267. *The Synthesis of Compounds related to the Sterols, Bile Acids, and Oestrus-producing Hormones. Part XI. A "Diene-Synthesis" of Phenanthrene and Hydrophenanthrene Derivatives.*

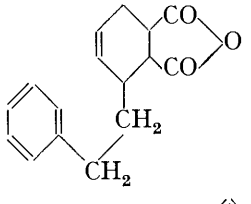
By A. COHEN and (in part) F. L. WARREN.

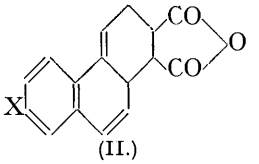
THE failure to cyclise 3-β-phenylethyl-1 : 2 : 3 : 6-tetrahydrophthalic anhydride (I) (Cohen, J., 1935, 429) presented a serious obstacle to the synthesis of *as.*-octahydrophenanthrene derivatives by the Diels reaction. Alternative routes were therefore investigated involving the condensation of maleic anhydride with derivatives of naphthalene and 3 : 4-dihydronaphthalene containing a 1-vinyl group; the conjugation of an aromatic nucleus with an ethylenic linkage to give an active diene system had been observed in the case of *as.*-diphenylethylene (Wagner-Jauregg, *Annalen*, 1931, **491**, 1).

Ethyl 3 : 4-dihydro-1-naphthylacetate was prepared through the Reformatsky reaction between α-tetralone and ethyl bromoacetate (Schroeter, Zadek, and Hoffmann, *Ber.*, 1925, **58**, 713), but this could not be reduced to the required β-(3 : 4-dihydro-1-naphthyl)ethyl alcohol by the Bouveault–Blanc method, the only product being the saturated β-1-tetrahydronaphthylethyl alcohol. This result was anticipated in view of the known facility with which a double bond conjugated with a benzene nucleus is reduced by sodium and alcohol, and is in agreement with the subsequently recorded finding of Robinson and Walker (J., 1935, 1530).

1-Vinylnaphthalene, however, combines readily with maleic anhydride, affording 1 : 2 : 3 : 11-*tetrahydrophenanthrene*-1 : 2-*dicarboxylic anhydride* (II; X = H), and the present communication describes experiments of this nature which were mostly completed by April, 1936, when circumstances caused the work to be interrupted. A preliminary note on some of these experiments has already been published (*Nature*, 1935, **136**, 869).

(I.)





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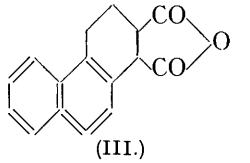
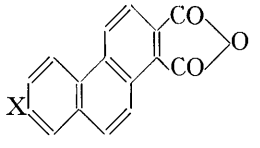
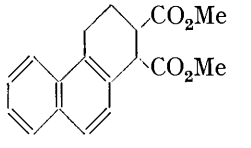


(III.)

(IV.)





(V.)

Formula (II) is that of the theoretical primary addition product from 1-vinylnaphthalene and maleic anhydride, and it was realised that such a molecule could easily isomerise to a naphthalene derivative (III) which might well represent the product actually obtained. Experimental evidence, however, demonstrated the correctness of (II). The adduct is found by fractional dissolution to be homogeneous; it rapidly consumes cold alkaline permanganate, and perbenzoic acid titration gives a value of 1·7 for the number of ethylenic linkings, the alternatives being 2 for (II) and 0 for (III). Moreover, (II) is readily isomerised by hydrogen chloride to a *compound* which must be represented by (III). The latter has the same chemical composition, is far more stable to alkaline permanganate, and is much more soluble in benzene. Its saturated character is shown by the negligible absorption of oxygen from perbenzoic acid.

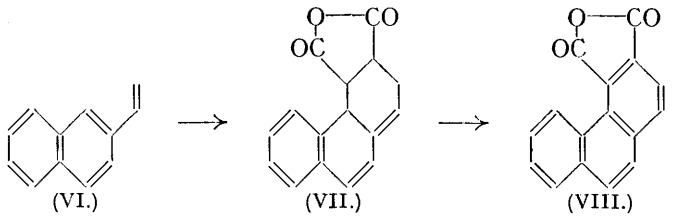
The ease of isomerisation of (II) to (III) was shown by treatment of the former with cold alkaline methyl sulphate, which, without introducing any acid factor, gave the same *methyl* ester (V) as was obtained in the methyl alcohol–sulphuric acid esterification of the free acid obtained from (III).

