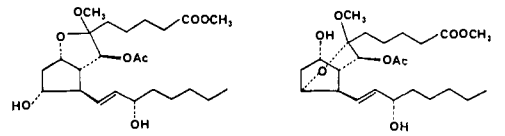
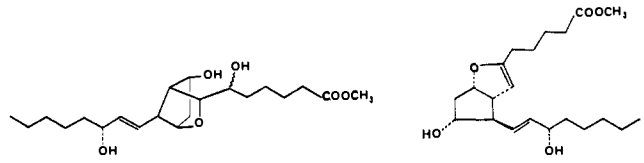
structures **2** and **3a,b.** Thus treatment of **2** in methanol with potassium carbonate at 25 °C for 2 h afforded the diol **4.**[7] The presence of an internal ketal moiety was evidenced by transketalization. Reaction of **2** with methanol in the presence of boron trifluoride etherate at 25 °C for 1 h gave **5**[8,9] and **6.**[8]



5 **6**

Similar methanolysis of **3a,b** at 25 °C for 15 min furnished the isomeric methyl ketals **7a,b**[8] which, using acetic anhydride-pyridine at 25 °C for 30 min, were converted to **8a,b.**[8] The masked oxo function of **3a,b** could be reduced by sodium bobohydride in ethanol, yielding the readily separable isomeric triols **9a** and **9b.**[8]



9a,9b **10**

Formation of **2** and **3a,b** upon the action of thallium triacetate may be interpreted by assuming **10** as the intermediate, produced via formation of the 6,9α-oxido ring and a carbenium ion at C-5 after the heterolysis of the primary C-Tl bond, which is followed by hydride shift and the loss of a proton from C-6 or C-7. Occurrence of the highly unstable **10** in the enzymatic conversion of arachidonic acid by rat stomach homogenates has been reported recently by Sih et al.[10] The reaction of an additional mole of thallium triacetate[11] with the endo double bond, aided by the OH group at C-11 and the solvent molecules as nucleophiles, produces **2**[12] and **3a,b** simultaneously. This mechanism readily explains the stereochemistry at C-6 and C-7 in **2** and **3a,b.**

We believe that the underlying reactions may have implications also outside the prostaglandin field.

Acknowledgments. The authors are grateful to Dr. Gyula Horváth (Research Institute for Pharmaceutical Chemistry) for the recording and interpretations of the mass spectra and to Dr. István Tömösközi (Chinoin) for helpful discussions.

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(3) Mass spectra were taken on Varian MAT SM-1 instrument.

(4) (a) Mass spectrum of **2** showed $M^{+}\cdot$ at 424.2419 (calcd for $C_{23}H_{36}O_7$, 424.2461) and the characteristic fragment ions at *m/e* 364, 346, 174, 143 (base peak), and 99. (b) Mass spectrum of **3a,b** showed $M^{+}\cdot$ at 382.2344 (calcd for $C_{21}H_{34}O_6$, 382.2355) and prominent fragment ions at *m/e* 222.1598 ($M - HOOC(CH_2)_4COOCH_3$) (calcd for $C_{14}H_{22}O_2$, 222.1620), 204, 161, 143, and 99 (base peak). Ions *m/e* 161 (formed via H rearrangement) and 143 (from 161 $- H_2O$ and from 6-keto form $M^{+}\cdot$) indicate the presence of C-6 lactol. Ion *m/e* represents the C-7–C-20 moiety of **3;** the high abundance of ions formed in this fragmentation pathway is assumed to be due to the 7,11α-oxido group.

(5) ^1H and ^{13}C NMR spectra were recorded on a Varian XL-100 FT spectrometer operating at 100.1 and 25.16 MHz, respectively.

