Synthesis of 3-Alkyl-8-substituted- and 4-Hydroxy-8-substituted-2,3,4,5-tetrahydro-1*H*-2-benzazepines

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Based on the Schmidt reaction and an iodolactone ring expansion reaction, two different synthetic routes to substituted 2,3,4,5-tetrahydro-1*H*-2-benzazepines were developed. The Schmidt reaction on 2,3-dihydro-2*H*-1-naphthalenone (**1**) gave **3**, the product resulting from the alkyl group migration, as the major product instead of the tetrazole **2**. This prompted the investigation of the Schmidt reaction on aromatic ketones **8** and **12**. The product **9** due to alkyl group migration was the major product of the Schmidt reaction on 2-methyl-3,4-dihydro-2*H*-1-naphthalenone (**8**). The β-keto diester **12** gave a mixture of decarboxylated lactams after the Schmidt reaction. In this case, the lactam **13** resulting from the migration of the aromatic ring dominated over the other lactam **14**. When lactam **14** was subjected to nitration, a single regioisomer was produced and transformed to the bromo alcohol **19**. The other approach was based on the single pot ring expansion of the iodolactone **22** to the lactam **23** in the presence of methanolic ammonia. The iodolactone **22** was readily prepared from 2-allylbenzoic acid.

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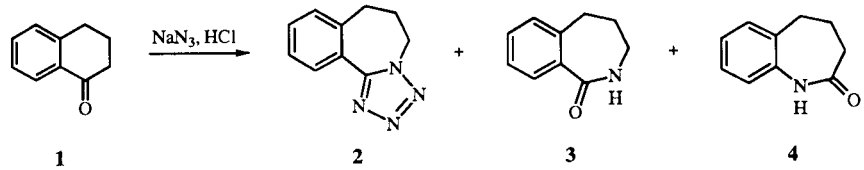
In our program directed towards the synthesis of selective and potent inhibitors of epinephrine biosynthesis some 3-alkyl-8-substituted and 4-hydroxy-8-substituted-2,3,4,5-tetrahydro-1*H*-2-benzazepines were sought. Previously a novel synthetic procedure for LY 134046 (8,9-dichloro-2,3,4,5-tetrahydro-1*H*-2-benzazepine) was developed in our laboratory [1]. The most common methods used in the synthesis of 2-benzazepines are summarized in the earlier report [1]. However, this new procedure is unsuitable for introducing a 3-hydroxymethyl substituent and is incompatible with electron-withdrawing substituents like a nitro group at the 8-position on the benzazepine ring.

Our attention was diverted to the approach based on the Schmidt reaction when the literature reaction [2] was repeated on 1-tetralone (**1**) in concentrated hydrochloric acid. Instead of isolating the described tetrazole **2** as the major product, we obtained a mixture of 2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one (**3**) and 2,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one (**4**) along with unreacted starting material (Scheme I). In the original report [2] no attempts were made to isolate other products that were formed and only **2** was isolated by fractional crystallization. In our hands the ratio of **2** to **3** to **4** was about 2:4:1. Although some undesired **4** was obtained, this procedure could be scaled up and gram quantities of **3** were readily obtained after flash chromatography.

According to other literature reports the major product of the Schmidt reaction on **1** is **4** [3,4,5]. This difference may be accounted for by the reaction medium [6,7] employed in this transformation as compared with the other literature reports which utilize trichloroacetic acid [3], polyphosphoric acid [4] and sulfuric acid [5]. The dependence of the migratory aptitude on the acidity of the reaction medium in the Schmidt reaction has been interpreted in terms of a change in the reaction mechanism [7]. In non-aqueous acids steric effects dictate the formation of the intermediate iminodiazonium ion which then rearranges to the lactam. The unfavorable steric interactions of the diazonium group with the peri hydrogen atom precludes the formation of the *syn*-iminodiazonium ion **7** (Scheme II). Such deleterious steric effects are absent in the *anti*-iminodiazonium ion **6**, in which the leaving diazonium group is *anti* to the peri hydrogen. After the migration of the aromatic ring, the iminocarbonium ion formed is hydrated to lactam **4**. However, in aqueous acids the reaction probably proceeds *via* a concerted rearrangement of an α-hydroxyhydrazidinium ion **5** intermediate and the migratory aptitude of the aryl and alkyl group governs the ratio of the isomeric amide products.

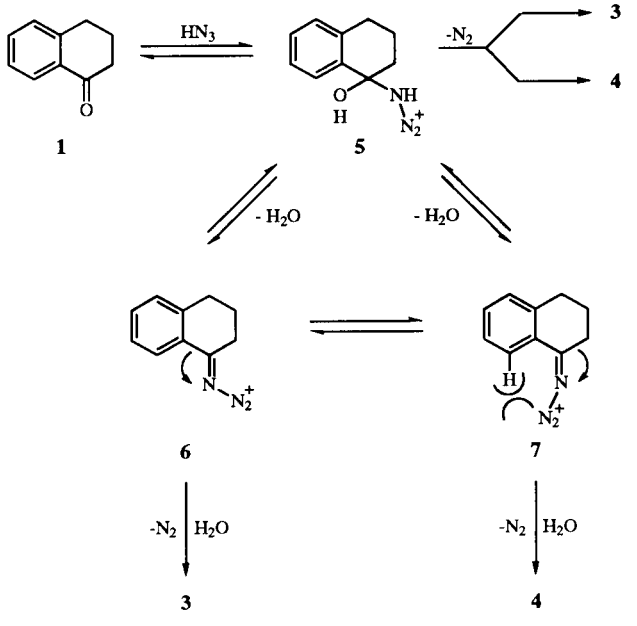
α-Alkyl-substituted tetralones like **8** could likely exist in the enol form under the strongly acidic conditions of the Schmidt reaction (concentrated hydrochloric acid in this case), and therefore the reaction was expected to be

Scheme I



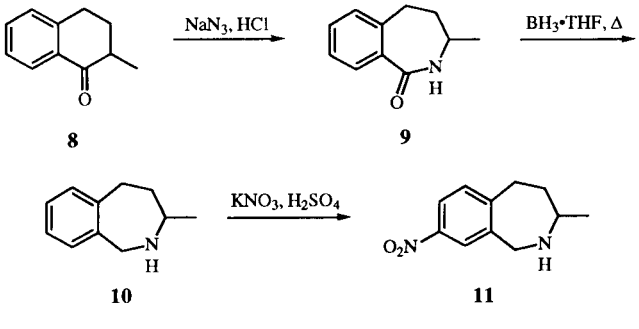
1 **2** **3** **4**

Scheme II



more sluggish. In order to synthesize 3-methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepinone (**9**), the Schmidt reaction was performed on 2-methyl-3,4-dihydro-2*H*-1-naphthalenone (**8**) (Scheme III). The major product **9** was isolated in 34% yield and some unreacted **8** was also recovered. The low electrophilicity of the aromatic ketones as compared to the aliphatic ketones resulted in the incomplete Schmidt reaction, especially under aqueous acidic conditions. According to pmr and cmr spectra, the other product seemed to be a mixture of the corresponding tetrazole and isomeric benzazepinone. A clean separation of these products could not be achieved. This is the first report to the best of our knowledge which describes the Schmidt reaction on **8** to get **9**.

