nitrogen, protected with a calcium chloride tube, and then cooled. A heavy white precipitate formed very quickly and the reaction mixture was left overnight. To work up, ice-water was added, and the organic layer was extracted with 5% sodium hydroxide solution. The aqueous layer, after dilution to 160 ml., was added to the basic extract, which was then extracted once with ether and slowly distilled. The distillate, which was collected until 50 ml. had been gathered after the condensing vapors gave a single phase, was saturated with salt and extracted with ether. The ether extract was washed with water and dried over magnesium sulfate. Removal of the ether gave 2,2-dimethylcyclohexanone which was purified by distillation to give 5.3 g. (40%, based on XV) of pure XVII, b.p. 80–82° (38 mm.), $n^{21.0}$D 1.4481. The identity of the product was demonstrated by its oxidation to α,α-dimethyladipic acid and by its infrared spectrum, which showed carbonyl absorption at 5.87 μ as reported by Corey.[12]

2,2-Dimethyl-6-ethylcyclohexanone (XVIII) (Method A).—A series of experiments were performed in an attempt to ethylate XVII substantially by the methylation procedure described above. A variety of bases (commercial sodium amide, freshly prepared sodium amide, lithium amide), ethylating agents (ethyl iodide, diethyl sulfate), solvents (ether, benzene) and reflux times (5–72 hours) were used. In each case, distillation of the crude product gave a fraction of pure starting material and a small amount of higher boiling mixture which contained some of the desired compound.

2,2-Dimethyl-6-ethylcyclohexanone (Method B).—A solution of potassium *t*-butoxide was prepared by dissolving 7.9 g. of potassium in 250 ml. of anhydrous *t*-butyl alcohol. To this solution were added 12.6 g. of 2,2-dimethylcyclohexanone and 62.4 g. of ethyl iodide. After the reaction had subsided the mixture was allowed to stand for at least three hours. The solid phase was filtered off, and most of the solvent removed under vacuum. The product was poured into 250 ml. of water, extracted with ether and after washing with dilute acid and water, was dried and partially purified by distillation. Pure XVIII was most easily obtained by conversion of the high boiling portion to a semicarbazone. Recrystallization and regeneration in the usual way gave XVIII, b.p. 110° (30 mm.), $n^{22.6}$D 1.4550.

A semicarbazone and a 2,4-dinitrophenylhydrazone were prepared and had melting points of 182–184° and 114–116°, respectively.

Anal. Calcd. for $C_{11}H_{21}ON_3$: C, 62.52; H, 10.02; N, 19.89. Found: C, 62.87; H, 10.08; N, 20.21. Calcd. for $C_{16}H_{22}O_4N_4$: C, 57.47; H, 6.63; N, 16.76. Found: C, 57.87; H, 6.65; N, 17.02.

2,2-Dimethyl-6-oxoöctanoic Acid (V).—To a solution of 7.7 g. of 6-ethyl-2,2-dimethylcyclohexanone in 100 ml. of glacial acetic acid was added 6.7 g. of chromic anhydride at a rate sufficient to maintain the reaction mixture at a temperature of 35–45°. After all the anhydride had been added this temperature was held for 1.5 hr. and then most of the solvent was removed under vacuum at a bath temperature no greater than 50°. The crude product was poured into brine and extracted with ether. The acidic materials were extracted with aqueous sodium hydroxide. The basic extract was acidified, and the organic portion extracted with ether. The acidic product was purified by distillation to give 1.5 g. (16%) of V, b.p. 162–163° (1.5 mm.), neutralization equivalent 180 (calcd. 186).

A 2,4-dinitrophenylhydrazone, m.p. 124–125°, was prepared and a mixed melting point with the same derivative of the rearrangement product of III showed no depression. The infrared spectra of the two 2,4-dinitrophenylhydrazones were indistinguishable.

Anal. Calcd. for $C_{16}H_{22}O_6N_4$: C, 52.45; H, 6.05; N, 15.29. Found: C, 52.64; H, 5.40; N, 15.06.

ITHACA, N. Y.

(12) E. Corey, T. Topie and W. Wozniak, THIS JOURNAL, **77**, 5415 (1955).

