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# SYNTHESIS BASED ON β-PHENYLETHYLAMINES X. SYNTHESIS OF NEW DERIVATIVES OF PHENYLETHYLAMINOMETHYLBENZO-CROWN ETHERS

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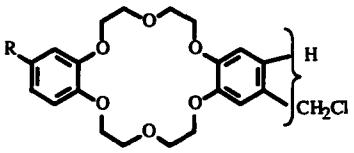
*Three methods have been developed for the introduction of a β-phenylethylamine fragment into a benzo-crown ether molecule.*

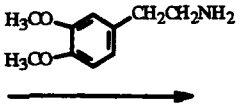
β-Phenylethylamine derivatives possess a broad spectrum of biological activity, fulfilling an important function in animal metabolism [1]. Synthetic β-phenylethylamines are intermediates in the synthesis of isoquinoline alkaloids and many drugs [2, 3], such as papaverine [4]. The present paper is devoted to the synthesis of new β-phenylethylamine derivatives with benzo-15-crown-5 (B15C5) and dibenzo-18-crown-6 (DB18C6) fragments.

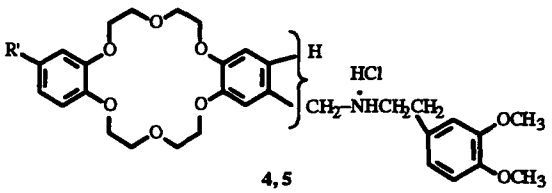
Derivatives of B15C5 and DB18C6 containing dopamine fragments are known in the literature [5]. This synthesis is based on Pedersen's method, which uses as the initial compounds substances containing structural elements capable of cyclization with polyethyleneglycols or their chlorides to form macrocycles.

We have developed a new method for obtaining such compounds by condensation with a preformed benzo-crown ether. We have previously attempted to introduce a β-phenylethylamine fragment into the DB18C6 molecule using an acetyl halide derivative of DB18C6 with the subsequent replacement of the halogen by an alkylamine. However, this route did not lead to satisfactory results, since the chloroacetylation reaction gives the desired product in very low yield (≈10%). Therefore, as the initial compounds we have now used chloromethyl and formyl derivatives of the benzo-crown ethers. For this purpose we synthesized 4′,4″(5″)-dichloromethyl-DB18C6 (**1**) and 4′-tert-butyl-4″(5″)-chloromethyl-DB18C6 (**2**) as described in [6], and 4′-formyl-B15C5 (**3**) as in [7].

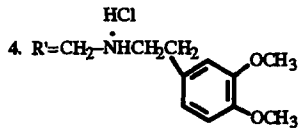


**1.** R=$CH_2Cl$
**2.** R=$C(CH_3)_3$





**4, 5**



**4.** R′=$CH_2$–$\overset{\cdot}{N}H$HCl$CH_2CH_2$

**5.** R′=$C(CH_3)_3$

*Deceased.

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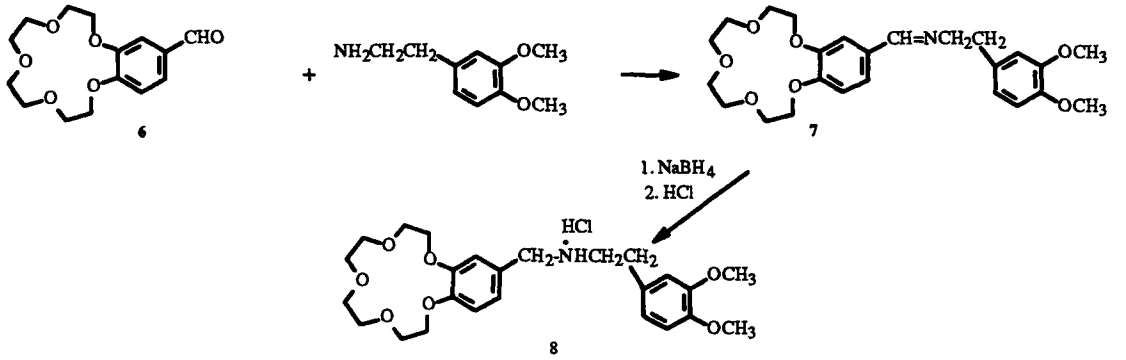
The condensation of 3,4-dimethoxy-β-phenylethylamine, obtained according to [8], with 4′,4″(5″)-dichloromethyl-DB18C6 (**1**) gave product (**4**) with a yield of 50% in the form of the hydrochloride, with mp 62—67°C. According to its PMR spectrum, the product was a mixture of structural isomers.

