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LIQUID CHROMATOGRAPHY STUDY OF BROMINATED ANILINES AND INVESTIGATION OF PRODUCT FORMATION IN THE BROMINATION REACTION

II. ANILINES WITH ALKYL GROUPS IN THE *meta*-POSITION

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SUMMARY

Straight- and reversed-phase liquid chromatography (LC) have been used to study product formation in the quantitative coulometric bromination of various anilines. The coulometric method yields, up to the end-point, predictable unambiguous products by exchange of hydrogen for bromine in free *ortho*- and *para*-positions. After the end-point, oxidation products may be formed from primary anilines and N-alkyl groups split off from secondary and tertiary anilines.

A detailed study of retention behaviour of some 30 bromoanilines in straight- and reversed-phase LC has been made. An increase in retention generally took place on the introduction of bromine into the aniline nucleus, except on formation of *o*-bromoanilines in straight-phase LC, where retention decreased. A semi-linear relationship was found to exist between capacity factors of brominated and non-brominated anilines in both the LC systems.

INTRODUCTION

In a previous paper¹ product formation in the quantitative coulometric bromination of anilines with alkyl groups in the *ortho*- and *para*-positions was studied, and retention behaviour of the formed bromoanilines in straight- and reversed-phase liquid chromatography (LC) was investigated. The present work is a continuation of this study applied to *meta*-alkyl-substituted anilines.

EXPERIMENTAL

The experimental conditions were described in detail in the previous paper in this series¹. In order to identify certain of the anilines formed on bromination, 3-methyl-4,6-dibromoaniline, 3-ethyl-6-bromoaniline, N-ethyl-3-methyl-4,6-dibromoaniline, N,N-dimethyl-3-methyl-4,6-dibromoaniline and N,N-diethyl-3-methyl-4,6-dibromoaniline were prepared at this laboratory.

RESULTS AND DISCUSSION

Choice of liquid chromatographic system

The reversed-phase octadecylsilane (C_{18}) system was used with methanol-aqueous buffer (80:20, v/v, pH 7.0) as eluent, and the straight-phase system on nitrile phase was used with isooctane containing 0.2% (v/v) 2-propanol as eluent.

Product formation in coulometric bromination

In the coulometric bromination method for the titration of anilines described by Truedsson and Smith², the reaction is carried out in a water-acetic acid medium and the reactivity is controlled by varying the water content and the bromide ion concentration and by the addition of pyridine. The reaction is believed to involve substitution with bromine at free *ortho*- and *para*-positions. For anilines with several such positions, the titration can be carried out to either the fully brominated stage or to a stage corresponding to the introduction of a smaller number of bromine atoms than the number of available free *ortho*- and *para*-positions. For a certain aniline, the outcome of a titration is dependent both on the structure and on the bromination-promoting properties of the titration medium.

In the present investigation the aim was to study product formation during titration in the pyridine-free medium III-1, containing acetic acid and water in the proportions 60:40 (v/v) and with a bromide concentration of 0.1 M. For this purpose samples were removed from the titration vessel at various stages of the titration and injected on to the LC column either directly (C_{18} phase) or after extraction (nitrile phase). A typical titration curve, with points of sample removal indicated, is given in Fig. 1 of ref. 1.

At the quantitative bromination in medium III-1 (point B on the titration curve), primary anilines studied in this work consume bromine corresponding to the number of free *ortho*- and *para*-positions, secondary anilines consume one bromine

