systems investigated. Rearrangement to isopropyl ions was found to be favored under all conditions, but its rate further increases with increasing internal energy content of the ion,[23] a particularly significant feature in view of the highly exothermic character of process 3a.

As a whole, it can be concluded that the experimental results of this work and the available evidence from mass spectrometric and radiolytic studies exclude the role of $n$-$C_3H_7^+$ as a gas-phase $n$-propylating reagent in the systems investigated in favor of the longer-lived protonated cyclopropane.

**Isomerization of Gaseous Arenium Ions and Substrate Selectivity.** The isomeric composition of alkylated products from toluene is characterized by a large proportion of the meta isomer from the $H_2$/c-$C_3H_6$/$C_7H_8$ and the $H_2$/$C_3H_6$/$C_7H_8$ systems at 720 torr, the extent of meta substitution further increasing at lower pressures to a maximum value of 85% measured at 50 torr.

The positional selectivity measured in this work is undoubtedly affected by extensive isomerization of the primary arenium ions into the thermodynamically most stable meta isomer (IV), according to the process outlined in eq 7. The isomerization is much more pronounced than in gaseous hydrocarbons at comparable pressures. As a comparison, the isomeric composition of cymenes from the irradiation of $C_3H_8$ (720 torr), $C_7H_8$ (0.87 torr), and $O_2$ (10 torr) is 53% ortho, 27% meta, and 20% para, in good agreement with previously reported data.[6,7] The difference can be traced to the reaction environment, as collisional deactivation by $H_2$, the bulk constituent of the system, is undoubtedly less efficient than that by $C_3H_8$ at the same pressure. In addition, the average excitation level of the $C_3H_7^+$ ions when they undergo a reactive collision with $C_7H_8$ is conceivably higher in the present study, owing to the strongly exothermic character of reactions 3 and again to the comparatively less efficient collisional deactivation in $H_2$ gas.

The view that the observed composition of products is heavily affected by secondary isomerization is supported by the *lower* proportion of the meta isomer found in $n$-propyltoluenes with respect to cymenes under the same experimental conditions. This of course reflects the incipient ionic character of the migrating alkyl group in the transition state of the isomerization process, irrespective of its intramolecular or intermolecular nature, and the higher stability of free $i$-$C_3H_7^+$ with respect to $n$-$C_3H_7^+$.

Finally, no particular kinetic significance should be attached to the measured $k_T$:$k_B$ ratio *lower* than unity. The ratio refers, in fact, exclusively to the alkylation channel rather than to the overall nucleophilic reactivity of the substrates. The lower alkylation rate of $C_7H_8$ can be traced to the competition of other processes, e.g., reactions 10 and 11, that affect exclusively, or predominantly, toluene with respect to benzene.

## Conclusions

The propyl ions formed from the protonation of cyclopropane and propene, respectively, with $H_3^+$ display a significantly different reactivity toward arenes in that $n$-propylation is a major channel for the reagent from cyclopropane and a barely detectable one for that from propylene.

Evaluation of the main reaction features denies the role of $n$-$C_3H_7^+$ as the $n$-alkylating reagent and points to the intervention of protonated cyclopropane, whose lifetime must then exceed $10^{-7}$ s. These results are consistent with evidence previously derived from widely different sources. Existence of c-$C_3H_7^+$ had been inferred from experiments involving the decay of $^3H_2$, but the lower limit of the protonated cyclopropane lifetime must be set at only $10^{-10}$ s, owing to the composition and the pressure of the systems investigated.[21] Mass spectrometric measurements indicate that isomerization of c-$C_3H_7^+$ to $i$-$C_3H_7^+$ requires $10^{-5}$ to $10^{-7}$ s, an estimate[16] supported by the present results. Observation of gaseous $C_3H_7^+$ ions that react as protonated cyclopropane in hydride ion abstraction from alkanes has been reported in connection with radiolysis of $n$-$C_4H_{10}$/$n$-$C_4D_{10}$ mixtures in the pressure range from 20 to 200 torr.[24] The minute but well-measurable yields of $n$-propylated arenes from the $H_2$/propene systems parallel the formation of traces of cyclopropane from the deprotonation of $C_3H_7^+$ ions from the radiolysis of propane,[25] indicating a (very limited) cyclization of originally linear cations.

Finally, the present results represent a direct extension to the dilute gas state of those typical Friedel-Crafts reactions that rely on the protonation of alkenes and cycloalkanes for the preparation of the alkylating reagent. It is worth noting in this connection that under conditions designed to reduce isomerization $n$-propylbenzene, formed via a process analogous to reaction 14, is the major product from the alkylation of $C_6H_6$ with cyclopropane in concentrated $H_2SO_4$.[26]

**Acknowledgments.** We are indebted to the National Research Council of Italy for financial support and to Mr. A. Grisanti and G. Grisanti for irradiation of the samples.

(25) Ausloos, P.; Rebbert, R. E.; Lias, S. G. *J. Am. Chem. Soc.* **1968**, *90* 5031.

(26) Stolyarov, B. V.; Isidorov, V. A.; Ioffe, B. V. *Dokl. Akad. Nauk SSSR* **1970**, *191*, 369, and references cited therein.

# "1,4" Alkyl Migrations in Fischer Indole Cyclizations

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*Contribution from the Department of Chemistry, University of Massachusetts, Amherst, Massachusetts 01003.* *Received August 13, 1979*

**Abstract:** The product from Fischer indole cyclization and dehydrogenation of cyclohexanone 2,4,6-trimethylphenylhydrazone (1) was determined to be 2,3,4-trimethylcarbazole (3) resulting from a formal 1,4-methyl migration, as previously proposed. To determine the destinations of migrating groups in these rearrangements, the Fischer indole cyclization and dehydrogenation of cyclohexanone 2-ethyl-6-methylphenylhydrazone (17) were studied. The products obtained were 1-ethylcarbazole, 1-methylcarbazole, 2-ethyl-1-methylcarbazole (18), and an apparent mixture of 1-ethyl-4-methylcarbazole (21) and 4-ethyl-1-methylcarbazole (22). However, no 1-ethyl-2-methylcarbazole (19), which would have been obtained by a "1,4"-methyl migration, was obtained. Analysis of the product ratios suggested that the apparent [1,4] ethyl shift in formation of 18 actually proceeded by a formal [1,5] shift of either an ethyl or a methyl group, followed by a [1,2] ethyl shift. Cyclization of 3-pentanone 2,4,6-trimethylphenylhydrazone (26) proceeded to give the product of "1,4" methyl migration, demonstrating that such reactions can occur with phenylhydrazones of ketones other than cyclohexanone. It is proposed that steric factors play a major role in determining whether migrating groups undergo [1,2] or "1,4" shifts during Fischer indole cyclizations.

Migrating groups in rearrangements of butenyl carbonium ions may in principle undergo either [1,2] or [1,4] migrations (eq 1). The distances between the migration origins and the migration termini for most potential [1,4] migrations, however, would make

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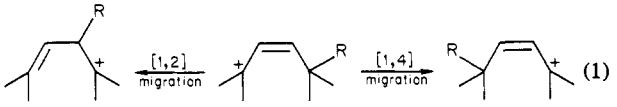
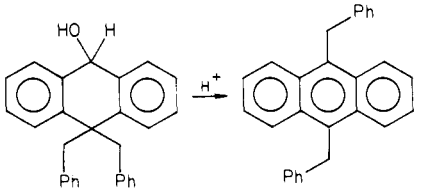


(1)

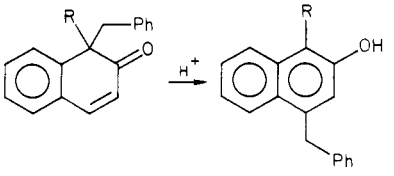
it difficult for the migrating groups to maintain satisfactory bonding to both sites throughout the reaction. This difficulty would usually be compounded by the requirement for inversion of migrating groups in [1,4] rearrangements of carbonium ions.[2] As a result, [1,4] migrations have been commonly observed only in rearrangements of bicyclo[3.1.0]hexenyl carbonium ions,[3] in which migrating groups are held in close proximity to the migration termini and the bond angles approximate those necessary for migration with inversion of the migrating carbons.

