Nitrene Insertion Selectivities. The Reaction of Ethyl Azidoformate with Saturated Cyclic Hydrocarbons

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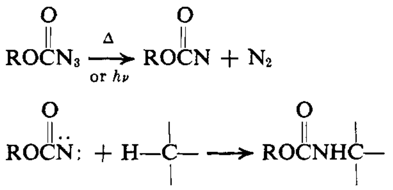
Abstract: The relative reactivities of the various positions of several hydrocarbons–cyclohexane, norbornane, bicyclo[2.2.2]octane, and adamantane—toward nitrene insertion were determined. The nitrene was generated by thermal decomposition of ethyl azidoformate at 120°. The secondary positions of the various substrate molecules had similar relative reactivities, but the 7-norbornyl C–H bonds were exceptional: attack occurred only about a fifth as readily there. The bridgehead positions of the polycyclic hydrocarbons showed a larger reactivity spread, some 14-fold, but this variation was much less than that observed for typical carbonium ion or free-radical processes. The relative reactivities of nitrene insertion correlated quantitatively better with data for free-radical than with data for carbonium ion reactions. One interpretation of this behavior, that the nitrene insertion transition state has "free-radical character," seems less likely than an alternative explanation: both free-radical and nitrene insertion reactivities are governed similarly by structural variations.

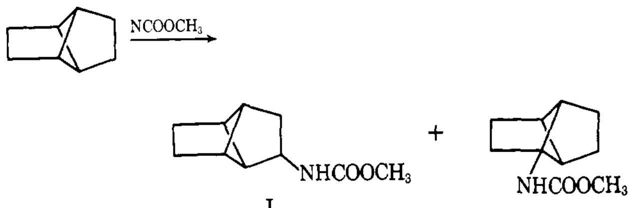
Azidoformates have been shown to decompose thermally[2] and photolytically[3] in a variety of solvents to eliminate molecular nitrogen and form electron-deficient nitrogen species, formylnitrenes. In saturated hydrocarbon solvents, the major reaction of such nitrenes is insertion into C–H bonds.[4] The evidence appears to be quite conclusive[2,5] that these nitrenes are formed first as singlets which insert into C–H bonds by a concerted mechanism with essentially complete retention of configuration.[6,7] The relative reactivities of primary, secondary, and tertiary C–H bonds toward thermally generated ethoxycarbonylnitrene have been shown to be 1:10:32 with 2-methylbutane as substrate;[2] these relative reactivities are practically independent of the method used to generate the nitrene.[8]



$$\mathrm{RO\overset{\overset{O}{\|}}{C}N_3 \xrightarrow[\text{or } h\nu]{\Delta} RO\overset{\overset{O}{\|}}{C}N + N_2}$$

$$\mathrm{RO\overset{\overset{O}{\|}}{C}\ddot{N}\colon + H{-}\underset{|}{\overset{|}{C}}{-} \longrightarrow RO\overset{\overset{O}{\|}}{C}NH\underset{|}{\overset{|}{C}}{-}}$$

Other nitrenes, for example, those generated from phenyl azide[9] or from pivaloyl azide,[10] give somewhat different insertion selectivity ratios. Nevertheless, the results obtained by Meinwald and Aue,[11] published while this work was in progress, surprised us. The insertion of methoxycarbonylnitrene into the secondary and bridgehead tertiary C–H bonds of tricyclo[3.3.0.0^{2,6}]octane took place in an apparently random fashion, since a 2:1 ratio of products I and II was obtained.[11]



I

II

To learn more about the nature of the insertion reaction and the structural factors governing positional selectivity, we carried out a systematic study of the reaction of ethoxycarbonylnitrene with a number of cyclic substrates. These reactions have synthetic potential as methods for functionalizing polycyclic and other saturated hydrocarbons.

Results

Three bridged ring hydrocarbons were investigated: bicyclo[2.2.2]octane and adamantane, whose bond angles do not deviate markedly from the tetrahedral value, and the highly strained norbornane. Decompositions were carried out in methylene chloride, using an approximately 10 mol % concentration of hydrocarbon and 1 mol % of ethyl azidoformate, at 120°. The solutions were cooled and analyzed by glpc, each carbamate being identified by comparing its retention time with that of a sample of known structure. It is quite apparent (Table I) that there are no large differences in reactivity among the various positions in any one of the individual hydrocarbons. Thus, there is only a 3- to 5-fold difference between the 2-*exo* and the

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[2] D. S. Breslow, T. J. Prosser, A. F. Marcantonio, and C. A. Genge, *J. Amer. Chem. Soc.*, **89**, 2384 (1967); R. J. Cotter and W. F. Beach, *J. Org. Chem.*, **29**, 751 (1964).

