306. *Aminophenoxazines as Possible Antitubercular Agents. Part II.**

By B. Boothroyd and Edward R. Clark.

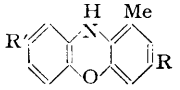
A number of 1-amino- and 3-amino-phenoxazines have been synthesised, including 3-amino-8-chloro-1-methylphenoxazine (I; R = NH_2, R′ = Cl), 1-amino-8-chlorophenoxazine (II; R = H, R′ = Cl), 3-aminophenoxazine-1-carboxylic acid (III), 3-amino-1-methylphenoxazine (I; R = NH_2, R′ = H), and 1 : 3-diaminophenoxazine (II; R = NH_2, R′ = H).

The reaction between 1-chloro-2 : 4 : 5-trinitrobenzene and *o*-benzylaminophenol yields a mixture of 10-benzyl-2-chloro-3-nitro- and 10-benzyl-2 : 3-dinitro-phenoxazine; catalytic reduction of the latter failed to yield any identifiable product.

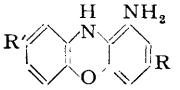
While some of the compounds have shown marked tuberculostatic activity *in vitro*, no influence on the course of tubercular infection in guinea pigs has been observed.

3-Amino-1-methylphenoxazine (I; R = NH_2, R′ = H) and its 8-chloro-analogue (I; R = NH_2, R′ = Cl) have been prepared in order to determine the influence of the halogen substituent on antitubercular activity.

The 2-chloro-3 : 5-dinitrotoluene needed was obtained from phosphorus oxychloride, diethylaniline, and 2-hydroxy-3 : 5-dinitrotoluene, this method giving a better yield than Ullmann and Sane's toluene-*p*-sulphonyl chloride method (*Ber.*, 1911, **44**, 3735). 1-Methyl-3-nitrophenoxazine (I; R = NO_2, R′ = H) was prepared by Ullmann and Sane (*loc. cit.*) by condensation of 2-chloro-3 : 5-dinitrotoluene with *o*-aminophenol and cyclisation of the purified 2′-hydroxy-6-methyl-2 : 4-dinitrodiphenylamine by using dilute alcoholic sodium hydroxide. Considerably improved yields are obtained when the intermediate diphenylamine is not isolated before cyclisation. The 8-chloro-analogue (I; R = NO_2, R′ = Cl) was prepared in one operation by use of aqueous alcoholic sodium hydroxide on 2-amino-4-chlorophenol and 2-chloro-3 : 5-dinitrotoluene.



(I)



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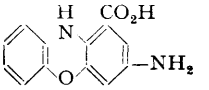

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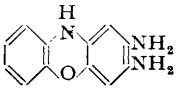

(IV)

The corresponding aminophenoxazines were obtained by catalytic reduction by using Adams's platinum oxide and acetic acid. This was preferred to the use of stannous chloride or tin and hydrochloric acid which give the tin complexes from which it is difficult to isolate the free bases. The bases were isolated in their oxidised forms as hydrochlorides; recrystallisation of these was not possible and attempts to purify them by reprecipitation failed to remove a very small amount of water-insoluble material. It appears that a little of the free base is precipitated with the hydrochloride.

1-Amino- (II; R = R′ = H) and 1-amino-8-chloro-phenoxazine (II; R = H, R′ = Cl) were then prepared; these compounds can be oxidised to *ortho*-quinones. 1-Nitrophenoxazine has been prepared by Ullmann (*Annalen*, 1909, **366**, 110) and its reduction, by

* Part I, preceding paper.

using stannous chloride and hydrochloric acid, was reported by Kehrmann and Lowry (*Ber.*, 1911, **44**, 3006). The hydrochloride, and that of the 8-chloro-analogue have been obtained. The former was rather insoluble in water as also was the oxidised form. 1-Aminophenoxazine-3-carboxylic acid (II; R = CO_2H, R′ = H) was therefore synthesised, since it could be tested as its sodium salt.

The preparation of 1-nitrophenoxazine-3-carboxylic acid has been claimed by Ullmann (*Annalen*, 1909, **366**, 96) but neither melting point nor analytical data were given. By using a similar method, an analytically pure sample has been obtained. Reduction of the nitro-carboxylic acid by using stannous chloride gave a highly insoluble product, recrystallisation of which yielded what was apparently a mixture of the hydrochloride and the free amino-acid.

