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GAS CHROMATOGRAPHIC SEPARATION OF TRICYCLIC COMPOUNDS WITH BRIDGEHEAD NITROGEN ATOMS

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SUMMARY

The diastereoisomeric mixtures of a series of unsubstituted and substituted perhydrodipyrido[1,2-*c*;2',1'-*e*]imidazoles (I), perhydropyrido[1,2-*c*]pyrrolo[2,1-*e*]imidazoles (II) and perhydrodipyrido[1,2-*c*;2'1'-*f*]pyrimidines (III), have been separated by preparative gas–liquid chromatography. Correlations have been made between the retention times and stereochemistry of the isomers in each mixture.

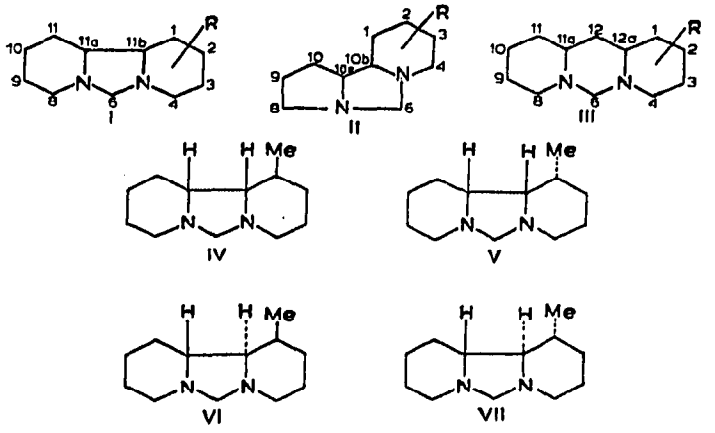
INTRODUCTION

As part of a detailed investigation into the use of NMR and IR spectroscopy in assigning the configurations and preferred conformations of bicyclic and tricyclic compounds with a nitrogen atom at a ring fusion a series of substituted perhydrodipyrido-[1,2-*c*; 2'1'-*e*]imidazoles (I)[1], perhydropyrido[1,2-*c*]pyrrolo[2,1-*e*]imidazoles (II)[2] and perhydrodipyrido[1,2-*c*; 2'1'-*f*]pyrimidines (III)[3] have been prepared. Since each compound possesses two and usually three asymmetric centres there can exist a number of possible stereoisomers. For example structures IV–VII represent the four diastereoisomeric 1-methylperhydrodipyrido[1,2-*c*; 2',1'-*e*]imidazoles.* In addition, because of the conformational mobility of the bridgehead nitrogen atoms, each isomer may exist in a number of possible conformations with the AB and BC ring fusions *cis cis*, *cis trans*, *trans cis* or *trans trans*.**

The diastereoisomeric relationship between each compound permits separation of a mixture by physical means and this report describes the preparative gas chromatographic separation of mixtures of I, II and of III into their components. Configurations and preferred conformations have been assigned to the pure isomers by NMR and IR spectroscopy and as a result it has been possible, in most instances, to establish a correlation between structures and column retention times. This correlation may then be used as a guide in establishing the stereochemistry of similar types of heterocyclic compounds.

*All the compounds discussed in this paper exist as racemates or in certain case optically inactive forms.

**See Fig. 2 for the various configurations and preferred conformations of these compounds.



EXPERIMENTAL

Column packing materials

(a) 20% w/w Carbowax 1540 on 60–80 Celite (B.D.H. Ltd.) was prepared by adding a solution of Carbowax 1540 (25 g) in chloroform (500 ml) to the Celite (100 g), thoroughly stirring the slurry and then removing the solvent by rotary evaporation, followed by drying the material in an oven at 110° for 6 h.

(b) 12% w/w Carbowax 20M terminated with T.P.A. on 60–72 DMCS (supplied by J.J.'s Ltd., Kings Lynn, Norfolk, Great Britain) was prepared as above except that methylene chloride was used as solvent.

Construction of columns

Packing (a) was used to prepare a 22 ft. × 3/8 in. O.D. coiled aluminium column for use in a Wilkens A700 Autoprep. The column was packed under vacuum (25 mm Hg) and the packing added continuously with constant vibration. The column was conditioned at 155° for 48 h in a stream of nitrogen.

