729. *The Preparation of o-Aminophenyl Sulphates.*

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Methods for the synthesis of a number of *o*-aminophenyl sulphate derivatives are described. The oxidation of aromatic amines with persulphate in alkaline solution yields *ortho*-substituted derivatives, and the reaction is a convenient method of preparation of *o*-aminophenyl sulphates.

The metabolism of aromatic amines in animals normally leads to the production of aminophenols and acetamidophenols, which are usually excreted in conjugated forms as the sulphuric esters or glucuronides. Usually the hydroxyl group is introduced in the *para*-position with respect to the amino-group, and in the *ortho*-position if the *para*-position is blocked. In some cases, however, hydroxylation in the *ortho*-position occurs when the *para*-position is free; *e.g.*, dimethylaniline, when given to dogs, is excreted as *o*-aminophenyl hydrogen sulphate (Horn, *Z. physiol. Chem.* 1936, **238**, 84; **242**, 23). 2-Naphthylamine is excreted mainly as 2-amino-1-naphthyl hydrogen sulphate in dogs (Wiley, *J. Biol. Chem.*, 1938, **124**, 627), in which species 2-naphthylamine produces cancer of the bladder, and mainly as 6-amino-2-naphthol derivatives in rats and rabbits (Dobriner, Hoffman, and Rhoads, *Science*, 1941, **93**, 600; Manson and Young, *Biochem. J.*, 1950, **47**, 170) in which it does not induce bladder cancer. Some *o*-aminophenols, *e.g.*, 2-amino-1-naphthol (Hueper, *Arch. Path.*, 1938, **25**, 856), 3 : 3′-dihydroxybenzidine (Baker, *Acta Un. int. Cancer*, 1950, **7**, 46), and 1-amino-2-naphthol (Bonser, Clayson, and Jull, in the press) have been shown to be carcinogenic. Investigation of the metabolism of aromatic amines necessitated the preparation of aminophenyl esters for comparison, and for the study of chemical oxidation which might resemble biological oxidation.

The preparation of 2-amino-1-naphthyl hydrogen sulphate from the corresponding aminophenol and chlorosulphonic acid as described by Wiley (*loc. cit.*), gave very small yields, but it was readily prepared by (1) treatment of the 2-phthaloylamino-1-naphthol

with chlorosulphonic acid and removal of the phthaloyl group with acetic acid, (2) reduction of 2-nitro-1-naphthyl hydrogen sulphate, and (3) oxidation of 2-naphthylamine with persulphate in alkaline solution. The last method is new, and seems to be of general application.

In studying the reaction of phenols with chlorosulphonic acid, Burkhardt and Lapworth (*J.*, 1926, 684) found that the order of addition of the reagents affected the yield. When *o*-aminophenol was treated with chlorosulphonic acid in dimethylaniline (without carbon disulphide), potassium 2-hydroxyphenylsulphamate, *o*-$HO{\cdot}C_6H_4{\cdot}NH{\cdot}SO_3K$, was the main product, and *o*-aminophenyl hydrogen sulphate could not be detected.

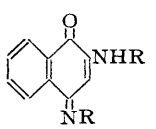
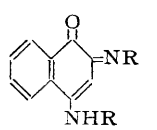
Burkhardt and Wood (*J.*, 1929, 141) prepared many aminoaryl hydrogen sulphates by reduction of the corresponding nitro-derivatives with ferrous hydroxide, and we have now prepared 2-amino-1-naphthyl hydrogen sulphate by this method. Catalytic reduction of the nitro-group has also been employed (Bernstein and McGilvery, *J. Biol. Chem.*, 1952, **198**, 195). Attempted preparation of 2-nitro-1-naphthyl sulphate by heating 2-nitro-1-naphthol with potassium pyrosulphate in dimethylaniline was unsuccessful. The use of carbon disulphide as a diluent is probably not necessary, and 1-nitro-2-naphthyl potassium sulphate described by Burkhardt and Wood (*loc. cit.*) has been prepared by using pyridine as the solvent (cf. Feigenbaum and Neuberg, *J. Amer. Chem. Soc.*, 1941, **63**, 3529).