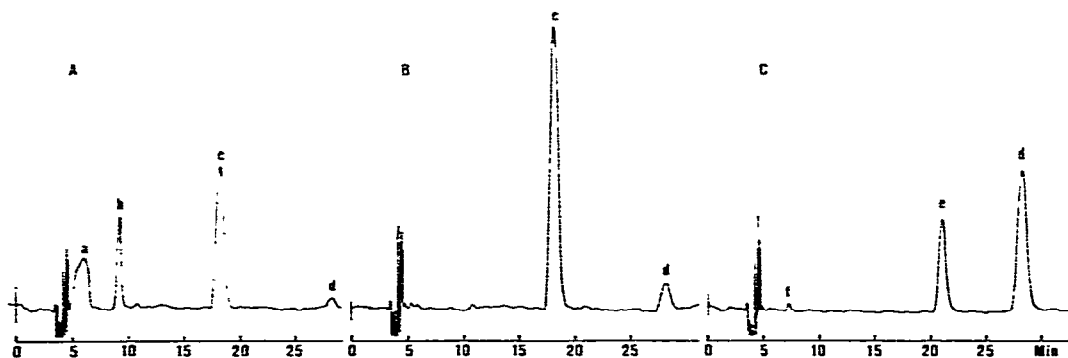


Fig. 1. Chromatograms of the product mixture after bromination of N-methyl-3-methylaniline. Column, Nucleosil C_{18} ; eluent, methanol-aqueous buffer (80:20, v/v, pH 7.0), 45 ml h^{-1} ; wavelength, 280 nm; volume injected, 20 μ l. Peaks: a = N-methyl-3-methylaniline; b = N-methyl-3-methyl-4-bromoaniline; c = N-methyl-3-methyl-2,4-dibromoaniline + N-methyl-3-methyl-4,6-dibromoaniline; d = N-methyl-3-methyl-2,4,6-tribromoaniline; e = 3-methyl-2,4,6-tribromoaniline; f = oxidation product. A, B and C refer to points at which samples were taken (see text).

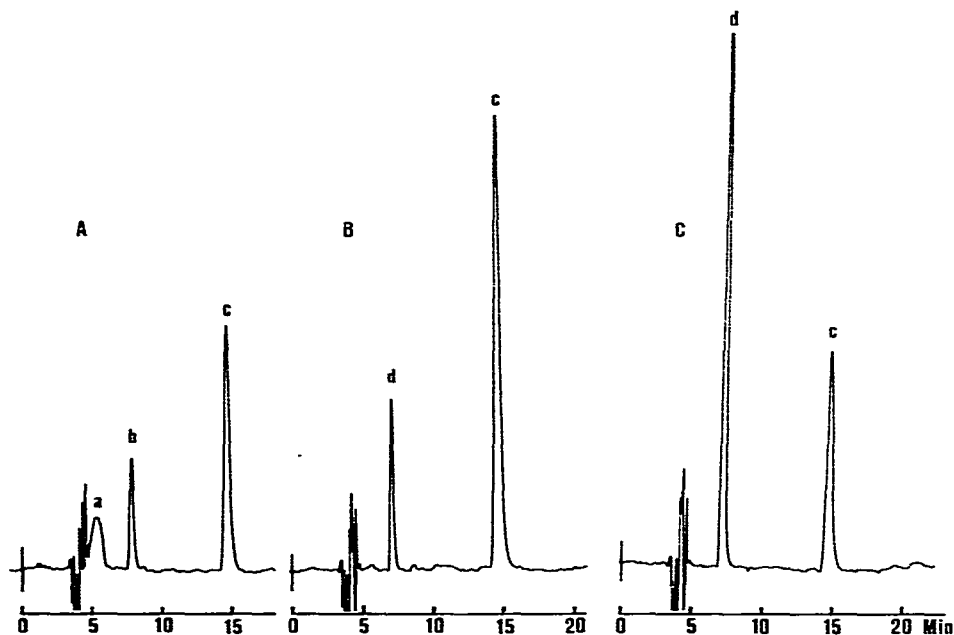


Fig. 2. Chromatogram of the product mixture after bromination of 2,5-dimethylaniline. Column, Nucleosil C_{18} ; eluent, methanol-aqueous buffer (80:20, v/v, pH 7.0), 45 ml h^{-1} ; wavelength, 280 nm; volume injected, $20 \mu\text{l}$. Peaks: a = 2,5-dimethylaniline; b = 2,5-dimethyl-4-bromoaniline; c = 2,5-dimethyl-4,6-dibromoaniline; d = oxidation product. A, B and C refer to points at which samples were taken (see text).

atom less and tertiary anilines two bromine atoms less². From the chromatograms of the samples taken at the end-point B, it was established that e.g. 3-methylaniline was converted into 2,4,6-tribromo-3-methylaniline, N-methyl-3-methylaniline into a mixture of the 2,4- and 4,6-dibromo-derivatives and N,N-dimethyl-3-methylaniline into the 4-bromo derivative.

