Identification and Synthesis of Di-(1-phenylisopropyl)methylamine, an Impurity in Illicit Methamphetamine

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Abstract □ The isolation, purification, and identification of di-(1-phenylisopropyl)methylamine, present in illicit samples of methamphetamine, are described. The identity of the substance was confirmed by synthesis. It is commonly present in amounts ranging between 3 and 15% relative to methamphetamine.

Keyphrases □ Di-(1-phenylisopropyl)methylamine—identification in illicit methamphetamine, NMR, IR, and mass spectroscopy □ Methamphetamine—identification and synthesis of di-(1-phenylisopropyl)methylamine as an impurity in illicit samples

Methamphetamine (I) is a drug popularly used and readily available on the illicit market. It is synthesized in clandestine laboratories on the North American continent and may contain various contaminants. A major impurity in illicit methamphetamine was recently identified as *N*-methyl-*N*-(α-methylphenylethyl)formamide (*N*-formylmethamphetamine, II) (1). A second substance in illicit methamphetamine has now been isolated and identified spectroscopically as di-(1-phenylisopropyl)methylamine (III). The identity was confirmed by synthesis of III.

EXPERIMENTAL[1]

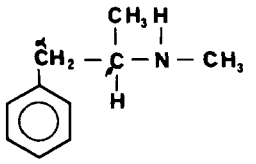
Isolation and Purification of III—The sample of illicit methamphetamine hydrochloride (about 1 g) was dissolved in 0.5 *N* HCl (about 20 ml) and extracted with ether. The ethereal extract contained the *N*-formylmethamphetamine (II) present (1). The aqueous phase was extracted with chloroform and the chloroform was evaporated, leaving a residue of crude III-HCl which, after triturating and washing with ether, had a melting range of 125–184°. (Methamphetamine could be recovered from the aqueous phase.) The material was recrystallized from a mixture of isopropanol and hexane, which raised the melting point to 183–192°, but scarcely changed the proton NMR or IR spectra. The free base was liberated from the salt with potassium carbonate solution, extracted into ether, and recovered as an almost colorless oil.

Synthesis of III—*d,l*-Amphetamine (2.70 g) and phenylacetone (2.68 g) were mixed in ethanol (20 ml) and kept at room temperature for 65 hr. The resulting solution was hydrogenated overnight in a Parr apparatus using 10% palladium-on-carbon (100 mg) as catalyst and an initial hydrogen pressure of 40 psi. The solution was filtered, concentrated, and adsorbed onto a column of silica gel (250 g) packed with chloroform. Elution with chloroform (2 liters) afforded unidentified products; elution with 5% methanol in chloroform yielded di-(1-phenylisopropyl)amine (IV, 360 mg), which was kept with formic acid (90%, 1 ml) and formaldehyde solution (36%, 1.4 ml) at 80° overnight.

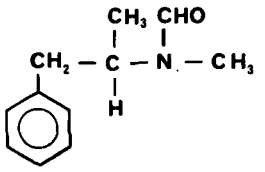
The mixture was cooled, made basic with 2 *N* NaOH, and extracted with ether. The extract was dried, concentrated, and adsorbed onto silica gel packed with hexane in a Pasteur pipet. Elution with hexane afforded the tertiary amine III (60 mg), which was identical by NMR, IR, mass spectrometry, and GLC analyses with the free base isolated from illicit methamphetamine. Attempts to convert the base into a crystalline hydrochloride were not successful. A product chromatographically and spectroscopically indistinguishable from synthesized III resulted when the reaction sequence was applied to *d*-amphetamine.

RESULTS AND DISCUSSION

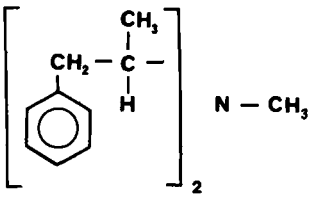
The isolated solid was readily soluble in water, giving a solution of pH about 5 (to test papers) which produced a whitish precipitate (soluble in ammonium hydroxide solution) on adding silver nitrate solution. Therefore, the solid was suspected to be the hydrochloride salt of an amphetamine derivative. The NMR spectrum of the salt, mp 125–184°, is shown in Fig. 1, and the effect of adding deuterium oxide is illustrated in Fig. 2.



