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Mass spectra of derivatives of phenylalkylamines

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The mass spectra of 18 synthetic and naturally occurring phenylalkylamine derivatives and compounds having a similar pharmacological effect were taken and evaluated and possible fragmentation mechanisms for each are discussed.

THE mass spectrometer has proved useful for the identification and elucidation of the structure of small amounts of substances. We have been interested in the detection of catecholamines and similar transmitter substances in animal tissues and sympathetic ganglia and in body fluids, which after chromatographic separation are usually available in less than mg amounts.

The mass spectrometer appeared to be suitable for identifying these substances. To obtain meaningful results, we have run and evaluated the mass spectra of several substances of this kind. A problem is that they give only small or no molecular ions (Teeter, 1966). The mass spectra to be described should simplify the identification of compounds of this type. Transmitter substances usually contain as their basic structure a phenylalkylamine.

Experimental

All spectra were taken on a Hitachi-Perkin Elmer RMU-6D Mass Spectrometer with an electron beam energy of 70 eV using the direct heated inlet system.

Results and discussion

Amphetamine, methamphetamine (Beckett, Tucker & Moffat, 1967), phentermine, chlorphentermine and 2-dimethylamino-1-phenylpropane, e.g., undergo a common β-fission process. The alkylamine residue normally appears as the base peak. The molecular ion is less than 1%

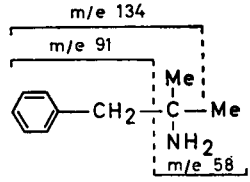

FIG. 1.

of the base peak or does not appear at all. In addition a peak at M-1 is present for all compounds when no further substituent is present on the benzene ring. This has also been observed with other aliphatic amines

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(Djerassi & Fenselau, 1965). The benzyl residue, which appears with an intensity between 30–50% of the base peak, fragments further as described by Beynon (1960), while the *p*-chlorobenzyl residue decomposes analogously to that described for *p*-chlorotoluene (Cornu & Massot, 1966). Fig. 1 shows the main fragmentation of phentermine.

When one or more OH groups are present on the benzene ring as with tyramine and dopamine, the molecular ion appears at an intensity of between 5 and 10% of the base peak which is the m/e 30 peak resulting from β-fission. A second important fragmentation involves the loss of COH from the phenolic portion (Beynon, 1960). A possible path is shown in Fig. 2 for tyramine.

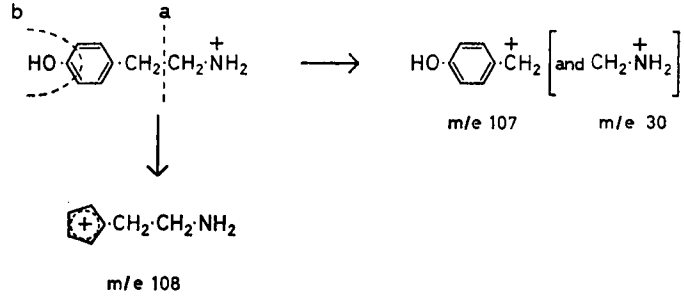


FIG. 2.

When an hydroxyl group is placed α to the benzene ring (β to the amino-group) as in norephedrine and ephedrine, no observable molecular ion is obtained. The base peak is m/e 44 or 58, respectively, resulting from β-fission. The benzylic residue also appears (m/e 107), however only to the extent of 1–2% of the base peak. Another interesting aspect is the presence of the benzoyl ion radical (m/e 105), as shown in Fig. 3 for ephedrine.

Some of the common transmitter substances possess hydroxyl groups both on the benzene ring and the carbon α to the benzene, e.g., noradrenaline, adrenaline, and isoprenaline. Among this type of compound

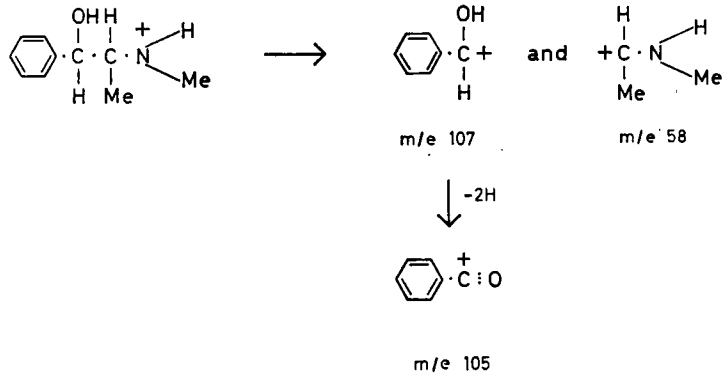


FIG. 3.