Packing (b) was used to prepare a 15 ft. × 3/8 in. O.D. coiled glass column for use in a Pye 105 chromatograph. The packing was introduced under a pressure of 20 p.s.i. of nitrogen and vacuum applied to the outlet. The column was conditioned at 185° for 48 h in a stream of nitrogen.

Analytical data were obtained from a Perkin-Elmer F11 instrument with flame ionisation detector using a 2 m × 1/8 in. O.D. stainless steel column packed with 20% w/w Carbowax 1540 on 60–80 Chromosorb supplied by Perkin-Elmer. Conditions: column temp., 155°; injection temp., 200°; nitrogen carrier with inlet pressure of 30 p.s.i. and a 30 ml/min flow rate. Preparative gas chromatography of the perhydrodipyrido[1,2-*c*;2',1'-*e*]imidazoles was carried out on the Wilkens Autoprep A700 using the 22-ft. column at 200 ml/min and temperatures between 150 and 165°. In all cases hydrogen was used as carrier gas at an inlet pressure of 40 p.s.i. and an inlet port temperature of 220°. The perhydropyrido[1,2-*c*]pyrrolo[2,1-*e*]imidazoles and perhydrodipyrido[1,2-*c*; 2',1'-*f*]pyrimidines were separated on a Pye 105 preparative gas chromatograph fitted with the 15-ft. glass column packed with 12% Carbowax 20M terminated with TPA with a 200 ml/min of nitrogen flow at an inlet pressure of 80 p.s.i. and a column temperature between 150–200° depending on the mixture being separated. Sample sizes on both instruments varied from between 50 μl to 300 μl and depended on

the complexity and resolution of the individual mixtures. The Pye 105 instrument was programmed to separate the individual mixtures automatically and gave a total recovery of 75–80%. The Autoprep A700 was used manually and gave poorer recovery of separated components.

RESULTS AND DISCUSSION

As previously stated the configurations and preferred conformations of the isomers separated from each mixture were assigned using IR and NMR spectroscopy. Although the conformations are those existing in chloroform solution at room temperature the reasonable assumption has been made that the conformational preferences will be the same during the chromatographic separation.

Under the above experimental conditions the analytical column gave similar resolutions to the 15-ft. and 20-ft. preparative columns and the former was used to assign the approximate (±5 %) composition of each mixture and the retention times for each isomer. Fig 1. shows chromatograms for some typical mixtures. The details of separation of the mixtures of the perhydrodipyrido[1,2-*c*; 2′1′-*e*]imidazoles (I) is reported in Table I. Not all possible isomers were present in some of the mixtures but in every separation the isomers with an *anti* 11a11b configuration had shorter retention times than the corresponding *syn* 11a11b isomers. It is also of note that *syn* and *anti* isomers substituted with an axial methyl group had shorter retention times than the corresponding isomers with an equatorial methyl group.

The mixture of 3-methylperhydrodipyrido [1,2-*c*; 2′,1′-*e*]imidazoles contained all four possible diastereoisomers. However, preparative GLC showed only two peaks and separation gave two fractions each shown by NMR to contain two isomers. These pairs were then separated into the individual components by column chromatography using alumina as adsorbent. In each separation, elution with light petroleum (60–80°)/ether removed the axial methyl-substituted isomer initially, a result consistent with the above observations.

