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Stereochemistry and Mechanism of the Schmitz Diaziridine Synthesis Leading to 2,4,6-Trisubstituted 1,3,5-Triazabicyclo[3.1.0]hexanes[1]

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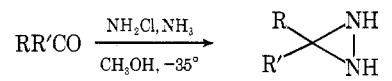
The Schmitz reaction of aldehydes with chloramine and methanolic ammonia leads to a mixture of two epimeric 2,4,6-trisubstituted 1,3,5-triazabicyclo[3.1.0]hexanes, each with exocyclic C-6 substituent; the major product (**3a**) and minor one (**3b**) have substituents at C-2, C-4 with trans and at C-2, C-4 with cis exocyclic stereochemistry, respectively. Isolation of Schmitz products under alkaline (kinetic) conditions yields a mixture of **3a,b** and a small amount of an epimer (**3c**) with endocyclic C-6 substituent and C-2, C-4 cis exocyclic substituent stereochemistry. The acid-catalyzed equilibration of **3a–c** generally yields a ca. 1:1 mixture of **3a** and **3b** (12 examples with alkyl, phenyl, and benzyl substituents); the equilibration mechanism is discussed. ^1H and ^{13}C NMR spectroscopy were employed in determination of product assay and stereochemistry. Oxidation of all equatorial 2,4,6-trialkyl-1,3,5-hexahydrotriazines (**17**) with *tert*-butyl hypochlorite in alkaline medium leads to a mixture of **3a** (predominantly) and **3b,c**; the reaction mechanism of this oxidation is discussed. It is concluded that a diaziridine intermediate, not a 2,4,6-trisubstituted 1,3,5-hexahydrotriazine, is involved in the Schmitz synthesis of **3**.

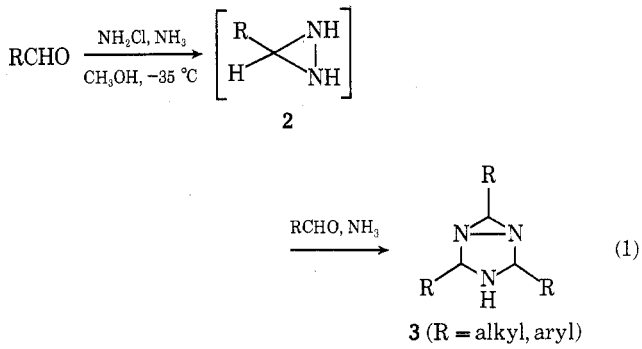
The Schmitz diaziridine synthesis involves reaction of a ketone or aldehyde and ammonia with a chloramine or hydroxylamine *O*-sulfonic acid.[3] For example, to prepare 3,3-disubstituted diaziridines (**1**) a ketone is added to cold



1 (R, R′ = alkyl, aryl)

methanolic ammonia containing chloramine (conveniently generated from *tert*-butyl hypochlorite[4]). The reaction was discovered independently by Abendroth and Henrich[5] and by Paulsen.[6] Many substituted diaziridines have been synthesized from imines including 1,3-disubstituted and 1,2,3- and 1,3,3-trisubstituted types.[7-10] Diaziridine formation is described as an intramolecular displacement of chloride ion from an *N*-chloroaminal intermediate.[3]

The Schmitz reaction of aldehydes with ammonia and chloramine leads to 2,4,6-trisubstituted 1,3,5-triazabicyclo[3.1.0]hexanes (**3**), rather than monocyclic diaziridines as the isolated products (eq 1).[7e,g,11] 3-Substituted diaziridines (**2**) are proposed to be intermediates which give **3** by further reaction with ammonia and aldehyde;[11] this suggestion has been confirmed in the present work. It has not been possible to prepare **2** directly by use of an excess of ammonia over aldehyde, nor from **3** by direct fractional hydrolysis.[7c] Indirect methods are required to prepare **2**.[7e,g] The present work is concerned principally with the stereochemistry and mechanism of formation of **3**.



2

3 (R = alkyl, aryl) (1)

Synthesis. 2,4,6-Trisubstituted 1,3,5-triazabicyclo[3.1.0]-hexanes (**3**) were synthesized by two methods. The principal procedure, that of Schmitz, was employed with slight modifications.[7g,11,12] *tert*-Butyl hypochlorite was added to 10 M methanolic ammonia followed by addition of the aldehyde; reaction proceeded at ca. −35 °C for 1 h followed by warming to ambient temperature. Workup gave mixtures of epimers in high yields (60–90%) from which the less soluble, predominant isomer (trans) could be readily isolated in pure form by crystallization from hexane (25–50% yield). Thirteen of these compounds (**4a–16a**) were prepared (Table I). Pure cis epimers were isolated with difficulty from the mother liquors by fractional crystallization.

In a second route to the title compounds, 2,4,6-trialkyl-1,3,5-triazacyclohexanes (**17**) were oxidized with *tert*-butyl hypochlorite in methanol containing 1 molar equiv of sodium carbonate (−35 °C), eq 2. The reactant monocyclic hexahydrotriazines (**17**) were prepared by reaction of aldehydes with ammonia at 0 °C.[12,13] Yields of **3** by this alternate procedure are poor (2–20%). Mixtures of epimers are produced despite the steric homogeneity of the reactant, **17**.[12,13]

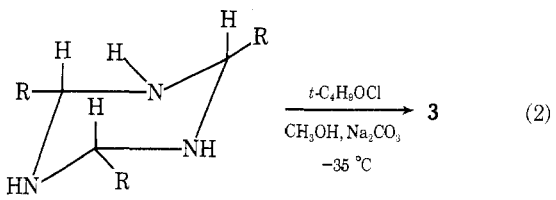
The bicyclic triazines (Table I) are stable, white, crystalline

Table I. 2,4,6-Trialkyl-1,3,5-triazabicyclo[3.1.0]hexanes

Compd	R	Prepn method[a]	Yield %[b]	Mp, °C[c]	Molecular formula[d]
4a	CH_3	A	75	113–114[e]	$C_6H_{13}N_3$
4c	CH_3	B	(6)	133–134	$C_6H_{13}N_3$
5a	C_2H_5	A (B)	90 (9)	98–100[f]	$C_9H_{19}N_3$
6a	n-C_3H_7	A (B)	90 (20)	82–84[g]	$C_{12}H_{25}N_3$
7a	i-C_3H_7	A (B)	58 (16)	140–143	$C_{12}H_{25}N_3$
8a	n-C_4H_9	A (B)	82 (6)	68–69	$C_{15}H_{31}N_3$
9a	i-C_4H_9	A (B)	89 (6)	134–139	$C_{15}H_{31}N_3$
10a	t-C_4H_9	A	27	93–95[h]	$C_{15}H_{31}N_3$
11a	n-C_5H_{11}	A (B)	90 (6)	51–55	$C_{18}H_{37}N_3$
11b	n-C_5H_{11}	A	10[i]	50–54	$C_{18}H_{37}N_3$
12a	$(C_2H_5)_2CH$	A	65	145–147	$C_{18}H_{37}N_3$
13a	C_6H_5	A	42	162–164[j]	$C_{21}H_{19}N_3$
14a	n-C_6H_{13}	A (B)	86 (8)	65–67	$C_{21}H_{43}N_3$
15a	$C_6H_5CH_2$	A (B)	94 (4)	172–175[k,l]	$C_{24}H_{25}N_3$
16a	$C_6H_5(CH_3)$-CH	A (B)	3 (2)	161–165[k]	$C_{27}H_{31}N_3$

[a] Method A: from alkanal and chloramine in methanolic ammonia. Method B: from 2,4,6-trialkyl-1,3,5-hexahydrotriazines by *tert*-butyl hypochlorite oxidation. [b] Yields of crystalline product mixtures by method A. Values in parentheses are yields of recrystallized products prepared by method B. [c] Capillary metling point of analytically pure sample crystallized from hexane, heptane, or ether; recovery yields are 30–50%. [d] Satisfactory analytical data (±0.3% for C, H, and N) and molecular weight data (±4%, by vapor osmometry in chloroform) for all compounds were submitted for review. [e] Lit.[11] mp 114–115 °C. [f] Lit.[11] mp 104–104.5 °C. [g] Lit. mp 84–86 °C. [h] Lit.[7g] mp 92–93 °C. [i] Prepared by fractional crystallization of product mixture. [j] Lit.[11] mp 160–162 °C. [k] Data reported in ref 12. [l] A material, mp 133–145 °C, isolated by fractional crystallization of the Schmitz reaction product was found to contain 73% of cis isomer **15b** (^{13}C NMR assay).

solids which may be stored indefinitely in air at ambient temperature, in contrast to the derived 3-substituted diaziridines (**2**) which decompose rapidly under such conditions.



