UDC 547. 314

N.Merkhatuly[1], P.Vojtíšek[2], S.B.Abeuova[1], G.Bakytzhan[1], Z.S.Suleimbekova[1]

[1]Ye.A.Buketov Karaganda State University;
[2]Charles University, Prague, Czech Republic
(E-mail: merhatuly@ya.ru)

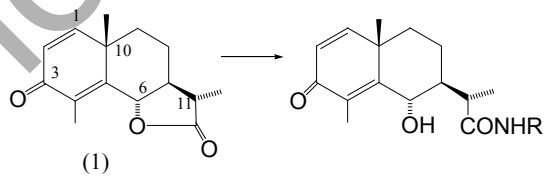
Synthesis and biological activity of nitrogen-containing derivatives of α-santonin

The reactions of eudesmanolide α-santonin with primary and secondary amines were investigated. It was shown that the reactions occured regioselectively at the carbonyl group of γ-lactone ring with formation of the products of aminolysis — hydroxyamides. Furthermore, it was found that the reaction of santonin with semicarbazide and phenylhydrazine flowed through carbonyl group of cross-conjugated cyclodienone to form condensation products and the reaction of santonin with hydroxylamine flowed to give tandem reactions products of Michael-type and condensation. It was revealed that synthetic nitrogen-containing derivatives of α-santonin had antibacterial and antioxidant activity.

Key words: sesquiterpene lactone, eudesmanolide, cross-conjugation, cyclodienone, santonin, Michael reaction, tandem reaction, desmotropsantonin.

The sesquiterpene γ-lactone eudesmanolide α-santonin induces interest for study of nucleophilic addition reactions of amines and synthesis of new potentially biologically active nitrogen-containing derivatives [1, 2]. The cross-conjugated cyclodienonic system of santonin tends to aromatization. For example, it is easily exposed to Wagner-Meerwein dienone-phenol rearrangement with the formation of desmotropsantonin [3, 4].

In this article the reactions of α-santonin (1) with different aliphatic and aliphatic-aromatic amines were investigated. Interaction of α-santonin (1) with primary amines as monoethanolamine, methylamine and benzylamine in ethanol medium at reflux gave only 6-hydroxy-amides, (2) in 81 % yield, (3) in 74 % yield and (4) in 50 % yield. The 6-hydroxy-amides are α-santonin lactone ring aminolysis products (^{1}H-NMR spectrum data are shown in Table 1). Apparently, low yield of amide (4) is a cause of weak-base properties of benzylamine in comparison with primary aliphatic amines.

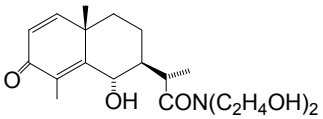


(1)

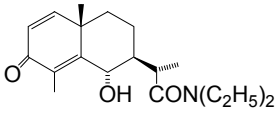
R= - C_2H_4OH (2)
- Me (3)
-CH_2Ph (4)

In the above conditions the reaction of compound (1) with secondary aliphatic amines like diethanolamine and diethylamine generally leads to γ-lactone ring aminolysis products — amides (5) and (7), in 53 and 58 % yields, and the products of Michael conjugate addition to the cyclodienone system — adducts (6) and (8) in 14 and 15 % yields.

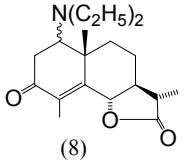
On the one hand formation of Michael reaction products confirms the hypothesis about cross-conjugated nature of α-santonin cyclodienone system (not the predominant aromatic character) and from the other hand the high reactivity with manifestation of the properties of the secondary aliphatic amines boundary bases. Strong evidence about cross-conjugation of α-santonin cyclodienone system obtained in reactions (1) with hydroxylamine, phenylhydrazine and semicarbazide is presented below.



