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Note

Gas chromatographic separations of dialkyl barbiturate derivatives

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Numerous gas chromatographic (GC) procedures have been published for the analysis of barbiturates as free acids and as N,N-dialkyl derivatives. A review article by Jain and Cravey[1] details much of the literature on this subject. Retention times have been reported for free acid barbiturates[2,3] and various derivatives such as: N,N-dimethyl[3], N,N-diethyl[4] and N,N-dibutyl[5]. Recently the retention times for N,N-dialkyl derivatives (dimethyl through didecyl) of aprobarbital, phenobarbital and secobarbital on a 3% SE-30 column were published[6].

Previous work has shown that alkylated barbiturates exhibit less tailing and absorption to GC columns than do the free acid barbiturates[1]. It is also known that under the same GC conditions that a free acid barbiturate will have a longer retention time than that same barbiturate as its N,N-dimethyl derivative and about the same retention time as its N-ethyl-N-propyl derivative[6].

This study was undertaken to determine the relationship between the length of the N-alkyl groups and the separation of several barbiturates (allylbarbital, amobarbital, butabarbital, pentobarbital, phenobarbital, and secobarbital), which are commonly analyzed for by GC due to their extensive use and abuse[7].

EXPERIMENTAL

Reagents

The N,N-dimethylformamide dialkyl acetals used to prepare the barbiturate derivatives were obtained from Aldrich (Milwaukee, Wisc., U.S.A.), while the alcohols used were obtained from Fisher Scientific (Pittsburgh, Pa., U.S.A.) and J. T. Baker (Phillipsburg, N.J., U.S.A.).

Procedure

The following barbiturate solutions in chloroform were prepared (10 μg/ml of each barbiturate included): the common barbiturates (allylbarbital, amobarbital, butabarbital, ibomal, pentobarbital, phenobarbital and secobarbital); heptabarbital and ibomal; and alphenal and ibomal.

The N,N-dialkylated derivatives of the barbiturates were prepared on-column through the use of the appropriate N,N-dimethylformamide dialkyl acetals and *n*-alkyl alcohols as described in our earlier work[6]. The dimethyl through dipropyl derivatives were made by injecting 1 μl of the barbiturate solution and 1 μl of the

appropriate N,N-dimethylformamide dialkyl acetal together into the 3% SE-30 column. The higher derivatives (dibutyl through dioctyl) were made by injecting 1 μl of the barbiturate solution, 1 μl of N,N-dimethylformamide dineopentyl acetal, and 1 μl of the appropriate alcohol together into the column. The retention times (*RT*) and relative retention times (*RRT*) were determined for each barbiturate derivative prepared.

RESULTS AND DISCUSSION

The N,N-dialkyl derivatives from dimethyl through dioctyl of a solution containing allylbarbital, amobarbital, butabarbital, ibomal, pentobarbital, phenobarbital, and secobarbital were synthesized on a 3% SE-30 column. These barbiturates (except for ibomal) were chosen for study because they are commonly used and, therefore, commonly subject to analysis by GC. *RT* and RRT values of these derivatives are shown in Table I. It can be seen that the *RRT* values for each barbiturate derivative remain essentially constant. It can also be seen that butylation and

TABLE I

RETENTION TIMES OF DIALKYL BARBITURATE DERIVATIVES ON 3% SE-30

Conditions: 6 ft. × 2 mm (I.D.) glass column packed with 3% SE-30 on Chromosorb W AW DMCS (80–100 μm). Oven temperature, 200°; injector 240° and detector 250°.

Dialkyl derivative		*Drug*						
		Allylbarb	*Butabarb*	*Amobarb*	*Pentobarb*	*Secobarb*	*Ibomal*	*Phenobarb*
Methyl	*RT* (min)	1.3	1.3	1.6	1.8	2.1	2.8	3.9
	RRT	0.48	0.48	0.56	0.64	0.75	1.00	1.42
Ethyl	*RT*	1.9	1.9	2.1	2.4	2.8	3.9	4.8
	RRT	0.48	0.48	0.54	0.62	0.72	1.00	1.23
Propyl	*RT*	3.3	3.3	3.7	4.2	4.9	6.8	8.4
	RRT	0.48	0.48	0.54	0.62	0.71	1.00	1.23
Butyl	*RT*	5.7	5.9	6.6	7.7	8.6	12.0	14.8
	RRT	0.48	0.50	0.55	0.64	0.72	1.00	1.24
Amyl	*RT*	11.1	11.6	12.8	14.6	16.5	23.1	28.3
	RRT	0.48	0.50	0.55	0.63	0.71	1.00	1.23
Hexyl	*RT*	20.9	22.1	23.9	27.9	30.7	43.5	52.6
	RRT	0.48	0.51	0.55	0.64	0.70	1.00	1.21
Heptyl	*RT*	40.8	43.6	46.8	53.8	60.6	84.9	103.9
	RRT	0.48	0.51	0.55	0.63	0.71	1.00	1.22
Octyl	*RT*	81.2	87.2	93.1	108.0	121.7	168.8	203.8
	RRT	0.48	0.52	0.55	0.64	0.72	1.00	1.21

higher alkylations lead to a separation of allylbarbital and butabarbital that is not obtained with shorter derivatives (Fig. 1). The separation is slight, as the *RRT* values still remain essentially constant.

