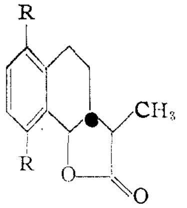
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF HOPE COLLEGE]

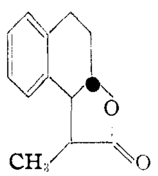
The Malonic Ester Reaction with 3,4-Dihydronaphthalene-1,2-oxide

BY EUGENE E. VAN TAMELEN,[1] GERRIT VAN ZYL AND GEORGE D. ZUIDEMA

It has been shown previously that α-carbethoxy-γ-butyrolactones may be prepared readily by condensing 1,2-epoxides with sodium malonic ester[2]; these carbethoxy lactones may be hydrolyzed and decarboxylated to the corresponding γ-lactones. The extension of this mode of synthesis using 3,4-dihydronaphthalene-1,2-oxide and methyl malonic ester should lead to a lactone of either structure Ia or II, depending upon whether attack by the methyl malonic ester anion occurs at the 1- or 2-position in the oxide. Compounds possessing the lactone system I are of interest because of their similarity to the natural product santonin[3] and its degradation products (*e. g.*, hyposantonin, Ib). In addition, the juncture between the cyclohexane and the lactone ring in Ia should be *trans*, since the epoxide ring opening by malonic ester has been definitely shown to proceed with Walden inversion[4,5]; the *trans* ring system is also a structural feature of hyposantonin, Ib, and, presumably, santonin.[6] Although two forms of Ia have been previously synthesized by another method,[7] their stereochemistry was not investigated.



Ia, R = H
Ib, R = CH_3



II

The course of the proposed reaction did not proceed as desired, however, since evidence presented herewith proves II to be the structure of the lactone obtained.

The lactone II (or VIb) may be conveniently prepared by either of two procedures: (1) condensation of 3,4-dihydronaphthalene-1,2-oxide (III) and methyl malonic ester (IV), which yields exclusively VIb. The intermediate carbethoxy lactone was not isolated, but was cleaved directly to the lactone by refluxing for thirty hours with sodium ethoxide in absolute ethanol[8]; upon cooling, VIb crystallized out in an essentially pure state. (2) Condensation of 2-bromo-1,2,3,4-tetrahydronaphthol-1 (VII) with IV, whereby the over-all result is *not* displacement of the *halogen* by a propionic acid residue, but rather of the *hydroxyl* group. This course of reaction may be rationalized quite readily. The initial attack of the strong base IV upon the halohydrin promotes ring closure to the epoxide rather than direct halogen displacement; this preference would be predicted, since such a ring closure is a very rapid reaction,[9] while the malonic ester reaction with halides—especially secondary halides—proceeds considerably less readily.[10,11] Condensation of the oxide with excess IV takes place with subsequent cleavage to VIb. Actually the whole series of steps was performed in a single operation by slowly adding an ethanolic solution of VII to a refluxing solution of IV (Chart I).

The structure represented by VIb possesses three asymmetric carbon atoms, and therefore four racemic forms are theoretically possible. Only one was obtained by the methods outlined above. The possibilities are decreased to unity because of the following considerations: the lactone ring juncture is exclusively *trans*,[4,5] allowing for a total of only two *dl*-modifications. In the presence of sodium ethoxide, however, the α-hydrogen in the lactone ring will enolize; upon ketonization, the more stable configuration with reference to the lactone ring juncture will be assumed at the α-carbon atom, leaving but one *dl*-compound as the end-product of the series of transformations.

If Ia were the structure of the lactone obtained, it would be expected to exhibit reactions characteristic of hyposantonin, Ib. The results were almost entirely dissimilar. VIb did not give the color test with sulfuric acid–ferric chloride which is characteristic of Ib.[12] Ib, upon dissolution in strong aqueous base followed by acidification with mineral acids, gives an isomeric lactone, isohyposantonin, formulated as the *cis* lactone.[12] The present lactone, upon similar treatment, was merely regenerated. The *cis* lactone, VIII, can be gotten from VIb, however, by using more drastic conditions, *viz.*, refluxing in a 45% solution of concentrated sulfuric acid in ethanol. The reagents used to effect the reduction of Ib to α-2-(5,8-dimethyl-1,2,3,4-tetrahydronaphthyl)-propionic acid,[13] aromatization to α-2-(5,8-dimethylnaphthyl)-propionic acid[14] and ring-

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[1] Present address: Harvard University, Cambridge, Massachusetts.

