Variations of the Fischer and Piloty Syntheses

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Received August 3, 1973

The methyl iodide induced conversion of *N*-methylphenylhydrazones to indoles has been studied and an enehydrazine intermediate **3c** has been isolated. N′-Protonation of the enehydrazine leads to a facile electrocyclic ring closure. Ketazinium methiodides have been converted to pyrroles by heating. Action of acetic anhydride on cyclopentylketazine intercepted an intermediate in the pyrrole synthesis as the acetyl derivative of a tautomer **15.** Some modifications of the known reaction of carbonyl compounds with *N*′-methylhydrazines and phenylhydrazines are described.

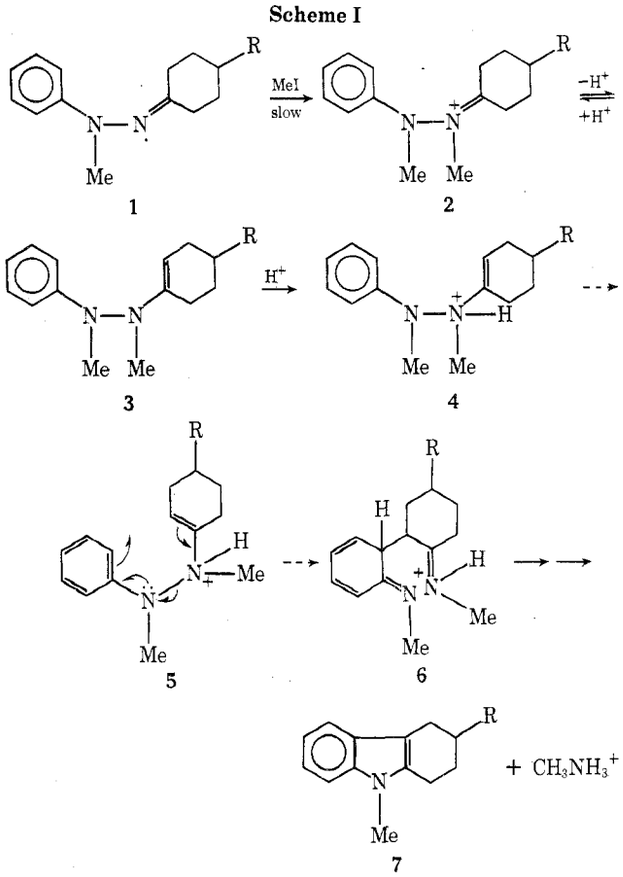
During the course of another research program, 4-cyclohexylcyclohexanone α-methylphenylhydrazone (**1b**) was treated with methyl iodide with the expectation that a hydrazonium salt would result from methylation at the α-nitrogen atom; instead cyclization to the indole **7b** occurred. The unusually mild conditions involved, especially the absence of deliberately added acid, suggested that further study of this system might lead to better understanding of some of the steps of the Fischer indole synthesis.[2] The ideas developed during this phase of the work led to investigation of other indolization procedures, and of the similar Piloty[3] synthesis of pyrroles.

Results and Discussion

Reaction of Phenylhydrazones with Methyl Iodide. A solution of hydrazone **1b** in excess methyl iodide began to deposit a solid within 30 min and precipitation continued slowly at room temperature. After 12 hr the precipitate comprised a nearly quantitative yield of methylammonium iodide, and from the filtrate a good yield of indole **7b** was isolated. Attack of methyl iodide on the hydrazone appears to occur exclusively at the β-nitrogen atom, rather than at the α-nitrogen atom as is true with dimethylhydrazones.[4] No intermediates were observed when the reaction was carried out in the sample cell of an infrared spectrometer, with repeated scanning over several hours; therefore the first step in the reaction sequence, presumably formation of the hydrazinium salt **2** (Scheme I), is rate determining. Hence all subsequent steps are quite rapid at room temperature, including the key conversion of **4** into **6.** This conclusion is supported by the fact that no products are found that result from further methylation of intermediates; these react faster along the path leading to indole than they react with methyl iodide.

To explore the question of acid catalysis in steps following the initial methylation, the reactions of hydrazones **1a, 1b** and **1c** with methyl iodide were carried out under a variety of proton-scavenging conditions. A limitation on the choice of bases which might be employed is that they must not react with methyl iodide. In the presence of an excess of the hindered amines 2,6-diisopropylpyridine and *N,N*,2,6-tetramethylaniline,[5] **1b** again furnished the indole and methylammonium iodide, although the isolated yield of **7b** from the second solvent was only 28% owing to separation problems. Although these media are formally basic, proton transfer from various ammonium ions which might be present is not precluded. It was found that in methanol solution at room temperature, *N,N*,2,6-tetramethylanilinium iodide slowly catalyzes indole formation from the hydrazone, but methylammonium iodide does not. In the methyl iodide promoted reactions, since methylammonium iodide is produced, direct acid catalysis of indolization by the anilinium ion is eliminated, but acid catalysis of subsequent steps by the methylammonium ion remains a possibility.

Scheme I

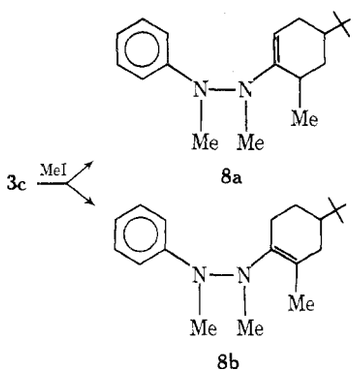


a, R = H
b, R = cyclohexyl
c, R = *tert*-butyl

Treatment of hydrazone **1b** with methyl iodide in a vigorously stirred suspension of anhydrous potassium carbonate in 2-butanone still produced the indole in substantial yield. When the ketone was replaced by the more basic dimethylformamide (DMF), no indole was found. High-vacuum distillation of the product of this reaction gave a viscous oil which could not be purified further nor completely characterized. Spectral and chemical evidence suggested that it was a mixture of enehydrazines containing some C-methylated components. To resolve the problem, two other hydrazones were subjected to similar reaction conditions. Cyclohexanone α-methylphenylhydrazone (**1a**) still gave the indole **7a.** This indicates that the 4-cyclohexyl group of **1b** decreases its rate of indolization, probably by conformational effects in the transition state for cyclization; there-

fore the even bulkier *tert*-butyl group was employed in the next experiments.