3-Aminophenoxazine-1-carboxylic acid (III) was synthesised by reduction of the corresponding nitro-compound with stannous chloride in hydrochloric acid. Recrystallisation from 50% hydrochloric acid yielded the hydrochloride monohydrate.

1 : 3-Diamino- (II; R = NH_2, R′ = H) and 2 : 3-diamino-phenoxazine (IV) are of interest, the former, since it is capable of conversion into both *ortho*- and *para*-quinonoid structures and, the latter, since it bears a close resemblance to the tuberculostatic 2 : 3-diaminophenazine (Erlenmeyer, *Helv. Chim. Acta*, 1949, **32**, 605). 1 : 3-Dinitrophenoxazine was reduced by Kehrmann (*Ber.*, 1899, **32**, 2603) by using stannous chloride in hydrochloric acid. Catalytic reduction in acetic acid solution with platinum oxide proceeded smoothly, and is to be preferred. The product was characterised as the sulphate and by oxidation to the imine from which the picrate was formed.

Owing to the absence of any $C_{(1)}$-substituent, the synthesis of 2 : 3-diaminophenoxazine was approached along similar lines to those used for 3-aminophenoxazine (see Part I).

According to Nietzki and Zänker (*Ber.*, 1903, **36**, 3953) 5-chloro-2 : 4-dinitroaniline can be obtained by the action of ammonia on 1-chloro-2 : 4 : 5-trinitrobenzene, giving rhombic plates, m. p. 174—176°, or on 1 : 3-dichloro-4 : 6-dinitrobenzene, giving long needles, m. p. 182°. No experimental details are given. When 1-chloro-2 : 4 : 5-trinitrobenzene and ammonia reacted in alcoholic solution in the presence of a little sodium carbonate, 5-chloro-2 : 4-dinitroaniline, m. p. 184·5—185° and some 1 : 3-diamino-4 : 6-dinitrobenzene were obtained, the former being identified as the acetanilide (Kehrmann and Stanoyevitch, *Helv. Chim. Acta*, 1925, **8**, 664). Recrystallisation of the aniline from benzene–ligroin gave a product, m. p. 176—176·5°. Five crystallisations of this form from 50% aqueous alcohol raised the m. p. to 184—185°; a mixture of approximately equal parts of the two forms melted at 181—182°.

The use of dry benzene as solvent in the preparation of the aniline caused a marked improvement in the yield. Samples obtained by both methods gave high analytical results for carbon, due presumably to excessive formation of nitrous fumes on combustion.

Kehrmann and Stanoyevitch (*loc. cit.*) obtained 5-acetamido-2 : 4-dinitrodiphenylamine from 5-chloro-2 : 4-dinitroacetanilide and aniline. By using *o*-aminophenol, in place of aniline, and sodium acetate in aqueous ethanol as the condensing agent, only a dark tar was obtained. Only 5-chloro-2 : 4-dinitroaniline was identified in the products of the attempted cyclisation of this material.

The reaction between 1-chloro-2 : 4 : 5-trinitrobenzene and *o*-benzylaminophenol yielded 10-benzyl-2 : 3-dinitro- and 10-benzyl-2-chloro-3-nitro-phenoxazine. The production of the former is remarkable, but the ratio of the dinitrophenoxazine to the chloronitrophenoxazine, approximately 3 : 1, is even more so. No conclusions can be drawn from this result, however, as only 26% of the starting materials was accounted for.

Preliminary biological tests have been carried out. 3-Imino-1-methylphenoxazine hydrochloride and its 8-chloro-analogue inhibited the growth, *in vitro*, of *M. tuberculosis* (H37Rv) at dilutions of 1 in 100,000, while 1-aminophenoxazine hydrochloride inhibited growth at dilutions down to 10^9.

Despite the poor analytical figures obtained for the product of reduction of 1-nitrophenoxazine-3-carboxylic acid, it was believed to be the required amino-acid, probably, as stated above, as a mixture of hydrochloride and free amino-acid. It was therefore neutralised with sodium carbonate solution and the resulting sodium salt tested; no

inhibition of the growth of *M. tuberculosis* was observed, even at concentrations of 1 in 1000.

