

it should be recalled that a mixture of butenyl bromides comparable to that reported by Delaby and Lecomte was actually fractionated<sup>3</sup> at low temperatures into fractions comparable in size to those expected from refractive index analysis.

Further confirmation of the above conclusions has been obtained in this Laboratory<sup>8</sup> from experiments on the *controlled* conversion of alkylvinylcarbinols into bromides with phosphorus tribromide. In each case approximately 47% secondary bromides was present.

### Summary

Several pure primary and secondary alkenyl

bromides of the type  $R-\overset{\text{H}}{\text{C}}=\overset{\text{H}}{\text{C}}-\text{CBr}$  and  $R-\overset{\text{H}}{\text{C}}-\overset{\text{H}}{\text{C}}=\overset{\text{H}}{\text{C}}\text{H}$  ( $R = \text{Et to Bu}$ ) have been isolated for the first time.

The isomeric bromides have been rearranged at 100° to equilibrium mixtures the compositions of which have been determined.

The refractive index method of analysis of alkenyl bromide mixtures has been tested further with pentenyl bromide mixtures.

Conflicting reports in the literature concerning the composition of bromides made from alkylvinylcarbinols have been discussed and corrected values calculated.

LOS ANGELES, CALIF.

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[CONTRIBUTION FROM THE UNIVERSITY OF MARYLAND]

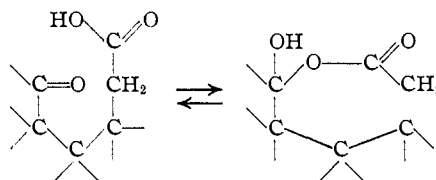
## Cerin and Friedelin. V. A Study of Friedonic Acid<sup>1</sup>

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Friedonic acid, a monobasic keto acid, is produced from friedelin by vigorous oxidation.<sup>3</sup> The acid is esterified readily, but neither free acid nor ester yields the ordinary derivatives of a carbonyl compound. However, the fact that the acid can be reduced both by sodium and alcohol and by hydrogen in the presence of a catalyst to an hydroxy acid which spontaneously undergoes inner esterification to yield a lactone, make it clear that friedonic acid is a keto acid and not an hydroxy acid. It is the purpose of this paper to present additional evidence of the presence of a carbonyl group in friedonic acid, and to show the relation of carbonyl to carboxyl.

From the reaction products of one of many routine oxidations of friedelin was isolated a substance, isomeric with friedonic acid, which melted at 126–127°. The same compound had been isolated earlier by Campbell,<sup>4</sup> but never in quantity sufficient to warrant further investigation. We have found that this product, which is unaffected by dilute sodium hydroxide in the cold, can be converted into a methyl ester identical with the methyl ester of friedonic acid, and that friedonic acid, when allowed to stand at room temperature for

some time in alcoholic solution containing sodium ethoxide, is converted in part into this same compound (m. p. 126–127°). We shall call this substance "isomer A." The possibility that this substance is an hydroxylactone formed by interaction of the carboxyl and carbonyl of friedonic acid has been considered



Such a formulation would account for the fact that both isomer A and friedonic acid yield the same methyl ester, and that isomer A cannot be titrated with alkali in the cold, but does give normal values of saponification equivalent. The failure of "isomer A" to take up alkali in the cold makes it very unlikely that stereoisomerism only is involved in the difference between friedonic acid and this isomer. However, our ignorance of a suitable method of preparing the substance has rendered further work upon it impossible. Our supply of this material has been limited to several grams obtained for some unknown reason during a routine preparation of friedonic acid, and a very small amount formed by the action of sodium alkoxide on friedonic acid as mentioned above.

(1) Presented before the Division of Organic Chemistry at the Baltimore meeting of the American Chemical Society, April, 1939.

(2) From the Ph.D. dissertation of John K. Wolfe.

(3) Drake and Campbell, *THIS JOURNAL*, **58**, 1681 (1936).

