[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

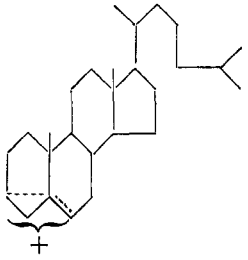
Mechanism of Formation of Cholesterylisothiuronium Tosylate from Thiourea and Cholesteryl Tosylate[1]

BY RALPH G. PEARSON, L. CARROLL KING AND STANLEY H. LANGER[2]

The reaction between cholesteryl tosylate and 0.4 *M* thiourea in methanol-chloroform solvent to form cholesterylisothiuronium tosylate proceeds through an *i*-ether intermediate to the extent of 67% and goes directly to the extent of 33%. The kinetics have been treated quantitatively by an expression developed for two concurrent first order reactions, one of which is followed by a second order reaction. The total rate of ionization of cholesteryl tosylate is increased only 40% by the addition of 0.4 *M* thiourea. A carbonium ion mechanism is indicated.

Current theories[3] on the reaction of cholesteryl derivatives with nucleophilic reagents postulate that an *i*-cholesteryl derivative is first formed, which then may or may not rearrange to a normal cholesteryl structure. The formation of high yields of *i*-ethers (80–90%) in the reaction of cholesteryl halides and tosylates with alcohols under buffered conditions,[4] and the ready rearrangement of *i*-ethers to normal ethers under acid conditions show that such a mechanism can operate.

Also it is believed[3b,3d,5] that a common intermediate in the interconversion of normal and *i*-cholesteryl derivatives may be the carbonium ion which is stabilized by hyperconjugative resonance.



To check the general validity of these theories the reaction of cholesteryl tosylate I with thiourea in methanol–chloroform solvent to form 3-β-cholesterylisothiuronium tosylate II[6] was studied kinetically. Since thiourea is a very powerful nucleophilic reagent, any tendency for direct reaction should be enhanced.

The experimental results presented here show that the total rate of reaction of I in a solvent consisting of 10 parts of methanol to 1 part of chloroform by volume is increased by only 40% in going from zero to 0.4 molar thiourea. Analysis of a reaction mixture containing initially 0.00425 molar I and 0.4 molar thiourea, for hydrogen ion as a function of time shows that 67% of the reaction goes by way of *i*-cholesteryl methyl ether III and 33% goes by way of a "direct" reaction of I with thiourea not involving *i*-cholesteryl methyl ether. III is known to react with thiourea and *p*-toluenesulfonic acid to give high yields of II.[6] The reaction sequence can be formulated as

