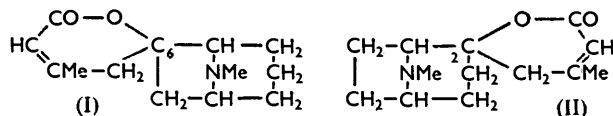


123. *An Alkaloid of Dioscorea hispida, Dennstedt. Part V.\**  
*The Degradation of Dioscorinol.*

By J. B. JONES and A. R. PINDER.

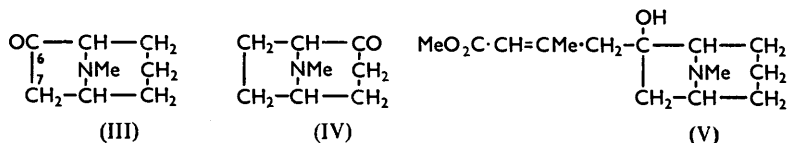
Evidence is presented which suggests that the  $C_8H_{13}ON$  keto-base obtained by degradation of dioscorinol is tropan-2-one (IV), and not tropan-6-one (III) as proposed by other workers. Dioscorine is therefore formulated as (II), and more exactly as (X).

PREVIOUS work<sup>1</sup> has shown that in dioscorine, an alkaloid occurring in the tubers of *Dioscorea hispida*, Dennst., an  $\alpha\beta$ -unsaturated six-membered lactone ring is linked in a *spiro*-manner with a tropane system, in the 2- or 6-position of the latter. Two possible constitutions, (I) and (II), were advanced for the alkaloid, the former being preferred on



the grounds that it is derived from tropan-6-ol, from which several familiar alkaloids are derived.

Strong evidence favouring structure (I) has been described recently by Büchi, Ayer, and White,<sup>2</sup> who have degraded dioscorine by successive reduction with lithium aluminium hydride, ozonolysis, and alkaline decomposition. The final product was an optically active ketonic base  $C_8H_{13}ON$ , which on reduction by desulphurisation of its ethylene thioketal, afforded tropane. The compound is therefore a tropanone, and must be formulated as either tropan-6-one (III) or tropan-2-one (IV). For two main reasons, structure (III) was preferred. First, the  $C_8H_{13}ON$  base showed a carbonyl infrared band at  $1730\text{ cm.}^{-1}$ , which these authors considered in better agreement with the location of the carbonyl group in a five-membered ring, as in (III), than with its location in a six-membered ring, as in (IV). Secondly, the tropanone methiodide underwent Hofmann degradation with remarkable facility (sodium hydrogen carbonate at  $30^\circ$ ), which gave strong support to structure (III) since here a methylene group  $\beta$  to the nitrogen atom is activated by a neighbouring carbonyl group. No such activation is possible with (IV).



Whilst the chemical evidence for the structure of the ketonic base appeared convincing, it seemed to us that the position of the carbonyl band at  $1730\text{ cm.}^{-1}$  was, in fact, more in agreement with the presence of the group in a six-membered ring, if the assumption is made that ketonic carbonyl frequencies in heterocyclic nitrogen systems are analogous to those in carbocyclic systems.<sup>3</sup> Nevertheless, we contemplated a synthesis of compound

\* Part IV, *Tetrahedron*, 1957, **1**, 301. For a preliminary account of the present results see *Chem. and Ind.*, 1958, 1000.

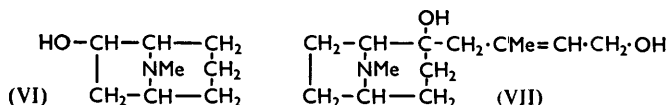
<sup>1</sup> Pinder, *Chem. and Ind.*, 1957, 1240; *Tetrahedron*, 1957, **1**, 301.

<sup>2</sup> Büchi, Ayer, and White, XVIth Internat. Congress Pure & Applied Chem., Paris, July, 1957.

<sup>3</sup> Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 1954, chapter 9; Jones and Sandorfy, in "Technique of Organic Chemistry," ed. Weissberger, Interscience, New York, 1956, pp. 443 *et seq.*

(I) by a Reformatsky condensation between the ketone (III) and methyl  $\gamma$ -bromosuccinate, to give the hydroxy-ester (V), which on hydrolysis and lactonisation would afford the base (I).

