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Research Article

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Influence of substituents 5-substituted 1,4-naphthoquinones on regioselectivity Diels-Alder reaction

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ABSTRACT

A Diels-Alder reaction between 5-substituted 1,4-naphthoquinones and 1-acetoxy-1,3-butadiene was carried out. The optimization of reaction conditions [4 + 2] –cycloaddition were carried out. The dependence of the nature of the substituent in the 5th position of 1,4-naphthoquinone on the regioselectivity of Diels-Alder reaction was established. Tricarbocyclic derivatives of 5-R-1,4-naphthoquinones were synthesized.

Keywords: 5-R-1,4- naphthoquinones, cycloaddition, regioselectivity.

INTRODUCTION

Over the last decade, microorganisms that cause bacterial and viral infections are becoming increasingly resistant to drugs. For this reason, the scientific world was extremely high need in the synthesis of new bioactive compounds that can be used in the treatment of these infections. Tricyclic nucleus is part of various therapeutic agents that have shown antimicrobial activity. Condensation of the carbocycle with different pharmacofore fragments, including 1,4-quinoid, enables design tricyclic systems that can have potential anti-microbial, anti-tumor and anti-inflammatory activity [1-6]. First Diels-Alder reaction, which includes cycloaddition diene to quinones, is valuable in the synthesis of many natural derivatives. Cycloaddition to p-benzoquinones is key in the synthesis of steroids, cortisone, reserpine, yohimbine, estrone and terramicyn [7-9]. Corey achievement is stereospecific synthesis using gibberellic acid regioselectively Diels-Alder cycloaddition involving substituted benzoquinones [10]. In addition, interest in cycloaddition involving quinones growing, as already synthesized tetracycline antibiotics such as adriamycin and daunomicyn, these two molecules are effective in anticancer chemotherapy [11-25].

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded on spectrometer "Varian VXR" (300 MHz) (^{1}H chemical shifts are expressed in δ-scale relative to standart- tetrametylsilan and integrated intensity correspond to the allocation made).

Elemental analysis performed on a standard apparatus for microanalysis. Monitoring the progress of the reaction and individuality substances carried by TLC on plates "Silufol UV-254."

Methods of preparation

(4a,9a)-8-Hydroxy-9,10-dioxo-1,4,4a,9,9a,10-hexahydroanthracene-1-yl acetate (7)

To 0.61 g (0.0047 mol) of 5-hydroxy-1,4-naphthoquinone (**1**) dissolved in 10 ml of benzene was added 0.39 g (0.0039 mol) of 1-acetoxy-1,3-butadiene (**6**). The reaction mass was heated for 5 hours at 750-85^{0}C and stirring with reflux in argon. Then the reaction mixture was cooled within 10-12 hours. The product was filtered and washed with benzene, dried. Prepared (4aR,9aR)-8-hydroxy-9,10-dioxo-1,4,4a,9,9a,10-hexahydroanthracene-1-yl

acetate as yellowish crystals with a yield of 0.69 g (69%). The solution filtrate evaporated on a rotor-vacuum evaporator, precipitate recrystallized from benzene light yellow crystals obtained with the release of 0.27 g (27%).
^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 7,62 (t, J=7,80, 7,71, 1H, CH); 7,48 (d, J=7,80, 1H, CH); 7,15 (d, J=7,71, 1H, CH); 6,09-6,03 (m, 1H, CH); 5,98-5,90 (m, 1H, CH); 5,78-5,71 (m, 1H, CH); 3,90 (d, J=8,03, 6,00, 1H, CH); 3,43 (t, J=8,03, 7,42, 1H, CH); 2,70-2,55 (m, 2H, CH_2); 2,17 (s, 3H, $OCOCH_3$).