[3] W. Lwowski and T. W. Mattingly, Jr., *ibid.*, **87**, 1947 (1965).

[4] Compare the analogous behavior of cyanonitrene: A. G. Anastassiou and H. E. Simmons, *ibid.*, **89**, 3177 (1967); A. G. Anastassiou, *ibid.*, **89**, 3184 (1967).

[5] W. Lwowski, *Angew. Chem.*, **79**, 922 (1967); *Angew. Chem. Int. Ed. Engl.*, **6**, 897 (1967).

[6] G. Smolinsky and B. I. Feuer, *J. Amer. Chem. Soc.*, **86**, 3085 (1964).

[7] S. Yamada, S. Terashima, and K. Achiwa, *Chem. Pharm. Bull.* (Tokyo), **13**, 751 (1965).

[8] W. Lwowski and T. J. Maricich, *J. Amer. Chem. Soc.*, **87**, 3630 (1965).

[9] J. H. Hall, J. W. Hill, and H. C. Tsai, *Tetrahedron Lett.*, 2211 (1965).

[10] G. T. Tisue, S. Linke, and W. Lwowski, *J. Amer. Chem. Soc.*, **89**, 6303 (1967).

[11] J. Meinwald and D. H. Aue, *Tetrahedron Lett.*, 2317 (1967).

Table I. Thermal Decomposition of Ethyl Azidoformate in Various Hydrocarbons

Hydrocarbon	Carbamate position	Concn, mg/ml[b]	Type of H	Rel reactivity per H
Norbornane[a]	1	0.83, 0.79	Tertiary	0.32, 0.31
	2-*exo*	5.18, 5.17	Secondary	1.00
	2-*endo*	1.77, 1.75	Secondary	0.34, 0.34
	7	0.51, 0.60	Secondary	0.20, 0.23
Bicyclo[2.2.2]octane[a]	1	0.43, 0.38	Tertiary	1.94, 1.74
	2	1.33, 1.31	Secondary	1.00
Adamantane[a]	1	3.10, 3.05	Tertiary	6.65, 6.74
	2	1.40, 1.36	Secondary	1.00
Tricyclo[3.3.0.0^{2,6}]octane[11]	1		Tertiary	1
	2		Secondary	1
2-Methylbutane[2]	2		Tertiary	3.2
	3		Secondary	1

[a] At 120° in CH_2Cl_2 solution. [b] By glpc. Average of three determinations on two separate runs: aliquots for the norbornane runs, individual solutions for the others.

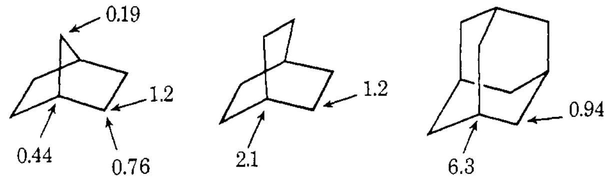
Table II. Decomposition of Ethyl Azidoformate in a Mixture of Hydrocarbons[a]

Hydrocarbon	Carbamate position	Concn, mg/ml[b]	Type of H	Rel reactivity per H
Cyclohexane		1.9, 1.8	Secondary	1.00, 1.00
Norbornane	1	0.14[c]	Tertiary	0.44
	2-*exo*	0.8, 0.8	Secondary	1.2, 1.2
	2-*endo*	0.5, 0.5	Secondary	0.74, 0.78
	7	0.06[c]	Secondary	0.19
Bicyclo[2.2.2]octane	1	0.8, 0.7	Tertiary	2.2, 2.0
	2	2.6, 2.6	Secondary	1.2, 1.2
Adamantane	1	5.4, 4.7	Tertiary	6.5, 6.0
	2	2.3, 2.2	Secondary	0.93, 0.94

[a] At 120°, equimolar hydrocarbon concentration in CH_2Cl_2. [b] By glpc. Average of three determinations in two separate runs. [c] After concentrating the solution. Amount estimated by comparison with bicyclo[2.2.2]octane carbamates.