Some years ago, Beckwith and his co-workers reported that rearrangements of 10,10-dibenzyl-9-anthranols in acid give, in part, 9,10-dibenzylanthracenes (eq 2).[4a] They proposed that these



(2)

rearrangements proceed by a series of [1,2] migrations,[4a] but more recent evidence indicates that direct [1,4] shifts of the benzyl groups occur.[5] Miller and his co-workers have shown that benzyl groups undergo apparent [1,4] migrations in acid-catalyzed rearrangements of β-naphthalenones (eq 3).[6] These reactions cannot

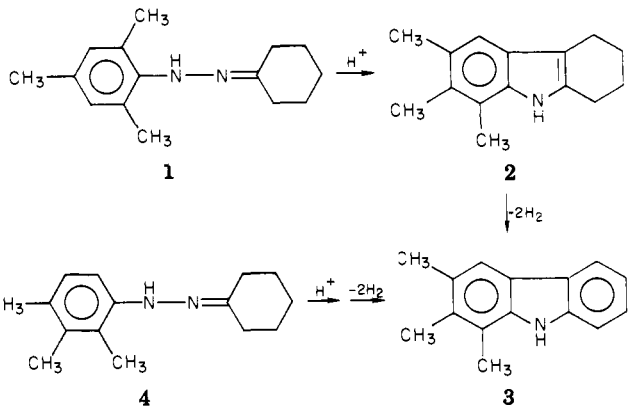


(3)

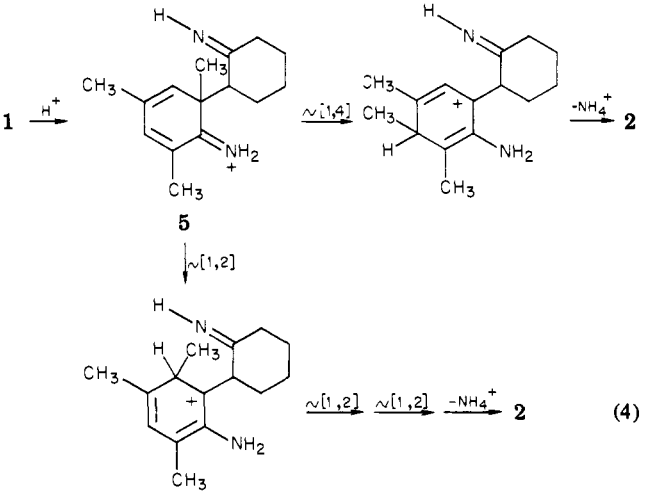
proceed entirely by [1,2] shifts, but the possibility that they proceed by initial [1,2] shifts to the carbonyl carbons followed by [1,3] migrations to C-4 cannot be discounted.

1,4-Migrations of simple alkyl groups (as distinct from benzyl groups or carbons in cyclopropyl rings) have been reported only in Fischer indole cyclizations of 2,6-disubstituted phenylhydrazones of cyclohexanones. This type of reaction was first reported by Carlin and Moores,[7] who found that rearrangement of hydrazone **1** in hot acetic acid gave a tetrahydrocarbazole formulated as **2**. The structure of **2** was established by chloranil dehydrogenation to form carbazole **3**, which was independently synthesized by Fischer indole rearrangement of cyclohexanone 2,3,4-trimethylphenylhydrazone (**4**) followed by dehydrogenation.

Carlin and Moores suggested that formation of **2** proceeds by a direct [1,4] migration of a methyl group in the intermediate carbonium ion **5**. Although they considered the possibility that




**2** might instead be formed by a series of [1,2] methyl shifts, they rejected that mechanism on the grounds that carbonium ion **6** should lose a proton to form an aromatic ring, rather than undergo further methyl migrations. Dewar, however, later suggested that aromatization of **6** might be slowed by steric repulsions between substituents in the transition state leading to the planar aromatic ring, and favored the [1,2] shift mechanism.[8]



(4)

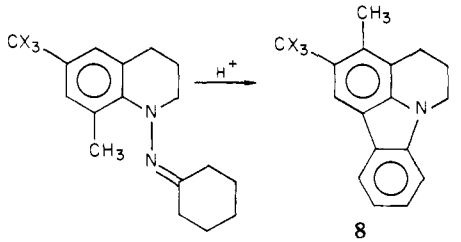
Convincing evidence against [1,2] migrations proceeding through intermediates such as **6** was provided by Fusco and Sannicolô, who found that Fischer indole cyclization of the tetrahydroquinolylhydrazone **7a** gave (after dehydrogenation) the [1,4] rearrangement product **8**.[9] Rearrangement of the deuterated analogue **7b** gave a product lacking one of the two methyl signals of **8** (X = H) in its NMR spectrum. Rearrangement via a series of [1,2] shifts similar to those in eq 4 would have formed intermediate **9**. Further rearrangement of **9** to **8** would form a product with *two* methyl signals, each of 1.5 H intensity. Fusco and Sannicolô thus favored the direct [1,4] methyl migration mechanism for formation of **8**.[9]

In view of the unique aspects of the postulated [1,4] methyl migrations in these rearrangements, we have reinvestigated the rearrangements of hydrazone **1** and its analogues. This paper reports the details of that investigation.

### Structures of Products of Fischer Indole Rearrangements

Carlin and Moores as well as Fusco and Sannicolô attempted to demonstrate the structures of their rearrangement products by independent syntheses employing other, presumably unequivocal, Fischer indole cyclizations. As mentioned above, Carlin and Moores showed that the product of Fischer cyclization and dehydrogenation of **4**, presumably **3**, was identical with the product

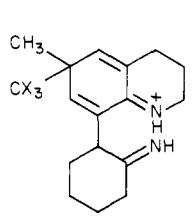
(1) Part of this work was reported in a preliminary communication: Miller, B.; Matjeka, E. R. *Tetrahedron Lett.* **1977**, 131.
(2) Woodward, R. B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Academic Press: New York, 1971.
(3) E.g., Swatton, D. W.; Hart, H. *J. Am. Chem. Soc.* **1967**, *89*, 5075. Hart, H.; Rodgers, T. R.; Griffiths, J. *Ibid.* **1969**, *91*, 754. Childs, R. F.; Winstein, S. *Ibid.* **1968**, *90*, 7146; **1974**, *96*, 6409. See also: Zimmerman, H. E.; Crumrine, D. S. *Ibid.* **1968**, *90*, 5612. Brennan, T. M.; Hill, R. K. *Ibid.* **1968**, *90*, 5614. Zimmerman, H. E.; Crumrine, D. S.; Döpp, D.; Huyffer, D. S. *Ibid.* **1969**, *91*, 434.
(4) (a) Beckwith, A. L. J.; Renfrow, W. B.; Renfrow, A.; Teubner, J. K. *Tetrahedron Lett.* **1968**, 3463. See also: (b) Karger, M. H.; Mazur, Y. *J. Org. Chem.* **1971**, *36*, 540.
(5) Creedon, V. C. Ph.D. Dissertation, University of Massachusetts, Amherst, Mass., 1979.
(6) Miller, B.; Saidi, M. R. *J. Am. Chem. Soc.* **1976**, *98*, 2227. Miller, B.; Lin, W.-O. *J. Org. Chem.* **1979**, *44*, 887.
(7) Carlin, R. B.; Moores, M. S. *J. Am. Chem. Soc.* **1959**, *81*, 1259; **1962**, *84*, 4107.
(8) Dewar, M. J. S. In "Molecular Rearrangements"; de Mayo, P., Ed.; Wiley: New York, 1963; Vol. I, pp 304–308.
(9) Fusco, R.; Sannicolô, F. *Tetrahedron Lett.* **1975**, 3351.



7a, X = H
b, X = D



8



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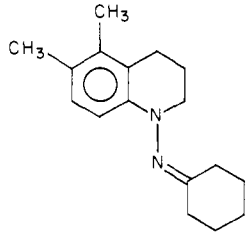
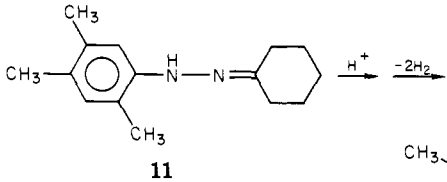


10

obtained by rearrangement of **1**. Furthermore, the Fischer indole cyclization and dehydrogenation product of hydrazone **11**, expected to be **12**, the product which would have been obtained by a simple



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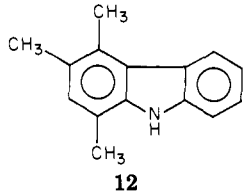
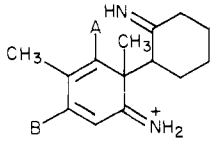


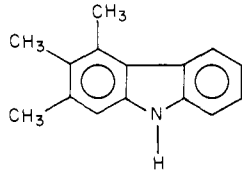
12

[1,2] shift in rearrangement of **1**, was not identical with the product obtained from **1**. Fusco and Sannicolò similarly prepared **8** by Fischer indole cyclization and dehydrogenation of hydrazone **10**, and showed the product to be identical with that obtained from **7a**.

However, unequivocal structural proofs for products of Fischer indole cyclizations are difficult to obtain by means of "independent" syntheses employing other Fischer indole cyclizations. Cyclizations of **4**, **10**, and **11** might each occur at substituted ortho positions of the aromatic rings, as has been observed in other reactions,[10,11] rather than at unsubstituted positions. Rearrangement of intermediate **13a** (formed from **11**) would then yield carbazole **14** rather than the expected **12**. Rearrangement



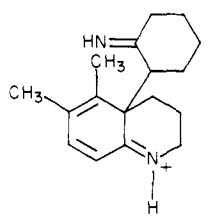
13a, A = H; B = $CH_3$
b, A = $CH_3$; B = H



14

of intermediate **13b** (formed from **4**) would be expected to form **14**, but might instead yield **12**, either by a [1,5] methyl shift or a series of [1,2] shifts. A [1,5] methylene shift, or cleavage of the heterocyclic ring followed by realkylation of the aniline ring in **15** (formed by cyclization at the substituted ortho position of **10**), would yield **16**, the product expected of a simple [1,2] methyl shift in rearrangement of **7a**.

