TIGLIC AND ANGELIC ACIDS

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CONTENTS

I. INTRODUCTION

The purpose of this review is to discuss the natural occurrence, uses, configurations, properties, syntheses, and reactions of the geometric isomers, tiglic acid (m.p. 62–64°C.) and angelic acid (m.p. 44–46°C.), and of their derivatives. These trivial names, which are the ones used in the index of *Chemical Abstracts*, will be used throughout this review. For the purpose of clarifying the configurations it will also be convenient to use the name 2-methyl-*trans*-crotonic acid for tiglic acid (I) and the name 2-methyl-*cis*-crotonic acid for angelic acid (II). This method of nomenclature is an adaptation of that suggested (61) for olefinic hydrocarbons.

Because no review on these acids has been published, considerable historical material is included in this review. The literature has been covered through 1953.

II. NATURAL OCCURRENCE AND USES

Tiglic and angelic acids, which have the isoprene carbon skeleton, have been found to be quite widely distributed in plants—usually as esters. The first isolation of an impure acid, which was probably a mixture of tiglic and angelic acids with other acids, was reported (135) in 1820. The mixture was isolated from the saponification of cevadilla seeds (*Schoenocaulon officinale* A. Gray) and was named cevadic acid. Even in recent years this name for tiglic acid is sometimes encountered (53). Further investigation of cevadilla showed that the acid was in the form of an alkaloid ester, cevadine, which could also be isolated

from *Veratrum album* L. The acid isolated from the saponification of the alkaloid has been reported to be tiglic acid (95, 200), angelic acid (1, 169), and a mixture of the two (81, 158). The most reasonable explanation of such discrepancies, which are common among the reports on these acids, is the isomerization of angelic acid to tiglic acid which has been observed to take place under conditions of saponification or acid hydrolysis, especially when fairly high temperatures were used (56, 65, 73, 75). The reverse isomerization of tiglic acid to angelic acid showed little tendency to take place. Cevadine, then, appears to be an ester of angelic acid and the amino alcohol cevaginine (169).

The first clean-cut isolation of angelic acid was reported (30) in 1842. The acid was isolated by the saponification of the root of *Angelica archangelica* L., for which it was named (30). A more complete description of the acid and its properties was given in 1845 (121). No tiglic acid could be isolated from this source (85, 152, 153). The first reported isolation (151) of tiglic acid in 1858 was by the saponification of croton oil from *Croton tiglium* L. It was said (151) at that time to be accompanied by angelic acid, but subsequent reports (57, 85, 86, 152, 156, 157) discounted this fact and also established the identity of tiglic acid with synthetic 2-methylcrotonic acid (79).

For early investigations the best method (192) of preparation of tiglic and angelic acids was by the saponification of Roman camomile oil from *Anthemis nobilis* L. Angelic acid had originally been isolated from this source (42, 54, 55, 56, 84, 85, 101), but later work appears to have established the fact that tiglic acid esters were also present in the oil (17, 67, 68, 73, 75, 152, 157) and that the tiglic acid was not formed by isomerization during saponification. The isolation (54) of butyl and amyl alcohols from the saponification mixture indicated that esters of these alcohols were present. A fractional distillation of the oil yielded three fractions, reported (74) to be isobutyl angelate, isoamyl angelate, and isoamyl tiglate. The presence of isobutyl esters was questioned however, since only *n*-butyl alcohol could be isolated (20) from the saponification.

Similarly to cevadine, the alkaloid turneforcine, from *Tournefortia sibirica* L., has been reported to give angelic acid and the amino alcohol turneforcidine on saponification (120). Tiglic acid has been isolated, along with amino alcohols, from the saponification of several alkaloids: from meteloidine (*Datura meteloides* D. C.) along with teloidine (141); from tigloidine (*Duboisia myoporoides* R. Br.) along with ψ-tropine (16, 176); from lindelofamine (*Lindelofia anchusoides* Lehm.) along with trachelanthic acid and *d*-isoretronecanol (110).

Tiglic acid has been isolated from the saponification of jegosapogenin from *Styrax japonicus* Sieb. et Zucc. (7, 163), while angelic acid was obtained by the saponification of theasaponin from the tea plant (*Thea sinenis* L.) (99, 177). The substance laserpitin from *Laserpitium latifolium* L. was found on saponification to give two moles of angelic acid per mole of a dihydroxylactone, laserol (66, 126, 149). The red coloring matter alkannin, from *Alkanna tinctoria* Tausch, has been found (27) to occur naturally in the form of an easily hydrolyzable ester of angelic acid.

Tiglic acid has been reported on numerous occasions from the saponification of oil of geranium obtained from various sources (181, 182). It has been pre-

sumed that the main constituent of these oils is geranyl tiglate (138, 181, 182), and this ester, as well as (+)-citronellyl tiglate and phenethyl tiglate, has been synthesized (15, 134) for use in perfumes (138) and flavoring agents (100).

Angelic acid has also been obtained by saponification from *Ferula sumbul* Hook. (91, 154), *Thapsia garganica* L. (39), and *Cynomarathrum nuttallii* A. Gray (129). Tiglic acid has been obtained by saponification from *Convolvulsus scammonia* L. (140), *Ipomoea orizabensis* Led. (109, 139, 140), *Ipomoea hederacea* Jacq. (8), French oil of lavender (*Lavandula officinalis* Chaix) (161), and anise seed oil (*Illicium verum* Hook.) (19). It was also isolated as a constituent of the crude pyroligneous acid obtained from the dry pyrolysis of beech wood (160). In two cases tiglic acid has been isolated from the metabolic products of microorganisms: from *Ascaris lumbricoides* (37) and from crude sodium penicillin (44).