(6) Selected ^1H and ^{13}C NMR chemical shifts follow (* indicates exo C-6 OH). ^1H NMR (δ, $CDCl_3$): **2,** 2.86 (m, 1 H, C-8 H), 3.00 (m, 1 H, C-12 H), 4.05 (m, 1 H, C-15 H), 4.32 (m, 1 H, $J_{10,11} = 1.5 + 1.5$ Hz, $J_{9,11} = 2$ Hz, C-11 H), 4.77 (m, 1 H, C-9 H), 4.96 (d, 1 H, $J_{7,8} = 0.5$ Hz, C-7 H), 5.38 (dd, 1 H, C-13 H), 5.52 (dd, 1 H, C-14 H), 3.66 (s, 3 H, $-COOCH_3$), 2.06 (s, 3 H, $7-OCOCH_3$); **3a,b,** 2.89 + 3.10* (m, 1 H, C-8 H), 2.95 (m, 1 H, C-12 H), 3.9 (m, 1 H, C-15 H), 4.15 + 4.08* (m, 1 H, $J_{10,11} = 1.5 + 1.5$ Hz, $J_{9,11} = 1$ Hz, C-11 H), 4.48 + 4.52* (m, 1 H, C-9 H), 3.92 + 3.95* (dd, 1 H, $J_{7,8} = 3$ Hz, $J_{7,9} = 1$ Hz, C-7 H), 5.42 (dd, 1 H, C-13 H), 5.55 (dd, 1 H, C-14 H), 3.56 (s, 3 H, $-COOCH_3$). ^{13}C NMR (δ, $CDCl_3$): **2,** 30.94 (C-5), 107.66 (C-6), 81.39 (C-7), 47.56 (C-8), 80.79 (C-9), 36.42 (C-10), 78.36 (C-11), 52.96 (C-12), 128.65 (C-13), 135.28 (C-14), 72.43 (C-15), 21.16 + 170.27 ($-O-CO-CH_3$); **3a,b,** 37.81 + 36.46* (C-5), 106.0 + 107.0* (C-6), 82.62 + 83.87* (C-7), 51.02 + 49.56* (C-8), 77.75 + 78.47* (C-9), 39.16 + 39.77* (C-10), 78.90 + 79.08* (C-11), 52.72 + 51.92* (C-12), 125.15 + 126.14* (C-13), 137.03 + 136.66* (C-14), 72.32 (C-15).

(7) Relevant ^{13}C NMR acetylation shifts (Δ_{2-4}: -1.35 (C-6), + 1.02 (C-7), and -2.21 (C-8).

(8) ^1H and ^{13}C spectral data of all derivatives were consistent with their structures.

(9) The formation and cleavage of the intramolecular oxygen bridges as in **2** and **3** involving C-11 OH are accompanied by characteristic changes of the C-11 H coupling constants; substantially smaller values are observed for **2** and **3** than for **1** and **5.**

(10) Sih, C. J.; Huang, Fu-Chih. *J. Am. Chem. Soc.* **1978**, *100*, 643–645.

(11) With 1 mol of thallium triacetate, besides unchanged **1,** only small amounts of **2** and **3** could be detected.

(12) After completion of this manuscript, we learned about the paper by Shimoji, K., et al. *J. Am. Chem. Soc.* **1978**, *100*, 2547–2548, describing the synthesis of **10** and a derivative of **2.**

Vilmos Simonidesz, Zsuzsa Gombos-Visky, Gábor Kovács*
Chinoin Pharmaceutical and Chemical Works Ltd.
H-1325 Budapest, Hungary

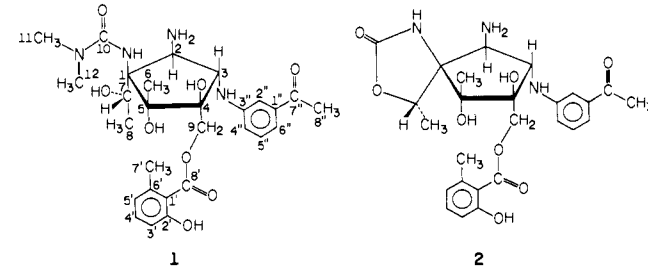
Eszter Baitz-Gács, Lajos Radics
Central Research Institute of Chemistry
H-1525 Budapest, Hungary