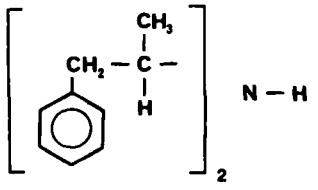
I



II



III



IV

[1] GLC was carried out on a Bendix 2500 instrument fitted with 1.8-m (6-ft) glass columns containing 3% OV-1 on Chromosorb W-H-P, 80–100 mesh, and on a Varian Aerograph 1520 fitted with 1.8-m (6-ft) glass columns containing 5% OV-7 on 80–100-mesh Chromosorb W; the carrier gas was nitrogen at 30 ml/min. Optical rotation was measured on a Perkin-Elmer 141 polarimeter (courtesy of Carleton University, Ottawa, Canada). NMR spectra were recorded at 40° on a Varian A-60A spectrometer using solutions in deuterochloroform containing tetramethylsilane as the internal standard. IR spectra were measured on a Unicam SP 1000 spectrophotometer using natural films between sodium chloride plates for the free bases and mineral oil mulls for the salts. A Hitachi Perkin-Elmer RMU-6L mass spectrometer was used for determining mass spectra, with the probe at 160° and an ionizing voltage of 70 ev.

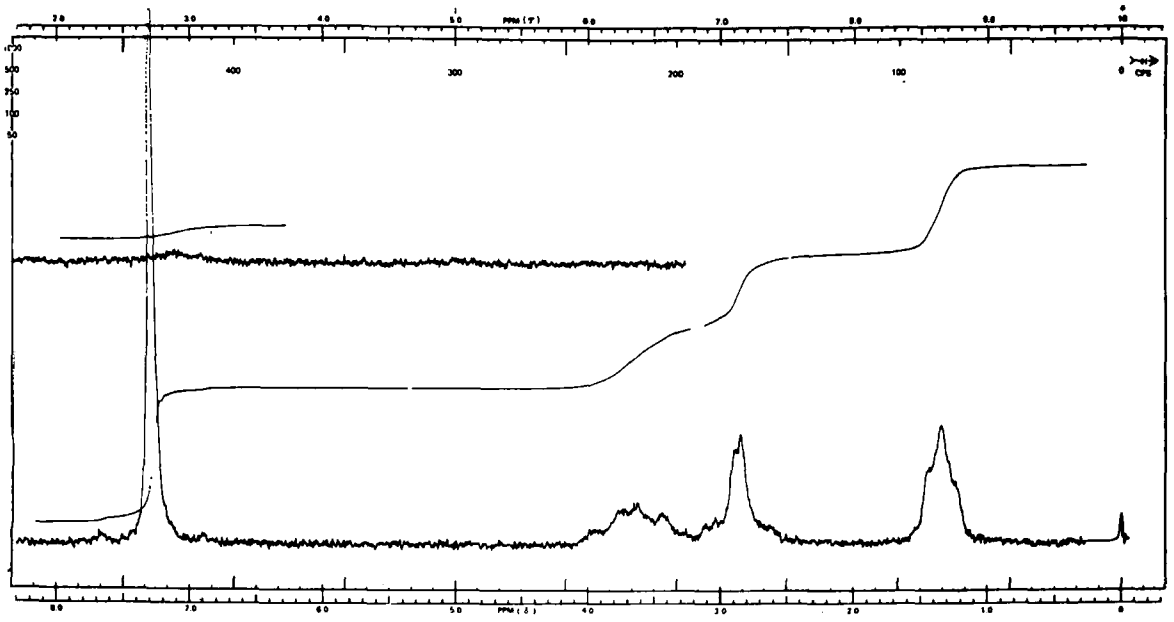


Figure 1—*NMR spectrum of di-(1-phenylisopropyl)methylamine hydrochloride in $CDCl_3$.*