Scheme III

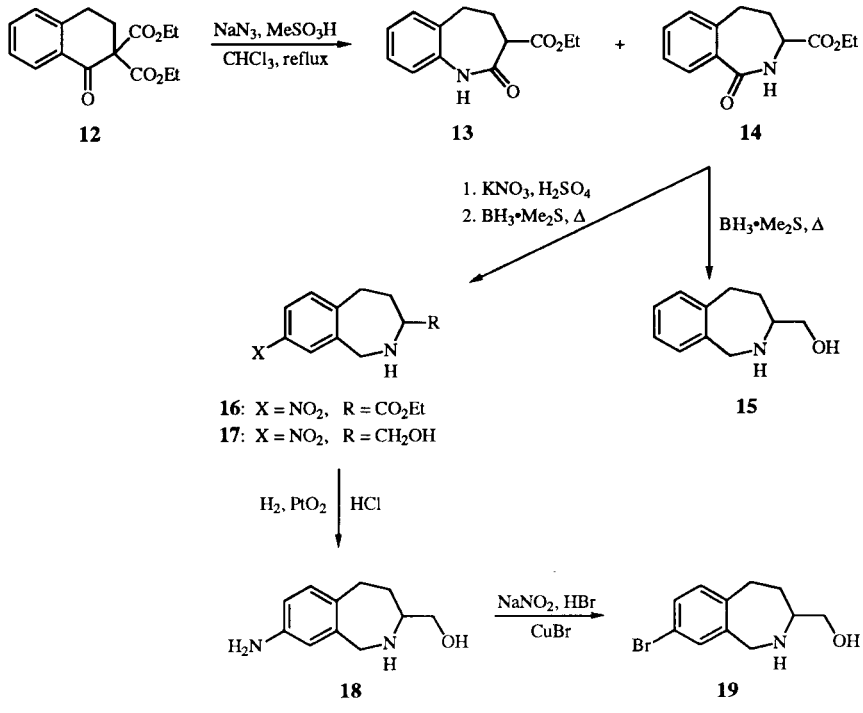


There have been other literature examples wherein the only product of the Schmidt reaction on 2-phenyl-3,4-dihydro-2*H*-1-naphthalenone is the product arising from aryl migration [8,9]. Introduction of a methoxy group at the 6-position produced a mixture of regioisomeric lactams. A similar result was obtained when 3- or 4-phenyl-1-tetralones were subjected to the Schmidt reaction. In the case of 2-alkylcyclohexanone the only product obtained after the Schmidt reaction in sulfuric acid was the lactam resulting from the migration of the carbon bearing the alkyl group. This was attributed to the steric effect exerted by the alkyl group in the formation of *anti*-iminodiazonium ion and the electron releasing effect of the alkyl group [10].

Compound **9** was then reduced with borane to get the benzazepine **10**. Nitration of **10** using potassium nitrate and sulfuric acid produced 3-methyl-8-nitro-2,3,4,5-tetrahydro-1*H*-2-benzazepine (**11**) as the major product. A small amount of the 6,8-dinitro product was also observed. The regiochemistry of the product was in agreement with the aromatic splitting pattern in the proton nmr and was further confirmed by a one dimensional difference nuclear Overhauser effect experiment, wherein, irradiation of the H-1 proton resulted in an increased intensity of the more down field H-9 proton. This experiment was also used to ascertain the regiochemistry of the resulting products in the subsequent nitration reactions described in this report. Although in this series we have not attempted any other aromatic electrophilic substitution reactions, it is conceivable that bromination or chlorosulfonation can be attempted on the amide **9**. Only the 8-regioisomer would be obtained due to the directing effect of the amido group. Also, a different alkyl group at the 2-position in the starting 1-tetralone could be used. This method provides a simple and straight forward route to 8-substituted-3-alkyl-2,3,4,5-tetrahydro-1*H*-2-benzazepines.

To prepare 3-ethoxycarbonyl-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one (**15**), the precursor to the 3-hydroxymethyl derivative of benzazepine, the Schmidt reaction was done on 2,2-bis(ethoxycarbonyl)-3,4-dihydro-2*H*-1-naphthalenone (**12**). It was thought that **14** could be obtained after the decarboxylation of the Schmidt reaction products (Scheme IV). When **12** was subjected to the Schmidt reaction, under the same conditions as employed for **1** and **8**, no reaction occurred even after stirring for 20 hours at room temperature and only starting material was recovered. The Schmidt reaction was done in non-aqueous conditions using methanesulfonic acid in chloroform with sodium azide at reflux, the conditions described by Georg [11] for the Schmidt rearrangements of α,α-bisalkylated-β-ketoesters. The reaction was sluggish and even after refluxing for 36 hours, the starting material was present along with the decarboxylated products **13** and **14**. It is possible that **13** and **14** might be formed after decarboxylation under ambient reaction conditions. If the decarboxylation occurred prior to the Schmidt reaction, then the Schmidt reaction on this decarboxylated product would be slow because the decarboxylated product would

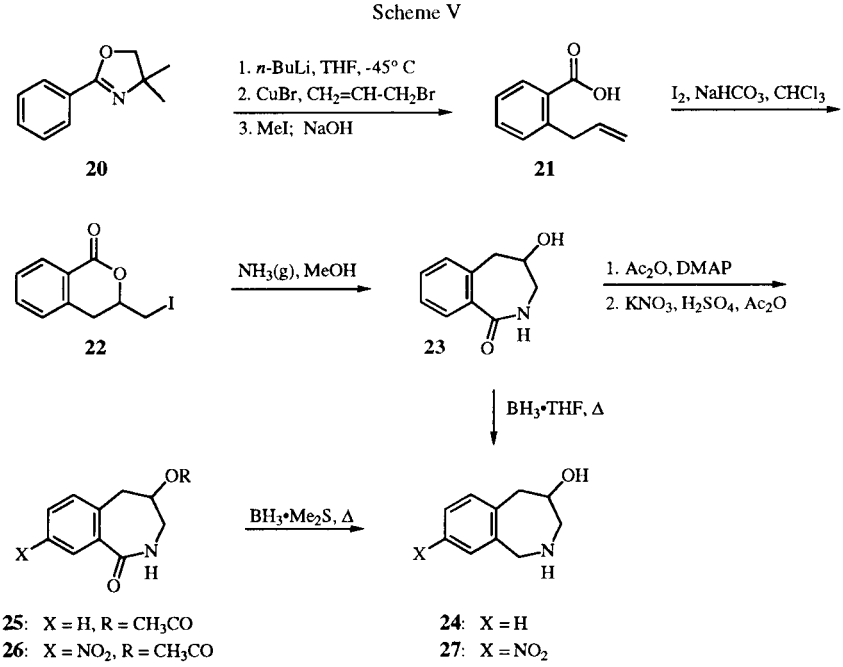
Scheme IV



exist predominantly in the enol form. In an attempt to improve the yield, the Schmidt reaction was performed in trifluoroacetic acid at 80°, but the reaction was quite slow, indicated by the presence of **14** (tlc) after 22 hours. The lactam **13** resulting from the migration of the aromatic ring was the major product. This may be accounted for by the electron-withdrawing effect of the ethoxycarbonyl groups at the 2-position which retards the migration of the alkyl group. But, 2-ethoxycarbonylcyclohexanone has been reported to undergo a Schmidt reaction with hydrazoic and sulfuric acids to produce the lactam *via* migration of the carbon bearing the ethoxycarbonyl group [10]. This difference may be due to the lack of peri hydrogen interaction in cyclohexanones which allows the formation of the *anti*-iminodiazonium ion.

