APPLICATION OF CHROMATOGRAPHIC MASS SPECTROMETRY IN THE ANALYSIS OF MIXTURES OF THE STEREOISOMERS IN THE 1,2-DIMETHYL- AND 1-ETHYL-2-METHYL-4-ALKYLPERHYDRO-4-QUINOLOL SERIES

V. G. Zaikin, V. I. Smetanin,
N. S. Vul'fson, A. A. Akhrem,
and L. I. Ukhova

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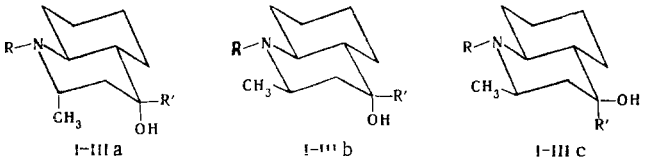
It is shown on the basis of a comparison of the mass-spectral data obtained by admission of the individual substances into the ion source through direct introduction and by introduction of mixtures of the stereoisomers through a gas chromatograph that the chromatographic mass-spectrometric method can be successfully used for the qualitative and quantitative analysis of mixtures of stereoisomers in the 1,2-dimethyl- and 1-ethyl-2-methyl-4-alkyldecahydro-4-quinolol series.

The combined gas chromatographic-mass spectrometric method is presently widely used in the analysis of mixtures of organic compounds.

However, there are practically no special papers devoted to the elucidation of the possibilities of this method in the investigation of mixtures of stereoisomers formed during synthesis or isolable from natural objects. However, research of this sort is expedient, since the application of mass spectrometry to the solution of stereochemical problems, as a rule, involves rather rigid requirements demanded by the experimental conditions. In particular, it is important that the temperature be maintained as low as possible in the region of vaporization of the sample and in the ionization chamber [1]. At the same time, during chromatographic mass-spectrometric analysis the substance passing along the column and through the molecular separator for a rather long time comes in contact with heated surfaces, the temperature of which usually is rather high. In this case the thermal effect may substantially distort the mass spectrum of the substance and, in the case of mixtures of stereoisomers, may lead to a decrease in the quantitative differences in their spectra.

For the present investigation we used mixtures of stereoisomers in the 1,2-dimethyl- (I, III) and 1-ethyl-2-methyl-4-alkyldecahydro-4-quinolol (II) series, the presence of a hydroxy group in which may be responsible for the thermal lability of these compounds. We have previously developed [2-4] a mass-spectrometric approach to the determination of the configurations of the 2 and 4 centers in the molecules of these compounds, and it was therefore interesting to ascertain whether the quantitative differences in the mass spectra of these stereoisomers observed when direct introduction into the ion source is used would be retained if the substance was introduced in a mixture with other stereoisomers through a gas chromatograph.



I-III a I-III b I-III c

I $R=CH_3$, $R'=C_2H_5$; II $R=C_2H_5$, $R'=C_2H_5$; III $R=CH_3$, $R'=C_4H_9$-*n*

A. V. Topchiev Institute of Petrochemical Synthesis, Academy of Sciences of the USSR, Moscow. M. M. Shemyakin Institute of Bioorganic Chemistry, Academy of Sciences of the USSR, Moscow. Institute of Bioorganic Chemistry, Academy of Sciences of the Belorussian SSR, Minsk. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1537-1539, November, 1976. Original article submitted February 13, 1976.

TABLE 1. Ratio of the Intensities of the Ion Peaks

Compound	$J_{[M-CH_3]^+}/J_{[M]^+}$		$J_{[M-R']^+}/J_{[M]^+}$	
	MS	GCMS	MS	GCMS
Ia	7,4	7,2	5,0	4,7
Ib	3,8	4,6	3,4	4,2
Ic	4,4	5,1	8,0	9,8
IIa	6,2	7,5	5,3	6,3
IIb	4,0	4,8	3,6	4,9
IIc	3,1	4,4	8,5	8,8
IIIa	7,2	8,1	5,1	5,8
IIIb	4,4	4,1	4,3	5,6
IIIc	4,2	5,0	8,5	9,6

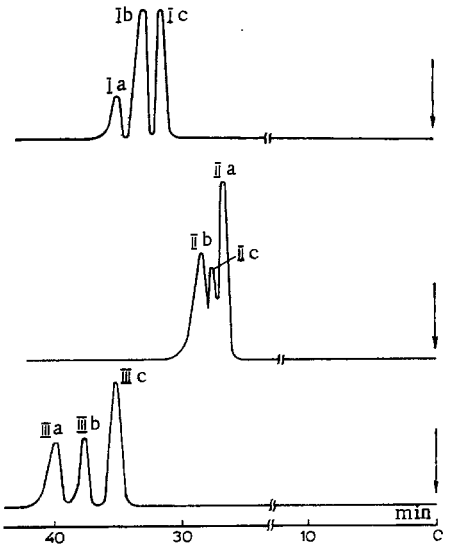


Fig. 1. Chromatograms of the mixtures of stereoisomers.