In compound (**4**), the signal of the protons of the $NH_2$ group at 8.3 ppm had disappeared and a signal of the proton of a NH group had appeared at 10 ppm, while the signal of the protons of the $CH_2Cl$ group at 4.47 ppm had also disappeared. The methylene protons were shown by a multiplet in the 2.86—3.4 ppm region and by a singlet at 2.0 ppm. Since in such a 3,4-dimethoxyphenylethylamine the signals of the $CH_2$ groups are shown by two multiplets at 3.1—3.34 and 2.9—3.1 ppm, we assumed that in compound (**4**) these signals had come together and given a single multiplet in the 2.86—3.4 ppm region, while the singlet appearing at 2.0 ppm and corresponding to 4H related to the signals of the $CH_2$ groups located between NH and the benzene ring of DB18C6. The signals of the two methoxy groups almost fused with the signals of the $OCH_2$ groups of the macrocycle. The signals of the aromatic protons gave a common complex multiplet in the 6.4—9.04 ppm region.

The condensation of 3,4-dimethoxy-β-phenylethylamine with 4′-tert-butyl-4″(5″)-chloromethyl-DB18C6 (**2**) took place far better, the yield of product (**5**), the hydrochloride of which had mp 76—82°C, amounting to 90%. It was characterized by its PMR spectrum and shown to consist of a mixture of isomers. In the PMR spectrum of compound (**5**) the proton of the NH group was shown by a symmetrical multiplet with its center at 9.9 ppm. The methylene protons of the $N—CH_2—CH_2$ group gave a multiplet in the 2.86—3.26 ppm region, and the methylene protons between the nitrogen and the crown-ether fragment a singlet at 1.92 ppm. The protons of the methoxy groups were revealed by two singlets at 3.80 and 3.82 ppm. The protons of the $OCH_2$ groups of the macrocycle were shown by two multiplets in the 4.06—4.36 and 3.88—4.06 ppm regions (α- and β-$OCH_2$, respectively). In contrast to compound (**4**), in the spectrum of (**5**) the protons of the 3,4-dimethoxy-β-phenylethylamine fragment and of the benzene rings of the crown ether were represented by two multiplets in the 6.8-6.96 and 6.5—6.8 ppm regions, respectively.

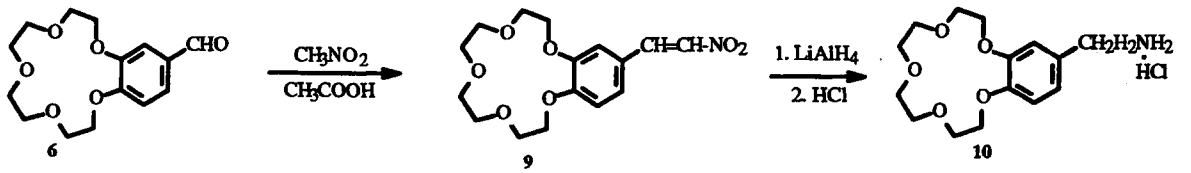
Another route to the introduction of a β-phenylethylamine fragment into a benzo-crown ether is condensation with the formyl derivative (**6**) via the formation of the azomethine derivative (**7**) and its subsequent reduction.




6 7 8

The final product (**8**) was isolated in 64% yield in the form of the hydrochloride with mp 85—87°C. Its structure was shown by the PMR spectrum. This contained a multiplet corresponding to the signal of the proton of the NH group at 9.9 ppm. The methylene protons were also shown by a multiplet at 3.04 ppm and a singlet at 1.82 ppm. The signals of the methoxy groups were superposed on the signals of compound (**6**) and had the form of two singlets at 3.78 and 3.79 ppm between the signals of the protons of the β-, γ-, and δ-$OCH_2$ groups of the macrocycle. The protons of the $OCH_2$ groups of B15C5 were revealed, as usual, by three groups of signals; a multiplet in the 4.06—4.24 ppm region (α-$OCH_2$), a multiplet at 3.88—4.06 ppm (β-$OCH_2$), and a singlet at 3.66 ppm (γ- and δ-$OCH_2$). Aromatic protons were shown by a complex multiplet in the 6.62—7.0 ppm region.

