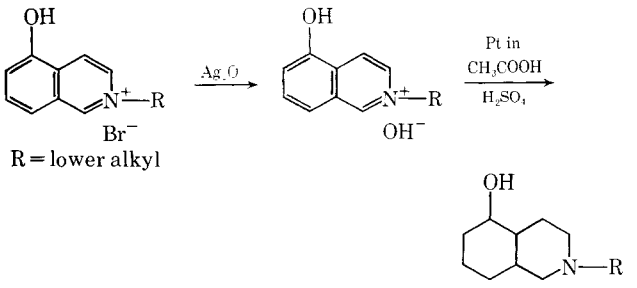
Hydrogenation of Substituted Isoquinolines over Nickel Catalyst I: The Effects of Pressure and Temperature on the Hydrogenation of 5-Nitro-2-alkylisoquinolinium Salts

IAN W. MATHISON and WILEY L. FOWLER, JR.

Abstract □ The nickel catalyzed high-pressure/high-temperature hydrogenation of a 5-nitroisoquinolinium salt is described. This has been studied at varying pressures and temperatures and the effects of these parameters have been evaluated in regard to product yield, degree of hydrogenolysis, and their effect on the stereochemistry of the desired 5-aminodecahydroisoquinolines. The advantages of this procedure over previously reported syntheses of 5-aminodecahydroisoquinolines are noted.

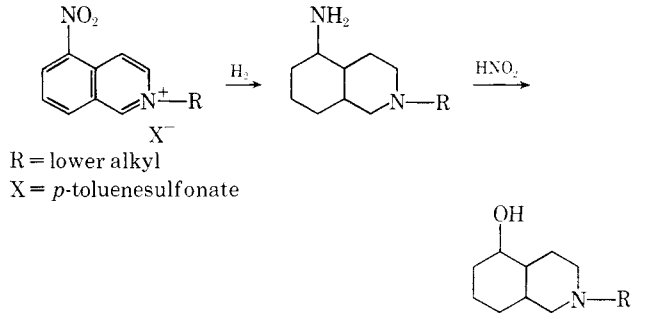
Keyphrases □ Isoquinolines, hydrogenation—nickel catalysts □ 5-Nitro-2-alkylisoquinolinium salts—hydrogenation □ Temperature effect—isoquinolines hydrogenation □ Pressure effect—isoquinolines hydrogenation □ Vapor phase chromatography—analysis

One of the main objectives of the authors' laboratory has been an investigation of the stereochemistry of variously substituted fully-reduced isoquinolines (1) and attempts at correlating cardiovascular activity with the type of substituent and the stereochemical conformation of the isoquinoline ring system (2–4). The synthetic procedures involved the low-pressure, platinum-catalyzed hydrogenation of isoquinolinium salts at room temperature in a one-stage reduction to the corresponding substituted decahydroisoquinoline. The syntheses initially centered on the hydrogenation of 5-hydroxy-2-alkylisoquinolinium bromide; the novel condensation (5) occurring during this step necessitated the conversion to the corresponding hydroxide salt which on hydrogenation yielded the desired 5-hydroxy-2-alkyldecahydroisoquinoline (see Scheme I).



Scheme I

The poor yields led the authors to a modified synthesis involving the reduction of 5-nitro-2-alkylisoquinolinium salts to the corresponding 5-amino-2-alkyldecahydroisoquinoline which on deamination with nitrous acid yielded the 5-hydroxy-2-alkyldecahydroisoquinoline (1) (see Scheme II). While the hydrogenation yields in the latter experiments were superior to the hydrogenation of the 5-hydroxyisoquinolinium salt, the time element (hydrogenation takes approximately 6 days) coupled with the high catalyst:compound ratio was a severe limitation on the synthesis. Since their work had also demonstrated significant pharmacological differences between stereoisomers of some derivatives of these 5-aminodecahydroisoquinolines (2) the authors decided to investigate a one-stage high-pressure/high-temperature hydrogenation of a 5-nitroisoquinolinium salt over Raney nickel catalyst to determine the effects of temperature and pressure on both the yield and isomer content of the product.