The possibility that Fischer indole cyclizations of **1** and **7a** proceed normally but that the cyclizations carried out as proofs



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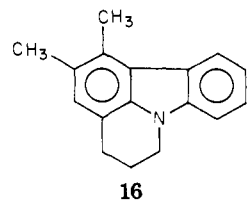
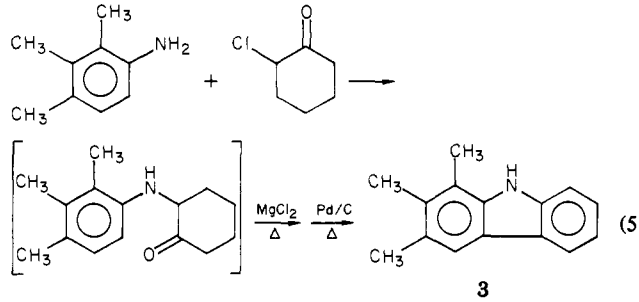


16

of structure proceed abnormally could therefore not be ignored.

To provide independent evidence for the structure of the product obtained by rearrangement and dehydrogenation of **1**, carbazole **3** was synthesized by reaction of 2,3,4-trimethylaniline with 2-chlorocyclohexanone, followed by cyclization and dehydrogenation (eq 5).[12] Carbazole **3** prepared in this manner was identical with the product from Fischer indole cyclization and dehydrogenation of **1**.



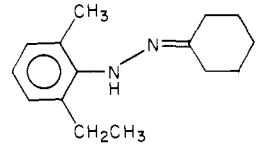
(5)

3

To help eliminate the faint possibility that a methyl migration might have taken place under the mild acid conditions required for cyclization of the intermediate anilino ketone in reaction 5, the NMR spectra of the four monomethylcarbazoles were compared with that of **3**. As can be seen in Table I, a methyl group at C-4 of a carbazole, in the deshielding region of the second aromatic ring, appears ca. 0.4 ppm downfield from signals for methyls at the other three ring positions. The product of rearrangement of carbazole **11**, formulated as **12** by Carlin and Moores,[7] similarly showed one methyl singlet at $\delta$ 2.70, ca. 0.35 ppm downfield from the other methyl signals, in accord with the assigned structure. On the other hand, the spectra of carbazole **3** had all methyl signals around $\delta$ 2.3, showing that it has no methyl group at C-4. The product of Fischer indole rearrangement of **1** must therefore have the structure 1,2,3-trimethylcarbazole, as proposed by Carlin and Moores.

### Destinations of the Migrating Groups

The fact that all the ring substituents in **1** are identical makes it impossible (without isotopic labeling) to determine the original locations of each methyl group in **3**. To determine the destination of a migrating group, we studied the rearrangement of cyclohexanone 2-ethyl-6-methylphenylhydrazone (**17**). To help in

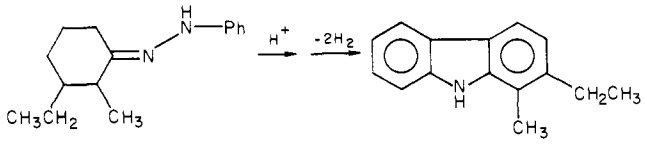


17

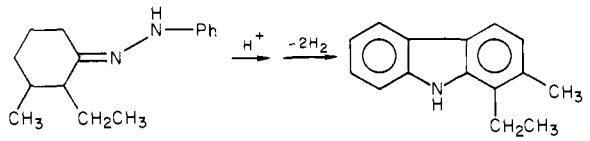
identifying the reaction products, the two possible products of "1,4" migrations, **18** and **19**, were synthesized by Fischer indole cyclizations of the phenylhydrazones of 3-ethyl-2-methylcyclohexanone and 2-ethyl-3-methylcyclohexanone, respectively.

Fischer cyclization of **17** in refluxing acetic acid followed by dehydrogenation by chloranil in xylene gave a mixture which apparently contained four components. The components were isolated by preparative GLC. The component with the longest

(10) Heath-Brown, B.; Philpott, P. *J. Chem. Soc.* **1965**, 7185.
(11) Fusco, R. *Chim. Ind. (Milan)* **1973**, *60*, 903.
(12) Campaigne, E.; Lake, R. D. *J. Org. Chem.* **1959**, *24*, 478.

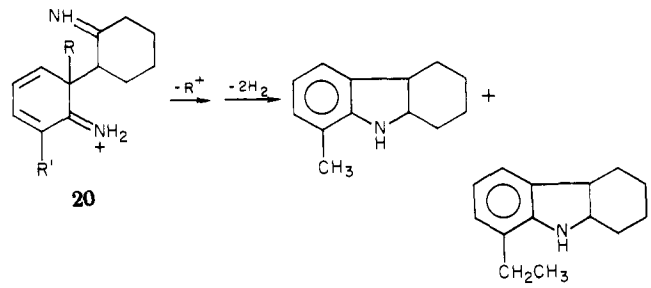


18



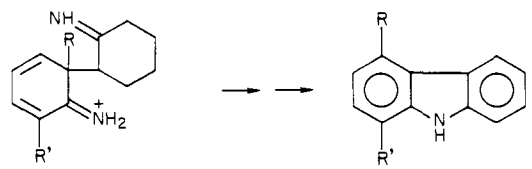
19

retention time was identified as 2-ethyl-1-methylcarbazole (**18**). The two components with the shortest retention times were identified by their melting points and spectra as 1-methylcarbazole and 1-ethylcarbazole. These products were presumably formed by cleavage of substituents from the quaternary carbon in the intermediate ion **20**.[13]



20

Although attempts employing several different GLC columns to separate the remaining GLC peak into separate peaks failed, this component seemed to have too complex a spectrum to be accounted for by a single carbazole structure. In addition to aromatic hydrogen peaks, its spectrum showed methyl singlets (in area ratio 1.3:1) at $\delta$ 2.48 and 2.84 ppm and methylene quartets at $\delta$ 3.24 and 2.8 ppm, the higher field quartet being partially covered by the singlet at $\delta$ 2.84. The ratio of aromatic to substituent protons in the spectrum indicates that the constituents of the mixture are disubstituted carbazoles, as suggested by its GLC retention time, which also suggests that the constituents are isomers. The low-field positions of one methyl and one methylene absorption indicate that one constituent has a methyl group at C-4 and the other an ethyl group at that position. Although these compounds cannot be unequivocally identified, the available structural information and the structure of the starting material strongly suggest that this component of the reaction products consists of a 1.3:1 molar mixture of 1-methyl-4-ethylcarbazole (**21**) and 1-ethyl-4-methylcarbazole (**22**) formed by [1,2] alkyl migrations in intermediates **20a** and **20b**, respectively. The



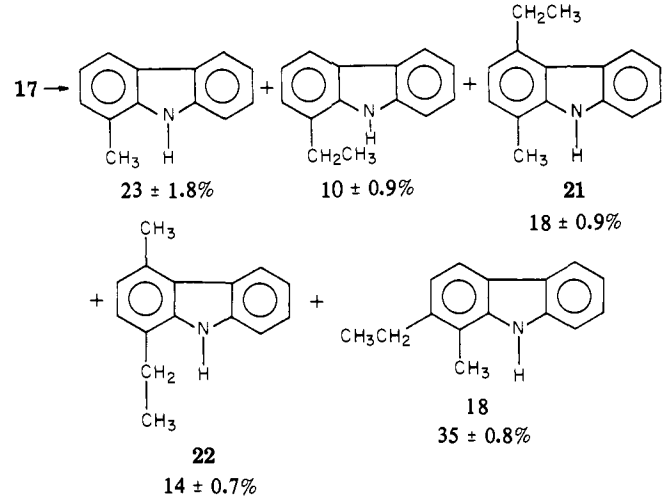
**20a**, R = $C_2H_5$; R' = $CH_3$
**b**, R = $CH_3$; R' = $C_2H_5$

**21**, R = $C_2H_5$; R' = $CH_3$
**22** R = $CH_3$; R' = $C_2H_5$

apparent formation of **21** and **22** is the first evidence for "normal" alkyl migrations in Fischer indole cyclizations of 2,6-dialkylphenylhydrazones of cyclohexanones, although such migrations are dominant processes in rearrangements of 2,6-dialkylphenylhydrazones of other ketones.[14]

(13) The loss of ortho substituents during Fischer indole cyclizations has previously been reported: Bajwa, G. S.; Brown, R. K. *Can. J. Chem.* **1968**, *46*, 1927; **1969**, *47*, 786; **1970**, *48*, 2294. Fusco, R.; Sannicolò, F. *Gazz. Chim. Ital.* **1973**, *103*, 197; **1974**, *104*, 813.