A convenient route to tropan-6-one (III) started with 6-hydroxytropinone, available by a Robinson tropinone-type synthesis from maleic dialdehyde, methylamine, and acetone-dicarboxylic acid.<sup>4</sup> We have been able to improve this preparation slightly. Wolff-Kishner reduction of the hydroxy-ketone afforded tropan-6-ol (VI), m. p. 65°. A compound formulated as tropan-6 $\beta$ -ol, m. p. 91°, has been described by Kovács and Banfi,<sup>5</sup> who obtained it by successive treatment of tropane-3 $\alpha$ :6 $\beta$ -diol with thionyl chloride and a base, followed by hydrogenation. We have not been able to compare these two products directly, but the infrared spectra of our compound and of 6 $\beta$ -hydroxytropinone in the 3400—3650  $\text{cm}^{-1}$  region are very similar, and we conclude that our product is tropan-6 $\beta$ -ol, the configuration of the 6-hydroxyl group in 6 $\beta$ -hydroxytropinone having been established as  $\beta$  by chemical methods.<sup>6</sup> Kovács and Banfi's product is presumably the 6 $\alpha$ -isomer, epimerisation having occurred.



Oxidation of tropan-6 $\beta$ -ol by chromic acid gave, in 25% yield, tropan-6-one (III), together with a considerable amount of unchanged alcohol. Our failure to obtain the ketonic base in good yield, even when more than the theoretical amount of chromic acid was used, is paralleled by the observations that the alkaloid valeroidine<sup>7</sup> (3 $\alpha$ -isovaleryloxy-tropan-6 $\beta$ -ol) and 6 $\beta$ -hydroxytropinone<sup>8</sup> are not oxidised to the corresponding ketones by chromic acid or by other methods. Further comment on this behaviour, which is probably explained by interaction between the hydroxyl group and the nitrogen atom, is reserved until the completion of certain model experiments.

Tropan-6-one is a colourless, strongly basic syrup, and in harmony with its structure as an  $\alpha$ -amino-ketone is rapidly oxidised in air and reduces ammoniacal silver nitrate and Fehling's solution readily. It shows strong infrared carbonyl bands at 1750 (in  $\text{CCl}_4$ ) and 1752  $\text{cm}^{-1}$  (liquid film), unexpectedly high values compared with that of 1730  $\text{cm}^{-1}$  for the  $\text{C}_8\text{H}_{13}\text{ON}$  ketone obtained by Büchi *et al.* (see above). Its methiodide shows a similar band at 1778  $\text{cm}^{-1}$  (Nujol mull).

It appeared from these figures that the degradative ketonic base was not tropan-6-one, so the projected synthesis was abandoned, and the degradation described by Büchi *et al.*<sup>2</sup> was repeated.

Dioscorinol was obtained as described previously<sup>1</sup> by lithium aluminium hydride reduction of dioscorine, purified *via* its picrate. The American workers have apparently obtained this diol as a crystalline compound, m. p. 101°, but in spite of many repetitions we have obtained it only as a thick syrup. Ozonolysis of dioscorinol in acetic acid afforded a saturated, basic keto-alcohol  $\text{C}_{11}\text{H}_{19}\text{O}_3\text{N}$ , showing infrared bands (in  $\text{CCl}_4$ ) at 1718 (saturated, acyclic C=O) and 3535  $\text{cm}^{-1}$  (broad, OH), with strong intramolecular hydrogen-bonding between the two functional groups. It has not so far been possible to prepare a crystalline derivative of this compound: its picrate and methiodide were oils. With

<sup>4</sup> Nedenskov and Clauson-Kaas, *Acta Chem. Scand.*, 1954, **8**, 1295; see also Sheehan and Bloom, *J. Amer. Chem. Soc.*, 1952, **74**, 3825; Stoll, Becker, and Jucker, *Helv. Chim. Acta*, 1952, **35**, 1263; Sandoz, Ltd., B.P. 737,419/1955; Schöpf and Arnold, *Annalen*, 1947, **558**, 109.

<sup>5</sup> Quoted by Fodor, Tóth, Koczor, and Vincze, *Chem. and Ind.*, 1955, 1260.

