1-OXOTETRAHYDRO-2-BENZAZEPINES FROM 1-METHYL-3,4-DIHYDRO-5H-2-BENZAZEPINES: SYNTHESIS OF N-METHYL-7,8,9-TRIMETHOXY-2,3,4,5-TETRAHYDRO-1H-2-BENZAZEPINE

Ricardo Alonso, Kimio Takahashi, Bernhard Schönenberger, and Arnold Brossi
Medicinal Chemistry Section, Laboratory of Analytical Chemistry, NIDDK, National Institutes of Health, Bethesda, Maryland 20892, U.S.A.

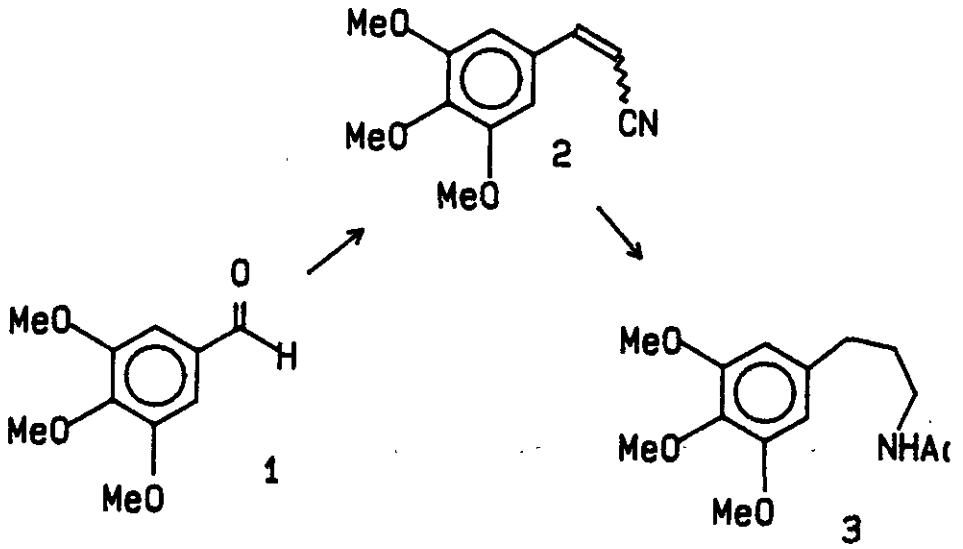
Abstract- A new approach to 1-oxo-2,3,4,5-tetrahydro-1H-2-benzazepines is described, the key step being the ruthenium catalyzed oxidative cleavage of 1-methylene-2-benzazepine 5 obtained by N-acetylation of the Bischler-Napieralski cyclization product of N-acetyl-3-(3',4',5'-trimethoxyphenyl)-propylamine (3). Aromatic bromination instead of benzylic oxidation took place upon irradiation of the 1-oxo-2-benzazepine 8 with visible light in the presence of $CaCO_3$ and NBS.

1-Oxo-2,3,4,5-tetrahydro-1H-2-benzazepines substituted with a 7,8-methylenedioxy group represent valuable intermediates for synthesis of Amaryllidaceae alkaloids[1,2], and 1-(3',4',5'-trimethoxybenzyl)-substituted 2-benzazepines were found effective inhibitors of platelet aggregation induced by bacterial phospholipase.[3] Whereas 1-substituted 2-benzazepines are accessible from N-acylated 3-phenylpropylamines by Bischler-Napieralski cyclization[3,4], similar synthesis of 1-unsubstituted analogs from N-formyl-3-phenylpropylamines is complicated because of an acid catalyzed interconversion of 3,4-dihydro-5H-2-benzazepine monomers into dimers.[5,6] We have overcome this problem by the reaction sequence shown in Scheme 2, explored earlier with 1-methyl-3,4-dihydroisoquinolines.[7,8,9] Since the compounds utilized for the synthesis of alkaloids are methylenedioxy-substituted, we aimed at the preparation of 7,8,9-trimethoxy-substituted 2-benzazepines, to learn whether a subsequent introduction of a 5-oxo group by photooxidation in the presence of N-bromosuccinimide[2] would be impaired by the different substitution.

