Nitrogen evolution was measured by displacement of *n*-butyl phthalate in a 100-ml gas buret. In the abortive Koelsch radical work, a pressure transducer was used,[14] and a Beckman DU was used to measure the optical density. A Radiometer Model 26 pH meter was employed; measurements were in water using 1.000 *M* hydrochloric acid; back-titration with base gave the same shaped curve. A Sargent 15 polarograph with ir compensator and rotating platinum electrode was used to measure the oxidation potential of **1a**.

Acknowledgment. We wish to thank the National Science Foundation and the Wisconsin Alumni Research Foundation for generous support of this work. S. F. N. thanks the Sloan Foundation for general support. We thank Mr. M. Micke for measuring some of the nitrogen evolution kinetics runs.

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[14] The apparatus was a simplified version of that of L. R. Mahoney, R. W. Beyma, A. Warnicle, and C. H. Rust, *Anal. Chem.*, **36**, 2516 (1964).

Carbethoxynitrene. The Stereochemistry of the Intermolecular Singlet Carbon–Hydrogen Insertion

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Abstract: Carbethoxynitrene inserts into the C–H bonds of 3-methylhexane with a selectivity that does not change over a concentration range from 100 to 1.2 mol % of the hydrocarbon. The selectivity is also unaffected by the presence of a triplet nitrene trap, α-methylstyrene, and by using a heavy atom solvent, dibromomethane, instead of dichloromethane. The insertion into the tertiary C–H bond of optically active 3-methylhexane proceeds with 100% retention of configuration, under all reaction conditions, and irrespective of the path by which the nitrene is generated. It is concluded that only the singlet state of carbethoxynitrene participates to a measurable extent in the insertion reaction.

Carbethoxynitrene,[3] EtOOCN, inserts into C–H bonds to form N-substituted carbamates, EtOOCNHR. The order of reactivities of various types of C–H bonds has been studied,[4–8] and it has been found that the C–H bonds of saturated, unstrained hydrocarbons are reactive in the order tertiary > secondary > primary. With 2-methylbutane, for example, the relative reactivities for tertiary, secondary, and primary C–H bonds are about 30:10:1, respectively. Bridgehead C–H bonds react readily.[9,10]

It has been shown that carbethoxynitrene can exist, in solution, in both the singlet and the triplet states, and that both these species can undergo a number of intermolecular reactions.[11–16] For example, both the singlet and the triplet nitrene give aziridines with C=C double bonds, albeit with different stereochemistry,[11–13] but only the singlet carbethoxynitrene expands the benzene ring to give N-carbethoxyazepine.[17] The rate with which singlet carbethoxynitrene decays to the triplet (ground) state is comparable to the rate of intermolecular reactions of the singlet.[11–13] Generating the singlet, one can thus adjust the fraction of triplet in the nitrene population by adjusting the concentration of the reactant. Alternatively, one can reduce this fraction by using triplet carbethoxynitrene traps, such as α-methylstyrene.[12,13]

The reaction of carbethoxynitrene with cyclohexene gives more insertion products (into the C–H bonds in the 3 and 4 positions) as more of the nitrene is in the singlet state. This is true both for the absolute yields of insertion products and for the fraction of insertion products in the product mixture (of aziridine and insertion products).[18] Thus, it appears that singlet carbethoxynitrene inserts much more efficiently than the triplet. A question remains: Are the rates of C–H insertion (into unactivated C–H bonds) for singlet and triplet carbethoxynitrene different by just an order of magnitude, or is the triplet slower by a large factor, perhaps

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[11] W. Lwowski and J. S. McConaghy, *ibid.*, **87**, 5490 (1965).

[12] J. S. McConaghy and W. Lwowski, *ibid.*, **89**, 2357 (1967).

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[14] A. Mishra, S. N. Rice, and W. Lwowski, *J. Org. Chem.* **33**, 481 (1968).

[15] A. L. J. Beckwith and J. W. Redmond, *Aust. J. Chem.* **19**, 1859 (1966).

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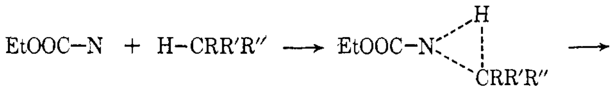
[18] W. Lwowski and F. P. Woerner, *J. Amer. Chem. Soc.*, **87**, 5491 (1965).

unmeasurably slow? There is reason to expect (formal) insertion by the triplet; Nozaki[19] found indications for triplet insertion into C–H bonds adjacent to ether functions, triplet cyanonitrene reacts with tertiary C–H bonds,[20] and triplet phenylnitrene forms N-cyclohexylaniline with cyclohexane.[21] Consequently, a more sensitive experiment had to be devised to probe for triplet carbethoxynitrene insertion into unactivated C–H bonds. This is the first problem the present paper deals with.

The second question our results bear on is that of a stepwise *vs.* a concerted mechanism of the C–H insertion. Stepwise mechanisms could involve ion pairs or free-radical pairs, such as $EtOOCNH^- \ ^+CRR'R''$, or $EtOOCNH\cdot \ \cdot CRR'R''$. Ion pair mechanisms seem to be excluded by the order of reactivities of the C–H bonds in unstrained hydrocarbons, together with the substantial reactivities of bridgehead C–H bonds (see above). The available data are, however, compatible with a radical-pair mechanism (eq 1), as well as with a concerted mechanism, such as in eq 2. The problem of the electron distribution in the transition state of the C–H insertion has been discussed in some detail, and it has been said that the reactivity is governed by "free-radical character"[22,23] or that "both free-radical and nitrene insertion reactivities are governed similarly by structural variations".[10] The question "stepwise *vs.* concerted" is not answered by the data on reactivities, but more information is available in the literature. Paired intermediates of any appreciable lifetime should lead to racemization when the insertion is carried out at an asymmetric carbon, while a concerted process would have to be stereospecific. Smolinsky[24] has studied the cyclization of optically active 2-methylbutyl azidoformate to give optically active 4-ethyl-4-methyloxazolidin-2-one, and Yamada[25] has shown that this cyclization proceeds with "nearly 100%" retention of configuration—data which support the concerted mechanism. Two questions can be raised, however, as to the general validity of these results. Asymmetric induction may increase the degree of stereospecificity in the cyclization of an optically active nitrene. On the other hand, the 82% retention calculated from Yamada's data might be too low, because the crystalline comparison compound (thought to be 46% optically pure[25]) might really have been of higher optical purity, as fractionation of partially resolved compounds by simple crystallization is fairly common.

