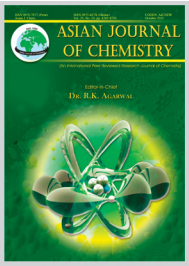
Asian Journal of Chemistry; Vol. 24, No. 5 (2012), 2013-2016

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in



Synthesis of a Progesterone-Carbachol Derivative: Relationship with Some Parameters Involved in its Geometry and Electronic Structure

LAURO FIGUEROA-VALVERDE[1,*], FRANCISCO DÍAZ-CEDILLO[2], MARÍA LÓPEZ-RAMOS[1], ELODIA GARCÍA-CERVERA[1] and EDUARDO POOL-GOMEZ[1]

[1]Laboratorio de Farmacoquímica, Facultad de Ciencias Químico-Biológicas, Universidad Autónoma de Campeche, Av. Agustín Melgar, Col Buenavista C.P. 24039 Campeche Cam., México
[2]Escuela Nacional de Ciencias Biológicas del Instituto Politécnico Nacional. Prol. Carpio y Plan de Ayala s/n Col. Santo Tomas, C.P. 11340, México, D.F.

*Corresponding author: Fax: +981 8119800 Ext. 73002; Tel: +981 8119800 Ext. 73006; E-mail: lauro_1999@yahoo.com

(*Received*: 6 April 2011; *Accepted*: 9 December 2011) AJC-10815

In this study, a progesterone-carbachol (**3**) derivative was synthetized and its relationship with some physicochemical parameters involved in its geometry and electronic structure wasevaluated. The results showed an increase in the HOMO/LUMO, logP and π values of compound **3** with respect to progesterone. All this datasuggest that changes in the chemical structure of progesterone to form progesterone-carbacholexert variations in HOMO/LUMO, logP and π values.

Key Words: Progesterone, Carbachol, Physicochemical parameters, log P.

INTRODUCTION

In previous years, some amino steroid derivatives were synthesized with a wide spectrum of biological actions, as antibacterial[1,2], antimalarial[3] and antiviral[4] drugs. For example, there are reports[4,5], which show the synthesis of 17β-[*N*-methyl-*N*(aminoethyl)amino-5a-androsterone by reduction of oxime-androsterone derivative using $LiAlH_5$. Additionally, other reports[6] showed the synthesis of a series of 7-amino-sterol squalamine analogues through a stereoselective titanium reductive amination reaction. Walker and coworkers[7] reported the synthesis of several amino-steroids derivatives by the reaction between methyl ester of cholic acid with polyamines (spermine, pentamine or hexamine) using *N*-hydroxy-succinamide. Other studies made by Acs *et al.*[8] showed the synthesis of 11-carboxamido-androstan-4,9(11)-diene using palladium as catalyst. In addition, another reports indicate the synthesis of 7a-[4´-(aminophenyl) thio]pregna-4-ene-3,20-dione by the reaction between pregna-4,6-diene-3,20-dione with 4-aminothiophe-nol[9]. In addition, there are some studies which show the synthesis of a quaternary nitrogen-steroid using 1-ethyl-3(3-dimethylaminopropyl)-carbodiimide as catalyst[10]. Other reports show the synthesis of 17α-amino-3α, 16α-dihydroxy-5β-pregnane-11,20-dione was prepared from 3α-acetoxy-5β-pregnane-11,20-dione[11]. Recently, an amino-steroid derivative was synthetized using 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide[12]. All these experimental data show several protocols for synthesis of amino steroid-derivatives, nevertheless, the use of some reagents requires of special conditions. Therefore in this work our initial design included a facile synthesis of nitrogen-steroid derivative in presence of boric acid. It is important to mention that this steroid derivative contain in the A-ring of steroid nucleus an arm with quaternary nitrogen.