Synthesis of phenylpropylamine 3 was accomplished from benzaldehyde 1 by condensation with acetonitrile (67%)[10], followed by catalytic reduction of the cis-trans mixture of nitriles 2

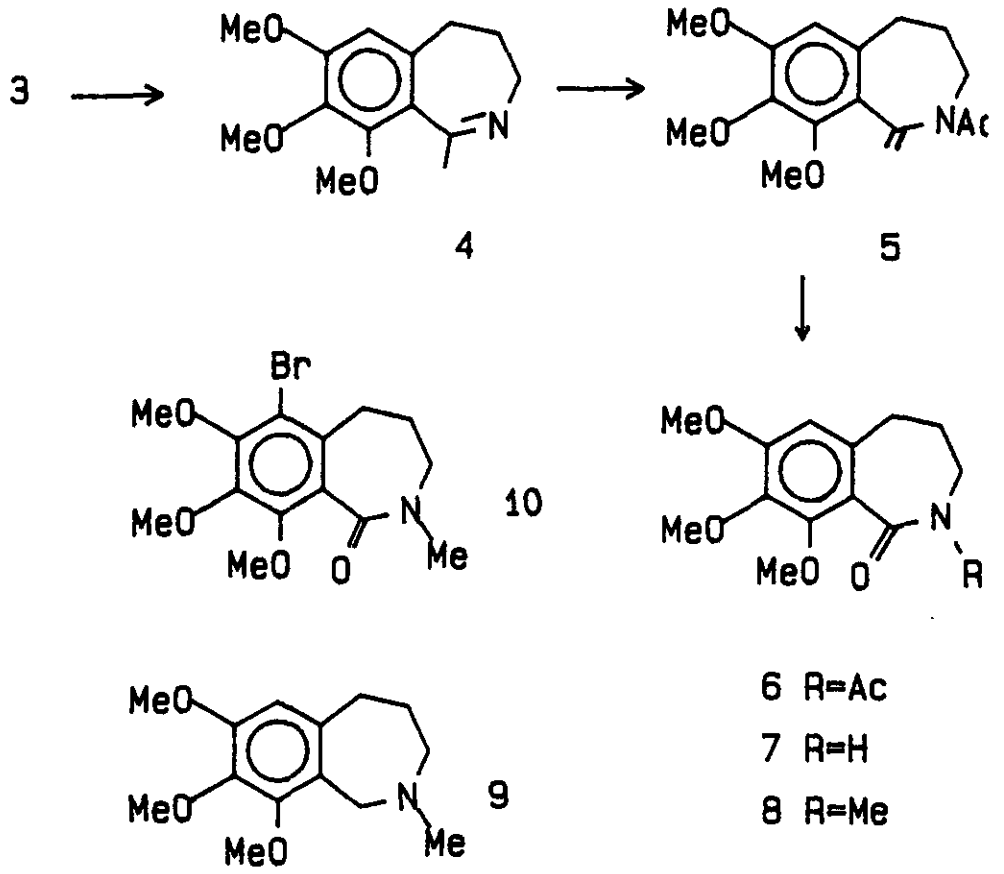
Dedicated to Professor Edward C. Taylor, Department of Chemistry, Princeton University, New Jersey, U.S.A., at the occasion of his 65th birthday.

(E/Z = 6.2 (PMR)) over PtO_2 catalyst in acetic anhydride (76%) (Scheme 1).



SCHEME 1

Cyclization of 3 with phosphorus oxychloride in acetonitrile afforded 3,4-dihydro-5H-benzazepine 4 as an oil (47%). Subsequent treatment with acetic anhydride in pyridine afforded crystalline amide 5 (95%) (Scheme 2), with a characteristic signal in the ^{1}H-NMR spectrum at δ 5.52 ppm for the methylene group. Ozonolysis of 5 (CH_2Cl_2, -61°C) gave a complex mixture of products in contrast to the result obtained with 3,4-dihydroisoquinoline analogs.[7] Oxidative cleavage, however, was accomplished by treatment of 5 with sodium metaperiodate and catalytic amounts of ruthenium trichloride (72%).[11] The dilactam 6 thus obtained was converted into N-methyllactam 8 by smooth acid hydrolysis to lactam 7 followed by methylation of 7 with methyl iodide. Reduction of 8 with LAH afforded the 1-unsubstituted 2,3,4,5-tetrahydro-1H-2-benzazepine 9. The photooxidation step, used to introduce a 5-oxo group in the series of 7,8-methylenedioxy substituted analogs,[2] did not work in the 7,8,9-trimethoxy-series since irradiation of 8 with visible light in the presence of NBS and $CaCO_3$ yielded bromolactam 10 as the only isolated product.



