Orbital Symmetry Control in the Thermal and Photoinduced Pericyclic Reactions of Some 1,2-Dihydropyrazines with Dimethyl Acetylenedicarboxylate[1a]

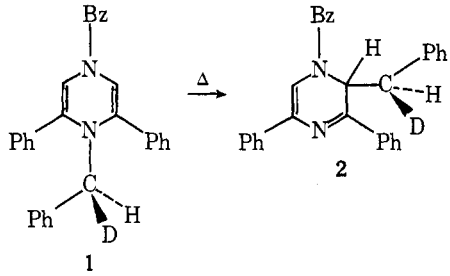
J. William Lown,* M. Humayoun Akhtar,[1b] and W. Michael Dadson

Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2E1

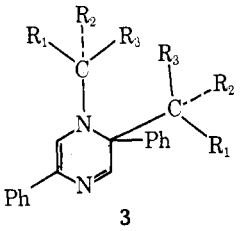
Received May 12, 1975

Reaction of several 1,2-dialkyl-2,5-diphenyl-1,2-dihydropyrazines **3** with dimethyl acetylenedicarboxylate (**4**) affords a series of dimethyl 1,2-dialkyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylates (**6**) the structures of which were proven by specific deuterium labeling. Thermolysis of chiral examples of the latter leads to sequential valence tautomerism via the 1,2-dihydro-1,4-diazocine **7**, [1,3] sigmatropic (C → N) alkyl shift with inversion of configuration, and cycloreversion of an intermediate 1,4-dihydro-1,4-diazocine **11** to pyrroles **10** and ketenimine **12**; the latter was isolated as the chiral amide **14**. Photolysis of chiral **6g** and **6h** takes a parallel chemical pathway except that the analogous [1,3] sigmatropic shift now displays the predicted orbital symmetry allowed retention. Reaction of **6i** with excess of **4** traps **11** to produce the 1,6-diazecines **25** (which in contrast to **11** is stable up to 150°) in addition to the azepines **26**. The latter provides evidence for intermediate **7** since it plausibly arises by trapping of **7**, [1,3]-sigmatropic shift and cycloreversion of the isomeric 1,4-diazecine **24**.

We have recently prepared 1,4-dibenzyl-2,6-diphenyl-1,4-dihydropyrazine (**1**) and have shown that it undergoes a stereospecific thermally induced suprafacial [1,3] sigmatropic benzyl shift with inversion of configuration to give the corresponding 1,2-dihydropyrazine **2** with a 12 ± 6% contribution from a radical dissociation–recombination mechanism.[2,3] Relatively few reports exist of stereochemical investigations of the applicability of the orbital symmetry rules to [1,3] shifts. Elegant examples by Berson,[4] Doering,[5] Masamune,[6] and Baldwin[7] all involve highly strained molecules. In view of the sensitivity of the stereochemical course of certain examples of [1,3] sigmatropic shifts to molecular environment[8] and the predicted dependence on substituent effects[9] it was of interest to examine the stereochemistry of the corresponding rearrangements of the 1,4-dialkyl-2,5-diphenyl-1,4-dihydropyrazines which proceeds regiospecifically to the 1,2-dihydropyrazines **3**.[10]



1 **2**



3

Since chiral examples of **3** proved resistant to the degradative procedures developed for investigating the absolute configuration of **2**,[3,11] a different approach was adopted. We report that the reactions of 1,2-dihydropyrazines **3** with dimethyl acetylenedicarboxylate (**4**) leading to a series of novel pericyclic reactions[12] permits the establishment of the stereochemistry of [1,3] alkyl sigmatropic shifts in both directions (N → C and C → N) and under both thermal and photochemical conditions and thus permits a detailed examination of these processes. In addition a number of novel nitrogen heterocycles become accessible.

Treatment of 1,2-dicyclohexyl-1,2-dihydro-2,5-diphenylpyrazine (**3a**) with 1 equiv of **4** at room temperature for 3 days in tetrahydrofuran afforded a 1:1 adduct **6a**, formulated as dimethyl 1,2-dicyclohexyl-2,5-diphenyl-3,5-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (see Scheme I and Table II). The ring expansion of enamine systems with acetylenic esters has several literature precedents.[13] Structure proof for **6a** is provided by a parallel experiment with 6-deuterio-**3b** (95% *d*) (prepared by the self-condensation of $C_6H_5COCD_2NHC_6H_{11}$ in which the 3 deuteron is selectively exchanged during work-up) which gives **6b** in which the methine AB quartet exhibited by **6a** was simplified to a broad singlet at δ 4.64. In view of the marked propensity for reversibility of the [1,3] sigmatropic shifts noted below, this key experiment permits the exclusion of an alternative mechanism for the formation of compounds of type **6** (see Scheme II) which would have resulted in label scrambling through the intermediate **8**.

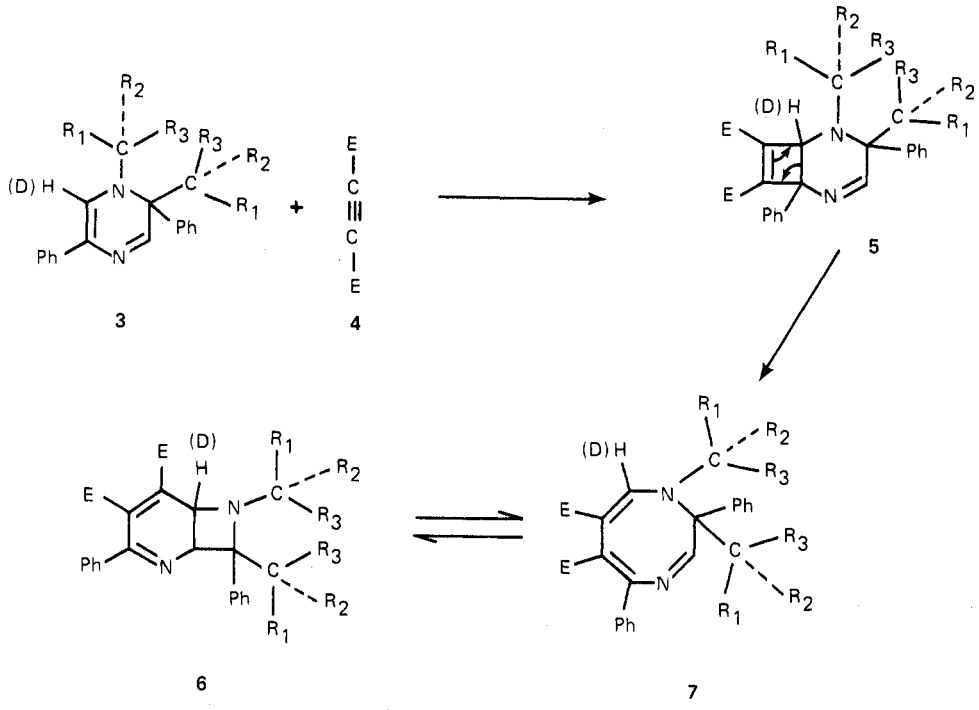
Analytical and spectral data for a series of similarly prepared 1,2-dialkyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylates are summarized in Table I.

Table I
1,2-Dialkyl-1,2-dihydro-2,5-diphenylpyrazines 3

Compd	Yield, %	δ ($CDCl_3$)
3c(d)[a] (oil)	77	0.17 [(d, 3 H, J = 6.5 Hz, $-CH(CH_3)$], 1.39 [d, 3 H, J = 6.5, Hz, $-NCH(CH_3)$], 1.92–2.30 [m, 1 H, $-CH(CH_3)$], 2.54–3.21 (m, 4 H, $-CH_2Ph$), 3.82–4.41 [(m, 1 H, $-NCH-(CH_3)$], and 6.69–7.81 (m, 12 H, aromatic and C_3H and C_5H)
3e(f)[a] (oil)	81	1.21 (d, 3 H, J = 6.5 Hz, $CHCH_3$), 1.53 (d, 3 H, J = 6.5 Hz, $-NCHCH_3$), 1.87–2.35 (q, J = 6.5 Hz, $-CH-$), 3.86–4.31 (q, 1 H, $-CH-$), 6.82 (s, 1 H, C_6H), and 7.04–7.71 (m, 20 H, aromatics)
3g(h)[a] (oil)	86	0.52–0.89 [m, 8 $CH(CH_3)$, (C_2H_5)], 1.22–1.85 [m, 8 H, $NC(CH_3)$, (C_2H_5)], 2.51–2.94 [m, 1 H, $-CH(CH_3)(C_2H_5)$], 3.71–4.11 [m, 1 H, $NCH(CH_3)(C_2H_5)$], 6.79 (s, 1H, C_6H) and 7.31–7.87 (m, 1 H, aromatic and C_3H)

[a] Satisfactory combustion analytical data for C, H, N (±0.3%) and "exact mass" mass spectral data were provided for these compounds. Ed.

