Impurities in Illicit Drug Preparations: 3,4-(Methylenedioxy)amphetamine and 3,4-(Methylenedioxy)methylamphetamine

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REFERENCE: Verweij AMA: Impurities in illicit drug preparations: 3,4-(methylenedioxy)amphetamine and 3,4-(methylenedioxy)methylamphetamine; *Forensic Sci Rev* 4:137; 1992.

ABSTRACT: Attention is given here to the mass spectral data of impurities present in illicit drug preparations of 3,4-(methylenedioxy)amphetamine and 3,4-(methylenedioxy)methylamphetamine. These "designer" drugs, having emphatic properties, were synthesized following well-known procedures such as the reductive amination route, the Leuckart reaction, and the nitropropene and the bromopropane routes. Based on the structure elucidation of impurities — especially those so-called "route specific" ones — present in these illicit drug preparations conclusions can be drawn about the method of preparation of a drug sample. Furthermore, on the basis of this kind of information methods can be developed for the comparison of drug samples, by which questions about the origin of drug samples can be solved (commonly known as the signature method).

KEY WORDS: Designer drugs, dioxyamphetamine, synthesis, impurities, mass spectrometry.

I. INTRODUCTION

Clandestine manufacturing of 3,4-(methylenedioxy)-amphetamine (MDA) analogs and homologs was thoroughly discussed by Dal Cason [1]. Central nerve system activities, synthesis potentialities, ease of chemical handling, and availability of precursors were reviewed. Achieving synthesis of the desired compounds through the reductive amination route (with several hydrogenation steps), the Leuckart reaction, the bromopropane route, the Ritter reaction, the nitropropene route, and the substituted cinnamic acid route were also focused on [1].

As MDA and 3,4-(methylenedioxy)methylamphetamine (MDMA) are nearly always illicitly produced in clandestine laboratories, the preparations produced very often contain precursors, intermediates, or other impurities in addition to the targeted drugs. In fact, the presence of these contaminations derived from different origins in MDA or MDMA preparations can assist in establishing the route of synthesis [2] adopted by the individuals illegally producing these amphetamines.

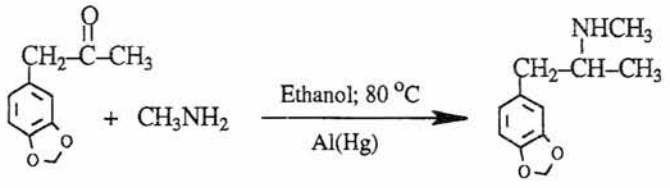
Structure elucidation of the impurities in MDA and MDMA preparations by mass spectrometric and other methods can be found in literature: the reductive amination route [3,4], the Leuckart reaction [4,5], the nitropropene route [5,6], and the bromopropane route [7,8]. In this article the MS data of the impurities present in preparations of MDA and MDMA are collected and arranged in tables, in according to the synthetic routes used.

The data given here are obtained mostly by low resolution MS using the electron impact (EI) ionization method. The compounds were identified by consulting MS data bases, synthesis of the assumed compounds, interpretation of the fragmentation properties known in MS, or sometimes by using analytical methods other than MS. For full details the reader is referred to references [2-8].

II. SYNTHESIS ROUTES

A. The Reductive Amination Route

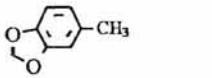
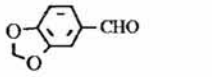
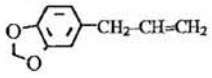
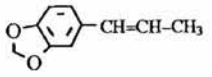
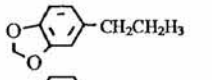
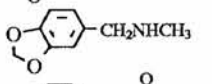
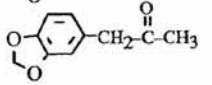
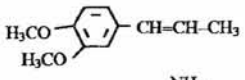
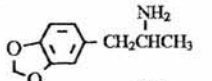
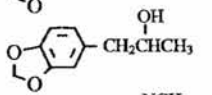
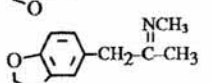
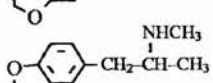
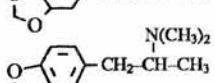
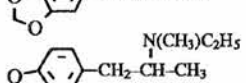
The most frequently used method to prepare MDMA in The Netherlands can be described as a low pressure reductive amination at slightly elevated temperatures [3,4] (Scheme 1).