R = lower alkyl
X = *p*-toluenesulfonate

Scheme II

While the use of Raney nickel catalyst as a high-temperature/high-pressure hydrogenation catalyst is not new (6), its application in a one-stage reduction of substituted isoquinolines to their fully saturated analogs has received little attention (7). The numerous attempts (8) to reproduce the reductive alkylation experiments of Georgian *et al.* (7) prompted a more detailed study of the reduction of isoquinolines using nickel catalyst. The hydrogenation of 5-nitro-2-methylisoquinolinium *p*-toluenesulfonate has been studied at various high temperatures and pressures. The influence of these parameters on the isomer content of the product, the product yield, and the degree of hydrogenolysis is discussed.

EXPERIMENTAL

Apparatus—All hydrogenations were run in a 1-l. rocker-type pressure reactor (Parr, Series 4000) utilizing the ground-glass bomb insert liner. The temperature of hydrogenation was controlled by a temperature controller (Honeywell No. 4811) connected to the inner bomb wall *via* a standard 1.5-m. (5-ft.) iron-constantin thermocouple. This system allowed a ±0.50% deviation at a selected temperature and a ±0.75% deviation in reproducibility for any given temperature. Vapor phase chromatograms were recorded on

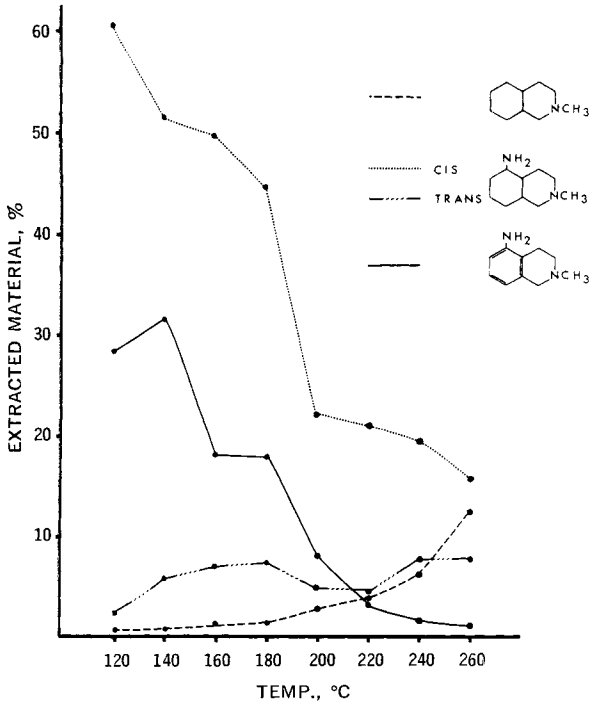


Figure 1—*Effect of temperature on reaction products at 2000 p.s.i.*

a chromatograph (Varian Aerograph model 700 Autoprep) 3.05 m. × 0.62-cm. (10 ft × 0.25-in.) SE-30 (15%) on a diatomite aggregate column (Chromosorb W) at 170° and a thermal conductivity detector (He gas) at a flow rate of 30 ml./min.

Hydrogenation Procedure—Each hydrogenation experiment consisted of the reduction of 10.0 g. of 5-nitro-2-methylisoquinolinium *p*-toluenesulfonate salt [prepared by the method outlined by Mathison (1)] over 3.0 g. of W7 Raney nickel catalyst [prepared as described by Billica and Adkins (9)] in 150 ml. of methanol. The temperature was preset on a thermostat (Honeywell) and the time of hydrogenation was standardized by allowing the reaction to continue with heat and constant agitation for 4 hr. after the bomb had reached the desired temperature. The heat was discontinued and the bomb then allowed to cool to room temperature (~23°). Constant agitation was extended for 12 hr. following the termination of the heating period. The pressure was then released and the hydrogenated products were removed and treated immediately with 5.0-ml. concentrated HCl. The hydrogenation mixture was filtered to remove the exhausted catalyst and the catalyst was washed well with fresh solvent. The filtrate was concentrated by rotary evaporation to yield a viscous mass which was then made alkaline with NaOH, extracted with ether, and the ether extract dried over anhydrous Na_2SO_4. The ether was removed by distillation. The residual viscous oil was weighed and gas chromatographic examinations were then carried out. Five major components of the reaction products were identified by comparing their retention times with known analytical samples and by peak potentiation with these known samples. The area under each peak was measured using a planimeter (Dietzgen model D-1803-8). An average of at least three reproducible measurements (±1%) for each peak area was determined.