<sup>6</sup> Fodor and Kovács, *J.*, 1953, 2341; Fodor, Tóth, and Vincze, *Helv. Chim. Acta*, 1954, **37**, 907; Fodor, *Tetrahedron*, 1957, **1**, 94.

<sup>7</sup> Martin and Mitchell, *J.*, 1940, 1155.

<sup>8</sup> Meinwald and Chapman, *J. Amer. Chem. Soc.*, 1958, **80**, 633.

Brady's reagent it gave a deep red precipitate, suggestive of the presence of an  $\alpha\beta$ -unsaturated carbonyl grouping, although the base itself showed no intense absorption in the ultraviolet region. We have confirmed the previous observation<sup>1,2</sup> that the base gives a positive iodoform test, and therefore contains a  $\text{CH}_3\cdot\text{CO}\cdot\text{C}\leq$  grouping.

We have confirmed also that the ozonolysis product, in warm dilute alkali, breaks down into acetone and a syrupy ketonic base  $\text{C}_8\text{H}_{13}\text{ON}$ . This base is presumably the same as that isolated by Büchi *et al.*,<sup>2</sup> although it shows infrared carbonyl bands at 1737 (liquid film) and 1740  $\text{cm}^{-1}$  (in  $\text{CCl}_4$ ); its methiodide shows a similar band at 1720  $\text{cm}^{-1}$ . An infrared comparison between this base and synthetic tropan-6-one differentiated the two compounds; this was confirmed by a similar comparison of the two crystalline picrates and methiodides, and the two methiodides showed a depression in m. p. on admixture. These differences were too pronounced to be ascribed merely to the fact that the "natural" ketone is optically active, and the synthetic product racemic, and in any case such a difference would not be manifest in the infrared curves, in the liquid state or in solution.<sup>9</sup>

We have not yet obtained a sufficient quantity of the degradative base  $\text{C}_8\text{H}_{13}\text{ON}$  to confirm that on reduction by desulphurisation of its ethylene thioether it yields tropane, although we have not been able to reduce tropinone or 6 $\beta$ -hydroxytropinone by this method, owing to our inability to prepare their ethylene thioethers under the usual conditions. If we accept the validity of this step, and recall earlier evidence<sup>10</sup> for the presence of a tropane system in dioscorine, the only possible structure for the  $\text{C}_8\text{H}_{13}\text{ON}$  base is apparently that of tropan-2-one (IV), and dioscorine is to be formulated as (II). Dioscorinol therefore has structure (VII), and the ozonolysis product is the aldol (VIII), which on treatment with alkali undergoes retroaldol cleavage to acetone and the ketone (IV). The reaction of the aldol (VIII) towards Brady's reagent is explained by a preliminary dehydration to the  $\alpha\beta$ -unsaturated ketone (IX).



The position of the carbonyl band of tropan-6-one (III) at a somewhat high wave-number than that for *cyclopentanones* has prompted us to study the infrared spectra of several model ketones. Little has been recorded concerning the position of carbonyl absorption in heterocyclic ketones such as 3-oxopyrrolidine and 3- and 4-oxopiperidine. Our investigations will be described in detail later, but a few preliminary results indicate that in 1-methyl-3-oxopyrrolidine the carbonyl stretching band occurs at a higher frequency (1765  $\text{cm}^{-1}$ ) than in *cyclopentanone* (1745  $\text{cm}^{-1}$ ). A similar effect is noted with *N*-substituted 2:3-dioxopyrrolidines,<sup>11</sup> and a smaller one with 1-methyl-4-oxopiperidine and tropinone, compared with *cyclohexanone*. We conclude that the carbonyl frequency of 1730  $\text{cm}^{-1}$ , quoted by Büchi *et al.*,<sup>2</sup> is too low to accommodate the presence of a 1-methyl-3-oxopyrrolidine system in the  $\text{C}_8\text{H}_{13}\text{ON}$  ketone.

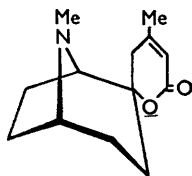
The ease of Hofmann decomposition of the  $\text{C}_8\text{H}_{13}\text{ON}$  keto-base, mentioned by the American workers, led us to study the effect of the mild conditions specified on tropan-6-one methiodide. We found that this quaternary salt was stable to aqueous sodium hydrogen carbonate at 30° for several hours. Even when the temperature was raised to 60° for 6 hr. the methiodide was mainly recovered unchanged. It is of interest that in tropinone two methylene groups  $\beta$  to the nitrogen atom are activated by the carbonyl group, yet the

<sup>9</sup> Jones and Sandorfy, ref. 3, p. 324.

