The Synthesis of N^{π}-Alkylhistamines

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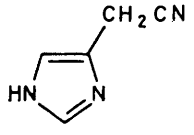
The use of the phthaloyl and pivaloyloxymethyl protecting groups in a new synthesis of N^{π}-alkylhistamines is described. The N^{α}-phthaloyl-N^{τ}-pivaloyloxymethyl-protected derivative of histamine was obtained by selective alkylation of N^{α}-phthaloylhistamine with chloromethyl pivalate. Quaternisation at the N^{π}-nitrogen atom with either methyl iodide or benzyl bromide followed by removal of the protecting groups, either simultaneously or sequentially, furnished the required N^{π}-methyl- and N^{π}-benzyl-histamines.

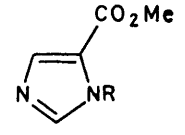
THE investigation in these laboratories of the classification and blockage of histamine H_2-receptors [1] has recently culminated in the synthesis and characterisation of histamine H_2-receptor antagonist drugs typified by burimamide,[1] metiamide,[2,3] and cimetidine.[4,5] The natural agonist molecule histamine was chosen as the starting point in these studies.[6] The need to substitute in histamine by methyl [7] and other selected alkyl groups called for the development of several new synthetic routes, some of which have been briefly reported.[7] In this paper a convenient new synthesis of N^{π}-alkylhistamines † is described.

RESULTS AND DISCUSSION

Two routes to N^{π}-methylhistamine have been reported,[9,10] one [9] *via* methylation of 4(5)-imidazolylacetonitrile (1) and the other *via* chain extension of the ester (2a). Since neither of these routes seemed to be



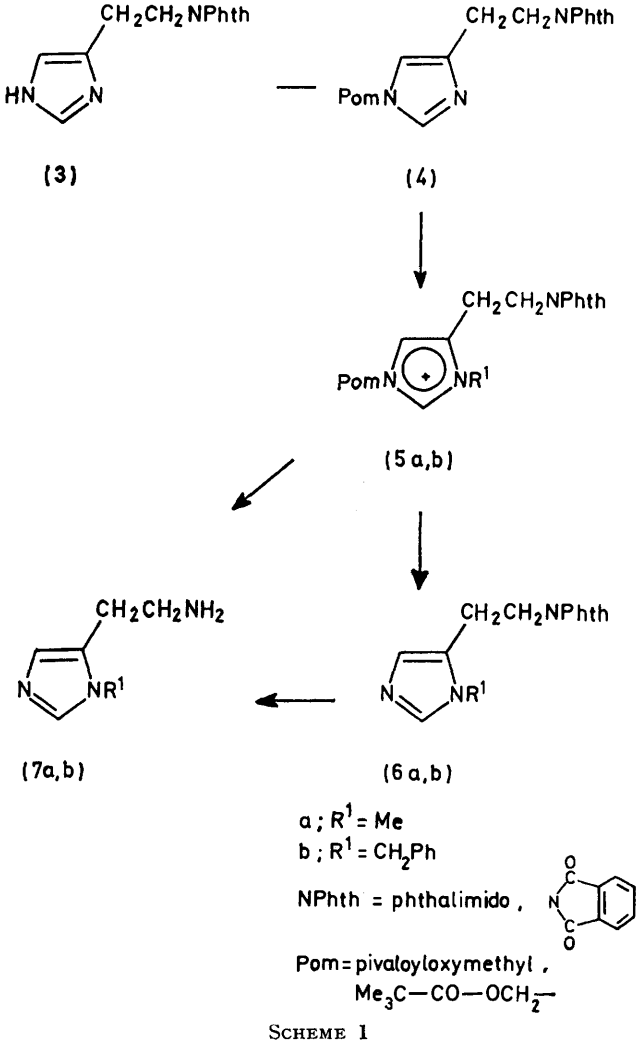
(1)



(2)
a ; R = Me
b ; R = CH_2Ph

generally applicable to the synthesis of other analogues we were prompted to investigate methods which would allow the selective alkylation at the N^{π}-atom of suitably protected (N^{α}- and N^{τ}-) forms of histamine. This principle of selective protection followed by alkylation has been successfully used previously in the synthesis of N^{τ}-methylhistamine.[7]