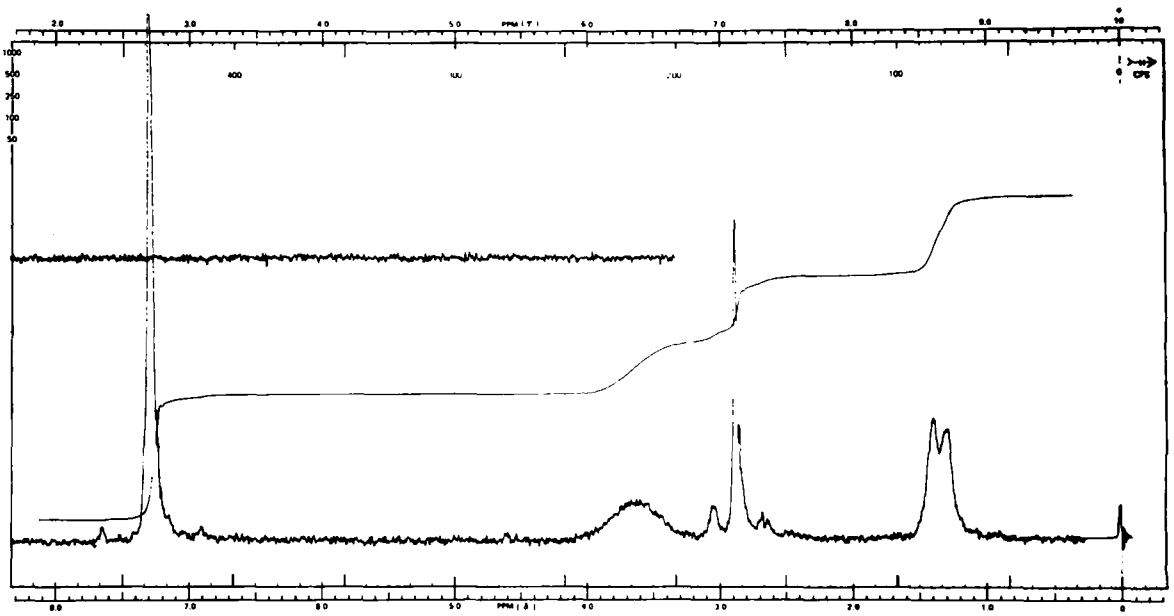


Figure 2—*NMR spectrum of di-(1-phenylisopropyl)methylamine hydrochloride in $CDCl_3$ with D_2O added.*

In Fig. 1, the smallest integration occurs at δ 12.1 (ppm downfield of tetramethylsilane) and is assigned to $^+$N—H; the remaining signals then account for about 26 protons and, with reference to Structure III, are assigned as follows: δ 7.2–7.35 (10), protons of two equivalent monosubstituted aromatic rings; 2.5–4.1 (10), α, β, and N—CH_3 protons (N—CH_3 at 2.86 ppm; the integration between 2.5 and 4.1 ppm indicates that there is one more proton present which could be due to moisture); and 1.35 (six), β-CH_3 protons.

The spectrum of the free base is shown in Fig. 3 and assignments are: δ 7.2, aromatic ring protons; about 2.3–3.3, α, β, and N—CH_3 protons (N—CH_3 at 2.87 ppm); and 0.96, β-CH_3 protons. Protonated III (Fig. 1) shows coupling between the $^+$NH and the β-CH_3 and the $^+$NH and the N—CH_3 protons, which is lost on adding D_2O (Fig. 2) or liberation of the base (Fig. 3), with the β—CH_3 and N—CH_3 then appearing as a doublet and singlet, respectively. The small signal at δ 1.27 in Fig. 3 arises from the long-chain aliphatic protons of portions of an impurity. Apart from this, the NMR spectra of the base III synthesized from either *d*- or *d,l*-amphetamine were identical.

The IR spectrum of the salt, mp 125–184°, was unchanged on recrystallization (Fig. 4). The IR spectra of the base from either illicit drug or synthetic III starting from *d,l*- or *d*-amphetamine were essentially identical (Fig. 5). Of particular note are the bands at 2450 cm^{-1} in Fig. 4, assigned to $^+$N—H stretching, the lack of N—H stretching bands (about 3300–3500 cm^{-1}) in Fig. 5, and the bands at about 700 and 745 cm^{-1} in Figs. 4 and 5, indicative of a monosubstituted benzene ring (2).

Virtually identical mass spectra resulted from the salt or free base of illicit or synthetic III from *d,l*- or *d*-amphetamine (Fig. 6). The molecular ion for III is at *m/e* 267. The very intense peak at *m/e* 176 and other major peaks are compatible with the cracking pattern for amphetamines (3, 4) depicted in Fig. 7 for Structure III.

