IMPROVED METHOD FOR THE ISOLATION OF GERANYL ESTERS OF (4E/Z,8E)-AND (4E/Z,8Z)-FARNESYLACETIC ACID

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The geranyl esters of 4E,8E-farnesylacetic acid and its stereomers are effective agents for the prophylaxis and treatment of gastric ulcers [10]. The synthesis utilizing malonic ester is a simple method for the isolation of these compounds [6, 8]. We improved this principal scheme by the modification and simplification of the separate stages of the synthesis. The scheme permits the isolation of the mixture of the geranyl esters of (4E,8E)farnesylacetic (I-EE) and (4Z,8E)-farnesylacetic (I-ZE) acids from E-geranylacetone (IIa), and the mixture of the geranyl esters of (4E,8Z)-farnesylacetic (I-EZ) and (4Z,8Z)-farnesylacetic (I-ZZ) acids from Z-geranylacetone (IIb).

The starting compound - linalool - was converted into the mixture of (IIa) and (IIb) by a modified method [2] in the yield of 74%. The 1:2 molar ratio of linalool/acetoacetic ester, which was recommended in the work [2], was thereby substituted by the 1:1 ratio without a loss of the yield. It gave the individual compounds (IIa) and (IIb) in the respective yields of 54 and 41% by the vacuum rectification on a column with 100 theoretical plates. The ethynylation of (IIa) by the method of [1] led to the E-dehydronerolidol (IIIa) in the yield of 93-95%; the Z-dehydronerolidol (IIIb) was obtained from (IIb) with the same yield. The best variant of the hydrogenation of (IIIa) to E-nerolidol (IVa) and of (IIIb) to Z-nerolidol (IVb), guaranteeing a quantitative yield and complete selectivity, was found to be the hydrogenation in hexane over Pd/BaSO<sub>4</sub> with twice the mass amount of KOH; the catalyst was first poisoned with NH<sub>3</sub> gas. The yields of (IVa) and (IVb) from linalool comprised ~38 and ~27% respectively at this stage of the synthesis.

In previous work [6, 8] for the isolation of farnesylmalonic esters from (IVa) or (IVb), the latter were first converted to the corresponding farnesyl bromides by the action of PBr<sub>3</sub>. We established that malonic ester can be successfully alkylated by impure "farnesyl chlorides" (mixtures of isomeric allyl chlorides) obtained by the treatment of (IVa) or (IVb) with conc. HCl. The reaction of the chloride, obtained from (IVa), with malonic ester in acetone in the presence of  $K_2CO_3$  and 2 mole % of KI (catalyst) gave the mixture of the farnesylmalonic esters (Va) with the 3:1 ratio of the (4E,8E)- and (4Z,8E)-isomers in the yield of 57-64% based on the amount of (IVa) taken. For the reaction of the distilled farnesyl bromide with malonic ester in EtOH in the presence of EtONa, the yield of (Va) comprised from 41% [8] to 59% [6]; this corresponds with the yields of 34 and 52.5% from the nerolidol (IVa). The alkylation of malonic esters (Vb) with the analogous 3:1 ratio of the (4E,8Z)- and (4Z,8Z)-isomers.

We compared the effectiveness of three variants for the comparison of the mixture (Va) to the mixture of (I-EE) and (I-ZE). On heating (Va) with 2 moles of geraniol according to [7], the yield of (I-EE) + (I-ZE) comprised 70%. With the object of economizing on the geraniol, 1 mole of which is lost as  $\beta$ -myrcene in this method, two two-stage variants with the intermediate isolation of the mixture of the (4E,8E)- and (4Z,8E)-isomers of ethyl farnesylacetate (VIa) were investigated. In the first of them, (Va) was subjected to partial alkaline saponification with the subsequent decarboxylation of the acid monoester at 170°C according to [3]. In the second, the direct desethoxycarbonylation of (Va) was performed by the method of Krapcho by heating it with LiCl in moist HMTPA according to [5]. In both cases, the yield of (VIa) comprised 80%. The transesterification of (VIa) by the action of 1.2 moles of geraniol in boiling xylene in the presence of 2 mole % of KOH led to the 80% yield of the mixture of (I-EE) and (I-ZE) (3:1) ratio). therefore, the yield of the desired product from (Va) comprised ~64% for each of the two-stage variants. The yield of the mixture

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 21, No. 7, pp. 854-858, July, 1987. Original article submitted August 19, 1986. of (I-EE) + (I-ZE) in the conversion from E-nerolidol (IVa) comprised ~40% in the first variant; the yield in the two other variants comprised ~37%, which corresponds with the yields of 15 and 14% based on the initial linalool.



We accomplished the conversion of the mixture of the farnesylmalonic esters (Vb), with the 8Z-configuration, to the 3:1 mixture of (I-EZ) and (I-ZZ) according to the method of [7]; it gave precisely the same yield as in the case of the isolation of (Va). The yield of the mixture of (I-EZ) and (I-ZZ) based on linalool comprised 12%.

