[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

Molecular Rearrangements in the Sterols. IV. The Structure of *i*-Cholestanone[1]

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In parts I, II and III[4,5,6] of this series, experiments on the preparation and on the determination of the structure of a new isomer of cholesterol, designated by us as *i*-cholesterol, and shown to be the parent alcohol of the isomeric dextrorotatory cholesteryl ethers, have been described. Although our experimental results were confirmed at once by other investigators,[7] our interpretation and proposed formulation of the structure of this new isomer was sharply questioned.

In this paper we wish to report the results of certain experiments which establish more rigidly the original formulation proposed in this Laboratory of the structure of these highly interesting compounds. Before the existence of *i*-cholesterol was suspected, Windaus and Dalmer[8] had treated α-3-chlorocholestanone-6 with alcoholic potassium hydroxide, and had obtained a halogen-free ketone which they believed to contain a true double bond, and which they named "heterocholestenone." That this "heterocholestenone" was in reality *i*-cholestanone was first pointed out by Heilbron and co-workers,[9] who prepared *i*-cholestanone not only by the method of Wallis, *et al.*,[4] by oxidation of *i*-cholesterol, but also obtained it from *i*-cholesteryl acetate and from *i*-cholesterol methyl ether. We are now able to report that we have prepared the isomer of *i*-cholestanone containing a true double bond by refluxing α-3-bromocholestanone-6 with quinoline. The double bond so produced by the removal of hydrogen bromide shifts from the C_3:C_4 position to the position conjugated to the ketone group as is indicated by its absorption spectra; the compound shows absorption in the ultraviolet, maximum at 2450 Å., the wave length characteristic for conjugation across two rings. Therefore, we have assigned to it the structural formula III. This new ketone melts at 105°; its oxime melts at 185°. The same compound is also obtained in somewhat smaller yields from α-3-chlorocholestanone-6 by treatment with quinoline. It is, thus, the "true heterocholestenone."

In Part III of this series it was shown that the cyclopropane ring of *i*-cholestanone can be opened without difficulty. Thus when treated with dry hydrogen chloride α-3-chloro-cholestanone-6 is formed. We have found that a similar reaction takes place when aqueous hydrogen bromide is added to an acetic acid solution of *i*-cholestanone; α-3-bromo-cholestanone-6 (m. p. 123°) crystallizes out quantitatively. Another interesting observation is the fact that when an acetic acid solution of *i*-cholestanone is refluxed with dilute sulfuric acid, it is converted into β-3-hydroxy-cholestanone-6 (m. p. 142–143°) identical with the compound prepared by the method of Windaus.[10]

To establish further proof of the structure of *i*-cholestanone (II), a study of degradative oxidations of this ketone has been made. The following experiments show that there is no double bond in the molecule. Hydrogen peroxide, when heated with an acetic acid solution of the ketone, has no effect. Neither is the compound oxidized by neutral or alkaline potassium permanganate, reagents which attack violently compounds containing a double bond. However, when a pyridine solution of *i*-cholestanone is shaken for twenty-four hours with an aqueous solution of potassium hypobromite, an acid (IV) is obtained. This acid melts at 233°. It is dibasic and does not decolorize bromine solution nor does it give an active Liebermann reaction. Unlike the ketone, it does not add water or halogen acid; its analysis agrees with the assigned formula IV.

The facts mentioned above show the marked difference in the stability of the cyclopropane ring in the series: *i*-cholesterol, *i*-cholestanone, *i*-cholestane diacid. *i*-Cholesterol has been prepared from cholesterol by molecular rearrangement, and can be converted back into cholesterol under certain conditions; *i. e.*, the cyclopropane linkage can shift to a double bond and *vice versa*. *i*-Cho-

(1) The experimental results herein described were placed before the Society in a paper read before the Division of Organic Chemistry at the Society meeting in Boston, September 11–15, 1939.

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(4) Wallis, Fernholz and Gephart, THIS JOURNAL, **59**, 137 (1937).

(5) Ford and Wallis, *ibid.*, **59**, 1415 (1937).

(6) Ford, Chakravorty and Wallis, *ibid.*, **60**, 413 (1938).