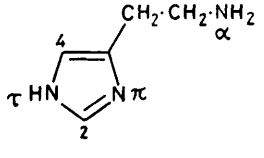
Not unexpectedly, methylation of N^{α}-acetylhistamine gives a mixture of both ring-methylated products, the N^{τ}-methyl derivative predominating.[11] We reasoned, however, that the use of a bulky N^{α}-protecting group such as phthaloyl might allow the selective introduction of another bulky protecting group at the N^{τ} ring-nitrogen and thereby permit specific alkylation at the free N^{π}-position. This was in fact achieved by utilising the little used pivaloyloxymethyl (Pom) protecting group [12] for protection of the N^{τ}-nitrogen atom (Scheme 1). N^{α}-Phthaloylhistamine (3) was readily prepared by



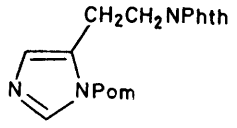
SCHEME 1

reaction of histamine with *N*-ethoxycarbonylphthalimide, a more convenient reagent than phthalic anhydride.[13] Alkylation of (3) with chloromethyl pivalate [12] in dimethylformamide, followed by chromatographic removal of unreacted starting material, gave the $N^{\pi}N^{\alpha}$-bis-protected derivative (4), apparently pure

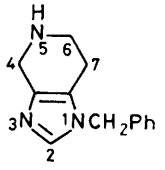
† Histamine numbering according to ref. 8.



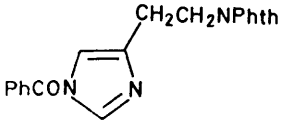
according to microanalysis and t.l.c. However, the n.m.r. spectrum showed the presence of another compound containing a pivaloyloxymethyl group, which, if assumed to be the isomer (8), was present to the extent of 15% from a comparison of the peak heights of the t-butyl groups. A single recrystallisation of (4) gave a



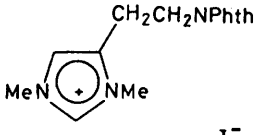
(8)



(9)



(10)



(11)

Pom = pivaloyloxymethyl
NPhth = phthalimido

product containing <5% impurity. This material was reacted with either methyl iodide or benzyl bromide to give the quaternary salts (5a and b) which could be purified by recrystallisation. Sequential removal of the protecting groups from the benzyl derivative (5b) was achieved by treatment with methanolic ammonia to give N^{π}-benzyl-N^{α}-phthaloylhistamine (6b), followed by acid hydrolysis to give N^{π}-benzylhistamine (7b). This product was shown to be identical to the material obtained [14] from side-chain elaboration of the ester (2b) according to the method of Jones.[10] When the quaternary salt (5b) was heated with acid in an attempt to remove both protecting groups simultaneously, the bicyclic spinaceamine (9) was the sole product isolated. The formation of this product is presumably due to reaction of N^{π}-benzylhistamine (7b) with formaldehyde produced *in situ* from fission of the Pom substituent, a well-documented cyclisation for histamine.[15] In the synthesis of N^{π}-methylhistamine (7a) simultaneous removal of both protecting groups was successfully achieved by reaction of the methiodide (5a) with hydrazine followed by diethyl phthalate (to remove excess of hydrazine). The dihydrochloride of N^{π}-methylhistamine obtained from the dipicrate, was identical to the product obtained using the Jones synthesis.[10] The use of hydrazine to achieve simultaneous removal of the two protecting groups was not attempted with the N^{π}-benzyl derivative (5b). In our judgement, however, this method should provide the most convenient procedure for obtaining 4-unsubstituted N^{π}-alkylhistamines from their corresponding N^{τ}-pivaloyl-N^{α}-phthaloyl derivatives. When a substituent is present in the 4-position removal of both groups by acid should also be feasible, since 'spinaceamine' formation is blocked.

In selecting a suitable protecting group for the N^{τ}-atom some consideration was given to the use of the benzoyl group, which has been employed recently in conjunction with oxonium alkylating agents to provide a useful synthesis of N^{π}-methyl- and N^{π}-ethyl-histidine.[16] Since this route, which is clearly analogous to the one described here, is somewhat limited in scope by the inaccessibility of many alkyloxonium salts, we felt that some investigation of the use of alkyl halides in conjunction with an N^{τ}-benzoyl protecting group deserved investigation. We found, however, that treatment of N^{τ}-benzoyl-N^{α}-phthaloylhistamine (10) with methyl iodide in dimethylformamide led to loss of the benzoyl group with the formation of the dimethyl quaternary salt (11),[17] thus indicating that an N^{τ}-benzoyl protecting group may only prove of use in this synthesis when coupled with a powerful oxonium alkylating agent.