(4) Campbell, Thesis, U. of Md., 1936.

We have attempted again and again to produce isomer A, but all experiments, except the one mentioned above from which only a very small quantity of product was isolated, have failed. When isomer A was treated with methylmagnesium iodide<sup>5</sup> in the "Grignard machine," 0.58 mole of methane was evolved, and 3.0 moles of reagent consumed. A similar experiment with friedonic acid resulted in the liberation of 1.57 moles of methane and the consumption of 4.15 moles of reagent. The methyl ester of friedonic acid liberated 0.52 mole of methane and consumed 3.0 moles of reagent. Apparently enolization of a carbonyl group of methyl friedonate is responsible for the evolution of methane when this substance is treated with methylmagnesium iodide, and the results obtained with isomer A would lead one to conclude that the same carbonyl group is present in this substance. This situation would not be possible in the "hydroxylactone" formula.

The possibility that isomer A is the lactone of an hydroxy keto acid also has been considered, but the practically quantitative formation of methyl friedonate from it definitely eliminates this possibility.

When friedonic acid is treated with acetic anhydride a mixed anhydride results. It was hoped that this reaction might yield the acetyl derivative of the "hydroxylactone" from which gentle hydrolysis or alcoholysis might form isomer A. However, treatment of the mixed anhydride with 70% ethanol regenerates friedonic acid. An attempt was made to prepare a similar mixed anhydride from isomer A, but the substance was recovered unchanged from the reaction mixture.

In order to obtain additional evidence supporting the presence of a carbonyl function in friedonic acid, its absorption spectrum in the near ultraviolet was determined.<sup>6</sup> A decided maximum of absorption ( $\log \epsilon = 1.55$ ) was found at 2900 Å. Many alicyclic ketones show absorption in this range.<sup>7</sup> Conjugation of a double bond with the unsaturation of the carbonyl group causes a shift of the characteristic carbonyl absorption into the neighborhood of 2500 Å. ( $\log \epsilon = 4.1$ ). The observed absorption spectrum of friedonic acid confirms our earlier belief that the acid is not an  $\alpha,\beta$ -unsaturated ketone.

(5) Philip Wingate, Thesis, U. of Md., 1939.

(6) We are indebted to Mr. P. A. Cole of the Washington Biological Institute for the absorption spectrum data.

(7) Waters and Lowry, "Physical Aspects of Organic Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 1937, pp. 398-399.

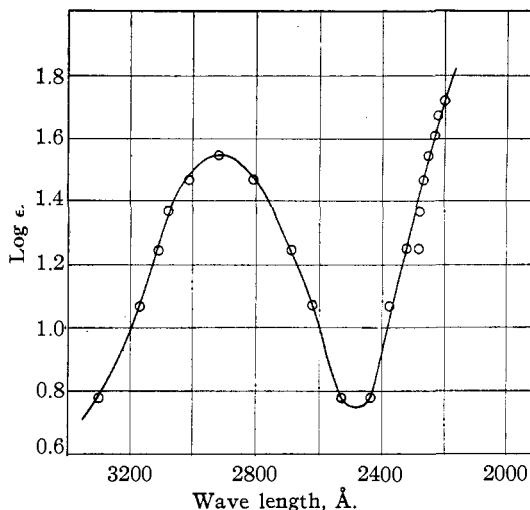


Fig. 1.—Absorption spectrum of friedonic acid. 1% in cyclohexane.

When friedonic acid was heated to a temperature about 40° above its melting point in an atmosphere of nitrogen, a new product was formed by elimination of water and loss of carbon dioxide. Quantitative determination of the water and carbon dioxide formed showed that approximately one mole of each was produced per mole of acid. The product, norfriedelene, gave a strong test for unsaturation using tetranitromethane, and absorbed one mole of hydrogen to yield norfriedelane which gave no color with tetranitromethane. In keeping with its unsaturated character, norfriedelene reacted with one mole of perbenzoic acid in chloroform and was transformed into an epoxide. These transformations are quite comparable to the behavior of 12-ketocholanic acid, which when heated to 300° loses water and carbon dioxide to yield dehydronorcholene.<sup>8</sup> Apparently the condensation involves the  $\alpha$ -methylene group of friedonic acid; the subsequent decarboxylation, characteristic of  $\alpha,\beta$ -unsaturated acids,<sup>9</sup> produces norfriedelene.