$$EtOOC{-}N + H{-}CRR'R'' \longrightarrow EtOOC{-}\dot{N}H \ \dot{C}RR'R'' \longrightarrow EtOOC{-}NH{-}CRR'R'' \quad (1)$$



$$EtOOC{-}N + H{-}CRR'R'' \longrightarrow EtOOC{-}N\overset{H}{\underset{CRR'R''}{\vdots}} \longrightarrow EtOOC{-}NH{-}CRR'R'' \quad (2)$$

In this paper we wish to report our results on the reaction of carbethoxynitrene with 3-methylhexane: the absence of a concentration dependence of selectivity, and the stereochemistry of the intermolecular insertion into the tertiary C–H bond of (+)-3-methylhexane. While this work was in progress, similar experiments were done on the system cyanonitrene–*cis*- and *trans*-1,2-dimethylcyclohexanes.[20]

Results and Discussion

1. Selectivity. Carbethoxynitrene can be made, in the singlet state, by thermolysis of ethyl azidoformate or by α elimination from N-(*p*-nitrobenzenesulfonoxy)-urethan, $p\text{-}O_2NC_6H_4SO_2ONHCOOEt$.[12,13] In the absence of a high concentration of a suitable substrate, much of the singlet nitrene has time to cross to the triplet state before a reactive collision of singlet and reactant occurs.[11–17] If both singlet and triplet undergo C–H insertion, one would expect them to do so with different selectivities, because the transition states (or intermediates) in going from a singlet *vs.* a triplet to one and the same product should be quite different, especially in an exothermic reaction. Thus, the apparent selectivity of C–H insertion should change when the substrate (3-methylhexane) concentration is changed. If, on the other hand, only one of the two nitrene states produces insertion product, one would expect the apparent selectivity to be independent of substrate concentration. The yield of insertion products, however, should depend on this concentration; when it is low, the yield should be low if the singlet is responsible for insertion product formation, and high if the triplet is the reactive state.

Carbethoxynitrene, generated under various conditions in the presence of 3-methylhexane, led to all seven of the possible C–H insertion products. None of them had been reported previously, but all were easily made by unambigous synthesis, to serve as comparison compounds, as shown in Scheme I. Together with the insertion products **3** through **9**, ethyl carbamate, $EtOOCNH_2$ (**22**), was formed when ethyl azidoformate was used as the nitrene precursor. When the nitrene was made by base-induced decomposition of $p\text{-}O_2NC_6H_4SO_2ONHCOOEt$, ethyl carbamate and diethyl hydrazodiformate, EtOOCNHNHCOOEt (**23**), were the by-products. The compounds were separated and determined by gas chromatography. The insertion product from the tertiary C–N bonds could readily be separated. The products from the secondary C–H functions were difficult to separate, and for the quantitative determinations they were collected and measured together. The products from the primary positions separated easily, but were formed in equal amounts, so that there is only one value for the reactivity of the primary C–H groups in the tables. All values are corrected for the number of C–H groups of each kind, the figures for secondary C–H groups being a composite, derived from the total yield of products **4**, **5**, and **6**.

The photolysis of ethyl azidoformate at 38°, with the light of a low-pressure mercury arc, has been shown to produce carbethoxynitrene, one-third of which is initially in the triplet state, the rest in the singlet state.[13] Under

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[19] H. Nozaki, S. Fujita, H. Takaya, and R. Noyori, *Tetrahedron*, **23**, 45 (1967).

[20] A. G. Anastassiou, *J. Amer. Chem. Soc.*, **88**, 2322 (1966); **89**, 3184 (1967).

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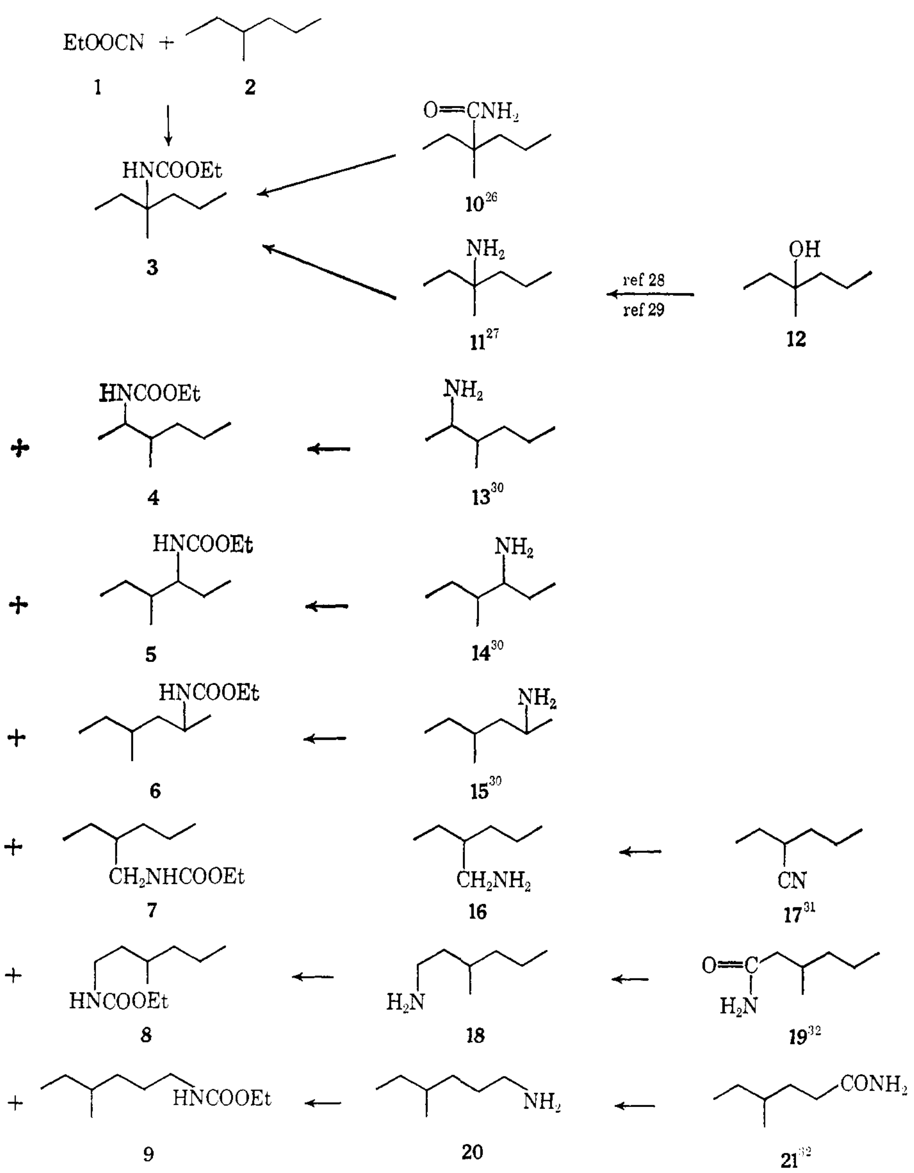
[24] G. Smolinsky and B. I. Feuer, *ibid.*, **86**, 3085 (1964); G. Smolinsky, *Trans. N. Y. Acad. Sci. Ser. II*, **30**, 511 (1968).

