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SHORT PAPER

PRODUCTS FROM FURAN VII: A SYNTHETIC ROUTE TO C-SUBSTITUTED AMINODEOXYPOLYOLS AND THEIR *cis*-Pt-COMPLEXES

GEORGIADIS P. MINAS, COULADOUROS A. ELIAS

Chemistry Laboratory, Agricultural University of Athens, Iera Odos 75, Athens 118 55, Greece

CHONDROS P.COSTAS[1]

Araetaion University Hospital, 76 V.Sofias Ave., Athens 611, Greece

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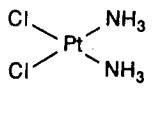
INTRODUCTION

Cisplatin, 1, (cis-diaminedichloroplatinum-II), is used today as anticanser agent[2]. The fact that it has no selectivity against various tissues[3] and the dose-related, cummulative and only partialy reversible renal toxicity[4], are the more serious disadvantageous of 1.

There is evidence that the presence of a hydrophylic[5] sugar-moiety on the ligand, may degrease the toxicity of the drug. On the other hand, the importance of the receptor binding ability (RBA), of several ligants has also been reported[3,6].



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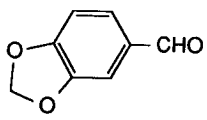
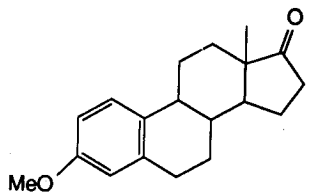


2a



2b

Having the above in mind, a catechol derivative, as well as, a steroidal one (namely, 3,4-methylendioxy-benzaldehyde, **2a**, and 3-methoxy-estrone, **2b**), were chosen in order to demonstrate our methodology of producing 1,2 diamines and the related cis-Pt complexes, having a combination concerning hydrophilisity and possible RBA properties.

The synthetic strategy was the following :

1) Introduction of the selected substituent into C-5 of an 1-O-acetyl-pentopyranulose.

2) Transformation of the C-substituted pentopyranulose to an open-chained 1,2-diaminodeoxypentitol.

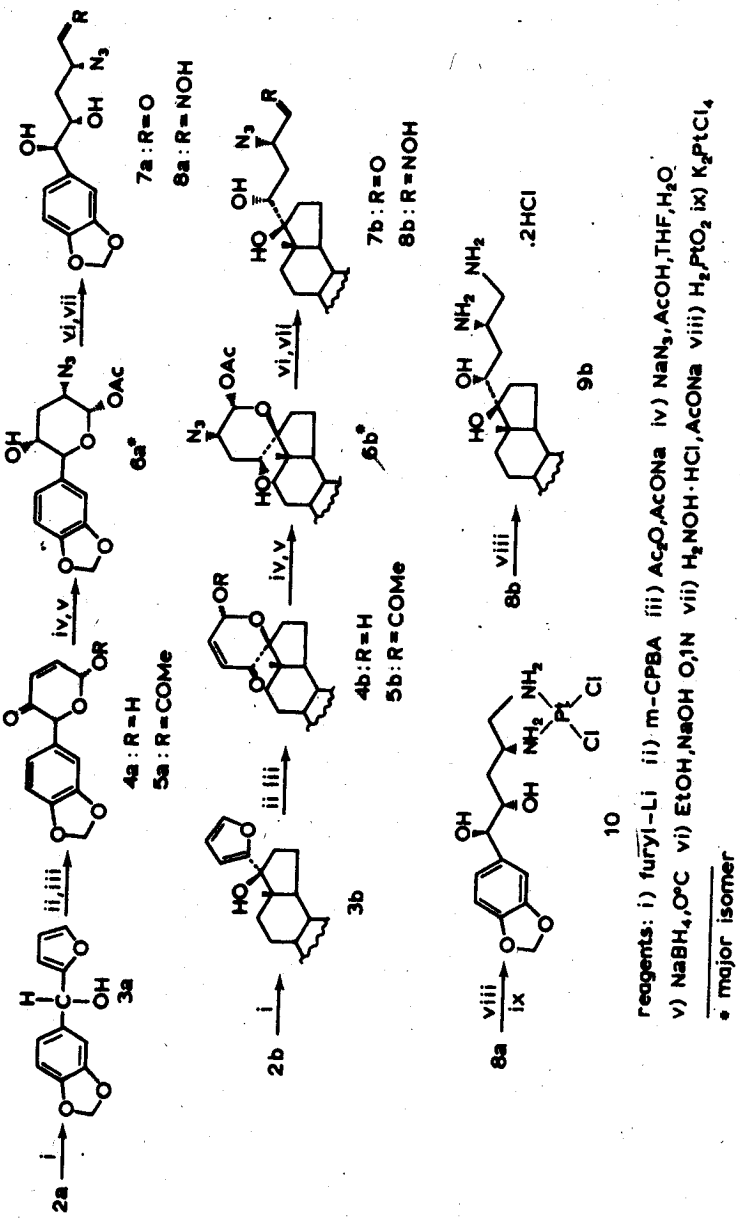
3) Complexation of the latter compound with K_2PtCl_4.