The testing of the samples of (I), which we obtained, for antiulderogenic activity showed that the mixture of (I-EE) + (I-ZE) gives a significant protective effect in relation to the gastric ulcer induced in rats by injections of noradrenaline.

## EXPERIMENTAL CHEMICAL

The bps of all the compounds obtained were uncorrected. The monitoring of the chemical purity and the ratio of the geometrical isomers was carried out by the method of gas-liquid chromatography (GLC) on an LKhM-8MD instrument with a stainless steel column of 2 m by 3 mm and a flame-ionization detector. The stationary phase was 5% XE-60 on Chromaton N-AW-DMCS with the supplementary silanization by  $(Me_3Si)_2NH$ ; the gas carrier was N<sub>2</sub> at the pressure of 0.495 MPa. The qualitative monitoring of the reaction masses was performed on Silufol plates in the 9:1 system of hexane-AcOEt. The PMR spectra were taken on a Tesla BS-467 instrument (60 MHz) in CCl<sub>4</sub>. The IR spectra were taken on a UR-20 instrument in CCl<sub>4</sub>. The mass spectra were taken on an MX-1303 instrument. The isolation of pure geraniol and its technical mixture with nerol was carried out via the complex with CaCl<sub>2</sub> according to [9]. The properties of the compounds obtained are presented in Table 1.

<u>(E)-Geranylacetone (IIa) and (Z)-Geranylacetone (IIb).</u> The mixture of 2 moles of linalool and 2 moles of acetoacetic ester was rapidly heated to 160-180°C, and was held at this temperature for 3 h until the separation of  $CO_2$  and EtOH ceased. Vacuum distillation afforded the mixture of (IIa) and (IIb) with the bp 125°C (11 mm); the yield of the mixture of (IIa) and (IIb) was 286 g. The rectification of 200 g of such a mixture on a column with a copper packing (100 theoretical plates, r from 20 to 100) gave initially 82 g of the cisisomer (IIb), bp 69-70°C (0.3 mm) and  $np^{18}$  1.4686, and then 108 g of (IIa), bp 71-72°C (0.3 mm) and  $np^{18}$  1.4689.

E-Nerolidol (IVa) and Z-Nerolidol (IVb). The ethynylation of 108 g of (IIa) according to [1] gave the virtually pure E-dehydronerolidol (IIIa), which was characterized by the PMR

TABLE 1. Characteristics of the Compounds Obtained

M <sup>+</sup> , nı/z	402 (M+ - - 2 ), 400 (M+), cf. [4]	402 (M+ -{- 2), 400 (M+), cf. [4]	222 (M+)	222 (M+)	364 (M+)	364 (M+)	292 (M+), 277, 247	292 (M+), 277, 247
δ, ppm (in CCl <sub>4</sub> )	1,5−1,7 broad, s, (2111, δ 1,55>1,65); 1,8−2,1 m (1211); 2,2−2,4 m (411); 4,5 d (211); 5,05 m ≫ 5,30 m (511)	$\begin{array}{l} 1,5-1,7 \ \text{broad, s} \ (2111, \ \delta \ 1,55<1,65); \\ 1,8-2,1m \ (1211); \ 2,2-2,4 \ m \ (411); \ 4,45 \ d \ (211); \\ 5,05 \ m \gg 5,30 \ m \ (511) \end{array}$	1,2 s (3H); $1,52$ s > 1,7 s (9H); $1,9-2,1$ (7H); $5,05-6,06$ m (3H)	The same $1,55 \ s < 1,65 \ s$ (9H)	1,24 t (6H); 1,55 broad, s > 1,65 broad, s (12H); 1,9-2,1 (8H); 2,5 t (2H); 3,2 t (1H); 4,1 q (4H); 5,05 m (3H)	The same $1,55 s < 1,67 s$ (12H)	$\begin{array}{l} 1,20t  (3H); \ 1,55 \ broad, \ s > 1,67 \ broad, \ s \ (12H); \\ 1,87-2,08m \ (8H); \ 2,10-2,32m \ (4H); \ 4,02 \ q \ (2H); \\ 5,05 \ m \ (3H) \end{array}$	The same , $1,55 s < 1,67s$ (1211)
$\nu$ , cm <sup>-1</sup> (in CCl <sub>4</sub> )	37, 1670, 50, 1380,	37, 1670, 50, 1380,		:	40, 1670, 50, 1375,	:	40, 1668, 75, 1255	
	3040, 17 1652, 14 1255	3040, 17 1655, 14 1250		•	3040, 17 1650, 14 1250	•	3040, 17 1448, 13	•
n <sup>(</sup> D. (t°, C)	1,4920 (20)	1,4918 (20)	1,4766 (24)	1,4764 (24)	1,4735 (21)	1,4732 (21)	1,4758 (19)	1,4755 (19)
bp, *C (mm)	17880 (0,07)	174	75—6 (0,07)	73,5-75 (0,07)	128—35 (0,06)	126-8 (0,06)	1147 (0.09)	113-4 (0,09)
Ratio of isomers	3:1	3:1			3:1	3:1	 e	3:1
Compound	I-EE and I-ZE	I-EZ and I-ZZ	IVa	IVb	Va, (E/Z)	VIb, (E/Z)	VIa, (E/Z)	VIh (E/Z) div