Besides the use of their esters in perfumes and flavoring agents, tiglic and angelic acids have been mentioned in a patent (178), along with other acids of relatively low molecular weight, as being useful as emulsoid breakers. Angelic acid, along with other α,β-unsaturated acids, when incorporated in branched-chain olefin polymers, yielded acids whose multivalent metallic salts have been said to be good driers for use in varnishes or inks (60).

III. STEREOCHEMISTRY

Perhaps the most difficult problem encountered in the history of tiglic and angelic acids was the nature of the isomerism relating the two compounds. The fact that they were isomers was recognized at the time that tiglic acid (2-methylcrotonic acid) was first synthesized (79). This synthesis (79, 125) from ethyl 2-hydroxy-2-methylbutyrate by way of ethyl tiglate established the branched-carbon skeleton for tiglic acid, but angelic acid was believed (79) to be a straight-chain isomer. The fact that they had the same carbon skeleton was established by the identity of the dibromides obtained by the addition of bromine (55, 76, 153). This dibromide on debromination gave tiglic acid (55, 105, 153). The two acids gave different hydroiodides which, on reduction by zinc in sulfuric acid, gave 2-methylbutyric acid (152, 153), as did the unsaturated acids themselves on treatment with hydrogen iodide and red phosphorus (9, 156, 157). Oxidation of both tiglic and angelic acid by permanganate in the cold under conditions not expected to give rise to isomerization yielded acetaldehyde and acetic acid along with carbon dioxide (17). Of interest also were the observations that strong base cleaved both acids to propionate ion and acetate ion (55, 79, 101) and that angelic acid was relatively easily isomerized to tiglic acid (56, 65, 73, 75, 193).

Around 1880 the difference between tiglic and angelic acid was believed to involve the position of the double bond (69, 152, 153), and the most likely structure (70) for angelic acid identified it with ethylacrylic acid. This acid was not synthesized independently until 1891 (108), at which time it was still believed possibly to be angelic acid because of its relatively easy isomerization to tiglic acid.

In 1887 Wislicenus (190) made use of the ideas which le Bel, in 1882, had

published (18) concerning maleic and fumaric acids, and presented the general concept of geometric isomerism to explain the isomerism in such cases as that of tiglic and angelic acids (190, 191). At that time the configurations proposed were the reverse of those now accepted. The stereospecific *trans* additions of hydrogen iodide to tiglic and angelic acids, which were interpreted (122) as consistent with the fact that the acids were geometric isomers, are illustrated in chart I. Also illustrated are the stereospecific *trans* eliminations (48, 49, 87) of carbon dioxide and iodide ion from the salts of the iodo acids. These reactions were used (198) to relate the configurations of tiglic and angelic acids to those of the 2-butenes. They were also used as methods of synthesis for the pure isomeric 2-butenes (189, 201). Although tiglic and angelic acids were reported (55, 76, 153) to give the same dibromide, it was eventually established (72, 192) after some controversy (71, 196) that the addition of bromine in the dark was stereospecific. Also, the two dibromides which were formed gave different 2-bromo-2-butenes on *trans* elimination of carbon dioxide and bromide ion (64, 194, 196), and different bromo acids on *trans* dehydrohalogenation (195) as outlined in chart II.

On the basis of stereospecific *trans* additions and *trans* eliminations such as those outlined in charts I and II, Pfeiffer (137) proposed the configurational assignments for tiglic acid (I) and angelic acid (II) and for the isomeric crotonic acids which are now accepted. A comparison of tiglic and angelic acids based on the dispersions and molar refractions of the acids and their esters (12) resulted in the same assignment of configurations (10). This comparison of isomers was related to that of the *cis*- and *trans*-crotonic acids, whose configurations were established by the chemical relationships of the acids to maleic and fumaric acids (14). This configurational assignment of tiglic acid as 2-methyl-*trans*-crotonic acid and angelic acid as 2-methyl-*cis*-crotonic acid was further substantiated by the comparison of relative properties with those of analogously

