LOW-MOLECULAR-WEIGHT BIOREGULATORS.
4.* SYNTHESIS OF 2-ISOPROPYL-2,5-DIMETHYL-2,3-DIHYDROFURAN — THE SEX PHEROMONE OF THE LEATHER-WINGED SAILOR *Hylecoetus Dermestoides L.*

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*A new four-stage method has been developed for obtaining racemic 2-isopropyl-2,5-dimethyl-2,3-dihydrofuran — the sex pheromone of the "leather-winged sailor"** Hylecoetus Dermestoides L.

Previously, from females of an active forest pest — the "leather-winged sailor" *Hylecoetus Dermestoides L* — a sex pheromone was isolated and identified as 2-isopropyl-2,5-dimethyl-2,3-dihydrofuran (I) [2]. Its structure was proved by synthesis of the racemate [3] and also the corresponding S-enantiomer on the basis of D-glucose [3, 4]. The stereoisomers of this pheromone were subsequently obtained by a scheme including as the key stage the Sharpless asymmetric oxidation of 2-methylene-3-methylbutanol [5, 6]. There is no information in the literature on the comparative biological activity of the racemic pheromone and its optically active forms; it is known, however, that the racemate is the female's attractant in the above-mentioned species [3]. With the aim of obtaining an effective preparation for combating the "leather-winged sailor" and introducing this preparation into forest protection practice, we have developed a new and simpler method for synthesizing the racemic dihydrofuran I.

The key compound in the synthesis of the dihydrofuran I is 5-isopropenyl-3-carbethoxy-2,5-dimethyl-4,5-dihydrofuran (II), which we obtained by a known procedure through the reaction of 2,3-dimethyl-1,3-butadiene (III) with acetoacetic ester, initiated by trivalent manganese acetate [7]. We have examined two possible variants in the transformation of the intermediate II into the desired pheromone I. The first of these assumes initial decarbethoxylation of the ester II and subsequent hydrogenation of the isopropenyl group of the product that is formed, 2-isopropenyl-2,5-dimethyl-2,3-dihydrofuran (IV). The second variant includes the same stages but in reverse order.

We were not able to accomplish the direct decarbethoxylation of compound II to the dihydrofuran IV by the action of sodium chloride in DMSO at 160°C [8], nor by the action of basic aluminum oxide (Merck, Type T) in moist dioxane [9]. In the first case, we observed 100% conversion of II, but the reaction product was completely converted to tar. In the second case, the original compound II was recovered in unchanged form at the end of the experiment. In view of these results, we then investigated the possibility of a two-stage conversion of the ester II into the dihydrofuran IV. As a result of hydrolysis by aqueous alcoholic caustic, we obtained 5-isopropenyl-3-carboxy-2,5-dimethyl-4,5-dihydrofuran (V), which was then subjected to decarboxylation through the action of copper in quinoline [10], trivalent manganese acetate [11], or bivalent mercury chloride [12]. In all of the reactions that were studied, the decarboxylation reaction did take place, but it proved impossible to recover the expected product IV or any other compounds from the reaction mixture, as they had been completely converted to tar. We were able to effect the transformation by means of copper oxide [13]. With the aim of finding the optimal process conditions, a number of the process parameters were varied: substrate/CuO mole ratio, temperature, and depth of vacuum used.

The yield of compound IV is 66% with a 1:2 mole ratio of substrate to CuO under the following conditions: T 125-155°C at 760 mm Hg (time 3 min), then T 155-175°C at 100 mm Hg (time 7 min) (see scheme below).

The decarboxylated product IV proved to be extremely sensitive to moisture. The addition of a water molecule apparently takes place at the double bond of the dihydrofuran ring with reversible opening of the ring, as had been shown previously in the example of a compound that is structurally related [5]. The corresponding hydroxyketone, 3-hydroxy-2,3-dimethyl-1-hepten-6-one, can be detected in the product IV as a minor component by means of mass spectrometry and IR spectroscopy. The concluding stage of the synthesis was selective hydrogenation of the isopropenyl group of the 2,3-dihydrofuran derivative IV by the action

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*For Communication 3, see [1].

†The Russian name for this insect is "kozhistokrylyi korabel'schik," of which "leather-winged sailor" is a literal translation; the alternative is "skin-winged sailor" (or shipbuilder); no common English name has been found for this insect — Translator.