Calculated ($C_{16}H_{14}O_5$), %: C=67.13, H=4.93, O=27.94.
Found, %: C=67.04, H=4.95.
Yield - 0,69 g (69%), M.p. 187-189 ^{0}C

By this method received the following derivatives of 5-substituted 1,4-quinones **8-16**

(4a,9a)-5-Hydroxy-9,10-dioxo-1,4,4a,9,9a,10-hexahydroanthracene-1-yl acetate (8)
^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 7,62 (t, J=7,80, 7,71, 1H, CH); 7,50 (d, J=7,80, 1H, CH); 7,16 (dd, J=7,71, 1,44, 1H, CH); 6,03-5,99 (m, 1H, CH); 5,96-5,94 (m, 1H, CH); 5,79-5,71 (m, 1H, CH); 3,41-3,34 (m, 1H, CH); 3,30-3,24 (m, 1H, CH); 2,66-2,57 (m, 2H, CH_2); 2,17 (s, 3H, $OCOCH_3$).

Calculated ($C_{16}H_{14}O_5$), %: C=67.13, H=4.93, O=27.94.
Found, %: C=67.06, H=4.92.
Yield - 0,27 g (27%), M.p. 177-179 ^{0}C

(4a,9a)-8-Nitro-9,10-dioxo-1,4,4a,9,9a,10-hexahydroanthracene-1-yl acetate (9)
^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 8,08 (dd, J=7,50, 2,00, 1H, CH); 7,97 (dd, J=7,73, 2,00, 1H, CH); 7,46 (t, J=7,73, 7,50, 1H, CH); 6,05-5,97 (m, 1H, CH); 5,92-5,88 (m, 1H, CH); 5,79-5,71 (m, 1H, CH); 3,97-3,88 (m, 1H, CH); 3,92 (d, J=8,03, 6,00, 1H, CH); 3,32 (t, J=8,03, 7,42, 2H, CH); 2,17 (s, 3H, $OCOCH_3$).

Calculated ($C_{16}H_{13}NO_6$), %: C=60.95, H=4.16, N=4.44, O=30.45.
Found, %: C=60.92, H=4.12, N=4.40.
Yield - 0,71 g (71%), M.p. 210-211 ^{0}C

(4a,9a)-5-Nitro-9,10-dioxo-1,4,4a,9,9a,10-hexahydroanthracene-1-yl acetate (10)
^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 8,13 (dd, J=7,50, 2,00, 1H, CH); 7,97 (dd, J=7,73, 2,00, 1H, CH); 7,44 (t, J=7,73, 7,50, 1H, CH); 6,08-6,02 (m, 1H, CH); 5,92-5,84 (m, 1H, CH); 5,79-5,71 (m, 1H, CH); 3,50-3,44 (m, 1H, CH); 3,40-3,32 (m, 1H, CH); 2,66-2,57 (m, 1H, CH); 2,17 (s, 3H, $OCOCH_3$).
Calculated ($C_{16}H_{13}NO_6$), %: C=60.95, H=4.16, N=4.44, O=30.45.
Found, %: C=60.90, H=4.13, N=4.41.
Yield - 0,29 g (29%), M.p. 167-169 ^{0}C

(4a,9a)-8-Amino-9,10-dioxo-1,4,4a,9,9a,10-hexahydroanthracene-1-yl acetate (11)
^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 7,87 (s, 2H, NH_2); 7,47 (t, J=7,87, 7,73, 1H, CH); 7,38 (d, J=7,73, 1H, CH); 6,98 (dd, J=7,87, 1,60, 1H, CH); 5,98-5,90 (m, 1H, CH); 5,88-5,82 (m, 1H, CH); 5,79-5,71 (m, 1H, CH); 3,93 (d, J=8,03, 1H, CH); 3,17 (t, J=8,03, 7,42, 1H, CH); 2,61-2,52 (m, 2H, CH_2); 2,17 (s, 3H, $OCOCH_3$).
Calculated ($C_{16}H_{15}NO_4$), %: C=67.36, H=5.30, N=4.91, O=22.43.
Found, %: C=67.39, H=5.27, N=4.85.
Yield - 0,70 g (70%), M.p. 162-163 ^{0}C