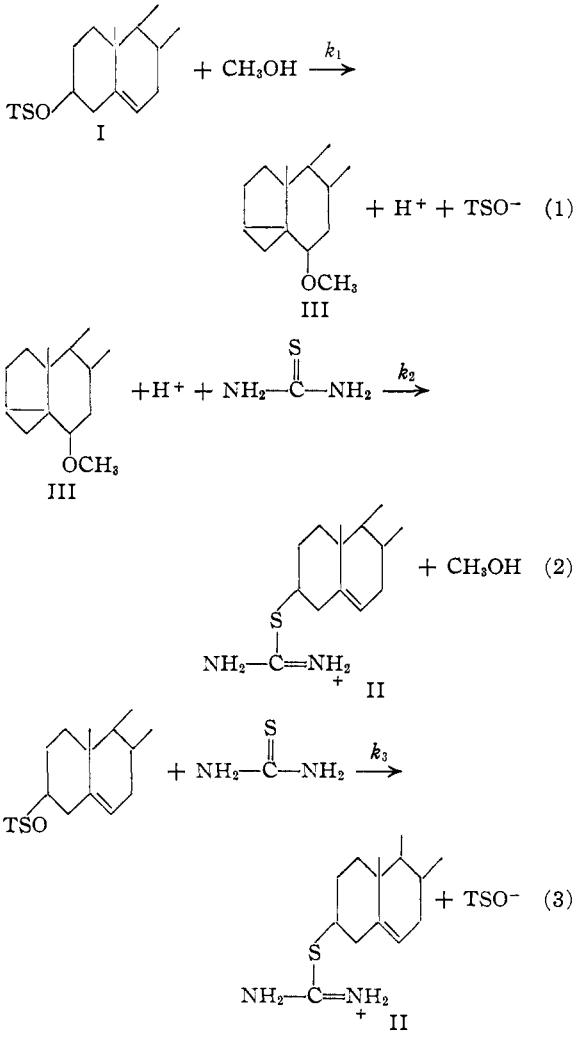


TABLE I

FIRST ORDER SOLVOLYSIS OF CHOLESTERYL TOSYLATE AT 34.85 ± 0.07°

Cholesteryl tosylate = 0.00425 *M*

Added substance	k_1, min^{-1}
.....	0.00460
.....	.00466
0.00425 *M* *p*-toluenesulfonic acid	.00447
.0084 *M* triethylamine	.00466
.4 *M* thiourea, 0.0084 *M* triethylamine	.00644
.4 *M* thiourea, .0084 *M* triethylamine	.00652
.34 *M* urea	.00540

(1) Presented at the Chicago Meeting of the American Chemical Society, September, 1950.

(2) Public Health Pre-doctoral Fellow 1949–1951.

(3) (a) E. S. Wallis and co-workers, THIS JOURNAL, **59**, 137, 1415 (1937); **60**, 413 (1938). (b) E. W. Meyer, Ph.D. thesis, Northwestern University, 1943. (c) C. W. Shoppee, *J. Chem. Soc.*, 1147 (1946). (d) R. M. Dodson and B. Riegel, *J. Org. Chem.*, **13**, 424 (1948). (e) L. C. King, THIS JOURNAL, **70**, 2685 (1948).

(4) Byron Riegel, private communication.

(5) (a) S. Winstein and R. Adams, THIS JOURNAL, **70**, 838 (1948); (b) R. G. Pearson, L. A. Subluskey and L. C. King, *ibid.*, **70**, 3479 (1948); (c) S. Winstein and A. Schlesinger, *ibid.*, **70**, 3528 (1948).

(6) L. C. King, R. M. Dodson and L. A. Subluskey, *ibid.*, **70**, 1176 (1948).

TABLE II

RATE OF FORMATION OF CHOLESTERYLISOTHIURONIUM TOSYLATE FROM *i*-ETHER, THIOUREA AND *p*-TOLUENESULFONIC ACID AT 34.85°

Thiourea = 0.4 *M*, Acid = 0.00425 *M*

i-ether concentration	k_2, l./mole-min.
0.00636	3.01
.00642	2.99
.00425	2.97
.00425	2.95
.00425	3.2[a]

[a] This rate was followed by conductometric titration and the constant is not very accurate.

In the presence of excess thiourea both k_1 and k_3 may be treated as first order rate constants. Also k_1 can be found independently by measuring the rate of solvolysis of I. Table I gives data for the experimental values of k_1 in solvent alone and in the presence of various addends. These were all determined by measuring the change in resistance with time as I solvolyzed.

The rate constant k_2 is a pseudo-second order constant in excess thiourea and may be separately evaluated by starting with pure III instead of I.[5b] Table II gives values of k_2 obtained in this study.

Knowing the values of k_1 and k_2 and the expression given by Chien[7] for a first order reaction followed by a second order one, an attempt was made to analyze the over-all reaction kinetically. This was first done by putting $k_1 = 0.0065$, $k_2 = 2.96$ and $k_3 = 0$. The results are shown in the full line of Fig. 1 which shows hydrogen ion concentration (equal to *i*-ether concentration) plotted against time. The circles in Fig. 1 represent experimentally observed points. A maximum is found when hydrogen ion concentration is plotted against time because the solvolysis of I produces acid but the reaction with *i*-ether and thiourea removes acid.

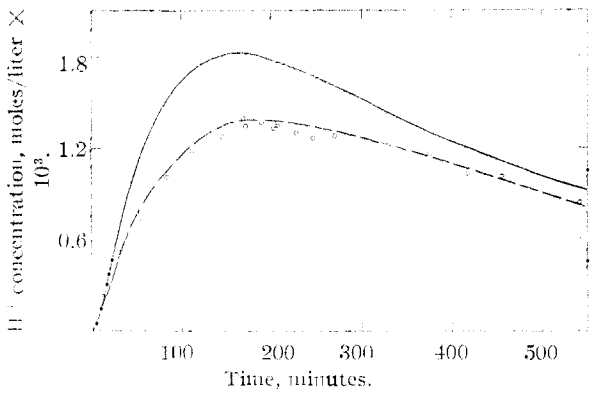


Fig. 1.—Reaction of cholesteryl tosylate with 0.4 *M* thiourea: full line, $k_1 = 0.0065$ and $k_3 = 0$; dotted line, $k_1 = 0.0044$ and $k_3 = 0.0021$; circles, experimental points.