4-*tert*-Butylcyclohexanone α-methylphenylhydrazone (**1c**) was treated with 1.2 equiv of methyl iodide in a stirred K_2CO_3–DMF suspension at room temperature, furnishing a 90% yield of the enehydrazine **3c** after appropriate work-up. When only 1 equiv of methyl iodide was used, some unreacted hydrazone remained; when a large excess of methyl iodide was used, the product was a mixture of the C-methylated enehydrazines **8a** and **8b.** Apparently C-methylation of the enehydrazine is somewhat slower than N-methylation of the hydrazone.



It was curiously difficult to find efficient conditions for the cyclization of **3c,** considering that **1c** in methyl iodide alone gave the indole in high yield at room temperature. With catalytic or equivalent amounts of strong acids at room temperature, no indole was formed during several hours. After **3c** was allowed to stand overnight at room temperature with 0.5 equiv of trifluoroacetic acid in methanol, aqueous work-up gave approximately 0.5 equiv each of recovered **3c** and 4-*tert*-butylcyclohexanone.The latter probably arises by hydrolysis of the iminium salt **2c** produced by C-protonation of **3c.** The best yield of indole (45%) when using fairly strong acid catalysts was obtained by refluxing **3c** with 0.05 equiv of trifluoroacetic acid in DMF for 3 hr.

Acetic acid alone does not promote indolization, but when **3c** was refluxed in acetic acid for 10 min in the presence of excess solid ammonium chloride, a 25% yield of **7c** was isolated. This was encouraging, but it was felt that the low solubility of ammonium chloride was deleterious. *tert*-Butylammonium chloride, which is quite soluble in acetic acid, proved to be an effective catalyst. When a cold solution of this salt in acetic acid was added to **3c,** the solution warmed spontaneously, and ir monitoring indicated that the reaction was complete within 15 min. Addition of water afforded a 95% yield of crystalline **7c.**

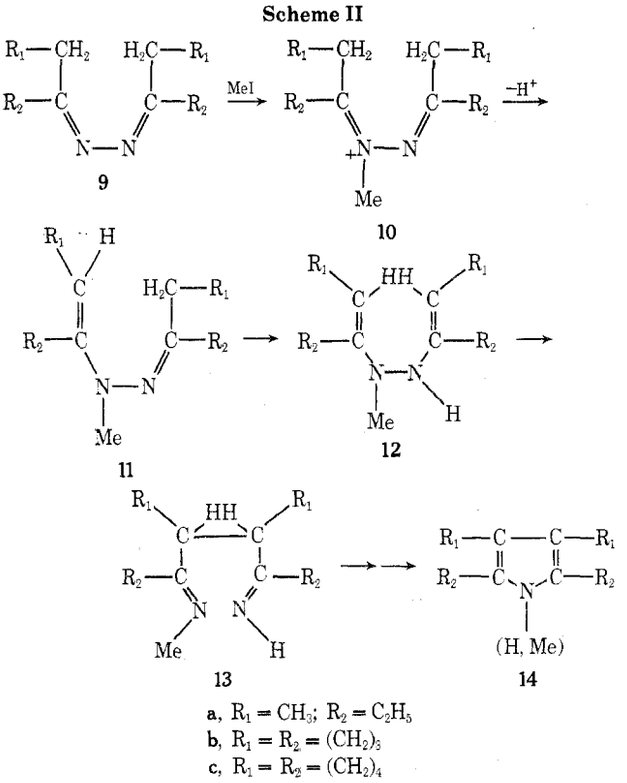
The foregoing results suggest that the carbon–carbon bond-forming step in a typical Fischer indole synthesis is a rapid electrocyclic reaction of the N′-protonated enehydrazine, structure **4.**[2c] N-Protonation may be effected by moderately strong acids, ammonium ions being especially effective. Strong acids, however, result in C-protonation to the iminium salt **2,** which is kinetically immobile under these conditions and does not lead directly to the indole.

Thermal, *i.e.,* non-acid-catalyzed, cyclizations of phenylhydrazones have been reported, but the intervention of trace amounts of acid is difficult to preclude.[6] When **3c** was refluxed with rapid stirring for 7 hr in a K_2CO_3–DMF suspension, a 15% yield of **7c** was produced. This may represent the non-acid-catalyzed cyclization of the enehydrazine, but if so, it is about 10^6 times slower than the acid-catalyzed process described in the preceding paragraphs.

Reaction of Ketazines with Methyl Iodide. Previous workers[3,7] have converted a number of ketazines into pyrroles, usually under rather vigorous conditions similar to those ordinarily employed in the Fischer synthesis. In a number of instances pyrazolines were formed in part or exclusively, especially with methyl ketones.

In an extension of the work described in the first section, three ketazines, diethylketazine, cyclohexylketazine, and cyclopentylketazine, were treated with methyl iodide and monomethiodides were obtained.[8] Heating the ketazinium iodides under various conditions afforded pyrroles in moderate yields. That heat is required for cyclization, in contrast with indole formation from **2,** is not too surprising, since loss of a proton from the ketazinium ion **10** (Scheme II) would produce an enehydrazine function in only one half of the molecule **11.** Presumably conversion of **11** into the dienehydrazine **12** is relatively slow, as in the usual Piloty reactions.