(4a,9a)-5-Amino-9,10-dioxo-1,4,4a,9,9a,10-hexahydroanthracene-1-yl acetate (12)
^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 7,87 (s, 2H, NH_2); 7,47 (t, J=7,87, 7,73, 1H, CH); 7,40 (d, J=7,73, 1H, CH); 6,95 (dd, J=7,87, 1,60, 1H, CH); 6,03-5,97 (m, 1H, CH); 5,84-5,71 (m, 2H, 2CH); 3,59-3,51 (m, 1H, CH); 3,45-3,37 (m, 1H, CH); 2,68-2,58 (m, 2H, CH_2); 2,17 (s, 3H, $OCOCH_3$).
Calculated ($C_{16}H_{15}NO_4$), %: C=67.36, H=5.30, N=4.91, O=22.43.
Found, %: C=67.38, H=5.26, N=4.87.
Yield - 0,28 g (28%), M.p. 159-161 ^{0}C

(4a,9a)-5-Methoxy-9,10-dioxo-1,4,4a,9,9a,10-hexahydroanthracene-1-yl acetate (13)
^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 7,67 (t, J=8,14, 7,80, 1H, CH); 7,61-7,56 (m, 1H, CH); 7,43-7,37 (m, 1H, CH); 6,04-5,98 (m, 1H, CH); 5,97-5,90 (m, 1H, CH); 5,79-5,71 (m, 1H, 1CH); 3,94 (s, 3H, OCH3); 3,86-3,77 (m, 1H, CH); 3,36 (t, J=8,03, 7,42, 1H, CH); 2,70-2,61 (m, 2H, CH_2); 2,17 (s, 3H, $OCOCH_3$).
Calculated ($C_{17}H_{16}O_5$), %: C=67.99, H=5.37, O=26.64.

Found %: C=67.93, H=5.32.
Yield - 0,68 g (68%), M.p. 132-133 ^{0}C

(4a,9a)-8-Methoxy-9,10-dioxo-1,4,4a,9,9a,10-hexahydroanthracene-1-yl acetate (14)
^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 7,65 (t, J=8,14, 7,80, 1H, CH); 7,60-7,56 (m, 1H, CH); 7,40 (dd, J=8,14, 1,44, 1H, CH); 6,03-5,97 (m, 1H, CH); 5,95-5,88 (m, 1H, CH); 5,76-5,68 (m,1H, CH); 3,96 (s, 3H, OCH3); 3,92-3,87 (m, 1H, CH); 3,36 (t, J=8,03, 7,42, 1H, CH); 2,68-2,59 (m, 2H, CH_2); 2,17 (s, 3H, $OCOCH_3$).
Calculated ($C_{17}H_{16}O_5$), %: C=67.99, H=5.37, O=26.64.
Found, %: C=67.95, H=5.34.
Yield - 0,31 g (31%), M.p. 184-185 ^{0}C

(4a,9a)-9,10-Dioxo-1,4,4a,9,9a,10-hexahydroanthracene-1,5-diyl diacetate (15)
^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 7,73 (dd, J=7,90, 7,80, 1H, CH); 7,67 (dd, J=7,80, 1,44, 1H, CH); 7,56-7,51 (m, 1H, CH); 6,04-5,98 (m, 1H, CH); 5,94-5,87 (m, 1H, CH); 5,79-5,71 (m,1H, CH); 3,76-3,67 (m, 1H, CH); 3,49 (t, J=8,03, 7,42, 1H, CH); 2,73-2,64 (m, 2H, CH_2); 2,44 (s, 3H, $OCOCH_3$); 2,17 (s, 3H, $OCOCH_3$).
Calculated ($C_{18}H_{16}O_6$), %: C=65.85, H=4.91, O=29.24.
Found, %: C=65.89, H=4.93.
Yield - 0,72 g (72%), M.p. 181-183 ^{0}C

