large. The criterion given above should also apply to the permissible tube to tube velocity variations in a multiple tube system.

The immediate remedy to packing nonuniformity would seem to lie in more careful packing. However, it may be taken as fundamental that center and wall regions of the tube are never equivalent, and cannot be subjected to the same influences and forces. The proximity of a wall must always influence packing structure. Even in vibration, tapping and beating, different forces are operating because of energy absorption by the packing, etc. Possible solutions may be found in, (1) the trial and error discovery of packing methods which properly compensate divergent factors, (2) the use of uniform packing particles, perhaps machine made, and (3) the use of column geometries which, by symmetry or otherwise, lend themselves to uniform packing. The latter appears most promising; the annular space between two concentric cylinders has angular equivalence by symmetry and the effect of the radial nonuniformity can be obviated through control of the gap width while still maintaining very high capacities[3]. This column can also be adopted to continuous use.

This work was supported by the Atomic Energy Commission under Contract AT-(11-1)-748.

Department of Chemistry, University of Utah, Salt Lake City, Utah (U.S.A.)

J. CALVIN GIDDINGS
EDWARD N. FULLER

[1] M. J. E. GOLAY, *Second Intern. Conf. Gas Chromatog.*, East Lansing, 1959.
[2] F. H. HUYTEN, W. VAN BEERSUM AND G. W. A. RIJNDERS, in R. P. W. SCOTT, *Gas Chromatography 1960*, Butterworths, London, 1960, p. 224.
[3] J. C. GIDDINGS, *Anal. Chem.*, in the press.
[4] J. PYPKER, in R. P. W. SCOTT, *Gas Chromatography 1960*, Butterworths, London, 1960, p. 240.
[5] A. E. SCHEIDEGGER, *The Physics of Flow Through Porous Media*, Macmillan,, New York, 1957, p. 126.

Received October 9th, 1961

J. Chromatog., 7 (1962) 255–258

Gas chromatography of some pharmacologically active phenothiazines

While there has been widespread application of gas chromatography to the separation of naturally occurring, biologically active compounds[1-8], little work has been directed to similar compounds of synthetic origin. Since the phenothiazine derivatives are widely used in medicine, their gas chromatographic behavior is of interest to chemists, pharmacologists, and toxicologists involved in synthetic, metabolic, and analytical studies.

TABLE I

RELATIVE RETENTION TIMES

Conditions: 6 ft. × 5 mm i.d. glass column, 2 % SE-30 on 80–100 mesh Gas-chrom S, ^{90}Sr argon ionization detector. Retention times relative to chlorpromazine.

Generic name	*Chemical name*	*Time*
	*Column temp., 205°C**	
Trifluomeprazine	2-Trifluoromethyl-10-(3-dimethylamino-2-methylpropyl)-phenothiazine	0.43
Triflupromazine	2-Trifluoromethyl-10-(3-dimethylaminopropyl)-phenothiazine	0.46
Promethazine	10-(2-Dimethylaminopropyl)-phenothiazine	0.53
Trimeprazine	10-(2-Dimethyl-3-dimethylaminopropyl)-phenothiazine	0.58
Promazine	10-(3-Dimethylaminopropyl)-phenothiazine	0.60
Ethopropazine	10-(2-Diethylaminopropyl)-phenothiazine	0.70
Ethyl isobutrazine	2-Ethyl-10-(3-dimethylamino-2-methylpropyl)-phenothiazine	0.91
Methdilazine	10-(1-Methyl-3-pyrrolidylmethyl)-phenothiazine	0.92
Chlorpromazine	2-Chloro-10-(3-dimethylaminopropyl)-phenothiazine	1.00**
Pyrathiazine	10-[2-(1-Pyrrolidyl)-ethyl]-phenothiazine	1.11
Mepazine	10-[(1-Methyl-3-piperidyl)-methyl]-phenothiazine	1.13
Methopromazine	2-Methoxy-10-(3-dimethylaminopropyl)-phenothiazine	1.20
Trifluoperazine	2-Trifluoromethyl-10-[3-(1-methyl-4-piperazinyl)-propyl]-phenothiazine	1.69
Propiopromazine	2-Propionyl-10-(3-dimethylaminopropyl)-phenothiazine	2.38
	*Column temp., 270°C****	
Chlorpromazine	2-Chloro-10-(3-dimethylaminopropyl)-phenothiazine	1.00†
Prochlorperazine	2-Chloro-10-[3-(1-methyl-4-piperazinyl)-propyl]-phenothiazine	2.72
Thioridazine	2-Methylmercapto-10-[2-(N-methyl-2-piperidyl)-ethyl]-phenothiazine	3.47
Thiopropazate	2-Chloro-10-{3-[1-(2-acetoxyethyl)-4-piperazinyl]-propyl}-phenothiazine	6.97
Pipamazine	2-Chloro-10-[3-(4-carbamoylpiperidino)-propyl]-phenothiazine	8.83
Perphenazine	2-Chloro-10-{3-[1-(2-hydroxyethyl)-4-piperazinyl]-propyl}-phenothiazine	>23.90
Fluphenazine	2-Trifluoromethyl-10-{3-[1-(2-hydroxyethyl)-4-piperazinyl]-propyl}-phenothiazine	>23.90

* Flash heater 225°, 20 p.s.i. inlet pressure, outlet pressure was atmospheric.
** Time, 24.9 min.
*** Flash heater 305°, 16 p.s.i. inlet pressure, outlet pressure was atmospheric.
† Time, 3.80 min.