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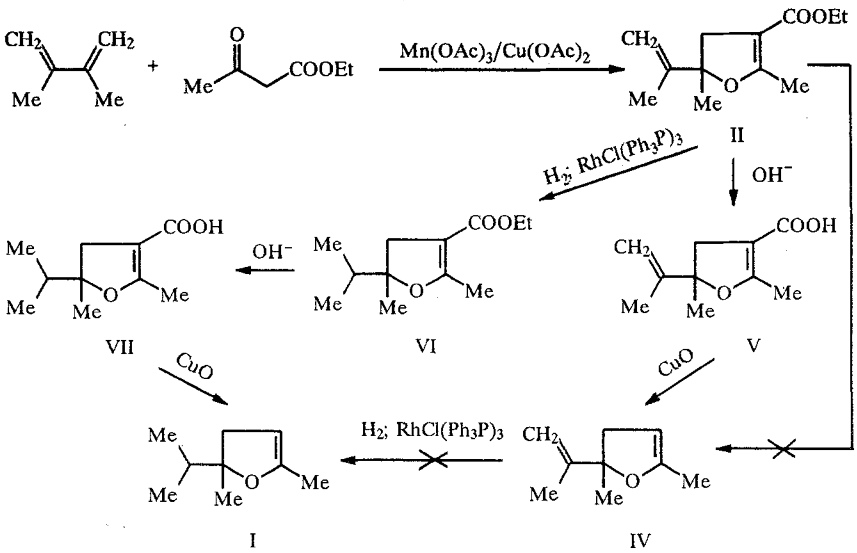

of molecular hydrogen in the presence of rhodiumchloro-tris(triphenylphosphine) [14]. However, despite detailed investigation of the unpurified reaction mixture, isolating the expected product of hydration I, as with the initial compound IV or other products failed.

Thus, chief among marked variants (hydrolysis of ester II with subsequent decarboxylation and hydration) is that pheromone I is not available.

The second variant is the noticeable reduction in intermediate II action of molecular hydrogen in the presence of rhodiumchloro-tris(triphenylphosphine) [14]. This reaction proceeded selectively at the isopropenyl group and led to the formation of 5-isopropyl-3-carbethoxy-2,5-dimethyl-4,5-dihydrofuran (VI). The VI was then subjected to alkaline hydrolysis, and the resulting acid, 5-isopropyl-3-carboxy-2,5-dimethyl-4,5-dihydrofuran (VII), was decarboxylated by the action of copper oxide as described above for compound IV. The desired product, the dihydrofuran I, was formed with a yield of 59%, and it had spectral characteristics identical to those described in [3, 5]. Compound I, the same as its dehydro derivative IV, is extremely sensitive to moisture: In the process of taking the IR spectrum in a thin layer, it became completely dehydrated, with disappearance of frequencies that are characteristic for the corresponding hydroxyketone: 3430 (OH) and 1715 cm^{-1} (C=O). A satisfactory IR spectra can be obtained in a cuvette using carbon tetrachloride as the solvent. It should be noted that the sensitivity of this pheromone to moisture was the source of an erroneous determination of the sign and magnitude of the angle of rotation of its S-enantiomer [3-5].

With the scheme of synthesis that we have developed, the racemate of the sex pheromone of the "leather-winged sailor" can be obtained in four stages with an overall yield of 31% as calculated on the original compound III. It should be noted that the scheme can also be used to obtain enantiomers of this pheromone by splitting the racemic acid VII by means of optically active amines [15]. The lability of the pheromone I in relation to moisture creates rather severe difficulties in formulating this pheromone into a preparation suitable for use in forest protection. It may be that the lifetime of the active substance in the preparative form can be prolonged by formulating the pheromone with a moisture-absorbing substance or by depositing it on an inert, moisture-absorbing support.

EXPERIMENTAL

PMR spectra were obtained in a Perkin—Elmer R-12B spectrometer (60 MHz) in CCl_4 (in the case of compound I, in C_6D_6), with TMS internal standard. The IR spectra were taken in a UR-20 instrument in a thin layer; mass spectra were obtained in an MX-1320 spectrometer with an ionizing electron energy of 70 eV. TLC analysis was performed on Silufol UV-254 plates, with development by a saturated $KMnO_4$ solution. As the sorbent for column chromatography we used Brockman II Al_2O_3 (neutral) and silica gel (40-100 μ).

The spectral characteristics of the synthesized compounds are summarized in Table 1. The results of elemental analysis for C and H were in agreement with the calculated values.