RESULTS AND DISCUSSION

As indicated in the *Experimental* section, GC was utilized to evaluate the effects of the various parameters on the products of the hydrogenation. A number of plots of the results of this study have been made; each point represents the average area under each identified peak of duplicate gas chromatographic determinations of at least two separate hydrogenations. Identification of the compounds included on the graphs was made by comparison of retention times with the known standards (1) shown below and by peak potentiation of the hydrogenated mixture with these known samples. The retention times for these standards run under the conditions outlined in the *Experimental* section are as follows: 2-methyl-1,2,3,4-tetrahydroisoquinoline retention time = 20.4 min.; *cis*-2-methyldecahydroisoquinoline retention time = 4.5 min.; *trans*-2-methyldecahydroisoquinoline retention time = 4.2 min.; *cis*-5,9,10 - H - 5 - amino - 2 - methyldecahydroisoquinoline retention time = 10.5 min.; *trans*-9,10-*trans*-5-H-5-amino-2-methyldecahydroisoquinoline retention time = 9.2 min.

Effect of Temperature at Constant Pressure—The authors' study was approached by an initial range finding examination of the effect of temperature on the reduction of the 5-nitroisoquinolinium salt at an initial bomb pressure (at room temperature) of 2000 p.s.i. The results obtained are shown in Figs. 1, 2, 3. As anticipated the authors were able to demonstrate (Fig. 1) that as the temperature was increased from 120 to 260° the extent of hydrogenation increased; this was evidenced by the sharp decrease in the amount of 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline produced. Accompanying this, however, was a marked falloff in the quantity of *cis*-5,9,10-H-5-amino-2-methyldecahydroisoquinoline produced above 180°. It was apparent that this was primarily due to extensive deamination, decomposition, and probable alkylation (10) of the products; this was well demonstrated at 260° by the production of 23 detectable compounds by GC and by an increase in the amount of 2-methyldecahydroisoquinoline formed (*i.e.*, deaminated 5-amino-2-methyldecahydroisoquinoline). It has been well established that in many hydrogenations there is a threshold temperature below which little or no reduction takes place (11). It is apparent from this study (Fig. 1) that significant hydrogenation occurs at temperatures of 140° and above, as evidenced by the decrease in the amount of partially saturated isoquinoline, however, the optimum range is 140–160° (Fig. 3).

It is known (11) that low temperature hydrogenations are specific in regard to the stereochemistry of the products and that the hydrogenation becomes more random as the temperature is increased. The results of this study shown in Fig. 2 demonstrate this phenomenon in that the desired *cis*-5,9,10-H-5-amino-2-methyldecahydroisoquinoline was heavily favored over the corresponding *trans*-9,10-*trans*-5-H-5-amino-2-methyldecahydroisoquinoline at 120° (13:1) and as the temperature increased, more randomization occurred resulting in isomer ratios of 2:1 at the extremes of this study. The predominant production of the *cis* ring junction decahydroisoquinolines in this investigation is in line with the findings of Linstead and Levine (12) in their *cis* reduction of polycyclic aromatics over Raney nickel but contrasts with a study of Witkop in 1949 (13) in which he was able to produce selectively *trans*-decahydroisoquinoline from the hydrogenation of isoquinoline over Raney nickel at a temperature of 164° at 3000 p.s.i.; the authors can only intimate that the presence of the 5-nitro-substituent and the type of Raney nickel used were influencing factors in the isomer