Finally, the close relationship between (II) and (III) was demonstrated by dehydrogenating both with platinum-black at 300° to the same phenanthrene-1 : 2-dicarboxylic

anhydride (IV; X = H), which had just previously been described by Fieser and Hershberg (*J. Amer. Chem. Soc.*, 1935, **57**, 1508, 1853).

In a parallel series of experiments β-1-(6-methoxynaphthyl)ethyl alcohol was dehydrated to 6-*methoxy*-1-*vinylnaphthalene*, which also reacts with maleic anhydride. To the *adduct*, of which only a very small quantity has been available, the structure (II; X = OMe) is assigned by analogy with the results in the case where X = H. Its reduction of permanganate has been observed, and on dehydrogenation, it is converted into 7-methoxyphenanthrene-1 : 2-dicarboxylic anhydride, identical with a specimen synthesised by another route (Part IX; J., 1936, 52).

As a third example of this type of Diels reaction, 2-vinylnaphthalene (VI) reacts with maleic anhydride, though much less readily, furnishing 2 : 3 : 4 : 12-*tetrahydrophenanthrene*-3 : 4-*dicarboxylic anhydride* (VII). The assumed location of the double bonds in (VII) is



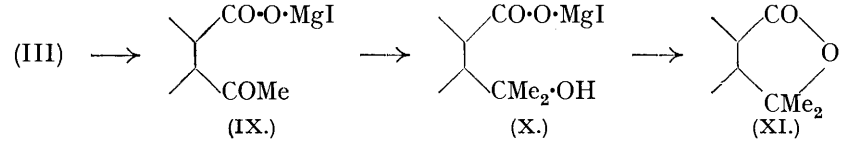
(VI.) (VII.) (VIII.)

once more based on analogy. The phenanthrene type of structure is, however, definitely established, and the anthracene type (which would result from condensation of maleic anhydride in the only alternative manner) excluded by the identity of the dehydrogenation *product* (VIII) obtained from (VII) with a specimen independently synthesised by Dr. C. L. Hewett, to whom the author is grateful.

The anhydride (II; X = H) in dioxan solution was submitted to catalytic hydrogenation with palladium-black, with a view to converting it into an octahydrophenanthrene derivative more closely resembling an oestrone type of compound. Nearly half of the calculated volume of hydrogen was absorbed, resulting in an obviously mixed product of a gummy nature. The only homogeneous product isolated did not depress the melting point of the isomer (III). This migration of the ethylenic linking by means of the catalyst recalls the isomerisation of β- to α-pinene (Richter and Wolff, *Ber.*, 1926, **59**, 1733) effected by platinum and palladium, and of γ- to α-ergostenol (Reindel and Walter, *Annalen*, 1928, **460**, 214; v. Reichel, *Z. physiol. Chem.*, 1934, **226**, 146). Hydrogenation in alkaline solution failed, as was to be expected from the ease with which (II) passes into (III) in alkaline medium.

Further experiments, aimed at the building up of a five-carbon ring in place of the anhydride ring, were confined to the naphthalenic isomer (III) in order to avoid the complications associated with the labile compound (II; X = H). Bouveault-Blanc reduction did not yield a hydroxy-acid or lactone, and only the dibasic acid corresponding to unchanged material was obtained.

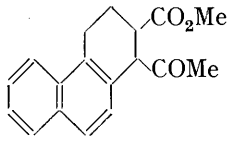
The reaction between the anhydride (III) and one molecular equivalent of methylmagnesium iodide afforded a mixture of compounds. This was resolved after esterification treatment with methyl alcohol and sulphuric acid into (*a*) the characteristic crystalline *dimethyl-lactone* (XI; in this formula CMe_2 and CO are interchangeable, as the exact orientation has not been determined) arising from reaction between initially formed ketone (IX) with more Grignard reagent, followed by lactonisation of the resulting tertiary

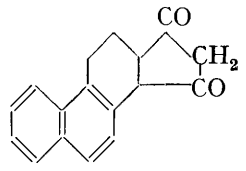


(IX.) (X.) (XI.)

carbinol-acid corresponding to (X); (*b*) the methyl ester (V) of the original dibasic acid; and (*c*) a compound, b. p. 185—190°/0·2 mm., obtained in very small yield, which is

probably the desired keto-ester (XII). The last yields an acid on alkaline hydrolysis, but further investigation was prevented by the small quantity available. It was hoped to

(XII.) 



