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ON THE ELIMINATION OF METHANOL FROM STEREOISOMERIC ARYLCYCLOHEXYL METHYL ETHERS UNDER ELECTRON IMPACT

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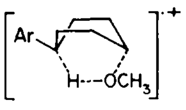
Abstract—The elimination of methanol from 3- and 4-arylcyclohexyl methyl ethers under electron impact exhibits stereoselectivity, which is similar to that found for the elimination of H_2O from the corresponding arylcyclohexanols. The two eliminations also exhibit a similar substituent effect correlation. The similarity holds in the site specificity of these processes *only* for the *trans*-isomers. The *cis*-ethers undergo elimination of methanol by a mechanism which is different from that for the elimination of H_2O from the *cis*-alcohols.

In a previous publication we have shown that the introduction of an aryl substituent at the 3 or 4 positions in cyclohexanol enhances the stereospecific *cis*-elimination of H_2O under electron impact by increasing the mobility of the tertiary H-atom which is involved in this process.[1] This enhancement is best seen in the stereoisomeric 3-arylcyclohexanols which differ considerably in their mass spectral dehydration in contrast to the 3-alkyl analogs.

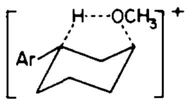
It is always useful to generalize. With this in mind, and in view of our long and favorable experience with stereoselective methanol eliminations,[2] we decided to examine the behavior of the corresponding methyl ethers.

It has been shown that the difference in the elimination of MeOH between *cis*- and *trans*-4-t-butylcyclohexyl methyl ethers is less pronounced than the difference in the dehydration of the corresponding stereoisomeric alcohols.[3] It has been suggested that the *cis*-1,4-elimination in the *trans*-ether is not as great as the loss of H_2O from the alcohol because of charge stabilization on the ether O atom due to the inductive effect of the Me group. On the other hand the higher abundance of $[M\text{-}MeOH]^{\cdot+}$ ion in the *cis*-isomer (both the lower abundance in the *trans*- and higher in the *cis*-ether are suggested to contribute to the observed lower stereoselectivity) has been attributed to a 1,3-elimination, which is accelerated in the ether because of a larger steric strain.[3]† As expected by analogy to the alcohols, both 3- and 4-arylcyclohexyl methyl ethers **1–9** exhibited stereoselective elimination of methanol under electron impact at 70 eV and at low ionizing energies. Comparison of data listed in Table 1 with those reported for the corresponding alcohols shows that there is no decrease in stereoselectivity in the ethers. On the contrary, the ratio $\{[M\text{-}ROH]^{\cdot+}/M^+\}_{trans}/\{[M\text{-}ROH]^{\cdot+}/M^+\}_{cis}$ (R = H for alcohols and CH_3 for ethers), which seems to be the best criterion for stereoselectivity, is higher for most ethers (it is considerably lower only for **1**). Moreover, in analogy to the alcohols the *trans*-ethers exhibit a strong substituent effect. There is a linear correlation of $\log Z/Z_0$ with σ^- (with the exception of **6t**), and the slopes have values similar to that of the *trans*-alcohols. There is no significant substituent effect in the elimination of CH_3OH from the *cis*-ethers, which is again similar to the behavior of the *cis*-arylcyclohexanols.

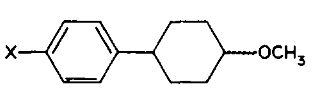
All these data would suggest that the elimination of methanol from the ethers takes place by mechanisms similar to that of the dehydration of the corresponding alcohols. Labelling with deuterium at the benzylic position (C-4 in **1**, **2** and **5**, and C-3 in **6**, **7** and **9**) of the ethers was undertaken to test this suggestion. Data listed in Table 2 show that as expected the elimination of methanol from the *trans*-ethers involves mainly the benzylic H-atom both in the 3- and 4-aryl series. This result together with the stereoselectivity and the substituent effect may be considered as proof that this process is indeed mainly a *cis*-elimination, occurring through cyclic transition states **A** and **B** in which the original configuration has been retained.



