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REACTIONS OF ETHYL AZODICARBOXYLATE WITH AMINES

BY

FRANK ROSS FARR

A thesis submitted
in partial fulfillment of the requirements for the
degree Master of Science, Major in
Chemistry, South Dakota State
University

1968

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REACTIONS OF ETHYL AZODICARBOXYLATE WITH AMINES

The following is a summary of the work done during the course of the investigation. The first part of the work was devoted to the study of the reaction of ethyl azodicarboxylate with primary amines. It was found that the reaction proceeds in a stepwise manner, the first step being the formation of a diazo intermediate. The second step is the decomposition of this intermediate to give the final product. The rate of reaction was found to be first order with respect to the concentration of ethyl azodicarboxylate and zero order with respect to the concentration of the amine.

The second part of the work was devoted to the study of the reaction of ethyl azodicarboxylate with secondary amines. It was found that the reaction proceeds in a similar manner to that observed with primary amines. The rate of reaction was found to be first order with respect to the concentration of ethyl azodicarboxylate and zero order with respect to the concentration of the amine. The results of the investigation are discussed in the following chapters.

This thesis is approved as a creditable and independent investigation by a candidate for the degree, Master of Science, and is acceptable as meeting the thesis requirements for this degree, but without implying that the conclusions reached by the candidate are necessarily the conclusions of the major department.

Thesis Adviser

Date

Head, Chemistry Department

Date

ACKNOWLEDGMENTS

The author wishes to express his appreciation to Dr. William S. Wadsworth, Jr. for his suggestions and guidance, and the Chemistry Department for supplying the materials and equipment which made this work possible.

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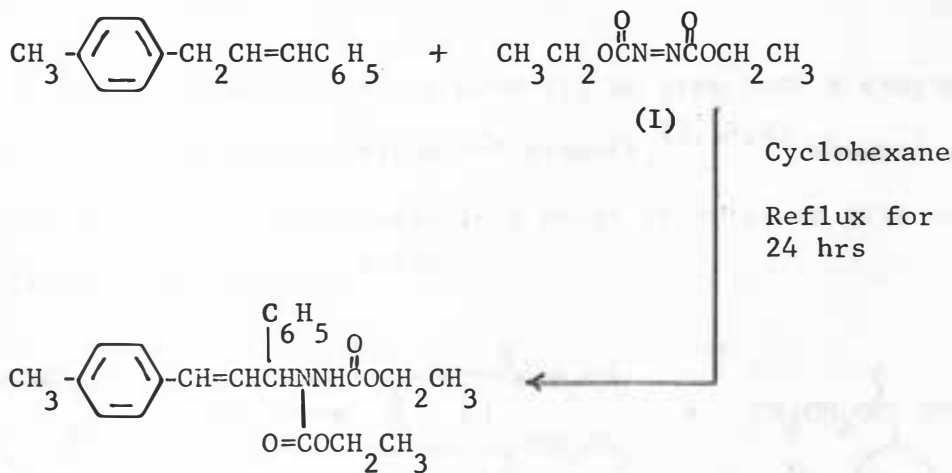
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INTRODUCTION

The purpose of this investigation was to clarify some literature reports dealing with the reactions of ethyl azodicarboxylate with primary and secondary aliphatic amines. The chemistry of azodicarboxamides was also investigated.

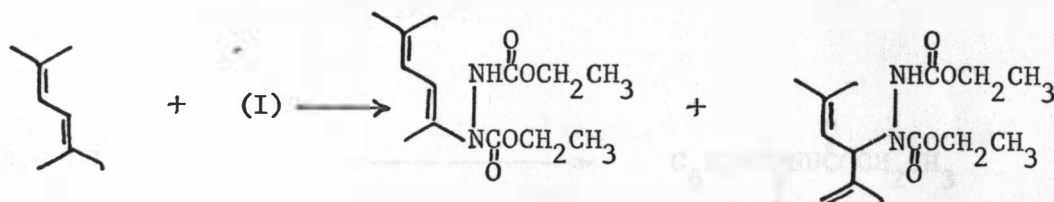
Much of the work with ethyl azodicarboxylate (I) was done prior to 1930. It was found that (I) reacts with olefins in two different ways depending upon the conditions and the type of olefin. Monoolefins react with (I) to give an addition product.^{1,2,3,4,5} A multicenter process with cyclic electron shifts was proposed for this reaction.³



