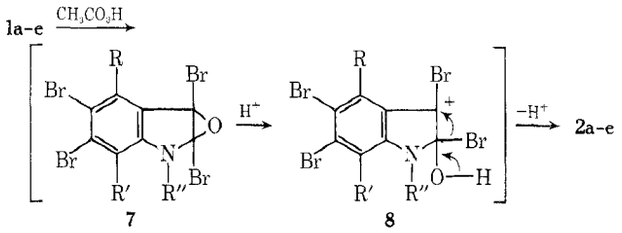
Since all 2,3-dibromoindoles were converted to 3,3-dibromooxindoles, this method could be used as a diagnostic tool in the structure determination of 2,3-dibromoindoles.

One possible explanation of the unusual oxidative reaction could involve the formation of an epoxide intermediate **7**, followed by opening of the epoxide ring to give a carbonium ion **8**, a 1,2 shift, and expulsion of the proton




to yield the observed 3,3-dibromooxindole. Similar molecular rearrangements have been already observed in the peracid epoxidation of several haloalkenes.[11]

**Acknowledgment.** This work was supported by a grant from the Consiglio Nazionale delle Ricerche.

**Registry No.**—**1a**, 17826-06-1; **1b**, 51417-37-9; **1c**, 51417-38-0; **1d**, 51417-39-1; **1e**, 25055-55-4; **2a**, 51417-40-4; **2a** β-phenylhydrazone, 51417-41-5; **2b**, 51417-42-6; **2b** β-phenylhydrazone, 51417-43-7; **2c**, 51417-44-8; **2c** β-phenylhydrazone, 51417-45-9; **2d**, 51417-46-0; **2d** β-phenylhydrazone, 51417-47-1; **2e**, 25055-56-5; **2f**, 51417-48-2; **2f** β-phenylhydrazone, 51417-49-3; **3b**, 51417-50-6; **4**, 51417-51-7.

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(11) See, *e.g.*, (a) R. N. McDonald and P. A. Schwab, *J. Amer. Chem. Soc.*, **85**, 4004 (1963); (b) R. N. McDonald and T. T. Tabor, *ibid.*, **89**, 6573 (1967); (c) R. N. McDonald and R. N. Steppel, *ibid.*, **92**, 5664 (1970); (d) W. A. Denny, V. Kumar, G. D. Meakins, J. Pragnell, and J. Wicha, *J. Chem. Soc., Perkin Trans. 1*, 486 (1972).

# Stereochemistry and Mechanism of the Thermal [1,3] Alkyl Shift of Stable 1,4-Dialkyl-1,4-dihydropyrazines[1a,b]

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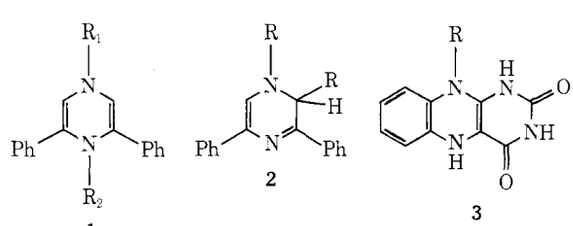
Stable 8-π-electron 1,4-dialkyl-1,4-dihydropyrazines are readily prepared by reaction of *N*-benzyldiphenacylamine hydrobromide with primary aliphatic amines provided care is taken to avoid the subsequent rearrangement. The previously postulated intermediacy of 1,4-dibenzyl-1,4-dihydro-2,6-diphenylpyrazine (**1a**) in the rearrangement to 1,2-dihydropyrazine **2a** is demonstrated and the reaction proceeds in 95 ± 2% yield with first-order kinetics. Crossover recombination experiments show 12 ± 6% intermolecular contribution from a radical dissociation–recombination process which is prevented with butanethiol scavenger. Chiral **24** rearranges in the presence of the scavenger with ≥95% stereospecificity and with inversion of the migrating group indicating an 88 ± 6% component of a concerted [1,3] sigmatropic shift with suprafacial allylic utilization.

We wish to report the general synthesis and chemistry of novel 1,4-dialkyl-2,6-diphenyl-1,4-dihydropyrazines[1] **1** and a study of the stereochemistry and mechanism of their thermally induced rearrangement to the isomeric 1,2-dialkyl-3,5-diphenyl-1,2-dihydropyrazines **2**. Compounds of structure **1** are of interest in possessing an 8π available electron system which is potentially antiaromatic[2] or homoaromatic.[3] In addition, the structural similarity between the 1,4-dihydro-1,4-dialkylpyrazines and the reactive ring of the isoalloxazine portion of the reduced flavin coenzymes **3**[4] and the marked propensity of both to undergo redox reactions (which see) renders **1** of interest as model compounds for the latter. The structurally related 5,10-dihydrophenazines **4** have been employed as analogs of riboflavin.[4,5] The recent discovery of the importance of the 1,4-dihydropyrazine moiety in the biolumi-



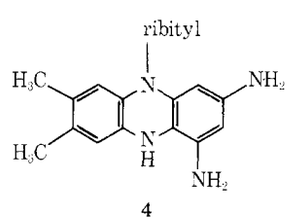
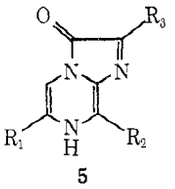



**Table I**
**1-Benzyl-4-alkyl-2,6-diphenyl-1,4-dihydropyrazines[c] (1, $R_1$ = $CH_2Ph$)**

| Compd | $R_2$ | Mp, °C | Yield, % | $\lambda_{max}$,[a] nm | Log ε | δ |
|---|---|---|---|---|---|---|
| **1a** | $CH_2Ph$ | 107–108.5 | 73 | 442<br>338 | 3.22<br>3.48 | ($C_6D_6$) 3.20 (s, 2 H, $-CH_2Ph$), 3.76 (s, 2 H, $-CH_2Ph$), 5.57 (s, 2 H, vinylic, $C_3$ and $C_5$ H), and 7.17–7.57 (m, 20 H, aromatic |
| **1b** | $(CH_2)_2Ph$ | 135–137 | 90 | 427<br>339<br>237 | 3.49<br>3.41<br>4.17 | ($C_5D_5N$) 3.25 [br s, 4 H, $-(CH_2)_2Ph$], 4.26 (s, 2 H, $-CH_2Ph$), 6.57 (br s, 2 H, vinylic H, $C_3$ and $C_5$ H), and 6.96–7.85 (m, 20 H, aromatic |
| **1c** | $(CH_2)_2CH_3$ | 103–105 | 64.4 | 428<br>338<br>238 | 3.41<br>3.29<br>4.22 | *b* |
| **1d** | $(CH_2)_3CH_3$ | 115–117 | 78.1 | 428<br>338<br>237 | 3.53<br>3.38<br>4.27 | *b* |
| **1e** | $CH_2CH(CH_3)_2$ | 106–107.5 | 79.4 | 429<br>337<br>239 | 3.21<br>3.51<br>4.21 | *b* |
| **1f** | $(CH_2)_2CH(CH_3)_2$ | 126–128 | 68.7 | 429<br>341<br>237 | 3.21<br>3.47<br>4.17 | *b*<br>*b* |
| **1g** | $CH_3$ | 133–135 | 22.3 | 428<br>340<br>237 | 3.41<br>3.51<br>4.15 | *b* |
| **1h** | c-$C_3H_5$ | 111–112.5 | 77.2 | 428<br>340<br>238 | 3.42<br>3.48<br>4.17 | *b* |
| **1i** | c-$C_5H_9$ | 107–108.5 | 30.4 | 409<br>329<br>245 | 3.64<br>3.47<br>4.09 | ($C_6D_6$) 0.92–2.02 (m, 8 H, cyclopentyl), 3.20–3.60 (br, 1 H, methine), 3.80 (s, 2 H, $CH_2Ph$), 6.35 (s, 2 H, vinylic H, $C_3$ and $C_5$ H), and 6.96–7.79 (m, 15 H, aromatic) |
| **1j** | c-$C_6H_{11}$ | 138–139.5 | 36.5 | 410<br>328<br>245 | 3.61<br>3.48<br>4.11 | ($C_6D_6$) 0.77–2.21 (m, 10 H, cyclohexyl), 2.64–3.30 (br, 1 H, methine), 3.76 (s, 2 H, $CH_2Ph$), 6.30 (2, 2 H, vinylic H, $C_3$ and $C_5$ H), and 6.95–7.91 (m, 15 H, aromatic) |
| **1k** | c-$C_7H_{13}$ | 120–121.5 | 31.4 | 409<br>329<br>243 | 3.61<br>3.45<br>4.08 | *b* |
| **1l** | c-$C_8H_{15}$ | 96–97.5 | 15.2 | 425<br>327<br>244 | 3.58<br>3.44<br>4.12 | *b* |

[a] Measured in $CH_3CN$. [b] The nmr signals were not visible owing to paramagnetic broadening by the odd-electron species present. [c] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds listed in the table: Ed.



