

Reference to the hydrogen-ion concentration of these various acids gives no apparent reason for the behavior of the various acids. A view to be considered is that the action is selective and follows along the same lines as that of heating the chlorate alone, when rearrangement takes place, 3 molecules of the chlorate being oxidized at the expense of another molecule. In the cases of the action of certain acids on the chlorate, we have the same general character of reaction going on, only at lower temperatures than when the chlorate is heated alone.

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VICTOR LENHER,
HOSMER W. STONE
AND HELEN H. SKINNER.

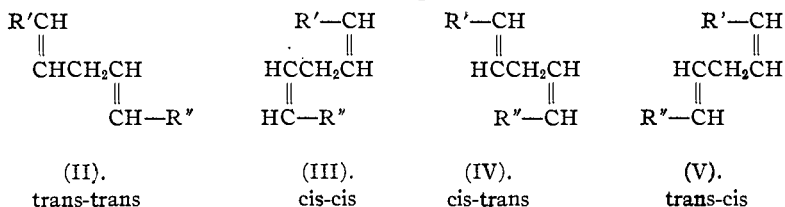
[CONTRIBUTION FROM THE KENT CHEMICAL LABORATORY OF THE UNIVERSITY OF CHICAGO.]

C₁₈ ACIDS. III. FOUR TETRAHYDROXY-STEARIC ACIDS DERIVED FROM LINOLIC ACID, AND THEIR SIGNIFICANCE WITH REGARD TO THE LINOLIC ACID OF COMMON OILS.

BY BEN H. NICOLET AND HENRY L. COX.¹

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In spite of the relatively considerable amount of work that has been done on linolic acid, C₁₈H₃₂O₂, our knowledge of its chemistry is rather strikingly limited. There is a moderate amount of evidence² that its formula is represented by (I) CH₃(CH₂)₄CH=CHCH₂CH=CH(CH₂)₇CO₂H. Four space isomers of such a substance are possible.



in which R' represents the radical CH₃(CH₂)₄— and R'' represents (CH₂)₇CO₂H. No attention has apparently been paid to the question of which, or how many of these occur in natural glycerides, except for Bedford's³ suggestion that there are two different acids of this formula, because the addition of bromine yielded two tetrabromides. Takahashi⁴ has shown further that the α-tetrabromide (m. p. 114°) of linolic acid, when treated with zinc under proper conditions for the elimination of bromine, gives a linolic acid which, on re-bromination, yields two or more tetrabromides (two crystalline products, and an oil which may or may not have been a mixture of these). Each of these products, on removal of bromine, re-

¹ The material here presented is used by Henry L. Cox in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Chicago.

² Goldsobel, *Chem. Ztg.*, 1906, 825.

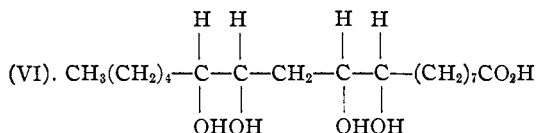
³ Bedford, *Dissertation*, Halle a. S., 1908.

⁴ Takahashi, *J. Tokyo Chem. Soc.*, 40, 233-89 (1919); *C. A.*, 13, 1583 (1919).

generates a "linolic acid" which, when again brominated, yields the same three products as before, and in approximately the same proportions, whichever tetrabromide served as a starting point. The elimination, and perhaps also the re-addition, of bromine occurs in more than one way.

Again, the oxidation of linolic acid with alkaline permanganate gives at least two (the published data might suggest a larger number)⁵ tetrahydroxy-stearic (sativic) acids. This list of things unknown need not be further extended to indicate the need for further information concerning linolic acid.

Since sativic acid (VI) contains 4 asymmetric carbon atoms, it is ob-



vious that 16 optically active forms are possible, or 8 inactive forms (*dl*-mixtures or racemates). As has been suggested, 2 of these 8 are probably known, as products of permanganate oxidation.

