An Entry into the Novel Tetracyclic System 6*H*-Pyrido[1′,2′:4,5]pyrazino[1,2-*a*]benzimidazole. Synthesis and Conformational Study of the 1,2,3,4,13,13a-Hexahydro-3,3-ethylenedioxy and 3-Ketone Derivatives

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The synthesis of the tetracyclic title compounds, acetal **5** and ketone **6**, is presented. The key step, formation of the imidazole ring to give compound **5**, involved the acid catalysed dehydration of the 2-(*o*-aminophenyl)lactam **7b**. This was generated from lactam **4** *via* *N*-substitution with *o*-nitrofluorobenzene and reduction of the nitro group. Deprotection of acetal **5** afforded ketone **6** which through a temperature dependence study of vicinal coupling constants was shown to occur as an equilibrium of *trans*- and *cis*-fused forms **A** and **B**.

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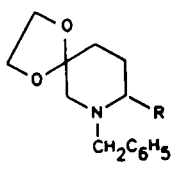
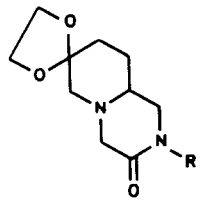
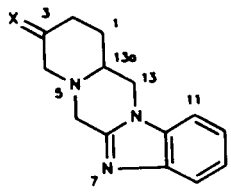
Recently we disclosed a synthetic route to compound **1**; this involved regioselective Hg^{2+} oxidation and trapping of the resulting iminium ion with cyanide [1]. The versatility of this synthon in providing access to 2,5-substituted piperidines was demonstrated by its conversion to aldehyde **2**, primary amine **3** and bicyclic lactam **4** [2]. Further transformation of **1**–**4** to the tetracyclic benzimidazole derivatives **5** and **6** is an attractive goal since these compounds represent an original heterocyclic system. Furthermore, the benzimidazole moiety and angular N-5-atom clearly remind of numerous indole alkaloid structures, suggesting an interesting potential for biologic activity. Finally, modulation of such activity should be possible by functionalisation of the 3-ketone group in synthon **6** or by variation of the substitution pattern of the benzene ring.



1: R = CN
2: R = CHO
3: R = CH_2NH_2



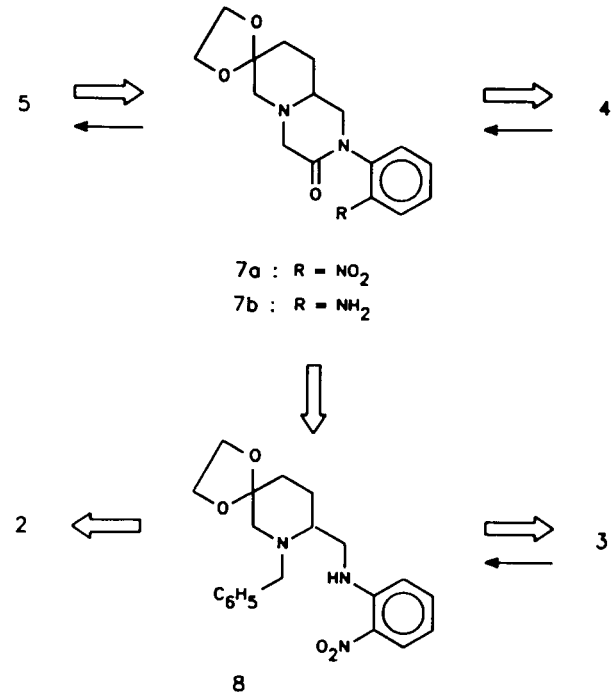
4: R = H



5: X = OCH_2CH_2O
6: X = O

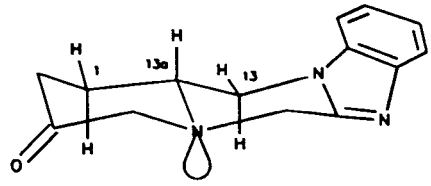
Our approach to the synthesis of target compounds **5** and **6** is illustrated in the retrosynthetic Scheme 1. The key step producing the imidazole ring is based on the gain in energy expected from conversion of the amide group of amino lactam **7b** into the benzimidazole ring system of **5**. A suitable precursor of **7b**, the 2-(*o*-nitrophenyl)lactam **7a**, could result from arylation of the 2-NH position of lactam **4**. Another viable route to **7a** involves cyclisation of the *N*-chloroacetyl derivative of nitroaniline **8**; this method has been used previously [2] to prepare similar lactam products from the aniline and *o*-anisidine analogues of **8**.