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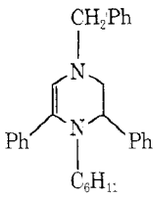
nescence of certain luciferins, *e.g.*, **5**, increases the general interest of the present study.[6] The logical approach to the synthesis of a representative of **1**, *e.g.*, the condensation of benzylamine with *N*-benzyldiphenacylamine hydrobromide, originally considered to afford 1,4-dihydro-1,4-dibenzylpyrazine,[7] has been shown to give the 1,2-dibenzyl-3,5-diphenyl-1,2-dihydropyrazine[8,9] (**4**, R = $PhCH_2$) and a 1,3-alkyl migration from the initially formed but unisolated 1,4-dibenzyl-1,4-dihydropyrazine isomer was postulated.[8]

We found that, in a general reaction with *N*-benzyldiphenacylamine, primary aliphatic amines, containing groups which are less prone to migrate, react to give the series of 1,4-dialkyl-1,4-dihydropyrazines indicated in Table I, often in excellent yield.[1] The simplicity of the nmr spectra is consistent with the $C_{2v}$ symmetry of structures of type **1**. Catalytic hydrogenation of **1j** at atmospheric pressure over Pd/C afforded the 1,2,3,4-tetrahydropyrazine **6** as an oil in 84% yield. The addition of only 1 equiv of hydrogen under these conditions is held to be characteristic of a 1,4-dihydropyrazine.[9] The new 1,4-dialkyl-1,4-dihydropyrazines described in Table I are stable as orange-red solids in the crystalline state but are sensitive to light and atmospheric oxygen and are reactive in solution, especially with halogen-containing solvents. The solutions are readily oxidized in air to stable paramagnetic species which give persistent epr signals. The sensitivity to oxygen of compounds **1a–f** results in considerable paramagnetic nmr line broadening in many cases even though they analyze correctly. Structure proof was, however, obtained with two additional representative examples, **1d** and **1h**, by catalytic hydrogenation to the 1,2,3,4-tetrahydro compounds, the nmr spectra of which were normal.[10] The epr spectra of the paramagnetic species formed by oxidation of **1j** (Table II) gave *g* values of 2.0025, close to the free-electron value of $g = 2.00232$,[11] indicative of an organic free radical, and the spectrum width for **1h**, 51 G, closely corresponds to those values previously reported for the reduction in concentrated sulfuric acid solutions of substituted pyrazines.[12] These analogies, together with



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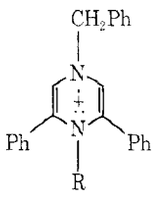

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**Table II**
**Esr Data on Paramagnetic Species Formed from the Oxidation of 1,4-Dialkyl-2,6-diphenyl-1,4-dihydropyrazines 1 in Benzene**

| Substrate | Spectrum width, G | Appearance |
|---|---|---|
| **a** | 62.5 | Multiplet |
| **b** | 110.0 | Multiplet |
| **c** | 167.0 | Multiplet |
| **d** | 68.0 | Multiplet |
| **e** | 58.0 | Multiplet |
| **f** | 87.0 | Multiplet |
| **g** | 64.5 | Multiplet |
| **h** | 51.0 | 8 lines, hfs 7.5 G |
| **i** | 48.0 | 7 lines, hfs 7.5 G |
| **j**[a] | 50.0 | Multiplet |
| **m**[b] | 72.0 | 9 lines, hfs 8.6 G |

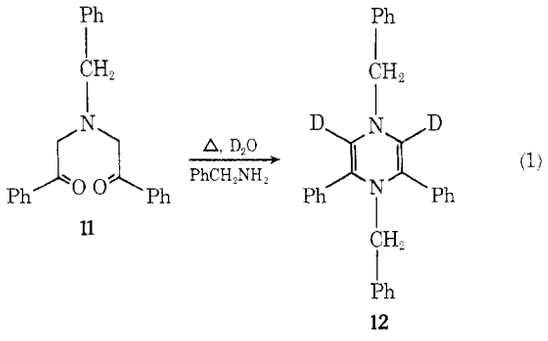
[a] $g$ value = 2.0025. [b] 1,4-Dimethyl-2,6-diphenyl-1,4-dihydropyrazine.

the recent announcement that stable pyrazine radical cations may be generated under mild conditions by the action of daylight,[13] point to the 7-$\pi$-electron radical cation structure (**7**) for these species.

It was possible by employing lower reaction temperatures to isolate the very reactive 1,4-dibenzyl-2,6-diphenyl-1,4-dihydropyrazine (**1a**) as an orange, crystalline solid. This permits confirmation of the previously postulated mechanism[8,9] and an examination of this unusually facile [1,3] alkyl shift.

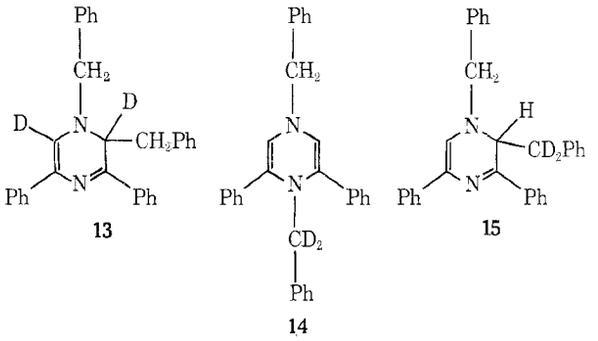
Examples of thermally induced [1,3] shifts involving heteroatoms at the migration origin or terminus have been reported in several cases.[14,15] However, in very few of these cases has it yet been established whether the rearrangements are concerted or proceed *via* a radical mechanism.[16] Thus we hoped to contribute to the general problem of [1,3] shifts. The 1,4-dibenzyl-2,6-diphenyl-1,4-dihydropyrazine rearranges smoothly in benzene in the temperature range of 40–80° to **2** (R = $PhCH_2$) in a yield of ≥95 ± 2% as determined spectroscopically. Because of the photosensitivity and propensity of 1,4-dialkyl-1,4-dihydropyrazines to air oxidize to stable odd-electron species[1,13] it was necessary to degas carefully and protect the solution from the light.

To establish whether the reaction is intramolecular or intermolecular we performed a crossover recombination experiment with differentially deuterium-labeled 1,4-dialkyl-1,4-dihydropyrazines. The ring-labeled compound **12** was formed readily by deuterium exchange (eq 1) with



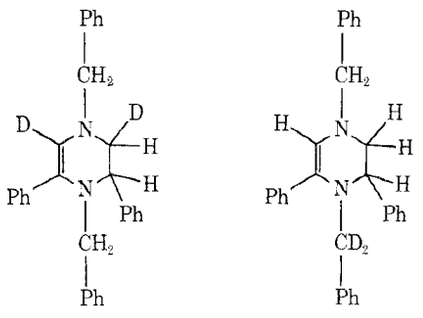

(1)

≥80% incorporation as shown by nmr, which showed the diminution of the 2 H singlet at $\delta$ 6.25. Rearrangement of **12** in benzene gave a quantitative yield of the 2,6-dideuterio-1,2-dihydropyrazine **13**, which allowed assignment of the methine and vinyl nmr absorptions in **2a** as $\delta$ 4.76 and 6.55, respectively. The isotopic labeling isomer of **12**, compound **14**, was prepared by treating **11** with $PhCD_2NH_2$ and contained 100 ± 2% deuterium incorporation at the 1-benzyl methylene positions. Thermal rearrangement of **14** to **15** proceeded smoothly and permitted assignment of




the methylene group nmr signals at the 1 and 2 positions of **2a** as $\delta$ 3.96 ($J$ = 15.5 Hz) and 2.70 ($J$ = 14.0 Hz), respectively.

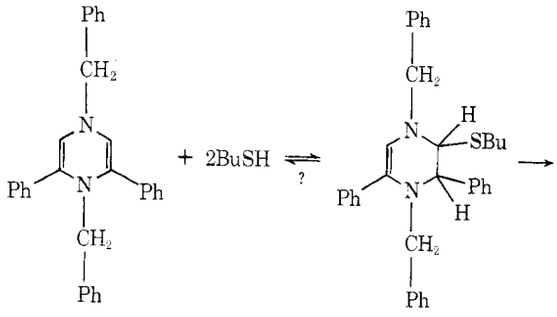
Additional assignments of the vicinal coupling constants were readily accessible by rapid catalytic hydrogenation of compounds **12** and **14**. Under these conditions 1,4-dihydropyrazines add only 1 equiv of hydrogen[9] and no deuterium scrambling was observed, giving compounds **16** and **17** from **12** and **14** respectively. An intimate mixture



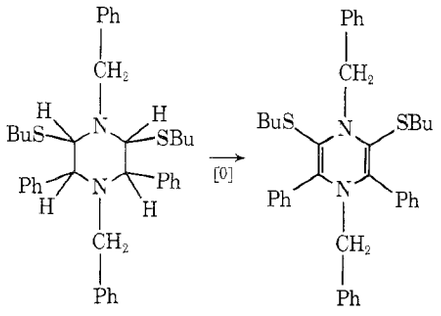

**of 12** and **14** in a ratio of 5:4 was heated in benzene at 55° until the rearrangement was completed and the product mixture was examined by mass spectrometry. The isotopic content was consistent only with 12% being formed by crossover recombination.[17]

The results therefore indicate a largely intramolecular reaction with a small intermolecular component. Since free radicals are implicated in the extra cage reaction by scavenging experiments (which see), the crossover recombination evaluates the extent to which the initially formed radicals in the intermediate are independent (*i.e.*, escape the solvent cage). Similar crossover experiments in hexane (14%) and tetrahydrofuran (12% crossover) indicate that the somewhat higher figure for the former solvent may reflect its lower viscosity.[18] Combination of pyrazinyl radicals to form a dimer was not detected. The 10% or so of free pyrazinyl radicals formed may tend to scavenge benzyl radicals rather than permit the formation of detectable quantities of bibenzyl. The measured M + 4 peak, after correction for the $^{13}C$ isotope peak,[19] represents ¼ of the rearrangement product formed outside the solvent cage. In agreement with this interpretation it was found that, when the rearrangement of the mixture of **12** and **14** was performed in the presence of the radical scavenger butanethiol, crossover recombination, represented by the M + 4 peak, was prevented completely, and with the formation of butane disulfide. Since the yield of **2a** in the presence of the scavenger was 75 ± 3%, corresponding fairly well to a 95 ± 2% yield diminished by the extra-cage yield, this would tend to rule out a free-radical chain mechanism. A competing slow addition of the butanethiol

to the 1,4-dihydropyrazine is evident when a large excess of the thiol (20 equiv) is used, resulting in the formation of 1,4-dibenzyl-2,6-diphenyl-3,5-di(butylthiol)-1,4-dihydropyrazine (**20**) in 36% yield.[20] The loss of hydrogen from



**1a** **18**



**19** **20**

18 or 19 to form 20 may be due to disproportionation or air oxidation. This ready reversion of adducts of **1** to the 1,4-dihydrostructure, particularly when they bear five or more ring substituents, is surprising but common and attests to the unexpected stability of this new heterocyclic system.

