

one-half hours for the absorption of an equivalent amount of hydrogen. The product, camphane-2,3- d_2 (plus impurity from the bornylene) was isolated in the same manner used for camphane and gave no test for unsaturation. The physical constants are listed in Table I. In measuring the rotation and in making comparisons with the hydrogen analog, care was exercised to maintain identical conditions throughout. In no instance was there any observable difference between the optical activity of the samples of camphane and camphane-2,3- d_2 .

Summary

l-Bornylene upon reduction with hydrogen gives a camphane having a rotation of +0.02 (± 0.01) due to some impurity. Reduction with deuterium results in a molecule of identical rotation. The densities of camphane and camphane-2,3- d_2 were shown to be markedly different.

URBANA, ILLINOIS

RECEIVED JUNE 8, 1936

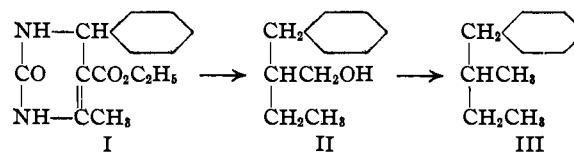
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY, AND THE RESEARCH LABORATORY OF MERCK AND CO., INC.]

Hydrogenation and Hydrogenolysis of a 2-Keto-1,2,3,4-tetrahydropyrimidine Derivative to 2-Benzyl- and 2-Hexahydrobenzylbutanol-1¹

BY KARL FOLKERS²

The action of hydrogen on 2-keto-1,2,3,4-tetrahydropyrimidines over nickel and copper-barium-chromium oxide catalysts at approximately 200 atmospheres pressure and at temperatures up to 200° was recently described.³ It was shown that 2-keto-4-phenyl-5-carbethoxy-6-methyl-1,2,3,4-tetrahydropyrimidine, I, was reduced to a mixture of at least two isomeric hexahydropyrimidine derivatives. The reduction of the pyrimidine 5,6-double bond took place at 200°, and the yield of the isolated hexahydropyrimidines was 77%. There was evidence for the presence of side products resulting from further reactions with hydrogen. It was to be expected that a higher temperature would increase the extent of these reactions, and this paper summarizes the results of allowing the 2-keto-1,2,3,4-tetrahydropyrimidine derivative, I, to react with hydrogen at 250° over a copper-barium-chromium oxide catalyst.

It could be predicted that, as the temperature of the reaction neared 250°, a rather complex combination of hydrogenation and hydrogenolysis reactions would occur. Thus, the pyrimidine 5,6-double bond and the carbethoxy group would be definitely susceptible to reduction. The formed carbinol group would be somewhat susceptible to reduction to a methyl group. The ring 3,4-bond



and the 1,6-bond would be susceptible to cleavage because of the neighboring activating influences. Theoretically, it could be said that the initial reaction of hydrogen might follow four courses leading to four different products. These four products, on further reaction with hydrogen, could lead to seven new products, and these, in their turn, could lead to seven more. These last seven molecules could lead to four products, and these four would lead to a single molecule, 2-benzylbutane, III. Thus, in this theoretical stepwise transformation of I to III, there are twenty-two intermediates to be considered, exclusive of stereoisomers, and exclusive of change in the -NH-CO-NH-grouping.

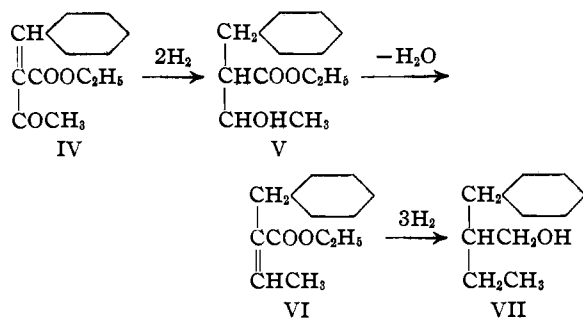
It was never possible, in this hydrogenation at 250°, to obtain full hydrogen absorption, and there was isolated a small amount of a low boiling fraction which appeared to be the product II, 2-benzylbutanol-1. After repeated purifications, only traces of impurities containing nitrogen remained, and the carbon and hydrogen analyses were not quite satisfactory for 2-benzylbutanol-1.

For further identification, the alcohol, II, was synthesized in order that comparable derivatives, etc., could be made. It was readily obtained by the following series of reactions

(1) Researches on Pyrimidines CLII.

(2) Post-doctorate Research Fellow, 1933-1934, Yale University. The greater part of this study was made at Yale University under the administration of Professor Treat B. Johnson. The courtesy of Dr. Randolph T. Major for permission to complete the investigation in the Merck Laboratory is gratefully acknowledged.

(3) Folkers and Johnson, *THIS JOURNAL*, **56**, 1180 (1934).



In carrying out the last step, VI \rightarrow VII, the second stage, or carboxy group reduction, reached completion very readily, and if the reaction were not stopped, further hydrogenation slowly took place.