It has been shown that, at least for the stereo-isomeric oleic and elaidic acids, addition takes place in only one way in the course of oxidation with permanganate. Thus oleic acid yields only a dihydroxy acid, m. p. 132–3°, while elaidic acid yields only an isomer, m. p. 99–100°. Albitzky⁶ has described a method by which addition seems to occur only in the reverse direction. This consists in the addition of hypochlorous acid to the double bond, with subsequent replacement of the chlorine by hydroxyl, by means of caustic alkali. By this method, Albitzky obtained from oleic acid a dihydroxy-stearic acid corresponding to the product obtained from elaidic acid with potassium permanganate. Similarly treated, elaidic acid gave the dihydroxy acid obtained from oleic acid by direct oxidation.

If it be assumed that linolic acid will behave, with reference to permanganate and hypochlorous acid, as Albitzky showed oleic acid to act with these reagents, it follows that a study of the sativic acids obtained by these different methods, can throw some light on the space structures of the original linolic acids. This has been found to be the case.⁷

The oxidation of linolic acid with permanganate produces 2 different sativic acids,⁸ m. p. 170° and 153°, respectively. The existence of 2

⁵ Cf. Lewkowitzsch, "Chemical Technology of Oils, Fats and Waxes," 5th Ed., 1913, vol. I, pp. 232–3, for list of references.

⁶ Albitzky, *J. prakt. Chem.*, [2] 61, 65 (1900).

⁷ Strictly speaking the results and conclusions here reported, apply to linolic acid regenerated from the tetrabromide, m. p. 114°. But the natural linolic acid gives, so far as reported, such similar results on bromination and oxidation, that the acid of ordinary oils may be at least suspected of being identical with the regenerated acid.

⁸ Meyer and Beer (*Monatsh.*, 33, 325 (1912)) oxidized the fatty acids of the seed oil of "Jimson weed" (*Datura stramonium*) and obtained an "α-sativic acid," m. p.

sativic acids, as indicated by various previous observers,⁵ is thus confirmed by the work here reported, in which for the first time both acids are isolated from a single oxidation experiment. The fact that 2, and essentially only 2, sativic acids were isolated (although a relatively much smaller quantity of lower melting material, which may perhaps be an isomeric sativic acid, was obtained) points to the fact that 2 stereo-isomers of linolic acid were present originally. It is conceivable, though not in accord with the behavior of oleic acid on oxidation, that both of these acids might come from a single linolic acid; but this would not account for the additional sativic acids later described.

The addition of hypochlorous and hypobromous acids to linolic acid⁹ was found to take place smoothly, and a method was developed which permitted the transformation of these substances to sativic acids, though the yields, never over 14%, left much to be desired. The first step in this transformation, the formation of tetra-acetyl-sativic acid, was accomplished with a yield of 85%. Hydrolysis of the tetra-acetate, however, gave a large amount of by-products, probably due to a splitting off of acetic acid from the partially hydrolyzed molecule to give ring compounds containing oxygen.¹⁰

Two new sativic acids, m. p. 144.5° (γ -acid), and 135° (δ -acid), were thus obtained, differing in melting point and solubility from those obtained by direct oxidation. No indications of the formation of α - or β -acid were obtained in this product.

Since only 2 sativic acids were obtained by the permanganate oxidation of linolic acid, while 2 and only 2 additional sativic acids were obtained from the hypobromous acid addition product, it is concluded that 2 and essentially only 2 of the possible stereo-isomeric forms (II-V) are present in "ordinary" linolic acid. This limits the possibilities to six combinations, as follows:

A, II and III	C, II and V	E, III and V
B, II and IV	D, III and IV	F, IV and V

Further, as *cis* (or *trans*) addition yields α - and β -sativic acids, while *trans* (or *cis*) addition yields the γ - and δ -acids, it is not unreasonable to eliminate 2 of these pairs, A and F. Examination of the space formulas will show that *trans* addition at the double bonds of (II) or (V) will give 163°, and a " β -sativic acid," m. p. 173°. As the same oil yielded a tetrabromo-stearic acid, m. p. 117°, whereas the highest recorded melting point of linolic acid tetrabromide is 114°, it is not certain that these were true linolic acid derivatives. However, in conformity with their system, the acid of higher melting point (170°) obtained in this work, will be called the β -acid, and the second, (m. p. 153°) the α -acid.

⁹ Albitzky, Ref. 6, has prepared the corresponding addition products of several acids of the oleic series.

¹⁰ There is here the possibility of forming oxide rings containing from 3 to 6 atoms. The relative ease of formation and stability of 5- and 6-membered rings, is well known.

the same product as *cis* addition at the corresponding bonds of (III) and (V), and *vice versa*.