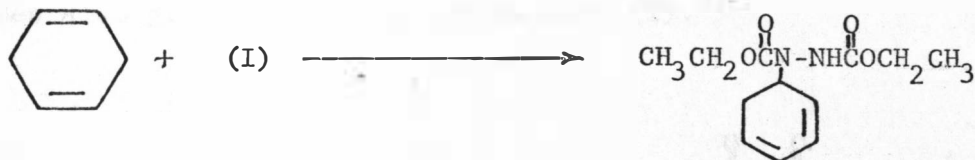
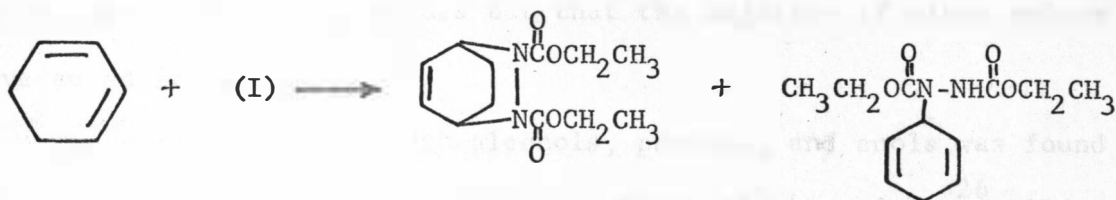
It was found that (I) is a very good dienophile and reacts readily with conjugated dienes to give a Diels-Alder type reaction.^{6,7,8,9,10,11}

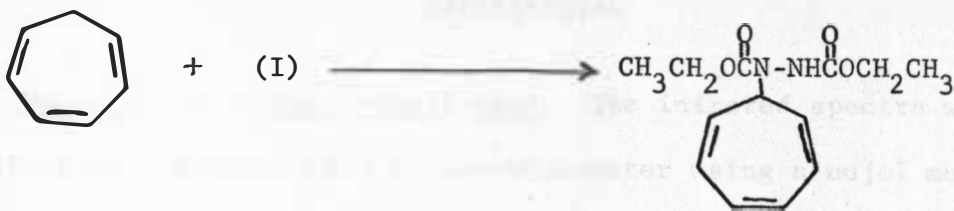


Conjugated dienes which are sterically hindered do not undergo a Diels-Alder type reaction but form simple addition products.¹²

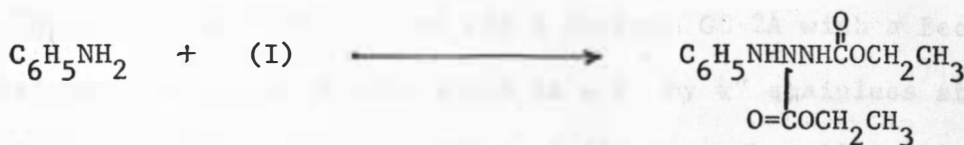


1,3-cyclohexadiene reacts with (I) to give both a simple addition product and a Diels-Alder product,^{13,14,15} whereas 1,4-cyclohexadiene and cycloheptatriene react with (I) to give only simple addition products.^{13,16}





It has been reported that aromatic amines react with (I) to give only addition products^{17,18} but that primary and secondary amines react with (I) to give both addition products^{19,20} and substituted amides.^{19,21,22,23,24,25}



Diels proposed that strongly basic aliphatic amines react with (I) to give substituted amides but that the majority of other amines give an addition product.²³

The reaction of (I) with alcohols, phenols, and enols was found to give addition products analogous to those of the amines.²⁶ Aldehydes also give addition reactions with (I).²⁷



EXPERIMENTAL

Description of Instruments used. The infrared spectra were obtained on a Beckman IR-5 spectrophotometer using a nujol mull or neat sample on NaCl plates.

The nuclear magnetic resonance (nmr) spectra were obtained on a 60 MHz Varian A-60A spectrophotometer, using tetramethyl silane (TMS) as an internal standard.

The visible and ultraviolet spectra were obtained on a Beckman DK-2A spectrophotometer using quartz cells 1 cm thick.

The gas chromatograph used was a Beckman GC-2A with a Beckman general purpose column #74346 which is a 6' by $\frac{1}{4}$ " stainless steel column packed with a ratio of 100 g of 42--60 mesh C-22 Johns-Manville firebrick to 30 g of Dow Corning silicone fluid, type 550.

Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee, and by Miss Carol Myers at South Dakota State University, Chemistry Department, Brookings, South Dakota.

Melting points were taken on a Thomas Hoover capillary melting point apparatus and are uncorrected. Temperatures are in degrees centigrade unless otherwise specified.

Molecular weights were determined on a Mechrolab 301-A vapor pressure osmometer, using the solvents indicated.

Preparation of Ethyl Hydrazodicarboxylate.²⁸ A mixture of hydrazine, 32.0 g (1.00 mole), and ethanol, 500 ml, was cooled to 10° and ethyl chloroformate, 108.5 g (1.00 mole), was added drop-

wise with stirring at such a rate as to maintain a temperature of 15--20°.

Following this addition another 108.5 g of ethyl chloroformate and a solution of sodium carbonate, 106 g (1.00 mole) in 500 ml of water, were added simultaneously keeping the temperature below 20°. The addition of the ethyl chloroformate was completed slightly ahead of the sodium carbonate solution. Water, 150 ml, was added and the solution stirred for 30 minutes to allow the reaction to be completed.

The mixture was filtered and the precipitate washed with 500 ml of water and dried in a vacuum oven at 60° (15 mm). The yield of crude ethyl hydrazodicarboxylate was 170 g (96.5%) which melted at 130--132° (lit.²⁸ mp 131--133°). It is sufficiently pure without recrystallization for the preparation of ethyl azodicarboxylate.

An unsuccessful attempt was made to prepare ethyl hydrazodicarboxylate from diethyl carbonate and hydrazine. A polymeric substance which was insoluble in ethanol was obtained.

Preparation of Ethyl Azodicarboxylate.²⁹ A mixture of crude ethyl hydrazodicarboxylate, 176 g (1.00 mole), and 70% nitric acid, 110 ml, was cooled to 5°. (If this solution was not cold enough a very violent reaction took place when the fuming nitric acid was added).

Ice cold 90--95% nitric acid (yellow fuming), 195 ml, was added to the above solution. The solution was stirred for two hours at 0--5°. The reaction was quenched by pouring it carefully into crushed

ice, 900 g, and dichloromethane, 90 ml, in a 2-l Erlenmeyer flask. The mixture was stirred until all the ice melted and the layers were separated, using a separatory funnel.

The aqueous layer was washed with three 90 ml portions of dichloromethane and the combined organic layers were washed with two 90 ml portions of ice water. The organic layer was stirred for ten minutes with 10% sodium bicarbonate solution, 500 ml, and the layers separated. The final wash was with ice water, 90 ml. The dichloromethane solution was dried quickly with a small amount of anhydrous magnesium sulfate, filtered, and dried overnight with a fresh portion of anhydrous magnesium sulfate.

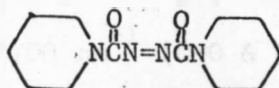
The dichloromethane was evaporated under reduced pressure, and the residue was vacuum distilled using an oil bath and raising the temperature of the bath slowly from 75° to 130°. This distillation should be well shielded. The yield of ethyl azodicarboxylate (I) was 105 g (60%); bp 73--75° (1 mm) [lit.²⁹ bp 93--95° (5 mm)].

Reaction of Ethyl Azodicarboxylate with Piperidine.²¹ The reaction was carried out under varying conditions. Because the procedure for each reaction was quite similar to that of the other reactions, a typical example of the procedure is given, followed by a table showing how each reaction varies, TABLE I.

A mixture of ethyl azodicarboxylate (I), 8 g (0.046 mole), and petroleum ether, 5 ml, was placed in a 200-ml three-necked flask fitted with a condenser, thermometer, dropping funnel, and a magnetic stirrer. The reaction flask was cooled in an ice bath to

0--5°. Piperidine, 8 g (0.094 mole), was added dropwise with stirring so as to maintain a temperature of 0--5°. The mixture was allowed to stand for several hours, filtered, and the precipitate washed with 10 ml of petroleum ether. The precipitate was recrystallized from methanol and found to be di-N,N-pentamethylene azodicarboxamide, 3.4 g (27.6%); mp 134--135° (lit.²⁵ mp 130--132°); ir (nujol) 1700 cm⁻¹ (C=O & N=N); nmr (CCl₄) δ3.4 & 1.6 (typical piperidine absorption with no extraneous peaks).