Administration of 3-imino-1-methylphenoxazine hydrochloride, its 8-chloro-analogue, and 1-aminophenoxazine hydrochloride to infected guinea pigs during 40 days had little influence on the course of the tubercular infection. Further biological tests are in progress. The results of these and full details of the above biological examinations will be published elsewhere.

Experimental

Some of the analyses are by Mrs. Richards.

2-Chloro-3 : 5-dinitrotoluene.—Diethylaniline (60 c.c.) was added, with cooling, to a solution of 2-hydroxy-3 : 5-dinitrotoluene (40 g.) in phosphorus oxychloride (235 c.c.), which was then heated on the steam-bath for 2 hr., allowed to cool, and carefully poured on crushed ice (1·5 kg.). 2-Chloro-3 : 5-dinitrotoluene (37·9 g.) was recrystallised from alcohol, yielding pale yellow plates, m. p. 63—64°.

1-Methyl-3-nitrophenoxazine.—A solution of *o*-aminophenol (11 g.) and 2-chloro-3 : 5-dinitrotoluene (21·6 g.) in *ca.* 2N-sodium acetate (60 c.c.) and ethyl alcohol (100 c.c.) was stirred and heated under reflux for 5 hr. *ca.* 2N-Sodium hydroxide solution (75 c.c.) was slowly added and the red solution boiled for 30 min. and then set aside overnight in the ice-box. The dark brown product was washed with dilute sodium hydroxide and a little ethanol, and then recrystallised from toluene, yielding 1-methyl-3-nitrophenoxazine (18·9 g.), m. p. 212—213° (decomp.) (Found : C, 64·5; H, 4·2; N, 11·3. Calc. for $C_{13}H_{10}O_3N_2$: C, 64·4; H, 4·1; N, 11·6%).

8-Chloro-1-methyl-3-nitrophenoxazine.—To a refluxing solution of 2-amino-4-chlorophenol (3·6 g.) and 2-chloro-3 : 5-dinitrotoluene (5·4 g.) in ethyl alcohol (30 c.c.), *ca.* 2N-sodium hydroxide (25 c.c.) was added slowly, with stirring. The mixture was heated on the steam-bath and stirred for a further 2 hr., set aside overnight in the ice-box and then filtered, yielding a slightly sticky solid which was washed with dilute sodium hydroxide and alcohol. *8-Chloro-1-methyl-3-nitrophenoxazine* formed red needles (5·0 g.), m. p. 272—273° (decomp.) (from nitrobenzene or chlorobenzene) (Found : C, 56·6; H, 3·2; N, 10·4; Cl, 13·15. $C_{13}H_9O_3N_2Cl$ requires C, 56·4; H, 3·3; N, 10·1; Cl, 12·85%).

3-Imino-1-methylphenoxazine.—1-Methyl-3-nitrophenoxazine (2·7 g.) in suspension in glacial acetic acid (50 c.c.) was reduced at room temperature by using Adams's platinum oxide (0·1 g.) and an initial hydrogen pressure of 5 atmospheres; the calculated amount of hydrogen was absorbed during 14 hr. The resulting colourless solution, which rapidly became red on exposure to the air, was filtered, concentrated *in vacuo* to 10 c.c., and made alkaline with dilute sodium hydroxide. Dry hydrogen chloride was passed through the dried (Na_2SO_4) benzene solution of the precipitated solid, giving the imine hydrochloride (2·4 g.), which was filtered off, washed with benzene, and dried in a vacuum.

The bulk of the product was very soluble in ethyl alcohol, water, and acetone, but entirely insoluble in benzene, ligroin, and other non-polar solvents.

In an attempt to remove the small amount of water-insoluble material, a filtered aqueous solution of the hydrochloride was made alkaline with sodium hydroxide solution, the imine extracted with benzene, and the hydrochloride precipitated from the dried solution as before. The product again contained a very small amount of water-insoluble material which appeared to be the free base.

Addition of a saturated picric acid solution to a filtered aqueous solution of imine hydrochloride immediately gave a red precipitate. Recrystallisation from a mixture of ethyl alcohol and 30% by volume of saturated aqueous picric acid yielded *3-imino-1-methylphenoxazine picrate*, m. p. >300° (Found : C, 51·9; H, 3·4; N, 16·2. $C_{13}H_{10}ON_2,C_6H_3O_7N_3$ requires C, 51·9; H, 3·0; N, 15·95%).

