A New Procedure for Regioselective Synthesis of 8,9-Dichloro-2,3,4,5-tetrahydro-1*H*-2-benzazepine (LY134046) and its 3-Methyl Analogue as Inhibitors of Phenylethanolamine *N*-Methyltransferase (PNMT) [1a]

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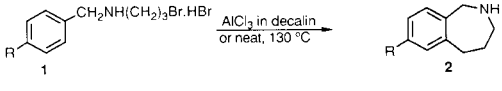
Received April 9, 1991

A regioselective synthesis of 8,9-dichloro-2,3,4,5-tetrahydro-1*H*-2-benzazepine (LY134046, **10**) and its 3-methyl analogue **26** from 6,7-dichloro-3-hydroxyphthalide (**16**) is described. The key step involved 1,4-hydride addition to the α,β-unsaturated nitrile **17** to give the saturated nitrile **18** using sodium borohydride in 2-propanol. In the preparation of LY134046 **10**, the COOH group in **18** was first esterified and then the nitrile function was selectively reduced with borane to yield the aminoester **20**. The aminoester **20** was then cyclized to the azepinone **21** which on reduction with borane provided LY134046 **10** in an overall yield of 22%. The route is adaptable to the preparation of hitherto unknown 3-substituted-2-benzazepines as demonstrated by the preparation of the 3-methyl analogue **26**. In this case the nitrile **18** was reacted with an excess methylmagnesium iodide to give the ketoacid **22**. Esterification of **22** followed by reductive amination with sodium cyanoborohydride and ammonium acetate provided the aminoester **24**, which was then converted to the target benzazepine **26** as described earlier for the title compound. The reaction conditions and the reagents used throughout the sequence are fairly mild and many functional groups may be tolerated. The only limitation to this procedure is the availability of the corresponding hydroxyphthalide. A variation in the choice of reagent in the Grignard reaction of **18** should provide an access to a variety of 3-substituted-2-benzazepines.

J. Heterocyclic Chem., **28**, 1587 (1991).

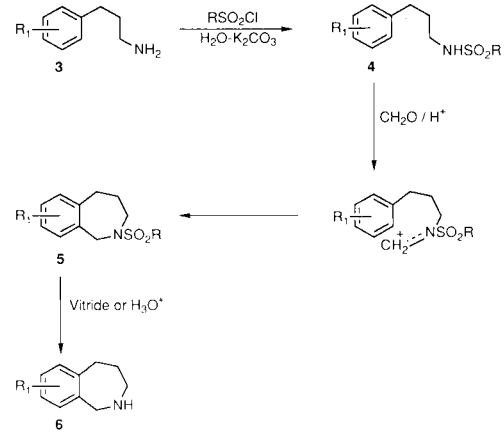
2-Benzazepine derivatives substituted either on the benzene ring or on the azepine ring are of considerable medicinal interest [2-5]. The prototype compound LY134046 (8,9-dichloro-2,3,4,5-tetrahydro-1*H*-2-benzazepine, **10**) is a widely studied inhibitor of the enzyme phenylethanolamine *N*-methyltransferase [2]. The most commonly used methods for the preparation of 2-benzazepines involve intramolecular electrophilic aromatic substitution as depicted in Scheme I. The reaction involves heating a substituted *N*-(3-bromopropyl)benzylamine hydrobromide (**1**) with anhydrous aluminum chloride either neat or in decalin at 130° [6]. The harsh conditions employed in this reaction preclude its use for the preparation of 2-benzazepines with substituents sensitive to heat and/or Lewis acids. Furthermore, the yield of benzazepine in this reaction declines considerably when the substituent is an electron-withdrawing group.

Scheme I



In an alternate method (Scheme II), sulfonamide **4** is cyclized with formaldehyde and acid to the *N*-sulfonyl-2-benzazepine **5** [7]. The sulfonyl group is then removed either by acid hydrolysis or reductively by sodium *bis*(2-methoxyethoxy)aluminum hydride (Vitride). It was proposed that the presence of the electron-withdrawing sulfonyl group on the nitrogen in **4** increases the reactivity of the intermediate carbocation, thereby allowing the use of substrates with a non-activated aromatic moiety. However, no examples were cited for the preparation of 2-benzazepines with electron-withdrawing substituents [7].