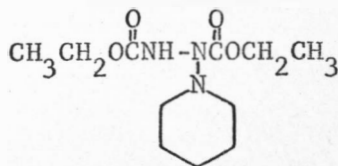
Structure:



Analysis: Calculated for C₁₂H₂₀N₄O₂: C, 57.12; H, 7.99; N, 22.21. Found: C, 56.88; H, 7.88; N, 22.15.

The filtrate was stirred vigorously for 30 minutes and again filtered. The precipitate this time was recrystallized from diethyl ether and found to be 1,2-dicarboethoxy-N-piperidylhydrazine, 3.8 g (32%); mp 80--82°; ir (nujol) 3130 cm⁻¹ (N-H), 1750 cm⁻¹ & 1700 cm⁻¹ (C=O), 1500 cm⁻¹ (CONH); nmr (CCl₄) δ7.6 (s, 1, NH), 4.1 (m, 4, J = 7 Hz, OCH₂CH₃), 2.7 & 1.6 (m, 10, C₅H₁₀N-), 1.2 (t, 6, J = 7 Hz, CH₂CH₃).

Structure:

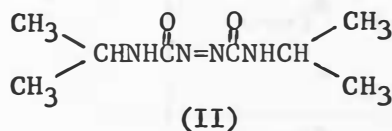


Analysis: Calculated for $C_{11}H_{21}N_3O_4$: C, 50.95; H, 8.16; N, 16.21. Found: C, 50.95; H, 8.19; N, 16.86.

Reaction of Ethyl Azodicarboxylate with Isopropyl Amine. A mixture of ethyl azodicarboxylate (I), 8.5 g (0.05 mole), and diethyl ether (or benzene), 25 ml, was cooled to $0--5^{\circ}$, and isopropyl amine, 5.9 g (0.10 mole), was added dropwise keeping the temperature below 5° .

The mixture was allowed to stand for 30 minutes, filtered, and the precipitate recrystallized from benzene to yield N,N'-diisopropyl azodicarboxamide (II), 5.00 g (50.0%); mp $168--169^{\circ}$; ir (nujol) 3150 cm^{-1} (NH), 1700 cm^{-1} (C=O & N=N), 1525 cm^{-1} (CONH); nmr ($CDCl_3$) $\delta 4.0$ (m, $(CH_3)_2CH$), 1.2 (d, CH_3 & NH).

Structure:



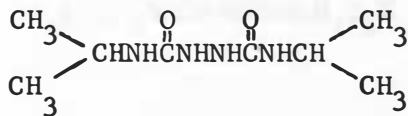
Analysis: Calculated for $C_8H_{16}N_4O_2$: C, 47.99; H, 8.05; N, 27.98. Found: C, 48.06; H, 8.11; N, 28.04.

Reacting ethyl azodicarboxylate (I) with isopropyl amine (1:2 ratio) in refluxing benzene gave some unidentifiable liquids and 1,6-diisopropyl biurea, 1.01 g (10%); mp $221--223^{\circ}$; ir (nujol) $3320, 3220, \& 3080\text{ cm}^{-1}$ (NH), $1660, 1690\text{ cm}^{-1}$ (C=O), 1550 cm^{-1} (CONH).

TABLE I

REACTION NO.	MOLE ^a RATIO	SOLVENT	TEMP.	PRODUCTS ^b	
				% YIELD A	% YIELD B
1 ^c	2:1	Petroleum ether 5 ml	0--5°	27.6	32.0
2	1:1	None	50°	----	41.5
3	1:1	None	70--120° ^d	----	----
4	1:1	Benzene 60 ml	70--80°	----	43.0
5	2:1	Petroleum ether 10 ml	35--45°	8.7	33.8
6	2:1	Benzene 20 ml	0--5°	6.3	36.8
7	2:1	Diethyl ether 20 ml	0--5°	29.0	----
8	2:1	Dioxane 20 ml	5--10°	28.0	----

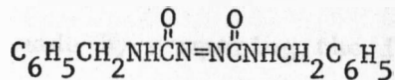
- a. Moles of piperidine per mole of ethyl azodicarboxylate (I)
- b. A = di-N,N-pentamethylene azodicarboxamide
B = 1,2-dicarboethoxy-N-piperidylhydrazine
- c. Example written up on preceding page
- d. A small explosion occurred at 120°. Analysis of the residue showed the presence of ethyl hydrazodicarboxylate and ethyl N,N-pentamethylene urethane.