EXPERIMENTAL

Progesterone and the other compounds evaluated in this study were purchased from Sigma-Aldrich Co., Ltd. The melting points for the different compounds were determined on an Electrothermal (900 model). Infrared spectra were recorded using KBr pellets on a Perkin Elmer Lambda 40 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-300/5 FT NMR spectrometer at 300 and 75.4 MHz in DMSO-d_6 using TMS as internal standard. EIMS spectra were obtained with a Finnigan Trace GC Polaris Q. spectrometer. Elementary analysis data were acquired from a Perkin Elmer Ser. II CHNS/0 2400 elemental analyzer.

[2-17-Acetyl-10-13-dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro- cyclo-penta[a]phenanthren-3-yl-denecarbamoyloxy)-ethyl]-trimethyl-ammonium chloride: A solution of progesterone (100 mg, 0.32 mmol), carbachol (117 mg, 0.64 mmol), boric acid (40 mg, 0.65 mmol) in 10 mL

of ethanol:water (1:2) was stirring for 24 h to room temperature. The reaction mixture was evaporated to a smaller volume. The reaction mixture was diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol:water (4:1) yielding 75 % of product, m.p. 98-100 ºC; IR (ν_{max}, cm^{-1}):1712, 1670; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 0.67 (s, 3H), 0.93-1.02 (m, 2H), 1.04 (s, 3H), 1.11-1.32 (m, 2H), 1.33-1.51 (m, 4H), 1.52-1.63 (m, 2H), 1.65-1.90 (m, 3H), 2.05-207 (m, 2H), 2.12 (s, 3H), 2.19-2.58 (m, 5H), 3.13 (s, 9H), 3.70 (t, 2H, J = 6 Hz), 4.42 (t, 2H, J = 6 Hz), 6.28 (m, 1H). ^{13}C NMR (74.5 MHz, DMSO-d_6) δ_C: 13.21 (C-18), 17.76 (C-24), 20.78 (C-5), 23.44 (C-15), 23.75 (C-9), 27.19 (C-8), 29.92 (C-25), 31.31 (C-11), 31.62 (C-16), 32.12 (C-10), 34.10 (C-3), 35.26 (C-17), 38.07 (C-6), 43.83 (C-1), 51.97 (C-4), 54.90 (C-31, C-32), 56.02 (C-2), 59.66 (C-27), 63.41 (C-7), 64.17 (C-28), 118.99 (C-13), 150.17 (C-22), 158.48 (C-12), 159.71 (C-14), 206.67 (C-19) ppm. MS (70 ev): m/z 443.50 [M+ Cl^-]; Anal. calcd. For $C_{27}H_{43}ClN_2O_3$: C, 67.69; H, 9.05; Cl, 7.40; N, 5.85; 0, 10.02. Found: C, 67.63; H, 9.08.

Evaluation of physico-chemical parameters: To estimate the logarithmic octanol-water partition coefficient (log P) and π of progesterone (**1**) and progesterone-carbachol derivative (**3**), the ACDlab program was used[13-19]. The log K_{ow} method (atom/fragment contribution), introduced by Mannhold and Waterbeemd[20], available as the KOWWIN software was used. Ina addition, the hyperchem 6.0 software to evaluate the electronic parameters of compounds studied.