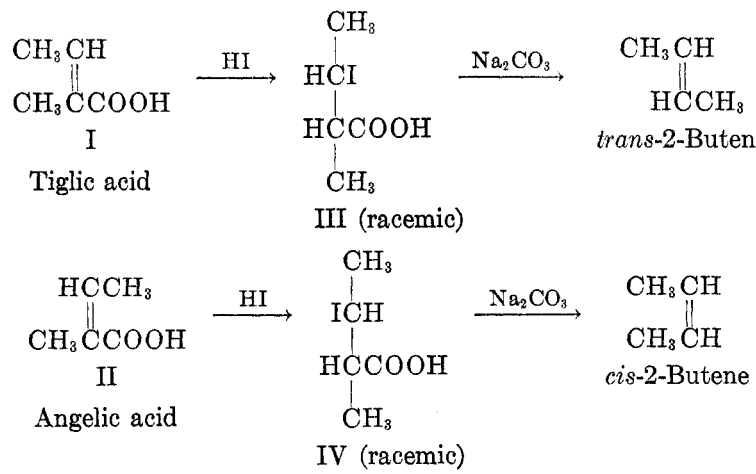


CHART I

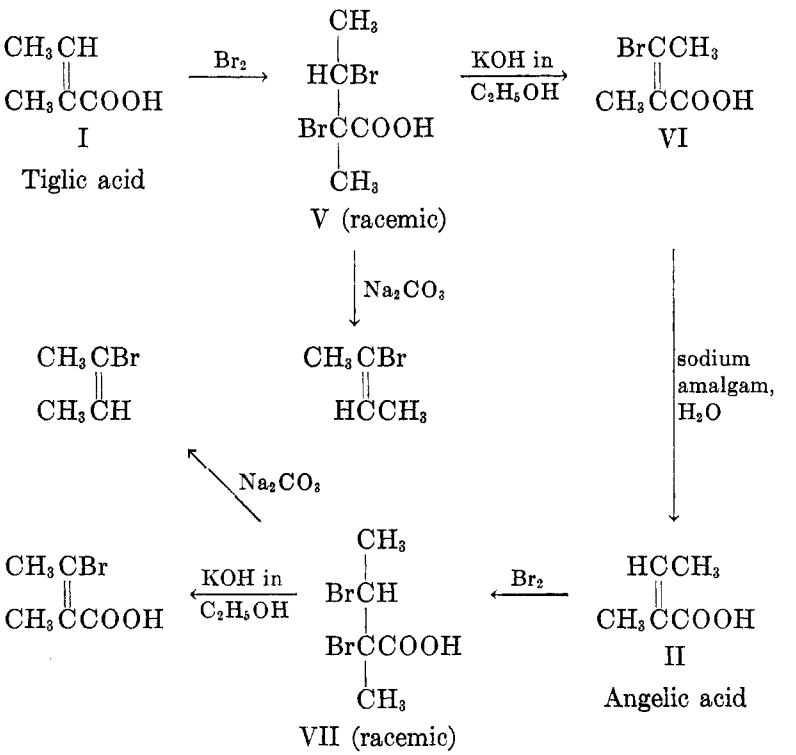


CHART II

substituted benzene derivatives, as shown in table 1 (29, 175). In such comparisons, which have been used fairly often in assignments of configuration (115, 180, 185, 199), it is assumed that the steric relationship of two *cis* groups on a double bond is the same as that of the two groups ortho on a benzene ring, and that the same analogy between *trans* groups and para groups is valid.

IV. PHYSICAL PROPERTIES OF THE ACIDS AND THEIR DERIVATIVES

Various lists of the melting points of solid derivatives of tiglic and angelic acids have been published (96, 116, 162), but no complete list is available. In table 2 are given the melting points of all of the solid derivatives which seem to

TABLE 1

Physical properties of tiglic acid, angelic acid, and derivatives and of analogously substituted benzene derivatives

Property	Tiglic Acid	Angelic Acid	3,4-Dimethylbenzoic Acid	2,5-Dimethylbenzoic Acid
Melting point of acid (175)	65°C.	45°C.	165°C.	132°C.
Dissociation constant, $K_{25°}$ (90, 131, 175)	9.6×10^{-6}	5.0×10^{-5}	3.3×10^{-5}	1.20×10^{-4}
Melting point of amide (29)	75–76°C.	127–128°C.	130–131°C.	186°C.
Boiling point of nitrile (29)	136–137°C.	120–121°C.	232°C.	223°C.

TABLE 2

Solid derivatives of tiglic and angelic acids

Derivative	Melting Point of Angelic Acid Derivative	Melting Point of Tiglic Acid Derivative	References
	°C.	°C.	
Acid*	45.0–45.5	63.5–64.0	(201)
Amide†	127–128	75–76	(29, 128)
Anilide	126	77	(22)
β-Naphthylamide	135	96	(22)
p-Toluidide		70.0–71.5	(57)
Symmetrical hydrazide		182–183	(80)
p-Nitrobenzyl ester		63.9	(96)
p-Bromophenacyl ester	67	68.5–69	(37, 111)
ψ-Tropeine hydrobromide		234.5	(16)
Tropeine hydrobromide		207	(16)
Dibromide	86–87 (V)	87–88 (VII)	(72, 192)
Hydroiodide	59.5–60.5 (III)	86.5–87.0 (IV)	(198)
Hydrobromide		66.0–66.5	(76, 78)
Molecular compound with desoxycholic acid		171.5–172.0	(145)
Molecular compound with apocholic acid		168–168.5	(145)

* Boiling point of tiglic acid, 95.0–96.0°C. at 11.5 mm.; of angelic acid, 85.5–87.5°C. at 12–13 mm. (201).

† The crystallographic properties of the amides have also been investigated (174).

be useful for the identification and characterization of tiglic and angelic acids. In table 3 liquid derivatives of the acids are listed along with properties useful for identification.

The amides of tiglic acid were prepared by way of the acid chloride, which was prepared from the acid and phosphorus trichloride (16, 22). The amides of angelic acid were prepared from an ester, either by ammonolysis or by reaction with an arylaminomagnesium bromide (22). The simple amides were also prepared by hydration of the nitriles (29). *p*-Bromophenacyl tiglate and *p*-nitrobenzyl tiglate were prepared by displacement reactions of the carboxylate ion with a halide. Methyl and ethyl angelate were also prepared in this way in order to insure their identity as angelates (33). The rest of the simple alkyl esters in table 2 were prepared by direct esterification or were isolated from Roman camomile oil (74). The other esters in tables 2 and 3 were made from the acid chlorides.

Density and dispersion measurements have been made on tiglic and angelic acids above their melting points (12, 58). Dispersion measurements have also been made on the ethyl esters (12) and on the nitriles (28).

The dissociation constants of the acids are given in table 1. The fact that angelic acid is a stronger acid than tiglic acid has been interpreted as being consistent with their configurations about the double bond (90).

