Benzylpiperazine Derivatives. XI.[1] Synthesis of Compounds Related to the Metabolites of 1-[Bis(4-fluorophenyl)methyl]-4-(2,3,4-trimethoxybenzyl)piperazine Dihydrochloride (KB-2796)

Hiroshi OHTAKA,* Manabu HORI, Ryuichi IEMURA and Hiroya YUMIOKA

Pharmaceuticals Research Center, Kanebo Ltd., 5–90, Tomobuchi-cho, 1-chome, Miyakojima-ku, Osaka 534, Japan. *Received March 28, 1989*

The metabolites of 1-[bis(4-fluorophenyl)methyl]-4-(2,3,4-trimethoxybenzyl)piperazine dihydrochloride (KB-2796, 1), a cerebral vasodilator, and related compounds were synthesized to confirm the proposed structures. The structures of the metabolites (3—5) in rats were identified by means of synthesis of the authentic compounds.

Keywords benzylpiperazine derivative; metabolite; Reimer–Tiemann reaction; Leuckart–Wallach reaction; structural identification; cerebral vasodilator

In the previous paper, we described the synthesis and the cerebral vasodilating activity of 1-benzyl-4-diphenylmethylpiperazine derivatives.[2] Among them, 1-[bis(4-fluorophenyl)methyl]-4-(2,3,4-trimethoxybenzyl)piperazine dihydrochloride (KB-2796, **1**) was selected as the most promising compound, and is now under clinical trial. Metabolism studies are an integral part of all programs of new drug development and are essential to the assessment of safety and efficacy of medicines. Recently, a study on the metabolism of **1** in biological fluids of rat was presented[3] and two demethylated derivatives (**3** and **4**) and a hydroxylated derivative (**5**) in addition to the degradation products (**7**, **8** and **9**) were proposed as the metabolites. The present study was undertaken to confirm the structures of the metabolites unequivocally through synthesis of three possible isomers of demethylated derivatives (**2**, **3** and **4**) and two isomers of hydroxylated derivatives (**5** and **6**).

The demethylated compounds were prepared by the methods shown in Chart 2. 2-Hydroxy-3,4-dimethoxybenzaldehyde (**10**)[4] was condensed reductively with 1-[bis(4-fluorophenyl)methyl]piperazine (**9**) to give 1-[bis(4-fluorophenyl)-methyl]-4-(2-hydroxy-3,4-dimethoxybenzyl)piperazine (**2**). Recrystallization from ethanol gave **2** as colorless prisms.

Although Leuckart–Wallach reaction of 3-hydroxy-2,4-dimethoxybenzaldehyde (**11**)[5] and **9** gave 1-[bis(4-fluorophenyl)methyl]-4-(3-hydroxy-2,4-dimethoxybenzyl)piperazine (**3**), the method of synthesis and the yield of **11** were unsatisfactory. On the other hand, condensation of OH-protected 3-benzyloxy-2,4-dimethoxybenzaldehyde (**12**)[6] with **9** followed by deprotection afforded **3** in nearly quantitative yield.

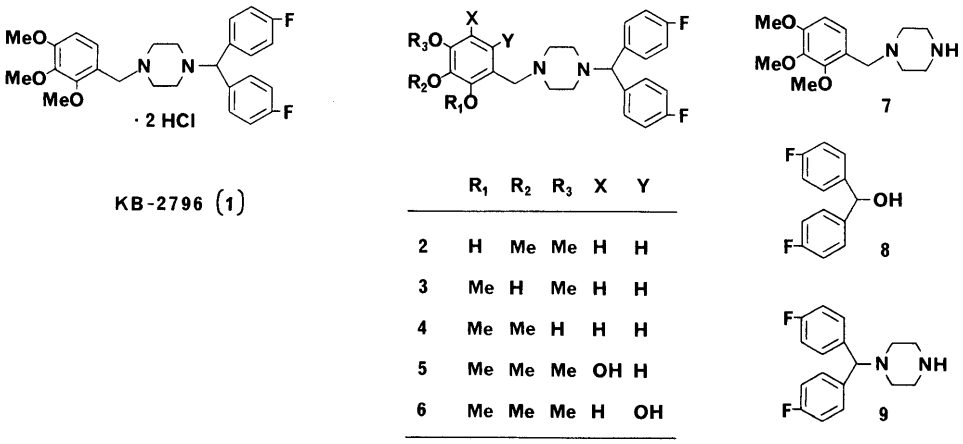
4-Hydroxy-2,3-dimethoxybenzaldehyde (**14**) has not been described in the literature. Several attempts to cleave the ether bond of 2,3,4-trimethoxybenzaldehyde selectively to afford **14** failed. Although usual formylation of 2,3-dimethoxyphenol (**13**) gave the *ortho*-formylated product (**10**),[7] selective *para*-formylation of substituted phenols to *p*-hydroxybenzaldehyde derivatives in the presence of β-cyclodextrin has been reported recently.[8] Applying this method, Reimer–Tiemann reaction of **13** in the presence of β-cyclodextrin gave a mixture of **10** and **14** (*ca.* 1:4) together with the starting material. Chromatographic separation gave **14** in 16% yield. Thus, 1-[bis(4-fluorophenyl)-methyl]-4-(4-hydroxy-2,3-dimethoxybenzyl)piperazine (**4**) was obtained from **14** and **9**.