It seemed probable that aminoaryl hydrogen sulphates could be prepared more readily from the aminophenols if the amino-groups were protected. 2-Phthaloylamino-1-naphthol was treated with chlorosulphonic acid, but the sulphuric ester fraction obtained failed to give 2-amino-1-naphthyl hydrogen sulphate with hydrazine. Treatment of the sulphuric ester with dilute acetic acid, which caused little hydrolysis of the sulphate group, gave 2-amino-1-naphthyl hydrogen sulphate in low yield. This method could not be applied to the synthesis of *o*-aminophenyl hydrogen sulphate because here too hydrazine was without effect, and acetic acid caused hydrolysis of the sulphate.

The oxidation with persulphate is of interest as it provides a new and easy route for the preparation of some *o*-aminophenols, and it is in many ways different from the Elbs persulphate oxidation. The reaction is remarkable in that it yields only *o*-aminophenols, in which it resembles that process of biological oxidation which appears to be associated with carcinogenesis.

Although the sulphate of 3 : 3′-dihydroxybenzidine could not be isolated from the persulphate oxidation of benzidine, treatment of aniline with persulphate yielded *o*-aminophenyl potassium sulphate, which resembled the product obtained by Burkhardt and Wood (*loc. cit.*) by reduction of 2-nitrophenyl potassium sulphate. The free acid was not precipitated when a saturated solution of the salt was treated with mineral acid (*p*-aminophenyl hydrogen sulphate is precipitated under these conditions; Burkhardt *et al.*, *loc. cit.*); the *N*-acetyl derivative of the potassium salt was readily obtained. Hydrolysis with hot mineral acid afforded *o*-aminophenol. A neutral amorphous product obtained in this oxidation was apparently a mixture, but the constituents could not be identified.

Dimethylaniline, under similar conditions, afforded *o*-dimethylaminophenyl potassium sulphate, which, when treated with cold mineral acid, gave *o*-dimethylaminophenyl hydrogen sulphate. This was hydrolysed by hot mineral acid to *o*-dimethylaminophenol. 1-Naphthylamine was oxidised to 1-amino-2-naphthyl potassium sulphate from a solution of which (contrary to a statement by Burkhardt *et al.*, *loc. cit.*) the free acid separated on acidification. Hydrolysis with hot mineral acid yielded 1-amino-2-naphthol.

(I)   (II)

Oxidation of 2-naphthylamine with persulphate afforded crude 2-amino-1-naphthyl hydrogen sulphate which was best purified by crystallisation of the sodium or potassium salt. Hydrolysis with hot dilute acid yielded 2-amino-1-naphthol. The neutral by-product from the oxidation was examined in detail for comparison with the products

obtained on use of benzoyl peroxide (to be discussed in a later paper). Chromatography of the benzene-soluble fraction (the benzene-insoluble fraction was a brown amorphous substance) showed the presence of 1 : 2-5 : 6-dibenzophenazine, 2-2′-naphthylamino-1 : 4-naphthaquinone 4-2′-naphthylimide (I; R = 2-$C_{10}H_7$) [or possibly the isomer (II; R = 2-$C_{10}H_7$)], and a small amount of an unidentified red substance of m. p. 279°. The imide (I or II; R = 2-$C_{10}H_7$) has previously been prepared by Meldola (*J.*, 1884, 156) by the action of 2 : 4-dibromo-1-naphthol on 2-naphthylamine. The isomer (I or II; R = 1-$C_{10}H_7$) has been prepared by the condensation of 1-naphthylamine with 2-nitroso-1-naphthol (Fischer and Hepp, *Annalen*, 1893, **272**, 306), and aniline gives similarly (I or II; R = Ph) (Bromme, *Ber.*, 1888, **21**, 391). The imide (I or II; R = 2-$C_{10}H_7$), m. p. 246—247°, was prepared in a similar manner by the condensation of 2-naphthylamine with 2-nitroso-1-naphthol and was identical with the imide, m. p. 252—253°, obtained from the persulphate oxidation. 1 : 2-5 : 6-Dibenzophenazine is a product of the oxidation of 2-naphthylamine with lead dioxide (Clemo and Dawson, *J.*, 1939, 1114) or ferric chloride.