(4a,9a)-9,10-Dioxo-1,4,4a,9,9a,10-hexahydroanthracene-1,8-diyl diacetate (16)
^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 7,75 (dd, J=7,90, 7,80, 1H, CH); 7,65 (dd, J=7,80, 1,44, 1H, CH); 7,54-7,49 (m, 1H, CH); 6,08-6,02 (m, 1H, CH); 5,98-5,90 (m, 1H, CH); 5,78-5,70 (m,1H, CH); 4,03-3,98 (m, 1H, CH); 3,31 (t, J=8,03, 7,42, 1H, CH); 2,68-2,59 (m, 2H, CH_2); 2,44 (s, 3H, $OCOCH_3$); 2,17 (s, 3H, $OCOCH_3$).
Calculated ($C_{18}H_{16}O_6$), %: C=65.85, H=4.91, O=29.24.
Found, %: C=65.82, H=4.89.
Yield - 0,27 g (27%), M.p. 182-184 ^{0}C

1-Hydroxyanthracene-9,10-dione (17)
For the dehydrogenation 1.27 g (0.0045 mol) of the resulting product(4aR,9aR)-8-hydroxy-9,10-dioxo-1,4,4a,9,9a,10-hexahydroanthracene-1-yl acetate (**7**) was dissolved in 12 ml of 5% KOH in alcoholic solution in three throatflask with reflux and missed the air for 24 hours. Yellow product was filtered and washed with 4 ml of water, 2 ml of ethanol and 1 ml ether, dried.

^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 8,25-8,21 (m, 1H, CH); 8,19-8,15 (m, 1H, CH); 7,99-7,90 (m, 2H, 2CH); 7,82 (t, J=7,76, 7,71, 1H, CH); 7,71 (d, J=7,76, 1,18, 1H, CH); 7,38 (d, J=7,71, 1,18, 1H, CH).
Calculated ($C_{14}H_8O_3$), %: C=75.00, H=3.60, O=21.41.
Found, %: C=75.03, H=3.58.
Yield - 0,94 g (94%), M.p. 215-217 ^{0}C

By this method received the following derivatives of 5-substituted 1,4-quinones **18-21**

1-Methoxyanthracene-9,10-dione (18)
^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 8,21 (dd, J=7,48, 1,59, 1H, CH); 8,17 (dd, J=7,48, 1,59, 1H, CH); 7,96 (t, J=7,48, 7,22, 1H, CH); 7,84 (t, J=7,48, 7,22, 1H, CH); 7,78 (t, J=8,14, 7,76, 1H, CH); 7,70 (dd, J=7,76, 1,04, 1H, CH); 7,55 (d, J=8,14, 1H, CH); 3,97 (s, 3H, OCH_3).
Calculated ($C_{15}H_{10}O_3$), %: C=75.62, H=4.23, O=20.15.
Found, %: C=75.64, H=4.28.
Yield - 0,93 g (93%), M.p. 199-201 ^{0}C

9,10-Dioxo-9,10-dihydroanthracene-1-yl acetate (19)
^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 8,25 (dd, J=7,76, 1,20, 1H, CH); 8,20 (dd, J=7,48, 1,59, 1H, CH); 8,16 (dd, J=7,48, 1,59, 1H, CH); 8,01 (t, J=7,90, 7,76, 1H, CH); 7,90 (t, J=7,48, 7,22, 1H, CH); 7,81 (t, J=7,48, 7,22, 1H, CH); 7,64 (dd, J=7,90, 1,20, 1H, CH); 2,45 (s, 3H, $OCOCH_3$).
Calculated ($C_{16}H_{10}O_4$), %: C=72.18, H=3.79, O=24.04.
Found, %: C=72.22, H=3.78.
Yield - 0,91 g (91%), M.p. 186-188 ^{0}C

1-Nitroanthracene-9,10- dione (20)
^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 8,32 (dd, J=7,50, 2,00, 1H, CH); 8,26-8,20 (m, 1H, CH); 8,17-8,13 (m, 1H, CH); 8,10 (dd, J=7,50, 2,00, 1H, CH); 7,89-7,83 (m, 2H, 2CH); 7,59 (t, J=7,50, 7,50, 1H, CH).