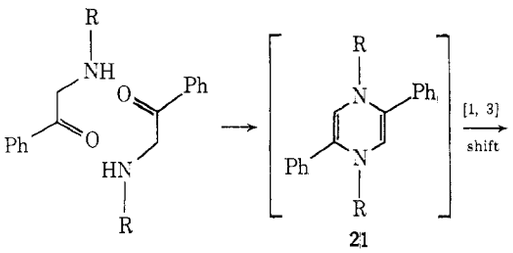
With firm evidence for the intervention of free radicals in the rearrangement an estimate of their lifetime was sought using CIDNP. The experimental conditions were established first by a control with picoline *N*-oxide–acetic anhydride system.[21] Rearrangement of the latter in benzene at 83° gave a strong CIDNP emission signal. However, in the present system no sign of a CIDNP effect was detected under a variety of conditions. In view of recent caveats concerning the conclusions to be drawn from such experiments[22] this negative result does not rule out the possibility of a rapid intramolecular rearrangement involving a tight radical pair. Closs[23] recently estimated the limiting lifetime of a free radical detectable by CIDNP at $10^{-10}$ sec. Owing to the tendency of benzyl groups to cleave as benzyl radicals, additional migrating alkyl groups were examined, namely cyclohexyl and cyclopentyl. The corresponding 1,4-dihydropyrazines rearranged smoothly to the 1,2-dihydropyrazines, both in good yield.

The kinetic order of the rearrangements was established conveniently by measuring the rate of disappearance of **1** by absorption spectrophotometry at 500 nm at which wavelength there was no overlap with the product. Compounds **1a**, **1i**, and **1j** obeyed Beer's law. The rearrangement of **1a** to **2a** strictly obeyed first-order kinetics over 80% of the reaction and at 55.4° gave $k = 6.44 \times 10^{-4}$ $sec^{-1}$. Measurement of the reaction rate in the temperature range 40.4–75.3° allowed the evaluation of Arrhenius parameters of $\Delta E^* = 15.6$ kcal $mol^{-1}$ and $\Delta S^* = -16.3$ eu.[24] The cyclopentyl and cyclohexyl analogs **1i** and **1j** similarly rearrange at somewhat higher temperatures but again strictly according to first-order kinetics.

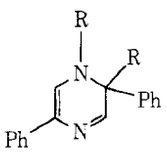
These examples indicate that relief of steric compression of the groups at the 1, 2 and 6 positions may contribute to the driving force of the migration, since the direction of migration is such as to favor formation of less stable migrating radical and migration terminus. By comparison the analogous rearrangement of the symmetrical 2,5-diphenyl substituted 1,4-dihydropyrazines **21** is regiospecific, giving exclusively migration to the substituted carbon in **22**. In view of the proposed intermediacy of ion

**Table III**

| Rates (55.4°) | Solvent | Dielectric constant |
|---|---|---|
| $6.44 \times 10^{-4}$ | $C_6H_6$ | 2.28 |
| $7.95 \times 10^{-4}$ | Tetrahydrofuran | 7.95 |
| $11.80 \times 10^{-4}$ | *o*-$Cl_2C_6H_4$ | 9.93 |



**21**



**22**

pairs in certain rearrangements of analogous 1,2-dihydropyridines[25] and of ostensibly antiaromatic 2-azirines,[26] the effects of changes in solvent dielectric constant on the rate of rearrangement of **1a** to **2a** at 55.4° was examined (Table III). A slight trend toward higher rate at higher dielectric constant was observed but was clearly insufficient to warrant consideration of the intervention of charged species. The rate of a concerted [1,3] sigmatropic shift or of a stepwise reaction involving radical intermediates where no significant charge build-up develops should be relatively independent of solvent polarity.[27] As remarked upon above, unless care is exercised to exclude air from solutions of 1,4-dialkyl-1,4-dihydropyrazines, strong and persistant epr signals are detected.[1] Thus the possibility of a molecule-induced homolysis mechanism must be considered.[28] However, the rate of rearrangement of **1** in the presence of 2.5 equiv of the scavenger butanethiol (measured by the rate of disappearance of the dihydropyrazine) at the midrange temperature was comparable with that observed in the absence of the scavenger. The small rate difference is probably not due to a solvent effect, since a slight rate enhancement should have been anticipated on the basis of the study of solvent dielectric constant on rate. We rather attribute the rate reduction to the slow competing reversible addition of the scavenger to **1** discussed in the preparative experiment.

The above data point to an unusually facile unimolecular rearrangement which proceeds to the extent of ≥88% in an intracage process with a 12% contribution from intermolecular extracage free-radical pathway. Orbital symmetry theory recognizes two thermally allowed pathways for a [1,3] sigmatropic shift in an allylic moiety,[29] inversion at the migrating center with suprafacial allylic utilization and retention at the migrating carbon with antarafacial allylic participation. The latter alternative is excluded by geometrical constraints. Recently interest has

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## EXPERIMENTAL SECTION

### General

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 421 spectrophotometer, and only the principal sharply defined peaks are reported. Nuclear magnetic resonance spectra were recorded on Varian A-60 and A-100 analytical spectrometers. The spectra were measured on approximately 10–15% (w/v) solutions in $CDCl_3$ with tetramethylsilane as a standard. Line positions are reported in parts per million from the reference. Absorption spectra were recorded in "Spectro" grade solvents on a Beckman DB recording spectrophotometer. Mass spectra were determined on an Associated Electrical Industries MS-12 double-focusing high resolution mass spectrometer. The ionization energy, in general, was 70 eV. Peak measurements were made by comparison with perfluorotributylamine at a resolving power of 15,000. Eastman Kodak precoated sheets were used for thin layer chromatography. Microanalyses were carried out by Mrs. D. Mahlow of this department.

### N,N-Diphenacylbenzylamine

To a suspension of 8.5 g (20 mmole) of diphenylacylbenzylamine hydrobromide in cold water was added dropwise a 10% sodium bicarbonate solution (50 ml). The free base was extracted with ether and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave a yellow oil 6.2 g (91%) of N,N-diphenacylbenzylamine; which turns dark on standing at room temperature; nmr $\delta_{TMS}$ ($CDCl_3$): 4.01 (s, 2H, $-N-CH_2Ph$), 4.25 (S, 4H, $-CH_2-COPh$), and 7.25 - 8.05 (m, 15H, aromatics); ir($CHCl_3$) $1670\ cm^{-1}$ (C=O).

Anal. Calcd. for $C_{23}H_{21}NO_2$ (mol. wt. 343.1736). Found (343.1731, mass spectrum).

### 1,4-Dialkyl-1,4-dihydropyrazines

A representative preparation of one of the more stable examples is given, thereafter the physical data on other compounds similarly prepared are summarized in Table I.

### 4-Benzyl-1-phenethyl-2,6-diphenyl-1,4-dihydropyrazine

To a solution of 4.25 g (10 mmole) of diphenacylbenzylamine hydrobromide in 5 ml of toluene was added 2.45 g (20 mmole) of phenethylamine. The reaction mixture was heated under nitrogen in an oil bath at 100 ± 2° for 4 h. The thick oil was treated with benzene and washed twice with cold water. The dark red solution was dried ($Na_2SO_4$). Removal of the solvent *in vacuo* gave an oil which on trituration with 95% ethanol deposited the dihydropyrazine 1b as a dark red solid 3.89 g (90%) m.p. 135–7°. Mass spectrum (70 eV) 428.2245 (calcd. for $C_{31}H_{28}N_2$, 428.2253).

Anal. Calcd. for $C_{31}H_{28}N_2$: C, 86.88; H, 6.58; N, 6.54. Found: C, 86.74, H, 6.70; N, 6.21.

### 1,4-Dibenzyl-1,4-dihydro-2,6-diphenylpyrazine

To a suspension of 4.25 g (10 mmole) of diphenacylbenzylamine hydrobromide[1] in 5 ml of benzene[44] was added 2.15 g (20 mmole) of benzylamine. The mixture, in a pressure bottle was kept in an oil bath maintained at 40 ± 1° for 18 h. The reaction mixture was cooled to room temperature, diluted with 200 ml of ether and the precipitated benzylamine hydrobromide removed by filtration. The filtrate was washed with 30 ml of cold water and dried ($Na_2SO_4$). Removal of the solvent *in vacuo* at ambient temperature yielded a red semi-solid which was purified by chromatography on 100 g of B.D.H. alumina using benzene:hexane (1:9) as eluent. The initial colorless eluant was discarded then further elution gave a red solution. Removal of the solvent from the first 100 ml of the colored solution *in vacuo* at 35 ± 1° gave 1a as a red solid, 2.45 g (59%) m.p. 109–110.5° (95% ethanol)[45]; nmr $\delta_{TMS}$ (pyridine-$d_5$): 3.85 (s, 2H, 4-benzyl $CH_2$); 3.96 (s, 2, 1-benzyl $CH_2$), 6.23 (s, 2,3 and 5 protons); 7.16 - 7.9 (m, 20, aromatic protons); $\lambda_{max}$ ($C_6H_6$) 442 (log ε 3.33) and 338 (log ε 3.84); mass spectrum (70 eV) 414.2106 (calcd for $C_{30}H_{26}N_2$, 414.2096).

Anal. Calcd. for $C_{30}H_{26}N_2$: C, 86.95; H, 6.32; N, 6.76; Found: C, 87.07; H, 6.20; N, 6.96.