Scheme 1. Reductive amination

The structural information and eight-peak MS data of the impurities that are reported for this route of synthesis are summarized in Table 1. The compounds given in the table include starting materials and their impurities, hydrogenated compounds originating from starting materi-

Table 1. Impurities found in MDMA synthesized with the reductive amination

	MW	Formula	Structure	Name	Most intense EI ions and relative intensity[a]							
1	136	$C_8H_8O_2$		4-Methyl-1,2-(methylenedioxy)benzene	135	136	77	79	51	106	52	105
					100	85	24	15	7	7	5	5
2	150	$C_8H_6O_3$		3,4-(Methylenedioxy)benzaldehyde, piperonal	149	150	121	63	65	61	91	119
					100	89	55	40	29	20	15	7
3a	162	$C_{10}H_{10}O_2$		4-Allyl-1,2-(methylenedioxy)benzene, safrole	162	104	131	103	77	78	51	135
					100	45	44	32	26	21	18	18
3b				1,2-(Methylenedioxy)-4-propenylbenzene, isosafrole								
4	164	$C_{10}H_{12}O_2$		1,2-(Methylenedioxy)-4-propylbenzene	135	77	164	51	79	136	105	91
					100	26	24	12	12	10	8	3
5	165	$C_9H_{11}NO_2$		3,4-(Methylenedioxy)benzyl-*N*-methylamine	135	42	51	77	136	165	164	79
					100	84	75	67	45	40	36	32
6	178	$C_{10}H_{10}O_3$		3,4-(Methylemedioxy)phenylpropanone	135	77	51	43	178	79	136	105
					100	44	21	21	20	19	13	12
7	178	$C_{11}H_{14}O_2$		1,2-(Dimethoxy)-4-propenylbenzene	162	163	178	147	135	107	136	91
					100	99	70	48	37	32	28	27
8	179	$C_{10}H_{13}NO_2$		1,2-(Methylenedioxy)-4-(2-aminopropyl)benzene, 3,4-(methylene-dioxy)amphetamine, MDA	44	136	135	77	51	179	45	78
					100	20	8	8	7	3	2	2
9	180	$C_{10}H_{12}O_3$		1-(3,4-Methylenedioxy)phenylpropanol-2	135	136	77	51	106	180	79	43
					100	66	27	20	16	15	13	12
10	191	$C_{11}H_{13}NO_2$		1,2-(Methylenedioxy)-4-(2-*N*-methyliminopropyl)benzene	56	191	135	77	57	51	105	160
					100	17	9	9	9	8	2	1
11	193	$C_{11}H_{15}NO_2$		*N*-Methyl-[1,2-(methylenedioxy)-4-(2-aminopropyl)]benzene, 3,4-(methylenedioxy)methylamphetamine, MDMA, Ecstasy	58	136	135	59	77	51	89	193
					100	17	15	15	14	9	6	5
12	207	$C_{12}H_{17}NO_2$		*N,N*-Dimethyl-[1,2-(methylenedioxy)-4-(2-aminopropyl)]benzene	72	56	44	73	58	70	77	135
					100	11	10	10	5	4	4	4
13	221	$C_{13}H_{19}NO_2$		*N*-Ethyl,*N*-methyl-[1,2-(methylenedioxy)-4-(2-aminopropyl)]benzene	86	58	87	56	44	77	72	135
					100	21	7	4	3	3	2	2

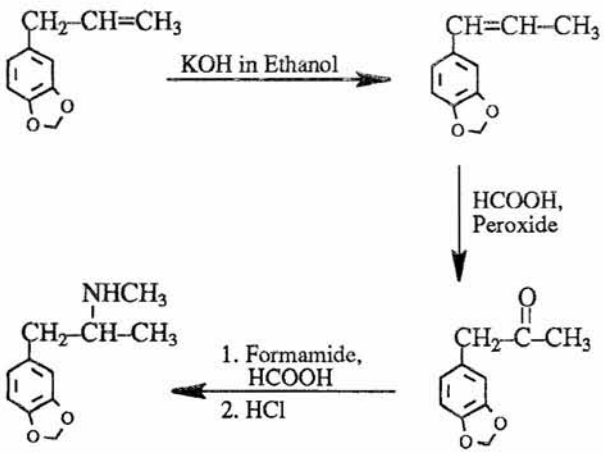
[a] The relative intensities of the ions listed for each compound are shown on the line below it.

als, and nitrogen-containing compounds — intermediate substances resulting from the reaction of phenylpropanone with impurities in methylamine such as ammonia and higher alkylated amines.

