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Hydrogenation of Substituted Isoquinolines over Nickel Catalyst II: Effects of Pressure and Temperature on the Hydrogenation of 5-Hydroxy-2-alkylisoquinolinium Salts

IAN W. MATHISON, WILEY L. FOWLER, Jr., and KATHLEEN C. FOWLER

Abstract □ A study of the effect of high pressure and high temperature on the nickel-catalyzed hydrogenation of 5-hydroxy-2-ethylisoquinolinium salt is described. The effects of these parameters on the yield and stereochemistry of the 5-hydroxy-2-ethyldecahydroisoquinolines produced are discussed. Comparisons of these data with those from analogous hydrogenations of the 5-nitro-2-methylisoquinolinium salt are included.

Keyphrases □ 5-Hydroxy-2-alkylisoquinolinium salts—hydrogenation □ Hydrogenation, isoquinolinium salts—temperature, pressure effect □ Vapor phase chromatography—analysis □ GLC—analysis □ IR spectrophotometry—structure

In a continuing study of the stereochemistry of variously substituted, fully reduced isoquinolines possessing pharmacological activity (1, 2), the authors have been recently interested in the hydrogenation of 5-substituted isoquinolines at high temperature and high pressure over Raney nickel catalyst (3). Their initial attention was directed toward the hydrogenation of a 5-nitroisoquinolinium salt in which they were able to demonstrate that increases in temperature were effective in inducing changes in the specificity of the hydrogenation while increases in pressure played little or no role in determining the stereochemistry of the desired 5-aminodecahydroisoquinolines produced. The results in regard to the effects of temperature were not totally unanticipated (4); however, an unexpected result was that increases in temperature initially resulted in increased specificity of hydrogenation up to a certain point which was then followed by a more randomized reduction. It was of significance that the *cis* ring junction decahydroisoquinoline was the heavily favored isomer produced (approximately 13:1 to 2:1, depending on conditions) (5, 6). The authors demonstrated that hydrogenolysis occurred to a significant extent at temperatures of 200° and above, while at 160° and 1500 p.s.i. an optimum yield of 71% of the desired 5-aminodecahydroisoquinolines was produced (*cis*:*trans*, 7.7:1). In view of the reported pharmacological activity of derivatives of 5-hydroxy-2-alkyldecahydroisoquinolines (2, 7) and the need for a rapid, efficient synthesis of these compounds, the authors wish to report the effects of increased pressure and temperature on the one-stage hydrogenation of 5-hydroxy-2-ethylisoquinolinium *p*-toluenesulfonate over W7 Raney nickel catalyst. The effects of these parameters on the stereochemistry of the hydrogenation and yields of the 5-hydroxy-2-ethyldecahydroisoquinolines produced will be discussed and comparisons will be drawn with the previously reported study (3).

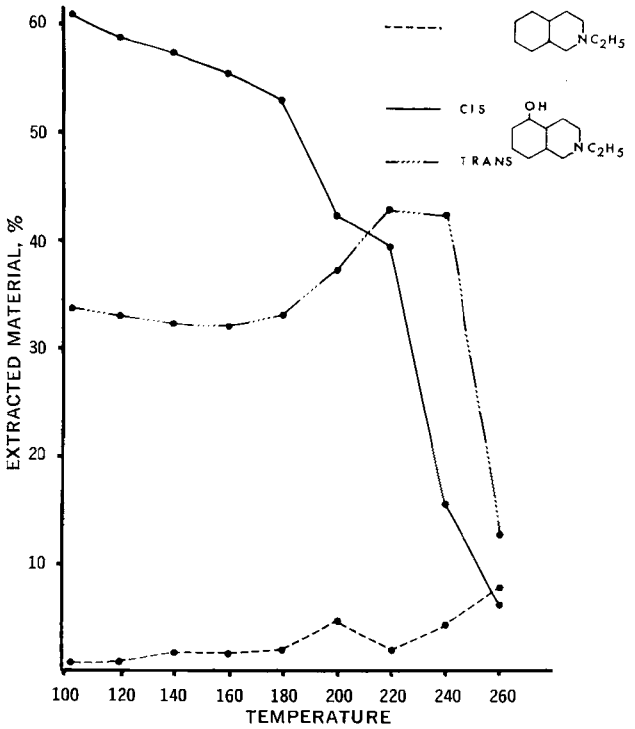

Figure 1—*Effect of temperature on reaction products at 2000 p.s.i.*

EXPERIMENTAL

The melting point is corrected. Analyses were run by Galbraith Laboratories, Knoxville, Tenn. Vapor phase chromatograms were recorded on a Varian Aerograph model 700 Autoprep chromatograph. Chromatographic peak areas were determined using a Dietzgen model D-1803-8 planimeter.