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF CORNELL UNIVERSITY AND THE BROOKHAVEN NATIONAL LABORATORY]

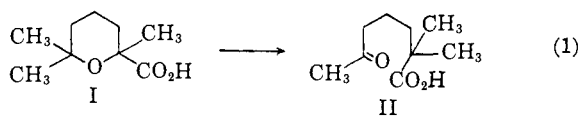
The Acid-catalyzed Rearrangement of Cinenic Acid. V. Evidence for a Decarbonylation–Recarbonylation Mechanism

BY JERROLD MEINWALD, HO CHIEN HWANG, DAVID CHRISTMAN AND ALFRED P. WOLF

RECEIVED MAY 23, 1959

A series of steps involving the loss and subsequent recapture of carbon monoxide is suggested to account for the carboxyl group transfer characteristic of the cinenic acid rearrangement (I → II). This reaction sequence is compatible with all earlier observations, and can be supported by analogies at every stage. The participation of carbon monoxide is indicated by an experiment in which the rearrangement, carried out in the presence of excess carbon monoxide, gave a significantly increased yield of geronic acid (II). Rearrangement in the presence of C^{14}-labeled carbon monoxide yielded labeled geronic acid. The possibility that this incorporation is due to exchange of the carboxylic carbon of either the starting material I or the product II with the externally supplied carbon monoxide is excluded by appropriate control experiments.

Introduction.—The rearrangement of α-cinenic acid (I) to geronic acid (II) was discovered by Rupe and Liechtenhan over a half century ago.[1] Even at that time the transformation appeared unusual, because it seemed to involve a long range migration of a methyl group (implicit in equation 1). As recently as 1952 this rearrangement



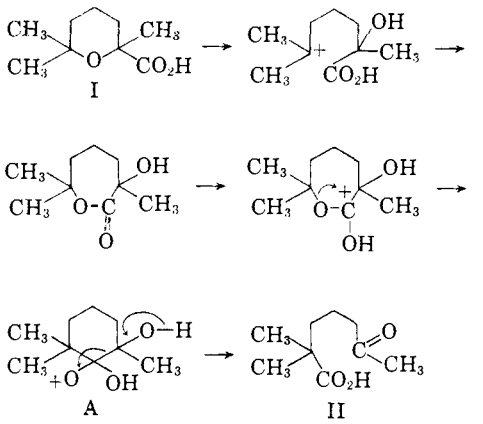
(1)

remained a unique and puzzling phenomenon.[2] Earlier papers in this series have described results which required a modification of the methyl migration theory.[3,4] It is the purpose of the present paper to outline a rational mechanism for the cinenic acid rearrangement, and to present experimental evidence supporting this new mechanism.

Discussion.—The demonstration by two discrete lines of evidence that the cinenic acid rearrangement involves a carboxyl-group transfer rather than a methyl migration[3,4] has led us to a more careful consideration of the mechanistic details of this unusual process. Our original hypothesis, which served to motivate the reinvestigation of the problem, involved the series of steps shown below in Chart I. The key feature in this postulated scheme is the formation of the electron-deficient species A, in which an oxygen atom with an open

(1) H. Rupe and C. Liechtenhan, *Ber.*, **41**, 1278 (1908).
(2) H. Dahn and T. Reichstein, *Helv. Chim. Acta*, **35**, 1 (1952).
(3) K. Meinwald, THIS JOURNAL, **77**, 1617 (1955).
(4) J. Meinwald and J. T. Ouderkirk, *ibid.*, **82**, 480 (1960).

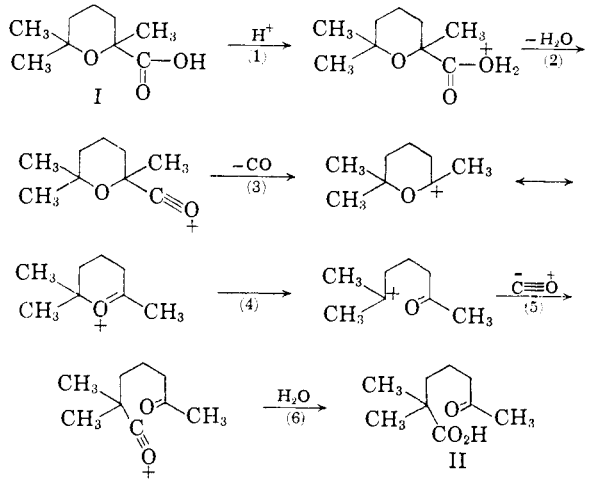
CHART I



sextet is generated. A much more direct route from I to II *via* A has also been discussed.[3] Although analogies could be found for each of these reaction steps, convincing evidence for the participation of ion A in the rearrangement was lacking, and other possible mechanisms were sought.