1 or 7 positions in norbornane,[12] and the maximum variation is the 6.7-fold one between the two positions in adamantane. However, when comparisons are made among the several hydrocarbons, much larger variations are found. Thus, if one considers the 2-*exo* position as the "normal" reaction site in norbornane, there is over a 20-fold difference in the relative tertiary/secondary reactivity ratios between norbornane and adamantane. The ratio appears to decrease with increasing ring strain in the cyclic compound, with Meinwald and Aue's tricyclooctane[11] fitting into the series between norbornane and bicyclooctane. On this basis, the observed tertiary/secondary ratio of 1 for this compound would appear to be fortuitous.[13]

In order to compare the different hydrocarbons more accurately, the decomposition of ethyl azidoformate in an equimolar mixture of cyclohexane, norbornane, bicyclo[2.2.2]octane, and adamantane in methylene chloride was carried out. The results are shown in Table II. Although the values are less precise than those from the individual experiments, because of the considerable difference in reactivities and the much greater analytical complexity, the results in Table II differ surprisingly little from those in Table I. These relative reactivities are summarized in the figures shown below.



Relative reactivitives (per H), cyclohexane = 1

All of the secondary positions—save only the 7-norbornyl—have almost the same reactivity. The 7 position of norbornane is highly strained,[14] and both carbonium ion and free-radical reactions are inhibited there (*vide infra*). The 2-*exo* position of norbornane is somewhat more reactive than the 2-*endo* position, presumably because of steric and/or torsional effects.[15]

A greater reactivity range is found at the bridgehead position; the lowest in norbornane, the highest in adamantane, with bicyclo[2.2.2]octane intermediate. This sequence is suggestive of those found for both carbonium ion and free-radical processes at the same positions (Table III), but the magnitudes are quite different.

It might be expected that nitrene and carbene insertion processes would be quite similar. A study of the reaction of methylene, carbomethoxycarbene, and bis(carbomethoxy)carbene with norbornane and with bicyclo[2.2.2]octane has been carried out by Willcott.[16] Unfortunately, the products from norbornane and the substituted carbenes could not be separated completely by gas chromatography, and

(12) Lwowski[5,10] has recently referred to unpublished work in which it was determined that all the secondary positions in norbornane were 1.7 times more reactive (per H atom) than the bridgehead positions, a result in excellent agreement with our value, 1.8, similarly computed.

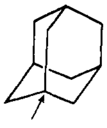
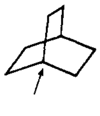
(13) Although Meinwald and Aue carried out their decompositions without additional solvent, the comparison with our results is still valid. We obtained essentially identical results in molten pure norbornane and in a methylene chloride solution of norbornane. Lwowski[5] has reported the same lack of solvent dependence with acyclic hydrocarbons.

(14) J. F. Chiang, C. F. Wilcox, Jr., and S. H. Bauer, *J. Amer. Chem. Soc.*, **90**, 3149 (1968), and references cited therein.

(15) P. von R. Schleyer, *ibid.*, **89**, 699, 701 (1967).

(16) M. R. Willcott, III, Ph.D. Thesis, Yale University, 1963

Table III. Comparison of Bridgehead Relative Reactivities

			
Nitrene insertion	1	0.3	0.07
Carbonium ion			
(bromide solvolyses)[a]	1	10^{-3}	10^{-10}
Free radical			
(*t*-butyl perester decomposition)[b]	1	0.07	0.001
(decarbonylation)[c]	1	0.5	0.003

[a] R. C. Fort, Jr., and P. von R. Schleyer, *Advan. Alicyclic Chem.*, **1**, 283 (1966). [b] L. B. Humphrey, B. Hodgson, and R. E. Pincock, *Can. J. Chem.*, in press. See also R. C. Fort, Jr., and R. E. Franklin, *J. Amer. Chem. Soc.*, **90**, 5267 (1968), and J. P. Lorand, S. D. Chodroff, and R. W. Wallace, *ibid.*, **90**, 5266 (1968). [c] D. E. Applequist and L. Kaplan, *ibid.*, **87**, 2194 (1965).

only a general tertiary/secondary ratio could be determined for all secondary positions together. Willcott's carbene data and our nitrene work are summarized in Table IV.