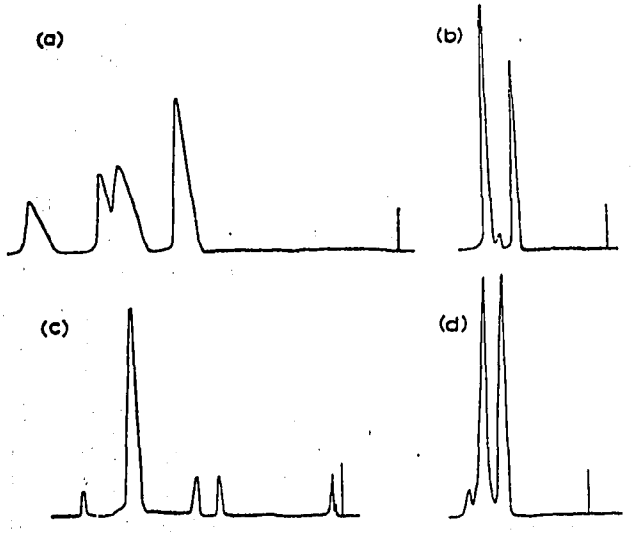


Fig. 1. Chromatograms of some of the mixtures. (a) 3-Methylperhydrodipyrido [1,2-*c*; 2′,1′-*f*]-pyrimidines, (b) 2-methylperhydropyrido[1,2-*c*]pyrrolo[2,1-*e*]imidazoles, (c) 1-methylperhydrodipyrido[1,2-*c*; 2′,1′-*e*]imidazoles, (d) 2,10-dimethylperhydrodipyrido[1,2-*c*; 2′,1′-*e*]imidazoles.

TABLE I

ISOMER DISTRIBUTION AND RETENTION TIMES OF PERHYDRODIPYRIDO[1,2-*c*; 2',1'-*e*]IMIDAZOLES (I)

Mixture	*Retention time (min)*	*Isomer distribution*	*Configuration and preferred conformation*	*Configuration of substituent*
Perhydrodipyrido[1,2-*c*; 2'1'-*e*]-imidazoles	9.2	50	*trans anti trans*	
	13.5	50	*trans syn trans*	
6-methyl	10.0	50	*trans anti trans*	eq
	12.6	45	*trans syn trans*	eq
	14.7	5	*trans syn trans*	ax
6-isopropyl	13.2	50	*trans anti trans*	eq
	16.7	50	*trans syn trans*	eq
1-methyl	10.6	10	*trans anti trans*	ax
	13.4	10	*trans anti trans*	eq
	19.2	75	*trans syn trans*	ax
	26.0	5	*trans syn cis*	ax
3-methyl	11.4	20	*trans anti trans*	ax
	11.4	30	*trans anti trans*	eq
	15.7	5	*trans syn trans*	ax
	15.7	45	*trans syn trans*	eq
4-methyl	10.4	50	*trans anti trans*	eq
	14.5	50	*trans syn trans*	eq
2,10-dimethyl	11.5	50	*trans anti trans*	di-eq
	15.8	45	*trans syn trans*	di-eq
	18.2	5	*trans syn trans*	eq-ax

TABLE II

ISOMER DISTRIBUTION AND RETENTION TIMES OF PERHYDROPYRIDO[1,2-*c*]PYRROLO[2,1-*e*]IMIDAZOLES (II)

Mixture	*Retention time (min)*	*Isomer distribution*	*Configuration and preferred conformation*	*Configuration of methyl group*
II (R = H)	10.2	50	*trans syn cis*	
	13.4	50	*trans anti cis*	
II (R = 1-Me)	13.2	6	*trans syn cis*	eq
	18.9	65	*trans syn cis*	ax
	20.2	29	*cis anti cis*	eq
II (R = 2-Me)	11.5	50	*trans syn cis*	eq
	15.2	46	*trans anti cis*	eq
	13.7	4	*cis anti cis*	eq
II (R = 3-Me)	11.3	25	*trans syn cis*	ax
	13.1	25	*trans syn cis*	eq
	17.3	40	*trans anti cis*	eq
	17.3	10	*cis anti cis*	eq
II (R = 4-Me)	10.8	50	*trans syn cis*	eq
	15.2	47	*trans anti cis*	eq
	16.6	3	*cis anti cis*	eq

Table II shows the details of separation and retention times of the mixtures of the perhydropyrido [1,2-*c*]pyrrolo[2,1-*e*]imidazoles (II). As with compounds of type I, there is again a close correlation between the relative retention times of the isomers in a particular mixture and their structure and preferred conformations. Isomers with a

trans syn cis stereochemistry have the shortest retention time followed by *trans anti cis* and then *cis anti cis*.

The retention times of the perhydrodipyrido[1,2-*c*; 2',1'-*f*]pyrimidines (III) are shown in Table III. Mixtures of the 1-methyl- and 4-methyl-substituted isomers were separated by preparative gas chromatography but, for convenience, the parent compounds III (R = H), and the 2- and 3-methyl-substituted isomers, which were solids of long retention times, were separated by column chromatography on alumina using light petroleum (60–80°)/ether as eluant. It is significant that in each separation on alumina the elution pattern was identical to that observed using analytical GLC. Again it is clearly apparent that a correlation exist between the retention times and stereochemistry of the isomers in a particular mixture.