Fig. 1 illustrates the bromination course for N-methyl-3-methylaniline. At point A, half-way to the end-point, the main bromination products formed are N-methyl-3-methyl-4-bromoaniline (b) and the corresponding 2,4- and 4,6-dibromo derivatives (c). In addition, a small amount of N-methyl-3-methyl-2,4,6-tribromoaniline (d) is present. At the end-point (B) only the mixture of the dibromo derivatives and somewhat of the tribromo derivative are present. The formation of the latter compound is in agreement with the slight overconsumption of bromine found for N-methyl-3-methylaniline on quantitative coulometric bromination in medium III-1².

As shown by Table I, a mono-*ortho*-brominated derivative is generally not formed on bromination of *meta*-alkyl-substituted anilines with a free *para*-position. There is only one example of such a compound being formed, *viz.* in the case of 3-ethylaniline. It appears that the steric hindrance, exerted by a more bulky substituent in the *meta*-position than methyl, decreases the speed of the *para*-bromination reaction enough to allow the formation of a 3-alkyl-6-bromoaniline.

On dibromination of 3-alkylanilines with free *ortho*- and *para*-positions two isomers can be formed, *viz.* 2,4- and 4,6-dibromo-3-alkylanilines. As shown by Table I, both isomers are formed from primary and secondary anilines, whereas tertiary

TABLE I
CAPACITY FACTORS AND SEPARATION FACTORS FOR *meta*-ALKYL-SUBSTITUTED ANILINES AND THEIR BROMINATION PRODUCTS IN
THE REVERSED-PHASE LC SYSTEM

Column, Nucleosil C₁₈; eluent, methanol-aqueous buffer (80:20, v/v, pH 7.0)

No.	Aniline (substituent)	Capacity factor, <i>k'</i>						Separation factor, α								
		Non-brominated			Dibrominated			Tri-brominated		Mono-/non-		Di-/mono-para-		Tri-/di-		
		Ortho	Para	2,6-	2,4-	4,6-	Ortho	Para	Ortho	Para	2,4-	4,6-	2,4-	4,6-	2,4-	4,6-
1	3-Methyl	0.51	0.88		2.17	2.17	2.17	5.14		1.73	2.47	2.47	2.37	2.37	2.37	2.37
2	3-Ethyl	0.67	1.12		2.57	2.73	6.24		1.96	1.67	2.29	2.44	2.43	2.43	2.29	2.29
3	2,3-Dimethyl	0.74	1.25			3.23				1.69		2.58				
4	2,5-Dimethyl	0.75	1.29			3.26				1.72		2.53				
5	3,4-Dimethyl	0.69		3.14					1.99							
6	N-Methyl-3-methyl	0.89	1.66		4.33	4.24	7.18			1.87	2.61	2.55	1.66	1.66	1.69	1.69
7	N-Ethyl-3-methyl	1.14	2.11		6.55	6.30	10.3			1.85	3.10	2.99	1.57	1.57	1.63	1.63
8	N,N-Dimethyl-3-methyl	1.82	3.42			5.18	17.7			1.88		1.51			3.42	3.42
9	N,N-Diethyl-3-methyl	3.08	5.83			10.1	31.9			1.89		1.73			3.16	3.16

anilines only yield the 4,6-dibromo derivative. This is undoubtedly caused by increased steric hindrance to bromine substitution at the 2-*ortho*-position.

Effect of over-bromination. Primary, 3-alkylanilines without *ortho* alkyl groups are comparatively stable to excess bromine. At 50% excess (point C on the titration curve), small early peaks appear at separation on the C₁₈ phase. Spectra evidence indicates that their structure is quinoidic.

If the aniline contains an *ortho* as well as a *meta* alkyl group, it becomes more sensitive to excess bromine, and quinoidic oxidation products can appear already at the end-point B. At 50% excess of bromine (point C), a considerable amount of the oxidation product has been formed. This is shown for 2,5-dimethylaniline in Fig. 2. Early peaks also appear on the straight-phase system, indicating the formation of substituted diphenylamines, as was reported in the previous paper on *ortho*-substituted anilines¹.

