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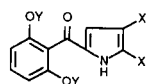
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Enol esters **3a** and **3b**, from cyclohexane-1,3-dione and pyrrole-2-carbonyl chloride and indole-2-carbonyl chloride, respectively, rearranged in the presence of triethylamine to the enamino acids **7** and **12**. In the presence of cyanide, **3b**, also underwent the expected rearrangement to **4b**, whereas only **7** was formed from **3a**. Treatment of **7** with mercuric acetate in hot acetic acid resulted in decarboxylation and aromatization to phenol **9**.

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Pyoluteorin **1a** is an antibiotic compound that has been isolated from, among other sources, *Pseudomonas* spp. that are symbiotic with planthoppers (*Sogatella furcifera*) and other insects [1]. Virtually all reported synthetic approaches to **1a** have utilized the reaction of 2,6-dimethoxybenzoyl chloride with an appropriate pyrrole [2,3,4]. Two procedures [3,4] have featured chlorination of **1c** to **1b**.

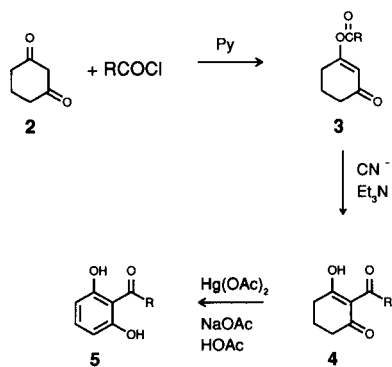
Figure 1

**1 a - d**

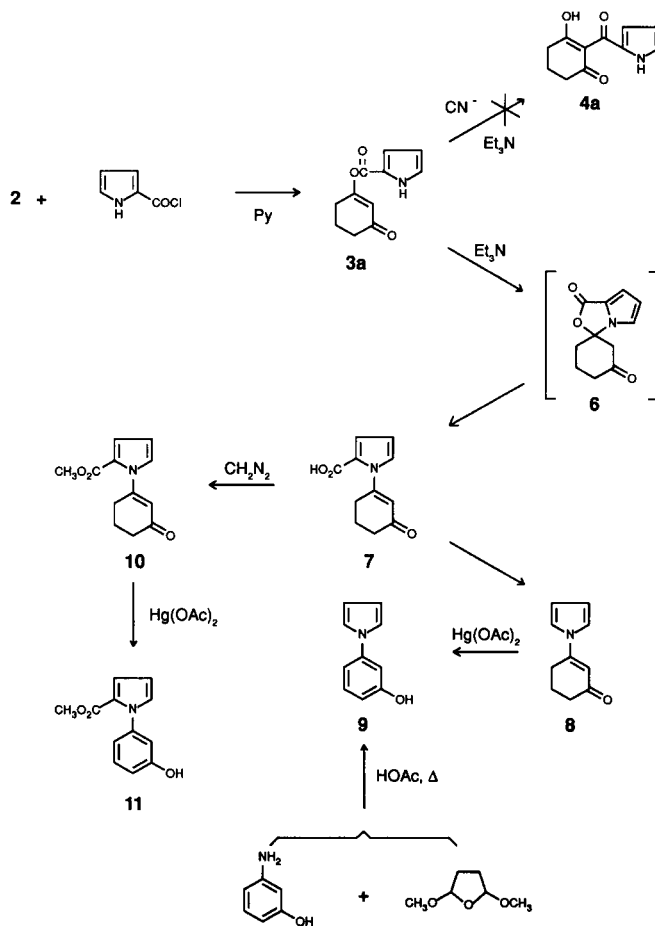
- a X = Cl, Y = H
b X = Cl, Y = CH₃CO
c X = H, Y = CH₃CO
d X = Y = H

We recently developed the sequence illustrated in Scheme 1 as a general synthesis of 2',6'-dihydroxyalkano-phenones **5** [5], the key step being the mercuric acetate oxidation of **4** to **5**. If a parallel sequence beginning with pyrrole-2-carbonyl chloride (Scheme 2) were successful, the oxidation product of **4a** would be **1d**, and a simple synthesis of **1a** would be at hand.