RESULTS AND DISCUSSION

In this study, a straightforward route is reported for the synthesis of progesterone-carbachol derivative(**3**). This stage was achieved by reacting progesterone(**1**) with carbachol using boric acid as catalyst to form a progesterone derivative (Fig. 1). It is important to mention that several amino-steroid derivatives are available in the literature[21-24]. Nevertheless, despite their wide scope, these procedures suffer from several drawbacks. Some of the reagents are of limited stability and preparation can be dangerous. Analyzing these data and the report of Chaudhuri *et al.*[25] show that the boric acid efficiently catalyzes the addition of aliphatic amines to α,β-unsaturated compounds to produce β-amino compounds. In this work, boric acid was used as catalyst in the reaction between progesterone and carbachol to form the compound **3**. The results indicate that ^{1}H NMR spectrum of **3** showed several signals at 0.67, 1.04 ppm corresponding to methyls presents in the steroid nucleus; at 1.11-2.07, 2.19-2.58 and 6.10 ppm for methylenes involved in the steroid nucleus; at 2.12 ppm for methyl bound to carbonyl group. Finally, other signals at 3.10 ppm for methyl groups bound to quaternary amine; at 3.70 and 4.42 ppm for methylenes involved in arm bound to steroid nucleus were found. The ^{13}C NMR spectra display chemical shifts at 13.18 and 17.70 ppm for the carbons of methyls presents in the steroid nucleus of **3**. Another chemical shifts at 20.78-27.19, 31.31-51.97, 56.02, 63.41, 118.70 and 158.70-159.68 ppm for carbons of methylenes involved in the steroid nucleus were exhibited. Additionally, several signals at 29.92 ppm for methyl bound to carbonyl group; at 54.90 ppm for methyl groups bound to quaternary amine; at 59.60 and 64.16 ppm for methylenes involved in the arm bound to steroid nucleus. Finally, two signals at 150.17 ppm for carbonyl bound to nitrogen atom and at 206.60 ppm for ketone group were exhibited. Additionally, the presence of the compound **2** was further confirmed from mass spectrum which showed a molecular ion at m/z 443.50.

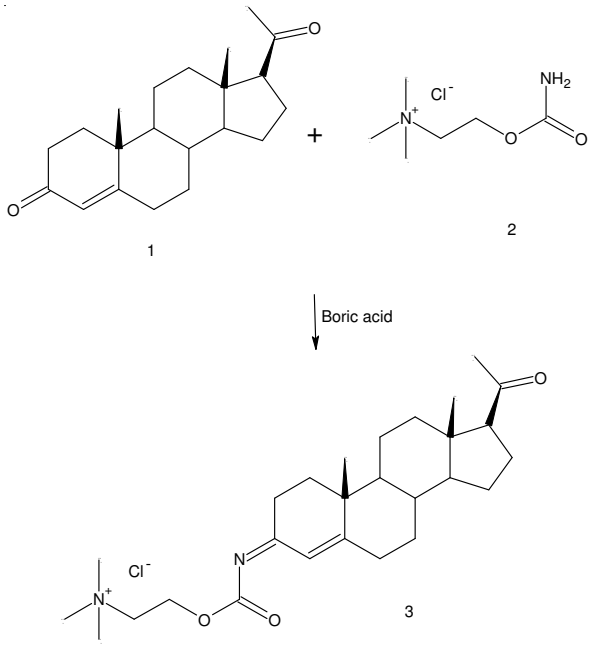


Fig. 1. Synthesis of progesterone-carbachol derivative (**3**). Reaction between progesterone (**1**) and carbachol (**2**) using boric acid as catalyst

Evaluation of physicochemical parameters: There are reports[26,27], which indicate that biological activity of steroid derivatives is a consequence of physicochemical parameters involved in its geometrical (*i.e*. configuration, conformation) and electronic structure of steroids (*i.e*. energy, electron distribution, charge and reactivity). Nevertheless, there are little data about the electronic structure of progesterone derivatives. Therefore, in this study some physicochemical parameters involved in the chemical structure of **3** were evaluated.

Electronic parameters: Some methods have been developed within the mathematical framework of the molecular orbital theory to evaluate the electronic properties of several compounds. For example, there are studies, which showed the evaluation of the frontier molecular orbitals (HOMO-LUMO gap) of some steroids using the MINDO and ZINDO models[28,29]. In this study, HOMO-LUMO gap of compound **3** were evaluated using a theoretical method (ZINDO/S, hyperchem 6.0). The results showed two energy levels for HOMO (-302.70 eV) and for LUMO (4.76 eV) in the compound **3**. These frontier orbital molecular values were compared with the data obtained for the compounds **1**, in order to evaluate if changes in their structure chemical affect the energy levels. The results showed that HOMO/LUMO were low for **3** in comparison with **1** (Table-1). This phenomenon could be conditioned by π orbital which are localized in the arm bound to A-ring (C=N) and carbonyl group (C=O) of