5-Hydroxy-2-ethylisoquinolinium *p*-Toluenesulfonate (I)—5-Hydroxyisoquinoline (25 g., 0.17 mole) and ethyl *p*-toluenesulfonate (35.5 g., 0.18 mole) were dissolved in dimethylformamide (100 ml.) and allowed to stand at room temperature for 72 hr. The precipitated crystals (50 g., 83%) of 5-hydroxy-2-ethylisoquinolinium *p*-toluenesulfonate were recrystallized from methanol to yield yellow needles, m.p. 212–213°.

Anal.—Calcd. for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06; S, 9.28. Found: C, 62.74; H, 5.67; N, 4.05; S, 9.57.

The IR spectrum (KBr) was consistent with the proposed structure (3200 cm.$^{-1}$; 1230 cm.$^{-1}$, —OH).

HYDROGENATION PROCEDURE

The catalytic reduction of I (10 g.) was carried out in methanol (150 ml.) over W7 Raney nickel catalyst (8) (3.0 g.) in a Parr series 4000 hydrogenator under varying conditions of temperature and pressure. The temperature was carefully controlled using a Honeywell temperature controller No. 4811. Standardization of each hydrogenation experiment regarding time of heating and agitation has been previously described in detail (3). At the termination of the reduction, the hydrogenated solution was removed from the bomb and the exhausted catalyst was filtered using diatomaceous earth (Celite) as a filtering aid. The methanol filtrate was evaporated on the rotary evaporator to yield a pale-yellow viscous oil which was suspended in water, made strongly alkaline with sodium hydroxide, and extracted with ether. The dried ether extract was then distilled to yield a yellow oil. This oil was assayed gas chromatographically on a 6.09 m. × 0.95 cm. (20 ft. × 0.375 in.) SE 30 (30%) on Chromosorb W column at 215° using a thermal conductivity detector at a gas (helium) flow rate of 100 ml./min. Authentic samples, which were used for identification of the chromatographic peaks of the reaction product mixture, included:

1. *cis*-5,9,10-*H*-5-Hydroxy-2-ethyldecahydroisoquinoline (2). Retention time = 28.4 min.
2. *trans*-9,10-*trans*-5-*H*-5-Hydroxy-2-ethyldecahydroisoquinoline.[1] Retention time = 26.8 min.
3. *cis*-2-Ethyldecahydroisoquinoline.[2] Retention time = 14.3 min.
4. *trans*-2-Ethyldecahydroisoquinoline.[2] Retention time = 13.4 min.

RESULTS AND DISCUSSION

The average areas under each identified peak of duplicate gas chromatograms of at least two separate hydrogenations were plotted and Figs. 1–6 were obtained.

Effect of Temperature at Constant Pressure

The study was approached by an initial examination of the influence of temperature on the reduction of 5-hydroxy-2-ethylisoquinolinium *p*-toluenesulfonate. An initial bomb pressure of 2000 p.s.i. was utilized, since it allowed comparisons with the previous investigation (3). Examination of Figs. 1–3 shows clearly the overall effects of temperature on the hydrogenation. As anticipated, increases in temperature resulted initially in an increase in yield of the desired 5-hydroxy-2-ethyldecahydroisoquinolines (Fig. 3); this was followed by a decreased yield concurrently with increased hydrogenolysis (Figs. 1 and 3). It was apparent that the optimum temperature was in the region of 200°, a significantly higher temperature than that for the corresponding nitroisoquinolinium salt (3). The influence of temperature on the stereochemistry of the products yielded some interesting results (Figs. 1 and 2). It is evident (Fig. 1) that increased temperature resulted in increased yields of the *trans* ring junction product accompanied by a comparable decrease in the *cis* product. This holds up to 200–220°, at which point marked decreases in both isomers occur, primarily due to hydrogenolysis and decomposition. This trend, while evident