[2] Traube and Lehman, *Ber.*, **34**, 1977 (1901).

[3] Clemo, Haworth and Walton, *J. Chem. Soc.*, 1110 (1930).

[4] Grigsby, Hind, Chanley and Westheimer, THIS JOURNAL, **64**, 2606 (1942).

[5] Newman and VanderWerf, *ibid.*, **67**, 233 (1945).

[6] Grassi-Cristaldi, *Gazz. chim. ital.*, **23**, I, 65 (1893).

[7] Schroeter and Gluschke, German Patent 511,887.

[8] The cleavage of α-alkyl-α-carbethoxy-γ-butyrolactones to the corresponding α-alkyl lactones has been previously reported by Skinner, Stokes and Spiller, THIS JOURNAL, **69**, 3083 (1947).

[9] Straus and Rohrbacher, *Ber.*, **54**, 40 (1921).

[10] Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 154.

[11] Pearson, THIS JOURNAL, **71**, 2212 (1949).

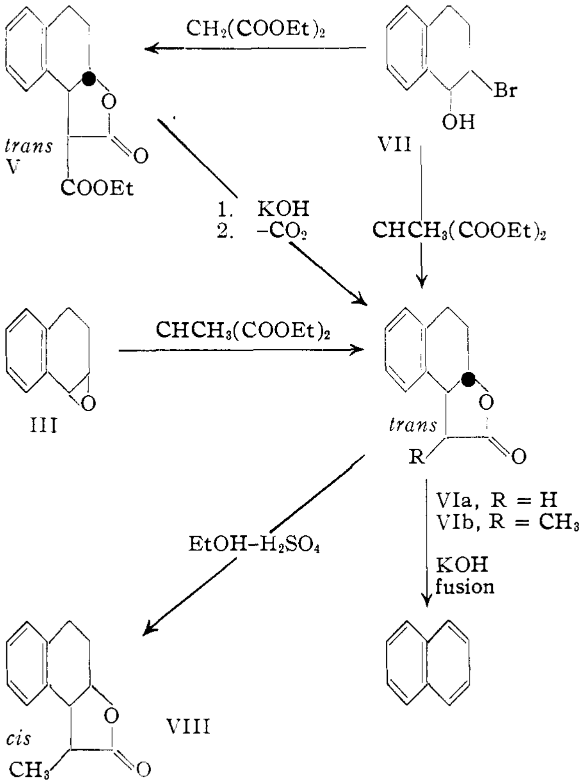
[12] Grassi-Cristaldi, *Gazz. chim. ital.*, **19**, 382 (1889).

[13] Grassi-Cristaldi, *ibid.*, **26**, II, 451 (1896).

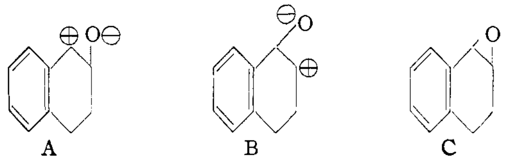
[14] Grassi-Cristaldi and Gucci, *ibid.*, **22**, I, 1 (1892).

opening to the ethyl ester of α-2-(5,8-dimethyl-3,4-dihydronaphthyl)-propionic acid[14,15] were without effect on VIb. Fusion with solid potassium hydroxide was the only degradation method which exhibited a parallel effect. Ib is known to give 1,4-dimethylnaphthalene by this treatment[16]; VIb gave naphthalene in good yield.

Both of the possible (*cis* and *trans*) racemic forms of 2-(1,2,3,4-tetrahydronaphthol-1)-acetic acid lactone (IX) (m. p.'s 67–69° and 106°) have been prepared by Schroeter and Gluschke.[7] Method (2), outlined above, with malonic ester yielded a lactone isomeric, but not identical (m. p. 147.0–147.5°), with either form of IX. This result is in agreement with the formulation of this lactone and, therefore, the α-methyl derivative as VIa and VIb, respectively.[17] Conclusive proof resulted from catalytic dehydrogenation studies in that VIb yielded 1-ethylnaphthalene, which was identified as the picrate.