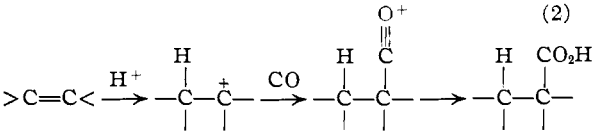
A new mechanism has now come to light which we consider to be distinctly more attractive than any previously considered scheme. It would be initiated by an acid-catalyzed decarbonylation of the α-cinenic acid as shown in steps 1–3 of Chart II. This type of decarboxylation is a well known

CHART II



reaction of α-hydroxy acids (for example, the classical synthesis of acetonedicarboxylic acid from citric acid),[5] and would be expected to occur generally whenever the decarboxylated fragment would have appreciable stabilization. In this particular instance, an additional steric factor can be seen to favor the decarboxylation reaction. Thus, α-cinenic acid can relieve itself of a 1,3-diaxial interaction (either between two methyl groups or between a methyl and a carboxyl) by loss of the carboxyl substituent. The resultant fragment, a cyclic hybrid oxonium ion, can then isomerize by a simple electronic shift to give an acyclic tertiary carbonium ion (step 4). Finally, interaction of this ion with carbon monoxide (step 5) might yield an acylium ion which could react with the solvent (step 6) to give the observed final product, geronic acid (II).

It is the final part of this sequence which may at first appear to be the most unprecedented. It would certainly be unfair to claim that the carbonylations exploited by Reppe and his coworkers,[6] involving nickel-carbonyl catalysis, provide analogies for a reaction of the type shown in step 5. However, excellent examples of the carbonium ion carboxylation process have been provided by recent work in two independent laboratories. Thus, Stork and Bersohn have shown that the transformation of olefins into carboxylic acids in sulfuric acid solution, using carbon monoxide under pressure, is a laboratory operation of great synthetic value[7] in certain instances. Their over-all results conform to the generalized scheme shown in equation 2.



Koch and Haaf have developed a technique for the carboxylation of olefins which promises to be especially convenient in the laboratory,[8] and which uses experimental conditions exceedingly similar to those of the cinenic acid rearrangement. These authors have shown that olefins (or preferably alcohols) will react with carbon monoxide, generated *in situ* from a mixture of sulfuric acid and formic acid, to give carboxylic acids in good yield. These carboxylations are carried out at room temperature and atmospheric pressure. From the structures of the products produced, it is clear that the reaction path followed is essentially that shown in equation 2, the alcohols serving as alternate precursors for the requisite carbonium ions. In several cases the final products are derived from rearranged carbonium ions, but this in no way obscures the general features of this important synthetic technique.

A preliminary experimental indication that decarbonylation might be playing a role in the cinenic acid rearrangement was provided by a heretofore disregarded observation that slight foaming occurs when α-cinenic acid is dissolved in sulfuric acid. Since carbon monoxide has only a low solubility in sulfuric acid,[9] the evolution of some of the gas under these conditions would hardly be surprising. Although we have not tried to capture and characterize the gas evolved, we have carried out the rearrangement with a steady stream of carbon monoxide being bubbled through the reaction medium. Under these conditions, the yield of geronic acid is doubled (from 40 to 80%). This result would certainly seem to indicate that carbon monoxide is incorporated into the product.

With this encouraging preliminary finding in hand, an experiment was carried out in which α-cinenic acid was shaken with concentrated sulfuric

(5) H. Gilman and A. H. Blatt, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 10.

(6) J. W. Copenhaver and M. H. Bigelow, "Acetylene and Carbon Monoxide Chemistry," Reinhold Publishing Corp., New York, N. Y., 1949, pp. 246–280.

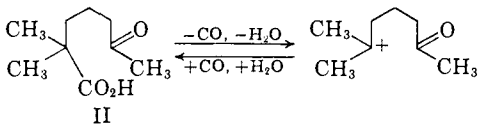
(7) G. Stork and M. Bersohn, private communication.

(8) H. Koch and W. Haaf, *Ann.*, **618**, 251 (1958).