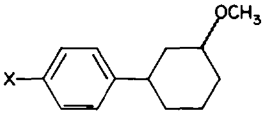
A



B



1: (*cis* and *trans*). X = NO_2
2: (*cis* and *trans*) X = H
3: (*cis* and *trans*)· X = CH_3
4: (*cis* and *trans*) X = OCH_3
5: (*cis* and *trans*)· X = NH_2



6: (*cis* and *trans*) X = NO_2
7: (*cis* and *trans*): R = H
8: (*cis* and *trans*). R = OCH_3
9: (*cis* and *trans*)· R = NH_2

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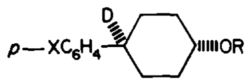
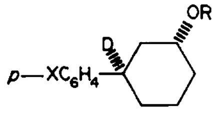
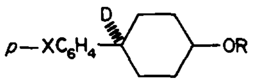
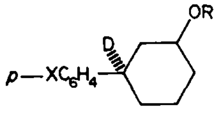
†This assumption is open to question, if the ΔG°_x values[4] are considered to be relevant in the reactions of gas-phase ions.

Table 1. The abundances of $[M-CH_3OH]^{\cdot +}$ in the 70 eV mass spectra of stereoisomeric 4- and 3-arylcyclohexyl methyl ethers

		% $\Sigma_{40}[M-CH_3OH]^{\cdot +}$		Rel. Abundance		$[M-CH_3OH]^{\cdot +}/M^{\cdot +}$		Ratio trans/cis
Cpd.	X	cis	trans	cis	trans	cis	trans	
1	NO_2	7.7	15.5	16.4	63.0	3.1	63.0	20.3
2	H	4.6	15.8	32.6	100	0.96	28.6	29.8
3	CH_3	3.9	16.1	33.9	100	0.56	16.8	30.0
4	OCH_3	6.0	19.3	37.9	100	0.55	3.5	6.4
5	NH_2	6.1	13.2	33.3	100	0.47	1.3	2.8
6	NO_2	9.2	10.7	95.7	100	1.2	130	108
7	H	7.2	15.6	75.0	100	1.2	78	65
8	OCH_3	6.3	10.1	69.8	100	0.73	3.9	5.3
9	NH_2	6.2	13.3	51.4	100	0.52	1.3	2.5

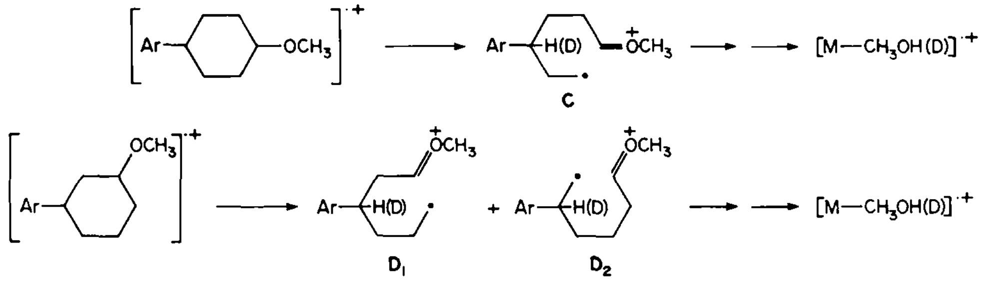
Table 2.

		R = CH_3		R = H	
	X	$[M-CH_3OD]^{\cdot +}$	$[M-CH_3OH]^{\cdot +}$	$[M-HOD]^{\cdot +}$	$[M-H_2O]^{\cdot +}$
	NO_2	96%	4%	85%	15%
	H	88%	12%	84%	16%
	NH_2	90%	10%		
	NO_2	93%	7%		
	H	78%	22%	85%	15%
	NH_2	90%	10%		
	NO_2	90%	10%	24%	76%
	H	69%	31%	33%	67%
	NH_2	63%	37%		
	NO_2	51%	49%		
	H	50%	50%	3%	93%
	NH_2	79%	21%		

Thus far the expectation of similar behavior of the alcohols and ethers has been fulfilled. The unexpected appeared upon examination of the deuterium labelling results of the *cis*-isomers (Table 2); there is a significant dissimilarity between these two groups of compounds, despite the excellent correlation in stereoselectivity and substituent effect. The elimination of methanol from the *cis*-arylcyclohexyl methyl ether involves the benzylic hydrogen to a great extent (the site specificity is never below 50%, and reaches 90% in one case), in contrast to the alcohols in which the involvement of the benzylic H-atom is much lower (3% and 33% are the extreme values).