Scheme 1

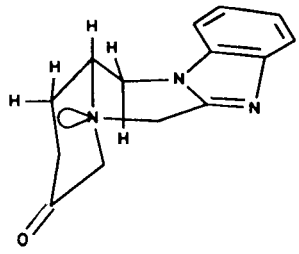


Reductive amination (sodium cyanoborohydride, methanol, *p*H 6) of aldehyde **2** with *o*-nitroaniline was not successful for the preparation of intermediate **8**. However, the desired compound was obtained in good yield by arylation of the primary amine **3** with *o*-nitrofluorobenzene. In this reaction, the nucleophilic properties of the amine were enhanced by hydrogen bond formation with tetrabutylammonium fluoride [3,4]. Unfortunately, chloroacetylation of **8** did not succeed, thereby precluding the cyclisation route **8** → **7a**.

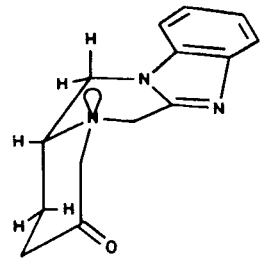
We then resorted to direct arylation of lactam **4** with *o*-nitrofluorobenzene. In a first method, this was effected by generation of the anion of **4** using potassium hydroxide powder in tetrahydrofuran under phase-transfer catalysis (tetrabutylammonium bromide). A slightly better yield (62% instead of 40-60% with the former method) and a cleaner product **7a** were obtained by exploiting again the enhancement of nucleophilicity brought about by the tetrabutylammonium fluoride reagent. Without addition of any further base, smooth *N*-arylation was effected in this way. The spectral data for **7a** were in agreement with the *N*-(*o*-nitrophenyl)lactam structure. In the infrared spectrum strong absorptions corresponding to the carbonyl (1675 cm^{-1}) and nitro groups (1530 and 1360 cm^{-1}) were observed. Hydrogenation of **7a** (10:1 ethyl acetate-acetic acid, palladium on activated carbon) afforded a mixture of intermediate **7b** and the already cyclised benzimidazole **5**. The intermediate **7b** was isolated by using tlc (mass spectrum M^+ 303) and was readily converted to **5** by refluxing in acetic acid. Deprotection (6*N* hydrogen chloride, reflux) finally gave the required ketone **6**.



trans–fused A



cis–fused B



cis–fused C

Table 1

^{1}H NMR Data for **5** and **6** [a]

Proton	5	6
H-13a	2.63 (tt) ^3J = 10.5, 10.5, 4.1 and 3.5 Hz	3.08 (ddt) ^3J = 10.5, 8.2, 4.55 and 4.15 Hz
H-13ax	3.77 (t) ^2J = 11.7 Hz, ^3J = 10.5 Hz	3.87 (t) ^2J = 11.7 Hz, ^3J = 10.5 Hz
H-13eq	4.14 (dd) ^2J = 11.7 Hz, ^3J = 4.1 Hz	4.27 (dd) ^2J = 11.7 Hz, ^3J = 4.15 Hz
H-1ax(A) [b]	1.82 (tdd) ^2J = 13 Hz, ^3J = 12.8, 10.5 and 3.5 Hz	1.95 (dddd) ^2J = 13.8 Hz, ^3J = 10.95, 8.2 and 5.1 Hz
H-1eq(A) [b]	1.98 (dq) ^2J = 13 Hz, ^3J = 4.3, 3.5 and 3 Hz	2.30 (dtd) ^2J = 13.8 Hz, ^3J = 5.9, 5.9 and 4.55 Hz
H-2ax(A) [b]	1.72 (td) ^2J = 12.5 Hz, ^3J = 12.8 and 4.3 Hz	2.48 (ddd) ^2J = 15.4 Hz, ^3J = 10.95 and 5.9 Hz
H-2eq(A) [b]	1.89 (dq) ^2J = 12.5 Hz, ^3J = 3.5 and 3 Hz, ^4J = 2.4 Hz	2.65 (dt) ^2J = 15.4 Hz, ^3J = 5.9 and 5.1 Hz, ^4J = 1.4 Hz
H-4ax(A) [b]	2.36 (d) ^2J = 11.5 Hz	3.12 (d) ^2J = 15.4 Hz
H-4eq(A) [b]	2.99 (dd) ^2J = 11.5 Hz, ^4J = 2.4 Hz	3.53 (dd) ^2J = 15.4 Hz, ^4J = 1.4 Hz
H-6ax	3.56 (d) ^2J = 15.9 Hz	3.72 (d) ^2J = 16 Hz
H-6eq	4.25 (d) ^2J = 15.9 Hz	4.34 (d) ^2J = 16 Hz
H-8	7.67 (m)	7.75 (m)
H-9, 10, 11	7.27-7.17 (m)	7.32 (m)
OCH_2CH_2O	4.07-3.97 (m)	