Table IV. Comparison of Carbene and Nitrene C–H Insertion Reactivities

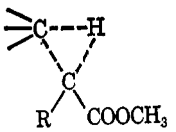
	Reactivity ratio tertiary/secondary (per H)			
	Carbene[16]			Nitrene
Hydrocarbon	$:CH_2$[a]	$:CHCOOCH_3$[a]	$:C(COOCH_3)_2$[a]	$:NCOOC_2H_5$[a]
Norbornane[b]	1.0 (0.8)	0.7 (0.5)	0.2 (0.1)	0.6[c,12] (0.2)
Bicyclo[2.2.2]octane	1.0 (0.8)	1.0 (0.8)	0.7 (0.3–0.5)	1.8[c] (0.5–0.7)
Typical acyclic alkanes[d]	1.2[17] (1.0)	1.3[17] (1.0)	1.5–2.1[17] (1.0)	2.5–3.8[28] (1.0)

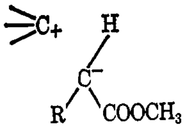
[a] Values in parentheses obtained for each carbene or nitrene by dividing the bicyclic hydrocarbon ratio by the one typical for acyclic alkanes. [b] All secondary positions combined. [c] This work. [d] Estimated by dividing the tertiary/primary by the secondary/primary ratios given in the references cited.

Although methylene itself is quite nonselective (especially in the liquid phase),[16] both carbomethoxycarbenes and carbethoxynitrene show inhibited reactivity at the norbornane bridgehead positions. The same is true for the bicyclo[2.2.2]octane bridgeheads, when one takes the "typical" tertiary/secondary reactivity ratios into account (values in parentheses in Table IV). On this basis, the selectivity of carbethoxynitrene toward norbornane and bicyclo[2.2.2]octane is intermediate between that of carbomethoxycarbene and bis(carbomethoxy)carbene. The limited data available do not permit a more detailed comparison of univalent nitrogen with bivalent carbon species.

Discussion

The Mechanism of C–H Insertion Reactions. Doering and Knox[17] have attributed the enhanced discrimination of substituted carbenes ($:CH_2 < :CHCOOCH_3 < :C(COOCH_3)_2$, see Table IV) for tertiary and secondary over primary positions to contributions of polar structures, such as III and IV, to the insertion transition states. These authors were careful to point out, however, that "there are other consistent explanations, so that the one offered should not be considered as uniquely established." Despite this warning, the original explanation has proven to be a popular one for the rationalization of carbene insertion behavior.[16,18,19] Reduced reactivity at small ring bridgehead positions has been attributed to the known instability[20] of carbonium ions at such positions.[16,19]





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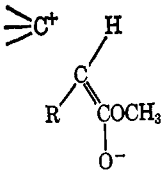

IV

The nature of the (singlet) nitrene insertion process has been discussed,[4] chiefly by Lwowski.[5,10] Although he concedes that the "pronounced preference for insertion into tertiary C–H bonds. . .could be interpreted as indicating a partial positive charge on carbon in the transition state of the insertion," he is more impressed by the only slightly diminished reactivity of norbornane bridgehead C–H bonds (see Table IV) and concludes "that only little, if any, positive charge is created on the carbon, in the transition state."[10]

Thus, the diminished reactivity at the norbornane bridgehead toward C–H insertion has been used both to support and to discredit the postulate of "carbonium ion character" in the transition state for such processes!

The stability of free radicals, as well as that of carbonium ions, decreases in the order: tertiary > secondary > primary. Hence, as Lwowski has pointed out,[5] the C–H insertion behavior is compatible not only with "carbonium ion character," but also with "free-radical character" for the carbon atom involved. Whereas it is perhaps best to think of these nitrene and carbene insertion states as having their own "character," it is useful to examine the extent to which similarities exist. The wider sampling of insertion relative reactivities we have determined permits a broader comparison than has been possible before; data for carbonium ion, free-radical, and nitrene insertion processes are collected in Table V.

A plot of carbonium ion reactivities *vs.* nitrene insertion data (Figure 1) shows only a relatively poor correlation (correlation coefficient = 0.884).[21] The low slope of the least-squares line, 0.099, attests to the

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(17) W. von E. Doering and L. H. Knox, *J. Amer. Chem. Soc.*, **83**, 1989 (1961); *cf.* M. Jones, Jr., W. Ando, and A. Kulczycki, Jr., *Tetrahedron Lett.*, 1391 (1967).

(18) W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964, p 97.

(19) R. R. Sauers and R. J. Kiesel, *J. Amer. Chem. Soc.*, **89**, 4695 (1967).

(20) See footnote *a*, Table III.

(21) This correlation is improved significantly (to a coefficient of 0.926) if the *unassisted* rates estimated[22] for 2-*exo*-norbornyl and for 2-bicyclo[2.2.2]octyl tosylates are employed instead of the observed rates. Anchimeric assistance should pertain only in carbonium processes and not in nitrene insertions.

(22) P. von R. Schleyer, *J. Amer. Chem. Soc.*, **86**, 1856 (1964).