Received June 6, 1978

Biosynthesis of the Antitumor Antibiotic Pactamycin. A Methionine-Derived Ethyl Group and a C_7N Unit[1]

Sir:

Pactamycin (**1**), an antibiotic isolated from *Streptomyces pactum* var. *pactum,*[2a] is one of the more potent cytotoxic agents in vitro, inhibiting KB cells at 0.003 μg/mL (ID_{50}), and it has in vivo activity against a number of mammalian tumors.[2b] It is also active against gram-positive bacteria (MIC 0.8



1 **2**

μg/mL vs. *B. subtilis*), though its toxicity[2b] prevents any clinical applications, and it has proved valuable as a biochemical tool in studies of protein synthesis.[3] In addition to its bioactivity the uniquely branched, multiply hydroxylated and aminated, cyclopentane ring[4] is of considerable interest for its obscure biosynthetic origin. We report here that pactamycin is derived from a mixed biosynthetic pathway involving glucose, acetate, and methionine.

Administration of labeled precursors to a culture of *S. pactum* (Table I) showed that L-[*methyl*-^{14}C]methionine was incorporated into pactamycin to the extent of 0.020%, while [*carboxy*-^{14}C]acetate and D-[1-^{14}C]glucose were incorporated into pactamycate (**2**), which is coproduced in this medium, to the extent of 0.093 and 0.061%, respectively. Conversion of pactamycin labeled by [*methyl*-^{14}C]methionine to pactamycate indicated loss of 40% of the label; thus, the *N*-methyl groups are derived from methionine.

Administration of ^{13}C-labeled precursors was followed by

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Table I. Incorporation of Labeled Precursors into Pactamycin and Pactamyçate[a]

	precursor			pactamyçate			
compd	sp act., μCi/mmol	amt, g	vol, L	sp act., μCi/mmol	amt, mg	dilution	incorporation, %
D-[6-^{14}C]glucose	1.76	3.0	0.5[b]	2.92	3.2	0.60	0.062
sodium [1-^{14}C]acetate	2.17	0.8	0.4[c,d]	1.15	8.9	1.89	0.091
L-[*methyl*-^{14}C]methionine	1.86	4.0	2.0	3.43[g]	1.6[g]	0.54[g]	0.021[g]
				2.07[h]		0.89[h]	0.014[h]
	enrichment, %			av enrichment, %[i]			
D-[6-^{13}C]glucose	61	4.2	0.7[f]	9.0	5.0	6.7	0.14[j]
D-[1-^{13}C]glucose	24.5	3.5	0.7[e,f]	1.6	5.0	15	0.070[j]
sodium [1-^{13}C]acetate	92	1.4	0.7[d,f]	0.8	12	115	0.055[j]
sodium [2-^{13}C]acetate	91	1.4	0.7[d,f]	1.7	11	54	0.11[j]
L-[*methyl*-^{13}C]methionine	60	1.6	0.8	2.7	6.0	22	0.13[j]

