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GAS CHROMATOGRAPHIC DECOMPOSITION OF 2-AMINOPROPIOPHENONES

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SUMMARY

Decomposition of 2-aminopropiophenones, observed during gas chromatography on KOH-coated columns, did not correspond to the known reaction of beta elimination caused by the presence of an alkali. Decomposition products were characterised by gas chromatography and gas chromatography–mass spectrometry and it was confirmed that dehydrogenation occurred, caused by the presence of KOH and the temperature used. N-Primary, secondary and tertiary 2-aminopropiophenones decomposed to significantly different extents.

INTRODUCTION

The instability of the α-aminoketone-type compounds in the presence of alkalis has been reported[1,2]. Their extraction from alkaline solutions has been stated to be impractical[2,3]. Also, decomposition or rearrangement of diethylpropion and its ketone metabolites during gas chromatographic (GC) analysis on KOH-treated supports has been mentioned[3–5].

Testa and Beckett[4] stated that under the GC conditions used (stainless-steel column containing support coated with 10% KOH, 2% Carbowax 20M and 10% Apiezon L) diethylpropion (retention time, t_R = 7.7 min) partially decomposed to give a secondary peak (t_R = 9.0 min) which partly interfered with the peak of the corresponding alcohol metabolite.

Banci *et al.*[5] analysed diethylpropion and its metabolites by GC using two KOH-coated (5%) columns, 2% Carbowax 20M and 10% Apiezon L, and observed that diethylpropion, even after crystallization, showed always two peaks on both columns, which were attributed to a keto–enolic equilibrium or to another rearrangement. Also, they mentioned decomposition of 2-ethylaminopropiophenone after storage for some hours in alkaline solution, and the impossibility of detection of 2-aminopropiophenone because of its thermolability.

The problem of decomposition of sympathomimetic amines used as anorectics

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(among which was diethylpropion) during GC analysis was mentioned as a process promoted by the high temperatures and probably by some stationary phases[6].

On the contrary, Beckett *et al.*[7] reported that GC using KOH-treated columns was completely satisfactory for the identification and determination of the majority of sympathomimetic amines used in anorectic formulations. Although, in general, they recommended alkaline coating of the support before application of the stationary phase, in order to prevent phenomenon of decomposition of amines, they mentioned that in certain cases a non-KOH coated support may be preferable, *e.g.*, for diethylpropion.

Both instability of 2-aminopropiophenones in alkaline medium and decomposition during GC analysis were considered to involve the same process. Two neutral and one acidic products (benzoic acid), as a result of their instability during alkaline extraction and GC analysis, were found[1].

Following our experimental observations during GC analysis of 2-aminopropiophenones on KOH-coated supports and the conflicting data in the literature, we now investigate the stability of members of 2-aminopropiophenones and the structures of their decomposition products.

EXPERIMENTAL

Gas chromatography

The compounds were chromatographed on a Pye-104 gas chromatograph in which a flame ionization detector was incorporated. The following columns were used: (A) Glass column (1 m × 4 mm I.D.) containing 10% KOH, 2% Carbowax 20M and 10% Apiezon L on Chromosorb G AW DMCS (100 120 mesh); carrier gas, nitrogen; pressures, 87, 100 and 135 kPa; flow-rates, 1, 1.25 and 1.66 cm^3/sec, respectively; column temperature, 200°C; air and hydrogen pressures, 135 kPa. (B) Glass column (1 m × 4 mm I.D.) containing 2% Carbowax 20M and 10% Apiezon L on Chromosorb G AW DMCS (100–120 mesh); carrier gas, nitrogen; pressures, 100, 135 and 168 kPa; flow-rates, 1.25, 1.66 and 2 cm^3/sec, respectively; column temperature 200°C; air and hydrogen pressures, 135 kPa.

The compounds were also chromatographed on a Perkin-Elmer F11 gas chromatograph with a flame ionization detector, using 1-m glass columns containing 5% KOH and 2% Carbowax 20M on Chromosorb G (column temperature 150°C), or 10% KOH and 10% Apiezon L on Chromosorb W (column temperature 200°C).