(7) Beynon, Heilbron and Spring, *J. Chem. Soc.*, 1459 (1937); see also, Heilbron, Hodges and Spring, *ibid.*, 759 (1938).

(8) Windaus and Dalmer, *Ber.*, **52**, 168 (1919).

(9) Heilbron, Hodges and Spring, *J. Chem. Soc.*, 759 (1938).

(10) Windaus, *Ber.*, **36**, 3754 (1903).

lestanone does not undergo isomerization. The cyclopropane linkage, however, can be opened without difficulty. In the dicarboxylic acid the cyclopropane linkage exhibits the greatest stability and resists strongly efforts to rupture it. Thus, it can be concluded that the stability of the cyclopropane ring depends on the nature of the state of oxidation of the C_6 carbon atom. Exactly the same relationship has been observed with sabina ketone and its derivatives.[11]

In an attempt to relate the above diacid (IV) to a known compound, β-3-chloro-cholestane-diacid-6,7 (VI) was prepared from β-3-chlorocholestanone-6 (V) according to the method of Windaus and Stein.[12] When this compound is treated with alcoholic potassium hydroxide, hydrogen chloride is not removed. Treatment with sodium ethylate, however, at higher temperature results in a halogen-free dicarboxylic acid (VII), m. p. 231°. This compound gives no reaction characteristic of the ethylenic double bond but exhibits all those properties associated with the presence of a cyclopropane ring. Experiments show that it is not identical with the acid obtained from *i*-cholestanone. Thus this second acid is an isomer of *i*-cholestane-diacid (IV).

This isomerism can be explained as being due to the relative positions of the groups at C_3, since the two acids were obtained from the α- and β-chloro ketones, respectively. However, the isomerism may be due to the relative positions of the groups at C_5.

The following experiments show that the stereochemical positions of both asymmetric centers, C_3 and C_5, are involved.

In order to establish the isomeric relationship of the above dicarboxylic acids, α-3-chlorocholestane-diacid-6,7 (VIII) was prepared from α-3-chlorocholestanone-6 according to Windaus and Staden.[13] This diacid loses hydrogen chloride with greater difficulty than the other halogen compounds studied in this series. But it can be removed when the acid is treated with sodium ethylate at 150°. When this procedure is followed, a halogen-free diabasic acid (IX), melting at 265°, is obtained. This third acid also gives no reactions of the double bond and is an isomer of the other two. Since, like the diacid (IV), it also has been derived from α-3-chlorocholestanone-6, the steric position of the hydrogen at C_3 with respect to the methyl group at C_{10} should be the same in these two diacids (IV and IX), and the latter will be designated as α_2-*i*-cholestane-diacid-6,7. We believe that its non-identity with the α_1-*i*-cholestane-diacid-6,7 (IV) is due to a difference in the steric position of the carboxyl group at C_5, the inversion being caused by the influence of the alkaline reagent on α-3-chlorocholestane-diacid-6,7 (VIII). The mechanism of such an inversion may be explained by the formation of an enol. Thus, the carboxyl group at C_5 in the diacid (IX) is believed to have a *trans* orientation with respect to the methyl group at C_{10}. In the diacid (IV), however, the carboxyl group at C_5 should be in *cis* position to the methyl group at C_{10} since in the oxidation of the ketone (II) to the acid (IV) inversion cannot take place, there being no available hydrogen at C_5.

Theoretically there should exist a fourth isomeric acid of the structure (XI) which should be obtained by the oxidation of the isomer of *i*-cholestanone (X). As yet this acid has not been prepared. This diacid (XI) should have the same stereochemical configuration at C_3 as the diacid (VII) but would differ from the latter in the steric position of the carboxyl group at C_5. In accordance with the naming of the α-diacids, the diacid (VII) will be designated as β_2-*i*-cholestane-diacid-6,7. The method of preparation of the β_1-*i*-cholestane-diacid-6,7 is being studied at the present time.

The chart contains in outline the reactions discussed.