TABLE-1
PHYSICO-CHEMICAL PARAMETERS (HOMO AND LUMO), ΔH_f, RMS_g (RM GRADIENT) AND DIPOLAR MOMENT (μ) OF COMPOUNDS **1** AND **3**

Compound	HOMO (eV)	LUMO (eV)	$\Delta H_f RMS_g$ (Kcal/mol)	μ (Kcal/Å mol)	(Debyes)
1	-567.8763	-0.2464529	-157750.6	2018	0.8596
3	-615.4523	-0.477154	-172552.3	1874	2.3900

compound **3** in comparison with **1**. These data suggest that functional groups involved in the arm bound to A-ring could induce changes in the organic superconductivity of compound **3** as it happens in other steroid derivatives, which show that molecular orbitals (C-2p) are aligned along of the molecular axes[30]; this phenomenon could bring like consequence variations in the electronic transmittance (Figs. 2 and 3).

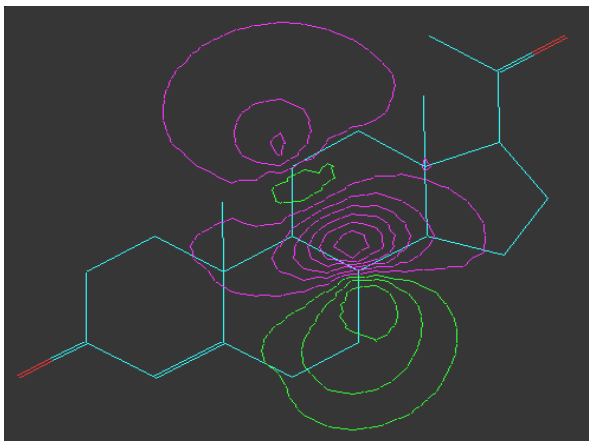


Fig. 2. LUMO of progesterone using Hyperchem 6.0 software

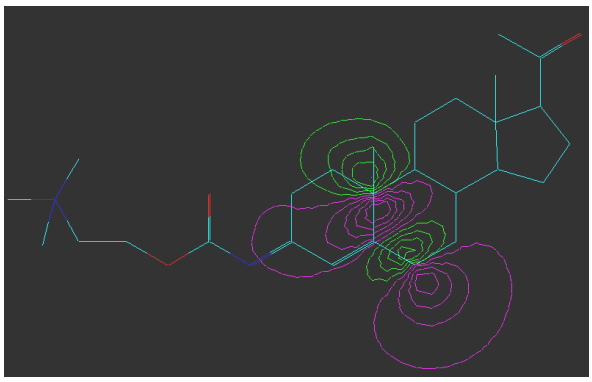


Fig. 3. LUMO of progesterone-carbachol derivative using Hyperchem 6.0 software.

On the other hand, it is important to mention that the relation HOMO/LUMO gap has been relationship with the changes in the dipole moment on other compounds[31]. Therefore, in this study the dipole moment of **3** was evaluated and compared with the values of **1**. The results showed that dipole moment was high in **3** in comparison with **1** (Table-1). This data indicate that increase in the length of chain induce greater dipole moment.

