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The Use of Carbon-13 Nuclear Magnetic Resonance Spectra in the Identification and Authentication of Monomethoxyamphetamines and Dimethoxyamphetamines

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ABSTRACT: The ^{13}C nuclear magnetic resonance (NMR) spectra of amphetamine, the three monomethoxyamphetamines, and the six dimethoxyamphetamines and their hyrochlorides were determined. The spectra are distinctive and suitable for identification and authentication purposes. The signals may be assigned by comparisons of chemical shifts with those of model compounds and by an internally consistent analysis of chemical shift differences, supported by the results of appropriate proton-decoupling techniques. Data from the spectra and details of their interpretation are presented. Ortho methoxyl groups relatively shield the α and β side-chain carbon signals. The ring substituents affect the resonances of the ring carbons in a consistent manner. The data should be valuable in the forensic science identification and structural authentication of these and related substances and further confirm the power of ^{13}C NMR spectroscopy in distinguishing between isomeric structures.

KEYWORDS: toxicology, chemical analysis, amphetamine

The monomethoxyamphetamines and dimethoxyamphetamines (Fig. 1) form a series of compounds whose members are generally held to be psychoactive in man. 2,5-Dimethoxyamphetamine (2,5-DMA) and 4-methoxyamphetamine (*p*-methoxyamphetamine, PMA) are hallucinogenic [*1*]. Both have been found on the illicit drug market for several years, and chromatographic and spectroscopic data suitable for their identification have been published [*2-4*]. The authentication of reference material from which the individual parameters for identification are obtained is obviously essential. All of the supporting data, especially spectrometric data, must be entirely consistent with the purported chemical structure and existing chemical-spectroscopic theory. The use of ^{13}C nuclear magnetic resonance (NMR) spectroscopy [*5*] for confirming the authenticity of reference materials can be expected to increase with the availability of sensitive spectrometers and the continued demonstration of its power in discriminating among similar compounds. Thus, ^{13}C NMR data have been published for several classes of abused drugs, including arylcyclohexylamines (phencyclidine analogs) [*6*], barbiturates [*7*], cannabinoids [*8*], and opiates [*9*]. The analysis of ^{13}C NMR spectra reported here confirms the authenticity of

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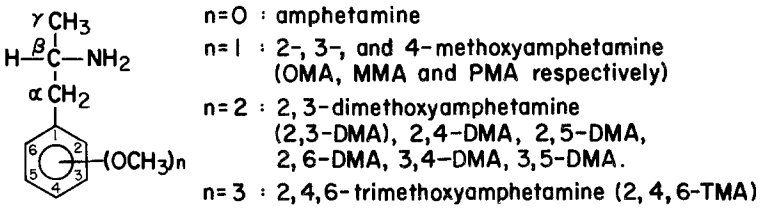

FIG. 1—*Structures and numbering system for methoxyamphetamines.*

monomethoxyamphetamines and dimethoxyamphetamines used in the generation of identification data [*2,3*], provides additional reference characteristics, and further demonstrates the power of ^{13}C NMR spectroscopy as a unique tool for drug identification. Their interpretation is also relevant to the conformational behavior of aromatic methoxyl groups in this series, which has been investigated recently in similar compounds by ^{13}C NMR spectroscopy [*10*].

Experimental Procedure

The methoxyamphetamines and their hydrochlorides were obtained and characterized as previously described [*2,3*]. Carbon-13 NMR spectra were determined at 20.1 MHz on a Brüker WP 80 Fourier transform spectrometer. Spectra were recorded at ambient temperature by using the deuterium resonance of the solvent as the internal lock. Hydrochlorides were examined in deuterium oxide and free bases in deuterochloroform, containing internal standards of sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) and tetramethylsilane (TMS), respectively. Solution concentration was about 100 mg/1.7 mL solvent in 10-mm tubes. Protons were decoupled by broad-band irradiation (4 or 5 W, offset 6000 Hz) except in single frequency off-resonance decoupling (SFORD) experiments (4 W, offset 4700 Hz) [*11*]. Some 2000 or more interferograms of 5000-Hz sweep width were stored for output in 4K data points following transform (address separation 0.06 ppm). Pulse widths were 1.5 μs (19.2° flip angle) with no pulse delay following data acquisition. The chemical shift reagent Eu-Resolve® (Ventron Corp., Danvers, Mass.) was added incrementally (5, 25, and 50 mg) to a solution of amphetamine (300 mg) in deuterochloroform (1.7 mL), and ^{13}C NMR spectra were recorded at each stage. Bar graphs of the spectra were prepared by normalizing the strongest signal to 100%.