Gas chromatography–mass spectrometry (GC–MS)

Mass spectra were recorded on a VG 12F mass spectrometer with VGDS 2135 data system (ionization potential 70 eV) linked to a Pye-104 gas chromatograph (columns A and B; carrier gas, nitrogen; pressure, 100 kPa; column temperature 200°C).

Direct inlet mass spectra of the compounds examined were obtained on the same instrument at an ionization potential of 70 eV.

Compounds

The compounds investigated (Table I) were kindly supplied by: Temmler-Werke, Marburg/Lahn, F.R.G. (diethylpropion · HCl, dimethylpropion · HCl, 2-

ethylaminopropiophenone · HCl and 2-aminopropiophenone · HCl, as well as phenyl vinyl ketone and phenyl methyl diketone) and by Pharmaceutical Development, The Wellcome Foundation Ltd., Dartford, U.K. (bupropion · HCl).

Solutions

Solutions of the compounds examined (Table I) were obtained by dissolving their hydrochlorides in methanol or chloroform, or by extracting alkaline aqueous solutions of their salts with freshly distilled diethyl ether. Each solution contained approximately 2 g base per l, with the exception of the solution of 2-aminopropiophenone (comp. 5, Table I) examined on column (B), where concentrations were *ca.* g/l. A 2–3-μl aliquot of the prepared solutions was chromatographed.

RESULTS AND DISCUSSION

Using column A in GC analysis of diethylpropion and its metabolites (system A used by Testa and Beckett[4], where glass instead of stainless-steel column was used), we observed two peaks from diethylpropion (compound 1, Fig. 1) and 2-ethylaminopropiophenone (compound 4), and a single peak from 2-aminopropiophenone (compound 5) (compounds 4 and 5 are ketone metabolites of diethylpropion).

We extend our investigations to other 2-aminopropiophenones and examined dimethylpropion (compound 2) and bupropion (compound 3). From dimethylpropion two peaks were obtained, while bupropion showed one peak with pronounced tailing (Fig. 1).

Very similar GC results were obtained using KOH-coated columns of Carbowax 20M or Apiezon L.

The smaller peaks derived from compounds 1, 2 and 4 (however, sometimes the second peak from compound 4 was higher than the first peak), and tailing off of compound 3 had a longer t_R than the main peaks (Table I).

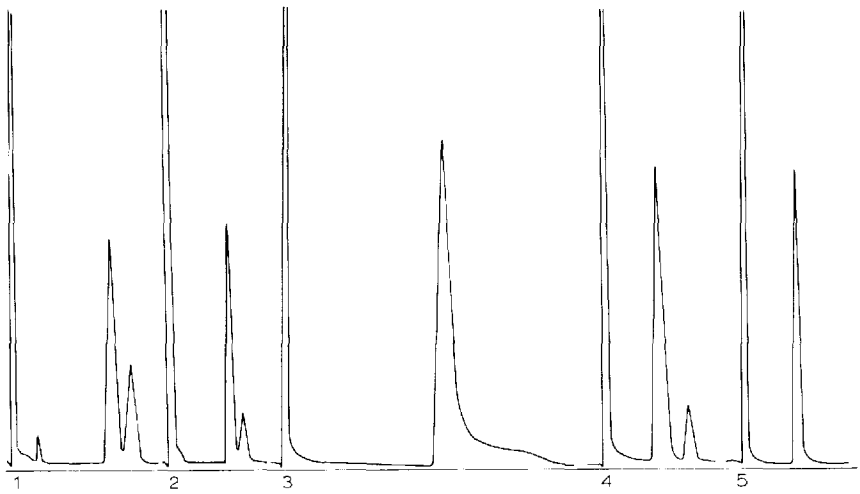
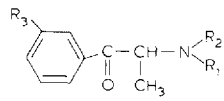
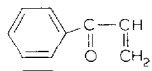
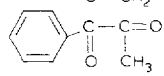


Fig. 1. Gas chromatograms of the compounds examined on column A. Column temperature: 200°C. Peaks 1 = diethylpropion; 2 = dimethylpropion; 3 = bupropion; 4 = 2-ethylaminopropiophenone; 5 = 2-aminopropiophenone; 6 and 7 are shown in Fig. 2.

