66768-81-8; **19**, 66768-82-9; **20**, 66768-83-0; **21**, 66768-84-1; **23**, 66768-85-2; **31**, 66768-86-3; **32**, 66768-87-4; **33**, 66768-88-5; 2-bromo-4-chloro-5-methyl-1-benzothiepin, 66768-89-6; 2-chloro-1-methylnaphthalene, 20601-21-2; 2-bromo-1-methylnaphthalene, 20601-22-3.

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Direction of Cyclization in the Fischer Indole Synthesis. Mechanistic Considerations

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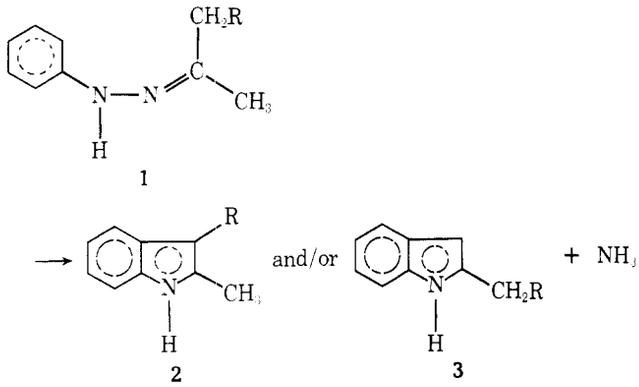
The effects of acid catalysts and temperature in the uncatalyzed reaction on the direction of cyclization of unsymmetrical ketone phenylhydrazones in the Fischer indole synthesis have been examined. Higher acidity, as previously reported, and higher temperature in the thermal process cause cyclization toward the less substituted position. The observations are considered in terms of a refined version of the first two stages of the mechanism of the reaction.

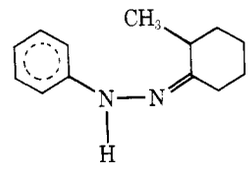
A perplexing aspect of the Fischer indole synthesis[2] has been the cyclization of phenylhydrazones of unsymmetrical ketones to form two possible indoles. The early generalizations of Plancher,[3] suggesting that the course of the reaction depends only on the structure of the ketone moiety of the

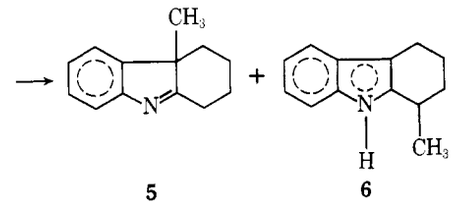


phenylhydrazone, have not been sustained by more recent investigations[4-7] in which the ratio of the products has been found to vary with the nature of the acid used as the catalyst, its concentration, or its absence in a thermal cyclization.

While Lyle and Skarlos[5] suggested that the direction of cyclization was an effect of the size of the acid, Illy and Funderburk[6] and Palmer and McIntyre[7] independently provided convincing evidence that the course of the reaction was governed by the acidity of the reaction medium. The trend evident in the results of these more recent studies[5-7] is that weaker acids or lower acid concentrations promote cyclization toward the more branched carbon atom (**1** → **2**) and stronger acids or higher acid concentrations enhance the extent of cyclization at the less branched position (**1** → **3**).

Most of these observations have been made on a variety of phenylhydrazone structures with several acid catalysts under nonuniform conditions. Since the direction of enolization is necessarily central to the mechanism[2] of the Fischer indole synthesis, a systematic examination of this phenomenon should provide further information regarding the character of the mechanistic steps. For this purpose, 2-alkylcyclohexanone phenylhydrazones were selected for cyclization under varying conditions of acidity and temperature. This substrate provides two reaction pathways of similar energy requirements since both products are known to form in good yield under moderate reaction conditions.[4c,c,8]





In Table I are listed the product ratios observed in the cyclization of 2-methylcyclohexanone phenylhydrazone (**4**) with various acids at 80 °C. The trend is similar to that found previously.[4a,8a] The results also parallel those of Illy and Funderburk[6] for the phenylhydrazone of methyl isopropyl ketone.