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

Scheme I



these conditions, ethyl azidoformate was photolyzed in nitrogen-saturated solutions of 3-methylhexane in dichloromethane. The results are shown in Table I. Thermolysis of ethyl azidoformate gives only the singlet nitrene as the initial product.[13] The thermolysis was done at 92° in pure 3-methylhexane, and in sealed tubes in dichloromethane solution, at 100°. All solutions were oxygen-free and saturated with nitrogen. The results are given in Table II. Generating the nitrene by α elimination produces it in the singlet state.[12] Because of the insolubility of the precursor, N-(p-nitrobenzene-

Table I. Photolytic Decomposition of Ethyl Azidoformate in Dichloromethane Solutions of 3-Methylhexane

Concn in CH$_2$Cl$_2$, mol %	Yields, %: Insertion	Yields, %: Ethyl carbamate	Rel reactivities of C–H bonds: Tertiary	Secondary	Primary	Tertiary	Secondary
1.2	16.3	10.8	17.4	6.2	1	2.8	1
5.4	18.8	12.4	15.2	5.0	1	3.0	1
8.6	19.2	11.7	17.3	6.4	1	2.7	1
15.0	22.4	8.7	13.0	4.9	1	2.7	1
26.8	25.8	10.9	13.9	5.2	1	2.7	1
100	28.1	11.8	16.0	5.3	1	3.0	1
	Av selectivities		15.5	5.5	1	2.8	1

Table II. Thermal Decomposition of Ethyl Azidoformate in Dichloromethane Solutions of 3-Methylhexane

Concn in CH$_2$Cl$_2$, mol %	Yields, %: Insertion	Yields, %: Ethyl carbamate	Rel reactivities of C–H bonds: Tertiary	Secondary	Primary	Tertiary	Secondary
1.2	17.1	20.6	17.6	6.0	1	2.9	1
8.6	21.4	23.4	17.4	6.1	1	2.8	1
26.8	23.2	20.0	18.4	6.6	1	2.7	1
100	25	20	17.0	6.0	1	2.8	1
	Av selectivities		17.6	6.2	1	2.8	1

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(26) F. S. Prout, *J. Org. Chem.*, **25**, 836 (1960). References to Scheme I refer to first reports of the compounds, not necessarily to the method of synthesis employed; see Experimental Section.

(27) M. Montagne, *Ann. Chim.*, [10] 13, 40 (1930); *Chem. Abstr.*, **24**, 2718 (1930).

(28) R. Graf, German Patent 870,856 (1940); French Patent 902,342 (1944); *Chem. Zentralbl.*, 6341 (1954); F. Möller in "Methoden der Organischen Chemie," Vol. XI/1, E. Müller, Ed., G. Thieme, Stuttgart, 1957, p 994.

(29) J. J. Ritter and P. P. Minieri, *J. Amer. Chem. Soc.*, **70**, 4045 (1948).

(30) E. Rohrman and H. A. Shonle, *ibid.*, **66**, 1516 (1944).

(31) M. Murayama, *Chem. Pharm. Bull.* (Tokyo), **6**, 186 (1958); *Chem. Abstr.*, **52**, 20162g (1958).

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Table III. Base-Induced Decomposition of N-(*p*-Nitrobenzenesulfonyloxy)urethan in Dichloromethane Solutions of 3-Methylhexane

Concn in CH_2Cl_2, mol %	Yields, %			Rel reactivities of C–H bonds				
	Insertion	Ethyl carbamate	Diethyl hydrazodiformate	Tertiary	Secondary	Primary	Tertiary	Secondary
1.2	3.0	14.0	26.8	14.5	5.8	1	2.5	1
5.4	8.5	11.6	19.4	14.3	5.5	1	2.6	1
8.6	8.8	11.4	18.3	13.2	4.8	1	2.8	1
15.0	10.7	12.8	14.8	15.6	6.3	1	2.5	1
26.8	16.3	11.7	12.5	13.5	4.7	1	2.8	1
			Av selectivities	14.2	5.4	1	2.6	1

Table IV. Reaction of Carbethoxynitrene, Generated by α Elimination, with 3-Methylhexane in the Presence of α-Methylstyrene

Concn in CH_2Cl_2, mol %		Yield of insertion products, %	Rel reactivities of C–H bonds		
3-Methylhexane	α-Methylstyrene		Tertiary	Secondary	Primary
5.4	0	8.5	14.3	5.5	1
5.4	1.2	8.2	14.5	5.7	1
5.4	5.4	4.6	13.8	4.9	1

Table V. Thermolysis of Ethyl Azidoformate in Dichloromethane and Dibromomethane Solutions of 3-Methylhexane