(XIII.)

cyclise this keto-ester to 1′ : 3′-diketo-3 : 4-dihydro*cyclo*pentanophenanthrene (XIII). An attempt to obtain this diketone by the alternative method of condensing the methyl ester (V) with ethyl acetate, followed by hydrolysis and decarboxylation, led to a small yield of a crystalline product, but dehydrogenation had occurred at some stage, as the analytical figures and properties were in very good agreement with the phenanthrene analogue of (XIII), which has been described by Fieser and Hershberg (*J. Amer. Chem. Soc.*, 1936, **58**, 2322).

Note on Biological Testing [By F. L. WARREN].

Lactonic degradation products of oestriol methyl ether, of somewhat analogous structure to some of the synthetic compounds now described, were reported by MacCorquodale, Levin, Thayer, and Doisy (*J. Biol. Chem.*, 1933, **101**, 753) to have a higher oestrogenic activity than oestrone, and Fieser and Hershberg (*J. Amer. Chem. Soc.*, 1935, **57**, 1852) claimed a moderately high order of oestrogenic activity for the anhydride of phenanthrene-1 : 2-dicarboxylic acid and its 3 : 4-dihydro-derivative. Hence tests for oestrogenic activity have been carried out with many of the compounds described in this and a previous communication (Cohen, Cook, and Hewett, J., 1936, 52). The technique used was the ordinary Allen and Doisy procedure of examining vaginal smears after injection of the substances into ovariectomised mice. The compounds were mostly very sparingly soluble, and in the higher doses were injected in suspension in sesame oil. Contrary to expectation, no oestrogenic activity whatever was shown by any of the compounds in the doses in which they were administered. Five mice were normally used for each test, and the doses were spaced so that six injections were given during 48 hours; smears were examined up to 96 hours after the last injection. The compounds tested, with the total amount administered to each mouse, were as follows :

Compound.	Doses, mg.
Phenanthrene-1 : 2-dicarboxylic anhydride	0·1, 0·5, 5·0
1 : 2 : 3 : 4-Tetrahydrophenanthrene-1 : 2-dicarboxylic anhydride	5·0
1 : 2 : 3 : 11-Tetrahydrophenanthrene-1 : 2-dicarboxylic anhydride	0·1, 0·5, 5·0
7-Methoxyphenanthrene-1 : 2-dicarboxylic anhydride	0·5, 5·0
7-Methoxy-3 : 4-dihydrophenanthrene-1 : 2-dicarboxylic anhydride	0·1, 0·5, 5·0
7-Hydroxy-3 : 4-dihydrophenanthrene-1 : 2-dicarboxylic anhydride	0·1, 0·5
Dimethyl-lactone (XI) from 1 : 2 : 3 : 4-tetrahydrophenanthrene-1 : 2-dicarboxylic anhydride and methylmagnesium iodide	10

On account of the low solubility of these anhydrides in sesame oil absorption by the animals must be very slow, and additional tests were made by injecting aqueous solutions of sodium 7-methoxy-3 : 4-dihydrophenanthrene-1 : 2-dicarboxylate in both mice and rats, so that each mouse received 10 mg. of material, and each of 4 rats received 100 mg. There was no sign of oestrus in any animal.

From these results it is evident that none of the compounds examined has any oestrogenic activity when examined in accordance with the standard procedure. It subsequently transpired that the activity originally claimed for phenanthrene-1 : 2-dicarboxylic anhydride and its 3 : 4-dihydro-compound (Fieser and Hershberg, *loc. cit.*) was estimated by a new method of assay (Pincus and Werthessen, *Science*, 1936, **84**, 45) and it was afterwards admitted by Fieser and Hershberg (*J. Amer. Chem. Soc.*, 1936, **58**, 2315) that their earlier statement was misleading and that the anhydrides gave negative results when tested by the standard technique. Also MacCorquodale, Levin, and Thayer (*J. Biol Chem.*, 1934, **105**, lv) appear to have withdrawn their earlier claim (*loc. cit.*), for in a note on the degradation products of oestriol methyl ether they state " none of the derivatives of

theelin and theelol so far obtained has any significant oestrogenic activity." * Thus there is now general agreement that compounds of the type under review in the present communication have no oestrogenic activity of any practical importance [The Research Institute, The Royal Cancer Hospital (Free)].