SCHEME 2

EXPERIMENTAL

Melting points were taken on a Fisher-Johns Apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab Inc. (Atlanta, Georgia). IR spectra were recorded on a Beckman IR 4230 instrument. NMR spectra were determined by using a Varian XL-300 spectrometer with $(CH_3)_4Si$ as the internal reference. Chemical-ionization (CI) mass spectra were obtained by using a Finnigan 1015D spectrometer with a Model 6000 data collection system. Thin-Layer Chromatography (TLC) plates were purchased from Analtech, Inc. Preparative Chromatography columns were packed with Silica gel 60 (0.015-0.040 mm) purchased from EM laboratories. In all the reactions carried under a dry atmosphere of N_2, the glassware material was oven dried, assembled while hot and allowed to cool while flushing with dry N_2.

(E)- and (Z)-3,4,5-Trimethoxycinnamonitrile (2): A 50 ml, two-necked, round-bottomed flask,

equipped with a pressure equalizing addition funnel, reflux condenser, N_2 purge, and a magnetic stirring bar, was charged with KOH (674 mg, powdered under a nitrogen atmosphere immediately prior to use) and dry MeCN (10 ml, freshly distilled from CaH_2). The mixture was heated to reflux and a solution of 3,4,5-trimethoxybenzaldehyde (1) (2g, 10.2 mmol) in dry MeCN (10 ml) was added in a stream. After the addition was complete, stirring was continued for 10 min and the hot solution was poured onto cracked ice (50 g). This mixture was extracted with four 10 ml portions of CH_2Cl_2, dried with anhydrous Na_2SO_4, and evaporated in the rotavapor (bath temperature not exceeding 30°C). The crude product was purified by column chromatography (2x20 cm) using Et_2O as the eluent. The nitrile 2 (1.15 g, 67%) was obtained as a mixture of isomers (E/Z = 6.2 (PMR)). Crystallization from Et_2O-hexane yielded a pure sample of the E-isomer as colorless plates (mp 99°C). PMR ($CDCl_3$) δ : 3.89 (s, 9H, OMe), 5.79 (d, 1H, J = 16.6 Hz), 6.66 (s, 2H), 7.31 (d, 1H, J = 16.6 Hz); IR ν_{max} (KBr) 2210 cm^{-1}. A pure sample of the Z-isomer (Rf value slightly higher than the E-isomer) was obtained as a colorless oil by column chromatography using mixtures of hexane-Et_2O of increasing polarity. PMR ($CDCl_3$) δ: 3.90 (s, 3H), 3.91 (s, 3H) 3.92 (s, 3H), 5.39 (d, 1H, J = 12.0 Hz), 7.04 (d, 1H, J = 12.0 Hz), 7.10 (s, 2H). When starting with 30 g of the aldehyde 1 the yield was 66% of the nitrile mixture.

N-acetyl-3-(3',4',5'-trimethoxyphenyl)-propylamine (3).

PtO_2 (500 mg) was added to a solution of (E)-3,4,5-trimethoxycinnamonitrile (2) (9.9 g, 45.20 mmol) in acetic anhydride (80 ml). The mixture was hydrogenated at 35 psi and room temperature overnight. The catalyst was removed by filtration through Celite and the filtrate was concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 and washed with a dilute aqueous solution of $NaHCO_3$ and with brine, dried with $MgSO_4$ and concentrated under reduced pressure to give a slight yellow oil. Compound (3) (9.12g, 76%) was obtained after column chromatography (5x16cm, using CH_2Cl_2 progressively polarized with MeOH as the eluent) as a white crystalline solid, mp 68-69°C (isopropyl ether- CH_2Cl_2). PMR ($CDCl_3$) δ: 1.83 (m, 2H), 1.96 (s, 3H), 2.59 (m, 2H), 3.29 (m, 2H), 382 and 3.85 (s each, 9H), 5.55 (s, b, 1H), 6.40 (s, 2H); IR ν_{max} (KBr) 3300, 1640 cm^{-1}. The same result was achieved starting from the mixture of isomers E and Z.

1-Methyl-7,8,9-trimethoxy-3,4-dihydro-5H-2-benzazepine (4).