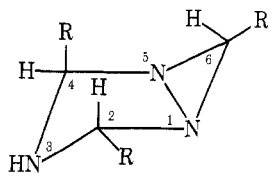
(2)

17 (R = alkyl)

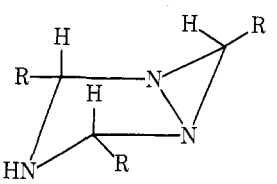
Results and Discussion

Stereochemistry of the Schmitz Reaction. The stereochemistry of 2,4,6-trisubstituted 1,3,5-triazabicyclo[3.1.0]-hexanes has not been studied by others.[1] Schmitz assumed that the ethyl groups in **5a**, obtained from propanal by his procedure, were all pseudoequatorial.[7f] No evidence was offered for this assignment, however. It has now been established that the predominant isomer formed (and isolated) in the Schmitz reaction is **3a**, with trans C-2 and C-4 substituents and an exocyclic C-6 substituent.[14] Previously reported bicyclotriazines have now been shown to exist in this configuration. A second isomer formed in smaller amounts is the cis-exo form (**3b**), having all pseudoequatorial substituents. Virtually none of the cis-endo isomer (**3c**) is produced under the reported conditions of the Schmitz reaction.

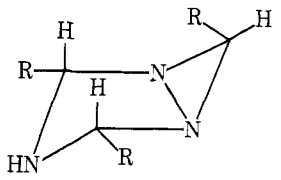
Although spectroscopic evidence suggests that the parent hydrocarbon, bicyclo[3.1.0]hexane,[15] and its diaziridine analogue, 1,5-diazabicyclo[3.1.0]hexane,[16] exist in boat or twist-boat forms, the actual departure from planarity of the five-membered ring is not great and would doubtless be strongly influenced by the orientation of substituents. We have, accordingly, treated the five-membered ring in 1,3,5-triazabicyclo[3.1.0]hexane as nearly planar.



3a (trans-exo)



3b (cis-exo)



3c (cis-endo)

The assignment of stereochemistry in the title compounds rests on ^1H and ^{13}C NMR spectral data as well as equilibration studies. ^1H NMR data are summarized in Table II and ^{13}C data in Table III. The trans compounds (**3a**) are each characterized by separate ^{13}C signals for the C-2 and C-4 ring carbons. In trans compounds having simple ring methine proton spectra (e.g., **4a, 7a, 10a, 13a**) separate signals are readily observed for the C-2 and C-4 ring methine protons. In the cis compounds (**3b,c**) only one signal is seen for the C-2, C-4 carbons and ring methine protons. The differentiation of cis-exo (**3b**) and cis-endo (**3c**) forms rests on ^{13}C NMR, kinetic, and equilibration data.

The most striking chemical shift differences in the carbon-13 spectra of the three epimers are seen at C-6, the diaziridine carbon (Table III). For typical alkyl substituents the shielding is greatest for the cis-exo form, 5 ppm less for the trans-exo, and 12 ppm less for the cis-endo. A possible explanation is the change in dihedral angle between the two rings caused by steric repulsion between endo substituents. Thus, in the cis-exo epimer with no endo substituents, the angle should approach the value of 116 ± 5° found for the parent hydrocarbon.[15] The trans-exo epimer with the endocyclic C-4 substituent would show some steric repulsion and an increased angle. The cis-endo epimer with the C-6 substituent in the position of greatest steric interaction would have the largest dihedral angle. Apparently, as the molecule becomes more planar due to steric repulsion, the change in bond character at C-6 results in progressively greater deshielding. This effect is even more noticeable with bulky substituents. In the trans-exo epimer of the *tert*-butyl derivative (**10b**) the shielding at C-6 is reduced 8.5 ppm; little or no cis-endo form is found to be present. In the diethylmethyl derivative (**12b**) trans-exo substitution leads to a 6.5 ppm deshielding, and cis-endo substitution (**12c**) gives a 15.8 ppm reduction of the shielding value, the largest change observed.

The kinetic composition of epimer mixtures produced in the Schmitz reaction has been established (Table IV). A kinetic preference for the trans isomer is observed. Substantial amounts of the cis-exo and cis-endo forms are also present. Products were obtained by adding excess sodium hydroxide to the ammoniacal reaction mixture prior to workup; ammonium chloride, an equilibration catalyst, was thereby removed from the isolated products.

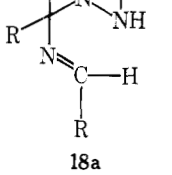
The transition state leading to the bicyclic triazine favors a repulsion of bulky groups in a monocyclic precursor at or removed from the bond-forming site (e.g., **18a** favored over **18b**). Aldol cyclization stereochemistry (formation of a C–C bond) exhibits a similar transition state.[17] The presence of an

Table II. ^{1}H NMR Spectra of 2,4,6-Trisubstituted 1,3,5-Triazabicyclo[3.1.0]hexanes[a]

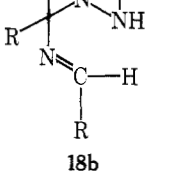
Compd	R	Chemical shift, δ, ppm: Ring CH at C-2; C-4	Ring CH at C-6	R-Substituted protons[b]
4a	CH_3	4.25 (q, 6.0); 4.14 (q, 6.0)[c]	2.20 (q, 4.8)	1.38 (d, 5.9, CH_3 at C-2); 1.27 (d, 4.9, CH_3 at C-6); 1.26 (d, 6.5, CH_3 at C-4)
4b	CH_3	4.39 (q, 6.0)	2.31 (q, 5.0)	1.36 (d, 5.8, CH_3 at C-2,4); 1.27 (d, 4.9, CH_3 at C-6)
4c	CH_3	4.42 (q, 6.5)	2.13 (q, 5.0)	1.26 (d, 6.4, CH_3 at C-2,4); 1.15 (d, 5.0, CH_3 at C-6)
5a	C_2H_5	4.07 (t, 5.5); 3.99 (t, 5.0)[c]	2.09 (dd, 4.5, 6.5)	1.3–1.9 (m, CH_2); 1.15 (t, 6.5, CH_3); 0.98 (t, 6.5, CH_3)
5b	C_2H_5	4.05 (t, 7.0)	2.02 (t, 5.5)	1.2–1.8 (m, CH_2); 1.00 (t, 7.0, CH_3)
6a	n-C_3H_7	4.13 (t, 5.5); 4.06 (t, 5.5)	2.11 (t, 4.5)	1.2–1.8 (m, CH_2CH_2); 0.9–1.1 (m, CH_3)
7a	i-C_3H_7	3.75 (d, 7.0); 3.70 (d, 7.0)[c]	2.04 (d, 7.5)	1.2–1.7 (m, CH); 1.12 (d, 6.0, CH_3); 1.01 (d, 6.0, CH_3); 0.92 (d, 6.0, CH_3)
7b	i-C_3H_7	3.60 (d, 8.5)	1.90 (d, 7.5)[e]	1.2–1.7 (m, CH); 0.98 (d, 6.0, CH_3); 0.90 (d, 6.0, CH_3)
8a	n-C_4H_9	3.9–4.2 (m)	2.10 (m)	1.2–1.7 (m, CH_2); 0.8–1.2 (m, CH_3)
9a	i-C_4H_9	4.13 (t, 7.0)[c]	2.12 (t, 5.5)	1.2–1.8 (m, CH_2CH); 0.8–1.2 (m, CH_3)
10a	t-C_4H_9	3.92 (s); 3.60 (s)[c]	1.93 (s)	1.07 (s, CH_3); 0.96 (s, CH_3); 0.94 (s, CH_3)
10b	t-C_4H_9	3.70 (s)[d]	2.34 (s)	1.09 (s, CH_3); 0.95 (s, CH_3)
10c	t-C_4H_9	3.52 (s)	2.32 (s)	1.03 (s, CH_3); 0.85 (s, CH_3)
11a	n-C_5H_{11}	3.9–4.2 (m)	1.9–2.1 (m)	1.2–1.8 (m, CH_2); 0.9–1.2 (m, CH_3)
11b	n-C_5H_{11}	3.9–4.2 (m)	1.9–2.1 (m)	1.2–1.8 (m, CH_2); 0.9–1.2 (m, CH_3)
12a	$(C_2H_5)_2CH$	3.92 (dd, 7.2, 5.5[d]); 3.84 (dd, 8.5, 9.5[d])	1.92 (d, 6.7)[e]	1.2–1.8 (m, CH, CH_2); 0.7–1.2 (m, CH_3)
12b	$(C_2H_5)_2CH$	3.86 (d, 8.5)	2.12 (d, 7.0)	1.2–1.8 (m, CH, CH_2); 0.7–1.2 (m, CH_3)
13a	C_6H_5	5.60 (d, 6.0[d]); 5.22 (d, 9.5[d])	3.20 (s)	7.2–7.9 (m, C_6H_5); 3.05 (broad t, NH)
13b	C_6H_5	5.51 (d, 10.5[d])	3.17 (s)	7.2–7.9 (m, C_6H_5)
14a	n-C_6H_{13}	4.0–4.3 (m)	2.1–2.3 (m)	1.2–1.8 (m, CH_2); 0.8–1.2 (m, CH_3)
15a	$C_6H_5CH_2$	4.26 (t, 4.2); 4.18 (t, 5.5)	2.20 (t, 5.5)	7.0–7.5 (m, C_6H_5); 2.6–3.2 (m, CH_2)
15b	$C_6H_5CH_2$	4.27 (t, 5.5)	2.08 (t, 6.0)	7.0–7.5 (m, C_6H_5); 2.5–3.1 (m, CH_2)
16a	$C_6H_5(CH_3)$-CH	4.20 (d, ~8); 4.10 (d, ~8)	2.30 (d, ~8)	7.3 (m, C_6H_5); 2.0–3.0 (m, CH); 1.0–1.6 (m, CH_3)