It is interesting that despite the involvement of the benzylic hydrogen in the elimination of methanol from the *cis*-ethers, no significant substituent effect has been observed. We suggest that a great part of the elimination from the *cis*-ethers occurs after ring-opening caused by the cleavage of C–C bonds adjacent to the ether function (intermediate-ions C and D). The benzylic H-atom is then transferred to the OCH_3 group, and the elimination of MeOH occurs after additional transformations. The lack of substituent effect indicates that the transfer of the benzylic hydrogen is not the rate determining step in this multi-step fragmentation.

On the other hand the *cis*-alcohols prefer to ring-open



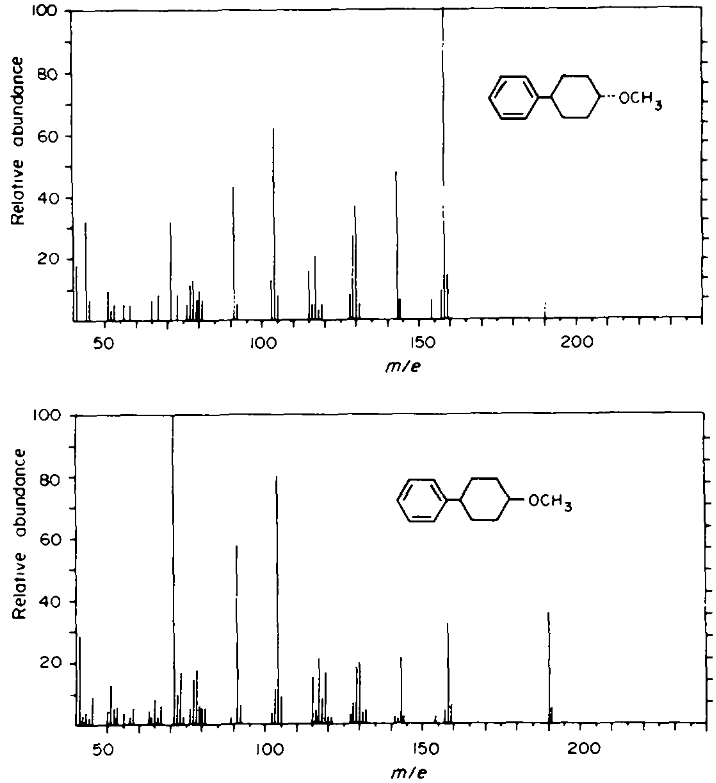


Fig. 1. 70 eV mass spectra of *trans*- and *cis*-4-phenylcyclohexyl methyl ethers (**2**-*trans* and **2**-*cis*).

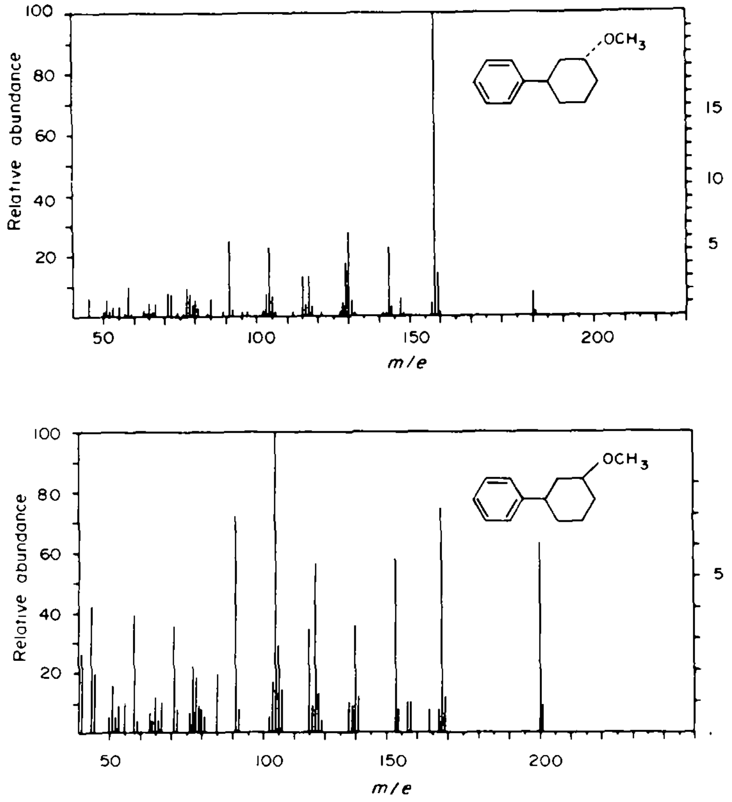


Fig. 2. 70 eV mass spectra of *trans*- and *cis*-3-phenylcyclohexyl methyl ethers (**7**-*trans* and **7**-*cis*).

