CLANDESTINE MANUFACTURE OF 3,4-METHYLENEDIOXY-METHYLAMPHETAMINE (MDMA) BY LOW PRESSURE REDUCTIVE AMINATION. A MASS SPECTROMETRIC STUDY OF SOME REACTION MIXTURES

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Summary

Attention is paid here to a synthesis of MDMA consisting of a low pressure reductive amination of 3,4-(methylenedioxy)phenylpropanone with methylamine. The structures of several compounds present in reaction mixtures were elucidated by means of mass spectrometry.

Keywords: 3,4-Methylenedioxymethylamphetamine; Synthesis; Reductive amination; Reaction mixtures; Impurities; Fingerprinting

Introduction

As a result of the increasing popularity amongst drug users of 3,4-methylenedioxymethylamphetamine (MDMA), the drug was brought under the regulations of the Dutch Opium Law in the course of 1988. Rumours began to circulate last Autumn, concerning the production of MDMA (ECSTASY) in this country and these lasted several months until an actively operating production location was discovered and dismantled by police.

The process of synthesizing MDMA followed there can be described as a low pressure reductive amination at slightly elevated temperatures. The recipe was: a mixture of 3,4-(methylenedioxy)phenylpropanone and methylamine in alcohol was added slowly and under temperature control to aluminium powder freshly treated with mercuric chloride in ethanol. Then the temperature of the reaction mixture was raised and kept at the boiling temperature of alcohol for several hours. MDMA was isolated by distillation under reduced pressure, and a further cleanup was done by introducing hydrochloric acid gas into an alcoholic solution of MDMA.

Results are given here of the gas chromatographic-mass spectrometric investigation of several reaction mixtures at different reaction stages of the

low pressure reductive amination, found in an illegal laboratory. This was done in order to get a better understanding of the synthesis followed by the producers of illegal MDMA, and to ascertain the impurities which might be present in the final MDMA preparations.

Experimental

Spectroscopic conditions

Electron impact mass spectra at 70 eV were taken on a Finnigan MAT 212 GC-MS combination, coupled to a Kratos DS90 computer system. In the low resolution mode $M/\Delta M = 1000$ was used. Ion source and GC-MS interface temperatures were 250 °C. The accelerating voltage was 3 kV, whilst an ionization current of 0.8 mA was used.

Chromatographic conditions

Column: Phase Sep OV-1 on fused Silica, length 50 m, inner diameter 0.32 mm and 0.15 μm film thickness. The oven was programmed from 50 °C to 250 °C at 5 °C per min. The carrier gas was helium, flow rate was approximately 1.8 ml/min and the split ratio was 5 : 1.

Results and Discussion

In our previous work regarding impurities in illicit drug preparations [1,2] attention was paid principally to the syntheses of amphetamine and methylamphetamine. Especially the Leuckart process for the production of amphetamine was discussed in detail [3]. A high pressure reductive amination procedure for the production of methylamphetamine was found [4] to be operative in this country. Benzylmethylketone and methylamine were the starting materials in that process, and hydrogenation took place with Raney nickely and hydrogen. Impurities like amphetamine, *N,N*-dimethylamphetamine and phenylpropanol-2 were found in minor quantities in illegal methylamphetamine. The explanation of the existence of phenylpropanol-2 was straightforward, it was thought to originate from the hydrogenation of benzylmethylketone. The other two impurities stem from the reductive amination of benzylmethylketone with ammonia or dimethylamine, both impurities are present in the other starting material methylamine.

The low pressure reductive amination of 3,4(methylenedioxy)phenylpropanone with methylamine under hydrogenation by Al(Hg) in boiling ethanol (see Fig. 1), is a synthesis of similar nature as the procedure for the production of methylamphetamine. It is to be expected, therefore, that impurities to be found in MDMA, are as common as those in methylamphetamine.