[a] All measurements at 60 or 100 MHz, $CDCl_3$ solvent (+1% Me_4Si) ca. 27 °C. Multiplicity of signal and coupling constant (Hz) in parentheses. [b] A broad NH signal (~20 Hz) appears near δ 2.0–2.5 in all spectra except where noted otherwise. [c] Broadened signal (~2 Hz) which sharpens on addition of D_2O, apparently due to unresolved NH proton coupling. [d] Indicated splitting due to NH proton, collapses on addition of D_2O.

acyclic imine precursor related to **18** [i.e., i-$C_3H_7CH{=}N$-$CH(i$-$C_3H_7)NHCH(i$-$C_3H_7)NH_2$], derived from the very labile monocyclic triazine **17d** (R = i-C_3H_7), is seen in the ^{13}C NMR spectrum (Table V, footnote *b*).[13]



18a



18b

Equilibration of the bicyclic triazines is observed in methanolic ammonium chloride or hydrogen chloride at ambient temperature; recovery of epimerized products is quantitative. No observed epimerization occurs in basic media. In neutral protic solvents such as methanol a slow epimerization is sometimes observed. At equilibrium the cis-endo isomer virtually disappears leaving trans-exo and cis-exo epimers (**3a,b**) in a nearly 1:1 ratio (Table IV). A preference for the trans-exo form at equilibrium is observed for compounds with substituents methyl, *tert*-butyl, and phenyl.

The rate of acid-catalyzed equilibration of the bicyclic triazines depends on reaction conditions, structure, and stereochemistry of reactants. In 1% methanolic ammonium chloride solution at 25 °C equilibration is complete within 2–6 h in all cases examined except the cis- and trans-exo methyl and phenyl compounds **4** and **13**, which were unaffected after 48 h. However, these substances and all others are equilibrated in methanolic hydrogen chloride (pH 1–2, 25 °C) very rapidly (less than 10 min). Prolonged exposure of the bicyclic triazines to such strongly acidic conditions causes degradation (formation of aldehydes, hydrazine, and diaziridines).[7]

The rate of acid-catalyzed epimerization of cis-endo epimers (**3c**) is much more rapid than that of the exo isomers **3a,b.** For example, although methanolic ammonium chloride will not equilibrate trans- or cis-exo methyl isomers (**4a,b,** R = CH_3) the cis-endo form (**4c**) is converted quantitatively into the trans-exo form in this medium within 10 min. Similar results are observed with other cis-endo isomers. Mixtures containing three isomers (**3a–c**) in methanolic ammonium chloride are converted into mixtures containing only two isomers (**3a,b**) within 10 min. In each instance during this short reaction period the cis-endo form (**3c**) is converted exclusively into the trans-exo form; the amount of cis-exo form (**3b**) remains unchanged. Only on more extended exposure (2–6 h) is equilibrium attained involved interconversion of cis-exo and trans-exo forms. In methanol a slow, uncatalyzed cis-endo → trans-exo conversion is observed. This epimerization is most rapid with the methyl compound (1–2 days), but very slow with others (several weeks).

Epimerization of bicyclic triazines was found to involve no incorporation of deuterium at the C-2 or C-4 positions when the reaction was conducted in methanol-*O*-*d* containing ammonium chloride (**3,** R = C_2H_5, i-C_3H_7) or hydrogen chloride (**3,** R = CH_3).

A mechanism for the acid-catalyzed equilibrations and epimerizations is suggested by the above observations (Scheme I). Acid-catalyzed ring opening of cis-endo **3c** at N-1,C-2 would lead to iminium ion **19a.** Diaziridine nitrogen inversion would provide invertomer **19b;** ring closure would then give trans-exo **3a** only. The other possible epimer derived by ring closure of **19b** would be an unobserved, disfavored cis isomer (**3d**), having two endocyclic substituents (at C-2, C-4).

Table III. ^{13}C NMR Spectra of 2,4,6-Trisubstituted 1,3,5-Triazabicyclo[3.1.0]hexanes [a]

		Chemical shift, ppm					
		Ring carbons [b]			Substituent α carbon [b]		
R	Compd	C-2	C-4	C-6	C-2	C-4	C-6
CH_3	**4a**	75.3	72.4	46.2	15.2	17.0	21.4
	4b	74.9		41.0	15.3		17.1
	4c	75.7		53.2	24.9		23.0
C_2H_5	**5a**	81.1	78.2	52.1	24.1	24.3	28.1
	5b	80.2		47.0	24.1		24.2
	5c	81.9		59.2	31.2		24.6
n-C_3H_7	**6a**	79.5	76.8	50.9	33.4	33.6	37.4
	6b	78.8		45.8	33.4		33.4
	6c	80.4		58.2	40.6		33.6
i-C_3H_7	**7a**	84.2	86.1	58.2	32.0	33.1	30.4
	7b	84.9		52.3	31.5		30.1
	7c	87.7		66.4	35.0		30.8
n-C_4H_9	**8a**	79.6	77.0	50.9	30.8	31.0	34.8
	8b	78.8		45.9	30.9		31.0
	8c	80.3		57.9	38.0		31.2
i-C_4H_9	**9a**	78.0	75.4	49.7	40.4	40.4	44.0
	9b	77.5		44.5	40.4		40.4
	9c	78.8		57.1	47.2		40.4
t-C_4H_9	**10a**	87.4	89.9	62.7	32.8	31.3	36.5
	10b	86.2		54.2	32.8		32.8
n-C_5H_{11}	**11a**	79.7	77.0	50.9	31.5	31.2	35.2
	11b	78.9		45.8	32.0		31.7
	11c	80.4		58.1	38.3		30.9
$(C_2H_5)_2CH$	**12a**	82.4	80.4	55.5	43.3	42.7	44.4
	12b	81.4		49.0	43.2		42.0
	12c	83.5		64.8	46.1		44.0
C_6H_5	**13a**	81.4	80.5	51.9	136.2	136.1	140.4
	13b	82.3		48.1	136.2		140.4
n-C_6H_{13}	**14a**	79.9	77.2	51.3	31.7	31.5	35.4
	14b	79.1		46.1	31.8		31.8
	14c	80.6		58.4	38.4		32.0
$C_6H_5CH_2$	**15a**	81.1	72.1	53.0	36.5	38.3	41.6
	15b	78.8		48.3	36.5		41.4
$C_6H_5(CH_3)CH$	**16a** [c]	84.7	81.4	58.3	44.4	42.9	41.0
	16a'	85.3	82.8	58.6	45.1	43.4	41.6

[a] Fourier transform mode (proton decoupled) 25.14 MHz, $CDCl_3$ solvent with tetramethylsilane internal reference. [b] Substituent at C-2 is assumed to be exocyclic in the trans compounds. [c] Mixture of four diastereoisomers. Spectrum of recrystallized sample consists of the two sets of relatively strong lines shown and two sets of weaker lines that have not been assigned.

