Proc. Estonian Acad. Sci. Chem., 1992, 41, 4, 169—174
https://doi.org/10.3176/chem.1992.4.03

UDC 547.594.4

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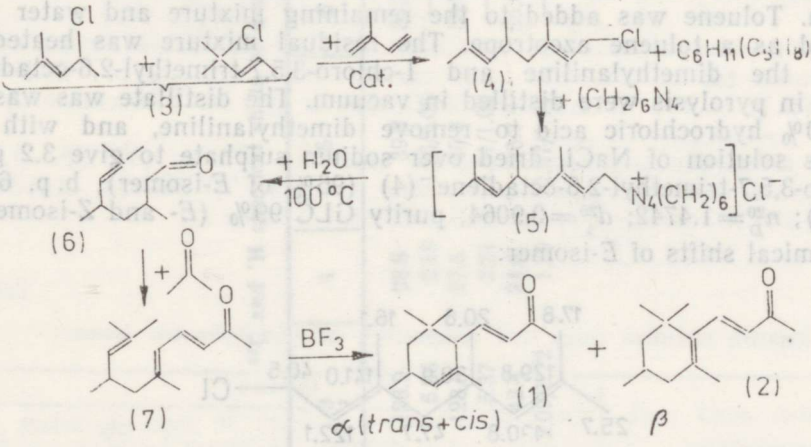
SYNTHESIS OF 4-METHYLIONONE

A seven-step synthesis of 4-methylionones (1, 2) from 4-bromo-2-methyl-2-pentene is known [1]. We have prepared these isomers by a five-step method from the mixture of methylchloropentenes (3) (4-chloro-2-methyl-2-pentene and 4-chloro-4-methyl-2-pentene) with twice the yield compared to [1, 2].

In the well-known synthesis of ionone and irone ([3], p. 375 and 398, respectively) the first step is alkylation of acetone with primary allylic chloride (1-chloro-3-methyl-2-butene or 1-chloro-2,3-dimethyl-2-butene) to get 6-methyl-5-heptene-2-one or 5,6-dimethyl-5-heptene-2-one, respectively. By this method it is practically impossible to synthesize 4-methylionones (1) because the alkylation of acetone with secondary allylic chloride (2-methyl-4-chloro-2-pentene) gives a very low yield of the desired intermediate 4,6-dimethyl-5-heptene-2-one. We have elaborated a new scheme for the synthesis of 4-methylionones: *trans*- and *cis*-α (1) and β (2).



Methylchloropentenes are obtained by hydrochlorination with gaseous hydrogen chloride from the mixture of methylpentadienes (2-methyl-1,3-pentadiene and 4-methyl-1,3-pentadiene). The starting methylpentadienes were prepared by dehydratation of 2-methylpentane-2,4-diol.

The addition of methylchloropentenes to isoprene proceeds in the presence of $SnCl_4$ at 20 °C. The yield of 1-chloro-3,5,7-trimethyl-2,6-octadiene (4) was 58%. Primary allylic chloride (4) is separated as a

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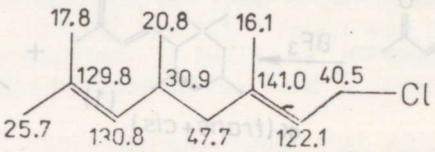
hexamethylenetetramine quaternary salt (5). From the latter 3,5,7-trimethyl-2,6-octadienal (6) was synthesized by steam distillation (the Sommelet-reaction) (yield 52%). Condensation of (6) with acetone in the presence of alkali yields 6,8,10-trimethyl-3,5-9-undecatriene-2-one (7) (pseudo 4-methylionone). By the cyclization of (7) in the presence of BF_3 the target 4-(2,4,6,6-tetramethyl-2-cyclohexene-1-yl)-3-buten-2-one (1) is formed as a mixture of *trans*- and *cis*-isomers along with 4-methyl-β-ionone (2). The odour of the synthesized 4-methylionone (1) is very similar to that of α-irone and it can replace more expensive α-irone in perfumery compositions.

Experimental

Synthesis of 1-chloro-3,5,7-trimethyl-2,6-octadiene (4). To a mixture of 173 g of methylchloropentene isomers and 147 g of isoprene the 2% solution of anhydrous tin tetrachloride was dropwise added by stirring. The reaction temperature was kept at 20 °C. The reaction was quenched by the addition of 10 g of carbamide to the mixture. After stirring, settling, and filtration the unreacted starting compounds were distilled off from the mixture in moderate vacuum. They should be recycled. From the 126 g at residue the fraction of 1-chloro-3,5,7-trimethyl-2,6-octadiene (4) was distilled off at 58—62 °C (2 torr) with a 74% content of (4), yield 58,2%. 8.1 g of crude product, 5.4 g of dimethylaniline, and 5.4 g of methanol were stirred and left overnight. Then 25 to 50 ml of 50% methanol and 30 ml of petroleum ether were added, mixed, and the layers were separated. The aqueous methanol solution was washed twice with petroleum ether and the methanol was distilled off under moderate vacuum. Toluene was added to the remaining mixture and water was removed as a toluene azeotrope. The residual mixture was heated to 120 °C; the dimethylaniline and 1-chloro-3,5,7-trimethyl-2,6-octadiene formed in pyrolysis were distilled in vacuum. The distillate was washed with 10% hydrochloric acid to remove dimethylaniline, and with an aqueous solution of NaCl, dried over sodium sulphate to give 3.2 g of 1-chloro-3,5,7-trimethyl-2,6-octadiene (4) (96% of *E*-isomer), b. p. 65 °C (2 torr); $n_D^{20}=1.4742$; $d_4^{20}=0.9064$; purity GLC 99% (*E*- and *Z*-isomers). ^{13}C chemical shifts of *E*-isomer:



Synthesis of 3,5,7-trimethyl-2,6-octadienal (6). 100 g of the fraction of 1-chloro-3,5,7-trimethyl-2,6-octadiene (74%), 66.5 g of hexamethylenetetramine, 80 ml of dichloroethane, and 15 ml of methanol were mixed at room temperature for 24 h and then 200 ml of water was added. The mixture was stirred and the layers were separated. The upper aqueous layer was washed with dichloroethane, added to 100 ml of 10% acetic acid and 800 ml of an aqueous solution of NaCl, and stirred. The obtained solution was dropwise added to the distillation flask containing an aqueous saturated solution of sodium chloride, 10% acetic acid. Live steam was simultaneously passed through the flask. Water was distilled off and 39.7 g of 3,5,7-trimethyl-2,6-octadienal (6) was obtained. The purity of the product was 86% (*E*- and *Z*-isomers), yield 51.8%.

Table 1

^{13}C and ^{1}H chemical shifts of 4-methylionone isomers [a] (δ_{TMS})

Isomers	1	2	3	4	5	6	7	8	9	10	11	12	13	14
cis-α δ_C	54.1	131.1	128.9	28.5	39.8	33.3	148.3	131.9	197.1	26.8	22.5	21.6	29.0	26.8
δ_H	2.23	—	5.36	2.18	1.26/1.09	—	6.60	6.02	—	2.20	1.57	0.99	0.85	0.95
trans-α δ_C	54.0	131.1	128.8	27.8	45.8	33.7	148.3	134.0	196.9	26.8	22.7	21.8	29.8	22.1
δ_H	2.51	—	5.37	2.21	1.51/1.02	—	6.59	6.10	—	2.24	1.55	0.96	0.91	0.86
β δ_C	135.1	135.6	42.4	24.8	48.7	35.0	142.5	131.7	197.4	27.0	21.5	22.0	30.0	28.1
δ_H	—	—	2.09/1.72	1.79	1.47/1.14	—	7.26	6.09	—	2.26	1.76	0.94	1.06	1.09

[a] see also [4].

Synthesis of 4-methylionone (1). A mixture containing 70 g of acetone and 10 g of 42% caustic soda was dropwise added during 20 min at 20 °C to stirred mixture of 43 g of aldehyde (6). After that the mixture was stirred at 40 °C for 3 h. The mixture was neutralized with acetic acid. Acetone was evaporated and the residue was extracted with toluene. The toluene solution was dried over anhydrous sodium sulphate. The dry toluenic solution was saturated with 19 g of BF_3 at 0 °C. The mixture was stirred at 38 °C for 30 min, neutralized with a 10% caustic soda solution, stirred, and separated. The organic layer was washed with a saturated solution of NaCl at 60 °C. Then toluene was evaporated and 23.4 g of 4-methylionone was isolated from the residue at 85—86 °C (1 torr), purity by GLC 95.1% (ketones), $n_D^{20}=1.4951$, $d_4^{20}=0.9211$.

Methylionone isomers were analysed from their mixture by ^{13}C and ^1H NMR spectroscopy, using 2D ^1H-^1H and ^1H-^{13}C COSY correlations. For the differentiation of *cis*- and *trans*-isomers of (1) chemical shifts of C-5 and geminal methyl groups at C-6 are the most diagnostic. The observed differences (Table 1) give information about the preferred conformations of 1-*trans* and 1-*cis* isomers. C-5 in 1-*cis* and one of the geminal methyls in 1-*trans* have additional gauche interactions, which are reflected in the ^{13}C chemical shifts of the corresponding carbon atoms.

Elemental analysis:
Found, %: C 81.6, H 10.9. Calculated, %: C 81.58, H 10.75. IR-spectrum (cm^{-1}): 830—CH—C<; 1.140; 1.180; 1.195>$C(CH_3)_2$; 980—993; 1.295—CH=CH; 1.365—C(O)CH_3; 1.383;. 1.430—CH_3; 1.460; 1.475—CH_3, —CH_2—, 1.625; 1.635>C=CH—C(O)—; 1.685; 1.700>C=O; 2.730 (2×1.365).

GLC of chlorides: chromatograph Chrom 5 (Czechoslovakia), glass capillary column (41 m, i. d. 0.25 mm) coated with a mixture of TCEP and DEGS (4:1) at 100 °C, sampler 180 °C, carrier gas Ar (1.5 cm^3/min).