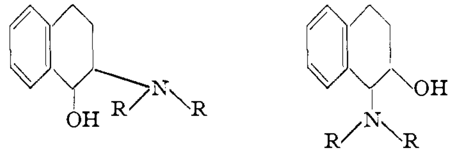
Recently Russell and VanderWerf[18] condensed styrene oxide and malonic ester and showed that attack occurred at the unsubstituted carbon atom of the oxide ring, since γ-phenyl-γ-butyrolactone was obtained rather than β-phenyl-γ-butyrolactone. This result was interpreted by them as evidence that the phenyl group exhibits a +I (electron-releasing) effect, thus increasing the electron density at the carbon atom to which it is attached; this partial negative charge would be expected to repel the malonic ester anion, which would then attack the alternative position. This conclusion seems to us unwarranted, however, since it may well be that ring opening in this case proceeds as observed simply because nucleophilic displacement occurs more readily at a primary carbon atom than at a secondary.[10] Although it has been sometimes assumed that this order is a consequence of the +I effect of alkyl substituents (thus increasing the electron density at the carbon atom bearing the displaceable group and thereby retarding the approach of the nucleophilic particle),[19] recent evidence[20] indicates that the *steric effects* of substituents may actually determine the facility of such reactions.[21] The present case is worthy of notice, since the 1- and 2-positions of 3,4-dihydronaphthalene-1,2-oxide (III) are more nearly sterically equivalent than the corresponding positions in styrene oxide. Identification of the lactone as VIb shows that III, in contrast to styrene oxide, is opened at the same carbon atom to which the phenyl group is attached. This result can be rationalized either by assuming that the phenyl ring exhibits here the −I (electron-attracting) effect usually attributed to this substituent,[22] or possibly more satisfactorily by noting that of the three contributions to the resonance hybrid, that of A is



A B C

considerably greater than that of B (because of the participation of π-electrons in the benzene ring), and in any case sufficient to lead to products of reaction at the α-carbon atom as in the cases studied in this paper. That the electronic effect may be overshadowed by steric factors is shown by the case of styrene oxide mentioned earlier.

The product of the reaction of the epoxide III with amines presents two structural possibilities: 2-alkylamino-1,2,3,4-tetrahydronaphthol-1 (X) or 1-alkylamino-1,2,3,4-tetrahydronaphthol-2 (XI). Straus and Rohrbacher[9] decided in favor



X XI

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[15] The procedures used in the present work were duplications of those in the literature; no further account will be given in the "experimental" section.

[16] Bertolo, *Gazz. chim. ital.*, **32**, II, 371 (1902).

[17] Since cleavage of an α-carbethoxy lactone with no α-alkyl substituent does not occur, saponification and thermal decarboxylation of the intermediate V became necessary (Chart I).

[18] Russell and VanderWerf, THIS JOURNAL, **69**, 11 (1947).

[19] Hinshelwood, Laidler and Timm, *J. Chem. Soc.*, 848 (1938).

[20] Brown and Eldred, THIS JOURNAL, **71**, 445 (1949).

[21] Meer and Polanyi, *Z. physik. Chem.*, **B19**, 164 (1932), advanced the steric hindrance effect in explaining the relative reaction rates of aliphatic primary, secondary and tertiary halides.

[22] Ingold, *Chem. Revs.*, **15**, 225 (1934).

of structure X solely by analogy with the ring opening of styrene oxide by diethylamine, a reaction which was unequivocally shown to lead to 1-phenyl-2-diethylaminoethanol-1.[23] In the light of the present results, not only does such an analogy become untenable, but XI would be favored as the structure of the amino alcohols.

