1-PHENETHYL-2,3,4,5-TETRAHYDRO-1H-2-BENZAZEPINES FROM 2-ACETYL-1-METHYLENE-2,3,4,5-TETRAHYDRO-1H-2-BENZAZEPINES

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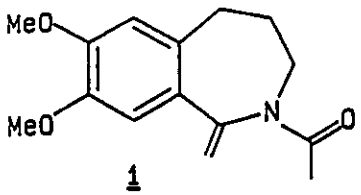
Abstract- (±)-1-(3',4',5'-Trimethoxyphenethyl)-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-2-benzazepine (7) and its N-acetyl derivative 8, of which the 1-phenyl analogs have potent platelet antiaggregatory properties, have been synthesized from 2-acetyl-1-methylene-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-2-benzazepine (1). The chemical reactivity of 2-benzazepines in this transformation has shown to be very similar to that of isoquinolines.

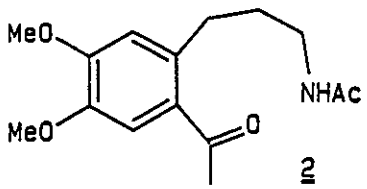
Recently[1] we developed a new approach to the preparation of 1-oxo-2,3,4,5-tetrahydro-1H-2-benzazepines based on the ruthenium catalyzed oxidative cleavage of 1-methylene-2,3,4,5-tetrahydro-1H-2-benzazepines and found that 1-methyl-3,4-dihydro-5H-2-benzazepines, obtained from N-acetyl-phenylpropylamines by Bischler-Napieralski cyclization, underwent chemical reactions similar to those observed earlier with 1-methyl-3,4-dihydroisoquinoline.[2,3,4] This finding has now been extended to the transformation of 2-acetyl-1-methylene-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-2-benzazepine (1) into (±)-1-(3',4',5'-trimethoxyphenethyl)-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-2-benzazepine (7), and its N-acetyl derivative (8). These two compounds are of potential pharmacological interest since their 1-benzyl analogs were recently reported to have potent platelet antiaggregatory properties.[5]

Synthesis of 2-acetyl-1-methylene-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-2-benzazepine (1) was accomplished from 3,4-dimethoxybenzaldehyde following the same sequence employed for its 7,8,9-trimethoxy analog.[1] Subsequent treatment with dilute HCl at 39°C afforded crystalline benzophenone 2 (91%) which was condensed with 3,4,5-trimethoxybenzaldehyde in the presence of sodium ethoxide to yield the trans αß unsaturated ketone 3. Catalytic hydrogenation at room temperature and atmospheric pressure in the presence of PtO_2 afforded considerable quantities of the alcohol 5 as by-product. Since compound 4 has the same Rf value as the starting material 3 (TLC, silica gel, MeOH-CH_2Cl_2 (5:95)), the course of the reaction had to be followed by

measuring the dissapearance of the enone band (335 nm) from the reaction mixture. In this way, ketone 4 was obtained with 10% Pd-C catalyst in 87% yield. Cyclization of 4 with 2 M HCl and catalytic reduction of the intermediate imine 6, afforded the desired (±)-1-phenethyl-2,3,4,5-tetrahydro-1H-2-benzazepine 7. The N-acetyl derivative 8, of interest because of its resemblance to structural features of colchicine, was prepared in the usual way.



1



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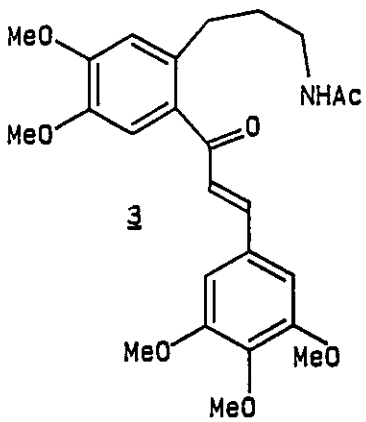

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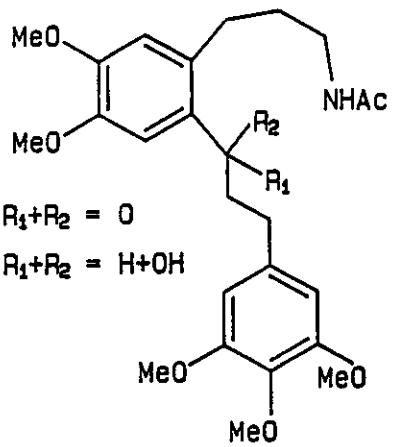
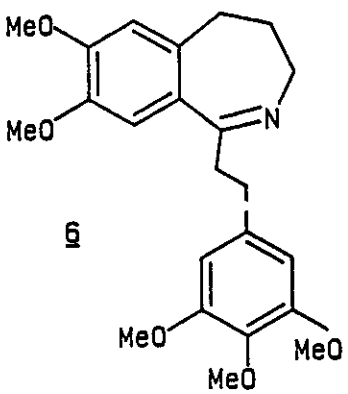