In Fig. 2 a total ion chromatogram is given of a representative reaction mixture of the reductive amination of 3,4-(methylenedioxy)phenylpropanone and methylamine. The chromatographic peaks are numbered according to increasing molecular weight of the compounds. The nomenclature used

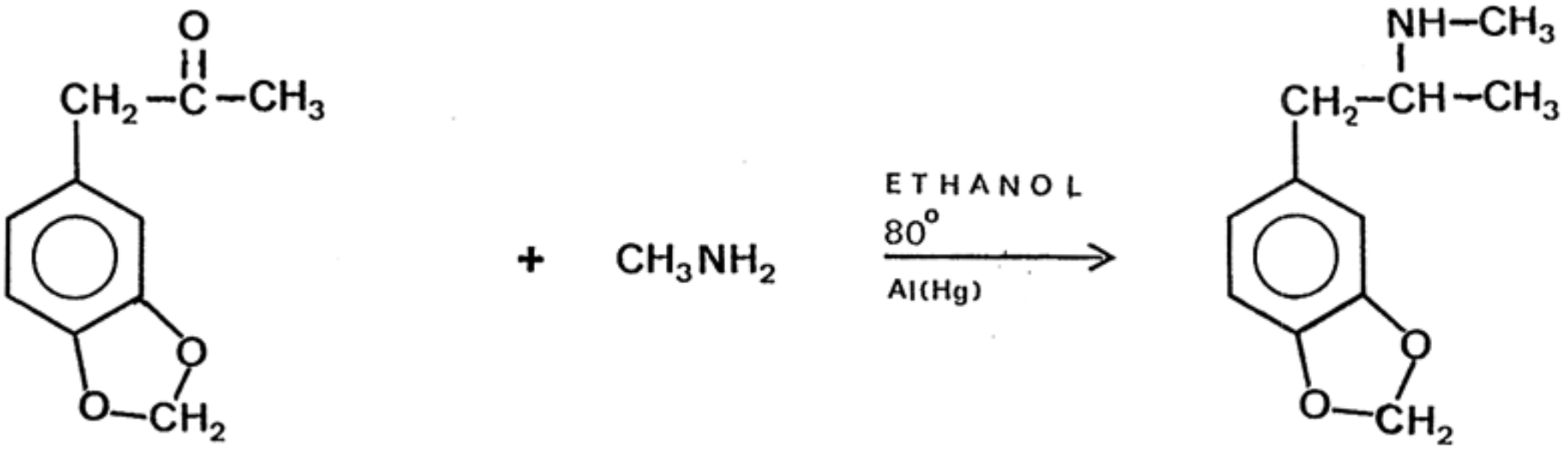

Fig. 1. Reaction scheme for the reductive amination of 3,4-(methylenedioxy)phenylpropane and methylamine.