The concomitant reduction of the amide and the ester

Scheme V



functionalities in **14** gave 3-hydroxymethyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (**15**). Compound **14** was nitrated to yield **16** as the single product in 71% yield. In this nitration the amido group directs the regiochemistry to produce the desired regioisomer. Borane reduction followed by catalytic hydrogenation provided the diamine **18** from **16**. Diazotization of **18** in the presence of hydrobromic acid and cuprous bromide yielded the bromo compound **19** in a moderate yield (46%). In this transformation the aliphatic amine is unreactive as it is protonated under the reaction conditions, while the aromatic amine participates in the Sandmeyer reaction. This methodology, based on the Schmidt reaction, allows a reasonable synthesis of **18**, which is difficult to obtain by other conventional methods used in the synthesis of 2-benzazepines.

The methodology for the synthesis of 3-alkyl-2,3,4,5-tetrahydro-1*H*-2-benzazepines based on the Schmidt reaction suffers from the major drawback of getting the undesired lactam in the key step. But, the ease of synthesis of the starting materials and the ability to functionalize the 2-benzazepine nucleus outweigh this disadvantage.

The synthesis of 4-hydroxy-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one **23** is based on the lactone to lactam rearrangement. This type of reaction has been documented in the synthesis of 4-hydroxy-1,2,3,4-tetrahydroisoquinoline [12]. The main intermediate 2-allylbenzoic acid (**21**) was readily prepared from the commercially available 4,4-dimethyl-2-phenyl-2-oxazoline (**20**). The *ortho*-lithiation procedure described by Ellefson [13] was used in introducing the allyl group and further hydrolysis of the oxazoline [14] (iodomethane followed by sodium hydroxide) provided **21** in an overall 52% yield. Other literature *ortho*-lithiation procedures [15,16,17] were unsatisfactory and tended to give a mixture of alkylated products. Acid **21** (Scheme V) was subjected to iodolactonization [18] to get an almost quantitative yield of the iodolactone **22**. Prolonged treatment of **22** with saturated methanolic ammonia under high dilution conditions provided **23** in 61% yield after column chromatography.

This method of converting the iodide **22** to the intermediate amine under high dilution conditions with ammonia precluded the need of a stepwise procedure where the iodide was converted to the azide and then reduced to the amine. The intermediate amine then rearranges to the thermodynamically more stable **23** under the ambient reaction condition. Even though the expansion of the six-membered iodolactone **22** to the seven-membered benzazepinone **23** was disfavored, the formation of the amide bond from the ester likely provided the necessary driving force.

Compound **23** was reduced to provide the unsubstituted 4-hydroxybenzazepine (**24**). To introduce a nitro group at the 8-position, **23** was first cleanly converted to the acetate **25** and then subjected to the usual nitration procedure. Addition of acetic anhydride to the nitration mixture and a bicarbonate workup improved the yield of the nitration reaction. A concomitant reduction of 4-acetoxy-8-nitro benzazepinone **26** with borane provided 4-hydroxy-8-nitro-2,3,4,5-tetrahydro-1*H*-2-benzazepine (**27**).

This short procedure based on the ring expansion provides a quick entry to 4-hydroxybenzazepines. The only limiting step was the availability of the appropriate 2-allyl-benzoic acid, which could be prepared from the phenyl oxazolines by the *ortho*-lithiation procedure. Also, the introduction of an alkyl substituent on the allyl group should afford a route to the 3-alkyl-4-hydroxybenzazepines. Enantiopure benzazepines may be obtained by separating the diastereomers formed with (-)-menthyl chloroformate [19].

EXPERIMENTAL

All reagents and solvents were reagent grade or were purified by standard methods before use. Melting points were determined on a Thomas Hoover melting point apparatus calibrated with known compounds, but are otherwise uncorrected. Infrared spectra were obtained on a Perkin Elmer 1420 infrared spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian XL-300 or a GE QE-300 instrument operating at 300 MHz for proton and 75.4 MHz for carbon-13. All chemical shifts were in parts per million (δ) downfield from tetramethylsilane. Multiplicity abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet. Electron impact mass spectra (EIMS) were obtained on Ribermag R10-10 mass spectrometer. Preparative centrifugal thin layer chromatography (PCTLC) was performed on a Harrison model 7924 Chromatotron (Harrison Research, Palo Alto, CA) using Merck silica gel 60 PF254/$CaSO_4$•0.5H_2O binder on 1, 2 or 4 mm thickness plates. Silica gel 60 (230-400 mesh) used for flash chromatography [20] was supplied by Universal Adsorbents, Atlanta, Georgia. Analytical tlc was performed by using silica gel with a fluorescent indicator coated on 1 x 3 inch glass plates in 0.2 mm thickness (Whatman MKGF silica gel 200μ). Combustion analyses were performed on a Hewlett-Packard Model 185B CHN Analyzer at the University of Kansas by Dr. Nguyen. Amine hydrochloride salts were prepared by adding a solution of methanolic hydrogen chloride to the methanolic solution of the amine, followed by evaporation and crystallization of the resulting hydrochloride from methanol-ether. Bulb to bulb distillations were carried out on a Kugelrohr distillation apparatus (Aldrich Chemical Co.) and oven temperatures were recorded.

2,3,4,5-Tetrahydro-1*H*-2-benzazepin-1-one (**3**).

To an ice-cold stirred mixture of **1** (5.00 g, 35.2 mmoles) in hydrochloric acid (26 ml) was added sodium azide (2.34 g, 36.0 mmoles) in small portions over a period of 20 minutes. The resulting pale yellow-red suspension was stirred at the ice-bath temperature for 2 hours and then stirred at room temperature for an additional 2 hours. The reaction mixture was poured over ice and neutralized with solid potassium carbonate. The reaction

mixture was extracted with chloroform, dried over anhydrous sodium sulfate and evaporated to yield a brown-red oil (6.00 g). Purification of the crude reaction mixture by flash chromatography (silica gel, hexanes:ethyl acetate 1:1 as the eluent) led to isolation of starting material (1.23 g), tetrazole **2** (1.44 g, 23%) and isomer **4** (0.73 g, 13%). Finally, elution of the column with ethyl acetate gave **3** (2.40 g, 42%).

Compound **3** was crystallized as a colorless solid from ethyl acetate-hexanes, mp 98-100° (lit [21] mp 99-101°); ir (potassium bromide): 3180 (NH), 1650 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.25 (broad s, 1H, deuterium oxide-exchangeable, N*H*), 7.71 (dd, 1H, J = 1.5, 7.4 Hz, H-9), 7.27 (m, 2H, H-7 and H-8), 7.18 (d, 1H, J = 7.8 Hz, H-6), 3.11 (q, 2H, J = 6.4 Hz , H-3), 2.85 (t, 2H, J = 7.1 Hz, H-5), 2.00 (p, 2H, J = 6.8 Hz, H-4); ^{13}C nmr (deuteriochloroform): δ 174.3 (CO), 138.2, 135.0, 130.9, 128.3, 128.3, 126.6, 39.2, 30.4, 30.0; ms: m/z 162 (M+1, 26), 161 (M^+, 100), 132 (77), 131 (80), 104 (92), 103 (56).