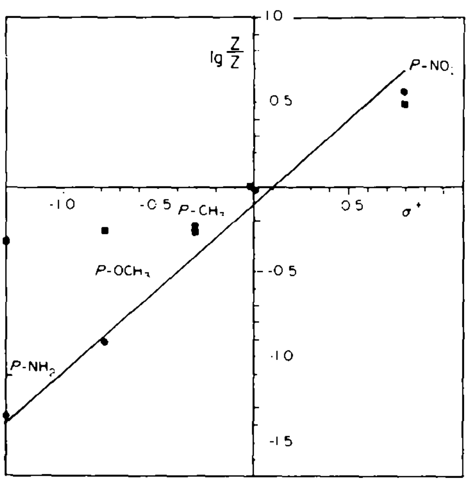


Fig. 3. Log Z/Z_0 ($Z = [M-CH_3OH]^{+\cdot}/[M]^{+\cdot}$, $Z_0 = Z$ for the unsubstituted phenylcyclohexyl methyl ether) vs σ^+ for stereoisomeric 4-arylcyclohexyl methyl ethers at 70 eV: ●-*trans*; ■-*cis*.

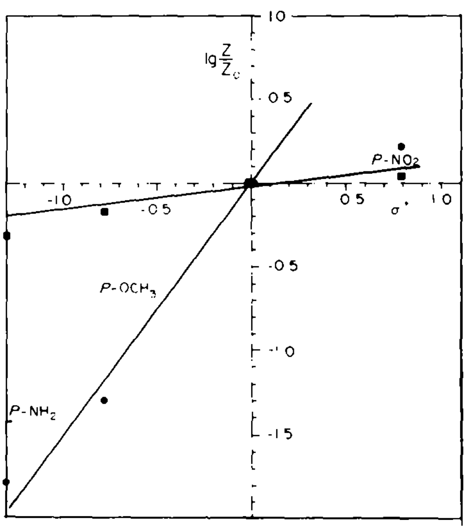
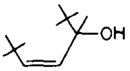


Fig. 4. Log Z/Z_0 ($Z = [M-CH_3OH]^{+\cdot}/M^{+\cdot}$) vs σ^+ for stereoisomeric 3-arylcyclohexyl methyl ethers at 70 eV: ●-*trans*; ■-*cis*.

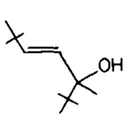
by cleavage of the C–C bond adjacent to the aryl group, giving **E** and **F** prior to dehydration. Relatively a small portion of the dehydration takes place via intermediates analagous to C and D. These different tendencies of alcohols and ethers can be explained either by different charge distribution in their molecular ions or by different stability of the corresponding oxonium ions (C=O–H from alcohols vs C=O–Me from methyl ethers).

The difference in the mechanism of MeOH elimination between *cis*-arylcyclohexanols and their methyl ethers apparently stems from the different tendencies of alcohols and ethers to undergo H-transfers and β-fissions. Aliphatic alcohols and ethers are entirely different in this respect, the former preferring elimination of H_2O while the latter undergo mainly β-cleavages[5] (the $[M-ROH]^{+\cdot}$ ion in ethers may also arise by a two-step fragmentation: $M^{+\cdot} \rightarrow [M-RO]^{+} \xrightarrow{-H} [M-ROH]^{+\cdot}$).[6] These different tendencies can also explain the difference in the source of H-atoms involved in dehydration upon electron impact of cyclohexanol (42% from C-4 and 42% from C-3 and C-5) as compared to cyclohexyl methyl ether (23% from C-4 and 66% from C-3 and C-5).[7]