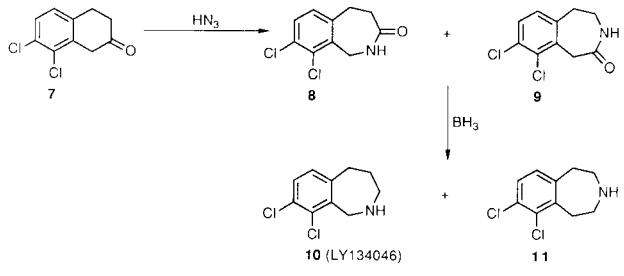
Scheme II



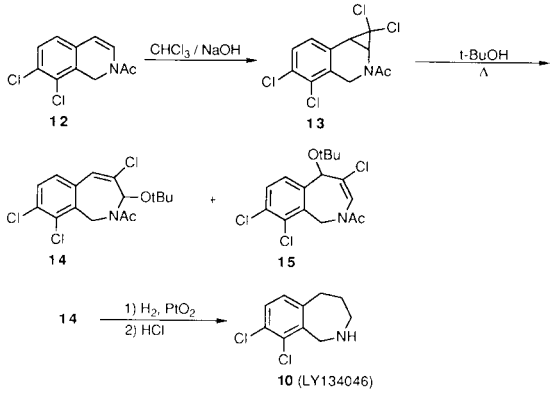
The currently available methods for the preparation LY134046 involve either a Schmidt reaction of 7,8-dichloro-2-tetralone (**7**) as described in a Canadian patent [8] (Scheme III) or a cyclopropanation ring enlargement of 2-acetyl-7,8-dichloro-1,2-dihydroisoquinoline (**12**) (Scheme IV) [9]. The Schmidt reaction results in a mixture of 8,9-dichloro-1,2,4,5-tetrahydro-3*H*-2-benzazepin-3-one (**8**) and 8,9-dichloro-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one (**9**). After reduction of this mixture of azepinones, LY134046 is

separated from its regioisomer by chromatography. In addition to the use of hazardous hydrazoic acid in the Schmidt reaction and the need for chromatographic separation of the regioisomers formed, the preparation of 7,8-dichloro-2-tetralone (**7**) involves seven steps from the commercially available 2,3-dichloroaniline and the overall yield of LY134046 is only about 1%. In the cyclopropanation-ring enlargement of 2-acetyl-7,8-dichloro-1,2-dihydroisoquinoline (**12**), one ends up with a mixture of two dihydro-2-benzazepine derivatives **14** and **15** (see Scheme IV) of which only the former has been converted into LY134046 after chromatography. The starting dihydroisoquinoline **12** itself is prepared from 2,3-dichlorobenzaldehyde in three steps and the overall yield of LY134046 is only 9%. Furthermore, neither of these two methods can be adapted to the preparation of 3-substituted-2-benzazepines of which there are no examples in the literature. We wish to describe a general method for the regioselective preparation of LY134046 [10] and its hiterto unknown 3-methyl analogue **26** from 6,7-dichloro-3-hydroxyphthalide (**16**) as depicted in Schemes V and VI respectively.