Apparently, the benzenoid nucleus was slowly undergoing reduction. Analysis of the product showed a low percentage of carbon and a high percentage of hydrogen, such as would be expected; and when this product was hydrogenated completely over nickel, a low amount of hydrogen was absorbed as calculated for 2-benzylbutanol-1, and analysis of the product indicated that it was 2-hexahydrobenzylbutanol-1.

Interpreting the pyrimidine hydrogenation in accord with the above results, the alcohol product undoubtedly was essentially a mixture of 2-benzyl- and 2-hexahydrobenzylbutanol-1. There were fractions which might have contained the corresponding butane derivatives, but the quantity was much smaller than that of the alcohol fraction.

These experiments contributed toward the knowledge of a characteristic of the copper-barium-chromium oxide catalyst. It has been generally expressed that copper-chromium oxide catalyst is inactive for true benzenoid nuclei reduction.⁴ This study would suggest that it is probably a question of relative activity for these catalysts. In other words, there is usually a tremendous difference in the rates of phenyl group reduction with respect to the other many reactions for which these catalysts are valuable, and the control of the reactions and isolation of pure phenyl substituted products is entirely practicable. However, when certain factors (temperature, time, catalyst amounts and ratios, etc.) are forced, advertently or not, the amount of phenyl group reduction may become appreciable, as in the case of ethyl α -benzylcrotonate. In the case

(4) Adkins and Connor, *THIS JOURNAL*, **53**, 1091 (1931); **54**, 4689 (1932); Wojcik and Adkins, *ibid.*, **56**, 2421 (1934).

of complex heteronuclear phenyl substituted compounds, such as the pyrimidine I, the extent of phenyl group reduction may be sufficient as to make impracticable the isolation of pure phenyl substituted products, when rather drastic conditions must be employed in order to secure appreciable conversion of the hydrogen acceptor.

Experimental Part⁵

Hydrogenation of the Pyrimidine, I.—The literature citations on apparatus, catalysts, and special methods have already been recorded.³ The preparation of 2-keto-4-phenyl-5-carboxy-6-methyl-1,2,3,4-tetrahydropyrimidine, I,⁶ and the corresponding hexahydropyrimidine have been described.³

When 10 g. (0.038 mole) of the pyrimidine I was hydrogenated at 250° for 7.25 hours over 5 g. of copper-barium-chromium oxides in 100 ml. of ethanol solvent, the resulting solution was colorless and practically free from volatile ammonia or amines. The catalyst, to all appearances, was in an active state. The hydrogen absorption was not over 0.176 mole. The residue, after ethanol removal, was distilled: Fraction I, b. p. essentially 77–79° at 2.5 mm., 1.8 g. (approximately 28.6%); Fraction II, b. p. 80–160° continuous, and large resinous residue.

When the hydrogenation was conducted over 3 g. of catalyst, first for two hours at 200°, then for four hours at 250°, there was isolated only 0.5 g. (8.0%) of Fraction I boiling essentially at 70–72° at 1.5 mm.

Fraction I was also obtained in small yield from the hydrogenation of 2-keto-4-phenyl-5-carboxy-6-methyl-hexahydropyrimidine under similar conditions.

The residues from distillation of Fraction I (or Fraction II, continuous b. p. of 80–160–200° plus its residue) were dissolved in alcoholic sodium hydroxide solution and the mixture refluxed for two to three hours. After removal of the ethanol, there were no basic or neutral substances present other than an occasional trace of Fraction I. On acidification there precipitated carboxy acids. The properties of the acid indicated a complex mixture, and, in one instance, some impure 2-keto-4-phenyl-5-carboxy-6-methylhexahydropyrimidine was isolated.

When the product from the hydrogenation of 20 g. of pyrimidine I under similar conditions was directly saponified, etc., there was obtained 2.6 g. (20.6%) of Fraction I, and the distillation residue of 4.3 g. comprised the remaining basic or neutral products.

The various Fractions I were combined and fractionated. The forerun of b. p. 47–74° at 2 mm. darkened in color on standing and was found to contain 2–3% nitrogen. The greater amount of the material boiled at 75–78° at 2 mm., and, after treatment with acid and alkali, was found to distil at 77–77.2° at 2 mm. Undoubtedly, this liquid was essentially 2-benzylbutanol-1. *Anal.* Calcd. for C₁₁H₁₆O: C, 80.42; H, 9.82. Found: C, 79.25, 79.20; H, 9.38, 9.33; N, trace (0.1–0.2%). The discrepancy on carbon

(5) Acknowledgment is made to Mr. D. Hayman and Mr. S. Adler for the greater part of the analytical work.

(6) Folkers, Harwood and Johnson, *THIS JOURNAL*, **54**, 3751 (1932); see also Folkers and Johnson, *ibid.*, **56**, 3784 (1933).

and hydrogen content was probably due in part to the presence of 2-hexahydrobenzylbutanol-1, as explained elsewhere, and to the nitrogen containing impurities.⁷

Ethyl α -Benzalacetoacetate.—This ester was made by the method of Knoevenagel.⁸ It was finally distilled through a Widmer column, b. p. 129–130° at 2.5 mm.