Besides these impurities relating to chemical synthesis and the substances used in it, the MDA and the MDMA preparations can be contaminated by a host of strange compounds [4] including caffeine, cocaine, ketamine, quinine, and amphetamine; the latter substance also contains typical impurities aziridines, pyrimidines, and di-(β-phenylisopropyl)amine.

B. The Leuckart Reaction

This reaction is seldom used for the synthesis of the substituted amphetamines [4,5]. Using safrole as a starting compound in order to produce the phenylpropanone, the reaction can be schematically depicted as shown in Scheme 2.



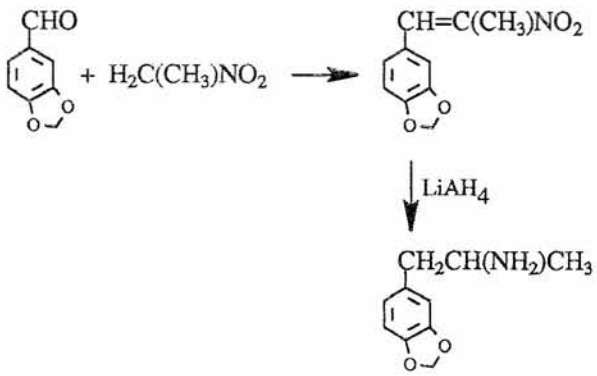
Scheme 2. Leuckart reaction

The structural information and eight-peak MS data of the impurities that are reported for this route of synthesis are summarized in Table 2. Again, many impurities derive from starting materials and accompanying chemicals; others originate from condensations between the starting material and the end product.

C. The Nitropropene Route

The condensation reaction (Scheme 3) between nitroethane and piperonal has been adopted for the production of MDA [5,6].

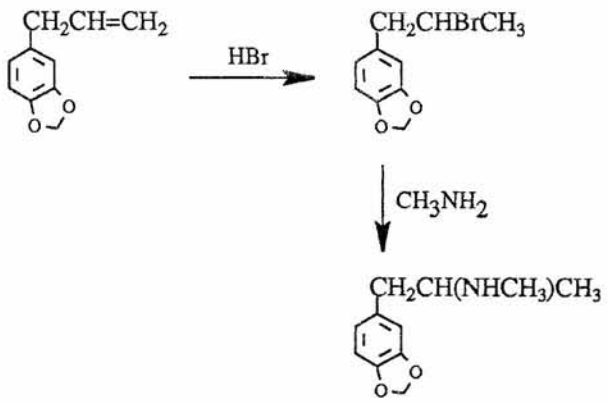
The structural information and eight-peak MS data of the reported impurities that are known for this route of synthesis are summarized in Table 3. Again, the presence of impurities in the starting materials was noticed, while the most of the other impurities found can best be explained by assuming condensation reactions between starting materials, intermediate, and final products.



Scheme 3. Nitropropene route

D. The Bromopropane Route

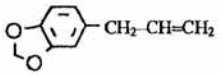
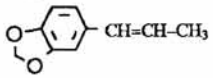
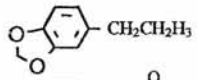
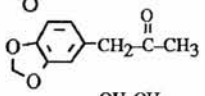
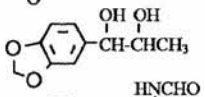
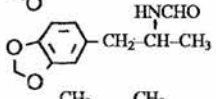
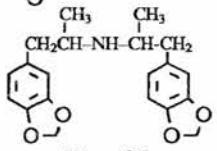
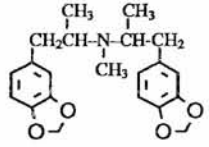
The reaction of safrole (obtained from sassafras oil) with hydrobromic acid shown in Scheme 4 was intensively studied [7,8].



