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A CONVENIENT SYNTHESIS OF PHOSPHATE ESTERS OF DOPAMINE AND EPININE

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***Abstract**: The title compounds were prepared with a route which is characterized by the regioselective preparation of 3 or 4 oxydryl protected dopamine and epinine precursors.*

Introduction

The growing body of knowledge of the physiological role of dopamine and its complex pharmacological profile[1] when it is exogenously administered point to important clinical applications of orally bioavailable forms of dopamine, suitable to overcome the first pass metabolic inactivation. Then, the usefulness of these forms would be increased if they could be designed to specifically deliver dopamine in the therapeutically relevant organs or districts.

The fast metabolic inactivation of the catecholamines, including dopamine, is essential for their physiological functions as neurotransmitters or short-range hormones. An enormous amount of work, with a great deal of success, has been devoted to molecular modification of catecholamine-related agonists. This work was equally aimed at modulating receptorial

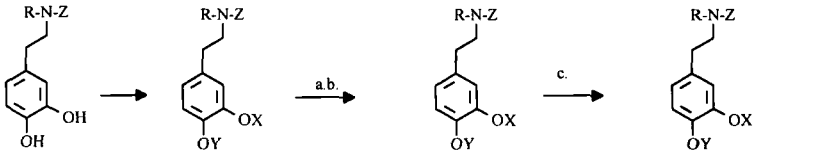
selectivity and at improving bioavailability and duration of action. On the other hand, the prodrug approach is appealing because it appears more suitable to achieving site-specific delivery, but up to now it has produced only few drugs having a proven clinical efficacy[2].

We have undertaken an investigation of synthesis of phosphate esters of catecholamines, i.e. 1-4 corresponding to the general formula of scheme 1, and we are exploring their pharmacological activity which is dependent upon their activation by phosphatases or by phosphodiesterases[3].

Chemistry

The synthesis of this class of compounds faced an intrinsic difficulty of lack of regioselectivity both in the phosphorylation of the 3- an 4-hydroxy group of the cathechol system and in any reaction introducing a protective group on either of the two hydroxy groups. Thus, the simplest approach investigated and outlined in scheme 1 was the use of N-benzyloxycarbonyldopamine or epinine as starting material[4]. The mono-introduction of benzyl group upon the catechol group by a completely non regiospecific reaction, led to a pair of isomers **5-6** and **7-8** which were easily separated by chromatography. These monobenzyl ethers were converted to the corresponding sodium salt, then they reacted with dibenzylphosphorochloridate[5] to give compounds **9-12**. Deprotection by hydrogenolysis of all benzyl groups gave phosphate esters **1-4**.

However, despite the few steps such a scheme allows the preparation of only a small amount of phosphate esters **1-4** and we were forced to find a more feasible scheme. Regioselective syntheses were designed by taking advantage of intermediates carrying an electron-withdrawing carbonyl group in meta/para position to the catechol system. Under this influence, the alkylation of the mono-anion of the catechol yielded the ether of the



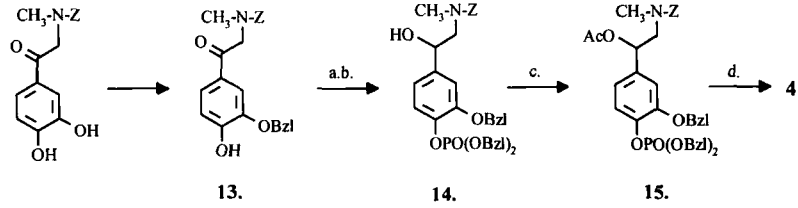
5. R=H, X=H, Y=Bzl
6. R=H, X=Bzl, Y=H
7. R=CH_3, X=H, Y=Bzl
8. R=CH_3, X=Bzl, Y=H

9. R=H, X=$PO(OBzl)_2$, Y=Bzl
10. R=H, X=Bzl, Y=$PO(OBzl)_2$
11. R=CH_3, X=$PO(OBzl)_2$, Y=Bzl
12. R=CH_3, X=Bzl, Y=$PO(OBzl)_2$