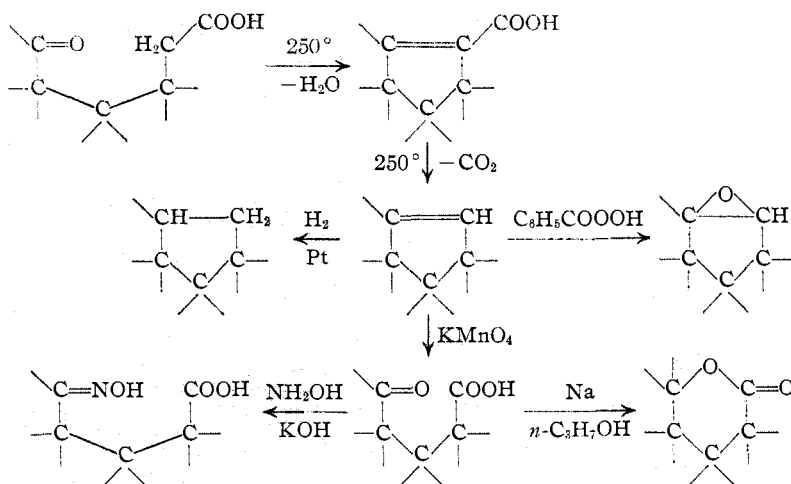
Oxidation of norfriedelene by means of potassium permanganate in glacial acetic acid according to Wieland<sup>10</sup> produced a new acid ( $C_{29}H_{48}O_3$ ), norfriedonic acid, a keto acid differing from friedonic acid by methylene group and by its ability to form the usual derivatives of the carbonyl group. The lactone of the related hydroxy acid was obtained earlier directly from friedelin.<sup>3</sup> The

(8) Wieland and Schlichting, *Z. physiol. Chem.*, **150**, 273 (1925).

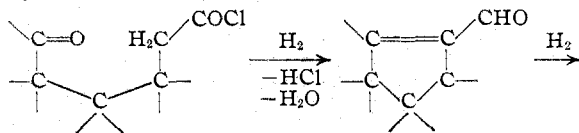
(9) Hurd, "The Pyrolysis of Carbon Compounds," The Chemical Catalog Co., New York, N. Y., 1929, pp. 349-354.

(10) Wieland and Wiedensheim, *Z. physiol. Chem.*, **186**, 229 (1930).

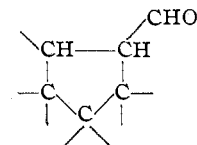
fact that carbonyl derivatives are readily obtained both from norfriedonic acid and its methyl ester indicates very clearly that some interaction of carbonyl and carboxyl groups is responsible for the failure of friedonic acid (and methyl friedonate) to yield such derivatives. The pyrolysis of friedonic acid and the other reactions given above can be represented



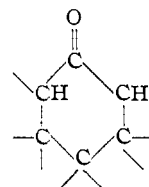
Friedonic acid yields a non-crystalline acid chloride when treated with thionyl chloride. Reduction of the acid chloride in xylene by hydrogen in the presence of a palladium-barium sulfate catalyst<sup>11</sup> produced a substance  $C_{30}H_{50}O$ , isomeric with friedelin. This new substance differs markedly from friedelin in regard to the reactivity of its carbonyl group. A 2,4-dinitrophenylhydrazone formed readily and the compound gave no test for unsaturation with tetranitromethane. This new substance also differed from friedelin by being easily oxidized to an acid containing the same number of carbon atoms and only two oxygen atoms. The isomer of friedelin must, therefore, be a saturated aldehyde, formed by a process quite analogous to the one involved in the production of norfriedelene from friedonic acid. Reduction of the double bond first formed may take place before production of the aldehyde, but more likely involves 1,4-addition to the  $\alpha,\beta$ -unsaturated system in the aldehyde first produced. The formation of this aldehyde, norfriedelanylformaldehyde, can be represented



(11) Rosenmund, *Ber.*, **54**, 437 (1921).