Since agreement between experimental and calculated values is clearly not obtained (nor would it be with $k_1 = 0.0046$ and $k_3 = 0$), it was necessary to assume that k_3 was not zero. Chien's formulation was adapted to the case of two concurrent first order reactions, one of which is followed by a second order process. Holding $(k_1 + k_3) = 0.0065$, various values of k_3 were tried until the best fit was obtained between the experimental points and the theoretical curve. The broken line in Fig. 1 corresponds to $k_3/(k_1 + k_3) = 0.33$ so that $k_1 = 0.0044$ and $k_3 = 0.0021$.

The reaction sequence that we are dealing with consists of

$$A \xrightarrow{k_1} 2B \xrightarrow{k_2} C \qquad (4)$$

$$A \xrightarrow{k_3} C \qquad (5)$$

The equation used to find the hydrogen ion concentration as a function of time is as follows: (B is *i*-ether, III, or hydrogen ion which are present in equal concentrations from their method of formation, and $[A]_0$ is the initial concentration of cholesteryl tosylate)

$$[B] = [A]_0 \frac{k_1}{(k_1 + k_3)} \sqrt{\tau/K} \frac{iJ_1(2i\sqrt{K\tau}) - \beta H_1^{(1)}(2i\sqrt{K\tau})}{J_0(2i\sqrt{K\tau}) + \beta i H_0^{(1)}(2i\sqrt{K\tau})} \qquad (6)$$

where

$$\tau = e^{-(k_1+k_3)t} \quad K = \frac{k_1 k_2 [A]_0}{(k_1 + k_3)^2} \quad \beta = \frac{iJ(2i\sqrt{K})}{H_1^{(1)}(2i\sqrt{K})}$$

and the J's and H's are Bessel functions.[8]

The calculation of values of [B] at various times is a laborious procedure. The first assumption made that $k_1 = 0.0065$ and $k_3 = 0$ is equivalent to assuming that the increase in solvolysis rate of I found in thiourea solution is due to a general solvent effect without any change in the nature of the products. The second assumption makes $k_1 = 0.0044$ which is nearly the value found for k_1 in pure solvent.

The small increase in the rate of solvolysis caused by the presence of large amounts of the powerful nucleophilic reagent thiourea, is good evidence for a carbonium ion mechanism in the case of *i*-ether formation. The "direct" reaction with thiourea can be interpreted as either a displacement reaction of thiourea on I or as a reaction of the carbonium ion with thiourea without ever going through the *i*-ether stage. Since only a single stereoisomeric product is formed (very probably the 3-β configuration, see reference 6), the nature of the displacement reaction is hard to visualize since I also has the β-configuration. A double inversion is possible in which thiourea attacks the 6-carbon atom of I forming the *i*-cholesterylisothiuronium salt, and this in turn is attacked by a second molecule of thiourea at the 3-carbon forming II. All that is known of the *i*-cholesterylisothiuronium ion is that its salts are not stable enough to be isolated, and that it is not formed in any amount even as an unstable intermediate in the reaction of III to give II.[5b]

At the present time we prefer to believe that a carbonium ion is involved in the "direct" reaction but that the incipient ion is preferentially solvated by a molecule (or several molecules) of thiourea. Thus when the carbonium ion is released it immediately reacts with the closely attached thiourea molecule. If reaction occurred at the 3-position, the β-

(7) J. Y. Chien, THIS JOURNAL, **70**, 2256 (1948).

(8) Values of the Bessel functions are given in Jahnke and Emde, "Tables of Functions," Dover Publications, New York, N. Y., 1943, pp. 224–229, 236–249.

isomer would be formed because of the participation of the double bond in maintaining the steric configuration.[3d,5a] Reaction might also occur at the 6-position, giving the *i*-cholesterylisothiuronium salt which would eventually revert to II.

Experimental

Materials.—Methanol used was either a Baker C.P. grade or dried by the method of Lund and Bjerrum.[9] Chloroform was also a Baker C.P. grade or purified according to Fieser.[10] Triethylamine was purified by successive distillations from phthalic anhydride and barium oxide.