Scheme III

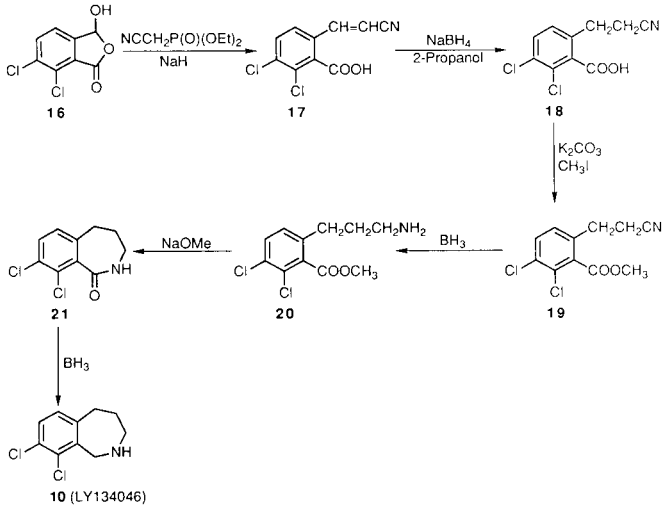


Scheme IV

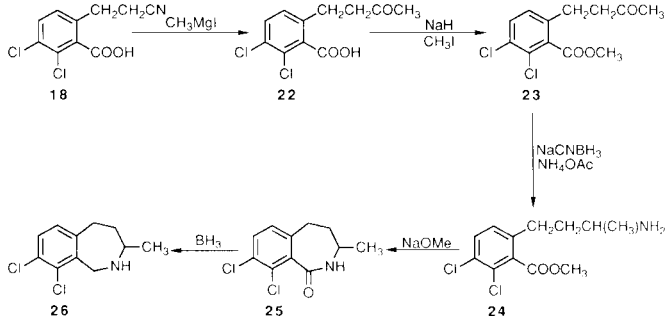


The key intermediate, 6,7-dichloro-3-hydroxyphthalide (**16**), previously prepared in our laboratory [11], was reacted with diethyl cyanomethylphosphonate and 2 equivalents of sodium hydride to give a 9:1 mixture of *trans:cis* o-carboxycinnamonitrile **17** (Scheme V). Attempts to selectively reduce the double bond of the α,β-unsaturated nitrile **17** with magnesium in methanol [12] led to simultaneous dechlorination of the aromatic ring. Pépin *et al.* have reported a selective reduction of the double bond of cinnamonitrile in 90% yield using a large excess of sodium borohydride in 2-propanol [13]. The reaction probably involves 1,4-hydride addition. Although there are several other reagents reported for this conversion [14-16] many of them are difficult to handle, particularly on a large scale, and can affect other functional groups such as those present in **17**. Sodium borohydride reduction of **17** in 2-propanol proceeded smoothly to give the saturated nitrile **18** in 80% yield. The esterification of **18** with potassium carbonate-methyl iodide followed by selective reduction of the nitrile function with borane gave the aminoester **20**. The aminoester **20** was cyclized with sodium methoxide in methanol to the azepinone **21** which was then smoothly reduced to LY134046 **10** with borane in tetrahydrofuran at reflux. The overall yield of LY134046 was *ca.* 22% starting from 6,7-dichloro-3-hydroxyphthalide (**16**). It is noteworthy that no chromatography was required.

Scheme V



Scheme VI



As a part of the program directed towards the design and synthesis of selective inhibitors of the enzyme phenylethanolamine *N*-methyltransferase, we were interested in analogues of 2-benzazepines with an alkyl group at the 3-position. The prototype compound 8,9-dichloro-3-methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (**26**) was prepared by a modification of the above method as illustrated in Scheme VI. The key reaction in the sequence was the addition of a Grignard reagent to nitrile **18**. The yield of this reaction is generally low with alkyl Grignard and alkyl nitrile as in the present case (<50%) [22,23]. The use of benzene containing 1 equivalent of ether as the solvent is supposed to improve the yield in such cases [17]. We carried out this reaction using excess methylmagnesium iodide and either benzene containing 1 equivalent of ether or ether alone as the solvent. In either case the ketoacid **22** was not purified but converted directly into the ketoester **23**. The combined yield of these two steps in both cases was almost identical but the latter solvent was preferred for operational simplicity. The crude ketoacid **22** was treated with 1 equivalent of sodium hydride and methyl iodide to yield the ketoester **23** in 38% yield based on **18**. Reductive amination of ketoester **23** with sodium cyanobrohydride and ammonium acetate produced a 62% yield of the aminoester **24**. Aminoester **24** was cyclized in 77% yield to the azepinone **25** which was then reduced (80%) with borane to **26**, the 3-methyl analogue of LY134046.