The GLC retention times on OV-7 were the same for nonrecrystallized and recrystallized salts and the free base of illicit or synthetic III.

Mixtures of illicit and synthetic III were not separated. The method for illicit methamphetamine synthesis (1) would be expected to give an optically inactive product, and no optical rota-

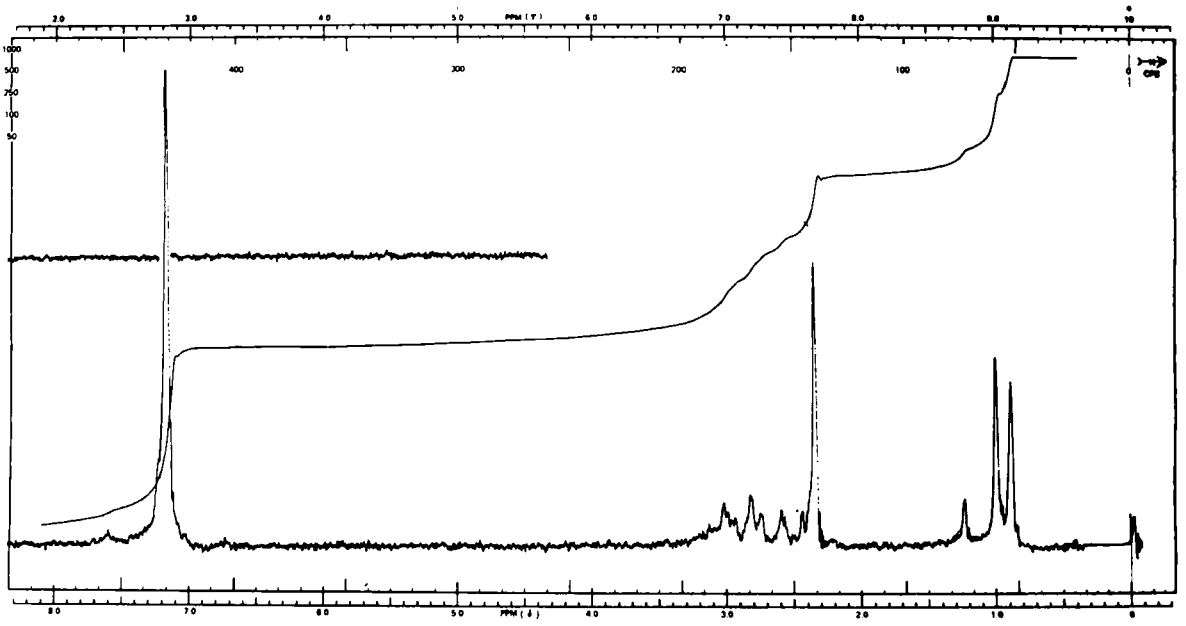


Figure 3—*NMR spectrum of di-(1-phenylisopropyl)methylamine base in $CDCl_3$.*

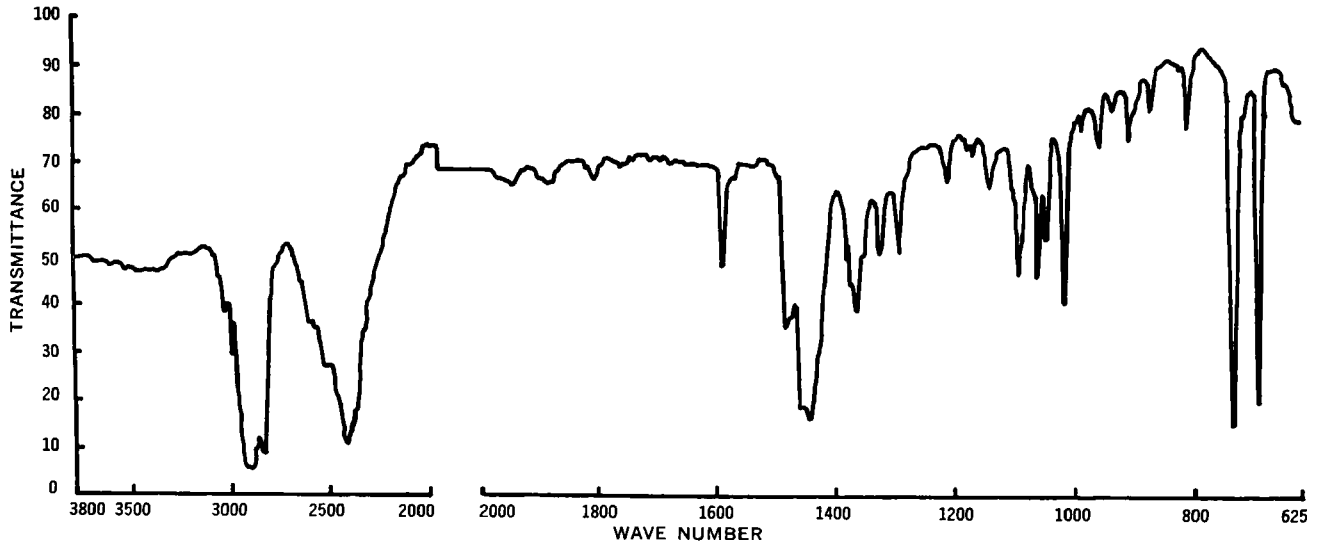


Figure 4—*IR spectrum of di-(1-phenylisopropyl)methylamine hydrochloride in mineral oil.*