Experimental[24]

α-1-(1,2,3,4-Tetrahydronaphthol-2)-propionic Acid Lactone (*trans*), VIb. Method (1).—A solution of 0.1 mole of sodium methyl malonic ester in 100 cc. of absolute ethanol was brought to boiling, and 14.7 g. (0.1 mole) of 3,4-dihydronaphthalene-1,2-oxide[9] (diluted to a volume of 25 cc. with absolute ethanol) was added with stirring over a period of twenty-five minutes. A few boiling chips were added, and refluxing and stirring were continued for thirty hours. Upon cooling to room temperature, colorless crystals precipitated, which were collected by filtration, washed well with ether and dried (8.7 g., 43%). The alcoholic filtrate was acidified with a slight excess of glacial acetic acid and the excess alcohol removed *in vacuo* while the mixture was churned slowly. Addition of water yielded an oily solid (contaminated with the cleavage product diethyl carbonate). Systematic investigation of this solid gave only additional amounts of VIb. The lactone was recrystallized from 95% ethanol, giving opaque, stout needles, m. p. 152.5–153.5°.

The infrared spectrum showed the intense band at 5.70 microns characteristic of five-membered lactones.

Anal. Calcd.: C, 77.21; H, 6.97. Found: C, 77.09; H, 7.24.

Method (2).—A solution of 0.1 mole of sodium methyl malonic ester in 50 cc. of absolute ethanol was heated to boiling and 22.7 g. (0.1 mole) of 2-bromo-1,2,3,4-tetrahydronaphthol-1[9] (dissolved in 200 cc. of absolute ethanol) was added dropwise with stirring to the gently refluxing ester solution over a period of ten hours. After cooling to 5°, the lactone was filtered off and triturated with water to dissolve the sodium bromide. After drying at room temperature overnight, the m. p. was 151.5–152.5°, which was undepressed upon admixture with the lactone obtained by method (1). The alcoholic filtrate was refluxed with a solution of 3 g. of sodium in 50 cc. of absolute ethanol for forty hours. After cooling to room temperature, the alcoholic solution was stirred into 500 cc. of water and immediately acidified to congo red with concentrated hydrochloric acid. Additional lactone (6.1 g.) slowly precipitated over a period of several days, making a total of 11.6 g. (55%) obtained.

The lactone was added to an aqueous solution of sodium hydroxide and refluxed for one hour. The clear solution was cooled, diluted with water and acidified with concentrated hydrochloric acid. A colorless gummy solid precipitated which partially crystallized on standing overnight. To effect complete lactonization, the mixture was heated at the boiling point for fifteen minutes, whereupon a crystalline solid formed, m. p. 152.5–153.5° (undepressed by starting material).

Fusion of VIb with Potassium Hydroxide.—Two hundred milligrams of VIb was placed in a round-bottom flask along with 1.2 g. of 85% potassium hydroxide pellets. A condenser was attached and the flask immersed in an oil-bath. The temperature of the bath was gradually raised until it reached 325°; heating was then discontinued. White crystals (20 mg.) had sublimed into the condenser (m. p. 79–80°, mixed m. p. with naphthalene 79–80°). After the fusion mixture had cooled to room temperature, 50 cc. of water was added and the excess potassium hydroxide dissolved with stirring. The naphthalene (56 mg.) remained undissolved (m. p. 78–80°). The total yield was 58%.

Dehydrogenation of VIb to 1-Ethylnaphthalene.—Five hundred milligrams of VIb, 250 mg. of 10% palladium-charcoal catalyst and 1.5 cc. of acetone were sealed in a Carius tube. The tube was suspended vertically in a bath and heated at 300–310° for ten hours. After opening the tube, ether was added and the catalyst removed by filtration. The solvent was evaporated off on the steam-bath and the residue used directly for the preparation of the picrate (m. p. 97–98°). The m. p. of the picrate of 1-ethylnaphthalene is 98°,[25] while that of the picrate of 2-ethylnaphthalene has been reported as 69°[26] and 71°.[27]

α-1-(1,2,3,4-Tetrahydronaphthol-2)-propionic Acid Lactone (*cis*), VIII.—Five grams of VIb and 80 cc. of absolute ethanol were placed in a 250-cc. flask, and 20 cc. of concentrated sulfuric acid was carefully poured in with swirling. Upon raising the temperature of the reaction mixture to the boiling point, the lactone dissolved; the resulting solution was refluxed for sixteen hours. An additional 10 cc. of acid was added, and refluxing was continued for six more hours. The solution was cooled, poured into 250 cc. of water and allowed to stand in the refrigerator overnight. The lactone which had precipitated was filtered off, washed with water and dried. Recrystallization from 95% ethanol gave fine needles (m. p. 120–121°). The yield was 3.8 g. (76%).