Continued elution and following the procedure described above gave a mixture of 1a and the rearranged product 2a, 0.900 g (80:20) as estimated by nmr. The pure 1,4-dihydropyrazine 1a was stable indefinitely at 0° and in the dark, otherwise it became gummy and discolored either by oxidation or due to a photochemical process.

### Thermal Rearrangement of 1,4-Dibenzyl-1,4-dihydro-2,6-diphenylpyrazine

A solution of 0.725 g (1.75 mmol) of 1a in 50 ml of benzene was heated under reflux for 4 h. Removal of the solvent *in vacuo* gave a red oil, trituration of which with 95% ethanol gave 1,2-dibenzyl-1,2-dihydro-3,5-diphenylpyrazine 4 as an orange solid 0.643 g (89%) m.p. 105–106.5° [lit. m.p. 94–98°[6,7]. The nmr spectrum of 2a was identical with that reported by Chen and Fowler.[8] Absorption spectrum $\lambda_{max}$ ($C_6H_6$): 2422 nm (log ε = 3.785), and 327 (log ε 4.08).

In a separate control experiment the yield of 2a as determined spectroscopically was 92 ± 3%.

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### Thermal Rearrangement of 1,4-Dibenzyl-1,4-dihydro-2,6-diphenylpyrazine in the Presence of Butanethiol

A solution of 0.732 g (1.75 mmol) of 1a and 0.183 g (2 mmol) of butanethiol in 50 ml of benzene was heated under reflux for 4 h. Removal of the solvent *in vacuo* afforded a red oil. The yield of 2a determined spectroscopically was found to be 75 ± 3%. Chromatography of the red oil on 50 g of B.D.H. alumina and elution with benzene:hexane (1:5) gave first a colorless fraction which provided butane disulfide 0.055 g, m/e = 178 (mass spectrum). Further elution with benzene:hexane (1:5) gave pure 2a as an orange oil 0.496 g (67%) which solidified on standing to give an orange solid m.p. 108–109.5°.

### 1,4-Dibenzyl-3,5-dideuterio-1,4-dihydro-2,6-diphenylpyrazine

To a suspension of 6.3 g (15 mmol) of diphenacylbenzylamine hydrobromide in 15 ml of tetrahydrofuran (freshly distilled from lithium aluminum hydride) was added 3.8 g (35 mmol) of benzylamine in 25 ml of deuterium oxide (99.7%, Merck, Sharp and Dohme of Canada). The mixture was stirred at room temperature for 7 days. The usual work-up procedure and chromatography on B.D.H. alumina gave the labelled 1,4-dihydropyrazine 1d as a dark red solid, 3.26 g (54%) m.p. 107.5–109°. nmr $\delta_{TMS}$ (pyridine-$d_5$): 3.86 (s, 2,4-benzyl $CH_2$); 3.97 (s, 2,1-benzyl $CH_2$), 6.25 (s, 0.4, 3 and 5 protons, 80% ring deuterium incorporation); 7.17–7.94 (m, 20, aromatic protons). Mass spectrum (70 eV) 416.2219, (calcd. for $C_{30}H_{22}D_2N_2$, 416.2221).

### 1,2-Dibenzyl-2,6-dideuterio-1,2-dihydro-3,5-diphenylpyrazine

To a solution of 6.6 g (20 mmol) of di(phenacyl-1-$d_2$)-benzylamine (80% deuterium incorporation, prepared by treating diphenacylbenzylamine with deuterium oxide in dry tetrahydrofuran solution with a trace of sodium hydroxide as catalyst), in 50 ml of tetrahydrofuran was added 4.5 g (45 mmol) of benzylamine in 40 ml of deuterium oxide. The reaction mixture was heated under reflux for 24 h. The usual workup procedure gave compound 1j 5.75 (70%) m.p. 105–106.5°, nmr $\delta_{TMS}$ ($CDCl_3$): 2.69 (ABq, $J_{AB}$ = 14.0 Hz, 2;2-benzyl methylenes)] 3.95 (ABq, $J_{AB}$ = 15.0 Hz, 2;1-benzyl methylenes), 6.85–8.01 (m, 20, aromatic protons). Mass spectrum (70 eV) 416.2218 (calcd. for $C_{30}H_{24}D_2N_2$, 416.2221).

### 1-(Benzyl-$\alpha,\alpha$-$d_2$)-4-benzyl-2,5-diphenyl-1,4-dihydropyrazine

To a solution of 3.5 (10 mmol) of diphenacylbenzylamine in 5 ml of benzene was added 1.1 g (10 mmol) of $\alpha,\alpha$-$d_2$-benzylamine prepared by a literature procedure.[46] The solution was set aside at 40 ± 1° for 18 h. The usual workup procedure gave the benzyl labelled 1,4-dihydropyrazine 1d 2.63 g (60% yield) m.p. 108–109.5°, nmr $\delta_{TMS}$ (pyridine-$d_5$): 3.87 (s, 2;4-benzyl methylenes), 6.22 (s, 2; 3 and 5 proton); 7.18–7.92 (m, 20, aromatic protons). The disappearance of the 3.96 absorption represents 100% incorporation of deuterium. Mass spectrum (70 eV) 416.2217 (calcd. for $C_{30}H_{24}D_2N_2$, 416.2221).

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### 1-Benzyl-2-(benzyl-$\alpha,\alpha$-$d_2$)-1,2-dihydro-3,5-diphenylpyrazine

The thermal rearrangement of compound 1d carried out in the usual manner gave compound 1j in 80% yield, m.p. 105–106.5, nmr $\delta_{TMS}$ ($CDCl_3$): 3.96 (ABq, $J_{AB}$ = 15.0 Hz, 2;1-benzyl methylenes), 4.78 (s, 1;2 methine), 6.61 (d, $J_{2,6}$ = 1.5 Hz, 6-proton) and 6.87–7.97 (m, 20 aromatic protons).

### Catalytic Hydrogenation of 1,4-Dibenzyl-2,6-diphenyl-3,3-dideuterio-1,4-dihydropyrazine 1d and 1d

(i) A solution of 0.60 g (1.41 mmole) of 1d in 80 ml of ethyl acetate was hydrogenated over 100 mg of 10% palladium on charcoal at atmospheric pressure for 48 h. The residual oil, obtained by filtration through Celite and removal of the solvent *in vacuo*, was chromatographed on 40 g of B.D.H. alumina. Elution with benzene:hexane gave 1,2,3,4-tetrahydro-3,5-dideuterio-1,4-dibenzyl-2,6-diphenylpyrazine 1e as an oil 0.302 g (50%); nmr $\delta_{TMS}$ ($CDCl_3$): 2.93 (d, 1H, $J_{2,3}$ = 2.0 Hz, $C_2H$), 3.55 and 4.33 (two doublets, 2H, J = 13.5 Hz, $N-CH_2Ph$), 3.65 (ABq, 2H, J = 12.5 Hz, $-NH-CH_2Ph$), 4.10 (d, 1H, J = 2.0 Hz, $C_3H$) and 6.94 - 7.78 (m, 20H, aromatics).

Anal. Calcd. for $C_{30}N_{26}D_2N_2$ (mol. wt. 420.2304). Found: (420.2309, mass spectrum).

(ii) A similar catalytic hydrogenation of 1-($\alpha$,$\alpha$-dideuteriobenzyl)-4-benzyl-2,6-diphenyl-1,4-dihydropyrazine 1e gave 1,2,3,4-tetrahydro-1-($\alpha,\alpha$-dideuteriobenzyl)-4-benzyl-2,6-diphenyl-1,4-dihydropyrazine 1f as an oil in 52% yield; nmr $\delta_{TMS}$ ($CDCl_3$) 2.85–3.25 (m, 2H, $C_3H$), 3.87 (center of ABq, 2H, J = 12.5 Hz), $-NHCH_2PH$), 4.11 (t, 1H, J = 2.0 Hz, $C_2H$), 6.07 (s, 1H, $C_5H$) and 6.94–7.81 (m, 20H, aromatics).

Anal. Calcd. for $C_{30}N_{26}D_2N_2$ (mol. wt. 420.2304). Found: (420.2311, mass spectrum).

### Cross-over Recombination Experiments with Deuterium Labelled 1,4-Dibenzyl-1,4-dihydropyrazines.

A solution of 0.104 g (0.25 mmol) of 1j (99% deuterium incorporation) and 0.131 g (0.315 mmol) of 1d (80% deuterium incorporation) in 25 ml of the solvent (benzene, hexane, or tetrahydrofuran) was heated under reflux for 6 h. Removal

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of the solvent *in vacuo* and trituration of the residual oil with 95% ethanol resulted in the crystallization of the rearranged labelled products m.p. 105–106.5° The product was examined by high resolution mass spectrometry as summarized in Table III.

### Reaction of 1,4-Dibenzyl-2,6-diphenyl-1,4-dihydropyrazine with Butanethiol

A solution of 0.83 g (1 mmole) of 1a and 1.38 g (15 mmole) of butanethiol in 5 ml of benzene was set aside at room temperature for 4 days. Removal of the solvent *in vacuo* gave a red oil which was subjected to chromatography on 60 g of B.D.H. alumina. Elution with hexane:benzene (2:1) gave a light yellow oil, 0.501 g (42%) (of 1,4-dibenzyl-2,6-diphenyl-3,5-dibutylthio-1,4-dihydropyrazine 2b); nmr $\delta_{TMS}$ ($CDCl_3$) 0.91 (t, 6H, $CH_3$), 1.12–1.65 (m, 8H, $-(CH_2)_2-$), 1.85 (t, 4H, $-CH_2-S-$), 4.24 (bs, 2H, $-CH_2Ph$), 4.64 (bs, 2H, $-CH_2Ph$) and 6.98–7.98 (m, 30H, aromatics).

