*Arch. Pharm. Res.* **15**(3), 191-195 (1992)

# Synthesis of 6′-Substituted Dobutamine Analogues

**Sung-Hwa Yoon**
*Department of Applied Chemistry, Ajou University, Suwon 441-749, Korea*
*(Received July 6, 1992)*

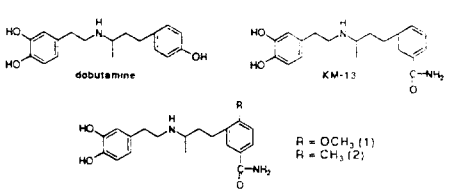
**Abstract** □ Two 6′-substituted dobutamine analogues (**1, 2**) were synthesized from the coupling reaction of dopamine with the corresponding ketones. The ketone (**8**) was obtained from 4-nitrosalicylaldehyde via 6 synthetic steps while the ketone (**12**) was prepared from 2-methyl-5-nitrobenzoic acid *via* 7 synthetic steps. Another synthetic attempts were also reported.

**Keywords** □ Dobutamine, inotrope, 4′-(2′-methoxy-5′-carbamyl)phenyl-2-oxobutane, 4′-(2′-methyl-5′-carbamyl)phenyl-2-oxobutane.

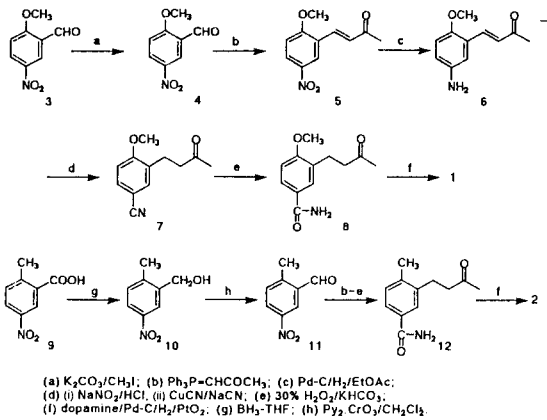
Among the currently available cardiotonics in the market[1], dobutamine is one of most extensively used drugs to treat cardiac failure due to its potentially beneficial pharmacological profile[2]. However, as a result of inconvenience of intravenous administration method of dobutamine, various chemical manipulations[3-9] of dobutamine were tried to achieve longer duration of action and/or oral bioavailability. Recently, KM-13[10], analogue of dobutamine which replaces the para hydroxy group in dobutamine with carbamyl one, showed not only increased inotropic potency three folds without changing the inotropic selective profile of dobutamine but also a little oral effectiveness. This report led us to investigate the substituent effects on phenyl ring containing carbamyl group, and further structural requirements to meet oral effectiveness in catecholamine type inotropes.

In this report, we describe general synthetic methods of 6′-substituted dobutamine analogues **1, 2**.

As shown in Scheme 1, dobutamine analogues

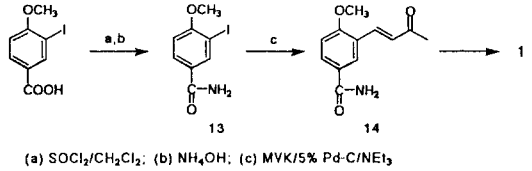



**1, 2** were prepared from coupling reaction of dopamine with the corresponding ketones, 4′-(2′-methoxy-5′-carbamyl)phenyl-2-oxobutane **8**, 4′-(2′-methyl-5′-carbamyl)phenyl-2-oxobutane **12**, respectively, under hydrogenation condition (Pd-C/$H_2$). Since dopamine is commercially available, the ketone **8** was first synthesized from 5-nitrosalicylaldehyde[11] for the synthesis of dobutamine analogue **1**. Reaction of 5-nitrosalicylaldehyde with methyl iodide under basic condition afforded **4**, which was used for Wittig olefination with 1-triphenylphosphoranylidine-2-propanone in benzene to give **5** in 70% yield. Hydrogenation of **5** in ethyl acetate under low pressure (15 psi) reduced both nitro group and double bond simultaneously to give amine compound **6** without formation of secondary alcohol although hydrogenation of **5** in ethanol under high pressure (50 psi) resulted in the formation of secondary alcohol in significant amounts. Diazotization of **6** followed by Sandmeyer reaction gave **7**, which was oxidized with 30% hydrogen peroxide under basic condition to give 4′-(2′-methoxy-5′-carbamyl) phenyl-2-oxobutane. Finally, the reaction of the ketone **8** with dopamine under hydrogenation condition ($PtO_2$, Pd-C/$H_2$) gave the dobutamine analogue **1** with samll amounts of starting material. It is noted that this reductive amination reaction using sodium cyanoborohydride instead of hydrogenation