<sup>10</sup> Pinder, *J.*, 1956, 1577.

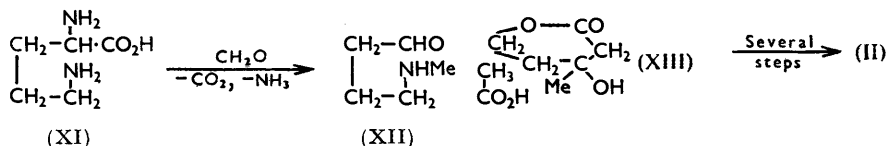
<sup>11</sup> Southwick, Pevic, Casanova, and Carlson, *J. Org. Chem.*, 1956, **21**, 1087; Vaughan and Covey, *J. Amer. Chem. Soc.*, 1958, **80**, 2197.

methiodides of this base<sup>12</sup> and of several substituted tropinones<sup>8,13</sup> and compounds of analogous structure<sup>14</sup> require treatment with base at 100° for decomposition. We have found that tropinone methiodide is stable to aqueous sodium hydrogen carbonate at 30° for 24 hr., and previous workers<sup>12</sup> have shown that steam distillation with this reagent for 30 min. is necessary for decomposition.



(X) As a result of our earlier infrared studies<sup>1</sup> on dihydrodeoxy-dioscorinol we may write the three-dimensional structure (X) as a more accurate representation of dioscorine.

From the biogenetic viewpoint the structure (II) may perhaps be derived from ornithine (XI) [via  $\gamma$ -methylaminobutyraldehyde (XII)], mevalonic lactone (XIII), and acetic acid (1 mol.), according to the annexed scheme.<sup>17</sup>



### EXPERIMENTAL

**$6\beta$ -Hydroxytropinone.**—This compound was most conveniently prepared from 2 : 5-dihydro-2 : 5-dimethoxyfuran<sup>15</sup> (hydrolysed and hydrated *in situ* to maleic dialdehyde), methylamine hydrochloride, and acetonedicarboxylic acid, essentially as outlined by Nedenskov and Clauson-Kaas.<sup>4</sup> Continuous ether-extraction for several days gave a nicely crystalline product which, recrystallised from benzene, had m. p. 123° (yield 35–40%),  $\nu_{\text{max}}$  (in  $\text{CCl}_4$ ) 1718 (C=O), 3450 (broad), 3598, and 3635  $\text{cm}^{-1}$  (all OH).

**Tropan-6 $\beta$ -ol (VI).**— $6\beta$ -Hydroxytropinone (4.16 g.) in ethanol (40 c.c.) was heated with 100% hydrazine hydrate (8.4 g.) at 100° for 2 hr., the ethanol being allowed to distil off gradually. The solvents were then removed under reduced pressure and the syrupy hydrazone was heated with powdered potassium hydroxide (8.0 g.) at 100° for 2 hr., then at 150° for a further hr. The total nitrogen evolution corresponded to 1 mol. The solid residue was cooled and thoroughly extracted with boiling ether, and the extract dried ( $\text{K}_2\text{CO}_3$ ) and evaporated, leaving *tropan-6 $\beta$ -ol* (3.0 g.), b. p. 87–90°/0.1 mm. (2.75 g.). The distillate solidified, and crystallised from light petroleum (b. p. 40–60°) in rhombic prisms, m. p. 65° (Found: C, 67.7; H, 10.4; N, 9.5.  $\text{C}_8\text{H}_{15}\text{ON}$  requires C, 68.1; H, 10.6; N, 9.9%), hydroxyl bands (in  $\text{CCl}_4$ ) at 3450 (broad), 3601, and 3635  $\text{cm}^{-1}$ . The *picrate* separated from methanol in yellow needles, m. p. 259° (decomp.) (Found: C, 45.1; H, 4.7; N, 15.3.  $\text{C}_{14}\text{H}_{18}\text{O}_8\text{N}_4$  requires C, 45.4; H, 4.9; N, 15.2%). The *methobromide* crystallised from ethanol in rhombs, m. p. >330° (Found: C, 45.6; H, 7.3; N, 5.6.  $\text{C}_9\text{H}_{10}\text{ONBr}$  requires C, 45.75; H, 7.6; N, 5.9%). Treatment of the base with ethanolic hydrogen peroxide afforded the syrupy amine oxide, the *picrate* of which separated from ethanol in yellow needles, m. p. 225° (decomp.) (Found: C, 43.5; H, 4.5; N, 14.2.  $\text{C}_{14}\text{H}_{18}\text{O}_9\text{N}_4$  requires C, 43.5; H, 4.65; N, 14.5%).

