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IDENTIFICATION OF N-ALKYL SUBSTITUTED PRODUCTS BY A DEALKYLATION REACTION IN THE PRESENCE OF ADSORPTION CHROMATOGRAPHY SUBSTRATES

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SUMMARY

Some N-alkyl substituted products are partially or completely dealkylated when heated in the adsorbed state on silica gel or alumina. This reaction could be carried out either on a microscale, by direct heating of the thin-layer chromatography plates on which the sample has been spotted and eluting it together with the untreated product and with the probable degradation products, or on a macroscale, by adsorbing the sample on alumina or silica, heating and then extracting the dealkylation products with suitable solvents.

Advantage could be taken of this reaction to identify unknown substances as the dealkylation product of an unknown product could be identified after comparison with standards by thin-layer chromatography. Furthermore, by working on a macroscale, it is possible to prepare the dealkylated product in amounts sufficient for elementary analysis and infrared spectrophotometry. The reaction mechanism is discussed.

INTRODUCTION

The fast growing number of papers published by specialized journals is a manifestation of the potentialities of chromatography for the identification of unknown substances. This particular application of chromatography is of importance when either impure products or product mixtures difficult to separate by conventional chemical methods are to be analyzed. The main techniques normally used are briefly outlined below.

Direct chromatographic examination of an unknown sample in comparison with known products; in such a case the identification is based directly on the mobility and color of the bands obtained.

Chromatographic examination of products obtained by chemical reactions on the test sample (*e.g.*, reduction, hydrolysis, oxidation, diazotization and coupling, etc.) in comparison with the probable conversion products; in this case, very useful data for the establishment of the constitution of the unknown product become available through the identification of the reaction products.

In both of the above cases, the chromatographic technique could be coupled further with other analytical techniques.

Finally, there is the case where a reaction is allowed to take place after the test sample has already been deposited on the chromatographic substrate.

In this short communication a reaction carried out by the latter identification technique, and applied with good results to some N-alkyl substituted products, is described. Products of importance in the dye industry were studied such as:

N-alkylaminoanthraquinones

N-alkylanilines and toluidines

Azo dyes, the coupling components of which are N-alkyltoluidines.

This reaction involves, according to the reaction conditions, the complete or partial dealkylation of the sample with the possibility of pinpointing the basic structure exhibiting a free primary amino group. The technique described is a rapid and simple method of obtaining information on the structure of an unknown N-alkylated product. It is the author's intention to continue the work with a view to determine the suitability of the reaction to other functional groups.

EXPERIMENTAL

The dealkylation reaction is carried out by a simple thermal treatment of the chromatographic substrate on which the test product has been adsorbed; the conditions of the treatment in an oven generally range as follows: temperature 110–160°; heating period 1–16 h.

This reaction could be carried out either on a microscale by thin-layer chromatography or on a preparative scale by using substrates for column adsorption chromatography. The chromatographic stage follows the thermal treatment. The following substrates were tested:

Silica Gel G and Alumina G (Merck), for the reactions on a microscale

Silica gel 0.05–0.2 mm and activated basic alumina for column chromatography (Merck), for the reactions on a preparative scale.

Microscale reaction and thin-layer chromatography

Normal thin-layer chromatography is adequate when the dealkylation reaction is carried out on a practically uniform product.

In this case, 10 μl of a 1% sample solution are placed at $\sim$ 3 cm from the end of the chromatographic plate and, after the dealkylation treatment in an oven under the optimum conditions previously determined by preliminary tests, the sample is eluted together with an untreated sample and the probable partial or total dealkylation products. The choice of eluent and of chromatographic substrate depends upon the results of preliminary tests carried out by the qualitative analysis.

After elution, examination of the chromatogram makes it possible, firstly, to see whether conversion has taken place and, secondly, to identify the dealkylation product of the sample, if the required reference standards are available. Normally, the main reaction products correspond to dealkylation products; in certain cases, however, other side reactions, product which vary from case to case and are difficult to identify, could be formed.

