# Substrate Specificity with Palladium-on-Silica Gel Catalysts

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**Hydrogenation studies using palladium deposited upon silica gels prepared in the presence of various alkaloids indicate substrate selectivity. The selectivity appears analogous to that observed with enzymes (biocatalysts).**

PADGETT and Beamer (1) have demonstrated the stereospecific hydrogenations of $\alpha$-methylcinnamic acid catalyzed by palladium deposited upon silica gels precipitated in the presence of various cinchona alkaloids. That similarly prepared silica gels possess adsorption specificity has been demonstrated by Dickey (2) and Haldeman and Emmett (3). Beckett and co-workers (4) have shown stereoselective absorption on gels prepared in the presence of various alkaloids.

The present work is concerned with extending the hydrogenation studies of Padgett and Beamer (1) to include substrates in addition to $\alpha$-methylcinnamic acid and silica gel carriers prepared in the presence, not only of cinchona alkaloids, but a modification of the cinchona alkaloidal structure (quinene). Studies using gels prepared in the presence of strychnine and brucine also were made.

## EXPERIMENTAL

**Reagents.**—$\alpha$-Methylcinnamic acid (K and K Laboratories), quinine sulfate N.F., quinidine sulfate U.S.P., cinchonine sulfate U.S.P. IX, cinchonidine sulfate U.S.P. X, strychnine sulfate N.F., brucine (Nutritional Biochemicals Corp.), propiophenone (Eastman Organic Chemicals), and ethylphenyl carbinol C.P. (Columbia Organic Chemicals).

**Quinene.**—Confusion exists in the literature concerning the melting point of quinene which reportedly melts indefinitely between 67 and 90° (5).

Comstock and Koenigs (6) first prepared quinene in 1884 and reported a melting point of 81–82° for the dihydrate. Giemsa and Halberkann (7) also prepared quinene but reported a melting point of 67°. The compound then resolidified and remelted from 90–91°. Both papers describe the preparation of quinene by dehydrohalogenations of 9-chloro-9-deoxyquinene using alcoholic potassium hydroxide, but differ in their methods of isolation.

The isolation described by Comstock and Koenigs proceeded through the zinc chloride–hydrochloric acid double salt (6). Giemsa and Halberkann crystallized quinene from a 50% acetone–water solution without prior conversion to the zinc chloride–hydrochloric acid double salt (7).

The discrepancy in melting points possibly could arise from the different isolation procedures. Therefore, we chose to isolate quinene by both procedures and to compare the products as to melting point, infrared spectra, and optical rotation.

Quinene was prepared by dehydrohalogenation of 9-chloro-9-deoxyquinine as described by both Koenigs and Giemsa. The product was isolated by use of each of the described procedures (6, 7) and compared as to yield, melting point, infrared spectra, and optical rotation. The infrared spectra were obtained in chloroform solution using a Perkin-Elmer Infracord model 137 spectrophotometer and were identical for the products of each separation. The specific rotation values were obtained using a Rhudolph spectropolarimeter model 200. The data for the yields, melting points, and specific rotations are summarized in Table I. A mixed melting point of the two products produced no depression.

The authors also prepared quinene by starting with 9-chloro-9-deoxyquinidine. The product of this reaction was identical with that prepared from 9-chloro-9-deoxyquinine. These results are in accord with those reported by Koenigs (8).

**9-Chloro-9-deoxyquinine.**—Preparation of this compound followed the procedure of Pouwels and Veldstra (9) which involves the replacement of the hydroxy group of quinine by chlorine through thionyl chloride.

**9-Chloro-9-deoxyquinidine.**—This compound was prepared according to the thionyl chloride procedure of Pouwels and Veldstra (9).

**Propiophenone Oxime.**—Thirty grams of hydroxylamine hydrochloride were added to 33.5 Gm. of propiophenone in 150 ml. of pyridine and 150 ml. of absolute alcohol. The mixture was refluxed 24 hr. Following the reaction period, the mixture was concentrated *in vacuo* with a rotary evaporator and left stoppered in the hood for 3 days, during which time white crystals formed.