Ethyl α -Benzyl- β -hydroxybutyrate.—The ethyl α -benzalacetoacetate was hydrogenated at 150° and 160 atm. in absolute ethanol solvent, and over copper-barium-chromium oxide catalyst. The yield of ethyl α -benzyl- β -hydroxybutyrate was 90%, b. p. 124–126° at 3 mm. *Anal.* Calcd. for $C_{18}H_{18}O_3$: C, 70.22; H, 8.16. Found: C, 70.14, 69.96; H, 8.12, 8.34.

Ethyl α -Benzylcrotonate.—To 20 ml. of dry benzene and 8 g. of phosphorus pentoxide in a distilling flask and cooled in an ice-bath was added 22.8 g. of ethyl α -benzyl- β -hydroxybutyrate. Benzene was now slowly distilled by immersing the flask in an oil-bath and heating slowly to a temperature of 140°. The pressure was then reduced to 15 mm., and, after removal of the last benzene, the dehydrated ester distilled at 133–138° (bath temp. 190–200°), yield 17.1 g. or 81.4%. The ester was purified by washing its ethereal solution with a sodium carbonate and chloride solution and then a sodium chloride solution. The ester after ether removal, on distillation yielded a few drops of a yellow low boiling fraction and then distilled at 125–127° at 13 mm. *Anal.* Calcd. for $C_{18}H_{16}O_2$: C, 76.42; H, 7.89. Found: C, 76.38, 76.29; H, 7.80, 7.67.

2-Benzylbutanol-1.—A solution of 15.5 g. of ethyl α -benzylcrotonate and 25.5 ml. of absolute ethanol was hydrogenated over 4 g. of copper-barium-chromium oxide at 250° and 190 atm. for five minutes. The product was dissolved in alcoholic sodium hydroxide solution and refluxed for five hours. The alcohol, on ether extraction, etc., distilled at 81–81.5° at 2 mm. It was a rather viscous liquid and its odor was not so characteristic or pleasant as that of the hexahydrobenzylbutanol. *Anal.* Calcd.

for $C_{11}H_{16}O$: C, 80.42; H, 9.82. Found: C, 80.65, 80.55; H, 9.75, 9.64.

2-Benzylbutyric Acid.—The alkaline solution of the above experiment, freed from 2-benzylbutanol, was acidified and ether extracted. A few drops of acid were obtained and distilled in a minute flask, b. p. 123–124° at 2 mm. *Anal.* Calcd. for $C_{11}H_{14}O_2$: C, 74.11; H, 7.92. Found: C, 74.17, 73.88; H, 8.12, 8.14.

2-Hexahydrobenzylbutanol-1.—When 15.3 g. of ethyl α -benzylcrotonate was hydrogenated as described above, except for a period of five and one-half hours, the product, on fractionation, gave a forerun, undoubtedly containing the corresponding butane derivatives, and then the principal fraction, b. p. 86–87.5° at 3 mm. This fraction was, nevertheless, taken in three parts, and the middle one, representing 21% of the total, was estimated to contain 44% of 2-hexahydrobenzylbutanol-1 and 56% of 2-benzylbutanol-1. *Anal.* Calcd. for $C_{11}H_{16}O$: C, 77.56; H, 13.02. Found: C, 79.30, 79.16; H, 11.32, 11.14.

When this mixture of butanols was hydrogenated to completion over Raney nickel catalyst at 180°, 2-hexahydrobenzylbutanol-1 was obtained, b. p. 83–84° at 2 mm. *Anal.* Found: C, 77.01, 77.09; H, 12.94, 12.67. This completely saturated alcohol had a very characteristic and perfume-like odor, and there seemed no doubt but that the odor of Fraction I from the pyrimidine hydrogenation was due to the presence of this alcohol.

Summary

The principal final product of hydrogenation of 2-keto-4-phenyl-5-carbethoxy-6-methyl-1,2,3,4-tetrahydropyrimidine over copper-barium-chromium oxides at 250° under elevated pressures was a mixture of 2-benzyl- and 2-hexahydrobenzylbutanol-1. These two alcohols were synthesized by other reactions. It appears that copper-barium-chromium oxide catalyst has a very weak activity for hydrogenation of the phenyl group, and that this slight activity is exhibited only under certain forced conditions.

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RECEIVED JUNE 11, 1936

(7) Guerbet [*Compt. rend.*, **146**, 1406 (1908); *Bull. soc. chim.*, [4] **3**, 944 (1908)] described 2-benzylbutanol as an oil of lilac odor, as obtained from the reaction of *n*-butanol and sodium benzyolate. The above analytical product had a very characteristic and pleasant odor.

(8) Knoevenagel, *Ber.*, **29**, 172 (1896); **31**, 730, note 4 (1898); see also Claisen and Matthews, *Ann.*, **218**, 178 (1883).