(a) $K_2CO_3/CH_3I$; (b) $Ph_3P{=}CHCOCH_3$; (c) Pd-C/$H_2$/EtOAc; (d) (i) $NaNO_2$/HCl, (ii) CuCN/NaCN; (e) 30% $H_2O_2$/$KHCO_3$; (f) dopamine/Pd-C/$H_2$/$PtO_2$; (g) $BH_3$-THF; (h) $Py_2$ $CrO_3/CH_2Cl_2$

**Scheme 1**



(a) $SOCl_2/CH_2Cl_2$; (b) $NH_4OH$; (c) MVK/5% Pd-C/$NEt_3$

**Scheme 2**

method resulted in lower yield of product.

The ketone **12**, which was used for the synthesis of dobutamine analogue **2**, was prepared from 2-methyl-5-nitrobenzoic acid. Reduction of starting material with 1.0 M $BH_3$-THF solution followed by partial oxidation of the resulting benzyl alcohol **10** with Collin's reagent gave 2-methyl-5-nitrobenzaldehyde in good yield. From this aldehyde **11**, the ketone **12** was prepared in a manner similar to the synthesis of the ketone **8**. Finally, coupling reaction between dopamine with **12** gave the dobutamine analogue **2**.

Before attempting the synthetic methods described in Scheme 1, the shorter synthetic way of the ketone **8** from 3-iodo-4-methoxybenzoic acid was attempted (Scheme 2). However, substitution of iodine atom in **13** by methyl vinyl ketone in the presence of catalytic amounts of 10% Pd-C and triethylamine was not successful although same reaction with 3-iodobenzamide resulted in 70% yield of the corresponding oxo-compound[12]. It is believed that failure of this reaction in **13** resulted from steric hinderance of methoxy group.

## EXPERIMENTAL SECTION

### *Materials and method*

Melting points were determined on a Fischer-Johns melting point apparatus and were uncorrected. Proton nuclear magnetic resonance spectra were recorded on a Varian EM 390 spectrophotometer. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard. The solvent used are given in parentheses for each spectrum reported. Multiplicities of proton are designated as singlet(s), doublet(d), triplet(t), quartet(q) or multiplet(m). Infrared (IR) spectra were recorded on Perkin-Elmer 281 spectrophotometer. Solid samples were run as either a KBr pellet or a nujol mull; liquid samples were analyzed neat as a thin film between NaCl plates. Elemental analyses were performed by Atlantic Microlab. Inc., Atlanta, Georgia in U.S.A. and were within ± 0.4% of the theoretical values unless otherwise indicated. Silica gel 60 (Merck) for column chromatography was used.

### *5-Nitrosalicylaldehyde, 3*

was obtained from salicylaldehyde by following the reported method[11]. (47.0% yield)

mp.: 127-128.5℃ (ref.[11], 126℃).

### *2-Methoxy-5-nitrobenzaldehyde, 4*

A solution of 2.47g (0.0148 mol) of 5-nitrosalicylaldehyde and 2.65g (1.3 eq) of $K_2CO_3$ in 30 m*l* of DMF was stirred at 60℃ for 1 hr and was treated with 1.10 m*l* (1.2 eq) of methyl iodide dropwise at room temperature. The resulting mixture was stirred for 2 hrs at 60℃ again. When reaction was completed, the reaction mixture was poured into 50 m*l* of ice-water. The yellow precipitate was collected, washed with water and dried to give 2.52g of crude product. Recrystallization from ethanol gave 2..31g of pure product (86.3% yield).

mp.: 85.5-87.5℃;. IR (KBr): 1680 (C=O), 1590 (-$NO_2$), 1340 (-$NO_2$) $cm^{-1}$;. $^1$H-NMR ($CDCl_3$): 4.13 (1H, s, -$OCH_3$), 7.20 (1H, d, $J_{AB}$=9 Hz, aromatic H), 8.40-8.75 (2H, m, aromatic H), 10.57 (1H, s, -CHO).