An interesting, although unexplained, anomaly occurred in the case of phenobarbital where the dimethyl derivative had a significantly longer *RRT* than the other seven dialkyl derivatives (Table I). Further investigation of this anomaly was undertaken. Three possible explanations to the problem were proposed: (1) This property

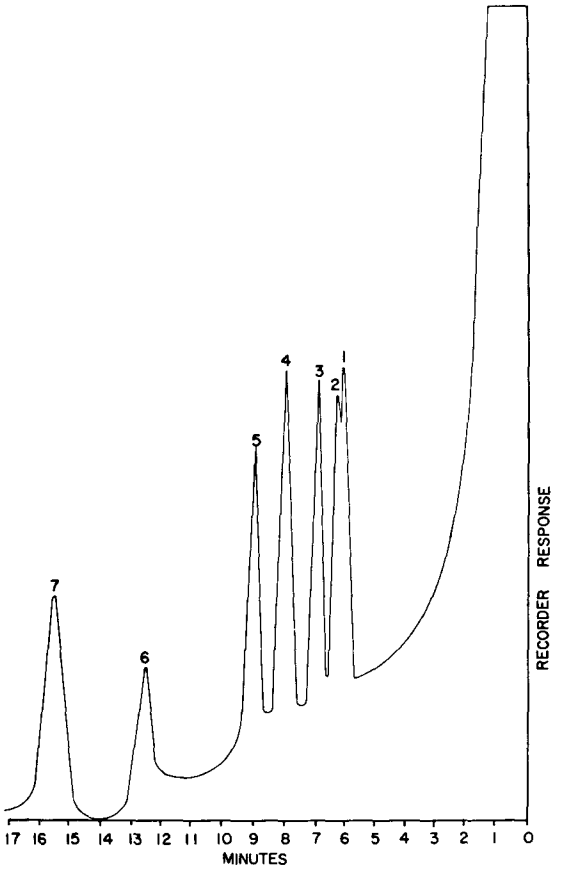

Fig. 1. Butylated barbiturates on 3% SE-30 glass column, 6 ft. × 2 mm, 195°; injector 270°; detector 280°; range 10^{-11}; attenuation × 32, injection: 1 μl containing 0.1 g/l each of the dibutyl derivatives of (1) allylbarbital, (2) butabarbital, (3) amobarbital, (4) pentobarbital, (5) secobarbital, (6) ibomal and (7) phenobarbital.

may occur for all barbiturates, but may only be observable for those barbiturates with long retention times (longer than ibomal); (2) it may occur for all barbiturates containing a 5-phenyl group; or (3) it may occur for only phenobarbital (5-ethyl-5-phenylbarbital). To investigate these possibilities, derivatives were made of heptabarbital (5-ethyl-5-(1-cyclohepten-1-yl)-barbital and alphenal (5-allyl-5-phenylbarbital), which both have longer retention times than ibomal. The *RRT* values of these barbiturates were compared with obimal (Table II). The *RRT* values for alphenal behaved as those of phenobarbital, while the *RRT* values of heptabarbital behaved as those of ibomal and the other barbiturates. Thus the anomaly must be related to the 5-phenyl group.

The synthesis of derivatives other than dimethyl allows differentiation of mephobarbital (1-methylphenobarbital) from phenobarbital, narconumol (1-methylaprobarbital) from aprobarbital, and metharbital (1-methylbarbital) from barbital. Thus, although dimethyl derivatives are the most frequently used derivatives in GC

TABLE II

RETENTION TIMES OF DIALKYL BARBITURATE DERIVATIVES

Conditions: 3ft. × 2 mm (I.D.) glass column packed with 3% SE-30 on Chromosorb W AW DMCS (80–100 μm). Oven temperature, 140°; injector 270° and detector 280°.

	Retention times (min)			*Relative retention times*		
	Ibomal	*Heptabarb*	*Alphenal*	*Ibomal*	*Heptabarb*	*Alphenal*
Dimethyl	3.85	9.4	7.78	1.0	2.4	2.0
Diethyl	5.9	13.5	10.2	1.0	2.3	1.7
Dipropyl	12.1	27.25	21.2	1.0	2.3	1.7
Dibutyl	26.45	61.9	45.35	1.0	2.3	1.7
Diamyl	64.8	–	111.0	1.0	–	1.7
Dihexyl	147.0	328.1	245.7	1.0	2.2	1.7
Ethyl propyl	8.1	18.5	13.85	1.0	2.3	1.7
Propyl butyl	17.15	–	29.0	1.0	–	1.7
Methyl ethyl	4.7	11.25	8.95	1.0	2.4	1.9
Methyl propyl	6.5	–	12.5	1.0	–	1.9
Methyl butyl	9.6	–	18.4	1.0	–	1.9
Methyl amyl	15.0	–	28	1.0	–	1.9
Methyl hexyl	25.2	57.4	45.5	1.0	2.3	1.8
Dihydrogen	8.95	19.7	23.1	1.0	2.2	2.6

procedures[1] and have the shortest retention times at a given temperature (Table I), the formation of barbiturate derivatives other than dimethyl may be advantageous for several reasons: (1) The shorter *RRT* for phenobarbital, (2) separation of allylbarbital from butabarbital, (3) differentiation of mephobarbital from phenobarbital, and (4) their ready formation[5–6].

It has been found that the dibutyl derivatives are the derivatives of choice since they are the shortest alkyl derivatives giving separation of allylbarbital and butabarbital.

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