Purity and Differentiation of N^{π}- *and* N^{τ}-*Alkylhistamines.*—Although our synthetic procedure should provide moderate to good yields of a wide range of N^{π}-alkylhistamines from histamine, n.m.r. spectral evidence suggested the possible formation of some of the unwanted isomer in the synthesis of N^{τ}-pivaloyloxymethyl-N^{α}-phthaloylhistamine (4). It was considered essential, therefore, that the identity and purity of the products should be established. In addition, it was necessary to ensure that contamination of the final products by the pharmacologically active starting material, histamine, was minimal. For these reasons t.l.c. systems, capable of separating histamine and its alkylated products, were developed. Inspection of the Table shows that the use of two systems, one basic and one acidic, effected complete separation of histamine from its corresponding N^{π}- and N^{τ}-alkylated products, which in turn could be separated from each other. The isomeric N^{τ}-alkylhistamines, which were obtained by the unambiguous route reported previously,[7] were not detected in the N^{π}-derivatives (50 μg loading), suggesting minimal contamination after purification. Using high loadings (1 000 μg), coupled with iodine visualisation, N^{π}-methyl- and N^{π}-benzyl-histamine were also shown to be free of histamine at the 0.2% level.

T.l.c. separation of histamine derivatives [a]

Compound	System A [b]	System B [c]
Histamine	0.52	0.70
N^{τ}-Methylhistamine	0.56	0.52
N^{π}-Methylhistamine	0.63	0.57
N^{τ}-Benzylhistamine	0.67	0.70
N^{π}-Benzylhistamine	0.75	0.70

[a] Compounds were run alongside histamine on one t.l.c. plate. [b] MeOH–NH_4OH (*d* 0.88)–H_2O (6 : 1 : 1); silica gel F_{524}. [c] $EtOCH_2CH_2OH$–HCl (11N)–H_2O (8 : 1 : 1); silica gel G.

N.m.r. spectrometry proved useful in structure determination, but, in general, could not be used for the absolute structural assignment of isomeric N^{π}- and

N^{τ}-alkylhistamines. The spectra of N^{π}- and N^{τ}-methylhistamines indicated, however, that with this pair of isomers, unequivocal structural assignment was possible from an examination of the methyl signals. Thus, in N^{τ}-methylhistamine the methyl signal appeared as a quartet due to coupling with both *ortho*-ring protons ($J_{2\text{-H,Me}}$ 0.5 Hz, $J_{4\text{-H,Me}}$ 0.2 Hz), whereas in N^{π}-methylhistamine the methyl signal appeared as a doublet ($J_{2\text{-H,Me}}$ 0.6 Hz) since, in this case, *para*-coupling to the imidazole 4-H is too small to be resolved. A method of differentiation of 1,4- and 1,5-disubstituted imidazoles on the basis of slightly different proton cross-ring coupling constants has recently been reported.[18] It is doubtful, however, whether this method allows the absolute determination of the structure of a derivative in the absence of its isomer. A more useful ^{13}C n.m.r. method of differentiating 1,4- and 1,5-imidazoles has also been reported.[19]

EXPERIMENTAL

M.p.s were recorded with an electrothermal apparatus, and are corrected. ^1H N.m.r. spectra were determined as solutions with tetramethylsilane as internal reference with a Varian A 60A spectrometer. H.p.l.c. analyses were determined on a Dupont 820 instrument at 254 nm.

N^{α}-*Phthaloylhistamine* (3).—Finely powdered *N*-ethoxycarbonylphthalimide (25 g, 0.11 mol) was added during 30 min to a vigorously stirred solution of histamine dihydrochloride (18.4 g, 0.1 mol) and sodium carbonate (21.2 g, 0.2 mol) in water (500 ml) at room temperature. After addition the mixture was stirred for a further 1 h, filtered, and the product recrystallised from aqueous ethanol to give N^{α}-phthaloylhistamine (22.7 g, 94%), m.p. 188—190 °C (lit.,[13] 189—190 °C).