### *2-Methoxy-5-nitro-3-(3'-oxobut-1-enyl)benzene, 5*

A mixture of 9.47g (0.0523 mol) of **4** and 20.0g (1.2 eq) of 1-triphenylphosphoanylidene-2-propanone in 250 m*l* of benzene was heated between

50 and 60℃ degree overnight. After evaporation of solvent, the remained crude product was purified by column chromatography on silica gel with ethyl acetate-hexane (1:2) to give a 9.13g of the product (79.0% yield).

mp.: 139.5-141.5℃; IR (KBr): 1690 (C=O), 1590 ($-NO_2$), 1340 ($-NO_2$) $cm^{-1}$; $^1$H-NMR ($CDCl_3$): 2.43 (3H, s, $-COCH_3$), 4.05 (3H, s, $-OCH_3$), 6.85 (1H, d, $J$=16.6 Hz, vinylic H), 7.04 (1H, d, $J_{AB}$=9.2 Hz, aromatic H), 7.81 (1H, d, $J$=16.6 Hz, vinylic H), 8.26 (1H, dd, $J_{AB}$=9.2 Hz, $J_{AC}$=3.0 Hz, aromatic H), 8.42 (1H, d, $J_{AC}$=3.0 Hz).

Elemental analysis for $C_{11}H_{11}NO_2$; Cald.: C, 59.72, H, 5.01, N, 6.33; Found: C, 59.80, H, 5.06, N, 6.30.

***5-Amino-2-methoxy-3-(3'-oxobutyl)benzene, 6***

A mixture of 2.00g (9.04 mmol) of **5** and 65 mg of 10% Pd-C in 90 ml of ethyl acetate was hydrogenated at 25℃ and initial pressure of 15 psi for 80 min. After the reaction was completed as indicated by TLC, the reaction mixture was filtered and concentrated to give desired product, which was used in the next reaction without further purification.

IR (KBr): 3330 (br. $-NH_2$), 1705 (C=O) $cm^{-1}$; $^1$H-NMR ($CDCl_3$): 2.12 (3H, s, $-COCH_3$), 2.75 (4H, s), 3.40 (2H, s, $-NH_2$), 3.73 (3H, s, $-OCH_3$), 6.40-6.85 (3H, m, aromatic H).

***5-Cyano-2-methoxy-3-(3'-oxobutyl)benzene, 7***

A mixture of 2.40g of the crude amine **6** in 5 ml of c-HCl and 5 ml of water was chilled to a slurry in ice-water bath. To this mixture, 1.02g (1.2 eq) of sodium nitrite in 4 ml of water was added dropwise and stirred for 20 min. at 0-5℃. After addition of a few crystal of urea to remove excess of sodium nitrite, the resulting mixture was carefully neutralized with an excess amount of calcium carbonate and filtered into a warm solution of mixture of 1.73g of CuCN and 2.31g of NaCN which was prepared in 25 ml of benzene. The resulting mixture was stirred for 1 hr at room temperature, and then extracted with 100 ml of ether. Combined organic layers were washed with 5% NaOH solution, 5% HCl solution, water and brine continuously. Finally, evaporation of solvent *in vacuo* gave a brown colored crude product, which was purified on silica-gel column chromatography with ethyl acetate-hexane (1:3) and recrystallized from ethanol to give 840 mg of pure product (33.3% yield).

mp.: 64.5-66℃; IR (nujol mull): 2230 (-CN), 1710 (C=O) $cm^{-1}$; $^1$H-NMR ($CDCl_3$): 2.12 (3H, s, $-COCH_3$), 2.80 (4H, m), 3.88 (3H, s, $-OCH_3$), 6.90 (1H, d, $J_{AB}$=9 Hz, aromatic H), 7.40-7.65 (2H, m, aromatic H).

Elemental analysis for $C_{12}H_{13}NO$; Cald.: C, 70.91, H, 6.44, N, 6.89; Found: C, 70.84, H, 6.47, N, 6.86.

***4-Methoxy-3-(3'-oxobutyl)benzamide, 8***

A mixture of 300 mg (1.40 mmol) of **7**, 170 mg of potassium bicarbonate and 1.00 ml of 30% hydrogen peroxide in 3.0 ml of methanol was stirred overnight at room temperature. After the reaction was completed, 25 ml of water was added to the reaction mixture and the resulting solution was extracted with 100 ml of ethyl acetate. The combined organic layers were washed with water and brine, dried, filtered and concentrated to give 287 mg of crude product which was recrystallized from EtOH-EtOAc (1:1) to give 265 mg of pure product (85.6% yield).

mp.: 128.5-130℃; IR (KBr): 3420, 3365 ($-CONH_2$), 1720 (C=O), 1660 (C=O) $cm^{-1}$; $^1$H-NMR ($CDCl_3$ + DMSO-$d_6$): 2.15 (3H, s, $-COCH_3$), 2.83 (4H, m), 3.90 (3H, s, $-OCH_3$), 6.85 (1H, d, $J_{AB}$=9 Hz, aromatic H), 6.00-7.50 (2H, br., $-CONH_2$), 7.65-7.85 (2H, m, aromatic H).