[a] 500 MHz spectra in deuteriochloroform. Multiplicity of a proton is given in parentheses after δ-values: d = doublet, t = triplet, q = quadruplet, m = multiplet, dd = doublet of doublets, tt = triplet of triplets, *ect.* [b] For compound **6** this assignment applies to the major *trans*-fused form **A**; the orientation of these protons is reversed for the minor *cis*-fused form **B**.

Table 2

Temperature Dependence of Vicinal Coupling Constant Values (Hz) for Protons H-13a, H-1, H-2 and H-13 in the ^{1}H NMR Specta of **6**

Temperature (°):	-40 [a]	-20 [a]	20 [b]	25 [b]	50 [c]	60 [d]	90 [d]
^{3}J[H-1ax(A),H-13a]	8.9	8.75	8.4	8.2	8.1	8.1	7.9
^{3}J[H-1eq(A), H-13a]	4.05	4.2	4.4	4.55	4.6	4.7	4.75
^{3}J[H-13ax(A),H-13a]	10.55	10.5	10.5	10.45	10.4	10.4	10.4
^{3}J[H-13eq(A), H-13a]	4.2	4.2	4.2	4.15	4.2	4.3	4.2
^{3}J[H-1ax(A),H-2ax(A),]	16.85	16.6	16.2	16.05	15.9	15.9	15.7
+^{3}J[H-1ax(A),H-2eq(A) [e]	(11.4+5.45)	(11.2+5.4)	(10.8+5.4)	(10.95; 5.1) [f]	(10.6+5.3)	(10.5+5.4)	(10.3+5.4)
^{3}J[H-1eq(A),H-2eq(A)]	11	11.2	11.4	11.8	11.8	11.8	11.8
+^{3}J[H-1eq(A),H-2ax(A)] [e]	(5.5+5.5)	(5.6+5.6)	(5.7+5.7)	(5.9; 5.9) [f]	(5.9+5.9)	(5.9+5.9)	(6+5.8)

[a] 250 MHz spectra in dichloromethane-d_2. [b] 500 MHz spectrum in chloroform-d. [c] 250 MHz spectrum in chloroform-d. [d] 250 MHz spectra in tetrachloroethane-d_2. [e] The sum of coupling constants is given; approximate values for the individual coupling constants are given in parentheses. [f] Real values determined from the 500 MHz spectra.

In analogy with the bicyclic quinolizidines [5], the piperidine-piperazine ring system can exist in a *trans*-fused and two *cis*-fused forms depicted as **A**, **B** and **C** for the tetracyclic ketone **6**.