Results and Discussion

A visual inspection of the spectra or bar graphs of both salts and bases enables them to be immediately and easily distinguished from one another. Bar graphs of the spectra of the monomethoxyamphetamine bases in deuterochloroform and hydrochlorides in deuterium oxide are reproduced in Figs. 2 and 3 as examples. Differences among the dimethoxy isomers are far more obvious than those seen in their mass spectra [*12*]. Data from the spectra and those from amphetamine are presented in Table 1.

The γ-CH_3 entity is easily recognizable as the signal at highest field, and it gives a quartet on SFORD. Its chemical shift is essentially unaffected by changes in the aromatic substitution pattern and is from about 20.0 to 20.4 ppm for the hydrochlorides and 23.0 to 23.6 ppm for the bases.

The β-CH entity gives a doublet on SFORD and appears at about 51.5 $\pm$ 0.6 ppm in the salts and 47.8 $\pm$ 0.8 ppm for the bases. It is apparent that compounds with an ortho methoxyl group exhibit this resonance at about 1 ppm to high field of the position observed

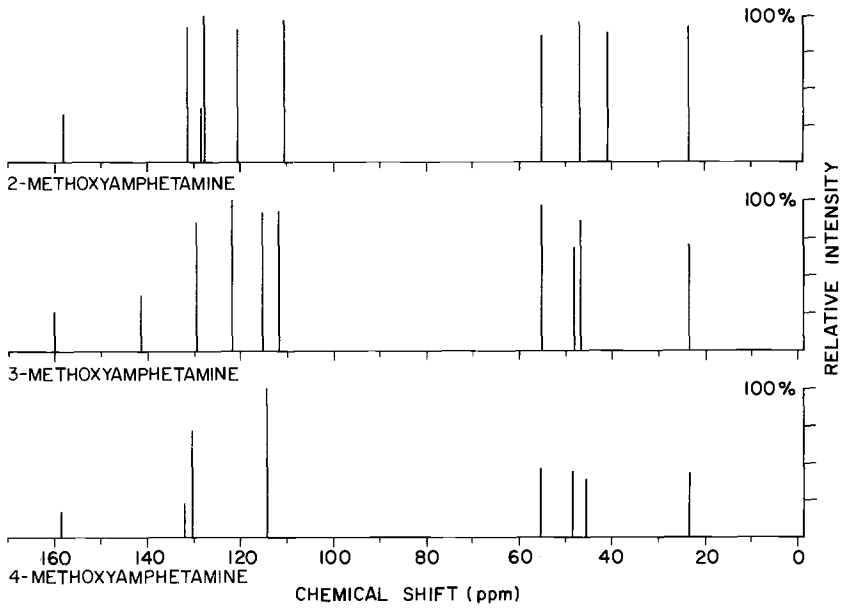

FIG. 2—*Normalized ^{13}C NMR spectra in deuterochloroform of 2-methoxyamphetamine* (upper), *3-methoxyamphetamine* (center), *and 4-methoxyamphetamine* (lower).