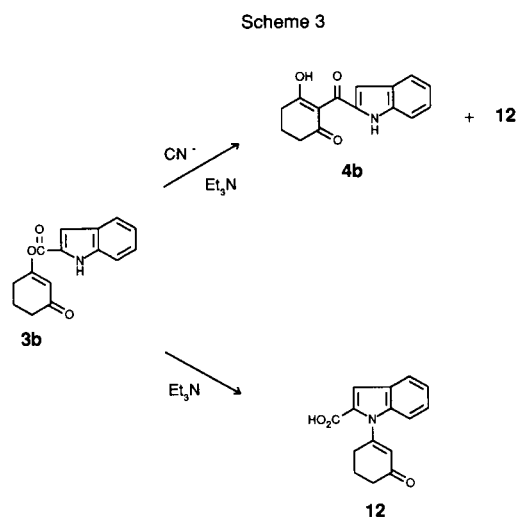
Scheme 1



Scheme 2



Pyrrole-2-carbonyl chloride reacted smoothly with cyclohexane-1,3-dione **2** to give the expected enol ester **3a**. Upon treatment with triethylamine and acetone cyanohydrin [6], **3a** underwent rearrangement at about the expected rate (\leq overnight at room temperature); the product, however, was not the anticipated **4a** but rather a



white solid extractable into aqueous sodium bicarbonate that was identified as the enamino carboxylic acid **7**. Acid **7** was readily decarboxylated (very brief warming in acetic acid containing either sodium acetate or hydrochloric acid) to **8**. Mercuric acetate aromatization of **8** (conveniently conducted with **7** because decarboxylation preceded oxidation) provided the phenol **9**, identical to a sample prepared from 3-aminophenol and 2,5-dimethoxytetrahydrofuran (Scheme 2). Decarboxylation could be circumvented by aromatizing methyl ester **10**; this reaction was slower than that with **7**, but gave a modest yield of ester **11**.

A straightforward explanation of the **3a** → **7** rearrangement would involve the intermediate spiro lactone **6** (Scheme 2). Consistent with this idea, we found that the **3a** → **7** rearrangement, unlike the general **3** → **4** conversion, does not require, and is uninfluenced by, cyanide (as acetone cyanohydrin); triethylamine alone is sufficient.

Indole-2-carbonyl chloride was similarly converted to enol ester **3b** (Scheme 3); when treated with triethylamine, **3b** rearranged to acid **12**, although this reaction was slower than the **3a** → **7** conversion. In contrast to the pyrrole derivative **3a**, **3b**, in the presence of acetone cyanohydrin, underwent the "normal" rearrangement and enol-dione **4b** was the major product; only a relatively small amount of acid **12** was formed. Acid **12** was less susceptible to decarboxylation than was **7**, remaining relatively unaffected by brief heating in the presence of either sodium acetate or hydrochloric acid.

EXPERIMENTAL

Mass spectra were obtained from a Finnigan model 4510 gas chromatograph-mass spectrometer equipped with a 30 m x 0.32 mm id DB-1 (J&W Scientific) fused silica column. Electron ionization spectra were collected at 70 eV and a source block tem-

perature of 150°. The ¹H-nmr spectra were obtained using a General Electric QE-300 nmr spectrometer. The ¹H chemical shift assignments were made by decoupling experiments and/or application of COSY. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Mention of a proprietary product does not imply endorsement by the U. S. Department of Agriculture.

1-(2-Cyclohexen-1-on-3-yl)pyrrole-2-carboxylic Acid **7**.