The average composition of the product mixture obtained from rearrangement of **17** (three runs) is shown below.



23 ± 1.8% 10 ± 0.9% **21** 18 ± 0.9%

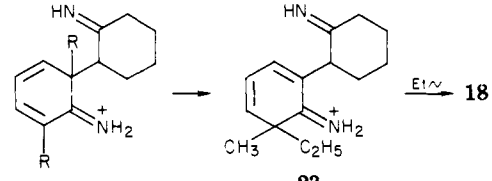
**22** 14 ± 0.7% **18** 35 ± 0.8%

Of particular interest is the fact that carbazole **19**, the product of a "1,4" methyl migration, is not detected, although analysis of synthetic mixtures shows that less than 0.5% of **19** would have been easily detected by GLC analysis.

Formation of the principal rearrangement product, **18**, could most simply be described as resulting from a direct [1,4] migration of an ethyl group in intermediate **20a**. If [1,4] alkyl migrations were feasible, however, it would be difficult to account for the complete absence of a [1,4] migration of a methyl group in **20b** to form **19**. Clearly **20b** does exist as an intermediate, since both 1-ethylcarbazole and **22** can only be obtained from **20b**. In view of the close similarity between **17** and **1**, in which "1,4" migration of the methyl group in intermediate **5** appears to be the principal process occurring, it seems quite unlikely that cleavage or [1,2] migration of a methyl group in **20b** would occur to the complete exclusion of "1,4" migration.

A second difficulty with assuming **18** to be formed solely via a [1,4] ethyl shift in **20a** is that the products assumed to arise from **20b** (1-ethylcarbazole and **22**) constitute only about 24% of the reaction products obtained, while those from **20a** constitute 76%. A priori, there seems to be no reason to expect formation of **20a** to be favored over formation of **20b**. Attack at a carbon bearing a methyl group should, in fact, be favored for steric reasons over attack at a carbon bearing an ethyl group. (Since the cyclization steps in the Fischer indole cyclizations involve cleavage of the N–N bonds they are undoubtedly irreversible, so that **20a** and **20b** would not be expected to be interconvertible.) Thus, if **18** is derived solely from **20a**, there seems to be an unexplained dearth of products from **20b**.

Both the absence of the "1,4" methyl migration product **19** and the apparent preference for cyclization of **17** at the carbon bearing the bulkier substituent can be accounted for if it is assumed that intermediates **20a** and **20b** could both rearrange to form intermediate **23**. A normal [1,2] migration in **23** would then yield, after dehydrogenation, a 1,2-disubstituted carbazole.



**20** **23**

If **23** is indeed an intermediate in formation of **18**, the fact that **19** is not formed in detectable amounts requires that migration of an ethyl group be very much faster than migration of a methyl

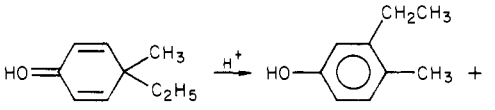
(14) Carlin, R. B.; Carlson, D. P. *J. Am. Chem. Soc.* **1957**, *79*, 3605; **1969**, *81*, 4673. Carlin, R. B.; Harrison, J. W. *J. Org. Chem.* **1965**, *30*, 563. Fusco, R.; Sannicolò, F. *Gazz. Chim. Ital.* **1975**, *105*, 465.

Table I. Physical Properties of Carbazoles

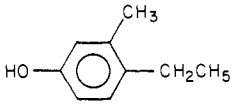
| carbazole | mp, °C (solvent) | lit. mp, °C | NMR absorptions, δ: Ar-H and N-H | Ar-$CH_3$ | Ar-$CH_2CH_3$ |
|---|---|---|---|---|---|
| 1-methylcarbazole | 120–122 (benzene) | 120.5[a] | 6.92–8.18 (m, 8 H) | 2.45 (s, 3 H) | |
| 2-methylcarbazole | 259–260 (ethanol) | 261–262[12] | 6.89–7.65 (m, 6 H)<br>7.75–8.30 (m, 2 H) | 2.45 (s, 3 H) | |
| 3-methylcarbazole | 205.5–207 (ethanol) | 206.5–207.5[12] | 6.85–7.70 (m, 6 H)<br>7.75–8.30 (m, 2 H) | 2.50 (s, 3 H) | |
| 4-methylcarbazole | 115–118 (ethanol) | 115–116[b]<br>129.5–130[12] | 6.87–8.25 (m, 8 H) | 2.85 (s, 3 H) | |
| 1-ethylcarbazole | 74–75 (benzene) | 74[c] | 6.98–8.18 (m, 8 H) | | 1.36 (t, 3 H)<br>2.86 (q, 2 H) |
| 1,2,3-trimethylcarbazole (**3**) | 127–131 (benzene) | 127.5–128.5[7] | 7.96 (1 H, d, $J$ = 7 Hz)<br>7.00–7.75 (m, 5 H) | 2.27 (s, 3 H)<br>2.31 (s, 3 H)<br>2.38 (s, 3 H) | |
| 1,3,4-trimethylcarbazole (**12**) | 143–152 (pet. ether) | 143–143.5[7] | 6.95–8.4 (m, 5 H) | 2.33 (s, 3 H)<br>2.36 (s, 3 H)<br>2.70 (s, 3 H) | |
| 2-ethyl-1-methylcarbazole (**18**) | 97.5–98 (benzene) | | 6.92–8.15 (m, 7 H) | 2.37 (s, 3 H) | 1.24 (t, 3 H)<br>2.78 (q, 2 H) |
| 1-ethyl-2-methylcarbazole (**19**) | 87–88 (benzene) | | 6.9–7.4 (m, 4 H)<br>7.65–8.10 (m, 3 H) | 2.39 (s, 3 H) | 1.15 (t, 3 H)<br>2.75 (q, 2 H) |
| 4-ethyl-1-methylcarbazole[d] (**21**) | | | | 2.48 (s) | 3.24 (q)<br>1.4 (t) |
| 1-ethyl-4-methylcarbazole[d] (**22**) | | | | 2.84 (s) | ~2.8 (q)<br>1.25 (t) |

[a] Ullman, F. *Justus Liebigs Ann. Chem.* **1904**, *332*, 82. [b] Pausacker, K. H.; Robinson, R. *J. Chem. Soc.* **1947**, 1557. [c] Pausacker, K. H. *J. Chem. Soc.* **1950**, 621. [d] NMR values from spectrum of mixture of **21** and **22**.

group. Although migratory aptitudes in rearrangements of cyclohexadieniminium cations such as **23** have not been studied, it has been reported that in acid-catalyzed rearrangements of cyclohexadienone **24** the ethyl group migrates 25–55 times as rapidly as the methyl group, depending on the conditions employed.[15]



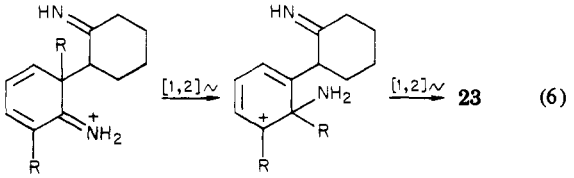
**24** major product



minor product

Since rearrangements of iminium salts such as **23** would be expected to be more selective than rearrangements of protonated cyclohexadienones, a preference of >70 for migration of ethyl rather than methyl in **23** is not unreasonable.

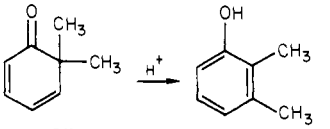
Rearrangements of **20a** and **20b** to form **23** represent overall 1,5-alkyl shifts. At present, however, it is impossible to distinguish between direct [1,5] shifts of the migrating groups and a sequence of [1,2] shifts, as in eq 6.



(6)

## Effects of the Nonaromatic Moieties on Rearrangement Paths

Although the mechanism offered above for "1,4" migrations of alkyl groups in Fischer indole cyclizations accounts for the nature of the products obtained, it does not, in itself, explain why such migrations have been observed only in reactions of phenylhydrazones of cyclohexanone, while phenylhydrazones of other ketones (acetone, acetophenone, acetoacetic ester) have only been reported to yield products resulting from [1,2] alkyl shifts.[14] Furthermore, it does not in itself explain why substituents in **20** should undergo [1,5] migrations (or [1,2] migrations to the imino carbons) while in the closely related rearrangement of **25** in acid only a [1,2] migration of a methyl group to a vinyl carbon is observed.[16] Migration to a vinyl carbon of **20** would similarly



**25**

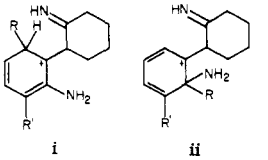
be expected to be preferred to migration to the imino carbon, since a more stable intermediate should be formed by that process.[17] While a [1,5] migration of the methyl group would give a more stable intermediate than that formed by either type of [1,2] methyl migration, such migrations of methyl groups in acid have never been observed.