4 R_1+R_2 = O

5 R_1+R_2 = H+OH



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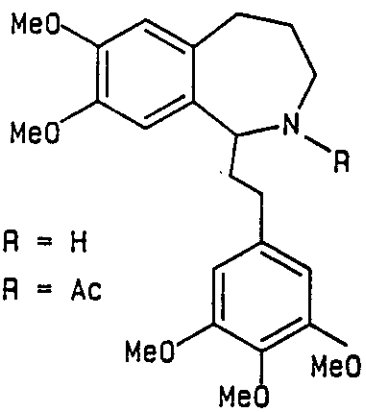

7 R = H

8 R = Ac

EXPERIMENTAL

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Ir spectra were recorded on a Beckman IR 4230 instrument. Nmr spectra were taken on a Varian XL-300 spectrometer Chemical shifts are reported in δ units downfield from internal tetramethylsilane. Chemical-ionization (CI) mass spectra were obtained from a Finnigan 1015D spectrometer with a Model 6000 data collection system. Uv spectra were measured with a Hewlet-Packard 8450A UV-VIS spectrometer. Thin-layer chromatography (TLC) plates (Analtech, Inc.) and preparative chromatography columns, packed with silica gel 60 (0.015-0.040 mm, EM Laboratories), were employed. In all the reactions carried under a dry atmosphere of N_2, the glassware was oven dried, assembled while hot and allowed to cool while flushing with dry N_2.

2-Acetyl-1-methylene-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-2-benzazepine (1).

For a detailed procedure see the synthesis of its 7,8,9-trimethoxy analog (ref. 1). 3,4-Dimethoxycinnamonitrile was obtained as a mixture of isomers (E/Z = 85/15 (Nmr)) in 85% yield by condensation of 3,4-dimethoxybenzaldehyde with MeCN. Crystallization from Et_2O-hexane yielded a pure sample of the E-isomer as colorless plates (mp 96°C). ^{1}H-Nmr($CDCl_3$) δ : 3.92 and 3.93 (s each, 6H), 5.73 (d, 1H, J = 16.6), 6.88 (d, 1H, J = 8.3), 6.94 (d, 1H, J = 2.0), 7.04 (dd, 1H, J = 8.3 and 2.0), 7.33 (d, 1H, J = 16.6); ir ν_{max} (KBr) 2300 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. ^{1}H-Nmr ($CDCl_3$) δ : 3.93 and 3.94 (s each, 6H), 5.30 (d, 1H, J = 11.9), 6.89 (d, 1H, J = 8.3), 7.02 (d, 1H, J=11.9), 7.25 (dd, 1H, J = 8.3 and 1.5) and 7.61 (d, 1H, J = 1.5); ir ν_{max} (film): 2300 cm^{-1}. Hydrogenation of the nitrile mixture (Ac_2O, PtO_2) afforded N-acetyl-3-(3',4'-dimethoxyphenyl)-propylamine as a colorless oil (69% after flash column chromatography). ^{1}H-Nmr ($CDCl_3$) δ : 1.82 (m, 2H), 1.95 (s, 3H), 2.60 (m, 2H), 3.28 (m, 2H), 3.86 and 3.87 (s each, 6H), 5.5 (s, b, 1H), 6.72 (m, 2H, ArH), 6.79 (d, 1H, J = 8.5); ir ν_{max} (film) 3290, 2930, 1645 cm^{-1}. Cyclization with $POCl_3$ in refluxing MeCN gave 1-methyl-7,8-dimethoxy-3,4-dihydro-5H-2-benzazepine as a colorless oil after column chromatography (53%). ^{1}H-Nmr ($CDCl_3$) δ: 2.25 (m, 2H), 2.39 (s, 3H), 2.49 (m, 2H), 3.25 (m, 2H), 3.90 (s, 3H), 3.92 (s, 3H), 6.73 (s, 1H) and 6.83 (s, 1H); ir ν_{max} (film): 2940, 1515, 1260, 1210, 1150 cm^{-1}; uv (MeOH, nm): λ 221, 261, 295; lg ϵ 4.488, 3.992, 3.937. Uv (MeOH + 2 drops of MeOH saturated with HCl, nm): λ 221, 245, 297, 341; lg ϵ 4.196, 4.296, 4.016, 4.075. CI ms m/z 220 (M^++1). Treatment with Py/Ac_2O afforded 1-methylene-2-benzazepine 1 (61%) which was crystallized from hexane-acetone, mp 110°C. ^{1}H-Nmr ($CDCl_3$) δ : 2.01 (m, 2H) 2.02 (s, 3H), 2.76 (m, 2H), 3.79 (m, 2H), 3.88 (s, 3H), 3.91 (s, 3H), 5.20 (s, 1H), 5.50 (s, 1H), 6.63 (s, 1H), 6.94 (s, 1H). CI ms m/z 262 (M^++1). Ir ν_{max} (KBr) 1650, 1630, 1610 cm^{-1}. Anal. Calc. for $C_{15}H_{19}O_3$:

C, 68.94; H, 7.33; N, 5.36. Found: C, 68.88; H, 7.36; N, 5.33.

N-Acetyl-3-(2'-acetyl-4',5'-dimethoxyphenyl)-propylamine (2).

A suspension of 1 (439 mg, 1.68 mmol) in 1.5 M HCl (15 ml) was magnetically stirred at 39°C for 18 h. THe clear solution thus obtained was basified with 10% aqueous NaOH and extracted with CH_2Cl_2 (5x13 ml). The organic extracts were washed with brine, dried over $MgSO_4$ and concentrated to afford a slightly yellow oil from which crystaline 2 was separated on treatment with benzene-Et_2O-hexane. After cooling in the refrigerator for 1/2 h, the crystals were filtered and washed with ethyl ether (425 mg, 91%). Mp 90°C. ^{1}H-Nmr ($CDCl_3$) δ: 1.79 (m, 2H), 2.03 (s, 3H), 2.59 (s, 3H), 2.88 (m, 2H), 3.26 (m, 2H), 3.92 and 3.93 (s each, 6H), 6.46 (s, b, 1H), 6.74 (s, 1H), 7.24 (s, 1H), ir ν_{max} (KBr) 3320, 1680, 1650 cm^{-1}. CI ms m/z 280 (M^++1). Anal. Calc. for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.42; H, 7.61; N,5.01.

αβ Unsaturated Ketone 3.

To a solution of propylamine 2 (500 mg, 1.79 mmol) and 3,4,5-trimethoxybenzaldehyde (358 mg, 1.82 mmol) in absolute ethanol (30 ml), sodium ethoxide (0.8 ml, 21% wt. solution in EtOH) was added. After stirring for 20 h at room temperature the solvent was evaporated, and the residue was taken up in methylene chloride, washed with 2% aqueous HCl and brine, dried over $MgSO_4$ and concentrated. Column chromatography of the crude product afforded ketone 3 (507 mg, 62%) as a yellow solid, mp 50-52°C. ^{1}H-Nmr ($CDCl_3$) δ : 1.87 (s, b, 2H), 1.99 (s, 3H), 2.77 (s, b, 2H), 3.26 (s, b, 2H), 3.89, 3.90 and 3.96 (s each, 15H), 6.54 (s, b, 1H), 6.80 (s, 3H), 7.03 (s, 1H), 7.04 (d, J = 15.9, 1H) 7.42 (d, J = 15.9, 1H). CI ms m/z 458 (M^++1). Ir ν_{max} (film) 3380, 3310, 1660 cm^{-1}. Uv (MeOH, nm): λ 335; lg ε 3.270. Anal. Cal. for $C_{25}H_{31}NO_7$: C, 65.63; H, 6.83; N, 3.06. Found: C, 65.54; H, 6.85; N, 3.02.

Ketone 4 and Alcohol 5.

To a solution of ketone 3 (557 mg, 1.22 mmol) in methanol (60 ml), 10% Pd/C (33 mg) was added and the mixture was hydrogenated at room temperature and 1 atm. The course of the reaction was monitored by the disappearance of the band at 335 nm in the uv spectra. The catalyst was removed by filtration through celite and the filtrate was concentrated under reduced pressure. Column chromatography afforded ketone 4 (487 mg, 87%) and alcohol 5 (71 mg, 12%) as oils.