6,7-Dihydro-5*H*-tetrazolo[4,5-*a*]benzo[*c*]azepine (**2**) was crystallized from ethyl acetate-hexanes as colorless plates, mp 98-100° (lit [2] mp 98-100°); ir (potassium bromide): 2970, 1480, 1440, 1400, 940, 780, 740 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.23 (dd, 1H, J = 1.6, 7.4 Hz, H-9), 7.48-7.38 (m, 2H, H-7 and H-8), 7.32 (d, 1H, J = 7.3 Hz, H-6), 4.62 (t, 2H, J = 6.6 Hz, H-3), 2.99 (t, 2H, J = 6.6 Hz, H-5), 2.47-2.39 (m, 2H, H-4); ^{13}C nmr (deuteriochloroform): δ 154.3 (C-1), 139.5, 131.4, 130.1, 129.9, 127.3, 123.0, 48.5 (C-3), 32.5 (C-5), 26.6 (C-4); ms: m/z 187 (M+1, 21), 186 (M^+, 100), 130 (33), 129 (58), 128 (38), 115 (72), 103 (28), 102 (32), 89 (16), 77 (23), 63 (17).

Anal. Calcd. for $C_{10}H_{10}N_4$: C, 64.50; H, 5.41; N, 30.09. Found: C, 64.46; H, 5.60; N, 30.26.

1,3,4,5-Tetrahydro-2*H*-1-benzazepine-2-one (**4**) was crystallized from ethyl acetate-hexanes as colorless crystals, mp 140-141° (lit [4] mp 140-141°); ir (potassium bromide): 3180 (NH), 1660 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.83 (broad, s, 1H, NH, deuterium oxide-exchangeable), 7.26-7.01 (m, 4H, aromatic), 2.82-2.70 (m, 2H, H-3), 2.38-2.18 (m, 4H, H-4 and H-5); ^{13}C nmr (deuteriochloroform): δ 175.7 (CO), 137.9, 134.2, 129.7, 127.4, 125.5, 121.8, 32.7, 30.3, 28.5.

(±)-3-Methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one (**9**).

Compound **8** was prepared from **1** by alkylation with methyl iodide (90%) of the intermediate sodium salt obtained by the reaction of **1** with sodium hydride (2 equivalents) and diethyl carbonate (1 equivalent) [22]. The intermediate 2-methyl-2-ethoxycarbonyl-3,4-dihydro-2*H*-1-naphthalenone was saponified and decarboxylated to **8** (82%) by refluxing with 45% potassium hydroxide.

The Schmidt reaction was performed as described above on 2-methyl-3,4-dihydro-2*H*-1-naphthalenone (**8**) (4.90 g, 20.6 mmoles) in hydrochloric acid (46 ml) and using sodium azide (2.20 g, 33.7 mmoles). The reaction was allowed to proceed for 7 hours at room temperature. A colorless solid (3.01 g) was obtained and purified by flash chromatography (silica gel, hexane-ethyl acetate 2.5:1, as the eluent). Because the crude product was insoluble in the solvent system used for the chromatography, it was adsorbed on silica gel and then added to the prepacked silica gel column. Flash chromatography yielded **8** (0.30 g), a colorless semisolid (0.73 g) showing multiple peaks in the cmr indicating it to be the mixture of at least two compounds, probably tetrazole and the other lactam, and **9** (1.82 g, 34%). Compound **9** was crystallized from ethyl acetate as colorless plates, mp 183-184°; ir (potassium bromide): 3180 (NH), 1640 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.70 (dd, 1H, J = 1.6, 7.3 Hz, H-9), 7.36 (m, 2H, H-7 and H-8), 7.17 (d, 2H, J = 8.2 Hz, H-6 and N*H*, deuterium oxide-exchangeable), 3.28 (m, 1H, H-3), 3.00 (m, 1H, H-5), 2.67 (m, 1H, H-5), 1.92 (m, 2H, H-4), 1.26 (d, 3H, J = 6.6 Hz, CH_3); ^{13}C nmr (deuteriochloroform): δ 172.7 (CO), 138.6, 135.3, 130.9, 128.4, 128.3, 126.7, 46.8 (C-3), 38.8 (C-5), 30.6 (C-4), 19.7 (CH_3); ms: m/z 176 (M+1, 10), 175 (M^+, 31), 133 (27), 104 (47), 44 (100).

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.28; H, 7.70; N, 8.18.

(±)-3-Methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (**10**).

To a solution of amide **9** (1.63 g, 9.30 mmoles) in dry tetrahydrofuran (10 ml) was added borane-tetrahydrofuran complex (1 *M* solution in tetrahydrofuran, 30 ml, 30 mmoles). The clear solution was refluxed under nitrogen for 20 hours and then cooled in an ice-bath. Excess borane was destroyed by careful addition of methanol and the reaction mixture was evaporated to dryness to yield a thick colorless oil. The oil was treated with methanol saturated with hydrochloride gas and refluxed for 3 hours. Removal of the solvent yielded a colorless oil which was mixed with water (30 ml) and washed with methylene chloride (thrice). The aqueous layer was cooled and basified with potassium hydroxide pellets and extracted with methylene chloride (thrice). The combined methylene chloride extracts were dried over anhydrous potassium carbonate and evaporated to yield a colorless oil (1.49 g). Bulb to bulb distillation (75-80°, 125 μ) gave **10** as a colorless oil (1.45 g, 97%), mp (hydrochloride salt) 231-232° dec; ir (film, free base): 3300-3240 (NH) cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.13-7.10 (m, 4H, aromatic), 3.93 and 3.87 (AB q, 2H, J_{AB} = 14.5 Hz, H-1), 3.08-2.97 (m, 2H, H-3 and H-5), 2.81-2.74 (m, 1H, H-5), 1.96-1.89 (m, 1H, H-4), 1.50-1.22 (m, 2H, H-4 and N*H*, deuterium oxide-exchangeable), 1.10 (d, 3H, J = 6.6 Hz, CH_3); ^{13}C nmr (deuteriochloroform): δ 142.4, 142.4, 128.9, 128.1, 127.0, 126.0, 58.8, 53.6, 37.4, 34.7, 23.9; ms: m/z 161 (M^+, 49), 160 (M^+-1, 33), 146 (M^+-CH_3, 30), 132 (52), 118 (40) 117 (100), 91 (56), 44 (97).

Anal. Calcd. for $C_{11}H_{15}N$•HCl: C, 66.83; H, 8.16; N, 7.08. Found: C, 66.63; H, 8.21; N, 6.90.

(±)-3-Methyl-8-nitro-2,3,4,5-tetrahydro-1*H*-2-benzazepine (**11**).

Sulfuric acid (5 ml) was chilled in an ice-bath and **10** (0.94 g, 5.8 mmoles) was added in small portions. Potassium nitrate (0.62 g, 6.1 mmoles) was added in small portions over a period of 30 minutes to yield a pale yellow-brown reaction mixture which was allowed to warm to room temperature. After stirring for 24 hours at room temperature, the reaction mixture was poured over ice, basified with concentrated ammonium hydroxide and extracted with methylene chloride (thrice). The combined methylene chloride layers were dried (potassium carbonate) and evaporated to afford a yellow oil that solidified on standing (1.25 g). Flash chromatography (silica gel, methylene chloride:methanol:ammonium hydroxide; 250:10:1 as the eluent) gave **11** as a pale yellow solid (0.75 g, 62%) which was recrystallized from benzene-hexanes as a pale yellow solid, mp 65-66°; mp (hydrochloride salt) >300° dec; ir (potassium bromide): 3220 (NH), 1520 (NO_2), 1340 (NO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.00-7.98 (m, 2H, H-7 and H-9), 7.29 (d, 1H J = 7.8 Hz, H-6), 4.04 and 3.99 (AB q, 2H, J_{AB} = 14.6 Hz, H-1), 3.16-3.03 (m, 2H, H-3 and H-5), 2.97-2.90 (m, 1H, H-5), 2.02-

1.95 (m, 1H, H-4), 1.55 (broad, s, 1H, N*H*, deuterium oxide-exchangeable), 1.14 (d, 3H, J = 6.3 Hz, CH_3); ^{13}C nmr (deuteriochloroform): δ 150.4, 146.1, 143.7, 129.9, 122.9, 122.2, 58.7 (C-1), 53.2 (C-3), 36.5 (C-5), 34.6 (C-4), 23.7; ms: m/z 207 (M+1, 13), 206 (M^+, 36), 191 (M^+-CH_3), 177 (25), 163 (12), 115 (73), 105 (23), 91 (46), 77 (33), 44 (100).