A major contribution of the *trans*-fused form was indicated by the observation of Bohlmann bands in the infrared spectra of acetal **5** (2760 and 2820 cm^{-1}) and ketone **6** (2740 and 2780 cm^{-1}). In the ^{1}H nmr spectrum (Table 1) of acetal **5**, exclusive *trans*-fusion was borne out by two diaxial couplings of the angular proton H-13a with the *trans*-disposed protons H-lax (^{3}J = 10.5 Hz) and H-13ax (^{3}J = 10.5 Hz). In the spectrum (Table 1) of ketone **6**, the angular proton H-13a was deshielded. An unchanged *trans*-diaxial relationship for protons H-13a and H-13ax, ruling out form **C**, was apparent from the coupling constant ^{3}J = 10.5 Hz. However, the low value ^{3}J = 8.2 Hz for protons H-13a and H-lax(**A**) suggested a contribution of form **B**, besides that of **A** shown by the infrared data. In this supposition proton H-lax(**A**) partly resides in the equatorial position H-leq(**B**). The existence of equilibrium **A** ⇌ **B** was confirmed by a temperature dependence study which revealed varying coupling constant values for those protons that are axial in **A** and equatorial in **B** (Table 2). For protons H-13a and H-lax(**A**), a continuous increase was observed from 7.9 Hz at 90° to 8.9 Hz at -40°. This result is consistent with a further shift from **B** to the more stable *trans*-fused form **A**. A parallel increase for ^{3}J[H-lax(**A**),H-2ax(**A**)] also appears from the data in Table 2. Although the low ratio $\Delta\nu/^2$J for protons H-2 in the 250 MHz spectra does not permit a first order analysis for proton H-lax(**A**), the increase is evident from the sum of coupling constants Σ^3J[H-lax(**A**),H-2] and from the line spacing in the second order pattern for proton H-lax(**A**).

The contribution of a *cis*-fused form was confirmed by comparing the coupling constant values ^{1}J[C-13a,H-13a] for **6** and **5** in the proton coupled ^{13}C nmr spectra (^{1}J = 133 and 130 Hz). A difference of about 10 Hz between ^{1}J[C,H] values for hydrogens α to nitrogen appears to be characteristic of their *gauche* and *anti* orientation relative to the nitrogen lone pair. Indeed, such a difference was observed not only for *cis*- and *trans*-fused quinolizidines [6], but also for the conformationally fixed protons H-6eq and H-6ax of 2-cyanopiperidine **1** (^{1}J = 139 and 131 Hz) [1]. In the ^{13}C nmr spectra of **5** and **6** (Table 3) no significant chemical shift variation was observed for C-13 in spite of two additional γ *gauche* interactions experienced in form **B** with C-2 and C-4. The upfield effect expected on the basis of a contribution of **B** to **6** probably is counterbalanced by the *anti* orientation of the nitrogen lone pair and C-13 in **B** [7].

Table 3

^{13}C NMR Data for **5** and **6** [a]

C-atom	5	6
1	27.5	27.1
2	32.5	36.8
3	105.5	204.8
4	60.9	63.4
6	53.6	53.0
13	47.1	46.8
13a	55.7	54.1
OCH_2CH_2O	64.4, 64.7	

[a] δ-values in ppm relative to TMS, measured at 62.9 MHz in deuteriochloroform. Assignments based on DEPT and heteronuclear decoupling experiments. Non-assigned δ-values for aromatic C-atoms: 108.7, 119.3, 121.9, 122.2, 133.8, 143.1, 148.3 for **5** and 108.8, 119.3, 122.3, 122.6, 133.8, 142.7, 147.8 for **6**.

Trans-quinolizidines are more stable than *cis*-quinolizidines by about 4 kcal/mol [5]. The occurrence of form **B** for ketone **6** can be attributed in part to decreased nonbonded interactions resulting from the presence of the 3-carbonyl group and the partially planar geometry of the

piperazine half-chair. A stereoelectronic factor involving the orientation of the nitrogen lone pair and the π-electron system of the imidazole ring can also be invoked. This orientation is parallel for **A** and **C** and perpendicular for **B**. Hence, repulsive interaction between nitrogen and the 1,3-related position C-6a may occur for **A** and **C**, as observed for a parallel arrangement of lone pair orbitals in fused 6/6 ring systems with an additional heteroatom located 1,3 relative to the bridgehead nitrogen atom [5].

The synthesis of the tetracyclic compounds **5** and **6** is only one example showing the versatility of synthons **1-4**. By suitable variations in synthetic design, poly-heterocyclic skeletons related to reserpine or the recently discovered imidazo-benzodiazepine anti-AIDS compounds [8] also should be accessible. The influence of additional aromatic rings, *e.g.* imidazole, indole or benzene, on the mode of ring fusion of the piperidine-piperazine ring system will be investigated further.