A suspension of pyrrole-2-carboxylic acid (1.11 g, 10 mmoles) in benzene (15 ml) was treated with oxalyl chloride (2.9 g, 23 mmoles) and *N,N*-dimethylformamide (10 μl). After standing overnight at room temperature, the solvent and excess oxalyl chloride were stripped *in vacuo* and replaced with dichloromethane (8 ml). This solution was stirred and treated dropwise with solution of cyclohexane-1,3-dione (1.15 g, 10 mmoles) in dichloromethane (8 ml) and pyridine (2 ml). After stirring at room temperature 1 hour, the mixture was partitioned between dilute hydrochloric acid and dichloromethane, and the organic phase was rinsed with water then with aqueous sodium bicarbonate. After drying over magnesium sulfate, the solution was filtered and concentrated to give 2.11 g of **3a** as a light tan oil that was used without purification (but *vide infra*). Acetonitrile (25 ml), triethylamine (2 ml) and acetone cyanohydrin (100 μl-subsequently found to be unnecessary, see text) were added and the solution was allowed to stand at room temperature. An aliquot was assayed by glc after five hours; *ca.* 50% conversion of **3a** to **7** had occurred at this point. After *ca.* 22 hours, the solution was concentrated *in vacuo* and the residue was partitioned between ethyl acetate and dilute hydrochloric acid. After rinsing with water, the ethyl acetate solution was extracted with saturated aqueous sodium bicarbonate. Acidification of this extract with dilute hydrochloric acid precipitated a white solid which was collected by filtration, rinsed with water, air dried (1.48 g, 72%), and recrystallized from toluene to give 1.18 g of **7**, mp 161.5-162°; ir (potassium bromide): ν 3550-2400 (br), 1675, 1627, 1536, 1446, 1423, 1373, 1348, 1293, 1127, 764, 744 cm⁻¹; ms: *m/z* (%) 205 (88, M⁺), 186 (8), 177 (9), 176 (15), 160 (25), 149 (57), 133 (27), 132 (12), 120 (12), 118 (20), 111 (100), 95 (30), 94 (66), 93 (70), 78 (17), 77 (14), 73 (13), 71 (13), 69 (12), 67 (46), 66 (31), 65 (33), 60 (10), 57 (20), 55 (45), 51 (23); ¹H-nmr (deuteriochloroform): δ 8.65 (br s, 1H, OH), 7.25 (m, 1H, H-5'), 6.94 (t, 1H, H-3'), 6.31 (t, 1H, H-4'), 6.06 (s, 1H, H-2), 2.74 (t, J = 5.7, 2H, H-4), 2.53 (t, J = 6.8, 2H, H-6), 2.19 (m, 2H, H-5).

Anal. Calcd. for C₁₁H₁₁NO₃: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.12; H, 5.42; N, 6.75.

In a separate experiment, a small amount of enol ester **3a** was prepared in order to obtain its mass and nmr spectra; ms: *m/z* (%) 205 (3.3, M⁺), 95 (8), 94 (100), 66 (20); ¹H-nmr (deuteriochloroform): **3a** δ 9.43 (br s, 1H, N-H), 7.0-7.15 (m, 2H, H-3' and 5'), 6.27-6.37 (m, 1H, H-4'), 6.08 (s, 1H, H-2), 2.65 (t, J = 5.7, 2H, H-4), 2.46 (t, J = 6.9, 2H, H-6), 2.05-2.17 (m, 2H, H-5). The material was not further characterized.

Methyl 1-(2-Cyclohexen-1-on-3-yl)pyrrole-2-carboxylate **10**.

A solution of **7** in tetrahydrofuran was treated with a slight excess of ethereal diazomethane to give methyl ester **10** as a white solid that was recrystallized from hexane, mp 64-65°; ms: *m/z* (%) 219 (46, M⁺), 186 (14), 176 (27), 163 (25), 160 (24), 159 (11), 148 (15), 132 (12), 125 (100), 118 (22), 117 (11), 104 (17), 95 (15), 94 (48), 93 (16), 67 (22), 66 (18), 65 (22), 55 (28); ¹H-nmr (deuteriochloroform): δ 7.09 (dd, J = 3.9 and 1.5, 1H, H-5'), 6.88 (t, J = 1.8,

1H, H-3'), 6.26 (t, J = 3, 1H, H-4'), 6.03 (s, 1H, H-2), 3.82 (s, 3H, OCH₃), 2.72 (t, J = 6, 2H, H-4), 2.52 (t, J = 6.3, 2H, H-6), 2.15-2.26 (m, 2H, H-5).

Anal. Calcd. for C₁₂H₁₃NO₃: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.77; H, 5.90; N, 6.30.

3-(1-Pyrrolyl)-2-cyclohexen-1-one **8**.