The product ratios observed with various concentrations of sulfuric acid in ethanol as the catalyst at 80 °C are given in Table II. As with the results reported by Illy and Funderburk[6] and Palmer and McIntyre[7] for acyclic ketone phenylhydraz-

Table I. Effect of Acid Catalyst on the Product Ratio at 80 °C

Acid	$-H_0$[a]	Ratio[b]
Acetic	ca. −2.5	40
H_2SO_4[c]	0.43	1.8
BF_3[d]	7–10	0.9
$ZnCl_2$[d]		0.3
PPA[e]	ca. 7	0.2

[a] C. H. Rochester, "Acidity Functions", Academic Press, New York, N.Y., 1970, Chapter 2. [b] Indolenine/indole. [c] 10% in ethanol. [d] Ethanol solvent. [e] Polyphosphoric acid.

Table II. Effect of Acid Concentration on the Product Ratio at 80 °C

% H_2SO_4[a]	$-H_o$[b]	Ratio[c]
10	0.43	1.8
20	1.10	0.8
40	2.54	0.4
60	4.51	0.5
80	7.52	0.7

[a] Ethanol solvent. [b] See footnote *a* in Table I. [c] Indolenine/indole.

Table III. Temperature Effect on the PPA-Catalyzed Reaction

Temp, °C	Ratio[a]
80	0.2
125	0.4
160	1.0[b]

[a] Indolenine/indole. [b] Minor decomposition observed (GC).

Table IV. Temperature Effect on the Uncatalyzed (Thermal) Reaction

Temp, °C	Ratio[a]
155	2.0[b]
200	0.5
245	0.2

[a] Indolenine/indole. [b] Some unreacted phenylhydrazone remained (GC).

Table V. Solvent Effect on the 10% H_2SO_4 Catalyzed Reaction at 80 °C

Solvent alcohol	Ratio[a]
Methyl[b]	1.4
Ethyl	1.8
2-Propyl	2.2
tert-Butyl	3.1

[a] Indolenine/indole. [b] At 65 °C.

Table VI. Product Ratios from the Cyclization of 2-Alkylcyclohexanone Phenylhydrazones with Various Acids at 80 °C

Acid catalyst	Product ratios[a]			
	2-Methyl	2-Ethyl	2-Isopropyl	2-*tert*-Butyl
Acetic	40	12	6.5	0[d]
H_2SO_4[b]	1.8	4.1	0.8	0
BF_3[c]	0.9	2.7	0.1	0
$ZnCl_2$[c]	0.3	3.0	0.5	0
PPA	0.2	4.4	0.6	0

[a] Indolenine/indole. [b] 10% in ethanol. [c] Ethanol solvent. [d] Only indole formed.

ones, these ratios show a trend toward the formation of more of the indole product **6** at higher acidities. Values for the Hammet acidity function, H_o, in Tables I and II are probably not valid for the present solvent and temperature, but they do indicate a gross correlation of product ratio with acidity. The reason for the formation of a maximum amount of the indole at a concentration of about 40% H_2SO_4 with some increase in the amount of indolenine at higher acid concentrations is not immediately obvious.

To examine the temperature effect in the cyclization of **4**, the PPA-catalyzed reaction was selected since the temperature could be increased without changing other reaction conditions. The product ratios are listed in Table III. In line with the previous observation that the formation of the indole **6** is favored by higher acidity, the decrease in the proportion of indole formed at higher temperatures suggests that a protonated intermediate leading to the indole dissociates at higher temperatures, permitting somewhat more of the indolenine **5** to form.

This increased formation of indolenine at higher temperatures in the acid-catalyzed reaction is in contrast to the trend in the uncatalyzed (thermal) cyclization (Table IV) in which higher temperatures increase the amount of indole produced. These opposite temperature effects are not inconsistent in a reaction involving two competing pathways, each favored by different factors.

A further examination of the effect of the extent of protonation was made by determining the product ratios from reactions catalyzed by 10% H_2SO_4 in a series of alcohols as solvent (Table V). Increased bulk of the R group in ROH_2^+ reduces the effectiveness of the acid in protonating the reaction intermediate involved in the formation of the indole, resulting in a larger indolenine/indole ratio.