Scheme II



a, $R_1 = CH_3$; $R_2 = C_2H_5$
b, $R_1 = R_2 = (CH_2)_3$
c, $R_1 = R_2 = (CH_2)_4$

The yields in the conversion of the ketazinium salts to pyrroles were fairly good for the salts derived from diethyl ketone and cyclohexanone, but that from cyclopentanone gave only 16%. This would seem to be due to the strain in the 5–5–5 ring system produced in the later stages of the reaction. Another difficulty which detracts from the utility of this pyrrole synthesis arises from the fact that at the stage of the heterocyclic ring closure and the subsequent elimination, either the substituted or the unsubstituted nitrogen atom may be retained. This problem is not encountered in indole syntheses, where it is invariably the anilino nitrogen that is retained.[9] In the cyclohexanone series, *N*-methyloctahydrocarbazolewas the only isolated product, although the presence of some of the nor compound was indicated by the rapid oxidation of the crude material with the production of a deep green color.[7,10] Starting with diethyl ketone, *N*-methyl and N-unsubstituted pyrroles were obtained in 1:2 ratio. With cyclopentanone, only the N-unsubstituted product was detected. If it is possible to generalize from such a small number of observations, it would

Table I
Indoles from 2-Substituted Phenylhydrazines

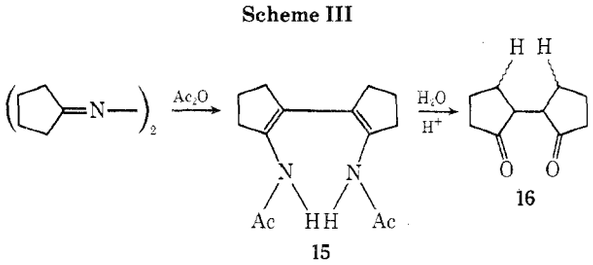
Phenylhydrazine	Registry no.	Carbonyl compd	Registry no.	Catalyst	Time, hr	Yield, %	Mp, °C	Bp, °C (1 mm)	Registry no.
2-Phenyl-	122-66-7	Cyclohexanone	108-94-1	Resin[a]	20	33	117–118		942-01-8
2-Methyl-	622-36-6	Cyclohexanone		Acetic acid	20	20	117		
2-Methyl-		Cyclohexanone		Resin	20	85	118		
2-Methyl-		Cyclopentanone	120-92-3	Resin	20	54	108[b]		2047-91-8
2-Methyl-		2-Heptanone	110-43-0	Resin	45	49[c]		120–122	51801-51-5
2-Methyl-		Heptanal	111-71-7	Resin	42	77		125–130	51801-52-6
2-Methyl-		Acetophenone	98-86-2	*p*-TsOH	20	64	189[d]		948-65-2
2-Methyl-		Propiophenone	93-55-0	Resin	45	25[e]	90–92[f]	155–160	10257-92-8
1,2-Dimethyl-[g]	29195-01-5	Cyclohexanone		Resin	20	29	48[h]	150	6303-88-4
1,2-Dimethyl-		4-Cyclohexylcyclohexanone	92-68-2	Resin	20	6	82		6623-15-0
1,2-Dimethyl-		2-Heptanone		Resin	20	10[i,j]		116–120	51801-53-7

[a] Amberlite IR-20. [b] Lit. mp 108°: W. H. Perkin and S. G. P. Plant, *J. Chem. Soc.*, **123**, 3242 (1923). [c] 2-Methyl-3-butylindole by nmr. [d] Lit. mp 188–189°: R. L. Shriner, W. C. Ashley, and E. Welch, *Org. Syn.*, **22**, 98 (1942). [e] Minimum, reaction not complete. [f] Lit. mp 90–92°: E. Leete, *J. Amer. Chem. Soc.*, **81**, 6023 (1959). [g] Products are *N*-methylindoles. [h] Lit. mp 50°: W. H. Perkin and S. G. P. Plant, *J. Chem. Soc.*, **119**, 1825 (1921). [i] Minimum, mechanical loss. [j] 1,2-Dimethyl-3-butylindole by nmr.

seem that cyclization of intermediate **13** is governed by electronic effects in the more facile reactions, as of the cyclohexyl compound, with the more nucleophilic methylated nitrogen attacking the more electrophilic unsubstituted imine function. When adverse steric factors due to the carbon skeleton are already present, the additional steric effect of the *N*-methyl substituent reverses the direction of addition, and becomes product determining.

Reaction of Ketazines with Acetic Anhydride. Suvorov[11] reported obtaining the diacetyl derivative of a vinyl phenylhydrazine by treatment of 2-butanone phenylhydrazone with acetic anhydride. In hope of similarly trapping an intermediate, the three ketazines mentioned in the previous section were treated with acetic anhydride under reflux. Cyclohexylketazine and diethylketazine gave the *N*-acetyl derivatives of the corresponding pyrroles in good yield.[7b] Cyclopentylketazine gave up to 37% yield of a solid, mp 187–189°, which was characterized as 2,2′-bis(acetamido)-1,1′-bicyclopentenyl (**15**) (Scheme III). Hydrolysis of **15** with dilute sulfuric acid gave the previously reported[12] bis-2,2′-cyclopentanone **16a** mp 70–71°, and its diastereoisomer **16b**, mp 37–40°.

Scheme III



15 16

Though conversion of **15** into a pyrrole was not achieved, its formation can nevertheless be considered as the trapping of a tautomeric form of an intermediate which in the methyl iodide promoted reaction did lead to pyrrole, albeit in low yield. That this trapping occurs in the cyclopentyl case, but not the other two, supports the contention made in the previous section that bond strain in the developing 5–5–5 ring system slows the conversion of **12b** to **14b**. A similar result was noted in the cyclization of α-keto-γ-butyrolactone phenylhydrazone,[13] though in that instance the intermediate was isolated as a salt of the imine tautomer. On the other hand, formation of **15** in reasonable yield demonstrates that the strain is less severe in the 5–6–5 ring transition state of the carbon–carbon bond-forming electrocyclic reaction.

Reaction of Carbonyl Compounds with *N*′-Methylphenylhydrazines. Initially it was found that hydrazobenzene reacted with cyclohexanone under appropriate conditions to give 1,2,3,4-tetrahydrocarbazole. The course of this reaction is highly dependent on the experimental conditions, since it is necessary to prevent benzidine rearrangement of the hydrazobenzene, which is the only process observed with strong acids in polar media. The best yields were obtained by prolonged refluxing in toluene with continuous water removal in the presence of a sulfonated cation exchange resin in the acid form. It was felt that the diprotonation which seems to be necessary for the benzidine rearrangement[14] would be less likely under these conditions. Reexamination of the literature showed that a similar transformation had been reported previously,[15] although under more vigorous conditions and in a different research area.