When impure products or mixtures are to be analyzed, two-dimensional chromatography should be carried out. In this case, the various constituents are separated by chromatography in the first dimension before carrying out the dealkylation treat-

ment. The second elution, orthogonal to the first, is then performed after the deal-kylation reaction and after having spotted the standards for the identification of the dealkylation products. In this way it is possible to see whether or not a reaction has taken place and, if so, which are the dealkylation products of single constituents and if all of the constituents tested have the same dealkylation product.

The reaction on a preparative scale

The reaction previously described also occurs when normal column adsorption chromatography substrates are used. A known volume of the test sample solution is adsorbed on the substrate and then thermally treated under the same conditions as described above. After the dealkylation, the reaction products could be extracted by suitable solvents and a preparative column or a thin-layer chromatographic sepa-ration could be performed, if the extract is not chemically uniform.

This preparative scale technique is very useful since substantial amounts of the chemically pure dealkylation product can be obtained. This is particularly ad-vantageous when the identification of the dealkylation product is not possible due to the lack of reference standards and one wishes to have recourse to other analytical methods (*e.g.* I.R. spectroscopy, elemental analysis, etc.). Furthermore, the reaction on a preparative scale enables one to obtain small amounts of products which are difficult to obtain by synthesis.

APPLICATIONS

As was briefly said in the introduction, the reaction has been applied experi-mentally to the following important derivatives in the dye industry:
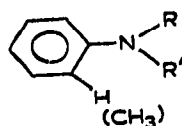
Alkylaminoanthraquinones of the following structure:
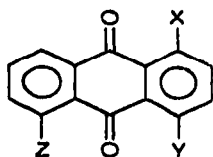
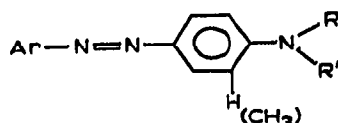| where	X	Y	Z
(a)	alkylamino	H	H
(b)	,,	OH	H
(c)	,,	alkylamino	H
	,,	H	alkylamino

The alkyl groups are linear or branched alkyl or cycloaliphatic groups.

N-alkyl substituted aromatic amines of the following type:

where R and R' = H, alkyl, cyanoethyl, hydroxyethyl, β-aminoethyl, β-succinimido-ethyl groups, etc.

Azo dyes of the following structure:

where Ar is an aromatic diazotizable amine moiety.

R and R′ = as above, under N-alkylated aromatic amines.

The results of the tests carried out on 25 products are reported in Tables I–III; in each case the reaction conditions and the dealkylation products formed are described where identification has been possible. Figs. 1 and 2 show sketches of the chromatograms obtained after dealkylation of some pure products and a product mixture.

DISCUSSION

Although the experiments do not enable us to make a complete analysis of the effect of chemical structure of the alkylamino derivative tested and of the chromatographic substrate used upon the reaction course, they permit us to make the following comments.

