## 194. *Experiments on the Synthesis of the Pyrethrins. Part II. The Structure of Cinerone.*

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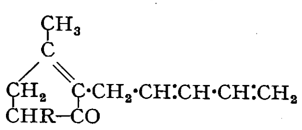
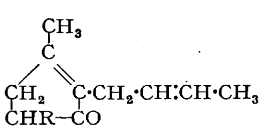
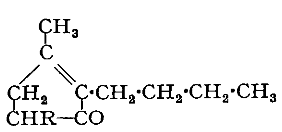
During the past year LaForge and Barthel have shown that "pyrethrolone", the keto-alcohol component of the pyrethrins, is a mixture of a $C_{11}$ keto-alcohol, pyrethrolone, and a $C_{10}$ keto-alcohol, cinerolone. In a synthetic approach to the structure of cinerolone and the related ketone, cinerone, a series of 3-*methyl*-2-*butenyl*-$\Delta^2$-cyclo*pentenones* have been prepared. However, neither the expected $\Delta^\beta$ nor the $\Delta^\gamma$ ketones are identical with cinerone. Possible structures for cinerone are considered.

Evidence has been presented during the past year by LaForge and Barthel (*J. Org. Chem.*, 1944, **9**, 242; 1945, **10**, 106, 114) that "pyrethrolone," the keto-alcohol component of the pyrethrins, is a mixture. By a combination of fractional distillation and crystallisation of suitable derivatives "pyrethrolone" was separated into the *d*- and *dl*-forms of a keto-alcohol, $C_{11}H_{14}O_2$, and the *d*- and *dl*-forms of a keto-alcohol, $C_{10}H_{14}O_2$. On the basis of analytical data the structure (I, R = OH) was assigned to the $C_{11}$ keto-alcohol and the name pyrethrolone retained. For the $C_{10}$ keto-alcohol structure (II, R = OH) was postulated and the name cinerolone suggested.


(I.)


(II.)


(III.)

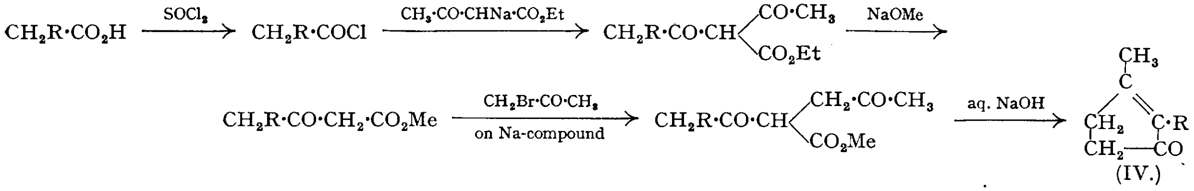
LaForge and Barthel found that the molecule of cinerolone was sufficiently stable to enable the hydroxyl group to be replaced by hydrogen, *via* the chloro-compound (II, R = Cl), to give cinerone (II, R = H), which was characterised by a semicarbazone and a *p*-nitrophenylhydrazone.

The radical nature of the suggestion that "pyrethrolone" is a mixture not merely of isomers rendered it desirable that this view based on analytical and degradative evidence should be supplemented by a synthetic approach. Of the two structures that of (II) seemed of the greater interest as being a formula with one carbon atom and one double bond less than previously assigned to " pyrethrolone." In a further paper (*ibid.*, 1945, **10**, 222), received after the work described in this paper had been started, LaForge and Barthel described the reduction of cinerolone to dihydrocinerolone (III, R = OH) and its conversion, *via* the chloro-compound (III, R = Cl), into dihydrocinerone (III, R = H). Derivatives of dihydrocinerone had melting points in moderate agreement with those from synthetic 3-methyl-2-*n*-butyl-$\Delta^2$-*cyclo*pentenone (III, R = H). Their identity was claimed, although apparently no mixed melting points were determined.