A solution of **7** (205 mg, 1 mmole) in acetic acid (4 ml) containing concentrated hydrochloric acid (50 μ l) was stirred and heated (80-95°) for 10 minutes. After cooling, the mixture was partitioned between water and ethyl acetate; the organic phase was washed successively with water, aqueous sodium bicarbonate, and brine, then was dried and concentrated to give 145 mg (90%) of **8** that consisted of a single component as judged by gas or thin layer chromatography. This material was combined with a sample similarly prepared (except that sodium acetate was substituted for the hydrochloric acid) and subjected to flash chromatography (6:4 hexane:ethyl acetate). Pure **8** was obtained as a clear oil that slowly crystallized, mp 62.5-63°. An analytical sample was recrystallized from hexane; ms: *m/z* (%) 161 (51, M⁺), 133 (37), 132 (34), 105 (8), 104 (5), 67 (100), 65 (9), 52 (5), 51 (10); ¹H-nmr (deuteriochloroform): δ 7.09 (t, J = 2.4, 2H, H-2' and 5'), 6.35 (t, J = 2.4, 2H, H-3' and 4'), 6.13 (s, 1H, H-2), 2.86 (t, J = 5.6, 2H, H-4), 2.46 (t, J = 6.4, 2H, H-6), 2.13-2.23 (m, 2H, H-5).

Anal. Calcd. for C₁₀H₁₁NO: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.50; H, 7.01; N, 8.67.

Decarboxylation and Aromatization of **7** to 3-(1-Pyrrolyl)phenol **9**.

A mixture of **7** (205 mg, 1 mmole), sodium acetate (320 mg, 3.9 mmoles), mercuric acetate (1.01 g, 3.17 mmoles), and acetic acid (5 ml) was stirred and heated to reflux. A clear tan solution resulted, followed by separation of a light tan solid. The latter quickly redissolved and a light brown solution resulted. After about 30 minutes (longer reaction times resulted in formation of higher molecular weight products and decreased yields of **9**) the mixture was cooled, 1 *N* hydrochloric acid (15 ml) was added, the mixture was stirred 10 minutes, ether (ca. 20 ml) was added, and after stirring a few more minutes, the entire mixture was filtered through Celite. The layers were separated, the aqueous phase was further extracted with ether-hexane (1:1), and the combined organic phases were washed twice with water, with saturated aqueous sodium bicarbonate, and then were extracted with 1*N* sodium hydroxide (10, 10, and 5 ml). After rinsing with ether, the alkaline phase was neutralized with 1*N* hydrochloric acid and extracted with ether. After rinsing with water, the ether solution was dried and concentrated to give a light tan oil (156 mg) that was purified by flash chromatography (8:2 hexane:ethyl acetate) to provide 142 mg (89%) of a slightly sticky white solid. Recrystallization from hexane plus ether gave 114 mg, mp 60-63° with a small amount of material remaining unmelted. This material was identical by gas chromatography and gas chromatography-mass spectrometry to the material synthesized from 3-aminophenol and 2,5-dimethoxytetrahydrofuran (*vide infra*); thin layer chromatography on silica gel (8:2 toluene:ethyl acetate) showed, in addition to the major spot with R_f 0.44, two minor components, R_f 0.33 and 0.29. Longer reaction times resulted in greater amounts of these latter two, presumably di- or polymeric, unknowns.

3-(1-Pyrrolyl)phenol **9** from 3-Aminophenol [7].