TABLE I

REACTION CONDITIONS AND RESULTS OF THE TESTS CARRIED OUT ON ALKYLAMINOANTHRAQUINONES

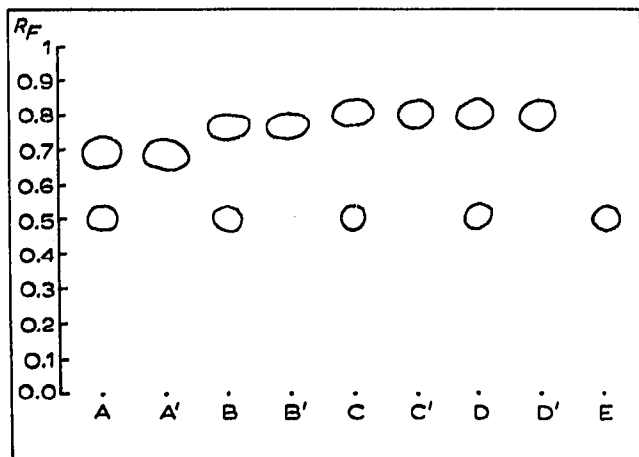| Product	Reaction conditions		Dealkylation products
	Temp. (°C)	Time (h)	
1-Methylaminoanthraquinone	150	16	1-Aminoanthraquinone
1-Isopropylaminoanthraquinone	150	16	1-Aminoanthraquinone
1-Isobutylaminoanthraquinone	150	16	1-Aminoanthraquinone
1-Cyclohexylaminoanthraquinone	150	16	1-Aminoanthraquinone
1-Hydroxy-4-isopropylaminoanthra-quinone	150	1	1-Amino-4-hydroxyanthraquinone
1,4-Diisopropylaminoanthraquinone	150	1	1,4-Diaminoanthraquinone 1-Amino-4-isopropylaminoanthra-quinone
1,4-Diisobutylaminoanthraquinone	150	1	1,4-Diaminoanthraquinone 1-Amino-4-isobutylaminoanthra-quinone
Mixtures of: 1,4-Dimethylaminoanthraquinone	150	1	1,4-Diaminoanthraquinone 1-Amino-4-methylaminoanthraquinone
1-(β-Hydroxyethylamino)-4-methyl-aminoanthraquinone			1,4-Diaminoanthraquinone 1-Amino-4-hydroxyethylaminoanthra-quinone 1-Amino-4-methylaminoanthraquinone
1,4-Di(β-hydroxyethylamino)anthra-quinone			1,4-Diaminoanthraquinone 1-Amino-4-hydroxyethylaminoanthra-quinone
1,5-Didodecylaminoanthraquinone	150	16	1,5-Diaminoanthraquinone 1-Amino-5-dodecylaminoanthraquinone

Fig. 1. 1-Alkylaminoanthraquinones. Reaction conditions: Silica Gel G; 150°; 16 h. Chromatography on Silica Gel G; eluent: toluene–ethyl acetate–pyridine–ammonia (80:10:7:3). A = 1-Methylaminoanthraquinone, after reaction; A' = 1-methylaminoanthraquinone; B = 1-isopropylaminoanthraquinone, after reaction; B' = 1-isopropylaminoanthraquinone; C = 1-isobutylaminoanthraquinone, after reaction; C' = 1-isobutylaminoanthraquinone; D = 1-cyclohexylaminoanthraquinone, after reaction; D' = 1-cyclohexylaminoanthraquinone; E = 1-aminoanthraquinone.

The –NRR' group is dealkylated at approximately the same rate when it is present either in N-alkylaniline derivatives or in azo dyes, where they are the coupling components. To prove this, a comparison test was carried out on both N-ethyl-*m*-toluidine and the corresponding azo dye

$$\text{Ar—N=N—Ar'—N}\begin{array}{c}\nearrow \text{H}\\ \searrow \text{C}_2\text{H}_5\end{array}$$
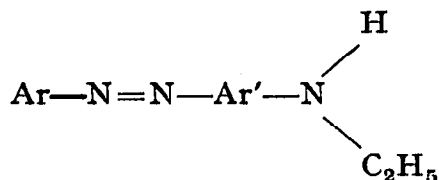
TABLE II