The crystals were collected by filtration and

TABLE I.—COMPARISON OF QUINENE BY DIFFERENT ISOLATION METHODS

| Method | Yield, Gm. | % Yield[a] | M.p.[b] | Specific Rotation[c] |
|---|---|---|---|---|
| Comstock-Koenigs | 3.67[d] | 39.7 | 76–80° | +48.93[e] |
| Giemsa-Halberkann | 3.40[d] | 36.8 | 75–78° | +45.98[e] |

[a] Based on 9-chloro-9-deoxyquinine and on quinene dihydrate (5). [b] Uncorrected. [c] In 95% alcohol using the dihydrate (C = 1.776 Gm./ml.), temperature = 20°, wavelength = 589 mμ, length of tube was 200 mm. [d] Starting with 9.4 Gm. of 9-chloro-9-deoxyquinine. [e] The literature value for the dihydrate was unavailable.

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washed with a small amount of water. The filtrate was concentrated further on the rotary evaporator and cooled in a refrigerator. The additional crystals were collected by filtration, washed with water, and recrystallized from ethanol and water. The weight of the product after recrystallization was 23.0 Gm., representing a yield of 62% of theory. The crystals melted from 52–55°. [Reported (10) m.p. 53°.]

**Preparation of Carriers.**—The silica gel carriers were prepared by the procedure of Padgett and Beamer (1). The silica gels were precipitated from an aqueous sodium silicate solution using a solution of the alkaloid in 5.7 *N* hydrochloric acid. The gel was dried under a current of air in a fume hood, and the alkaloid was removed by washing with methanol in a Soxhlet extractor.

**Hydrogenation Studies.**—The catalysts were prepared by the method of Hartung (11) using 100 mg. of palladous chloride per gram of gel and sodium acetate as a buffer. Hydrogenations were performed using 0.05-mole substrate in absolute ethanol on a low-pressure Parr hydrogenation apparatus at an initial pressure of 4.2 Kg./sq. cm. and using initially 1.0 Gm. of catalyst. Heating was accomplished with an infrared heat lamp. After 24 hr., an additional 1.0 Gm. of catalyst was introduced, and the hydrogenation continued for another 8 hr. for a total reduction time of 32 hr. The reaction period of 32 hr. was used in all experiments and was based on the time required for reduction of 0.05 mole of α-methylcinnamic acid (1). No kinetic studies were attempted because of the abnormally long reduction period and the lack of an adequate temperature control.

Following hydrogenation, the catalyst was removed by filtration, and the alcohol evaporated at room temperature.

**Infrared Studies.**—Infrared spectra of α-methylcinnamic acid, propiophenone, and quinene were determined in chloroform using a Perkin-Elmer model 137 Infracord spectrophotometer. The concentrations of the solutions were 10%. The spectra of α-methylcinnamic acid and dihydro-α-methylcinnamic acid were also determined as 5% solutions.

Infrared spectra of mixtures of varying proportions of α-methylcinnamic acid and dihydro-α-methylcinnamic acid were determined and their absorptions *versus* concentrations were plotted at 910 and 1625 cm.$^{-1}$.

The same degree of absorption at 1710 cm.$^{-1}$ (carboxyl group) was obtained with the spectra of each of the mixtures. Following evaporation of solvent, the infrared absorptions of the hydrogenation mixtures were determined at 910, 1625, and 1710 cm.$^{-1}$, and estimations of composition were made.