Scheme 4. Bromopropane route

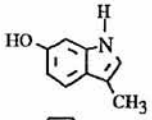
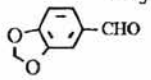
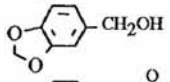
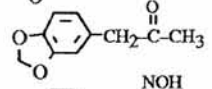
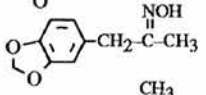
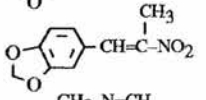
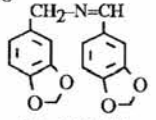
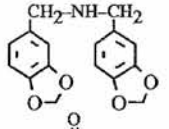
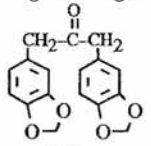
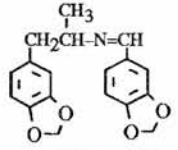
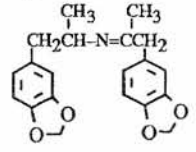
All bromination products of the other essential oils associated with the starting chemical safrole can be found in MDA or MDMA preparations, depending on the extent of purification attained by the individuals that are produc-

Table 2. Impurities found in MDA synthesized with the Leuckart reaction

	MW	Formula	Structure	Name	Most intense EI ions and relative intensity[a]							
1a	162	$C_{10}H_{10}O_2$		4-Allyl-1,2-(methylenedioxy)benzene, safrole	162	104	131	103	77	78	51	135
					100	45	44	32	26	21	18	18
1b				1,2-(Methylenedioxy)-4-propenylbenzene, isosafrole								
2	164	$C_{10}H_{12}O_2$		1,2-(Methylenedioxy)-4-propylbenzene	135	77	164	51	79	136	105	91
					100	26	24	12	12	10	8	3
3	178	$C_{10}H_{10}O_3$		3,4-(Methylenedioxy)phenylpropanone	135	77	51	43	178	79	136	105
					100	44	21	21	20	19	13	12
4	196	$C_{10}H_{12}O_4$		Isosafrole glycol	93	151	65	123	152	196	43	77
					100	79	53	18	18	7	7	6
5	207	$C_{11}H_{13}NO_3$		*N*-Formyl MDA	162	135	72	44	77	136	51	105
					100	99	82	68	46	28	26	14
6	341	$C_{20}H_{23}NO_4$		Di-[1-(3,4-methylenedioxy)phenyl-2-propyl]amine	163	135	206	105	133	77	70	79
					100	47	41	37	27	23	15	10
7	355	$C_{21}H_{25}NO_4$		Di-[1-(3,4-methylenedioxy)phenyl-2-propyl]methylamine	163	220	135	105	58	77	132	79
					100	55	46	42	37	28	23	16

[a] The relative intensities of the ions listed for each compound are shown on the line below it.

Table 3. Impurities found in MDA synthesized with the nitropropene route

	MW	Formula	Structure	Name	Most intense EI ions and relative intensity[a]							
1	147	C_9H_9NO		Hydroxyskatole	147 100	146 63	62 23	63 18	39 12	89 9	90 9	61 7
2	150	$C_8H_6O_3$		3,4-(Methylenedioxy)benzaldehyde, piperonal	149 100	150 92	121 24	63 16	65 15	91 6	118 6	51 4
3	152	$C_8H_8O_3$		3,4-(Methylenedioxy)phenylmethanol	152 100	137 51	93 45	65 35	151 34	122 25	123 25	94 19
4	178	$C_{10}H_{10}O_3$		3,4-(Methylenedioxy)phenylpropanone	135 100	178 46	77 42	51 40	43 22	136 17	105 12	79 11
5	193	$C_{10}H_{11}NO_3$		3,4-(Methylenedioxy)benzylmethylketoxime	135 100	193 54	136 34	77 32	146 29	178 23	51 22	118 15
6	207	$C_{10}H_9NO_4$		1-[3,4-(Methylenedioxy)phenyl]-2-nitro-1-propene	103 100	160 74	207 67	77 54	102 37	51 24	65 19	76 18
7	283	$C_{16}H_{13}NO_4$		*N*-[β-(3,4-Methylenedioxy)phenylmethyl]-3,4-(methylenedioxy)benzaldiimine	135 100	178 24	176 16	77 15	136 9	149 6	98 5	51 4
8	285	$C_{16}H_{15}NO_4$		*N,N*-Di-[3,4-(Methylenedioxy)phenylmethyl]amine	135 100	150 77	136 50	77 21	51 10	106 10	162 9	151 7
9	298	$C_{17}H_{14}O_5$		Di-[3,4-(methylenedioxy)phenylpropanone]	163 100	135 68	105 32	133 25	77 21	164 11	79 8	136 8
10	311	$C_{18}H_{17}NO_4$		*N*-{β-[3,4-(Methylenedioxy)]phenylisopropyl}-3,4-(methylenedioxy)benzaldiimine	176 100	149 14	177 10	77 10	135 10	91 7	168 6	118 5
11	339	$C_{20}H_{21}NO_4$		*N*-{β-[3,4-(Methylenedioxy)]phenylisopropyl}-3,4-(methylenedioxy)benzylketiimine	163 100	204 65	135 42	105 19	77 18	133 12	164 12	205 10