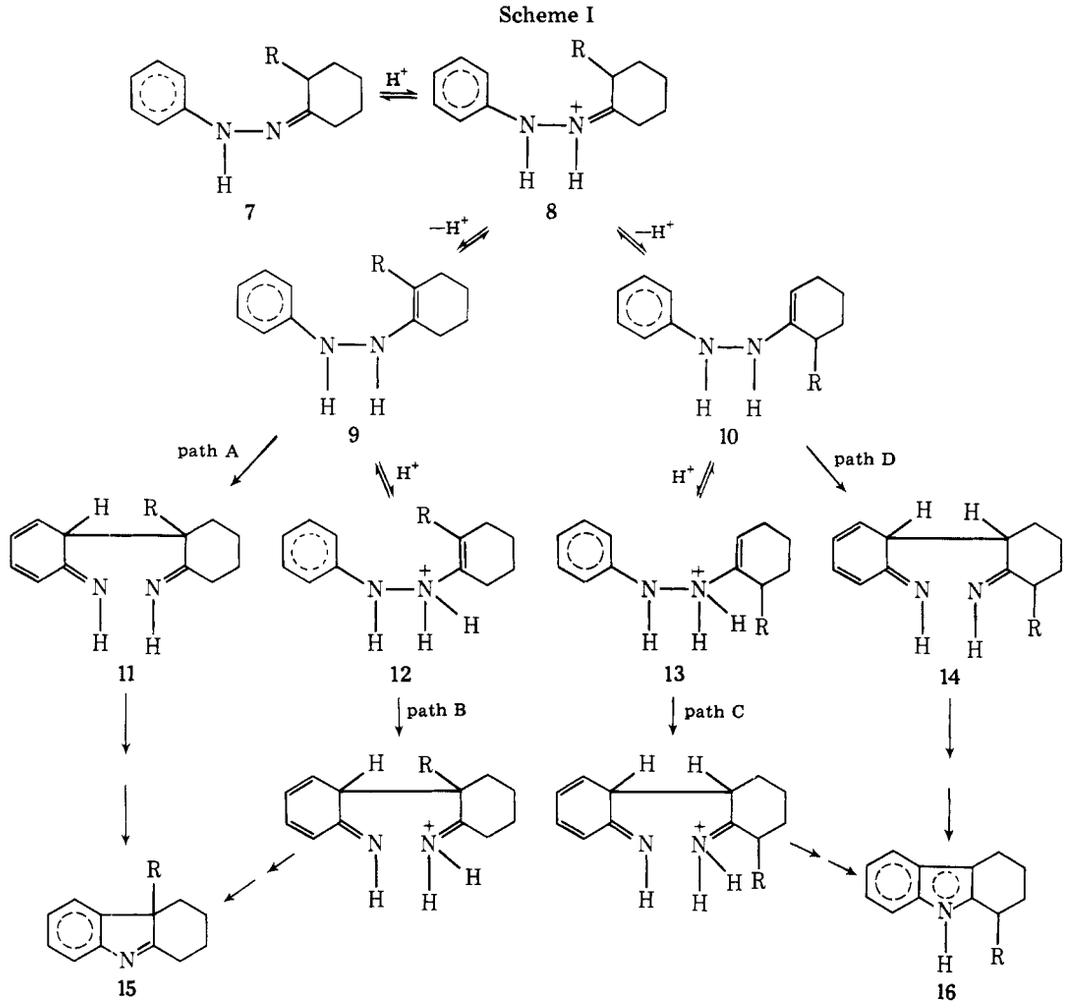
A measure of the steric control of the reaction was determined by examining the product ratio in the indolization of the phenylhydrazones of 2-ethyl-, 2-isopropyl-, and 2-*tert*-butylcyclohexanones with several acid catalysts (Table VI). The trends are generally parallel to those observed in the case of the 2-methyl compound except that $ZnCl_2$ and PPA produce somewhat more indolenine from the 2-ethyl and 2-isopropyl structures and that the 2-*tert*-butyl compound forms only indole. While the general picture evident from the data in Table VI is that increased bulk at the tertiary carbon atom favors the formation of indole by cyclization at the secondary position, there does not seem to be much indication that the size of the acid provides a significant directive influence on the course of the reaction.

The observations summarized in Tables I–IV can be interpreted in terms of the accepted mechanism[9] for the Fischer indole synthesis as outlined in Scheme I.