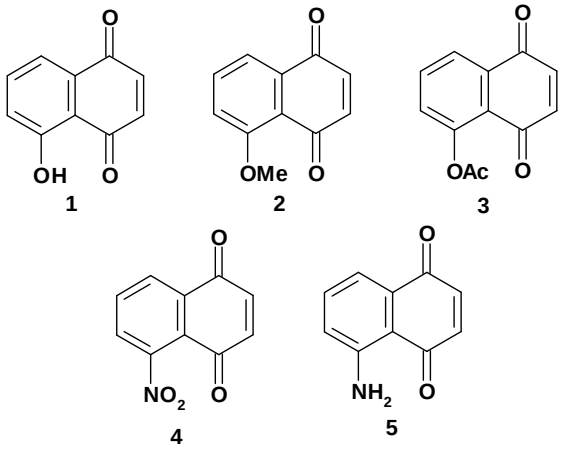
Calculated ($C_{14}H_7NO_4$), %: C=66.41, H=2.79, N=5.53, O=25.27.
Found, %: C=66.39, H=2.77, N=5.56.
Yield - 0,89 g (89%), M.p. ≥250 ^{0}C

1-Aminoanthracene-9,10-dione (21)
^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 8,20-8,14 (m, 1H, CH); 8,12-8,06 (m, 1H, CH); 7,83-7,76 (m, 2H, 2CH); 7,72 (s, 2H, NH_2); 7,58 (t, J=7,87, 7,60, 1H, CH); 7,52 (dd, J=7,60, 1,60, 1H, CH); 7,21 (dd, J=7,87, 1,60, 1H, CH).
Calculated ($C_{14}H_9NO_2$), %: C=75.33, H=4.06, N=6.27, O=14.33.
Found, %: C=75.30, H=4.11, N=6.25.
Yield - 0,90 g (90%), M.p. 185-186 ^{0}C

RESULTS AND DISCUSSION

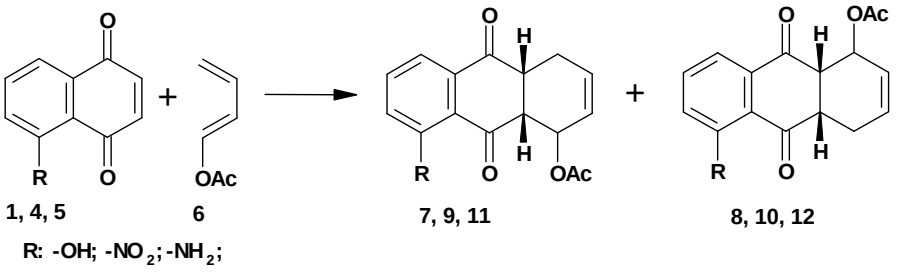
In the literature has not described the reaction of 5-substituted 1,4-naphthoquinones. Since the use of different substituents diene and heterodiene, Diels-Alder reaction will take place regioselectively to form two regioisomers in a ratio. In terms of finding promising bioactive compounds is to find methods of conducting regiospecific reactions [4 + 2] -cycloaddition.
In this paper, we have been tasked to get tricyclic condensed quinoid systems as initial building blocks for further construction on the basis drug-like molecules [26-27] by reaction between 5-R-substituted derivatives of 1,4-naphthoquinone and 1-acetoxy-1,3-butadiene. The synthesis of compounds was performed Diels-Alder reaction between dienophiles, as have been applied 5-hydroxy (**1**) methoxy-5 (**2**), 5-amino (**3**), 5-nitro (**4**), 5 acetoxy-1,4-naphthoquinone (**5**) and diene - 1-acetoxy-1,3-butadiene (**6**).