Accepting the identity of dihydrocinerone and the *n*-butyl ketone, it follows that in cinerone only the position of the double bond in the side chain is undetermined. LaForge and Barthel assigned this to the $\Delta^{\beta}$ position on the basis of terminal methyl values. Cinerolone gave 1·66 and its semicarbazone 1·64 terminal methyl groups, apparently indicating the presence of two such groups. It is to be observed, however, that while pyrethrolone, to which structure (I, R = OH) was assigned, gave 1·1 and its semicarbazone 1·1, tetrahydropyrethrolone, with a saturated side chain, gave 1·76 and its semicarbazone 1·85 terminal methyl groups. Reference to Table I will also show that for the synthetic ketones described in this paper there is an equal lack of consistency between terminal methyl content and structure. West, too (*J.*, 1945, 412), has found similar discrepancies in the terminal methyl values for this type of compound. Deductions from terminal methyl values in this series of compounds may therefore be misleading.

If the position of the double bond in cinerone is regarded as not yet settled, there are three possible structures, the $\Delta^{\alpha}$, $\Delta^{\beta}$, and $\Delta^{\gamma}$ ketones, of which the first two are theoretically capable of existing in *cis*- and *trans*-forms. The $\Delta^{\alpha}$ structure is unlikely, first, because the double bond would be cross conjugated with the $\alpha\beta$-unsaturated carbonyl group, which has been excluded by the examination of the absorption spectrum of " pyrethrolone " (Gillam and West, *J.*, 1942, 671), and secondly, because it would allow of the formation of propaldehyde on ozonisation of " pyrethrolone," which has never been observed (Staudinger and Ruzicka, *Helv. Chim. Acta*, 1924, **7**, 212; LaForge and Haller, *J. Org. Chem.*, 1938, **2**, 546). The $\Delta^{\beta}$ and $\Delta^{\gamma}$ structures are equally probable and would be spectroscopically indistinguishable, each showing only the characteristic absorption due to the $\alpha\beta$-unsaturated carbonyl group. LaForge and Barthel report for cinerolone, $\lambda_{\max.} =$ 2275 A. ($\epsilon$ = 15,500), and for cinerolone semicarbazone, $\lambda_{\max.} =$ 2630 A. ($\epsilon$ = 22,000), which are consistent with this explanation. These structures could, however, be distinguished unequivocally by ozonisation to give either acetaldehyde or formaldehyde. The separate existence of geometrical isomers in this type of compound has not yet been demonstrated. In the closely analogous case of jasmone (IV, R = $\Delta^2$-pentenyl), despite several syntheses by different routes (Treff and Werner, *Ber.*, 1935, **68**, 640; Hunsdiecker, *ibid.*, 1942, **75**, 460), only one form is known identical with natural jasmone. Moreover the configuration of this is uncertain, being based on that of $\Delta^3$-hexenol, which is itself in dispute (Takei, Ono, and Sinosaki, *ibid.*, 1940, **73**, 950; Stoll and Rouvé, *ibid.*, p. 1358).

As the first step, therefore, in an attempt to clarify this problem by synthesis, a series of 3-*methyl*-2-*butenyl*-$\Delta^2$-cyclo*pentenones* have been prepared by the following method (R = butenyl) from suitable hexenoic acids :



(IV.)

The pure ketones were regenerated from their *semicarbazones* and characterised by physical constants, absorption spectra, and the preparation of derivatives. These and the properties of cinerone recorded by LaForge and Barthel that are comparable are presented in Tables I and II. The $\Delta^{\gamma}$ structure for cinerone is clearly ruled out by the wide differences in melting points of the comparable derivatives. Likewise the divergences of melting points between the $\Delta^{\beta}$ ketone and cinerone are such as to make identity improbable. It has been possible, through the courtesy of Dr. LaForge, to test this point by making a direct comparison of the semicarbazones and the *p*-nitrophenylhydrazones of cinerone and the $\Delta^{\beta}$ ketone; in each case there was a marked depression of melting point. The two substances are therefore different. In view of this unexpected lack of identity, the structure (II, R = H) of the synthetic ketone was placed beyond doubt. The gross structure was confirmed by catalytic reduction of the semicarbazone to the known semicarbazone of 3-methyl-2-*n*-butyl-$\Delta^2$-*cyclo*pentenone (III, R = H) (Hunsdiecker, *Ber.*, 1942, **75**, 455), a specimen of which was prepared for comparison. The position of the double bond in the side chain was confirmed as the $\Delta^{\beta}$ by the production of acetaldehyde on ozonolysis. The geometrical configuration of the double bond is unknown. During the purification of the ketone no other semicarbazone was isolated. Moreover the starting material, $\Delta^4$-hexenoic acid, is only known in one form of undetermined configuration (Letch and Linstead, *J.*, 1934, 1994). It was then considered that cinerone might be a mixture of the $\Delta^{\beta}$ and $\Delta^{\gamma}$ ketones. Several mixtures of the synthetic semicarbazones were made, of which that containing 70% of the $\Delta^{\beta}$ semicarbazone had the same melting point as cinerone semicarbazone. Nevertheless a mixture gave a well marked depression. Cinerone is therefore different from either ketone singly or in combination.