TABLE I

2-AMINOPROPIOPHENONES AND DECOMPOSITION PRODUCTS INVESTIGATED

No.	Chemical name	Structure			Retention times (min)		
					Column A N_2 = 1.66 cm³/sec		Column B N_2 = 2 cm³/sec
		R_1	R_2	R_3	1st peak	2nd peak	
2-Aminopropiophenones							
1	2-Diethylaminopropiophenone (Diethylpropion)	C_2H_5	C_2H_5	H	6.6	7.9	5.9
2	2-Dimethylaminopropiophenone (Dimethylpropion)	CH_3	CH_3	H	4.1	5.0	3.7
3	2-(*tert.*-Butylamino)-*m*-chloropropiophenone (Bupropion)	H	$C(CH_3)_3$	Cl	10.4	12.2	8.9
4	2-Ethylaminopropiophenone	H	C_2H_5	H	3.6	5.6	4.1
5	2-Aminopropiophenone	H	H	H	3.5		3.1
Decomposition products							
6	Phenyl vinyl ketone				2.0		1.8
7	Phenyl methyl diketone				2.0		1.8

Compounds 6 and 7 (decomposition products of 2-aminopropiophenones) chromatographed under the same conditions showed very short t_R, 1.8–2.0 min (Table I and Fig. 2).

A process of beta-elimination occurred to a small extent during the process of extraction from alkaline medium, so that peak(s) with short t_R corresponding to compounds 6 and/or 7 were almost immeasurable.

As it was confirmed by GC that decomposition did not correspond to a beta elimination reaction, the structures of the decomposition products were examined by GC–MS.

The GC–MS results showed that the spectra of the first peaks of compounds 1–4 corresponded to the direct inlet mass spectra of these compounds. The compounds examined showed base peaks formed by α-cleavage ($CH_3-\overset{+}{C}H-N\begin{matrix}R_2\\R_1\end{matrix}$, $\overset{+}{C}H_2-CH_2\ N\begin{matrix}R_2\\R_1\end{matrix}$, $CH_3-CH=\overset{+}{N}\begin{matrix}R_2\\R_1\end{matrix}$): compound 1, peak at *m/e* 100 (100%; direct inlet: 100%); compound 2, peak at *m/e* 72 (100%; direct inlet: 100%); compound 3, peak at *m/e* 100 (26%; direct inlet: 15%); compound 4, peak at *m/e* 72 (100%; direct inlet: 100%). Direct inlet mass spectrum of compound 5 showed base peak at *m/e* 44.

Upon GC–MS, the second peaks from compounds 1, 2 and 4, and the tailing portion of the first peak of compound 3, and the single peak of compound 5, all showed as the highest masses observed, signals for two mass units lower than those corresponding to the molecular ions (M^+) of these compounds plus the characteristic fragments of the respective compounds. Peaks of *m/e* 203 (25%) and *m/e* 98 (76%)

were obtained from diethylpropion, peaks of *m/e* 175 (16%) and of *m/e* 70 (100%) from dimethylpropion, and a peak at *m/e* 98 (21%) from bupropion, peaks of *m/e* 175 (1%) and of *m/e* 70 (76%) from 2-ethylaminopropiophenone, and peaks of *m/e* 147 (6%) and of *m/e* 42 (100%) from 2-aminopropiophenone.

The longer t_R of the above decomposition products, supported by these GC–MS results, suggests the formation of a new double bond in the structures.

The GC and GC–MS results showed that decomposition was almost complete for the N-primary aminopropiophenone (2-aminopropiophenone). This compound showed one peak on column A and gave a mass spectrum in which *m/e* 147 ($M^+ - 2$) instead of *m/e* 149 (M^+) was obtained. Also, the t_R of this compound on column (A) was almost the same as the t_R of the main peak of 2-ethylaminopropiophenone (Table I), despite its smaller molecular mass, which suggested that the peak detected was produced by a decomposition product. Decomposition occurred less with the N-secondary aminopropiophenone (2-ethylaminopropiophenone, 20-55%) and much less with 2-*tert.*-butylaminopropiophenone (bupropion). Probably the *tert.*-butyl group on the nitrogen atom of the latter diminished the decomposition. For the N-tertiary aminopropiophenones (diethylpropion, 10–35% and dimethylpropion, 20–25%), the decomposition was less than for the N-secondary aminopropiophenone, 2-ethylaminopropiophenone.