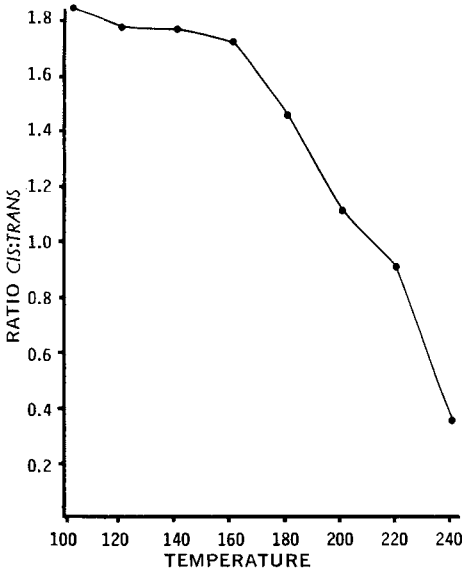

Figure 2—*Effect of temperature on the stereochemistry at 2000 p.s.i.*

during the reduction of the nitro analog (3), was not nearly so dramatic as in the present study on the hydrogenation of the hydroxy compound. Indeed, at 240° and above, the authors were able to produce predominantly the *trans* isomer, a situation never realized during the reduction of the nitro compound. More interesting were the data obtained regarding isomer ratios as temperature was increased (Fig. 2). At 100°, a favored *cis* ring junction hydrogenation occurred. As the temperature was increased to 200°, a more randomized hydrogenation resulted where the *cis*:*trans* ratio was 1:1. However, beyond 200° the randomization of hydrogenation was decreased which resulted in a *cis*:*trans* ratio of 0.8, *i.e.*, a reduction favoring the *trans* isomer. While it is acknowledged that increased temperature favors a more randomized hydrogenation (4), the authors are unaware of temperature increases resulting in increased randomization followed by a decrease in the randomization. Additionally, it was unanticipated that such a marked reversal of the favored stereochemistry would result. No comparable data were obtained during the reduction of the nitroisoquinoline (3). It is also pertinent that in the reduction of the nitro compound the *cis*-5-aminodecahydroisoquinoline was the very heavily favored product (*cis*:*trans* ratio of 14:1 to 2:1 depending on the temperature), while in the present study with the hydroxy compound the *cis* isomer was the most favored at best at isomer ratios of only 2:1.

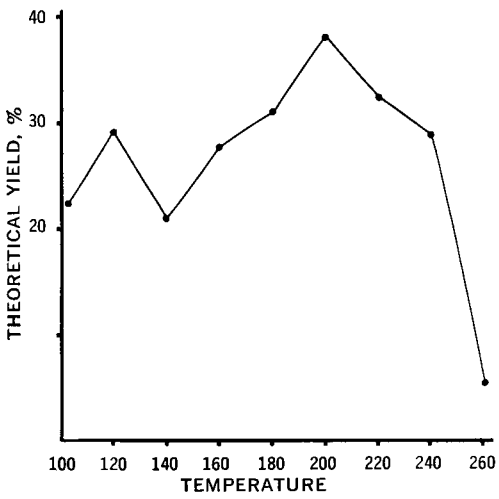

Figure 3—*Effect of temperature on yield of 5-hydroxy-2-ethyldecahydroisoquinolines at 2000 p.s.i.*

[1] Prepared from *trans*-9,10-*trans*-5-*H*-5-hydroxydecahydroisoquinoline using essentially the method of Blicke and Monroe (9) as outlined by Mathison *et al.* (2) for the corresponding *cis*-5,9,10-*H*-5-hydroxy-2-ethyldecahydroisoquinoline.

[2] Prepared by the catalytic hydrogenation of 2-ethylisoquinolinium *p*-toluenesulfonate using the general procedure outlined by Witkop (10).