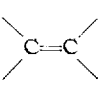
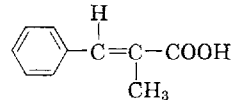
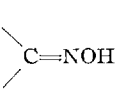
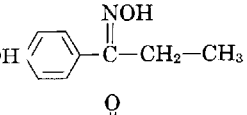
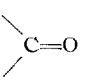
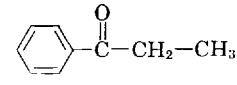
**Gas Chromatographic Studies.**—These determinations were made using a Beckman G.C.-2A gas chromatograph. The column was composed of silicone 550, 50% on C-22 firebrick (42/60 mesh). The column length was 6 ft. The instrument was equipped with a Bausch & Lomb Vom 7 recorder and a thermal conductivity detector.

The studies were made at a column temperature of 160° and with a flow rate of 60 ml./min. Helium was used as the carrier gas. The sample size was 0.005 ml. and was introduced using a Beckman 22400 liquid sampler.

## RESULTS

When substrates other than α-methylcinnamic acid are employed with palladium-on-quinine silica gel catalysts, a lowered reactivity or a lack of reactivity was noted. These results are summarized in Table II.

TABLE II.—HYDROGENATIONS WITH PALLADIUM-ON-QUININE SILICA GEL

| Group | Compd. Employed | % Yield |
|---|---|---|
|  |  | 81.1 |
|  |  | 0.0 (With alc. HCl)<br>15.6 (No. alc. HCl) |
|  |  | 0.0 |

It should be noted that of the substrates employed, only α-methylcinnamic acid and propiophenone oxime in the absence of alcoholic hydrogen chloride gave a detectable yield. A lack of reaction was determined by no significant fall in hydrogen pressure and isolation within experimental error of all the starting material.

The absence of hydrogen chloride from the propiophenone oxime reduction introduced the possibility of secondary amine formation. So far, no secondary amine has been detected by infrared spectroscopy.

Vapor phase chromatography produced only two peaks having retention times of 52 sec. and 18 min., respectively. The peak at 52 sec. was identified as the solvent, ethanol. The peak at 18 min. was identified as 1-phenyl-1-propyl amine. Treatment with benzenesulfonyl chloride followed by sodium hydroxide indicated only primary amine.

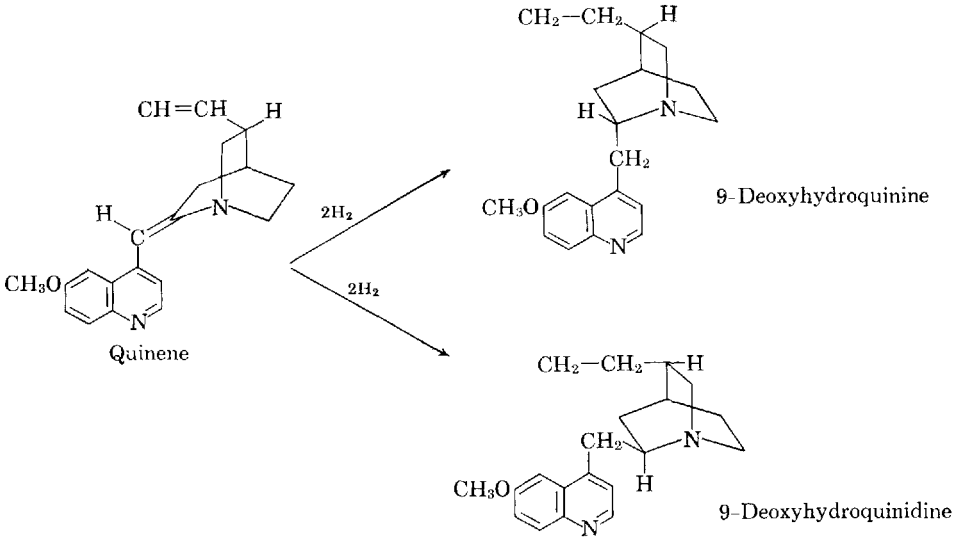
That only starting material was isolated from the attempted reduction of propiophenone was shown by infrared spectroscopy and gas chromatography and a comparison with known propiophenone. The possible hydrogenation products, ethylphenyl carbinol or *n*-propylbenzene (12), could not be detected by infrared spectroscopy or vapor phase chromatography.