The fact that, with simple aromatic amines, substitution apparently occurs only in the *ortho*-position relative to the amino-group suggests that a special mechanism may be functioning. In the oxidation of phenols with persulphate, where a free radical, the sulphate-ion radical, is thought to be responsible (Baker and Brown, *J.*, 1948, 2303), substitution normally takes place in the *para*-position, and *ortho*-substitution occurs only when the *para*-position is blocked. In the latter case yields are much reduced. With 1- and 2-naphthol, substitution occurs in the 4- and the 1-position respectively (Desai and Sethna, *J. Indian Chem. Soc.*, 1951, **28**, 213). Both the hydroxyl and the amino-group have similar orientating effects on further aromatic substitution, so that *para*-substituted aromatic amines might be expected as a result of persulphate oxidation. It is suggested, therefore, that, in these cases, there is addition to the 1 : 2-double bond, followed by elimination of a potassium hydrogen sulphate residue. In 2-naphthylamine, where, by this mechanism, addition across the 1 : 2- or the 2 : 3-bond is equally possible, addition to the 1 : 2-bond takes place because of its more unsaturated nature. The action of persulphate on nuclear-substituted aromatic amines is under investigation.

Experimental

Oxidation of Aniline.—Aniline (5 g.), in water (500 ml.) and 2N-potassium hydroxide (50 ml.), was treated at room temperature with potassium persulphate (14·5 g.) in saturated aqueous solution, added during 8 hr. with continuous stirring. The mixture was kept overnight and the precipitate (2·9 g.) collected. The filtrate was evaporated to 100 ml. under reduced pressure, washed with ether (3 × 100 ml.), and made acid to Congo-red with 2N-sulphuric acid. The filtered solution was extracted with butanol (6 × 100 ml.), slight excess of aqueous 2N-potassium hydroxide was added, and the butanol extract evaporated to dryness under reduced pressure. The residue was extracted with hot 95% aqueous ethanol (4 × 100 ml.), and the combined extracts were evaporated to 25 ml. and kept at 0° for some hours. *o*-Aminophenyl potassium sulphate (1·9 g., 15·5%*) was obtained, separating from 90% ethanol containing a trace of aqueous potassium hydroxide as light brown plates (Found: N, 6·3; K, 17·6. Calc. for $C_6H_6O_4NSK$: N, 6·2; K, 17·2%).

The N-*acetyl* derivative of the potassium salt separated from 80% ethanol as needles (Found: N, 5·1. $C_8H_8O_5NSK$ requires N, 5·2%).

Hydrolysis of the potassium salt (500 mg.) with concentrated hydrochloric acid (2 ml.) at 100° for 30 min. and partial neutralisation with 2N-potassium hydroxide afforded *o*-aminophenol (245 mg., 90%), separating from water containing a trace of sodium hydrogen sulphite as needles, m. p. and mixed m. p. 173—174° (Found: N, 12·6. Calc. for C_6H_7ON: N, 12·8%). The dibenzoyl derivative crystallised from ethanol as needles, m. p. and mixed m. p. 182—183° (Found: N, 4·4. Calc. for $C_{20}H_{15}O_3N$: N, 4·4%).

Oxidation of Dimethylaniline.—Dimethylaniline (5 g.) in water (250 ml.), acetone (400 ml.), and 2N-potassium hydroxide (30 ml.) was treated with potassium persulphate (11·2 g.) as before. The solution was evaporated to 250 ml., washed with ether (3 × 150 ml.), and evaporated to

* In the persulphate oxidations, yields are calculated on the amount of persulphate used. Unoxidised amines were present in the reaction mixtures from all these oxidations, but use of excess of persulphate generally resulted in more complex products.

dryness under reduced pressure, and the residue extracted with hot 95% ethanol (3 × 50 ml.). The combined extracts were diluted with ether (1·5 l.); *o-dimethylaminophenyl potassium sulphate* (4·2 g., 40%) was obtained, separating from 95% ethanol as elongated plates (Found : N, 5·2; K, 15·6. $C_8H_{10}O_4NSK$ requires N, 5·5; K, 15·3%).

The potassium salt (0·46 g.) in water (2 ml.) and hydrochloric acid (2 ml.) afforded *o-dimethylaminophenyl hydrogen sulphate* (310 mg., 82%), prisms (from aqueous ethanol), m. p. 217—219° (decomp.) (Found: C, 44·3; H, 5·3; N, 6·1; S, 15·0. $C_8H_{11}O_4NS$ requires C, 44·2; H, 5·1; N, 6·45; S, 14·8%).