(9) "International Critical Tables," Vol. III, McGraw-Hill Book Co., Inc., New York, N. Y., 1928, p. 265.

acid in the presence of a small amount of $C^{14}O$. The reaction mixture was worked up in the usual manner, and the acidic portion of the product (II) was found to contain a significant amount of radioactivity. The labeled geronic acid obtained in this way was converted into its 2,4-dinitrophenylhydrazone, which was subjected to rigorous purification. The high activity of this purified derivative verified the incorporation of the external carbon monoxide into the rearrangement product II.[10]

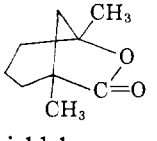
There are some obvious reservations one might have, before being willing to conclude that the above result implicates carbon monoxide in the rearrangement mechanism. One of these is the possibility that the geronic acid might have been formed initially unlabeled, but then acquired C^{14} by subsequent equilibration of its carboxyl carbon with the radiocarbon of the medium, as portrayed in equation 3. It is, in fact, quite conceivable that any



(3)

quaternary carboxylic acid might undergo a rather rapid reversible exchange with carbon monoxide in concentrated sulfuric acid solution. This possibility has been excluded, however, at least in the case of geronic acid, which was shown to acquire radioactivity at only a negligible rate under the conditions of the rearrangement experiment.

Another reservation might involve the possibility that the α-cinenic acid itself suffered a rapid reversible carboxyl group exchange *prior* to the rearrangement process. Ideally, this occurrence could be investigated by stopping the reaction before its completion and analyzing the unreacted starting material for C^{14}. We have not chosen to do this, because it would necessitate having knowledge which is not readily available about the rate of the rearrangement, and because it would involve a tedious separation of the starting material from the product. Instead, we have made use of the neutral by-product of the cinenic acid rearrangement, the lactone III.[11] This lactone is normally formed



III

in about 15% yield by a mechanism unrelated to that involved in producing geronic acid (II). Its production, which requires no skeletal rearrangement, represents an alternate reaction path that Compound I may follow in concentrated sulfuric acid solution. It is important to note that III must, however, be formed at a rate comparable to the rate of formation of II, and that it retains all of the carbon atoms of I intact. It follows that if, in the experiment involving $C^{14}O$, the α-cinenic acid had suffered a rapid, preliminary carboxyl group exchange, then the lactone III produced in this experiment would necessarily be radioactive. In actuality, the lactone isolated in this experiment showed only a very low radioactivity compared to the geronic acid (II). Thus, exchange before rearrangement is excluded.

We therefore conclude that the incorporation of external carbon monoxide is a key feature of the cinenic acid rearrangement, and is intimately connected with the rearrangement process itself.

The above findings cannot be reconciled with the original mechanism shown in Chart I. They provide strong support, however, for the new mechanism outlined in Chart II, and serve to transfer the cinenic acid rearrangement from its previous position in the exotic field of unusual molecular rearrangements to the less exciting area of comfortably rationalized organic reactions.

Acknowledgments.—The authors are indebted to Professor Saul Winstein for stimulating discussions of this problem during his tenure as George Fisher Baker Non-resident Lecturer in Chemistry at Cornell University. They would also like to express their appreciation to the National Science Foundation for their generous support of this work in the form of a research grant. Finally, we are pleased to acknowledge that this research was carried out in part under the auspices of the U. S. Atomic Energy Commission.

Experimental

Rearrangement of α-Cinenic Acid in the Presence of Carbon Monoxide.—Carbon monoxide was prepared by dropping 90% formic acid (250 ml.) into concentrated sulfuric acid (250 ml.). The gas was passed through a drying tower filled with potassium hydroxide pellets, and led into an ozonizer tube containing 20 ml. of concentrated sulfuric acid, pre-cooled in an ice-bath. When the sulfuric acid had been saturated with carbon monoxide, finely powdered α-cinenic acid (3.00 g.) was dissolved in the resultant solution. Carbon monoxide was bubbled through the reaction mixture for an additional 2.5 hours, and the mixture was allowed to stand overnight at room temperature. The wine-red colored solution was poured onto 150 g. of ice and diluted to 200 ml. with water. The organic products were extracted with five 50-ml. portions of ether, and the ethereal solution was extracted with five 100-ml. portions of saturated sodium bicarbonate solution. Acidification of the basic aqueous extract, followed by ether extraction, drying over anhydrous magnesium sulfate, and evaporation of the ether, gave 2.65 g. (83%) of geronic acid, identified by infrared comparison with an authentic sample.