Table IV. Composition of Epimeric Mixtures of 2,4,6-Trisubstituted 1,3,5-Triazabicyclo[3.1.0]hexanes (±2%) ^{13}C NMR Assay

		Kinetic mixture (base catalysis)			Equilibrium mixture (acid catalysis)			Schmitz reaction product mixture	
Compd	R	Trans-exo **a**	Cis-exo **b**	Cis-endo **c**	Trans-exo **a**	Cis-exo [a] **b**	Catalyst [b]	Trans-exo **a**	Cis-exo [a] **b**
4	CH_3	53	38	9	65	35 [c]	B	61	38 [c]
5	C_2H_5	61	31	8	55	45	A	69	31
6	n-C_3H_7	57	32	12	55	45	A	69	32
7	i-C_3H_7	71	20	9	45	55 [c]	A	80	20 [c]
8	n-C_4H_9	55	33	12	45	55	A	67	33
9	i-C_4H_9	49	35	16	47	53	A	65	35
10	t-C_4H_9	85	15	*a,c*	80	20	A, B	85	15
11	n-C_5H_{11}	56	31	13	50	50	A, B	69	31
12	$(C_2H_5)_2CH$	81	13	6	53	47	A	87	13
13	C_6H_5	70	30	*a,c*	70	30 [c]	B	70	30 [c]
14	n-C_6H_{13}	61	29	10	55	45	A	71	29
15	$C_6H_5CH_2$	43	47	10	50	50	A	53	47

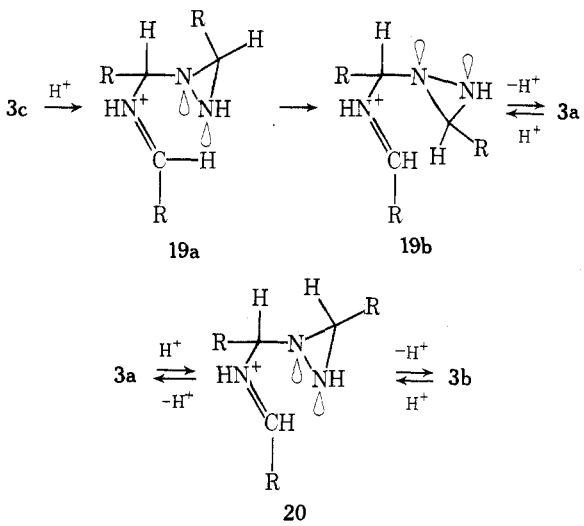
[a] Cis-endo (**c**) concentration <3%. [b] Catalyst: (A) ammonium chloride, (B) hydrogen chloride. [c] Assay by ^1H NMR gave the same results, ±2%.

Table V. ^{13}C NMR Spectra of 2,4,6-Trisubstituted 1,3,5-Triazacyclohexanes [a]

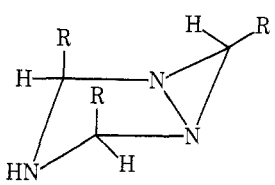
Compd	R	Chemical shift, ppm: Ring carbons	Chemical shift, ppm: Substituent carbons
17a	CH_3	66.2	22.8 (CH_3)
17b	CH_2CH_3	71.6	29.8 (CH_2); 9.3 (CH_3)
17c	$CH_2CH_2CH_3$	75.4	43.2, 21.3 (CH_2); 16.8 (CH_3)
17d	$CH(CH_3)_2$ [b]	75.9	33.7 (CH); 18.2 (CH_3)
17e	$C_6H_5CH_2$	73.2	139.1, 131.8, 130.8, 128.9 (C_6H_5); 45.1 (CH_2)
17f	$C_6H_5(CH_3)CH$ [c]	77.8, 77.6, 76.9	144.9, 130.6, 130.3, 129.9, 129.8, 128.8, (C_6H_5); 47.8, 47.7, 47.2 (CH); 19.6, 19.0, 18.7 (CH_3)

[a] Fourier transform mode, 25.14 MHz, $CDCl_3$ solvent with internal tetramethylsilane reference. [b] On standing in $CDCl_3$ solution at 25 °C for 12 h, peaks appear which are attributed to the acyclic dissociation product, i-$C_3H_7CH{=}NCH(i\text{-}C_3H_7)NHCH(i\text{-}C_3H_7)NH_2$: 168.4 (C=N); 96.8, 91.8 (NCHN); 34.1, 33.5 [$(CH_3)_2CH$]; 19.5, 17.4 (CH_3). [c] A statistical 1:3 mixture of two diastereoisomers. One component shows a single line of unit intensity. The other shows two lines with intensities in the ratio 1:2.

Scheme I



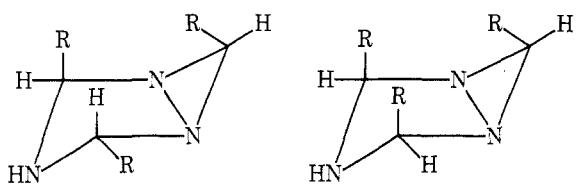
To achieve the slower cis-exo, trans-exo (**3a,b**) equilibration would involve iminium ion intermediate **20.**



3d

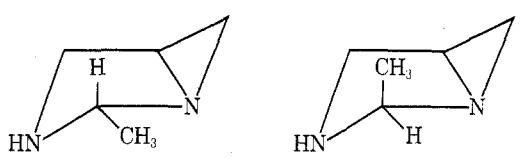
The epimer composition of reaction products obtained under normal Schmitz reaction conditions is different from that observed under kinetic conditions (alkaline workup) or at equilibrium (Table IV). Schmitz reaction products contain a higher percentage of trans isomer (**3a**) than either kinetic or equilibrium conditions, and very little cis-endo isomer (**3c**). The results are understandable in light of the equilibration and stereochemical studies. The normal workup procedure involves removal of excess ammonia and methanol by concentration of the reaction mixture to dryness at temperatures near 25 °C. During the final stages of concentration the methanolic solution changes from basic (excess ammonia) to weakly acidic (excess ammonium chloride). Under these conditions the cis-endo isomer (**3c**) is rapidly epimerized to the trans-exo form **3a.** The product contact time with ammonia-free methanolic ammonium chloride during workup is sufficiently short so that the relatively slower cis-exo to trans-exo (**3b,a**) equilibration occurs only slightly. These conclusions were confirmed by ^{13}C NMR assay of Schmitz reaction product mixtures. Also treatment of kinetic product mixtures (containing large amounts of cis-endo isomer) with ammonium chloride in 10 M methanolic ammonia followed by concentration to dryness (simulated Schmitz workup) gave reaction mixtures having compositions corresponding closely to those of Schmitz reaction products obtained by normal workup procedures.

Alternate structures with two or three endocyclic substituents could be written for the bicyclic triazines (e.g., **3d–f**).



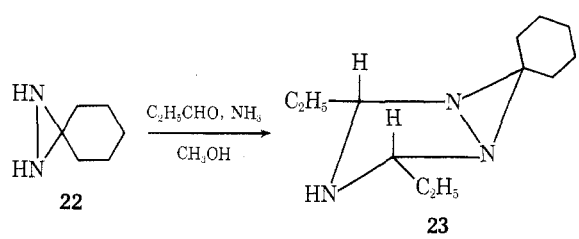
3e 3f

There is evidence against such sterically unfavorable configurations, however. For example, in the related simple monosubstituted 2-methyl-1,3-diazabicyclo[3.1.0]hexane the exo methyl structure (**21a**) is favored 3:1 over the endo (**21b**).[18]



21a 21b

2,4-Diethyl-6,6-pentamethylene-1,3,5-triazabicyclo-[3.1.0]hexane (**23**) was prepared by reaction of 6,6-pentamethylenediaziridine (**22**) with propanal under Schmitz reaction conditions. The crude reaction product contained only one isomer with cis stereochemistry of the C-2, C-4 substituents. The structure is supported by ^1H and ^{13}C NMR spectra. The ^1H NMR spectrum of **23** reveals a single triplet at δ 4.12 for the triazolidine ring protons. The ^{13}C NMR spectrum reveals the expected cis isomer signals. The ring C-6 signal appears in the region corresponding to those found for other cis-endo compounds (Table III). A line at δ 38.0 is assigned to the endocylic α-methylene carbon of the pentamethylene



22 23

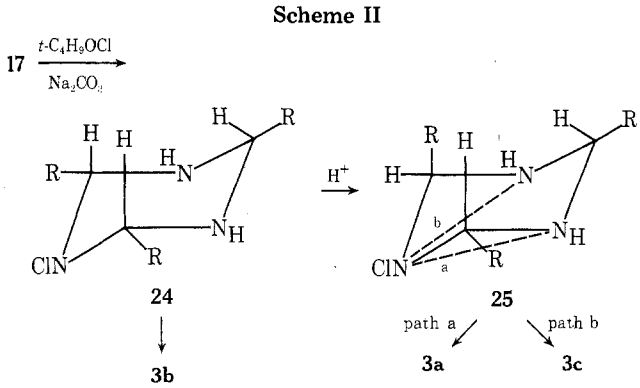
group owing to its position 13 ppm downfield from the other carbons of this ring. A similar deshielded α-carbon signal is observed in the methyl cis-endo compound **4c**, presumably arising from interaction with the triazolidine ring hydrogens. Such an interaction of the endocyclic methylene at C-6 disfavors a trans diethyl C-2, C-4 **23** epimer with two endocyclic substituents.