In summary, application of the present method to the preparation of 2-benzazepines with substituents on the aromatic ring is limited only by the availability of the starting hydroxyphthalide. The reagents used and the reaction conditions are fairly mild and a variety of substituents can be tolerated. Where the required hydroxyphthalide is not available, the *o*-carboxycinnamonitrile can be prepared from the corresponding anthranilic acid by Meerwein arylation reaction [18-21]. A variety of 2-benzazepines with alkyl or aryl substituents at the 3-position are accessible *via* Grignard reaction of the nitrile **18**. Although we have not used the present methodology to prepare 4-substituted-2-benzazepines, such an exercise should be possible by an appropriate choice of the Wittig reagent in the first step of Scheme V. The 3-methyl analogue **26** was about six times less potent than the parent compound **10** as an inhibitor of PNMT. A resolution of **26** and the biochemical profile of the individual enantiomers in relation to their absolute stereochemistry will be the subject of a future publication.

EXPERIMENTAL

All reagents and solvents were reagent grade or were purified by standard methods before use. Melting points were taken in open capillaries on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 1420 Infrared spectrophotometer. The pmr spectra were determined at 80 MHz using a Varian FT-80A spectrometer or at 300 MHz using a Varian XL-300 spectrometer. The ^{13}C nmr were recorded at 75.4 MHz using a Varian XL-300 spectrometer. All chemical shifts are reported in parts per million (δ) relative to tetramethylsilane. Microanalyses were performed either by Midwest Microlab Ltd., Indianapolis, Indiana, or on a Hewlett-Packard Model 185B CHN analyzer at the University of Kansas by Mr. Nguyen. Silica gel 60 (70-230 mesh ASTM) used for column chromatography was supplied by Universal Adsorbents, Atlanta, Georgia. Analytical thin-layer chromatography (tlc) was performed on silica gel with fluorescent indicator coated on 2.5 x 7.5 cm glass plates in 0.2 mm thickness. Bulb-to-bulb distillations were carried out by using a kugelrohr distillation apparatus (Aldrich Chemical Co.).

cis,trans-6-(2-Cyanoethenyl)-2,3-dichlorobenzoic Acid (**17**).

To a rapidly stirred suspension of sodium hydride (6.3 g, 157.5 mmoles, 60% dispersion in mineral oil) in 30 ml of dry 1,2-dimethoxyethane, a solution of 6,7-dichloro-3-hydroxyphthalide (**16**) (17.2 g, 78.5 mmoles) and diethyl cyanomethylphosphonate (14.0 g, 79.0 mmoles) in 220 ml of 1,2-dimethoxyethane was added dropwise at ice-bath temperature under argon. After the addition was over, the reaction mixture was brought to room temperature and stirred for 18 hours. The reaction mixture was quenched by addition of 50 ml of 6 *N* aqueous hydrochloric acid. Most of the solvent was removed on a rotary evaporator, and after dilution with water the contents were repeatedly extracted with ether. The ether layers were combined and extracted with 5% aqueous sodium carbonate. The carbonate layer was acidified to *p*H 2, and the precipitated product was extracted into ether. The ether layer was washed with water followed by brine, and after drying (magnesium sulfate) the solvent was evaporated to yield 15.0 g (79%) of a 9:1 mixture of *trans:cis*-**17**. The pmr spectrum of the crude product indicated the presence of *ca.* 10% of the *cis* isomer. A sample was recrystallized from hexane-ethyl acetate mp 175-196°; ir (potassium bromide): 3130 (OH), 2230 (CN), 1720 (CO), 1615 (C=C) cm^{-1}; pmr (80 MHz, DMSO-d_6): δ 6.60 (d, 1H, J = 17 Hz, ArC*H*), 7.40 (d, 1H, J = 17 Hz, C*H*CN), 7.87 (s, 2H, Ar *H*).

Anal. Calcd. for $C_{10}H_5Cl_2NO_2$: C, 49.58; H, 2.06; N, 5.78. Found: C, 49.52; H, 2.10; N, 6.00.

6-(2-Cyanoethyl)-2,3-dichlorobenzoic Acid (**18**).

