Journal of Chromatography, 169 (1979) 397–399

CHROM. 11,455

Note

Thermal decomposition of 1,3-dimethylphenobarbital in trimethylanilinium hydroxide

Reaction pathway

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(Received August 30th, 1978)

It has been reported[1] that extensive degradation of 1,3-dimethylphenobarbital (I) occurred when it was injected with trimethylanilinium hydroxide (II) in methanol into a gas chromatograph. The major products, identified by mass spectrometry, were N-methyl-2-phenylbutyramide (III), N,N-dimethyl-2-phenylbutyramide (IV), methyl 2-phenylbutyrate (V), N,N,N′-trimethylethylphenylmalondiamide (VI), and N,N,N′,N′-tetramethylethylphenylmalondiamide (VII). Although some speculations were made, the reaction pathway was not elucidated. A pathway based upon experiments carried out with the reaction intermediates and products is proposed in this note.

EXPERIMENTAL

Materials

Compounds I, II, III, IV, and V were obtained as previously described[1]. N,N′-Dimethylethylphenylmalondiamide (VIII) was prepared by hydrolyzing I in 0.7 *M* potassium hydroxide in aqueous methanol for 24 h, acidifying, and extracting the product with chloroform. The solid product melted at 106–110° (ref. 2: 108–109°). Compound IX was prepared by treating I with 0.1 *M* potassium hydroxide in aqueous methanol for a few minutes, acidifying, and extracting with chloroform. The chloroform layer was shaken with phosphate buffer, pH 7, and the organic layer discarded. Compound IX was then obtained by chloroform extraction of the acidified aqueous phase. All other chemicals were of reagent grade.

Methods

Gas chromatography was performed routinely on a 1.82 m × 2 mm I.D. silanized glass column packed with 3% OV-17 on Chromosorb W HP in a Hewlett-Packard 7620A research gas chromatograph. The carrier gas was nitrogen (30 ml/min), the injection port temperature was 280°, and the oven temperature was programmed from 160° to 260° at 10°/min. A flame ionization detector, maintained at 280°, was used. When mass spectrometry was performed, the apparatus described in a previous paper was used[1].

RESULTS AND DISCUSSION

It has been observed that 5,5-disubstituted barbituric acids are hydrolyzed in aqueous solution by hydroxide ions, the pyrimidine ring opening at the 1,6-position to form a malonuric acid or at the 1,2-position to yield an unstable carbamic acid derivative, followed by further degradation to the acetic acid and urea[3]. The ionization state of the barbituric acid and the size of the substituents on carbon 5 determine the relative extent to which the 1,6- or 1,2-ring opening occurs in a given compound[4]. We have found[5] that when compound I is hydrolyzed in 0.02–0.4 *M* potassium hydroxide in aqueous methanol, the ring opens predominantly at the 1,6-position yielding the malonuric acid IX which does not decarboxylate under the mild conditions used, but it can recyclize to compound I. The ring was also cleaved at the 1,2-position but at a much slower rate, to form compound VIII, which is presumably the decarboxylation product of the unstable carbamic acid derivative X. Owing to the irreversibility of this latter step the ultimate reaction product is the diamide VIII.

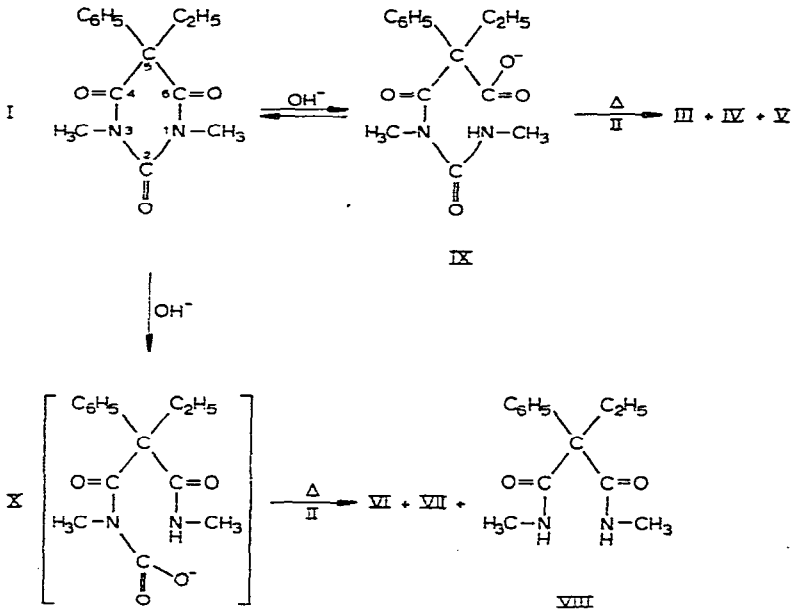
In order to gain some information about the reaction pathway for the degradation of I when injected into a gas chromatograph with II, compounds VIII and IX were treated with II in a similar manner, and the products identified by gas chromatography and mass spectrometry as previously described[1]. It was found that VIII, unlike ethylphenylmalondiamide itself[6], did not degrade under these conditions to the butyramides III and IV but simply was methylated to VI and VII. Interestingly, VII and VIII had the same retention time whereas the retention time of VI was slightly shorter. Consequently, although it was not apparent earlier, a closer examination of the mass spectral data shows that VIII is a product of I when injected into the gas chromatograph with II. Compound IX, on the other hand, did degrade to III and IV and formed the ester V. It was confirmed using [$^2H_3$]-methanol and [$^2H_3$]-II that the methyl group of the ester was derived from the methanol solvent, as had been reported in the decomposition of I[1].

The various reactions resulting from the interaction of I and II at high temperatures are summarized in Scheme 1. This reaction sequence is not only qualitatively in agreement with the observed reactions but is also quantitatively consistent in that the predominant products III, IV, and V are consequences of the preferred 1,6-ring cleavage.

It has been suggested[7] that the formation of III and IV during the on-column methylation of phenobarbital with II is due to the degradation of N-methyl-2-phenylbutyrylurea formed by the hydrolysis of N-methyl-phenobarbital initially produced during the methylation reactions. This suggestion is consistent with reactions reported here, although no formation of ester was mentioned in the report. It is possible that III and IV could also be formed from phenobarbital by the other route of a 1,2-ring cleavage, with a subsequent degradation of the resulting ethylphenylmalondiamide in the presence of II to form the butyramides III and IV. This, however, cannot be the case in the decomposition of I because of the stability of the methylated malondiamides.

ACKNOWLEDGEMENTS

I am indebted to Dr. Patrick S. Callery for the mass spectrometric analyses.



Scheme 1.

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