Summary

Heating of 1-oxides of 2-(N-acetoacetyl)pyridinesulfonamide, 4-methyl-2-(N-acetoacetyl)pyridinesulfonamide, 4-(N-acetoacetyl)pyridinesulfonamide, and 4-(N-acetoacetyl)-quinolinesulfonamide each in 10% sodium hydroxide at 90~95° causes rearrangement reaction with liberation of sulfur dioxide to form respectively, 2-pyridineacetic acid, 1-oxides of 4-methyl-2-pyridineacetic acid, 4-pyridineacetic acid, and 4-quiolineacetic acid. These substances were confirmed by their respective decarboxylation and derivation to 2-picoline 1-oxide, 2,4-lutidine 1-oxide, 4-picoline 1-oxide, and lepidine 1-oxide.

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11. **Shigehiko Sugasawa and Kitaro Mizukami** : Studies on the Synthesis of Dibenzoindolizine Derivatives. V. Synthesis of 4′,5′ : 4″,5″-Tetramethoxy-3,4-dihydro-(2′,1′ : 1,2 ; 2″,1″ : 5,6-dibenzoindolizine).**

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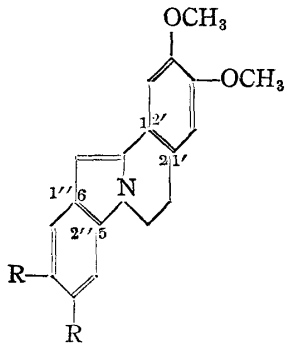
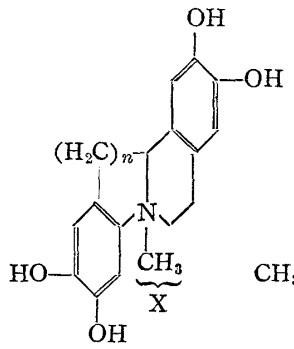
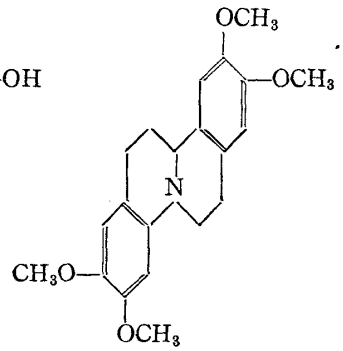
This paper describes the synthesis of dibenzoindolizine derivative (I) mentioned in the title, related to dehydrolaudanosoline salt (II), furnishing the synthetic support for the proposed structure (II) of the latter compound. This compound was first placed on record by Robinson and Sugasawa[1] as an unexpected dehydrogenation product of laudanoline salt, to which they ascribed the formula (II) chiefly based upon the experimental data in Hofmann and Emde degradations. Indirect synthetic support was, however, offered, when Sugasawa and Kakemi[2] succeeded in synthesizing the homo compound (III) related to (II), which was proved to be identical with the compound derived from dehydrohomolaudanosoline salt (IV), obtained by applying Robinson and Sugasawa's dehydrogenation method upon homolaudanosoline (V) salt.[3]



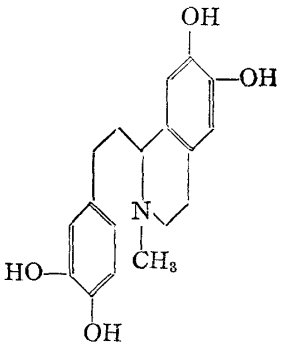
(I) R=OCH_3, (VI) R=H



(II) n=1, (IV) n=2



(III)



(V)

It may be considered rather unusual that the (II)-type alkaloid, the *in vitro*-formation of which proceeds with such an ease, has not yet been located in the vegetable kingdom. Though Folkers[4] once supposed this kind of skeleton for some of the erythrina alkaloids,

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** Part IV : Sugasawa, Kodama : Proc. Imp. Acad. (Tokyo), **18**, 565(1942); J. Pharm. Soc. Japan, **63**, 54(1943).

