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The Synthesis of 2,5-Dialkylcyclopentanones from Aliphatic Aldehydes and Formaldehyde

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Synopsis. Aliphatic aldehydes react with formaldehyde in the presence of dimethylamine hydrochloride at 200 °C to form 2,5-dialkylcyclopentanones in moderate yields. Propanal, butanal, and pentanal give 2,5-dimethyl-, 2,5-diethyl-, and 2,5-dipropylcyclopentanone respectively, but ethanal gives only a tarry material.

A large variety of methods are available for building up the cyclopentanone and cyclopentenone ring.[1-9] In the course of our study of the α-methylation of ketones,[10] we have found a novel method for the preparation of cyclopentanone derivatives by treating aliphatic aldehydes with formaldehyde in the presence of a secondary amine hydrochloride. The combination of straight chain aliphatic aldehydes with formaldehyde in the present method represents a unique pathway to the formation of the cyclopentanone ring.

Experimental

Reagent. The propanal and butanal were distilled and dried over Na_2SO_4. The other reagents were commercial products. Formaldehyde(guaranteed reagent 35% Wako Chemicals Co.,) was used.

Reaction Procedure. An autoclave with a 100-ml capacity, made of stainless steel and equipped with a magnetic stirrer, was used in each run. Forty mmol of aliphatic aldehyde, 35% aqueous formaldehyde (40—80 mmol as formaldehyde), 20 ml of a solvent, and 20—40 mmol of dimethylamine hydrochloride were put into it. After the replacement of the argon in the autoclave, it was kept at 200 °C by electrical heating for 4 h. The products, such as 2,5-dimethyl-, 2,5-diethyl-, 2,5-dipropyl-, and 2,5-dipentylcyclopentanone, were isolated by distillation or column chromatography. They were characterized by their IR, ^1H, ^{13}C-NMR, and mass spectra, and by elemental analysis. The 2,5-dimethylcyclopentanone formed was identified by a comparison of its mp, IR, and ^1H and the ^{13}C-NMR spectra of its 2,4-dinitrophenylhydrazone derivative with those of an authentic sample. GLC analysis was made using internal standards: a column (0.3 cmϕ × 3 m) packed with PEG 20M 10%.

2,5-Diethylcyclopentanone (**1b**); bp 71—76 °C/17 Torr (1 Torr = 133.3 Pa). Found as 2,4-dinitrophenylhydrazone, mp 113—115 °C: C, 56.01; H, 6.24; N, 17.48; O, 20.25%. Calcd for $C_{15}H_{20}N_4O_4$: C, 56.24; H, 6.29; N, 17.48; O, 19.98%. 2,5-Dipropylcyclopentanone (**1c**); bp, 89—92 °C/8 Torr. Found as semicarbazone, mp, 168—170 °C: C, 63.69; H, 10.36; N, 18.56%. Calcd for $C_{12}H_{23}N_3O$: C, 63.96; H, 10.29; N, 18.65%. 2,5-Dibutylcyclopentanone (**1d**); bp 86—92 °C/4 Torr. Found as semicarbazone, mp 118—120 °C: C, 65.80; H, 10.72; N, 16.12%. Calcd for $C_{14}H_{27}N_3O$: C, 66.34; H, 10.74; N, 16.31%. 2,4-Dipentylcyclopentanone (**1e**) was chromatographed on silica gel (3 cm × 30 cm), using benzene as an eluent. A light yellow liquid was obtained.[12]

Analytical Procedure. The infrared spectra were measured on a Hitachi model 215 grating spectrophotometer. The ^1H-NMR spectra were obtained at 60 MHz with a JEOL JNM-60, at 100 MHz with a JEOL JNM-100, and at 220 MHz with a Varian model HR-220 NMR spectrometer. The ^{13}C-NMR spectra were obtained at 25.05 MHz with a JEOL pulsed Fourier transform spectrometer model FX-100. Samples were dissolved in $CDCl_3$ and the chemical shift values were expressed in δ-values (ppm) relative to Me_4Si as an internal standard. The mass spectra were recorded on a JMS-O1SG mass spectrometer.