3-Aminophenol (0.55 g, 5 mmoles), 2,5-dimethoxytetrahydro-

furan (mixed isomers, 0.66 g, 5 mmoles), sodium acetate (0.51 g, 6.2 mmoles) and acetic acid (6 ml) were stirred together at room temperature 1.5 hours; no **9** was detectable by glc analysis. The solution was then heated to reflux; the color quickly darkened and a red-brown solid separated from solution. After 15 minutes the mixture was cooled, diluted with ether, and filtered. The filtrate was washed well with water and with aqueous sodium bicarbonate, then was extracted with 1 *N* sodium hydroxide. The alkaline extract was acidified with dilute hydrochloric acid and extracted with ether. The somewhat dark product was passed through a small pad of silica gel with 3:1 (v:v) hexane:ethyl acetate to give, after concentration, 0.18 g (23%) of **9** as a nearly colorless oil that crystallized, mp 62.5-64°. Similar results were obtained from another run that included no sodium acetate. An analytical sample was recrystallized from hexane, mp 63-64°; ms: *m/z* (%) 159 (100, M⁺), 131 (29), 130 (24), 103 (7), 79 (7), 77 (7), 65 (7), 63 (5), 51 (6); ¹H-nmr (deuteriochloroform): δ 7.26 (t, J = 8.1, 1H, H-5), 7.07 (t, J = 2.1, 2H, H-2' and 5'), 6.97 (dd, J = 7.8 and 2.1, 1H, H-4 or H-6), 6.87 (t, J = 2.1, 1H, H-2), 6.69 (dd, J = 2.4 and 8.1, 1H, H-6 or 4), 6.34 (t, J = 2.1, 2H, H-3' and 4').

Anal. Calcd. for C₁₀H₉NO: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.53; H, 5.57; N, 8.82.

Aromatization of Methyl Ester **10** to **11**.

A solution of **10** (224 mg, ca. 1 mmole), mercuric acetate (0.67 g, 2.1 mmoles) and sodium acetate (0.27 g, 3.2 mmoles) in acetic acid (5 ml) was stirred and refluxed 3.5 hours; glc analysis indicated 85% conversion to a material with a somewhat longer retention time. An additional portion (0.28 g) of mercuric acetate was added and refluxing was resumed for an additional 0.5 hour, then the mixture was cooled and worked up essentially as described for the conversion of **7** to **9**. Flash chromatography (8:2 hexane:ethyl acetate) and crystallization from hexane plus a little dichloromethane gave 91 mg of **11** as a white solid, mp 134-135°; ms: *m/z* (%) 217 (89, M⁺), 186 (100), 172 (7), 159 (8), 158 (8), 131 (5), 130 (8), 103 (7), 94 (11), 79 (5), 77 (8), 65 (11); ¹H-nmr (deuteriochloroform): δ 7.22 (t, J = 7.8, 1H, H-5), 7.10 (dd, J = 4.2 and 0.9, 1H, H-5'), 6.94 (t, J = 2.1, 1H, H-3'), 6.83 (d, J = 8.1, 1H, H-4 or H-6), ca. 6.75 (partially obscured doublet, 1H, H-6 or H-4), 6.74 (s, 1H, H-2), 6.27 (dd, J = 3.0 and 2.4, 1H, H-4'), 5.77 (br s, 1H, OH), 3.75 (s, 3H, OCH₃).

3-[(1*H*-Indol-2-yl)oxy]-2-cyclohexen-1-one **3b**.

A suspension of indole-2-carboxylic acid (4.02 g, 25 mmoles) in dichloromethane (20 ml) was stirred and a solution of oxalyl chloride (2.5 ml, 28.5 mmoles) in dichloromethane (20 ml) was added dropwise. A clear solution soon developed. After an hour at room temperature, the solvent and excess oxalyl chloride were stripped and replaced with dichloromethane (20 ml); this solution was stirred while a solution of cyclohexane-1,3-dione (2.80 g, 25 mmoles) and pyridine (3 ml) in dichloromethane (20 ml) was added dropwise. A white solid separated. After ca. 20 minutes, the mixture was transferred to a separatory funnel with additional dichloromethane (limited solubility of **3b**) and the solution was washed sequentially with cold, dilute hydrochloric acid, water, and aqueous sodium bicarbonate. After drying (magnesium sulfate) and filtration, the solution was concentrated to provide **3b** as a pale yellow solid (6.12 g, 96%). Most of this material was used without purification, but a small sample was recrystallized from acetonitrile to give a white solid, mp 152-154°; ms: *m/z* (%) 255 (11, M⁺), 145 (10), 144 (100), 116 (10), 89 (21); ¹H-nmr (deu-

teriochloroform): δ 9.18 (br s, 1H, NH), 7.20 (d, $J = 8.1$, 1H, H-4' or 7'), 7.46 (d, $J = 7.2$, 1H, H-7' or 4'), 7.38 (t, $J = 7.8$, 1H, H-5' or 6'), 7.36 (s, 1H, H-3'), 7.19 (t, $J = 7.8$, 1H, H-6' or 5'), 6.17 (s, 1H, H-2), 2.70 (t, $J = 6$, 2H, H-4), 2.49 (t, $J = 7.2$, 2H, H-6), 2.08-2.20 (m, 2H, H-5).