Since the best yield employing hydrazobenzene was only 33%, *N*′-methylphenylhydrazines were used in the subsequent experiments. Five ketones and one aldehyde were treated with 2-methyl-1-phenylhydrazineand furnished indoles in yields of 25–85% (Table I). Because of the experience with hydrazobenzene, the resin catalyst in refluxing toluene was used in most of these runs. Under these conditions methylamine was slowly evolved, as well as water, and was used to monitor the progress of the reactions (odor or pH paper). When hydrazobenzene was employed, the aniline expected as a by-product reacted with cyclohexanone to form *N*-cyclohexylideneaniline; therefore an excess of the ketone was required. This would seem to be unnecessary with the methylphenylhydrazines. It is probably also not necessary to use equivalent amounts of resin, though this was not investigated.

Acetophenone failed to react when the resin was used; substituting *p*-toluenesulfonic acid as the catalyst gave the indole in 63% yield. Propiophenone reacted quite slowly in the presence of the resin; this reaction was not carried to completion and the 25% yield is only a minimum value.

Three ketones were refluxed with 1,2-dimethyl-1-phenylhydrazine and the resin catalyst in toluene. Methylamine was evolved very slowly and the yields of indoles were poor, only 29% from cyclohexanone, although the reactions may not have been completed. This is in distinct contrast with the results of the standard Fischer method employing phenylhydrazones; alkylation of the anilino nitrogen great-

ly facilitates such reactions. Since the presumed iminium intermediate in the reaction of 4-cyclohexylcyclohexanone with 1,2-dimethyl-1-phenylhydrazine would be exactly the same, **2b**, as encountered in the methyl iodide promoted process described in the first section of this discussion, and which afforded a 96% yield of indole, the 6% yield under the more vigorous conditions currently being discussed indicates that the deleterious effect of the 1-methyl substituent operates in the steps leading to **2b**, probably during the nucleophilic attack by the 2-nitrogen atom upon the carbonyl group.

To assess the role of the anilino nitrogen atom in the electrocyclic process, **4** → **6**, an analogous carbon compound was subjected to the reaction conditions of this section. A solution of *N*-methylbenzylamine and cyclohexanone in toluene was refluxed with some *p*-toluenesulfonic acid. Water separation was complete in 6 hr, but no methylamine was evolved. Vacuum distillation gave a single product in good yield; the nmr spectrum indicated that it was the enamine, *N*-methyl-*N*-benzylcyclohexenylamine. Although the greater strength of the C–N bond may be partly responsible, this failure to cyclize suggests that with the enehydrazines, the nonbonding electrons of the 1-nitrogen atom play a part in the electrocyclic reaction. However, *N*-allyl vinylammonium ions have been reported to rearrange by a cyclic mechanism.[16]

Reaction of Ketones with Methylhydrazine and with 1,2-Dimethylhydrazine. Pyrroles were formed rapidly and conveniently when 2 equiv of the ketone was refluxed for a few minutes with 1 equiv of methylhydrazine in glacial acetic acid, followed by addition of an amine salt catalyst. Isolation of the ketone methylhydrazone was unnecessary.[17] In this type of reaction, as in the reaction of ketazines with methyl iodide, either methylamine or ammonia may be eliminated in the latter stages of the process. In numerous preliminary runs with cyclohexanone, besides *N*-methyl-1,2,3,4,5,6,7,8-octahydrocarbazole, a considerable amount of another, very easily oxidizable, material was obtained. This is probably the unmethylated compound, which is reported[7a,10] to be unstable and difficult to purify. The use of methylammonium chloride as the catalyst was found to suppress formation of by-product, and this technique was employed with the other ketones. Even under these conditions, diethyl ketone and cyclopentanone gave complex mixtures. Treatment of cyclohexanone with 1,2-dimethyl hydrazine[6] gave *N*-methyloctahydrocarbazole as a pure white product without unstable impurities. However, this reaction was slower than that with methylhydrazine under comparable conditions, and 1,2-dimethylhydrazine is quite expensive.

Experimental Section

Melting points were determined on a Fisher-Johns block calibrated to give corrected melting points. Infrared spectra were obtained with a Perkin-Elmer Model 21 spectrometer and are reported in microns. Nmr spectra were obtained with a Varian Model A-60 spectrometer, and are reported in parts per million downfield from tetramethylsilane internal standard. Mass spectra were determined on a Bendix Model 12-107 time-of-flight instrument. Analyses were performed by Micro-Tech Laboratories, Skokie, Ill., and by Mrs. G. Libovitz, Cornell University.

4-Cyclohexylcyclohexanone α-Methylphenylhydrazone (1b). 4-Cyclohexylcyclohexanone was prepared by CrO_3–acetic acid oxidation of technical 4-cyclohexylcyclohexanol (cis–trans mixture, Dow Chemical Co.) and was purified through the bisulfite adduct. The hydrazone was prepared by refluxing the ketone with α-methylphenylhydrazine in methanol, without acid catalyst, and was recrystallized from methanol: yield 73%; mp 88–89°; ir (Nujol mull) 6.09, 6.24, 6.67, 7.76, 9.17, 13.32, 14.43 μ.

Anal. Calcd for $C_{19}H_{28}N_2$: C, 80.21; H, 9.86; N, 9.86. Found: C, 80.38, H, 9.55; N, 9.99.

Addition of a small amount of hydrochloric acid to a warm methanolic solution of **1b** resulted in rapid crystallization of a nearly quantitative yield of **9-methyl-3-cyclohexyl-1,2,3,4-tetrahydrocarbazole (7b):** mp 90°; ir (Nujol mull) 6.16, 7.03, 7.60, 8.19, 8.45, 8.70, 9.86, 11.22, 13.57 μ.

Anal. Calcd for $C_{19}H_{25}N$: C, 85.32; H, 9.43; N, 5.24. Found: C, 85.26; H, 9.40; N, 5.42.

In an attempt to prepare an *N*-benzylphenylhydrazone, 4-cyclohexylcyclohexanone (9.5 g, 0.05 mol) was refluxed for 6 hr with a solution of α-benzylphenylhydrazine hydrochloride (11 g, 0.05 mol) and 10 ml of pyridine in 100 ml of methanol. The oily product was triturated with ether–petroleum ether and crystallized from isopropyl alcohol, yield 9.6 g (56%), mp 115–115.5°. The analysis indicates that cyclization to the indole, **9-benzyl-3-cyclohexyl-1,2,3,4-tetrahydrocarbazole,** had occurred.