Anal. Calcd. for $C_{38}H_{42}N_2S_2$[32] (mol. wt. 590.27905). Found: (590.2813, mass spectrum).

### Chemically Induced Dynamic Nuclear Polarization (CIDNP) Experiments

### (i) Control Experiment with γ-Picoline-N-oxide

A degassed solution of 100 mg of γ-picoline-N-oxide[47] m.p. 180–182° in 250 µl of acetic anhydride and 100 µl of benzene-$d_6$ was sealed in an nmr tube. In 35 sec after the sample tube had been placed in the heated (83°) cavity of the Varian 100 MHz nmr spectrometer, there appeared emission signals at δ 4.97 and 2.58 which reached a maximum in 120 sec and gradually disappeared.[21]

### (ii) 1,4-Dibenzyl-2,6-diphenyl-1,4-dihydropyrazine

Similarly a degassed solution of 125 mg of 1a in 0.7 ml of benzene-$d_6$ was sealed in an nmr tube and placed in the nmr cavity at 83°. The spectral data were stored in a computer at 5 sec intervals for a period of 10 min. The reproduction of these data did not show any emission and enhancement signals. However, at the end of the 10 min period approximately 85% of 1a had been converted into 2a.

### Thermal Rearrangement of 4-Benzyl-1-cyclohexyl-2,6-diphenyl-1,4-dihydropyrazine 1i

A solution of 1.05 g (2 mmole) of 1i in 30 ml of *p*-xylene was heated under reflux in an atmosphere of nitrogen for 10 h. Removal of the solvent *in vacuo* gave an orange oil which was subjected to chromatography on 50 g of BDH alumina.

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Elution with benzene:hexane (1:2) gave a light yellow oil 0.468 g (46.5%) which on trituration with ethanol and on cooling deposited yellow crystals of 1-benzyl-2-cyclohexyl-3,5-diphenyl-1,2-dihydropyrazine 2i, m.p. 127–8.5°, nmr $\delta_{TMS}$ ($CDCl_3$): 0.91–2.01 (m, 11H, $C_6H_{11}$), 4.32 (dd, 1H, J = 8.5, $J_{2c}$ = 1.5 Hz, $C_2H$), 4.52 (c, 2H, $J_{AB}$ = 12.5 Hz, $-CH_2Ph$), 6.53 (d, 1H, $J_{2c}$ = 1.5 Hz, $C_2H$), and 6.98–7.81 (m, 15H, aromatics).

Anal. Calcd. for $C_{29}H_{30}N_2$ (mol. wt. 406.2409) C, 85.65; H, 7.42; N, 6.92. Found: (405.2413, mass spectrum): C, 84.91; H, 7.33; N, 7.17.

### Kinetic Studies

$(1.0 - 5.0) \times 10^{-2}$ Molar solutions of the 1,4-dihydropyrazines were prepared in benzene or the other appropriate solvents at room temperature and transferred in 5 ml aliquots to reaction tubes which were sealed and protected from the light with aluminum foil. The reaction tubes were placed in a Colora constant temperature bath, and after thermal equilibrium was attained, one tube was withdrawn, quenched in a methanol-ice bath and the initial absorbance recorded. Seven or eight reaction tubes were withdrawn at convenient intervals and the concentration of the 1,4-dihydropyrazine established by absorption spectrophotometry using balanced 1 cm cells. The analysis was performed at 500 nm region where the rearranged 1,2-dihydropyrazine isomer had a negligible extinction coefficient. It was established that the three 1,4-dihydropyrazines studied obeyed Beer's Law in the optical density range of 0.04–1.2. The reactions followed good first order kinetics for the disappearance of the 1,4-dihydropyrazine and showed a linear relationship for $\log (E_t/E_0)$ *versus* time, where $E_0$ = the initial optical density and $E_t$ = the optical density at time t. A representative run is shown in full in Table IV, and subsequent kinetic data are summarized in Table V.

### Stereochemistry Experiments

### 1-[(+)α-d-Benzyl]-4-benzyl-2,6-diphenyl-1,4-dihydropyrazine

To a solution of 3.3 g (10 mmole) of diphenacylbenzylamine in 5 ml of benzene was added 1.1 g (10 mmol) of (S)(+)α-d-benzylamine $[\alpha]_{10}^{D}$ +-0.738 (neat) prepared by the prescribed procedure.[32] The mixture was set aside for 18 h at 40 ± 1°. The workup procedure described previously afforded the chiral 1,4-dihydropyrazine (S)-2d 2.51 g (60%) m.p. 108.5–110°; nmr $\delta_{TMS}$ (pyridine-$d_5$) 3.85 (s, 2;4-benzylmethylene), 3.97 (s, 1.2H, 1-benzyl methine, 80% deuterium label), 6.24 (s, 2;3 and 5 protons); 7.19–7 92 (m, 20, aromatic protons). Mass spectrum (70 eV) 415.2153 (calcd. for $C_{30}H_{25}DN_2$, 415.2159).

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### Rearrangement of (S)1-(α-d-Benzyl)-4-benzyl-2,6-diphenyl-1,4-dihydropyrazine in the Presence of Butanethiol.

A solution of 0.425 g (1 mmole) of the dihydropyrazine (S) 2d and 0.092 g (1 mmole) of butanethiol in benzene was heated under reflux in a nitrogen atmosphere for 8 h. Removal of the solvent *in vacuo* gave a red oil which was subjected to chromatography on 40 g of B.D.H. alumina. Elution with benzene:hexane (1:2) gave a light yellow oil 0.279 g (67%) of the 1-benzyl-2-(α-d-benzyl)-3,5-diphenyl-1,2-dihydropyrazine (-)(R) 2f which on trituration with ethanol gave yellow crystals m.p. 108–109.5° $[\alpha]_L^{25}$ -0.76 (c, 3.75, $C_6H_6$).

### (-)-(R)-3-Phenyl-2-deuteriopropiophenone

The title compound was prepared by the following sequence of reactions.

(a) (-)-(S)-α-d-Benzylamine 2j (80%) - $[\alpha]_D^{25}$ + 0.73 (21, neat); $[\alpha]_D^{25}$ + 0.71 (21, 4.01, $C_6H_6$) was prepared by the prescribed procedure.[32]

(b) (-)-(S)-N,N-Dimethyl-α-d-benzylamine 2k (80%), b.p. 71–73°/17mm, (85% yield), $[\alpha]_D^{25}$ - 1.94 (21, 7.0, $C_6H_6$) was prepared by the methylation of (+)-(S)-α-d-benzylamine by treatment with formic acid and formaldehyde[48], nmr $\delta_{TMS}$ ($CDCl_3$): 2.58 (s, 6H, $N(CH_3)_2$), 3.57 (t, 1.2DH, $J_{HD}$ = 1.7 Hz-CHD), and 7.25 (s, 5H, aromatic).

(c) (+)-(S)-N,N-Dimethyl-N-phenacyl-α-d-benzylammonium bromide 2l. This compound was prepared from the (-)-(S)-N,N-dimethyl-α-d-benzylamine by reaction of phenacylbromide in benzene, as a white granular solid m.p. 160–2°[49] (88%) $[\alpha]_D^{25}$ + 0.50 (21, 7.52 $CH_3OH$).

(d) (+)-(S)-α-Dimethylamino-β-deutero-β-phenylpropiophenone 2m. This compound was obtained by heating the quaternary salt with 10% excess of 1N sodium hydroxide. The propiophenone was crystallized from hot methanol as needles m.p. 67–68° (80%). $[\alpha]_D^{25}$ -3.34 (21, 10.2, $C_6H_6$), nmr $\delta_{TMS}$ ($CDCl_3$) = 2.40 (s, 6H, $-N(CH_3)_2$), 2.80–3.20 (b, 1.2d, -CHD), 4.21–4.91, (S, 1H, $-\underline{CH}-$), and 7.17–7.97 (m, 10Z, aromatics).

Anal. Calc. for $C_{17}H_{18}DNO$: C, 80.63; H, 7.50; N, 5.53. Found: C, 80.36; H, 7.79; N, 5.65.

(e) (-)-(R)-β-Deutero-β-phenylpropiophenone 2g. A magnetically stirred solution of 0.509 g (2 mmole) of the aminoketone in 25 ml of glacial acetic acid was heated under reflux with 0.49 g (5.1 mmole) of zinc dust for 45 min. The hot solution was filtered from the inorganic precipitate and excess zinc. The filtrate was diluted with an ice-water mixture (125 ml) to yield a yellow semi-solid which was taken up in ether dried ($MgSO_4$) and the solvent removed to give 2g 0.313 g (75%). Repeated recrystallization from ether-petroleum ether gave a pure sample as white needles, m.p. 67–68.5° (lit. m.p. 69–71°). $[\alpha]_D^{25}$ -1.387 (21, c, 3.3 $C_6H_6$).

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### Aqueous Acid Catalyzed Hydrolysis of 1,2-Dibenzyl-3,5-diphenyl-1,2-dihydropyrazine.

A solution of 0.63 g (1.52 mmole) of the 1,2-dihydropyrazine 2a in 50 ml of tetrahydrofuran and 20 ml of concentrated hydrochloric acid was heated under reflux for 18 h. The red solution was diluted with water and extracted with ether. The organic layer was washed twice with 5% sodium hydrogen carbonate solution, dried ($MgSO_4$), concentrated *in vacuo* to give a light yellow oil, 0.35 g which solidified on standing. Trituration with methanol-petroleum ether gave a light colored solid m.p. 143–146.5°, $\delta_{TMS}$ ($CDCl_3$): 4.23 (s, 4H, $\underline{CH_2}Ph$), 7.13 (s, 10H, aromatic) and 7.26 - 7.53 (m, 10H, aromatic).

Anal. Calcd. for $C_{30}H_{24}N_2$: C, 87.35; H, 5.82; N, 6.79. Found: C, 87.41; H, 5.73; N, 6.51.