From the data presented above and in earlier papers, it seems reasonable to conclude that friedonic acid is an epsilon-keto acid whose carbonyl group is highly sterically hindered, and that friedelin must contain the unit of structure



### Experimental

#### Preparation of Friedonic Acid.—

The procedure employed in oxidizing friedelin to friedonic acid was much the same as that used in earlier work.<sup>3</sup> The oxidation mixture was heated under reflux for ten hours, and at the

end of that time concentrated to about one-fifth of its original volume. Five volumes of water was then added to the boiling solution, and the resulting precipitate was filtered hot, washed thoroughly with water, and dried in a desiccator over potassium hydroxide to constant weight; yield, 24.5 g. of light green solid from 24 g. of friedelin. The crude acid was pulverized and shaken well with 800 ml. of cold ethyl ether. The residual friedelin was filtered off, washed with ether, and used again without purification in a subsequent oxidation; yield, 8.0 g. of friedelin. The ethereal solution was extracted repeatedly with 10% sodium hydroxide until no more sodium salt precipitated in the aqueous layer. The precipitated sodium salt was returned to the separatory funnel and washed twice with ether. When the resultant emulsion was centrifuged three layers were produced; the upper ethereal layer was decanted, and the lower green aqueous layer poured off through holes punched in the compact intermediate layer of sodium salt. A suspension of the sodium salt was then acidified with concentrated hydrochloric acid in a separatory funnel and separated from the aqueous layer by extraction. The ethereal solution was then evaporated to dryness, the gummy residue taken up in 25 ml. of 95% ethanol, seeded with a few crystals of friedonic acid and cooled in the icebox overnight; yield of crude friedonic acid, 7.3 g. (m. p. 196–198°). Recrystallization of the crude acid from ethanol yielded 6.0 g. of pure acid which crystallized as colorless needles having parallel extinction and melted at 205–207°. The ethereal solution from which the acid was originally extracted was combined with that obtained during centrifugation, washed free from sodium hydroxide and evaporated to dryness. The solid residue was diluted with alcohol and filtered; the product was nearly pure friedelin (3.5 g.). Of the 24 g. of friedelin sub-

jected to oxidation, 11.5 g. was recovered, 12.5 g. oxidized, and 6.0 g. of friedonic acid obtained (48% yield).

**Isomer A.**—Friedonic acid (0.2 g.) was dissolved in 25 ml. of ethyl alcohol, containing 1 g. of dissolved sodium, and was allowed to stand at room temperature for forty-eight hours. The mixture was acidified, diluted with water, and filtered. On recrystallization of the solid from ethyl alcohol, 0.1 g. of friedonic acid was obtained. The filtrate from the crystallization was evaporated to dryness and triturated with a little ethyl alcohol in the cold. The undissolved crystals were filtered and recrystallized from ethyl alcohol; a small quantity of a nicely crystalline substance melting at 126–127° was obtained. When treated with 0.02 *N* sodium hydroxide this product showed no acidic properties. A mixed melting point with the substance obtained from friedelin by oxidation showed no depression.

*Anal.* Calcd. for  $C_{30}H_{50}O_3$ : C, 78.54; H, 11.00. Found: C, 78.49, 78.65; H, 11.09, 11.08.

**Methyl Friedonate.**—One gram of friedonic acid (m. p. 205–207°) was dissolved in 50 ml. of methyl alcohol containing 0.1 g. of dissolved sodium. Five ml. of methyl sulfate was added and the mixture refluxed for one and one-half hours. Half of the solvent was evaporated, the mixture diluted with 100 ml. of water, and extracted twice with ether. The solid obtained by the removal of the ether was recrystallized from methyl alcohol, from which it formed silky needles, which after several recrystallizations melted at 157–158°.