The research was carried out with a LKV-2091 chromatographic mass spectrometer (ionizing-electron energy 70 eV, emission current 50 μA, ionization chamber and molecular separator temperature 250°C) with the application of a 3 m by 3 mm glass-packed column [stationary phase Carbowax 20-M, solid support Chromaton N-AW-DMCS, carrier-gas (helium) flow rate 20 ml/min]. The chromatograms of the mixtures of stereoisomers, which represent the recording of the change in the total ion current during passage of the substances into the ionization chamber of the mass spectrometer, are presented in Fig. 1 (temperature programming from 120° at a rate of 3°/min was used in the case of mixtures of Ia-c and IIIa-c, and temperature programming from 105° at a rate of 5°/min was used in the case of IIa-c).

Since the ionization cross sections of the stereoisomers were identical, the ratio of the areas of the chromatographic peaks is equal to the weight and molar ratios of the stereoisomers in the investigated mixtures. Mixtures having the following component ratios were compared: Ia-Ib-Ic = 7 : 18 : 12, IIa-IIb-IIc = 20 : 15 : 10, and IIIa-IIIb-IIIc = 19 : 11 : 17. The chromatographic peaks were identified by means of these values and the ratios of the peak areas.

In the case of mixtures Ia-Ic and IIIa-IIIc, which are satisfactorily resolved under the chromatographic conditions used, the mass spectra of the individual compounds were recorded when the maximum of the total ion current was reached. The mass spectra were recorded for the sides of the peaks for the poorer resolving conditions for IIa-IIc.

For the determination of the configurations of the 2 and 4 centers in the examined stereoisomers, we have previously used [2-4] the ratio of the intensities of the peaks of the $[M - CH_3]^+$ (elimination of a 2-CH_3 group) and $[M - R']^+$ ions (elimination of a 4-alkyl group) to the intensity of the molecular ion peak. These values, obtained, on the one hand, when direct introduction of the individual samples into the ion source (MS) [2-4] was used, and on the other, when gas-chromatographic introduction (GCMS) under the described conditions was used,

are presented in Table 1. Despite the fact that these values do not coincide in absolute value with one another (which may also be associated with the different geometries of the devices used), the character of their change on passing from one series of stereoisomers to another is retained. In fact, the $J_{[M-CH_3]^+}/J_{[M]^+}$ values also remain considerably higher in the case of Ia-IIIa, which contain an axial 2-CH_3 group, whereas the $J_{[M-R']^+}/J_{[M]^+}$ values for Ic-IIIc, with an axial 4-R' group, also remain higher than the values observed for their stereoisomers. It should be noted that no appreciable increase in the peaks of the dehydration ions was observed in the mass spectra obtained in the case of gas-chromatographic introduction.

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INDOLIZINES

IV.* PROTONATION OF 2-ALKYL(ARYL)-6- AND -7-CARBETHOXYINDOLIZINES AND THEIR FORMYL, ACETYL, AND NITROSO DERIVATIVES

L. M. Alekseeva, G. G. Dvoryantseva, M. S. Goizman, T. S. Loseva, A. D. Yanina, E. E. Mikhlina, Yu. N. Sheinker, and L. N. Yakhontov

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It was established by PMR spectroscopy that 2-alkyl(aryl)-6- and -7-carbethoxyindolizines are protonated at C_3, whereas their 3-formyl, 3-acetyl, and 3-nitroso derivatives are protonated at the oxygen atom of the substituent in the 3 position. The ionization constants of 24 indolizine derivatives in nitromethane relative to diphenylguanidine were measured by potentiometric titration. A correlation between protonation and electrophilic substitution in the 2-alkyl(aryl)-6- and -7-carbethoxyindolizine series was established.

In preceding communications of this series [1-3] we described the syntheses of 2-alkyl(aryl)-6- and -7-carbethoxyindolizines and their transformations under the influence of electrophilic and nucleophilic agents. In the present research we studied the protonation of 2-alkyl(aryl)-6- and -7-carbethoxyindolizines (I, V) and their formyl (II, VI), acetyl (III, VII), and nitroso (IV, VIII) derivatives, and the results were compared with the results of previously investigated transformations of these compounds under the influence of other electrophilic reagents.

The protonation centers of the investigated compounds were established on the basis of a study of the PMR spectra of the neutral molecules and conjugate acids (Table 1). In the spectra of neutral molecules the references of proton signals by the pyridine fragment are due to the character of their multiplicity. As in the case of 7-carbethoxyindolizines V-VIII, the proton in position 6 appears in the form of a quartet ($J_{5,6}$ = 7.5 Hz, $J_{6,8}$ = 1.8 Hz) in the region δ 6.90-7.20 ppm. The quartet of the proton at C_8 ($J_{5,8}$ = 0.9 Hz, $J_{6,8}$ = 1.8 Hz) is

*See [1] for communication III.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1540-1545, November, 1976. Original article submitted December 2, 1975.