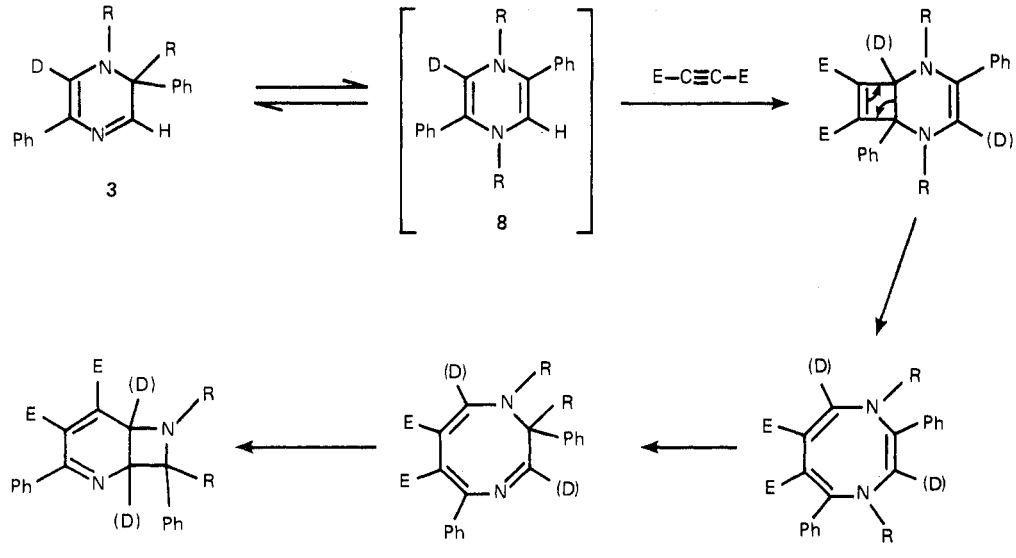
Scheme I



3 4 5 6 7

a, R_1 = H; R_2, R_3 = C_5H_{10}
b, R_1 = H; R_2, R_3 = C_5H_{10}; H_5 = D
c, R_1 = $PhCH_2$; R_2 = H; R_3 = CH_3
d, R_1 = CH_3; R_2 = H, R_3 = $PhCH_2$
e, R_1 = Ph; R_2 = H; R_3 = CH_3
f, R_1 = CH_3; R_2 = H; R_3 = Ph
g, R_1 = CH_3CH_2; R_2 = CH_3; R_3 = H
h, R_1 = CH_3; R_2 = CH_3CH_2; R_3 = H
i, R_1 = CH_3 R_2 = CH_3; R_3 = CH_3
j, R_1 = CH_3; R_2 = CH_3; R_3 = H
k, R_1 = H; R_2, R_3 = c-$C_{12}H_{23}$

Scheme II

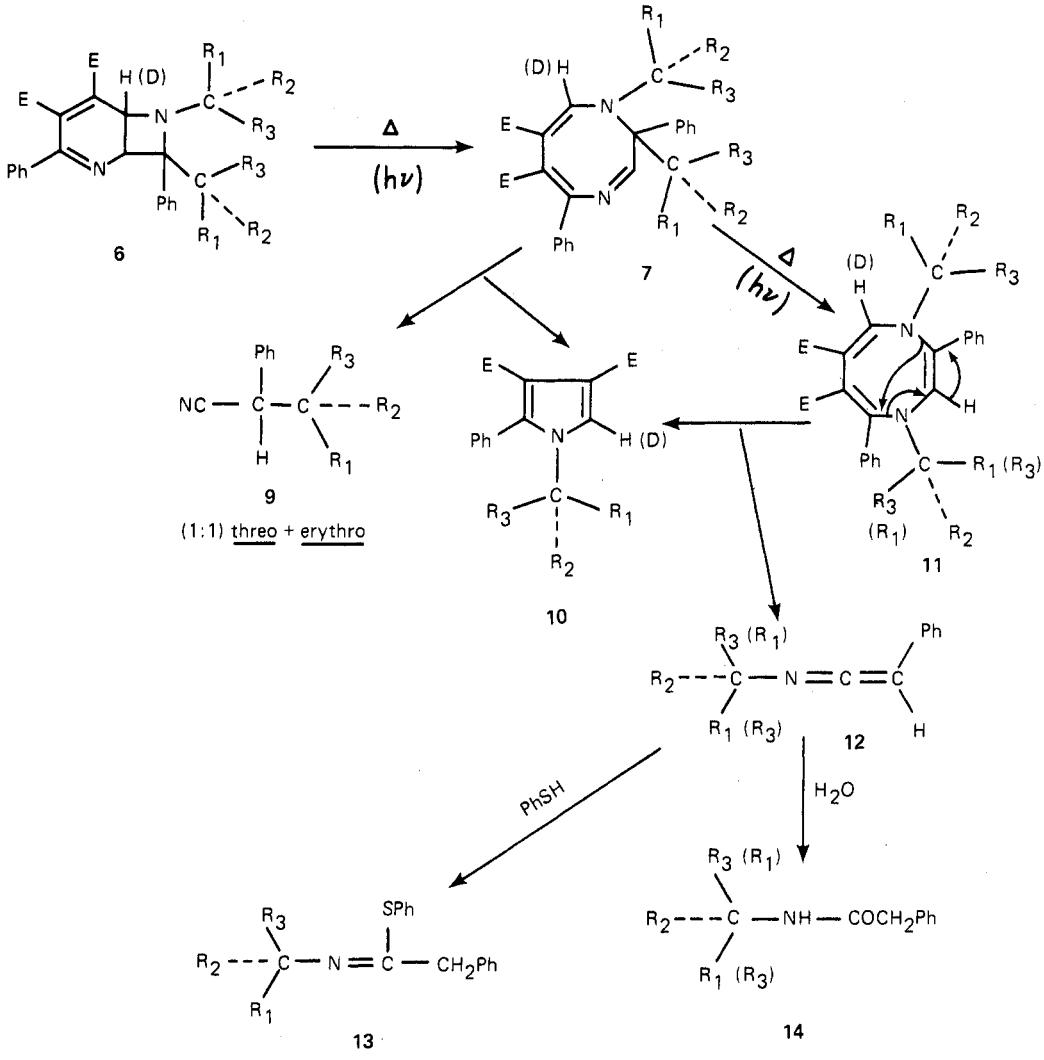


3 8

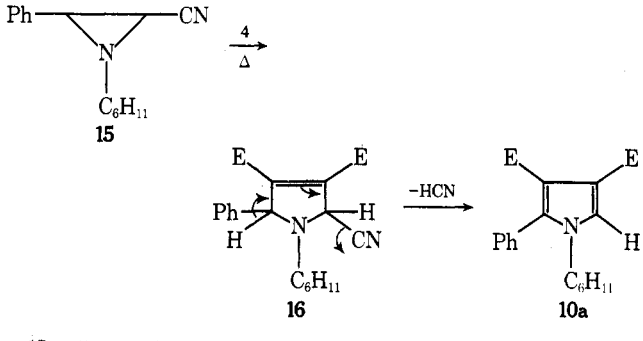
The conversion of **6** to **7** in Scheme I is represented as a reversible valence tautomerism,[14] since **6** upon heating briefly in benzene gave pyrroles **10** and ketenimines **12** in approximately equal quantities. The progress of the thermolysis of **6i** was conveniently followed by NMR and is rationalized as shown in Scheme III as sequential valence tautomerism of **6** to **7**, regiospecific [1,3] sigmatropic (C → N) alkyl shift to **11** followed by a formal orbital symmetry allowed [$_{\pi}6_s$ + $_{\pi}4_s$] cycloreversion[15] with an accompanying 1,2-hydride shift to give **10** and **12**.[16] Ketenimine **12i** was isolated during photolysis and characterized spectroscopically (see below) but all the ketenimines readily added water (e.g., during alumina column chromatography) to form the amides **14** which were identified by comparison with authentic samples. Further evidence for the intermediacy of the ketenimines is provided by their trapping with thiophenol to give a pseudothiourea **13** (see Scheme III).

The structure of the pyrrole products was proven in the case of **10a** by a 1,3-dipolar addition of **4** to the aziridine

Scheme III



The stereochemical pathway adopted upon photolysis is indicated in parenthesis.



15[17] followed by 1,4 elimination of hydrogen cyanide from **16**. Additional evidence in support of the proposed mode of cleavage of **11** in Scheme III is provided by the parallel experiment with 8-deuterio-**6b** which gave **10b** in which the 5 position was completely deuterated and **12b** in which the allenic proton was clearly visible in the NMR at δ 4.72. Substituted pyrroles produced by the thermolysis of compound **6** are summarized in Table III and the corresponding amides are reported in Table IV.

Stereochemistry of Thermal [1,3] Sigmatropic Shifts. The transformations in Schemes I and III provide the means for examining the stereochemistry of the [1,3] migrations, since the chiral center of interest is conveniently isolated in the amide **14**. Several examples of **3** containing chiral groups were prepared and treated with **4** (Scheme IV). Starting with **17c**, (−)-(*R*)-amphetamine,[18] the product **6c** (with one [1,3] sigmatropic shift during its formation via **19**) upon thermolysis affords pyrrole (*R*)-**10c** in 100% yield (required retention of configuration at position of 1 of **10c** by comparison with an authentic chiral compound) and amide *N*-(*R*)-**14c** in 100% yield (corresponding to 82% overall retention for the two successive [1,3] sigmatropic shifts during preparation, reaction with **4**, and subsequent cleavage). The comparable result from the (+)-(*S*)-amphetamine derivative **6d** corresponds to 82.5% overall retention in the double [1,3] sigmatropic shift (see Scheme III).

An experiment was performed with chiral (*S*)-(−)-α-methylbenzylamine (**17c**) which allowed a decision between the possible allowed double suprafacial inversion or disallowed double suprafacial retention. In this example **6f** upon thermolysis afforded products **9f** and **10f** (the structure of which was proven by independent synthesis) corresponding to the direct cleavage of **7c** [i.e., prior to the (C → N) [1,3] sigmatropic shift] thereby permitting the establishment of the stereochemistry of a single [1,3] alkyl shift (see Scheme III). The stereochemical results are summarized in Table V. The configuration of the known *erythro*-(*R*)-(−)-2,3-diphenylbutyronitrile (**9f**, $[\alpha]^{26}D$ −24°, C_6H_6)[19] has been correlated with that of (*R*)-(+)-α-phenethyl chloride by SN2 inversion, which in turn has been correlated with both (*R*)-(+)-glyceraldehyde[20] and (*S*)-(−)α-methylbenzylamine.[20]