*Anal.* Calcd. for  $C_{31}H_{52}O_3$ : C, 78.75; H, 11.09; methoxyl, 6.56. Found: C, 78.58, 78.87; H, 11.08, 11.22; methoxyl, 6.58, 6.52.

Methyl friedonate also was prepared from sodium friedonate by the action of methyl iodide, and from friedonic acid by use of diazomethane. Melting points and mixed melting points of all samples were the same.

**Reduction of Friedonic Acid. Friedololactone.**—Friedonic acid (0.5 g.) was hydrogenated in glacial acetic acid in the presence of Adams platinum catalyst. Twelve hours were required to complete the reduction. The catalyst was filtered off and the resulting solution was diluted with water (100 ml.). The jelly-like precipitate was filtered, dried, and recrystallized from ethyl acetate to a melting point of 308–312°. This product showed no depression in melting point when mixed with friedololactone previously obtained.<sup>3</sup>

**Methyl Friedonate from "Isomer A."**—One gram of "isomer A" (m. p. 126–127°) when treated with sodium methoxide and dimethyl sulfate in the same manner as friedonic acid above, yielded a product which after several recrystallizations from methyl alcohol melted at 157–158°. A mixed melting point with methyl friedonate prepared from pure friedonic acid showed no depression.

**Norfriedelene.**—Friedonic acid (2.93 g.) was heated in an atmosphere of nitrogen for two and one-half hours at 250°. The water and carbon dioxide evolved were collected and weighed in absorption tubes. The melt was cooled and the solid material obtained recrystallized three times from an ethyl acetate–benzene mixture to a constant melting point of 228.5–230°. The product, of which 1.82 g. was obtained, gave a yellow color with tetranitromethane, showing the presence of unsaturation.

*Anal.* Calcd. for  $C_{29}H_{48}$ : C, 87.79; H, 12.21. Found: C, 87.75, 87.94; H, 12.28, 12.26.

**Norfriedelane.**—One-half gram of norfriedelene was hydrogenated in ethyl ether–ethyl acetate solution in the presence of 0.1 g. of Adams platinum catalyst. After five hours the hydrogenation was complete; the solvent was removed and the product recrystallized from benzene to constant melting point. Norfriedelane gave no color with tetranitromethane and melted at 220–221°; it crystallized as colorless needles having a slight oblique extinction (about 3.2°).

*Anal.* Calcd. for  $C_{29}H_{50}$ : C, 87.36; H, 12.65. Found: C, 87.41, 87.44; H, 12.79, 12.82.

**Norfriedonic Acid.**—Two grams of powdered norfriedelene, 3 g. of powdered potassium permanganate, and 120 ml. of glacial acetic acid, previously distilled from chromic anhydride, were stirred vigorously for eight hours at room temperature. Five grams of sodium bisulfite was added and the mixture diluted with 400 ml. of water. The acid was extracted with ether and converted into sodium salt by addition of 10% sodium hydroxide. The mixture was centrifuged, separated, and the sodium salt acidified with hydrochloric acid. After several crystallizations from ethyl alcohol, 0.75 g. of acid melting at 215–217° was obtained. The residues from crystallizations contained 0.95 g. of amorphous material which could not be induced to crystallize.

*Anal.* Calcd. for  $C_{29}H_{48}O_3$ : C, 78.31; H, 10.89. Found: C, 78.20, 78.27; H, 11.02, 11.03.

Norfriedonic acid crystallizes in the form of colorless needles having parallel extinction.

**Methyl Norfriedonate.**—Esterification of norfriedonic acid by dimethyl sulfate and alkali and by diazomethane yielded a product which melted at 166–167°.