Anal. A portion of the lactone was recrystallized twice more to give the constant m. p. 121.0–121.5°. Calcd.: C, 77.21; H, 6.97. Found: C, 77.48; H, 7.09.

The *cis* lactone (100 mg.) was heated gently with a solution of 300 mg. of potassium hydroxide in 2.0 cc. of water until complete solution just took place (about five minutes was required). The flask was then cooled immediately under running tap water, diluted with 2.0 cc. of water and acidified to congo red with concentrated hydrochloric acid. A white solid melting at 119–120° precipitated immediately and completely; the mixed m. p. with the starting material was 120.0–121.5°. This extremely facile lactonization is consistent with the *cis* formulation.[5] If the lactone was heated for longer periods of time (one to six hours) with aqueous alkali, a mixture was obtained which melted at 104–116°. It is likely that this mixture consisted of starting lactone and an isomeric lactone in which the α-hydrogen has inverted. No attempt was made to separate them, however.

1-(1,2,3,4-Tetrahydronaphthol-2)-acetic Acid Lactone (*trans*), VIa.—The procedure was patterned after that used by Newman and VanderWerf[5] in a similar synthesis.

A solution of 0.07 mole of sodium malonic ester in 50 cc. of absolute ethanol was prepared in the usual manner. Fifteen and nine-tenths grams (0.07 mole) of VII (dissolved in 125 cc. of absolute ethanol) was added over a period of three hours to a stirred, refluxing solution of 0.07 mole of sodium malonic ester in 50 cc. of ethanol. The contents were then cooled somewhat, and 11.2 g. of potassium hydroxide and 50 cc. of water were added. The reflux condenser was replaced by a condenser set for distillation; 200 cc. of distillate was collected while stirring was continued and the flask heated by a mantle. Seventy more cc. of water was added, and heating and stirring were resumed until 70 cc. of distillate had come over and the contents of the flask turned solid. After cooling, a solution of 15 cc. of concentrated sulfuric acid in 15 cc. of water was added to the salt mixture. Upon shaking, an oily solid separated. The solid was extracted with ether and the combined ether extracts were boiled down on a hot-plate until a sirup remained. Decarboxylation was accomplished by gradually raising the temperature of the contents to 150°; the temperature was held at this point until the evolution of carbon dioxide ceased. The brown solid obtained on cooling was recrystallized from 1:2 ligroin (b. p. 30–75°)-benzene (m. p. 144–146°). The yield was 7.1 g. (54%).

Anal. A portion of the lactone was recrystallized to a

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(23) Tiffeneau and Fourneau, *Bull. soc. chim. France*, [4] **1**, 556 (1907).

(24) All melting points are corrected.

(25) Carnelutti, *Ber.*, **13**, 1672 (1880).

(26) Brunel, *ibid.*, **17**, 1180 (1884).

(27) Marchetti, *Gazz. chim. ital.*, **11**, 440 (1881).

constant m. p. (147.0–147.5°). Calcd.: C, 76.57; H, 6.43. Found: C, 76.81; H, 6.61.

Acknowledgment.—The authors wish to thank the Research Corporation for a grant-in-aid supporting this project.

Summary

Methyl malonic ester has been shown to add to the 1-position of 3,4-dihydronaphthalene-1,2-oxide, yielding α-1-(1,2,3,4-tetrahydronaphthol-2)-propionic acid lactone (*trans*). This lactone may also be obtained from 2-bromo-1,2,3,4-tetrahydronaphthol-1 and methyl malonic ester.

The theoretical implications of this result are discussed.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE JOHNS HOPKINS UNIVERSITY]

1,4,5,8-Tetramethyl-2,3,6,7-tetracarbethoxyporphyrin and Some Derivatives[1]

BY JOHN S. ANDREWS,*[2] ALSOPH H. CORWIN† AND ALVIN G. SHARP[3]

One of the most readily available pyrrole derivatives is 2,4-dimethyl-3,5-dicarbethoxypyrrole. Its conversion into a porphyrin should yield an easily prepared synthetic porphyrin. Several unsuccessful attempts to achieve this[4] have led certain investigators to the conclusion that carbethoxy groups hinder porphyrin formation.