Secondary and tertiary anilines are not fully brominated at the end-point, but still contain vacant *ortho*-positions. On over-bromination these free positions are substituted with bromine, producing the fully brominated aniline (see Table I). However, this reaction cannot be utilized for quantitative purposes. The fully brominated secondary and tertiary anilines are very sensitive to further excess of bromine and react with loss of N-alkyl groups to the corresponding primary and secondary anilines. This is demonstrated in Fig. 1C where N-methyl-3-methylaniline on over-bro-

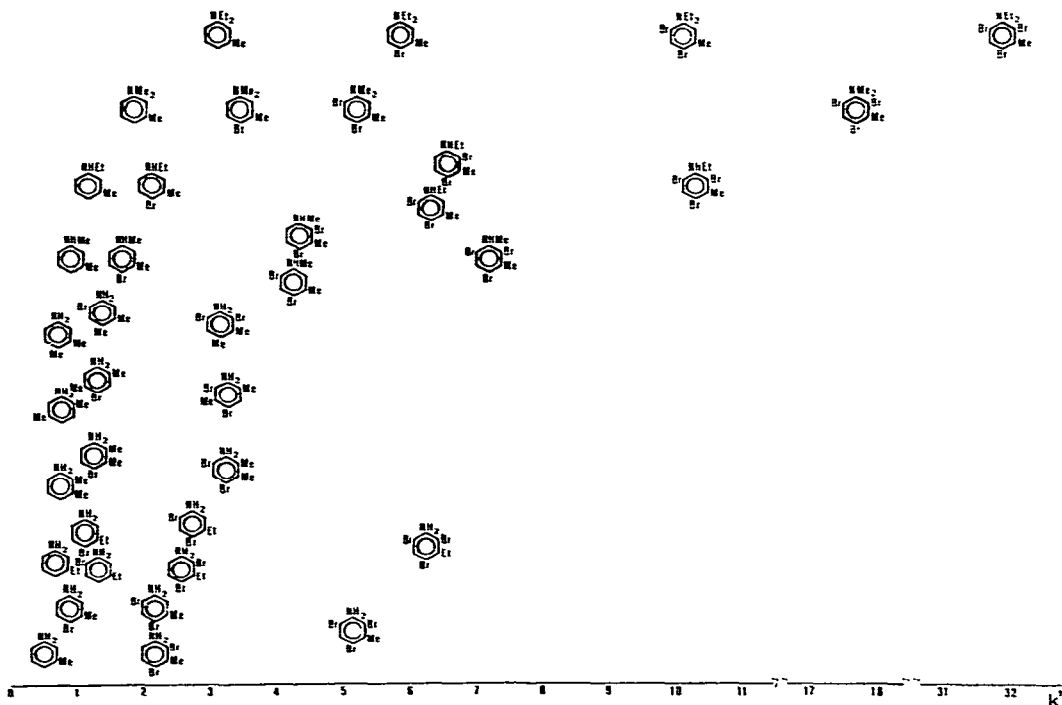


Fig. 3. Retention of primary, secondary and tertiary anilines and the corresponding bromination products in reversed-phase LC. Column, Nucleosil C₁₈; eluent, methanol-aqueous buffer (80:20, v/v, pH 7.0), 45 ml h⁻¹. Me = Methyl; Et = ethyl.

mination furnishes N-methyl-3-methyl-2,4,6-tribromoaniline (d) and 3-methyl-2,4,6-tribromoaniline (e). In addition a small amount of an oxidation product (f) is formed.

Retention behaviour of brominated anilines

Reversed-phase chromatography. The substitution of bromine into free *ortho*- and *para*-positions of *meta*-alkyl-substituted primary, secondary and tertiary anilines gives a considerable increase in retention in reversed-phase chromatography (Table I and Fig. 3). A semi-linear relationship exists between the k' values of the original anilines and those of the corresponding mono-, di-, and tribrominated derivatives, respectively (Fig. 4). Dibrominated tertiary anilines seem to fall on a line of their own (see broken line in Fig. 4).