1) J. Chem. Soc., **1932**, 789; cf. also Schöpf, Thielfelder : Ann., **497**, 22(1932); Harley-Mason : J. Chem. Soc., **1953**, 1465.
2) Ber., **71**, 1860(1938).
3) Sugasawa, Yoshikawa : J. Chem. Soc., **1933**, 1583.
4) J. Am. Chem. Soc., **73**, 589(1951).

his view was later rejected by Prelog, *et al.*[5]

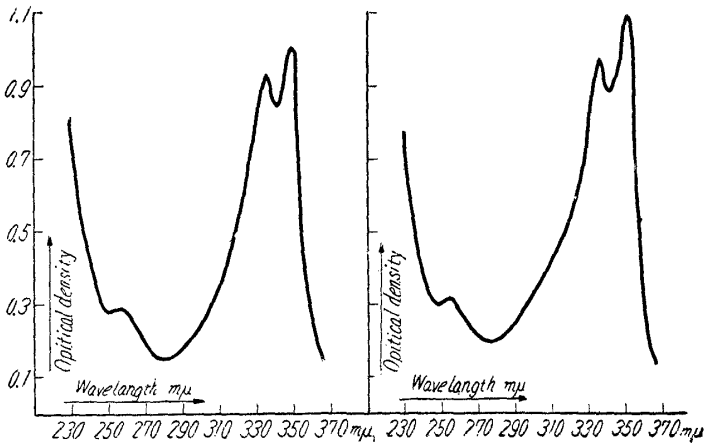
Ewig, *et al.*[6] were the first to find this type of natural product, when they made known that the new iodine-containing phenolic base, isolated from the bark of *Cryptocarya bowiei*, native to Qeensland, is a trimethyl ether derivative of (II, X=I)(position of one free phenolic hydroxyl group is not located) ; the methyl ether of this alkaloid being identified with the authentic specimen prepared from laudanosoline according to Robinson and Sugasawa.

Thus we decided to prove the structure of (II), from which (I) is derivable, by direct synthesis. First, the synthesis of the simpler analog (VI) was explored. For that purpose homoveratryl bromide was condensed with aniline, giving homoveratrylaniline (VII), which was chloroacetylated to furnish (VIII). The latter was fused with aluminum chloride under Stollé conditions,[7] when N-(β-3,4-dihydroxyphenyl)-ethyloxindole (IX) resulted, giving the compound (X) on being methylated with dimethyl sulfate and alkali. (X) was also produced by the condensation of the potassio derivative of oxindole with homoveratryl bromide in boiling xylene in the presence of copper, thus proving the structure of (X) beyond doubt. The latter was then cyclized with phosphoryl chloride, yielding directly (VI) rather than the quaternary salt, which responds to the Ehrlich reagent developing a pure blue coloration.

However, when this method was extended to the synthesis of (I) it failed at the oxindole stage. When chloroacetoanilide (XII), a nicely crystalline solid of m.p. 97~99° was heated with aluminum chloride, there resulted a brown resinous mass, from which no definite substance was isolated, either through methylation by means of dimethyl sulfate or phenyltrimethylammonium hydroxide, or acetylation. Tetrahydroxyoxindole (XIII) might have once been formed, which is, however, too susceptible to air oxidation to be worked up further. The alternative route proved successful.

The compound (XII) was therefore cyclized first to form N-3′,4′-dimethoxyphenyl-1-chloromethyl-6,7-dimethoxy-3,4-dihydroisoquinolinium salt (XIV), the structure of which was proved by converting this into the corresponding 1-methyl-1,2,3,4-tetrahydro derivative (XV) by gentle reduction with lithium aluminum hydride. When the compound (XIV), as the chloride, was fused with aluminum chloride, there was probably produced the phenolic base (XVI), which gave (I) on being treated with dimethyl sulfate and alkali. The identification of the latter was made by direct comparison with the specimen derived.