Anal. Calcd for $C_{25}H_{29}N$: C, 87.40; H, 8.52; N, 4.08. Found: C, 87.40; H, 8.59; N, 4.32.

Reactions of 1b with Methyl Iodide. A solution of 10 g (0.035 mol) of **1b** in 25 g of methyl iodide was allowed to stand overnight at room temperature. The precipitated solid was filtered, extracted twice with hot chloroform and then with ether, and dried. It was identified as methylammonium iodide, yield 5.0 g (90%), by ir comparison with an authentic sample and by reaction with NaOH solution and phenyl isothiocyanate to produce *N*-methyl-*N'*-phenylthiourea, mp 113° (no depression with an authentic sample). The purity was confirmed by analysis.

Anal. Calcd for CH_6NI: C, 7.55; H, 3.80; I, 79.81. Found: C, 7.44; H, 3.90; I, 80.01 (gravimetric).

The filtrate from the above reaction was evaporated and the residue was crystallized from methanol, yield 7.0 g (75%) of **7b**, mp 90°, no depression with the sample prepared above, ir identical.

In a similar reaction with commercial DMF as diluent, a comparable yield of **7b** was obtained. When the experiment was repeated with DMF dried over calcium hydride, a 96% yield of **7b** was realized.

Reactions in the Presence of Bases. A solution of 1 g of **1b** in 5 ml of methyl iodide and 2 ml of *N,N*,2,6-tetramethylaniline[5] was allowed to stand at room temperature for 4 days. By this time 0.127 g (23%) of methylammonium iodide, identified by ir and iodide determination, had precipitated. Work-up of the filtrate was more difficult than before, because of the necessity of avoiding acidic conditions, but 0.26 g (28%) of **7b** was isolated. A similar reaction in the presence of 2,6-diisopropylpyridine[5] as base gave 64% of **7b** and 26% of methylammonium iodide.

Hydrazone **1b** (1 g, 3.5 mmol) was stirred for 2 days with a suspension of anhydrous potassium carbonate (0.5 g, 3.5 mmol) in 5 ml of 2-butanone and 1 ml (17 mmol) of methyl iodide, yielding 0.55 g (58%) of **7b.** When the reaction time was cut to 12 hr, ir indicated a large amount of unreacted hydrazone.

When **1b** was treated with excess methyl iodide and potassium carbonate in dry DMF, no indole was formed if stirring was efficient enough. The ir of the product after molecular distillation at 0.01 mm (200–230°) showed over 90% conversion of the hydrazone into incompletely identified compounds (see discussion).

4-*tert*-Butylcyclohexanone α-Methylphenylhydrazone (1c). The ketone and the hydrazine were refluxed in methanol for 10 min. Slow addition of water gave a 75% yield of crude product, mp 63°, which was recrystallized from methanol–water, mp 63.5–64°.

Anal. Calcd for $C_{17}H_{26}N_2$: C, 79.07; H, 10.08; N, 10.85. Found: C, 79.05; H, 10.27; N, 10.82.

9-Methyl-3-*tert*-butyl-1,2,3,4-tetrahydrocarbazole (7c). An authentic sample was prepared by briefly refluxing a methanol solution of **1c** containing a small amount of hydrochloric acid: mp 65.5–66° (lit.[18] mp 66.5–67.5°); ir (melt) 6.3 (w), 6.92, 7.45, 8.53, 9.98, 13.8 μ (s).

A solution of 0.85 g of **1c** in 1 ml of methyl iodide was allowed to stand overnight. Water was added, the product was taken up in ether, and after drying the solvent was evaporated, giving 0.80 g (quantitative) of **7c,** mp after crystallization from ethanol 66.5–67.5°.

1,2-Dimethyl-1-phenyl-2-(4-*tert*-butylcyclohexenyl)hydrazine (3c). A suspension of 5 g (35 mmol) of powdered anhydrous K_2CO_3 in 15 ml of dry DMF was stirred for several minutes to scavenge traces of acid; then 2.58 g (10 mmol) of **1c** and 0.75 ml (12 mmol) of methyl iodide were added. Rapid stirring under nitrogen was continued overnight at room temperature. Pentane (50 ml) was added and the mixture was stirred vigorously for 15 min. After settling, the pentane layer was decanted and the extraction was repeated twice. The combined pentane extracts were stirred with

solid NaI for 15 min, then transferred to a fresh portion of NaI and stirred again. This treatment removed practically all of the dissolved DMF. The solvent was stripped and the residue (2.6 g, 95%) slowly crystallized when stored at −50° under nitrogen, mp 40–43°. An analytical sample was prepared by recrystallization from pentane at −50° under nitrogen: mp 44.5–45.5°; ir (melt) 6.11 (m), 6.31 (s), 6.74 (s), 6.89, 9.07, 13.45 (s), 14.52 μ (s); nmr ($CDCl_3$) δ 6.8–7.4 (5 H), 4.8 (br, 1 H, vinyl), 2.81 (s, 3 H) and 2.72 (s, 3 H)(NCH_3's), 2.1 (br, 4 H), 1.25 (br, 2 H), 0.88 (s, 9 H). The methine ring proton signal is buried under the ring methylenes and cannot be located.

Anal. Calcd for $C_{18}H_{28}N_2$: C, 79.41; H, 10.30; N, 10.30. Found: C, 79.26; H, 10.50; N, 10.21.

When only an equivalent amount of methyl iodide was used in the above preparation, the nmr indicated that the crude product contained about 20% of unreacted hydrazone.

Using a similar procedure, 1.6 g (6.5 mmol) of **1c** and 3 ml (6.7 g, 48 mmol) of methyl iodide gave 1.5 g (77%) of a solid, mp 57–60°. In subsequent runs the yield of crude product was quantitative. Upon crystallization from pentane at −50°, various fractions of differing melting points were obtained, 65–70, 65–73, and 70–74° The combustion analyses of these fractions (below) were nearly the same, and the mass spectra all showed a strong parent peak at *m/e* 286, corresponding to a monomethyl derivative of **3c**. The nmr spectra indicated that all fractions are probably mixtures of the double-bond isomers **8a** and **8b**. The lowest melting fraction had a higher integrated value (80% of theory) of the vinyl hydrogen signal at δ 4.6–4.9 and of the saturated-CH_3 doublet at δ 1.05. It evidently consists largely of **1,2-dimethyl-1-phenyl-2-(6-methyl-4-*tert*-butylcyclohexenyl)hydrazine (8a).** In the nmr spectra of the higher melting fractions, these signals were weaker, and the vinyl methyl singlet at δ 2.50 was stronger. These fractions apparently are richer in **1,2-dimethyl-1-phenyl-2-(2-methyl-4-*tert*-butylcyclohexenyl)hydrazine (8b).**

Anal. Calcd for $C_{19}H_{30}N_2$: C, 79.79; H, 10.45; N, 9.79; mol wt, 286. Found: C, 79.66; H, 10.60; N, 9.65; mol wt, 286.