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.56; H, 5.13; N, 5.49. Found: C, 70.44; H, 5.14; N, 5.45.

1-(2-Cyclohexen-1-on-3-yl)indole-2-carboxylic Acid **12**.

A solution of **3b** (5.81 g, 22.8 mmoles) in acetonitrile (40 ml) and tetrahydrofuran (20 ml) was treated with triethylamine (5 ml) and allowed to stand at room temperature *ca.* 18 hours, then was partitioned between ether and aqueous sodium bicarbonate. The ether fraction, after drying and concentration, provided 0.94 g of unreacted **3b** (16%). Acidification of the sodium bicarbonate extracts precipitated a white solid; extraction with dichloromethane plus a little tetrahydrofuran (limited solubility in dichloromethane alone), washing with water, drying (magnesium sulfate), and evaporation of solvent gave 4.12 g (71%) of **12** as a pale solid; recrystallization from toluene plus a little ethyl acetate provided nearly white crystals, mp 198-201°; ms: m/z (%) 255 (40, M⁺), 210 (30), 183 (19), 168 (10), 161 (47), 144 (20), 143 (100), 115 (32), 95 (18), 89 (18), 67 (22), 57 (13), 55 (22); ¹H-nmr (deuteriochloroform): δ 7.74 (d, $J = 8.1$, 1H, H-4' or H-7'), 7.61 (s, 1H, H-3'), 7.39 (m, 2H, H-4' and H-5' or H-6' and H-7'), 7.22-7.27 (seven peak multiplet, 1H, H-5' or H-6'), 2.69 (t, $J = 5.7$, 2H, H-4), 2.63 (t, $J = 6.6$, 2H, H-6), 2.26 (pent, $J = 6.6$, 2H, H-5).

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.56; H, 5.13; N, 5.49. Found: C, 70.72; H, 5.17; N, 5.50.

3-Hydroxy-2-(1H-indol-2-oyl)-2-cyclohexen-1-one **4b**.

A solution of **3b** (250 mg), triethylamine (250 μ l), and acetone cyanohydrin (50 μ l) in acetonitrile (2.5 ml) was stirred 5 hours at room temperature, then was partitioned between ethyl acetate and dilute hydrochloric acid. The organic phase was then extracted with aqueous sodium bicarbonate (both **12** and **4b** were

extracted into the bicarbonate solution); neutralization with dilute hydrochloric acid and extraction with ethyl acetate gave, after drying and concentration, *ca.* 250 mg of crude product that was flash chromatographed with 8:2 and 6:4 hexane:ethyl acetate, and finally with 100% ethyl acetate. The intermediate mixture eluted **4b** (113 mg, 45%) which was recrystallized from hexane-ether, mp 96-97°; ms: m/z (%) 255 (100, M⁺), 254 (32), 238 (8), 227 (6), 199 (5), 144 (33), 143 (27), 130 (16), 128 (7), 118 (7), 117 (35), 116 (12), 115 (14), 90 (6), 89 (30); ¹H-nmr (deuteriochloroform): δ 19.33 (s, 1H, enolic OH), 12.55 (br s, 1H, NH), 7.74 (br s, 1H, H-3'), 7.70 (d, $J = 8.1$, 1H, H-4' or 7'), 7.47 (d, $J = 8.1$, 1H, H-7' or 4'), 7.35 (t, $J = 7.8$, 1H, H-6' or 5'), 7.13 (t, $J = 7.5$, 1H, H-5' or 6'), 2.77 (m, 4H, H-4 and H-6), 2.05 (m, 2H, H-5).

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.56; H, 5.13; N, 5.49. Found: C, 70.70; H, 5.00; N, 5.60.

Elution with 100% ethyl acetate then provided 38 mg (15%) of the carboxylic acid **12**.

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