The evidence is thus fairly conclusive that there are 2 stereo-isomers present in ordinary linolic acid, and that choice of the 2 forms is limited to 4 possibilities, B, C, D, and E, above. A further limitation of choice cannot be definitely made in the present state of our knowledge of linolic acid and its derivatives; but it may be of interest to consider certain indirect evidence that makes possible a fairly plausible guess, for by making use of two not unreasonable assumptions the number of possibilities can be narrowed much further.

It has been shown that when bromine is added to oleic or elaidic acid, and subsequently removed with zinc, only the original acid is obtained. Linolic acid, however, behaves in a different manner.⁴ Isomerization takes place in the latter case, but not in the former; but even linolic acid produces only 2 of the 4 possible isomers, so that even here but one double bond has been affected. The first assumption, then, is that the double bond in the 9, 10 position (common to oleic and linolic acids) is the one *not* affected. This excludes the 2 combinations B and E (above), on account of the different space arrangement of the 9-10 double bond in these pairs of isomers. The choice is thus limited to the 2 pairs, C and D.

It is the universally observed rule that the naturally occurring higher fatty acids of the oleic series are the *trans* forms.¹¹ The *cis* forms are known only as artificially prepared from these.

The second assumption, then, is that linolic acid, also, should have a *trans* structure with regard to its 9-10 double bond. Inspection of the formulas shows that only (II) and (V) fulfil this condition, and these are accordingly the linolic acids most probably present in the natural glycerides, and in linolic acid as prepared from them by the usual methods.

It should be understood that present evidence is not definitely sufficient to limit the choice of stereo-isomers further than to the 4 pairs above mentioned, without the introduction of assumptions that have at present no particularly firm experimental foundation. A certain amount of speculation is however justified by the fact that present synthetical methods do not make likely the synthesis in the near future of any homogeneous sativic acid, by methods which would indicate a really definite space-structure.

Experimental Part.

Preparation of Linolic Acid Tetrabromide.—The starting material was the dried fatty acids of cottonseed oil. Of several methods tried, the following gave the best results. A slight excess of bromine (as shown by a faint permanent red color) was added gradually to a well-stirred solution of 200 g. of fatty acids in 1000 cc. of ligroin (b. p. 70–100°) cooled to 0°. The mixture was boiled, filtered hot, and allowed to crystal-

¹¹ Lewkowitsch, Ref. 5, pp. 178, 195, 213.

lize. After filtering and washing with ligroin of lower boiling point, 88 g. of tetrabromide, m. p. 113° without further purification, was obtained. More than a kilogram of tetrabromide was prepared by this method.

Linolic Acid.—This was prepared from the tetrabromide in the usual way, by refluxing it for 24 hours with zinc and 8% alcoholic hydrochloric acid, followed by saponification of the ester. The yields averaged 97%, and the purity, as judged by the iodine number, ranged from 86–99%.

Dichloro-dihydroxy-stearic Acid.—Linolic acid (11 g.) was dissolved in 500 cc. of 1% potassium hydroxide solution, and slightly more than 2 mols of 2 *N* potassium hypochlorite was added. (The sodium soaps are so slightly soluble that their use requires an almost prohibitive volume of solution.) A slow stream of carbon dioxide was then led through the solution. A white, gummy mass precipitated within a short time, but the gas was passed for several hours, or until a small sample of the solution, removed for testing, showed little or no test for hypochlorite. Excess of the latter was then destroyed with bisulfite and dil. sulfuric acid, and the solution extracted with ether. The light brown viscous oil obtained, would not crystallize, and could not be made to distil under 10 mm. pressure. The iodine number (2.3%) showed nearly complete reaction.

Analysis (Carius). Calc. for $C_{18}H_{34}O_4Cl_2$: 18.92. Found: Cl, 18.98.

All the products intermediate between linolic acid and γ - and δ -sativic acids, showed themselves incapable of crystallization or of distillation. Their definite characterization, and preparation in a high state of purity, must therefore be left for future work.

Dibromo-dihydroxy-stearic Acid.—This was prepared in very much the same manner as was the chloro compound, but saturation with carbon dioxide was carried out at 0°, on account of the less stability of hypobromous acid. From 40 g. of linolic acid, 59 g. of a viscous brown oil was obtained.