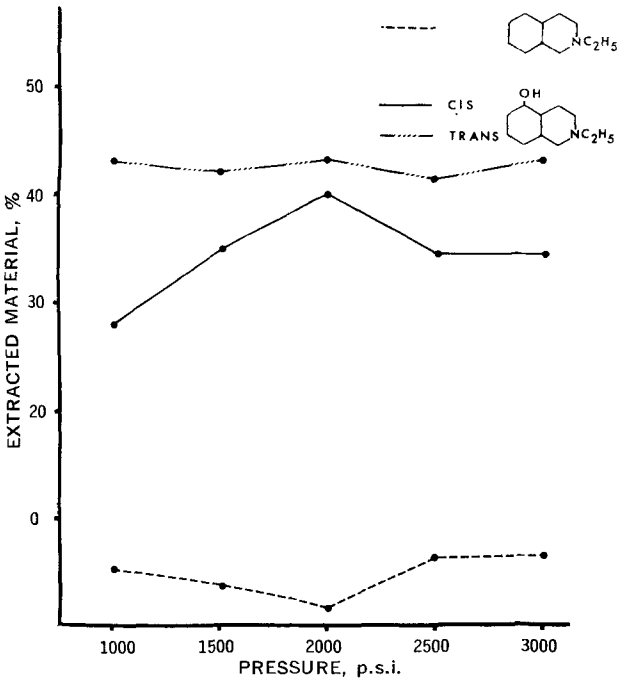

Figure 4—*Effect of pressure on reaction products at 220°.*

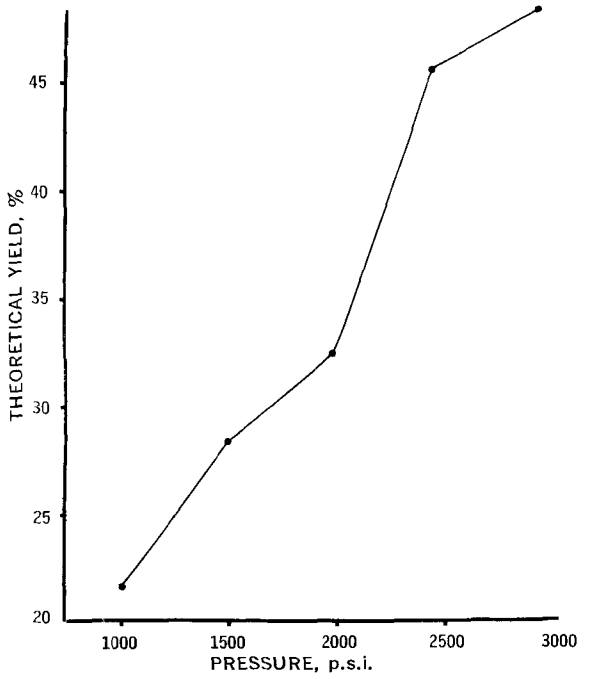

Figure 6—*Effect of pressure on yield of 5-hydroxy-2-ethyldecahydroisoquinolines at 220°.*

Effect of Pressure at Constant Temperature

In view of the superior yield and nearly equal isomer ratio, it was decided to examine the effects of pressure at 220°. The results are summarized in Figs. 4–6. Figure 4 shows clearly that the production of the *trans* ring junction isomer is virtually unaffected by increases in pressure. On the other hand, the amount of the *cis* analog produced undergoes marked changes during a similar pressure increase. Increased pressure up to 2000 p.s.i. results in increased quantities of *cis*-5,9,10-*H*-5-hydroxy-2-ethyldecahydroisoquinoline, while pressure increases beyond this point result in decreased product. The correlation between the amount of *cis* isomer produced and the amounts of hydrogenolyzed products is of interest. As the amount of the *cis* analog increases, the hydrogenolysis products decrease and vice versa. The summation of the amounts of *cis* product and the hydrogenolysis products remains at a figure of approximately 39% of extracted material throughout the pressure range 1500–3000 p.s.i. These data strongly suggest that the *cis* isomer is more readily hydrogenolyzed than the *trans* analog, a finding compatible with the data obtained during the temperature study on the hydrogenation of the nitro and hydroxy compounds. The authors were unable to demonstrate this trend in the analogous pressure experiments on the nitro compound (3). The results regarding the stereochemistry of the hydrogenation (Fig. 5) were comparable with the data obtained for the nitro compound. Increased pressure results in decreased specificity of hydrogenation up to a point (approximately 2000 p.s.i.); this is then followed by increased specificity. This finding is in contrast to the anticipated results (11). As pressure increases, hydrogen availability increases, and processes requiring hydrogen would be accelerated. One would expect, therefore, that greater *cis*:*trans* ratios would result since desorption from the catalyst surface would be less likely to occur prior to completion of the hydrogenation. The results concur with this rationale up to 2000 p.s.i; however, beyond this point the data contradict this theory. The authors can only assume that pressures beyond 2000 p.s.i. in some way perturb the adsorption of the compound to the catalyst prior to completion of the reduction which results in desorption and, therefore, decreased specificity of hydrogenation. As anticipated, pressure was more effective than temperature in inducing higher yields of the desired 5-hydroxydecahydroisoquinolines. Superior yields, however, were obtained with the nitro compound at increased pressures (3).