The hydroxylated compounds (**5** and **6**) were prepared by the methods shown in Chart 3. 5-Hydroxy-2,3,4-trimethoxybenzaldehyde (**17**) has not been described in the literature. Vilsmeier reaction of the benzyl ether of 2,3,4-trimethoxyphenol (**15**)[9] gave a mixture of two formylated compounds. Attempts to separate them by chromatography failed, but after removal of the benzyl moiety by hydrogenolysis 2-hydroxy-3,4,5-trimethoxybenzaldehyde (**16**)[10] and **17** were separated by chromatography. Condensation of **17** with **9** gave 1-[bis(4-fluorophenyl)methyl]-4-(5-hydroxy-2,3,4-trimethoxybenzyl)piperazine (**5**).

6-Hydroxy-2,3,4-trimethoxybenzaldehyde (**18**)[11] was condensed with **9** to give 1-[bis(4-fluorophenyl)methyl]-4-(6-hydroxy-2,3,4-trimethoxybenzyl)piperazine (**6**).

Compounds **3**—**6** were converted to dihydrochlorides and purified by recrystallization.

The metabolites (**3**,**4** and **5**) from the biological fluids



	R_1	R_2	R_3	X	Y
2	H	Me	Me	H	H
3	Me	H	Me	H	H
4	Me	Me	H	H	H
5	Me	Me	Me	OH	H
6	Me	Me	Me	H	OH