8-Chloro-3-imino-1-methylphenoxazine.—8-Chloro-1-methyl-3-nitrophenoxazine (2·8 g.) was reduced, and the imine hydrochloride (2·5 g.) isolated as described for the analogue not containing halogen. The *picrate* crystallised from ethanol containing 10% of a saturated aqueous solution of picric acid in long red needles, m. p. >300° (Found : C, 48·5; H, 2·85; N, 14·4. $C_{13}H_9ON_2Cl,C_6H_3O_7N_3$ requires C, 48·15; H, 2·5; N, 14·8%).

1-Chloro-2 : 6-dinitrobenzene.—Prepared from diethylaniline (10·5 c.c.), 2 : 6-dinitrophenol (7 g.), and phosphorus oxychloride (70 c.c.) as described above for 2-chloro-3 : 5-dinitrotoluene, 1-chloro-2 : 6-dinitrobenzene (5·6 g.) had m. p. 86—87° (Ostromisslensky, *J. pr. Chem.*, 1908, **78**, 260, recorded m. p. 87°).

1-*Aminophenoxazine Hydrochloride*.—1-Nitrophenoxazine (0·6 g.) (Ullmann, *Annalen*, 1909, **366**, 110) was reduced with stannous chloride (2·4 g.) and concentrated hydrochloric acid according to Kehrmann and Lowry's method (*Ber.*, 1911, **44**, 3006). To a filtered hot aqueous solution (240 c.c.) of the grey-green crystals (0·6 g.) concentrated hydrochloric acid (240 c.c.) was added; precipitation of the hydrochloride began immediately. Repetition of precipitation next day gave 1-*aminophenoxazine hydrochloride* (0·48 g.), m. p. 249—250° (decomp.) (Found: C, 61·0; H, 4·2; N, 12·3; Cl, 15·6. $C_{12}H_{10}ON_2$,HCl requires C, 61·4; H, 4·7; N, 11·9; Cl, 15·1%).

8-*Chloro*-1-*nitrophenoxazine*.—1-Chloro-2 : 6-dinitrobenzene (2 g.), 2-amino-4-chlorophenol (1·5 g.), ethyl alcohol (15 c.c.), and *ca.* 2N-sodium acetate (10 c.c.) were stirred and heated under reflux for 4 hr. *ca.* 2N-Sodium hydroxide (10 c.c.) was slowly added to the boiling solution and, after a further 30 min.' heating, the mixture was allowed to cool in the ice-box overnight. The mass of fine needles was filtered off, washed with dilute sodium hydroxide solution followed by ethanol, and recrystallised from chlorobenzene; 8-*chloro*-1-*nitrophenoxazine* (1·9 g.) had m. p. 240—241° (decomp.) (Found: C, 54·6; H, 2·6; N, 10·9; Cl, 13·9. $C_{12}H_7O_3N_2Cl$ requires C, 54·85; H, 2·7; N, 10·7; Cl, 13·5%).

1-*Amino*-8-*chlorophenoxazine Hydrochloride*.—8-Chloro-1-nitrophenoxazine (1 g.) was reduced with stannous chloride (3·6 g.) and concentrated hydrochloric acid (15 c.c.) as described for the halogen-free analogue. The crude *hydrochloride* (0·95 g.) was recrystallised from ethyl alcohol—concentrated hydrochloric acid (6 : 4) yielding long rectangular plates, m. p. 228—230° (decomp.) (Found: C, 53·2; H, 4·0; N, 10·5; Cl, 25·9. $C_{12}H_9ON_2Cl$,HCl requires C, 53·5; H, 3·7, N, 10·4; Cl, 26·4%).

1-*Nitrophenoxazine*-3-*carboxylic Acid*.—*o*-Aminophenol (3·3 g.), 4-chloro-3 : 5-dinitrobenzoic acid (7·5 g.), water (30 c.c.), and *ca.* 2N-sodium acetate (15 c.c.) were stirred and heated under reflux for 15 min. To the resulting thick paste was added *ca.* 2N-sodium hydroxide (15 c.c.), and the mixture was stirred and heated for a further 15 min. The dark purple sodium salt was washed with cold brine. More of the sodium salt was obtained by saturating the filtrate and washings with sodium chloride.