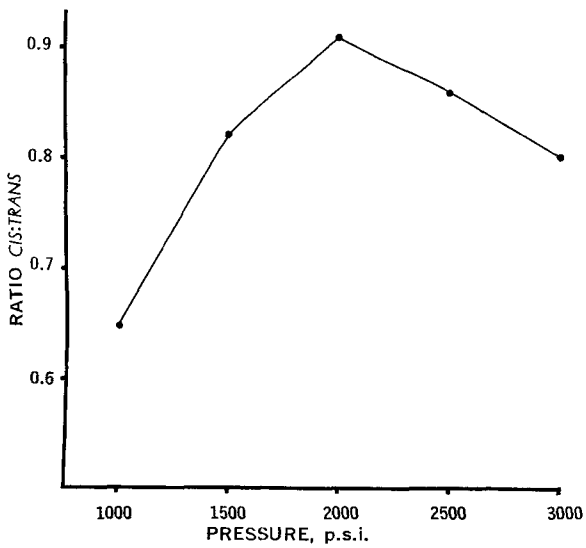

Figure 5—*Effect of pressure on stereochemistry at 220°.*

The differences in stereochemistry observed between the hydrogenations carried out on the 5-nitro-2-alkylisoquinolinium salts (3) and the present study on the hydroxy compounds may be related to the basicity of the products, the aminodecahydroisoquinolines produced in the former investigations being stronger bases than the hydroxydecahydroisoquinolines produced in this study. It is well established (12) that pH is an important factor in determining the steric course of catalytic reductions.

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Influence of Phase Equilibria on Properties of Emulsions

S. FRIBERG and L. MANDELL

Abstract □ An investigation was made concerning the phase equilibria in water–oil–emulsifier systems. The results have shown the presence of liquid crystalline phases and the pronounced influence of these on the properties of emulsions. The pronounced solubilizing power of emulsifier micelles in the oil phase, the changed stability due to these, and the drastic changes of volume ratios, water to oil, with increasing emulsifier concentration which this gives rise to, have been investigated.

Keyphrases □ Emulsions—phase equilibria effect □ Phase equilibria—w/o emulsions □ Stability, emulsions—emulsifier concentration □ Liquid crystalline phase—emulsions

The complicated behavior of emulsions has been treated in numerous articles and reviews, due to the importance of such systems in chemical technology and in a vast number of systems of biological origin. In his bibliography, Becher (1) dealt with the different factors that had been found responsible for the behavior of emulsions. Davies discussed the stability of emulsions based on a collision theory (2). Sherman has made important contributions concerning the general properties and rheological behavior of emulsions (3). Recently, Shinoda has introduced the PIT value (4), which denotes the phase inversion temperature. Shinoda assumes this temperature to be more useful than the well-known HLB value in the prediction of the behavior of emulsions from the properties of the emulsifiers.

The HLB value is useful to a very high degree; its success in practical emulsion preparation has shown this beyond doubt, but its shortcomings are obvious. As an example, Sherman (5) pointed out the inversion of emulsions when the amount of emulsifier is increased, and Davies (2) showed the difference in emulsion behavior when the oil phase was changed from benzene to petroleum ether. Neither of these examples can be explained by the HLB value of the emulsifier.

Preliminary results on the influence of phase equilibria on the properties of emulsions showed a sudden increase in stability in the presence of a mesomorphous phase (6). Further investigations (7) showed a pronounced change in phase equilibria when the aromatic *p*-xylene in the oil phase was replaced by hexadecane. These results gave a tentative explanation to the problem stated by Davies (2). The rather complicated rheological behavior of emulsions when the emulsifier concentration was changed could also be satisfactorily explained by interpretation of phase equilibria (8). Since these results appeared to be promising, it was considered that further investigations of phase equilibria in the water–emulsifier–oil systems could be of general value.

Emulsions of w/o type are considerably more difficult to treat theoretically due to the low electric field strength in the continuous medium. Taking this into consideration, the authors chose a set of emulsifiers of the w/o type and determined the phase equilibria of the systems.

EXPERIMENTAL

Materials—The water was twice distilled. The nonylphenol diethyleneglycol ether was of commercial origin (Berol AB, Sweden), which was purified from polyglycols; other impurities are less than 0.01%. Other chemicals used were: octylamine (puriss. gas chromatographic >99%) and *p*-xylene (puriss. gas chromatographic >99.5%) (Fluka A.G., Switzerland); monocapryline (synthesized at the Institute of Medical Biochemistry, University of Gothenburg, Sweden); tricapryline (Eastman Distillation Products Industries); and lecithin, prepared from egg yolk according to a simplified method (9).

Phase Equilibria—The samples for investigation of the phase equilibria in the three-component systems given in Fig. 1 (A–D) were weighed directly into glass ampuls which were sealed. The samples were heated to homogeneity, slowly cooled to 20° under agitation, and allowed to stand at this temperature. The different phases were separated by ultracentrifugation and identified by visual observation under a polarizing microscope or by X-ray methods according to previous work on phase equilibria in ternary systems (10, 11).

Emulsion Preparation and Properties—The components were weighed into ampuls which were treated in an ultrasonic device at 20° for 1 min. followed by vacuum treatment to remove air. This was repeated five times.

The nature of the emulsion was determined by visual observation through a microscope of the spread of oil- or water-soluble dyes (Sudan III and Brilliant Blue F.C.F.). The emulsions with an