In regard to the first point—the apparently unique ability of phenylhydrazones of cyclohexanone to form products resulting from "1,4" alkyl migration—it was noted that phenylhydrazones of cyclohexanone have been the only 2,6-dialkylphenylhydrazones studied which were not derivatives of methyl ketones. To see whether derivatives of other ketones lacking a methyl bonded to the carbonyl would yield "1,4" migration products, the mesitylhydrazone of 2-pentanone (**26**) was prepared and rearranged to yield a single indole. To identify the product, it was compared

(15) Pilkington, J. W.; Waring, A. J. *Tetrahedron Lett.* **1973**, 4345. Marx, J. N.; Argyle, J. C.; Norman, L. R. *J. Am. Chem. Soc.* **1974**, *96*, 2121. See also: Miller, B.; Margulies, H. *Ibid.* **1965**, *87*, 5706. Carlin, R. B.; Sivaramakrishnan, K. P. *J. Org. Chem.* **1970**, *35*, 3368.

(16) Marvell, E. N.; Magoon, E. *J. Am. Chem. Soc.* **1955**, *77*, 2542. Miller, B. *Ibid.* **1970**, *92*, 6252.

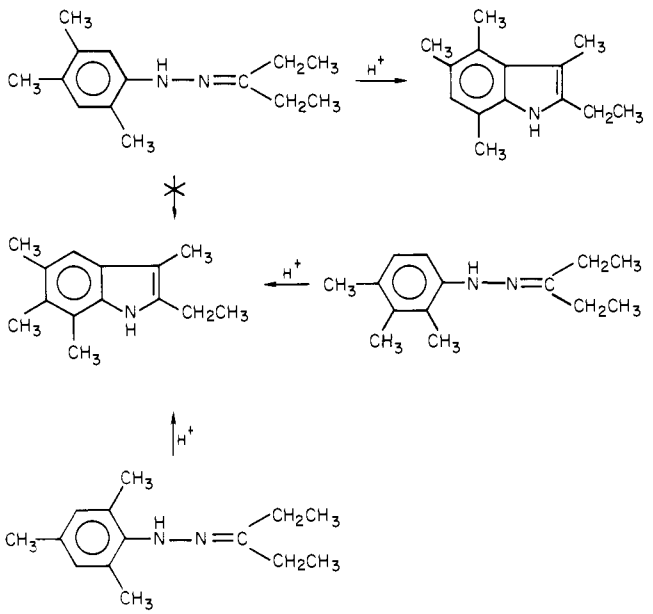
(17) Migration of R to the adjacent vinyl carbon would form a vinylamine (i), while migration to the amine carbon would form an allylic amine (ii). By



i ii

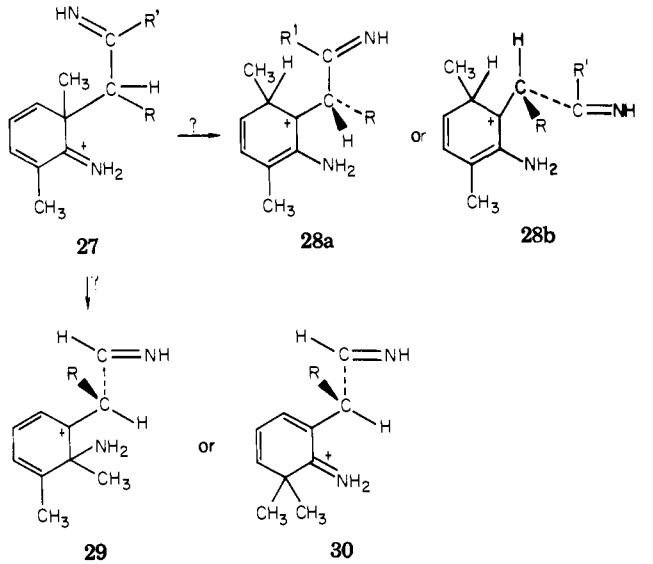
analogy with the properties of vinyl and allylic ethers, halides, and sulfides (Hine, J.; Flachskam, N. W. *J. Am. Chem. Soc.* **1973**, *95*, 1179) i would be expected to be appreciably more stable than ii.

with the indoles independently synthesized by Fischer indole cyclizations of the phenylhydrazones obtained from reaction of 2-pentanone with 2,3,4-trimethylphenylhydrazine and 2,4,5-trimethylphenylhydrazine. The indole prepared from the former precursor was found to be identical with the product from rearrangement of **26**. Thus, **26** cyclizes with a "1,4" migration of the methyl group.



**26**

This result suggests that "1,4" migrations of alkyl groups in Fischer indole cyclizations can occur when the substituent R in an intermediate such as **27** is an alkyl group, but not when R is a hydrogen atom.



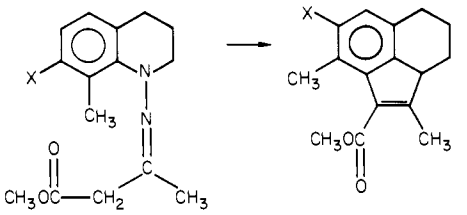
**27** **28a** **28b**



**29** **30**

The effect of the substituent R on the nature of the migration of a methyl group in **27** must almost certainly be steric in origin, since the polar effect of changing a hydrogen atom on the side chain of **27** to an alkyl group should be minimal. Inspection of molecular models shows that in carbonium ion **28**, which would result from a [1,2] methyl shift to the vinyl carbon of **27**, there is no conformation which does not require severe crowding of substituents on the former aromatic ring. (Crowding would be much less severe if **28** were derived from a methyl ketone.) On the other hand, either a [1,2] methyl migration to the imino carbon or a [1,5] migration would yield intermediates such as **29** and **30** which could adopt relatively uncrowded conformations. As a result, such reactions should be favored over the normal shift to a vinyl carbon.

While it is tempting to ascribe the abnormal "1,4" migrations of alkyl groups to these steric effects, it does not appear that they can be the only factors involved. Fusco and Sannicolò have reported that the heterocyclic hydrazones **31a** and **31b** rearrange to form products derived from [1,2] methyl shifts rather than 1,4 shifts.[9,11] On the basis of the steric argument presented above,



**31a**, X = H
**b**, X = $CH_3$

predominant 1,4 migrations would have been expected. It is thus clear that further work is needed to obtain a detailed understanding of the factors affecting the nature of alkyl migrations in Fischer indole cyclizations.

## Experimental Section

**General.** All melting points and boiling points are uncorrected. NMR spectra were recorded on a Perkin-Elmer Model R12A spectrometer, in chloroform solution using $Me_4Si$ as an internal standard unless otherwise noted. IR spectra were recorded on a Perkin-Elmer Model 727 spectrometer. Mass spectra were obtained using a Perkin-Elmer Model RMU6L mass spectrometer coupled to a Perkin-Elmer Model 990 gas chromatograph.

***N,N'*-Dicarbethoxy-2,4,6-trimethylphenylhydrazine, *N,N'*-dicarbethoxy-2,3,4-trimethyhenylhydrazine,** and ***N,N'*-dicarbethoxy-2,4,5-trimethylphenylhydrazine** were prepared by reaction of ethyl azodicarboxylate and boron trifluoride with the appropriate trimethylbenzenes, as described by Carlin and Moores.[7]

**2,4,6-Trimethylphenylhydrazine, 2,4,5-trimethylphenylhydrazine,** and **2,3,4-trimethylphenylhydrazine** were prepared from the corresponding *N,N'*-dicarbethoxyphenylhydrazines by reaction with refluxing ethanolic potassium hydroxide, as described by Carlin and Moores,[7] and used immediately without further purification.

**6,7,8-Trimethyl-1,2,3,4-tetrahydrocarbazole picrate** was prepared in 27% yield from cyclohexanone 2,4,6-trimethylphenylhydrazone and in 45% yield from cyclohexanone 2,3,4-trimethylphenylhydrazone, and **5,6,8-trimethyl-1,2,3,4-tetrahydrocarbazole picrate** was prepared in 62% yield from cyclohexanone 2,4,5-trimethylphenylhydrazone by refluxing the hydrazones in glacial acetic acid and then adding 1.0–2.5 equiv of picric acid to the reaction mixtures.[7]

**1,2,3-Trimethylcarbazole (3)** was prepared from 6,7,8-trimethyl-1,2,3,4-tetrahydrocarbazole picrate and **1,3,4-trimethylcarbazole (12)** was prepared from 5,6,8-trimethyl-1,2,3,4-tetrahydrocarbazole picrate by neutralizing the picrates with aqueous base and oxidizing the tetrahydrocarbazoles with 2 equiv of chloranil in refluxing xylene.[7]

**2,3,4-Trimethylaniline.** Raney nickel (15.0 g) was added to a solution of 2,3,4-trimethylphenylhydrazine (3.4 g, 0.0227 mol) in 50 mL of 95% ethanol. The mixture was refluxed for 4 h, cooled, and filtered. The filtrate was evaporated under vacuum and the residue dissolved in methylene chloride, dried over sodium carbonate, filtered, and evaporated to yield 3.2 g of brown oil. Distillation gave 1.3 g (9.6 mmol, 42%) of 2,3,4-trimethylaniline as a golden-yellow oil, bp 121–123 °C (4 mm) [reported[18] bp 136–140 °C (20 mm)].