1. R,Y=H, X=PO_3H_2
2. R,X=H, Y=PO_3H_2
3. R=CH_3, Y=H, X=PO_3H_2
4. R=CH_3, X=H, Y=PO_3H_2

SCHEME 1

Z=benzyloxycarbonyl, Bzl=benzyl a. NaH/DMF, b. $CIPO(OBzl)_2$/toluene c. H_2,10%Pd/C

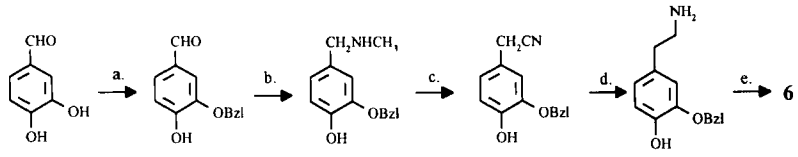


13. 14. 15.

SCHEME 2

a. 1) NaH/DMF, 2)$CIPO(OBzl)_2$/toluene b. $NaBH_4/CH_3OH$, c. $(CH_3CO)_2O$/pyridine
d. H_2, 10% Pd/C

more acidic para oxydryl group. On the other hand, the alkylation of the di-anion resulted in the preparation of the meta-ether[6]. Starting from this information we used as a precursor of epinine, the N-benzyloxycarbonyladrenalone (scheme 2) which was first mono-benzylated[4] in meta position and then phosphorylated to give the ketone **14**. The carbonyl group was reduced to alcohol and we tried the direct hydrogenolysis of oxydryl group but without success. However, its corresponding acetyl ester was easily reduced. So, the final hydrogenolysis removed, besides the acetyl group, all benzyl groups as well. However, a



16 17 18 19

SCHEME 3

a. NaH/DMF, BzlCl; b. CH_3NH_2/C_2H_5OH, $NaBH_4$; c. NaCN/DMSO; d. $BH_3.S(CH_3)_2$/THF; e. BzlOCOCl/toluene

similar strategy could not be followed for dopamine derivatives since noradrenalone is not commercially available or easily prepared and we elaborated a similar strategy starting from 3,4-dihydroxybenzaldehyde (Scheme 3). We started from the aldehide **16** which we obtained with a higher yield than previously reported[8]. Then the carbonyl group was converted to amine **17** and the amino group was easily substituted with a cyanide ion in DMSO; the mechanism of the reaction goes through a quinone-methide intermediate with shows a high reactivity[7]. Reduction of the nitrile group with borane-dimethylsulfur complex, followed by protection of amine group gave **6** with a good overall yield. Then, the synthesis went on as reported in scheme 1. It is worthwhile noting that, following these last two schemes every intermediates were obtained with high yield and moreover, when necessary easily cristallized.

In conclusion, this work reports the preparation in multigrams scale of intermediates which are regioselectively protected on either oxydryl group of the cathecol ring. This scheme could be useful for obtaining other regioselective derivatives of cathecolamines.

Experimental Section

Melting points were determined with a Buchi apparatus in open capillary

tubes and are uncorrected. Electron impact mass spectra (EIMS), chemical ionization mass spectra (CIMS), were recorded on Finnigan 4006.

^{1}H-NMR spectra were recorded on Varian EM 360L (60 MHz) spectrometer or Varian XL 300 (300 MHz). Chemical shifts are expressed in parts per million (ppm) on the δ scale relative to tetramethylsilane unless otherwise stated.

Microanalyses were performed on a Perkin Elmer 240 B elementar analyzer and are within 0.4% of theoretical values when indicated by symbols of the elements. Merck silica gel F_{254} (0.25 mm) plates were used for thin-layer chromatography and visualization was effected with UV light or iodine vapour. All reactions were conducted under nitrogen atmosphere. Organic extracts were dried over Na_2SO_4.

