SYNTHESIS OF METHYL ESTER OF PHENYLALANINE - GOSSYPOL DERIVATIVE

Nguyễn Kim Phi Phụng,
Nguyễn Ngọc Sương, Phạm Đình Hùng.

Department of Chemistry

College of Natural Sciences

(Received Dec.30,1997)

Abstract: Gossypol, a polyphenolic aldehyde from cottonseed oil, has attracted much attention as a potential male antifertility drug. Selective toxicity of gossypol againts various cancer cell lines and experimental tumors has been demonstrated, suggesting its possible therapeutic use. More recently, a numbers of researchs indicated that the derivatives of the aldehydic functions of(...) gossypol with twenty monoamines and polyamines were of biological and industrial interest. A series of peri-acylated gossypylic nitriles had also antiviral activities. The present report presents the synthesys of analogue of gossypol such as methyl ester of phenynlalanine-gossypol derivative, an attempt to find more effective and/or less toxic entities.

TỔNG HỢP DẪN XUẤT ESTER METIL PHENILALANIN CỦA GOSSYPOL

(Nhận được ngày 30/12/1997)

Tóm tắt: Gossypol, poliphenol-aldehyd, tách chiết từ dầu hạt cây bông, đã từ lâu gây chú ý do tính vô sinh. Độc tính chọn lọc của gossypol đối với nhiều loại tế bào ung thư và khối u đã được thử nghiệm. Gần đây, nhiều nghiên cứu đã cho biết là các dẫn xuất của nhóm aldehyd của (....) gossypol với 20 monoamin và poliamin đều có hoạt tính sinh học. Vài hợp chất nitril của acetat gossypol có tính kháng khuẩn.

Chúng tôi thử nghiên cứu tổng hợp dẫn xuất mới của gossypol, ester metyl của phenilalanin-gossypol, hầu tìm ra một hợp chất ít độc hơn và có thể hữu hiệu hơn về hoạt tính sinh học.

1 Introduction

Gossypol, [1,1',6,6',7,7'-hexahydroxy-5,5' -diisopropyl-3,3' -dimethyl-(2,2' -binaphtalene)-8,8' - dicarboxyaldehyde] is a polyphenol aldehyde found in the seeds of Gossypium species (Malvaceae). It is a chiral molecule because of steric hindrance to rotation about the internaphthyl bond and so it is obtained in the form of optically inactive, racemic (±) material.

This natural compound has been studied for its antifertility effect on males and females as well [3,4,10]. Gossypol exhibits a number of interesting types of biological

activity, including antitumor, anti-amoebic and anti-HIV effects [9]. Gossypol could be potentially very useful for the treatment of human breast cancer, especially for patients who have developed multidrug resistance [1,6,8,12].

INCHULL KIM and al.[7] proved that derivatives od gossypol with aldehyde groups substituted with hydrophobic functionalities showed equivalent or more inhibitory effects on lactase dehydrogenase- X than gossypol, whereas some other derivatives of gossypol with aldehyde groups substituted with hydrophilic functional groups lost the ability of that inhibition. RADLOFF and al. [10] considered that toxicity of gossypol may be a result of a schiff-base type of reaction between the aldehyde group of gossypol and cellular protein, they found that the modification of the aldehyde group of gossypol lowered the toxicity of the drug but did not abolish its antiviral properties.

Currently, a number of research groups are engaged in the synthesis of analogues of gossypol in an attempt to find more effective and/ or less toxic entities.

A variety of new anil derivatives of gossypol have prepared in order to determine the scope of the reaction and to obtain potentially useful gossypol derivatives. The amines selected for anil formation with gossypol were in general the following types: amines containing other functional groups which would permit further reactions of the gossypol anils, physiologically active amines which might impart biological activity to the anil formed and amino acid, dipeptide esters.

2 Material and Methods

The IR spectra was accomplished with an apparatus SHIMAZDU IR 470. NMR spectra were recorded in $CDCl_3$ on a BRUKER AC200 spectrometer (at 50 MHz for ^{1}H_RMN; at 200 MHz for 13 C_NMR); the chemical shifts are expressed in ppm from TMS taken at 0.00 (δ-units).

3 Experiments

Reactions to form Schiff'bases were run in solution.