An aqueous solution of the combined precipitates was acidified (Congo-red) with dilute hydrochloric acid, the free acid forming a dark gelatinous precipitate. Recrystallisation from 50% aqueous pyridine or acetic acid yielded dark purple needles of 1-*nitrophenoxazine*-3-*carboxylic acid* (6·3 g.), m. p. 320—321° (Found: C, 57·1; H, 3·1; N, 10·4. $C_{13}H_8O_5N_2$ requires C, 57·35; H, 2·9; N, 10·3%).

Reduction of 1-*Nitrophenoxazine*-3-*carboxylic Acid*.—A suspension of 1-nitrophenoxazine-3-carboxylic acid (2·5 g.) in boiling ethyl alcohol (40 c.c.) was reduced by being heated for 3 hr. with stannous chloride (9·0 g.) and concentrated hydrochloric acid (40 c.c.). After cooling the pale green product (2·4 g.) was filtered off. Recrystallisation from large quantities of distilled water containing about 1 c.c. of concentrated hydrochloric acid and a small amount of sodium dithionite gave a mixture (2·3 g.) of 1-aminophenoxazine-3-carboxylic acid and its hydrochloride, crystallising in fine pale-green needles, m. p. $>340°$.

Attempts to form the acetyl derivative and the *S*-benzylthiuronium salt were unsuccessful.

3-*Aminophenoxazine*-1-*carboxylic Acid Hydrochloride*.—A solution of stannous chloride (3·6 g.) in concentrated hydrochloric acid (20 c.c.) was added to 3-nitrophenoxazine-1-carboxylic acid (1·2 g.) in boiling alcohol (20 c.c.). After 2 hr.' heating the hot solution was filtered and allowed to cool, whereupon precipitation of green needles occurred. (The amount of precipitate was increased by passage of dry hydrogen chloride.) The crystalline product was dissolved in alcohol (10 c.c.), and *ca.* 2N-sodium carbonate (15 c.c.) added. The precipitated stannic hydroxide was filtered off and dilute acetic acid added to the filtrate. The free amino-acid was recrystallised from 50% hydrochloric acid, yielding fine greenish-brown needles of 3-*aminophenoxazine*-1-*carboxylic acid hydrochloride monohydrate* (1·05 g.) (Found: C, 52·1; H, 4·7; N, 9·9. $C_{13}H_{10}O_3N_2$,HCl,H_2O requires C, 52·6; H, 4·4; N, 9·45%).

1 : 3-*Diaminophenoxazine*.—1 : 3-Dinitrophenoxazine (4 g.) in glacial acetic acid (100 c.c.) was reduced with hydrogen at a maximum pressure of 5 atmospheres, in the presence of Adams's platinum oxide (0·1 g.). Reduction was complete in 5 hr. The filtered solution was concentrated under reduced pressure to 20 c.c., sealed under nitrogen, and stored in the ice-box overnight. Recrystallisation of the fine needles from 2N-sulphuric acid, containing a little sodium dithionite, yielded 1 : 3-*diaminophenoxazine sulphate* (2·6 g.), m. p. 221—223° (decomp.) (Found: S, 10·0. $C_{12}H_{11}ON_3$,H_2SO_4 requires S, 10·3%).

1-*Aminophenoxazim Picrate*.—1 : 3-Diaminophenoxazine sulphate (0·1 g.) was oxidised by passage of oxygen through its solution in water (10 c.c.) for 30 min. Saturated aqueous picric

acid solution (20 c.c.) was added and the yellowish-brown precipitate recrystallised from saturated aqueous picric acid–ethyl alcohol (3 : 4) yielding **1-*aminophenoxazim picrate***, m. p. 231—233° (decomposition appears to commence at 180°) (Found : C, 48·7; H, 2·8; N, 19·0. $C_{12}H_9ON_3,C_6H_3O_7N_3$ requires C, 49·1; H, 2·8; N, 19·1%).