N-Methyldopamine 4-O-phosphate 4. A suspension of 50% NaH in mineral oil (1.44 g, 33 mmol) and **8**[4] (11.7 g, 30 mmol) in 20 ml of DMF was stirred for 30 minutes at 25°C. After the mixture was cooled to O°C, a solution of dibenzylphosphorochloridate[5] (10.65 g, 36 mmol) in toluene (106 ml) was added drop by drop. The solution was stirred at room temperature for 15 minutes and then diluted with cold water and extracted with ether. The ether solution was washed with water, dried and evaporated under reduced pressure to give **12** as a colorless oil which was used directly in the following reaction. A solution of **12** (19.5 g, 29 mmol) in 85% ethanol (330 ml) was hydrogenated in a Parr apparatus at a initial pressure of 50 psi in presence of 10% Pd supported on carbon (2 g). After theoretical absorption of hydrogen, the catalyst was filtered, washed with cold water and suspended in 2N NH_4OH (70 ml) at 50°C. The suspension was filtered, washed with water and concentrated at reduced pressure at

50°C to a volume of about 50 ml. The solution was filtered, acidified with HCl and after dilution of ethanol (240 ml) the compound was crystallized from the solution. Filtration of the solution provided 5.5 g (72%) of **4** as white solid; m.p. 175-178°C. ^{1}N-NMR (D_2O, 300 MHz) δ 2.75 (s, 3H, CH_3N), 300 (t, J=7.2 HZ, 2H, CH_2Ph), 3.34 (t, J=7.2 Hz, 2H, CH_2N) 6.88 (dd, J=8.4 Hz, J=2.1 Hz, 1H), 6.95 (d, J=2.1 Hz, 1H), 7.28 (d, J=7.2 HZ, 1H). Anal. ($C_9H_{14}NO_5P$) C, H, N.

N-Methyldopamine 3-O-phosphate 3. Compound **3** was prepared from **7**[4] according to the procedure previously described for **4**. Yield was 79%; m.p. 198-210°C. ^{1}N-NMR (D_2O, 300 MHz) δ 2.68 (s, 3H, CH_3N), 2.92 (T, J=6.8 Hz, 2H, CH_2Ar), 3.27 (t, J=6.8 Hz, 2H, CH_2N), 6.96 (s, 2H), 7.18 (s, 1H). Anal. ($C_9H_{14}NO_5P$) C,H,N.

Dopamine 4-O-phosphate 2. Compound **2** was prepared from **6**[4] according to the procedure previously described for **4**.Yield was 81%: m.p. 210-225°C (slow decomposition). ^{1}N-NMR (D_2O, 300 MHz) δ 2.94 (t, 3H, CH_2Ar), 3.26 (t, 3H, CH_2N), 6.82 (dd, J=8.2 HZ, J=2.1 Hz, 1H), 690 (d, J=2.1 Hz, 1H), 7.21 (d, J=8.2 Hz, 1H). Anal. ($C_8H_{12}NO_5P$) C,H,N.

Dopamine 3-O-phosphate 1. Compound **1** was prepared from **5**[4] according to the procedure previously described for **4**. Yield was 53% m.p. 210-220°C (slow decomposition). ^{1}N-NMR (D_2O, 300 MHz) δ 2.92 (t, 2H, CH_2Ar), 3.27 (t, 2H, CH_2N), 6.98 (s, 2H), 7.20 (s, 1H). Anal. ($C_8H_{12}NO_5P$) C,H,N.

2-[3-Benzyloxy)-4-(dibenzylphosphonyloxy)phenyl]-2-hydroxy-N-benzyloxy carbonyl-N-methyl-ethylamine 14. A suspension of 50% in