Compound **9f** was formed in an approximately equal

Scheme IV

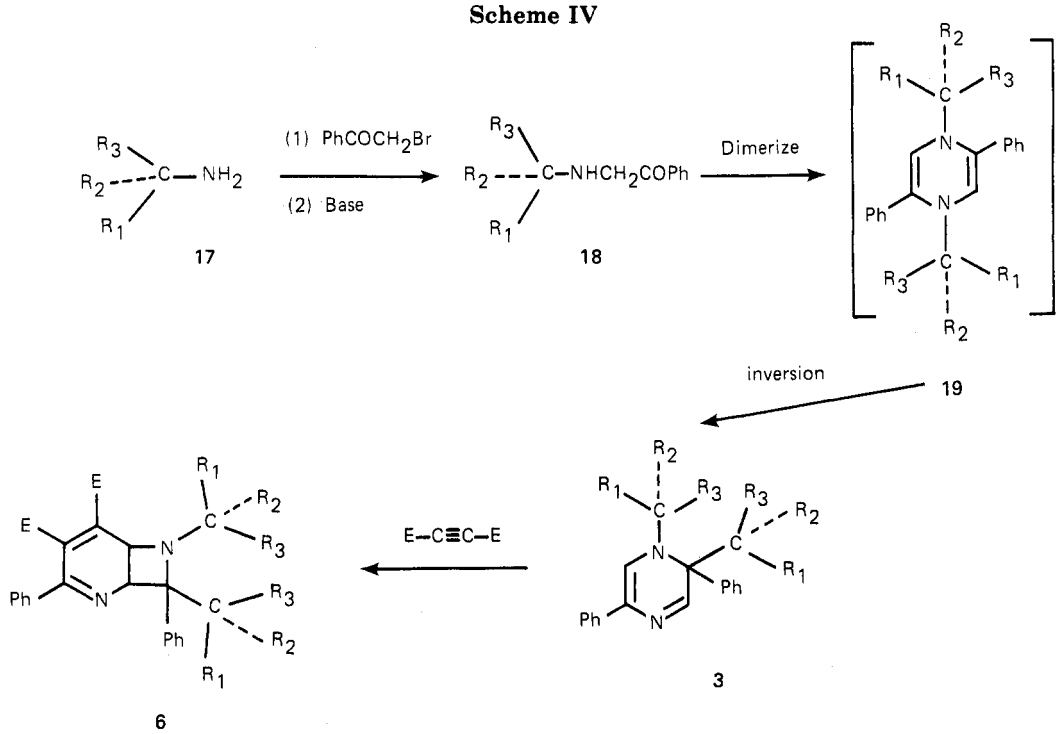


Table II
Dimethyl 1,2-Dialkyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylates 6

Compd	Mp, °C	Yield %	H_3, H_8 AB q	J_{38}	Ester methyl	1,2-Alkyl groups	Alkyl methine
6a[a]	144–145.5	87	4.18, 4.64	4.0	3.27, 3.86	0.51–1.95	2.05–2.49 2.67–3.17
6b[a]	144–145.5	87	4.18 (br s)		3.27, 3.86	0.50–1.96	2.05–2.49
6c,d[a]	Oil	72	4.18, 4.67	4.0	3.23, 3.83	0.67–1.33 (CH_3) 1.82–2.21 ($-CH_2$) 2.51–2.93 ($-CH_2$)	3.43–3.82 4.21–4.64
6e,f[a]	Oil	75	4.11, 4.61	4.5	3.27, 3.88	0.97–1.31	3.37–3.73 4.16–4.48
6g,h[a]	127–129	85	4.13, 4.62	4.2	3.28, 3.88	0.52–1.51	2.12–2.62 2.82–3.33
6i[a]	135–137	91	4.17, 4.76	4.5	3.25, 3.90	0.82, 1.03 (s)	
6j[a]	118–119	88	4.14, 4.61	4.2	3.27, 3.86	0.36–1.18	2.36–2.91 3.01–3.59
6k[a]	122–123.5	73	3.98, 4.60	4.2	3.40, 3.90	0.77–2.01	2.89–3.41

[a] See footnote *a*, Table I.

mixture of threo and erythro diastereomers implying little or no asymmetric induction during the cleavage of **7f** to **9f**. The isolated and purified erythro diastereomer, mp 135° from **9c** ($[\alpha]^{25}D$ − 21.85, C_6H_6),[21] therefore corresponds to 91.3% overall inversion (i.e., a single inversion in the step **19** to **3** and retention in the step **7** to **9**). We conclude that formation of **14** in 82% overall retention corresponds to two successive N → C (**19** to **3**) and C → N (**7** to **11**) allowed suprafacial [1,3] sigmatropic shifts, i.e., double inversion.

As we reported previously, the analogous [1,3] sigmatropic shift **1** to **2** proceeded with 95% stereospecific inversion of configuration and also in the absence of a scavenger exhibits a 12 ± 6% contribution from the parallel radical dissociation–recombination mechanism[11] which probably accounts for the loss of 18% optical activity observed here. In support of this contention it was observed that thermolysis of **6e** or **6f** at a higher temperature produced some 2,3-diphenylbutane from α-methylbenzyl coupling in addition to **10e** and **14e**. To that extent example **6f** is not ideal and may not be typical of the behavior of this system. A better model is provided by chiral *sec*-butyl, which would have less tendency to form radicals either under photolytic or thermolytic conditions (see below).

The 3,8-dihydroazetidino[3,2-*b*]pyridines **6** contain three chiral carbons and a nitrogen which may be inverting rather slowly. The influence of the relative stereochemistry of the groups in **6** on the stereochemical outcome of the processes described above remains to be investigated. Also the fortuitous formation of **9** rather than **12** in the case of α-methylbenzyl derivatives is currently being investigated employing a range of model compounds to see if the division of reaction pathways in Scheme III may be attributed to steric factors, for example.

Stereochemistry of Photoinduced [1,3] Sigmatropic Shifts. It was now necessary to ascertain the behavior of these systems upon photolysis. It was by no means obvious that [1,3] sigmatropic shifts, if they could be induced to proceed under photolytic conditions, would do so with the predicted retention of configuration. For example, Cookson and Kemp have reported that the photoisomerization of **20**

Table III
Dimethyl 1-Alkyl-2-phenylpyrrole-3,4-dicarboxylates 10

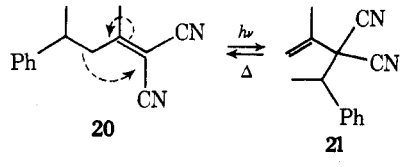
Compd	Mp, °C	Yield, %	CO_2CH_3	Alkyl	Alkyl methine	Ir spectrum [$CHCl_3$ (C=O)] cm^{-1}
10[a]	Oil	89	3.63 3.84	0.85–2.23 (m, 10 H, cyclohexyl)	3.46–4.07	1720 (b)
10c,d[a]	94–95	88	3.56 3.82	1.28 (d, 3 h, J = 6.5 Hz, CH_3), 2.55–3.15 (m, 2 H, CH_2Ph)	3.80–4.46 (m, 1 H)	1720 (b)
10e,f[a]	Oil	89	3.59 3.75	1.67 (d, 3 H, J = 7.0 Hz, CH_3)	5.05–5.40 (q, 1 H, J = 7.0 Hz)	1715 (b)
10g,h[a]	118–119.5	94	3.63 3.81	1.33 (d, 3 H, J = 6.5 Hz, CH_3) 0.71 (t, 3 H, J = 7.0 Hz, CH_2CH_3)	3.36–4.15	1720 (b)
10i[a]	92–93	92	3.55 3.82	1.43 [s, 3 H, $-C(CH_3)_3$]		1715 (b)
10j[a]	145–146.5	92	3.64 3.85	1.35 (d, 6 H, J = 7.0 Hz, CH_3)	3.88–4.58 (1 H, septet J = 7.0 Hz)	1720 (b)
10k[a]	106–107.5	87	3.66 3.65	0.72–2.21 (m, 22 H, cyclooctyl)	3.71–4.31	1720 (b)

[a] See footnote *a*, Table I.

Table IV
***N*-Alkyl-2-phenylacetamides[a] 14**

Compd	Mp, °C	Found molecular ion (mass spectrum)	Calcd molecular ion (mass spectrum)	δ ($CDCl_3$)
14a	132–133.5	217.1461	217.1464	0.85–2.08 (m, 10 H, cyclohexyl), 3.53 (s, 2 H, CH_2), 3.47–4.15 (br, 1 H, methine), 5.17–5.73 (br s, 1 H, NH, D_2O exchangeable), and 7.29 (s, 5 H, aromatic)
14c(d)	90–91.5 (lit. mp 95°[25])	215.1416	253.1419	1.04 (d, 3 H, J = 6.5 Hz, CH_3), 2.62 (d, 2 H, J = 6.7 Hz, $-CH_2Ph$), 3.43 (s, 2 H, $PhCH_2$), 3.78–4.47 (m, 1 H, –CH), 5.64–6.09 (br, 1 H, exchangeable with D_2O, NH), 6.91–7.63 (m, 10 H, aromatic)
14g(h)	57–58.5	191.1308	191.1306	0.83 (t, 3 H, J = 6.5 Hz, $-CH_2CH_3$), 1.08 (d, 3 H, J = 6.5 Hz, CH_3), 1.06–1.54 (m, 2 H, $-CH_2CH_3$), 3.58 (s, 2 H, CH_2), 3.62–4.15 (m, 1 H, methine), 5.31–5.92 (br, 1 H, NH, exchangeable with D_2O), and 7.33 (s, 5 H, aromatics)
14i	135–136.5	191.1304	191.1306	1.30 [s, 9 H, $C(CH_3)_3$], 3.50 (s, 2 H, CH_2), 5.11–5.47 (br, 1 H, exchangeable with D_2O), 7.30 (s, 5 H, aromatics)
14j	102–103.5	177.1159	177.1156	1.67 (d, 6 H, J = 6.5 Hz, CH_3), 3.50 (s, 2 H, $C_6H_5CH_2$), 3.69–4.38 (septet, 1 H, –CH–), 5.82–6.31 (br, 1 H, NH, D_2O exchangeable), and 7.30 (s, 5 H, aromatics)
14k	134–135	301.2504	301.2498	1.61 (br s, 22 H, cyclododecyl), 3.52 (s, 2 H, CH_2), 3.74–4.31 (br, 1 H, methine), 4.95–5.61 (br, 1 H, D_2O exchangeable, NH), and 7.28 (s, 5 H, aromatic)

[a] Authentic sample was prepared in each case by treating phenylacetyl chloride with the appropriate amine.



20 21

to **21** takes place with ca. 85% retention of configuration.[8] However, thermal reversion of the rearrangement occurred with >90% retention and also with ≈10% inversion. In the latter process the concerted suprafacial [1,3] shift with retention may therefore have become sufficiently allowed to permit it to compete successfully with the sterically more strained route with inversion. Cookson therefore warns against uncritical extension of the orbital symmetry rules from the parent system to which they apply to strongly perturbed analogs in which, e.g., substituent electronic effects, the introduction of heteroatoms, and steric strain operate.