One consideration fundamental to a reaction in which two products are formed competitively is the relative stability of the two products and the possibility of their interconversion. Intuitively, the indole structure **16**, because of its greater aromaticity, might be expected to be at a lower energy level than the indolenine **15**. Support for this assumption is found in the well-established rearrangements of 3,3-disubstituted indolenines to 2,3-disubstituted indoles.[10] However, the suggested[11a] stability of the trisubstituted indolenine **15** toward rearrangement was confirmed under the experimental conditions of the present investigation.[11b]

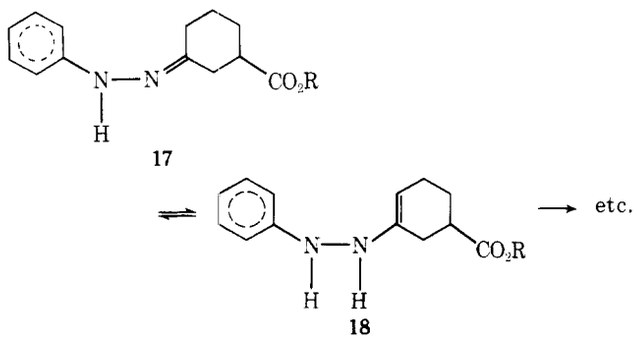
The rate-determining step of the Fischer indole synthesis has not been identified. The kinetics of the reaction have received only cursory examination[8a,12] to indicate that the reaction is first order in phenylhydrazone when carried out in acetic acid solution and first order each in phenylhydrazone

Scheme I



and acid when the cyclization occurs in sulfuric acid solution. However, the effect of substituent groups on the rate of the reaction[12] and the analogy[13] to the Claisen rearrangement are compatible with a rate determining [3,3] sigmatropic rearrangement of the enehydrazine to the diimine (steps A, B, C, or D in Scheme I).

The two possible pathways which the reaction of an unsymmetrical phenylhydrazone may follow are determined by the two enehydrazines, **9** and **10**, the formation of which would be facilitated by protonation of the phenylhydrazone, although acid catalysis is not essential. Equilibrium concentrations of N-unsubstituted enehydrazones are too low to be detected by physical methods,[2] but the relative tendency of **9** and **10** to form should be in favor of the more highly substituted double-bond isomer **9**.[14] Support for this idea is found in the significant amount of cyclization at the more substituted carbon atom, even at relatively high acidities, in the case of the phenylhydrazones of methyl ketones.[6,7] Among other examples,[2] the cyclization of **17** shows a preference for



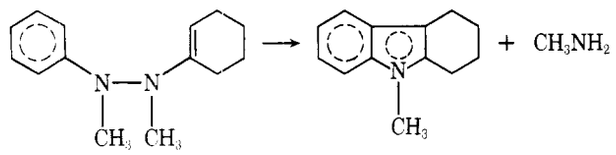
enehydrazone **18**, estimated to be about 0.6 kcal/mol more stable than the alternate possibility, although the same degree of substitution at the α-carbon atoms is involved in each case.[15]

In the uncatalyzed reaction at low temperatures, the greater stability of the more substituted π bond (**9**) prevails, forming more of the indolenine and suggesting that the energy requirements are less along this pathway (kinetic control). At higher temperatures, sufficient energy is available to permit formation of more of the less substituted enehydrazine **10**, shifting the product ratio from 2:1 indolenine **15** to 5:1 indole **16** (thermodynamic control). Steric hindrance to the cyclization through the more stable enehydrazine **9** intervenes as the size of the alkyl group is increased (Table VI).

At low acidities, e.g., with acetic acid, the large proportion of indolenine formed suggests that the acid is serving only to catalyze enehydrazine formation.

The role of the acid catalyst at higher acidities in the shifting of the product ratio toward larger proportions of indole was considered by earlier investigators to be the consequence of further protonation of reaction intermediates. Illy and Funderburk[6] did not specify the site of this protonation. Palmer and McIntyre[7] pictured the reaction course to be controlled by acid-catalyzed formation of the enehydrazines.

Schiess and Grieder[16] prepared a series of *N,N'*-dimethyl enehydrazines, including **19**, and studied their conversion to the corresponding indoles, both thermally and under acid catalysis. The acid-catalyzed reaction was found to be many times faster than the thermal process, suggesting the intervention of an N-protonated form such as **12** or **13** in a *charge induced pericyclic reaction.*[13a]



19 20

Therefore, the energy barrier for the rearrangement of **12** or **13** is apparently less than that for the corresponding rearrangement of the unprotonated enehydrazines **9** or **10**, and under conditions of higher acidity pathways B or C should be followed to a greater extent than A or D. If routes B or C are both relatively fast, the fact that C is preferred to B could be a reflection of the greater stability of the indole product compared to the indolenine (thermodynamic control).