Structure:

Analysis: Calculated for $\text{C}_8\text{H}_{18}\text{N}_4\text{O}_2$: C, 47.51; H, 8.97; N, 27.70. Found: C, 47.46; H, 8.83; N, 27.99.

Positive identification was made by reducing N,N'-diisopropyl azodicarboxamide, using 50 lbs of hydrogen with Palladium on charcoal as a catalyst and ethanol as the solvent. The product of this reaction had the same melting point and infrared spectrum as the product of the reaction of isopropyl amine with ethyl azodicarboxylate (I) in refluxing benzene.

Reaction of Ethyl Azodicarboxylate with Benzyl Amine. A mixture of ethyl azodicarboxylate (I), 7.3 g (0.042 mole), and diethyl ether, 25 ml, was cooled to 5° and benzyl amine, 8.9 g (0.084 mole), was added dropwise with stirring at such a rate as to keep the temperature between 5° and 10° . The mixture was filtered, and the precipitate was washed with diethyl ether. A small amount was recrystallized from acetonitrile. The yield was crude N,N'-dibenzyl azodicarboxamide, 11.0 g (88.5%); mp $208\text{--}209^\circ$; ir (nujol) 3100 cm^{-1} (NH), 1700 cm^{-1} (C=O), 1530 cm^{-1} (CONH), $740\text{ \& } 695\text{ cm}^{-1}$ (C_6H_5).

Structure:

Analysis: Calculated for $\text{C}_{16}\text{H}_{16}\text{N}_4\text{O}_2$: C, 64.85; H, 5.44; N, 18.99. Found: C, 64.26; H, 5.51; N, 18.18.

Pyrolysis of N,N'-Diisopropyl Azodicarboxamide. In a 25-ml flask fitted with a condenser, N,N'-diisopropyl azodicarboxamide (II), 2.0 g (0.01 mole), was heated to 140° . After approximately 30 minutes the solid melted, and a gas evolved. The residue in the reaction flask and condenser was recrystallized from acetone and found to be 1,3-diisopropyl urea, 0.20 g (13.9%); mp $185\text{--}189^\circ$ (lit.³⁰ mp 192°); ir (nujol) 3150 cm^{-1} (NH), 1600 cm^{-1} (C=O), 1500 cm^{-1} (CONH).

Positive identification was made by comparing the infrared spectrum of this compound with that for N,N'-diisopropyl urea.³⁰

Reaction of N,N'-Diisopropyl Azodicarboxamide with Acetic Anhydride. A mixture of N,N'-diisopropyl azodicarboxamide (II), 5 g (0.025 mole), and acetic anhydride, 2.75 g (0.027 mole), was refluxed for 30 minutes. The acetic acid which was produced and the excess acetic anhydride were evaporated in vacuo. The residue in the flask was vacuum distilled, and the fraction between 65° and 75° at 0.20 mm was found to be N-isopropyl acetamide, 2.66 g (52.6%); ir (neat) 3150 cm^{-1} (NH), 1650 cm^{-1} (C=O), 1500 cm^{-1} (CONH); nmr

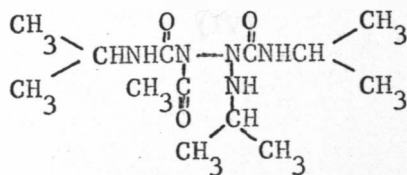
(neat) δ 0.82 (d, 6, $(\text{CH}_3)_2\text{CH}$), 1.68 (s, 3, CH_3 -), 3.75 (m, 1, CH), 4.25 (s, 1, NH).

Identification was made by comparing the infrared spectrum and the retention time on the gas chromatograph of this liquid with those of a known sample of N-isopropyl acetamide.

Reaction of N,N'-Diisopropyl Azodicarboxamide with Acetic Acid.