The third method of introducing a β-phenylethylamine fragment consists in the condensation of a formyl derivative of a benzo-crown ether with nitromethane, followed by reduction of the nitrovinyl derivative, by analogy with [8]:




6 9 10

The product of condensation with nitromethane was obtained in 53% yield, mp 160—162°C. The structure of (**9**) was established by PMR spectroscopy The proton of the vinyl group located adjacent to the benzene ring had a signal in the form of a doublet at 8.12 ppm. The proton adjacent to the nitro group was revealed by a doublet signal at 7.55 ppm.

Reduction of the substituted nitrostyrene (**9**) was successfully achieved with lithium tetrahydroaluminate only in the mixed solvent ether—dioxane (3:1). Isolation of the product in crystalline form presented particular difficulties. The hydrochloride of compound (**10**) was obtained with a yield of 33%, mp 97—99°C. Its structure was determined by PMR. The two methylene protons adjacent to the amino group were revealed by a triplet at 3.6 ppm and the methylene protons linked with the benzene ring were revealed by a triplet at 3.0 ppm. The aromatic protons and the protons of the macrocycle had signals characteristic for substituted benzo-crown ethers.

Thus, we have developed three methods for introducing a β-phenylethylamine fragment into a benzo-crown ether molecule, consisting in its condensation with chloromethyl and formyl derivatives of the benzo-crown ethers. The proposed methods are simpler than those known in the literature.

## EXPERIMENTAL

4′,4″(5″)-Dichloromethyl-DB18C6 and 4′-tert-butyl-4″(5″)-chloromethyl-DB18C6 were obtained as described in [6]. The 4′,4″(5″)-dichloromethyl-DB18C6 — a mixture of structural isomers — was obtained with a yield of 37%, mp 137—140°C. The 4′-tert-butyl-4″(5″)-chloromethyl-DB18C6 consisted of a mixture of structural isomers with mp 110—112°C, yield 80%. 4′-Formyl-B15C5 was obtained as in [7]. Its yield was 55%, mp 78—80°C. 3,4-Dimethoxy-β-phenylethylamine was obtained as in [8]. Yield 50%, mp of the hydrochloride 154°C. Nitromethane was obtained as described in [9], yield 31%, bp 95—100°C.

**Condensation of 3,4-Dimethoxy-β-phenylethylamine with 4′,4″(5″)-Dichloromethyl-DB18C6.** A solution of 0.25 g (0.00054 mole) of 4′,4″(5″)-dichloromethyl-DB18C6 with 0.25 g (0.0013 mole) of 3,4-dimethoxy-β-phenylethylamine in chloroform was boiled for 5 h and was then washed with 5% KOH solution and with water. The chloroform was distilled off and the residue was washed with hexane and treated with acidified benzene. After repeated trituration with hexane, 0.22 g (50%) of the salt (**4**) was obtained, with mp 62—67°C. PMR spectrum (δ, ppm): 10 (2H, br. s)-NH; 6.40-7.04 (12H, m)-ArH; 3.90-4.40 (16H, m)-$OCH_2$; 3.84-3.80 (12H, s)-$OCH_3$; 2.86-3.40 (8H, m)-N-$CH_2$-$CH_2$; 2.00 (4H, s)-N-$CH_2$-Ar (crown).

**Condensation of 3,4-Dimethoxy-β-phenylethylamine with 4′-tert-Butyl-4″(5″)-chloromethyl-DB18C6.** Similarly, 0.94 g (0.0052 mole) of 3,4-dimethoxy-β-phenylethylamine and 0.81 g (0.0017 mole) of 4′-tert-butyl-4″(5″)-chloromethyl-DB18C6 gave in 7 h a product which was separated on silica gel in the chloroform—alcohol (3:1) system. After acidification and trituration with hexane, 1.0 g (90%) of substance (**5**) was obtained in the form of the hydrochloride with mp 76—82°C. PMR spectrum (δ, ppm): 9.90 (1H, m)-NH; 6.80-6.96 (3H, m)-ArH; 6.50-6.80 (6H, m)-ArH-(crown); 4.06-4.36 (8H, m)-α-$OCH_2$; 3.88-4.06 (8H, m)-β-$OCH_2$; 3.82, 3.90 (6H, s)-$OCH_3$; 2.86-3.26 (4H, m)-$NCH_2CH_2$; 1.92 (2H, s)-$NCH_2Ar$ (crown); 1.22 (9H, s)-$C(CH_3)_3$.