Sodium borohydride (15.0 g, 396.5 mmoles) was added portionwise to a stirred solution of **17** (15.0 g, 62.0 mmoles) in 300 ml of 2-propanol at room temperature. The reaction mixture was heated at reflux for 48 hours under argon. After cooling to room temperature, the solvent was evaporated, water was added and the *p*H was adjusted to 2 with 6 *N* aqueous hydrochloric acid in the cold. The precipitated product was extracted in ether. The ether layer was extracted twice with 5% aqueous sodium bicarbonate, followed by water. The *p*H of the combined aqueous extracts was adjusted to 2 and the separated oil was extracted in ether. The ether layer was washed with water followed by brine and after drying (magnesium sulfate) the solvent was evaporated to yield 12.0 g (79%) of **18** as a pale yellow oil; ir (film): 3300-2400, 2240 (CN), 1720 (CO) cm^{-1}; pmr (80 MHz, deuteriochloroform): δ 2.50-2.75 (m, 2H, CH_2), 2.80-3.05 (m, 2H, CH_2),

7.15 (d, 1H, J = 8 Hz, Ar *H*), 7.50 (d, 1H, J = 8 Hz, Ar *H*), 9.30 (br s, 1H, COO*H*, deuterium oxide exchanged).

A satisfactory elemental analysis was obtained on the methyl ester of **18** (see below).

Methyl 6-(2-Cyanoethyl)-2,3-dichlorobenzoate (**19**).

A mixture of **18** (12.0 g, 49.2 mmoles), anhydrous potassium carbonate (13.7 g, 99.3 mmoles) and methyl iodide (14.1 g, 99.3 mmoles) in 180 ml of dry acetone was heated at reflux for 24 hours under argon. After cooling to room temperature, the reaction mixture was filtered and the solid was washed with acetone. The combined filtrate and washings were evaporated to leave a residue, which was partitioned between water and ether. The ether layer was washed with water followed by brine, and after drying (magnesium sulfate) the solvent was evaporated to give a dark viscous oil. A bulb-to-bulb distillation (bath temperature 150° at 0.6 mm) of this crude product provided 9.8 g (77%) of **19** as a pale yellow oil (R_f 0.41 in hexane-ethyl acetate 4:1); ir (film): 2940, 2235 (CN), 1728 (CO), 1555 cm^{-1}; pmr (80 MHz, deuterium oxide δ 2.40-2.90 (m, 4H, CH_2CH_2), 3.95 (s, 3H, OCH_3), 7.05 (d, 1H, J = 8 Hz, Ar *H*), 7.37 (d, 1H, J = 8 Hz, Ar *H*).

Anal. Calcd. for $C_{11}H_9Cl_2NO_2$: C, 51.18; H, 3.51; N, 5.42. Found: C, 51.20; H, 3.65; N, 5.43.

Methyl 6-(3-Aminopropyl)-2,3-dichlorobenzoate (**20**).

A 1 *M* solution of borane in tetrahydrofuran (45.0 ml, 45.0 mmoles) was added dropwise to a solution of **19** (9.8 g, 38.0 mmoles) in 50 ml of dry THF at ice-bath temperature under argon. After stirring for 24 hours at room temperature, the excess borane was destroyed carefully with methanol. The solvent was evaporated, the residue was taken up in methanol and acidified to *p*H 2 with methanolic hydrochloric acid. The contents were heated at reflux for 5 hours to decompose the amine-borane complex. On evaporation of methanol, dry ether was added to precipitate 8.6 g (76%) of **20** as the hydrochloride salt. A sample recrystallized from ethanol-ether had mp 183-184°; ir (hydrochloride salt, potassium bromide): 2800-2300 (RNH_3^+ Cl^-), 1735 (CO), 1600 cm^{-1}; pmr (hydrochloride salt, 80 MHz, DMSO-d_6): δ 1.50-2.00 (m, 2H, ArCCH_2), 2.30-2.85 (m, 4H, ArCH_2C and CH_2N), 3.85 (s, 3H, OCH_3), 7.30 (d, 1H, J = 8 Hz, Ar *H*), 7.65 (d, 1H, J = 8 Hz, Ar *H*), 8.05 (br s, 3H, RNH_3^+, deuterium oxide exchanged).

Anal. Calcd. for $C_{11}H_{13}Cl_2NO_2$·HCl: C, 44.24; H, 4.72; N, 4.69. Found: C, 44.34; H, 4.75; N, 4.68.