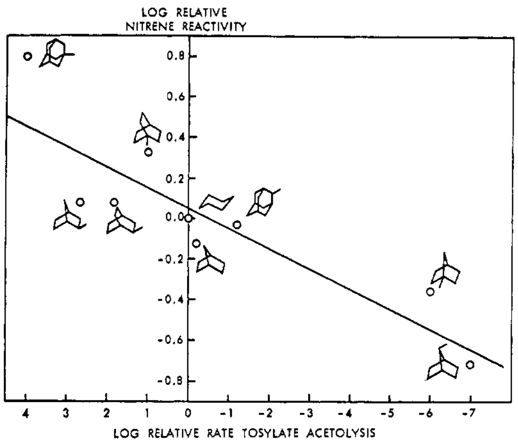

Figure 1. Plot of the log of the relative rates of tosylate acetolysis *vs.* the log of the relative nitrene reactivities in cyclic hydrocarbons; correlation coefficient, 0.884.

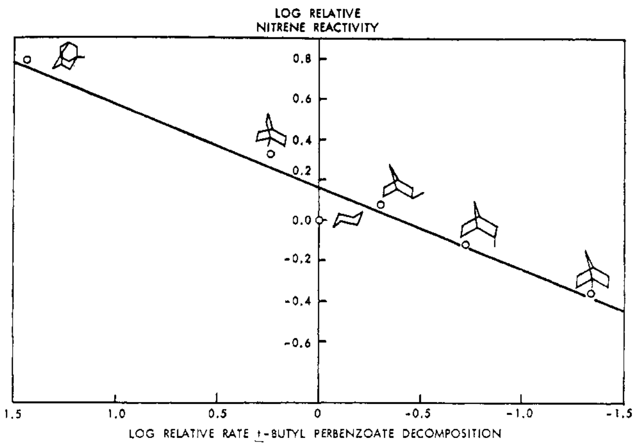

Figure 2. Plot of the log of the relative rates of *t*-butyl perbenzoate decomposition *vs.* the log of the relative nitrene reactivities in cyclic hydrocarbons; correlation coefficient, 0.978.

much greater effect of structural variations on carbonium ion reactivities than on nitrene insertion behavior.

Table V. Comparison of Nitrene Insertion, Carbonium Ion, and Free-Radical Relative Reactivities

Hydrocarbon	Position	Nitrene reactivity (per H)[a]	Tosylate acetolysis[b]	*t*-Butyl perester decomposition[c]	Chlorination ratios (per H)
Cyclohexane		1.00	1.00	1.00[d]	
Norbornane	1	0.44	10^{-6}	0.046[h]	. . .
	2-*exo*	1.2	510	0.50[d]	~17.5[e]
	2-*endo*	0.76	1.5	0.19[d]	~6.3[e]
	7	0.19	10^{-7}		1.0[e]
Bicyclo[2.2.2]-octane	1	2.1	10	1.75[h]	6.8[f]
	2	1.2	71		1.0[f]
Adamantane	1	6.3	10^4	27.8[h]	1.7–2.4[g]
	2	0.94	0.066		1.0[g]

[a] Average values from Table II, 120°, CH_2Cl_2. [b] Solvolysis rates at 25°.[22] [c] Reactivities calculated at 100° from literature data, cumene solvent. [d] P. D. Bartlett and J. M. McBride, *J. Amer. Chem. Soc.*, **87**, 1727 (1965). This paper summarizes and discusses prior literature data. [e] Free-radical photochlorination of norbornane in methylene chloride gave 7-chloro-, 2%; 2-*exo*-chloro-, 70% and 2-*endo*-chloronorbornane, 25%: E. C. Kooyman and G. C. Vegter, *Tetrahedron*, **4**, 382 (1958). [f] Free-radical photochlorination of bicyclo[2.2.2]octane in carbon tetrachloride gave 53% 1-chloro product and 47% 2-chloro product: A. F. Bickel, J. Knotnerus, E. C. Kooyman, and G. C. Vegter, *ibid.*, **9**, 230 (1960). [g] Photochlorination of adamantane in carbon tetrachloride gave a 0.63 ratio of 1-chloro- to 2-chloroadamantane: G. W. Smith and H. D. Williams, *J. Org. Chem.*, **26**, 2207 (1961). A higher ratio of 0.80 was obtained by C. R. Carpenter, Ph.D. Thesis, Pennsylvania State University, 1967. Also see I. Tabushi, J. Hamuro, and R. Oda, *J. Amer. Chem. Soc.*, **89**, 7127 (1967). [h] See footnote *b*, Table III.