Stereochemistry of 2,4,6-Trialkyl-1,3,5-hexahydrotriazine Oxidations. Despite the steric homogeneity of reactant 2,4,6-trialkyl-1,3,5-hexahydrotriazines (**17**) their oxidation with *tert*-butyl hypochlorite in basic medium leads to epimeric mixtures of 2,4,6-trialkyl-1,3,5-triazabicyclo-[3.1.0]hexanes (**3**, eq 2). No equilibration of products occurs under the reaction conditions. The all equatorial stereochemistry of the parent 2,4,6-trialkyl-1,3,5-hexahydrotriazines (**17**) is indicated by their simple NMR spectra. The proton spectra of these materials have been discussed.[12,13] Their ^{13}C NMR spectra have now been determined and support the structure assignments. For example, the spectrum of 2,4,6-trimethyl-1,3,5-hexahydrotriazine (**17a**) reveals two lines, one each for the three ring carbons and three methyl substituents (Table V).

The stereochemistry and mechanism of 2,4,6-trialkyl-1,3,5-hexahydrotriazine oxidation was examined with the aid of ^{13}C NMR spectroscopy. Oxidation of anhydrous 2,4,6-trimethyl-1,3,5-hexahydrotriazine (**17a**) in methanol containing 1 equiv of sodium carbonate with 1 molar equiv of *tert*-butyl hypochlorite at −35 °C gave a crude reaction product containing only trans-exo and cis-endo bicyclic triazines (**4a** and **4c**, respectively). The reaction mixture is alkaline throughout; no epimerization occurs during the reaction period. The pure cis-endo form (**4c**) is readily isolated from the reaction mixture by extraction with hexane.

When the crude original product mixture was dissolved in deuteriochloroform the cis-exo compound **4b**, which was absent initially, was observed to appear slowly on standing (^{13}C NMR). After 3 days a nearly 1:1 equilibrium mixture of trans and cis-exo forms (**4a,b**) appeared; the cis-endo form (**4c**) had disappeared. The equilibration catalyst is believed to be hydrogen chloride formed from *N*-chloro-2,4,6-trimethyl-1,3,5-hexahydrotriazine (**24a**, R = CH_3, Scheme II) present

Scheme II



in the crude reaction mixture. This *N*-chloro compound is characterized by ^{13}C lines at δ 90.1 and 145.3. After 3 days these lines had disappeared and a spectrum appeared corresponding only to trans-exo and cis-exo bicyclotriazines (**4a,b**). Oxidation of 2,4,6-trimethyl-1,3,5-hexahydrotriazine-*2,4,6-d*$_3$ in methanol-*O-d* gave no CH deuterium incorporation into the bicyclic triazine products.

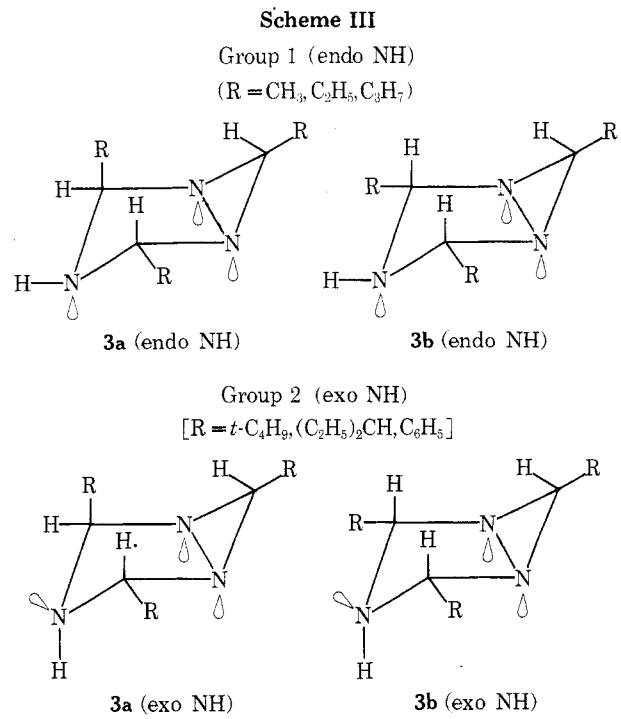
The above observations may be explained by the steps shown in Scheme II. The initially formed all-equatorial *N*-chloro compound **24a** (R = CH_3) rapidly epimerizes to yield a sterically favored 2-axial methyl isomer **25a** (R = CH_3) via an acyclic iminium intermediate formed by acid-catalyzed ring opening. The rate-limiting ring closure reactions in **25** lead to **3a** and **3c** by intramolecular chloride ion displacements (paths a and b, respectively); path a predominates.

With other triazines (**17**, R = alkyl) similar results are observed: the predominant reaction products are the trans-exo isomers (**3a**). However, in addition to the cis-endo form (**3c**), cis-exo form (**3b**) is also observed. The latter isomer could form by ring closure in **24** which may be favored to some extent over **25** when R is larger than methyl. Thus, depending on structure and method of workup, bicyclic triazines derived by oxidation of monocyclic triazines could have various epimer compositions. However, the predominant product isomer obtained is trans (**3a**). Our original report[1] describing the hexahydrotriazine oxidation products as only cis-exo (**3b**) and trans-exo (**3a**) was incorrect. The present findings permit a distinction between cis-endo and cis-exo products, and the rather surprising conclusion that despite the all-equatorial configuration of reactant **17**, the oxidation initially yields products having little or none of this stereochemistry.

NH Stereochemistry. The ^1H NMR data of Table II provide evidence of two different orientations of the NH proton in rigid bicyclic triazines ($CDCl_3$ solvent). Line broadening of one of the ring proton signals (H-2,4) which is observed in some trans-exo compounds (group 1—**4a, 5a, 7a**; R = CH_3, C_2H_5, *i*-C_3H_7, respectively) is absent in the corresponding cis-exo and/or cis-endo epimers. This broadening, presumably arising from a weak unresolved spin coupling to the NH proton, disappears on addition of deuterium oxide. In a second group of compounds (group 2) characterized by bulky substituents, line broadening or an observable strong NH spin coupling is observed for H-2 or H-4 of the trans-exo compounds [**10a, 12a, 13a**; R = *t*-C_4H_9, $(C_2H_5)_2CH$, and C_6H_5, respectively] *and* for both H-2 and H-4 in the cis-exo forms. In the phenyl-substituted trans compound **13a**, –NH spin-coupling values of 6.0 and 9.5 Hz were observed for H-2 and H-4, while the cis compound **13b** showed only one splitting of 10.5 Hz for the two ring protons. In the remaining compounds studied the NMR spectra were not sufficiently resolved to reveal NH coupling information.

The above observations suggest an endocyclic NH in the group 1 compounds (**4, 5, 6**) and an exocyclic NH in group 2 compounds (**10, 12, 13**) (Scheme III).