N^{τ}-*Pivaloyloxymethyl*-N^{α}-*phthaloylhistamine* (4).—Potassium carbonate (5 g, 0.036 mol) was added to a solution of N^{α}-phthaloylhistamine (8.4 g, 0.036 mol) in dimethylformamide (DMF) (120 ml) and to this stirred mixture was added, during 30 min, a solution of pivaloyloxymethyl chloride [12] (5.4 g, 0.036 mol) in DMF (120 ml), while the temperature was maintained at 40—50 °C. After addition the mixture was stirred at 90 °C overnight, cooled, filtered, and the filtrate evaporated to dryness *in vacuo*. The residue was dissolved in chloroform, filtered, and the filtrate chromatographed on silica gel. Elution with ethyl acetate–methanol (10 : 1), which separated the product from starting material, gave N^{τ}-*pivaloyloxymethyl*-N^{α}-*phthaloylhistamine* (4) (9.5 g, 76%), m.p. 122—124 °C, after evaporation and recrystallisation of the residue from carbon tetrachloride–light petroleum (Found: C, 63.8; H, 6.0; N, 11.9. $C_{19}H_{21}N_3O_4$ requires C, 64.2; H, 6.0; N, 11.8%); δ($CDCl_3$) 1.14 (s, Bu^t), 2.96 (t, CH_2CH_2N), 4.0 (t, CH_2CH_2N), 5.76 (s, CH_2O), 6.88 (s, imidazole 4-H), 7.55 (m, imidazole 2-H), and 7.75 (m, phthalimido-H). Two additional singlets at δ 1.2 (Bu^t) and 5.92 (CH_2O) were consistent with the presence of *ca.* 15% of the N^{π}-isomer (8). This product showed one spot in all t.l.c. systems, but separated into two components using h.p.l.c. [ODS, MeOH–H_2O (1 : 3), 1 000 lb in^{-2}, 50 °C]. A further recrystallisation from carbon tetrachloride–light petroleum afforded a 38% yield of material, m.p. 128—130 °C, containing <5% isomeric impurity. This material was used for quaternisation.

1-*Pivaloyloxymethyl*-3-*methyl*-4-(2-*phthalimidoethyl*)*imidazolium Iodide* (5a).—A solution of N^{τ}-pivaloyloxymethyl-N^{α}-phthaloylhistamine (9.0 g, 0.025 mol) and methyl iodide (29 g) in dry DMF (50 ml) was heated under reflux overnight. After cooling, the mixture was filtered, the filtrate evaporated to dryness, and the residue recrystallised from methanol–ether to give the *quaternary iodide* (5a) (11.7 g, 93%), m.p. 167—169 °C; δ[$(CD_3)_2SO$] 1.1 (s, Bu^t), 3.15 (t CH_2CH_2N), 3.92 (t, CH_2CH_2N), 3.96 (s, Me), 6.1 (s, CH_2O), 7.75 (m, imidazole 4-H), 7.9 (s, phthalimido-H), and 9.45 (m, imidazole 2-H). Two additional singlets at δ 1.19 (Bu^t) and 6.2 (CH_2O) were consistent with the presence of a small amount of the N^{τ}-methyl isomer. Recrystallisation from ethanol–ether gave a pure sample, m.p. 170—171 °C (Found: C, 48.6; H, 4.9; N, 8.2; I, 25.75. $C_{20}H_{24}IN_3O_4$ requires C, 48.3; H, 4.9; N, 8.45; I, 25.5%).

1-*Pivaloyloxymethyl*-3-*benzyl*-4-(2-*phthalimidoethyl*)*imidazolium Bromide* (5b).—A solution of (4) (2.7 g) in benzyl bromide (25 ml) was heated with stirring at 90 °C overnight. After removal of excess of benzyl bromide *in vacuo* the residual oil was dissolved in ethanol and the solution poured into a large volume of ether to give the quaternary bromide (5b) (4 g, 95%), as a hygroscopic oily solid, which was reacted without further purification, δ(D_2O) 1.22 (s, Bu^t), 3.15 (t, CH_2CH_2N), 3.85 (t, CH_2CH_2N), 5.58 (s, CH_2Ph), 6.24 (s, OCH_2), 7.26 (m, Ph), 7.8 (m, phthalimido-H + imidazole 4-H), and 9.28 (d, imidazole 2-H).