In the event photolysis of the dihydroazetidino[3,2-*b*]pyridines both in benzene at room temperature and in ether at −70° with a 200-W Hanovia medium-pressure lamp gave clean products of pyrroles and ketenimines in good isolated yields (i.e., ketenimines isolated as the amides). Next the chiral 1,2-dihydropyrazine **3g** was prepared in 74% yield from (*S*)-(+)-*sec*-butylamine (29% enantiomeric excess). Treatment of 1-(*S*)-2-(*R*)-**3g** with **4** in tetrahydrofuran gave 1-(*S*)-2-(*R*)-**6g**, mp 128–128.5°, in 85% yield. Photolysis of **6g** at −78° in ether afforded chiral 1-(*S*)-pyrrole **10g**

Table V
Optical Activity of Products from Reaction of Chiral 1,2-Dihydropyrazines 3 and Dimethyl Acetylenedicarboxylate under Thermal Conditions, $[\alpha]^{25}D$ (C_6H_6)

General structure	Chiral amine employed			
	(−)-(*R*)-17c	(+)-(*S*)-17d	(−)-(*S*)-17f	(+)-(*R*)-17e
3	−105.6	+108.8	−76.4	+72.8
6	−70.7	+74.3	−85.40	+88.9
9[a]			−21.85	+20.95
9[b]			−22.40	
10[c]	−77.8	+75.6	−57.25	+57.80
10[d]			−59.80	
14[c]	+6.55 (82%)[e]	−6.85 (82.5%)	−54.30[f]	+53.80[f]
14[d]	+7.9	−8.45	−55.5	+55.60

[a] Purified erythro diastereomers. [b] Value in presence of scavenger *n*-BuSH. [c] Product from thermolysis. [d] Authentic synthetic sample. [e] % overall retention. [f] Isolated in 2–3% yield.

Table VI
Optical Activity of Products from Reaction of Chiral 1,2-Dihydropyrazines 3 and Dimethyl Acetylenedicarboxylate under Thermal and Photolytic Conditions, $[\alpha]^{25}D$ (C_6H_6)

General structure	Mp, C	Chiral amine	
		(*S*)-(+)-17g	(*R*)-(-)-17h
3	Oil	+5.65	−5.85
6	128–8.5	+4.95	−5.15
10[a]	118–119	+3.6	−3.8
10[b]	118.5–119.5	+3.2	−3.3
14[c]	57–58.5	+4.95	−5.2
14[a]	55–56.5	+4.7 (95%)[d]	−4.9 (94%)[d]
14[b]	56–57.5	−3.8 (77%)[e]	+3.7 (71%)[e]

[a] Product from thermolysis. [b] Product from photolysis. [c] Authentic synthetic sample. [d] % overall retention. [e] % overall inversion.

in 73% yield and the *N*-(*R*)-ketenimine **12h** (80% yield as estimated by NMR). The latter was isolated as the chiral *N*-(*R*)-**14h**, mp 55–56.5°, in 67% yield, with an optical purity which corresponded to about 80% retention of configuration in the [1,3] sigmatropic rearrangement by comparison with an authentic sample. By contrast, thermolysis of **6g** affords chiral *N*-(*S*)-**14g** with 95% overall retention from two successive suprafacial [1,3] sigmatropic shifts.

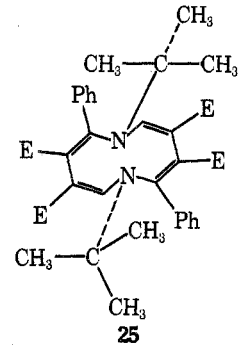
Parallel experiments were performed with *R*-(−)-*sec*-butylamine with comparable results. The isolated pyrroles **10g** and 10h showed 100% retention of configuration of the *N*-*sec*-butyl group in both cases. The stereochemical results are summarized in Table VI.

Trapping of Diazocine Reaction Intermediates. The photolysis of **6** (R = *t*-Bu, see Scheme V) at −70° produced a small quantity of an isomer as a yellow oil. The NMR spectrum shows absence of the AB quartet characteristic of the methine hydrogens in **6** confirming that the 3–8 bond has been broken. Comparison with the known lability and chemical reactivity of compound **11** points to structure **7** (R = *t*-Bu) for this isolated intermediate, although the small quantities available prevented further characterization.

Efforts were now made to obtain more direct evidence for the existence of intermediates **7** and **11** by trapping experiments using **4**. Trapping of **7** or **11** as dienes was possible, or if [1,3] migration from **7** to **11** proved competitive, the latter could conceivably be trapped as an enamine. In the event, reaction of **6** (R = *t*-Bu) or **6** (R = C_6H_{11}) with 1 equiv of **4** thermally succeeded in trapping the enamine moiety of **11** to form the 1,6-diazecines **25** (R = *t*-Bu) and **25** (R = C_6H_{11}), respectively, plausibly via **22**. Compound **25** was isolated in low yield as a yellow oil together with the corresponding pyrrole **10e** and amide **14**. Formation of **25** thus parallels the initial formation of intermediate **5** from the enamine moiety of **3** reacting with **4**. In the presence of a large excess of the ester **4** (as solvent) the facile thermal cycloreversion of **11** to pyrrole and ketenimine is somewhat suppressed and a higher yield of **25i** may be obtained together with substantial amounts of the crystalline tetramer of **4**.[22]

Evidence in support of structure **25** (R = *t*-Bu) is the composition as determined by mass spectroscopy and the NMR spectrum, which shows two equivalent *tert*-butyl groups at δ 1.45, two different methyl ester peaks at δ 3.62 and 3.68, and two equivalent vinyl protons at δ 6.97. The NMR data are consistent with the molecular environments predicted for these groups from a model. The trans disposition of the large *tert*-butyl substituents may also explain the reluctance of **25** to undergo catalytic hydrogenation, since they would be expected to interfere with absorption on the catalyst surface.

Supporting evidence for the formation of **25** is provided by a control reaction of the dihydroazetidino[3,2-*b*]pyridine from α-methylbenzylamine. Previous work had established this compound upon thermolysis to undergo valence tautomerism and then selective cleavage to pyrrole and nitrile only, to the exclusion of the [1,3] (C → N) sigmatropic shift. Reaction with an excess of **4** therefore permitted discrimination between species **7** and **11** as reactants with **4** to yield **25**. In this experiment the corresponding **9e** and **10e** were obtained from cycloreversion of **7** and no product corresponding to **25** was observed. A second control experiment between the ketenimine **12** (R = *t*-Bu) and **4** gave no reaction. Although the formal orbital symmetry allowed [$_\pi6_s$ + $_\pi4_s$] thermal cycloreversion of **11** to **10** and **12** proceeds smoothly, the vinylog of **11**, compound **25**, is thermally stable up to 150°. It is tempting to suggest that the analogous cycloreversion here to the pyrrole would be a [$_\pi6_s$ + $_\pi6_s$] process and is precluded since it is predicted to be thermally disallowed.

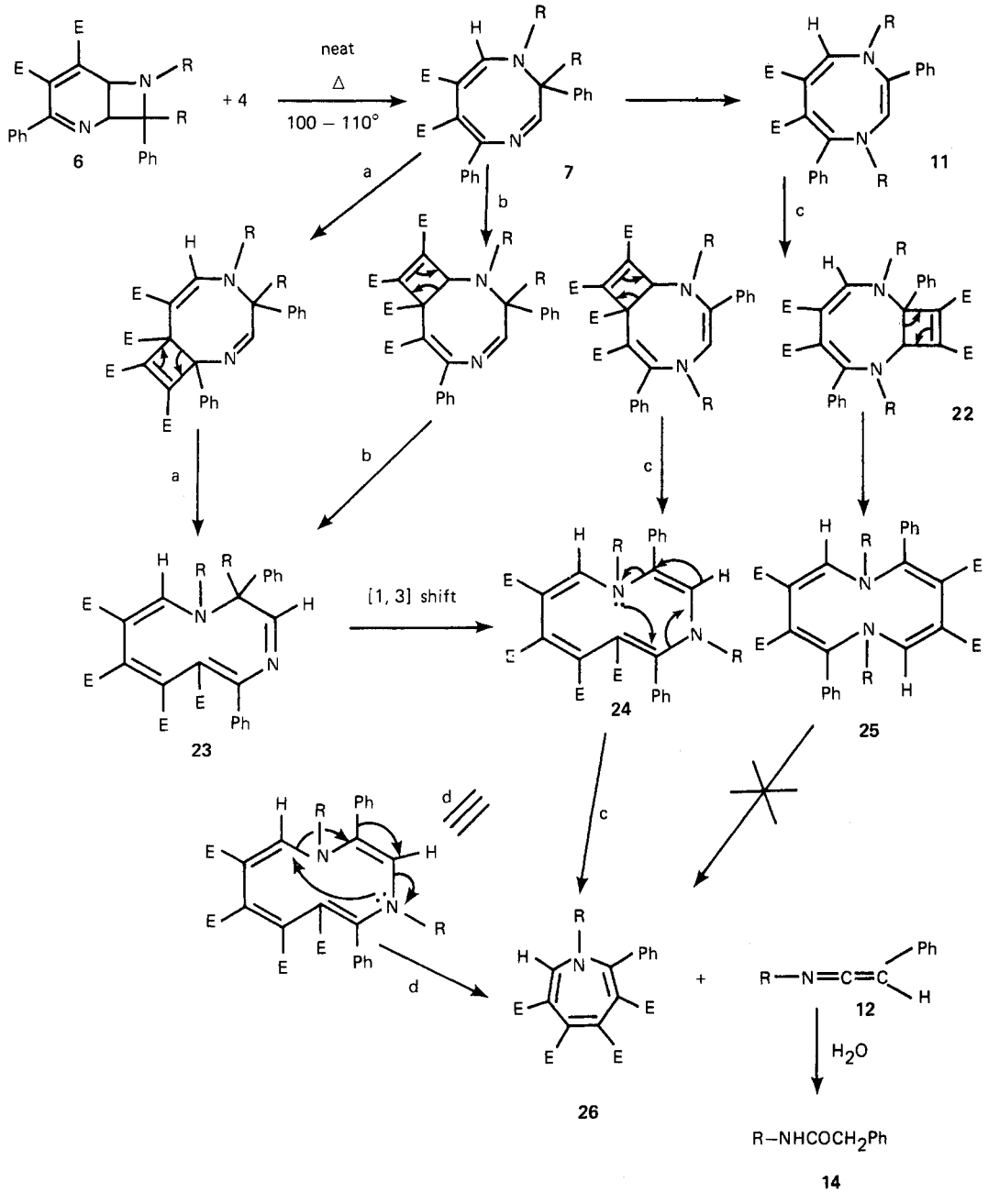


25

An alternative mode of addition of **4** to the valence tautomer of the azetidinopyridine requiring the formation and cycloreversion of an isomeric 1,4-diazecine was uncovered. Reaction of **6** (R = *sec*-Bu) with in **4** as solvent at 100–110° afforded the azepine **26** (R = *sec*-Bu) and the corresponding amide **14**. Several possible pathways to these products may be formulated, some of the alternatives being given in Scheme V.