**Condensation of 2,3,4-Trimethylaniline with 2-Chlorocyclohexanone.** A mixture of 2,3,4-trimethylaniline (1.2 g, 8.9 mmol), 2-chlorocyclohexanone (1.05 g, 8.5 mmol), 5 g of anhydrous sodium carbonate, and 15 mL of methyl Cellosolve was heated under reflux with stirring under nitrogen for 1 h. The reaction mixture was cooled to room temperature under nitrogen and filtered, and the filter cake was washed three times with 10-mL portions of methyl Cellosolve. Anhydrous magnesium chloride (4.0 g, 0.042 mol) was added to the mixture, which was heated under reflux for 4 h. The mixture was cooled to room temperature, poured onto ice, and allowed to stand overnight. It was then filtered, and the solid product was washed with water and 50% aqueous ethanol to give a black residue. This was suspended in 30 mL of xylene and 5 g of 10% Pd on C added. The mixture was heated under reflux for 48 h, cooled

(18) Buu Hoi, N. P.; Jacquinon, P.; Roussel, O. *Bull Soc. Chim. Fr.* **1965**, 372.

to room temperature, and filtered. The residue was washed with ethyl acetate, and the ethyl acetate and xylene solutions were evaporated under vacuum. The residue was chromatographed on an 18 × 1/2 in. dry silica gel column, eluting with methylene chloride, to yield 132 mg of dark brown powder. Recrystallization from ethanol gave 74 mg (0.35 mmol, 4%) of 1,2,3-trimethylcarbazole, mp 127–130 °C.

**2-Ethyl-6-methylphenylhydrazine.** 2-Ethyl-6-methylaniline (33.3 g, 0.25 mol) was added drop by drop to 90 mL of 12 M hydrochloric acid. The resulting solution was cooled to −10 °C and a solution of sodium nitrite (17.4 g, 0.27 mol) in 28 mL of water was added below the surface of the acid solution. The rate was adjusted to maintain the reaction temperature below −5 °C. When addition of the sodium nitrite solution was complete a solution of stannous dichloride hydrate (126 g, 0.56 mol) in 169 mL of 6 M hydrochloric acid was added over a 3-h period, during which the temperature of the reaction mixture was maintained below −5 °C. The resulting cream-colored mixture was allowed to stand overnight at room temperature and filtered. The solid was washed with ether and suspended in 200 mL of water, and the suspension was cooled to 5 °C and stirred while a solution of 63 g of sodium hydroxide in 85 mL of water was added at a rate sufficient to maintain the temperature of the reaction mixture below 15 °C. The resulting solution was extracted three times with ether and the ethereal solutions were combined and dried over anhydrous magnesium sulfate. The dry ether solution was heated with decolorizing charcoal and filtered to yield a gold-colored solution. Hydrogen chloride gas was then introduced beneath the surface of the ethereal solution until no further precipitate formed. Filtration yielded 48.3 g of pale yellow crystals, which were dissolved in ethanol, decolorized with carbon, and filtered. The solution was concentrated on a steam bath and cooled to yield 14.8 g (0.080 mol, 32%) of **2-ethyl-6-methylphenylhydrazine hydrochloride** as white crystals.

The crystalline hydrochloride was reacted with a solution of 10 g of sodium hydroxide in 100 mL of water and extracted twice with ether. The ether layers were dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated under vacuum to give 12.0 g of **2-ethyl-6-methylphenylhydrazine** as a yellow oil. Its IR spectrum showed peaks at 2960 and 3345 $cm^{-1}$.

**Fischer Indole Cyclization of Cyclohexanone 2-Ethyl-6-methylphenylhydrazone (17).** 2-Ethyl-6-methylphenylhydrazine (6.3 g, 0.042 mol) was added to cyclohexanone (4.5 g, 0.043 mol). The reaction temperature rose to 45 °C and the mixture turned a deep orange. Acetic acid (5.3 mL), which had previously been degassed by refluxing for 1 h while a stream of nitrogen was passed through it, was added and the mixture was heated at 130 °C for 30 min. The reaction mixture was then cooled in ice and extracted with ether. The ethereal solution was washed with 1 M hydrochloric acid solution, then twice with water, and finally with a saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and filtered, and the solvent evaporated to give 5.6 g of a brown oil. The oil was passed through a column of neutral alumina and eluted with petroleum ether to give 3.95 g of an orange oil, to which were added chloranil (9.12 g, 0.0371 mol) and 50 mL of xylene which had been degassed by refluxing for 1 h while a stream of nitrogen was passed through it. The mixture was refluxed under nitrogen for 24 h and cooled to room temperature. Most of the xylene was distilled out at atmospheric pressure and the remainder evaporated under vacuum to give 17.8 g of a black residue. The residue was extracted in succession with hot petroleum ether (bp 30–60 °C), ether, and methylene chloride. The three fractions were each individually washed with 1 M potassium hydroxide solution and twice with saturated sodium chloride solutions and dried over anhydrous magnesium sulfate, and the solvent was evaporated under vacuum. The petroleum ether extract yielded 0.69 g of product, the ether extract 1.0 g, and the methylene chloride extract 0.64 g. VPC analysis showed the three fractions to be essentially identical, so they were combined and chromatographed on neutral alumina, eluting with petroleum ether and benzene. VPC analysis showed that little separation was accomplished by chromatography, so the products were combined to give 1.0 g of a brown oil. VPC analysis on a 6 ft × 1/8 in., 10% SE-30 on Chromosorb W column at 225 °C showed four components at retention times of 4.3, 5.3, 7.5, and 8.6 min. These components were isolated by preparative VPC on a 12 ft × 3/8 in., 20% SE-30 on Chromosorb W column at 225 °C. The component with a retention time of 4.3 min was identified as **1-methylcarbazole**, that with a retention time of 5.3 min as **1-ethylcarbazole**, and that with a retention time of 8.6 min as **2-ethyl-1-methylcarbazole**, by comparison of their retention times, spectra, and melting points with those in the literature and of samples prepared as described below. The component with a retention time of 7.5 min was considered to be a mixture of **1-ethyl-4-methylcarbazole** and **4-ethyl-1-methylcarbazole** from analysis of its NMR spectrum.

This procedure was repeated twice more, except that the extracts from the chloranil dehydrogenation were combined before washing. The products obtained from the three runs were similar except for a slight difference in the product ratios. The molar ratios of the four products from each run are listed in Table II, and were obtained by VPC analysis after calibrating for detector sensitivity by use of a standard mixture of 1-methylcarbazole, 1-ethylcarbazole, and 2-ethyl-1-methylcarbazole. It was assumed that the components of the peak with a retention time of 7.5 min (present in a 1.3:1 ratio) would yield detector responses identical with that of 1-methyl-2-ethylcarbazole.

**Table II.** Molar Ratios

| run | 1-methylcarbazole | 1-ethylcarbazole | mixture | 2-ethyl-1-methylcarbazole |
|---|---|---|---|---|
| 1 | 2.8 | 1 | 3.4 | 3.8 |
| 2 | 1.8 | 1 | 3.0 | 2.9 |
| 3 | 2.4 | 1 | 3.1 | 3.6 |

**3-Ethyl-2-methylcyclohexanone.** Cuprous iodide (4.2 g, 0.022 mol) was added to a solution of ethylmagnesium bromide (0.220 mol) in 150 mL of ether. The mixture was stirred at 0 °C for 15 min and a solution of 2-methyl-2-cyclohexenone (23.0 g, 0.209 mol) in 50 mL of ether was added dropwise over a 45-min period. The reaction mixture was warmed to room temperature, stirred overnight, and poured into a mixture of ice and saturated ammonium chloride solution. The mixture was filtered and the ether layer separated. The aqueous layer was washed twice with 50 mL of ether, the combined ether solutions were washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed by use of a rotatory evaporator. The residual liquid (37.9 g) was distilled to yield 9.98 g (0.072 mol, 34%) of 3-ethyl-2-methylcyclohexanone, bp 89–96 °C (18 mm). Its IR spectrum (neat) showed a carbonyl absorption at 1700 $cm^{-1}$. Its NMR spectrum showed a singlet (3 H) at $\delta$ 1.05 and a triplet (3 H, $J$ = 7.5 Hz) at $\delta$ 1.23. Anal. Calcd for $C_9H_{16}O$: C, 77.10; H, 11.50. Found: C, 77.24; H, 11.67.