mineral oil (8.87 g, 0.20 mol) and **13**[4] (75 g, 0.185 mol) in DMF (500 ml) was stirred for 2 hours at 0-5°C. Then, a solution of dibenzylphosphorochloridate (65.82 g, 0.222 mol) in toluene (0.5 l) was added drop by drop. After the addition was complete, the reaction mixture was stirred for 30 min and then diluted with water. The toluene was separated and the aqueous phase was extracted again with toluene. The organic phase was dried and the solvent removed in vacuo. The resulting colorless oil (138 g, 123 g theoretical yield) was used directly in the next reaction without further purification. Sodium borohydride (10.4 g, 0.27 mol) was slowly added to a solution of the previous crude residue in methanol (0.75 l) at 15-20°C. The solution was stirred for 30 min, cooled at 0°C and acidified with 6N HCl. The mixture was concentrated in vacuo to 1/3 of volume, diluted with ether, washed three times with water, dried and evaporated in vacuo. Chromatography on silica gel (eluent CH_2Cl_2/ethyl acetate, 90/10) afforded **14** (98 g, 80%) as a clear viscous oil which cristallized after standing. ^{1}N-NMR ($CDCl_3$, 60 MHz) δ 2.85 (s, 3H, CH_3N), 3.42 (d, 2H, CH_2), 4.94 (t, 1H, CHOH), 3.03-3.32 (m, 8H, CH_2O), 6.30-7.46 (m, 23H). Anal. ($C_{38}H_{36}NO_8P$)C,H,N.

2-[3-Benzyloxy)-4-(dibenzylphosphonyloxy)]-2-acetyloxy-N-benzyloxy-carbonyl-N-methyl-ethylamine 15. A solution of **14** (98 g, 0.146 mol), acetic anhydride (98 ml, 1.03 mol) in pyridine (600 ml) was stirred for **4** hours. Then the mixture was evaporated at the reduced pressure (bath temperature 50°C). The residue was dissoved in ethyl acetate, washed with water, 5% HCl and water up to neutrality, dried and evaporated at reduced pressure to give **15** as a colorless oil (100 g, 96%) which was used directly in the next step without further purification. ^{1}N-NMR ($CDCl_3$, 60 MHz) δ

2.05 (s, 3H, CH_3CO), 2.92 (s, 3H, CH_3N), 3.63 (d, 2H, CH_2N), 4.94-5.13 (m, 8H, CH_2O), 5.82 (t, 1H, CHOH), 6.80-7.44 (m, 23H).

N-Methyldopamina 4-O-phosphate 4. Compound **15** (100 g, 0.14 mol) was dissolved in ethanol (3.2 l) and then diluted with water (0.8 ml). Palladium (10%) on carbon (25 g) was added and the mixture was submitted at hydrogenation at initial pressure of 40 atm. After 24 hours, the reaction was discarded and the suspension was filtered. The catalyst was suspended in a solution of water (350 ml) basified with 12 g of $NaHCO_3$ for one hour at room temperature, filtered and washed with water (250 ml). The filtered was acidified at pH=2 with HCl conc. and immediately diluted with ethanol (2.4 l). The colorless crystals were filtered, washed with ethanol and dried in vacuo to afford **4** (19 g, 54%).

4-Hydroxy-3-benzyloxybenzaldehyde 16. A solution of 3,4-dihydroxybenzhaldehyde (89 g, 2.1 mol) in DMF (1.4 l) was added to a suspension of NaH 60% in oil (16.8 g, 4.2 mol) in DMF (1.5 l) at room temperature. After 30 minutes at the same temperature, benzyl chloride (18.35 g, 0.145 mol) was dropped keeping the temperature at about O°C and the resulting mixture was stirred for 24 h at the same temperature. The mixture was concentrated at reduced pressure and the residue, diluted with water (1.3 l). The 3,4-dibenzyloxybenzaldehyde was extracted off with CH_2Cl_2 which was extracted with water (200 ml). The aqueous phase was diluted with ethanol (1.5 l) and then acidified with acetic acid (290 ml). After cooling the compound crystallized and was collected by filtration to obtain the desired product **16** (248 g, 52%) as colorless solid m.p. 112-114°C (lit.[8] 110-113°C). ^{1}N-NMR (DMSO-d_6, 300 MHz) δ 5.20 (s, 2H,

CH_2O), 6.98 (d, 1H), 7.30-7.2 (m, 7H), 9.75 (s, 1H, CHO). Anal. ($C_{14}H_{12}O_3$)C,H.