In the GC–MS spectra of all compounds examined there were no *m/e* units corresponding to the normal decomposition products, phenylvinylketone and phenylmethyldiketone (compounds 6 and 7, Table I), when direct inlet mass spectra of these compounds 6 and 7 were scanned. Beckett *et al.*[8] also found that GC breakdown of the 2-methylaminopropiophenone to product 6 (Table I) and methylamine, whilst possible, was not consistent with GC–MS evidence obtained from the main GC peak.

Decomposition of the compounds examined on KOH-coated columns always took place, but the extent of the change depended on the gas chromatographic conditions and varied daily. Decomposition did not depend on the solvent used, *i.e.* similar results were obtained using methanol, chloroform and diethyl ether solutions of the compounds.

The use of three different stationary phases all treated with KOH gave similar decomposition of these compounds, to indicate the influence of the KOH rather than the stationary phase. Therefore, chromatography of the compounds was investigated using a column similar to A but without treatment with KOH (*i.e.* column B).

Under the same GC conditions, as used for column A, compounds 1–4 (Table I) showed only single peaks using column B (Fig. 2).

The GC–MS spectra of the compounds giving these peaks corresponded to the direct inlet mass spectra of the parent 2-alkylaminopropiophenones. For compound 5 (Table I), 2-aminopropiophenone, it was necessary to use 10–20 times higher concentrations to give a detectable GC peak, which was shown to be of 2-aminopropiophenone by GC–MS. The peak from 2-aminopropiophenone on column B was not as sharp as it was on column A, and GC–MS results showed that some dehydrogenation had occurred even without the presence of KOH. Using column B, small amounts of the fragments corresponding to the decomposition products (1–3% with compounds 1 and 2, up to 10% with compound 4, and in almost equal amounts as unchanged fragments with compound 5), but none from compound 3, were demonstrated by GC–MS.

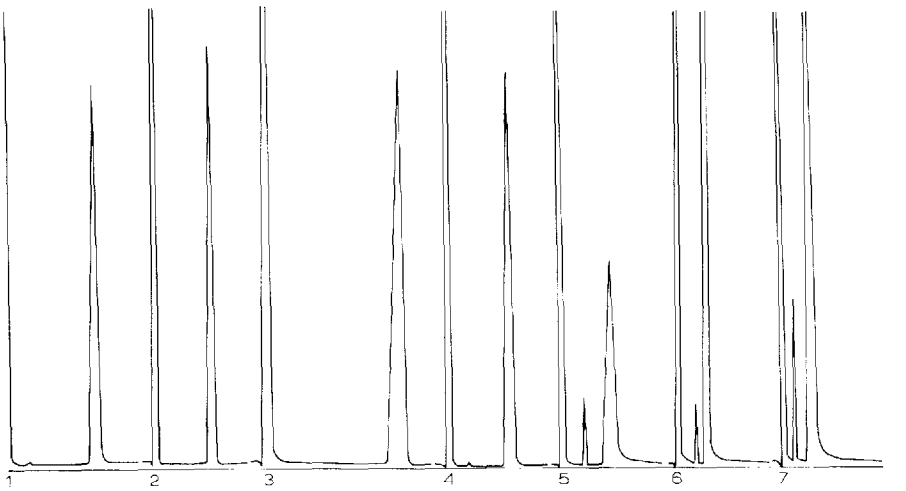
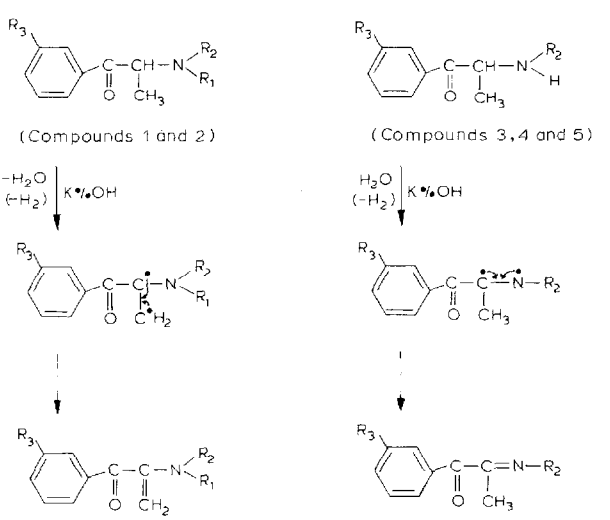