Analysis (Carius). Calc. for $C_{18}H_{34}O_4Br_2$: 33.7. Found: Br, 31.3, 31.1.
Iodine number. Calc., 0.0. Found: 8.5.

The bromine determination thus indicates a purity of 93%, while the iodine absorption points to a 95% conversion of the linolic acid. It appears to be possible to prepare this acid with a purity of more than 90%, and in view of the character of the product, better results were scarcely to be expected.

Tetrahydroxy-stearic Acid Tetra-acetate (Sativic Acid Tetra-acetate).—When dichloro-dihydroxy-stearic acid was heated with sodium acetate and acetic anhydride for periods of 3 to 21 hours, the product contained much chlorine, and gave no sativic acid on saponification. The substitution of silver acetate for sodium acetate gave no better results. When potassium acetate was used, and the mixture refluxed 45 hours, an oil was obtained which gave the following analytical data.

Acid number. Calc.: 92.2. Found: 83.2, 88.8.
Saponification number. Calc.: 543. Found: 489.2

Obviously, therefore, the product was rather impure, but consisted chiefly of sativic acid tetra-acetate. It still contained 2.3% of chlorine.

When dibromo-dihydroxy-stearic acid was refluxed with dry potassium acetate and acetic anhydride, the reaction was much more rapid. A precipitate of potassium bromide began to appear almost at once, and at the end of 5 hours, represented 74% of the bromine theoretically present. This method, with slightly longer heating, proved to be the best for preparing the tetra-acetyl derivative.

Saponification of Sativic Acid Tetra-acetate.—Sativic acid is somewhat soluble in hot water, and insoluble in ether. It was by these preliminary tests that the success of various methods of hydrolysis of its tetra-acetate was judged. Alcoholic sodium or

potassium hydroxide gave yields of sativic acid of 3-4%, regardless of whether the reaction was carried out at ordinary or higher temperatures. Sodium carbonate in aqueous-alcoholic solution gave about the same result. Hydrolysis with a 1% alcoholic solution of hydrochloric acid (Gattermann's method for saponification of ethylene di-acetate) gave less good results, although important amounts of ethyl acetate were formed. Dil. aqueous sulfuric acid was equally unsuccessful in giving the desired results.

The best yields of sativic acid were obtained by hydrolysis of the tetra-acetyl derivative with hot aqueous sodium hydroxide, for a period of one hour. The solution, diluted to 1 liter for each 10 g. of original substance, acidified, allowed to stand overnight, and washed with ether, gave 12-14% of sativic acid. Better yields could not be obtained. The exceptional opportunity for the formation of cyclic oxides in this case, has already been mentioned.

The ether-soluble portions of the residues from these hydrolyses were saved, and an attempt made to distil them. Under a pressure of less than 1 mm., distillation occurred only in part, and with obvious decomposition, above 300°.

Sativic Acids Derived from Dihalogeno-dihydroxy-stearic Acids.—As the product obtained directly from the hydrolysis of dichloro-dihydroxy-stearic acid was the same in melting point, 140-3°, and in all of its observed properties, as that from the bromine analog, the two were used interchangeably in the later work.

Preliminary attempts to purify the sativic acid obtained by hydrolysis of the tetra-acetyl derivative, indicated separation into 2 portions, m. p. 135° and 144° respectively. Accordingly, 3 g. of these sativic acids, previously recrystallized once from water was boiled for 15 minutes with 200 cc. of water, containing a few drops of hydrochloric acid, filtered hot, and this extraction process repeated as long as any residue remained. Flocculent precipitates were deposited as all the filtrates cooled. After filtration and washing with ether, the following 5 fractions were obtained.

TABLE I

Fraction	Wt. G.	M. p. ° C.
1	1.25	Below 120
2	0.45	135
3	0.25	135
4	0.22	144-5
5	0.05	145

Fractions 2 and 3 were combined and recrystallized from 50% acetic acid, then from 50% alcohol. As the melting point remained constant at 135°, the material was considered to be pure, and designated δ -sativic acid. Similarly treated, Fraction 4 retained its melting point, 144.5°, and was designated γ -sativic acid. Analysis gave the following results.