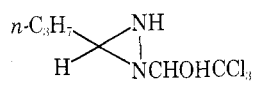
Scheme III



In group 1 the endocyclic NH proton of **3a** nearly eclipses H-2 and a weak coupling would be predicted, while it is almost trans to H-4 and should couple strongly with it. In **3b** both H-2 and H-4 eclipse the endocyclic NH proton and only weak coupling is expected. In group 2 the spectra of **3a** and **3b** both show at least one strong coupling of H-2 and H-4 to the NH proton. Since the R groups should be exocyclic because of their bulk, it follows that the NH proton must also be exocyclic to permit the observed spin coupling. In the trans compounds of group 1 the ring proton signal at highest field represents exocyclic H-4, while in the group 2 compounds it is the endocyclic H-2. In flexible heterocycles with 1,3-heteroatom substitution there is a preference for an axial NH.[19,20] However, configurations in these and other heterocycles are known to depend on substituent bulk.[21,22]

Mechanism of the Schmitz Reaction. Two mechanisms may be considered for formation of 2,4,6-trisubstituted 1,3,5-triazabicyclo[3.1.0]hexanes: (1) the Schmitz mechanism[11] involving reaction of a 3-substituted diaziridine (**2**) with aldehyde and ammonia to yield **3** (eq 1), and (2) oxidation of initially formed 2,4,6-trisubstituted 1,3,5-hexahydrotriazine (**17**) to yield **3** (eq 2).

Evidence obtained previously favoring the Schmitz mechanism includes trapping of a 3-substituted diaziridine intermediate with chloral to form 1-(2-trichloromethyl-1-hydroxyethyl)-3-propyldiaziridine (**26**) in low yield (8%).[7e] The possibility that **26** had formed by cleavage of the bicyclic triazine **6** has been discounted. In the present study treatment



26

of bicyclic triazine **6a** (trans-exo, R = n-C_3H_7) in methanol with chloral at 25 °C gave quantitative recovery of reactants after 20 h.

Other evidence favors the Schmitz mechanism. Certain bicyclic triazines are formed in the Schmitz reaction which form no monocyclic triazines (**17**) under the reaction conditions [e.g., **10a**, R = t-C_4H_9, **12a**, R = $CH(C_2H_5)_2$, **13a**, R = C_6H_5].[13] Also, the rate of bicyclic triazine formation in the Schmitz reaction (1–2 h) is more rapid than formation of comparable yields of most monocyclic triazines (**17**) under the same conditions (several days except for those derived from acetaldehyde and propanal).[13]

Finally, the stereochemistry of the Schmitz reaction leading to **3** is somewhat different from that found for 2,4,6-trialkyl-1,3,5-hexahydrotriazine oxidation under comparable conditions (basic medium, −35 °C). The Schmitz reaction gives a mixture of three epimers (**3a–c**) under kinetic conditions (Table IV). The oxidation of 2,4,6-trimethyl-1,3,5-hexahydrotriazine, on the other hand, can yield trans-exo and cis-endo isomers (**4a,c**) only. All evidence of this study favors the originally proposed Schmitz mechanism involving a diaziridine intermediate (eq 1).

Experimental Section[23]

Aldehydes. All aldehydes were commercial samples, reagent grade, distilled immediately before use.

2,4,6-Trimethyl-1,3,5-hexahydrotriazine-*1,3,5-d*$_3$ was prepared by dissolving a 2.5-g sample of the anhydrous protiotriazine[13] in 25 ml of deuterium oxide and concentrating the solution to dryness under reduced pressure at 25 °C; the process was repeated. Final drying in a vacuum desiccator over calcium chloride gave 2.25 g of trideuteriotriazine showing no NH or H_2O in its ^1H NMR spectrum.

Preparation of 2,4,6-Trialkyl-1,3,5-triazabicyclo[3.1.0]hexanes. A. General Schmitz Procedure. The procedure of Schmitz was employed with slight modifications and is illustrated with preparation of ***cis*- and *trans*-2,4,6-tris(*n*-pentyl)-1,3,5-triazabicyclo[3.1.0]hexanes** (**11b** and **11a**, respectively). A solution of *tert*-butyl hypochlorite (2.71 g, 0.026 mol) in 3 ml of *tert*-butyl alcohol was added dropwise, stirring magnetically during 5 min, to 25 ml of 10 M methanolic ammonia contained in a 125-ml Erlenmeyer flask (reaction temperature maintained at ca. −35 °C by immersing the flask in an ethylene dichloride/dry ice bath). Hexanal (5.0 g, 0.05 mol) was added dropwise with stirring during 5 min and stirring continued (calcium chloride tube attached) for 1 h, maintaining the reaction temperature near −35 °C. The flask was removed from the cold bath and allowed to stand at ambient temperature (no stirring) for 2.5 h. The mixture was concentrated to dryness under reduced pressure and the residue extracted thoroughly with boiling hexane; concentration of the extracts gave 4.26 g (87%) of a mixture of cis-exo and trans-exo triazines **11b** (33%) and **11a** (67%), respectively; assay by ^{13}C NMR. Fractional crystallization from heptane gave pure samples of the less soluble trans-exo **11a**, 0.67 g, mp 51–55 °C, and more soluble cis-exo **11b**, mp 50–54 °C.

The above procedure was employed to prepare the trans triazines listed in Table I, procedure A. Pure trans products were obtained by recrystallization from hexane, ethanol, or ether to constant melting point (assay by ^1H and ^{13}C NMR). Fractional crystallization of mother liquors gave material enriched in the cis-exo isomers. NMR data of these products are summarized in Tables II (^1H) and III (^{13}C).

To a 0.10-g (0.50 mmol) sample of *trans-exo*-2,4,6-tri-*n*-propyl-1,3,5-triazabicyclo[3.1.0]hexane (**6a**) dissolved in 1.0 ml of methanol was added 0.080 g (0.50 mmol) of chloral hydrate. After standing at 25 °C for 20 h the solution was concentrated to dryness and the residue fractionally crystallized from hexane to yield 0.095 g (95%) of unreacted **6a** in successive crops, mp 79–84 °C; chloral was also recovered.

B. The general kinetic procedure is illustrated by preparation of 2,4,6-triisobutyl-1,3,5-triazabicyclo[3.1.0]hexane isomer mixture (**9a–c**). The general Schmitz procedure above was followed (using 0.05 mol of isovaleraldehyde and 0.025 mol of *tert*-butyl hypochlorite) except that prior to concentration of the reaction mixture excess aqueous sodium hydroxide solution was added (2.5 mol of 50% solution, 1.9 g, 0.047 mol, of sodium hydroxide) to assure conversion of the ammonium chloride to sodium chloride. The alkaline reaction mixture was concentrated to dryness at 25 °C and the residue extracted thoroughly with methylene chloride. Concentration of the extracts gave 3.75 g (89%) of crude product: small prisms, mp 124–131 °C [mixture of 48% trans-exo (**9a**), 35% cis-exo (**9b**), and 16% cis-endo (**9c**) by ^{13}C NMR assay]. Total yields of crude triazine mixtures by the above procedure were essentially the same as obtained by the general Schmitz procedure (A). Data are summarized in Table IV.

2,4,6-Trimethyl-1,3,5-triazabicyclo[3.1.0]hexane (4c, Cis-Endo). Oxidation of 2,4,6-Trimethyl-1,3,5-hexahydrotriazine (17a). A solution of anhydrous 2,4,6-trimethyl-1,3,5-hexahydrotriazine (**17a**, 2.58 g, 0.02 mol)[13] in methanol (100 ml) mixed with sodium carbonate (1.06 g, 0.01 mol) was chilled to −35 °C (ethylene dichloride/dry ice bath). While stirring, *tert*-butyl hypochlorite (2.2 g, 0.02 mol) was added dropwise during 2 min. A calcium chloride tube was attached and stirring continued at ca. −35 °C for 1 h. The cold bath was removed and the mixture allowed to warm to 25 °C during 1 h and then filtered. The filtrate was concentrated to dryness at 25 °C and the residue extracted several times with hot hexane. The extracts were immediately concentrated under reduced pressure to ca. 20 ml and chilled at −15 °C to deposit a solid which was fractionally crystallized from hexane to yield 0.15 g (6%) of **4c** as long needles, mp 133–134 °C. A solution of **4c** dissolved in methanol was concentrated after standing at 25 °C for 48 h to yield trans-exo **4a**, mp 111–114 °C.