are norphenylephrine, ethyladrianol, and nylidrin, all of which undergo the usual β-fission process under electron bombardment. Norphenylephrine and ethyladrianol, besides giving a small molecular ion, have as their base peak m/e 30 and m/e 58 respectively. In addition, peaks corresponding to the loss of COH (from the phenolic portion) and peaks for the hydroxybenzoyl ion, as with norephedrine and ephedrine, can be observed. Because of the branched chain substituent on the nitrogen, nylidrin presents a more complex spectrum. Besides the usual β-fission, a fragmentation (A) α to the nitrogen and one (B) β to the non-phenolic benzene ring in the side chain occurs. It should be noted that the m/e 44 peak is the base peak as in the spectrum of isopropylamine (Cornu & Massot, 1966). Fig. 4 shows the proposed fragmentation for nylidrin.

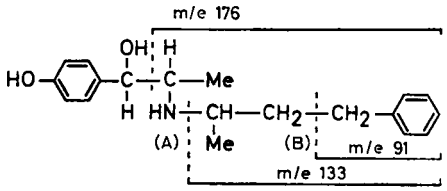


FIG. 4.

Noradrenaline, adrenaline, and isoprenaline with two phenolic hydroxyl groups all give an observable molecular ion. The peaks m/e 30 (noradrenaline), 44 (adrenaline), and 72 (isoprenaline) are again present.

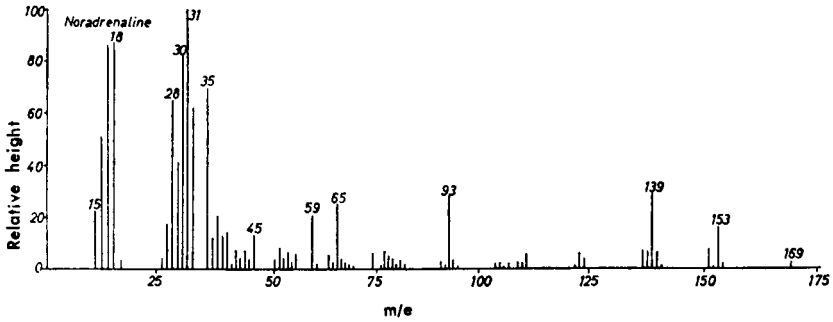


FIG. 5. Mass spectrum of noradrenaline.

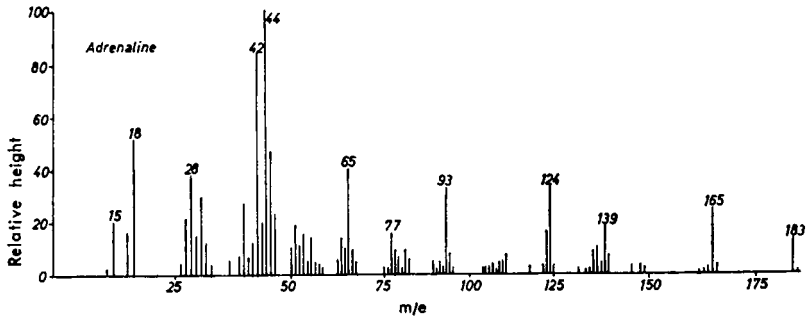
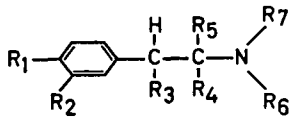


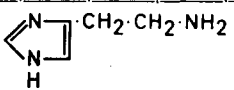
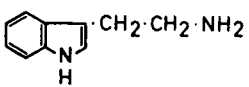
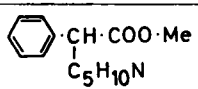
FIG. 6. Mass spectrum of adrenaline.