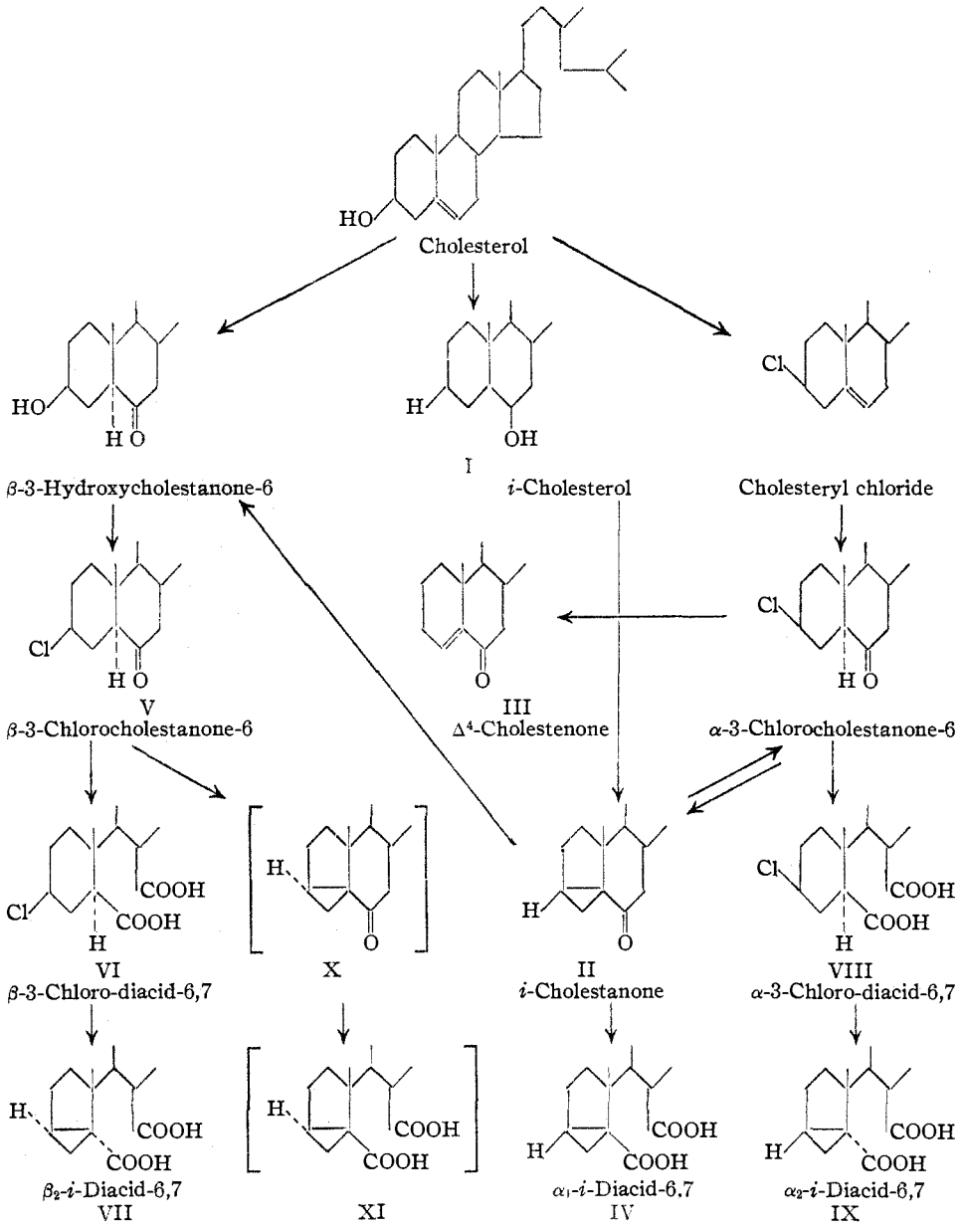
While the nature of the isomeric relationship between these acids is clear, the assignment of the steric position of the hydrogen at C_3 and of the carboxyl at C_5 is difficult. It is possible, however, to make certain deductions based on some observations of other investigators[14] in closely allied fields. If one considers for example the α- and β-cholestanols, one sees that these two compounds each yield different chlorides depending on whether they are treated with phosphorus pentachloride or with thionyl chloride. With cholesterol, however, the same product in each case results. Ruzicka assumes that the β-cholestyl chloride (m. p. 105°) is the *trans* form and the α-isomeride (m. p. 116°) is the *cis* form, basing his assumption on the fact that in the cholestanols

(11) Wallach, *Ann.*, **359**, 265 (1908); Thomson, *J. Chem. Soc.*, **97**, 1502 (1910).