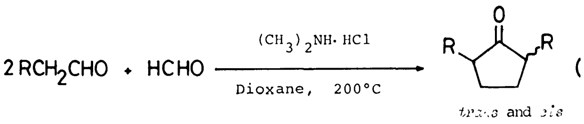
Results and Discussion

Two molecules of aldehydes reacted with one molecule of formaldehyde in the presence of dimethylamine hydrochloride to form 2,5-dialkylcyclopentanones in moderate yields. The results are summarized in the Tables. Each of the C_3—C_7 aldehydes with a straight chain structure, such as propanal, butanal, pentanal, hexanal, and heptanal, gives the corresponding 2,5-

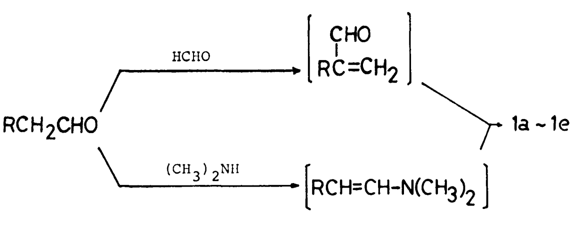
TABLE 1. SYNTHESIS OF 2,5-DIALKYLCYCLOPENTANONES FROM ALIPHATIC ALDEHYDES AND FORMALDEHYDE[a)]

Run	Aldehyde	Substituted cyclopentanone	Yield/%
1	Ethanal	Tarry material	
2	Propanal	2,5-Dimethyl-(**1a**)	16[b)]
3	Butanal	2,5-Diethyl-(**1b**)	22[b)]
4	Pentanal	2,5-Dipropyl-(**1c**)	26[c)]
5	Hexanal	2,5-Dibutyl-(**1d**)	19[c)]
6	Heptanal	2,5-Dipentyl-(**1e**)	21[c)]
7[d)]	Butanal	None	≈0

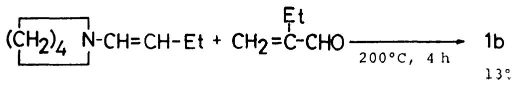
a) Aldehyde 40 mmol, $NH(CH_3)_2 \cdot HCl$ 40 mmol, HCHO, 80 mmol, 200 °C, 4 h, dioxane 20 ml, HCOOH 20 mmol. b) Determined by GLC. Based on the amount of aldehyde used. c) Isolated yield. d) Without $NH(CH_3)_2 \cdot HCl$.



1a~1e
(1)



(2)



(3)

Table 2. Spectroscopic data of 2,5-dialkylcyclopentanones

		IR $\nu_{C=O}/cm^{-1}$	M^+	^{13}C-NMR (ppm from TMS)				
				C=O	CH	CH_2 (in ring)	CH_2 (side chain)	CH_3
1b	*trans*	1740	140	222.2	51.0	27.0	23.0	11.7
	cis			222.8	49.9	26.2	23.1	12.0
1c	*trans*	1740	168	222.2	49.3	27.7	32.3 20.7	14.0
	cis			222.6	48.2	26.8	32.4 20.8	
1d	*trans*	1740	196	223.0	49.4	27.7	29.8 29.6 22.7	13.9
	cis			223.6	48.3	26.7		
1e	*trans*	1740	224	222.5	49.5	27.7	31.8 30.0 27.1 22.5	14.0
	cis				(48.4)	(26.8)		

dialkylcyclopentanone. Ethanal failed to give cyclopentanone, but provided only a tarry material. The amine salt is necessary for this ring formation (see Run 7).

The ^{13}C-NMR spectra of the products from butanal, pentanal, hexanal, and heptanal exhibited two sets of peaks with different intensities, assignable to *trans*- and *cis*-2,5-dialkylcyclopentanone.[11] The *trans* isomers predominate in **1b**, **1c**, and **1d**, and the *trans* to *cis* mole ratios are estimated to be about 2 : 1 from the height of peaks of ^{13}C-NMR spectra. With **1e**, the *trans* isomer highly predominates, and only a trace of the *cis* isomer is formed.

Though the mechanism of this reaction is not yet clear, the following two condensates are considered to be the reaction intermediates: the 2-alkylpropenal derived by the reaction of the aldehyde with formaldehyde, and an enamine (Eq. 2). 2,5-Dialkylcyclopentanones may be derived from these condensates *via* several steps. This consideration may be supported by the fact that the reaction between 2-ethylpropenal and 1-(1-pyrrolidinyl)-1-butene at 200 °C for 4 h gave 2,5-diethylcyclopentanone in a 13% yield, while 2-alkylpropenals were readily formed under the conditions used.

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12) Although **1e** could not be isolated in an analytically pure form and failed to give its semicarbazone and 2,4-dinitrophenylhydrzaone, it was identified on the basis of its spectral data.