TABLE 1. STRUCTURAL FORMULAE AND M/E VALUES OF COMPOUNDS INVESTIGATED



Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7	M	100% peak	m/e (% relative height)
Amphetamine				Me				135	44	135 (0), 134 (1), 120 (3), 91 (20), 77 (3)
Methamphetamine				Me		Me		149	58	149 (<1), 148 (1), 134 (3), 91 (20), 77 (3)
Phentermine				Me	Me			149	58	149 (<1), 148 (<1), 134 (15), 117 (5), 91 (50), 77 (3)
Chlorphentermine	Cl			Me	Me			183	58	183 (0), 168 (5), 127 (2), 125 (10), 89 (7), 77 (2)
2-Dimethylamino-1-phenylpropane ..				Me		Me	Me	163	72	163 (1), 162 (2), 148 (10), 135 (5), 117 (8), 115 (8), 103 (5), 91 (60), 89 (7), 77 (50)
Tyramine	OH							137	30	137 (15), 120 (2), 109 (5), 108 (35), 107 (25), 91 (2), 77 (25)
Dopamine	OH	OH						153	30	153 (4), 124 (55), 123 (25), 105 (1), 77 (15)
Norephedrine			OH	Me				151	44	151 (0), 149 (1), 141 (1), 132 (1), 118 (1), 117 (1), 107 (5), 105 (5), 91 (5), 77 (15)
Ephedrine			OH	Me		Me		165	58	165 (0), 146 (1), 132 (2), 131 (2), 117 (3), 107 (10), 105 (10), 91 (10), 77 (70)
Norphenylephrine		OH	OH					153	30	153 (10), 124 (60), 123 (15), 121 (15), 107 (5), 95 (40), 77 (35)
Ethyladrianol		OH	OH			Me		181	58	181 (1), 162 (2), 152 (3), 138 (2), 121 (50), 107 (10), 95 (10), 93 (5), 77 (15)

TABLE 1—*continued*

Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7	M	100% peak	m/e (% relative height)
Noradrenaline	OH	OH	OH					169	31	169 (3), 153 (17), 151 (8), 139 (30), 137 (7), 124 (4), 123 (6), 111 (5), 93 (30), 77 (7)
Adrenaline	OH	OH	OH			Me		183	44	183 (13), 165 (25), 139 (18), 137 (10), 124 (35), 123 (15), 111 (7), 93 (30), 77 (15)
Isoprenaline	OH	OH	OH			$CHMe_2$		211	44	211 (0), 148 (1), 141 (2), 124 (20), 123 (15), 107 (4), 106 (3), 105 (4), 95 (3), 91 (2), 78 (5), 77 (4)
Nylidrin	OH		OH	Me		$CH<^{Me}_{CH_2CH_2Ph}$		299	44	299 (0, 1), 282 (1), 267 (1), 177 (5), 176 (25), 148 (2), 133 (2), 91 (50), 77 (5)
Histamine								111	82	111 (5), 83 (10), 82 (100), 81 (60), 77 (2)
Tryptamine								160	30	160 (10), 132 (20), 131 (90), 130 (90), 118 (10), 117 (10), 103 (10), 102 (10), 89 (5), 77 (50)
Methylphenidate								233	84	233 (0), 232 (1), 172 (2), 150 (2), 130 (3), 118 (5), 117 (5), 115 (4), 103 (2), 91 (40), 85 (45), 84 (100), 77 (20)

Noradrenaline and adrenaline also show the complements to these β-fission peaks, i.e. m/e 139 (10–15% of the base peak). This m/e 139 peak then fragments in at least two ways; in one, loss of 2 hydrogens gives the corresponding benzoyl ion which has appeared in every case where a hydroxyl group is present on the benzyl carbon; the second mode is the loss of CO (Reed, 1966) followed by a splitting off of water to give m/e 93. Also characteristic for these three catecholamines is the appearance of the m/e 124 peak, which could be derived by loss of water from the molecular ion and loss of CHN, C_2H_3N, or C_4H_7N, respectively. Figs 5 and 6 show the mass spectra of noradrenaline and adrenaline as representative examples.

Three chemically and pharmacologically similar compounds, histamine, tryptamine, and methylphenidate, were also subjected to mass spectrum analysis. With histamine the base peak m/e 82 was produced by β-fission with parallel rearrangement of one amine hydrogen to the imidazole ring. A second important process appears to be simple β-fission. Tryptamine undergoes the same two processes. The resulting peaks, m/e 131 and m/e 130, then fragment further as 3-methyl indole (Budzikiewicz, Djerassi & Williams, 1964). With methylphenidate the base peak is that at m/e 84 (). Two accompanying fragmentation modes are (i) the loss of protonated methylformate (fission of the C–C bond α to the carbonyl with abstraction of two hydrogens) and (ii) the formation of the methylbenzoate ion (m/e 150). This ion then decomposes in the normal fashion to give the benzyl ion. Table 1 shows the formulae of the compounds investigated and the characteristic m/e peaks in the mass spectrum of each along with the intensity of each expressed as percent of the largest peak (arbitrarily set at 100%).

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