Despite the absence of positive identification it is considered probable that cinerone is the $\Delta^{\beta}$-butenyl ketone of opposite geometrical configuration to the synthetic ketone described in this paper.* Work is being continued in an attempt to obtain more certain evidence on this point.

TABLE I.

| Ketone (IV). | B. p. | $n_D^{25°}$. | $d_{4°}^{25°}$. | $[R_L]_D$* Found. | $[R_L]_D$* Calc. | Exaltation. | Terminal methyl values. Found. | Terminal methyl values. Calc. |
|---|---|---|---|---|---|---|---|---|
| R = $CH_2\cdot CH{:}CH\cdot CH_3$ | 119°/15 mm. | 1·4983 | 0·9472 | 46·51 | 45·26 | 1·25 | 1·15 | 2·00 |
| R = $CH_2\cdot CH_2\cdot CH{:}CH_2$ | 110°/13 mm. | 1·4948 | 0·9407 | 46·54 | 45·26 | 1·28 | 1·30 | 1·00 |
| Cinerone ................. | — | 1·5067 (29°)<br>1·4978 (31°) | — | — | — | — | — | — |
| R = $CH_2\cdot CH_2\cdot CH_2\cdot CH_3$ | 105°/10 mm. | 1·4794 | 0·9192 | 46·99 | 45·72 | 1·27 | 2·00 | 1·00 |
| Dihydrocinerone ...... | 115°/17 mm. | 1·4800 (24°) | 0·9150 (24°) | 47·25 | 45·72 | 1·53 | — | — |

* Using the values C = 2·418, H = 1·100, :O = 2·211, and C:C = 1·733.

TABLE II.

| Ketone (IV). M. p.'s of : | Semicarbazone. | *p*-Nitrophenylhydrazone. | 2 : 4-Dinitrophenylhydrazone. |
|---|---|---|---|
| R = $CH_2\cdot CH{:}CH\cdot CH_3$ ............... | 220° | 162° | 161° |
| R = $CH_2\cdot CH_2\cdot CH{:}CH_2$ ............ | 188 | 127 | 146 |
| Cinerone ................................. | 214—215 | 148<br>140—142 | — |
| R = $CH_2\cdot CH_2\cdot CH_2\cdot CH_3$ ........... | 193 | 133 | 155 |
| Dihydrocinerone ..................... | 191·5—192·5 (corr.) | 128—131 (corr.) | 149—151 (corr.) |

## EXPERIMENTAL.

(Melting points are uncorrected. Microanalyses, including terminal methyl values by the micro Kuhn–Roth procedure, are by Drs. Weiler and Strauss, Oxford.)

$\Delta^3$-Hexenoic acid was prepared from *n*-butaldehyde and malonic acid (Boxer and Linstead, *J.*, 1931, 748; Linstead and Noble, *J.*, 1933, 559) and purified by low temperature crystallisation. $\Delta^3$-Hexenoyl chloride, prepared using thionyl chloride, had b. p. 50°/17 mm. and 54°/20 mm. $\Delta^4$-Hexenoic acid was prepared from crotyl chloride and ethyl malonate (Eccott and Linstead, *J.*, 1929, 2163). $\Delta^4$-Hexenoyl chloride, prepared using thionyl chloride, had b. p. 56°/20 mm. $\Delta^5$-Hexenoic acid was prepared from $\Delta^3$-butenyl bromide and ethyl malonate (Linstead and Rydon, *J.*, 1934, 1998; Michael and Mason, *J. Amer. Chem. Soc.*, 1943, **65**, 684). $\Delta^5$-Hexenoyl chloride, prepared using thionyl chloride, had b. p. 50°/15 mm. *n*-Hexoyl chloride, prepared using thionyl chloride, had b. p. 54°/20 mm.