Chart 1

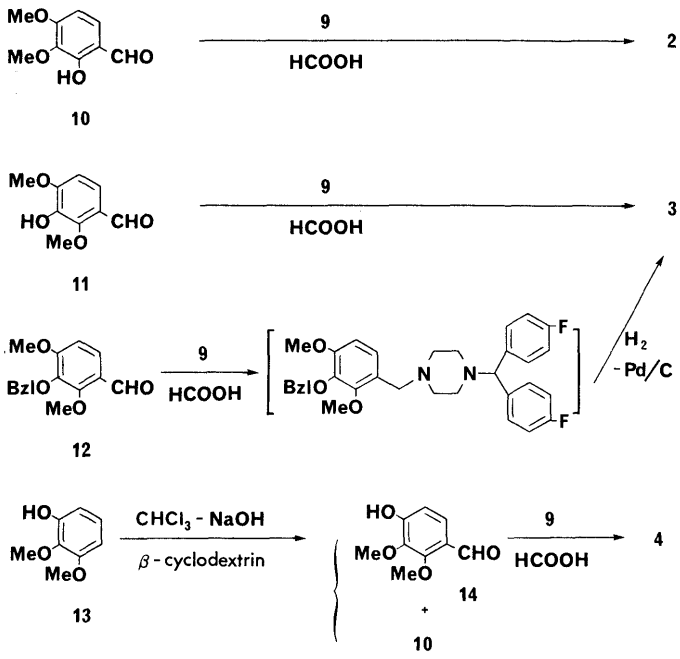


Chart 2

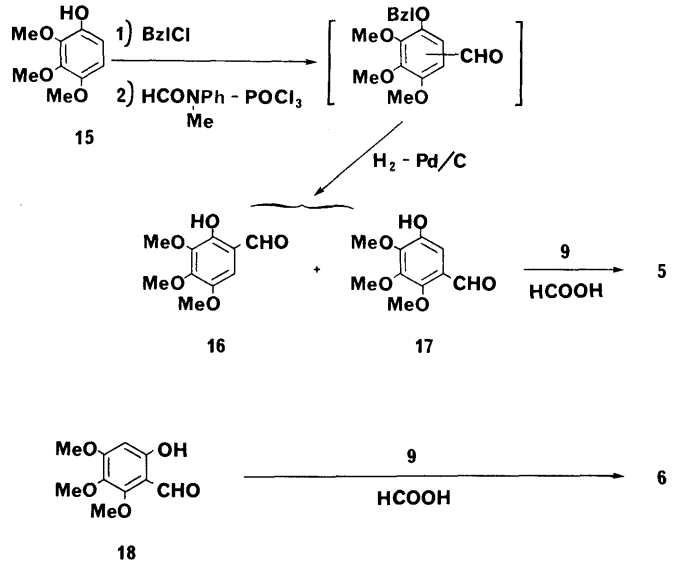


Chart 3

were identical with the corresponding synthetic compounds on the basis of direct comparisons of thin-layer chromatographic (TLC) behavior, mass spectra (MS) and proton nuclear magnetic resonance (^{1}H-NMR) spectra.

Experimental

Melting points were determined on a Yamato capillary melting point apparatus, model MP-21, and are uncorrected. MS were taken on a Hitachi M-80 spectrometer. ^{1}H-NMR spectra were determined on a Hitachi R-24B or a Bruker AM-300 spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given as δ (ppm). Abbreviations are as follows: s, singlet; d, doublet; m, multiplet; br, broad. Infrared (IR) spectra were obtained on a Hitachi 270-50 infrared specrophotometer. Silica gel 60 (Merck) TLC plates were used for thin layer chromatography. For column chromatography, Silica gel 60 (Merck) was used.

1-[Bis(4-fluorophenyl)methyl]-4-(2-hydroxy-3,4-dimethoxybenzyl)piperazine (2) A mixture of **10**[4] (3.0 g) and **9** (9.0 g) was melted in an oil bath at 130 °C, and formic acid (1.5 ml) was added dropwise. The mixture was stirred for 10 min at this temperature, and allowed to cool. Then the mixture was diluted with $CHCl_3$, washed successively with 3 N HCl, 1 N NaOH and saturated NaCl and dried over $MgSO_4$. After removal of the solvent, the residue was recrystallized from EtOH to give **2** as colorless prisms (4.6 g, 61%). mp 75.5—77.5 °C. MS *m/z*: 454 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.20—2.75 (8H, m), 3.65 (2H, s), 3.80 (3H, s), 3.84 (3H, s), 4.21 (1H, s), 6.32 (1H, d, J=8.4 Hz), 6.62 (1H, d, J=8.4 Hz), 6.87—7.00 (4H, m), 7.22—7.36 (4H, m). *Anal.* Calcd for $C_{26}H_{28}F_2N_2O_3 \cdot 0.5C_2H_5OH \cdot 0.25H_2O$: C, 67.27; H, 6.59; N, 5.81. Found: C, 67.00; H, 6.71; N, 5.81.

1-[Bis(4-fluorophenyl)methyl]-4-(3-hydroxy-2,4-dimethoxybenzyl)piperazine (3) a) Compounds **11**[5] (2.6 g) and **9** (4.1 g) were condensed in a similar manner to that described for compound **2** using formic acid (0.64 ml). After usual work-up of the reaction mixture, the product was chromatographed on silica gel with $CHCl_3$–MeOH (50 : 1) to give **3** as a pale yellow oil (5.92 g, 91%). MS *m/z*: 454 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.20—2.60 (8H, m), 3.48 (2H, s), 3.85 (3H, s), 3.86 (3H, s), 4.17 (1H, s), 5.40—5.65 (1H, br), 6.57 (1H, d, J=8.4 Hz), 6.74 (1H, d, J=8.4 Hz), 6.86—7.00 (4H, m), 7.22—7.37 (4H, m), This was converted into the dihydrochloride in a usual manner, mp 189—191 °C (EtOH). *Anal.* Calcd for $C_{26}H_{28}F_2N_2O_3 \cdot 2HCl \cdot H_2O$: C, 57.25; H, 5.91; N, 5.14. Found: C, 57.20; H, 5.81; N, 5.00.