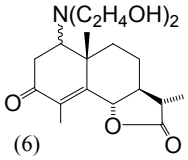
(5)



(7)



(8)



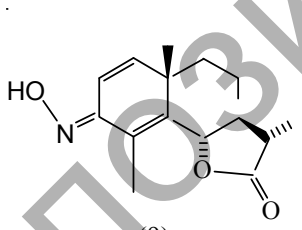
(6)

Table 1

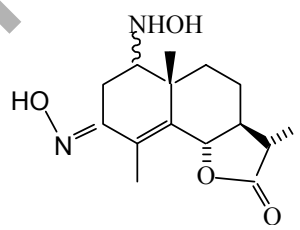
Chemical shifts (δ, ppm) and spin-spin interaction constants (in Hz) of santonin and its derivatives (2)-(4)

Protons	Compounds			
	(1)	(2)	(3)	(4)
Me-4	2,15 broad singlet	2,61 s.	2,69 s.	2,70 s.
Me-10	1,33 s.	1,03 s.	1,04 s.	1,04 s.
H-1	6,28 d. (10)	6,32 d. (10)	6,34 d. (10)	6,34 d. (10)
H-6	4,80 broad singlet (11)	4,77 broad singlet (11)	4,76 d. (10)	4,72 d. (10)
Other protons	–	$CONH(CH_2)_2OH$: 3,55 qui. (1H, 7,5; 4Hz); 3,78 qui. (1H, 12,5; 5 Hz); 4,01 t. (1H, 5Hz); 5,05 broad singlet (1H)	$–CONHCH_3–$ 3,51 qui. (1H, 6,5; 4Hz); 2,92 d. (3H, 5Hz)	$–COCH_2Ph–$ 3,50 d. (2H, 6,5 Hz); Aromatic nucleus 7,06 broad singlet (5H)

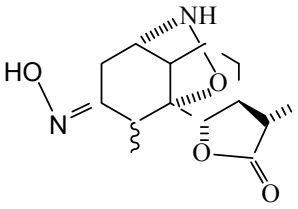
It is known that the reaction of α-santonin oximation with hydroxylamine hydrochloride leads to the formation of not only the final E-oxime (9) in 20 % minor yield, but also two products of tandem Michael-type reactions and condensation — compounds (10) and (11) [5]. The reaction is carried out in the presence of sodium methoxide in methanol or ethanol in the presence of sodium acetate at reflux (10–12 hours). Presumably the formation of the reaction products occurred as a result of the Michael conjugated addition and then only by the condensation reaction. The dominant implementation of the Michael reaction results in the conjugated addition products (10) and (11). It supports the hypothesis that hydroxylamine is a border basis. Phenylhydrazine and semicarbazide (analogs of hydroxylamine) are more strong bases because of their interaction with α-santonin (1) at the above conditions, leading to condensation products: E-semicarbazone (12) and E-phenylhydrazone (13) in 60 and 65 % yields (^{1}H-NMR spectrum data are shown in Table 2).



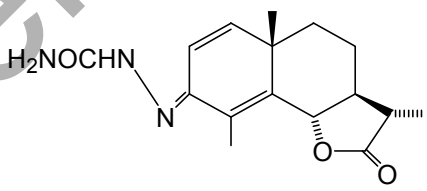
(9)



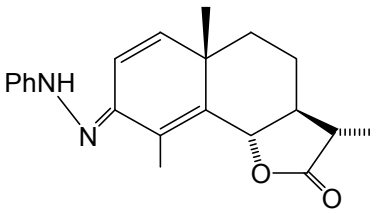
(10)



(11)



(12)



(13)

For high yield synthesis of the oxime (9), which is a key molecule in the synthesis of new nitrogen-containing derivatives, it was necessary to increase basicity of hydroxylamine.

A single-step preparative method of synthesis of E-oximesantonin (9) was developed as a result of numerous experiments. According to this method the reaction of α-santonin (1) is carried out with hydroxylamine hydrochloride in pyridine at reflux for 4–5 hours. Finally, E-oximesantonin (9) forms in 96–98 % quantitative yield.