	Analyses		
	γ -Acid M. p. 144.5° %	δ -Acid M. p. 135° %	Calc. for C ₁₈ H ₃₆ O ₈ %
Carbon.....	61.87 62.26	61.89	62.03
Hydrogen.....	10.42 10.50	10.21	10.42
	Solubility		
	G.	G.	
100 g. of boiling water dissolves.....	0.20	0.39
	Equiv. wt.		
(By titration).....	351.5	348.4

Although these two acids differ rather strikingly in melting point and in solubility, the melting point of the δ -acid is not lowered by admixture of a small amount of the γ -acid. Accordingly, a series of mixtures was made containing known amounts of each acid, and the temperatures estimated at which melting began, and was complete. The results, plotted in Fig. 1, Curve 2, showed that mixtures melted over much wider ranges than the pure substances, and that the formation of solid solutions (rather common among the higher fatty acids) was indicated. All the evidence, therefore, indicates the formation of 2 different sativic acids in this series of reactions.

Oxidation of Linolic Acid.—The procedure adopted was that of A. Rollet,¹² essentially an oxidation with cold, dilute, alkaline permanganate. The product was dried and extracted with ether for 8 hours, the residue being a white powder which constituted a 54% yield of crude sativic acid. It melted at 162–8°, and recrystallization from alcohol had very little purifying effect. This was also the experience of Rollet; but his further results¹³ were not in accordance with those here described. Treatment with benzol had no appreciable effect. The crude product was therefore treated with water, as in the case of the γ - and δ -acids.

Twelve g. of ether-extracted sativic acid was boiled for several minutes with 2.5 liters of water containing 4 cc. of conc. hydrochloric acid. The solution was filtered hot, and the filtrate allowed to cool. The residue was boiled again with acidified water, and the process repeated as long as any material crystallized as the solution cooled. To prevent too great loss, the mother liquor from the first fraction was used as solvent for the third and fifth fractions, and that from the second, for the fourth and sixth. Six fractions were collected as shown.

TABLE II

Fraction	Wt. G.	M. p. °C.	Fraction	Wt. G.	M. p. °C.
1	2.30	148–150	4	0.85	170–171
2	1.95	153.5–4.5	5	0.95	169–170
3	1.50	165–169	6	0.45	169–171

Other samples were treated in the same way with similar results. The melting points indicate a partial separation into at least two substances.

The various fractions of several preparations were recombined to form three new fractions: A, all fractions melting from 145° to 150°; B, all fractions melting from 152° to 155°; C, all fractions melting from 170° to 172°.

Fraction A was fractionated into 14 portions by the procedure outlined above. All but the first and last two melted between 150° and 154°, and were combined and crystallized several times from glacial acetic acid and from alcohol. After the first time, the product melted constantly at 153°, and was considered to be pure α -sativic acid. A further quantity of identical material was obtained by crystallizing fraction B from acetic acid.

When Fraction C was crystallized from acetic acid, the melting point, after the first time, remained constant at 170°. This material is evidently the sativic acid commonly described, and is here called the β -acid.

While it is fairly obvious from the data given that these two products are different and isomeric, the melting point of the α -acid is not depressed by admixture with the other. Curve 1 (Fig. 1), which shows the temperatures at which melting begins, and at which it is complete, for mixtures of various compositions, indicates the formation of solid

¹² A. Rollet, *Z. physiol. Chem.*, **62**, 410 (1909).

¹³ A. Rollet, Ref. 12. "When, however, the substance (*i. e.*, crude sativic acid) was boiled with 50 parts of benzol, in which only a minimal trace dissolved, and was again crystallized from alcohol, the melting point was 171–3°."

Analyses			
	α -Acid M. p. 153° %	β -Acid M. p. 170° %	Calc. for C ₁₈ H ₃₄ O ₆ %
Carbon.....	61.66	62.14	62.03
	61.96	62.11	
Hydrogen.....	10.37	10.50	10.42
	10.55	10.40	
Solubility			
	G.	G.	
100 g. of boiling water dissolves...	0.10	0.04	
Equiv. wt.			
(By titration).....	349.0	345.0	348.4

solutions. At the same time, it adds one more proof that the two acids are different.