When the acid (0·4 g.) was heated at 100° with concentrated hydrochloric acid (5 ml.) for 1 hr. and the ice-cold solution partially neutralized with 2N-sodium hydroxide, *o*-dimethylaminophenol (210 mg., 83%) separated as needles, m. p. and mixed m. p. 44—45°, raised to 46° by crystallisation from aqueous ethanol.

Oxidation of 1-*Naphthylamine.*—1-Naphthylamine (5 g.) in water (600 ml.), pyridine (200 ml.), and 2N-potassium hydroxide (36 ml.) was treated with potassium persulphate (9·5 g.) as before. The mixture was evaporated to 100 ml. under reduced pressure, unchanged 1-naphthylamine separated, and the cooled solution washed with ether (2 × 100 ml.). The solution was kept at 0° overnight, 1-amino-2-naphthyl potassium sulphate separating. The filtrate was acidified to Congo-red with 2N-sulphuric acid, and the solution filtered and extracted with butanol (6 × 100 ml.). The extract was dried (Na_2SO_4), treated with slight excess of 2N-potassium hydroxide, and evaporated under reduced pressure. Crystallisation of the residue from 90% ethanol gave more of the potassium salt. 1-Amino-2-naphthyl potassium sulphate (1·7 g., 17·5%) crystallised from 90% ethanol as hexagonal plates (Found : S, 12·0; K, 13·8. Calc. for $C_{10}H_8O_4NSK$: S, 11·6; K, 14·1%). The *sodium* salt (prepared in a similar manner with sodium persulphate) separated from 90% ethanol as hexagonal plates (Found : S, 12·8. $C_{10}H_8O_4NSNa$ requires S, 12·3%). Treatment of a saturated solution of the potassium or sodium salt with concentrated hydrochloric acid produced 1-*amino-2-naphthyl hydrogen sulphate*, separating from water as prismatic needles, decomp. 203—204° (Found: S, 13·3 $C_{10}H_9O_4NS$ requires S, 13·4%). Aqueous and aqueous-alcoholic solutions of the sodium and potassium salts had a faint blue fluorescence in daylight and the acid and salts had a bright blue fluorescence in ultra-violet light.

The acid (0·5 g.) was heated to 100° with concentrated hydrochloric acid (2 ml.) for 30 min. 1-Amino-2-naphthol hydrochloride (0·35 g.) separated from the cooled solution. The dibenzoyl derivative crystallised from ethanol as needles, m. p. and mixed m. p. 225—226° (Found : N, 3·9. Calc. for $C_{24}H_{17}O_3N$: N, 3·8%), and the diacetyl derivative from ethanol as leaflets, m. p. and mixed m. p. 202—203° (Found: N, 5·9. Calc. for $C_{14}H_{13}O_3N$: N, 5·8%).

2-*Amino*-1-*naphthyl Hydrogen Sulphate.*—(*a*) 2-Nitro-1-naphthol (9·7 g.) (Burkhardt and Wood, *loc. cit.*) was added to chlorosulphonic acid (8·4 g.) in dry dimethylaniline (40 ml.) and carbon disulphide (40 ml.) as described by Burkhardt and Lapworth (*loc. cit.*). After 3 days, the mixture was poured into 6% aqueous potassium hydroxide (200 ml.). The solution was filtered, and the filtrate was washed with benzene and acidified at 0°. 2-Nitro-1-naphthol was separated, and the inorganic sulphate was removed from the filtrate with a slight excess of potassium hydroxide and barium chloride at 50°. The solution was concentrated; at 0° potassium 2-nitro-1-naphthyl sulphate (5·7 g.) separated in pale yellow needles, contaminated with red crystals of potassium 2-nitro-1-naphthoxide. Aqueous potassium 2-nitro-1-naphthyl sulphate (5·7 g.) was added during 1 hr., with stirring, to hydrated ferrous sulphate (47·5 g.) and barium carbonate (45 g.) in water (200 ml.) at 70°. After 2 hr., the solution was filtered hot, made alkaline with aqueous potassium hydroxide, and concentrated under reduced pressure. Ethanol (4 vols.) was added, and the solution was treated with charcoal. Acidification of the cold filtrate with concentrated hydrochloric acid yielded the ester (1·5 g.) as prisms, m. p. 224—225° (decomp.) (Found: N, 5·8; S, 13·2. Calc. for $C_{10}H_9O_4NS$: N, 5·9; S, 13·4%).