The nature of the products requires a reverse C → N [1,3] sigmatropic shift in one of the intermediates prior to cycloreversion. Paths a and b are indistinguishable. Pathway c is likely in view of precedents given in Scheme III representing then the vinylog of the cycloreversion of, e.g.,

Scheme V



11 to 10 and 12. Pathway d is unlikely since it requires the postulation of a 1,2-phenyl shift.

The Cope rearrangement that occurs with 7 is evidently not favored for intermediate 23 presumably because this would produce a bridgehead phenyl group.

It is evident that in this first report on these novel and complex reactions the mechanisms proposed can only be viewed as tentative at this stage. The detailed investigation is being continued.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer Model 421 spectrophotometer, and only the principal, sharply defined peaks are reported. The NMR 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. Mass spectra were determined on an Associated Electrical Industries MS-9 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 15000. Kieselgel DF-5 (Camag, Switzerland) and Eastman Kodak precoated sheets were used for thin layer chromatography. Microanalyses were carried out by Mrs. D. Mahlow of this department.

Materials. The amines, *d*- and *l*-α-methylbenzylamine and *d*- and *l*-α-methylphenethylamine, were available commercially (Aldrich Chemical Co.). The *d*- and *l*-*sec*-butylamines were prepared in 29% enantiomeric excess by resolving the *dl*-*sec*-butylamine into diastereomeric tartrate salts and subsequent regeneration of the enantiomeric amines according to the described procedure.[23] The (*S*)-*sec*-butylamine had $[\alpha]^{25}D$ +2.14° (neat) compared with $[\alpha]^{25}D$ +7.44° for enantiomerically pure compound.[23]

1,2-Dialkyl-2,5-diphenyl-1,2-dihydropyrazines 3. Representative examples of the preparation are given; thereafter the physical data of other compounds similarly prepared are summarized in Table I.

6-Deuterio-1,2-dicyclohexyl-2,5-diphenyl-1,2-dihydropyrazine (3b). A mixture of 10 g (5 mmol) of α,α-dideuterio-2-bromoacetophenone (prepared from bromination of acetophenone-d_3) and 10 g (10 mmol) of cyclohexylamine-*N*-d_2 (prepared by repeated deuterium oxide exchange of cyclohexylamine) in dry benzene was stirred at room temperature for 6 hr, then heated at reflux

temperature for 8 hr. The precipitated salt was collected, the filtrate was washed with deuterium oxide (2 × 10 ml) and dried ($MgSO_4$), and the solvent was removed to give a yellow oil. The oil on trituration with methanol deposited 13.5 g (67% yield) of the 1,2-dihydropyrazine **3b**, mp 97–98.5°. During the work-up with methanol the 3-deuterium atom is preferentially exchanged as shown by the NMR spectrum: δ_{Me_4Si} ($CDCl_3$) 0.72–2.04 (br, 20 H, C_6H_{11}), 2.33–2.83 (br, 1 H, methine), 3.47–4.01 (br, 1 H, *N*-methine), and 7.18–7.85 (m, 11 H, aromatic and C_3H).

Anal. Calcd for $C_{28}H_{33}N_2D$: mol wt 399.2728. Found: mol wt, 399.2724 (mass spectrum).

1-(*S*)-2-(*R*)-Di-*sec*-butyl-2,5-diphenyl-1,2-dihydropyrazine (3g). (*S*)-(+)-*sec*-Butylamine, $[\alpha]^{25}D$ 2.14° (neat) (4.54 g, 60 mmol), was added to a benzene solution of 5.0 g (25 mmol) of α-bromoacetophenone, and the mixture was stirred at room temperature for 2 hr, then heated under reflux for 16 hr. Upon cooling, the resulting *sec*-butylamine hydrobromide was removed by filtration. The filtrate was washed with cold water and dried ($MgSO_4$) and the solvent was removed in vacuo to give a reddish-orange oil which was purified by chromatography on B. D. H. alumina. Elution with hexane–benzene (3:1) gave **3g** as an orange oil which resisted crystallization: 3.2 g (74% yield); $[\alpha]^{25}D$ +5.67° (*c* 9.37, C_6H_6); NMR δ_{Me_4Si} ($CDCl_3$) 0.5–0.98 [m, 11 H, $-CH(C_2H_5)$, CH_3, $-CH_2CH_3$], 1.33 (d, 3 H, J = 6.5 Hz, $-NCHC_2H_5CH_3$), 1.12–1.67 [m, 2 H, $-NCH(CH_2CH_3)CH_3$], 2.51–2.85 (m, 1 H, methine), 3.57–4.16 (m, 1 H, *N*-methine), 6.77 (s, 1 H, C_3H), and 7.02–7.86 (m, 11 H, C_3H aromatics); absorption spectrum λ_{max} (CH_3CN) 265 nm (log ε 4.23).

Anal. Calcd for $C_{24}H_{30}N_2$: mol wt, 346.2409. Found: mol wt, 346.2415 (mass spectrum).

Dimethyl 1,2-Dialkyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (6). A representative preparation of one example is given; thereafter the physical data on other compounds similarly prepared are summarized in Table II.

(+)-Dimethyl-1-(*S*)-2-(*R*)-di-*sec*-butyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (6g). A solution of 2.6 g (7.5 mmol) of the 1,2-dihydropyrazine **3f**, $[\alpha]^{25}D$ +5.67°, in 15 ml of dry tetrahydrofuran and 1.15 g (8 mmol) of **4** was stirred at room temperature for 6 days. Removal of the solvent gave a dark oil which was subjected to chromatography on 80 g of B. D. H. alumina. Elution with hexane–benzene (1:3) gave as the main fraction an oil, 2.94 g (85% yield), which on trituration with hexane deposited the azetidinopyridine **6g** as a white solid: mp 127–128.5°; $[\alpha]^{25}D$ +4.95° (*c* 8.35, C_6H_6); NMR δ_{Me_4Si} ($CDCl_3$) 0.37–1.83 (m, 16 H, CH_3, C_2H_5), 2.03–2.71 (m, 1 , H, methine), 2.48–2.81 (m, 1 H, methine), 3.33 (s, 3 H, CO_2CH_3), 3.92 (s, 3 H, CO_2CH_3), 4.13 (d, 1 H, J = 4.0 Hz, C_3H), 4.63 (d, 1 H, J = 4.0 Hz, C_8H), and 7.11–7.76 (m, 10 H, aromatic); absorption spectrum λ_{max} (CH_3CN) 314 nm (log ε 3.26).

Anal. Calcd for $C_{30}H_{36}N_2O_4$ (mol wt 488.2846): C, 73.55; H, 7.34; N, 5.75. Found (mol wt 488.2840, mass spectrum): C, 73.41; H, 7.47; N, 5.81.

Dimethyl 8-Deuterio-1,2-dicyclohexyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (6b). A solution of 8.0 g (20 mmol) of the 6-deuterio-1,2-dihydropyrazine **3b** in 35 ml of dry tetrahydrofuran and 2.9 g (20 mmol) of **4** was set aside at room temperature for 4 days. Removal of the solvent gave a yellow oil which in trituration with hexanes deposited yellowish-white crystals of the pyridine **6b**: 9.3 g (86% yield); mp 144–146°; NMR δ_{Me_4Si} ($CDCl_3$) 0.51–1.95 (m, 20 H, cyclohexyl), 2.05–2.49 (br, 1 H, methine), 2.67–3.18 (br, 1 H, methine), 3.28 (s, 3 H, CO_2CH_3), 3.86 (s, 3 H, CO_2CH_3), 4.18 (t, 1 H, C_3H), and 7.11–7.78 (m, 10 H, aromatic).

Anal. Calcd for $C_{34}H_{39}DN_2O_4$: mol wt, 541.2208. Found: mol wt, 541.2210 (mass spectrum).

Thermolysis of Dimethyl 8-Deuterio-1,2-dicyclohexyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (6b). A solution of 1.35 g (2.5 mmol) of the azetidinopyridine **6b** in dry toluene was heated under reflux for 10 hr. Removal of the solvent in vacuo gave a light yellow oil, the NMR spectrum of which exhibited the allenic proton of the ketenimine at δ 4.72. Chromatography of the oil on B. D. H. alumina afforded dimethyl *N*-(cyclohexyl)-2-phenyl-5-deuteriopyrrole-3,4-dicarboxylate (**10b**, 0.704 g, 82% yield) which was compared with an authentic sample of **10a**: NMR δ_{Me_4Si} ($CDCl_3$) 0.95–1.30 (br, 10 H, cyclohexyl), 3.65 (s, 3 H, CO_2CH_3), 3.83 (s, 3 H, CO_2CH_3), 3.4–4.05 (br, 1 H, methine), 7.32–7.59 (m, 5 H, aromatics).

Anal. Calcd for $C_{20}H_{22}DNO_4$: mol wt, 342.1688. Found: mol wt, 342.1676 (mass spectrum).

Further elution with benzene–chloroform gave the amide *N*-cyclohexyl-2-phenylacetamide (**14b**, 0.48 g, 90% yield), mp 131–132.5°; mixture melting point with an authentic sample was undepressed; NMR δ_{Me_4Si} ($CDCl_3$) 0.8–2.08 (br, 10 H, cyclohexyl), 3.53 (s, 2 H, $-CH_2C_6H_5$), 3.48–4.15 (br, 1 H, methine), 5.17–5.73 (br, 1 H, NH, D_2O exchangeable), and 7.29 (s, 5 H, aromatic).

Synthesis of Dimethyl *N*-(*S*)-(−)-α-Methylbenzyl]-2-phenylpyrrole-3,4-dicarboxylate (10f). The title compound was prepared by the following sequence of reactions.