Table 2

Chemical shifts (δ, ppm) and spin-spin interaction constants (in Hz) of santonin and its derivatives (9), (10), (12) and (13)

Protons	Compounds				
	(1)	(9)	(10)	(12)	(13)
Me-4	2,15 broad singlet	2,06 s.	1,7 s.	2,43 s.	2,43 s.
Me-10	1,33 s.	–	–	1,14 s.	1,14 s.
H-1	6,28 d. (10)	5,96 d. (10)	5,19 d. (10)	6,05 d. (10)	6,05 d. (10)
H-6	4,80 broad singlet (11)	–	–	4,87 d. (10)	4,87 d. (10)
Other protons	–	=NOH; 9,21 broad singlet (1H)	CHNH–OH 3,5 t. (1H)	–HNCO–NH_2; 5,04 broad singlet (3H)	–HN–NH_2; 4,54 broad singlet (1H). Aromatic nucleus 7,02 broad singlet (5H)

Thus, it is shown that the interaction of the primary and secondary amines occurs at the carbonyl group of α-santonin γ-lactone ring regioselectively to form products of aminolysis — hydroxy amides. Reactions of α-santonin with semicarbazide and phenylhydrazine implemented by carbonyl group of cross-conjugated cyclodienone to form condensation products. The reaction of α-santonin with hydroxylamine generally leads to products of Michael tandem and condensation reactions. The single-step preparative method of oximesantonin synthesis was developed for the first time. The oximesantonin is a key molecule in the purposeful synthesis of practically important derivatives of natural compounds.

The biological activity of the synthesized nitrogen-containing derivatives of α-santonin (1) was studied. It was found that monoethanolamide (2), methylamide (3) and oxime (9) had antibacterial activity against 16 strains of gram-positive bacteria (Staphylococcus aureus, St.epidermidis et al.), gram-negative bacteria (*Salmonella* spp, *Klebsiella* spp. et al.) and gram positive nonspore-forming anaerobic bacteria (*Propionibakterium* spp., *Eubacterium* spp.) and coccus (*Reptococeus* spp.) and also have fungicidal action against fungal strains of the genus *Candida albicans* and *Mucor*.

Furthermore, it was found that derivatives of santonin (2), (3), (9) and (13) have antioxidant activity. The relationship between their structure and biological activity was identified (Table 3).

Table 3

Antioxidant activity of α-santonin (1) and its derivatives (options of initiated chemiluminescence in the presence of synthesized compounds)

No	Code and the number of compounds	*H*, arbitrary units	τ, min	tg, α	*H*, arbitrary units
1	SN (1)	2,75±2,01	1,86±0,12	6,64±0,58	6,41±0,44
2	SN-NOH (9)	2,4±0,11	2,0±0,08	8,0±0,05	15,2±1,2
3	SN-MA (3)	3,6±0,09	1,0±0,08	9,0±0,08	43,75±2,1
4	SN-BA (4)	3,0±0,1	2,7±0,07	6,0±0,11	9,0±0,08
5	SN-MEA (2)	3,5±0,19	1,5±0,06	9,0±0,07	37,5±3,5
6	Ionol	2,17±0,13	7,64±0,15	2,69±0,13	6,34±0,51
7	Control	2,6±0,1	2,0±0,09	3,5±0,29	7,1±0,55

Derivatives of (2), (3) and (9) have intensification of pro-oxidant effect when methylamide (3) in the structure of molecule has the methyl group. In this case the emission intensity of methylamide (3) increases in 6.16 times compared with the control slowly. A similar effect of initiated emission growth is detected for monoethanolamide (2) where a hydroxyethyl moiety existed. Moreover, among all the studied substances a new property was detected. It is not characteristic for exogenous anti — and pro-oxidants. This property is preservation of the latent period value.

Thus, synthesized biologically active nitrogen-containing derivatives of α-santonin are interesting for investigating their pharmacological activity and creating effective new drugs.