Hydrophobicity parameters: The most common properties[32] that are correlated to biological activity are electronics (π) in and lipophilicity (log P). log P describes the logarithmic octanol-water partition coefficient at room temperature. Therefore, it represents the lipophilic effects of a molecule that includes the sum of the lipophilic contributions of the parent molecule and its substituent[33]. The difference between the substituted and unsubstituted log P values is conditioned by the π value for a particular substituent. Hammett showed that π values measure the free energy change caused by a particular substituent to relate to biological activity[34]. In this study it was interesting to evaluate these physicochemical descriptors (log P and π) involved in the chemical structure of compound **3** using the method reported by Mannhold and Waterbeemd[20]. It is important to mention that fragments **3** involved in the chemical structure of **3** were also evaluated with the purpose to know if the compound **1** induce changes in the lipophilicity degree of **3**. The results showed an increase in log P and π values in the **3** compound with respect to **1**. This phenomenon is conditioned mainly by the contribution of all substituent atoms involved in the chemical structure of the different compounds, as is showed in Tables 2 and 3. These results showed that aliphatic carbons ($-CH_3$, $-CH_2$ and -C) in compound **3** contribute to the high lipophilicity in comparison with **1**.

TABLE-2
PHYSICOCHEMICAL PARAMETERS log K_{ow} AND π OF DIHYDROTESTOSTERONE-VITAMIN B1 CONJUGATE (3)

Compound	log K_{ow} fragment	Contributions
1	$-CH_3$ [aliphatic carbon]	1.6419
	$-CH_2-$ [aliphatic carbon]	3.9288
	-CH [aliphatic carbon]	1.4456
	=CH- or =C< [olefinc carbon]	0.7672
	-C(=O) [carbonyl, aliphatic attach]	-1.5586
	-tert Carbon [3 or more carbon attach]	0.5352
	-C(=O)- [carbonyl, olefinic attach]	-1.2700
	Fused aliphatic ring unit correction	-2.0526
	Equation constant	0.2290
	log K_{ow}	3.6665
	π	

TABLE-3
PHYSICOCHEMICAL PARAMETERS log K_{ow} AND π OF THE DANAZOL-VITAMIN B1 CONJUGATE (5)

Compound	log K_{ow} Fragment	Contributions
2	CH_3 [aliphatic carbon]	3.3838
	$-CH_2-$ [aliphatic carbon]	4.9110
	-CH [aliphatic carbon]	1.4456
	-C [aliphatic carbon - No H, not tert]	0.9723
	=CH- or =C< [olefinc carbon]	0.7672
	-C(=O)- [carbonyl, aliphatic attach]	-1.5586
	-C(=O)O [ester, aliphatic attach]	-0.9505
	-tert Carbon [3 or more carbon attach]	0.5352
	-N=C [aliphatic attach]	-0.0010
	>N< [+5 valence; single bonds; H attach]	-4.6000
	Fused aliphatic ring unit correction	-2.0526
	Reaction: nitrogen[+5] / ester	0.7000
	Equation constant	0.2290
	log K_{ow}	3.6814
	π	0.0164

Conclusion

All this data suggest that changes in the chemical structure of progesterone to form progesterone-carbachol exert variations in HOMO/LUMO, log P and π values.