b) Compounds **12**[6] (3.9 g) and **9** (4.1 g) were condensed in a similar manner to that described for compound **2** using formic acid (0.64 ml). After usual work-up of the reaction mixture, the product was chromatographed on silica gel with $CHCl_3$–MeOH (50 : 1) to give 1-[bis(4-fluorophenyl)methyl]-4-(3-benzyloxy-2,4-dimethoxybenzyl)piperazine as a pale yellow oil (6.86 g, 88%). A mixture of the above oil (1.5 g), 5% Pd/C (0.5 g) and EtOH (30 ml) was shaken under a hydrogen atmosphere for 1.5 h. After usual work-up, a pale yellow oil (1.1 g, 88%) was obtained which was identical with **3** described above.

1-[Bis(4-fluorophenyl)methyl]-4-(4-hydroxy-2,3-dimethoxybenzyl)piperazine (4) A mixture of **13** (5.0 g), β-cyclodextrin (9.0 g) and 10% NaOH solution (169 ml) was warmed at 60 °C. Chloroform (10 ml) was added dropwise within 5 h at 60 °C. The reaction mixture was stirred for 2 h, then dilute HCl was added. Precipitated solid (β-cyclodextrin) was filtered off and the product was extracted with AcOEt. After usual work-up of the extract, the product was chromatographed on silica gel with hexane–AcOEt (2 : 1) to give **13** (1.5 g), **10**[7] (0.3 g) and **14** (1.0 g). **14**; mp 71.5—73 °C (ligroin). IR (KBr): 3150, 1658 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.95 (3H, s), 4.05 (3H, s), 6.55 (1H, s, OH), 6.80 (1H, d, J=9 Hz), 7.55 (1H, d, J=9 Hz), 10.20 (1H, s). *Anal.* Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.34; H, 5.49. Compounds **14** (1.3 g) and **9** (4.0 g) were condensed in a similar manner to that described for compound **2** using formic acid (0.7 ml). After usual work-up of the reaction mixture, the product was chromatographed on silica gel with $CHCl_3$–MeOH (15 : 1) to give **4** as a pale yellow oil (2.5 g, 74%). MS *m/z*: 454 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.23—2.60 (8H, m), 3.45 (2H, s), 3.84 (3H, s), 3.90 (3H, s), 4.19 (1H, s), 6.64 (1H, d, J=8.4 Hz), 6.85—7.02 (5H, m), 7.28—7.37 (4H, m). This was converted into the dihydrochloride in a usual manner, mp 209.5—212 °C (CH_3CN–EtOH). *Anal.* Calcd for $C_{26}H_{28}F_2N_2O_3 \cdot 2HCl \cdot 0.5H_2O$: C, 58.21; H, 5.82; N, 5.22. Found: C, 58.14; H, 5.78; N, 5.12.

1-[Bis(4-fluorophenyl)methyl]-4-(5-hydroxy-2,3,4-trimethoxybenzyl)piperazine (5) A mixture of $POCl_3$ (5.2 g) and *N*-methylformanilide (4.5 g) was cooled in ice-water and 1-benzyloxy-2,3,4-trimethoxybenzene (6.2 g), obtained in a usual manner from 2,3,4-trimethoxyphenol,[9] was added. The reaction mixture was stirred for 21 h at room temperature, then poured into an ice-water and the product was extracted with AcOEt. After usual work-up of the extract, the product was chromatographed on silica gel with hexane–AcOEt (5 : 1) to give the starting material (0.2 g) and a mixture of formylated compounds (5.2 g). A mixture of the formylated compounds (5.2 g), 10% Pd/C (0.5 g) and AcOEt (150 ml) was shaken under a hydrogen atmosphere for 3 h. After usual work-up, the product was chromatographed on silica gel with $CHCl_3$–MeOH (30 : 1) to give **16** (1.1 g) and **17** (1.6 g). **16**: mp 35—36 °C (ligroin–AcOEt, lit[10] 39—40 °C). IR (KBr): 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.87 (3H, s), 3.97 (3H, s), 4.07 (3H, s), 6.80 (1H, s), 9.77 (1H, s), 10.97 (1H, s, OH). **17**: mp 93—95 °C (hexane–AcOEt). IR (KBr): 3200, 1672 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.93 (3H, s), 3.95 (3H, s), 4.05 (3H, s), 6.45 (1H, s, OH), 7.15 (1H, s), 10.20 (1H, s). *Anal.* Calcd for $C_{10}H_{12}O_5$: C, 57.60; H, 5.70. Found: C, 56.65; H, 5.60.