8,9-Dichloro-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one (**21**).

A solution of amine hydrochloride **20** (8.6 g, 28.8 mmoles) in 75 ml of dry methanol was added at room temperature to a fresh solution of sodium methoxide in methanol (prepared by addition of sodium metal (2.0 g, 87.0 mmoles) to 25 ml of dry methanol). After heating at reflux for 36 hours the solvent was removed on a rotary evaporator, water was added, and after acidification the separated solid was extracted with methylene chloride. The methylene chloride layer was washed with water followed by brine. After drying (magnesium sulfate), the solvent was evaporated to yield 5.8 g (87%) of **21** as a pale yellow solid (R_f 0.17 in hexane-ethyl acetate 1:1). A sample recrystallized from ethyl acetate had mp 204-206°; ir (potassium bromide): 3240 (NH), 2940, 1660 (CO), 1580, 1550 cm^{-1}; pmr (80 MHz, deuteriochloroform): δ 1.60-2.40 (m, 2H, ArCCH_2C), 2.50-3.50 (m, 4H, ArCH_2 and CH_2N), 6.95 (d, 1H, J = 8 Hz, Ar *H*), 7.20 (br s, 1H, N*H*, deuterium oxide exchanged), 7.40 (d, 1H, J = 8 Hz, Ar *H*).

Anal. Calcd. for $C_{10}H_9Cl_2NO$: C, 52.17; H, 3.94; N, 6.08. Found: C, 52.25; H, 3.80; N, 5.98.

8,9-Dichloro-2,3,4,5-tetrahydro-1*H*-2-benzazepine (**10**).

A 1 *M* solution of borane in tetrahydrofuran (75 ml, 75.0 mmoles) was added dropwise to a suspension of lactam **21** (5.8 g, 25.2 mmoles) in 75 ml of dry tetrahydrofuran at ice-bath temperature. The resulting solution was heated at reflux for 72 hours under argon. After cooling to room temperature, the excess borane was destroyed by dropwise addition of methanol and the contents were evaporated to dryness. The residue was taken up in methanol, acidified with methanolic hydrochloric acid, and heated at reflux for 6 hours to destroy the amine-borane complex. The reaction mixture was cooled to room temperature and the methanol was evaporated under reduced pressure. The residue was taken up in water and basified to *p*H 11 with aqueous sodium hydroxide. The separated oil was extracted into ether and the ether layer was washed with water followed by brine. After drying (potassium carbonate) the ether was removed to yield 3.9 g (71%) of **10** as the free base, mp 58° (lit [8] mp 61-63°). The hydrochloride salt recrystallized from 2-propanol had mp 268-270° (lit [9] mp 268-270°); ir (hydrochloride salt, potassium bromide): 2800-2300 ($R_1R_2NH_2^+$ Cl^-), 1560 cm^{-1}; pmr (hydrochloride salt, 80 MHz, DMSO-d_6): δ 1.60-2.00 (m, 2H, ArCCH_2C), 2.75-3.50 (m, 4H, ArCH_2C and CH_2N), 4.50 (s, 2H, ArCH_2N), 7.20 (d, 1H, J = 8 Hz, Ar *H*), 7.60 (d, 1H, J = 8 Hz, Ar *H*), 9.75 (br s, 2H, $R_1R_2NH_2^+$); ^{13}C nmr (hydrochlorilde salt, DMSO-d_6): δ 24.28, 32.74, 45.81, 48.74; 129.06, 129.75, 130.45, 131.67, 132.97, 144.52.

Anal. Calcd. for $C_{10}H_{11}Cl_2N$·HCl: C, 47.54; H, 4.80; N, 5.54. Found: C, 47.71; H, 4.90; N, 5.65.

2,3-Dichloro-6-(3-oxobutyl)benzoic Acid (**22**).