REFERENCES

1. F. Smith, D. Shay and N. Doorenbos, *J. Bacteriol.*, **85**, 1295 (1963).
2. B. Ding, U. Taotofa, T. Orsak, M. Chadwell and P. Savage, *Org. Lett.*, **6**, 3433 (2004).
3. U. Sharma, K. Srivastava, S. Puri and C. Singh, *Med. Chem. Res.*, **17**, 326 (2008).
4. J. Giner and J. Faraldos, *J. Org. Chem.*, **67**, 2717 (2002).
5. M. Merlani, L. Amiranashvili, K. Mulkidzhanyan and E. Kemertelidze, *Chem. Nat. Comp.*, **42**, 313 (2006).
6. C. Loncle, C. Salmi, Y. Letourneux and J. Brunel, *Tetrahedron,* **63**, 12968 (2007).
7. S. Walker, M. Sofia, R. Kakarla, N. Kogan, L. Wierichs and C. Longley, *Proc. Nat. Acad. Sci. USA.*, **93**, 1585 (1996).
8. P. Acs, B. Jakab, A. Takas and L. Kollar, *Steroids*, **72**, 627 (2007).
9. F. Leonessa, J. Kim, A. Ghiorghis, R. Kulawiec, C. Hammer, A. Talebian and R. Clarke, *J. Med. Chem.*, **45**, 390 (2002).
10. L. Figueroa-Valverde, F. Díaz-cedillo, M. López Ramos, E. García-Cervera, *Int. J. Chem. Tech. Res.*, **2**, 1553 (2010).
11. F. Winternitz and R. Engel, *Steroids,* **6**, 805 (1965).
12. L. Figueroa-Valverde, F. Díaz-cedillo, A. Camacho-Luis, M. López Ramos and E. García-Cervera, *Int. J. Chem. Tech. Res.*, **2**, 557 (2010).
13. I.V. Tetko and V.Y. Tanchuk., *J. Chem. Inf. Comput. Sci.*, **42**, 1136 (2002).
14. I.V. Tetko, V.Y. Tanchuk and A.E. Villa, *J. Chem. Inf. Comput. Sci.*, **41**, 1407 (2001).
15. I.V. Tetko, V.Y. Tanchuk, T.N. Kasheva and A.E. Villa, *J. Chem. Inf. Comput. Sci.*, **41**, 1488 (2001).
16. I.V. Tetko and G.I. Poda, *J. Med. Chem.*, **47**, 5601 (2004).
17. I.V. Tetko and P. Bruneau, *J. Pharm. Sci.*, **93**, 3103 (2004).
18. V.N. Viswanadhan, A.K. Ghose, G.R. Revankar and R.K. Robins, *J. Chem. Inf. Comput. Sci.*, **29**, 163 (1989).
19. I. Moriguchi, S. Hirono, Q. Liu, I. Nakagome and Y. Matsushita, *Chem. Pharm. Bull.*, **40**, 127 (1992).
20. R. Mannhold and H. Waterbeend, *J. Comput. Aided. Mol. Design.*, **15**, 337 (2001).
21. T. Curran, G. Flynn, D. Rudisill and P. Weintraub, *Tetrahedron Lett.*, **36**, 4761 (1995).
22. J. Lovett, M. Darby and R. Counsell, *J. Med. Chem.*, **27**, 734 (1984).
23. J. Braughler, J. Pregenzer, R. Chase, L. Duncan, E. Jacobsen and J. McCall, *J. Biol. Chem.*, **262**, 10438.
24. D. Morrow, M. Butler and E. Huang, *J. Org. Chem.*, **30**, 579 (1965).
25. M.K. Chaudhuri, S. Hussain, M.L. Kantam and B. Neelima, *Tetrahedron Lett.*, **46**, 8329 (2005).
26. W. Tong, D. Lowis, R. Perkins, Y. Chen, W. Welsh, D. Goddette, T. Heritage and D. Sheehan, *J. Chem. Inf. Comput. Sci.*, **38**, 669 (1988).
27. L. Figueroa-Valverde, F. Díaz-Cedillo, M. Lopez-Ramos and E. Garcia-Cevera, *Monatsh.Chem.*,**141**, 373 (2010).
28. H.K. Srivastava, F.A. Pasha and P.P. Singh, *Int. J. Quant. Chem.*, **103**, 237 (2005).
29. N. Ferro, J.E. Tacoronte, T. Reinard, P. Bultinck and L.A. Montero, *J. Mol. Struct*., **758**, 263 (2006).
30. T. Cvitas, B. Kovac, L. Pasa-Tolic, B. Rusic and L. Klasinc, *Pure Appl. Chem.*, **61**, 2139 (1989).
31. A.R. Katritzky, M. Karelson and V.S. Lobanov, *Chem. Rev.*, **96**, 1027 (1996).
32. A.J. Leo, P.Y.C. Jow, C. Silipo and C. Hansch, *J. Med. Chem.*, **18**, 865 (1975).
33. A.J. Leo and D. Hoekman, *Perspect. Drug Discov. Design.*, **18**, 19 (2000).
34. C. Hansch, A. Leo and R.W. Taft, *Chem. Rev.*, **91**, 165 (1991).