A mixture of N,N'-diisopropyl azodicarboxamide (II), 10 g (0.05 mole), and acetic acid, 50 ml, was refluxed for three hours. The acetic acid was evaporated in vacuo, and the residue taken up in boiling ether. The ether mixture was filtered hot, and the white, ether insoluble solid was found to be 1,6-diisopropyl biurea, 1.25 g (12.4%). The ether was evaporated in vacuo, and the residue vacuum distilled. The fraction boiling from 60° to 65° at 0.2 mm was found to be N-isopropyl acetamide, 3.63 g (36%). The residue left in the distilling flask was recrystallized from water to yield 1-acetyl-1,2-diisopropylcarboxamido-3-isopropyl triazane (III), 0.50 g (4.0%); mp $167\text{--}168^\circ$; ir (nujol) 3150 cm^{-1} (NH), 1710, 1680, and 1650 cm^{-1} (C=O), 1560, 1520, and 1500 cm^{-1} (CONH); nmr (CCl_4) δ 7.78 (d, 3, NH), 3.85 (m, 3, CH), 2.1 (s, 3, CH_3), 1.18 (d, 12, $\underline{J} = 6.5\text{ Hz}$, $(\text{CH}_3)_2\text{CH}$); 1.12 (d, 6, $\underline{J} = 6.0\text{ Hz}$, $(\text{CH}_3)_2\text{CH}$); mw (ethanol) 279.2, Calculated 301.

Structure:

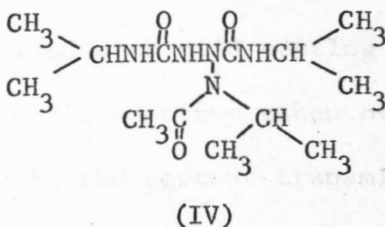


(III)

Analysis: Calculated for $C_{13}H_{27}N_5O_3$: C, 47.60; H, 9.75; N, 25.2. Found: C, 49.29; H, 8.58; N, 24.50.

Reaction of N,N'-Diisopropyl Azodicarboxamide with N-Isopropyl Acetamide. A mixture of N,N'-diisopropyl azodicarboxamide (II), 10.0 g (0.05 mole), N-isopropyl acetamide, 6.06 g (0.06 mole), and toluene, 15 ml, was refluxed for 20 hours at 120--130°. During this period a white precipitate formed. The toluene was evaporated in vacuo, and the residue washed with ether, recrystallized from water, and found to be 1,6-diisopropyl biurea, 1.00 g (10%). The ether was evaporated in vacuo, and the residue vacuum distilled. The fraction boiling from 60° to 65° at 0.25 mm was found to be N-isopropyl acetamide. The residue in the distilling flask was recrystallized from acetonitrile and found to be 1-acetyl-1-isopropyl-2,3-diisopropylcarboxamidotriazane (IV); mp 183--186°; ir (nujol) 3140 cm^{-1} (NH), 1590 and 1500 cm^{-1} (C=O), 1500 cm^{-1} (CONH); nmr ($CDCl_4$) δ 4.5 (m, 2, CHNHCO), 3.9 (m, 3, CH), 2.2 (s, 3, COCH₃), 1.2 (d, 18, $J = 6.5$ Hz (CH₃)₂CH).

Structure:



Analysis: Calculated for $C_{13}H_{27}N_5O_3$: C, 47.60; H, 9.75.

Found: C, 51.51; H, 9.59.

Preparation of Azobenzene.³¹ A mixture of nitrobenzene, 50 g (0.4 mole), methanol, 500 ml, a solution of sodium hydroxide, 65 g (1.62 mole) in 150 ml of water, and zinc dust, 53 g (0.82 mole), was refluxed on a steam bath with stirring for 10 hours. The mixture was filtered while hot, and the precipitate of sodium zincate was washed with a small amount of warm methanol. The methanol was distilled from the filtrate, the residue chilled, and the crystalline azobenzene removed by filtration.

To remove the zinc salts from the crude azobenzene, the latter was added to 500 ml of 2% hydrochloric acid solution. The mixture was warmed up to approximately 70° to melt the azobenzene and stirred rapidly for five minutes. The stirring was continued while the mixture was chilled to solidify the azobenzene. The product was filtered, washed with water, recrystallized from 80% ethanol, and found to be azobenzene, 25 g (68%); mp $64--66^{\circ}$.