[a] Fermentations were at 32 °C, 250 rpm, in 500-mL wide-mouthed Erlenmeyer flasks. The initial production medium (PAS) in all runs contained K_2HPO_4 (25.8 mM), KH_2PO_4 (12.9 mM), NH_4Cl (41.3 mM), $MgSO_4$ (2.1 mM), $FeSO_4$ (36 μM), $CaCl_2$ (125 μM), $MnSO_4$ (182 μM), $CoCl_2$ (16.9 μM), $CuSO_4$ (15.7 μM), $ZnSO_4$ (15.3 μM), and $NaMoO_4$ (10.4 μM). Glucose (1.0%) and yeast extract (Difco, 0.1%) were also added. Except as noted, precursors were added at 36 h. In those runs noted, mycelia were harvested, washed, and resuspended in fresh PAS solution, and the precursor and other materials, as necessary, were then added. After 84 h of shaking beyond the addition of precursor, the medium was adjusted to pH 8.3 and shaking was continued for 24 h. The combined broths were acidified to pH 2.5 for 10 min, filtered through Celite, neutralized to pH 8.3, and extracted with ethyl acetate. The combined organic layers were extracted with 0.1 N H_2SO_4, the aqueous phase was reneutralized and washed with ethyl acetate, and the crude bases were chromatographed on silica gel ($CHCl_3$-CH_3OH, 97:3). [^{14}C]Pactamycin was purified by repetitive chromatography on Florisil (acetone-hexane) or silica. [^{14}C]Pactamyçate was purified by recrystallization from ethanol, [^{13}C]pactamyçate was used directly following the initial silica gel chromatography. [b] Cells (from 1000 mL of medium) were washed and resuspended in 500 mL of PAS solution. [c] Cells (from 800 mL of medium) were washed and resuspended in 400 mL of PAS solution. [d] The final medium also contained glucose (0.5%). [e] The final medium also contained sodium acetate (0.2%). [f] Cells (from 1400 mL of medium) were washed and resuspended in 700 mL of PAS solution. [g] Pactamycin. [h] Pactamyçate derived from pactamycin (2 N HCl-CH_3OH, 9:1, 25 °C, 48 h). [i] Calculated by summing the values in Table II and dividing by the total number of carbons (26) to give the percent ^{13}C per carbon and then subtracting natural abundance ^{13}C (taken as 1.0%). [j] Calculated from ^{13}C data using enrichment values.

Table II. Chemical Shifts of Pactamyçate Carbons and Their Relative Enrichments by Labeled Precursors

		relative enrichment from individual precursors[b]				
		L-Met	sodium acetate		D-glucose	
pactamyçate carbon	chemical shift[a]	[*methyl*-^{13}C]	[1-^{13}C]	[2-^{13}C]	[6-^{13}C]	[1-^{13}C]
1	69.8	1.01	0.81	0.85	0.81	1.99
2	57.6	1.14	1.11	0.88	0.97	1.29
3	70.2	1.17	0.86	0.94	0.98	8.44
4	80.3	1.20	1.03	0.92	1.81	1.09
5	82.0	1.09	1.11	0.99	1.09	1.07
6	17.3	23.1	1.21	2.81	17.5	3.34
7	75.7	20.3	1.05	2.42	16.3	3.30
8	16.3	23.7	1.22	2.85	18.1	3.48
9	67.2	1.62	1.03	1.04	34.5	3.27
10	158.1	0.93	7.71	5.48	6.37	2.01
1′	119.9	1.25	1.12	6.72	15.4	2.59
2′	154.8	0.84	8.14	2.23	1.81	0.96
3′	113.3	1.02	1.11	7.32	17.2	3.33
4′	130.2	1.49	8.14	2.81	2.40	2.38[c]
5′	120.2	1.53	1.14	8.40	16.2	3.32
6′	136.9	1.10	7.47	3.04	1.84	1.13
7′	19.5	1.63	1.21	9.25	18.1	3.49
8′	167.9	1.47	8.17	3.15	2.87	0.93
1″	137.2	1.44	1.88	1.88	1.34	1.28
2″	111.4	1.27	1.12	1.05	32.7	3.63
3″	149.9	1.17	1.02	1.26	0.90	1.00
4″	116.6	1.32	1.39	1.14	1.84	1.56
5″	128.6	1.52	1.34	1.12	1.02	1.87
6″	115.6	1.47	1.06	1.62	21.5	5.17
7″	198.4	1.41	1.86	1.92	1.40	1.42
8″	26.6	1.82	1.42	12.3	25.4	3.58