**Tropan-6-one (III).**—To a solution of *tropan-6 $\beta$ -ol* (4.7 g.) in acetic acid (40 c.c.), previously heated to 60–70°, was added gradually, during 15 min., with stirring, chromic acid (2.34 g.) dissolved in water (2 c.c.) and acetic acid (10 c.c.). The mixture was heated at 85–90° for 3 hr., then cooled, diluted with water (100 c.c.), basified with excess of solid potassium carbonate, and subjected to continuous ether-extraction for 24 hr. Evaporation of the dried ( $\text{Na}_2\text{SO}_4$ ) extract gave a brown oil (3.0 g.), which when fractionated *via* a short Vigreux column yielded *tropan-6-one*, b. p. 78–90°/6 mm. (1.05 g.), unchanged *tropan-6 $\beta$ -ol*, b. p. 109–111°/6 mm., m. p. 65°

<sup>12</sup> Büchi, Yang, Emerman, and Meinwald, *Chem. and Ind.*, 1953, 1063; *J. Amer. Chem. Soc.* 1955, **77**, 4401.

<sup>13</sup> Meinwald and Chapman, *ibid.*, 1956, **78**, 4816; van Tamelen, Barth, and Lornitzo, *ibid.*, 1956, **78**, 5442.

<sup>14</sup> Meinwald and Koskenkyla, *Chem. and Ind.*, 1955, 476.

<sup>15</sup> Imperial Chemical Industries (Billingham Division), Ltd., personal communication; T. and H. Smith, Ltd., B.P. 703,929/1954.

(1.25 g.), and involatile residue (0.7 g.). The keto-base, purified *via* its crystalline picrate (see below) with decomposition with ammonia, distilled at 82°/7 mm. (Found: C, 69.5; H, 9.35; N, 10.3.  $C_8H_{13}ON$  requires C, 69.1; H, 9.35; N, 10.0%), C=O bands (in  $CCl_4$ ) at 1750 and 1752  $cm^{-1}$  (liquid film). Tropan-6-one is a colourless syrup rapidly oxidised by air; it reduces ammoniacal silver nitrate and Fehling's solution readily. The *picrate* separated from 50% aqueous ethanol in yellow needles, m. p. 269° (decomp.) (Found: C, 46.0; H, 4.2; N, 15.2.  $C_{14}H_{16}O_8N_4$  requires C, 45.7; H, 4.4; N, 15.2%), C=O band (in KCl) at 1770  $cm^{-1}$ . The *methiodide* crystallised from aqueous ethanol in rhombic prisms, m. p. 289° (decomp.) or 303—304° (decomp.) (Found: C, 38.7; H, 6.2; N, 5.0.  $C_9H_{16}ONI$  requires C, 38.4; H, 5.7; N, 5.0%). C=O band (in Nujol mull) at 1778  $cm^{-1}$ .

*Dioscorine*.—The alkaloid, obtained as described previously,<sup>16</sup> was purified *via* its picrate,<sup>16</sup> which was prepared in methanol solution in the usual manner, recrystallised from acetone, collected, dried in air, suspended in ether, and shaken repeatedly with ice-cold, 50% potassium hydroxide solution until the aqueous layer was no longer coloured. The dried, ethereal solution was evaporated, and the residual alkaloid distilled (b. p. 140—145°/0.2 mm.). It crystallised readily overnight and had  $[\alpha]_D^{20} = -32.0^\circ$  (in chloroform,  $c$  3.4),  $\lambda_{max}$ . (in methanol) 215  $\mu$  ( $\epsilon$  10,160).\*