Elemental analysis for $C_{12}H_{15}NO_2$; Cald.: C, 65.14, H, 6.83, N, 6.33; Found: C, 65.02, H, 6.89, N, 6.28.

***3,4-Dihydroxy-N-(3-(2'-methoxy-5'-carbamoylphenyl)-1-methyl-n-propyl)-β-phenethylamine. hydrochloride, 1***

A mixture of 900 mg (4.07 mmol) of **8**, 580 mg of dopamine (3.79 mmol), 10 mg of 10% $PtO_2$ and 200 mg of 10% Pd-C in 25 ml of methanol and 8 ml of acetic acid was hydrogenated for 72 hrs at an initial pressure of 30 psi. After the reaction was completed as indicated by TLC, the reaction mixture was filtered and added 1 ml of c-HCl. The solution was concentrated to give a white colored foam product, which was chromatographied on silica gel with $CHCl_3$-MeOH-Acetic acid (6:2:0.5) and treated with 20% hydrogen chloride-methanol to afford 1.21g of the desired hydrogen chloride salt of compound **8** as a powder (80.9% yield).

$^1$H-NMR ($CD_3OD$): 1.75 (3H, d, $-CH_3$), 1.70-2.40 (3H, m), 2.67-3.37 (8H, m), 3.40 (1H, m), 3.95 (3H,

s, -$OCH_3$), 6.55-6.87 (3H, m, aromatic H), 7.05-7.10 (1H, d, aromatic H), 7.90 (2H, m, aromatic H).

Elemental analysis for $C_{20}H_{26}N_2O_4 \cdot 3HCl \cdot 3H_2O$; Cald.: C, 46.51, H, 6.79, N, 5.42, Cl, 17.88; Found: C, 46.46, H, 6.42, N, 5.29, Cl, 17.59.

***3,4-Dihydroxy-N-(3-(2'-methyl-5'-carbamoylphenyl)-1-methyl-n-propyl)-β-phenethylamine. hydrochloride, 2***

was prepared from 12 by analogy with the synthetic methods of analogue **1**.

mp.: 165-169℃; $^1$H-NMR ($CD_3OD$): 1.75 (3H, d, -CH-$CH_3$), 1.90-2.40 (3H, m), 2.70 (3H, s, -$CH_3$), 2.90-3.30 (4H, m), 3.40-3.60 (2H, m), 6.95 (3H, m, aromatic H), 7.55 (1H, d, aromatic H), 7.95 (2H, m, aromatic H).

Elemental analysis for $C_{20}H_{26}N_2O_3 \cdot 1.4HCl \cdot 1.0H_2O$; Calc.: C, 58.66, H, 6.99, N, 6.84, Cl, 12.12; Found: C, 58.40, H, 6.90, N, 6.63, Cl, 12.36.

***2-Methyl-5-nitrobenzaldehyde, 11***

was prepared from 2-methyl-5-nitrobenzylalcohol by following the reported method[13] (91.3% yield).

mp.: 54.5-55.5℃ (ref.[13], 55℃).

***4-Methyl-3-(3'-oxobutyl)benzamide, 12***

was prepared from **11** by analogy of the synthetic methods of **8** from **4**.

mp.: 127-128℃; IR (KBr): 3370 (-$CONH_2$), 1705 (C=O), 1640 (C=O) $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): 2.13 (3H, s, -$COCH_3$), 2.30 (3H, s, -$CH_3$), 2.80 (4H, s, -$CH_2CH_2$-), 7.22 (2H, d, $J$=5 Hz, aromatic H), 7.65 (1H, d, aromatic H), 7.60-7.95 (2H, br., -$CONH_2$).

Elemental analysis for $C_{12}H_{15}NO_2$; Cald.: C, 70.22, H, 7.37, N, 6.82; Found: C, 69.66, H, 7.41, N, 6.76.

***3-Iodo-4-methoxybenzamide, 13***

To a solution of 3.00g (0.0108 mol) of 3-iodo-4-methoxybenzoic acid in 150 m*l* of benzene was added 1.54g (1.2 eq) of thionyl chloride and one drop of pyridine at room temperature. The reaction mixture was heated for 2 hrs at 65℃ and then cooled in ice-water bath before the reaction was quenched with an excess of 28% saturated ammonium hydroxide solution. The white precipitate which formed immediately was collected and recrystallized from 50% aqueous ethanol to give 2.12g of pure product (70.6% yield).

mp.: 151-152.5℃; IR (nujol mull): 3370 (-$CONH_2$), 1650 (C=O) $cm^{-1}$; $^1$H-NMR (DMSO-$d_6$): 3.96 (3H, s, -$OCH_3$), 7.18 (1H, d, $J_{AB}$=9 Hz, aromatic H), 8.10 (1H, m, $J_{AB}$=9 Hz, $J_{AC}$=2 Hz, aromatic H), 8.45 (1H, d, $J_{AC}$=2 Hz, aromatic H), 7.1-7.5 (2H, br., $CONH_2$).