spectrum. The product was not distilled; it was hydrogenated in a long-necked hydrogenation flask over 0.6 g of 5% Pd/BaSO<sub>4</sub> with the addition of 1.2 g of powdered KOH (in 100 ml of hexane, 20°C, 0.98 MPa). Before the beginning of the hydrogenation, H<sub>2</sub> was passed through the catalyst; it was saturated with NH<sub>3</sub> gas, and H<sub>2</sub> was again passed through prior to the addition of (IIIa). After 3 h, 12.5 liters of H<sub>2</sub> were absorbed, and the hydrogenation was terminated. The reaction mass was filtered through a column with 10 g of SiO<sub>2</sub>. The column was washed with hexane; the filtrate and the washing were concentrated. The pure (IVa) was obtained by distillation; the yield was 118 g [94% based on (IIa)].

The pure (IVb) was obtained analogously from 81 g of (IIb); the yield of (IVb) was 84 g (90%).

<u>4E/Z,8E-Farnesylmalonic Ester (Va).</u> The mixture of 52 g (0.235 mole) of (IVa) and 50 ml of conc. HCl was stirred intensively for 10 min while cooling it to 0-5°C; the mixture was allowed to settle. The organic layer was separated prior to the addition of a further 50 ml of conc. HCl to it, and the repetition of the same procedure. A saturated solution of NaCl (50 ml) was added; the organic layer was separated, washed with water, washed with NaHCO<sub>3</sub> solution, and washed again with water. The resulting farnesyl chloride was dried over CaCl<sub>2</sub>. Then, 38 g of (0.235 mole) of malonic ester, 102 g (0.75 mole) of K<sub>2</sub>CO<sub>3</sub>, and 0.8 g of KI in 80 ml of dry acetone were added to the mixture. The mixture was boiled for 4-5 h (monitoring by GLC and TLC); the acetone was evaporated. Water was added to the residue until the complete solution of the salts was effected, and the separated oil was extracted with ether. The extract was dried over Na<sub>2</sub>SO<sub>4</sub>; it was concentrated, and the residue was distilled in vacuo. We obtained 48.8 g of (Va); the yield was 57.5% based on the amount of (IVa) taken.

We obtained a 64% yield of 4E/Z,8Z-farnesylmalonic ester (Vb) analogously from (IVb).

<u>Mixture of the Geranyl Esters of (4E,8E)- and (4Z,8E)-Farnesylmalonic Acid, (I-EE) and (I-ZE).</u> The mixture of 36.4 g (0.10 mole) of the diester (Va) and 30.8 g (0.20 mmole) of geraniol was heated under Ar at 185-190°C for 8 h; it was treated according to [7]. The vacuum distillation of the residue led to the 3:1 mixture of (I-EE) and (I-ZE) (GLC and PMR spectral data). The yield was 28.1 g (70%). The form of the PMR and mass spectra agreed with the spectra presented in the works [4, 6].

<u>Mixture of the Geranyl Esters of (4E,8Z)- and (4Z,8Z)-Farnesylmalonic Acid, (I-EZ) and (I-ZZ). These were obtained analogously from the diester (Vb) with the same yield; there was the 3:1 ratio of (I-EZ) to (I-ZZ). The form of the PMR and mass spectra agreed with the spectra of [6, 4].</u>

## EXPERIMENTAL PHARMACOLOGICAL\*

The antiulcerogenic activity of the mixtures of (I-EE) and (I-ZE) and of (I-EZ) and (I-ZZ) were studied in experiments on intact rats of both sexes, weighing 160-200 g. The gastric ulcer was induced in the rats of the control group by a single ip dose of noradrenaline. For 3 h before the injection, the rats of the experimental group received a solution of the mixture of (I-EE) and (I-ZE) in olive oil at the dose of 100 mg/kg. The surviving animals in both groups were killed after 4 days; the extent of the ulceration of the stomach walls was determined macroscopically for the animals of the control and experimental groups. In the control group, the mortality comprised 75%; the mean index of ulceration was equal to 273 mm<sup>2</sup>. In the experimental group, the corresponding values were 25% and 123 mm<sup>2</sup>.

Therefore, the method of the isolation of the geranyl esters of (4EZ,8E)- and (4EZ,8Z)farnesylacetic acids by the malonate synthetic scheme was improved as a result of the investigations carried out; the method permitted their isolation from linalool with the total respective yields of 15 and 12%, based on seven stages. The utilization of the mixture of the chlorides, formed by the action of conc. HCl on the E- or Z-nerolidols, was proposed for the isolation of the farnesylmalonic esters. When diethyl malonate was alkylated by them in acetone with anhydrous  $K_2CO_3$  and 2 m = 7 KI as the catalyst, the yield of the farnesylmalonic esters was higher than that obtained by using the pure farnesyl bromides in the EtONa/EtOH system. The method for the isolation of nerolidols from dehydronerolidols was improved. Data confirming the antiulcerogenic activity of the geranyl esters of farnesylacetic acid were obtained.

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