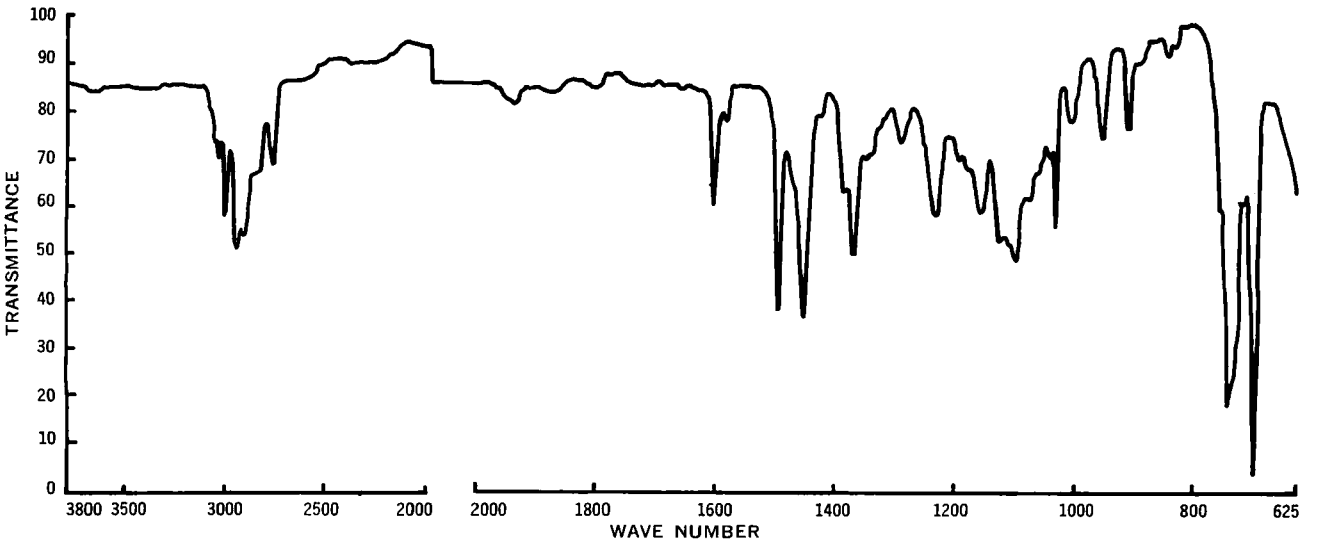


Figure 5—*IR spectrum of di-(1-phenylisopropyl)methylamine base as film.*

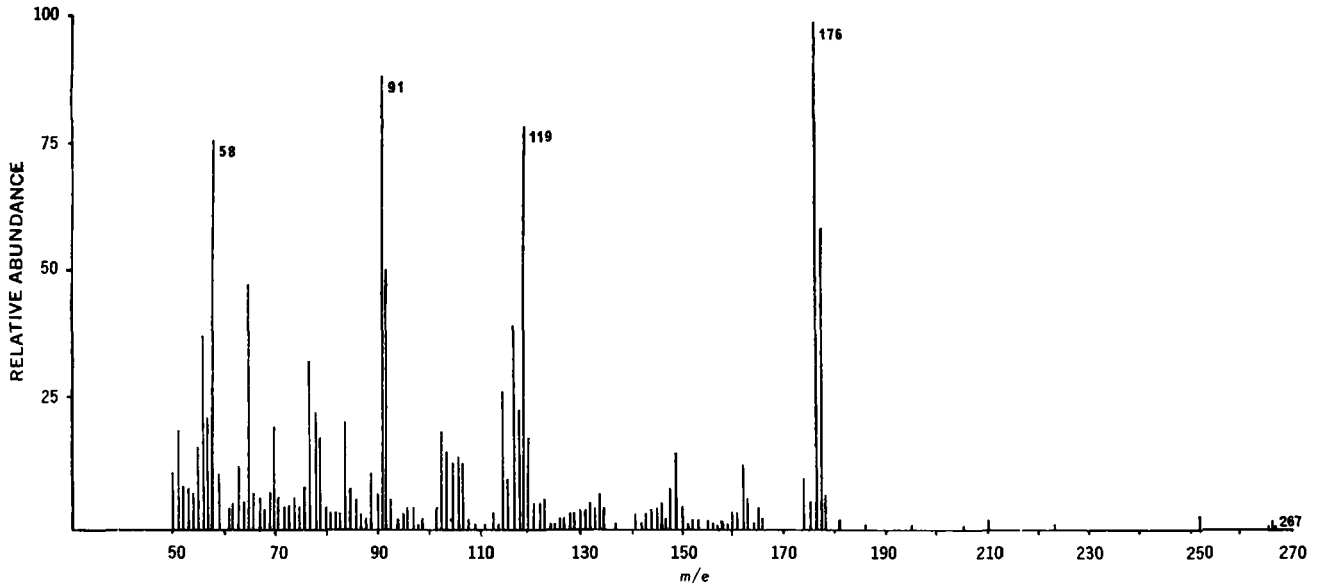


Figure 6—*Normalized mass spectrum of di-(1-phenylisopropyl)methylamine.*

tion was found for methanolic solutions of illicit III at the sodium d line. The synthesis described here, starting from *d,l*-amphetamine, would give a racemic mixture of the *d*- and *l*- and *meso*-forms of III; attempts to convert this mixture into a crystalline hydrochloride salt were not successful. Elemental analyses of the illicit salt, mp 125–184° (found: C, 72.29; H, 8.76) and mp 183–192° (found: C, 72.35; H, 8.53), were indicative of water content (for III, $C_{19}H_{25}N{\cdot}HCl{\cdot}\frac{1}{2}H_2O$ requires C, 72.90; H, 8.70), in corroboration of the NMR result already described.