The effect on retention of the successive introduction of bromine into a *meta*-

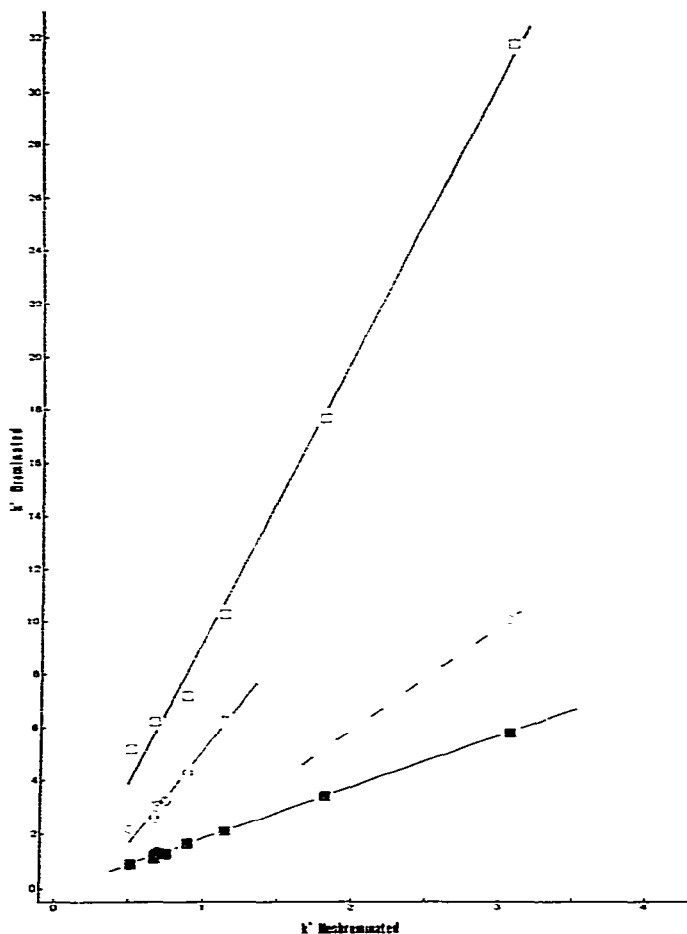


Fig. 4. Relationship between capacity factor, k' , for alkyanilines and the corresponding bromination products in reversed-phase LC. Column, Nucleosil C_{18} , eluent, methanol-aqueous buffer (80:20, v/v, pH 7.0), 45 ml h^{-1} . ■ = Mono-*para*-brominated; ● = mono-*ortho*-brominated; ○ = *ortho-para*-brominated; ▽ = di-*ortho*-brominated; □ = tribrominated.