Although fewer data points are available, the correlation between *t*-butyl perester decomposition rates—a typical free-radical process—and nitrene insertion relative reactivities (Figure 2) is remarkably good (correlation coefficient = 0.978). Furthermore, the slope of the correlation line, 0.413, suggests that both processes have more nearly comparable sensitivities toward structural variations.

Table V includes photochlorination data permitting a rough estimate of the relative free-radical reactivity of the positions (7-norbornyl, 2-bicyclo[2.2.2]octyl, and 2-adamantyl) for which no perester decomposition data are yet available. The chlorination ratios are at least in qualitative agreement with expectation, although the bridgehead/secondary ratio for adamantane seems lower than the nitrene selectivity would suggest. It would be good to complete the collection of perester data so that Figures 1 and 2 could be put on a comparable basis with regard to the number of points.

Nitrene insertion reactivities seem to be mirrored more accurately by free-radical rather than by carbonium ion processes. We do not think that this should be interpreted as indicating that the transition state for nitrene insertion reactions has more free-radical character than carbonium ion character. Rather, it seems more probable to us, nitrene insertion, free-radical, and perhaps to a lesser extent,[23] carbonium ion reactivities are all dependent in a similar fashion on the same structural features of the substrate molecules. It could be primarily for this reason that the correlations shown in Figures 1 and 2 are observed and not because of any electronic similarity of the transition states of the various processes.

Nevertheless, the observed correlations, if confirmed by comparison of a wider selection of data, can be of considerable predictive and interpretive utility.

Experimental Section

Melting points were obtained on a Hoover Unimelt (capillary) melting point apparatus (Arthur H. Thomas Co.) and, like the boiling points, are reported uncorrected. The nmr spectra were taken on a Varian A-60A spectrometer; chemical shifts are reported in δ units (parts per million (ppm) from tetramethylsilane internal standard). Infrared spectra were obtained on a Perkin-Elmer Model 257 infrared spectrophotometer. X-Ray diffraction patterns were determined on a Norelco diffraction unit with powder cameras, copper target 2, and nickel filter.

Materials. Cyclohexane (Eastman Spectroquality), norbornane (Aldrich), and methylene chloride (Fisher reagent grade) were commercial materials used as received. Adamantane was obtained as a gift from the du Pont Co., for which courtesy we express our gratitude.

Bicyclo[2.2.2]octane was prepared by hydrogenation of bicyclo[2.2.2]oct-2-ene (Columbia Organic Chemical Co.) according to the

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(23) Although a plot of the solvolysis data in Table V *vs.* the available perester decomposition rates is unsatisfactory (correlation coefficient = 0.815), it would be of considerable interest to have a much wider collection of data for this purpose.

Table VI. Urethan Standards

Urethan	Yield, %[a]	Mp, °C[b]	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1-Adamantylurethan	86	90	69.90	9.48	6.27	69.92	9.57	6.63
2-Adamantylurethan	55	85–86	69.90	9.48	6.27	70.36	9.66	6.57
Bicyclo[2.2.2]octyl-1-urethan	100	67–68	66.97	9.66	7.10	66.99	9.84	7.17
Bicyclo[2.2.2]octyl-2-urethan	100	97–98	66.97	9.66	7.10	66.59	9.80	7.04
Cyclohexylurethan	98	56.5–57.5[c]						
Norbornyl-1-urethan	76.5	Oil	94.6% 1-urethan[d]					
Norbornyl-7-urethan	100	57–58	65.54	9.35	7.64	65.46	8.98	7.28
Norbornyl-2-*endo*-urethan	82	Oil	46.6% 2-*endo*-urethan, 25.1% 2-*exo*-urethan, 28.5% unknown[d,e]					
Norbornyl-2-*exo*-urethan	100	51–52	65.54	9.35	7.64	65.81	9.42	7.23

[a] Crude product. [b] Recrystallized product. [c] Lit.[3] mp 55.5–56.5°. [d] By glpc, crude product. [e] Reduction of ketoximes of bridged ring systems with lithium aluminum hydride can give products other than the expected amines, *e.g.*, aziridines. See K. Kitahonoki, Y. Takano, and H. Takahashi, *Tetrahedron*, **24,** 4605 (1968).