Cyclization of the Enehydrazine 3c. A solution of 1.2 g (10 mmol) of *tert*-butylammonium chloride in 15 ml of glacial acetic acid was cooled to 20° and 2.7 g (10 mmol) of **3c** was added. Within a few minutes the solution warmed spontaneously to 30–35°. After 15 min a little ethanol was added to assist crystallization, and then water was added slowly. The product was filtered and dried, yield 2.3 g (95%), mp 63–64°. After recrystallization from ethanol, the melting point was 66–66.5°, not depressed by authentic **7c,** ir and nmr identical.

Reaction of Ketazines with Methyl Iodide. A. A solution of 168 g (1 mol) of diethylketazine in 284 g (2 mol) of methyl iodide was allowed to stand at room temperature for 5 days (or alternatively, refluxed for several hours) under nitrogen. Crystallization of the oil which separated was induced by trituration with dry ether, and the product was dried under vacuum, yield 279 g (98%), mp 57–60°. The salt was too hygroscopic for satisfactory analysis, but the spectral data indicate that it is ***N*-methyldiethylketazinium iodide (10a):** ir (KBr) 5.68 μ; nmr ($CDCl_3$) δ 4.00 (s, 3 H, NCH_3), 3.13 (q, 2 H), 2.62 (m, 6 H), 1.60–0.90 (m, 12 H).

A solution of 55 g of **10a** in 100 ml of 1-propanol was refluxed under nitrogen for 4 hr. The solvent was stripped, and ether was added to the residue. The crystalline material was collected, washed with ether, and dried. Ir comparison with authentic samples indicated that the solid was a mixture of methylammonium iodide and ammonium iodide, the estimated yields being 30 and 18%, respectively. The ethereal filtrate was distilled, and the higher boiling fractions were separated by preparative glc (Carbowax 20M, 5 ft). In addition to a 6% recovery of diethylketazine, the major products were **3,4-dimethyl-2,5-diethylpyrrole,** yield 37%, bp 210–215° (lit.[3] bp 215°)(750 mm), ir 2.9 μ (NH), nmr (CCl_4) δ 7.02 (br, 1 H, exchanged by D_2O, NH), 2.42 (q, 4 H), 1.83 (s, 6 H), 1.10 (t, 6 H), and **1,3,4-trimethyl-2,5-diethylpyrrole,** yield 18%, ir no HN, nmr (CCl_4) δ 3.32 (s, 3 H, NCH_3), 2.48 (q, 4 H), 1.83 (s, 6 H), 1.03 (t, 6 H).

B. When cyclopentylketazine (164 g, 1 mol) was added to methyl iodide (284 g, 2 mol), a mildly exothermic reaction occurred. After standing for 2 hr, the crystalline mass was extracted with tetrahydrofuran (THF) and dried, yield 295 g (89%), mp 101–103°. A portion was recrystallized from $CHCl_3$–THF (1:10), ***N*-methylcyclopentylketazinium iodide (10b):** mp 107–108°; ir (KBr) 5.68, 5.88 μ; nmr ($CDCl_3$) δ 3.98 (s, 3 H, NCH_3), 3.40 (m, br, 2 H), 2.83 (m, br, 6 H), 2.10 (m, br, 8 H).

Anal. Calcd for $C_{11}H_{19}N_2I$: C, 43.14; H, 6.24; N, 9.14. Found: C, 42.80; H, 6.28; N, 9.08.

Mild hydrolysis of **10b** gave cyclopentanone and methylhydrazinium iodide in a ratio of 2:1.

When a solution of 27.8 g (0.09 mol) of **10b** in 100 ml of 1-butanol was warmed to 75°, an exothermic reaction began. The temperature was then held at 120° for 5 hr. After concentration under vacuum and dilution with chloroform, 3.1 g (21%) of methylammonium iodide separated, identified by ir comparison. The filtrate was distilled, and the fraction boiling at 78–116° (0.4 mm) was further separated by preparative glc (Carbowax 20M, 10 ft). The major component of the complex mixture was collected, yield 2.08 g (16%), mp 84–87°. Because of ease of oxidation, a characteristic of pyrroles with an N–H bond, a completely satisfactory analysis was not obtained, but the nitrogen content excludes a pyrazoline structure. The spectral data indicate that the structure is **bis(cyclopenteno)[*b,d*]pyrrole 14b:** ir 2.9 (w, NH), 6.19, 7.06 μ; nmr ($CDCl_3$) δ 7.31 (s, 1 H, exchanged by D_2O, NH), 3 (m, 8 H) shown by spin decoupling to be two triplets at 2.97 (4 H) and 2.85 (4 H), 2.09 (pentet, 4 H).

Anal. Calcd for $C_{10}H_{13}N$: C, 81.58; H, 8.85; N, 9.51. Found: C, 82.84; H, 8.18; N, 8.83.

C. A solution of 192 g (1 mol) of cyclohexylketazine in 284 g (2 mol) of methyl iodide was allowed to stand at room temperature under nitrogen for 1 day. The crystalline product was filtered, washed with ether and THF, and dried under vacuum, yield 330 g (98%) of ***N*-methylcyclohexylketazinium iodide (10c):** mp 124–126°; ir (KBr) 5.68 μ (cyclohexylketazine 6.18 μ); nmr ($CDCl_3$) δ 3.96 (s, 3 H, NCH_3), 3.30 (m, 2 H), 2.63 (6 H), 1.86 (s, 12 H).

Anal. Calcd for $C_{13}H_{23}N_2I$: C, 46.71; H, 6.93; N, 8.38. Found: C, 46.65; H, 6.95; N, 8.37.