Scheme 1



Thus the reaction of interaction of compounds **1, 4, 5** with diene **6** held in ethanol at 75-85^{0}C for 5 hours. In analyzing the products of the reaction mixture was found that the interaction took place regioselectively. As a result, each reaction was allocated two regioisomers dominated compounds **7, 9, 11** outputs with 69%, 71%, 70% and compounds **8, 10, 11** fewer - 27%, 29%, 28%. This explains the reaction of electron-acceptor substituents influence in position 5 and 1,4-naphthoquinones appropriate orientation unsymmetrical diene - 1-acetoxy-1,3-butadiene.

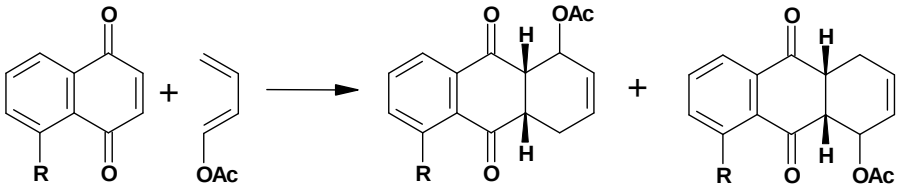
Scheme 2



In case of a 5-position of 1,4-naphthoquinone electron-donor - methoxy and acetoxy groups, Diels-Alder reaction is the formation of regioisomers in the opposite ratio. So, interaction of 1,4-naphthoquinones **2, 3** with 1-acetoxy-1,3-butadiene **6** was conducted in ethanol in the temperature range 75-85^{0}C for 5 hours. Analysis of the products of the

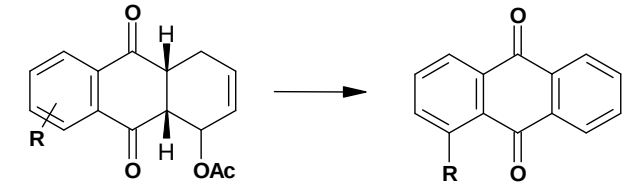
reaction mixture showed the formation of compounds **13** and **15** outputs with 68% and 72%, and **14** compounds, **16** of - 31% and 27%.

Scheme 3



It was further shown that the resulting dihydroantracenediones **7 - 16** can oxidise operates under manganese oxide to form a full antraquinoid derivatives **17 - 21**. Output reaction products was 89-94%.

Scheme 4



CONCLUSION

The paper describes the main route of synthesis of potentially bioactive compounds from 5-R-1,4-naphthoquinones. A Diels-Alder reaction between 5-R-substituted derivatives of 1,4-naphthoquinone and 1-acetoxy-2,3-butadiene. It is established that the products Diels-Alder contain a double bond between C2-C3 carbon atoms in the ring side of antracenedione. Found that the action of an excess of 5-R-1,4-naphthoquinone for products [4 + 2] -cycloaddition is dehydrogenetion of connection between the carbon atoms in positions 4a and 9a, in the case of oxidation dehydrogenetion takes place in the side to form an aromatic ring system 9,10-anthraquinone derivatives.