Experimental.

1-Vinylnaphthalene (cf. Sontag, *Ann. Chim.*, 1934, **1**, 359).—1-β-Naphthylethyl alcohol (24 g.) was added dropwise to solid potassium hydroxide in pellet form (16 g.), maintained at 165°/15 mm. in a Claisen flask fitted with a cooled receiver, in which a wet distillate accumulated. This was dissolved in ether, dried with calcium chloride, and freed from solvent. The product, a colourless refractive liquid (17·6 g.), was used directly for condensation with maleic anhydride.

1 : 2 : 3 : 11-Tetrahydrophenanthrene-1 : 2-dicarboxylic Anhydride (II; X = H).—A solution of 1-vinylnaphthalene (7·5 g.) and maleic anhydride (5 g.) in xylene (15 c.c.) was heated on the water-bath for 20 minutes and allowed to cool; it set to a crystalline mass, which was washed with benzene after 3 days. The *adduct* (4 g.) crystallised from glacial acetic acid, acetic anhydride, or, better, dioxan, in fine needles, sintering at 176°, m. p. 186—189° (Found: C, 75·9; H, 5·0. $C_{16}H_{12}O_3$ requires C, 76·15; H, 4·8%). It was insoluble in cold dilute sodium hydroxide solution, dissolved on warming, and the chilled solution reduced permanganate instantly. Perbenzoic acid titration corresponded to a consumption of 1·7 atoms of oxygen per molecule, against the required value of 2.

1 : 2 : 3 : 4-Tetrahydrophenanthrene-1 : 2-dicarboxylic Anhydride (III).—When the above adduct (10 g.) was boiled for 45 minutes with glacial acetic acid saturated with hydrogen chloride (100 c.c.), it passed readily into solution and, on cooling, the isomeric *anhydride* crystallised (8·5 g.). The latter was much more soluble in hot glacial acetic acid and crystallised from it in compact colourless prisms, m. p. 167—168° (Found: C, 76·0; H, 4·8. $C_{16}H_{12}O_3$ requires C, 76·15; H, 4·8%). It gradually became yellow when crystallised from benzene or sublimed in a vacuum. Brief heating in alkaline solution, followed by acidification, yielded *1 : 2 : 3 : 4-tetrahydrophenanthrene-1 : 2-dicarboxylic acid*, which crystallised from glacial acetic acid in minute rhombs, m. p. 220° (decomp.) (Found: C, 71·0; H, 5·3. $C_{16}H_{14}O_4$ requires C, 71·05; H, 5·2%).

Homogeneity of the Adduct (II; X = H).—The crystallised adduct (1 g.), m. p. 186—189°, was finely powdered and refluxed with pure benzene (20 c.c.) for 1 hour. Most of it remained undissolved and was unchanged. The solution was evaporated to dryness, yielding 0·15 g. of crystalline material, which was slightly less pure adduct, m. p. 180—185°, and gave no depression in m. p. with the original. There was no evidence of the presence of the naphthalene isomer which is much more soluble in benzene (not less than 0·5 g. in 20 c.c.).

Methyl 1 : 2 : 3 : 4-Tetrahydrophenanthrene-1 : 2-dicarboxylate (V).—(*a*) The recrystallised adduct (1 g.) was dissolved in warm dilute sodium hydroxide solution, cooled, and treated with methyl sulphate (2 g.) at room temperature, the mixture being constantly shaken and kept alkaline. After an hour the insoluble material was extracted with ether, from which 0·2 g. of the *ester* was isolated; this crystallised from methyl alcohol in stout rhombic prisms, m. p. 105—106° (Found: C, 72·2; H, 6·0. $C_{18}H_{18}O_4$ requires C, 72·5; H, 6·1%), not depressed by the product from (*b*).

(*b*) The naphthalenic isomer (III) (5 g.) was esterified in the usual way with 50 c.c. of methyl alcohol which was saturated with dry hydrogen chloride, or treated with concentrated sulphuric acid (5 c.c.). The product (4 g.) was identical with that from (*a*).