Possible structures for this product are 2,6-dibenzyl-3,5-diphenylpyrazine m.p. 146–7°[7] or 3,6-dibenzyl-2,5-diphenyl pyrazine m.p. 145–147°.[8]

### Ozonolysis of 1,4-Dibenzyl-3,5-d-phenyl-2,6-dihydropyrazine at −52 ± 2°

A slow stream of ozone was passed into a solution of 1.0 g (2.36 mmole) of the dihydropyrazine 2a in 40 ml of ethyl acetate placed in a dry ice-acetone bath until moistened potassium iodide-starch paper gave a positive iodine test (approximately 9–10 min). The reaction mixture was then poured into 150 ml of water containing 2 g of zinc dust. The mixture was stirred at room temperature for 24 h. The filtered solution was extracted with ether to give an oil, which was purified by chromatography on BDH alumina. Elution with benzene:hexane (7:3) gave 0.483 g of an oil 3la nmr $\delta_{TMS}$ ($CDCl_3$): 2.67–3.57 (m, 2H, $-CH_2Ph$), 4.41 (ABq, J = 14.5 Hz, $N-CD_2Ph$), 4.72–5.45 (m, 0.5H), 8.32 (s, 2.5H, J = 8.0 Hz), 7.09–8.09 (m, 15H, aromatics) 8.23 (s, 0.5H, -CHC) and 8.40 (s, 0.4H, CHO).

Anal. Calc. for $C_{23}H_{21}NC_2$ (mol. wt. 343.1862. Found: (343.1871, mass spectrum).

Compound 3l was taken up in dry tetrahydrofuran and treated with potassium carbonate and deuterium oxide and the mixture heated under reflux for 10 h allowed to cool and extracted with ether. The extract was dried ($MgSO_4$) and the solvent removed to give an oil 3lc nmr $\delta_{TMS}$ ($CDCl_3$) 2.67–3.58 (m, 2H, $-CH_2Ph$), 4.41 (ABq, J = 14.5 Hz, $-NCD_2Ph$), 7.05–8.39 (m, 15H, aromatics), 8.23 (s, 0.6H) and 8.40 (s, 0.4H) (-CHO).

Similarly, the ozonolysis of 1,2-dibenzyl-3,5-diphenyl-2,6-dideuterio-1,2-

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dihydropyrazine under the conditions given above gave 2lb nmr $\delta_{TMS}$ ($CDCl_3$): 2.67–3.58 (m, 2H, $-CH_2Ph$), 4.41 (ABq, J = 14.5 Hz, $NCH_2Ph$), 4.72–5.45 (m, 0.5H), 8.33 (t, 0.5H, J = 8.0 Hz), and 7.03–8.09 (m, 15H, aromatics).

### Ozonolysis of 1,2-Dibenzyl-3,5-diphenyl-1,2-dihydropyrazine at Ambient Temperatures.

A slow stream of ozone was passed into a solution of 1.0 g (2.36 mmole) of 2a in 40 ml of ethyl acetate until moistened potassium iodide-starch paper gave a positive test. The reaction mixture was then poured into a flask containing 2 g of zinc dust and 50 ml of glacial acetic acid. The mixture was stirred at room temperature for 24 h, filtered and the filtrate diluted with 250 ml of water. The solution was extracted with ether and the extract washed with 5% aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and the solvent removed. Chromatography of the residual oil on BDH alumina and elution with benzene gave an oil, which on trituration with methanol deposited 3d 0.280 g as a white solid m.p. 102–103.5°, nmr $\delta_{TMS}$ ($CDCl_3$): 3.56 (ABq, 2H, J = 14.0 Hz), 4.58 (ABq, 2H, J = 14.0 Hz) and 7.15–8.01 (m, 15H, aromatics), ir ($CHCl_3$) 1667 $cm^{-1}$ (C=O).

Anal. Calcd. for $C_{22}H_{19}NO$ (mol. wt. 313.1553). Found: (313.1551), mass spectrum).

Evaporation of the filtrate afforded 3le as an oil identified by its spectral characteristics.

Further elution of the column with benzene:ethanol (9:1) gave benzoic acid m.p. 119–120°, mmp with an authentic sample undepressed.

### Reduction Cleavage of 1-Benzyl-2(α-d-benzyl)-3,5-diphenyl-1,2-dihydropyrazine with Zinc and Acetic Acid.

A magnetically stirred solution of 0.830 g (2 mmole) of the dihydropyrazine 2f in 40 ml of glacial acetic acid was heated under reflux with 1.31 g (20 mmole) of zinc dust for 2 h, during which time the solution became colorless. The hot solution was filtered and the filtrate diluted with ice-water. The solution upon standing overnight deposited a yellow semi-solid which was taken up in ether. The extract was washed twice with 5% aqueous sodium hydrogen carbonate, dried ($MgSO_4$) and the solvent removed to give a light yellow oil, which was subjected to chromatography on 60 g of BDH alumina. Elution with hexane:benzene (3:1) gave an oil which solidified on standing (+)-(S)-α-phenyl-α-deuteriopropiophenone 2g. Repeated recrystallization from ether-petroleum ether afforded the pure ketone as white crystals m.p. 67–68.5°, $[\alpha]_D^{25}$ + 1.387 (21, 1.86, $C_6H_6$).

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Further elution with benzene:hexane (1:1) gave a yellow oil which on trituration with ethanol and cooling gave yellow crystals of 1,2-dibenzyl-2,5-diphenyl-1,2-dihydropyrazine, m.p. 99-102°, mmp with an authentic sample -5° was undepressed.

TABLE III

| Compound | (M+d) Peak [% of Base Peak M] Isotope Peak Calcd | Observed | Average | Increase |
|---|---|---|---|---|
| 13 | 5.6 | (i) 5.9 (ii) 5.8 (iii) 6.0 | 5.9 | - |
| 15 | 5.6 | (i) 5.9 (ii) 6.0 (iii) 6.1 | 6.0 | - |
| Cross-over | | | | |
| 12 + 14 (Benzene) | 5.6 | (i) 5.6 (ii) 9.7 (iii) 9.6 | 9.63 | 3.63 |
| 12 + 14 (THF) | 5.6 | (i) 9.7 (ii) 9.6 (iii) 9.5 | 9.72 | 3.70 |
| 12 + 14 (Hexane) | 5.6 | (i) 10.2 (ii) 9.9 (iii) 10.0 (iv) 10.2 | 10.1 | 4.1 |
| 12 + 14 (Benzene with Butanethiol Scavenger) | 5.6 | (i) 5.9 (ii) 6.1 (iii) 6.2 | 6.06 | ~0 |

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TABLE IV

Kinetics of Rearrangement of 1,4-Dibenzyl-2,6-diphenyl-1,4-dihydropyrazine [a] 1a in Benzene at 55.3 ± 0.1°

| Time (min) | Optical Density (320 nm) | k x 10^6 sec^-1 |
|---|---|---|
| 0 | 0.83 | - |
| 10 | 0.54 | 7.16 |
| 20 | 0.40 | 6.06 |
| 30 | 0.27 | 6.23 |
| 40 | 0.20 | 6.15 |
| 50 | 0.13 | 6.17 |
| 65 | 0.065 | 6.51 |
| 80 | 0.04 | 6.32 |

a Initial concentration = 1.0 x 10^-2 M.

REFERENCES TO EXPERIMENTAL

(44) Use of larger volumes of benzene results in the formation of substantial quantities of the rearranged product 2a.

(45) The 1,4-dibenzyl-1,4-dihydro-2,6-diphenylpyrazine should not be left in contact with ethanol for prolonged periods, since it undergoes a slow reversible addition.

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TABLE V

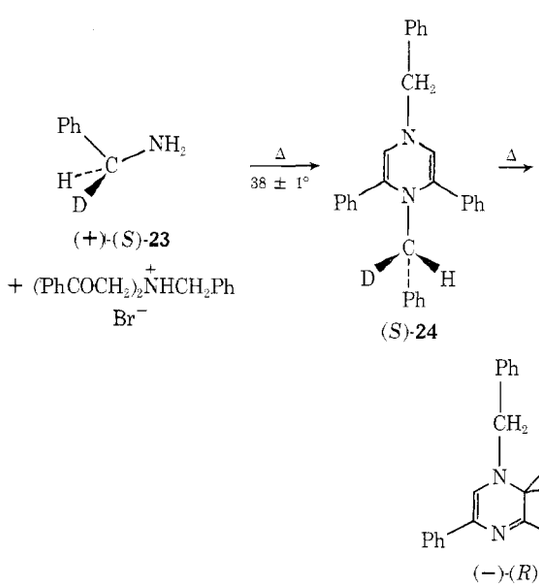
Summary of the Rate Constants

| Reactant and Initial Concentration | T°C | Rate constant [k x 10^6 sec^-1] |
|---|---|---|
| 1a (1.0-1.15) x 10^-2 M | 40.4 ± 0.1 | 1.96 |
| | 50.4 ± 0.1 | 4.62 |
| | 55.3 ± 0.1[a] | 6.37 |
| | 60.1 ± 0.1 | 8.02 |
| | 70.2 ± 0.1 | 14.58 |
| | 85.3 ± 0.1 | 16.71 |
| 11 (4.5-5.0) x 10^-2 M | 99.8 ± 0.1 | 1.12 |
| | 110.1 ± 0.1 | 1.78 |
| | 120.2 ± 0.1 | 2.84 |
| | 129.8 ± 0.2 | 2.69 |
| | 140.2 ± 0.2 | 4.88 |
| | 150.1 ± 0.2 | 7.05 |
| 12 (4.5-5.0) x 10^-2 M | 100.1 ± 0.1 | 2.98 |
| | 110.2 ± 0.1 | 4.51 |
| | 120.3 ± 0.1[b] | 5.32 |
| | 130.4 ± 0.2 | 6.54 |
| | 140.3 ± 0.2 | 7.89 |
| | 150.3 ± 0.2 | 10.87 |