Attempted Reduction of Azobenzene. A mixture of N,N'-diisopropyl azodicarboxamide, 12 g (0.06 mole), and azobenzene, 13.5 g (0.074 mole), was dissolved with mild heating in glacial acetic acid, 50 ml, and the visible spectrum taken over the region from 700--350 m μ . A minimum in the percent transmittance was observed

at 440 μ . To get the proper concentration 0.10 ml of the reaction mixture was diluted with glacial acetic acid to 100 ml.

The percent transmittance of the solution at 440 μ and the number of hours the solution was refluxed before the sample was taken are given in TABLE II. Since the concentration of azobenzene did not change significantly with refluxing time, the reaction appeared to be more complex than a simple reduction.

TABLE II

Sample No.	Time (hrs)	%T
1	0	19.6
2	20	14.0
3	47	10.0
4	97	20.0
5	120	18.0

Oxidation of Hydrazobenzene. A mixture of N,N'-diisopropyl azodicarboxamide (II), 10 g (0.05 mole), hydrazobenzene, 9.3 g (0.05 mole), and toluene, 100 ml, was refluxed for two hours. The mixture was filtered hot, and the precipitate washed with cold toluene, recrystallized from ethanol, and identified as 1,6-diisopropyl biurea, 3.0 g (30%), by comparing the melting point and the infrared spectrum of this compound with that of a known sample of 1,6-diisopropyl biurea. The visible spectrum

was taken of the toluene filtrate, and an absorption at 440 m μ indicated the presence of azobenzene.

Oxidation of Cyclohexanol. A solution of cyclohexanol, 3.0 g (0.03 mole), and toluene, 25 ml, was chromatographed at 160 $^{\circ}$. The attenuation was adjusted so that the size of the peak for cyclohexanol was about 50% of the chart width. To this mixture was added N,N'-diisopropyl azodicarboxamide (II), 6.0 g (0.03 mole), and the entire solution was refluxed. The reaction mixture was monitored by vapor phase chromatography, TABLE III. The ratios of the cyclohexanol peak to the cyclohexanone peak are only approximate values since they overlapped considerably.

TABLE III

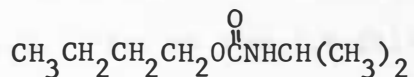
Sample No.	Time (hrs)	Ratio of Peaks (app)
1	0	1:0
2	2.5	5:1
3	23	2:1
4	44	2:1
5	170	2:1

Oxidation of n-Butanol. A mixture of n-butanol, 8.1 g (0.11 mole), and toluene, 50 ml, was chromatographed at 130 $^{\circ}$. The attenuation was adjusted so the size of the peak for n-butanol was about 90% of the chart width. This mixture was added to N,N'-diisopropyl azodicarboxamide (II), 20.0 g (0.10 mole),

and the entire solution was refluxed at 130° for 48 hours. The reaction mixture was filtered, and the white solid was found to be 1,6-diisopropyl biurea, 5.2 g (26%).

The toluene and n-butanol were removed by distillation at atmospheric pressure, and the liquid residue was chromatographed. The residue was then vacuum distilled to yield n-butyl-N-isopropyl urethane, 4.0 g (25%); bp (12 mm) 95--97°; ir (neat) 3150 cm⁻¹ (NH), 1670 cm⁻¹ (C=O), 1530 cm⁻¹ (CONH); nmr (neat) δ 0.9 (d, J = 7.0 Hz, (CH₃)₂CH), 1.0 (n-butyl), 3.6 (m, CH(CH₃)₂), 3.9 (m, CH₃CH₂CH₂CH₂), 6.1 (d, NH).

Structure:



Oxidation of n-Octanol. A mixture of n-octanol, 1.30 g (0.01 mole), and toluene, 8 ml, was chromatographed at 190°. The attenuation was adjusted so the size of the peak for n-octanol was about 40% of the chart width. This mixture was added to N,N'-diisopropyl azodicarboxamide (II), 4.0 g (0.02 mole), and the entire solution was refluxed at 130--140°. The reaction mixture was monitored by vapor phase chromatography. Since the amount of (II) was increased in this reaction, the oxidation was more complete, and after 24 hours the n-octanal peak was three times as large as the n-octanol peak. Another smaller peak was also observed, showing the presence of the higher boiling urethane, n-octyl-N-isopropyl urethane.