Condensation of Methyl 1 : 2 : 3 : 4-Tetrahydrophenanthrene-1 : 2-dicarboxylate with Ethyl Acetate.—To a solution of the methyl ester (V) (3·3 g.) in ethyl acetate (40 c.c.) were added 1·5 g. of fine sodium wire, which readily dissolved under reflux. More sodium wire was added (2 g.), and the mixture refluxed overnight and cooled for a day. The solid which separated was collected after addition of anhydrous ether (100 c.c.). It was heated at 100° for 1 hour with 5*N*-hydrochloric acid (20 c.c.). Vigorous evolution of carbon dioxide ensued. The cooled product (0·2 g.) crystallised from benzene or acetone in fine, pale yellow needles, m. p. 240° (corr.) in a Pyrex tube, and decomposing above 240° in soft glass; this compound gives no colour with ferric chloride, absorbs bromine readily, and gives a red alkaline solution, and is no doubt identical with 1′ : 3′-diketo*cyclo*pentenophenanthrene, which has been described by Fieser and Hershberg (*loc. cit.*) [Found (micro.): C, 82·8; H, 3·9. Calc.: C, 82·9; H, 4·1%].

* Thayer, MacCorquodale, and Doisy (*J. Pharm. Exp. Ther.*, 1937, **59**, 52) now explain that faulty technique was responsible for their original claim that these compounds were highly active.

The Action of Methylmagnesium Iodide on 1 : 2 : 3 : 4-*Tetrahydrophenanthrene*-1 : 2-*dicarboxylic Anhydride*.—A solution of the anhydride (III) (5 g.) in sodium-dried benzene (50 c.c.) was chilled in a freezing mixture and to the fine suspension was slowly added with shaking the Grignard reagent prepared from methyl iodide (3 g.), magnesium (0·5 g.), and anhydrous ether (20 c.c.). The mixture was allowed to reach room temperature, warmed at 50° for 1 hour, and after standing at room temperature for 1 hour was decomposed with ice and dilute sulphuric acid. The insoluble product was collected and added to the resinous residue from the benzene–ether solution in the filtrate. The total product so obtained was dried in a vacuum over sulphuric acid, and refluxed for 3 hours in methyl alcohol (50 c.c.) containing concentrated sulphuric acid (5 c.c.). The solvent was removed under reduced pressure, and the residue treated with water and extracted with ether. The ethereal solution was washed with cold sodium carbonate solution, which, on acidification, gave a small amount of acid methyl ester as shown by titration and by the fact that further esterification yielded the dimethyl ester (V). The washed and dried ethereal solution was evaporated till a white solid separated. This was filtered off (0·8 g.) from the chilled solution, and crystallised from glacial acetic acid, affording the *dimethyl-lactone* (XI) in colourless flat needles, m. p. 213·5—214·5° [Found (micro.): C, 81·0; H, 6·8. $C_{18}H_{18}O_2$ requires C, 81·15; H, 6·8%]. When this was heated with alcoholic potash, the water-soluble potassium salt of the corresponding hydroxy-acid was obtained; and acidification regenerated the lactone.

When the ethereal mother-liquor was allowed to evaporate slowly, the methyl ester (V) was obtained (1·5 g. of recrystallised material). The final ethereal mother-liquor yielded a gum, which was distilled, giving 0·5 g. of a viscous yellow oil, b. p. 185—190°/0·2 mm., insoluble in alkali but soluble on heating. Acidification yielded an acidic product. A small quantity of this oil appeared to react readily with sodium in toluene solution, but a satisfactory product such as might be expected from the keto-ester (XII) could not be isolated.

Hydrogenation of the Adduct (II; X = H).—(*a*) A dioxan solution (50 c.c.) of the adduct (1·26 g.) was shaken at 45—50° with palladium-black (0·5 g.) in an atmosphere of hydrogen, under a pressure of 70 cm. of water. After 150—175 c.c. of hydrogen had been absorbed (calc. for two double bonds, *ca.* 250 c.c.) in 5 hours, reaction appeared to have ceased. The filtered solution gave, on evaporation under reduced pressure, a brownish gum, which partly solidified on rubbing with glacial acetic acid–*cyclo*hexane; yield, 0·75 g. This crystallised from glacial acetic acid in prisms, m. p. 166—168°, not depressed by the anhydride (III).