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded as solids in potassium bromide pellets on a Perkin Elmer 297 grating ir spectrophotometer. The ^1H and ^{13}C nmr spectra were recorded on Bruker WM 250 and AM 500 instruments. The spectra were run in deuteriochloroform with TMS as the internal reference. The values ^1J[C-13a,H-13a] for **5** and **6** were determined at 62.9 and 125 MHz, respectively. Mass spectra were obtained on a Kratos MS50 instrument and DS90 data system; the ion source temperature was 150-200° as required. Exact mass measurements were performed at a resolution of 10,000.

2-(2-Nitrophenyl)-7,7-(ethylenedioxy)-1,3,4,6,7,8,9,9a-octahydro-2*H*-pyrido[1,2-*a*]pyrazin-3-one **7a**.

Method A.

To a solution of lactam **4** (305 mg, 1.44 mmoles) in anhydrous tetrahydrofuran (30 ml) was added *o*-nitrofluorobenzene (0.3 ml, 2.84 mmoles), tetrabutylammonium bromide (90 mg, 0.28 mmole) and powdered potassium hydroxide (120 mg, 2.14 mmoles). The solution was stirred at 0° under nitrogen for ten hours. The reaction mixture then was partitioned between dichloromethane (100 ml) and water (10 ml). The aqueous layer was further extracted with dichloromethane (50 ml). The combined organic layers were evaporated *in vacuo* and the residue was chromatographed on a silica gel column using 5% methanol/ethyl acetate as eluent to yield 290 mg (61%) of **7a** as a yellow crystalline product, mp (ethyl acetate) 153-154°.

Method B.

To a solution of lactam **4** (160 mg, 0.75 mmole) in 15 ml of anhydrous tetrahydrofuran was added *o*-nitrofluorobenzene (0.1 ml, 0.95 mmole) and 1.5 ml of a 1*M* solution of tetrabutylammonium fluoride in tetrahydrofuran. This mixture was refluxed under nitrogen for four hours. Direct application of the mixture onto a silica gel column and elution with 5% methanol/ethyl acetate yielded 155 mg (62%) of **7a**; ir: ν 2820 and 2800 (Bohlmann bands), 1675 (C=O), 1532 and 1360 (NO_2) cm^{-1}; ^1H nmr: δ 1.6-1.95 (m, 4H, H-8 and H-9), 2.2 (d, J = 11 Hz, 1H, H-6ax), 2.68 (dddd, J = 10.5, 10, 4 and 3 Hz, 1H, H-9aax), 2.85 (dd, J = 11 and 2 Hz, 1H, H-6eq), 3.03 (d, J = 16.5 Hz, 1H, H-4ax), 3.52 (dd, J = 11 and 4 Hz, 1H, H-1eq), 3.63 (d, J = 16.5 Hz, 1H, H-4eq), 3.72 (dd, J = 11 and 10.5 Hz, 1H, H-1ax), 4.2 (m, 4H, OCH_2CH_2O), 7.33 (dd, J = 8.5 and 2 Hz, 1H, H-6'), 7.47 (td, J = 8.5 and 2 Hz, 1H, H-4'), 7.65 (td, J = 8.5 and 2 Hz, 1H, H-5'), 7.9 (dd, J = 8.5 and 2 Hz, 1H, H-3'); ms: (m/z) 333 (M^+), 316, 304, 303, 288, 234 (100%), 216, 200, 155, 122, 99.

High resolution ms. Calcd. for $C_{16}H_{19}N_3O_5$: m/z 333.1325. Found: m/z 333.1316.

Anal. Calcd. for $C_{16}H_{19}N_3O_5$: C, 57.65; H, 5.75; N, 12.61. Found: C, 57.47; H, 5.80; N, 12.58.

3,3-(Ethylenedioxy)-1,2,3,4,13,13a-hexahydro-6*H*-pyrido[1',2':4,5]-pyrazino[1,2-*a*]benzimidazole (**5**).