Ketone 4: ^{1}H-Nmr ($CDCl_3$) δ : 1.71 (m, 2H), 2.06 (s, 3H), 2.81 (m, 2H), 2.99 (m, 2H), 3.22 (m, 4H), 3.82, 3.84, 3.87 and 3.93 (s each, 15 H), 6.4 (s, b, 1H), 6.45 (s, 2H), 6.73 (s, 1H), 7.12 (s, 1H). Ir ν_{max} (film): 3380, 3300, 1665 cm^{-1}. CI ms m/z 460 (M^++1). Alcohol 5: ^{1}H-Nmr ($CDCl_3$) δ: 1.62 (m, 2H), 1.88 (s, b, 4H), 2.14 (m, 1H), 2.49 (s, b, 2H), 2.6-2.8 (m, 2H), 3.11 (m, 2H), 3.82, 3.83, 3.84 and 3.86 (s each, 15H), 4.81 (m, 1H), 5.9 (s, b, 1H), 6.44 (s, 2H), 6.60 (s, 1H) and 7.02 (s, 1H). Ir ν_{max} (film): 3360, 1645 cm^{-1}. CI ms m/z 444 (MH^+-18).

(±)-1-(3',4',5'-Trimethoxyphenethyl)-7,8-dimethoxy-3,4-dihydro-5H-2-benzazepine (6).

Ketone 4 (380 mg, 0.83 mmol) was treated with 2 M HCl (30 mL) and refluxed for 24 h. After concentration to one half volume, the reaction mixture was extracted with ethyl acetate (2x10 ml). The organic layer was washed with 5% HCl (5 ml), the aqueous extracts combined and basified with 10% NaOH. Extraction with ethyl acetate (4x30 ml) followed by column chromatography of the crude product afforded benzazepine 6 (287 mg, 87%) as a colorless oil. ^{1}H-Nmr ($CDCl_3$) δ : 2.22 (m, 2H), 2.34 (m, 2H), 2.86 (m, 2H), 2.95 (m, 2H), 3.28 (m, 2H), 3.81 (s, 9H), 3.87 (s, 3H), 3.92 (s, 3H), 6.39 (s, 2H), 6.71 (s, 1H), 6.74 (s, 1H). CI ms m/z 400 (M^++1). Uv (MeOH, nm): λ 212, 283, 297; log ϵ 4.597, 3.734, 3.630; uv (MeO + 2 drops of MeOH saturated with HCl, nm): λ 210, 245, 300, 348; log ϵ 4.581, 4.008, 3.685, 3.746.

(±)-1-(3',4',5'-Trimethoxyphenethyl)-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-2-benzazepine (7).

To a solution of dihydrobenzazepine 6 (1226 mg, 3.61 mmol) in methanol (30 ml), PtO_2 (60 mg) was added and the mixture was hydrogenated at room temperature and atmospheric pressure for 3 h. Filtration through celite afforded benzazepine 7 as an oil in quantitative yield. ^{1}H-Nmr ($CDCl_3$) : 1.7-1.9 (m, 2H), 2.24 (m, 2H), 2.67 (m, 1H), 2.80 (m, 1H), 2.92 (m, 2H), 3.12 (m, 1H), 3.30 (m, 1H), 3.8-3.9 (15 H), 3.95 (m, 1H), 6.45 (s, 2H), 6.68 (s, 1H) and 6.70 (s, 1H). Hr ms calcd. for $C_{23}H_{31}NO_5$ 401.2202, found 401.2211.

2-Acetyl-1-(3',4',5'-trimethoxyphenethyl)-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-2-benzepine (8).

A solution of benzazepine 7 (31 mg, 0.077 mmol) in Ac_2O (2 ml) was stirred overnight at room temperature. After evaporation of the solvent and purification by PTLC (silica gel, MeOH-CH_2Cl_2 (1:9)), acetyl-2-benzazepine 8 was obtained as a colorless oil (32 mg, 93%). ^{1}H-Nmr ($CDCl_3$) δ : 1.99 and 2.12 (s each, 3H, CH_3CO of two rotamers), 3.8-3.9 (15H) and 6.38, 6.41, 6.49, 6.62 and 6.65 (s each, 4H, ArH of two rotamers). CI ms m/z 444 (M^++1). Ir ν_{max} (film): 1640 cm^{-1}.

REFERENCES

1. R. Alonso, K. Takahashi, B. Schönenberger, and A. Brossi, Heterocycles, 1987, 26, 1595.
2. A. Brossi, J. Würsch, and O. Schnider, Chimia, 1958, 12, 114.
3. A. Brossi, H. Besendorf, B. Pellmont, M. Walter, and O. Schnider, Helv. Chim. Acta, 1960, 43, 1459.
4. A. Brossi, L. A. Dolan, and S. Teitel, Org. Synth., 1977, 56, 3.
5. M. T. Clark, J. Chang, S. S. Navran, Huzoor-Akbar, A. Mukhopadhyay, H. Amin, D. R. Feller, and D. D. Miller, J. Med. Chem. 1986, 29, 181.

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