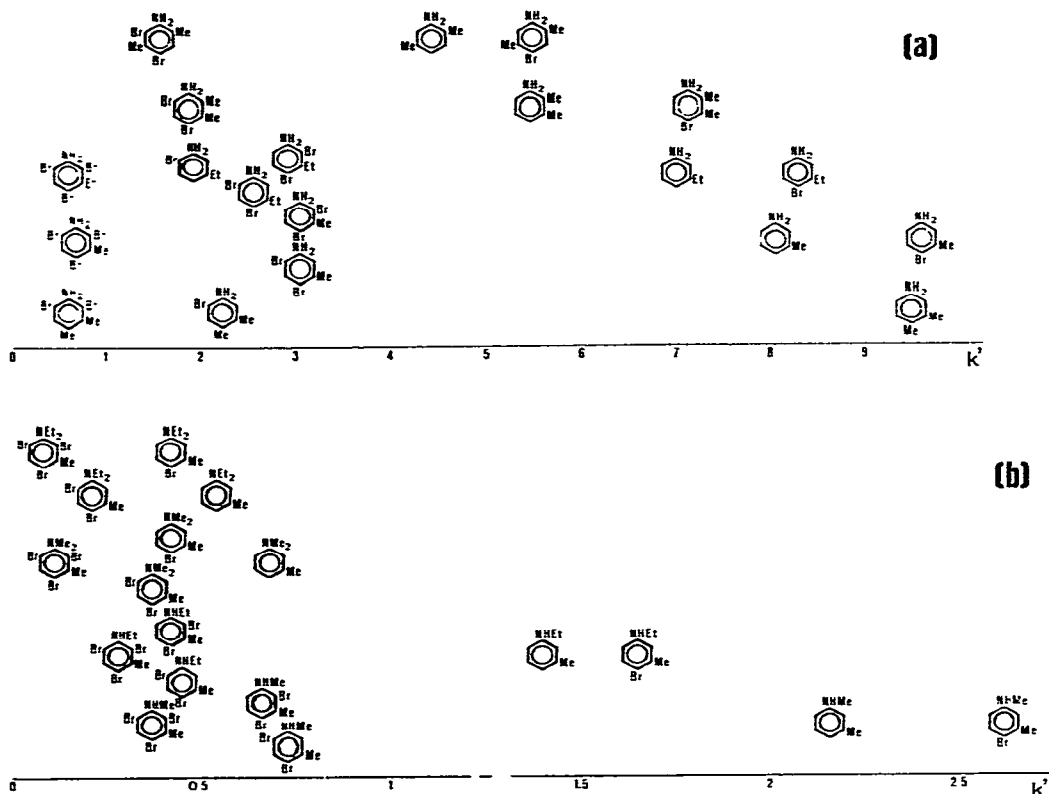


Fig. 5. Retention of primary, secondary and tertiary anilines and the corresponding bromination products in straight-phase LC. Column, Nucleosil CN; eluent, 0.2% (v/v) 2-propanol in isooctane, 45 ml h⁻¹. (a) Primary anilines. (b) Secondary and tertiary anilines.

alkyl-substituted aniline is demonstrated in Table I, where the separation factors, α , between the various bromination stages are given. As already established, the sensitivity of the values to the environmental structure is considerable. This is especially evidenced by their variation in the dibromo- to monobromo- and tribromo- to dibromo- series, respectively.

A kind of brominated aniline that has not been encountered previously is tribromoaniline containing a nuclear alkyl group. Comparison of k' values of these compounds with those of corresponding tribromoanilines without a nuclear alkyl group¹ indicates certain anomalies. Thus, it appears that the retention difference is abnormally high between N,N-dimethyl-3-methyl-2,4,6-tribromoaniline and N,N-dimethyl-2,4,6-tribromoaniline, the relationship between the k' values being 3.5. For the corresponding primary and secondary (N-methyl) aniline pairs the same relationship is only 1.4. Since the anilines, constituting a pair, must be considered to be of similar type, the retention differences between the members in each pair should, following Locke³, be due mainly to solubility differences in the mobile phase.

Straight-phase chromatography. A great decrease in retention in straight-phase chromatography for *ortho*-brominated alkyilanilines in comparison with correspond-

TABLE II

CAPACITY FACTORS AND SEPARATION FACTORS FOR *meta*-ALKYL-SUBSTITUTED ANILINES AND THEIR BROMINATION PRODUCTS IN THE STRAIGHT-PHASE LC SYSTEM

Column, Nucleosil CN; eluent, 0.2% (v/v) 2-propanol in isoctane.

No.	Aniline (substituent)	Capacity factor, <i>k'</i>						Separation factor, α							
		Non-brominated			Dibrominated			Tri-brominated		Mono-/non-		Di-/mono-para-		Tri-/di-	
		Ortho	Para	2,6-	2,4-	4,6-	Tri-brominated	Ortho	Para	2,4-	4,6-	2,4-	4,6-	2,4-	4,6-
1	3-Methyl	8.07	9.62		3.06	3.06	0.68		1.19	0.32	0.32	0.22	0.22	0.22	0.22
2	3-Ethyl	7.02	8.31		2.93	2.57	0.60	0.27	1.18	0.35	0.31	0.20	0.20	0.23	0.23
3	2,3-Dimethyl	5.48	7.15		1.88	1.88			1.30		0.26				
4	2,5-Dimethyl	4.45	5.50		1.57	1.57			1.24		0.29				
5	3,4-Dimethyl	9.51		0.60				0.24							
6	N-Methyl-3-methyl	2.16	2.62		0.66	0.73	0.37		1.21	0.25	0.28	0.56	0.56	0.51	0.51
7	N-Ethyl-3-methyl	1.40	1.65		0.42	0.45	0.28		1.18	0.25	0.27	0.67	0.67	0.62	0.62
8	N,N-Dimethyl-3-methyl	0.68	0.42		0.37	0.37	0.11		0.62		0.88			0.30	0.30
9	N,N-Diethyl-3-methyl	70.54	0.42		0.21	0.21	0.08		0.78		0.50			0.38	0.38