Rearrangement of α-Cinenic Acid in the Presence of Labeled Carbon Monoxide.—Labeled carbon monoxide (3.1 mg., 0.11 mmole, 2 mc.) was introduced into an evacuated reaction vessel containing 20 ml. of concentrated sulfuric acid. The vessel was equipped with a side arm previously charged with 1.29 g. (7.75 mmoles) of finely ground α-cinenic acid. The vessel was sealed and shaken for one hour before introducing the cinenic acid into the sulfuric acid solution. The reaction mixture was then shaken overnight and poured into *ca.* 150 ml. of ice-water. The quenched reaction mixture was continuously extracted with ether, and the ether solution was extracted with three 50-ml. portions of saturated sodium bicarbonate solution. Following a procedure essentially the same as that described in the previous experiment, 0.68 g. (53%) of crude, radioactive geronic acid was obtained.

(10) The extent to which the radioactivity of the $C^{14}O$ was incorporated into the geronic acid (II) produced is difficult to interpret quantitatively. Calculations based on (1) the total C^{14} used in the exchange experiment, (2) the C^{14} in solution at the moment the cinenic acid was added or (3) the C^{14} in solution assuming the cinenic acid decarbonylated and the resultant CO had time to mix freely with the $C^{14}O$ before appreciable recarbonylation occurred, all give quite different results. Calculation 3 corresponds to a quite high degree of C^{14} incorporation. Because of the ambiguities involved, space will not be devoted to these details, although the relevant experimental data are given in the Experimental section.

(11) J. Meinwald and H. C. Hwang, THIS JOURNAL, **79**, 2910 (1957).

This material was converted into its 2,4-dinitrophenylhydrazone which was recrystallized from aqueous ethanol to give fine needles, m.p. 135–136° (lit.[12] 135–137°). This derivative was subjected to eight successive recrystallizations, and the crystals, assayed at the fifth and eighth stages of purification, were found to possess constant activity. Specific activity of the initially obtained geronic acid 2,4-dinitrophenylhydrazone: 146.3 mμc./mg. C; specific activity after fifth recrystallization: 146.1 mμc./mg. C; specific activity after eighth recrystallization; 147.9 mμc./mg. C.

The ether solution remaining after the extraction with aqueous sodium bicarbonate was dried over anhydrous magnesium sulfate and evaporated to give 0.310 g. (23%) of crude lactone III. This lactonic fraction resisted attempts at crystallization, and was therefore subjected to vacuum sublimation. A 20.6-mg. sample of the sublimate (recognized as III by its infrared spectrum) was dissolved in a small volume of ether containing 122.8 mg. of authentic, non-radioactive lactone III. The ether solution was evaporated to dryness under a stream of nitrogen, and the solid residue was recrystallized twice from petroleum ether (30–60°) to give plate-like crystals, m.p. 50–51°. An assay of this product gave a specific activity of 0.923 mμc./mg. C.

Treatment of Geronic Acid with Labeled Carbon Monoxide.—Concentrated sulfuric acid (20 ml.) was shaken with labeled carbon monoxide (5.7 mg., 0.20 mmole, 3 mc.) for one hour, using the technique described in the previous experiment. Geronic acid (0.53 g., 3.1 mmoles) was then mixed with this solution. After shaking overnight, the reaction mixture was poured into *ca.* 150 ml. of ice and water. The resultant solution was subjected to continuous extraction with ether. The ether solution was washed twice with water, dried over anhydrous magnesium sulfate, and evaporated. The recovered geronic acid was converted into its 2,4-dinitrophenylhydrazone, which was recrystallized from aqueous ethanol to give fine needles, m.p. 135–136°, showing a specific activity of 2.75 mμc./mg. C; specific activity after fourth crystallization, 2.30 mμc./mg. C; after seventh recrystallization, 1.98 mμc./mg. C.

(12) H. H. Strain, THIS JOURNAL, **57**, 758 (1935).

ITHACA, N. Y.