The molar heat of combustion for tiglic acid has been given as 635.1 kcal. and that for angelic acid as 626.6 kcal. (168). The difference between these values is 8.5 kcal. and is a measure of the stability of tiglic acid with respect to angelic acid. It is comparable with the differences in heats of formation reported (144) for ethyl tiglate and ethyl angelate. At constant volume the value for ethyl tiglate was 953.2 kcal., that for ethyl angelate 963.1 kcal., and the difference 9.9 kcal.; at constant pressure the value for ethyl tiglate was 954.4 kcal., that for ethyl angelate 964.2 kcal., and the difference 9.8 kcal.

TABLE 3

Liquid derivatives of tiglic and angelic acids

Derivative	Boiling Point	Pressure	$n_D^{20°}$	$d_4^{20°}$	References
	°C.	mm.			
Methyl angelate	127.6–128	764	1.4321	0.9413	(128)
Methyl tiglate	139.4–139.6	766	1.4370	0.9498	(128)
Ethyl angelate	48.5–49.5	11	1.4304	0.9178[a]	(12)
Ethyl tiglate	55.5	11	1.4350	0.9247[a]	(12)
n-Butyl angelate	177–179	Atmospheric			(54)
Isobutyl angelate[b]	177–177.5	Atmospheric			(74)
Isobutyl tiglate	180	760			(184)
n-Amyl angelate	198–200	Atmospheric			(54)
Isoamyl angelate	200–201	Atmospheric			(74)
Isoamyl tiglate	204–205	Atmospheric			(74)
Phenyl tiglate	124–126	12	1.5237[c]	1.047[c]	(43)
Phenethyl tiglate	139–140	7		1.0257[d]	(15)
Geranyl tiglate	149–151	7		0.9279[d]	(15)
(+)-Citronellyl tiglate[e]	144–145	7		0.9090[d]	(15)
Chaulmoogryl tiglate	190–192	0.05	1.4740[f]		(38)
(−)-Menthyl angelate[g]	140–141	10.25			(150)
Angelonitrile	121–122	772	1.4230	0.8197	(28, 128)
Tiglonitrile	138–138.4	760	1.4319	0.8313	(28, 128)
Angelic acid chloride[h]					(150)
Tiglic acid chloride	64	35			(16)
	45	12			(22)

[a] The density in this case was measured at 19.5°C. instead of at 20°C.

[b] The identity of this compound has been questioned (20). It may have been the *n*-butyl ester.

[c] Measured at 20.5°C.

[d] The specific gravity was measured at 15°C. and referred to water at 15°C.

[e] $\alpha_D = 2.1°$.

[f] The index of refraction was measured at 19.5°C.

[g] $[\alpha]_D^{20°} = -84.38°$.

[h] This compound was synthesized from the sodium salt of the acid and phosphorus oxychloride and was used immediately without purification.

The ultraviolet absorption spectra of tiglic and angelic acids (37, 40) and of the corresponding amides (40) and nitriles (40) have been measured. The only peaks reported were for the acids: with tiglic acid at 216–217 mμ, $\epsilon = 10.7 \times 10^3$ and with angelic acid at 217 mμ, $\epsilon = 5.15 \times 10^3$ (37). Infrared spectra have been reported for the acids and for their *p*-bromophenacyl esters (37).

Partition chromatography has been used for the separation and identification of tiglic acid (37) and angelic acid (37, 177).

The properties of metal salts were used for the identification of tiglic and angelic acids in early investigations. The salts most usually prepared were those of barium (75, 79, 147), silver (75, 79, 147), sodium (147), zinc (147), potassium (75), and calcium (73, 75). The differences in solubility of the calcium salts were useful in the isolation of the two acids (73). Calcium angelate was much more soluble in water than calcium tiglate.

V. METHODS OF SYNTHESIS

A. Relative stabilities of tiglic and angelic acids

Besides the isolation of tiglic and angelic acids from natural sources synthetic methods have been developed for their preparation. Most of the methods give mainly tiglic acid, the more stable isomer. In fact, the tendency of angelic acid

to isomerize to tiglic acid illustrates this relative stability. The isomerization took place when catalyzed by acid (65, 75), when heated with base at temperatures substantially above 100°C. (73), when heated in water in a sealed tube (56, 73), and when illuminated in carbon disulfide in the presence of a trace of iodine or bromine (193). None of these methods caused appreciable isomerization of tiglic acid to angelic acid. The illumination of the stable forms of α,β-unsaturated acids and their amides in the absence of halogen has been reported to give the labile forms in appreciable yields (148, 164, 165, 166). The illumination of tiglic acid in solution by tropical sunlight for 75 days gave no isolable amount of angelic acid (112). The ultraviolet illumination (135a) of powdered tiglic acid gave a mixture of tiglic and angelic acids. Identification was confirmed by preparation of the *p*-phenylphenacyl esters: the tiglate melted at 105–106°C. and the angelate at 89–90.5°C. Such results have also been reported for such illuminations of crotonic acid, and in this case isomerization was possible with a quartz ultraviolet lamp (167). Ultraviolet illumination of tiglamide gave angelamide (29), just as *trans*-crotonamide gave *cis*-crotanamide (167), but the angelamide on hydrolysis or on deamination with nitrous acid yielded only tiglic acid (29).

It has been possible to handle angelic acid under mild conditions without appreciable isomerization. Treatment with base at relatively low temperatures caused little isomerization (73). Angelic acid was also stable to steam distillation (68). Crystalline angelic acid has been kept for years on laboratory shelves with no isomerization observed (71, 155).