**2-Ethyl-1-methylcarbazole (18).** A mixture of 3-ethyl-2-methylcyclohexanone (3.3 g, 0.024 mol) and phenylhydrazine (2.6 g, 0.024 mol) was flushed with nitrogen and then heated under nitrogen at 100 °C for 1 h, after which time no ketone remained unreacted (GLC). A solution of 20% (by volume) sulfuric acid in water (50 mL) was then added to the reaction mixture, and the resulting mixture was stirred and heated under nitrogen for an additional 15 min. The mixture was cooled and extracted three times with methylene chloride, and the methylene chloride solutions were combined and dried over anhydrous magnesium chloride. Decolorizing charcoal was added, the mixture was filtered, and the solvent was evaporated to give 3.6 g of a red-brown oil, which was chromatographed on 120 g of silica gel, eluting with benzene, to yield 1.8 g of 2-ethyl-1-methyl-1,2,3,4-tetrahydrocarbazole. This was combined with an additional 1.35 g obtained from a second run, and suspended in 50 mL of xylene. Chloranil (7.28 g, 0.038 mol) was added, and the mixture was refluxed for 24 h. The mixture was then cooled, 100 mL of petroleum ether added, and the mixture filtered. The solid residue was extracted three times with hot petroleum ether, and the combined liquid layers were evaporated under vacuum to give a gray solid, which was again extracted with hot petroleum ether and filtered. The filtrate was evaporated to give 2.2 g of brown powder, which was chromatographed on 75 mL of silica gel, eluting with benzene, to yield 1.9 g of brown solid. Three recrystallizations from benzene yielded 1.00 g (4.8 mmol, 11%) of **18** as white needles. Anal. Calcd for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.70. Found: C, 86.19; H, 7.21; N, 6.59.

**2-Ethyl-3-methylcyclohexanone.** Cuprous iodide (2.6 g, 0.0136 mol) was added to a solution of methylmagnesium bromide (0.136 mol) in 100 mL of ether at 0 °C under an atmosphere of nitrogen. The temperature was maintained at 0 °C and the mixture stirred for 15 min. A solution of 2-ethyl-2-cyclohexenone (13.5 g, 0.109 mol) in 25 mL of ether was added dropwise. When addition was complete, stirring was continued for an additional 15 min at 0 °C and then overnight at room temperature. Saturated ammonium chloride solution (50 mL) was then added dropwise and the reaction mixture worked up as described for preparation of 3-ethyl-2-methylcyclohexanone to give 12.4 g (0.09 mol, 81%) of 2-ethyl-3-methylcyclohexanone as a colorless liquid, bp 83–88 °C (26 mm) [lit.[20] bp 80–82 °C (21 mm)]. Its IR spectrum showed a carbonyl peak at 1705 $cm^{-1}$.

**1-Ethyl-2-methylcarbazole (19).** 2-Ethyl-3-methylcyclohexanone (5.0 g, 0.036 mol) and phenylhydrazine (3.9 g, 0.36 mol) were flushed with nitrogen and then stirred and heated under nitrogen at 95 °C for 45 min.

(19) Prepared by the general procedure of Gassman, P. G.; Gruetzmacher, G. D. *J. Am. Chem. Soc.* **1974**, *96*, 5487.

(20) Colonge, J.; Dreux, J.; Thiers, M. *Bull. Soc. Chim. Fr.* **1959**, 450.

Table III. Physical Properties of Phenylhydrazines and Picrates of Tetrahydrocarbazoles[a]

| | mp, °C (solvent) | lit. mp, °C | NMR absorptions, δ | | | | |
|---|---|---|---|---|---|---|---|
| | | | Ar-H | Ar-$CH_3$ | N-H | Ar-$CH_2$- or O-$CH_2$- | $CH_2CH_3$ |
| **Phenylhydrazines** | | | | | | | |
| *N,N'*-dicarbethoxy-2,4,6-trimethylphenylhydrazine | 159-161 (ethanol) | 159-160[7] | 6.92 (s, 1 H) | 2.32 (s, 6 H) | 7.77 (bs, 1 H) | 3.95-4.5 (2 q, 4 H) | 1.20 (t, 3 H)<br>1.39 (t, 3 H) |
| *N,N'*-dicarbethoxy-2,3,4-trimethylphenylhydrazine | 150.5-152 (ethanol) | 148-149[7] | 6.96 (d, $J$ = 8.3 Hz, 1 H)<br>7.25 (d, 1 H, $J$ = 8.3 Hz) | 2.17 (s, 3 H)<br>2.19 (s, 3 H)<br>2.24 (s, 3 H) | 7.78 (bs, 1 H) | ~4.17 (2 q, 4 H) | 1.2 (m, 6 H) |
| *N,N'*-dicarbethoxy-2,4,5-trimethylphenylhydrazine | 115-116 (ethanol) | 114-116[7] | 6.99 (m, 1 H)<br>7.24 (m, 1 H) | 2.18 (s, 9 H) | 7.73 (bs, 1 H) | ~4.2 (2 q, 4 H) | 1.2 (m, 6 H) |
| 2-ethyl-6-methylphenylhydrazine | | | 6.96 (s, 3 H) | 2.32 (s, 3 H) | 3.90 (bs, 2 H) | 2.68 (q, 3 H) | 1.21 (t, 3 H) |
| 2-ethyl-6-methylphenylhydrazine hydrochloride | 187-189 dec (ethanol) | | 7.20 (s, 3 H) | 2.40 (s, 3 H) | 4.72 (bs) | 2.76 (q, 2 H) | 1.19 (t, 3 H) |
| **Picrates of Tetrahydrocarbazoles** | | | | | | | |
| 6,7,8-trimethyl-1,2,3,4-tetrahydrocarbazole picrate | 170.5-172 (benzene) | 171-172[7] | 8.75 (s, 2 H)[b]<br>6.83 (m, 1 H) | 2.13 (s, 3 H)<br>2.17 (s, 3 H)<br>2.22 (s, 3 H) | | | |
| 5,6,8-trimethyl-1,2,3,4-tetrahydrocarbazole picrate | 167-168 (benzene) | 171 dec[7] | 8.90 (s, 2 H)[b] | 2.21 (s, 3 H)<br>2.38 (s, 3 H)<br>2.25 (s, 3 H) | | | |

[a] $D_2O$ was employed as the solvent for NMR spectra. [b] Aromatic protons on picrate ring.

Table IV. Physical Properties of Indoles and Picrates

| indoles and picrates | NMR absorptions, δ | | | | | |
|---|---|---|---|---|---|---|
| | Ar-H | Ar-$CH_3$ | N-H, O-H | Ar-$CH_2$ | $CH_2$-$CH_3$ | mp, °C |
| 2-ethyl-3,5,6,7-tetramethylindole picrate | 6.75 (1 H, m)<br>8.70 (2 H, s)[a] | 2.03 (s, 3 H)<br>2.15 (s, 3 H)<br>2.25 (s, 6 H) | 7.5 (bs, 2 H) | 2.65 (q, 2 H) | 1.22 (t, 3 H) | 161-162 (benzene) |
| 2-ethyl-3,5,6,7-tetramethylindole | 6.88 (1 H, m) | 2.15 (s, 3 H)<br>2.23 (s, 3 H)<br>2.33 (s, 6 H) | 7.2 (bs, 1 H) | 2.69 (q, 2 H) | 1.21 (t, 3 H) | |
| 2-ethyl-3,4,5,7-tetramethylindole picrate | 6.62 (m, 1 H)<br>8.92 (2 H, s)[a] | 2.23 (s, 3 H)<br>2.28 (s, 3 H)<br>2.33 (s, 3 H)<br>2.48 (s, 3 H) | 7.95 (bs, 2 H) | 2.69 (q, 2 H) | 1.23 (t, 3 H) | 168-169 (benzene) |
| 2-ethyl-3,4,5,7-tetramethylindole | 6.65 (m, 1 H) | 2.29 (s, 3 H)<br>2.35 (s, 3 H)<br>2.40 (s, 3 H)<br>2.57 (s, 3 H) | 7.0 (bs, 2 H) | 2.72 (q, 2 H) | 1.24 (t, 3 H) | |

[a] Aromatic protons on picrate ring.