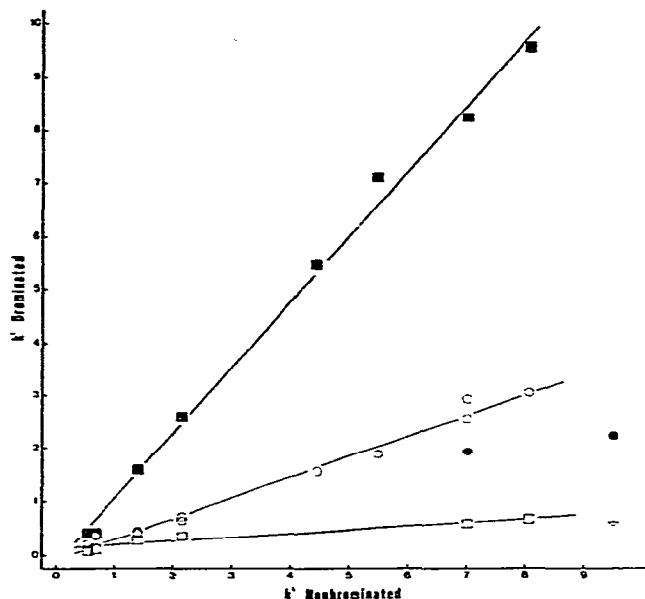


Fig. 6. Relationship between capacity factor, k' , for alkyranilines and the corresponding bromination products in straight-phase LC. Column, Nucleosil CN; eluent, 0.2% (v/v) 2-propanol in isooctane, 45 ml h^{-1} . ■ = Mono-*para*-brominated; ● = mono-*ortho*-brominated; ○ = *ortho-para*-brominated; ▽ = di-*ortho*-brominated; □ = tribrominated.

ing non-*ortho*-brominated compounds, has already been established¹. *Meta*-alkyl-substituted anilines behave similarly, as shown by the k' and α values given in Table II.

Substitution of bromine into the *para*-position leads to either an increase or a decrease in retention. An increase is observed for primary and secondary anilines and a decrease for tertiary anilines. A similar behaviour was previously noticed for other kinds of alkyranilines and for non-alkyl-substituted anilines and its cause discussed in terms of steric hindrance, base strength and solubility in the mobile phase¹.

Among the tribrominated *meta*-alkyl-substituted anilines the retention decreases in the order primary, secondary and tertiary anilines, *i.e.* with increased steric hindrance around the nitrogen atom. The very low k' values of the tribrominated tertiary anilines in Table II indicate that these compounds behave on the whole as hydrocarbons on the nitrile phase.

The elution order on the nitrile phase for some *meta*-alkyl-substituted anilines and their bromination products is further illustrated in Fig. 5. The semi-linear relationship between k' values of brominated and corresponding non-brominated anilines, previously established for the C_{18} phase, is also valid for the nitrile phase (Fig. 6). As can be seen, the position of a bromoaniline is governed by the number of *ortho*-situated bromine atoms and by the presence of a *para*-situated bromine atom.

CONCLUSIONS

For the investigated *meta*-alkyl-substituted anilines the quantitative coulomet-

ric bromination method described by Truedsson and Smith² yields, up to the end-point, mainly *o*- and *p*-bromoanilines by exchange of hydrogen for bromine at free *ortho*- and *para*-positions. Primary *m*-alkylanilines are not particularly sensitive to excess of bromine, unless *ortho*-situated alkyl groups are also present. In that case, oxidation products appear on over-bromination. Secondary and tertiary anilines are not fully brominated at the end-point, but still contain vacant *ortho*-positions. On over-bromination, these positions are substituted with bromine and, on further bromination, loss of N-alkyl groups occurs with the formation of primary and secondary anilines.

Introduction of bromine into the *ortho*- and *para*-positions causes an increase in retention in the reversed-phase LC system. In the straight-phase system, *ortho*-bromination occasions a decrease in retention and *para*-bromination leads to an increase for primary and secondary anilines and a decrease for tertiary anilines.

In both the LC systems studied, there is a semi-linear relationship between k' values of brominated and non-brominated anilines, respectively.

ACKNOWLEDGEMENT

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