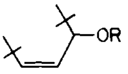
Delving in mass spectral data listed without comments in the experimental sections of unrelated papers is hard work, but it is sometimes rewarding.† In our case "out of the strong came forth sweetness",[9] as an interesting analogy could be extracted from the experimental data published by House and Weeks for compounds **10–12**.[10] The tertiary alcohols **10** *cis* and **10** *trans* exhibit different fragmentation patterns. The *cis*-alcohol gives rise to a more abundant $[M-H_2O]^{+\cdot}$ ion than the *trans*-isomer (rel. abundance 16% vs 1%). This can be explained by the proximity of the OH group to the three Me groups on the other side of the double bond in *cis* −**10**. The most abundant fragment in the mass spectrum of *cis* −**10** is formed by the loss of a t-Bu radical (*m/e* 127, 100%). This fragmentation is rather unimportant in *trans* −**10** (16%). This difference may be attributed to the greater steric strain in the *cis*-isomer.[11] These differences (together with other, which appear more difficult to explain) clearly show

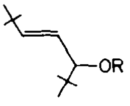


10: *cis*



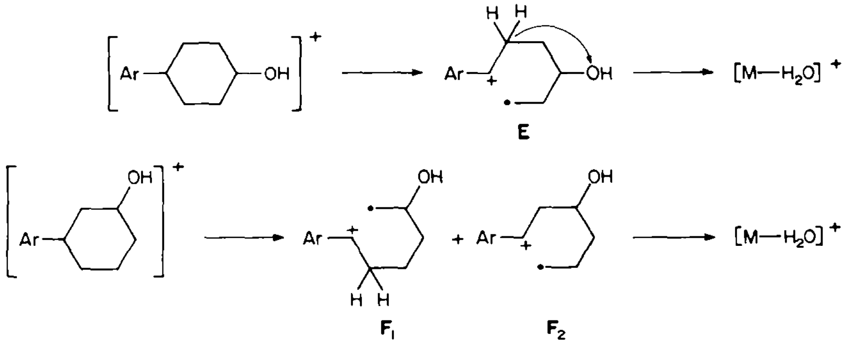
10: *trans*





11: *cis* R = H
12: *cis* R = Me

11: *trans*. R = H
12: *trans*. R = Me



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†This is in keeping with the ancient statement by R. Itzhak: "If a man says to you 'I have labored and not found', do not believe him; if he says 'I have labored and found', you may believe him".[8]

the great extent of configuration retention of the molecular ions of these isomers prior to main fragmentation processes.

The secondary alcohols *cis* $-$**11** and *trans* $-$**11** do not appear to lose H_2O according to the reported data, and only *cis* $-$**11** exhibits loss of the t-Bu radical giving rise to a relatively low abundance $[M-57]^+$ ion (*m/e* 113, 14%). On the other hand the loss of the t-Bu radical affords most abundant ions (*m/e* 127) in the mass spectra of both isomeric corresponding methyl ethers *cis* $-$**12** and *trans* $-$**12**, which are identical to each other in the high mass range. This remarkable difference between the fragmentations of **11** and **12** is another example of the effect of the different tendency of alcohols and ethers to undergo β-fission upon electron impact.

EXPERIMENTAL

Mass spectra were measured with an Atlas CH-4 mass spectrometer fitted with a EB4 ion source and direct inlet system.

NMR spectra were measured with a Varian T-60 spectrometer in $CDCl_3$ with tetramethylsilane as internal reference compound.

Gas chromatographic analyses and collections were performed on a Varian Aerograph 90-P instrument using 3% SE-30 or 3% XE-60 columns on Chromosorb Q (1.8 m × 1/4 in).

Materials

4- and 3-Phenylcyclohexyl methyl ethers **2** *and* **7**, *4-p-tolylcyclohexyl methyl ethers* **3**, *and 4- and 3-p-anisylcyclohexyl methyl ethers* **4** *and* **8**. Prepared by Grignard reaction of the appropriate arylmagnesium bromides and 4- and 3-methoxycyclohexanone followed by hydrogenolysis of the resulting hydroxy-ethers. A typical procedure: A soln of the methoxycyclohexanone (1 mmole) in dry ether (5 ml) was added to a cooled ether soln (20 ml) of the Grignard reagent (10 mmole). After several hr reflux water (2 ml) was added and the ether soln was separated, washed, dried and evaporated off. The crude product dissolved in MeOH (30 ml) was hydrogenolyzed at atmospheric pressure on Pd/C 30% (20 mg) until 1 mole equivalent of H_2 was absorbed (several hr to 1 week). Solvent evaporation from the filtered solution yielded a crude mixture of stereoisomers, which were separated by preparative TLC on 1 mm thick 20 × 20 cm alumina plates. Data are listed in Table 3.