5-Chloro-2 : 4-dinitroaniline.—(*a*) A stream of ammonia was passed through a mixture of 1-chloro-2 : 4 : 5-trinitrobenzene (10 g.), sodium carbonate (2·5 g.), and ethyl alcohol (50 c.c.), the temperature being kept below 50°. During the first 10 min. nearly all the solid dissolved, and the temperature then began to fall. The solution was evaporated to dryness and the residue extracted with hot 50% aqueous ethanol. The hot filtered extract, on cooling, deposited pale fawn needles of 5-chloro-2 : 4-dinitroaniline (4 g.), m. p. 184·5—185° (Found : C, 33·8; H, 2·2; N, 19·3; Cl, 16·0. Calc. for $C_6H_4O_4N_3Cl$: C, 33·1; H, 1·8; N, 19·3; Cl, 16·3%).

The insoluble residue from the alcohol extraction was crystallised from 75% acetic acid, yielding 1 : 3-diamino-4 : 6-dinitrobenzene (0·8 g.), m. p. 300—301° (Nietzki and Schedler, *Ber.*, 1897, **36**, 1667, give m. p. 300°) (Found : C, 37·0; H, 3·2. Calc. for $C_6H_6O_4N_4$: C, 36·4; H, 3·0%).

(*b*) Ammonia was passed for 10 min. into a cooled (<25°) mixture of 1-chloro-2 : 4 : 5-trinitrobenzene (10 g.) and sodium carbonate (2·5 g.) in dry benzene (20 c.c.). Next morning the precipitated yellow solid was recrystallised from 50% aqueous ethanol, yielding 5-chloro-2 : 4-dinitroaniline (6·4 g.), m. p. and mixed m. p. 184—185°.

Recrystallisation from benzene–ligroin (b. p. 60—80°) (4 : 1) yielded yellow crystals, m. p. 176—176·5° (Found : C, 33·8; H, 1·7; N, 19·0; Cl, 16·0%).

The 5-chloro-2 : 4-dinitroaniline (m. p. 184—185°) was acetylated to 5-chloro-2 : 4-dinitroacetanilide, m. p. 136·5—137° (Found : C, 37·4; H, 2·4; N, 16·1; Cl, 13·5. Calc. for $C_8H_6O_5N_3Cl$: C, 37·0; H, 2·3; N, 16·2; Cl, 13·7%.

Condensation between 1-Chloro-2 : 4 : 5-trinitrobenzene and o-Benzylaminophenol.—1-Chloro-2 : 4 : 5-trinitrobenzene (3·9 g.) and *o*-benzylaminophenol (3 g.) (Boothroyd and Clark, Part I) were stirred and heated under reflux for 4 hr. with alcohol (50 c.c.) and *ca.* 2N-sodium acetate (9 c.c.), after which *ca.* 2N-sodium hydroxide (9 c.c.) was added, and the heating and stirring continued for a further 30 min. The mixture was allowed to cool and the precipitated solids (2·2 g.) washed with dilute sodium hydroxide and water, and finally dried. Recrystallisation from ethyl acetate gave brownish-red, long rectangular plates of **10-*benzyl*-2 : 3-*dinitrophenoxazine*** (1·1 g.), m. p. 238—240° (Found : C, 63·3; H, 3·8; N, 11·4. $C_{19}H_{13}O_5N_3$ requires C, 62·8; H, 3·6; N, 11·6%).

The mother liquors from the ethyl acetate recrystallisation were evaporated to dryness and the residue extracted with hot *cyclo*hexane, giving **10-*benzyl*-2-*chloro*-3-*nitrophenoxazine*** (0·4 g.), as red needles, m. p. 198·5—199·5° (from *cyclo*hexane) (Found : C, 65·0; H, 3·6; N, 8·3; Cl, 10·6. $C_{19}H_{13}O_3N_2Cl$ requires C, 64·7; H, 3·7; N, 7·9; Cl, 10·1%).

Reduction of 10-Benzyl-2 : 3-dinitrophenoxazine.—Catalytic reduction and debenzylation of 10-benzyl-2 : 3-dinitrophenoxazine was attempted under conditions similar to those described in Part I, acetic acid and ethanol being used as solvents. In neither case was any identifiable material isolated, the product being apparently very readily oxidised (colour changed from light yellow through green to blue). A small amount of an impure hydrochloride, which was only partly soluble in water, was obtained from the oxidised product. Treatment with picric acid yielded a dark red precipitate, which could not, however, be recrystallised without decomposition.

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