Solvent	Mol % of 3-methylhexane	Yields, %		Rel reactivities of C–H bonds				
		Insertion	Ethyl carbamate	Tertiary	Secondary	Primary	Tertiary	Secondary
CH_2Cl_2	8.6	21.4	23.4	17.4	6.1	1	2.8	1
CH_2Br_2	8.6	7.0	44.0	16.9	5.9	1	2.9	1

sulfonoxy)urethan, in hydrocarbons, substrate concentrations higher than 27 mol % were not studied. The precursor was decomposed by slow addition of 1.5 equiv of triethylamine, after deoxygenating the mixture by evacuation at Dry Ice temperature and then bubbling nitrogen through it. Table III gives the results. It has been shown[12,13] that triplet carbethoxynitrene can be trapped by α-methylstyrene. If the triplet participated in the insertion reaction (with a selectivity different from that of the singlet), addition of α-methylstyrene should alter the observed selectivities. Table IV shows this not to be the case. Conversely, conducting the reaction in dibromomethane, rather than in dichloromethane, should favor singlet–triplet crossing, and should alter the selectivities if the triplet is involved in the insertion reaction. Table V shows this not to be the case.

Inspection of Tables I–V shows (1) that there is no correlation between hydrocarbon concentration and selectivities, (2) that the yield of insertion products increases with increasing hydrocarbon concentration, and (3) that neither the reduction nor the enhancement of the triplet : singlet ratio in the nitrene population changes the selectivities. These data are consistent with attributing the C–H insertion reaction to the singlet nitrene alone.

The selectivities in the insertion of carbethoxynitrene into the C–H bonds of 3-methylhexane are somewhat lower than in the reaction with 2-methylbutane. This is probably due to the greater steric hindrance at the tertiary C–H bond of 3-methylhexane, corresponding to the replacement of a methyl by a propyl group. With 3-methylhexane, the selectivity is greatest in the azide thermolysis, conducted at a temperature 60° higher than that of the photolysis. This could be du to a smaller excess vibrational energy in the nitrene produced by the thermolysis, as compared to photolytically produced nitrene. We prefer to think, however, that the reason is greater accessibility of the sterically hindered positions in the 3-methylhexane, due to thermal motion of the molecule. Such an effect should make a greater difference for the tertiary than for the primary positions, enhancing reaction at the tertiary site relative to that at primary sites. The reduced selectivity in the α-elimination reaction can hardly be attributed to excess energy in the nitrene. A steric explanation is more likely. Hindrance by the departing *p*-nitrobenzenesulfonate ion reduces reaction at the tertiary site, relative to the primary and secondary ones. Ionic strength in the solution might also exert an influence.

2. **Stereochemistry.** The reaction of carbethoxynitrene and (+)-(*S*)-3-methylhexane was investigated to distinguish between a stepwise (eq 1) and a concerted (eq 2) mechanism for the insertion. In such an intermolecular reaction, asymmetric induction should be unimportant, and a stepwise mechanism should lead to at least some racemization. A concerted mechanism should proceed with retention or inversion of configuration—the latter a little hard to envision, and made unlikely by the ready insertion into the bridgehead positions of bicyclic hydrocarbons. Insertion by a singlet nitrene could, *a priori*, involve a concerted as well as a stepwise mechanism. The triplet nitrene would be expected—if it inserts at all—to do that in a stepwise fashion, both because of the difficulty of making a bond and inverting an electron spin simultaneously, and by analogy with the addition to double bonds.

Absolute configuration[33] and maximum rotation[34] of 3-methylhexane are known. For the product of insertion into the tertiary C–H bond, 3-carbethoxyamino-3-methylhexane, these data were determined by making a sample independently from the half-ester of α-methyl-α-ethylsuccinic acid of known[35] absolute configuration and 49% optical purity. This was done without crystallizing any intermediate, thus avoiding the possibility

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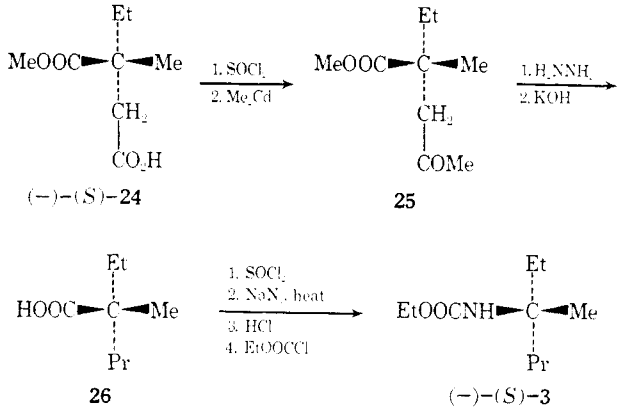
(33) K. Freudenberg and W. Hohmann, *Ann. Chem.*, **584**, 54 (1953).

(34) B. C. Easton and M. K. Hargreaves, *J. Chem. Soc.*, 1413 (1959).

(35) J. Porath, *Arkiv Kemi*, 3, 276 (1952).

of fractionation by preferred crystallization of either the racemate or of one of the pure enantiomers. The correlation is shown in Scheme II.

Scheme II

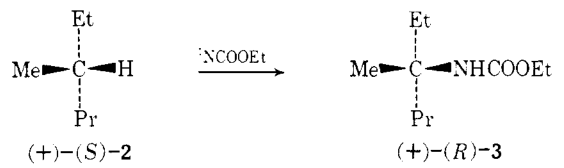


Carbethoxynitrene was generated, by azide photolysis, azide thermolysis, and α elimination, in the presence of (+)-(*S*)-3-methylhexane of 79% optical purity, in dichloromethane solutions. The reactions were run and worked up as before, the insertion product **3** was separated by vpc, and its rotation measured. Table VI shows the results. The insertion takes place with 100% retention of configuration under all reaction conditions—independent of 3-methylhexane concentration. The stereochemistry is summarized in Scheme III. The results again indicate a one-step, concerted, insertion by only the singlet carbethoxynitrene. The accuracy of our experiments (see Experimental Section) admits the possibility of a few per cent of the insertion product being formed by triplet nitrene. The result of our work can perhaps best be summarized by saying that carbethoxynitrene reacts with unactivated C–H bonds, such as in 3-methylhexane, in a stereospecific (presumably concerted) insertion reaction, in which singlet carbethoxynitrene is at least 20 times faster than the triplet.