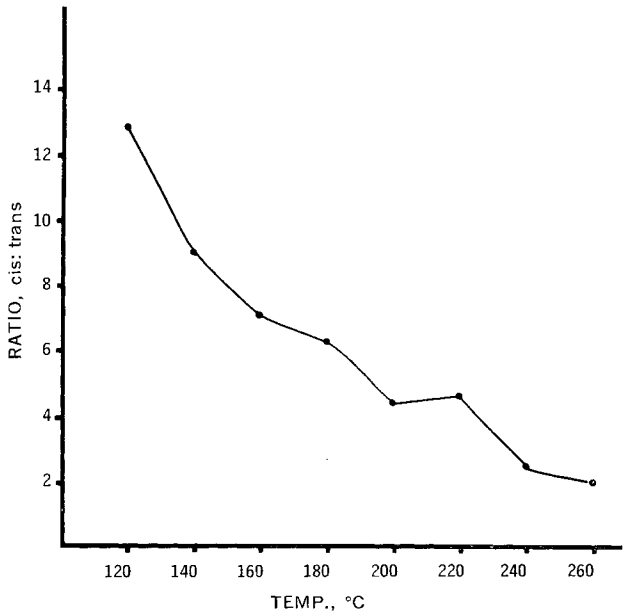


Figure 2—*Effect of temperature on stereochemistry at 2000 p.s.i.*

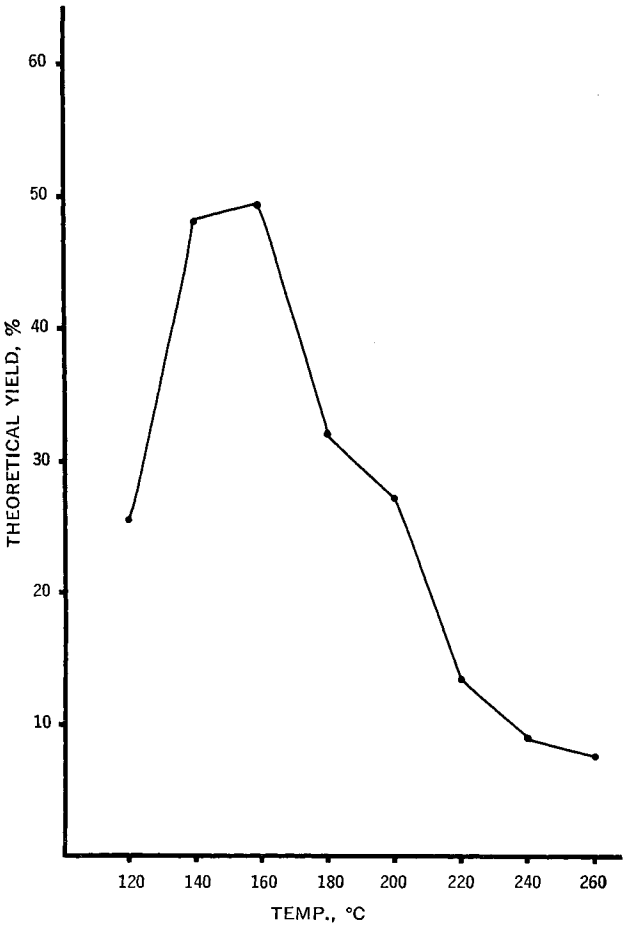


Figure 3—*Effect of temperature on yield of 5-amino-2-methyldecahydroisoquinolines at 2000 p.s.i.*

ratios obtained. It is pertinent to note (Fig. 3) that the maximum yield of the desired 5-amino-2-methyldecahydroisoquinolines was 50%. This contrasts with a 88% yield for the low-pressure platinum-catalyzed reduction (1).

Effect of Pressure at Constant Temperature—It has been stated (11) that pressure is an important variable in the chemistry and economics of catalytic hydrogenation and that its effect is not always predictable. In general, however, increases in pressure cause an increased rate of reduction associated with an increase in yield of the reduced product. It has also been shown by Levin and Pendergrass (14) that increased pressure favors hydrogenation over hydrogenolysis; as a result of the findings in regard to increases in temperature this factor is of some significance.