The following generalised procedures were used :

*Ethyl a-Hexenoylacetoacetates.*—Ethyl acetoacetate (71·5 g.; 0·55 mol.) was added in portions to sodium wire (12·7 g.; 0·55 atom) under dry ether (500 c.c.). Gentle refluxing was maintained for 4 hours to complete the formation of the sodio-compound. The mixture was then cooled and the hexenoyl chloride (66·3 g.; 0·5 mol.) added in small portions with shaking to moderate the violent reaction. Reaction was completed by refluxing for 30 minutes. Ice-water, acidified with sulphuric acid, was added, and the ethereal layer was separated, washed, and dried ($Na_2SO_4$). Removal of the ether and fractional distillation of the residue gave the required ester. The $\Delta^4$-*hexenoyl* ester (65% yield) had b. p. 143°/15 mm. (Found : C, 63·6; H, 8·2. $C_{12}H_{18}O_4$ requires C, 63·7; H, 8·0%); the $\Delta^5$-*hexenoyl* ester (60% yield) had b. p. 148°/16 mm. (Found : C, 64·1; H, 7·75%); the *n*-hexoyl ester (79% yield) had b. p. 145°/15 mm. Each ester gave a deep red colour with alcoholic ferric chloride. The product from $\Delta^3$-hexenoyl chloride tended to decompose on distillation (b. p. 140—155°/20 mm.) and the bright yellow distillate was heterogeneous. This could be overcome by using a higher vacuum; the product then had b. p. 100—110°/0·5 mm. (41% yield) (Found : C, 64·5; H, 7·8%). This ester gave only a pale red colour with alcoholic ferric chloride.

*Methyl γ-Butenylacetoacetates.*—The ethyl a-hexenoylacetoacetate (113 g.; 0·5 mol.) was added to a cold solution of sodium (12·5 g.; 0·55 atom) in methanol (250 c.c.). After 24 hours, water and dilute sulphuric acid were added, and the esters extracted with ether. The ethereal extract was washed and dried ($Na_2SO_4$), and the ether removed. Fractional distillation of the residue gave, after a forerun of methyl hexenoate, the required methyl γ-butenylacetoacetate. The $\Delta^2$-*butenyl* ester (65% yield) had b. p. 118°/15 mm. (Found : C, 63·3; H, 8·6. $C_9H_{14}O_3$ requires C, 63·5; H, 8·3%); the $\Delta^3$-*butenyl* ester (71% yield) had b. p. 125°/23 mm. (Found : C, 63·8; H, 8·3%); the *n*-butyl ester (64% yield) had b. p. 114°/15 mm. and 120°/20 mm. Each ester gave a deep purple red colour with alcoholic ferric chloride. The $\Delta^3$-hexenoyl condensation product failed to give a fraction corresponding to methyl γ-$\Delta^1$-butenylacetoacetate. Apart from a low boiling fraction of methyl hexenoate and methyl acetoacetate, the remaining material had a b. p. similar to that of the original condensation product (135—155°/17 mm.; 100—105°/0·3 mm.) and like it gave only a pale red colour with alcoholic ferric chloride (Found : C, 66·1; H, 7·1. $C_{10}H_{12}O_3$ requires C, 66·6; H, 6·7%). It seems probable that under the conditions employed the original condensation has proceeded abnormally, at least in part, with the elimination of $C_2H_6O$ (alcohol?) from the expected hexenoylacetoacetate, to give a *product* that does not suffer alcoholysis with sodium methoxide. This condensation is being studied in the hope of making the $\Delta^a$-butenyl ketone available by this route.

*Methyl a-Hexenoyl-lævulates.*—The methyl γ-butenylacetoacetate (42·5 g.; 0·25 mol.) was added in portions to sodium wire (6·3 g.; 0·27 atom) under dry ether (250 c.c.). The sodio-compound was moderately soluble in ether thus facilitating reaction of the sodium. After being refluxed for 1 hour the mixture was cooled, and freshly distilled bromoacetone (34 g.; 0·25 mol.) (*Org. Synth.*, Coll. Vol. **2**, 88) added in small portions with shaking; a transient bright pink colour being formed initially. Reaction was completed by refluxing for 30 minutes. Ice-water, acidified with sulphuric acid, was added, and the ethereal layer was separated, washed, and dried ($Na_2SO_4$). The ether was distilled off and low-boiling fractions removed by a water pump at 100°. The residual condensation product was used directly for cyclisation. Attempted distillation of part of the $\Delta^4$-hexenoyl ester led to partial decomposition (b. p. 165—170°/20 mm.) and the distillate was discoloured.