An alternative explanation of the acidity effect exists as the consequence of the fact that substitution on the β-carbon atom of enamines lowers basicity.[17] Thus, at higher acidity enehydrazine **10** should be more readily protonated than the isomeric structure **9**, favoring the formation of **13** and reaction path C leading to indole.[18]

Therefore, the effects of acidity and temperature on the direction of cyclization in the Fischer synthesis appear to be accommodated in terms of a partitioning of the reaction between the two pathways shown in Scheme I. Confirmation of these suggestions lies in a study of the activation parameters of the reaction.

Experimental Section

Melting points were observed on a Fisher-Johns apparatus using a calibrated thermometer. Boiling points are uncorrected. Gas chromatographic (GC) analysis was performed on a Varian Aerograph Model 2700 (thermal conductivity detector) using a 5 ft, 3% SE 30 on 100–200 mesh Varaport 30 column. Pure samples of the indolenine **5**, mp 71 °C (lit.[4a] mp 72 °C), and the indole **6**, mp 68 °C (lit[4a] mp 68 °C), were prepared for the determination of retention times.

2-Alkylcyclohexanols. The 2-alkylphenol (10 g) in 80 mL of 95% aqueous ethanol was hydrogenated over 1.0 g of 5% Ru/C at 125 °C and 1500 psi for 7 h.[19] The catalyst was removed by filtration, water was added, and the cyclohexanol was extracted with ether. The dried (Na_2SO_4) ether solution was evaporated and the product distilled under vacuum. The yields were essentially quantitative: **2-ethylcyclohexanol,** bp 50 °C (1 mm) [lit.[20] bp 75 °C (12 mm)]; **2-isopropylcyclohexanol,** bp 56 °C (1 mm) [lit.[21] bp 114 °C (28 mm)]; **2-*tert*-butylcyclohexanol,** bp 65 °C (1 mm) [lit.[22] by 99–103 °C (23 mm) (cis isomer)], mp 54 °C [lit.[22] mp 56.8–57.7 °C (cis isomer)].

2-Alkylcyclohexanones.[23] The 2-alkylcyclohexanol, dissolved in a small amount of acetone (distilled over $KMnO_4$), was titrated with Jones reagent to a slight excess of the equivalence point (1.0 mL of Jones reagent per 0.5 g of the cyclohexanol). During the addition period, the mixture was stirred and the temperature was maintained between 20 and 25 °C by a water bath. The reaction mixture was stirred overnight, water was added, and the 2-alkylcyclohexanone was removed by extraction several times with ether. The dried (Na_2SO_4) ether solution was evaporated, and the cyclohexanone was purified by vacuum distillation. **2-Ethylcyclohexanone:** 75% yield; bp 54 °C (4 mm) [lit.[24] bp 42 °C (2 mm)]. **2-Isopropylcyclohexanone:** 80% yield; bp 58 °C (1 mm) [lit.[21] bp 72 °C (9 mm)]. **2-*tert*-Butylcyclohexanone:** 85% yield; bp 62 °C (4 mm) [lit.[22] bp 62.5 °C (4 mm)].

2-Alkylcyclohexanone Phenylhydrazones. Equimolar amounts of the ketone and phenylhydrazine were heated with stirring in a water bath at 90–95 °C for 3 h, and the resulting phenylhydrazone was purified by vacuum distillation; the yields were 85–95%: **2-methylcyclohexanone phenylhydrazone,** bp 140 °C (1 mm); **2-ethylcyclohexanone phenylhydrazone,** bp 147 °C (1 mm); **2-*tert*-butylcyclohexanone phenylhydrazone,** bp 160 °C (1 mm).

Cyclization of the Phenylhydrazones. A. Acetic Acid. A solution of 1.0 g of the phenylhydrazone in 10 mL of glacial acetic acid was heated in a water bath at 80 °C for 0.5 h. The reaction mixture was diluted with water and made alkaline, and the products were extracted with benzene. The dried (Na_2SO_4) benzene solution was analyzed by GC.