A. 1-(*S*)-α-Methylbenzyl-3-cyano-2-phenylaziridine (15). To a solution of 4.35 g (15 mmol) of 1,2-dibromo-1-cyano-2-phenylethane[24] in 200 ml of dry benzene stirred at 0–5° was added dropwise a solution of 7.2 g (0.06 mol) of (*S*)-(−)-α-methylbenzylamine, $[\alpha]^{25}D$ −39° (neat), in 50 ml of benzene. The solution was then stirred at room temperature for a period of 10 days. The precipitated α-methylbenzylamine hydrobromide was collected and the yellow filtrate was concentrated in vacuo and subjected to chromatography on 100 g of B. D. H. alumina. Removal of the solvent from the main fraction gave 1-(*S*)-α-methylbenzyl-3-cyano-2-phenylaziridine as a white solid: mp 135–137.5° (67%); NMR δ ($CDCl_3$) 1.42 (d, 3 H, $-CH_3$, J = 6.5 Hz), AB quartet centered at 2.32 and 3.08 (J = 6.0 Hz, 2 H and 2, 3 ring protons), 2.89 (q, 1 H, J = 6.5 Hz, methine), and 7.27–7.70 (multiplet, 10 H, aryl protons); $[\alpha]^{25}D$ +18.5° (*c* 5.5, C_6H_6); mass spectrum (70 eV) *m/e* 248.1309 (calcd for $C_{17}H_{16}N_2$, 248.1314); ν_{max} ($CHCl_3$) 2250 cm^{-1} (C≡N).

Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.25; H, 6.45; N, 11.30. Found: C, 82.41; H, 6.51; N, 10.99.

B. Reaction of 1-(*S*)-(+)-α-Methylbenzyl-3-cyano-2-phenylaziridine with 4. A solution of 0.5 g (2 mmol) of the chiral aziridine and 0.285 g (2 mmol) of **4** was heated under reflux in xylene for 24 hr. The yellow solution was cooled and solvent removed in vacuo, giving a yellow oil. The oil was subjected to chromatography on 50 g of B. D. H. alumina to give *N*-[(*S*)-(−)-α-methylbenzyl]-2-phenylpyrrole-3,4-dicarboxylate (**10f**): 0.54 g (74%); $[\alpha]^{25}D$ −59.80° (*c* 10.01, C_6H_6); NMR δ ($CDCl_3$) 1.68 (d, 3 H, J = 6.5 Hz, $-CH_3$), 3.59 (s, 3 H, CO_2CH_3), 3.75 (s, 3 H, CO_2CH_3), 5.21 (q, 1 H, J = 6.5 Hz, methine), 6.65–7.31 (m, 10 H, aromatics), and 7.43 (s, 1 H, C_5 H); mass spectrum *m/e* 363.1484 (calcd for $C_{22}H_{21}NO_4$, 363.1471).

Anal Calcd for $C_{22}H_{21}NO_4$: C, 72.72; H, 5.78; N, 3.86. Found: C, 72.94; H, 5.62; N, 4.01.

Dimethyl *N*-Cyclohexyl-2-phenylpyrrole-3,4-dicarboxylate (10a). A solution of 0.45 g (2 mmol) of 1-cyclohexyl-2-cyano-3-phenylaziridine[17] and 0.285 g (2 mmol) of **4** was heated under reflux in 35 ml of xylene for 24 hr. Removal of the solvent in vacuo and chromatography on 50 g of B. D. H. alumina eluting with benzene–hexane (1:4) gave **10a** as a light yellow oil which resisted crystallization: 0.58 g (85%); NMR δ ($CDCl_3$) 0.87–2.15 (m, 10 H, cyclohexyl methylenes), 3.63 (s, 3 H, CO_2CH_3), 3.82 (s, 3 H, CO_2CH_3), 3.45–4.01 (br, 1 H, cyclohexyl methine), and 7.32–7.54 (m, 5 H, aromatic and C_5H); mass spectrum *m/e* 341.1616 (calcd for $C_{20}H_{23}NO_4$, 341.1627).

Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.38; H, 6.74; N, 4.10. Found: C, 70.47; H, 6.43; N, 4.09.

Thermolysis of Dimethyl 1-(*R*)-2-(*S*)-Di(α-methylphenethyl)-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (6c) in the presence of Thiophenol. A solution of 1.25 g (2 mmol) of the pyridine **6c** and 0.330 g (3 mmol) of the thiophenol in 75 ml of dry toluene was heated under reflux for 10 hr. Removal of the solvent in vacuo gave a light yellow oil which was subjected to chromatography on B. D. H. alumina. Elution with hexane–benzene (2:1) afforded the pseudothiourea **13c**, 0.593 g (86% yield), as a yellow oil: NMR δ_{Me_4Si} ($CDCl_3$) 1.30 (d, 3 H, J = 6.0 Hz, $-CH_3$), 2.91–3.14 [m, 2 H, $-CH(CH_2Ph)$], 3.58 (s, 2 H, $-CH_2Ph$), 3.90–4.65 (m, 1 H, methine), and 6.68–7.54 (m, 15 H, aromatics); ν_{max} ($CHCl_3$) 1665 cm^{-1} (C=N).

Anal. Calcd for $C_{23}H_{23}NS$ ($M^+ - C_6H_5S$, $C_{17}H_{18}N$, 236.1439): C, 80.01; H, 6.67; N, 4.05. Found ($C_{17}H_{18}N$ 236.1450, mass spectrum): C, 79.93; H, 6.42; N, 4.33.

Further elution with benzene gave dimethyl *N*-[(*R*)-α-methylphenethyl]-2-phenylpyrrole-3,4-dicarboxylate (**10c**, 0.670 g, 89% yield) as a pale yellow oil which on trituration with hexane deposited yellowish-white crystals, mp 93–95.5°. Repeated crystallization from methanol and petroleum ether gave an analytical sample: mp 94.5–95.5°; $[\alpha]^{25}D$ −78.5° (*c* 10.1, C_6H_6); NMR δ_{Me_4Si} ($CDCl_3$) 1.28 (d, 3 H, J = 6.5 Hz, $-CH_3$), 2.55– 3.15 (m, 2 H, CH_2Ph), 3.56 (s, 3 H, CO_2CH_3), 3.82 (s, 3 H, CO_2CH_3), 3.80–4.46 (m, 1 H, methine), 6.67–7.41 (m, 10 H, aromatic), and 7.45 (s, 1 H, C_5H).

Anal. Calcd for $C_{23}H_{23}NO_4$ (mol wt 377.1813): C, 73.19; H, 6.10; N, 3.72. Found (mol wt 377.1804, mass spectrum): C, 73.17; H, 6.48; N, 3.81.

Thermolysis of Dimethyl 1-(*S*)-2-(*R*)-Di(α-methylbenzyl)-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (6f). A solution of 1.8 g (3 mmol) of the pyridine **6f** in 75 ml of dry toluene was heated under reflux for 10 hr. Removal of the solvent in vacuo gave a light yellow oil which was subjected to chromatography on B. D. H. alumina. Elution with hexane–benzene (4:1) gave as a yellow oil a mixture of *threo*- and *erythro*-(*R*)-2,3-diphenylbutyronitriles **9f** in a ratio of 1:1 as estimated by NMR: δ_{Me_4Si} ($CDCl_3$) 1.33 (d, 3 H, J = 6.5 Hz, CH_3), 1.45 (d, 3 H, J = 6.5 Hz, CH_3), 2.93–3.48 (m, 2 H, methine, C_3H), 3.98 (d, 2 H, J = 6.5 Hz, C_2H), and 7.12–7.47 (m, 20 H, aromatics); infrared ν_{max} ($CHCl_3$) 2230 cm^{-1} (C≡N). The oil on trituration and repeated recrystallization from hot ethanol gave the pure *erythro*-(*R*)-(−)-2,3-diphenylbutyronitrile **9f** as a white solid: mp 132–133.5° (lit.[19] mp 133–134.5°); $[\alpha]^{25}D$ −21.85° (*c* 8.9, C_6H_6); NMR δ_{Me_4Si} ($CDCl_3$) 1.43 (d, 4 H, J = 6.5 Hz, CH_3), 302–3.50 (quintuplet, 1 H, J_{23} = 6.5, J_{CH_3-H} = 6.5 Hz, C_3H), 3.98 (d, 1 H, J = 6.5 Hz, C_2H), and 7.09–7.48 (m, 10 H, aromatics); infrared ν_{max} ($CHCl_3$) 2235 cm^{-1} (C≡N).

Further elution with benzene gave dimethyl *N*-[(*S*)-(−)-α-methylbenzyl]-2-phenylpyrrole-3,4-dicarboxylate (**10f**, 0.95 g, 86% yield) as a yellow oil: $[\alpha]^{25}D$ = −57.25° (*c* 10.5, C_6H_6); authentic sample $[\alpha]^{25}D$ −59.80° (*c* 10.8, C_6H_6); NMR δ_{Me_4Si} ($CDCl_3$) 1.72 (d, 3 H, J = 7.0 Hz, CH_3), 3.65 (s, 3 H, CO_2CH_3), 3.82 (s, 3 H, CO_2CH_3), 5.07–5.42 (q, 1 H, J = 7.0 Hz, methine), 6.92–7.41 (m, 5 H, aromatics), and 7.45 (s, 1 H, C_5H).

Anal. Calcd for $C_{22}H_{21}NO_4$ (mol wt, 363.1471): C, 70.21; H, 5.78; N, 3.85. Found (mol wt, 363.1459, mass spectrum): C, 70.09; H, 5.54; N, 4.01.

Thermolysis of (+)-Dimethyl 1-(*S*)-2-(*R*)-Di-*sec*-butyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (6g). A solution of 0.987 g (2 mmol) of the chiral azetidinopyridine **6g** in 50 ml of dry toluene was heated under reflux for 10 hr. Removal of the solvent in vacuo gave a light orange oil which on trituration with hexanes deposited yellowish-white crystals of dimethyl *N*-[1-(*S*)-*sec*-butyl]-2-phenylpyrrole-3,4-dicarboxylate (**10g**, 0.597 g, 94% yield): mp 118–119.5° (MeOH–petroleum ether); NMR δ_{Me_4Si} ($CDCl_3$) 0.71 (t, 3 H, J = 7.0 Hz, $-CH_2CH_3$), 1.33 (d, 3 H, J = 6.5 Hz, $-CH_3$), 1.01–1.86 (m, 2 H, $-CH_2CH_3$), 3.63 (s, 3 H, $-CO_2CH_3$), 3.81 (s, 3 H, CO_2CH_3), 3.36–4.15 (br, 1 H, methine), and 7.17–7.65 (m, 6 H, aromatic and C_5H); absorption spectrum λ_{max} (CH_3CN) 255 nm (log ε 4.04); $[\alpha]^{25}D$ +3.6° (*c* 9.91, C_6H_6).