The choice of quinene as a substrate for hydrogenation with palladized quinine silica gel as the catalyst was made because of its structural similarities to quinine.

The complete reduction of quinene is shown in Scheme I and leads to either dihydro-9-deoxyquinine or dihydro-9-deoxyquinidine. It was hoped that a stereoselective carrier would direct the reduction to one of the possible diastereoisomers.

Thus far, only quinene has been isolated from the reaction mixture. However, partial reduction could also lead to 9-deoxyquinine, 9-deoxyquinidine, or dihydroquinene. The authors are currently using other isolation techniques to attempt isolation of any of the possible products.

In view of the substrate selectivity with the




Hydrogenation of Quinene

Scheme I

palladium-on-quinine silica gel catalyst, varying the catalysts while employing the same substrate should give further information concerning the substrate selectivity of these catalysts. The results of these experiments are summarized in Table III.

TABLE III.—HYDROGENATIONS OF α-METHYLCINNAMIC ACID USING PALLADIUM-ON-SILICA GELS

| Carriers | % Yield (After 32 hr.) |
|---|---|
| QN 0.5 SG[a] | 81.1 |
| QDN 0.5 SG | 68.0 |
| CN 0.5 SG | 77.1 |
| CDN 0.5 SG | 87.9 |
| Strych. SG | 00.0 |
| Brucine SG | 00.0 |
| Quinene SG | 00.0 |
| Plain SG | 44.3 |

[a] Quinine silica gel which was prepared using 0.5 Gm. of quinine sulfate in the gel preparation. QDN = quinidine sulfate; CN = cinchonine sulfate; CDN = cinchonidine sulfate.

Only the catalysts prepared with the plain gel and the cinchona gels, with the exception of quinene, afforded reduction with α-methylcinnamic acid. Attempted hydrogenations employing catalysts prepared in the presence of strychnine, brucine, or quinene showed no indication of reduction after 32 hr. of hydrogenation and all of the unreacted α-methylcinnamic acid could be accounted for following the hydrogenation period.

However, the presence of large amounts of the starting material, α-methylcinnamic acid, can interfere with the isolation of dihydro-α-methylcinnamic acid by vacuum distillation (1). Therefore, we were never certain that where we have indicated no reduction that such was entirely the case. In other words, reduction too slight to be noted by a fall in the hydrogen gauge pressure might have occurred. Infrared spectra were determined with both α-methylcinnamic acid and D,L-dihydro-α-methylcinnamic acid. These spectra are shown in Figs. 1 and 2, respectively. The following absorption peaks are applicable to this work.

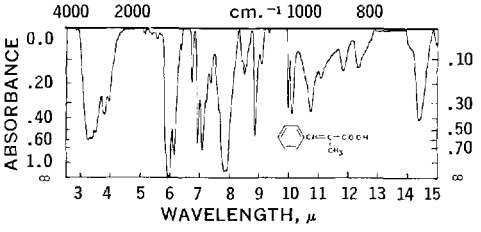



Fig. 1.—Infrared spectrum of α-methylcinnamic acid.

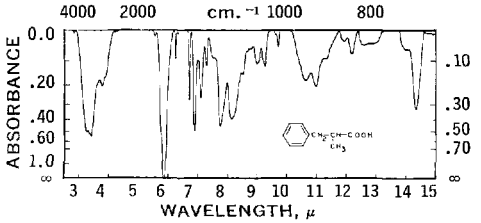



Fig. 2.—Infrared spectrum of D,L-dihydro-α-methylcinnamic acid.