Table VI. Reaction of Carbethoxynitrene with (+)-(*S*)-3-Methylhexane in Dichloromethane

Mode of nitrene generation	Concn of (+)-3-methylhexane, mol %	Rotation, $[\alpha]^{25}\text{D}$, deg, of **3**	Retention of configuration, %
α elimination	1.2	+1.32	98 ± 7
Azide thermolysis	100	+1.33	99 ± 5
Azide photolysis	1.2	+1.38	102 ± 3
	26.8	+1.35	100 ± 6
	100	+1.31	97 ± 5
			Av 99.2

Scheme III



(+)-(*S*)-**2** (+)-(*R*)-**3**

Experimental Section

Synthesis of Authentic N-Carbethoxyamino-3-methylhexanes. 3-N-Carbethoxyamino-3-methylhexane (3). To a solution of 0.04 mol of sodium ethoxide in 50 ml of absolute ethanol was added 2.9 g (0.02 mol) of 3-methylhexyl-3-carboxamide[26] and then 1.1 ml (0.02 mol) of bromine, over a period of 20 min. After 30 min at reflux temperature, the mixture was cooled and acidified with acetic acid, the ethanol removed *in vacuo*, and the residue distributed between water and petroleum ether (bp 30–60°). The aqueous layer was extracted several times with petroleum ether. From the organic phases, 2.4 g of **3** (64% yield), bp 70–73° (1 mm), was isolated; ir NH 3456 (sharp), 3375 (broad); C=O 1722 cm^{-1} in CCl_4; nmr NH δ 4.6 (broad, 0.8), -OCH_2CH_3 3.95 (q, 2.0), other C–H 0.6–1.8 (m, 18.2). *Anal.* Calcd for $C_{10}H_{21}NO_2$: C, 64.17; H, 11.32; N, 7.49. Found: C, 64.26; H, 11.19; N, 7.58.

To make larger quantities of **3**, it proved more convenient to make the parent amine by the Graf–Ritter reaction[28,29] and acylate it.

3-Methyl-3-aminohexane. A mixture of 250 g of sulfuric acid and 125 ml of acetic acid was added over a period of 3 hr to a mixture of 125 ml of acetic acid, 55 g (1 mol) of 90% sodium cyanide, and 116 g (1 mol) of 3-methyl-3-hexanol, bp 138–140°. The mixture was stirred and maintained at 40° for 12 hr, then poured onto ice, neutralized, heated to reflux for 3 hr, and steam distilled. The distillate was extracted three times with ether. The dried extracts gave 53.6 g (47% yield) of 3-methyl-3-aminohexane, bp 130–132° (lit.[27] 131–132°). A solution of 2.8 g (0.026 mol) of ethyl chloroformate in 25 ml of ether was slowly added to a solution of 3 g (0.026 mol) of the amine in 25 ml of ether. After half of the chloroformate had been added, a solution of 1.04 g of sodium hydroxide in 20 ml of water was added in 5-ml portions. After stirring for 2 hr, the ether layer yielded 90% of the theoretical amount of **3**, bp 71–74° (1 mm).

2-N-Carbethoxyamino-3-methylhexane (4) was prepared from the corresponding amine[30] and ethyl chloroformate, just as was **3**; ir (CCl_4) NH 3457 (sharp), 3360 (broad); C=O 1721 cm^{-1}; nmr NH δ 5.5 (broad, 0.8), -OCH_2CH_3 4.05 (q, 2.0), NC*H* 3.4–3.9 (m, 1.1), other aliphatic protons 0.7–1.6 (17.3).

Anal. Calcd for $C_{10}H_{21}NO_2$: C, 64.17; H, 11.32; N, 7.49. Found: C, 64.08; H, 11.32; N, 7.46.

4-N-Carbethoxyamino-3-methylhexane (5) was prepared from the corresponding amine,[30] ethyl chloroformate, and 1 equiv of triethylamine, in ether solution, in 85% yield, bp 82–83° (4 mm); ir (CCl_4) NH 3450 (sharp), 3355 (broad); C=O 1720 cm^{-1}; nmr NH δ 5.0 (broad, 0.8), OCH_2CH_3 3.94 (q, 2.0), NC*H* 3.2–3.6 (m, 1.0), other aliphatic protons 0.7–1.6 (16.9).

Anal. Calcd for $C_{10}H_{21}NO_2$: C, 64.17; H, 11.32; N, 7.49. Found: C, 64.17; H, 11.17; N, 7.62.

5-N-Carbethoxyamino-3-methylhexane (6) was prepared from the corresponding amine[30] just as **5**, in 92% yield, bp 85–88° (3 mm); ir (CCl_4) NH 3449 (sharp), 3350 (broad); C=O 1718 cm^{-1}; nmr NH δ 5.1 (broad, 0.9), OCH_2CH_3 3.96 (q), NC*H* 3.4–3.8 (m, 3.0 together with the q centered at 3.96), other aliphatic protons 0.7–1.5 (17.0). *Anal.* Calcd for $C_{10}H_{21}NO_2$: C, 64.17; H, 11.32; N, 7.49. Found: C, 63.92; H, 11.13; N, 7.64.

3-Cyano-3-hexanol was prepared from 3-hexanone by the method of Frank,[36] in 60% yield, bp 62–70° (1 mm). Its ir spectrum showed no carbonyl band. It was dehydrated with thionyl chloride[37] to give a mixture of **3-cyanohex-2-ene** and **3-cyanohex-3-ene** in 55% yield, bp 72° (25 mm); ir 3020 and 2217 cm^{-1}. Hydrogenation of 2.7 g of the mixture in 25 ml of ethanol with 5% Pd–C catalyst and 50 psi for 10 hr gave 2.2 g (80% yield) of **3-cyanohexane,** bp 68–71° (30 mm) (lit.[31] bp 164–165° (760 mm)); ir 2235 cm^{-1}. From this, **3-aminomethylhexane** was made after Freifelder,[38] by hydrogenation in ammoniacal ethanol with Rh–C catalyst at 50 psi for 12 hr. After removal of the ammonia, the crude ethanol solution was treated with ethyl chloroformate and triethylamine, to give **3-(carbethoxyaminomethyl)hexane (7),** isolated by vpc on a 10 ft 20% QF-1-6500 fluorosilicone on Chromosorb W column; ir NH 3455 (sharp), 3355 (broad); C=O 1720 cm^{-1}; nmr NH δ 5.2 (broad, 0.8), OCH_2CH_3 3.93 (q, 2.0), NCH_2– 2.96 (split t, 2.0), other protons 0.6–1.5 (16.0). *Anal.* Calcd for $C_{10}H_{21}NO_2$: C, 64.17; H, 11.32; N, 7.49. Found: C, 64.06; H, 11.21; N, 7.56.