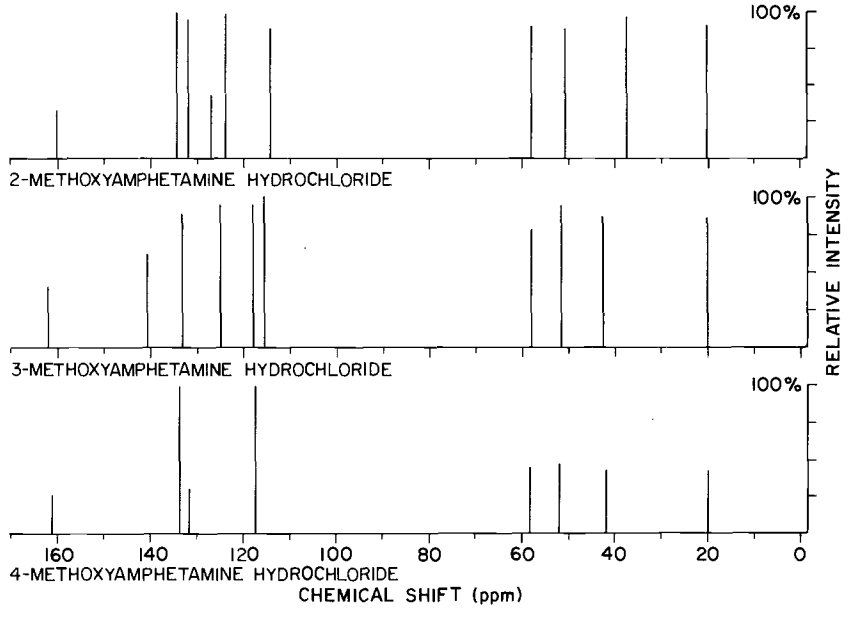

FIG. 3—*Normalized ^{13}C NMR spectra in deuterium oxide of the hydrochlorides of 2-methoxyamphetamine* (upper), *3-methoxyamphetamine* (center), *and 4-methoxyamphetamine* (lower).

in the other compounds. The nature of the interaction that is responsible for this effect has not been determined, but it is possibly related to the known differences in the populations of side-chain rotamers in ortho versus meta and para methoxyamphetamines [*13*].

The benzylic CH_2 appears between the foregoing signals and gives a triplet on SFORD. Its chemical shift is very sensitive to the aromatic substitution pattern. Reference to Table 1 shows that the signal appears between about 42.0 and 43.0 ppm for the hydrochlorides and 45.7 and 47.1 ppm for the bases of compounds that have no OCH_3 group ortho to the side chain. The substitution of one ortho OCH_3 results in upfield shifts of this signal of some 5 to 7 ppm. Thus, the high-field signal of the (benzylic) α-CH_2 of 2,6-dimethoxyamphetamine (2,6-DMA) is shifted upfield by about 13 ppm, which makes the compound immediately distinguishable. Confirmation of this effect was made by recording the spectra of 2,4,6-trimethoxyamphetamine, and data are reported in Table 1.

The OCH_3 signals appear from 58.1 to 58.5 ppm in the salts and 55.2 to 56.1 ppm in the bases, with the very notable exception of 2,3-DMA where one of the methoxyl carbons is shifted about 5 ppm downfield (Table 1). The situation appears to be analogous to that encountered in 2,3,4-trimethoxybenzaldehyde and 2,3,4-trimethoxyacetophenone and presumably an analogous conformational explanation can be offered [*10*], that is, that the "sandwiched" methoxyl group is forced out of the plane of the benzene ring; this results in loss of conjugation with the ring and the signal is consequently shifted downfield. (The β carbon of amphetamines is asymmetric, and in consequence the 2-OCH_3 group can assume one of two "diastereotopic" configurations, but there was no evidence of splitting of this or other signals. Presumably one of these configurations would be favored for each epimer in interactions with putative pharmacological receptors.) The unique position of the low-field methoxyl carbon enables 2,3-DMA to be recognized immediately in this series. Under our conditions of measurement, the methoxyl signals from 2,4- and 3,4-DMA were not resolved from one another and, although separated in 2,5-DMA, could not be confidently assigned.

The aromatic carbons give signals whose chemical shifts are characteristic for the individual compounds of the series. Thus, even though the conditions of measurement were such that the intensities of the signals were not absolutely proportional to the number of carbons giving rise to the individual signals (insufficient time for spin-lattice relaxation), their identification was not difficult [*5*]. Only PMA and 2,6- and 3,5-DMA have symmetric substitution and give rise to four signals. 2,6-DMA is recognizable from its α-CH_2 signal (see above), and 3,5-DMA from its characteristic C-4 signal at about 100 ppm; PMA has two strong signals from C-2,6 and C-3,5. There is no chance of confusing the four-line patterns of these three compounds. The remaining compounds are distinguishable even in the absence of reference spectra. 2-Methoxyamphetamine (OMA) and 3-methoxyamphetamine (MMA) yield six distinct signals resulting from their aromatic carbons, four of which give rise to doublets on SFORD, and no two of the six aromatic carbon signals appear at the same chemical shift for either bases or hydrochlorides.