Anal. Calcd for $C_{18}H_{21}NO_4$ (mol wt 315.1470): C, 68.55; H, 6.71; N, 4.44. Found (mol wt, 315.1460, mass spectrum): C, 68.44; H, 6.79; N, 4.42.

The filtrate on evaporation gave a yellow oil which was subjected to chromatography on 30 g of B. D. H. alumina. Elution with benzene–chloroform (4:1) gave a light yellow oil, 0.277 g (78% yield), which on trituration with hexanes and on cooling deposited *N*-[*S*-(+)-*sec*-butyl]-2-phenylacetamide (**14g**): mp 57–58.5°; mixture melting point with an authentic sample was undepressed; $[\alpha]^{25}D$ +4.75° (*c* 10.2, C_6H_6); NMR δ_{Me_4Si} ($CDCl_3$) 0.83 (t, 3 H, J = 6.5 Hz, CH_2CH_3), 1.08 (d, 3 H, J = 6.5 Hz, $-CH_3$), 1.06–1.54 (m, 2 H, $-CH_2CH_3$), 3.58 (s, 2 H, $-CH_2C_6H_5$), 3.62–4.15 (m, 1 H, $-CH_2CH_3$), 5.31–5.92 (br, 1 H, NH, exchangeable with D_2O), and 7.33 (s, 5 H, aromatic); infrared ν_{max} ($CHCl_3$) 1667 cm^{-1} (=O); absorption spectrum (CH_3CN) ν_{max} 270 nm (log ε 2.38), 266 (2.56), and 248 (2.49).

Anal. Calcd for $C_{12}H_{17}NO$: mol wt, 191.1306. Found: mol wt, 191.1308 (mass spectrum).

***N*-[(*S*)-(+)-*sec*-Butyl]-2-phenylacetamide (14g).** To a cold benzene solution of 1.65 g (1 mmol) of phenacyl chloride was added dropwise a benzene solution of 1.62 g (2 mmol) of (*S*)-(+)-*sec*-butylamine **17g** during 30 min. The reaction mixture was set aside at room temperature for 2 hr and then diluted with cold water. The organic layer was washed twice with cold water and dried ($MgSO_4$) and the solvent was removed to give a pale yellow oil. Trituration with hexane and cooling deposited *N*-[(*S*)-(+)-*sec*-butyl]-2-phenylacetamide (**14g**) as white needles: mp 57–58°; $[\alpha]^{25}D$ +4.95° (*c* 9.95, C_6H_6); NMR δ_{Me_4Si} ($CDCl_3$) 0.83 (t, 3 H, J = 6.5 Hz, CH_2CH_3), 1.07 (d, 3 H, J = 6.5 Hz, $-CH_3$), 1.06–1.54 (m, 2 H, $-CH_2CH_3$), 3.58 (s, 2 H, $-CH_2C_6H_5$), 3.62–4.15 (m, 1 H, $-CH_2CH_3$), 5.31–5.92 (br, 1 H, NH, exchangeable with D_2O), and 7.33 (s, 5 H, aromatic).

Photolysis of (+)-Dimethyl 1-(*S*)-2-(*R*)-Di-*sec*-butyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (6g). An ethereal solution of 1.0 g (2 mmol) of the azetidinopyridine **6g**, $[\alpha]^{25}D$ 4.95° (*c* 8.35, C_6H_6), in 100 ml of dry ether was cooled in an acetone–Dry Ice bath at −70 to −80° and irradiated with a 200-W Hanovia medium-pressure lamp for 2.25 hr. The progress of the reaction was followed by thin layer chromatography [Eastman alumina fluorescence coated plate using benzene–hexane (1:2) solution] by following the disappearance of the pyridine. Removal of the solvent in vacuo gave a yellow oil which was chromatographed on 50 g of B. D. H. alumina. Elution with hexane–benzene (1:2) gave a light yellow oil (0.603 g) which on trituration with hexane deposited yellowish white crystals (0.503 g, 80% yield) of dimethyl *N*-[(*S*)-(+)-*sec*-butyl]-2-phenylpyrrole-3,4-dicarboxylate (**10g**), mp 118.5–119°, $[\alpha]^{25}D$ +3.2° (*c* 10.1, C_6H_6).

Continued elution with benzene–chloroform (4:1) gave a light yellow oil (0.201 g, 52% yield) which on trituration with hexanes and on cooling deposited *N*-[(*R*)-*sec*-butyl]-2-phenylacetamide (**14h**), mp 57–58°, $[\alpha]^{25}D$ −3.8° (*c* 9.95, C_6H_6). A similar experiment was performed with dimethyl 1-(*R*)-1-(*S*)-di-*sec*-butyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (**6h**) giving comparable results (see Table IV).

Photolysis of Dimethyl 2,3-Di-*sec*-butyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate [6g(h)]. An ethereal solution of 0.200 g of the racemic azetidinopyridine **6g(h)** in 100 ml of ether was cooled in an acetone–Dry Ice bath (−70 to −80°) and irradiated under N_2 with a 200-W Hanovia medium-pressure lamp for 30 min. Removal of the solvent in vacuo at 15–18° gave a yellow oil which was chromatographed on B. D. H. alumina. Elution with hexane–benzene (4:1) gave a reddish-yellow oil (35 mg) which resisted crystallization and which is assigned structure **7g(h)** tentatively: NMR ($CDCl_3$) δ 0.75–1.84 [m, 14 H, $-CH(CH_3)(CH_2CH_3)$], 2.35–3.31 (m, 4 H, $-CHCH_2CH_3$), 3.76 (s, 6 H, $-CO_2CH_3$), and 7.02–7.68 (m, 12 H, aromatics, two ring protons); ν_{max} ($CHCl_3$) 1710 cm^{-1} (C=O).

Anal. Calcd for $C_{30}H_{36}N_2O_4$: mol wt, 488.2675. Found: mol wt, 488.2665 (mass spectrum).

Further elution with hexane–benzene (1:2) gave dimethyl *N*-*sec*-butyl-2-phenylpyrrole-3,4-dicarboxylate [**10g(h)**], mp 117–119° (60%), and continued elution with benzene–chloroform gave *N*-*sec*-butyl-2-phenylacetamide [**14g(h)**], mp 55–57° (52%).

Thermolysis of Dimethyl1,2-di-*tert*-butyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (6i) in Excess of Dimethyl Acetylenedicarboxylate. A suspension of 0.97 g (2 mmol) of the azetidinopyridine **6i** and 14.2 g (0.1 mol) of **4** was maintained at 75 ± 2° under a nitrogen atmosphere. The solid slowly dissolved and the mixture was then heated for 10 hr. Upon cooling and removing the excess of **4** a dark oil was obtained, which on trituration with methanol deposited the tetramer of **4** (**18**). The latter was collected and the filtrate concentrated and subjected to chromatography on 100 g of B. D. H. alumina. Elution with hexane–benzene (4:1) gave tetramethyl 1,6-di-*tert*-butyl-2,7-diphenyl-1,6-diazecine-3,4,8,9-tetracarboxylate (**25i**), 0.869 g (69% yield), as a light yellow oil: NMR δ_{Me_4Si} ($CDCl_3$) 1.45 [s, 18 h, $C(CH_3)_3$], 3.62 (s, 6 H, CO_2CH_3), 3.68 (s, 6 H, CO_2CH_3), 6.97 (s, 2 H, C_2H and C_7H), and 7.17–7.42 (m, 10 H, aromatic); ν_{max} ($CHCl_3$) 1673 cm^{-1} (ester C=O); mass spectrum *m/e* 630.2962 (calcd for $C_{36}H_{42}N_2O_8$, 630.2941).

Anal. Calcd for $C_{36}H_{42}N_2O_8$: N, 4.42. Found: N, 4.08.

Further elution with benzene gave 0.157 g (25% yield) of the pyrrole **10i.**

Thermolysis of Dimethyl 1,2-Dicyclohexyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate (6a) with Excess of Dimethyl Acetylenedicarboxylate. A suspension of 1.10 g (2 mmol) of the pyridine **6a** and 14.2 g (0.1 mol) of **4** was maintained at 100 ± 2° under nitrogen atmosphere. The solid slowly dissolved and the resulting reaction mixture was heated for 14 hr. Removal of the excess of **4** gave a dark red oil, which on trituration with methanol precipitated the tetramer of **4** as a white solid, mp 109–110.5°. The latter was removed by filtration, the filtrate was concentrated, and the residual oil was subjected to chromatography on 100 g of B. D. H. alumina. Elution with hexane–benzene (4:1) gave tetramethyl 1,6-dicyclohexyl-2,7-diphenyl-1,6-diazecine-3,4,8,9-tetracarboxylate (**25b**) as a light yellow oil: 0.35 g (25% yield); NMR δ ($CDCl_3$) 0.82–2.04 (m, 20 H, cyclohexyl), 3.61 (s, 6 H, CO_2CH_3), 3.67 (s, 3 H, CO_2CH_3), 6.90–7.92 (m, 12 H, aromatic, C_2H and C_7H).

Anal. Calcd for $C_{40}H_{46}N_2O_8$: mol wt, 682.3588. Found: mol wt, 682.3582 (mass spectrum).

Further elution with hexane–benzene (1:3) gave dimethyl *N*-(cyclohexyl)-2-phenyl-5-deuteriopyrrole-3,4-dicarboxylate (**10b**),

0.381 g (56% yield). Continued elution with benzene–chloroform (2:1) gave *N*-cyclohexyl-2-phenylacetamide (**14a**), mp 130–132°, 0.261 g (60% yield).