Anal. Calcd. for $C_{11}H_{14}N_2O_2$•HCl: C, 54.44; H, 6.23; N, 11.54. Found: C, 54.57; H, 6.20; N, 11.80.

(±)-3-Ethoxycarbonyl-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one (**14**).

Compound **12** was prepared from **1** by alkylation with ethyl chloroformate (86%) of the intermediate sodium salt obtained by treatment of **1** with sodium hydride (2 equivalents) and diethyl carbonate (1 equivalent) [22].

Methanesulfonic acid (6.20 g, 4.20 ml, 64.9 mmoles) was added to a solution of **12** (2.0 g, 6.9 mmoles) in chloroform (30 ml). The yellow colored solution was cooled in an ice-bath and sodium azide (1.34 g, 20.6 mmoles) was added in small portions. The yellow-orange colored suspension was refluxed under nitrogen for 36 hours, cooled, poured onto ice and carefully neutralized with ammonium hydroxide. Extraction of the aqueous layer with methylene chloride (thrice), followed by drying (sodium sulfate) and evaporation yielded an orange red oil (2.20 g). Purification by flash chromatography (silica gel, hexanes-ethyl acetate 1:1 as the eluent) gave starting material (0.39 g), compound **13** (0.80 g, 50%), and the slightly more polar compound **14** (0.43 g, 27%).

3-Ethoxycarbonyl-1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one (**13**) was crystallized as colorless plates from ethyl acetate, mp 136-138°; ir (potassium bromide): 3180 (NH), 1740 (CO_2Et), 1660 (CONH), cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.78 (broad, s, 1H, N*H*, deuterium oxide-exchangeable), 7.28-7.11 (m, 3H, aromatic), 7.04 (d, 1H, J = 7.8 Hz, H-6), 4.10 (q, 2H, J = 7.1 Hz, OCH_2CH$_3$), 3.49-3.43 (m, 1H, H-3), 2.93-2.71 (m, 3H, H-5 and H-4), 2.35-2.27 (m, 1H, H-4), 1.19 (t, 3H, J = 7.1 Hz, OCH$_2$CH_3); ^{13}C nmr (deuteriochloroform): δ 171.6, 169.2, 136.8, 134.2, 129.6, 127.5, 126.1, 122.4, 61.1 (OCH$_2$CH$_3$), 48.7 (C-3), 31.2 (C-4), 29.0 (C-5), 14.0 (OCH$_2$CH$_3$); ms: m/z 234 (M+1, 7), 233 (M^+, 23), 232 (M^+-1, 16), 188 (M^+-OEt), 186 (20), 160 (M^+-CO_2Et), 159 (49), 146 (14), 133 (41), 132 (34), 130 (33), 119 (46), 118 (29), 117 (21), 106 (100), 91 (16), 77 (41), 73 (22).

Anal. Calcd. for $C_{13}H_{15}NO_3$•0.25H_2O: C, 65.65; H, 6.58; N, 5.89. Found: C, 65.40; H, 6.20; N, 5.89.

Compound **14** was crystallized from ethyl acetate-hexanes as colorless needles, mp 93-94°; ir (potassium bromide): 3380 (NH), 1740 (CO_2Et), 1665 (CONH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.71 (d, 1H, J = 7.5 Hz, H-9), 7.45-7.30 (m, 2H, H-7 and H-8), 7.22 (d, 1H, J = 7.3 Hz, H-6), 6.79 (broad, s, 1H, N*H*, deuterium oxide-exchangeable), 4.21 (q, 2H, J = 7.2 Hz, OCH_2CH$_3$), 3.94-3.86 (m, 1H, H-3), 3.06-2.95 (m, 1H, H-5), 2.83-2.77 (m, 1H, H-5), 2.42-2.31 (m, 1H, H-4), 2.24-2.10 (m, 1H, H-4), 1.25 (t, 3H, J = 7.2 Hz, OCH$_2$CH_3); ^{13}C nmr (deuteriochloroform): δ 171.1 (CO), 137.5, 134.5, 131.5, 128.7, 128.7, 61.9 (OCH$_2$CH$_3$), 52.6 (C-3), 34.7 (C-5), 29.8 (C-4), 14.0 (OCH$_2$CH$_3$); ms: m/z 234 (M+1, 7), 233 (M^+, 20), 160 (M^+-CO_2Et, 100), 131 (22), 117 (13), 103 (13), 77 (20).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.79; H, 6.51; N, 6.04.

(±)-3-Hydroxymethyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (**15**).

Amide **14** (0.40 g, 1.71 mmoles) was reduced by borane-methyl sulfide complex (2 *M* in tetrahydrofuran, 4.3 ml, 8.6 mmoles) using the same procedure as described for compound **10**. The crude product was isolated as a pale yellow oil (0.38 g) and purified by PCTLC (2 mm, silica gel, methylene chloride:methanol:ammonium hydroxide 250:20:1 as the eluent) to afford a pale yellow oil that solidified on standing (0.20 g, 67%), mp 88-90°, mp (hydrochloride salt) 206-207° dec; ir (potassium bromide): 3260 (NH), 3130 (OH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.25-7.10 (m, 4H, aromatic), 3.91 (s, 2H, 1-H), 3.48 (dd, 1H, J = 4, 10.6 Hz, CH_2O), 3.23 and 3.21 (AB q, 1H, J_{AB} = 8.8 Hz, CH_2O), 3.05-2.91 (m, 4H, H-3 and H-5, O*H*, N*H*), 2.87-2.80 (m, 1H, 5-H), 1.88-1.77 (m, 1H, 4-H), 1.28-1.16 (m, 1H, 4-H); ^{13}C nmr (deuteriochloroform): δ 142.0, 141.8, 129.2, 128.3, 127.2, 126.2, 65.7 (CH$_2$O), 64.7 (C-3), 53.2 (C-1), 34.4 (C-5), 31.7 (C-4); ms: m/z 178 (M+1, 16), 147 (27), 146 (M^+-CH_2OH, 100), 129 (26), 117 (56), 115 (25), 105 (15).

Anal. Calcd. for $C_{11}H_{15}NO$•HCl: C, 61.82; H, 7.55; N, 6.55. Found: C, 61.80; H, 7.86; N, 6.40.

(±)-3-Ethoxycarbonyl-8-nitro-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one (**16**).