*Ozonolysis of Dioscorinol*.<sup>1</sup>—Dioscorinol<sup>1</sup> (3.6 g.) in glacial acetic acid (30 c.c.) was ozonised for 5 hr. at 15°. To the cooled solution zinc dust (1.5 g.) was added, and the mixture kept for 2 hr., with occasional shaking, by which time the starch-iodide test was negative. After filtration, water (50 c.c.) was added to the solution, which was then rendered strongly alkaline with potassium carbonate at <20°. Continuous ether-extraction for 48 hr. yielded, after drying ( $K_2CO_3$ ) and evaporation, a brown, viscous oil (3.0 g.), which distilled at 80°/0.01 mm., 90—92°/0.04 mm. (1.0 g.) (Found: C, 67.5; H, 9.8; N, 7.3.  $C_{11}H_{19}O_2N$  requires C, 67.0; H, 9.4; N, 7.1%),  $\nu_{max}$ . (in  $CCl_4$ ) 1718 (C=O) and 3535  $cm^{-1}$  (broad, OH), having no intense absorption in the ultraviolet region. This product, considered to be *2-acetonilytropan-2-ol* (VIII), formed an oily picrate and methiodide. With 2 : 4-dinitrophenylhydrazine in ethanolic sulphuric acid it gave a deep red precipitate, indicative of dehydration. It gave a positive iodoform reaction.

*Alkaline Decomposition of the Ozonolysis Product*.—(a) The above ozonolysis product (1.0 g.) was heated on the water-bath for 30 min. with 0.2N-sodium hydroxide (50 c.c.). The cooled solution was saturated with potassium carbonate and extracted continuously with ether for 24 hr. Distillation of the dried ( $Na_2SO_4$ ) extract gave an *oil* (0.7 g.), b. p. 89—90°/8 mm. (0.25 g.), which was converted into its picrate in methanol. The *picrate* crystallised from 50% aqueous ethanol in yellow needles, m. p. 188° (decomp.) (Found: C, 46.2; H, 4.6; N, 14.9.  $C_{14}H_{16}O_8N_4$  requires C, 45.7; H, 4.4; N, 15.2%), C=O band (in KCl) at 1750  $cm^{-1}$ . Alkaline decomposition of the picrate afforded a colourless oily base, b. p. 102°/14 mm. (Found: C, 68.6; H, 9.3; N, 9.7.  $C_8H_{13}ON$  requires C, 69.1; H, 9.35; N, 10.0), C=O bands at 1737 (liquid film) and 1740  $cm^{-1}$  (in  $CCl_4$ ). This product, considered to be tropan-2-one (IV), showed reactions characteristic of a ketonic tertiary base; the *methiodide* separated from aqueous ethanol in rhombic prisms, m. p. 295° (decomp.) (Found: C, 38.1; H, 5.8.  $C_9H_{16}ONI$  requires C, 38.4; H, 5.7%), C=O band (in Nujol mull) at 1720  $cm^{-1}$ . A mixture of this methiodide and tropan-6-one methiodide, m. p. 289° (decomp.) (see above), had m. p. 282—283° (decomp.), with previous softening.

(b) A mixture of the ozonolysis product (1.0 g.) and 0.2N-sodium hydroxide (50 c.c.) was distilled until about 25 c.c. of distillate had been collected. Addition of an excess of a saturated solution of 2 : 4-dinitrophenylhydrazine in 2N-sulphuric acid gave a yellow precipitate which crystallised from ethanol in yellow needles, m. p. 126—127°, alone or mixed with acetone 2 : 4-dinitrophenylhydrazone.

We thank Sir Robert Robinson, O.M., F.R.S., and Dr. W. Klyne for their interest in this work, and we are indebted to Dr. G. Eglinton for the infrared measurements (carried out by Mr. F. Gisbey). Plant material was supplied by the Colonial Products Council and extraction

\* A misprint occurs in Part I of this series:<sup>16</sup> on p. 2238 for  $\epsilon$  16,160 read  $\epsilon$  10,160.

<sup>16</sup> Pinder, *J.*, 1952, 2236.

<sup>17</sup> Cf. James, in "The Alkaloids," ed. Manske and Holmes, Academic Press Inc., New York, 1950, Vol. I, pp. 56 *et seq.*; Robinson, "The Structural Relations of Natural Products," Clarendon Press, Oxford, 1955, pp. 59 *et seq.*

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