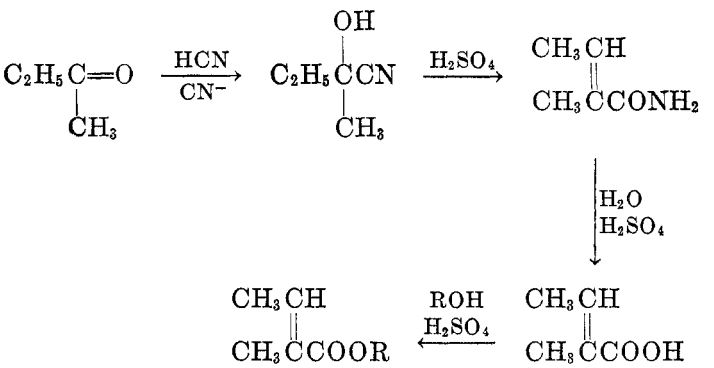
B. Synthesis of angelic acid

The most effective synthesis of angelic acid appears to be that involving the *trans* addition of bromine to tiglic acid, followed by the *trans* elimination of hydrogen bromide and the reduction of the 3-bromoangelic acid (VI) with 9 per cent sodium amalgam in water, as outlined in chart II (33, 103, 104). The overall yield was 33 per cent (33). The synthesis is similar to the general method which has been developed (94) for the synthesis of *cis*-olefins from *trans*-olefins.

The reaction of 3,3-dichloro-2-pentanone with bicarbonate ion has been reported (65) to yield angelic acid and tetramethylbenzoquinone. The identity of the angelic acid was established by its acid-catalyzed conversion to tiglic acid.

C. Syntheses by dehydration and related reactions

The most convenient method of synthesis for tiglic acid seems to be that based on the reaction of 2-hydroxy-2-methylbutyronitrile with 100 per cent sulfuric acid to give tiglamide, which on further hydrolysis gives tiglic acid (46, 47). Hydrogen cyanide was added to ethyl methyl ketone in the presence of cyanide ion, and the crude cyanohydrin was treated with 100 per cent sulfuric acid. Water was then added; steam distillation of the reaction mixture gave a 40–53 per cent yield of tiglic acid (33). Only in a few cases were mixtures containing angelic acid isolated as products. If an alcohol containing a limited amount of water was added to the sulfuric acid solution of the amide, the product was a tiglate ester in yields comparable to those obtained for the free acid (33, 46).



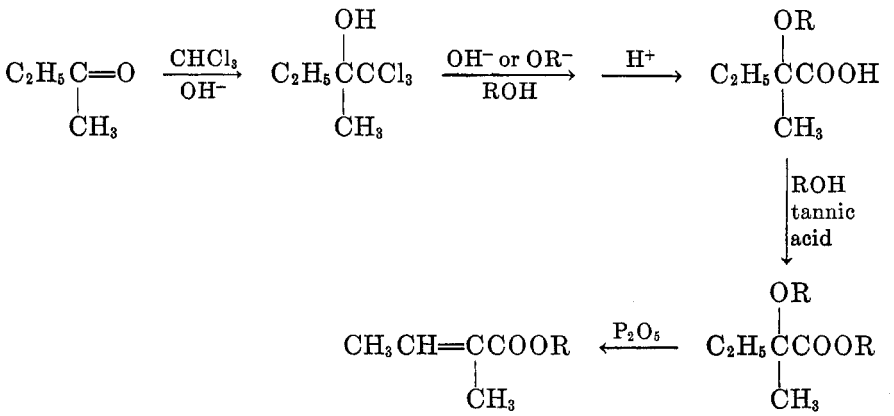
The pyrolysis of 2-hydroxy-2-methylbutyric acid was also developed (22) as a synthetic method. The hydroxy acid was conveniently prepared by hydrolysis of the cyanohydrin. The pyrolysis was carried out in a distilling flask, and the product was distilled at reduced pressure to yield tiglic acid (17 per cent), angelic acid (25 per cent), and the lactide of 2-hydroxy-2-methylbutyric acid (20–25 per cent) (201).

The dehydration of 3-hydroxy-2-methylbutyric acid, which was prepared by a sodium amalgam reduction of ethyl methylacetoacetate, followed by saponification, was used as a method of synthesis for tiglic acid (147, 197).

It has been reported that the condensation of methylmalonic acid with acetaldehyde in acetic anhydride gave a mixture of tiglic acid and 3-acetoxy-2-methylbutyric acid (124). The latter compound was pyrolyzed in order to augment the yield of tiglic acid. The condensation of acetaldehyde with propionic anhydride in the presence of sodium propionate has also been reported to yield tiglic acid (107).

The dehydration of ethyl 2-hydroxy-2-methylbutyrate has been used (33, 45, 79, 92) as a method of preparation for ethyl tiglate, but the ester product was usually reported to be a mixture. The dehydration of 2-hydroxy-2-methylbutyronitrile with thionyl chloride, followed by reaction of the unsaturated nitrile with ethyl alcohol containing sulfuric acid, has been used to synthesize ethyl tiglate of unconfirmed identity (41). The dehydration of ethyl 3-hydroxy-2-methylbutyrate has also been reported (20, 149) to give ethyl tiglate. The starting material was prepared either by the reduction of ethyl methylacetoacetate (149) or by the Reformatsky reaction (20).