B. Sulfuric Acid. The phenylhydrazone (1.0 g) was dissolved in 10 mL of a solution of sulfuric acid in ethanol (10, 20, 40, 60, or 80% H_2SO_4 by weight), and the solution was heated to 80 °C for 0.5 h. Water was added, the solution was made alkaline, and the products were extracted with benzene and analyzed as above. Similar runs were made with 10% H_2SO_4 in methyl, isopropyl and *tert*-butyl alcohols.

C. Zinc Chloride. The phenylhydrazone (12 g) was dissolved in 50 mL of absolute ethanol containing 70 g of anhydrous zinc chloride. The solution was protected from atmospheric moisture and refluxed for 5 h. Water was added and the mixture was made sufficiently alkaline to dissolve the $Zn(OH)_2$. The products were extracted with benzene and analyzed as above.

D. Boron Trifluoride. A solution of boron trifluoride in ethanol was prepared by distilling the ether from a 2:1 volume mixture of ethanol and boron trifluoride etherate. A solution of 10 g of the phenylhydrazone in 60 mL of the ethanolic BF_3 solution was refluxed until no more salt precipitation was evident (approximately 1 h). After dilution with water, the mixture was made basic and extracted with benzene and the products were analyzed as above.

E. Polyphosphoric Acid. PPA was heated to 80 °C in a water bath, and the phenylhydrazone (1.0 g/15 g of PPA) was added in small amounts so that the temperature did not rise. Heating was continued for 1 h. Ice was added, the mixture was made alkaline, and the products were extracted with benzene and analyzed as above. Other PPA runs were made at 125 and 160 °C with the 2-methyl compound.

F. Thermal Cyclization. Solutions of 5 g of 2-methylcyclohexanone phenylhydrazone in 30 mL of diethylene glycol were heated at 155, 200, or 245 °C (reflux). The reaction mixture was poured into water and extracted with benzene. These reactions were slow and required at least 10 h for reasonable completion. At 155 °C some phenylhydrazone remained unreacted.

Determination of Product Stability. Samples (1 g) of the indolenine **5** and the indole **6** were heated in the following solvents as indicated: 10 mL of 20% ethanolic H_2SO_4 at 80 °C for 1 h; 10 mL of 40% ethanolic H_2SO_4 at 80 °C for 1 h; 10 g of polyphosphoric acid at 125 °C for 3 h; 10 mL of diethylene glycol at 200 °C for 10 h. The reaction mixtures were diluted with water, the acid solutions were made basic, and the mixtures were extracted with benzene. The dried (Na_2SO_4) benzene solutions were analyzed by GC. In none of these cases was any of the isomeric substance detectable in the material following the heating.

Registry No.—**7** (R = Me), 1208-57-7; **7** (R = Et), 66675-14-7; **7** (R = *i*-Pr), 66675-15-8; **7** (R = *t*-Bu), 66675-16-9; **15** (R = Me), 18781-72-1; **15** (R = Et), 1504-31-0; **15** (R = *i*-Pr), 28658-98-2; **16** (R = Me), 17058-12-7; **16** (R = Et), 10257-86-0; **16** (R = *i*-Pr), 66675-17-0; **16** (R = *t*-Bu), 66675-18-1.

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Notes

Fischer Indole Synthesis from *cis*- and *trans*-9-Methyl-3-decalone

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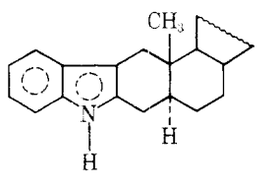
In the Fischer indole synthesis with the phenylhydrazone of an unsymmetrical ketone the direction of cyclization is governed in part by the relative stability of the two possible enehydrazines.[2] This regioselectivity has been well established[3] in the 3-keto steroid system in which 5α-cholestanone yields the linear indole **1** and the 5β isomer forms the angular product **2**. The same directions of enolization are observed in



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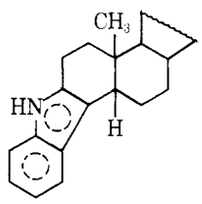
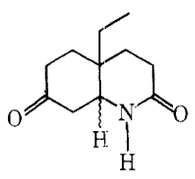
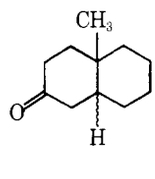