REFERENCES

[1] A. Husain, M. A. Naseer, M. Sarafroz // *Acta Pol. Pharm. Drug Res*., **2009**, 66, 135-140.
[2] S. Schenone, C. Brullo, O. Bruno, F. Bondavalli, A. Ranise, W. Filippelli, B. Rinaldi, A. Capuano, G. Falcone, *Bioorg. Med. Chem*.,**2006**,14, 1698-1705
[3] H. N. Dogan, A. Duran, S. Rollas, G. Sener, M. K. Uysal, D. Gülen, *Bioorg. Med. Chem.*, **2002**, 10, 2893-2898
[4] M.Kritsanida, A. Mouroutsou , P. Marakos , N. Pouli , S. Papakonstantinou-Garoufalias, C. Pannecouque, M. Witvrouw , E. De Clercq , *Farmaco* ,**2002**, 57, 253–257
[5] B. S. Holla, K. N. Poojary, B. S. Rao, M. K. Shivananda, *Eur. J. Med. Chem.*, **2002,** 37, 51-517
[6] B. Kalluraya, S. Sreenivasa, *Farmaco* ,**1998**, 53, 399-404
[7] Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. J. Am. Chem. *SOC.* **1952**, 74,4223**.**
[8] Sarett. L. H.: Arth. G. E.: Lukes. R. M.: Bevler. B. M.: Poos. G. I.: Johns, W. F.; Constantin, J. M. J. Am. Chem. Sic. **1952,** 74, 4974.
[9] Anand, N.; Bindra, J. S.; Ranganathan, S. "*Art in Organic Synthesis*"; Holden-Day: San Francisco, **1970.**
[10] Corey, E. J.; Danheiser, R. L.; Chandrasekan, S.; Siret, P.; Keck, G. E.; Gras, J.-L. J. Am. Chem. *SOC.* **1978,** 100, 8031.
[11] Kelly, T. R.; Gillard, J. W.; Goerner, R. N., Jr.; Lyding, J. M. *J. Am. Chem. SOC.* **1977,** 99, 5513.
[12] Kelly, T. R.; Goerner, R. N., Jr.; Gillard, J. W.; Prazak, B. K. *Tetrahedron Lett.* **1976,** 3869.
[13] Kelly, T. R.; Gillard, J. W.; Goerner, R. N., *Jr. Zbid.* **1976,** 3873.
[14] Kelly, T. R. *Jr. Zbid.* **1978,** 1387.
[15] Kelly, T. R.: Monturv. M. Zbid. *Jr. Zbid.* **1978,** 4309.
[16] Kellv. T. R.: Monturv. J. Ibid. *Jr. Zbid.* **1978,** 4311.
[17] Farina, F.**;** Prados, P. *Tetrahedron Lett.* **1979,** 477.
[18] Boeckman, R. K., Jr.; Dolak, T. M.; Culos, K. 0. *J. Am. Chem. SOC.* **1978,** 100, 7098.

[19] Grandmaison, J.-L.; Brassard, P. J. Org. Chem. **1978**, 43, 1435.
[20] Lee, E. W.; Martinez, **A.** P.; Smith, T. H.; Henry, D. W. *J. Org. Chem.* **1976,** 41, 2296.
[21] Wiseman, J. R.; French, N. I.; Hallmark, R. K.; Chiong, K. G. *Tetrahedron Lett.* **1978,** 3765.
[22] Kende, A. S.; Tsay, T.-G.; Mills, J. E. *J. Am. Chem. SOC.* **1976,** 98**.**
[23] Kende, A. S.; Curran, D. P.; Tsay, T.-G.; Mills, J. E. *Tetrahedron Lett.* **1977,** 3537.
[24] Jung, M. E.; Lowe, J. A. *J. Org. Chem.* **1977,** 42, 2371.
[25] Krohn, K.; Tolkiehn, K. *Tetrahedron Lett.* **1978,** 4023.
[26] S. Polovkovych, G. Zagoriy, O. Bondarchuk, R.Vynnytska, Y.Shakh, K. Bolibrukh, A. Karkhut, O. Kovalchuk, M.Ponomarenko, A.Komar, V.Novikov. // *Research Journal of Pharmaceutical, Biological and Chemical Sciences*:, **2013**, 4(2), 128-144.
[27] Yu. Dumanska, Yu. Shakh, A. Kudrinetska, Kh. Bolibrukh, A. Karkhut, B. Lytvyn, O. Kovalchuk, O. Marshalo k, M. Platonov, S. Polovkovych, V. Novikov // *Research Journal of Pharmaceutical, Biological and Chemical Scien ces*., **2013**, 4(4), 1471-1479.