[a] The relative intensities of the ions listed for each compound are shown on the line below it.

Table 4. Impurities found in MDA or MDMA synthesized with the bromopropane reaction

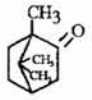
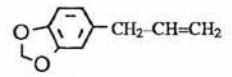
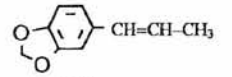
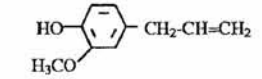
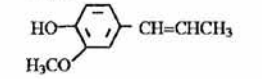
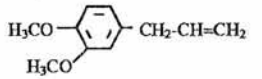
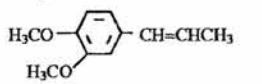
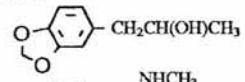
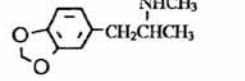
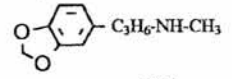
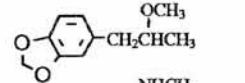
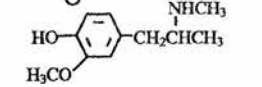
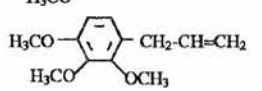
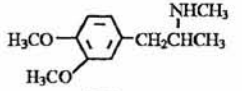
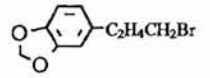
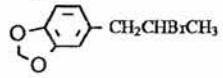
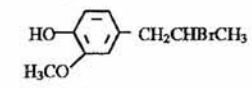
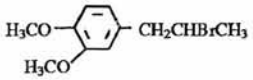
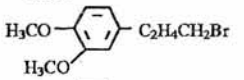
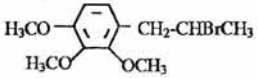
	MW	Formula	Structure	Name	Most intense EI ions and relative intensity[a]							
1	152	$C_{10}H_{16}O$		1,7,7-Trimethylbicyclo(2,2,1)heptan-2-one, Camphor	95 100	81 71	41 65	108 50	152 45	55 43	109 38	61 37
2a	162	$C_{10}H_{10}O_2$		4-Allyl-1,2-(methylenedioxy)benzene, safrole	162 100	104 45	131 44	103 32	77 30	78 21	51 18	135 18
2b				1,2-(Methylenedioxy)-4-propenylbenzene, isosafrole								
3a	164	$C_{10}H_{12}O_2$		2-Methoxy-4-(2-propenyl)phenol, eugenol	164 100	77 44	55 42	103 38	149 35	91 33	39 30	131 30
3b				2-Methoxy-4-propenylphenol, isoeugenol								
4a	178	$C_{11}H_{14}O_2$		4-Allyl-1,2-(dimethoxy)benzene	178 100	91 49	107 49	103 43	147 38	163 36	39 27	77 26
4b				1,2-(Dimethoxy)-4-propenylbenzene	178 100	107 76	163 53	91 48	103 36	77 24	79 23	41 22
5	180	$C_{10}H_{12}O_3$		1-(3,4-Methylenedioxy)phenylpropanol-2	135 100	136 66	77 27	51 20	106 16	180 15	79 13	43 12
6a	193	$C_{11}H_{15}NO_2$		*N*-Methyl-[1,2-(methylenedioxy)-4-(2-aminopropyl)]benzene, 3,4-(methylenedioxy)methylamphetamine, MDMA, Ecstasy	58 100	136 17	135 15	59 15	77 14	51 9	89 6	193 5
6b				*N*-Methyl-[1,2-(methylenedioxy)-4-(3-aminopropyl)]benzene	44 100	162 17	65 11	77 11	135 10	51 10	193 9	136 8
7	194	$C_{11}H_{14}O_3$		1-(3,4-Methylenedioxy)phenyl-2-methoxypropane	59 100	194 27	135 27	136 17	77 13	51 10	103 5	105 4
8	195	$C_{11}H_{17}NO_2$		*N*-Methyl-1-[1-(hydroxy)-2-(methoxy)]-4-(2-aminopropyl)]benzene	58 100	51 6	77 5	137 5	94 4	59 4	122 3	165 2
9	208	$C_{12}H_{16}O_3$		4-Allyltrimethoxybenzene	208 100	193 59	161 24	133 20	105 21	91 15	77 13	79 12