Thiourea (m.p. 178–179°) was purified from a medicinal grade by recrystallization from ethanol. Cholesteryl *p*-toluenesulfonate was prepared as recommended by Wallis. Several recrystallizations from acetone gave pure product, m.p. 132.5–133.5°. *i*-Cholesteryl methyl ether was prepared by the method of Stoll, m.p. 78–79°, $[\alpha]^{26}D$ 55.1° in chloroform.

p-Toluenesulfonic acid monohydrate was an Eastman Kodak Co. white label product, m.p. 102–104°. Sodium methoxide solution was prepared by dissolving freshly cut sodium in dry methanol through which dry nitrogen was passed for several hours previously.

All solvents used were tested by conductometric methods and titrated to ensure that there was no detectable acidity.

Methods. Solvolysis of I.—The cholesteryl derivatives were always dissolved in one volume of chloroform and the reaction initiated by diluting with ten volumes of methanol in which any other reagents were dissolved. The concentration of I in all reaction mixtures was 0.00425 *M*, thiourea when used was 0.4 *M*, and *p*-toluenesulfonic acid when used was 0.00425 *M*. The rate of solvolysis was found by measuring the change in conductance with time using methods previously outlined.[11] $\mathrm{Log}[R/(R - R_e)]$ was plotted against time to get the first order rate constant. Figure 2 shows some of the results. The value of R_e, the equilibrium resistance was obtained by direct measurement and checked by making up synthetic equilibrium solutions.

It is not possible to measure the rate of solvolysis of I in solutions containing thiourea by resistance measurements alone because not only the number but also the kind of ions present is changing with time. Accordingly 0.0084 *M* triethylamine was also added to remove any hydrogen ions which might react further. The equilibrium resistance of such a solution corresponds to that of triethylammonium tosylate. Evidently any II formed by direct reaction is decomposed by triethylamine. A separate experiment in which triethylamine was added to a solution of II showed that the conductance increased rapidly at first and then slowly to that of triethylammonium tosylate.[12]

Rate of Formation of II from III.—This reaction was studied conductometrically essentially as outlined in reference 5b. One change was made in that a ratio of *i*-ether to *p*-toluenesulfonic acid of 1.5 to 1 as well as 1 to 1 was used. This was done to establish the value of R_e with certainty. Even in 0.4 *M* thiourea some isomerization (about 6%) to normal cholesteryl methyl ether occurs. This leaves unreacted acid in solution. The error in the resistance is cumulative and is greatest for the equilibrium resistance. By using an excess of *i*-ether all of the hydrogen ion will react eventually. In this way an equilibrium resistance equal to the measured value of a synthetic solution of II can be obtained. This value of the resistance was also used in calculating the rate constant for those solutions where *i*-ether was not in excess. If the measured equilibrium resistance in these solutions is used, a rate constant some 15% higher is calculated. The function plotted against time to find the pseudo-second order rate constant k_2 was $R/(R_e - R)$ for equivalent concentrations and log $\left[\left(R_e + \left(\frac{2R_e}{R_0} - 1.5\right)R\right)/(R_e - R)\right]$ for a 1.5 to 1 ratio of reactants. R_0 was the experimental resistance of a 0.00425 *M* *p*-toluenesulfonic acid solution in 0.4 *M* thiourea.

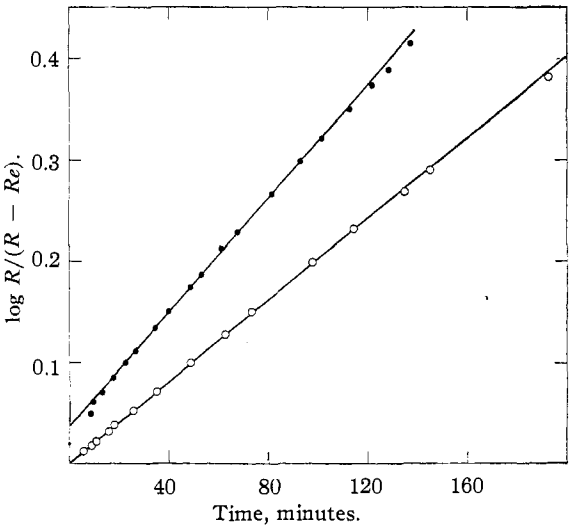


Fig. 2.—Solvolysis of cholesteryl tosylate: lower line nothing added; upper line 0.4 *M* thiourea and 0.0084 *M* triethylamine.