(*b*) The adduct (2·7 g.) was dissolved in warm 0·5*N*-sodium hydroxide (50 c.c.) and after the addition of palladium-black (0·5 g.) was shaken with hydrogen as in (*a*) but at room temperature. After a rapid initial absorption of hydrogen (90 c.c.), readily accounted for by the catalyst, absorption was slow and ceased after 1 hour. On acidification of the filtered solution, the dicarboxylic acid was obtained, which was converted into its anhydride, identified as (III).

6-*Methoxy*-1-*vinylnaphthalene*.—This was prepared in exactly the same manner as 1-vinylnaphthalene from β-1-(6-methoxynaphthyl)ethyl alcohol (Cohen, Cook, and Hewett, J., 1934, 657; 1935, 451) (8·5 g.) and potassium hydroxide (5 g.) at 160—170°/1 mm. The crude dry product crystallised spontaneously (4·1 g.) and separated from methyl alcohol in colourless leaflets, m. p. 41—42° (Found: C, 84·6; H, 6·4. $C_{13}H_{12}O$ requires C, 84·7; H, 6·6%), being readily obtained pure by regeneration from its *picrate*. This, prepared in the usual way in alcoholic solution, separated from alcohol in orange needles, m. p. 114·5° [Found (micro.): C, 54·7; H, 3·7. $C_{19}H_{15}O_8N_3$ requires C, 55·2; H, 3·7%].

7-*Methoxy*-1 : 2 : 3 : 11-*tetrahydrophenanthrene*-1 : 2-*dicarboxylic Anhydride* (II; X = OMe).—A solution of 6-methoxy-1-vinylnaphthalene (2·8 g.) and maleic anhydride (1·4 g.) in xylene (6 c.c.) was warmed on the water-bath for 15 minutes and left at room temperature for 4 days. The solid which separated was collected, washed with benzene, and digested with cold water to remove maleic anhydride; yield, 1·3 g. It crystallised from acetonitrile in small colourless rods, m. p. 171—175° (softening at 165°) to an opaque melt which decomposed with effervescence [Found (micro.): C, 72·2; H, 5·2. $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0%]. An alkaline solution instantly reduced permanganate.

Dehydrogenation. The above adduct (50 mg.) was heated with platinum-black (50 mg.) at 280° for 30 minutes. The temperature was raised to 300°, and the product sublimed (40 mg.) at the pressure of the water-pump. Crystallisation from glacial acetic acid yielded 7-methoxyphenanthrene-1 : 2-dicarboxylic anhydride (IV; X = OMe) in fine yellow needles, m. p. 252—254°, not depressed by a synthetic specimen (Cohen, Cook, and Hewett, J., 1936, 52).

2 : 3 : 4 : 12-*Tetrahydrophenanthrene*-3 : 4-*dicarboxylic Anhydride* (VII).—β-2-Naphthylethyl

alcohol (10 g.) was dehydrated with potassium hydroxide (7 g.) at 170°/14 mm. The crude dried product, 2-vinylnaphthalene (3·1 g.), was worked up as described above, and treated with maleic anhydride (2 g.) in xylene (10 c.c.) for 10 minutes on the water-bath. After 7 days at room temperature, the solid which had separated was collected (0·3 g.). The product crystallised from glacial acetic acid in prismatic needles of indefinite m. p. 170—180°, decomposing above 190° [Found (micro.): C, 75·8; H, 4·8. $C_{16}H_{12}O_3$ requires C, 76·15; H, 4·8%].

Dehydrogenation. This adduct (90 mg.) and platinum-black (50 mg.) were heated at 300° for 1 hour. The sublimed product, obtained as above, crystallised from glacial acetic acid in pale yellow needles, m. p. 243—244°, which was not depressed by an authentic specimen, m. p. 246—247°, prepared by Dr. C. L. Hewett by platinum dehydrogenation of 1 : 2-dihydrophenanthrene-3 : 4-dicarboxylic anhydride (Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1935, **57**, 1853; cf. Fieser, Fieser, and Hershberg, *ibid.*, 1936, **58**, 2323).

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