***4-Methoxy-3-(3'-oxybut-2'-enyl) benzamide, 14***

A solution of 0.276g (10 mmol) of **13**, a catalytic amount of 5% Pd-C, 0.081 m*l* of methyl vinyl ketone (1.1 eq.) and 0.15 m*l* of triethylamine in 10 m*l* acetonitrile was refluxed for 2.5 hrs. Next, the solution was cooled to room temperature, and another 0.073 m*l* of methyl vinyl ketone (1.0 eq.) and 0.115 m*l* of triethylamine (1.0 eq.) was added. After being refluxed again for 2 hrs, the solution was filtered to remove the catalyst and was concentrated to give a crude product which was identified as starting material with about five percents of desired product **14**. The product **14** was collected by column chromatography on silica-gel with ethyl acetate as an eluent and identified only with NMR.

$^1$H-NMR ($CDCl_3$): 2.32 (3H, s, -$COCH_3$), 3.95 (3H, s, -$OCH_3$), 6.83 (1H, d, $J$=16 Hz, vinylic H), 7.16 (1H, d, $J$=9 Hz, aromatic H), 7.25 (2H, br., -$CONH_2$), 7.80 (1H, d, $J$=16 Hz, vinylic H), 8.10 (1H, m, $J_{AB}$=9 Hz, $J_{AC}$=2 Hz, aromatic H), 8.45 (1H, d, $J_{AC}$=2 Hz, aromatic H).

## ACKNOWLEDGEMENT

This work was partly supported by Ajou University.

## LITERATURE CITED

1. Erhardt, P.W.: In search of digitalis replacement. *J. Med. Chem.* **30**, 232 (1987).
2. Weiner, N.: *The pharmacological basis of therapeutics*, A.G. Gilman, L.S. Goodman, A. Gilman Eds., Macmillan Publishing Co, New York (1980).
3. Minatoya, H., Tullar, B.F. and Conway, W.D.: Esters of β-aminoethyl-3-(hydroxy-hydroxymethyl)-4-hydroxybenzyl alcohol and their physiological activity. *Chem. Abstr.*, **74**, 53268 (1971).
4. Tullar, B.F., Minatiya H. and Lorenz, R.R.: Esters of N-tertbutylarterenol: Long-acting new bronochodilators with reduced cardiac effects. *J. Med. Chem.*, **19**, 834 (1976).

5. Larsen, A. A., Lish, P. M.: A new bio-isoster; Alkylsulphonamido-phenethanolamines. *Nature (London),* **203**, 1283 (1984).
6. Dungan, K. W., Cho, Y. W., Gomell, A. W., Aviado D. M. and Lish, P. M.: Pharmacologic potency and selectivity of a new bronchodilator agent; Soterenol. *J. Pharmacol. Exp. & Ther.* **64**, 290 (1968).
7. Hartley, D., Jack, D., Lunts L. H. C. and Ritchie, A. C.: New class of selective stimulants of β-adrenergic receptors. *Nature(London),* **219**, 861 (1968).
8. Kaiser, C., Colella, D. F., Schwartz, M. S., Garney E. and Wardell, J. R.: Adrenergic agents I; Synthesis and potential β-adrenergic agonist activity of some catecholamine analogs bearing a substituted amino functionality in the meta position. *J. Med. Chem.,* **17**, 49 (1974).
9. Wardell J. R. Jr., Colella, D. F., Shetzline A. and Fowler, P. J.: Studies on carbuterol (SK & F 40383-A); A new selective bronchodilator agent. *J. Pharmacol. Exp. & Ther.,* **189**, 167 (1974).
10. Caldwell, R. W., Nash, C. B., Smulkowski ,M. and Tuttle, R. R.: Cardiovascular effects of KM-13, a new, orally effective, cardiotonic sympathomimeticamine. *J. Cardiovasc. Pharmacol.* **9**, 375 (1987).
11. Miller, W. : Ueber nitrosalicylaldehyde. *Ber. Chem.* **488**, 1927 (1876).
12. Yoon, S.-H.: Unpublished results.
13. Patcliff, R. and Radehorst, R.: Improved procedure for oxidations with the chronium trioxide-pyridine complex. *J. Org. Chem.,* **35**, 4000 (1970).