Compound (I) by Robinson and Sugasawa



Compound (I) by the present synthesis

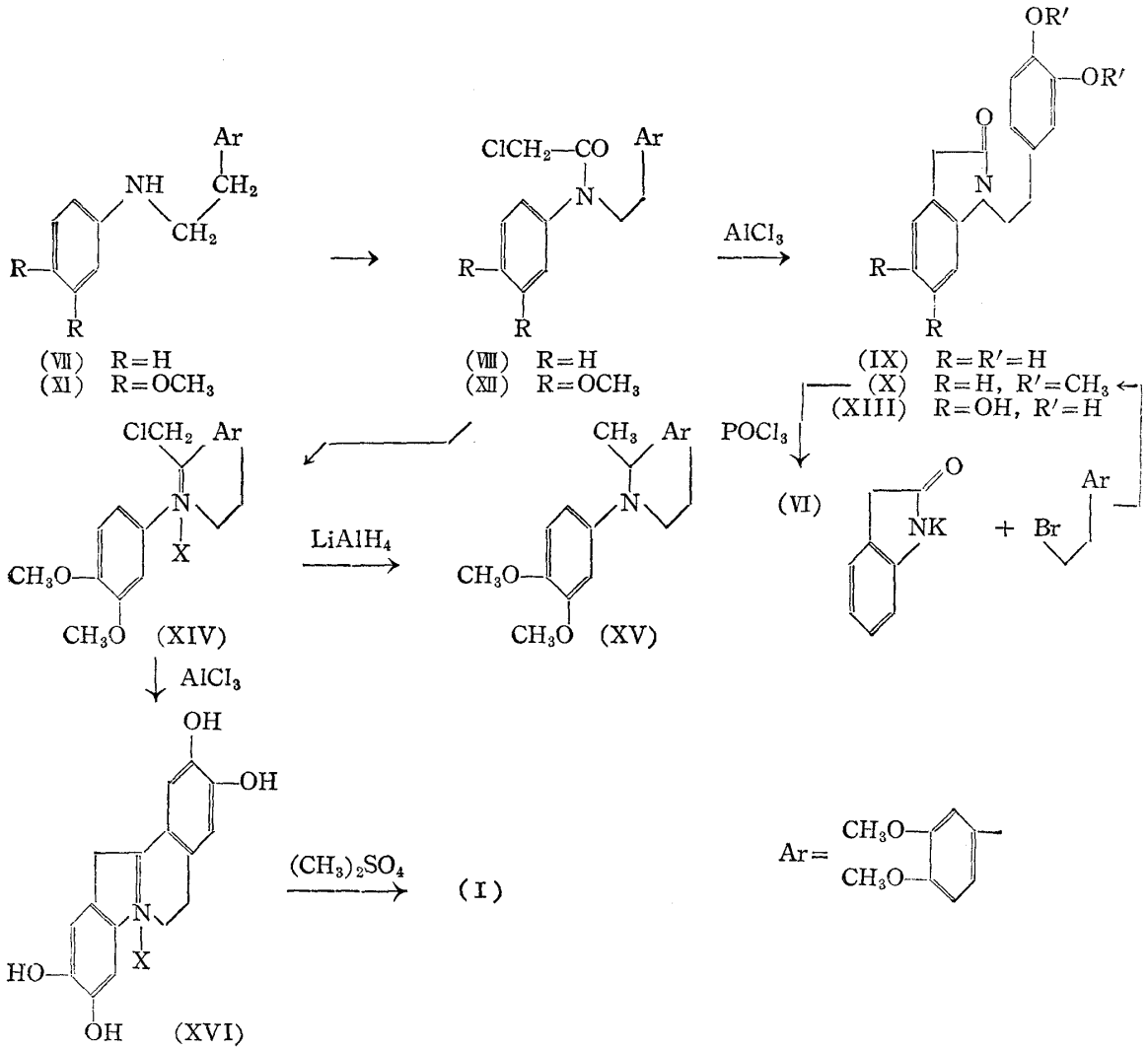
Fig. 1

5) Helv. Chim. Acta, **34**, 1601(1951).
6) Nature, **169**, 618(1952).
7) J. prakt. Chem., **128**, 1(1930).

from dehydrolaudanoline salt (II) prepared according to Robinson and Sugasawa. Both substances gave the same Ehrlich test (pure royal blue) and their ultraviolet spectra are also identical, as can be seen from Fig. 1. Ultraviolet spectra of related compounds are shown in Table I.

Table I.