Reaction of 1,2-Di-*tert*-butyl-2,5-diphenyl-1,2-dihydropyrazine (3i) with Excess of Dimethyl Acetylenedicarboxylate. A suspension of 0.7 g (2 mmol) of dihydropyrazine **3i** and 7.1 g (50 mmol) of **4** was heated at 75 ± 2° for 10 hr. Removal of the excess of **4** in vacuo gave a dark oil which was subjected to chromatography on B. D. H. alumina. Elution with hexane–benzene (4:1) gave the diazecine **25i**, 0.13 g (11% yield).

Further elution with benzene gave 0.38 g (60% yield) of the pyrrole **10i**. Continued elution with benzene–chloroform (9:1) gave *N*-(*tert*-butyl)-2-phenylacetamide (**14i**), 0.195 g (50% yield). Further elution with benzene–chloroform (3:1) gave unreacted dihydropyrazine **3i**, 0.153 g (20% yield).

Thermal Decomposition of Dimethyl 1,2-Di-*tert*-butyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate with 1 Equiv of Dimethyl Acetylenedicarboxylate. A solution of 0.97 g (2 mmol) of the pyridine **6i** and 0.285 g (2 mmol) of **4** in benzene was heated under reflux for 10 hr. Removal of the solvent and chromatography on B. D. H. alumina gave the diazecine **25i** as a light yellow oil, 52 mg (4% yield). Further elution gave the pyrrole **10i**, 0.54 g (85.7% yield), and *N*-(*tert*-butyl)-2-phenylacetamide (**14i**), 0.273 g (71% yield).

Thermolysis of Dimethyl 1,2-Di-*sec*-butyl-2,5-diphenyl-3,8-dihydroazetidino[3,2-*b*]pyridine-6,7-dicarboxylate with Excess of Dimethyl Acetylenedicarboxylate 6g(h). A suspension of 1.0 g of the racemic pyridine **6g(h)** and 14.2 g of **4** was maintained at 100° under N_2 atmosphere. The solid slowly dissolved and the resulting mixture was heated for 12 hr. Removal of the excess **4** in vacuo gave a dark red oil which on trituration with methanol deposited the tetramer of **4**, mp 108–110°.[22] The latter was removed by filtration, the filtrate concentrated, and the oil was subjected to chromatography on B. D. H. (150 g) alumina. Elution with hexane–benzene (3:1) gave a light yellow oil, 0.302 g (32%), which on trituration and on standing for 1 week deposited yellow solid, mp 135–137°, of tetramethyl 1-*sec*-butyl-2-phenylazepine-3,4,5,6-tetracarboxylate [**26g(h)**]: NMR ($CDCl_3$) δ 0.91 (t, 3 H, J = 6.5 Hz, $-CHCH_2CH_3$), 1.17 (d, 3 H, J = 6.2 Hz, $-CHCH_3$), 1.35–1.81 (m, 2 H, $-CHCH_2CH_3$), 3.15–3.56 (br, 1 H, –CH–), 3.42 (s, 6 H, $-CO_2CH_3$), 3.83 (s, 6 H, $-CO_2CH_3$), and 6.82–7.48 (m, 6 H, aromatic and C_6H); ir ($CHCl_3$) ν_{max} 1715 cm^{-1} (–C=O ester).

Anal. Calcd for $C_{24}H_{27}NO_8$: mol wt, 457.1737. Found: mol wt, 457.1757 (mass spectrum).

Further elution with hexane–benzene (1:2) gave dimethyl *N*-*sec*-butyl-2-phenylpyrrole-3,4-dicarboxylate [**10g(h)**], mp 117–118.5° (51% yield), and continued elution with benzene–chloroform gave *N*-*sec*-butyl-2-phenylacetamide, [**14g(h)**], mp 56–58.5° (46%).

Isolation of *N*-*tert*-Butyl-3-phenylketenimine (12i). Photolysis of dimethyl 2,3-di-*tert*-butyl-2,5-diphenyl-3,8-azetidino[3,2-*b*]pyridine-6,7-dicarboxylate (**6i**) in the manner described for **6g** and distillation of the oil obtained gave the ketenimine **12i**: bp ~100° (0.01 mmHg); NMR ($CDCl_3$) δ 1.28 (s, 9 H, *t*-Bu), 4.74 (s, 1 H, =CH), and 6.90–7.28 (m, 5 H, aromatic); ν_{max} 2020 cm^{-1} (N=C).

Registry No.—**3b**, 56572-07-7; **3c(d)**, 52168-80-6; **3e(f)**, 52168-81-7; **3g(h)**, 56572-08-8; **3i**, 40312-86-5; **4**, 762-42-5; **6a**, 51909-23-0; **6b**, 51852-18-7; **6c(d)**, 52168-82-8; **6e(f)**, 52168-83-9; **6g(h)**, 56572-09-9; **6i**, 51852-19-8; **6j**, 56572-10-2; **6k**, 50743-06-1; **7g(h)**, 56572-11-3; *threo*-(*R*)-**9f**, 56648-88-5; *erythro*-(*R*)-**9f**, 52195-01-4; **10a**, 50743-12-9; **10b**, 56572-12-4; **10c**, 52168-84-0; **10c(d)**, 56613-92-4; **10e(f)**, 56613-93-5; **10f**, 52168-86-2; **10g**, 56572-13-5; **10g(h)**, 56613-94-6; **10i**, 50743-08-3; **10j**, 56572-14-6; **10k**, 50743-07-2; **12i**, 50743-11-8; **13c**, 56572-15-7; **14a**, 10264-08-1; **14c(d)**, 56613-95-7; **14g**, 56572-16-8; **14g(h)**, 56649-69-5; **14h**, 56572-17-9; **14i**, 6941-21-5; **14j**, 5215-54-3; **14k**, 56572-18-0; **15a** (R = C_6H_{11}), 19521-14-3; **15f** (R = α-methylbenzyl), 56572-19-1; **17c**, 156-34-3; **17d**, 51-64-9; **17e**, 3886-69-9; **17f**, 2627-86-3; **17g**, 513-49-5; **25b**, 56572-20-4; **25i**, 56572-21-5; **26g(h)**, 56572-22-6; α,α-dideuterio-2-bromoacetophenone, 56572-23-7; cyclohexylamine-*N*-d_2, 2523-32-2; α-bromoacetophenone, 70-11-1; 1,2-dibromo-1-cyano-2-phenylethane, 19521-13-2.

References and Notes

(1) (a) We are indebted to the National Research Council of Canada (Grant A2305) for financial aid. (b) National Research Council of Canada Postdoctoral Fellow.
(2) J. W. Lown and M. H. Akhtar, *J. Chem. Soc., Chem. Commun.*, 829 (1972).
(3) J. W. Lown, M. H. Akhtar, and R. S. McDaniel, *J. Org. Chem.*, **39**, 1998 (1974).
(4) (a) J. A. Berson and G. L. Nelson, *J. Am. Chem. Soc.*, **89**, 5503 (1967); (b) *ibid.*, **92**, 1096 (1970); (c) W. R. Roth and A. Freidrich, *Tetrahedron Lett.*, 2607 (1969).
(5) (a) W. von E. Doering and H. D. Roth, *Tetrahedron*, **26**, 2825 (1970); (b) W. von E. Doering and L. Birladeanu, *ibid.*, **29**, 499 (1973).
(6) S. Masamune, S. Takada, N. Nakatsuka, R. Vukov, and E. N. Cain, *J. Am. Chem. Soc.*, **91**, 4322 (1969).
(7) J. E. Baldwin and R. H. Fleming, *J. Am. Chem. Soc.*, **94**, 2410 (1972).
(8) R. C. Cookson and J. E. Kemp, *Chem. Commun.*, 385 (1971).
(9) N. D. Epiotis, *J. Am. Chem. Soc.*, **95**, 1206 (1973).
(10) J. W. Lown and M. H. Akhtar, *J. Chem. Soc., Perkin Trans. 1*, 683 (1973).
(11) J. W. Lown and M. H. Akhtar, *J. Chem. Soc., Chem. Commun.*, 511 (1973).
(12) Part of this work has been published in preliminary form: J. W. Lown and M. H. Akhtar, *Tetrahedron Lett.*, 179 (1974).
(13) (a) L. A. Paquette and R. W. Begland, *J. Am. Chem. Soc.*, **88**, 4685 (1966); (b) G. A. Berchtold and G. F. Uhlig, *J. Org. Chem.*, **28**, 1459 (1963); (c) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *ibid.*, **28**, 1464 (1963); (d) A. K. Bose, G. Mina, M. S. Manhas, and E. R. Zucidlo, *Tetrahedron Lett.*, 1467 (1963).
(14) The suggested valence tautomerism is analogous to that of 2,3-dimethoxy-8-methyl-3,4-dihydroazocine to 7,8-dimethoxy-2-methyl-2,3-pyridocyclobutene [L. A. Paquette and T. Kakihana, *J. Am. Chem. Soc.*, **93**, 174 (1971)] and of the isomerization of *N*-carbethoxyazocine to an azepinocyclobutene [S. Masamune and N. T. Castellucci, *Angew. Chem., Int. Ed. Engl.*, **3**, 582 (1964)].
(15) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Academic Press, New York, N.Y., 1970, p 70. The precise synchronization of this rather unusual reaction and the nature of the intermediates leading to the ketenimine and pyrrole products clearly require separate experimental investigation which will be reported on separately.
(16) The cleavage of **11** to **10** and **12** may well be a two-step process, however.
(17) J. W. Lown, T. W. Maloney, and G. Dallas, *Can. J. Chem.*, **48**, 584 (1970).
(18) J. C. Craig, R. P. K. Chan, and S. K. Roy, *Tetrahedron*, **23**, 3573 (1967).
(19) W. J. Chambers, W. R. Brasen, and C. R. Hauser, *J. Am. Chem. Soc.*, **79**, 879 (1957).
(20) E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, N.Y., 1962, pp 89, 119, 122, 402.
(21) The value of the rotation was substantially unchanged when the cleavage of **7** to **9** and **10** was performed in the presence of the scavenger butanethiol.
(22) E. L. LeGoff and R. B. LaCount, *Tetrahedron Lett.*, 2333 (1967).
(23) L. G. Thomè, *Ber.*, **36**, 582 (1903).
(24) A. M. Birks and G. F. Wright, *J. Am. Chem. Soc.*, **62**, 2412 (1940).
(25) S. L. Shapiro, I. M. Rose, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 6065 (1958).