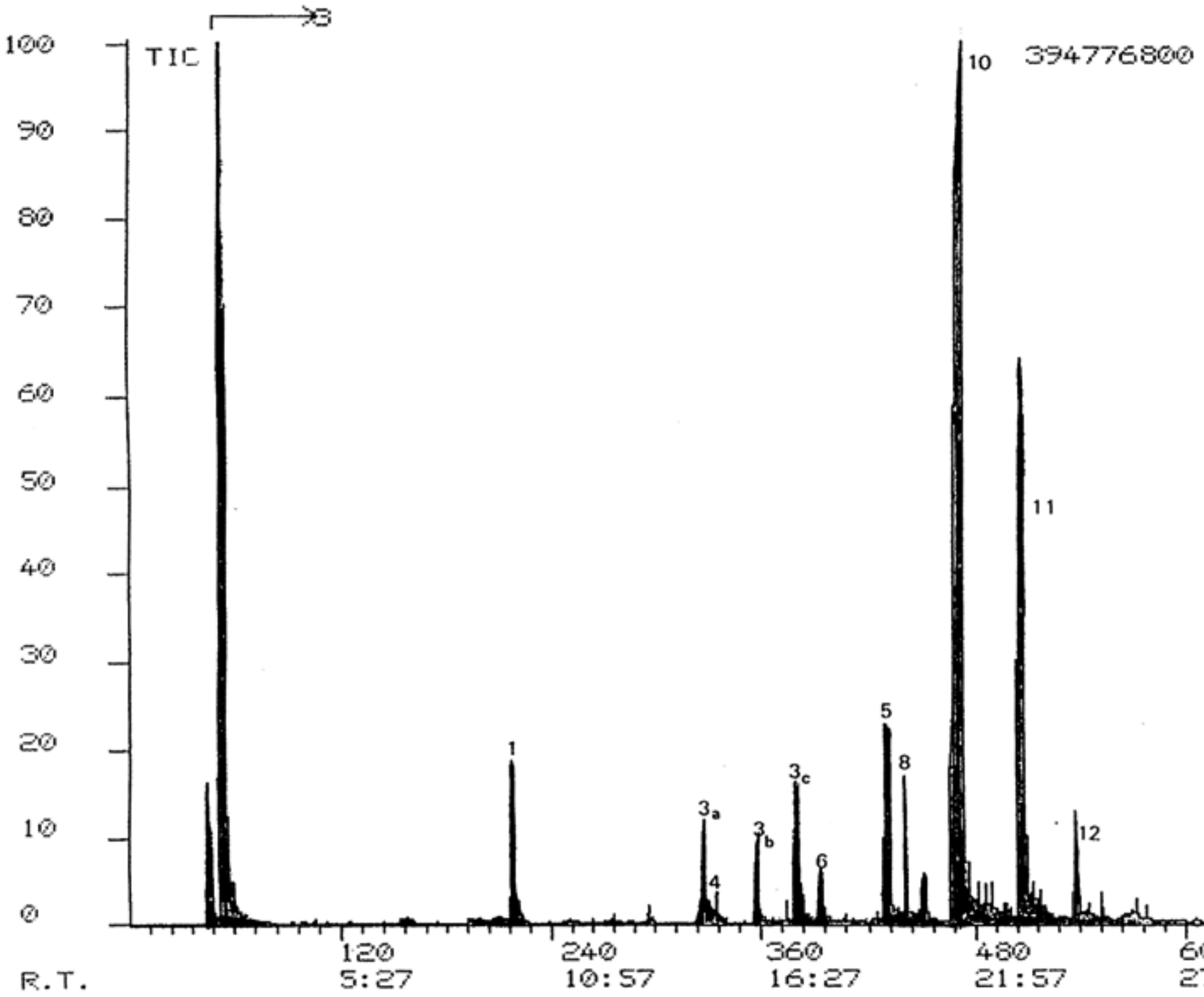

Fig. 2. Chromatogram of a representative reaction mixture. For experimental conditions and nomenclature of the peaks see text.

together with molecular weights of the compounds are collected in Table 1. Structure elucidation of the different compounds was obtained by using, if possible, the mass spectra and retention times of standard compounds. Some mass spectra were found in libraries [5—7], while in other cases the general properties of mass spectra were applied. The ions *m/z* 77, 105, 135 (in combination) appeared to be of diagnostic value for the methylenedioxymethylbenzene group, whereas the nitrogen containing compounds were governed by the ions *m/z* of either 44, 58, 72 or 86 due to charge localisation by nitrogen. In Table 2 an eight peak index of the mass spectra is given. Some additional compounds present in other reaction mixtures than the one mentioned complete the Tables. The nature and the origin of the compounds present in the reaction mixtures deserve some further attention. First the non-nitrogen compounds. The existence of safrole and isosafrole can be interpreted on the basis of the well known method of preparing the starting