A solution of **7a** (241 mg, 0.72 mmole) in ethyl acetate-acetic acid (10:1, 20 ml) was hydrogenated over 400 mg of 10% palladium on activated carbon at room temperature under 40 psi during three hours. The catalyst then was filtered off and washed with methanol. The combined organic layers were evaporated *in vacuo*. A sample of the residue was separated by tlc on silica gel (solvent 10% methanol/ethyl acetate) to give **7b** [R_f = 0.35; ms: (m/z) 303 (M^+), 285, 204, 186, 99] and the less polar **5**. The mixture was dissolved in acetic acid (5 ml) and the solution was heated at reflux for five minutes. The solution was evaporated *in vacuo* and the residue was partitioned between aqueous potassium carbonate (5 ml) and dichloromethane (50 ml). The aqueous layer was further extracted with dichloromethane (50 ml). The combined dichloromethane layers were evaporated *in vacuo* and the residue was chromatographed on a silica gel column (5% methanol/ethyl acetate) to yield 152 mg (74%) of **5** as a crystalline product, mp (ethyl acetate) 185°; ir: ν 2820 and 2760 (Bohlmann bands) cm^{-1}; ms: (m/z) 285 (M^+), 240, 213, 212, 186 (100%), 171, 131, 117, 99.

High resolution ms. Calcd. for $C_{16}H_{19}N_3O_2$: m/z 285.1477. Found: m/z 285.1476.

Anal. Calcd. for $C_{16}H_{19}N_3O_2$: C, 67.35; H, 6.71; N, 14.73. Found: C, 67.41; H, 6.73; N, 14.62.

1,2,3,4,13,13a-Hexahydro-6*H*-pyrido[1',2':4,5]pyrazino[1,2-*a*]benzimidazol-3-one (**6**).

A solution of **5** (500 mg, 1.75 mmoles) in 25 ml of 6*N* aqueous hydrogen chloride was heated at reflux for two hours. After evaporation and alkaline extraction with dichloromethane, the crude product was chromatographed on a silica column (6% methanol/ethyl acetate) to yield 375 mg (89%) of **6** as a crystalline product, mp (methanol) 201.5°; ir: ν 2800 and 2740 (Bohlmann bands), 1725 (C=O) cm^{-1}; ms: (m/z) 241 (M^+), 213, 212, 184, 183, 144 (100%), 131, 117, 77.

High resolution ms. Calcd. for $C_{14}H_{15}N_3O$: m/z 241.1215. Found: m/z 241.1211.

Anal. Calcd. for $C_{14}H_{15}N_3O \cdot CH_3OH$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.75; H, 7.08; N, 15.45.

7-Benzyl-8-(2-nitrophenylaminomethyl)-1,4-dioxa-7-azaspiro[4.5]-decane (**8**).

To a solution of the crude primary amine **3** [2] (335 mg, 1.28 mmoles) in 10 ml of tetrahydrofuran was added *o*-nitrofluorobenzene (0.27 ml, 2.55 mmoles) and 2.5 ml of a 1*M* solution of tetrabutylammonium fluoride in tetrahydrofuran. This mixture

was stirred at room temperature under nitrogen for one hour. The solvent then was evaporated *in vacuo* and the residue was chromatographed on a silica gel column (5% ethyl acetate/chloroform) to yield 400 mg (82%) of **8** as yellow crystals, mp 134°; ir: ν 3350 (NH), 1520 and 1355 (NO_2) cm^{-1}; ^1H nmr: δ 1.83 (m, 4H, H-3, H-4), 2.33 (d, J = 12.5 Hz, 1H, H-6), 2.8 (d, J = 12.5 Hz, 1H, H-6), 2.85 (m, 1H, H-2), 3.42 (dd, J = 10 and 5 Hz, 2H, CH_2NH), 3.6 and 4.09 (AB q, J = 13 Hz, 2H, NCH_2Ph), 3.88 (m, 4H, OCH_2CH_2O), 6.62 (t, J = 8 Hz, 1H, H-4′), 6.75 (d, J = 8 Hz, 1H, H-6′), 7.15-7.5 (m, 5H, phenyl), 7.33 (t, J = 8 Hz, 1H, H-5′), 8.18 (dd, J = 8 and 3 Hz, 1H, H-3′), 8.45 (broad s, 1H, NH); ms: (m/z) 383 (M^+), 382 (M^+-H), 364 (382-H_2O), 336 (M^+-HNO_2).

Anal. Calcd. for $C_{21}H_{25}N_3O_4$: C, 65.78; H, 6.57; N, 10.96. Found: C, 65.64; H, 6.68; N, 10.84.

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