[CONTRIBUTION FROM THE DIVISION OF NUCLEOPROTEIN CHEMISTRY SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH AND THE SLOAN-KETTERING DIVISION OF CORNELL UNIVERSITY MEDICAL COLLEGE]

Pyrimidine Nucleosides. V. 2-Oxo-hexahydropyrimidines and Their Nucleosides[1]

BY JACK J. FOX AND DINA VAN PRAAG

RECEIVED JUNE 22, 1959

Treatment of 4-thiothymidine and 4-thiouridine with activated Raney nickel led to the complete reduction of the heterocyclic nucleus. This unexpected nuclear reduction was shown to be characteristic of 4-thiouracils and of 2-hydroxypyrimidines. 2-Thiouracil and 4-hydroxypyrimidines, by contrast, do not undergo ring reduction with this catalyst. Rhodium-on-alumina catalyst will also reduce 2-hydroxypyrimidines to their corresponding N,N′-trimethyleneureas. Raney nickel or rhodium-on-alumina will reduce uracil and its 1-methyl homolog to their corresponding 5,6-dihydro derivatives. Syntheses of 4-thiouracil and 1-methyl-2-oxopyrimidine are described.

Previous papers in another series[2,3] dealt with the synthesis of 4-thiothymidine and 4-thiouridine by direct thiation of suitably blocked thymidine and uridine with phosphorus pentasulfide in pyridine. It was desired to prepare the desulfurized derivatives of these 4-thionucleosides by the use of activated Raney nickel catalyst. Bougault and associates[4] have shown that Raney nickel in neutral or in alkaline solutions removes sulfur from aliphatic sulfhydryl compounds and disulfides. Mozingo and co-workers[5] demonstrated that dibenzyl or di-*p*-tolyl disulfides may be desulfurized to benzene and toluene, respectively, under mild conditions by this catalyst without reduction of the benzenoid nucleus. On the other hand, examples in which nuclear reduction accompanied desulfurization have been noted. Alderton and Fevold[6] have observed that cyclohexylformyl-alanine may be prepared easily by refluxing benzoyl-*dl*-alanine with Raney nickel (prepared according to Mozingo[5]) in 80% alcohol.

Since the demonstration by Roblin and associates[7] that 2-mercapto-4,5-diamino-6-hydroxypyrimidine may be desulfurized by Raney nickel[5] to 4,5-diamino-6-hydroxypyrimidine, a host of 2-mercaptopyrimidines have been de-thiated in this fashion.[8] It was generally accepted, therefore, that mercapto groups of pyrimidines, having served their purpose in synthetic procedures, may be removed easily by this catalyst to yield the desulfurized pyrimidines. In the present paper, examples are reported in which nuclear reduction of certain mercaptopyrimidines accompanied desulfurization when activated Raney nickel[9] was employed.

Treatment of the 3′,5′-di-*O*-benzoate of I (R = H, R′ = CH_3) or the tri-*O*-benzoate (I, R = OBz, R′ = H) with Raney nickel[9] in refluxing ethanol for 15 minutes afforded crystalline, desulfurized derivatives (II). After removal of the protecting benzoyl groups with ethanolic ammonia in a sealed tube, a glass was obtained which was devoid of selective ultraviolet absorption. It is to be noted that 5,6-dihydropyrimidine derivatives (*i.e.*, of uracil or thymine) do exhibit selective absorp-

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, Public Health Service (Grant No. CY-3190) and from the Ann Dickler League.

(2) J. J. Fox, I. Wempen, A. Hampton and I. L. Doerr, THIS JOURNAL, **80**, 1669 (1958).

(3) J. J. Fox, D. Van Praag, I. Wempen, I. L. Doerr, L. Cheong, J. E. Knoll, M. L. Eidinoff, A. Bendich and G. B. Brown, *ibid.*, **81**, 178 (1959).

(4) J. Bougault, E. Cattelain and P. Chabrier, *Bull. soc. chim.*, [5]**7**, 781 (1940).

(5) R. Mozingo, D. E. Wolf, S. A. Harris and K. Folkers, THIS JOURNAL, **65**, 1013 (1943).

(6) G. Alderton and H. L. Fevold, *ibid.*, **73**, 463 (1951).

(7) R. O. Roblin, Jr., J. O. Lampen, J. P. English, Q. P. Cole and J. R. Vaughan, *ibid.*, **67**, 290 (1945).

(8) See D. J. Brown, *Rev. Pure and Applied Chem.*, **3**, 115 (1953), for a review of desulfurization reactions on pyrimidines.

(9) The activated Raney nickel used in these studies was prepared by the procedure of D. J. Brown, *J. Soc. Chem. Ind.*, **69**, 353 (1950). Similar results were obtained from commercially-available preparations of activated Raney nickel purchased from the Raney Catalyst Co., Chattanooga, Tenn., as well as from the Davidson Chemical Co., Cincinnati, Ohio.