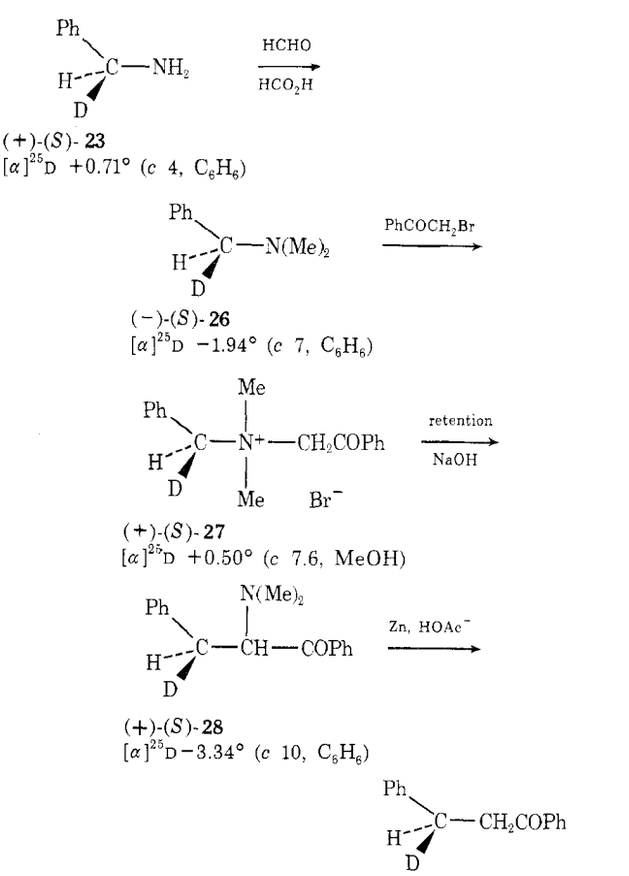
a) In the presence of Bu$H (3 mole) the rate of constant was 4.72 x 10^-6 sec^-1.

b) In the presence of Bu$H (3 mole) the rate of disappearance of this 1,4-dihydropyrazine was 3.16 x 10^-6 sec^-1.

been shown in the stereochemical consequences of intracage radical processes.[30] A stepwise reaction involving cleavage of the C–N bond to give a pair of radicals should lead to loss of optical acitivity only if the radical pair has a sufficiently long lifetime to permit reorientation of the planar radicals to occur.[30] A completely free radical necessarily results in racemization.[31] Thus the stereochemistry of the rearrangement permits a sensitive test of mechanism. An optically active product showing partial or total retention signifies a radical intracage mechanism where the radical lifetime is short compared with the rate of rotation, whereas overall inversion would only signify participation of the sigmatropic pathway inside the cage. The chiral 1,4-dibenzyl-1,4-dihydropyrazine **24** was prepared from chiral benzylamine-$\alpha$-*d*-(+)-(*S*)-benzylamine-$\alpha$-*d* **23** which has been prepared in 65% optical purity by Streitwieser and Wolfe.[32] and the absolute configuration established by Gerlach.[33] Upon heating compound **24** the labeled rearrangement product **25** was obtained quantitatively and proved to be optically active, $[\alpha]^{25}D$ −0.68 ± 0.01° (*c* 5.7, $C_6H_6$). To assess the degree of stereochemical integrity maintained inside the solvent cage, the rearrangement of **24** was examined in the presence of the butanethiol scavenger. From the crossover recombination experiments this must remove that portion of the rearranged product which is necessarily racemized by the extracage reaction. The rearranged product **25** under these conditions showed an increased specific rotation, $[\alpha]^{25}D$ −0.76 ± 0.02° (*c* 5.7, $C_6H_6$), in accord with this view. The configuration of the $\alpha$-*d*-benzyl group in **25** prepared in the presence of butanethiol was related to that in chiral 3-phenylpropiophenone-3-*d* by a Stevens rearrangement (Scheme I).



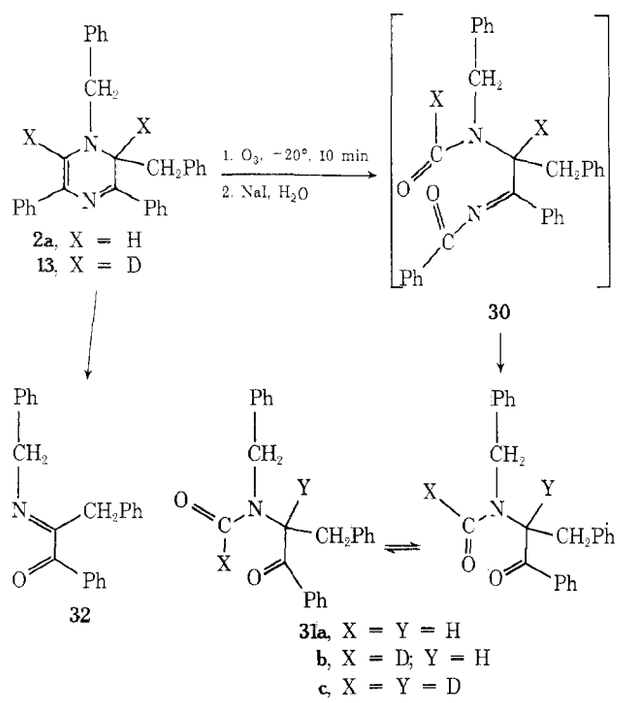

**Scheme I**



The scheme is based on a procedure developed by Brewster and Kline.[34] N-Methylation of the chiral benzylamine **23** afforded **26** in 85% yield, which was then quaternized with phenacyl bromide to give (−)-(*R*)-**27** quantitatively and converted into (−)-(*R*)-**29** as shown.[35]

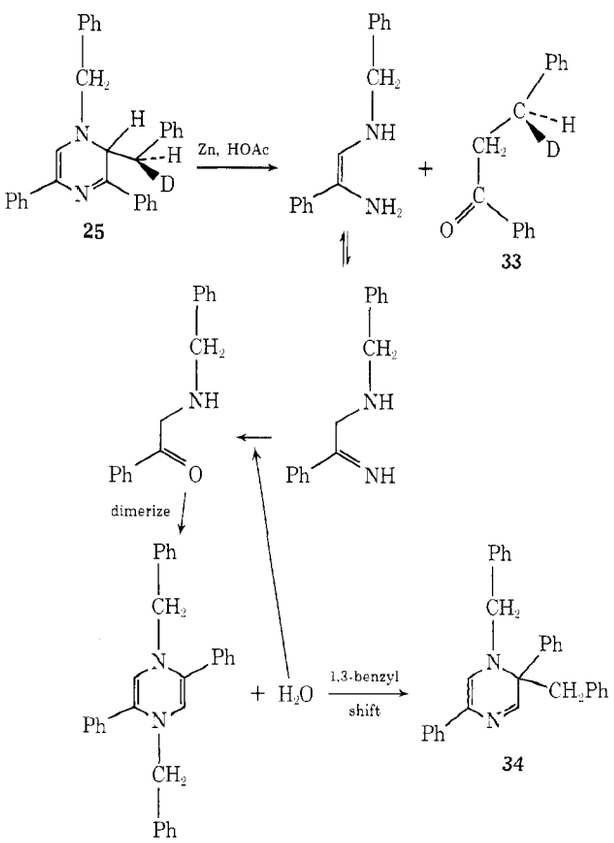
Attempts were made to relate the configurations of **25** and **29** directly by degradation of the former. Acid-catalyzed hydrolysis of **25** was found to be unsatisfactory, leading only to a dibenzyldiphenylpyrazine. Ozonolysis of **2a** in ethyl acetate solution at −20° resulted in the desired selective cleavage of the 5–6 bond and mild reductive work-up with sodium iodide and water (which was accompanied by hydrolysis of the intermediate **30**) afforded compound **31a** in about 65% yield. The nmr spectrum revealed a concentration-dependent equilibrium between the two possible geometrical isomers of **31a**, showing typically two formyl signals at $\delta$ 8.23 and 8.40 in a ratio of 60:40.

The ozonolysis must be carefully controlled, since at ambient temperatures and with longer exposure to ozone, further oxidative action affords **32**. Structure proof of **31a**



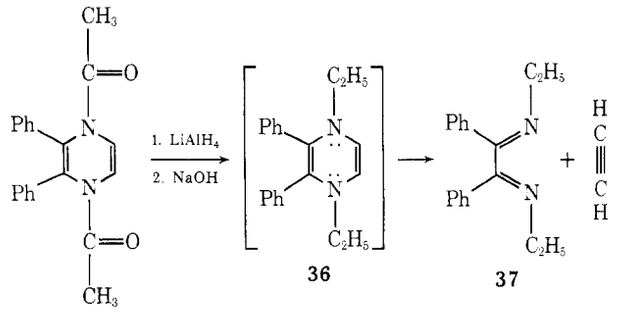

was provided by a parallel low-temperature ozonolysis of **13**, which gave **31b**. Inspection of the nmr spectrum showed that the formyl proton was completely exchanged with deuterium whereas the methine position $\alpha$ to the nitrogen was completely exchanged for protium. That this was due to base-catalyzed enolization of **31c** during work-up was confirmed by reverse exchange with potassium carbonate and deuterium oxide when Y was exchanged for deuterium. The formyl group in **31a** proved resistant to all attempts to convert it into the *N*-methyl compound, a prerequisite to the projected zinc and acetic acid reductive cleavage. Instead carefully controlled zinc and acetic acid cleavage of **25** afforded a mixture of the desired chiral ketone **26** and the known isomeric 1,2-dihydropyrazine[15] **34**. Compound **34** plausibly arises as shown in Scheme II. Chromatographic separation of **33** and **34** on alumina gave (+)-(*S*)-3-phenylpropiophenone-*3-d* (**33**), $[\alpha]^{25}D$ 1.37 ± 0.02° (*c* 1.86, $C_6H_6$). Assuming 96% retention in the Stevens rearrangement, then the specific rotation of (*R*)-**29** with 42% enantiomeric excess would be −1.45 ± 0.02°. Therefore that part of the rearrangement of **1** to **2** that proceeds intramolecularly proceeds with ≥95% stereospecificity and with inversion of configuration which demands a [1,3] sigmatropic shift with suprafacial allylic utilization.[29]