1-N-Carbethoxyamino-3-methylhexane (8) was made by reducing 2.0 g (0.016 mol) of 3-methylhexanoylamide[32] with 2 g of $LiAlH_4$

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(36) R. L. Frank, R. E. Berry, and O. L. Shotwell, *J. Amer. Chem. Soc.*, **71**, 3889 (1949).

(37) A. H. Cook and R. P. Linstead, *J. Chem. Soc.*, 956 (1934).

(38) M. Freifelder, *J. Amer. Chem. Soc.*, **82**, 2386 (1960).

in 35 ml of ether, at reflux for 10 hr. After destroying the excess $LiAlH_4$ with water, the dried ether layer was treated with ethyl chloroformate and triethylamine, as above, and the product **8** was isolated by vpc just as was **7**; ir (CCl_4) NH 3460 (sharp), 3359 (broad); C=O 1720 cm^{-1}; nmr NH δ 4.8 (broad, 0.9), OCH_2CH_3 3.96 (q, 2.0), NCH_2– 3.06 (m, 2.0), other protons 0.7–1.5 (15.9). *Anal.* Calcd for $C_{10}H_{21}NO_2$: C, 64.17; H, 11.32; N, 7.49. Found: C, 64.10; H, 11.34; N, 7.55.

1-N-Carbethoxyamino-4-methylhexane (9) was made from 4-methylhexanoylamide, just like **8**; ir NH 3460 (sharp), 3360 (broad); C=O 1718 cm^{-1}; nmr NH δ 5.3 (broad, 0.8), OCH_2CH_3 4.05 (q, 2.0), NCH_2– 3.1 (m, 2.0), other protons 0.7–1.4 (16.0). *Anal.* Calcd for $C_{10}H_{21}NO_2$: C, 64.17; H, 11.32; N, 7.49. Found: C, 64.09; H, 11.30; N, 7.49.

Photolysis of Ethyl Azidoformate in 3-Methylhexane. A solution of 1.73 g (0.015 mol) of ethyl azidoformate in 20 ml of 3-methylhexane was degassed by evacuation at −80°, then saturated with nitrogen. The solution was irradiated, in a silica tube, with the light of a low-pressure mercury arc at 38° until about 80% of the theoretical amount of nitrogen had been evolved (20 hr). Most of the excess solvent was removed *in vacuo* and the residue analyzed on a 15 ft × 0.25 in. cyanosilicone XF 1150 (20%, on Chromosorb W) column at 121° ("column B"). The first two peaks were identified by their retention times and ir and nmr spectra, as ethyl carbamate (**22**) and **3**. The third, broad, peak consisted of a mixture of the insertion products into secondary CH bonds, **4**, **5**, and **6**, as shown by retention times and ir and nmr spectra. This mixture could not be separated on four other columns (QF-1-6500, Carbowax 20M, neopentylglycol sebacate, Ucon Polar 50-HB-2000). The fourth peak consisted of a mixture of the insertion products into the primary C–H bonds, **7**, **8**, and **9**. It was separated into three peaks of equal areas on a 10 ft × 0.25 in. 20% Fluorosilicone QF-1-6500 on Chromosorb W column, at 121° ("column A"). The detector response was calibrated by injecting standard solutions, the peak areas were measured planimetrically, and the error was about ±2%. When *dichloromethane solutions* were photolyzed, a threefold excess of 3-methylhexane over ethyl azidoformate was maintained. The results are found in Table I. They are averages of three experiments for each reaction condition. The smallest error (±5%) occurred in the ratio tertiary:secondary insertion product, because these products were formed in about the same quantities (factor of 2). The error for the ratio secondary:primary insertion products is about ±15%, that for the yield of insertion products is about ±5%. A control irradiation of the insertion products, in 3-methylhexane–dichloromethane solution for 20 hr, and vpc analysis before and after, showed no change in amounts or ratios of the products.

Carbethoxynitrene by α Elimination in 3-Methylhexane–Dichloromethane Solutions. In a 250-ml flask was placed 2.9 g (0.01 mol) of N-(*p*-nitrobenzenesulfonoxy)urethan.[7] Approximately 130 g of 3-methylhexane–dichloromethane mixture (containing 27 mol % of hydrocarbon in the example used here) was added with rapid stirring, in a nitrogen atmosphere at 40°. A solution of 1.5 g (0.015 mol) of triethylamine in 20 ml of the 3-methylhexane–dichloromethane mixture was then added during 10 min. After 4 hr at 40°, the volume was reduced *in vacuo* to about 15 ml, and 50 ml of ether was slowly added. Triethylammonium *p*-nitrobenzenesulfonate crystallized and was washed several times with ether. Combination of the filtrates precipitated some more salt (total yield 95%, mp 122–123°). The filtrates were combined, concentrated *in vacuo*, and analyzed by vpc, like the photolysis reaction mixtures. Diethyl hydrazodiformate, the additional product, was analyzed on column A (see above) at 180°, and identified by its ir and nmr spectra. The results of the runs are found in Table III. Runs in the presence of α-methylstyrene (Table IV) were done in the same way and analyzed on column A.

Thermolysis of Ethyl Azidoformate. a. In 3-Methylhexane. A solution of 3.45 g of ethyl azidoformate in 30 ml of 3-methylhexane was heated to reflux for 27 hr in a flask, equipped with reflux condenser, and connected to a nitrometer. A 85% yield of nitrogen was evolved, the solvent was removed *in vacuo*, and the residue analyzed as before.

b. In 3-Methylhexane–Dichloromethane. Solutions of 0.115 g (0.001 mol) of ethyl azidoformate and 0.3 g of 3-methylhexane, in a suitable volume of dichloromethane, were placed in Pyrex tubes, nitrogen was bubbled through them, and the sealed tubes were heated to 100° in a water bath for 24 hr. Analyses were performed as above, and results are given in Table II. The runs in **dibromomethane** were done the same way, and the results are in Table V.