N^{π}-*Benzyl*-N^{α}-*phthaloylhistamine Hydrochloride* (6b).—A solution of the quaternary bromide (5b) (4 g, 0.008 mol) in methanol (60 ml) was saturated with ammonia gas while the temperature was maintained below 30 °C. After setting aside at room temperature for 30 min the mixture was evaporated to dryness and the residue extracted with chloroform. The chloroform extracts were concentrated and the solution chromatographed on silica gel, using a saturated solution of ammonia in ethyl acetate–methanol (9 : 1) as eluant. The combined fractions were evaporated to dryness, the residue was dissolved in propan-2-ol, and the solution acidified with hydrogen chloride in isopropyl alcohol to give, on setting aside at 0 °C, N^{π}-*benzyl*-N^{α}-*phthaloylhistamine hydrochloride* (1.89 g, 68%), m.p. 227—229 °C. An analytical sample (from isopropyl alcohol–ether) had m.p. 230—232 °C (Found: C, 65.2; H, 4.85; N, 11.6. $C_{20}H_{18}ClN_3O_2$ requires C, 65.3; H, 4.9; N, 11.4%); δ(D_2O) 3.15 (t, CH_2CH_2N), 3.87 (t, CH_2CH_2N), 5.6 (s, CH_2Ph), 7.35 (s, Ph), 7.62 (m, imidazole 4-H), 7.8 (m, phthalimido-H), and 9.03 (m, imidazole 2-H).

N^{π}-*Methylhistamine Dihydrochloride* (7a).—A solution of the quaternary iodide (5a) (1 g, 0.002 mol) and hydrazine hydrate (0.5 g, 0.01 mol) in ethanol (50 ml) was heated under reflux for 14 h. Diethyl phthalate (3.3 g, 0.015 mol) was then added and the solution heated under reflux for a further 6 h. The mixture was cooled (0 °C), filtered, and the filtrate evaporated to dryness. The residue was dissolved in a mixture of ethanol (20 ml) and water (5 ml) and a hot solution of picric acid in ethanol (20 ml) added. On setting aside the solution deposited N^{π}-methylhistamine dipicrate (1.03 g, 88%), m.p. 208—210 °C, which was recrystallised (ethanol–water) to give a sample, m.p. 212—214 °C (lit.,[9] 201 °C) (Found: C, 37.2; H, 2.8; N, 21.6. Calc. for $C_{18}H_{17}N_9O_{14}$: C, 37.1; H, 2.9; N, 21.6%). The dipicrate was converted to the dihydrochloride, m.p. 269—271 °C (lit.,[10] 265—266 °C), from aqueous ethanol (Found: C, 36.4; H, 6.4; N, 21.1; Cl, 35.5. Calc. for $C_6H_{13}Cl_2N_3$:

C, 36.4; H, 6.6; N, 21.2; Cl, 35.8%); δ(D_2O) 3.3 (m, CH_2CH_2N), 3.43 (m, CH_2CH_2N), 3.92 (s, NMe), 7.48 (s, imidazole 4-H), and 8.77 (s, imidazole 2-H). Under higher resolution the NMe signal was seen as a doublet due to coupling with the imidazole 2-H ($J_{2\text{-H,Me}}$ 0.6 Hz). Neither histamine nor N^{τ}-methylhistamine [7] were detected in this product on t.l.c. (Table).

N^{π}-*Benzylhistamine Dihydrochloride* (7b).—A solution of N^{π}-benzyl-N^{α}-phthaloylhistamine hydrochloride (2.1 g) in 5N-hydrochloride acid (50 ml) was heated under reflux overnight. After removal of phthalic acid and evaporation of the filtrate to dryness the crude product (1.54 g) was recrystallised from ethanol to give N^{π}-*benzylhistamine dihydrochloride* (1.08 g, 69%), m.p. 222—223 °C (Found: C, 52.4; H, 6.3; N, 15.2; Cl, 25.8. $C_{12}H_{17}Cl_2N_3$ requires C, 52.6; H, 6.25; N, 15.3; Cl, 25.9%); δ(D_2O) 3.2 (m, CH_2CH_2), 5.52 (s, CH_2Ph), 7.5 (m, Ph + imidazole 4-H), and 8.83 (m, imidazole 2-H). This product showed identical t.l.c., n.m.r., and i.r. characteristics as that (m.p. 216—218 °C) prepared from the reduction of 1-benzyl-5-(cyanomethyl)imidazole.[14] N^{τ}-Benzylhistamine [20] was not detected on t.l.c. (Table), but at high loading (1 000 μg) a trace (<1%) of an impurity, indistinguishable from histamine, was detected. Extraction of the base (in water) with chloroform and re-acidification gave 0.82 g of the dihydrochloride containing <0.2% histamine.

