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Note

The decomposition of trimethylanilinium hydroxide during pyrolysis methylation gas chromatography

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Flash heater methylation of barbiturates[1,2], cannabis metabolites[3], diphenylhydantoins[4], phenylurea herbicides[5] and fatty acids[6] with trimethylanilinium hydroxide (TMAH) has been shown to improve the GLC characteristics of these compounds. The derivatisation employing an alkylammonium salt is now accepted as the method of choice for routine urine and serum analysis for barbiturates and related drugs[7]. We have recently used "on-column" methylation for the derivatisation of phenolic and amino acids[8,9]. During this work, we observed the presence of a heretofore unreported by-product (A), having a relative retention time of 0.41 with respect to the dimethylaniline peak, in all our flash heater methylation experiments with TMAH. This product either was not observed or has been disregarded by other experimenters. This paper reports the identity of (A) along with the conditions affecting its formation.

EXPERIMENTAL

Material and methods

Apparatus. A Packard-Becker (Delft, The Netherlands) Model 419 gas chromatograph equipped with a 6 ft. × $^1/_8$ in. O.D. stainless-steel column packed with 3% Apiezon on Gas-Chrom Q was used.

For analysis by gas chromatography–mass spectrometry (GC–MS) a Varian (Walnut Creek, California, U.S.A.) Model 600D gas chromatograph coupled to an EAI (Palo Alto, Calif., U.S.A.) Model Quad 300 mass spectrometer via a Biemann separator was used.

Reagents and materials. Trimethylanilinium hydroxide (TMAH). A mixture of trimethylanilinium chloride (17.1 g, 0.1 mole) and silver oxide (17.4 g, 0.075 mole) was stirred for 3 h in anhydrous methanol (50 ml). After filtration the filtrate was stored at 0°.

N,N,N-Trimethyl-*p*-chloroanilinium iodide. A solution of N,N-dimethyl-*p*-chloroaniline[10] (1.0 g) in dry ethyl acetate (15 ml) was treated with an excess of methyl iodide (2.0 g). The iodide crystallised on standing over night (1.5 g, 80%; m.p. 203–204°).

N,N,N-Trimethyl-*p*-chloroanilinium hydroxide. N,N,N-trimethyl-*p*-chloro-

anilinium iodide (14 g) was stirred with silver oxide (2.0 g) in anhydrous methanol (20 ml) for 4 h at room temperature. After filtration the filtrate was stored at 0°. Solutions of N,N,N-trimethyl-*p*-chloroanilinium hydroxide in ethanol and propanol were similarly prepared.

N,N,N-Trimethyl-*p*-nitroanilinium sulphate[11]. N,N-dimethyl-*p*-nitroaniline[12] (2.6 g) and dimethyl sulphate (12 ml) were refluxed for 1 h. The crystalline material was filtered, washed with anhydrous diethyl ether and dried (4.1 g, 93%: m.p. 172–175°).

N,N,N-Trimethyl-*p*-nitroanilinium picrate[11]. The sulphate (2.0 g) in water (20 ml) was neutralised with sodium carbonate and the picrate precipitated with an aqueous picric acid solution. The product was recrystallised from aqueous alcohol (2.1 g, 73%: m.p. 180–181°).

N,N,N-Trimethyl-*p*-nitroanilinium chloride[11]. The picrate (2.0 g) was refluxed with concentrated HCl (20 ml) for 3 h and the liberated picric acid removed by diethyl ether extraction. The acid phase was evaporated to dryness and the chloride recrystallised from absolute alcohol (0.95 g, 90%: m.p. 169–170°).

N,N,N-Trimethyl-*p*-nitroanilinium hydroxide. A mixture of N,N,N-trimethyl-*p*-nitroanilinium chloride (0.50 g) and silver oxide (0.70 g) was stirred in anhydrous methanol (10 ml) for 2 h. After filtration the clear yellow filtrate was stored over molecular sieve (3A) at 0°.

The correct strength of the anilinium hydroxide solutions was in each case determined by titration of an aliquot with standard sulphuric acid solution (0.1 *N*) using phenolphthalein indicator. The base was then diluted with the appropriate quantity of anhydrous methanol to give a 0.20 *N* solution.

Gas chromatography

To a screw cap vial was added an internal standard (naphthalene, 10 μl; 0.10 *N* in methanol) and the respective anilinium hydroxide (100 μl, 0.2 *N*). After mixing, a sample (3 μl) was injected into the gas chromatograph. The GLC conditions were: injection port and detector temperature, 250°; oven temperature held at 80° for 1 min after injection and then programmed at 8°/min. Retention times with respect to the internal standard (1.0) were: anisole (0.36), N,N-dimethylaniline (0.70), *p*-chloroanisole (0.71), N,N-dimethyl-*p*-chloroaniline (1.28), *p*-nitroanisole (1.41) and N,N-dimethyl-*p*-nitroaniline (2.18).

RESULTS AND DISCUSSION

In the GLC of methanolic solutions of TMAH another product (A) was formed besides the expected N,N-dimethylaniline. The amplitude of (A) was constant when a constant quantity of TMAH reagent was injected. The mass spectrum of this material [$(M)^+$ 108 (84%); $(M^+ - CH_3)$ 93 (13%)] and the co-chromatography with an authentic sample identified (A) as anisole.

A possible explanation for the formation of (A) is that the strongly basic TMAH reagent is vulnerable to nucleophilic attack by the solvent in the injection heater of the GLC.

Since such a nucleophilic displacement reaction should be enhanced by the presence of electronegative substituents in the *ortho* or *para* positions of the aromatic

ring, methanolic solutions of $O_2N-C_6H_4-N(CH_3)_3^+ OH^-$ and $Cl-C_6H_4-N(CH_3)_3^+ OH^-$ were used for "on-column" methylation experiments. In these cases, $O_2N-C_6H_4-OCH_3$ (95%) and $Cl-C_6H_4-OCH_3$ (8%) were reaction products as predicted. Preparations of N,N,N-trimethyl-*p*-chloroanilinium hydroxide in ethanol and propanol gave the corresponding ethers $Cl-C_6H_4-OC_2H_5$ and $Cl-C_6H_4-OC_3H_7$.

The presence of the respective anisoles sometimes interferes with the GLC analysis of the fatty and amino acids. In such cases we recommend the use of solutions of the anilinium hydroxides in dimethylformamide, as more suitable methylation reagents.

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