REACTION CONDITIONS AND RESULTS OF THE TESTS CARRIED OUT ON N-ALKYL SUBSTITUTED AROMATIC AMINES

Product	Reaction conditions		Dealkylation products
	Temp. (°C)	Time (h)	
N-Methylaniline	110	1	Aniline
N-Ethylaniline	110	1	Aniline
N-(β-Hydroxyethyl)aniline	110	1	Aniline
N-(β-Cyanoethyl)aniline	110	1	Aniline
N-Ethyl-N-(β-hydroxyethyl)aniline	140	1	Aniline N-Ethylaniline N-(β-Hydroxyethyl)aniline
N-Ethyl-*m*-toluidine	110	1	*m*-Toluidine
N-(β-Cyanoethyl)-*m*-toluidine	110	1	*m*-Toluidine
N-(β-Aminoethyl)-*m*-toluidine	110	1	*m*-Toluidine
N-(β-Succinimidoethyl)-*m*-toluidine	110	1	*m*-Toluidine
N,N-Di(β-cyanoethyl)-*m*-toluidine	150	1	*m*-Toluidine N-(β-Cyanoethyl)-*m*-toluidine
N-Ethyl-N-(β-succinimidoethyl)-*m*-toluidine	150	1.5	*m*-Toluidine N-(β-Succinimidoethyl)-*m*-toluidine

TABLE III

REACTION CONDITIONS AND RESULTS OF THE TESTS CARRIED OUT ON AZO DYES

Product	Reaction conditions		Dealkylation product
	Temp. (°C)	Time (h)	
$Ar-N=N-Ar'-N \begin{smallmatrix} /C_2H_5 \\ \backslash H \end{smallmatrix}$	150	16	$Ar-N=N-Ar'-N \begin{smallmatrix} /H \\ \backslash H \end{smallmatrix}$
$Ar-N=N-Ar'-N \begin{smallmatrix} /C_2H_4CN \\ \backslash H \end{smallmatrix}$	150	16	$Ar-N=N-Ar'-N \begin{smallmatrix} /H \\ \backslash H \end{smallmatrix}$
$Ar-N=N-Ar'-N \begin{smallmatrix} /C_2H_5 \\ \backslash C_2H_4CN \end{smallmatrix}$	150	16	$Ar-N=N-Ar'-N \begin{smallmatrix} /H \\ \backslash H \end{smallmatrix}$ $Ar-N=N-Ar'-N \begin{smallmatrix} /H \\ \backslash C_2H_4CN \end{smallmatrix}$ $Ar-N=N-Ar'-N \begin{smallmatrix} /H \\ \backslash C_2H_5 \end{smallmatrix}$
$Ar-N=N-Ar'-N \begin{smallmatrix} /C_2H_5 \\ \backslash C_2H_4OH \end{smallmatrix}$	150	16	$Ar-N=N-Ar'-N \begin{smallmatrix} /H \\ \backslash H \end{smallmatrix}$ $Ar-N=N-Ar'-N \begin{smallmatrix} /H \\ \backslash C_2H_5 \end{smallmatrix}$
$Ar-N=N-Ar'-N \begin{smallmatrix} /C_2H_5 \\ \backslash C_2H_5 \end{smallmatrix}$	150	16	$Ar-N=N-Ar'-N \begin{smallmatrix} /H \\ \backslash H \end{smallmatrix}$ $Ar-N=N-Ar'-N \begin{smallmatrix} /H \\ \backslash C_2H_5 \end{smallmatrix}$

The dealkylation was carried out for 1 h at 110° on Silica Gel G. It was noticed that in both cases about 5% of the dealkylated product (*m*-toluidine and the corresponding azo dye, respectively) was formed.