(±) Gossypol-acetic acid (1mM), phenylalanine methyl ester (3mM) were added in 75ml CH_2Cl_2 and 0.7 ml DIPA. The solution was stirred in 12 hours at room temperature. The reaction solution was filtered and was evaporated to dryness by using a rotary evaporator. The residue was subjected to a silica column with the eluent of heptane: ethyl acetate 9:1 and different fractions were collected in the laboratory test-tubes which were then gathered together according to the results of thin layer chromatography. Methyl ester of phenylalanine- gossypol derivative was collected with the yield of 60%.

i./ Thin layer chromatography on silica gel CERA - LABO F 1800/LS250 on the product and gossypol-acetic acid was used as the reference. The eluents were acetone:cyclohexane (4:6). The product gave a spot (Rf = 0.62)

ii./ IR spectra: The IR spectra of the product showed absorption maximum (cm^{-1}) at 3460 (-OH st), 1732 (C=O st), 1601 (-C=N-st). (Appendix 1)

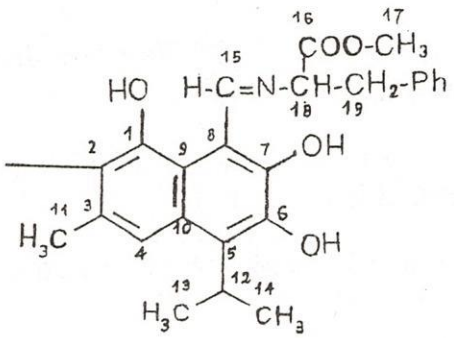
iii./ ^{1}H_NMR ($CDCl_3$): 1.47, 1.51 (d, 2x6H, gem-Me_2); 1.98 (s, 2x3H, H_11'); 3.67 (m, 2x1H, C<u>H</u>-CH_2-Ph), 3.75, 3.76 (s, 2x3H, 2x2H, -$CO_2C\underline{H}_3$, CH-C<u>H_2</u>-Ph); 4.62, 4.65 (m, 2x1H, H-12, H-12), 7.18, 7.19 (2s, 2x5H, arom H); 7.52 (s, 2x1H, H-4, H-4'); 9.48, 9.50 (s, 2x1H, -C<u>H</u>=N-) (Appendix 2)

iv./ ^{13}C_NMR ($CDCl_3$): 23.0, 23.3 (2-<u>C</u>H_3, C-11, C-11'); 30.6, 31.9, 32.2, 32.8 (4-<u>C</u>H_3 of gem-Me_2); 33.2, 33.6 (C-12, C-12'); 34.6 (C-18, C-18'), 42.6, 42.7 (-<u>C</u>H_2-Ph); 55.6, 67.2 (-$CO_2\underline{C}H_3$); 107.3, 118.6, 120.7, 121.6, 130.5, 130.7, 131.7, 132.1, 132.9, 133.0, 135.6, 135.7, 139.2, 139.3, 150.2, 153.5 (12 C of benzene ring and 20 C of naphtalen ring); 165.6 (-H<u>C</u>=N-); 173.9, 176.7 (-$C0_2CH_3$). (Appendix 3).

v./ ^{13}C_NMR_DEPT 135 spectra (Distortionless Enhancement Polarization Transfer): The product was dissolved in CD_3COCD_3 and the spectra showed signals which agree with the data of ^{13}C_NMR above (Appendix 4).

4 Conclusions

These above results confirmed that the product obtained was methyl ester of phenylalanine-gossypol derivative with the structure as below.



5 Acknowledgements

This work was supported by grants from International Foundation for Science (Ref/ 2405-1). The authors wish to thank for Doctor LENNART PRAGE. Scientific Secretary of for the kindness helping in the research.

References

[1] Aldar S. Bourinbaiar and Sylvia Lee-Huang., Contraception. **49**, 131-137 (1994).

[2] Carruth F. E., J. Am. Chem. Soc.. **40**, 647-663, (1918).

[3] Donald P. Waller, Lourens J. D. Zaneveld and Norman R. Farnsworth. Economic and Medicinal Plant Research, **1**, 87-112, Academic Press Inc. (London) Ltd., (1985).

[4] Dorsett Ph., Kerstine EE. and Powers L.J., J. Pharm. Sci., **64**, 1073-1075, (1975).

[5] Hu Y.F., CJ. G. Chang and Y. C. Lin., Life Sciences, **53**, 433-438, (1993).

[6] Inchull Kim, Guido B. Marcell, Donald P. Waller, Geoffrey A. Dordell and Harry H. S. Fong., Contraception, **35**, 289-297, (1993).

[7] Lin Ts., Schinazi Rf., Zhu J., Birks E., Carbone R. Si Y., Wu K., Huang I. and Prusoff Wh., Biochemical Pharmacology, **46**, 251-255, (1993).

[8] Quezia B. Cass, Elizabeth Tiritan and Stephen A., Phytochemistry. **30**, 2655-2657, (1991).

[9] Radloff Rj., Deck Lm., Royer Rc. and Van Der Jagt Dl., Pharmacol. Res. Commun., **18**, 1063-1073, (1986).

[10] Sherif A. Abou-Donia, Jerome L. Lasker and Mohamed B. Abou-Donia, Journal of Chromatography, **206**, 606-610, (1981).

[11] Wagner H., Economic and Medicinal Plant Research. **5**, 206-207, Academic Press Inc. (London) Ltd., (1991).