In view of the occurrence of minimal side reactions accompanied by a maximal yield of 5-amino-2-methyldecahydroisoquinolines (Fig. 3) at 160°, it was decided to investigate the effect of varying pressure on the hydrogenation of the 5-nitroisoquinolinium salt at this temperature. Figures 4, 5, and 6 summarize the results obtained. It is clearly shown (Fig. 4) that increased pressure causes a significant increase in the extent of hydrogenation; this is well demonstrated by the decrease in the percent yield of 5-amino-2-methyl-1,2,3,4-tetrahydroisoquinoline accompanied by increases in yield of both isomers of the desired 5-amino-2-methyldecahydroisoquinolines. Results from this laboratory also show that increases in pressure caused no detectable change in the amount of hydrogenolysis occurring as evidenced by the curve for the deaminated product in Fig. 4. However, rather surprising results were obtained in regard to the stereochemistry of the reduced products. These results (Fig. 5) suggest that increases in pressure initially result in increased specificity of hydrogenation which leads to a maximum *cis*:*trans* ratio 7.7:1; this is then followed by a more randomized reduction in which the *cis*:*trans* ratio is reduced to 5.9:1. It would appear that the pressure associated with maximum specificity is in the region of 1500 p.s.i. It is of interest to note that temperature changes are far more effective in inducing changes in specificity of hydrogenation than those brought about by variations in pressure (*cf.* Figs. 2 and 5). It should also be noted that pressure is much more significant an entity in inducing high yields of the desired hydrogenation products (5-amino-2-methyldecahydroisoquinolines) than is temperature and that at a pressure of 3000 p.s.i. a very respectable figure of 71% yield was obtained (Fig. 6).