Reaction of I with Thiourea.—A complete analysis of the kinetics of this reaction requires that the concentration of the intermediate hydrogen ion or *i*-ether be measured. The hydrogen ion is the logical choice since titration methods can be used. However, considerable difficulty was encountered in titrations using indicator or e.m.f. methods for finding the end-point. This is because the solutions are very dilute (0.001–0.002 *M* in acid) and are buffered by the presence of thiourea and cholesterylisothiuronium ion. A method of conductometric titration was finally used in which a 25-ml. aliquot was added to about 10 ml. of cold methanol in an open conductance cell and then rapidly titrated with 0.05 *M* sodium methoxide in methanol, with appropriate readings of the resistance. From 0.2 to 0.8 ml. of base were required for the first end-point, volumes being read to 0.002 ml.

TABLE III

CONDUCTOMETRIC TITRATIONS OF *p*-TOLUENESULFONIC ACID AND CHOLESTERYLISOTHIURONIUM TOSYLATE KNOWNS

Thiourea = 0.4 *M*

Acid. concn.	Chol. Iso. Tos. concn.	Acid found	Chol. Iso. Tos. found
0.00112	.....	0.00108	.....
.00112	0.00051	.00108	0.00066
.00112	.00101	.00107	.....
.00112	.00306	.00107	.....
.00112[a]	.....	.00108	.....
.00168	.....	.00163	.....
.00056	.....	.00053	.....
.....	.00425	.....	.00417
.....	.00425	.....	.00452
.....	.00425	.....	.00480

[a] Containing no thiourea.

Plots of the reciprocal of resistance against the volume of base gave good breaks indicating the end-point for the titration of all of the hydrogen ion including that bound by thiourea. If readings were continued a second break could be obtained for the titration of cholesterylisothiuronium ion. The second end-points were sharp but the concentrations calculated from them were not reliable. Table III shows the results of titrating a number of knowns by the conductometric method.

The blank runs of Table III indicate that the experimental points of Fig. 1 are all too low. Correcting them would give a better fit to the points around the maximum and a

(9) H. Lund and J. Bjerrum, *Ber.*, **64B**, 210 (1931).

(10) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Company, New York, N. Y., 1941, p. 361.

(11) R. G. Pearson, THIS JOURNAL, **69**, 3100 (1947).

(12) The resistance of II in this case was 10,000 ohms, the initial reading at three minutes was 8200 ohms, and overnight the resistance became 7000 ohms which corresponds to triethylammonium tosylate. Any error due to the incompleteness of this reaction can be shown to be negligible in our studies.

poorer fit to the latter points. However, the latter points would be expected to be high since some isomerization to normal ether occurs. At infinite time for example (1260 minutes), the acid concentration found is 0.00024 *M* instead of zero. Considering this side reaction and the inherent errors in the method of analysis, the agreement obtained is as good as can be expected.

Acknowledgment.—One of the authors (S. H. L.) is indebted to the United States Public Health Service for a fellowship held during the course of this work.

EVANSTON, ILLINOIS RECEIVED DECEMBER 8, 1950

[CONTRIBUTION FROM THE COAL RESEARCH LABORATORY, CARNEGIE INSTITUTE OF TECHNOLOGY]

Reactions of Benzofurans with Hydrogen[1]

BY JACOB ENTEL, CLARENCE H. RUOF AND H. C. HOWARD

The presence of linear and cyclic ethers has often been postulated to account for the inert character of oxygen in bituminous coals. Little information is available on the behavior of such ethers when subjected to reaction with hydrogen. In this work benzofuran, 2,3-dihydrobenzofuran and 2-methyl-2,3-dihydrobenzofuran have reacted with hydrogen at 200°, 250° and 300° using copper–chromium oxide as catalyst and the products have been separated and identified. The heterocyclic ring is ruptured and at higher temperatures a secondary hydrogenolysis removes the oxygen to form alkyl benzenes and cyclohexanes. A possible mechanism for the reaction, based on yields of the various products and the amenability of possible intermediate products to further reaction, is presented.