N-acetyl-3-(3',4',5'-trimethoxyphenyl)-propylamine (3) (15.326g, 57.40 mmol) and $POCl_3$ (5.35 ml, 57.40 mmol) in dry MeCN (300 ml) were heated at reflux for 2h. The solvent was evaporated under vacuum and the residue was taken in a mixture of benzene (20 ml) and 10% aqueous solution of NaOH (20 ml). After addition of concentrated NH_4OH until pH 8 the aqueous phase was extracted with benzene (4x20 ml). The organic extracts were washed with distilled water, dried over Na_2SO_4 and

concentrated. Column chromatography (petroleum ether - Et_2O (20:80 - 8:91)) afforded 4 (6.651 g, 47%) as an oil. PMR ($CDCl_3$) δ: 1.98 (s, b, 1H), 2.2-2.5(m, 3H), 2.37 (s, 3H), 2.89 (s, b, 1H), 3.60-3.65 (m, 1H), 3.85 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 6.52 (s, 1H). UV (MeOH, nm): λ 221, 259; log ε 4.187, 3.768. UV (MeOH + 1 drop of MeOH saturated with HCl, nm): λ 246, 314; log ε 3.635, 3.905.

2-Acetyl-1-methylene-7,8,9-trimethoxy-2,3,4,5-tetrahydro-1H-2-benzapine (5).

A solution of 4 (103 mg, 0.41 mmol) and acetic anhydride (0.3 ml) in pyridine (0.5 ml) was magnetically stirred overnight at room temperature. After elimination of the solvents under reduced pressure, the white solid was dissolved in Et_2O and filtered through a short column of silica gel 60 (0.015-0.040 mm). By eluting with more Et_2O 5 (114 mg, 95%) was obtained as a white crystalline solid: mp 151-153°C (MeOH). PMR ($CDCl_3$) δ: 1.93 (m, 2H), 2.04 (s, 3H) 2.81 (m, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 3.82-3.86 (m, 2H), 3.95 (s, 3H), 5.52 and 5.53 (s each, 2H), 6.45 (s, 1H). IR ν_{max} (KBr) 1640 cm^{-1}. Anal. Calc. for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 66.00; H, 7.30; N, 4.78.

2-Acetyl-7,8,9-trimethoxy-2,3,4,5-tetrahydro-1H-2-benzazepin-1-one (6).

A 50 ml round bottomed flask was charged with a magnetic stirring bar, CCl_4(10 ml), MeCN (10 ml), water (15 ml), N-acetyl-6,7,8-trimethoxy-9-methylene-5H-2-benzazepine (5) (1g, 3.44 mmol) and sodium metaperiodate (2.572 g, 12.02 mmol). To this biphasic solution $RuCl_3$ hydrate (50 mg) was added, and the mixture was stirred vigorously for 1 h at room temperature. Then 15 ml of CH_2Cl_2 was added and the phases were separated. The aqueous phase was extracted with more CH_2Cl_2 (4x15 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated. The resulting residue was diluted with Et_2O (30 ml), filtered through a Celite pad, washed with Et_2O (10 ml) and concentrated. After column chromatography (3x14 cm) (Et_2O), 6 (720 mg, 72%) was obtained as a white solid: mp 77-78°C (MeOH). PMR ($CDCl_3$) δ: 1.90 (m, 2H), 2.67 (m, 2H), 2.67 (s, 3H), 3.78 (m, 2H), 3.88 (s, 3H), 3.90 (s, 3H), 3.98 (s, 3H), 6.46 (s, 1H). CI MS m/z 294 (M^++1). IR ν_{max} (KBr) 1680, 1590 cm^{-1}. Anal. Calc. for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.77. Found: C, 61.31; H, 6.55; N, 4.76.

7,8,9-Trimethoxy-2,3,4,5-tetrahydro-1H-2-benzazepin-1-one (7).

A solution of 2-acetyl-7,8,9-trimethoxy-2,3,4,5-tetrahydro-1H-2-benzazepin-1-one (6) (1.136 g, 3.88 mmol) in 5% aqueous HCl (6 ml) and MeOH (12 ml) was stirred overnight at room temperature. The solvents were removed in vacuo and the residue was taken in CH_2Cl_2 (15 ml), washed with distilled water (2x3 ml), dried over $MgSO_4$, filtered and concentrated to give 7 in quantitative yield. It was crystallized from MeOH as white needles, mp 169-170°C. PMR ($CDCl_3$) δ: 1.85 (m, 2H), 2.68 (m, 2H), 3.05 (m, 2H), 3.81 (s, 3H, MeO), 3.82 (s, 3H, MeO), 3.89 (s, 3H, MeO), 6.41

(s, 1H, ArH), 6.55 (s, b, 1H, NH); CI MS m/z 252 (M^+ +1); IR ν_{max} (KBr) 3270, 3200, 1650, 1590 cm^{-1}. Anal. Calc. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.03; H, 6.86; N, 5.55.