The aromatic assignments proposed in Table 1 are based on internally consistent chemical shift and intensity data and the results of SFORD experiments. Those of C-2,6 and C-3,5 of amphetamine itself were made initially on the grounds that the chemical shift of C-3,5 should be very nearly the same as those in compounds with similar side chains [*14*]. Propylbenzene and isopropylbenzene were chosen as model compounds, for which the shifts of C-3,5 are reported as 128.6 and 128.4 ppm, respectively, and those of C-2,6 as 128.3 and 126.5 ppm, respectively [*15*]. Hence the signals at 128.75 and 129.54 ppm of amphetamine are assigned to C-3,5 and C-2,6, respectively. In support of this, the spectrum of "β-methylphenethylamine," in which the side-chain methyl group is shifted from its terminal location in amphetamine to the benzylic position, was determined. The signals at 145.09 and 126.81 ppm obviously arose from C-1 and C-4, respectively. The lower field of the remaining signals at 128.93 and 127.66 ppm shows an excellent correlation with that ascribed to C-3,5 in amphetamine (128.75 ppm). In further support, the upper-field signal is

TABLE 1—*Data from the ^{13}C NMR spectra of methoxyamphetamines.*[a]

Compound	Signal, ppm, at Position										
	C-1	C-2	C-3	C-4	C-5	C-6	α-CH_2	β-CH	γ-CH_3	OCH_3[b]	OCH_3[b]
Amphetamine	139.93	129.54	128.75	126.50	128.75	129.54	46.64	48.40	23.38	...	...
Amphetamine HCl	138.95	132.27[c]	131.85[d]	130.21	131.85[c]	132.27[d]	42.69	51.74	20.04	...	...
2-OCH_3	128.45	158.14	110.71	127.84	120.67	131.42	41.12	47.07	23.50	55.39 (2)	...
2-OCH_3 HCl	126.99	160.33	114.30	131.97	123.83	134.40	37.53	50.89	20.22	58.12 (2)	...
3-OCH_3	141.63	115.33	160.15	111.81	129.66	121.95	46.76	48.28	23.50	55.27 (3)	...
3-OCH_3 HCl	140.84	118.00	162.15	115.75	133.18	125.11	42.75	51.74	20.16	58.18 (3)	...
4-OCH_3	132.09	130.51	114.24	158.63	114.24	130.51	45.73	48.52	23.38	55.45 (4)	...
4-OCH_3 HCl	131.66	133.67	117.45	161.12	117.45	133.67	42.02	52.05	20.16	58.30 (4)	...
2,3-diOCH_3	133.79	148.06[c]	153.23[c]	111.08	124.01[d]	123.16[d]	40.75	47.80	23.62	60.61 (2)	55.81 (3)
2,3-diOCH_3 HCl	132.69	149.70[c]	155.41[c]	115.45	128.08[d]	126.02[d]	37.17	51.26	20.22	63.53 (2)	58.61 (3)
2,4-diOCH_3	120.86	159.06[c]	98.93	159.97[c]	104.28	131.67	40.51	47.19	23.50	55.45 (2)	55.45 (4)
2,4-diOCH_3 HCl	119.64	161.36[c]	101.54	162.64[c]	108.16	134.88	36.92	50.95	20.16	58.18 (2)	58.18 (4)
2,5-diOCH_3	129.72	152.50[c]	111.75[d]	111.75[d]	153.83[c]	117.70[d]	41.30	47.13	23.62	55.81 (2 or 5)	56.06 (5 or 2)
2,5-diOCH_3 HCl	128.39	154.93[c]	115.75[d]	116.48[d]	155.84[c]	120.49[d]	37.71	50.95	20.28	58.73 (2 or 5)	58.85 (5 or 2)
2,6-diOCH_3	116.67	159.12	104.03	127.54	104.03	159.12	33.40	47.19	23.50	55.75 (2)	55.75 (6)
2,6-diOCH_3 HCl	114.90	161.36	107.37	132.03	107.37	161.36	30.06	51.01	20.35	58.48(2)	58.48(6)
3,4-diOCH_3	132.76	113.02[c]	149.46[d]	148.06[d]	111.87[c]	121.58	46.28	48.46	23.50	56.12 (3)	56.12 (4)
3,4-diOCH_3 HCl	132.09	115.88[c]	151.34[d]	150.37[d]	115.09[c]	124.99	42.39	51.99	20.16	58.55 (3)	58.55 (4)
3,5-diOCH_3	142.54	107.68	161.36	98.57	161.36	107.68	47.13	48.28	23.62	55.45 (3)	55.45 (5)
3,5-diOCH_3 HCl	141.75	110.71	163.43	102.03	163.43	110.71	42.94	51.62	20.10	58.24 (3)	58.24 (5)
2,4,6-tri OCH_3	109.19	159.72	90.98	160.09	90.98	159.72	33.16	47.31	23.50	55.75 (2,6)	55.51 (4)
2,4,6-tri OCH_3 HCl	107.56	162.03	93.95	163.06	93.95	162.03	29.88	51.20	20.28	58.42 (2,6)	58.24 (4)