(12) Windaus and Stein, *Ber.*, **37**, 3699 (1904).

(13) Windaus and Staden, *Ber.*, **54**, 1059 (1921).

(14) Ruzicka, Wirz and Meyer, *Helv. Chim. Acta*, **18**, 998 (1935); Marker, Whitmore and Kamm, THIS JOURNAL, **57**, 1755, 2358 (1935).



the α-form (*cis* or *epi*) has a higher melting point than the β-form (*trans* or normal). It must be remembered that *cis* and *trans* here refer to the position of the functional group at C_3 with respect to the hydrogen at C_5. Therefore, if this be true, it follows that a Walden inversion takes place in the chlorination of cholesterol with either phosphorus pentachloride or thionyl chloride, whereas with the cholestanols only chlorination with thionyl chloride causes an inversion.

If we apply these relationships to the reactions described in this paper and assume inversion to take place in the chlorination of cholesterol but not with cholestanol, a *cis*- or *epi* configuration should be assigned to the α-chlorocholestanone-6 (m. p. 129°) and a *trans*- or normal configuration to the β-chloro ketone (m. p. 181°). It should be pointed out that this leads to confusion, when considered in the light of Ruzicka's rule, which assumes that of the two isomers the one of higher melting point has the *epi*- or *cis* configuration. It is interesting to note, however, that the two chloro diacids obtained from the α- and β-ketones, respectively, are in accordance with Ruzicka's assumption, the α-chloro diacid melting at 263° and the β-form melting at 243°.

We also can state that the stereochemical configurations so assigned to the α- and β-3-chlorocholestanone-6 are supported by certain experimental observations. Windaus[8] has observed that hydrogen chloride may be removed from the α-chloro ketone without difficulty by simply warming with alcoholic potassium hydroxide, whereas a similar or even more drastic treatment leaves the β-chloro ketone unchanged. Since it is now believed that the removal of the hydrogen chloride with an alkaline reagent involves the hydrogen atom at C_5 and not, as Windaus assumed, at C_4, the difference of the α- and β-chloro ketones in this particular reaction may well be attributed to the *cis* orientation of the chlorine atom to the hydrogen at C_5 in the α-compound and to the *trans* orientation in the β-isomer. It is also possible to follow this argument through to the 3-chloro diacids. If we consider that sodium ethylate first produces an inversion of the carboxyl group at C_5 before removal of hydrogen chloride from the chloro acids is attained, then the reaction would be expected to proceed more easily in the case of the β-form than in the case of the α-isomeride. This expectation is substantiated by the experiments.

Experimental Part

Preparation of *i*-Cholestanone (II) from *i*-Cholestanone-oxime.—*i*-Cholestanone-oxime (m. p. 143–144°) prepared by the method of Wallis, Fernholz, and Gephart was hydrolyzed with dilute sulfuric acid in alcohol solution. The solution was boiled for three hours, diluted with water, and extracted several times with ether. Evaporation of the ether and recrystallization of the residue gave a crystalline ketone which melted at 96°.[15] When mixed with an authentic specimen of the halogen-free ketone of m. p. 96° (oxime 143°) prepared from α-3-chlorocholestanone-6 by the Windaus and Dalmer method, no depression of the melting point was observed.

Preparation of β-3-Hydroxycholestanone-6 from *i*-Cholestanone.—One gram of *i*-cholestanone was dissolved in 200 cc. of acetic acid and 50 cc. of 5 *N* sulfuric acid. The solution was refluxed for two hours, diluted with water, and extracted with ether. After removing the solvent, the residue was taken up in alcoholic sodium hydroxide and refluxed for one hour to hydrolyze any acetate formed in the reaction. The hydroxy ketone was precipitated with water, filtered, and recrystallized from alcohol; yield 0.95 g. (91%), m. p. 142–143°. The acetate was prepared by refluxing 0.1 g. of the material with acetic anhydride for one hour. On making up the product in the usual manner, crystals were obtained from alcohol which melted at 127–128°. No depression of the melting point of the free hydroxy ketone as well as of its acetate could be observed when these compounds were mixed with specimens prepared according to Windaus.[10]

Preparation of the Oxime of β-3-Acetoxycholestanone-6.—The oxime was prepared in the usual manner. It melted at 194–195°.