3-*Methyl*-2-*butenyl*-$\Delta^2$-cyclo*pentenone.*—The crude methyl a-hexenoyl-lævulate (56·5 g.) was stirred at 70° (thermometer in flask) with 3% aqueous sodium hydroxide (800 c.c.) for 3 hours. The solution was cooled and acidified with

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* This is consistent with the results of the ozonisation of cinerolone (Dr. LaForge, private communication to the author).

sulphuric acid, and the liberated ketone extracted with ether (4 × 100 c.c.). The ethereal extract was washed and dried ($Na_2SO_4$), and the ether taken off through a column. The residue was distilled and the crude cyclic ketone (24 g.) collected as a fraction, b. p. 110—130°/20 mm. The crude ketone was converted into the semicarbazone by using the pyridine–ethanol method (Haller and LaForge, *J. Org. Chem.*, 1936, **1**, 38) and the sparingly soluble product recrystallised from methanol, ethanol, or ethyl acetate. The *$\Delta^{\beta}$-butenyl semicarbazone* had m. p. 220° (decomp.), $\lambda_{\max.} = 2660$ A. ($\epsilon = 21{,}800$) in alcohol (Found: C, 63·7; H, 8·4; N, 20·2. $C_{11}H_{17}ON_3$ requires C, 63·7; H, 8·3; N, 20·2%); the *$\Delta^{\gamma}$-butenyl semicarbazone* had m. p. 188° (decomp.) (Found: C, 63·5; H, 8·3%); the *n*-butyl semicarbazone had m. p. 193°.

*Regeneration of Ketones.*—The pure semicarbazone (5·0 g.) was added to a solution of oxalic acid (10 g.) in water (50 c.c.) and the suspension heated under reflux on the steam-bath for 1 hour in a stream of nitrogen. After cooling, the separated ketone was taken up in light petroleum (25 c.c.) and the extract dried ($Na_2SO_4$). After removal of the solvent through a column the residue was distilled from a small Claisen flask and the pure ketone collected as one fraction of constant b. p. (3·1 g.) (see Table I). Portions were immediately sealed for analysis and the physical constants (see Table I) determined without delay. All these ketones on analysis showed low carbon contents, owing presumably to the slow absorption of atmospheric oxygen. A similar phenomenon has been observed for pyrethrolone (LaForge and Haller, *J. Amer. Chem. Soc.*, 1936, **58**, 1779) and cinerolone (LaForge and Barthel, *J. Org. Chem.*, 1945, **10**, 118). The *$\Delta^{\beta}$-butenyl ketone* [Found (after 1 week): C, 78·9; H, 9·45; (after 3 weeks): C, 77·1; H, 9·5. $C_{10}H_{14}O$ requires C, 80·0; H, 9·4%] had $\lambda_{\max.} = 2350$ A. ($\epsilon = 12{,}000$) in alcohol. A portion left for 5 months in contact with air "dried" to a viscous resin, no longer soluble in light petroleum. The *$\Delta^{\gamma}$-butenyl ketone* (Found: C, 79·5; H, 9·25%) and *n*-butyl ketone (Found: C, 77·8; H, 10·95. Calc. for $C_{10}H_{16}O$: C, 78·9; H, 10·6%) had the constants shown.