Table VII. Amounts of Reactants in Thermal Decompositions of Ethyl Azidoformate in Presence of Cyclic Hydrocarbons

Hydrocarbon	Wt, g	mmoles	Ethyl azidoformate Wt, g	Ethyl azidoformate mmoles	Ethyl azidoformate mol %	Solvent,[a] ml
Adamantane	5.0	36.8	0.5	4.2	11.4	50
	5.0	36.8	0.5	4.2	11.4	50
Bicyclo[2.2.2]octane	3.01	27.4	0.294	2.56	9.3	30
	3.01	27.4	0.286	2.49	9.1	30
Norbornane	0.49[b]	5.12	0.067[b]	0.58	11.4	7
	0.49[b]	5.12	0.067[b]	0.58	11.4	7
Mixed Hydrocarbons						
Cyclohexane	*c*	4.85	*c*	0.605	12.5[d]	7[c]
Norbornane	*c*	4.85	*c*			
Bicyclo[2.2.2]octane	*c*	4.85	*c*			
Adamantane	*c*	4.85	*c*			

[a] Methylene chloride. [b] 1.76 g of norbornane and 0.2398 g of ethyl azidoformate were dissolved in methylene chloride, made up to 25 ml. A 7-ml portion of this solution was used for each decomposition. [c] 1.45 g of cyclohexane, 1.66 g of norbornane, 1.90 g of bicyclo [2.2.2]octane, and 2.35 g of adamantane (17.3 mmol of each) and 0.2484 g of ethyl azidoformate (2.16 mmol or 12.5 mol % relative to each individual hydrocarbon) were dissolved in methylene chloride and made up to 25 ml. Two 7-ml portions were used for decompositions. [d] Relative to each individual hydrocarbon.

procedure of Grob and coworkers.[24] Sublimation at 20 mm (bath at 100–105°) gave an 82% yield of hydrocarbon.

Anal. Calcd for C_8H_{14}: C, 87.19; H, 12.81. Found: C, 86.84; H, 12.50. The infrared spectrum showed no detectable olefin (<0.3%). The nmr spectrum in carbon tetrachloride consisted of a single sharp peak at δ 1.52.

Ethyl azidoformate was prepared from ethyl chloroformate and sodium azide in a manner similar to that described by Lwowski and Mattingly.[3] Because of the sensitivity of the azidoformate,[2] it was isolated in small portions, as needed, by removal of solvent and distillation through a 5-in. Vigreux column, bp 40–41° (34 mm).

Preparation of Amines. The following amines were prepared by reduction of the corresponding oximes: 2-*endo*-aminonorbornane,[25] 7-aminonorbornane,[26] and 2-aminoadamantane.[27]

The following amines were synthesized by Schmidt reactions[28] on the corresponding carboxylic acids: 2-*exo*-aminonorbornane,[28] 1-aminonorbornane,[29] 2-aminobicyclo[2.2.2]octane,[30] and 1-aminobicyclo[2.2.2]octane.

1-Aminoadamantane[31] was supplied as a gift from Dr. E. C. Hermann of E. I. du Pont de Nemours and Co.

The products of the above reactions were not characterized completely, but were converted to the corresponding urethans for this purpose.

Synthesis of Urethans. The above amines were converted into urethans by the method of Hartman and Brethen;[32] the solids were recrystallized several times from ethanol–water (Table VI).

Decomposition of Azidoformates. Methylene chloride solutions of hydrocarbon and ethyl azidoformate were chilled in Dry Ice, purged with nitrogen, and then sealed *in vacuo* (Table VII). Duplicate reaction mixtures were than heated at 120° for 20 hr to decompose all the azidoformate and analyzed by glpc. The results with the individual hydrocarbons are given in Table I, and those with the mixture of hydrocarbons in Table II. In the latter case the free space was kept to a minimum (*ca.* 8 ml of liquid and 3 ml of vapor space at reaction temperature) to minimize fractionation due to the different vapor pressures of the different hydrocarbons.

Analyses[33] were obtained with an F & M Model 700 gas chromatograph with an F & M Model 240 temperature programmer. The column was glass, 8 ft × 6 mm, packed with Carbowax 20M, 20% on ABS. Provision was made for on-column injection. Products containing urethans of adamantane or bicyclo[2.2.2]octane were temperature programmed; others were isothermal. Peak areas were measured by the product of their height and their width at half-height. Yields of the individual isomers were calculated by comparison with standard solutions of the separately prepared isomers of identical retention times. In the adamantane and bicyclo[2.2.2]octane experiments the pure urethans were used as standards; in the norbornane experiment the crude urethans were used. To confirm the identity of the *exo* and *endo* isomers, the crude *exo* amine was converted to the corresponding acetamide, mp 142.5–143° (lit.[27] 143–144°), not depressed when mixed with an authentic sample.[34] X-Ray powder patterns confirmed their identity. The major isomer was separated by glpc from the crude *endo* amine, and converted into the acetyl derivative, melting point of the crude amide, 110–116° (lit.[27] 131–132°; insufficient material was available for recrystallization). X-Ray diffraction patterns showed the material to be different from the *exo* isomer.