In a parallel run employing 6.36 g (0.05 mol) of anhydrous 2,4,6-trimethyl-1,3,5-hexahydrotriazine the resulting hexane extracts were concentrated to dryness to yield 3.9 g of a solid mixture of products. The ^{13}C NMR spectrum (in $CDCl_3$) of this material showed the bicyclic triazine component to be a mixture of 66% trans-exo **4a** and 34% cis-endo **4c**. Additional strong peaks were observed in the ^{13}C spectrum at δ 90.1 and 58.1 (intensity ratio 2:1) attributed to C-2, C-4, and C-6 ring carbons, respectively, of all-equatorial 1-chloro-2,4,6-trimethyl-1,3,5-hexahydrotriazine (**24a**, R = CH_3); peaks for the corresponding C-2, C-4, and C-6 methyl carbons appeared at δ 23.5 and 15.3, respectively, also in a 2:1 intensity ratio. On standing in deuteriochloroform the intensities of these *N*-chloro peaks diminished and after 72 h had completely disappeared. After 14 h the bicyclic triazine composition had changed to 80% **4a**, 15% **4b**, and 5% **4c**; after 72 h there was present 53% **4a**, 47% **4b**, and 0% **4c**. The *N*-chlorotriazine **24a** (R = CH_3) was also prepared in deuteriochloroform (3.5 ml) by reaction of anhydrous triazine **17a** (R = CH_3) (0.42 g) with *tert*-butyl hypochlorite (0.37 g) at −35 °C; examination of the ^{13}C NMR spectrum of the solution at 30 °C revealed the presence of all-equatorial *N*-chlorotriazine; no bicyclic triazine formation was ob-

served in 1 h, and only the trans form (**4a**) was evident after 16 h. The reaction of triazine **17a** (R = CH_3) (0.42 g) and sodium carbonate (0.18 g) in methanol (3 ml) with *tert*-butyl hypochlorite (0.37 g) at −35 °C was followed by ^{13}C NMR; no *N*-chlorotriazine peaks were evident and after 1 h only the trans bicyclotriazine (**4a**) spectrum appeared.

2,4,6-Trimethyl-1,3,5-hexahydrotriazine-*1,3,5-d*$_3$ (1.30 g, 0.01 mol) was oxidized in the same manner as the protio compound **17a** in methanol-*O-d* to yield a crude product (0.62 g) showing a ratio of CH_3/CH of 3:1 by ^1H NMR. Crystallization from hexane gave crude cis-endo triazine **4c-*N*-*d***, 0.05 g, mp 90–106 °C, showing no deuterium incorporation at ring CH positions.

Oxidation of 2,4,6-Trialkyl-1,3,5-hexahydrotriazines. The procedure employed with the trimethyltriazine **17a** (R = CH_3) was used with other anhydrous triazines, prepared as described previously.[13] 2,4,6-Triisopropyl-1,3,5-hexahydrotriazine (**17d**, *i*-C_3H_7) gave a crude product, mp 131–134 °C (16% yield), of a mixture containing 77% **7a**, 16% **7b**, and 6% **7c** by ^{13}C NMR; recrystallization from hexane gave trans-exo **7a**, mp 140–143 °C.

The crude product obtained from 2,4,6-triethyl-1,3,5-hexahydrotriazine (**17b**, R = C_2H_5) contained 70% **5a**, 30% **5b**, and only traces of **5c**; recrystallization from ether gave a 9% yield of crystalline trans **5a**, mp 99–102 °C. The crude product from the anhydrous tri-*n*-propyl compound (**17c**, R = *n*-C_3H_7) contained 90% trans **6a** and 10% **6b**; one recrystallization from hexane gave trans **6a**, mp 78–82 °C. Other 2,4,6-trialkyl-1,3,5-hexahydrotriazines were oxidized to yield trans bicyclotriazines after recrystallization from hexane. Yields are listed in Table I.

Epimerization Experiments. Procedure A. Methanolic Ammonium Chloride. A sample of 2,4,6-tri-*n*-propyl-1,3,5-triazabicyclo[3.1.0]hexane (**6a**, 0.30 g) was added to a solution of ammonium chloride (300 mg) in 30 ml of methanol. After standing at ambient temperature (25 °C) for 30 h the solution was concentrated to dryness and the mixture extracted with methylene chloride. Concentration of the extracts gave 0.30 g of recovered triazine which was assayed by ^{13}C NMR revealing a mixture of 51% trans **6a** and 49% **6b**, and only trace amounts of **6c**. The same procedure was employed with other triazines (pure cis or trans or mixtures of two or three epimers; reaction times 6–74 h). No epimerization was observed with the pure trans phenyl compound **13a** during 68 h nor with the trans methyl compound **4a** during 16 h (reactants recovered). Data are summarized in Table IV.

The rate of epimerization of the tri-*n*-pentylbicyclotriazine **11a** was evaluated using the same procedure. Starting with a mixture of 70% trans-exo **11a** and 30% cis-exo **11b**, samples were removed at intervals, quenched with excess sodium hydroxide, and assayed by ^{13}C NMR; observed time in hours followed by percent trans-exo **11a** in parentheses were as follows: 0 (70), 0.1 (68), 0.35 (60), 2.5 (54), 6 (50), 30 (50).

The ammonium chloride catalyzed epimerization of mixtures containing appreciable amounts of cis-endo isomer was examined using short reaction times. The equilibration reaction was stopped by addition of 50% aqueous sodium hydroxide to adjust the pH to ca. 10. A tri-*n*-propylbicyclotriazine mixture (57% **6a**, 32% **6b**, 12% **6c**) gave after 5 min 64% **6a**, 32% **6b**, 4% **6c**. A tris-isobutylbicyclotriazine mixture (49% **9a**, 35% **9b**, 16% **9c**) gave after 5 min 67% **9a**, 33% **9b**, and 0% **9c**.

Pure cis-endo trimethylbicyclotriazine (**4c**, mp 133–134 °C) in 1% methanolic ammonium chloride for 30 min gave the trans epimer only (**4a**, mp 111–114 °C, ^{13}C NMR assay).

A modified ammonium chloride catalyzed epimerization procedure was employed which approximates the workup procedure employed in the Schmitz reaction. A mixture of 0.36 g of *n*-pentylbicyclotriazine (containing 56% **11a**, 31% **11b**, and 13% **11c**), 0.36 g of ammonium chloride, and 36 ml of 10 M methanolic ammonium chloride was concentrated to dryness under reduced pressure during ca. 12 min. The residue was extracted with methylene chloride and the extracts concentrated to dryness to yield a product (0.36 g) containing 64% **11a**, 31% **11b**, and 5% **11c** (the crude product isolated from a 0.05-mol Schmitz reaction run requiring ca. 1 h concentration time during workup gave a mixture of 67% **11a**, 33% **11b**, and less than 2% **11c**). In a parallel experiment with a tri-*n*-propylbicyclotriazine sample containing 57% **6a**, 32% **6b**, and 12% **6c** there was obtained after ca. 12 min concentration time a mixture of 64% **6a**, 32% **6b**, and 4% **6c**.

Procedure B. Methanolic Hydrogen Chloride. A 0.30-g sample of 2,4,6-tri-*n*-pentyl-1,3,5-triazabicyclo[3.1.0]hexane (70% trans-exo, **11a**, and 30% cis exo, **11b**) was dissolved in methanol (30 ml). Hydrochloric acid (12 N) was added dropwise (5 drops) to adjust to pH ca. 2. After 10 min aqueous sodium hydroxide solution (50%) was added dropwise to adjust the pH to ca. 9. The solution was concentrated to dryness and the residue extracted with methylene chloride. Concentration of the extracts gave 0.30 g of epimerized product (48% trans, **11a**; 49%; cis-exo, **11b**; and 3% cis-endo, **11c**). Samples of certain other triazines were epimerized using the same conditions for 10 min. Product equilibrium mixture compositions agreed (±2%) with values obtained using methanolic ammonium chloride (procedure A). Data are summarized in Table IV.

Procedure C. Epimerizations in Methanol-*O-d*. A 0.20-g sample of trimethylbicyclotriazine (67% trans **4a**, 33% cis **4b**) was dissolved in 20 ml of methanol-*O-d*. Hydrochloric acid was added dropwise to adjust to pH 1. After standing for 2 h the solution was made alkaline (pH 8) by addition of 50% aqueous sodium hydroxide solution. The mixture was concentrated to dryness and the residue extracted with deuteriochloroform. The CH proton NMR spectrum was identical with that of the reactant mixture; the ratio of integrals for the C-2, C-4, C-6 ring CH and methyl protons remaining unchanged at 1:3.

A 0.10-g sample of triethylbicyclotriazine (55% trans **5a**, 45% cis **5b**) was exchanged with D_2O several times to prepare the *N*-deuterio compound. This material and deuterioammonium chloride (0.10 g) in 15 ml of methanol-*O-d* after standing at 25 °C for 16 h was concentrated to dryness and the residue extracted with deuteriochloroform. Except for the absence of an NH signal, the ^1H NMR spectrum of the product was identical with that of the reactant (no CH deuterium incorporation).