The chromatographic behavior of 20 phenothiazine derivatives was studied using the nonpolar silicone polymer SE-30 coated on "silanized" diatomaceous earth by the filtration technique[9]. The sample size was 1–2 μl of a 0.5% solution of the free base in ethyl acetate. No evidence of decomposition was observed and all eluted compounds gave distinct peaks. Relative retention times are given in Table I.

In general, the retention times increased with increasing molecular weight but notable exceptions occurred. No consistent correlations between relative retention times and boiling points or melting points were observed. All compounds containing a

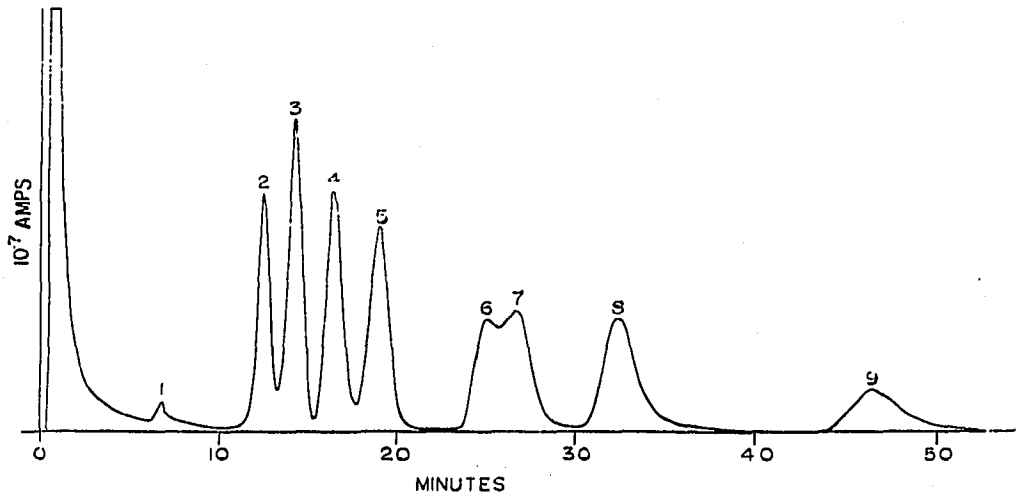

Fig. 1. Gas chromatographic separation of: (1) impurity in (6); (2) triflupromazine; (3) promethazine; (4) promazine; (5) ethopropazine; (6) methdilazine; (7) chlorpromazine; (8) methopromazine; (9) trifluoperazine. The conditions are described in Table I.

piperazine ring were slow to elute and required high temperatures. Two of these, perphenazine and fluphenazine, were not eluted after 90 minutes at 270°.

Preliminary experiments indicate that gas chromatography will be useful for the determination of the phenothiazines in biological fluids and viscera.

Department of Pharmacology and Toxicology,
University of Wisconsin,
Madison, Wisc. (U.S.A.)

M. W. ANDERS
G. J. MANNERING

[1] W. J. A. VANDENHEUVEL, C. C. SWEELEY AND E. C. HORNING, *J. Am. Chem. Soc.*, 82 (1960) 3481.
[2] W. J. A. VANDENHEUVEL, E. C. HORNING, Y. SATO AND N. IKEKAWA, *J. Org. Chem.*, 26 (1961) 628.
[3] W. J. A. VANDENHEUVEL AND E. C. HORNING, *J. Org. Chem.*, 26 (1961) 634.
[4] H. ZIFFER, W. J. A. VANDENHEUVEL, E. O. A. HAAHTI AND E. C. HORNING, *J. Am. Chem. Soc.*, 82 (1960) 6411.
[5] W. J. A. VANDENHEUVEL AND E. C. HORNING, *Biochem. Biophys. Research Communs.*, 3 (1960) 356.
[6] W. J. A. VANDENHEUVEL, C. C. SWEELEY AND E. C. HORNING, *Biochem. Biophys. Research Communs.*, 3 (1960) 33.
[7] H. A. LLOYD, H. M. FALES, P. F. HIGHET, W. J. A. VANDENHEUVEL AND W. C. WILDMAN, *J. Am. Chem. Soc.*, 82 (1960) 3791.
[8] J. NELSON AND A. MILUN, *Chem. & Ind. (London)*, (1960) 663.
[9] E. C. HORNING, E. A. MOSCATELLI AND C. C. SWEELEY, *Chem. & Ind. (London)*, (1959) 751.

Received October 9th, 1961