High yields of isobutyl tiglate have been reported (183, 184) from a procedure which involves the base-catalyzed condensation of ethyl methyl ketone with chloroform to give 1,1,1-trichloro-2-methyl-2-butanol from which the reaction with hydroxide ion or isobutoxide ion in isobutyl alcohol gave 2-isobutoxy-2-methylbutyric acid, possibly by way of an epoxide intermediate. Esterification of the acid with isobutyl alcohol containing tannic acid gave a 12.2 per cent yield of isobutyl tiglate and a 78.2 per cent yield of isobutyl 2-isobutoxy-2-methylbutyrate, which with phosphorus pentoxide gave a 94.5 per cent yield of isobutyl tiglate. The identity of the tiglate ester was reported as confirmed by its saponification to tiglic acid.



R = isobutyl.

The dehydration of ethyl 3-hydroxy-2,2-dimethylpropionate has been reported to take place with rearrangement and to give a mixture of ethyl tiglate and ethyl angelate, while the acid gave a polyester under dehydrating conditions (23). Ethyl 2-(hydroxymethyl)butyrate gave a mixture of ethyl ethylacrylate and ethyl tiglate on dehydration (24). The ethyl tiglate was formed by a rearrangement during the dehydration or by a rearrangement of the ethyl ethylacrylate. Under acid conditions ethylacrylic acid was rearranged to tiglic acid (25, 108).

D. Syntheses by dehydrohalogenation and dehalogenation

Dehydrohalogenation has also been used for the synthesis of derivatives of tiglic and angelic acids. Ethyl 2-bromo-2-methylbutyrate, prepared from 2-methylbutyric acid by way of the acid chloride and the brominated acid chloride, gave ethyl tiglate of unconfirmed identity when treated with dimethylaniline (82, 143). The nitriles of tiglic and angelic acids were prepared by the dehydrochlorination of 3-chloro-2-methylbutyronitrile (29, 128).

Debromination of tiglic acid dibromide by zinc (89, 105) or pyrolysis (55) gave tiglic acid. With zinc in pyridine a 96 per cent yield of tiglic acid was obtained (105).

E. Miscellaneous methods of synthesis

The oxidation by air of tiglaldehyde obtained from guaiacum resin gave tiglic acid (89). The reaction of potassium hypobromite with 3-methyl-3-buten-2-one also yielded tiglic acid (173). The heating of castor oil in aqueous sodium hydroxide solution, which usually gives 2-octanol and sodium sebacate, has been reported to give sodium tiglate (53).

The reaction of methyl methacrylate with diazomethane gave a pyrazoline which decomposed to give a product consisting of 63 per cent methyl tiglate and 37 per cent methyl 1-methylcyclopropane-1-carboxylate (11). Tiglic acid was reported as a by-product in the synthesis of 5-(1-methylpropenyl)isoxazole from

ethyl methyl ketone, acetylene, and sodium fulminate in dilute sulfuric acid (142).

The pyrolysis of 2-keto-3-carbethoxy-3-methyl-4-valerolactone gave ethyl tiglate, which on saponification yielded very impure tiglic acid (m.p. 52°C.) (93). It would seem possible that cleavage of this lactone with aqueous sodium bicarbonate, as in the synthesis of α-bromo-α,β-unsaturated esters and ketones (130), would be a more convenient way of synthesizing ethyl tiglate.

VI. REACTIONS OF THE ACIDS AND THEIR DERIVATIVES

A. Addition reactions

The stereospecific (72, 192) addition of bromine to tiglic and angelic acids has already been discussed in connection with the stereochemistry of the acids, and the reactions have been outlined in chart I. The products are listed in table 2. In one set of experiments it was found that the addition of bromine to angelic acid while the reaction mixture was illuminated with circularly polarized light gave a mixture of dibromides melting at 75°C. and having no measurable optical activity (132, 133).

A number of kinetic studies of the addition of bromine to α,β-unsaturated acids have been carried out, and tiglic and angelic acids have at times been included in the investigations.

In carbon tetrachloride as a solvent the results of such additions were erratic (35, 171, 172, 187). Oxygen of the air was found (35) to inhibit the addition of bromine to tiglic and angelic acids, just as it did addition to cinnamic acid (186). In one set of experiments angelic acid was found to add bromine in the dark somewhat faster than tiglic acid (172); in another the reverse was true (35). A marked catalysis by hydrogen bromide (187) was found to drop off rapidly as the reaction progressed (35). The initial effect of hydrogen bromide on the rate of addition to both tiglic and angelic acids appeared to involve roughly the second power of the concentration of hydrogen bromide. Spectrophotometrically no tribromide ion was detectable, so this does not appear to have been a case of catalysis by tribromide ion (35).

Nucleophilic attack by tribromide ion on the double bond has been found to be an important feature of the rate-determining process, both in the addition of bromine to crotonic acid in ethylene chloride in the presence of tribromide ion (36) and in the addition of bromine to tiglic acid and to crotonic acid in ethylene chloride when tribromide ion was the only brominating agent present (32, 36). In each case the reaction was considerably faster than that observed for bromine alone, and it was much less erratic. The kinetic results could not be explained by assuming that the tribromide ion merely dissociated to give molecular bromine.

The effects of such nucleophilic attacks on bromine addition have been investigated in a number of cases with α,β-unsaturated acids and their derivatives, using such salts as lithium halides (62, 88, 114, 127, 146). These studies have not been made under conditions such that the effects of the polyhalide ions themselves could be isolated and studied as they have been in the case (32, 36)

of tribromide ion in ethylene chloride. In connection with these studies on the effect of various anions, kinetic measurements were made on the addition of bromine to tiglic acid in acetic acid containing acetate ion (63).