Observations made in our studies of the mechanism of the aldehyde synthesis of dipyrrylmethenes[5] have led to the discovery of a unique porphyrin synthesis which proceeds smoothly at room temperature and yields the crystalline product directly from the reaction medium. The fact that a porphyrin containing four carbethoxy groups can be prepared readily suggests that previous assumptions regarding their influence on porphyrin formation can no longer be justified.

The success of the method depends upon two reactions which have been shown to exist when the N-methylpyrryl aldehyde I is condensed with the α-unsubstituted pyrrole II. The first is the formation of the tripyrrylmethane intermediate III and the second is the specific cleavage of this intermediate at the bond attaching the N-methylpyrryl group to the methane carbon (Chart I).

This reaction is comparable in effect to the formic acid condensation frequently employed for the synthesis of symmetrical dipyrrylmethenes in that the N-methylpyrryl aldehyde appears to serve solely as the source of the carbon joining the two pyrrole groups in the methene IV. Unlike the formic acid method, however, the reaction above proceeds quantitatively.

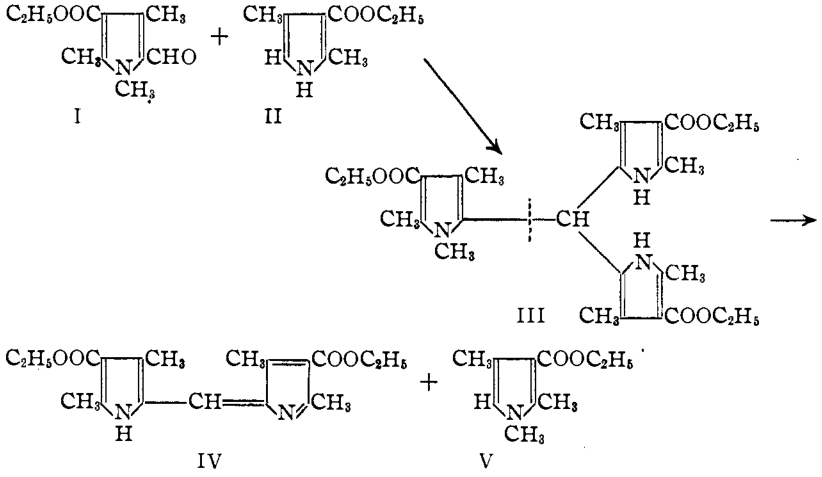

CHART I

These observations led to the prediction that substitution of a 5,5′-unsubstituted dipyrrylmethane VI for the α-unsubstituted pyrrole II should lead to the coupling of two molecules of the methane yielding the methene VII. This in turn should condense to the dihydroporphyrin VIII which should oxidize spontaneously to the porphyrin IX (Chart II).

The reaction has been carried out and the predictions realized by the isolation of the crystalline porphyrin. The high acid number of the porphyrin is of the magnitude expected for this type of material.

The complicated series of transformations necessary for the formation of the porphyrin is not

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* Harvard University A.M. 1927.

† Harvard University Ph.D. 1932.

(1) Porphyrin Studies, VIII. For previous porphyrin studies in this series see Corwin and Krieble, THIS JOURNAL, **63**, 1829 (1941); Corwin and Buc, *ibid.*, **66**, 1151 (1944); McEwen, *ibid.*, **68**, 711 (1946); Ellingson and Corwin, *ibid.*, **68**, 1112 (1946); Erdman and Corwin, *ibid.*, **68**, 1885 (1946); Corwin and Erdman, *ibid.*, **68**, 2473 (1946); Erdman and Corwin, *ibid.*, **69**, 750 (1947).

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(4) Fischer, *et al.*, *Ann.*, **452**, 270, 273 (1927); **448**, 194, note 1 (1926); **473**, 236 (1929).

(5) Corwin and Andrews, THIS JOURNAL, **58**, 1086 (1936).