To chilled sulfuric acid (4 ml), compound **14** (0.60 g, 2.57 mmoles) was added in small portions to give a suspension, followed by addition of potassium nitrate (0.29 g, 2.8 mmoles). After stirring for 4 hours at ice-bath temperature the reaction mixture was poured onto ice and extracted with methylene chloride (4 times). The combined methylene chloride extracts were washed with 5% sodium bicarbonate solution (once), brine (once) and dried (sodium sulfate). Evaporation of the solvent gave an oil that solidified on standing (0.72 g). Recrystallization from ethyl acetate-hexanes gave a pale brown crystalline solid (0.51 g, 71%), mp 135-136°; ir (potassium bromide): 3220 (NH), 1750 (CO_2Et), 1660 (CONH), 1520 (NO_2), 1340 (NO_2) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.56 (d, 1H, J = 2.5 Hz, H-9), 8.28 (dd, 1H, J = 2.5, 8.3 Hz, H-7), 7.45 (d, 1H, J = 8.3 Hz, H-6), 6.94 (broad, s, 1H, N*H*, deuterium oxide-exchangeable), 4.25 (q, 2H, J = 7.1 Hz, OCH_2CH$_3$), 3.93-3.85 (m, 1H, H-3), 3.12-2.95 (m, 2H, H-5), 2.48-2.27 (m, 2H, H-4), 1.27 (t, 3H, J = 7.1 Hz, OCH$_2$CH_3); ^{13}C nmr (deuteriochloroform): δ 170.4, 168.6, 147.3, 144.6, 136.2, 130.2, 126.0, 124.3, 62.3 (OCH$_2$CH$_3$), 52.3 (C-3), 34.0 (C-5), 29.9 (C-4), 14.0 (OCH$_2$CH$_3$); ms: m/z 279 (M+1, 13), 278 (M^+, 10), 206 (M^+-CO_2Et, 100), 176 (12), 159 (14), 130 (12), 103 (14), 89 (16), 77 (24).

Anal. Calcd. for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 55.78; H, 5.45; N, 10.40.

(±)-3-Hydroxymethyl-8-nitro-2,3,4,5-tetrahydro-1*H*-2-benzazepine (**17**).

Reduction of **16** (2.05 g, 7.36 mmoles) with borane-methyl sulfide complex (2.0 *M* in tetrahydrofuran, 15 ml, 30 mmoles) was done in a similar manner as that described for compound **10**. After the usual work up, a yellow oil (1.79 g) was obtained which was subjected to PCTLC (4 mm, methylene chloride: methanol:ammonium hydroxide 250:17:1, as the eluent) to afford a pale yellow solid (1.24 g, 76%), mp 123-124°, ir (potassium bromide): 3250 (NH), 3100 (OH), 1510 (NO_2), 1340 (NO_2); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.99-7.97 (m, 2H, H-7 and H-9), 7.43 (m, 1H, H-6), 4.65 (broad, s, 1H, O*H*, deuterium oxide-exchangeable), 3.95 (AB q, 2H, J_{AB} = 14.5 Hz,

H-1), 3.33-3.19 (m, 2H, C*H*$_2$O), 3.02-2.86 (m, 3H, H-5 and N*H*, deuterium oxide-exchangeable), 1.91-1.84 (m, 1H, H-4), 1.12-1.02 (m, 1H, H-4); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 151.1, 145.5, 144.8, 130.2, 122.4, 121.6, 65.3 (CH_2O), 64.3 (C-4), 52.1 (C-1), 33.6 (C-5), 30.8 (C-4); ms: m/z 223 (M+1, 2), 191 (M^+-CH_2OH, 100), 145 (19), 116 (14), 115 (18).

Anal. Calcd. for $C_{11}H_{14}N_2O_3$•HCl: C, 51.07; H, 5.84; N, 10.83. Found: C, 51.16; H, 5.90; N, 10.69.

(±)-3-Hydroxymethyl-8-amino-2,3,4,5-tetrahydro-1*H*-2-benzazepine (**18**).

A hydrogenation bottle was charged with **17** (1.23 g, 5.53 mmoles) as a solution in 95% ethanol (20 ml) and to it concentrated hydrochloric acid (2 ml) was added followed by platinum oxide (0.12 g). The suspension was hydrogenated at 50 psi for 5 hours (until no further uptake of hydrogen was observed). The suspension was filtered through Celite, concentrated to a volume of 10 ml and basified with potassium hydroxide pellets. The liberated free base was extracted with ethyl acetate (thrice), dried (potassium carbonate) and evaporated to yield a colorless semisolid (0.83 g, 78%), mp (dihydrochloride salt) 248° dec; ir (potassium bromide, dihydrochloride salt): 3510 (NH) 3260 (OH, NH_2) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 6.93 (d, 1H, J = 8.3 Hz, H-7), 6.48-6.45 (m, 2H, H-6 and H-9), 3.83 (s, 2H, H-1), 3.55 (dd, 1H, J = 3.9, 10.7 Hz, C*H*$_2$O), 3.27-2.88 (m, 7H, H-3 and H-5, C*H*$_2$O, N*H*$_2$, O*H* and N*H*, deuterium oxide-exchangeable), 2.79-2.72 (m, 1H, H-5), 1.84-1.78 (m, 1H, H-4), 1.25-1.13 (m, 1H, H-4); ^{13}C nmr (deuteriochloroform): δ 144.5, 142.8, 132.0, 130.3, 115.7, 113.3, 65.9 (CH_2O), 64.8 (C-3), 53.3 (C-1), 33.6 (C-5), 32.4 (C-4); ms: m/z 192 (M^+, 9), 161 (M^+-CH_2OH, 100), 144 (18), 132 (48), 120 (15), 106 (24), 60 (53).

Anal. Calcd. for $C_{11}H_{16}N_2O$•2HCl: C, 49.82; H, 6.84; N, 10.56. Found: C, 49.43; H, 6.86; N, 10.38.

(±)-8-Bromo-3-hydroxymethyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (**19**).

Diamine **18** (0.58 g, 3.0 mmoles) was taken up in 48% hydrobromic acid (1.4 ml in 4.8 ml of water), cooled in an ice-bath and sodium nitrite (0.23 g, 3.3 mmoles) was added dropwise as a solution in water (2.7 ml). After stirring for 20 minutes the presence of excess nitrous acid was checked by starch-iodide paper. Urea (0.12 g) was added to destroy the excess nitrous acid (negative starch-iodide test). This ice-cold diazotized solution was added dropwise to a well stirred warm (35°) mixture of cuprous bromide (1.3 g, 9.1 mmoles), 48% hydrobromic acid (3.1 ml) and water (7.5 ml). The reaction mixture was then heated to 75-80° and stirred at that temperature for 2 hours. The reaction mixture was then allowed to stand overnight and then basified with ammonium hydroxide, extracted with methylene chloride (4 times), dried (sodium sulfate) and evaporated to get a colorless solid (0.52 g). Purification by PCTLC (2 mm silica gel, methylene chloride:methanol:ammonium hydroxide 250:17:1 as the eluent) gave a colorless solid, (0.35 g, 46%), mp 133-134°; mp (hydrochloride salt) 298° dec; ir (potassium bromide): 3260 (NH), 3160 (OH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.27-7.24 (m, 2H, H-7 and H-9), 7.03-7.01 (m, 1H, H-6), 3.90 (s, 2H, H-1), 3.54 (dd, 1H, J = 3.9, 10.5 Hz, CH_2O), 3.24 (AB q, 1H, J_{AB} = 9.0 Hz, C*H*$_2$O), 3.04-2.93 (m, 2H, H-3 and H-5), 2.86-2.79 (m, 1H, H-5), 2.26 (broad, s, 2H, O*H* and N*H*, deuterium oxide-exchangeable), 1.87-1.80 (m, 1H, H-4), 1.27-1.14 (m, 1H, H-4); ^{13}C nmr (deuteriochloroform): δ 144.4, 141.0, 131.1, 130.0, 119.6, 66.0 (CH_2O), 64.7 (C-3), 52.9 (C-1), 34.0 (C-5), 31.7 (C-4), ms: m/z 258 (M+3, 1), 257 (M+2, 1), 256 (M+1, 1), 255 (M^+, 1), 226 (M+2-CH_2OH, 100), 224 (M^+-CH_2OH, 100), 145 (13), 128 (27), 116 (56), 115 (56), 103 (15), 90 (16), 89 (28).