*Anal.* Calcd. for  $C_{30}H_{50}O_3$ : C, 78.54; H, 11.00; mol. wt., 458. Found: C, 78.52, 78.63; H, 10.87, 10.94;  $-OCH_3$ , 6.87, 6.78; mol. wt. (from  $-OCH_3$ ), 452, 458.

**Norfriedololactone.**—Norfriedonic acid (0.1 g.) was dissolved in 10 ml. of *n*-propanol; the mixture was refluxed and 0.05 g. of sodium added. After cooling, the mixture was diluted with 30 ml. of water and made acid to Congo red with concd. hydrochloric acid. The white precipitate was filtered and recrystallized from ethyl acetate; 10 mg. of a product melting at 288–290° was obtained. This product showed no depression in melting point when mixed with norfriedololactone obtained in earlier work.<sup>3</sup>

**The Oxime of Norfriedonic Acid.**—Norfriedonic acid (0.25 g.) and 0.15 g. of hydroxylamine hydrochloride were dissolved in 10 ml. of ethyl alcohol. A solution of 0.15 g. of potassium hydroxide in 5 ml. of ethyl alcohol was added and the mixture was refluxed for thirty minutes. The resulting mixture was diluted with water (25 ml.) and acidified with 10% sulfuric acid. The solution was extracted twice with benzene and ethyl alcohol mixture (90–10). The solvent was removed and the solid residue recrystallized from a benzene–ethyl alcohol mixture (50–50). The oxime (0.22 g.) melted at 270.5–273°, and crystallized as colorless needles having parallel extinction.

*Anal.* Calcd. for  $C_{29}H_{48}O_3N$ : C, 75.75; H, 10.73. Found: C, 75.94, 75.93; H, 10.83, 10.90.

**The Oxime of Methyl Norfriedonate.**—Methyl norfriedonate (0.2 g.) and 0.15 g. of hydroxylamine hydrochloride were dissolved in 5 ml. of pyridine and allowed to stand at room temperature for twenty-four hours. The mixture was then diluted with water, filtered, and washed well with water. The product (0.17 g.) was recrystallized from methyl alcohol. The oxime melted at 193–195°, and crystallized in the form of colorless prisms having parallel extinction.

*Anal.* Calcd. for  $C_{30}H_{51}O_3N$ : C, 76.04; H, 10.86. Found: C, 75.93, 75.85; H, 11.01, 10.72.

**The 2,4-Dinitrophenylhydrazone of Methyl Norfriedonate.**—Methyl norfriedonate (0.2 g.) was dissolved in 5 ml. of ethyl cellosolve and 0.12 g. of 2,4-dinitrophenylhydrazine dissolved in 5 ml. of cellosolve was added to this solution; two drops of concd. hydrochloric acid was then added and the mixture refluxed for five minutes. The solution was allowed to stand overnight to complete crystallization, and the product formed was recrystallized from ethyl alcohol-benzene mixtures; it (0.15 g.) melted at 233–234°, and formed bright yellow prisms having oblique extinction.

*Anal.* Calcd. for  $C_{30}H_{53}N_4O_6$ : C, 67.62; H, 8.38. Found: C, 67.36; H, 8.40.

**Norfriedelanylformaldehyde (I).**—One gram of friedonic acid and 5 ml. of thionyl chloride were heated to reflux on a steam-bath for about thirty minutes. Excess thionyl chloride was removed *in vacuo* and the residue was placed in a desiccator over potassium hydroxide for forty-eight hours; the acid chloride could not be induced to crystallize. Xylene (15 ml.), previously dried over sodium, was added along with 2 g. of palladium-barium sulfate catalyst<sup>11</sup> and hydrogen was passed through the mixture at 150° for seven hours during which time 1 g. of fresh catalyst was added; the hydrogen chloride evolved was collected and titrated with 0.05 *N* sodium hydroxide. The quantity of hydrogen chloride produced was approximately 85% of that calculated for one mole per mole of substance. The solvent was removed under reduced pressure, and the partially crystalline mass was treated with ethyl acetate. After several recrystallizations from ethyl acetate, 0.20 g. of a substance which melted at 222–225° and crystallized in the form of colorless prisms having a slight oblique extinction (extinction  $\angle ca.$  19.4°) was obtained. From the mother liquors 0.3 g. of friedonic acid was recovered via its sodium salt.