[a] Parts per million from Me_4Si; Me_2SO-d_6 solutions. [b] Enrichments calculated as times natural abundance by a method previously described (A. Haber, R. D. Johnson, and K. L. Rinehart, Jr., *J. Am. Chem. Soc.*, **99**, 3541 (1977)). Intensities of peaks in labeled pactamyçate were divided by those in unlabeled pactamyçate and the resulting values were normalized to the average of the five smallest values, defined as 1.00 (assumed to be unlabeled). [c] Artifically high owing to instrumental problem of imaging. Presumed to be unlabeled like C-2′, C-6′, C-8′.

isolation of pactamyçate, since it was produced in larger amount than pactamycin itself. Location of label in pactamyçate was determined from its ^{13}C NMR spectrum, whose signals (Table II) have been assigned elsewhere.[5] From Table II it can be seen that methionine labels C-6, C-7, and C-8 of pactamyçate, and to approximately the same degree. Since these constitute 60% of the label provided by methionine, the *N*-methyl groups must each be labeled to the same extent

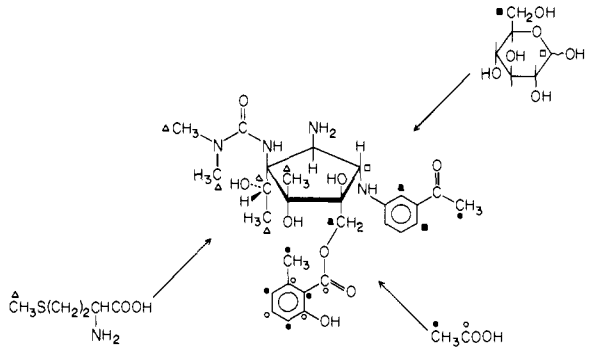

Figure 1. Labeling of pactamycin by [*methyl*-^{13}C]methionine, by [*methyl*-^{13}C]- and [*carboxy*-^{13}C]acetate, and by D-[6-^{13}C]- and [1-^{13}C]glucose.

(20%). Labeling of C-6, C-7, and C-8 accounts for the branching alkyl groups of the substituted cyclopentane unit except for C-9 (cf. below). Of particular interest is the labeling of both carbons of an ethyl group by methionine, a pattern observed previously only in sitosterol, stigmasterol, and related 24-ethyl steroids.[6]

As expected, [*carboxy*-^{13}C]acetate labeled C-2′, C-4′, C-6′, and C-8′ and [*methyl*-^{13}C]acetate labeled C-1′, C-3′, C-5′, and C-7′ of pactamycin's 6-methylsalicylate unit, a standard acetogenin product.[7] [*methyl*-^{13}C]Acetate and [*carboxy*-^{13}C]acetate both labeled C-10, the urea carbon, suggesting its derivation from [^{13}C]carbon dioxide produced in the tricarboxylic acid cycle.[8] In addition, [*methyl*-^{13}C]acetate labeled C-8″, in the *m*-aminoacetophenone unit, suggesting an acetate origin of the acetyl group.[9] However, [*carboxy*-^{13}C]acetate did not label C-7″ or any other carbon of *m*-aminoacetophenone. The origin of the remaining seven carbons of *m*-aminoacetophenone was established by the labeling pattern observed after administering D-[6-^{13}C]glucose. The latter compound labeled C-2″ and C-6″, the pattern expected if *m*-aminoacetophenone is derived, in part at least, from a shikimate-related pathway[10] involving erythrose 4-phosphate, phosphoenol pyruvate,[11] and 3-deoxy-D-arabinoheptulosonic acid 7-phosphate as intermediates. Direct analogies to the present unit are found in the "C_7N" units[13] of geldanamycin (carbons 15-21),[14] mitomycin (carbons 4a, 5, 6, 6a, 7, 8, and 8a),[15] rifamycin (carbons 1, 2, 3, 4, 8, 9. and 10),[16] and streptovaricin (carbons 21-27).[17] The first three have all been shown (and streptovaricin is presumed) to be derived from a shikimate-type pathway, which in the case of rifamycin (and presumably of the others) has been reported to branch from the shikimate pathway before chorismate.[18] In all of the cited antibiotics, except mitomycin, the "C_7N" unit serves as a starter for a poly(propionate-acetate) chain. In the present case it appears that the "C_7N" unit condenses with acetate (or malonate) to give a product which decarboxylates to give *m*-aminoacetophenone.