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(33) We are indebted to L. Anderson and J. Churchill of the Hercules Research Center for assistance with these analyses.

(34) We are indebted to Professor H. Brown, Purdue University, for an authentic sample of *exo*-2-acetamidobicyclo[2.2.1]heptane.

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A Total Synthesis of the Diazaphenanthrene Alkaloid Perlolidine

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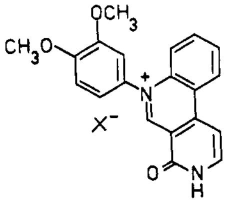
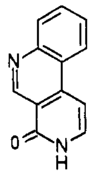
Contribution No. 2169 from the Department of Chemistry, University of California, Los Angeles, California 90024. Received July 3, 1968

Abstract: A total synthesis of the diazaphenanthrene alkaloid perlolidine is reported. A key intermediate, 3-cyano-4-phenylpyridone, was synthesized by two methods. This intermediate was then converted to 2-aza-1-keto-fluorenone by a polyphosphoric acid cyclization. Perlolidine was prepared from the corresponding fluorenol by a Schmidt rearrangement. Alkylation of perlolidine with 4-bromoveratrole gave an O-alkylated product instead of the alkaloid perloline. A synthetic route patterned after a proposed biosynthesis of perlolidine led to several compounds containing elements of the diazaphenanthrene skeleton.

Several alkaloids containing a diazaphenanthrene skeleton have been discovered in various species of grass. Perloline, the most abundant member of this family of alkaloids, was the target for most of the structural investigations. Chemical studies and an X-ray crystallographic investigation led to the establishment of the correct structure (**1**).[2] Perlolidine, one of the minor alkaloids, was first isolated from the New Zealand perennial rye grass *Lolium perenne* L.,[3] and has since been found in other species of grasses along with perloline.[4] Perloline is degraded into perlolidine by oxidizing agents or by storage of its hydrochloride. Since these transformations involve loss of the dimethoxyphenyl substituent,[3,5] the structure of perlolidine (**2**) is defined.[2] In the present paper we describe a total synthesis of this novel diazaphenanthrene alkaloid.[6]

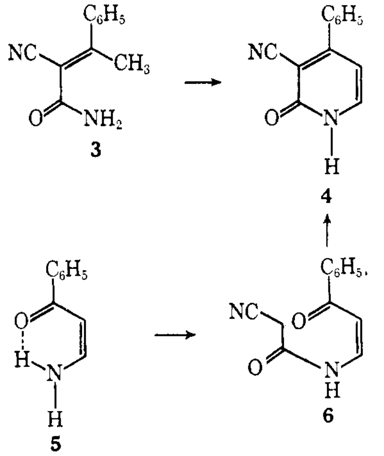


1



2

The pyridone **4** was an obvious intermediate for the synthesis of perlolidine. Once prepared, we planned to utilize the cyano group of **4** in the formation of the tricyclic diazaphenanthrene skeleton. Since the obvious route to **4**, condensation of cyanoacetamide with formylacetophenone or its equivalent, could be expected to give predominately the isomeric 6-substituted 2-pyridone,[7] our first synthesis of 3-cyano-4-phenyl-2-pyridone (**4**) utilized a new method for the formation of pyridone rings. A Knoevenagel condensation of cyanoacetamide with actophenone yielded 1-cyano-2-methylcinnamide which was predominately the *trans* isomer **3**.[8] Condensation of the product with ethyl formate using sodium hydride as a base gave a small yield of the desired pyridone **4**. The reasons for the low yield were soon apparent. The cinnamide **3** reacts readily with strong bases to yield a dimer, 3-cyano-3,4-dihydro-4,6-diphenyl-4-methyl-2-pyridone. And a reaction of ethyl formate with strong bases was causing the destruction of both the base and the formylating agent.[9]



A practical route to **4** was found in the reaction of ethyl cyanoacetate with the enamino ketone **5**. This synthesis was based on a report by Hauser and Basu[10]

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