TABLE 1. Spectral Characteristics of Compounds I and IV-VII

Compound	IR spectrum, cm^{-1} [*1]	PMR spectrum, δ ppm (and J, Hz) [*2]				
		2-CH$^+$ (3H)	5-CH$_3$, 3H	CH$_2$(CH) [*3] in ring, m	CH$_2$=C—CH$_3$ (i-C$_3$H$_7$)	
					CH$_2$, CH, 1H, m	CH$_3$, 3H
I	1680 (C=C)	1,20 s	1,68 m	2,30 (2H, J=14,4); 4,37 (1H)	1,5...2,0	0,86 d (J=7,2); 0,89 d (J=7,2)
IV	1648 (C=C), 1680 (C=C), 3102 (vicinal) C—H)	1,30 s	1,68 s	2,40 (2H), 4,24 (1H)	4,60, 4,82	1,68 s
V	1635 (C=C), 1680 (C=O), 2400...3300 (O—H)	2,13 t (J=1,5)	1,37 s	2,67 (2H)	4,70, 4,86	1,71 s
VI	1650 (C=C), 1700 (COOC$_2$H$_5$)	2,04 t (J=1,5)	1,17 s	2,48 (2H)	1,20...2,0	0,82 d (J=6,6); 0,85 d (J=6,6)
VII	1630 (C=C), 1678 (C=O), 2400...3300 (O—H)	2,14 t (J=1,5)	1,24 s	2,56 (2H)	1,20...2,0	0,86 d (J=6,6); 0,90 d (J=6,6)

[*1] In the case of compounds I, V, and VII, spectra were taken from solutions in CCl$_4$; the spectra of the dihydrofurans IV and VI were obtained in a thin layer.

[*2] In the spectrum of compound VI there are also signals of the COOCH$_2$CH$_3$ group: 1.17 (3H, t, J = 7.3 Hz, CH$_3$) and 4.02 ppm (2H, q, J = 7.3 Hz, CH$_2$).

[*3] For compounds I and IV.

[*4] For compounds I and VI.

[*5] Dihydrofuran ring.

5-Isopropenyl-3-carboxy-2,5-dimethyl-4,5-dihydrofuran (V, $C_{10}H_{14}O_3$). A mixture of 420 mg (2 mmoles) of compound II, 1.12 g (20 mmoles) of KOH, 5 ml of ethanol, and 2.5 ml of water was refluxed 4 h. The course of the reaction was monitored by TLC. Then most of the ethanol was driven off at 60°C (14 mm Hg); 5 ml of water was added to the residue, the mixture was chilled to 0°C, and 20% H_2SO_4 was added dropwise to bring the pH to 1. The aqueous layer was salted out and extracted with ether (5 × 20 ml); the extracts were dried with $MgSO_4$. After evaporating the ether, the residue was dried at 60°C (14 mm Hg), obtaining 330 mg (91%) of the acid V, mp 55-56°C, R_f 0.47 (heptane—ether, 1:3).

2-Isopropenyl-2,5-dimethyl-2,3-dihydrofuran (IV, $C_9H_{14}O$). A 218-mg quantity (1.2 mmoles) of the acid V and 192 mg (2.4 mmoles) of CuO were charged to a flanged flask in an argon atmosphere: the flask was then submerged in a Wood's metal bath and held for 3 min at 125-155°C, then 7 min at 155-175°C and 100 mm Hg. Obtained 110 mg (66%) of the product IV, n_D^{20} 1.4285. M$^+$ 138.

5-Isopropyl-3-carbethoxy-2,5-dimethyl-4,5-dihydrofuran (VI, $C_{12}H_{20}O_3$). A hydrogenation flask was charged with 420 mg (2 mmoles) of compound II, 370 mg (0.5 mmole) of $RhCl(Ph_3P)_3$, and 25 ml of degassed absolute benzene; the reaction mixture was shaken in a hydrogen atmosphere until the reaction was completed, as indicated by TLC (3 h). The reaction mixture was then filtered through Al_2O_3 (18 g) and the benzene was driven off, obtaining 380 mg (90%) of the ester VI, n_D^{20} 1.4770, R_f 0.72 (hexane—ether, 1:3).

5-Isopropyl-3-carboxy-2,5-dimethyl-4,5-dihydrofuran (VII, $C_{10}H_{16}O_3$). By a procedure analogous to that for compound V, compound VI was obtained from 2.0 g (9.4 mmoles) of the ester VI by treating with 3.76 g (94 mmoles) of NaOH in 30 ml of ethanol and 15 ml of water. Yield of acid VII 1.65 g (95%), mp 75-77°C, R_f 0.48 (hexane—ether, 1:3).

2-Isopropyl-2,5-dimethyl-2,3-dihydrofuran (I, $C_9H_{15}O$). By a procedure analogous to that for compound IV, compound I was obtained by decarboxylation of 184 mg (1 mmole) of the acid VII in the presence of 159 mg (2 mmoles) of CuO. Yield of I 82 mg (59%), n_D^{20} 1.4341, R_f 0.41 (hexane—ether, 1:1). M$^+$ 140.

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