Glucose also provides the source of the remaining six carbons of pactamycin, the cyclopentane ring plus C-9. D-[6-^{13}C]-Glucose labels C-9, while D-[1-^{13}C]glucose labels most heavily C-3.[19] This labeling pattern could arise by condensation of C-1 of glucose at its C-5 in an aldol-type reaction (perhaps mediated by 4-ketoglucose or a related intermediate) or by ring contraction of an initially formed inositol with expulsion of the carbon derived from glucose C-6 in a reaction related to the formation of dihydrostreptose from 4-keto-6-deoxyglucose.[22]

The origin of the skeleton of pactamycin can then be summarized as in Figure 1.

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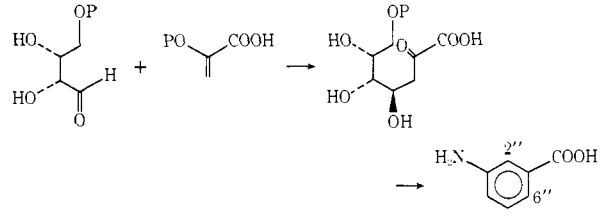
(9) In addition, [*methyl*-^{13}C]acetate labeled to a lesser degree C-6, C-7, C-8, C-2′, C-4′, C-6′, and C-8′, all of which have been shown to be derived more directly from [*methyl*-^{13}C]methionine (C-6, C-7, C-8) or [*carboxy*-^{13}C]-acetate (C-2′, C-4′, C-6′, C-8′), as well as C-1″, C-6″, and C-7″, which are part of the glucose-derived *m*-aminoacetophenone unit (cf. below) and presumably incorporated via phosphoenol pyruvate. Conversion of methyl-labeled to dilabeled acetate and formation of pyruvate from acetate via succinate and oxaloacetate in the tricarboxylic acid cycle are well-studied pathways.[8]
(10) E. Haslam, "The Shikimate Pathway", Wiley, New York, N.Y., 1974, pp 3-12.
(11) The slight enrichment of the *m*-aminoacetophenone unit at C-6″ by sodium [*methyl*-^{13}C]acetate (Table II)[8] suggests that phosphoenol pyruvate forms C-6″ (rather than C-2″) as well as C-1″ and C-7″ of *m*-aminoacetophenone via the scheme shown. This conclusion is supported by the results of the



[^{13}C]glucose feeding experiments. Following incorporation of [6-^{13}C]-glucose into pactamycate, relatively more ^{13}C label is observed at C-2″ than C-6″ (32.7 vs. 21.5), while in the [1-^{13}C]glucose experiment C-6″ is more enriched than C-2″ (5.17 vs. 3.63). These results closely parallel the incorporation of [6-^{14}C]- and [1-^{14}C]glucose into shikimic acid in *E. coli*,[12] and strongly support the argument that C-6″ derives from phosphoenol pyruvate and C-2″ from erythrose phosphate.
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(19) Carbon 6 of glucose is also an efficient precursor of many of the other carbons of pactamycin: C-6, C-7, C-8 by conversion to L-[*methyl*-^{13}C]-methionine via D-3-phospho[3-^{13}C]glycerate, L-[3-^{13}C]serine, and N^5-[*methyl*-^{13}C]methyltetrahydrofolate;[20,21] C-10, C-1′, C-3′, C-5′, C-7′, C-8″ by conversion to [*methyl*-^{13}C]acetate via pyruvate.[21] Carbon 1 of glucose labels the same carbons (C-6, C-7, C-8, C-10, C-1′, C-3′, C-5′, C-7′, C-8″), as well as those labeled more directly by D-[6-^{13}C]glucose (C-9, C-2″, C-6″), by routes discussed earlier.[22]
(20) Reference 8, Chapter 8.
(21) Reference 8, Chapter 11.