The impurity in illicit methamphetamine is concluded to be di-(1-phenylisopropyl)methylamine (III). Quantitation by GLC of eight illicit methamphetamine samples received recently indicated that between 3 and 15% of III was present relative to methamphetamine.

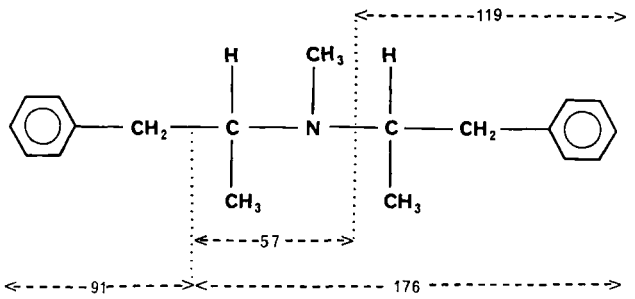


Figure 7—*Amphetamine cracking pattern for di-(1-phenylisopropyl)methylamine.*

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ACKNOWLEDGMENTS AND ADDRESSES

Received October 12, 1973, from the **Drug Research Laboratories, Health Protection Branch, Tunney's Pasture, Ottawa K1A OL2, Ontario, Canada,* and the ‡*Quebec Regional Laboratory, Health Protection Branch, 400 Youville Square, Montréal 125, Province of Quebec, Canada.*

Accepted for publication May 20, 1974.

The authors thank Mr. H. W. Avdovich for recording NMR spectra and the polarimetric measurement.

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