**Scheme II**



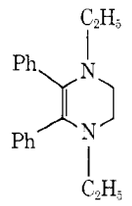

As far as we are aware this represents the first clear-cut example of a [1,3] sigmatropic shift with inversion involving nitrogen at the migrating center. The rearrangement therefore proceeds by a combination of sigmatropic and dissociative mechanisms and the contribution of the latter would be expected to be a function of the nature of the migrating group and reaction temperature. Baldwin and coworkers have encountered several examples of dual competing mechanisms in the rearrangement of ylides.[36]

**Nature of the 1,4-Dihydropyrazine System.** Theoretical considerations suggest that 4n-$\pi$ cyclic systems in general are antiaromatic,[2,37] *i.e.*, destabilized by increased electron delocalization. Molecular orbital calculations by Streitwieser on the 1,4-dihydropyrazine structure predicts thermodynamic destabilization in that the last two electrons must be placed in an antibonding orbital.[38] However, this presupposes that the geometry of the 1,4-dialkyl-1,4-dihydropyrazine allows the nitrogen lone pairs to interact conjugatively with the $\pi$ electrons of the ring. Some pieces of evidence suggest this may be so in certain structures. In contrast to the relative stability of the 1,4-dialkyl-1,4-dihydropyrazines described here, marked thermodynamic instability is inferred for the 1,4-diethyl-2,3-diphenyl-1,4-dihydropyrazine (**36**) postulated as a product of reduction of lithium aluminum hydride of the corresponding 1,4-diacetyl compound **35**.[9] While the electron-withdrawing 1,4 groups in **35** appear to stabilize the 1,4-dihydropyrazine system, compound **36** apparently undergoes a spontaneous retro Diels–Alder reaction and the diimine **37** was isolated. This implies destabilizing conjugative interaction of the nitrogen lone pairs of the $\pi$ electrons of the ring. This instability of **36** may also be con-



35 36 37

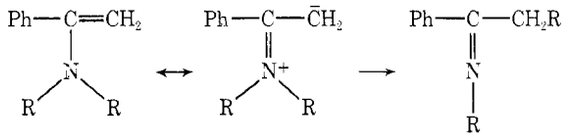
trasted with complete stability of **38**.[9] Evidently compounds **1** owe their relative stability and insolability to



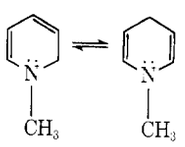
**38**

their substitution pattern, which imposes restrictions on full $\pi$ conjugation possibly owing to steric hindrance interactions at the 1, 2 and 6 positions. Further indications of this phenomenon follow from the regioselectivity of the [1,3] sigmatropic alkyl shift from **1** to **2**, implying relief of steric compression. The further contrast between the marked stability of **1** with the lability of the isomeric 1,4-dialkyl-2,5-diphenyl-1,4-dihydropyrazines[39] serves to emphasise this point. It is also tempting to suggest that destabilization inherent in **1** is relieved by the rapid oxidation to the 7-$\pi$ radical cation structures **7** described above.

An assessment of the role of the enamine to imine change of **1** to **4** must be made, however, Enamines are destabilized relative to the isomeric imine and Wittig has established a [1,3] shift in an acyclic example.[40] It must be

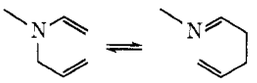


considered, therefore, that the unusual ease with which the groups migrate in **1a** could be due to the instability of the enamine moiety in **1a** compared to the imine in **2a**. Fowler points out that since **2a** is also an enamine containing and *N*-benzyl substituent its nonrearrangement under the reaction conditions indicates that there may be additional instability associated with enamine **1**.[8,9] However, the enediamine moiety of **1** may be different in character from a normal enamine. 1,4-Dihydropyridines show no tendency to rearrange to the 1,2 isomer. In equilibration, the *N*-methyl-1,4-dihydropyridine **40** is 2.29 ± 0.01 kcal mol$^{-1}$ more stable than the 1,2 isomer **39** at 91.6°.[41]



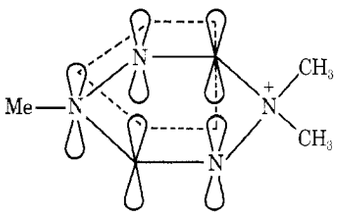
**39** **40**

Compounds of structure similar to **40** show unexpected stability which may be due to homoaromaticity or hyperconjugation.[41] The fact that the enamine to imine changes is not sufficient to account for the ease of rearrangement of **1** to **2** is also indicated by a comparison of the amino-Claisen rearrangement with the Claisen rearrangement. The former has an activation energy about 6 kcal mol$^{-1}$ higher than the latter and therefore is not so generally observed.[42] In conclusion, the evidence on the

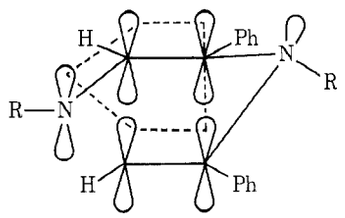


nature of the 1,4-dihydropyrazine system suggests a sensitive dependence of stability (determined by the extent of conjugative interaction of the nitrogen lone pairs) on the geometry of the heterocycle, which in turn is governed by the positioning of the substituents on the ring. For example, with two phenyl groups, 2,6 substitution confers stability[1] whereas 2,5[39] and2,3[8,9] substitution confers instability.

In a recent paper Kohn and Olofson[43] considered the geometry of the related 1,4-dimethyl-1,4-dihydro-1,2,4,5-tetrazine (**41**). Among other evidence, preferential N-alkylation at the substituted nitrogen may indicate a nonplanar homoaromatic structure for **41**. A similar nonpla-



**41**



**42**

nar structure **42** would appear to be plausible for the 1,4-dihydropyrazine structure at this time.

**Registry No.**—**1a**, 49570-21-0; **1b**, 38283-66-8; **1c**, 38283-67-9; **1d**, 38283-68-0; **1e**, 38283-69-1; **1f**, 38283-70-4; **1g**, 51381-06-7; **1h**, 38283-71-5; **1i**, 40312-97-8; **1j**, 38350-61-7; **1k**, 51381-07-8; **1l**, 51381-08-9; **1m**, 40312-93-4; **2a**, 25827-91-2; **2j**, 51381-09-0; **11**, 19264-38-1; **11** hydrobromide, 51381-10-3; **12**, 51381-11-4; **13**, 51381-12-5; **14**, 51381-13-6; **15**, 51381-14-7; **16**, 51381-15-8; **17**, 51381-16-9; **20**, 51464-56-3; (+)-(*S*)-**23**, 3481-14-9; (*S*)-**24**, 51381-17-0; **25**, 49570-23-2; (−)-(*S*)-**26**, 49570-26-5; (+)-(*S*)-**27**, 49570-27-6; (+)-(*S*)-**28**, 51424-69-2; (−)-(*R*)-**29**, 49570-24-3; **31a**, 51381-18-1; **31b**, 51381-19-2; **31c**, 51381-20-5; **32**, 51381-21-6; **33**, 51424-70-5; benzylamine, 100-46-9; phenethylamine, 64-04-0; propylamine, 107-10-8; butylamine, 109-73-9; isobutylamine, 78-81-9; isopentylamine, 107-85-7; methylamine, 74-89-5; cyclopropylamine, 765-30-0; cyclopentylamine, 1003-03-8; cyclohexylamine, 108-91-8; cycloheptylamine, 5452-35-7; cyclooctylamine, 5452-37-9; di(phenacyl-*1*-$d_2$)benzylamine, 51381-22-7; benzylamine-$\alpha,\alpha$-$d_2$, 15185-02-1; butanethiol, 109-79-5; 2,6- (or 3,6-) dibenzyl-3,5- (or 2,5-) diphenylpyrazine, 51380-76-8.

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# Synthetic and Mechanistic Aspects of the Sodium Hydride Promoted Acylation of Methylated Heteroaromatics[1]


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A series of representative α- and γ-methylated heteroaromatic azines and diazines were acylated with benzoate, trifluoroacetate, nicotinate, oxalate, and phthalate esters using sodium hydride as the condensing agent to afford heteroarylmethyl ketones, ethyl heteroarylpyruvates, and 2-heteroaryl-1,3-indandiones, respectively. Rates of acylation of quinaldine, as determined by hydrogen-evolution measurements, were shown to be independent of alkoxide concentration, but dependent upon both the concentration and polarity of the carbonyl group of the acylating ester. These results are attributed to accelerated ionization of a lateral proton from a complex involving ester and heterocycle.


Acylations of methylated heteroaromatics to afford ketones can be accomplished by initial lateral metalation of the heterocycle with a strong base, followed by treatment of the resulting carbanionic intermediate with an ester.[2] Essentials of the generally accepted mechanism for such reactions are illustrated in Scheme I by the acylation of quinaldine (1) with methyl benzoate.[3] On the basis of extensive studies by Levine and coworkers, alkali amides or alkali salts of certain dialkylamines currently appear to be the most satisfactory reagents for effecting these condensations.[4] Organolithium reagents have found some utility with heterocycles that are not susceptible to nucleophilic addition,[5] while alkoxides have been used in several instances where the acidity of side-chain protons is en-