CHEMISTRY

Introduction of a substituent to a sugar moiety by carbon-carbon bond formation, may be considered as a difficult task. That is why we have decided to construct the sugar sceleton upon a carbonyl group by using the well known rearengement of 2-furfuryl alcohols to 2H-pyran-3(6H)-ones[7]. Accordingly, aldehyde **2a** and ketone **2b** were treated with 2-furyl-lithium yielding the corresponding furfuryl alcohols **3a** and **3b** which by subsequent oxidation with m-CPBA rearenged to the anomeric mixture of 6-hydroxy-2-(3,4-methylenedioxyphenyl)-2H-pyran-3(6H)-one (yield 65%, two steps, mp 119-20°C), **4a** and 17β,24-epoxy-24-hydroxy-19,21-dinorchola-1,3,5(10),22-tetraene-20-one[8], (yield 62%, two steps, mp 191-2°C), **4b**, respectively.

Acetylation of alcohols **4a** and **4b** in benzene at room temperature for 4h (acetic anhydride, sodium acetate), gave as major product the α-anomer of **5a**, which was purified by column chromatography using hexane-AcOEt 7:3 as the eluant (yield 76%, mp 99-100°C, ^1H NMR: anomeric proton at 6.4 ppm, $J_{vicinal}$=3.5, $J_{allylic}$=0) while the α-anomer of hexenulose **5b** was purified by crystalization from acetone (yield 85%, mp 169-70°C, ^1H NMR: anomeric proton at 6.6 ppm, $J_{vicinal}$=3.2, $J_{allylic}$=0) .

Scheme I



reagents: i) furyl-Li ii) m-CPBA iii) Ac_2O,AcONa iv) NaN_3,AcOH,THF,H_2O
v) $NaBH_4$,0°C vi) EtOH,NaOH 0,1N vii) $H_2NOH \cdot HCl$,AcONa viii) H_2PtO_2 ix) K_2PtCl_4

* major isomer

Addition of the azide anion upon **5a** and **5b** under conditions of stereoelectronic control[9], (three-fold excess of sodium azide, in a mixture of THF:water:acetic acid 3:1:1 at room temperature for 6h) and *in situ* reduction[10] of the carbonyl group with $NaBH_4$ at 0°C, yielded predominately 1-O-acetyl-2-amino-2,3-dideoxy-5-(3,4-methylenedioxyphenyl)-α-DL-*ribo*-pentopyranose, **6a**, which was purified by column chromatography with hexane:AcOEt 1:1 as the eluant and crystalized from methanol-water (yield 70%, mp 127-9°C,^1H NMR: H-1=5.6ppm, $J_{1,2}$=3.2Hz ; H-5= 5.3ppm, $J_{5,4}$= 7.8Hz) and 24-acetyloxy-22-azido-17β,24-epoxy-20-hydroxy-19,21-dinorchola-1,3,5(10)-trien, **6b**, which was purified after three recrystallizations from AcOEt:hexane (yield 63%, mp 198°C, dec; ^1H NMR: anomeric proton at 5.9 ppm, J=2.9Hz), respactively. The ^1H NMR assignment of the above products were in agreement with analogous compounds[11,12] confirming the equatorial orientation of all but the anomeric substituents.