Table 4. (Continued)

	MW	Formula	Structure	Name	Most intense EI ions and relative intensity[a]							
10	209	$C_{12}H_{19}NO_2$		*N*-Methyl-1-[1,2-(dimethoxy)-4-(2-aminopropyl)]benzene	58	152	51	151	59	107	65	91
					100	11	6	5	5	4	4	3
11a	242	$C_{10}H_{11}BrO_2$		1-[3,4-(Methylenedioxy)]-4-(2-bromopropyl)]benzene	135	77	242	244	51	163	105	79
					100	18	16	16	15	14	12	9
11b				1-[3,4-(Methylenedioxy)]-4-(3-bromopropyl)]benzene	149	119	91	163	242	244	39	135
					100	20	19	14	14	13	9	8
12	244	$C_{10}H_{13}BrO_2$		2-Methoxy-4-(2-bromopropyl)phenol	137	244	246	165	135	122	105	77
					100	19	19	14	9	8	8	6
13a	258	$C_{11}H_{15}BrO_2$		1,2-Dimethoxy-4-(2-bromopropyl)benzene	151	179	107	258	260	91	77	65
					100	11	8	8	8	7	6	4
13b	258	$C_{11}H_{15}BrO_2$		1,2-Dimethoxy-4-(3-bromopropyl)benzene	165	162	258	260	119	105	204	91
					100	41	36	36	28	28	18	15
14	288	$C_{12}H_{17}BrO_3$		Trimethoxy-4-(2-bromopropyl)benzene	181	209	288	290	148	151	105	77
					100	18	15	15	7	6	5	5

[a] The relative intensities of the ions listed for each compound are shown on the line below it.

ing the illicit drugs. The structural information and eight-peak MS data of the impurities that are reported for this route of synthesis are summarized in Table 4. The impurities given here refer to various compounds present in safrole; the brominated products of these substances resulting from the reaction of different compounds in safrole with hydrobromic acid; and the amino compounds originating from the amination of the bromine-containing substances.

III. APPLICATIONS

The information collected in the tables was used in the author's laboratory [4] to differentiate between the various routes of synthesis followed for the production of MDMA samples. During the past year, very limited use of the data from the tables was made in cases in which the origin of different samples was questioned. These so-called "signature investigations" which utilize gas chromatographic profiles are now in a mature state of development. They are often used in cases in which amphetamine was involved. In particular, Strömberg's group at Linköping University has reported signatures of amphetamines of different origins for many years [9-12]. The literature [13-15] provides more of an overview of the subject. It stands to reason that the information from the tables can be used for similar purposes, depending on the popularity and future availability of these kinds of drugs.

IV. CONCLUSION

Mass spectral information in the tables is given about the different impurities found in either MDA or MDMA preparations that are produced along several routes. In most cases the nature of the impurities can be ascribed to starting chemicals, intermediates, and substances originating from condensations of reaction products in the various stages of the reaction. Some impurities are route specific, e.g., *N*-formyl MDA, 1-[3,4-(methylenedioxy)-phenyl]-2-nitro-1-propene, and the bromo compounds of the bromopropane route. Although there are other possible synthetic routes, only those the impurities of which are described in the literature, are reviewed in this article. In our opinion, proper use of information in the tables can assist in elucidating the nature of a reaction route that may be used for producing an MDA analog preparation.

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