Although oxygen is contained in all bituminous coals very little evidence as to its nature has been forthcoming. Even the simple soluble and volatile degradation products from coal often contain more oxygen than can be accounted for in reactive functional groups; as a result, linear and cyclic ether links have been postulated to account for the non-reactive character of the oxygen. Information on reactions of hydrogen with compounds containing cyclic oxygen is therefore of significance in studies on the hydrogenation and hydrogenolyses of coals and their degradation products; and, with the exception of the data on the hydrogenation of diphenylene oxide,[2] such information is limited.

In the present investigation on the reactions of oxygen heterocycles with hydrogen, benzofurans were chosen because of their importance in coal chemistry and their ready synthesis. The following compounds have been synthesized and studied: benzofuran (coumarone) (I), 2,3-dihydrobenzofuran (II) and 2-methyl-2,3-dihydrobenzofuran (III).[3]

Hydrogen Addition.—The simplest reaction of hydrogen with benzofuran is addition to the double bond of the furanoid ring to give 2,3-dihydrobenzofuran. To compare the ease of this addition to the hydrogenation of other unsaturated compounds, a semi-quantitative study (Fig. 1) of the rate of hydrogen absorption was made using palladium as a catalyst at room temperature. The rate of hydrogen absorption by benzofuran is shown to be much slower than that for indene and even furan, but is appreciable in contrast to that of benzene which shows no absorption under these conditions. Cyclohexene and 2-methylbutene show rapid hydrogenation.

A series of experiments was also run to compare the rates of hydrogenation of benzofuran using different catalysts and reaction conditions. While the Raney nickel at 93° gives the fastest reaction, as shown in Fig. 2, the temperature must be rigidly controlled to prevent benzene ring saturation.

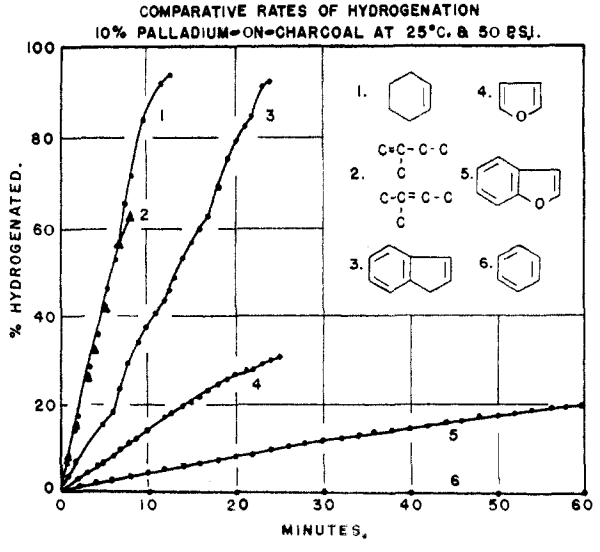


Fig. 1.

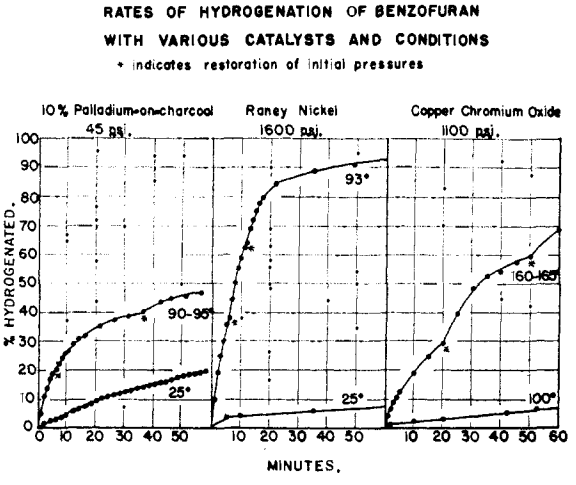


Fig. 2.

Hydrogenolysis Reactions.—In addition to the hydrogenation of the double bond, the reaction of

(1) Presented before the Gas and Fuel Division, American Chemical Society, 118th National Meeting, September 4-8, 1950, Chicago, Ill.

(2) C. C. Hall and C. M. Cawley, *J. Soc. Chem. Ind.*, **58T**, 7 (1939).

(3) For preparation of III, *cf.* J. Entel, C. H. Ruof and H. C. Howard, THIS JOURNAL, **73**, 2365 (1951).