Anal. Calcd. for $C_{11}H_{14}BrNO$•HCl: C, 45.15; H, 5.17; N, 4.79. Found: C, 45.38; H, 5.10; N, 4.80.

(±)-3-Iodomethyl-3,4-dihydro-1*H*-2-benzopyran-1-one (**22**).

To a stirred solution of sodium bicarbonate (0.34 g, 4.0 mmoles) in water (5 ml) was added 2-allylbenzoic acid (**21**, 0.32 g, 2.0 mmoles) and the suspension was stirred until a homogenous solution was obtained. Chloroform (5 ml) was added, the biphasic mixture was cooled in an ice-bath and iodine (1.1 g, 4.0 mmoles) was added in one portion. The dark brown mixture was stirred for 4 hours and a tlc taken at that point showed no starting material. The reaction mixture was diluted with water (20 ml) and chloroform (20 ml) and treated with saturated sodium thiosulfate solution to remove any excess iodine. The organic layer was separated and the aqueous layer was extracted with chloroform (twice). The combined chloroform layers were dried and washed with saturated sodium thiosulfate solution (once) and brine (once). Drying (sodium sulfate) followed by the removal of the chloroform gave a pale yellow oil which was further purified by PCTLC (2mm silica, hexanes-ethyl acetate 2:1, as the eluent) to afford a pale yellow oil (0.56 g, 97%); ir (film): 1720 (CO) cm^{-1}, ^{1}H nmr (deuteriochloroform): δ 8.08 (d, 1H, J = 7.8 Hz, H-8), 7.60-7.55 (m, 1H), 7.44-7.38 (m, 1H), 7.29 (d, 1H, J = 7.4 Hz), 4.60-4.51 (m, 1H, H-3), 3.54-3.34 (m, 2H, C*H*$_2$I), 3.26-3.08 (m, 2H, H-4); ^{13}C nmr (deuteriochloroform): δ 164.4 (CO), 137.8, 134.1, 130.3, 127.9, 127.6, 124.4, 76.9 (C-3), 33.1 (C-4), 5.5 (C-I); ms: m/z 289 (M+1, 9), 288 (M^+, 67), 161 (M^+-I, 40), 147 (M^+-CH_2I, 95), 119 (100), 118 (99), 91 (70), 90 (96); hrms: Calcd. for M+1: 288.9726. Found: 288.9738. A satisfactory elemental analysis could not be obtained on this compound.

(±)-4-Hydroxy-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one (**23**).

A solution of iodolactone **22** (5.85 g, 20.3 mmoles) in dry methanol (50 ml) was added dropwise over a period of 30 minutes to ice-cold methanol saturated with ammonia (400 ml). The reaction mixture was allowed to remain at room temperature for 4 days. The methanol was then removed by evaporation to yield a semisolid. The crude product was dissolved in methanol (20 ml) and ammonium hydroxide (1 ml) was added followed by silica gel (15 g). The suspension was evaporated on a rotary evaporator and dried on standing to yield a pale yellow powder. The crude product, adsorbed on silica gel, was loaded on a prepacked silica gel column and eluted with chloroform: methanol:ammonium hydroxide 9:1:0.1. A colorless solid was obtained (2.18 g, 61%) which was crystallized from hexanes-ethyl acetate, mp 184-185°; ir (potassium bromide): 3250 (OH), 3200 (NH), 1640 (CO) cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 8.10 (broad, s, N*H*, deuterium oxide-exchangeable), 7.53 (d, 1H, J = 7.3 Hz, H-9), 7.43-7.31 (m, 2H, H-7 and H-8), 7.24 (d, 1H, J = 7.3 Hz, H-6), 5.12-5.10 (m, 1H, O*H*, deuterium oxide-exchangeable), 4.20-4.05 (m, 1H, H-4), 3.02-2.91 (m, 2H, H-5), 2.77-2.52 (m, 2H, H-3); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 171.7 (CO), 136.2, 135.6, 130.5, 129.5, 128.3, 126.9, 71.7 (C-4), 46.4 (C-3), 39.5 (C-5); ms: m/z 178 (M+1, 3), 177 (M^+, 25), 159 (M^+-OH, 21), 148 (21), 147 (23), 119 (83), 118 (31), 105

(33), 91 (100), 90 (41).

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.43; H, 6.40; N, 7.92.

(±)-4-Hydroxy-2,3,4,5-tetrahydro-1*H*-2-benzazepine (**24**).

Amide **23** (0.40 g, 2.2 mmoles) was reacted with borane-tetrahydrofuran complex (1 *M* in tetrahydrofuran, 5 ml, 5 mmoles). After refluxing the reaction mixture for 24 hours, the usual workup procedure gave a colorless solid which was crystallized from hexanes-ethyl acetate to afford colorless small prisms (0.35 g, 94%), mp 143-144°, mp (hydrochloride salt) 193-194°; ir (potassium bromide): 3280 (NH), 3060 (OH) cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.22-7.07 (m, 4H, Ar*H*), 3.87 (s, 2H, H-1), 3.80-3.70 (m, 1H, H-4), 3.30-3.19 (m, 1H, H-3), 3.15-3.05 (m, 3H, H-3 and H-5), 3.00-2.75 (broad, s, 2H, O*H* and N*H*, deuterium oxide-exchangeable); ^{13}C nmr (deuteriochloroform): δ 142.3, 136.7, 131.0, 127.9, 127.1, 126.4, 67.1 (C-4), 58.8 (C-3), 54.3 (C-1), 43.3 (C-5); ms: m/z 163 (M^+, 10), 162 (M^+-1, 10), 145 (62), 144 (83), 118 (45), 117 (32), 105 (100), 104 (46), 91 (37), 77 (38).

Anal. Calcd. for $C_{10}H_{13}NO$•HCl: C, 60.15; H, 7.07; N, 7.01. Found: C, 59.95; H, 6.99; N, 6.92.

(±)-4-Acetoxy-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one (**25**).

To a suspension of **23** in methylene chloride (0.45 g, 2.5 mmoles) was added dimethylaminopyridine (0.03 g, 0.2 mmole) followed by acetic anhydride (2.4 ml, 25 mmoles). The suspension became a clear solution after stirring for 15 minutes and after 12 hours the reaction mixture was quenched with water and 1 *N* hydrochloric acid. Extraction with methylene chloride (thrice) and drying (sodium sulfate) followed by evaporation gave a yellow oil. Purification by PCTLC (2 mm silica, ethyl acetate as the eluent) gave a colorless solid (0.47 g, 84%), mp 138-139°; ir (potassium bromide): 3200 (NH), 1730 ($OCOCH_3$), 1660 (CONH) cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.77-7.75 (m, 1H, H-9), 7.46-7.35 (m, 2H, H-7 and H-8), 7.31-7.18 (m, 2H, H-6 and N*H*, deuterium oxide-exchangeable), 5.29-5.20 (m, 1H, H-4), 3.42-3.35 (m, 1H, H-3), 3.24-3.13 (m, 2H, H-5), 3.03-2.91 (m, 1H, H-4), 2.08 (s, 3H, $OCOCH_3$); ^{13}C nmr (deuteriochloroform): δ 173.5 (OCO), 170.4 (CONH), 134.8, 134.4, 131.4, 129.5, 129.1, 127.8, 75.0 (C-4), 44.3 (C-3), 36.3 (C-5), 21.1 (H_3CCO); ms: m/z 220 (M+1, 3), 176 (2), 159 (M^+-$OCOCH_3$, 88), 132 (18), 131 (16), 130 (28), 119 (62), 91 (52), 43 (100).