N-methyl-7,8,9-trimethoxy-2,3,4,5-tetrahydro-1H-2-benzazepin-1-one (8).

To a solution of (7) (300 mg, 1.19 mmol) in dry THF (freshly distilled from Na-benzophenone) (17 mL) under N_2, a 85% oil dispersion of NaH (75 mg) was added. After stirring at room temperature for 1/2 h, MeI (0.1 ml) was added and the stirring was continued for another hour. The solvents were evaporated on the rotavapor, and CH_2Cl_2 (10 ml) and brine (5 ml) were added. The aqueous phase was extracted with CH_2Cl_2 (3x15 ml). The combined organic extracts were washed with brine (10 ml), dried over $MgSO_4$ and concentrated to obtain 8 in quantitative yield: mp 91-92°C (2-propanol). PMR ($CDCl_3$) δ: 1.75 (b), 2.25 (b), 2.65 (b), 3.16 (s, 3H), 3.35 (b), 3.87 (s, 6H), 3.98 (s, 3H), 6.44 (s, 1H). IR ν_{max} (KBr) 1645 cm^{-1}. Anal. Calc. for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.42; H, 7.27; N, 5.26.

N-methyl-7,8,9-trimethoxy-2,3,4,5-tetrahydro-1H-2-benzazepine (9).

A mixture of 8 (192 mg, 0.72 mmol) and LAH (60 mg, 1.58 mmol) in dry THF (15 ml) was refluxed under N_2 for 15 h. The reaction mixture was allowed to cool until room temperature and quenched with a saturated aqueous solution of Na_2SO_4. The THF phase was decanted and the residue was washed with more THF and CH_2Cl_2. The combined organic extracts were evaporated and the crude product was taken in CH_2Cl_2, washed with brine, dried over $MgSO_4$ and concentrated to obtain a slightly yellow oil (178 mg). After column chromatography (1x12 cm) (CH_2Cl_2 progressively polarized with MeOH until 8%) 9 (155 mg, 85%) was obtained as a colorless oil. PMR ($CDCl_3$) δ: 1.76 (m, 2H), 2.36 (s, 3H), 2.80 (m, 2H), 2.92 (m, 2H), 3.77 and 3.84 (s each, 11H), 6.47 (s, 1H); HR MS calcd for $C_{14}H_{21}NO_3$ 251.1521, found 251.1521. The compound was converted into its hydrochloride salt, mp 172°C (ethyl acetate).

N-methyl-6-bromo-7,8,9-trimethoxy-2,3,4,5-tetrahydro-1H-2-benzazepin-1-one (10).

A solution of N-methyl-6,7,8-trimethoxy-2,3,4,5-tetrahydro-1H-2-benzazepin-1-one (8) (68 mg, 0.256 mmol) in wet THF (10% water) contained in a 25 ml round bottomed flask, was stirred at room temperature with freshly crystallized N-bromosuccinimide (137 mg, 0.77 mmol) and finally divided calcium carbonate (77 mg, 0.77 mmol) while being irradiated with visible light (crystal clear bulb, 120 v, 100 w, placed at 1 cm distance of the wall of the flask). The reaction mixture became progressively orange and finally colorless after 15 min. At this time the amount of product 10 was approximately, three times that of 8 (t.l.c. silica gel, CH_2Cl_2/MeOH (95:5)) and the reaction stopped. Addition of NBS (157 mg) and $CaCO_3$ (87 mg) conducted, after 0.5 h of stirring, to the nearly complete conversion of 8 into 10. The reaction mixture was concentrated

until a 1 ml suspension of a white solid material. CCl_4 (4 ml) and brine (3 ml) were added, and the organic layer was washed with distilled water (3 ml), dried over $MgSO_4$ and concentrated under reduced pressure. The obtained translucent oil (90 mg) was chromatographed on PTLC silica gel with CH_2Cl_2/MeOH (95:5) as eluent to give 10 (56 mg, 63%) as a colorless oil. PMR ($CDCl_3$) δ: 1.69 (m, 1H), 2.21 (m, 1H), 2.50 (m, 1H), 3.16 (s, 3H), 3.1-3.4 (m, 3H), 3.91 (s, 3H), 3.92 (s, 3H) 3.97 (s, 3H). CI MS m/z 346 (M^++1), 344 (M^+ -1). Two milligrams of the starting material was recovered.

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