Compound	λ_{max}	Ehrlich test
α-Phenylindole	312 mμ (in EtOH)	Bluish purple
Dihydrodibenzoindolizine	320 mμ (in $CHCl_3$)	Faint green
Compound (VI)	329 mμ (in EtOH)	Blue
Compound (I) by the present synthesis	335, 350 mμ (in EtOH)	Pure blue
Compound (I) by Robinson and Sugasawa	335, 350 mμ (in EtOH)	Pure blue



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Experimental

N-Homoveratrylaniline (VII)—Homoveratryl bromide (7 g.) and aniline (18 g., in excess) were heated on a steam bath, giving homogeneous liquid, from which crystalline solid (aniline•HBr) began to separate after about 30 mins. After being heated for 3 hrs. altogether, the whole was basified and steam distilled, recovering the unreacted aniline. The residual oil was taken up in ether and worked

up as usual. (Ⅶ) was obtained as viscous oil of b.$p_{0.05}$ 173~174°,[8] having characteristic basic odor. Yield, 6.5 g.

Picrate: Yellow needles from EtOH, m.p. 168~169°. *Anal.* Calcd. for $C_{18}H_{19}O_2N \cdot C_6H_3O_7N_3$: C, 54.2; H, 4.5; N, 11.5. Found: C, 54.0; H, 4.2; N, 11.2.

N-Homoveratryl Chloroacetanilide (VIII)—The amine (Ⅶ, 6.5 g.) in 25 cc. of pure acetone was added with pure pyridine (5 g.) and reacted with chloroacetyl chloride (5 g. in pure acetone) with stirring and cooling. After standing at room temp. for 2 hrs., the mixture was poured onto crushed ice, acidified with a little HCl, separating yellowish oily substance, which gradually solidified. This was collected on a filter, washed, and dried, giving 7.8 g. of a substance of m.p. 68~71°(sint. 65°), pure enough for the next stage. The pure substance, colorless prisms, m.p. 91~92°, was obtained from benzene–ligroine, after being purified through an alumina column. *Anal.* Calcd. for $C_{18}H_{20}O_3NCl$: N, 4.2; Cl, 10.6. Found: N, 4.2; Cl, 10.15.

N-(β-3,4-Dihydroxyphenyl)-ethyloxindole (IX)—An intimate mixture of the compound (Ⅷ, 6 g.) and powdered $AlCl_3$ (10 g.) was heated in an oil bath. At 130~140°(oil-bath temp.) evolution of HCl gas became rampant, after 30 mins. the temp. was raised to 150~160°, and kept there for additional 5 hrs. On cooling, the product was decomposed with crushed ice and acidified with HCl, yielding a dark resinous substance, weighing ca. 7 g. when air dried, soluble in EtOH, AcOEt, and dil. aq. NaOH, giving a reddish solution. The whole was dissolved in hot benzene and filtered from some resinous residue. On cooling, there separated 2.5 g. of a crystalline solid of m.p. 135~136°, which was raised to 143~145°(colorless plates) by further purification from the same solvent. The phenolic nature of this substance was disclosed by $FeCl_3$ color test (green in EtOH) and also by its being readily soluble in dil. NaOH solution.[9] *Anal.* Calcd. for $C_{16}H_{15}O_3N$: C, 71.4; H, 5.6; N, 5.2. Found: C, 71.3; H, 5.7; N, 5.5.

N-Homoveratryloxindole (X)—The compound (Ⅸ, 1.3 g.) was suspended in Me_2SO_4 (7.5 g., excess) and to this mixture was now added 20% KOH solution drop by drop in H_2 atmosphere, with stirring. After all the solid passed into solution, giving a faint rose-colored solution, there separated a reddish brown oil, while the aqueous layer became nearly colorless. After being stirred for ca. 3 hrs., the oil was taken up in benzene, washed, dried, and evaporated, leaving an orange yellow syrup, which solidified on being triturated with ether. Hexane was added to this and filtered; yield, 0.8 g. Purified from hexane, forming a solid of indistinct crystalline form of m.p. 98~100°. *Anal.* Calcd. for $C_{18}H_{19}O_3N$: C, 72.7; H, 6.4; N, 4.7. Found: C, 72.5; H, 6.4; N, 4.6.