[a]The bases were examined in deuterochloroform and the salts in deuterium oxide; see text for method of assignment.
[b]The numbers in parentheses refer to the position of substitution.
[c]These assignments may be reversed.

shifted upfield from that ascribed to C-2,6 of amphetamine, by 1.9 ppm, in close correspondence with the shift in C-2,6 from propylbenzene to isopropylbenzene (1.8 ppm). Similarly, the spectrum of phenylethylamine (PEA) was determined and the signal ascribed to C-3,5 was again found at 128.75 ppm and C-2,6 was identified at 129.05 ppm. The addition of the chemical shift reagent (50 mg; see Experimental Procedures section) to the amphetamine solution resulted in downfield shifts of the signals ascribed to C-1, C-2,6, C-3,5, and C-4 of 0.91, 0.73, 0.30, and 0.18 ppm, respectively; the progressive diminution with increased distance from the site of pseudo-contact (the amino function) [*16*] confirms the foregoing interpretation of assignments.

A comparison of the spectra of β-methylphenethylamine hydrochloride and amphetamine hydrochloride showed correspondence between the signal at 132.03 ppm in the former with both of those at 131.85 and 132.27 ppm in the latter. Evidently the signal at 132.03 ppm arises from C-3,5 and hence the signal from C-2,6 of β-methylphenethylamine hydrochloride was identified at 130.15 ppm. Both PEA hydrochloride and amphetamine hydrochloride showed signals at 131.85 ppm, and so this was ascribed to C-3,5 in both; the signal from C-2,6 of PEA hydrochloride was at 131.66 ppm. These chemical shift differences are too small for the assignments (Table 1) to be made with absolute confidence, but they are supported on the grounds of minimizing the change in chemical shift of the meta signals resulting from protonation [*6*].

The data for the methoxyamphetamines show that the methoxyl group has internally consistent shielding effects of some 11 to 18 and 5 to 8 ppm at ortho and para positions, respectively, and a deshielding effect of about 1 to 2 ppm at meta positions in this series. In the series of monomethoxyamphetamines, the chemical shifts of the aryloxy carbons compared with that of anisole (159.9 ppm) indicate that the side chain has a shielding effect on ortho and para signals of about 1.8 and 1.3, respectively, and a deshielding effect on meta signals of about 0.3 ppm; this is in contrast to the trends seen from the assignments for amphetamine itself. It is a warning that simple additivity effects must be applied with caution when they are used to assign signals, and it is a reminder that the effects would not be expected to be symmetrical in asymmetrically substituted compounds [*14*]. Some assignments should therefore be viewed with circumspection. For example, consider the assignments of C-2 and C-4 of MMA. Since the signal from C-4 of PMA is 0.5 ppm downfield of C-2 in OMA, a similar difference might be expected between C-2 and C-4 of MMA. However, if MMA is regarded as amphetamine substituted at C-3, the effects at C-2 and C-4 of the substituent would be equal and C-4 should be about 3 ppm upfield of C-2, as in amphetamine itself. The latter effects seem to outweigh the former. The experimental difference is 3.5 ppm for the base and 2.3 ppm for the hydrochloride, favoring the interpretation that C-4 is at field higher than that of C-2 (Table 1). Similar considerations apply to the assignments of C-6 and C-4 in OMA. However, in the case of 2,4-DMA, the upfield of the two aryloxy carbon signals has been ascribed to C-2, in conformity with the results in the monomethoxy and the shifts observed for 2,4,6-trimethyoxyamphetamine.