4- and 3-p-Nitrophenylcyclohexyl methyl ethers **1** *and* **6**. Prepared by nitration of **2** and **7** respectively by cupric nitrate in acetic anhydride.[1] Data listed in Table 3.

4- and 3-p-Aminophenylcyclohexyl methyl ethers **5** *and* **9**. Obtained by hydrogenation of the corresponding *p*-nitrophenylcyclohexyl methyl ethers at atmospheric pressure on Pd/C 10% in MeOH. The pure products were obtained by TLC on 1 mm thick silica 20 × 20 cm plates ($CHCl_3$–MeOH 95:5). The aminoethers tend to darken on standing. Data are listed in Table 3.

Deuterium labelling. Deuterium exchange of the benzylic hydrogen was achieved by heating a mixture of the phenylcyclohexyl ethers (400 mg of the mixture of stereoisomers) in d_6-dimethylsulfoxide (2 ml) and sodium hydride (140 mg) at 125–135° for 24 hr. Addition of D_2O (1 ml) followed by benzene extraction and evaporation yielded the product. Four treatments gave a relatively high degree of exchange, after which the stereoisomers were separated by preparative TLC. The yields were high (~90%) as well as the isotope incorporation, in contrast to the corresponding alcohols.[1] The following isotopic compositions have been found:

cis-4-d_1-4-phenylcyclohexyl methyl ether: d_0 4%; d_1–96%
trans-4-d_1-4-phenylcyclohexyl methyl ether: d_0–15%; d_1–85%
cis-3-d_1-3-phenylcyclohexyl methyl ether: d_0–9%; d_1–88%; d_2–3%
trans-3-d_1-3-phenylcyclohexyl methyl ether: d_0–16%; d_1–80%; d_2–4%.

The deuterated nitrophenyl- and aminophenylcyclohexyl methyl ethers were prepared by nitration followed by hydrogenation of the corresponding stereoisomeric deuterium labelled phenylcyclohexyl methyl ethers, without any loss in the label.

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[2] Refs. 9–15 in Ref. 1.

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Table 3. Experimental data for 3- and 4-arylcyclohexyl methyl ethers

Compd.	m.p.° (solvent)	b.p.°/torr	Analysis Found % C	 H	 N	 Calc. % C	 H	 N	NMR absorption of the carbinol proton
1 *cis*	97–9 (hexane)				6.12			5.95	3.55
1 *trans*	52–4 (hexane)				6.08			5.95	3.3
2 *cis*		105/0.8	81.90	9.41		82.06	9.54		3.55
2 *trans*		120/1	81.84	9.47		82.06	9.54		3.3
3 *cis*		105–110/0.9	77.27	8.42		77.55	8.68		3.55
3 *trans*		105–110/0.9	77.39	8.57		77.55	8.68		3.3
4 *cis*	35–6 (pentane)		76.54	9.24		76.32	9.15		3.55
4 *trans*	54–6 (pentane)		76.37	9.04		76.32	9.15		3.3
5 *cis*	194–5[a] (benzene-chloroform)				6.89			6.82	3.6
5 *trans*	51–3 (pentane)				6.93			6.82	3.35
6 *cis*	73–5 (hexane)				6.10			5.95	3.3
6 *trans*	85–7 (hexane)				6.06			5.95	3.6
7 *cis*		105/1							3.25[b]
7 *trans*		105/1							3.6[b]
8 *cis*		105–110/0.55	76.33	9.07		76.32	9.15		3.3
8 *trans*		105–110/0.55	76.44	9.17		76.32	9.15		3.55
9 *cis*	55–6 (hexane)				6.89			6.82	3.3
9 *trans*	53–5 (hexane)				6.75			6.82	3.5

[a] Hydrochloride.

[b] IR, NMR and MS in agreement with data reported in the literature.[12]

[5]H. Budzikiewicz, C. Djerassi and D. H. Williams, *Mass Spectrometry of Organic Compounds*, pp. 94–102; 227–231. Holden-Day, San Francisco (1967).

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[9]Judges, 14, 14.

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