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Dwight D. Weller, Kenneth L. Rinehart, Jr.*
Roger Adams Laboratory, University of Illinois
Urbana, Illinois 61801
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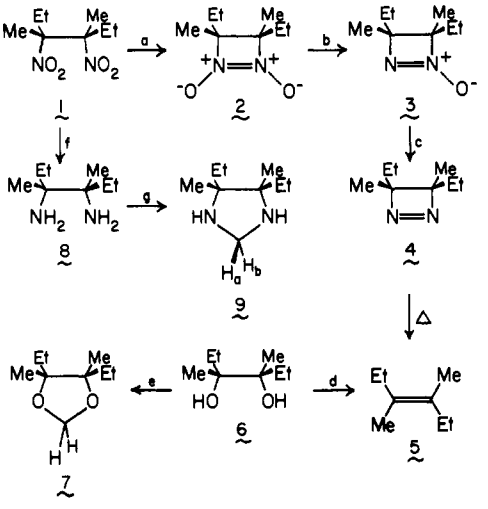
Decomposition of *meso*- and *dl*-3,4-Diethyl-3,4-dimethyldiazetine (a 1,2-Diaza-1-cyclobutene)[1]

Sir:

Study of the thermal decomposition of diazenes (azo compounds) has provided much information on the nature of diradicals and on the question of concerted vs. stepwise decomposition paths.[2] The four-membered-ring diazene—the 1,2-diazetine[3]—is of particular interest because of the variety of possible decomposition paths, and the relationships of these paths to orbital symmetry considerations and to questions associated with the high exothermicity in conversion of diazetines to olefins and N_2[3c] (e.g., the possibility of thermal generation of electronically excited states).[4] We report here the synthesis and stereochemistry of decomposition of *meso*- and *dl*-3,4-diethyl-3,4-dimethyldiazetine (*meso*-**4** and *dl*-**4**). The principal finding is that loss of N_2 from *meso*-**4** and *dl*-**4** is stereospecific and cis, affording *cis*- and *trans*-3,4-dimethyl-3-hexene, respectively.

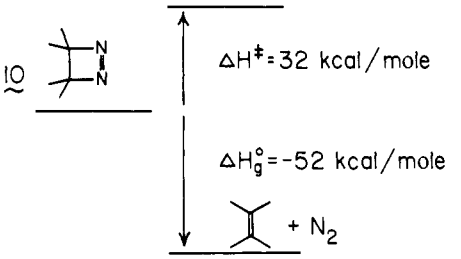
Synthesis of diazetines **4** (shown in Scheme I for the *dl* series): samples of **4** enriched in the meso or *dl* isomer were obtained by fractional recrystallization of *meso*- and *dl*-3,4-dimethyl-3,4-dinitrohexane (**1**),[5] followed by the sequence **1** → **2** → **3** → **4.** Assignments of stereochemistry (Scheme I): the meso and *dl* designations for diazetines **4** are based on conversion of dinitrohexane **1** to diamine **8** to imidazolidine **9;** NMR data of the ring methylene protons of imidazolidine **9** are definitive for stereochemical assignment (*meso*-**9** shows an AB quartet at δ 3.79, *dl*-**9** a singlet at δ 3.85). Assignment of olefin **5** stereochemistry is based on conversion of diol **6** to dioxolane **7** and to olefin **5.** In dioxolane **7,** the ring methylene protons appear as an AB quartet at δ 4.96 in the meso isomer and as a singlet at δ 4.98 in the *dl* isomer. The *dl*-dioxolane **7** was derived from the crystalline diol of mp 52–53 °C, thereby rigorously established as the *dl*-diol.[6] This same diol has been converted[7] by the cyclic thionocarbonate-triethyl phosphite reaction (known to involve overall cis elimination of the hydroxyl groups)[8] to one of the isomers of 3,4-dimethyl-3-hexene, established from the above relationships as the trans isomer.[9]