Other studies (2, 3, 4, 6) of the kinetics of the addition of bromine to tiglic acid and to other α,β-unsaturated acids in acetic acid led to the proposal (5) that hydrogen bromide catalyzes the reaction by activating the carbon–carbon double bond. It has been pointed out, however, that there is actually no evidence to support such a mechanism (113).

The addition of other halogens to tiglic and angelic acids has not been studied except for the use of iodine chloride in determining unsaturation (50).

The addition of hypochlorous acid to tiglic and angelic acids has been investigated and appears to be partly stereospecific (117, 118, 119). Tiglic acid (I) with hypochlorous acid gave a mixture of a 2-chloro-3-hydroxy-2-methylbutyric acid, m.p. 111.5°C. (VIII), and a 3-chloro-2-hydroxy-2-methylbutyric acid, m.p. 75°C. (IX) (117). Treatment of either of these chlorohydrins with hydroxide ion yielded a 2,3-epoxy-2-methylbutyric acid (X) melting at 62°C., which on treatment with hydrogen chloride gave the 3-chloro-2-hydroxy-2-methylbutyric acid (IX) melting at 75°C. Angelic acid (II) with hypochlorous acid gave a 2-chloro-3-hydroxy-2-methylbutyric acid (XI) melting at 103°C., along with the products obtained from tiglic acid (VIII and IX) (119). The chlorohydrin (XI) derived from angelic acid gave a liquid 2,3-epoxy-2-methylbutyric acid (XII) when treated with hydroxide ion. Treatment of this epoxide with hydrogen chloride gave a 3-chloro-2-hydroxy-2-methylbutyric acid (XIII) melting at 92°C. If the usual stereospecific *trans* addition and the usual formation of the oxide with inversion of configuration (188) took place, then the products formed were those outlined in chart III.

The effect of the carboxyl group on the polarization of the double bond in tiglic acid has been investigated in a study of the addition of hypochlorous acid (26). The chlorohydrin products were analyzed by a reduction with sodium amalgam which was preferential for chlorine on the α-position. With the acid the chlorine was found to go 38 per cent α and 62 per cent β; with the ethyl ester, which would have less effective polarization of the double bond, it was 50 per cent α and 50 per cent β; and with the tiglate ion, which would have much more effective polarization of the double bond, it was 20 per cent α and 80 per cent β.

Both tiglonitrile and angelonitrile have been reported to react with hypochlorous acid to give liquid 2-chloro-3-hydroxy-2-methylbutyronitriles boiling at 88–88.4°C./10 mm. and 85.4–85.6°C./10 mm. (83). The chlorohydrin from tiglonitrile on reaction with base gave a 2,3-epoxy-2-methylbutyronitrile boiling at 155–156°C., while that obtained from angelonitrile had a boiling point of 142–143°C.

The stereospecific additions of hydrogen iodide to tiglic and angelic acids (198) have been discussed in connection with the stereochemistry of the acids and are outlined in chart I. The addition of hydrogen bromide to tiglic acid gave a well-defined 3-bromo-2-methylbutyric acid (34, 78, 102), but the reaction with angelic acid gave only the tiglic acid derivative (76). The products of the addition of hydrogen halides are listed in table 2.