Since the cyclization to the aromatic ring in the above method was activated through CH_3O group (7-membered ring will be formed) or the double cyclization to form dibenzoindolizine derivative deemed not to be excluded, the compound (X) was prepared via an alternate route. Oxindole (1.33 g.) and K dust (0.4 g.) were heated in boiling xylene, separating potassio-oxindole (the formation of N-, O- and/or C-potassio derivative may also be possible) as white powdery solid. To this, homoveratryl bromide (2.4 g.) and Cu powder (0.1 g.) were added and the whole was refluxed for 5 hrs. The solvent was evaporated from the filtered reddish solution leaving a dark red viscous oil, which was dissolved in benzene and purified through an Al_2O_3 column. Benzene was evaporated from the filtrate and the residue was dissolved in ligroine added with a little benzene and kept in an ice chest. After about 2 weeks, there separated colorless solid, which was purified from hexane, forming a crystalline solid of m.p. 99~101° in a small yield. This was proved to be one and the same with the above-mentioned compound of m.p. 98~100°, making the structure of (X) beyond doubt.

4′,5′-Dimethoxy-3,4-dihydro-(2′,1′:1,2;2″,1″:5,6-dibenzoindolizine) (VI)—A mixture of the foregoing oxindole (0.7 g.), $POCl_3$ (3 cc.), and toluene (5 cc.) was refluxed for 2 hrs., giving a dark brown solution. Toluene and excess of $POCl_3$ were now removed *in vacuo*, the residue was treated with ice-water, and extracted with benzene. From the benzene solution some of the solvent was distilled off and the residual solution was filtered through an Al_2O_3 layer, giving yellowish solution having a faint fluorescence. On evaporating the solvent, there was obtained a crystalline solid, which was purified from benzene–hexane, forming a faint yellow amorphous solid of m.p. 147°. The positive Ehrlich test (pure blue) is proof of this being the indole derivative. *Anal.* Calcd. for $C_{18}H_{17}O_2N$: C, 77.4; H, 6.1; N, 5.0. Found: C, 77.3; H, 6.4; N, 5.0.

4-Homoveratrylaminoveratrole (XI)—Homoveratryl bromide (13.5 g.) and aminoveratrole (27 g., excess) were heated at 110~120°(oil bath temp.) for about 5 hrs. in H_2 atmosphere, giving a purple colored semisolid mass. The whole was added to 10% HCl and extracted with benzene to remove non-basic substance. The aqueous layer was basified and the separated oil was collected in benzene, washed, dried, and evaporated. The residue was then submitted to vacuum distillation, recovering

8) This compound is already mentioned in the literature by Wiesner, who gave b.$p_{0.1}$ 175~180°(C.A., 44, 9456(1950)).

9) cf. Wiesner (*loc. cit.*). According to this abstract he obtained dimethyl ether of (Ⅸ), therefore (X), directly by fusing (Ⅷ) with $AlCl_3$, which sounds rather extraordinary.

unreacted aminoveratrole (17.5 g.) coming over at 135~150°(10 mm. Hg). The product distilled at 240~245°(0.08 mm. Hg), forming a viscous oil; yield, 11 g. This solidified to a white solid on being triturated with ether and was purified from hexane-ligroine, forming prisms of m.p. 56~57°(with previous sintering), which gradually colors orange-purple in the air and satisfactory analysis could not be obtained. Its structure was, however, proved by identifying with the specimen prepared by $LiAlH_4$-reduction of homoveratroyl-3,4-dimethoxyanilide in poor yield.

4-(N-Chloroaceto-N-homoveratrylamino)-veratrole (XII)—This was prepared exactly in the same way as (Ⅷ). Crude (XII) forms a solid of m.p. 97~99°; yield 11 g. from 10 g. of (XI). Colorless prisms, m.p. 104~105°, from hexane-benzene. *Anal.* Calcd. for $C_{20}H_{24}O_5NCl$: C, 60.9; H, 6.1; N, 3.8. Found : C, 60.4; H, 5.7; N, 3.5.