Consider also the provisional assignments of C-3, C-4, and C-6 of 2,5-DMA hydrochloride (Table 1). These are equally intense signals that give doublets on SFORD. Consideration of the shifts at the methoxyl position in OMA, MMA, and PMA suggests that the order from low to higher field would be C-3, C-4, and C-6. A more satisfying approach is to attempt to calculate the positions of these signals thus: the C-6 signals should be about 1.5 ppm downfield from the C-2 signal in MMA hydrochloride, that is, about 119.5 ppm; the C-4 signal about 1.5 ppm downfield from C-4 in MMA hydrochloride, that is, about 117.3 ppm; and the C-3 signal about 1.5 ppm downfield from C-3 in OMA hydrochloride, that is, about 115.8 ppm. On this basis, the signals observed at 120.49, 116.48, and 115.75 ppm probably belong to C-6, C-4, and C-3, respectively. (Of course, these assignments of C-6 and C-4 will be reversed if the assignments of C-2 and C-4 in MMA hydrochloride are reversed.) Similarly, C-2 and C-5 have been assigned on the basis of a relative shielding effect of the am-

phetamine side chain at C-2, as observed on comparison of the shifts of C-2 and C-3 in OMA and MMA. The possibility of using selective proton-decoupling to resolve the ambiguity is precluded by uncertainties in proton assignments and the narrow range of the aromatic proton chemical shifts [*2*].

The large chemical shift difference between the aryloxy carbon signals in 2,3-DMA is interesting, since they are close in 3,4-DMA and the other DMAs. These signals were found at 149.95 ppm in 1,2-dimethoxybenzene. If C-2 appears at 153.23 ppm, the differences in chemical shifts at C-1 and C-3 (both ortho to the 2-methoxyl group) from their shifts in MMA are 7.84 and 12.09 ppm, respectively. Alternatively, if the C-3 signal is at 153.23 ppm, the differences are 7.84 and 6.92 ppm at C-1 and C-3, respectively; these are more nearly the same, as expected, and C-2 and C-3 were provisionally assigned on this basis. The spectrum of 2,3-dimethoxyphenylethylamine (2,3-DMPEA) was also recorded. The chemical shifts at C-3 and C-5 (meta to the side chain) were expected to be about the same in both compounds [*14*]. This approach confirmed C-3 (153.23 and 153.16 ppm in 2,3-DMA and 2,3-DMPEA, respectively) and C-5 (124.01 and 124.07 ppm in 2,3-DMA and 2,3-DMPEA, respectively). The signals from C-2 and C-6 of 2,3-DMPEA (at 147.88 and 122.62 ppm, respectively) are slightly upfield of their positions in 2,3-DMA (Table 1), as previously noted for the C-2,6 signals of PEA versus the C-2,6 signals of amphetamine itself.

Spectra of the salts in deuterium oxide show small upfield shifts at C-1 and downfield shifts at the remaining aromatic carbons compared with the bases in deuterochloroform. The α- and β-carbon signals and the γ-CH_3 signals of the salts are shifted by 3 to 4 ppm upfield, downfield, and upfield, respectively, from their positions in the bases.

Spectra of 2,3-, 2,5-, 3,4-, and 3,5-DMA (bases and hydrochlorides) were also determined at 400 mg/mL. The only chemical shift differences greater than 0.3 ppm were noted in the free bases of the last three isomers. The α-CH_2 and C-1 signals were shifted upfield by about 0.5 and 0.4 ppm, respectively, and they γ-CH_3 signal of 2,5-DMA was also shifted upfield by 0.5 ppm. Thus, concentration differences would not affect the ready identification of the spectra.

Conclusion

Data from the ^{13}C NMR spectra of monomethoxyamphetamines and dimethoxyamphetamines can be interpreted in an internally consistent manner that allows the majority of the signals to be confidently assigned. Despite ambiguities in some assignments, the spectra provide an excellent means of distinction, identification, and confirmation of structural authenticity.

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