α-methylcinnamic acid (Fig. 1):

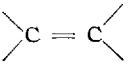
(a) —COOH absorption at 1710 cm.$^{-1}$

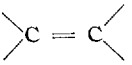
(b) $>C=C<$ absorption at 1625 cm.$^{-1}$

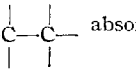
(c) $>C=C<$ absorption at 930 cm.$^{-1}$

D,L-dihydro-α-methylcinnamic acid (Fig. 2):

(a) COOH absorption at 1710 cm.$^{-1}$

(b) disappearance of  absorption at 1625 cm.$^{-1}$

(c) disappearance of  absorption at 930 cm.$^{-1}$

(d) appearance of  absorption at 910 cm.$^{-1}$

The absorption of mixtures of varying proportions of α-methylcinnamic acid and D,L-dihydro-α-methylcinnamic acid were plotted at 1625, 930, and 910 cm.$^{-1}$, as described earlier in this report. In each case a straight line was obtained. However, the plots at 910 and 1625 cm.$^{-1}$ were best applied to the determination of α-methylcinnamic acid and D,L-dihydro-α-methylcinnamic acid, and these are shown in Fig. 3. Use of these plots and the absorption at 1710 cm.$^{-1}$ (COOH) indicates the reaction mixture from the strychnine gel catalyst was 93% α-methylcinnamic acid and 7% dihydro-α-methylcinnamic acid.

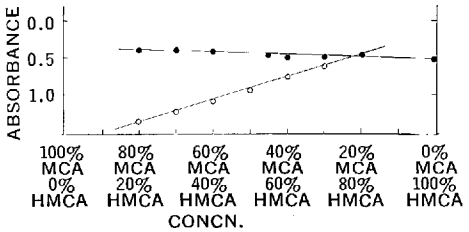



Fig. 3.—Plots of mixtures containing varying proportions of α-methylcinnamic acid and D,L-dihydro-α-methylcinnamic acid (HMCA). Key: ●, plot at 910 cm.$^{-1}$; ○, plot at 1625 cm.$^{-1}$.

## DISCUSSION

The data indicate that the substrate selectivity observed with palladium-on-silica gel catalysts is similar to that observed with enzymes.

Beckett and co-workers have attributed the stereospecific adsorption of alkaloids by cinchona and other alkaloidal silica gels to imprints left on the gel surface by the alkaloid present during the precipitation of the gel (4). Likewise, the substrate selectivity of palladium-on-silica gel catalysts must arise from imprints left on the catalytic surface. The nature of these imprints is not known but may arise from some charge distribution on the surface of the adsorbent.

Such an explanation necessitates the presence of catalytic centers or sites similar to those proposed to explain enzyme specificity (1, 13–15).

According to Beckett's hypothesis, quinene should have been hydrogenated to a greater extent than α-methylcinnamic acid. That such is not the case could arise from steric hindrance (16, 17).

Another explanation for the substrate selectivity of α-methylcinnamic acid over quinene involves the nature of the silica gel surface as influenced by the cinchona alkaloids. This hypothesis supposes the gel surface to be of basic character, thus attracting the carboxylic acid. The incorrectness of this explanation is indicated by the results with the brucine and strychnine, the reduction of propiophenone oxime in the absence of alcoholic hydrogen chloride, and by Beckett's observations (4).

Therefore, the most probable explanation appears to involve active sites of proper size, shape, and charge distribution to accommodate the substrate molecules. These sites are imprinted on the carrier surface by the alkaloid. That α-methylcinnamic acid is not hydrogenated by the catalysts prepared from the brucine and strychnine gels can be explained by sites of improper size, shape, and charge distribution to accommodate the substrate molecules. This does not preclude the possibility of other substrates being hydrogenated by palladized strychnine or brucine gels.

Before definite answers concerning the nature and extent of the substrate selectivity of these catalysts can be obtained, studies must be made employing other substrates and carriers.

## SUMMARY

Hydrogenations using palladium-on-quinine silica gel and various substrates indicate a degree of substrate selectivity by this catalyst. Substrate specificity also was shown in studies using α-methylcinnamic acid as a substrate and palladium deposited on various alkaloidal gels as catalysts. The selectivity may be explained by imprints left on the carrier surface by the alkaloid.

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