References

1 *Blay G., Cardona L., Garcia B.* Ring Opening Aminolysis of Sesquiterpene Lactones: An Easy Entry to Bioactive sesquiterpene Derivatives // Tetrahedron. — 1996. — Vol. 52, No. 31. — P. 10507–10518.

2 *Мерхатулы Н., Балмагамбетова Л.Т., Смоленков Ю.Ю.* Реакции нуклеофильного присоединения спиртов к (–)-α-сантонину // Вестн. Караганд. ун-та. Сер. Химия. — 2010. — № 4(40). — С. 47–50.

3 *Flohlich A., Maura P., Ishikowa K., McMurry T.B.H., Ranc D.* // Proc. r. Ir. Acad. — 1983. — Vol. 83. — P. 65–70.

4 *Merkhatuly N., Zhokizhanova S.K., Balmagambetova L.T., Adekenov S.M.* Reaction of the sesquiterpene γ-lactone α-santonin with alcoholic hydrogen chloride // Russ. J. Gen. Chem. — 2006. — Vol. 76. — P. 1347–1348.

5 *Edward J.T., Davis M.J.* Reaction of Santonin with Hydroxylamine // J. Org. Chem. — 1978. — Vol. 43, No. 4. — P. 537–539.

Н.Мерхатұлы, П.Войтичек, С.Б.Әбеуова, Г.Бақытжан, З.С.Сүлеймбекова

α-Сантониннің азотқұрамды туындыларының синтезі және биологиялық белсенділігі

Мақалада эвдесманолид α-сантониннің біріншілік және екіншілік аминдермен реакциялары зерттелінді. Реакция региоселективті γ-лактон сақинасындағы карбонил тобы бойынша аминолиз өнімі — гидроксиамидтерді түзіп жүретіндігі көрсетілді. Сонымен қатар сантониннің семикарбазид және фенилгидразинмен әрекеттесуі циклодиенонның *кросс*-қосарланған карбонилды тобы бойынша конденсация өнімін түзіп жүретіндігі, ал гидроксиламинмен әрекеттесуі Михаэль типі және конденсация тандемді реакция өнімдеріне әкелетіндігі анықталды. α-Сантониннің бірқатар азотқұрамды туындылары антибактериалды және антиоксидантты белсенділікке ие екендігі анықталды.

Н.Мерхатулы, П.Войтичек, С.Б.Абеуова, Г.Бакытжан, З.С.Сулеймбекова

Синтез и биологическая активность азотсодержащих производных α-сантонина

В статье изучены реакции эвдесманолида α-сантонина с первичными и вторичными аминами. Показано, что реакции протекают региоселективно по карбонильной группе γ-лактонного цикла, с образованием продуктов аминолиза — гидроксиамидов. Кроме того, установлено, что взаимодействие сантонина с семикарбазидом и фенилгидразином протекает по карбонильной группе *кросс*-сопряженного циклодиенона, с образованием продуктов конденсации, а взаимодействие с гидроксиламином приводит к продуктам тандемных реакций по типу Михаэля и конденсации. Выявлено, что ряд синтезированных азотсодержащих производных α-сантонина обладает антибактериальной и антиоксидантной активностью.

References

1 Blay G., Cardona L., Garcia B. *Tetrahedron,* 1996, 52, 31, p. 10507–10518.

2 Merkhatuly N., Balmagambetova L.T., Smolenkov Yu.Yu. *Bulletin of the Karaganda University*, Chem. ser., 2010, 4(40), p. 47–50.

3 Flohlich A., Maura P., Ishikowa K., McMurry T.B.H., Ranc D. *Proc. r. Ir. Acad.*, 1983, 83, p. 65–70.

4 Merkhatuly N., Zhokizhanova S.K., Balmagambetova L.T., Adekenov S.M. *Russ. J. Gen. Chem.*, 2006, 76, p. 1347–1348.

5 Edward J.T., Davis M.J. *J. Org. Chem.*, 1978, 43, 4. p. 537–539.