Heating was then continued for 30 min at 95 °C while the water produced in the reaction was evaporated at a pressure of 30 mm. A solution of 5 mL of sulfuric acid in 45 mL of ethanol was then added and the mixture heated under nitrogen at 95 °C for an additional 45 min. The mixture was cooled to room temperature and 5 g of potassium hydroxide added. Most of the ethanol was distilled off at atmospheric pressure, and a solution of 5 mL of sulfuric acid in 45 mL of water added to the mixture. The acidic mixture was extracted with methylene chloride and the methylene chloride solution washed in turn with water and saturated sodium bicarbonate solution. The organic layer was then dried over anhydrous magnesium sulfate and filtered and the solvent evaporated under reduced pressure to give 7.2 g of an orange oil. The oil was dehydrogenated with chloranil in xylene as described for the synthesis of **18**. After distillation of xylene from the crude mixture, the residue was dissolved in Claisen's alkali and filtered and the filter cake washed with hot petroleum ether. The filtrate was extracted repeatedly with petroleum ether, the combined extracts were washed with water, decolorized with charcoal, and dried over magnesium sulfate, and the solvent was evaporated under reduced pressure to give 3.1 g of a brown oil. Vacuum sublimation yielded off-white, oily crystals, which were chromatographed on alumina, eluting with petroleum ether. Recrystallization from benzene gave **1-ethyl-2-methylcarbazole** (**19**, 0.15 g, 2.1%) as white plates. Anal. Calcd for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.70. Found: C, 85.90; H, 7.41; N, 6.35.

**Preparation of 2-Methylcarbazole and 4-Methylcarbazole.** Anhydrous sodium carbonate (15 g) was added to a mixture of 2-chlorocyclohexanone (10.0 g, 0.076 mol) and *m*-toluidine (8.0 g, 0.075 mol) in 50 mL of methyl Cellosolve. The mixture was stirred and heated under reflux for 1 h. The mixture was cooled and filtered and the filter cake washed with methyl Cellosolve, which was added to the filtrate. *m*-Toluidine (5.0 g, 0.047 mol) and anhydrous magnesium chloride (18.0 g, 0.188 mol) were added, and the solution was heated under reflux for 4 h. The solution was cooled, poured into a mixture of concentrated HCl and ice, and allowed to stand overnight. It was filtered, washed with dilute HCl, water, and aqueous ethanol, and dried overnight in the atmosphere to give 18.0 g of a black, tarry residue. A portion (6.0 g) of the residue was dissolved in 50 mL of xylene and 10 g of 10% Pd on C added. The mixture was refluxed for 48 h, cooled, and filtered, and the solid washed with ethyl acetate, which was added to the xylene layer. Evaporation of the solvent left 4.2 g of brown solid, which was chromatographed on an 18 × 1 in. dry silica gel column, eluting with methylene chloride. The first fraction eluted (0.9 g) and the second (0.7 g) were mixtures of 2-methyl- and 4-methylcarbazole. The third fraction (0.9 g) was recrystallized from ethanol to yield 0.6 g of **2-methylcarbazole.** The first fraction was twice chromatographed on silica gel, eluting with 10% ethyl acetate in hexane, to yield 24 mg of **4-methylcarbazole.**

**3-Methylcarbazole** was similarly prepared from *p*-toluidine and 2-chlorocyclohexanone, following the procedure of Campaigne and Lake.[12]

**Rearrangement of 3-Pentanone 2,4,6-Trimethylphenylhydrazone (26).** To 2,4,6-trimethylphenylhydrazine (obtained by hydrolysis of 0.034 mol of *N,N'*-dicarbethoxy-2,4,6-trimethylphenylhydrazine) was added 2.92 g (0.034 mol) of 3-pentanone. A clear solution was obtained, to which 15 mL of acetic acid was added. The mixture was stirred and refluxed under nitrogen for 30 min. Picric acid containing 10% $H_2O$ (8.57 g, 0.034 mol) in 15 mL of hot acetic acid was added to the red solution, which immediately turned black. Upon cooling, black crystals were collected, which were digested several times with boiling water and recrystallized from benzene to yield 1.65 g (14%) of 2-ethyl-3,5,6,7-tetra-

methylindole picrate, mp 159-160 °C. A mixture with the picrate prepared below melted at 159-161 °C.

**2-Ethyl-3,5,6,7-tetramethylindole and Its Picrate.** A solution of 3-pentanone (1.70 g, 0.0195 mol) and 2,3,4-trimethylphenylhydrazine (obtained by hydrolysis of 0.0195 mol of *N,N'*-dicarbethoxy-2,3,4-trimethylphenylhydrazine) in 19 mL of acetic acid was refluxed for 0.5 h. A solution of 6.7 g (0.029 mol) of picric acid containing 10% $H_2O$ in 11.5 mL of hot acetic acid was added, and the flask containing the picric acid solution was washed with an additional 10 mL of acetic acid, which was added to the reaction mixture. Hot $H_2O$ (ca. 3 mL) was added to the solution, which was cooled and filtered. The black residue was boiled in $H_2O$, filtered, and dried in air to give 4.0 g (0.093 mol, 47.7%) of 2-ethyl-3,5,6,7-tetramethylindole picrate as black crystals, mp 161-162 °C (from benzene). Anal. Calcd for $C_{20}H_{22}N_4O_7$: C, 55.81; H, 5.15; N, 13.02. Found: C, 55.55; H, 5.39; N, 12.75.

A sample (0.080 g) of the picrate was shaken with aqueous potassium hydroxide solution, and the mixture was extracted with methylene chloride, washed three times with aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. Evaporation of the solvent left 2-ethyl-2,5,6,7-tetramethylindole as a tan oil which could not be crystallized.

**2-Ethyl-3,4,5,7-tetramethylindole and Its Picrate.** 3-Pentanone (2.92 g, 0.034 mol) and 2,4,5-trimethylphenylhydrazine (prepared from 0.034 mol of *N,N'*-dicarbethoxy-2,4,5-trimethylphenylhydrazine) in 15 mL of acetic acid were reacted as described for preparation of 2-ethyl-3,5,6,7-tetramethylindole. After addition of 7.79 g of picric acid in 18 mL of hot acetic acid, the product was worked up as previously described and recrystallized from benzene to give 1.71 g (0.0040 mol, 12%) of **2-ethyl-2,3,4,5-tetramethylindole picrate** as a reddish-brown solid. Anal. Calcd for $C_{20}H_{22}N_4O_7$: C, 55.81; H, 5.15; N, 13.02. Found: C, 56.02; H, 5.19; N, 12.48.

A sample of the picrate was converted to the free indole as described above to give a dark brown oil which did not crystallize.

Physical properties are given in Tables III and IV.

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# Carbon Isotope Effects in Proton Abstraction from 2-Nitropropane-2-$^{14}C$ by Pyridines. The Contribution of Tunneling[1]

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**Abstract:** The large kinetic isotope effects in the reaction of 2-nitropropane-*2-d* and 2-nitropropane-*2-t* with 2,6-dimethylpyridine are frequently cited as evidence for tunneling. We have found that 2-nitropropane-2-$^{14}C$ reacts with 2,6-dimethylpyridine in 60% *tert*-butyl alcohol-40% water to give a $^{14}C$ isotope effect, $k_{12}/k_{14}$, of 1.096 ± 0.003. The same reaction with pyridine gives $k_{12}/k_{14}$ of only 1.037 ± 0.002. Comparison with model calculations suggests that both carbon isotope effects contain a contribution from tunneling, and that the larger isotope effect with 2,6-dimethylpyridine as base arises from a larger tunnel correction. The calculations also suggest that significant rehybridization at C-2 has occurred in the transition state for the proton abstraction.

We recently reported evidence that tunneling contributes to carbon isotope effects on proton abstraction from carbon in E2 reactions of 2-phenylethyldimethylsulfonium and 2-phenylethyltrimethylammonium ions.[2,3] In order to obtain further evidence on this matter, we chose to study carbon isotope effects in a reaction for which a small change in the attacking base produces a dramatic change in the hydrogen isotope effect. This reaction is the pyridine-promoted ionization of 2-nitropropane. In 60% *tert*-butyl alcohol-40% water at 24.88 °C, the reaction with pyridine occurs with a $k_H/k_D$ of 9.8, but the reaction with 2,6-dimethylpyridine occurs with a $k_H/k_D$ of 24.1.[4] Although the reaction of 2-nitropropane-*2-d* with 2,6-dimethylpyridine is slow and difficult to follow, any doubt that the large isotope effect is essentially correct is allayed by the observations that $k_H/k_D$ is consistent with $k_H/k_T$[5] and that it agrees rather well with $k_H/k_D$ measurements by Bell and Goodall in aqueous solution.[6] In addition, a large $k_H/k_D$ value is found for the reaction of methyl 4-nitrovalerate with 2,4,6-trimethylpyridine.[7]

The tendency of 2,6-disubstituted pyridines to give unusually large isotope effects in proton abstractions has been ascribed to tunneling promoted by steric hindrance in the transition state.[4] The steric hindrance was suggested to lead to a high and narrow potential-energy barrier, a situation particularly favorable for tunneling. The temperature dependence of the isotope effect ($A_H/A_D$, the ratio of Arrhenius preexponential factors, is 0.15) with 2,4,6-trimethylpyridine was cited as additional support for tunneling. Later it was pointed out that the steric effect could also operate by hindering solvation of the proton in transit, thereby reducing the effective mass along the reaction coordinate and favoring tunneling.[8-10]

Coupling of internal heavy-atom motion with the proton transfer may have the same depressive effect as solvation on the isotope effect and the tunnel effect.[11,12] An unusually large isotope effect

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