Scheme I[a]



[a] (a) (1) Zn, NH_4Cl, (2) Br_2; (b) Si_2Cl_6, CH_2Cl_2; (c) $LiAlH_4$; (d) (1) RLi, CS_2, CH_3I, (2) Et_3P; (e) CH_2O; (f) Sn, HCl; (g) CH_2O.

Scheme II



Pyrolysis of samples of diazetine **4,** enriched in meso and *dl,* at 375 °C (GC injection point) gave the isomeric hexenes **5** (eq 1 and 2). Within the limits of these experiments,[10] the decompositions are stereospecific and involve cis elimination of N_2.

diazetine **4** → 3,4-dimethyl-3-hexene (**5**)

>95% *meso*-**4** → >95% *cis*-**5** (1)

58 ± 2% *dl*-**4** → 56 ± 2% *trans*-**5** (2)

The enthalpy changes associated with the decomposition of 3,3,4,4,-tetramethyldiazetine (**10**)[3b,c] to tetramethylethylene are summarized in Scheme II.[11] The energy liberated in going from the transition state of diazetine **10** decomposition to ground state of products is ~85 kcal/mol, substantially above the amount associated with the interconversion of cis and trans olefins. In spite of this, the thermal decomposition of *meso*- and *dl*-diazetine **4** proceeds with high stereospecificity. The high stereospecificity also indicates that crossover to the T_1 state of 3,4-dimethyl-3-hexene (**5**) has not taken place;[12,13] the S_1 state of **5,** lying more than 130[13c] kcal/mol above S_0, would be energetically inaccessible in this reaction.

It is also of interest to consider the implications of the stereochemical findings with regard to synchronous vs. stepwise decomposition of diazetines. Evidence favors the loss of nitrogen from cyclic azoalkanes by concerted two-bond cleavage.[3c] Engel has suggested that the sum of the ground-state strain energy and $\Delta H^{\ddagger}$ for thermolysis is approximately constant at 42–45 kcal mol^{-1} for monocyclic azoalkanes.[3c,14] For diazetine **10,** this sum is 56 kcal mol^{-1}, indicating that **10** decomposes with at least 11 kcal mol^{-1} more difficulty than the five- and six-membered-ring counterparts.[3c] This finding is in accord with orbital symmetry restrictions on a [2_s (olefin) + 2_s (N_2)] process in the four-membered-ring case.[3a] The cis elimination of N_2 from *meso*- and *dl*-**4** excludes the orbital symmetry allowed possibility of synchronous loss of N_2 by a [2_a (olefin) + 2_s (N_2)] path. The synchronous alternatives of [2_s (olefin) + 2_a (N_2)] or of [2_s (olefin) + "partial 2_a" (N_2)][15] remain.

Concerning possibilities for stepwise decomposition of diazetine **4** (shown in Scheme III), the finding of cis elimination of N_2 leads to two conclusions: (a) cleavage of a C–N bond in **4** does *not* occur via concomitant stretching and twisting to diradical A, since this species would inevitably afford both *cis*- and *trans*-hexenes **5;** (b) if cleavage occurs by C–N stretching to afford diradical B, then the rate of loss of N_2 from this diradical (k_{frag}) exceeds the rate of rotation around the central C–C bond (k_{rot}). Prediction of the relative magnitudes of k_{frag} and k_{rot}, both expected to be of low activation energy, is rather speculative; analysis of ESR data on bond rotations in radicals,[16] of the results of decomposition of an optically active diazene,[17] and of CIDNP data[18] leads us to conclude that for

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