(*b*) 2-Amino-1-naphthol hydrochloride (2·8 g.) in pyridine (15 ml.) was added to chlorosulphonic acid (1·9 g.) in dry dimethylaniline (10 ml.) and carbon disulphide (50 ml.) at 0°. Next day, the mixture was poured into 7·5% aqueous potassium hydroxide (100 ml.), and the solution was washed with benzene. When the solution was concentrated under reduced pressure and acidified, a violet precipitate (0·8 g.), m. p. 200—210°, was obtained, which was precipitated (4 times) with acid from aqueous-ethanolic potassium hydroxide (charcoal), to give the ester (0·2 g., 6%), m. p. 223—225° (decomp.), undepressed in admixture with material from (*a*).

(*c*) Via 2-*phthaloylamino-1-naphthol*. When 2-amino-1-naphthol hydrochloride (5·0 g.), phthalic anhydride (7·6 g.), and anhydrous sodium acetate (2·1 g.) in glacial acetic acid (250 ml.) were heated under reflux for 2 hr., and the solution allowed to cool, 2-*phthaloylamino*-1-*naphthol*

(5·2 g., 79%), m. p. 268—269°, separated (Found: N, 5·2. $C_{18}H_{11}O_3N$ requires N, 4·8%). The derivative was soluble in dilute sodium hydroxide and gave a red colour with diazotised sulphanilic acid.

Chlorosulphonic acid (2·3 g.) was added to pyridine (30 ml.) with cooling, followed by 2-phthaloylamino-1-naphthol (4·7 g.) dissolved in pyridine (20 ml.). The mixture was kept overnight and then poured into water (150 ml.) containing potassium hydroxide (10 g.), and the solution freed from inorganic sulphate with aqueous barium chloride and concentrated. Acidification (acetic acid) of the concentrate gave an unidentified substance (3·2 g.), m. p. 150—153°. The solution was filtered, boiled for 10 min., cooled, extracted with ether to remove acetic acid, the presence of which was found to prevent precipitation of the ester, and acidified with concentrated hydrochloric acid. One crystallisation of the product as before gave the ester (0·5 g., 12%), m. p. 224—225°, undepressed with material from (*a*).

In another experiment with 2-phthaloylamino-1-naphthol (1·65 g.), the substance of m. p. 150—153° was precipitated as before, the filtrate made alkaline, evaporated under reduced pressure, and extracted with 95% ethanol, and the filtered extract was heated under reflux with hydrazine hydrate (0·5 g.) for 4 hr. Concentration of the ethanolic solution to 10 ml. and dilution with an equal volume of water, followed by acidification with concentrated hydrochloric acid failed to yield the required ester. The solution was brought to pH 4 with aqueous sodium hydroxide and acetic acid, and the ester (75 mg., 5%), m. p. 222—225° (decomp.), isolated as above.

Oxidation of 2-Naphthylamine with Persulphate.—2-Naphthylamine (5 g.), in a mixture of pyridine (200 ml.), water (600 ml.), and 2N-sodium hydroxide (30 ml.), was treated with sodium persulphate (8·3 g.) in aqueous solution as before. After 24 hr. the solution was filtered, evaporated to 100 ml. under reduced pressure, and washed with ether (3 × 150 ml.). The ice-cold solution was acidified with concentrated hydrochloric acid and, after some hours, crude 2-amino-1-naphthyl hydrogen sulphate (2·8 g., 45%) collected, as a pink powder. The ester was purified by dissolving it in a minimum amount of aqueous N-sodium hydroxide, boiling the solution with charcoal for 30 min., and re-precipitating the acid in the presence of an equal volume of acetone and a trace of sodium dithionite. After three such treatments, the acid formed pale pink prisms, m. p. 225° (decomp.), undepressed in admixture with a specimen prepared by the reduction of 2-nitro-1-naphthyl hydrogen sulphate (Found: S, 13·8; N, 6·1. Calc. for $C_{10}H_9O_4NS$: S, 13·4; N, 5·9%).