Fig. 2. Gas chromatograms of the compounds examined on column B. Column temperature: 200°C. Peaks: 1 = diethylpropion; 2 = dimethylpropion; 3 = bupropion; 4 = 2-ethylaminopropiophenone; 5 = 2-aminopropiophenone; 6 = phenyl vinyl ketone; 7 = phenyl methyl diketone.

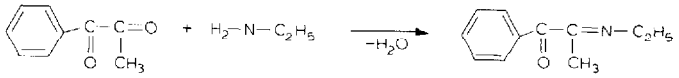
To confirm that both the compounds and their decomposition products were bases, and that alkali used during the process of extraction did not influence decomposition observed on the column, ether extracts of the compounds examined were washed with hydrochloric acid (1 *M*) and chromatographed; no peaks were observed. The acid layers were then made alkaline (5 *M* sodium hydroxide), extracted with ether and chromatographed; two peaks from the compounds examined were observed using column A and single peaks using column B.

On the basis of the above, the chemical mechanism for the GC decomposition of 2-aminopropiophenones on KOH-treated columns as shown in Scheme 1 is proposed.



Scheme 1.

The mechanism proposed by Scheme 1B was supported by the results obtained when phenyl methyl diketone solution (compound 7, Table I) and ethylamine–water (70:30, w/w) were mixed and the mixture left overnight. The mixture was diluted with diethyl ether to concentrations suitable fvor GC analysis and 2–3 μl injected on column A. Beside the peak corresponding to phenyl methyl diketone (ethylamine appears with the solvent peak), a peak with t_R = 5.6 min was observed. This peak corresponded to the second peak of compound 4 and it was formed according to the reaction shown in Scheme 2.



Scheme 2.

Hydrogen abstraction leading to dehydrogenation via free radical mechanisms is based on the following facts:

(i) The reaction takes place in the gas phase and under conditions which favour energetically the homolytic process. Reaction is initiated by KOH which under these conditions generates free radicals by heating[9,10].

(ii) The radical HO$^{\bullet}$ is known to be a very reactive hydrogen atom abstracting agent which reacts with most organic substrates[11]. Also, potassium atoms (like sodium atoms) exist as radicals in the gas phase and their reaction with organic compounds can produce radicals[12].

(iii) Hydrogen abstraction always occurs in preference to attack on carbon. As radicals abstract the hydrogen atoms from two adjacent atoms in the molecules giving diradicals, the energy necessary for bond breaking is partially supplied by making the new bond[12].

(iv) As for the HO$^{\bullet}$ radical in the gas phase (at 25°C), the relative reactivities for the reaction with alkyl hydrogens are: primary 1, secondary 7, tertiary 45[11] and this order also applies to bonds other than C–H (10), hydrogen abstraction is proposed by Scheme 1A for N-tertiary 2-aminopropiophenones (compounds 1 and 2) and by Scheme 1B for N-primary and N-secondary 2-aminopropiophenones (compounds 3, 4 and 5, Table I).

Although the heat of the reaction is of more importance, different extents of decomposition of compounds 3, 4 and 5 indicate steric, as well as inductive (+I) effects of the alkyl group on the nitrogen[10].

The above reactions are terminated by forming a new double bond in the molecule, which is conjugated not only with carbonyl group, but with the aromatic system[9].

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