solid that was crystallized from 150 ml. of ethyl acetate containing a little 60-90° petroleum ether, yield, 9.1 g. of a white solid, m.p. 93-96.5°. Another recrystallization gave material of m.p. 94-96° that was analyzed (7).

The ir spectrum (potassium bromide) showed ν co at 1625 cm^{-1}.

3-Acetyl-7-chloro-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**5b**).

Twenty-five and one-half g. (0.125 moles) of **3b** was diazotized in 50 ml. of water and 50 ml. of concentrated hydrochloric acid with a solution of 9 g. of sodium nitrite in 30 ml. of water in the usual way. The diazonium solution was added to a solution of cuprous chloride (0.156 mole), 15.4 g. in 63 ml. of concentrated hydrochloric acid. A thick paste resulted from which gas was slowly evolved. After stirring overnight at room temperature, the mixture was warmed to 60-80° for a brief time whereupon the solid dissolved. The resulting solution was cooled and extracted with six 100 ml. portions of benzene. After drying and distilling the solvent in the rotary evaporator 13.7 g. of an amber syrup remained. This was distilled from a small Claisen flask collecting the portion that boiled at 140-145°/0.1 mm. Yield of oil, that rapidly crystallized, 12.6 g. Recrystallization from 60-90° petroleum ether gave white crystals of m.p. 85-88°.

7-Chloro-2,3,4,5-tetrahydro-1*H*-3-benzazepine Hydrochloride (**5a**·HCl).

Eleven g. (0.0493 mole) of distilled **5b** was refluxed with 13.0 g. (0.325 mole) of sodium hydroxide in 125 ml. of 50% aqueous ethanol for 20 hours. The cooled mixture was poured into 300 ml. of ice water, the oil that separated was collected by three extractions with benzene, 75 ml. each, the combined extracts dried (potassium carbonate), and the solvent distilled in the rotary evaporator. The residual oil was converted to the hydrochloride in 2-propanol with a slight excess of hydrochloric acid. After two evaporations with 2-propanol, the crystalline residue was dissolved in 75 ml. of 2-propanol and the solution diluted with 350 ml. of ether. The pale yellowish crystals, 10.3 g., were recovered by filtration and recrystallized once more from 2-propanol-ether, using a little *Norite*. Creamy-white crystals, 5.12 g. of m.p. 177-178.5° were obtained, lit. 178-180°, (**2g**).

2,3,4,5-Tetrahydro-8-methoxy-1*H*-3-benzazepin-7-ol Hydrochloride (**9**·HCl).

Two and four-tenths g. (0.104 mole) of sodium was dissolved in 100 ml. of liquid ammonia to form a dark blue paste. To this stirred suspension at -78°, 5.4 g. (0.026 mole) of **7** in 25 ml. of tetrahydrofuran was added in several small portions over a 5-minute period. This mixture was stirred at the boiling point of ammonia until it reached room temperature (5 hours), then the sodium-sodamide was destroyed by the dropwise addition of 25 ml. of water. After removing the organic solvent in the rotary evaporator, the aqueous residue was extracted four times with 25 ml. portions of benzene to remove unreacted starting material. The aqueous residue was saturated with potassium carbonate and extracted 12 times with 20 ml. portions of chloroform. After drying the extract over potassium carbonate, distillation of the solvent gave 0.89 g. of the free base **9**. This was converted to the hydrochloride in 2-propanol and after repeated evaporation with 2-propanol, a brown solid was obtained. Two recrystallizations from aqueous 2-propanol gave 0.5 g. of brownish crystals, m.p. 240-242°.

The nmr spectrum (deuteriodimethylsulfoxide) showed δ = 3.05 (8H, s, CH_2-CH_2-N-CH_2-CH_2), 3.73 (3H, s, CH_3O), 6.79 (2H, s, CH-6 and -7) and 9.3 (3H, broad s, NH_2^+ and OH).

The low resolution mass spectrum showed the m.w. to be 193 in agreement with the calculated value.

2,3,4,5-Tetrahydro-7,8-dihydroxy-1*H*-3-benzazepine Hydrochloride (**10**·HCl)

Two-hundredths mole, 4.15 g., of **7** was refluxed with 125 ml. of 48% hydrobromic acid for 5 hours, the brown solution was freed of hydrobromic acid in the rotary evaporator, adding water and repeating the evaporation twice more. The grayish residue darkened at 225-230° and gradually liquified at 233-237°.

The hydrobromide was converted to the hydrochloride by ion-exchange using the chloride form of Amberlite IR-4 (32 ml.). The column effluent was evaporated to dryness giving 4.3 g. of grayish solid. This was recrystallized from 150 ml. of methanol and 250 ml. of ethyl acetate; yield 3.6 g. of a grayish brown solid. The appearance was unchanged after another recrystallization from methanol, yield 2.08 g., sintering at 225-227.0°, m.p. 263-270° to a dark tar.

Acknowledgment

The authors express their appreciation to Dr. F. Scheidl and his staff for the microanalyses reported here. The ir spectra were obtained by Mr. S. Traiman and the nmr spectra by Dr. T. Williams of our Physical Chemistry Department, (Director Dr. R. Scott).

REFERENCES

(1) For brevity, the term benzazepine will hereafter be used in this paper to mean 2,3,4,5-tetrahydro-1*H*-3-benzazepine.

(2) Among the most important methods for the synthesis of benzazepine, or benzazepinones which are reducible to benzazepines are the following: (a) J. von Braun and H. Reich, *Ann. Chem.*, 445, 225 (1925); (b) its modernization by J. O. Halford and B. Weissmann, *J. Org. Chem.*, 17, 1646 (1952); (c) P. Ruggli, B. S. Bussenmaker, W. Müller, and A. Staub, *Helv. Chem. Acta.*, 18, 1388 (1935), (d) F. Johnson and N. A. Nasutavicus, *J. Heterocyclic Chem.*, 2, 26 (1965); (e) J. H. Osborn, *Dissertation Abstr.*, 19, 2475 (1959); (f) M. D. Nair and P. A. Malek, *Indian J. Chem.*, 5, 169 (1967); and (g) Geigy, Netherlands Pat Appl. 1968, 02 257. Note especially the references given in (d).

(3) J. W. Wood, M. A. Perry, and C. C. Tung, *J. Am. Chem. Soc.*, 73, 4689 (1951).

(4) Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. IR spectra were determined on a Perkin-Elmer 621 recording spectrophotometer; NMR spectra were determined on a Varian A-60 spectrometer using TMS as internal standard and are recorded in terms of δ, parts per million.

Thin layer chromatography was carried out on plates of fluorescent Silica G using as developer a solvent mixture of ethanol, ether, and concentrated ammonium hydroxide (90-10-2-parts by volume). The spots were visualized under the ultraviolet lamp, with the Dragendorff reagent, or with iodine vapor.

(5) The two bases reported here have apparently caused some controversy in the older literature because of the proximity of their melting points. *Cf.* K. Fries, H. Bestian, and W. Klaudowitz, *Chem. Ber.*, 69, 715 (1936). The bases can be separated as described above; mixtures of the hydrochlorides show melting points from 218-220° to 235-238° depending on their composition. With the aid of tlc, nmr and elemental analyses both salts are now fully characterized, thus clarifying the variable melting points.

(6) Unless prefectly dry, the substance shows low broad melting points.

(7) Attempted methylation using diazomethane failed; the starting material was recovered after 18 hours contact with excess diazomethane in methanol solution.