The *sodium* (Found: N, 5·2. $C_{10}H_8O_4NSNa$ requires N, 5·4%) and *potassium* (Found: N, 5·0. $C_{10}H_8O_4NSK$ requires N, 5·05%) salts (prepared from the acid) separated from 90% ethanol as pale pink and silvery-grey plates respectively. Solutions of the salts had faint blue fluorescence in daylight and strong blue fluorescence in ultra-violet light.

Hydrolysis of the acid (0·5 g.) with 5N-sulphuric acid at 100° for 30 min. gave 2-amino-1-naphthol sulphate (0·46 g.), separating from the cooled solution as grey plates. The dibenzoyl derivative crystallised from ethanol as needles, m. p. and mixed m. p. 180° (Found: N, 3·9. Calc. for $C_{24}H_{17}O_3N$: N, 3·8%). The diacetyl derivative separated from aqueous ethanol as needles, m. p. and mixed m. p. 117—118°.

Investigation of the Neutral Fraction from the Oxidation of 2-Naphthylamine with Persulphate.—2-Naphthylamine (5 g.), dissolved in water (4 l.) and 2N-sodium hydroxide (20 ml.), was treated with sodium persulphate (8·5 g.) at 80°. After 8 hr. the precipitate (1·8 g.) was separated, and 2-amino-1-naphthyl hydrogen sulphate (3·4 g., 39·5 %) was recovered from the filtrate by extraction (20 times) with butanol. The neutral precipitate was extracted with boiling benzene (4 × 100 ml.) [to leave a dark amorphous residue (1·1 g.)], and the benzene-soluble fraction was chromatographed on alumina. Elution of the column with benzene yielded: (*a*) 1 : 2-5 : 6-dibenzophenazine (88 mg.) separating from glacial acetic acid as pale yellow needles, m. p. and mixed m. p. 282—283° (Found: N, 10·0. Calc. for $C_{20}H_{12}N_2$: N, 9·9%), and (*b*) a substance (5 mg.) separating from benzene as red needles, m. p. 279°. Elution of the column with benzene–ether gave 2-2′-naphthylamino-1 : 4-naphthaquinone 4-2′-naphthylimide (I; R = 2-$C_{10}H_7$) (230 mg.), which crystallised from benzene as red needles, m. p. 252—253° (Found: C, 84·7, 85·1; H, 4·9, 5·6; N, 6·65. Calc. for $C_{30}H_{20}ON_2$: C, 84·9; H, 4·75; N, 6·6%), undepressed in admixture with synthetic material (see below) of m. p. 246—247°.

2-2′-Naphthylamino-1 : 4-naphthaquinone 4-2′-Naphthylimide (I; R = 2-$C_{10}H_7$).—2-Nitroso-1-naphthol (1 g.) and 2-naphthylamine (1·8 g.) in glacial acetic acid (20 ml.) were heated under reflux for 30 min. The product crystallised from ethyl acetate as red needles (2·1 g., 85%), m. p. 246—247° (Found: C, 84·6; H, 4·9; N, 6·7%). Meldola (*loc. cit.*) gives m. p. 246—247° for an apparently identical product.

Potassium 2-Hydroxyphenylsulphamate.—Chlorosulphonic acid (25·6 g.) was added slowly with cooling and stirring to pyridine (150 ml.), followed by *o*-aminophenol (21·6 g.). After being kept at room temperature overnight, the mixture was poured into water (500 ml.), containing potassium hydroxide (45 g.). The solution was distilled down to 150 ml., crystallisation of the product commencing. *Potassium 2-hydroxyphenylsulphamate* was obtained and was purified by the addition of ether to a solution of the salt in aqueous ethanol; it separated as plates (12 g., 27%) (Found: N, 6·3. $C_6H_6O_4NSK$ requires N, 6·2%). Its aqueous solution gave a red colour with diazotised sulphanilic acid in alkali, and no colour with *p*-dimethylaminobenzaldehyde. *o*-Aminophenyl potassium sulphate does not couple with diazotised sulphanilic acid and gives a yellow colour with *p*-dimethylaminobenzaldehyde. Heating the salt with dilute hydrochloric acid produced inorganic sulphate and, after neutralisation, *o*-aminophenol was isolated, m. p. and mixed m. p. 172—174° (Found: N, 12·7. Calc. for C_6H_7ON: N, 12·8%).

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