Mild hydrolysis of **10c** produced cyclohexanone and methylhydrazinium iodide in a 2:1 ratio, both identified by ir and nmr comparison with authentic samples. A possible alternative formulation for **10c,** the pyrazoline hydriodide, is reported not to hydrolyze readily.[19]

A suspension of **10c** (8.8 g, 25 mmol) in 30 ml of 1,2-dimethoxyethane was refluxed under nitrogen. After about 10 min, a mildly exothermic reaction ensued and the solid dissolved completely. Refluxing was continued for 2 hr, when the mixture was diluted with some water and cooled. The product soon solidified and was recrystallized from ethanol–water, yield 3.6 g (73%) of **9-methyl-1,2,3,4,5,6,7,8-octahydrocarbazole (14c):** mp 93–95° (lit.[7a] mp 94°); nmr (CCl_4) δ 3.25 (s, 3 H, NCH_3), 2.7–2.1 (m, 8 H), 1.8–1.5 (m, 8 H). The aqueous solution remaining after removal of **14c** was evaporated and the residue was crystallized from chloroform–ethanol (5:1), giving 3.1 g (82%) of white crystals identified by ir comparison as ammonium iodide. Heating **10c** dry or in other solvents on the steam bath also gave **14c,** but in lower yield and purity.

In the nmr spectra of the ketazinium salts, one of the methylene signals is shifted downfield by about 0.6 ppm. Comparison with spectra in the literature suggests that these signals are probably due to the methylene groups on the neutral carbon–nitrogen double bond anti to the positively charged nitrogen atom. In the nmr spectrum of diethylketazine, the methylene region consists of two equal overlapping quartets separated by 0.07 ppm, and the methyl region of two equal overlapping triplets separated by 0.15 ppm, each measured from the respective centers. This must be due to the relative syn and anti positions of the four ethyl groups. With the cyclic ketazines, the α-methylene regions are broadened, but not resolved.

Reaction of Ketazines with Acetic Anhydride. A. A solution of 4.8 g (25 mmol) of cyclohexylketazine and 0.5 g of *p*-toluenesulfonic acid in 25 ml of acetic anhydride was refluxed for 1 hr. The solution was concentrated under vacuum and the residue was crystallized from methanol–water, yield 3.7 g (64%) of ***N*-acetyl-1,2,3,4,5,6,7,8-octahydrocarbazole:** mp 72–74° (lit.[7a] mp 73°); ir 5.9 μ; nmr ($CDCl_3$) δ 2.80 (m, 4 H), 2.44 (s, 3 H, acetyl), 2.34 (m, 4 H), 1.74 (m, 8 H).

B. A solution of 8.4 g (50 mmol) of diethylketazine and 0.2 g of *p*-toluenesulfonic acid in 50 ml of acetic anhydride was refluxed for 3 hr, then fractionally distilled, yield 7.8 g (68%) of ***N*-acetyl-3,4-dimethyl-2,5-diethylpyrrole:** bp 76–78° (0.03 mm) or 242° (750 mm) [lit.[3] bp 180° (88 mm)]; $n^{20}D$ 1.5079; ir 5.9 μ; nmr ($CDCl_3$) δ 2.70 (q, 4 H), 2.44 (s, 3 H, acetyl), 1.83 (s, 6 H), 1.07 (t, 6 H).

C. 2,2′-Bis(acetamido)-1,1′-bicyclopentenyl (15). A solution of 66 g (0.4 mol) of cyclopentylketazine in 200 ml of acetic anhydride was heated at 85° for 4 hr, then 200 ml of methanol was added cautiously to the warm solution. Three crops of crystals were taken by alternately cooling and concentrating the solution, and the combined products were recrystallized from methanol,

yield 37 g (37%) of **15:** mp 187–189°; ir (KBr) 3.0, 6.0 μ; nmr (deuteriopyridine at 80°) δ 8.66 (br, 2 H, NH), 2.99 (m, 4 H), 2.22 (m, 4 H), 2.08 (s, 6 H, acetyl), 1.75 (m, 4 H).

Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.75; H, 8.12; N, 11.28. Found: C, 68.20; H, 8.14; N, 11.20.

2,2'-Diketo-1,1'-bicyclopentyl (16a, 16b). Fifteen grams (60 mmol) of **15** was warmed on the steam bath with 150 ml of 50% sulfuric acid for 3 hr. The oily product was taken up in ether, dried, and distilled, yield 9.5 g (95%), bp 88–89° (0.2 mm). The semisolid product was apparently a mixture of diastereoisomers (meso and racemic) and was separated by repeated fractional crystallization from heptane. At a preliminary stage this afforded 2.5 g of material of mp 65–69° and 2 g of mp 33–37°. Further crystallization gave 1.8 g of **16a,** mp 70–71° (lit.[12] mp 67–69°), and 1.5 g of **16b,** mp 37–40°. The nmr spectra are complex multiplets and are useless for distinguishing the isomers, although consistent with the assigned structures. The ir spectra show some variations in the weaker bands: ir (melt) of **16a,** 5.80 (s), 8.58, 8.71, 8.97, 10.62, 11.07, 12.00, 12.24 μ; ir (melt) of **16b,** 5.80 (s), 8.72 μ. The simpler spectrum of **16b** suggests that it is the meso isomer, which would be centrosymmetric in the anti conformation. The mass spectra of the two isomers are nearly identical, and only that of **16a** is given: mass spectrum (70 eV) *m/e* (rel intensity) 166 (15), 148 (7), 138 (15), 111 (30), 98 (30), 84 (100), 83 (90), 68 (40), 67 (40), 55 (60), 44 (30), 41 (30), 40 (30), 39 (30).

The dinitrophenylhydrazones and semicarbazones melt with extensive decomposition and cannot be trusted for distinguishing **16a** and **16b.** The dioximes, prepared in pyridine–methanol and recrystallized from ethanol–water, are more satisfactory: **16a** dioxime, mp 182–186° with slight decomposition; **16b** dioxime, mp 200–201.5°.

Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.18; H, 8.16; N, 14.27. Found for **16a:** C, 61.14; H, 7.97; N, 14.27. Found for **16b:** C, 61.25; H, 8.16; N, 14.27.