TABLE 1

NOMENCLATURE USED THROUGHOUT THE TEXT

Compound	*M.W.*	*Formula*	*Name*
1.	136	$C_8H_8O_2$	1,2-(methylenedioxy)-4-methylbenzene.
2.	150	$C_8H_6O_3$	3,4-(methylenedioxy)benzaldehyde.
3a,3b	162	$C_{10}H_{10}O_2$	4-allyl-1,2-(methylenedioxy)-benzene, safrole c.q.
3c.			1,2-(methylenedioxy)-4-propenyl-benzene, isosafrole.
4.	164	$C_{10}H_{12}O_2$	1,2-(methylenedioxy)-4-propylbenzene.
5.	178	$C_{10}H_{10}O_3$	3,4-(methylenedioxy)phenylpropanone.
6.	178	$C_{11}H_{14}O_2$	1,2-(dimethoxy)-4-propenylbenzene.
7.	179	$C_{10}H_{13}NO_2$	1,2-(methylenedioxy)-4-(2-aminopropyl)benzene, M.D.A., 3,4-(methylenedioxy)amphetamine.
8.	180	$C_{10}H_{12}O_3$	1-(3,4-methylenedioxy)phenyl-propanol-2.
9.	191	$C_{11}H_{13}NO_2$	1,2-(methylenedioxy)-4-(2-*N*-methyl-iminopropyl)benzene.
10.	193	$C_{11}H_{15}NO_2$	*N*-methyl-(1,2-methylenedioxy)-4-(2-aminopropyl)benzene. 3,4-(methylenedioxy)methyl-amphetamine, Ecstasy.
11.	207	$C_{12}H_{17}NO_2$	*N*,*N*-dimethyl-(1,2-methylenedioxy)-4-(2-aminopropyl)benzene.
12.	221	$C_{13}H_{19}NO_2$	*N*-ethyl,*N*-methyl-(1,2-methylene-dioxy)-4-(2-aminopropyl)benzene.

TABLE 2

AN EIGHT PEAK INDEX OF THE MASS SPECTRA

Compound	*M.W.*	*Peaks*								*Intensities*							
1.	136	135	136	77	79	51	106	52	105	100	85	24	15	7	7	5	5
2.	150	149	150	121	63	65	61	91	119	100	89	55	40	29	20	15	7
3a./3b.	162	162	104	131	103	77	78	51	135	100	45	44	32	30	21	18	18
3c.	162	162	104	131	103	77	78	51	135	100	44	42	32	26	17	15	15
4.	164	135	77	164	51	79	136	105	91	100	26	24	12	12	10	8	3
5.	178	135	77	51	43	178	79	136	105	100	44	21	21	20	19	13	12
6.	178	162	163	178	147	135	107	136	91	100	99	70	48	37	32	28	27
7.	179	44	136	135	77	51	179	45	78	100	20	8	8	7	3	2	2
8.	180	135	136	77	51	106	180	79	43	100	66	27	20	16	15	13	12
9.	191	56	191	135	77	57	51	105	160	100	17	9	9	9	8	2	1
10.	193	58	136	135	59	77	51	89	193	100	17	15	15	14	9	6	5
11.	207	72	56	44	73	58	70	77	135	100	11	10	10	5	4	4	4
12.	221	86	58	87	56	44	77	72	135	100	21	7	4	3	3	2	2