On the contrary, the positions and the number of the N-alkylamino groups have a remarkable importance in anthraquinone derivatives. The 1,4-dialkylamino-
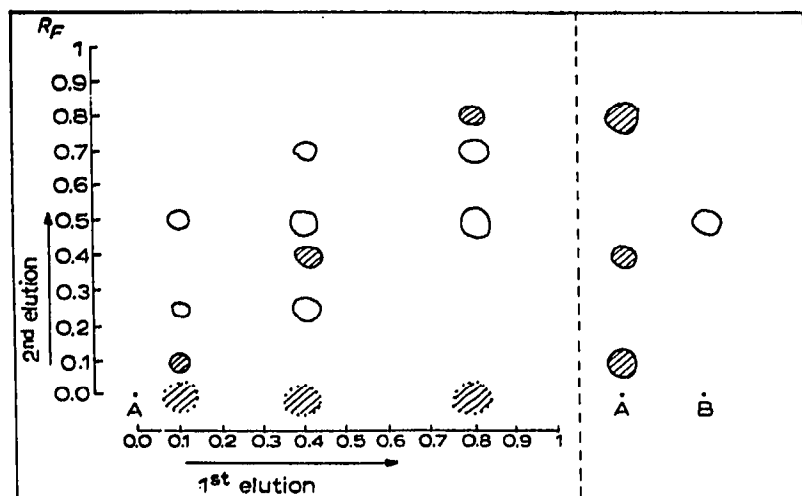
Fig. 2. Mixture of blue dyes: 1,4-dimethylaminoanthraquinone; 1,4-di(β-hydroxyethylamino)-anthraquinone; 1-(β-hydroxyethylamino)-4-methylaminoanthraquinone. Reaction conditions: Silica Gel G, 150°, 1 h; chromatographic conditions: Silica Gel G, bidimensional technique; eluent: toluene–ethyl acetate–pyridine–ammonia (60:20:16:4). Sequence: 1st elution; thermal treatment, application of standard; 2nd elution. A = Dye mixture; B = 1,4-diaminoanthraquinone; R_F 0.10 = 1,4-di(β-hydroxyethylamino)anthraquinone; R_F 0.25 = 1-amino-4-(β-hydroxyethylamino)anthraquinone; R_F 0.40 = 1-methylamino-4-(β-hydroxyethylamino)anthraquinone; R_F 0.50 = 1,4-diaminoanthraquinone; R_F 0.70 = 1-amino-4-methylaminoanthraquinone; R_F 0.80 = 1,4-dimethylaminoanthraquinone.

anthraquinone derivatives undergo a much faster reaction than 1-alkylamino- and 1,5-dialkylamino derivatives. This was corroborated by the experimental results shown in Table IV.

In most cases, with the same conditions of heating temperature and time, a higher yield in dealkylation product is obtained on using alumina instead of silica gel. Furthermore work is being carried out to establish, if possible, the reaction mecha-

TABLE IV

Product	Reaction conditions			% not dealkylated
	Adsorbent	Temp. (°C)	Time (h)	
1-Isopropylaminoanthraquinone	Silica Gel G	150°	1.5	~70
1,4-Diisopropylaminoanthraquinone	Silica Gel G	150°	1.5	~20
1,5-Didodecylaminoanthraquinone	Silica Gel G	150°	1.5	~70

nism. By subjecting 1,5-didodecylaminoanthraquinone to dealkylation on alumina for column chromatography according to the technique described and by examining the methanol extract by thin-layer chromatography, it has been possible to demonstrate the formation of dodecyl alcohol.

Alkylation reactions in the presence of alumina, silica and other catalysts (e.g. between aromatic amines and alcohols) are described in the literature[1–4]; these

reactions are considered equilibrium reactions, the equilibrium constants of which have been calculated for the various stages[1]. Connecting the above two data, a hypothesis is formulated that the alkylation occurs according to the following equilibrium equation:

$$Ar-N(R)R + 2H_2O \rightleftharpoons ArNH_2 + 2ROH$$
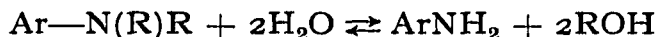
The water present in the substrate and surrounding atmosphere will favour an equilibrium shift toward the right side of the reaction.

In conclusion, attention is drawn to the fact that this property of many products of being easily dealkylated could be misleading in normal qualitative thin-layer analyses. For instance, it is current practice in many laboratories to evaporate, before eluting, the solvent used both for dissolving and depositing the sample, by heating in an oven at 100° or in a stream of hot air. Tests carried out on 1,4-diisopropylamino-anthraquinone have shown that this treatment is sufficient to provoke the formation of small amounts of 1-amino-4-isopropylaminoanthraquinone and to alter, therefore, the result of the qualitative analysis.

ACKNOWLEDGEMENT

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