To an ice-cold solution of methylmagnesium iodide (30 ml of 3.0 *M* solution in ether, 90.0 mmoles) a suspension of **18** (6.3 g, 25.8 mmoles) in 170 ml of ether was added slowly under argon with rapid stirring. After 36 hours at room temperature the reaction mixture was quenched by addition of saturated ammonium chloride solution. The *p*H of the aqueous layer was adjusted to 2 and the separated oil was extracted with ethyl acetate. The ethyl acetate layer was washed successively with water and brine. After drying (magnesium sulfate), the solvent was removed *in vacuo* to yield 6.2 g of crude **22**; ir (film): 3300-2400, 1710 (CO) cm^{-1}; pmr (80 MHz, dueteriochloroform): δ 2.10 (s, 3H, COCH_3), 2.80 (m, 4H, ArCH_2CH_2), 7.05 (d, 1H, J = 8 Hz, Ar *H*), 7.35 (d, 1H, J = 8 Hz, Ar *H*), 8.85 (br s, 1H, COO*H*).

A satisfactory elemental analysis was obtained on the methyl ester of **22** (see below).

Methyl 2,3-Dichloro-6-(3-oxobutyl)benzoate (**23**).

To an ice cooled suspension of sodium hydride (800 mg of 60% dispersion in mineral oil, 20.0 mmoles) in 20 ml of dimethylformamide a solution of ketoacid **22** (4.9 g, 18.8 mmoles) in 70 ml of dimethylformamide was added dropwise under argon. After stirring for an additional 20 minutes methyl iodide (12.5 g, 88.3 mmoles) was added and the dark brown solution was stirred overnight. The reaction mixture was poured into water and extracted with ether. The ether layer was washed successively with water and brine. Evaporation of the ether layer after drying (magnesium sulfate) gave a dark red oil. The ketoester **23** was isolated as a colorless oil, 2.1 g (38% based on **18**), by chromatography over

silica gel using benzene-chloroform (1:1) as the eluent (R_f 0.27 in the same solvent). The analytical sample was prepared by bulb-to-bulb distillation (bath temp 142° at 0.8 mm); ir (film): 2950, 1735 (CO), 1715 (CO) cm^{-1}; pmr (300 MHz, deuteriochloroform): δ 2.13 (s, 3H, $COCH_3$), 2.77 (m, 4H, $ArCH_2CH_2$), 3.96 (s, 3H, OCH_3), 7.11 (d, 1H, J = 8 Hz, Ar *H*), 7.40 (d, 1H, J = 8 Hz, Ar *H*); ^{13}C nmr (deuteriochloroform): δ 27.25, 29.95, 44.52, 52.87, 128.88, 129.20, 131.04, 135.41, 138.34, 167.02, 206.72, 216.19.

Anal. Calcd. for $C_{12}H_{12}Cl_2O_3$: C, 52.39; H, 4.40. Found: C, 52.40; H, 4.32.

Methyl 6-(3-Aminobutyl)-2,3-dichlorobenzoate (**24**).

A solution of ketoester **23** (1.38 g, 5.0 mmoles), ammonium acetate (7.8 g, 101.3 mmoles) and sodium cyanoborohydride (1.4 g, 22.6 mmoles) in 42 ml of dry methanol was stirred at room temperature for 3 days in the presence of 4 Å molecular sieves. The reaction mixture was acidified with methanolic hydrochloric acid to *p*H 2 and filtered. The filtrate was evaporated to dryness and the residue was partitioned between water and ether. The aqueous layer was cooled, basified to *p*H 11, and the liberated free base was extracted into ether. The ether layer was washed with water followed by brine and the solvent was evaporated after drying (potassium carbonate) to yield 857 mg (62%) of the aminoester **24** as a clear colorless oil. The hydrochloride salt recrystallized from methanol-ether had mp 149°; ir (hydrochloride salt, potassium bromide): 3000-2500 (RNH_3^+ Cl^-), 1720 (CO), 1600, 1580 cm^{-1}; pmr (free base, 80 MHz, deuteriochloroform): δ 1.05 (d, 3H, J = 6 Hz, CH_3), 1.40-1.75 (m, 4H, $ArCCH_2C$ and NH_2), 2.40-3.00 (m, 3H, $ArCH_2$ and CH_3CHNH_2), 3.95 (s, 3H, OCH_3), 7.05 (d, 1H, J = 8 Hz, Ar *H*), 7.4 (d, 1H, J = 8 Hz, Ar *H*).