Anal. Calcd. for $C_{29}H_{49}O_3N$: C, 75.77; H, 10.74; N, 3.04. Found: C, 75.96; H, 10.49; N, 3.08.

Preparation of α-3-Bromocholestanone-6.—To a solution of 0.25 g. of *i*-cholestanone in acetic acid, 2.5 cc. of a 34% aqueous hydrobromic acid solution was added. After standing overnight at room temperature, a crystalline product separated which was filtered and recrystallized from dilute acetic acid and alcohol. It melted at 123°, yield quantitative.

Anal. Calcd. for $C_{27}H_{45}OBr$: C, 69.65; H, 9.74; Br, 17.17. Found: C, 69.76; H, 9.84; Br, 17.47.

Preparation of Δ⁴-Cholestanone-6 (III).—Four grams of α-3-bromocholestanone-6 (m. p. 123°) was dissolved in 60 cc. of freshly distilled quinoline and the solution refluxed for one hour in an atmosphere of nitrogen. The product was precipitated with water and extracted with ether. The quinoline was removed with dilute sulfuric acid. The solvent was evaporated, and the residue was crystallized from alcohol. Crystals were obtained which melted at 104–105°, yield 2.6 g. (79%).

Anal. Calcd. for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.24; H, 11.31.

The oxime of Δ⁴-cholestenone-6 was prepared in the usual way, giving crystals from alcohol which melted at 184–185°.

Anal. Calcd. for $C_{27}H_{45}ON$: C, 81.14; H, 11.35; N, 3.51. Found: C, 80.98; H, 11.16; N, 3.72.

Preparation of α_1-*i*-Cholestane-diacid-6,7 (IV).—To a solution of 100 cc. of 10% potassium hydroxide and 2.5 cc. of bromine, 2.5 g. of *i*-cholestanone-6 (II) was added; the temperature was raised to about 50° so that all of the solid material became properly suspended. After cooling to room temperature, 250 cc. of pyridine was added and the solution was shaken vigorously for twenty-four hours; the solution was clear and almost colorless. After cooling to 0° sulfuric acid was added until the smell of pyridine was no longer noticeable, and the precipitate was taken up in ether. The ether was extracted with dilute alkali and the acidic product was precipitated with sulfuric acid. The precipitate was filtered and the product was recrystallized from dilute alcohol. Crystals were obtained which melted at 232–233°, yield quantitative, 18.1 mg. in 2 cc. of absolute acetone, α_D +0.16, $[\alpha]^{25}D$ +18° in absolute acetone.

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 74.95; H, 10.25; neut. equiv., 216. Found: C, 74.72; H, 10.13; neut. equiv., 216.

Preparation of β-*i*-Cholestane-diacid-6,7 (VII).—Two grams of metallic sodium was dissolved in 25 cc. of absolute alcohol in a bomb tube. To the clear solution 1 g. of β-3-chlorocholestane-diacid-6,7 (m. p. 243°), prepared according to Windaus and Stein, was added. The tube was sealed and heated in a furnace at 120° for one hour. A

(15) In the original recording of the melting point of this compound an error was made. We believe, however, that we are correct in our statement that the oxime melts at 143–144° and not at 122–123° as later reported by Heilbron, Hodges and Spring.[9] We have prepared this oxime many times by both methods, and never have we been able to obtain the melting point recorded by them.

successful reaction was indicated by the precipitation of sodium chloride. Water was added and the acidic reaction product was precipitated with sulfuric acid, filtered and recrystallized from dilute alcohol and dilute acetic acid. The crystals melted at 230–231°, 17.4 mg. in 2 cc. absolute acetone, α_D + 0.48, $[\alpha]^{24}D$ +55°. Experiment showed that this halogen-free dicarboxylic acid crystallizes with one molecule of water, which is still retained after drying in vacuum at 110°.

Anal. Calcd. for $C_{27}H_{44}O_4 \cdot H_2O$: C, 71.97; H, 10.29; neut. equiv., 226. Found: C, 72.16; H, 10.28; neut. equiv., 230.