The β -acid corresponds closely to the sativic acid obtained by Hazura,¹⁴ Rollet¹⁵ and others. With the possible exception of Meyer and Beer⁸ no previous investigators have mentioned separating more than a single sativic acid from the oxidation of linolic acid. However, among others, Fahrion,¹⁶ Krzizan,¹⁷ and Tsujimoto¹⁸ have described acids melting from 152° to 168°. These or some of them, may well have been the α -acid in various degrees of purity.

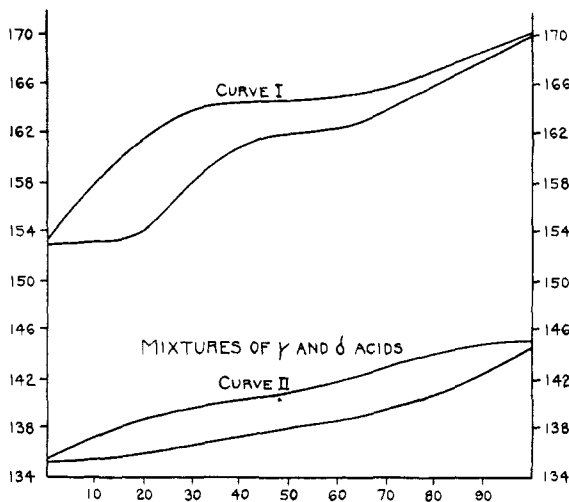


Fig. 1.

Mixtures of α and β acids.

Melting Points of Mixtures of Other Saticic Acids.—In the same way as has been described for the pairs γ and δ , and α and β , the melting points of mixtures of the other 4 pairs were investigated. The results are plotted in Figs. 2 and 3. In each of these 4 cases, the effect of mixing on melting-

¹⁴ Hazura, *Z. angew. Chem.*, **1**, 313 (1888).

¹⁵ A. Rollet, Ref. 12, p. 420.

¹⁶ Fahrion, *Z. angew. Chem.*, **17**, 1483 (1904).

¹⁷ Krzizan, *Chem. Rev. Fett Hartzind.*, **15**, 8 (1908); **16**, 3 (1909).

¹⁸ Tsujimoto, *ibid.*, **18**, 112 (1911).

point lowering was distinct, though sometimes rather slight. The β - δ , and to a lesser degree the α - δ combination showed evidence of solid solution formation. The α - β and α - γ mixtures, on the other hand, gave no such indications, the melting points being quite sharp.

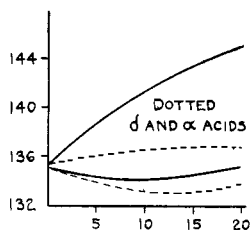


Fig. 2.

Solid curves.

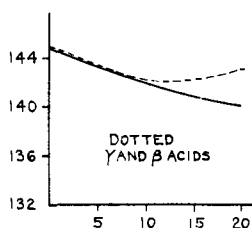
Mixture of δ and β acids.

Fig. 3.

Solid curves.

Mixture of γ and α acids.

Stability of α -Sativic Acid.—Acetic anhydride is recognized as a reagent which in certain cases is capable of bringing about the conversion of one stereo-isomer into another. It was therefore considered worth while to show that the γ - and δ -acids were not formed by a mere rearrangement of the α - and β -forms.

One g. of α -sativic acid was refluxed with 10 cc. of acetic anhydride and 1 g. of potassium acetate, under the same conditions as were used in the transformation of dibromo-dihydroxy-stearic acid. The product was saponified with aqueous alkali as already described. After one recrystallization, the product (0.75 g.) melted at 152–3°. No transformation, therefore, has occurred, and a further testing of this question would seem superfluous.

Summary.

1. Two distinct isomeric sativic acids (tetrahydroxy-stearic acids) have been obtained as the chief products of the oxidation of linolic acid by permanganate.
2. The additions of hypochlorous and hypobromous acids to linolic acid have been studied and shown to take place readily and with good yields.
3. These addition products give, on hydrolysis, two additional sativic acids, hitherto unknown.
4. Attention has been called to the fact that there are 4 possible stereo-isomers corresponding to the accepted structural formula for linolic acid. From a consideration of the 4 sativic acids described above, it is shown that only 2 of these isomeric forms occur (at least in important amounts) in linolic acid as usually prepared. It is further indicated that the most probable structures for this pair of isomers are those represented by Formulas II and V, above.

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