Anal. Calcd. for $C_{12}H_{15}Cl_2NO_2 \cdot HCl$: C, 46.10; H, 5.16; N, 4.48. Found: C, 46.14; H, 4.99; N, 4.46.

8,9-Dichloro-3-methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one (**25**).

A solution of aminoester **24** (764 mg, 2.77 mmoles) in 10 ml of methanol was added to a fresh solution of sodium methoxide in methanol (prepared by addition of 1.1 g (47.8 mmoles) of sodium to 28 ml of methanol). After heating at reflux for 24 hours under argon the solvent was removed *in vacuo* and the residue was partitioned between 1 *N* aqueous hydrochloric acid and methylene chloride. The methylene chloride layer was washed with water followed by brine and the solvent was removed after drying (magnesium sulfate) to yield an off-white solid. Chromatography over silica gel and elution with hexane-ethyl acetate (3:1) gave 524 mg (77%) of lactam **25** (R_f 0.27 in hexane-ethyl acetate 1:1). A sample recrystallized from ethyl acetate had mp 200°; ir (potassium bromide): 3200 (NH), 3070, 1650 (CO), 1580 cm^{-1}; pmr (80 MHz, deuteriochloroform): δ 1.15 (d, 3H, J = 6 Hz, CH_3), 1.50-2.00 (m, 2H, $ArCCH_2C$), 2.60-3.40 (m, 3H, $ArCH_2$ and CH_3CHN), 6.35 (br s, 1H, N*H*), 6.90 (d, 1H, J = 8 Hz, Ar *H*), 7.30 (d, 1H, J = 8 Hz, Ar *H*).

Anal. Calcd. for $C_{11}H_{11}Cl_2NO$: C, 54.12; H, 4.54; N, 5.74. Found: C, 54.27; H, 4.50; N, 6.00.

8,9-Dichloro-3-methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (**26**).

To a suspension of lactam **25** (524 mg, 2.15 mmoles) in 10 ml of tetrahydrofuran a 1 *M* solution of borane in tetrahydrofuran (21.5 ml, 21.5 mmoles) was added at room temperature under argon. The reaction mixture was heated at reflux for 24 hours. After cooling, the excess borane was destroyed with methanol and the solvent was removed to yield a white solid. The solid was dissolved in 20 ml of methanol, acidified with methanolic hydrochloric acid, and the contents were heated at reflux for 2 hours to decompose the amine-borane complex. After cooling to room temperature, the solvent was removed *in vacuo*, the residue was taken up in water and washed with ether. The aqueous layer was basified to *p*H 12 and extracted with ether. The ether layer was washed successively with water and brine, dried (potassium carbonate) and the solvent was removed to yield 397 mg (80%) of **26**. The hydrochloride salt recrystallized from 2-propanol-methanol had mp 298-302°; ir (hydrochloride salt, potassium bromide): 2800-2300 (RNH_2^+ Cl^-), 1575 cm^{-1}; pmr (free base, 300 MHz, deuteriochloroform): δ 1.10 (d, 3H, J = 6 Hz, CH_3), 1.20-1.65 (m, 2H, N*H*, $ArCCH_2$), 1.85-2.00 (m, 1H, $ArCCH_2C$), 2.75-3.20 (m, 3H, $ArCH_2$ and CH_3CHN), 3.80 (d, 1H, J = 16 Hz, $ArCH_2N$), 4.65 (d, 1H, J = 16 Hz, $ArCH_2N$), 6.95 (d, 1H, J = 8 Hz, Ar *H*), 7.20 (d, 1H, J = 8 Hz, Ar *H*); ^{13}C nmr (deuteriochloroform): δ 23.56, 34.55, 36.69, 49.11, 58.48, 128.11, 128.26, 130.64, 131.00, 141.65, 143.06.

Anal. Calcd. for $C_{11}H_{13}Cl_2N \cdot HCl$: C, 49.55; H, 5.29; N, 5.25. Found: C, 49.62; H, 5.32; N, 5.24.

Acknowledgements.

We thank Dr. James A. Monn for helpful discussions. This research was supported by USPHS Grant HL 34193.

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