Preparation of α_2-*i*-Cholestane-diacid-6,7 (IX).—This acid was prepared from α-3-chlorocholestane-diacid-6,7 (m. p. 263°) in a manner similar to the one described above. In this case, however, the reaction had to be carried out at 150°, and the time had to be increased to eight hours. The halogen-free dicarboxylic acid melts at 265°, 18.8 mg. in absolute dioxane, α_D +0.43, $[\alpha]^{25}D$ +46° in dioxane.

Anal. Calcd. for $C_{27}H_{44}O$: C, 74.95; H, 10.25; neut. equiv., 216. Found: C, 75.03; H, 10.46; neut. equiv., 217.

We wish to take this opportunity to express our thanks to Merck and Company, Inc., of Rahway, New Jersey, for the analyses published in this paper, for the determination of the absorption of Δ^4-cholestenone and for the cholesterol used as the starting material.

Summary

Further evidence has been given to show that Windaus' method of removing hydrogen chloride from α-3-chlorocholestanone-6 gives *i*-cholestanone and not the unsaturated ketone heterocholestenone.

The true heterocholestenone, Δ^4-cholestenone-6, has been obtained and characterized.

A new dicarboxylic acid, m. p. 233°, has been prepared from *i*-cholestanone. This acid has been shown to be an isomer of another new acid, m. p. 231°, obtained from β-3-chlorocholestanone-6. A third isomeric acid, m. p. 265°, has been prepared from α-3-chlorocholestanone-6.

A detailed discussion of the stereochemical relationships of these compounds has been given.

PRINCETON, N. J. RECEIVED SEPTEMBER 29, 1939

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF TEMPLE UNIVERSITY]

The Oxidation of Certain Heteronuclear-Substituted Polybromodiphenyls

BY FRANCIS H. CASE

In the course of various investigations in this Laboratory dealing with the structures of certain heteronuclear polybromodiphenyls, it seemed desirable to obtain more information as to the behavior of these compounds on oxidation. Although it is known, in general, that in the case of those diphenyls substituted by bromine in one ring only, the unsubstituted ring is destroyed by oxidation, there appears to be no information concerning the oxidation of those compounds in which bromine is a substituent in both rings. The method of oxidation employed utilizes chromic anhydride in approximately 75% acetic acid solution.[1] In each case a considerable amount of the total molecule was destroyed.

The oxidation of 3,4′-[2] and of 2,3′-dibromodiphenyls yielded *p*- and *m*-bromobenzoic acids, respectively, as the sole resulting products. The tribromodiphenyls investigated may (with the exception of 2,4,6-tribromodiphenyl) be divided into two groups in each of which the dibromo substituted nucleus remains the same, while the position of the monobromo substituent in the other nucleus is varied. Group A consists of 2,3′,5′-(I),[3] 3,3′,5′-(II), and 3′,4,5′-(III) tribromodiphenyls. Group B contains 2,2′,5′-(IV), 2′,3,5′-(V) and 2′,4,5′-(VI) tribromodiphenyls. The results of the oxidation of these six isomers are as follows: I and II yield only 3,5-dibromobenzoic acid; III, only *p*-bromobenzoic acid; IV, only 2,5-dibromobenzoic acid; V, both *m*-bromobenzoic and 2,5-dibromobenzoic acid; VI, both *p*-bromobenzoic and 2,5-dibromobenzoic acid.

The oxidation of 2,4,4′,6-tetrabromodiphenyl was found to yield only *p*-bromobenzoic acid, while 2,4,6-tribromodiphenyl, subjected to the same treatment, also yielded a certain amount of *p*-bromobenzoic acid. This surprising result was at first attributed to the presence of a small amount of 2,4,4′,6-tetrabromo-3-aminodiphenyl in the 2,4,6-tribromo-3-aminodiphenyl from which the 2,4,6-tribromodiphenyl was obtained by deamination. However, this explanation had to be

(1) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Inc., Boston, Mass., 1935, p. 230.

(2) Case, THIS JOURNAL, **60**, 424 (1938).

(3) Case, THIS JOURNAL, **61**, 767 (1939).