**Preparation of 4′-(3,4-Dimethoxy-β-phenylethylaminomethyl)-B15C5.** A solution of 0.24 g (0.0013 mole) of 3,4-dimethoxy-β-phenylethylamine and 0.3 g (0.001 mole) of 4′-formyl-B15C5 in 1 ml of alcohol was boiled for 3 h with the addition of traces of *p*-toluenesulfonic acid. The reaction mixture was treated with acidified benzene and the benzene was distilled off. The resulting oil was dissolved in 2 ml of alcohol, and a suspension of $NaBH_4$ in 2 ml of alcohol was added. The mixture was left overnight, the crystals that had deposited were separated off, and the mother solution was evaporated and acified with acidified benzene. The benzene was driven off and the residue was dissolved in acetone and precipitated with ether. The crystals so obtained were recrystallized from acetone. The yield of (**8**) was 0.32 g (64%), mp 85—87°C. PMR spectrum (δ, ppm): 9.90 (1H, m)-NH; 6.62-7.00 (6H, m)-ArH; 4.06-4.24 (4H, m)-α-$OCH_2$; 3.88-4.06 (4H, m)-β-$OCH_2$; 3.78, 3.79 (6H, 2s)-$OCH_3$; 3.66 (8H, s)-γ- and δ-$OCH_2$; 3.04 (4H, s)-$NCH_2CH_2$ (crown); 1.82 (2H, s)-N-$CH_2$-Ar (crown).

**Condensation of 4'-Formyl-B15C5 with Nitromethane.** A solution of 1.5 g (0.005 mole) of 4'-formyl-B15C5 in 15 ml of glacial acetic acid was treated with 0.4 g (0.005 mole) of ammonium acetate, and, with heating, 0.65 ml (0.012 mole) of nitromethane was added. The mixture was boiled for 2 h and was then poured onto ice, and the crystals that deposited were filtered off and recrystallized from acetone. Yield 0.9 g (53%), mp 160—162°C. PMR spectrum (δ, ppm): 8.12 (1H, d)-CH-Ar; 7.55 (1H, d)-CH-$NO_2$; 7.12 (1H, dd, J=2 Hz, 8 Hz); 7.00 (1H, d, J=2 Hz); 6.80 (1H, d, J=8.5 Hz)-ArH; 4.00-4.20 (4H, m)-α-$OCH_2$; 3.80-4.00 (4H, m)-β-$OCH_2$; 3.75 (8H, s)-γ- and δ-$OCH_2$.

**Preparation of Compound (10).** With stirring at room temperature, 0.7 g (0.002 mole) of nitrovinyl-B15C5 in 25 ml of abs. dioxane was added dropwise over 1.5 h to 0.4 g (0.01 mole) of lithium tetrahydroaluminate in 65 ml of abs. dioxane. The reaction mixture was boiled for 4.5 h and was then decomposed with water and filtered. The solvent was distilled off, leaving 0.47 g of an oil. This was boiled in hexane and the hexane extracts were treated with acidified ether. Thereupon a white curd-like precipitate deposited, and this was separated off and triturated with hexane. The amount of hydrochloride so obtained was 0.17 g, yield 33%, mp 97—99°C. PMR spectrum (δ, ppm): 7.12 (1H, d); 7.00 (1H, s); 6.92 (1H, d) -ArH; 4.12-4.37 (4H, m)-α-$OCH_2$; 3.87-4.12 (4H, m)-β-$OCH_2$; 3.77 (8H, s)-γ- and δ-$OCH_2$; 3.60 (2H, t)-CH-$NH_2$; 3.00 (2H, t)-CH-Ar.

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