(+)-(*S*)-3-Methylhexane was prepared from citronellal,[39] $\alpha^{24}\mathrm{D}$ +9.05° (homogeneous), by Wolff–Kishner reduction, ozonization of the **2,6-dimethyloctene-2** to give **(+)-4-methylhexanal,** and Wolff–Kishner reduction of the latter. Some **(+)-4-methylhexanoic acid** was formed in the ozonizations, $\alpha^{24}\mathrm{D}$ +9.24° (homogeneous), bp 83° (1 mm) (lit.[32] bp 217–218°); nmr COO*H* δ 12.15 (s, 1.0), CH_2COOH 2.31 (t, 2.0), other protons 0.7–1.8 (11.2). The acid was reduced with $LiAlH_4$ in ether, to give a 77% yield of **(+)-4-methylhexanol,** $[\alpha]^{28}\mathrm{D}$ +7.08° (*c* 13.7, EtOH), bp 73–75° (10 mm) (lit.[32] 173°). The alcohol was converted to the *p*-toluenesulfonate by the method of Tipson[40] in 58% yield, $[\alpha]^{28}\mathrm{D}$ +4.56° (*c* 26.5, EtOH); ir 3074, 3050, 3040, 1915, 1597, 1457, 1360, 1180, and 1170 cm^{-1}; nmr aromatic CH δ 7.30 and 7.73 (AB q, J = 8 Hz, 4.0), SO_2OCH_2– 3.94 (t, 2.0), $ArCH_3$ 2.43 (s, 3.1), other protons 0.5–1.8 (13.3). From the tosylate, **(+)-3-methylhexane** was prepared by $LiAlH_4$ reduction, similar to Strating's procedure,[41] in 50% yield after distillation through a 18-in. glass-helix-packed column. The ir and nmr spectra, as well as the rotation, of the (+)-3-methylhexane obtained by this procedure were identical with those of the product made by Freudenberg's method:[39] $\alpha^{28}\mathrm{D}$ 5.04° (homogeneous), d^{28}_{4} 0.676, $[\alpha]^{28}\mathrm{D}$ +7.42° (homogeneous), $[\alpha]^{28}\mathrm{D}$ +7.30° (*c* 10.2, EtOH), or 79.0% optically pure.

Carbethoxynitrene reactions with (+)-3-methylhexane were carried out as before. The 3-N-carbethoxyamino-3-methylhexane was separated using column A. Injection of the material onto three other columns showed it to be better than 99.5% pure. Rotations were determined neat, or on mixtures of known concentration with authentic, racemic **3**. From the runs in dichloromethane, (+)-3-methylhexane was recovered and purified by vpc (at 25° on a 20% silicone oil GE-SF-96 on Firebrick column). In all cases, its rotation had not changed. Compound **3** in a typical run (azide thermolysis) gave a read rotation of $\alpha^{25}\mathrm{D}$ 0.337° (homogeneous, mixture of 56.2% of reaction product plus 43.8% authentic racemic material, *l* 0.5 dm), $[\alpha]^{25}\mathrm{D}$ +1.33°. The Stanley photoelectric polarimeter employed has an accuracy of ±0.005°. The results are found in Table VI.

Racemic 3-methyl-3-ethyl-3-carbomethoxypropionic acid was prepared after Stallberg–Stenhagen:[42] mp 33–34° (lit.[42] 35.8–36.3°); nmr COO*H* δ 11.30 (s, 1.0), $COOCH_3$ 3.65 (s, 3.0), CH_2-COOH 3.38, 3.88 (AB q, J = 16 Hz, 2.0), other protons 0.85 (t, 3.1), 1.25 (s, 3.1), 1.60 (split q, 2.1). **Resolution** of 180 g of the acid with 380 g of quinine in 30% aqueous acetone gave, after four recrystallizations, a head fraction of 70.6 g of the quinine salt, mp 78°, $[\alpha]^{23}\mathrm{D}$ −80.8° (*c* 8.04, acetone), from which was prepared 23.1 g of acid, bp 110° (3 mm), $\alpha^{24}\mathrm{D}$ −6.152° (homogeneous), corresponding to 49.0% optical purity.[42]

4-Carbomethoxy-4-methylhexan-2-one (25) was prepared from the (−)-acid half-ester (**24**) by Cason's procedure.[43] **24** was converted to its chloride, bp 65–66° (0.5 mm), by thionyl chloride in 96% yield. The chloride (20 g, 0.104 mol) was treated with methylcadmium reagent in benzene,[43] made from 0.2 mol of magnesium, methyl bromide, and cadmium chloride. Work-up[43] gave 7.8 g of a colorless oil, bp 90–92° (7 mm). Gas chromatography (10% fluorosilicone QF-1-6500 on Chromosorb ABS at 132°) separated the oil into two fractions, **25** and its isomer **27**, in the ratio of 1:2. On spectral evidence, **27** was assigned the structure of **3-methyl-3-carbomethoxymethylpentan-2-one.** Formation of this isomer of the desired **25** is probably due to interchange of the functions in the ester acid chloride.[44] Spectra of **27**: ir C=O at 1735 and 1705 cm^{-1} in CCl_4; nmr $COOCH_3$ δ 3.53 (s, 3.0), CH_2COOMe 2.69 and 2.25 (AB q, J = 16 Hz, 2.1), $-COCH_3$ 2.07 (s, 3.0), other protons 1.52 (split q, 2.0), 1.18 (s, 3.0), 0.75 (t, 3.0). The desired compound **25** showed in the ir C=O at 1735 and 1717 cm^{-1}; nmr $COOCH_3$ δ 3.59 (s, 3.0), CH_2CO 2.69 and 2.18 (AB q, J = 16 Hz, 2.0), $COCH_3$ 2.05 (s, 3.0), other protons 0.75 (t, 3.0), 1.18 (s, 3.0), 1.52 (split q, 2.0). *Anal.* Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.58; H, 9.56.