Fig. 2 illustrates the different configurations and preferred conformation observed in the series of perhydrodipyrido[1,2-*c*; 2',1'-*e*]imidazoles (I), perhydrodipyrido-[1,2-*c*]pyrrolo[2,1-*e*]imidazoles (II) and the perhydrodipyrido[1,2-*c*; 2',1'-*f*]pyrimidi-

TABLE III

ISOMER DISTRIBUTION AND RETENTION TIMES OF THE PERHYDRODIPYRIDO[1,2-*c*; 2',1'-*f*]PYRIMIDINES (III)

Mixture	*Retention time (min)*	*Isomer distribution*	*Configuration and preferred conformation*	*Configuration of methyl group*
III (R = H)	26.4	50	*trans syn trans*	
	36.0	50	*trans anti cis*	
III (R = 1-Me)	33.4	55	*trans syn trans*	ax
	40.1	30	*trans anti cis*	ax
	45.0	15	*trans anti cis*	eq
III (R = 2-Me)	31.2	50	*trans syn trans*	eq
	40.4	50	*trans anti cis*	eq
III (R = 3-Me)	27.4	25	*trans syn trans*	ax
	35.4	25	*trans syn trans*	eq
	37.0	30	*trans anti cis*	ax
	46.0	20	*trans anti cis*	eq
III (R = 4-Me)	32.0	50	*trans syn trans*	eq
	40.8	50	*trans anti cis*	eq

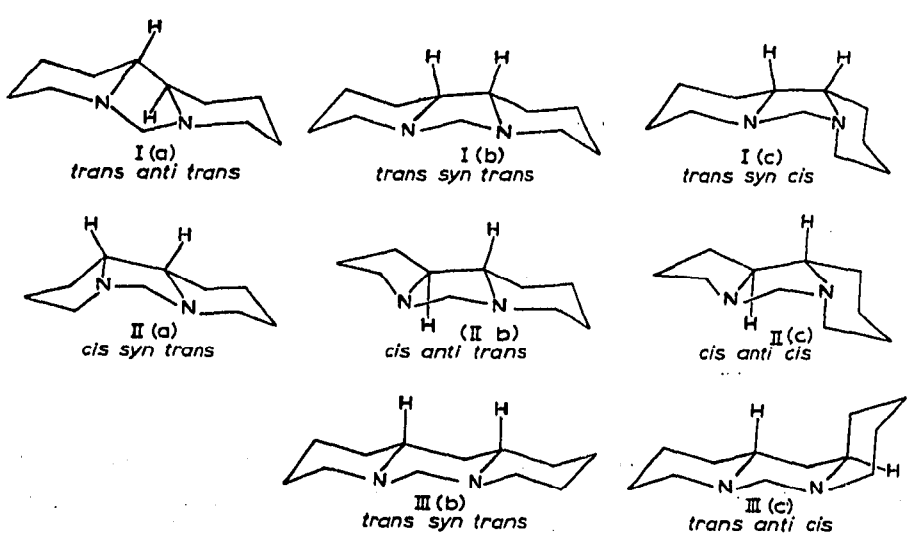


Fig. 2. Configuration and preferred conformations of compounds I, II and III.

nes (III). Each series is in order of increasing retention time (left to right). The close similarity between stereochemistry and relative retention times of compounds of types I and II is easily discernable. Isomers of shortest retention time are those with a 'planar' structure and with the nitrogen lone electron pairs on the opposite side of the molecule (Ia and IIa). A change in conformation to a more 'angled' molecule *e.g.* Ib, IIb and IIIb to Ic, IIc and IIIc, lengthens the retention times still further and isomers with equatorially substituted methyl groups tend to have longer retention times than the corresponding isomers with axial methyl groups. Presumably the 'flat' structures with nitrogen lone pairs on the same side are more strongly attracted by hydrogen bonding to the polar Carbowax stationary phase and puckering of the molecule facilitates this even more. Support for this observation is provided by attempts to separate the mixtures on non-polar columns such as Apiezon L and Silicone SE-30. Much poorer resolutions were obtained and the order of retention times of the various isomers were often changed. The boiling points of the individual isomers separated from a particular mixture also bore no special relationship to their elution pattern.

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