Using the freshly regenerated ketones, the following derivatives were prepared by standard methods:

The *$\Delta^{\beta}$-butenyl p-nitrophenylhydrazone*, red prisms from methanol, m. p. 162° (Found: C, 67·2; H, 6·8; N, 14·9. $C_{16}H_{19}O_2N_3$ requires C, 67·35; H, 6·7; N, 14·7%); *2 : 4-dinitrophenylhydrazone*, crimson needles from ethanol, m. p. 161° (Found: C, 58·2; H, 5·6; N, 16·9. $C_{16}H_{18}O_4N_4$ requires C, 58·2; H, 5·5; N, 16·9%); *oxime*, plates from light petroleum, m. p. 123° (Found: C, 72·4; H, 9·0; N, 8·4. $C_{10}H_{15}ON$ requires C, 72·6; H, 9·1; N, 8·5%). The *$\Delta^{\gamma}$-butenyl p-nitrophenylhydrazone*, red prisms from aqueous methanol, m. p. 127° (Found: C, 67·1; H, 6·9; N, 14·6%); *2 : 4-dinitrophenylhydrazone*, crimson needles from ethanol, m. p. 146° (Found: C, 58·5; H, 5·7; N, 16·6%). The *n*-butyl *p*-nitrophenylhydrazone, light red prisms from methanol, m. p. 133°; 2 : 4-dinitrophenylhydrazone, crimson needles from ethanol, m. p. 155°. The 2 : 4-dinitrophenylhydrazones were superior to the *p*-nitrophenylhydrazones for the purposes of characterisation, being obtained in much higher yield and being more readily crystallised.

*Ozonisation of Ketones.*—(1) The $\Delta^{\beta}$-butenyl ketone (500 mg.) in carbon tetrachloride (25 c.c.) was ozonised at 0° (30 minutes), the exit gases being passed through a solution of dimedone (1·2 g.) in water (300 c.c.). After completion of the ozonisation, water (25 c.c.) was added to the ozonide and aspiration continued for 24 hours, the volatile products from the decomposition of the ozonide being led through the dimedone. The dimedone derivative of acetaldehyde (298 mg.; 29% yield) was collected, dried at 90°, and had m. p. 140·5° (not depressed by admixture with an authentic specimen). There was no sign of the production of formaldehyde.

(2) Experiment (1) was repeated using as the absorbing solution 2 : 4-dinitrophenylhydrazine in 2N-sulphuric acid. Acetaldehyde 2 : 4-dinitrophenylhydrazone (240 mg.; 32% yield) was collected, and after crystallisation from ethanol had m. p. 168° (not depressed by admixture with an authentic specimen).

(3) The $\Delta^{\gamma}$-butenyl ketone (500 mg.) was ozonised as in (1), using dimedone as the absorbing solution. The dimedone derivative of formaldehyde (273 mg.; 28% yield) was collected and after crystallisation from aqueous ethanol had m. p. 190° (not depressed by admixture with an authentic specimen). There was no sign of the production of acetaldehyde.

*Hydrogenation.*—The $\Delta^{\beta}$-butenyl ketone semicarbazone (258 mg.) was added to previously reduced Adams's catalyst (50 mg.) in ethyl acetate (40 c.c.). The suspension was hydrogenated, absorption being slow owing to the sparing solubility. Hydrogen equivalent to one double bond was taken up in 3 hours. The product dissolved on boiling and after filtering from the catalyst separated as shining flakes on cooling (203 mg.), m. p. 193° alone or mixed with an authentic specimen of the *n*-butyl ketone semicarbazone.

*Mixed Melting Points with Derivatives of Cinerone.*—(1) A mixture of approximately equal parts of cinerone and $\Delta^{\beta}$-butenyl ketone semicarbazones, after being put in the melting point bath at 180°, went brown at 190°, softened at 200°, and melted with decomposition at 210°. At the same time cinerone semicarbazone went brown at 190°, softened at 200°, and melted with decomposition at 213°.

(2) A mixture of approximately equal parts of the *p*-nitrophenylhydrazones of cinerone and the $\Delta^{\beta}$-butenyl ketone melted on being put in the bath at 140° (m. p. 135—140°). At the same time cinerone *p*-nitrophenylhydrazone had m. p. 148—150°.

(3) The $\Delta^{\beta}$- (39·5 mg.) and the $\Delta^{\gamma}$-butenyl ketone semicarbazone (16·7 mg.) were mixed and crystallised from ethanol (5 c.c.). The product, on being put in the melting point bath at 180°, went brown at 190°, softened at 200°, and melted with decomposition at 215°. This mixture (12·5 mg.) and cinerone semicarbazone (12·5 mg.) were crystallised together from ethanol (2 c.c.). This mixed product, on being put in the melting point bath at 180°, went brown at 190°, softened at 200°, and melted with decomposition at 202°.

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