2,4-Diethyl-6,6-pentamethylene-1,3,5-triazabicyclo[3.1.0]-hexane (23). 3,3-Pentamethylenediaziridine[4] (2.0 g, 0.018 mol) was dissolved in 100 ml of dry methanol and cooled to −35 °C. To the stirred solution was added methanolic ammonia (4.46 ml of 8 N solution, 0.036 mol) in one portion. Propanal (2.32 g, 0.040 mol) was added in one portion to the stirred solution. The solution was stirred for 1 h at −30 °C and an additional 1 h at 25 °C. Removal of solvent gave 3.55 g of clear mobile oil. The oil was taken up in 40 ml of isopentane and dried over Drierite; its ^{13}C NMR spectrum shows **23** in one configuration only. Filtration and concentration gave 3.1 g (82%) of white solid: mp 37–41 °C; ir 3320 cm^{-1} (NH); ^1H NMR ($CDCl_3$) δ 4.18 (t, 2 H, ring CH), 2.52 [s (broad), 1 H, NH], 1.87 [s (broad), 14 H, CH_2], 1.17 (t, J = 7.5 Hz, 6 H, CH_3); the ^1H NMR spectrum in pyridine-d_5 showed one exchangeable proton upon addition of D_2O; ^{13}C NMR ($CDCl_3$) δ 77.3 (ring C-2, C-4), 64.6 (ring C-6), 38.0 [endocyclic α-C of $(CH_2)_5$], 31.3 (CH_2CH_3), 25.9, 25.4, 24.8, 24.1 [$(CH_2)_5$ carbons except endocyclic α-C], 10.7 (CH_3).

Anal. Calcd for $C_{12}H_{23}N_3$: C, 68.85; H, 11.08; N, 20.08; mol wt, 209.33. Found: C, 68.66; H, 11.04; N, 19.95; mol wt, 212 (osmometry, $CHCl_3$).

Registry No.—**4a**, 41807-88-9; **4b**, 41807-89-0; **4c**, 59829-85-5; **4c-*N*-*d*** (R = CH_3), 59812-99-6; **5a**, 41807-90-3; **5b**, 41807-91-4; **5c**, 59829-86-6; **6a**, 41807-92-5; **6b**, 41807-93-6; **6c**, 59829-87-7; **7a**, 41807-94-7; **7b**, 41807-95-8; **7c**, 59829-88-8; **8a**, 41807-96-9; **8b**, 49829-89-9; **8c**, 59829-90-2; **9a**, 41807-97-0; **9b**, 59829-91-3; **9c**, 59829-92-4; **10a**, 41807-98-1; **10b**, 59829-93-5; **10c**, 59829-94-6; **11a**, 41807-99-2; **11b**, 59829-95-7; **11c**, 59829-96-8; **12a**, 41808-00-8; **12b**, 59829-97-9; **12c**, 59829-98-0; **13a**, 41808-01-9; **13b**, 59830-03-4; **13c**, 59830-04-5; **14a**, 41808-02-0; **14b**, 59829-99-1; **14c**, 59830-00-1; **15a**, 51003-11-3; **15b**, 59830-01-2; **15c**, 59830-02-3; **16a** [R = Ph(CH_3)CH], 51003-93-1; **17a**, 41808-03-1; **17b**, 41808-70-9; **17c**, 41808-04-2; **17d**, 41808-05-3; **17e**, 59830-05-6; **17f**, 51003-91-9; **23**, 59813-00-2; **24a** (R = Me), 59813-01-3; 2,4,6-trimethyl-1,3,5-hexahydrotriazine-*1,3,5-d*$_3$, 59813-02-4; 3,3-pentamethylenediaziridine, 185-79-5.

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Diaziridines. 5. Reaction of Some 1-Aroyl- and 1,2-Diacyldiaziridines

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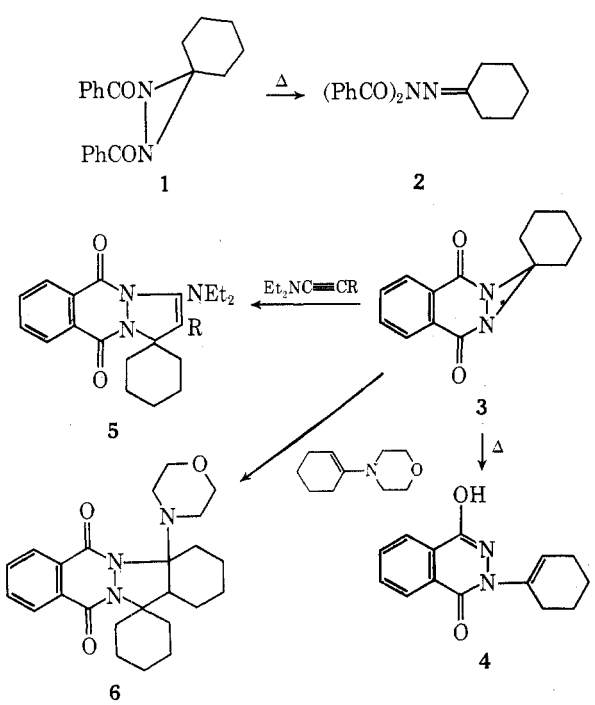
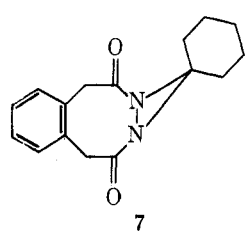
The diaziridine 4′,9′-dihydrospiro[cyclohexane-1,1′(1*H*)-diazirino[1,2-*c*][3,4]benzodiazocine]-3′,10′-dione (**7**) isomerizes in refluxing benzene into 3-(cyclohexylideneamino)-1*H*-3-benzazepine-2,4(3*H*,5*H*)-dione (**8**) and rearranges in refluxing benzene containing triethylamine hydrochloride into 3-(1-cyclohex-1-yl)-1,3,4,6-tetrahydro-3,4-benzodiazocine-2,5-dione (**9**). 1-*p*-Nitrobenzoyl-2,3,3-trialkyldiaziridines isomerize in chloroform or acetonitrile at ambient temperatures into labile 2-aryl-4,5,5-trialkyl-Δ^2-1,3,4-oxadiazolines (**11a–c**). The latter compounds react with both electrophiles and nucleophiles such as aromatic aldehydes and ynamines to give 2,5-diaryl-4-alkyl-Δ^2-1,3,4-oxadiazolines and pyrazoline derivatives, respectively.

Several studies on 1,2-diaroyldiaziridines have appeared recently. Schmitz and co-workers[1] reported the rearrangement of several 1,2-diaroyldiaziridines (**1**) to β,β-diaroylhydrazones (**2**) (Scheme I) and we[2,3] described the reactions of 1,1-dialkyl-1*H*-diazirino[1,2-*b*]phthalazine-3,8-diones (**3**). The latter compounds isomerize to 2-(1-alken-1-yl)-4-hydroxy-1(2*H*)-phthalazinones (**4**) in refluxing toluene and react with ynamines and enamines to give compounds **5** and **6**, respectively (Scheme I).

Scheme I



The difference in thermal behavior of **1** and **3** prompted us to undertake the preparation and thermolysis of a *N,N′*-diacyldiaziridine similar to **3** but less constrained, namely the benzodiazocine derivative **7**. For purposes of comparison with



7

N,N′-diaroyldiaziridines we also prepared several 1-aroyl-2,3,3-trialkyldiaziridines. These substances isomerize in chloroform or acetonitrile to labile 2-aryl-4,5,5-trialkyl-Δ^2-1,3,4-oxadiazolines which react readily with both electrophilic and nucleophilic substrates such as aromatic aldehydes and ynamines.

Results

Compound **7** was synthesized in 41% yield by reacting *o*-phenylenediacetyl chloride with excess 3,3-pentamethylenediaziridine. The NMR spectrum of **7** is consistent with the structure proposed (see Experimental Section). When heated in benzene **7** isomerizes into the benzazepine **8** (Scheme II). The structure of **8** was elucidated by NMR spectroscopy, mass spectroscopy, and elemental analysis. The NMR spectrum taken in $CDCl_3$ consists of two singlets at δ 7.25 and 4.12 for the aromatic and methylene protons, respectively, and two broad multiplets centered at δ 2.50 and 1.70. The two multiplets are characteristic of the cyclohexylidine moiety when bonded to nitrogen and they are observed in the NMR spectra of hydrazone derivatives of cyclohexanone[4] and cyclohexanone oxime. Compound **7** when refluxed in benzene containing