N-Methyl-3-benzyloxy-4-hydroxybenzylamina 17. A solution of methylamine 33% in ethanol (0.405 l, 3.24 mol) was added dropwise to a suspension of **16** (248 g, 1.08 mol) in methanol (1.25 mol) keeping the temperature below 30°C and stirred for one hour at room temperature. Then $NaBH_4$ (24.7 g, 0.65 mol) was added at portions cooling the mixture at 10°C. After another hour of stirring the solution was evaporated to half volume, diluted with water (0.5 l), evaporated the residue alcohol and finally diluted with other water (0.5 l). After cooling, the compound crystallized and was filtered to obtain the desired product **17** (244.5 g, 93%) m.p. 106-108°C. ^{1}N-NMR ($CDCl_3$, 60 MHz) δ 2.30 (s, 3H, CH_3N), 3.60 (S, 2H, CH_2N), 5.02 (s, 2H, CH_2O), 6.73-7.32 (m, 8H, aromatic hydrogen). Anal. ($C_{15}H_{17}NO_2$)C,H,N.

3-Benzyloxy-4-hydroxyphenylacetonitrile 18. A solution of **17** (255.6 g, 1.05 mol), NaCN (56.5 g, 1.15 mol) in dimethylsulphoxyde (1.3 l) was heated at 110°C for 5 hours. After cooling, the mixture was added dropwise to a solution of HCl conc. (173 ml, 1.73 mol) diluted with water (2.4 l). The product precipitated as oil which was slowly solidified after stirring. Filtration of the solid gave the desired compound **18** (199 g, 80%) which was used in the next step without further purification. An analytical sample was crystallized from ethyl acetate/petroleum ether m.p. 91°-93°C. ^{1}N-MR ($CDCl_3$, 60 MHz) δ 3.63 (s, 2H, CH_2N), 5.13 (S, 2H, CH_2O), 6.73-7.33 (M, 3H), 7.26-7.56 (M, 5H). Anal. ($C_{15}H_{13}NO_2$)C,H,N.

2-(3-benzyloxy-4-hydroxyphenyl)ethylamine hydrochloride 19. A solution of $BH_3.(CH_3)_2S$ (50.46 g, 0.66 mol) in tetrahydrofurane (0.4 l) was added dropwise to a solution of **18** (79.5 g, 0.332 mol) in tetrahydrofurane (1.2 l). The mixture was heated at reflux temperature for 2 hours and then cooled at room temperature. The excess of hydride was decomposed by carefully adding methanol (80 ml) and then a mixture of methanol (80 ml) and HCl conc. (27.7 mol), afterwards the solution was refluxed for 15 minutes. After evaporation to dryness under reduced pressure, the residue was redissolved in ethanol and evaporate again. The crude product was suspended in a saturated NaCl solution and by basification with ammonia the amine as free base (57 g) precipitated. After purification on a column of silica gel (eluent CH_2Cl_2 with increasing amount of CH_3OH up to 20%) the pure desired amine **19** was obtained (47.5 g, 58%). A sample was characterized as hydrochloride salt m.p. 154-156°C. ^{1}N-NMR ($CDCl_3$, 300 MHz) δ 2.53 (t, 2H, CH_2Ar), 2.72 (t, 2H, CH_2N), 5.08 (s, 2H, CH_2O), 6.58 (1H, dd), 6.72 (1H, d), 6.83 (1H, d), 7.28-7.49 (5H, m). Anal. ($C_{15}H_{17}NO_2$)C,H,N.

N-benzyloxycarbonyl-2-(3-benzyloxy-4-hydroxyphenyl)ethylamine 6. Compound **6** was prepared from **19** according to the procedure described for epinine in ref. 4. Yield was 81% m.p. 103-104°C (from isopropyl alcohol). ^{1}N-NMR ($CDCl_3$, 300 MHz) δ 2.74 (t, 2H, CH_2Ar), 3.42 (quartet, 2H, CH_2N), 5.05 (s, 2H), 5.10 (s, 2H), 6.68 (dd, 1H), 6.76 (d, 1H), 6.88 (1H, d), 7.29-7.42 (5H, m). Anal. ($C_{23}H_{23}NO_4$) C, H, N.

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