Acid Hydrolysis of (5b).—A solution of the quaternary bromide (5b) (1.93 g) in 5N-hydrochloric acid (25 ml) was heated under reflux overnight, cooled (0 °C), and filtered. The filtrate was washed with ether (2 × 30 ml), basified (K_2CO_3), extracted with chloroform (3 × 50 ml) and the chloroform extracts washed once with water and dried ($MgSO_4$). After evaporation to dryness the residue was dissolved in dry (molecular sieve) ethanol and acidified with ethanolic hydrogen chloride to give a hygroscopic solid (0.33 g, 32%), which was recrystallised twice from ethanol–ether to give 1-*benzyl*-4,5,6,7-*tetrahydroimidazo*[4,5-c]*pyridine dihydrochloride* (9), m.p. 192—194 °C (closed capillary) (Found: C, 54.3; H, 6.1; N, 14.6; Cl, 25.1. $C_{13}H_{17}Cl_2N_3$ requires C, 54.55; H, 6.0; N, 14.7; Cl, 24.8%); δ(D_2O) 2.95 (t, 7-H_2), 3.65 (t, 6-H_2), 4.5 (t, 4-H_2), 5.54 (s, CH_2Ph), 7.5 (m, Ph), and 8.87 (s, imidazole 2-H).

N^{τ}-*Benzoyl*-N^{α}-*phthaloylhistamine* (10).—A solution of benzoyl chloride (1.54 g, 0.011 mol) in THF (15 ml) was added dropwise with stirring to a suspension of N^{α}-phthaloylhistamine (2.4 g, 0.01 mol) in THF (150 ml) and triethylamine (1.1 g). After addition (45 min) the mixture was stirred for a further 75 min and then set aside at room temperature for 2 d. Triethylamine hydrochloride was filtered off, the filtrate was concentrated, and the product (3.02 g, 87%), m.p. 155—158 °C, obtained by addition of light petroleum. Recrystallisation from chloroform–light petroleum gave N^{τ}-*benzoyl*-N^{α}-*phthaloylhistamine* (10) (2 g, 58%), m.p. 157.5—158.5 °C (Found: C, 69.65; H, 4.4; N, 12.2. $C_{20}H_{15}N_3O_3$ requires C, 69.6; H, 4.4; N, 12.2%); δ($CDCl_3$) 3.02 (t, CH_2CH_2N), 4.04 (t, CH_2CH_2N), 7.32 (s, imidazole 4-H), *ca.* 7.7 (m, 2 Ph), and 7.99 (d, imidazole 2-H).

Attempted Quaternisation of (10) *with Methyl Iodide*.—Reaction of N^{τ}-benzoyl-N^{α}-phthaloylhistamine (0.75 g) with methyl iodide (8 g) in dry DMF (25 ml) at reflux temperature for 4 h gave, after addition of ether, an off-white solid (0.81 g), m.p. 235—240 °C (decomp.). Recrystallisation from ethanol–water gave 1,3-dimethyl-4-(2-phthalimidoethyl)imidazolium iodide (11) (0.3 g), m.p. 255 °C (decomp.) (lit.,[17] 255—257 °C) (Found: C, 45.2; H, 4.0; I, 32.0; N, 10.6. $C_{15}H_{16}IN_3O_2$ requires C, 45.35; H, 4.1; I, 31.95; N, 10.6%); δ[$(CD_3)_2SO$] 3.05 (m, CH_2CH_2N), 3.77 (s, Me), 3.85 (s, Me), *ca.* 3.8 (m, CH_2CH_2N), 7.56 (d, imidazole 4-H), 7.87 (m, phthalimido-H), and 9.06 (d, imidazole 2-H).

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