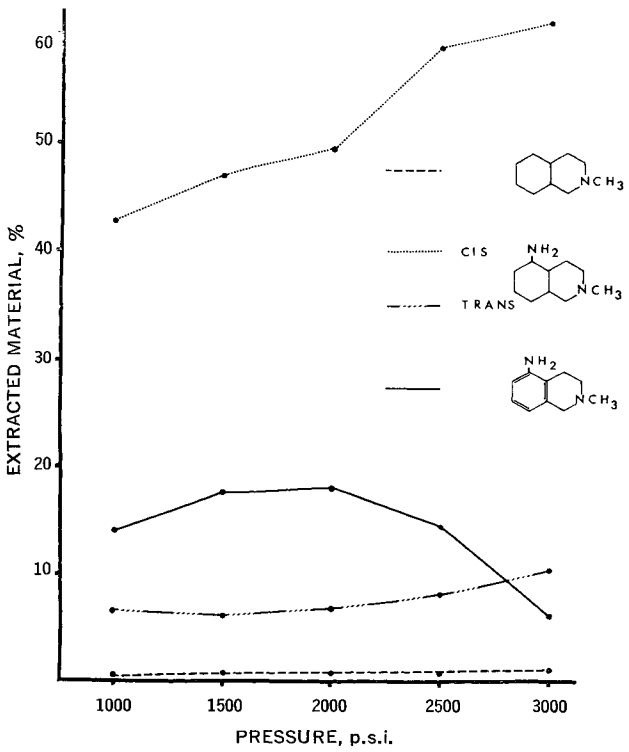


Figure 4—*Effect of pressure on reaction products at 160°.*

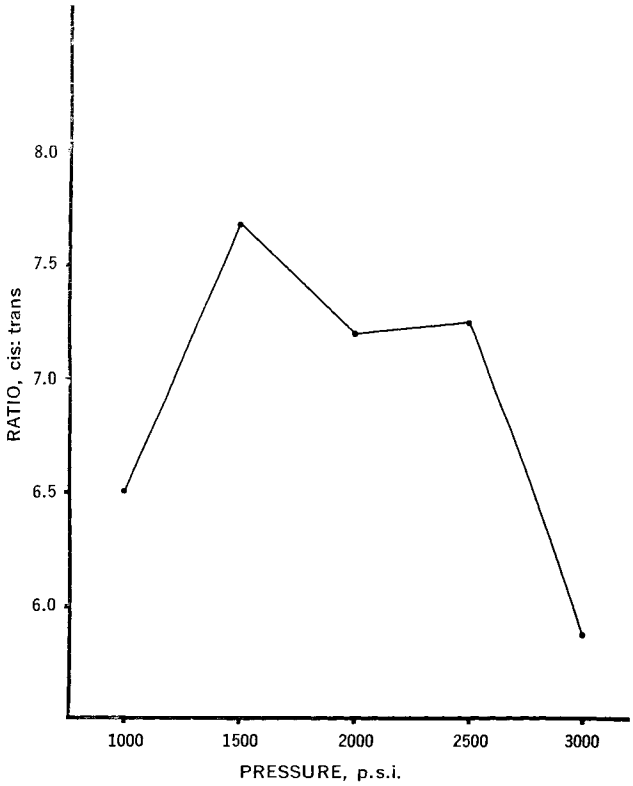


Figure 5—*Effect of pressure on stereochemistry at 160°.*

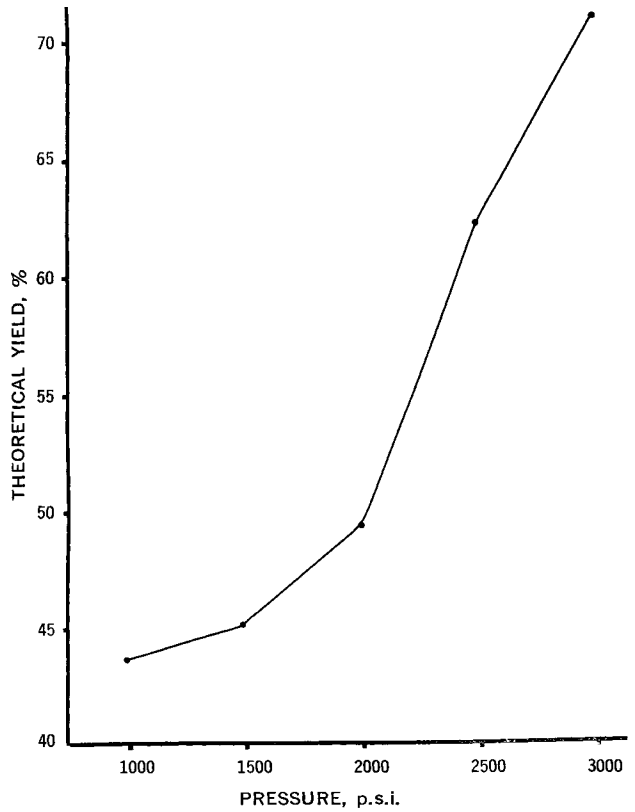


Figure 6—*Effect of pressure on yield of 5-amino-2-methyldecahydroisoquinolines at 160°.*

Other Factors—Many factors are instrumental in the successful completion of a catalytic hydrogenation. The present study was commenced in an effort to determine the effects of two of the major parameters influencing the course of hydrogenation reactions. However, it is appropriate to add some comments on other features of the investigation which the authors standardized in order to eliminate playing any significant role in the results obtained.

Primary consideration was given to the choice of catalyst. W7 Raney nickel was chosen in view of its ease of preparation, relative cheapness, and reported activity in the reduction of polycyclic ring systems (12). The amount of catalyst used was standardized for all hydrogenations and thus any effects (15) induced by this variable were eliminated. The choice of solvent was similarly considered; a neutral solvent capable of being subjected to high temperatures and of readily solubilizing the 5-nitroisoquinolinium salt was desirable. Methanol was selected since it met the needs; however, its possible role in alkylation (10) of the 5-amino function at very high temperatures (220° and above) was considered to be only a slight disadvantage. Indeed only at extremely high temperatures was there any evidence of this phenomenon having taken place. Adequate mixing of the catalyst and the hydrogenation mixture during the hydrogenation was standardized and is described in the *Experimental* section. The time of the hydrogenation (4 hr. heating followed by a 12-hr. cool-down period) was made uniform throughout and was considered adequate for the completion of the hydrogenation. It was estimated, by noting pressure changes within the reactor, that hydrogenation was essentially complete in all experiments within a 2-hr. period.

CONCLUSIONS

In the light of the above studies, it is evident that the high-pressure/high-temperature hydrogenation of 5-nitroisoquinolinium salts over Raney nickel catalyst is a more efficient procedure than the previously reported synthesis (1) of 5-amino-2-methyldecahydroisoquinolines. Furthermore, significant variations in the isomer content of the products may be brought about by variations in the temperature at which the hydrogenation is carried out. The pressure at which the hydrogenation is carried out should be carefully selected for maximum yield of the desired product.

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