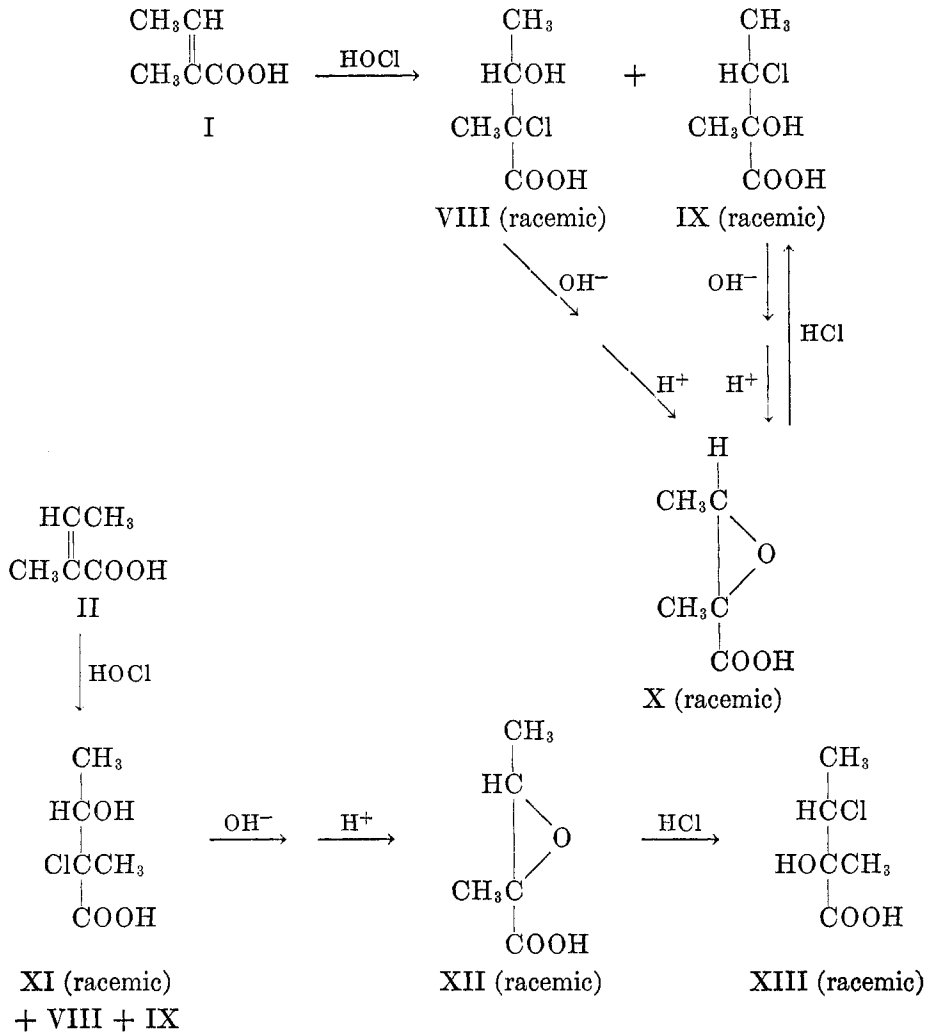


CHART III

Hydroxylation of tiglic acid by mild oxidation by neutral permanganate in the cold gave a 2,3-dihydroxy-2-methylbutyric acid melting at 88°C., while angelic acid gave one melting at 110–111°C. (77).

Catalytic hydrogenation of tiglic and angelic acids has been studied along with that of other *cis–trans* isomers in connection with the effect of structure on the rate of the reaction (51, 52). With some amounts of catalyst present one isomer reacted faster and with other amounts the other isomer reacted faster.

The complexing of tiglic acid with copper (I) chloride was investigated along with other unsaturated compounds (106). The two reactions represented in the following equations, where E is the unsaturated compound, were observed:

$$E + Cu^+ \rightleftarrows ECu^+$$
$$E + CuCl \rightleftarrows ECuCl$$

The equilibrium constants at 25°C. for tiglic acid were 2.1 for the first reaction and 5.4 for the second reaction.

The condensation of ethyl tiglate with the sodium salt of ethyl malonate gave ethyl 4-carbethoxy-2,3-dimethylglutarate, whether carried out in boiling alcohol for several hours (123) or at room temperature for several days (34, 82). Similarly, the condensation of ethyl tiglate with the sodium salt of ethyl cyanoacetate yielded ethyl 4-cyano-2,3-dimethylglutarate (21, 41, 123, 143). Each of these products on saponification gave 4-carboxy-2,3-dimethylglutaric acid, m.p. 145°C. (123, 143), which on decarboxylation gave 2,3-dimethylglutaric acid, m.p. 84–85°C. (21). The esters could be alkylated at the 4-position (41, 123, 143); in the case of the ethylation of ethyl 4-carbethoxy-2,3-dimethylglutarate the product was ethyl 4-carbethoxy-4-ethyl-2,3-dimethylglutarate, which was also prepared by the condensation of ethyl tiglate with ethyl ethylmalonate (82).

Only one such reaction has been reported for ethyl angelate (21). It was with the sodium salt of ethyl cyanoacetate for 11 days at room temperature and gave a 35 per cent yield of the same product that was obtained from ethyl tiglate. Ethyl angelate which had not undergone rearrangement was recovered, but no ethyl tiglate was detected.

Ethyl tiglate reacted with sodium cyanide to give, after saponification, a small yield of a product of melting point 175–185°C., which appeared to be *meso*-2,3-dimethylsuccinic acid mixed with some of the *dl*-isomer (34).

Tiglic acid underwent a Friedel–Crafts reaction with benzene in the presence of aluminum chloride to give 2-methyl-3-phenylbutyric acid, m.p. 132°C. (59). It has been reported that an analogous, internal reaction of phenyl tiglate failed to give the expected 3,4-dimethylhydrocoumarin (43).

The action of fuming nitric acid on tiglic acid was reported to give a poorly defined, unstable addition product which gave no amino compound on reduction (179).

The slow condensation of ethyl tiglate with ethyl diazoacetate yielded 3,5-dicarbethoxy-4,5-dimethyl-2-pyrazoline rather than the expected 3,5-dicarbethoxy-3,4-dimethyl-1-pyrazoline (13). Methyl angelate with hydrazine hydrate gave a dimethylpyrazolone melting at 268°C., while methyl tiglate gave a viscous product from which the pyrazolone was obtained only with difficulty (80).

B. Carboxyl reactions

The usual reactions of the carboxyl group of tiglic and angelic acids have been carried out. The derivatives formed are listed in tables 2 and 3, and the general methods of preparation are given in the discussion of the properties of derivatives. The only reference to acid anhydrides is a very early one (42) in which the preparations of angelic anhydride and of the mixed anhydride of angelic acid and benzoic acid are reported.

The rates of esterification of tiglic and angelic acids in methanol at 15°C. have been measured (170). The rate constant for tiglic acid was 0.408 liter per mole hour and that for angelic acid was 0.116 liter per mole hour.

The electrolysis of potassium tiglate at a current density of 0.07 amp. per

cm.^{2} has been reported to give 1-methylpropenyl tiglate (14 per cent) and dimethylacetylene (10 per cent) (136).

C. Reactions of the terminal methyl group

Two reactions involving the terminal carbon atom of tiglate esters have been reported. The bromination of methyl tiglate by *N*-bromosuccinimide gave a 69.5 per cent yield of methyl 4-bromotiglate, b.p. 109–114°C./24 mm. (31, 97 98). Ethyl tiglate was condensed with ethyl oxalate to give ethyl 4-oxalyltiglate, m.p. 91–92°C. (92).

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