Treatment of the above acetates (**6a, 6b**) with a dilute methanolic solution of NaOH (MeOH/NaOH 0.1N 4:1) afforted the pentital **7a** (from **6a**) and tetrital **7b** (from **6b**), which were identified spectroscopically[13]. The latter aldehydes, **6a** and **6b**, were coverted *in situ* to the oximes **8a** (colorless oil, yield 81%) and **8b** (crystals from AcOEt:hexane, mp 305°C, dec; yield 83%), by stirring the reaction mixture for 1h at 40°C with an excess of $H_2NOH.HCl$, while the pH was maintained at 4.5 with the addition of sodium acetate. Catalytic hydrogenation of **8a** and **8b** at 45 PSI with PtO_2, using a 2N HCl solution in MeOH/EtOH as the reaction solvent, yielded the hydrochloric salts of the coresponting 1,2-diamines: **9a** : 1,2-diamino-1,2,3-trideoxy-5-(3,4-methylenedioxyphenyl)-5R,S-ribitole (yield 85%, mp 112-4°C) and **9b** : 1,2-diamino-1,2,3-trideoxy-4-(17β-hydroxy-19,21-dinorcholan-1,3,5(10)-trienyl)-erythritol, (yield 71%, mp 329°C, dec). The later salts were both crystalized from ethanol-ether.

Finally the cis-Pt complex of diamine **9a** was prepared by stirring **9a** with a two-fold excess of K_2PtCl_4. in water, at room temperature. The rate of complexation was followed by monitoring the pH of the reaction , which was maintained at 6.5 by addition of 0.1N NaOH solution[14]. The

precipitate was recrystalized from DMF/ether. The characteristic doublet at 315cm^{-1} of the IR spectra of compound **10** confirmed the cis orientation of the ligants.

SUMMARY

The synthesis of C-substituted 1,2-diaminopolyols via 2H-pyran-3(6H)-ones, is presented. Estrone and catechol were chosen as the C-ligants, in order to produce cis-Pt complexes, having a combination concerning hydrophilicity and possible RBA properties.

The Griniard coupling of the selected ligand with furyl-Li and the subsequent oxidative rearengement of the furan to a pyran ring are the key steps of this general synthetic route to C-substituted aminodeoxypolyols.

Key Words : furfuryl alcohol, 2H-pyran-3(6H)-one, 2,3,6-trideoxy-2-amino-gluco-hexopyranose, 1,2-aminodeoypolyol, cis-Pt complexes, estrone, catechol, anti-cancer compounds.

ΠΕΡΙΛΗΨΗ

ΠΡΟΙΟΝΤΑ ΑΠΟ ΦΟΥΡΑΝΙΑ VII. ΣΥΝΘΕΤΙΚΗ ΠΟΡΕΙΑ ΠΡΟΣ ω-ΥΠΟΚΑΤΕΣΤΗΜΕΝΕΣ ΑΜΙΝΟ-ΔΕΟΧΥ-ΠΟΛΥΟΛΕΣ ΚΑΙ ΣΥΜΠΛΟΚΟΠΟΙΗΣΗ ΑΥΤΩΝ ΜΕ ΛΕΥΚΟΧΡΥΣΟ.

Στην παρούσα εργασία παρουσιάζεται μία πορεία σύνθεσις συμπλόκων λευκοχρύσου με υποκαταστάτες ομάδες με πιθανή ικανότητα σύνδεσις με ορμονικούς υποδοχείς (RBA). Στις ομάδες αυτές έχει προστεθεί η ανοικτή αλυσίδα ενός υδατάνθρακα με στόχο την αύξηση της υδροφιλικότητας του τελικού συμπλόκου. Αμφότερες οι βελτιώσεις, στοχεύουν στην ελάττωση της θεραπευτικής δόσης και της τοξικότητας που παρουσιάζει το αντίστοιχο αντικαρκινικό φάρμακο (Cisplatin).

Η συνθετική πορεία είναι η εξής :

1) Εισαγωγή του πυρανικού δακτυλίου στην καρβονυλομάδα του επιλεγμένου υποκαταστάτη.

2) Προσθήκη 1,4 HN_3 στην παραπάνω ένωση και μετατροπή της στην οξίμη του ανοικτού αναλόγου (πολυόλη).

3) Αναγωγή των N-ομάδων προς αμινομάδες και συμπλοκο-ποίηση αυτών με λευκόχρυσο.

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8. a) The assignment of 17-OH was made according to Lefebvre Y.; *Tetraheron Let.;* **2**, 133, (1972) b) All new compounds had consistent analytical and spectroscopical data.

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