*Anal.* Calcd. for  $C_{30}H_{50}O$ : C, 84.43; H, 11.82. Found: C, 84.51, 84.66; H, 11.80, 12.10.

**The Oxime of I.**—Prepared in the usual way, this oxime was purified by several recrystallizations from ethyl acetate. It separates from ethyl acetate in the form of very small colorless crystals which melt at 255–259°.

*Anal.* Calcd. for  $C_{30}H_{51}NO$ : C, 81.57; H, 11.65. Found: C, 81.50, 81.64; H, 11.62, 11.54.

**The 2,4-Dinitrophenylhydrazone of I.**—Fifty mg. of I was dissolved in 5 ml. of ethyl cellosolve and mixed with a solution of 25 mg. of 2,4-dinitrophenylhydrazine in 5 ml. of ethyl cellosolve. One drop of concd. hydrochloric acid was added and the mixture refluxed for fifteen minutes dur-

ing which time yellow needles separated from the mixture. After several recrystallizations from benzene 36 mg. of substance melting with decomposition at 312–314° was obtained. This material crystallized as bright yellow needles having parallel extinction.

*Anal.* Calcd. for  $C_{30}H_{54}N_4O_4$ : C, 71.26; H, 8.97. Found: C, 71.13, 71.21; H, 8.84, 8.85.

**Norfriedelanylformic Acid.**—To 0.3 g. of I dissolved in 50 ml. of glacial acetic acid at 100° was added a solution of 60 mg. of chromic anhydride dissolved in 30 ml. of acetic acid. The mixture was then evaporated to 20 ml. total volume and diluted with 50 ml. of water. The crystals formed were filtered, dried, dissolved in ether, and the ethereal solution extracted twice with 10% sodium hydroxide solution. The aqueous layer was centrifuged and acidified with hydrochloric acid. The solid formed was filtered and recrystallized from glacial acetic acid. The product was an acid (0.22 g.), which crystallized in the form of long colorless needles having parallel extinction and melted at 307–308°.

*Anal.* Calcd. for  $C_{30}H_{50}O_2$ : C, 81.37; H, 11.39. Found: C, 80.90, 81.10; H, 11.40, 11.46.

**Methyl Norfriedelanylformate.**—Norfriedelanylformic acid (0.04 g.) was dissolved in 10 ml. of methyl alcohol containing 0.05 g. of dissolved sodium. One ml. of dimethyl sulfate was added. The mixture was refluxed for one-half hour and crystals formed from the boiling mixture. The cooled mixture was filtered, and the crystals dried and recrystallized from a mixture of pyridine and methyl alcohol. Twenty-five mg. of methyl ester melting at 230–231.5° was obtained. This substance crystallizes in the form of very thin plates having parallel extinction.

*Anal.* Calcd. for  $C_{31}H_{52}O_2$ : C, 81.51; H, 11.49. Found: C, 81.15; H, 11.47.

## Summary

1. An isomer of friedonic acid, called for the present "isomer A," has been isolated and its conversion to methyl norfriedonate described.
2. Pyrolysis of friedonic acid has been shown to result in the production of an unsaturated hydrocarbon, norfriedelene, which has been hydrogenated to norfriedelane.
3. Oxidation of norfriedelene was found to yield norfriedonic acid, a monobasic keto acid of which carbonyl and carboxyl derivatives have been made.
4. Reduction of friedonyl chloride has been shown to result in the formation of an aldehyde isomeric with friedelin. The aldehyde has been oxidized to the corresponding acid.
5. Friedonic acid is apparently an epsilon-keto acid containing a highly blocked carbonyl group.