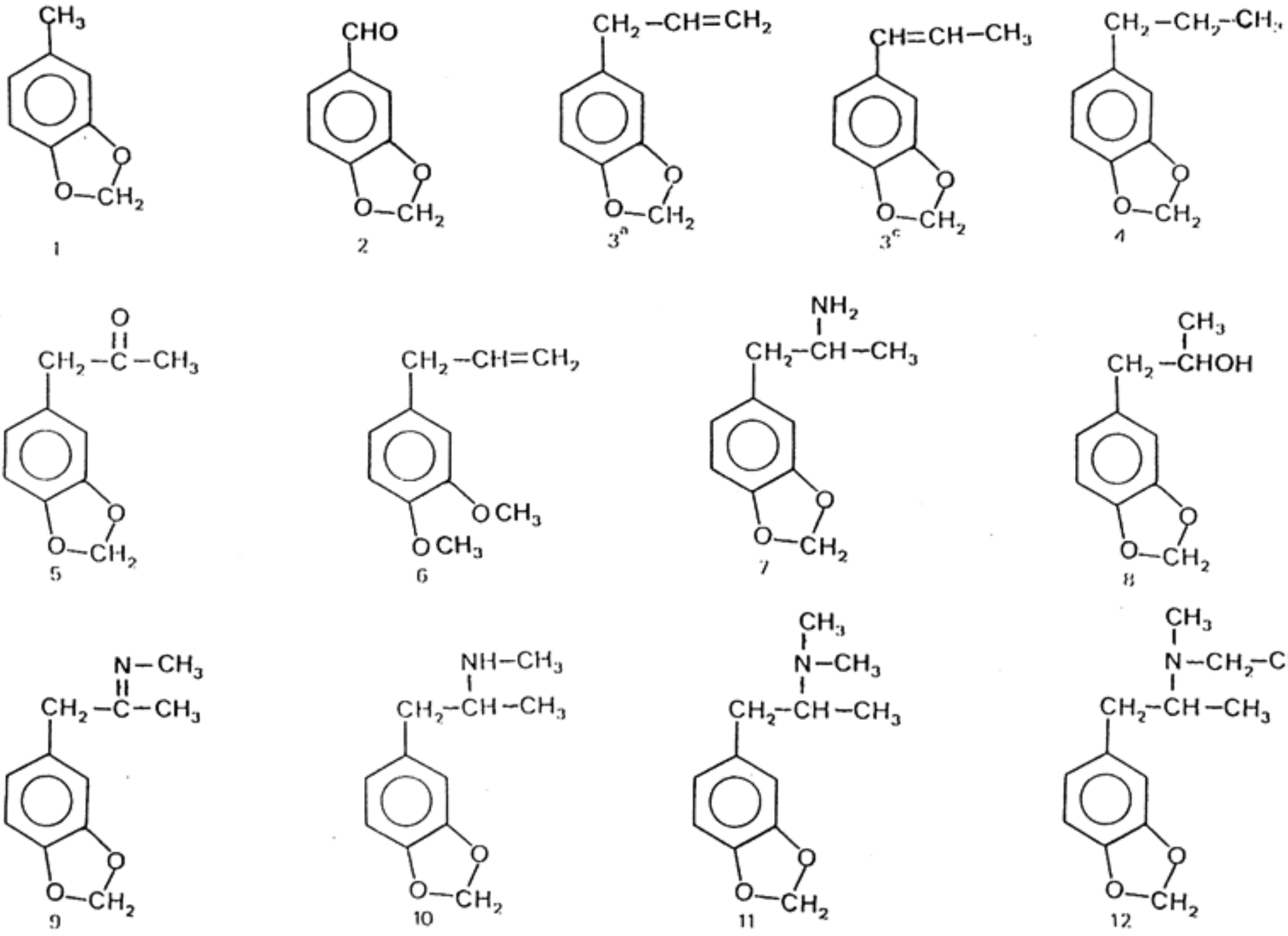

Fig. 3. Structural formulas of the compounds in Table 1.

ketone, 3,4-(methylenedioxy)phenylpropanone, of the MDMA synthesis by oxidising safrole or isosafrole by hydrogen peroxide in an acid medium. As hydrogenation is a basic step in the reaction the hydrogenated forms of the ketone, the alcohol 1-(3,4-methylenedioxy)phenylpropanol-2 can be present. Further hydrogenation of safrole, isosafrole and the alcohol can give rise to the presence of 1,2-(methylenedioxy)-4-propylbenzene. The aldehyde 3,4-(methylenedioxy)benzaldehyde is thought to be an impurity of the starting ketone, whereas 1,2-(methylenedioxy)-4-methylbenzene is its hydrogenation product. The dimethoxy compound 1,2-(dimethoxy)-4-propenylbenzene is likewise thought to be an impurity of the starting material.

Finally some remarks are given here on the nitrogen compounds found in the reaction mixtures. The synthesis of MDMA by reductive amination of 3,4-(methylenedioxy)phenylpropanone and methylamine was not unsuccessful as regards to the yields of MDMA. But a fair amount of nitrogen-containing impurities was found to be present in the reaction mixtures (see Fig. 2). As a matter of fact the methylamine could have been contaminated with ammonia, dimethylamine and ethylmethylamine, in that way the occurrence of the other nitrogen compounds can be explained. The presence of the imine 1,2-(methylenedioxy)-4-(2-*N*-methyliminopropyl)benzene, an intermediate product, points specifically to the type of reaction used by the producers of illegal MDMA and can be of importance as "route specific" impurity.

Of course the presence of the compounds as impurities in the final drug preparations, will depend on the degree of the purification of MDMA by the illegal producers.

Acknowledgement

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