Anal. Calcd. for $C_{12}H_{13}NO$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.45; H, 5.98; N, 6.29.

(±)-4-Acetoxy-8-nitro-2,3,4,5-tetrahydro-1*H*-2-benzazepinone (**26**).

Acetic anhydride (1 ml) and sulfuric acid (3 ml) were added to **25** (0.51 g, 2.3 mmoles) and the mixture was cooled in an ice-bath. Potassium nitrate (0.26 g, 2.6 mmoles) was added in small portions and the suspension was stirred for 14 hours at room temperature. The reaction mixture was cooled, diluted with ethyl acetate and poured onto ice-cold saturated sodium bicarbonate solution (30 ml). Extraction of the quenched reaction mixture with ethyl acetate (4 times) followed by drying (sodium sulfate) and evaporation gave a pale yellow solid (0.40 g, 67%) which was crystallized from ethyl acetate, mp 230-231°; ir (potassium bromide): 3200 (NH), 1730 ($OCOCH_3$), 1620 (CONH), 1520 (NO_2), 1300 (NO_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.52-8.48 (m, 1H, N*H*, deuterium oxide-exchangeable), 8.31-8.29 (m, 2H, H-7 and H-9), 7.66-7.63 (m, 1H, H-6), 5.27-5.18 (m, 1H, H-4), 3.32-3.19 (m, 2H, H-3), 3.02-2.90 (m, 2H, H-5), 2.04 (s, $OCOCH_3$); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 169.8, 169.3, 147.0, 142.2, 136.9, 131.5, 125.3, 123.4, 74.0 (C-4), 42.9 (C-3), 35.6 (C-5), 20.9 ($OCOCH_3$); ms: m/z 265 (M+1, 6), 205 (M^+-$OCOCH_3$, 11), 204 (23), 164 (4), 149 (3), 118 (6), 89 (7), 65 (6), 43 (100).

Anal. Calcd. for $C_{12}H_{12}N_2O_5$•$0.25H_2O$: C, 53.53; H, 4.70; N, 10.42. Found: C, 53.30; H, 4.39; N, 10.10.

4-Hydroxy-8-nitro-2,3,4,5-tetrahydro-1*H*-2-benzazepine (**27**).

Amido ester **26** (0.45 g, 1.70 mmoles) was reduced with borane-methyl sulfide complex (2 *M* in tetrahydrofuran, 4 ml, 8 mmoles) in the usual manner. The free base obtained was purified by PCTLC (2 mm, silica, methylene chloride: methanol: ammonium hydroxide 250:17:1 as the eluent) to afford a yellow solid (0.24 g, 69%) which was crystallized from ethyl acetate-hexanes as a pale yellow solid, mp 147-149°; mp (hydrochloride salt) 282-283° dec; ir (potassium bromide): 3300 (OH), 3280 (NH), 1510 (NO_2), 1340 (NO_2) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 8.01-7.95 (m, 2H, H-7 and H-9), 7.45 (d, 1H, J = 8.5 Hz, H-6), 4.81 (broad, s, 1H, O*H*, deuterium oxide-exchangeable), 3.91 and 3.81 (AB q, 2H, J_{AB} = 14.9 Hz, H-1), 3.58-3.40 (m, 1H, H-4), 3.20-3.01 (m, 3H, H-3 and H-5), 2.86-2.79 (m, 1H, H-5), 2.26 (broad, s, 1H, N*H*, deuterium oxide-exchangeable); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 147.0, 145.8, 145.6, 131.5, 122.1, 121.6, 67.2 (C-4), 59.4 (C-3), 52.9 (C-1), 43.9 (C-5); ms: m/z 209 (M+1, 24), 208 (M^+, 26), 207 (M^+-1, 21), 193 (20), 190 (71), 189 (100), 175 (19), 163 (20), 149 (33), 143 (19), 131 (19), 115 (28), 103 (43), 91 (41), 77 (67), 63 (29).

Anal. Calcd. for $C_{10}H_{12}N_2O_3$•HCl: C, 49.09; H, 5.36; N, 11.45. Found: C, 48.79; H, 5.50 N, 11.20.

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REFERENCES AND NOTES

[1] G. L. Grunewald, V. M. Paradkar, D. M. Stillons, and F. Ching, *J. Heterocyclic Chem.*, **28**, 1587 (1991).

[2] N. S. Hjelte and T. Agback, *Acta Chem. Scand.*, **18**, 191 (1964).

[3] P. A. S. Smith, *J. Am. Chem. Soc.*, **70**, 320 (1948).

[4] R. T. Conley, *J. Org. Chem.*, **23**, 1330 (1958).

[5] D. Evans and I. M. Lockhart, *J. Chem. Soc.*, 4806 (1965).

[6] M. Tomita, S. Minami, and S. Ueyo, *J. Chem. Soc. (C).*, 183 (1969).

[7] L. E. Fikes and H. Shechter, *J. Org. Chem.*, **44**, 741 (1979).

[8] L. H. Werner, S. Ricca, A. Rossi, and G. DeStevens, *J. Med. Chem.*, **10**, 575 (1967).

[9] L. I. Barsky and W. L. Bencze, *J. Med. Chem.*, **14**, 40 (1971).

[10] H. Shechter and J. C. Kirk, *J. Am. Chem. Soc.*, **73**, 3087 (1951).

[11] G. I. Georg, X. Guan, and J. Kant, *Tetrahedron Letters*, **29**, 403 (1988).

[12] S. Ram, A. K. Saxena, and P. C. Jain, *Indian J. Chem.*, **16B**, 1019 (1978).

[13] C. R. Ellefson, *J. Org. Chem.*, **44**, 1533 (1979).

[14] A. I. Meyers, D. L. Temple, R. L. Nolen, and E. D. Mihelich,

J. Org. Chem., **39**, 2778 (1974).

[15] A. I. Meyers and E. D. Mihelich, *J. Org. Chem.*, **40**, 3158 (1975).

[16] H. W. Gschwend and A. Hamdan, *J. Org. Chem.*, **40**, 2008 (1975).

[17] A. Padwa and A. Ku, *J. Am. Chem. Soc.*, **100**, 2181 (1978).

[18] F. B. González and P. A. Bartlett, *Org. Synth*, **64**, 175 (1984).

[19] J. F. Nicound and H. B. Kagan, *Israel J. Chem.*, **15**, 78 (1976-1977).

[20] W. C. Still, A. Mitra, and M. Kahn, *J. Org. Chem.*, **43**, 2923 (1978).

[21] N. Gilman, *Synth. Commun.*, **12**, 373 (1982).

[22] T. Miyashi, Y. Nishizawa, Y. Fujii, K. Yamakawa, M. Kamata, S. Akao, and T. Mukai, *J. Am. Chem. Soc.*, **108**, 1617 (1986).