Reaction of Cyclohexanone with Hydrazobenzene. A mixture of 5.75 g (30 mmol) of hydrazobenzene, 6 g (60 mmol) of cyclohexanone, and 20 ml (wet volume) of Amberlite IR-20 resin (30 mequiv) in 90 ml of toluene was refluxed with mechanical stirring to minimize bumping. Water was separated continuously by a Barrett trap. After water evolution ceased (20 hr), the resin was removed by filtration and the solvent was stripped. Repeated crystallization of the residue from ethanol gave 1.75 g (33%) of **1,2,3,4-tetrahydrocarbazole,** mp 117–118° (lit.[20] mp 117–118°), not depressed by an authentic sample.

Vacuum distillation of the mother liquors gave a fraction, bp 80–85° (0.4 mm), whose ir and nmr spectra matched those of an authentic sample of *N*-cyclohexylideneaniline prepared by refluxing cyclohexanone with aniline in the presence of the resin as in the foregoing preparation, bp 83–85° (0.4 mm) [lit.[21] bp 138–142° (19 mm)].

2-Methyl-1-phenylhydrazine was prepared by a variation of a reported method,[22] but employing sodium hydride in the methylation of formyl phenylhydrazine rather than metallic sodium. It was found advisable to recrystallize the 2-formyl-2-methyl-1-phenylhydrazine three times from ethanol, mp 78–79° (lit.[22] mp 79–80°), before hydrolyzing with base to avoid contamination of the product with 1,2-dimethylphenylhydrazine, whose presence in earlier samples was indicated by a small nmr peak at δ 2.8. **1,2-Dimethyl-1-phenylhydrazine** was prepared similarly, using sodium hydride in toluene for the methylation of 2-formyl-1-methyl-1-phenylhydrazine. In this case basic hydrolysis was unsatisfactory, and Harries' method of acidic alcoholysis[23] was employed.

The syntheses of indoles summarized in Table I were carried out by refluxing the carbonyl compounds with 1 equiv of the appropriate hydrazine and the acid catalyst in toluene with water removal by a trap. In some runs evolved methylamine was trapped in a methanol solution of phenyl isothiocyanate. Chromatography of the crude crystalline product on alumina, eluting with hexane–ethyl acetate, gave two fractions: A, mp 113°, not depressed by authentic *N*-methyl-*N'*-phenylthiourea,and B, mp 91°, whose nmr spectrum suggested that it was methyl *N*-phenylthiocarbamate (lit. mp 93°), derived from the methanol.

Pyrroles from Methylhydrazines.9-Methyl-1,2,3,4,5,6,7,8-octahydrocarbazole. A. A solution of 2.2 g (0.05 mol) of methylhydrazine and 10 g (0.1 mol) of cyclohexanone in 15 ml of glacial acetic acid was warmed on a steam bath for 5 min; hydrazone formation was indicated by the development of a golden yellow color. Upon addition of 1.5 g of methylammonium chloride to the warm solution, the solution immediately became cloudy, and soon an oily layer of product rose to the surface. After an additional 30 min of heating, the mixture was cooled, whereupon the oil solidified. The product was removed, washed with water, and crystallized from methanol, yield 7.5 g (80%), mp 93–94°, not depressed by the sample prepared above.

B. A mixture of 1.3 g (10 mmol) of 1,2-dimethylhydrazine dihydrochloride, 2 g (20 mmol) of cyclohexanone, and 2 g of methylammonium acetate in 10 ml of toluene was refluxed for 1 day with continuous water removal. After a preliminary wash with water, the product was extracted into 10% HCl, liberated by base, and crystallized from ethanol, yield 1.1 g (57%), mp 93°, not depressed by the previous sample.

1-Methyl-2,5-diphenyl-3,4-dibenzylpyrrole was made from dibenzyl ketone by procedure A (above): yield 24%; mp 161.5–162.5°; nmr (CCl_4) δ 7.1 (m, 20 H), 4.05 (s, 4 H), 3.05 (s, 3 H). A solution of this compound in dry chloroform oxidizes rapidly and turns dark blue when exposed to air, especially in the nmr probe.

Anal. Calcd for $C_{31}H_{27}N$: C, 90.00; H, 6.54; N, 3.55. Found: C, 90.03; H, 6.65; N, 3.35.

1,3,4-Trimethyl-2,5-diphenylpyrrole was made similarly in only 10% yield from phenylacetone, accompanied by large amounts of oily by-products: mp 142.5–143°; nmr (CCl_4) δ 7.1 (10 H), 3.50 (s, 3 H), 2.23 (s, 6 H).

Anal. Calcd for $C_{19}H_{19}N$: C, 87.45; H, 7.28; N, 5.36. Found: C, 87.51; H, 7.42; N, 5.47.

Registry No.—1b, 6623-14-9; **1c,** 51801-54-8; **3c,** 51801-55-9; **7c,** 22410-72-5; **8a,** 51801-56-0; **8b,** 51801-57-1; **9a,** 1530-17-2; **9b,** 20615-04-7; **9c,** 4278-87-9; **10a,** 51838-68-7; **10b,** 51801-58-2; **10c,** 51801-59-3; **14a** (H), 27301-66-2; **14a** (Me), 51801-60-6; **14b** (H), 51801-61-7; **14c** (Me), 23518-22-1; **15,** 51801-62-8; **16a,** 51820-21-4; **16a** dioxime, 51801-63-9; **16b,** 51820-22-5; **16b** dioxime, 51820-23-6; α-benzylphenyhydrazine hydrochloride, 51801-64-0; 9-benzyl-3-cyclohexyl-1,2,3,4-tetrahydrocarbazole, 51801-65-1; methylammonium iodide, 14965-49-2; *N*-acetyl-1,2,3,4,5,6,7,8-octahydrocarbazole, 51801-66-2; *N*-acetyl-3,4-dimethyl-2,5-diethylpyrrole, 51801-67-3; 1-methyl-2,5-diphenyl-3,4-dibenzylpyrrole, 51801-68-4; dibenzyl ketone, 102-04-5; 1,3,4-trimethyl-2,5-diphenylpyrrole, 24956-46-5; phenylacetone, 103-79-7;4-*tert*-butylcyclohexanone, 98-53-3.

References and Notes

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