N-3′,4′-Dimethoxyphenyl-1-chloromethyl-6,7-dimethoxy-3,4-dihydroisoquinolinium Iodide (XIV)—A mixture of the above-mentioned amide (1.5 g.), $POCl_3$ (4.5 cc.), and toluene (10 cc.) was gently refluxed, giving a dark brown solution. After 1.5 hrs.' heating, the solvent and $POCl_3$ were removed *in vacuo*, and the residue was decomposed with ice water, separating a little dark tarry substance. It was boiled with carbon and filtered through a wet filter, furnishing clear orange solution, from which the quaternary iodide separated on adding KI, which was collected on a filter, washed, and dried. Yield, 1.6 g. of m.p. 173~175°(with previous sintering). Since its purification did not appear to be advantageous, this was directly reduced with $LiAlH_4$ to yield the compound (XV) for the purpose of characterization.

N-3′,4′-Dimethoxyphenyl-1-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (XV)—$LiAlH_4$ (0.1 g.), suspended in 100 cc. of abs. ether, was added with the foregoing iodide (1.32 g.) in small portions with chilling (ice and NaCl) and stirring. After stirring for 1 hr., the mixture was added with hyd. ether to decompose unreacted $LiAlH_4$ and then acidified with dil. H_2SO_4. The aq. acid layer was now basified with dil. NaOH solution and the base was collected in ether-AcOEt mixture, washed, dried, and evaporated, leaving a viscous oil (0.6 g.), which solidified on being triturated with ether. Colorless scales of m.p. 109~110° from EtOH. *Anal.* Calcd. for $C_{20}H_{25}O_4N$: C, 69.5; H, 7.6; N, 4.0. Found : C, 70.0; H, 7.3; N, 4.0.

4′,5′:4″,5″-Tetrahydroxy-3,4-dihydro-8,9-dehydro-(2′,1′:1,2;2″,1″:5,6-dibenzoindolizinium) Salt (XVI)—The iodide (XIV) was converted into the corresponding chloride by the usual method. The latter (1.1 g., crude substance of m.p. 101~103°) was intimately mixed with powdered $AlCl_3$ (10 g.) and the whole was heated in an oil bath. At about 120°(oil bath temp.) the evolution of HCl became vigorous; the temperature was raised to 160~170°, kept there for 2 hrs.(HCl evolution becoming gentle), and at last heated at 190~200° for additional 2 hrs. On cooling, the content was powdered with a glass rod and added into crushed ice-HCl in small portions, separating greenish brown flocculent solid. This was collected on a filter and washed with a little cold water (XVI : X=Cl). This gives a positive $FeCl_3$-color test (bluish purple) and dissolves in dil. NaOH solution. Purification appeared difficult, and so it was methylated directly.

4′,5′:4″,5″-Tetramethoxy-3,4-dihydro-(2′,1′:1,2;2″,1″:5,6-dibenzoindolizine) (I)—The foregoing amorphous solid (wet and weight not certain) was suspended in 5 cc. of water and added with an excess of Me_2SO_4 (ca. 10 cc.). To this mixture was now added 15 cc. of 30% KOH solution, drop by drop in H_2 atmosphere, with stirring and cooling, giving a bluish purple solution, from which flocculent solid began to separate after some time. Additional 30 cc. of 30% KOH solution was introduced and the whole was stirred for 3 hrs. at room temperature. After neutralization with dil. H_2SO_4, the reaction mixture was extracted with benzene-AcOEt, washed, dried, and evaporated. The residue was dissolved in benzene and purified through an Al_2O_3 column, furnishing yellow fluorescent solution, from which a faint yellow solid was obtained on evaporating the solvent. Purified from AcOEt, it formed faint yellow plates of m.p. 199~200°, identical in every respect with a specimen prepared from laudanosoline according to Robinson and Sugasawa, by mixed melting point test and ultraviolet absorption curves.

Summary

Hofmann and Emde degradations had revealed that dehydrolaudanosoline salt, the dehydrogenation product of laudanosoline under specified conditions, is a derivative of the then unknown dibenzoindolizinium salt (II).[1] The correctness of this view is now fully supported by the present synthesis of 4′,5′ : 4″,5″-tetramethoxy-3,4-dihydro-(2′,1′: 1,2; 2″,1″ : 5,6-dibenzoindolizine)(I) which is readily derivable also from dehydrolaudanolinium salt (II). Both these compounds were found to be one and the same by direct comparison.

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