Separation of the isomers **25** and **27** was attempted by partial hydrolysis and physical means. While possible by vpc, it was cumbersome, and the mixture was used in the next step. **Wolff–Kishner reduction of 25 and 27** used 9 g of KOH in 45 ml of di-

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(42) S. Stallberg-Stenhagen, *Arkiv Kemi*, **3,** 276 (1952).

(43) J. Cason, *J. Amer. Chem. Soc.*, **68,** 2078 (1946).

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ethylene glycol, 6.9 g of the mixture of **25** and **27**, and 6.0 g of hydrazine hydrate, at 210° for 3 hr. The mixture was diluted with water, neutralized, and extracted three times with ether to give 1.7 g (about 30% yield) of an oil, bp 110–112° (2 mm). Gas chromatography on column A (see above) separated, with difficulty, **(−)-2-methyl-2-ethylpentanoic acid (26)** from its isomer **28, 3-methyl-3-ethylpentanoic acid.** The ir spectrum of **26** was identical with that of authentic material, made after Prout.[26] The mixture of **26** and **28** was used in the next step, in which 1.4 g of the mixture (0.01 mol) was treated with 3 ml of thionyl chloride at room temperature for 18 hr. After heating to reflux for 2 hr, the thionyl chloride was removed *in vacuo*, 0.5 g of activated sodium azide and 3 ml of xylene were added, the solution was heated to 80°, and another 0.5 g of sodium azide was added. After 5 hr, the temperature was raised to 180°. The filtrate was stirred for 12 hr with 4 ml of concentrated hydrochloric acid at about 80° and cooled, the aqueous layer separated, and the organic solution extracted once with hydrochloric acid. From the aqueous layers, the amine was liberated by base, extracted into ether, and acylated with ethyl chloroformate and sodium hydroxide. Analysis on column A readily separated **3** from its (optically inactive) isomer **29, 3-carbomethoxyaminomethyl-3-methylpentane.** Compound **3** was recognized by its retention time, spectra, and optical activity; compound **29** had the following spectra: ir NH 3450 (sharp), 3350 (broad); C=O 1720 cm^{-1}; nmr OCH_2CH_3 δ 4.03 (q, 2.0), $-CH_2$NHCOOEt 2.97 (d, 2.0), NH about 5 (very broad), other protons 0.5–1.5 (16.2). The rotation of **3** was found to be $[\alpha]^{25}\mathrm{D}$ −0.837° (homogeneous). It being 49% optically pure, the maximum rotation should be $[\alpha]^{25}\mathrm{D}$ −1.708°, and **3** obtained with full retention from 79% optically active (+)-(*S*)-3-methylhexane should have a $[\alpha]^{25}\mathrm{D}$ of +1.35° (compare Table VI).

Acknowledgments. We are greatly indebted to the National Science Foundation for support of this work, and to the National Institutes of Health for a predoctoral fellowship to J. M. S.

Stereochemical Studies. VIII. Asymmetric Selection *via* Elimination. Assignment of Nitrogen Chirality by Pyrolytic Elimination in Optically Active Amine Oxides[1]

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Abstract: The four possible optically active stereoisomeric N-methyl-N-neopentyl-4-methylcyclohexylamine oxides were individually prepared. The stereomeric secondary amines, *cis*- and *trans*-N-neopentyl-4-methylcyclohexylamines (**3** and **4**), obtained by reductive amination procedures, were separated and converted to the corresponding tertiary amines (**8** and **9**) by N-methylation. The *cis*- and *trans*-amine oxides (**10** and **11**) were obtained by oxidation of **8** and **9** with peracetic acid. A consistent correlation of nmr signal envelope shapes at each synthesis stage provided the basis for assignment of stereochemistry to these compounds. Resolution of the amine oxides gave the four optically active stereoisomers in undetermined enantiomeric purity. Each optically active amine oxide underwent asymmetrically selective pyrolytic elimination to optically active 4-methylcyclohexene of known configuration. Thus, the (−)-*cis*- and (+)-*trans*-amine oxides each gave (−)-(*S*) olefin, while the (+)-(*R*) olefin was the predominant enantiomer obtained from pyrolysis of the (+)-*cis*- and (−)-*trans*-amine oxides. These results, plus the reasonable assumption that neopentyl is bulkier than methyl, allowed for definition of nitrogen chirality in each of the amine oxides by a transition-state argument.

Although asymmetric selectivity[3] was observed during pyrolyses of optically active esters,[4] reliable interpretation regarding configurational correlations could not be made because of the low optical yields and because of a general lack of understanding of the factors governing conformational relationships in the carbalkoxy group. Unlike this situation, interpretation of the very high levels of asymmetric selectivity observed during pyrolyses of optically active sulfoxides[5] was straightforward because of the absence of these conformational questions. It was, therefore, of considerable interest to investigate pyrolyses of suitable optically active amine oxides, for, based upon the generally accepted view of the transition state,[6] here too no conformational questions would be involved. An additional point of interest lay in the realization that, with a reliable model of the transition state for the *syn* pyrolytic amine oxide process, and with a knowledge of the configurational details of other moieties present, the chirality at nitrogen could be uniquely defined. The system chosen for this undertaking was N-methyl-N-neopentyl-4-methylcyclohexylamine oxide, and we report herein on the synthesis of each of the four possible configurational isomers, stereochemical assignments (4-methylcyclohexyl group), individual pyrolyses, and transition-state analyses leading to specification of nitrogen chiralities.[7]

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(1) (a) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this research. (b) Presented in part at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968; see, Abstracts, No. P31.

(2) Taken in part from the dissertation submitted by F-L. L. to the Graduate School, University of South Carolina, 1966, in partial fulfillment of the requirements for the Ph.D. degree.

(3) Any reaction or process that gives, either directly or indirectly, enantiomers in unequal amounts.

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(7) During the early stages of the present investigation, G. Berti and G. Bellucci [*Tetrahedron Letters*, 3853 (1964)] reported that an optically active N-methyl-N-phenyl-4-methylcyclohexylamine oxide gave optically active 4-methylcyclohexene upon pyrolysis. No attempt was made by these authors to analyze their results under the concept presented herein.