2

the bromination of the respective 3-ketones[4] in which relief of strain is maximized by enolization of the trans isomer parallel to the ring fusion and of the cis isomer toward the ring fusion.[5] In contrast, Stork and Dolfini[6] observed a linear product from both the cis and trans isomers of the bicyclic azadecalin system **3**. This behavior is analogous to the formation of the 2-bromo derivative from both *cis*- and *trans*-9-methyl-3-decalone (**4**).[7]



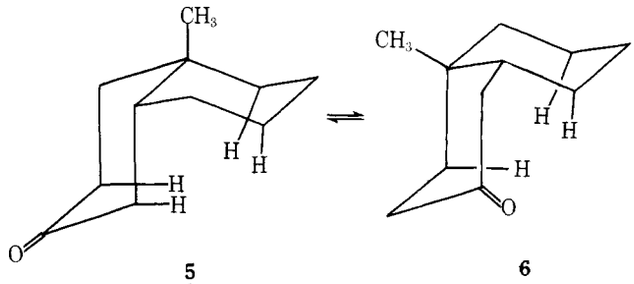
3



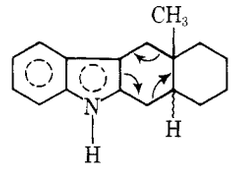
4a (cis)
4b (trans)

Unlike the more rigid cis steroid, the cis isomer of the bicyclic system can exist in two chair–chair conformations,[8] **5** and **6**. In the more stable of these two conformers, **6**, greater relief of strain results through enolization toward position 2 than toward position 4.

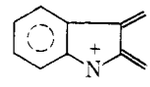
To confirm the course of cyclization in the Fischer indole synthesis with the decalin system, cyclization of the phenylhydrazones of both *cis*- and *trans*-**4** was carried out. That the product in each case was the linear indole **7** was determined from the mass spectral fragmentation to the *m/e* 143 ion (**8**), a fragmentation not available to the angular structure. The mass spectra of **7a** and **7b** are quite similar, showing only



5 **6**



7a (cis)
7b (trans)



8 (*m/e* 143)

slight intensity differences. Between the parent peak (*m/e* 239) and the base peak (*m/e* 143), the greatest difference lies in the presence of the *m/e* 224 (P − 15) peak in the trans isomer **7b**, reflecting a greater tendency of this isomer to lose the angular methyl group. In the mass region below the base peak, the spectra are both very similar to the mass spectrum of 1,2,3,4-tetrahydrocarbazole because of fragmentation of the common ion 8 and are typical of the spectra of alkylindoles.[9]

Experimental Section[10]

***cis*-9-Methyl-3-decalone (4a).** 9-Methyl-Δ^4-3-octalone was prepared by the procedure of Yanagita and Yamaka,[7] bp 93–96 °C (1.5 mm) [lit.[7] bp 102–110 °C (2.5 mm)]. Hydrogenation of the unsaturated ketone using 10% palladium on carbon at atmospheric pressure[7] afforded the cis saturated ketone **4a**: mp 46–47 °C (lit.[7] mp 47 °C); NMR δ 1.33 (CH_3).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.52; H, 10.84. Found: C, 79.38; H, 10.67.

***trans*-9-Methyl-3-decalone (4b).** Reduction of the unsaturated ketone with Li in liquid NH_3[11] furnished the trans isomer: bp 98–101 °C (5 mm) [lit.[11] bp 95–112 °C (7 mm)]; NMR δ 1.15 (CH_3).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.52; H, 10.84. Found: C, 79.34; H, 10.79.

Phenylhydrazones. Equimolar quantities of the above ketones and phenylhydrazine were stirred at room temperature for 24 h. The mixture was taken up in ether and dried over Na_2SO_4. The ether was removed under vacuum and the phenylhydrazone distilled under vacuum.

***cis*-9-Methyl-3-decalone Phenylhydrazone:** bp 174–178 °C (1 mm); NMR δ 1.35 (CH_3).

Anal. Calcd for $C_{17}H_{24}N_2$: C, 79.69; H, 9.38; N, 10.94. Found: C, 79.56; H, 9.16; N, 10.23.

***trans*-9-Methyl-3-decalone Phenylhydrazone:** bp 180–185 °C

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