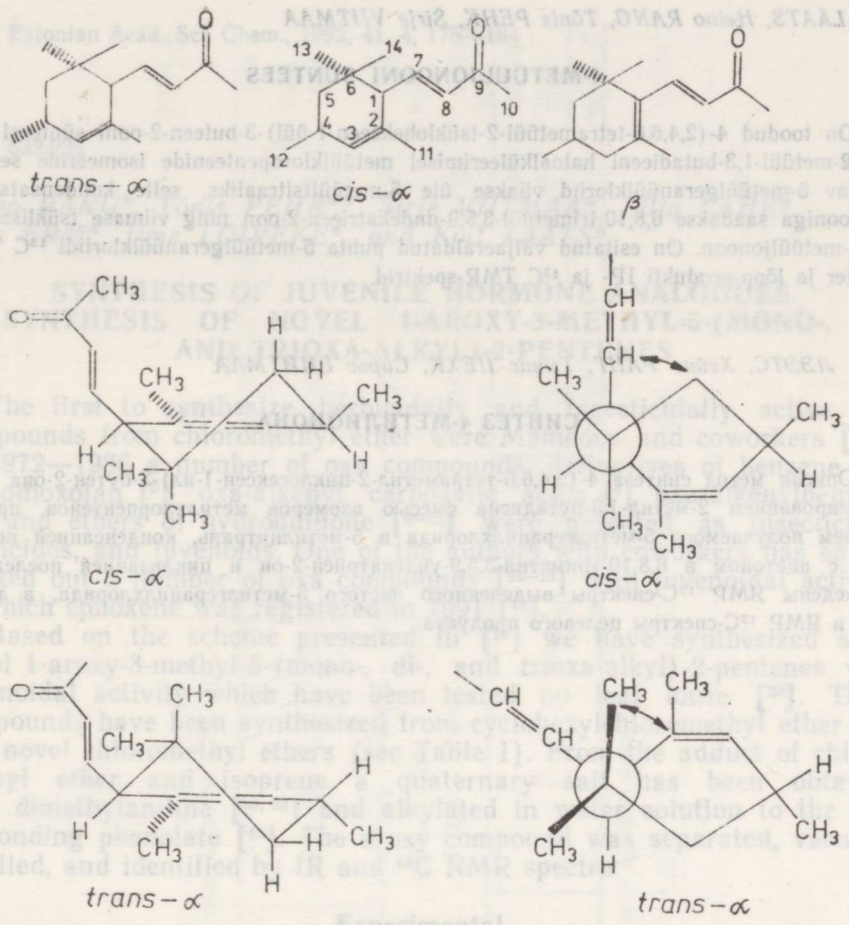
GLC of aldehydes and ketones: glass capillary column (47 m, i. d. 0.3 mm) coated with phenyldiethanolamine succinate (PDEAS) at 150 °C, sampler 260 °C, carrier gas Ar (1.5 cm^3/min) (Table 2).

Table 2

Relative retention times and composition of 4-methylionone isomers

Characteristics	Isomers					
	cis-α	Not identified		*trans*-α	Not identified	β
	1	2	3	4	5	6
Relative retention time	1	1.04	1.07	1.14	1.30	1.39
Content, %	35.2	2.6	3.5	46.7	2.7	9.3

NMR spectra were measured from $CDCl_3$ solutions on Bruker AM-500 spectrometer. Standard pulse programmes for 2D correlations were used. Chemical shifts are referenced from solvent signal ($\delta_C=77.0$, $\delta_H=7.27$ ppm).



Identified isomers of 4-methylionone

Newman projections along C-6–C-1

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Received
March 6, 1992
Revised
June 9, 1992

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4-METÜÜLJONOONI SÜNTEES

On toodud 4-(2,4,6,6-tetrametüül-2-tsüklohekseen-1-üül)-3-buteen-2-ooni sünteesi meetod 2-metüül-1,3-butadieeni haloalküleerimisel metüülkloropenteenide isomeeride seguga. Saadav 5-metüülgeranüülkloriid viiakse üle 5-metüültsitraaliks, selle kondensatsioonil atsetooniga saadakse 6,8,10-trimetüül-3,5,9-undekatrieen-2-oon ning viimase tsüklisatsioonil 4-metüüljonoon. On esitatud väljaeraldatud puhta 5-metüülgeranüülkloriidi ^{13}C TMR-spekter ja lõpp-produkti IP- ja ^{13}C TMR-spektrid.

Койт ЛЭЭТС, Хейно РАНГ, Тынис ПЕХК, Сирье ВИЙТМАА

СИНТЕЗ 4-МЕТИЛИОНОНА

Описан метод синтеза 4-(2,4,6,6-тетраметил-2-циклогексен-1-ил)-3-бутен-2-она галоалкилированием 2-метил-1,3-бутадиена смесью изомеров метилхлорпентенов, превращением получаемого 5-метилгеранилхлорида в 5-метилцитраль, конденсацией последнего с ацетоном в 6,8,10-триметил-3,5,9-ундекатриен-2-он и циклизацией последнего. Приведены ЯМР ^{13}C-спектры выделенного чистого 5-метилгеранилхлорида, а также ИК- и ЯМР ^{13}C-спектры целевого продукта.