Compounds **17** (240 mg) and **9** (720 mg) were condensed in a similar manner to that described for compound **2** using formic acid (0.1 ml). After usual work-up of the reaction mixture, the product was chromatographed on silica gel with hexane–AcOEt (2 : 1) to give **5** as a pale yellow oil (150 mg, 27%). MS *m/z*: 484 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.25—2.60 (8H, m), 3.47 (2H, s), 3.78 (3H, s), 3.91 (3H, s), 3.92 (3H, s), 4.20 (1H, s), 6.67

(1H, s), 6.90—7.02 (4H, m), 7.28—7.37 (4H, m). This was converted into the dihydrochloride in a usual manner, mp >170 °C (dec., EtOH–CH_3CN). *Anal.* Calcd for $C_{27}H_{30}F_2N_2O_4 \cdot 2HCl \cdot 1.5H_2O$: C, 55.48; H, 6.04: N, 4.79. Found: C, 55.49; H, 5.74; N, 4.74.

1-[Bis(4-fluorophenyl)methyl]-4-(6-hydroxy-2,3,4-trimethoxybenzyl)-piperazine (6) Compounds **18**[11] (1.2 g) and **9** (2.6 g) were condensed in a similar manner to that described for compound **2** using formic acid (0.64 ml). After usual work-up of the reaction mixture, the product was chromatographed on silica gel with benzene–AcOEt (8 : 1) to give **6** as a colorless oil (0.71 g, 26%). MS *m/z*: 484 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.15—2.85 (8H, m), 3.72 (2H, s), 3.77 (3H, s), 3.79 (3H, s), 3.81 (3H, s), 4.24 (1H, s), 6.18 (1H, s), 6.90—7.05 (4H, m), 7.28—7.48 (4H, m). This was converted into the dihydrochloride in a usual manner, mp >164 °C (dec., EtOH–Et_2O). *Anal.* Calcd for $C_{27}H_{30}F_2N_2O_3 \cdot 2HCl \cdot 0.5H_2O$: C, 57.25; H, 5.87; N, 4.95. Found: C, 57.19; H, 5.85; N, 4.87.

References and Notes

1) H. Ohtaka, K. Yoshida, K. Suzuki, K. Shimohara, S. Tajima and K. Ito, *Chem. Pharm. Bull.*, **36**, 4825 (1988).
2) H. Ohtaka, T. Kanazawa, K. Ito and G. Tsukamoto, *Chem. Pharm. Bull.*, **35**, 3270 (1987).
3) T. Kawashima, O. Satomi and N. Awata, Abstracts of Papers, The 108th Annual Meeting of the Pharmaceutical Society of Japan, Hiroshima, April 1988, p. 547.
4) C. Hansson and B. Wickberg, *Synthesis*, **1976**, 191.
5) J. F. W. McOmie and S. A. Saleh, *J. Chem. Soc., Perkin Trans. 1*, **1974**, 384.
6) D. M. X. Donnelly, P. J. Keenan and J. P. Prendergast, *Phytochemistry*, **12**, 1157 (1973).
7) T. Tomimatsu, S. Yamada and R. Yuasa, *Yakugaku Zasshi*, **97**, 2170 (1977).
8) M. Komiyama and H. Hirai, *Yuki Gosei Kagaku Kyokai Shi*, **44**, 49 (1986).
9) M. Matsumoto, H. Kobayashi and Y. Hotta, *J. Org. Chem.*, **49**, 4740 (1984).
10) T. Rios and R. M. Flores, *Rev. Latinoam. Quim.*, **7**, 33 (1976) [*Chem. Abstr.*, **85**, 17061*y* (1976)].
11) W. J. Horton and M. G. Stout, *J. Org. Chem.*, **26**, 1221 (1961).