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Methods for the Preparation of *trans*-3-Methyl-2-hexenoic Acid, the Malodorous Component of Schizophrenics' Sweat

Keyphrases □ *trans*-3-Methyl-2-hexenoic acid—schizophrenic sweat component, synthesis □ Schizophrenic sweat, malodorous component—synthesis of *trans*-3-methyl-2-hexenoic acid

Sir:

The malodorous component of schizophrenics' sweat (1) has been identified (2) as *trans*-3-methyl-2-hexenoic acid. Although recent studies failed to verify this observation, continued investigation was suggested (3). In the works cited, previously reported procedures (4, 5) were employed for the preparation of the ethyl ester of *trans*-3-methyl-2-hexenoic acid. Reinvestigation showed that these procedures yield four isomers of ethyl *trans*-3-methyl-2-hexenoic acid. The characterization of these isomers and development of alternate, more effective methods for preparing *trans*-3-methyl-2-hexenoic acid are described in this communication.

Table I—Products Formed with Methods A–D

Methods	Products	Ratio	Relative Retention Time ^a
A ^b	Ia	1	0.59
	Ib	2 ^c	0.71
	IIa	1 ^c	0.71
	IIb	2	1.00
B	IIc	4	0.47
	IId	9	0.64
C	IIa	2	0.69
	IIb	3	1.00
D	IIa	3	0.73
	IIb	7	1.00

^a Relative to ethyl *trans*-3-methyl-2-hexenoate (IIb), retention time (from solvent front) = 5.1 min. (eight determinations). ^b The same ratio of products was obtained when POCl₃ or P₂O₅ dehydration was employed. ^c Proportions of these isomers were determined by NMR analysis.

Four procedures were used in preparing the ethyl and methyl esters of *trans*-3-methyl-2-hexenoic acid.

Method A—A recently reported (6) Reformatsky procedure was used to condense ethyl bromoacetate with 2-pentanone. A 67% yield of 3-methyl-3-hydroxyhexanoate was obtained after workup and distillation (109–112°, 10 mm.). Dehydration was accomplished with POCl₃ or P₂O₅ using the procedure of Kon and Nargund (5); distillation (90–97°, 10 mm.) gave a mixture of ethyl *cis*-3-methyl-3-hexenoate (Ia), ethyl *trans*-3-methyl-3-hexenoate (Ib), ethyl *cis*-3-methyl-2-hexenoate (IIa), and ethyl *trans*-3-methyl-2-hexenoate (IIb) in 69% yield.

Method B—Hydrogenation (5% palladium-on-charcoal) and hydrolysis (5% KOH in ethanol) of the unsaturated ester mixture produced by Method A gave an 85% yield of 3-methylhexanoic acid which was homogeneous upon GC¹. By using a general procedure (7) for α -bromination, dehydrohalogenation, and esterification, 3-methylhexanoic acid was converted to a mixture of methyl *cis*-3-methyl-2-hexenoate (IIc) and methyl *trans*-3-methyl-2-hexenoate (IId) in 33% yield.

Method C—The procedure of Wadsworth and Emmons (8) was used to condense triethyl phosphonoacetate with 2-pentanone to form IIa and IIb in 55% yield.

Method D—Reaction of (carbethoxymethylene)-triphenylphosphorane with 2-pentanone, using benzoic acid as a catalyst (9), gave an 87% yield of IIa and IIb.

Ester mixtures were submitted to preparative GC². Compounds IIb and IId were hydrolyzed (5% KOH in ethanol) to form *trans*-3-methyl-2-hexenoic acid in 80–86% yield. *trans*-3-Methyl-2-hexenoic acid had a melting point of 20° (uncorrected), and its spectral characteristics agreed well with reported data (2).

Gas chromatograms¹ of ester mixtures resulting from Method A showed three peaks (Table I). Isolation by preparative GC² of the components represented

¹ Hewlett-Packard 5750B equipped with a flame-ionization detector and a 1.83-m. (6-ft.) × 6-mm. i.d. glass column packed with 3% OV-17 on Gas Chrom Q (100/120 mesh); operated at 84° with a flow rate of 120 ml./min. (He).

² Varian Aerograph A-700 fitted with a 6.09-m. (20-ft.) × 9-mm. i.d. aluminum column packed with 30% SE-30 on Gas Chrom P (45/60 mesh); operated at 90° with a flow rate of 150 ml./min. (He).

Table II—Important IR and NMR Bands of *trans*-3-Methyl-2-hexenoic Acid and Its Ester Analogs

Compound Number	Structure	NMR, Chemical Shift, p.p.m. ^a (Multiplicity ^b , Number of Protons ^c)							ν C=O, cm. ⁻¹
		a	b	c	d	e	f	g	
Ia		0.96 (t,3)	1.25 (t,3)	1.77 (d,3)	2.10 (m,2)	3.03 (s,2)	4.14 (q,2)	5.37 (m,1)	1735
Ib	<i>trans</i>	0.97 (t,3)	1.24 (t,3)	1.71 (d,3)	2.10 (m,2)	2.98 (s,2)	4.15 (q,2)	5.31 (m,1)	1731
IIa		0.97 (t,3)	1.24 (t,3)	1.53 (m,2)	1.88 (d,3)	2.63 (t,2)	4.15 (q,2)	5.70 (m,1)	1714
IIb	<i>trans</i>	0.91 (t,3)	1.28 (t,3)	1.67 (m,2)	2.15 (d,3)	2.15 (t,2)	4.16 (q,2)	5.67 (m,1)	1715
IIc		0.94 (t,3)	1.50 (m,2)	1.87 (d,3)	2.63 (t,2)	3.70 (s,3)	5.67 (m,1)		1717
IId	<i>trans</i>	0.90 (t,3)	1.50 (m,2)	2.15 (d,3)	2.15 (t,2)	3.70 (s,3)	5.67 (m,1)		1718
		0.91 (t,3)	1.50 (m,2)	2.16 (d,3)	2.16 (t,2)	5.69 (m,1)	11.0 (s,1)		1695

^a From tetramethylsilane internal standard, DCCl₃ solutions. ^b s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. ^c Spectrum integration.

by these peaks and spectral analysis (Table II) revealed that a 1:1 mixture of β,γ -: α,β -unsaturated esters was formed. Very similar results have been reported with pentenoic acid esters (5) prepared in an analogous fashion. These findings are in contrast to those recently reported (2, 3) which indicate that IIa and/or IIb exclusively result from reactions employed in Method A³.

Method B provides a product free of β,γ -unsaturated isomers; however, it requires several steps which reduce final yields of *trans*-3-methyl-2-hexenoic acid to less than 15%. Methods C and (especially) D represent considerably improved procedures for preparing *trans*-3-methyl-2-hexenoic acid since only two synthetic steps (*i.e.*, condensation and hydrolysis) are required. Attempts were made photolytically to isomerize (10) IIa to IIb in mixtures obtained from Method D. These experiments, however, were unsuccessful.

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³ The ethyl ester mixture arising from Method A was hydrolyzed in alkali and reesterified with methanol and bis(trimethylsilyl)acetamide. Gas chromatograms of the resulting methyl ester mixture were analogous to those of the original ethyl ester mixture. In addition, two peaks in the methyl ester product had identical retention times to that of IIc and IId. GC of the trimethylsilyl ester mixture revealed four peaks in the same ratio as the products obtained through Method A.

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