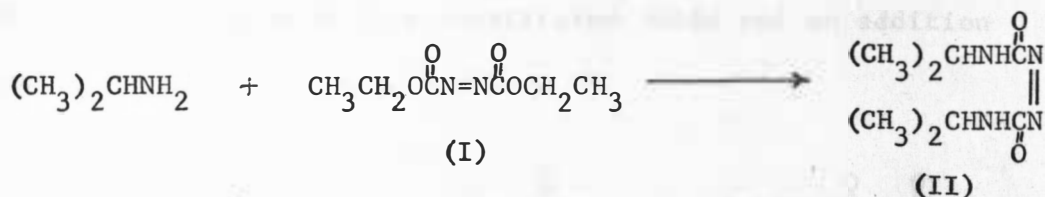
Oxidation of Isopropyl Alcohol. A mixture of N,N'-diisopropyl azodicarboxamide (II), 10 g (0.05 mole), isopropyl alcohol, 3.5 g (0.06 mole), and toluene, 25 ml, was refluxed at 120° for 72 hours. The mixture was cooled and filtered to remove the 1,6-diisopropyl biurea, and the filtrate extracted with water. The water layer was treated with a solution of 2,4-dinitrophenylhydrazine, and a precipitate formed seeming to indicate the presence of acetone. The vapor phase chromatograph of the filtrate at 190° showed no peak for the urethane.

Oxidation of n-Propyl Alcohol. A mixture of N,N'-diisopropyl azodicarboxamide (II), 5.0 g (0.025 mole), n-propyl alcohol, 3.0 g (0.05 mole), and toluene, 15 ml, was refluxed for 48 hours at 120°. The mixture was filtered to remove the 1,6-diisopropyl biurea, and the filtrate extracted with water. The water layer was treated with a solution of 2,4-dinitrophenylhydrazine, and a precipitate formed seeming to indicate the presence of n-propanal. The vapor phase chromatograph of the filtrate at 190° showed that n-propyl-N-isopropyl urethane was the major product.

Oxidation of Isopropyl Amine. A mixture of N,N'-diisopropyl azodicarboxamide (II), 5.0 g (0.025 mole), isopropyl amine, 3.0 g (0.05 mole), and toluene, 15 ml, was refluxed for four hours at 120°. The mixture was filtered to remove the 1,6-diisopropyl biurea, and the filtrate extracted with water. The water layer was treated with a solution of 2,4-dinitrophenylhydrazine, and a precipitate formed seeming to indicate the presence of acetone.

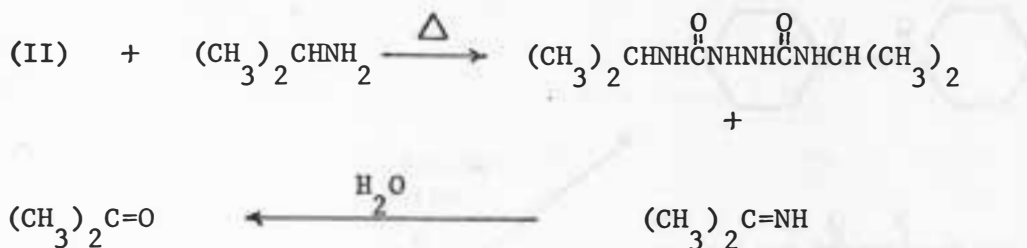
DISCUSSION OF RESULTS

It was found that primary aliphatic amines such as isopropyl amine or benzyl amine react with ethyl azodicarboxylate (I) to give only substituted amides. When the reaction was carried out in di-

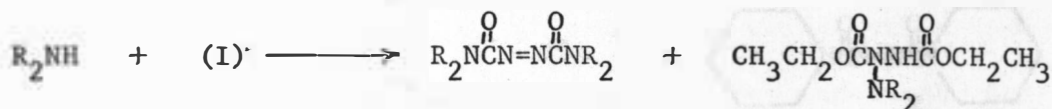


ethyl ether, the yield was better than when benzene was used as the solvent. The temperature was kept low to improve the yield of amide since at higher temperatures the N,N'-diisopropyl azodicarboxamide (II) oxidizes the isopropyl amine to form 1,6-diisopropyl biurea and isopropylidene amine. Since (II) was only slightly soluble in chloroform and insoluble in other suitable solvents, the nuclear magnetic resonance (nmr) spectrum was difficult to resolve. The infrared (ir) spectrum and the elemental analysis agreed with the assigned structure.

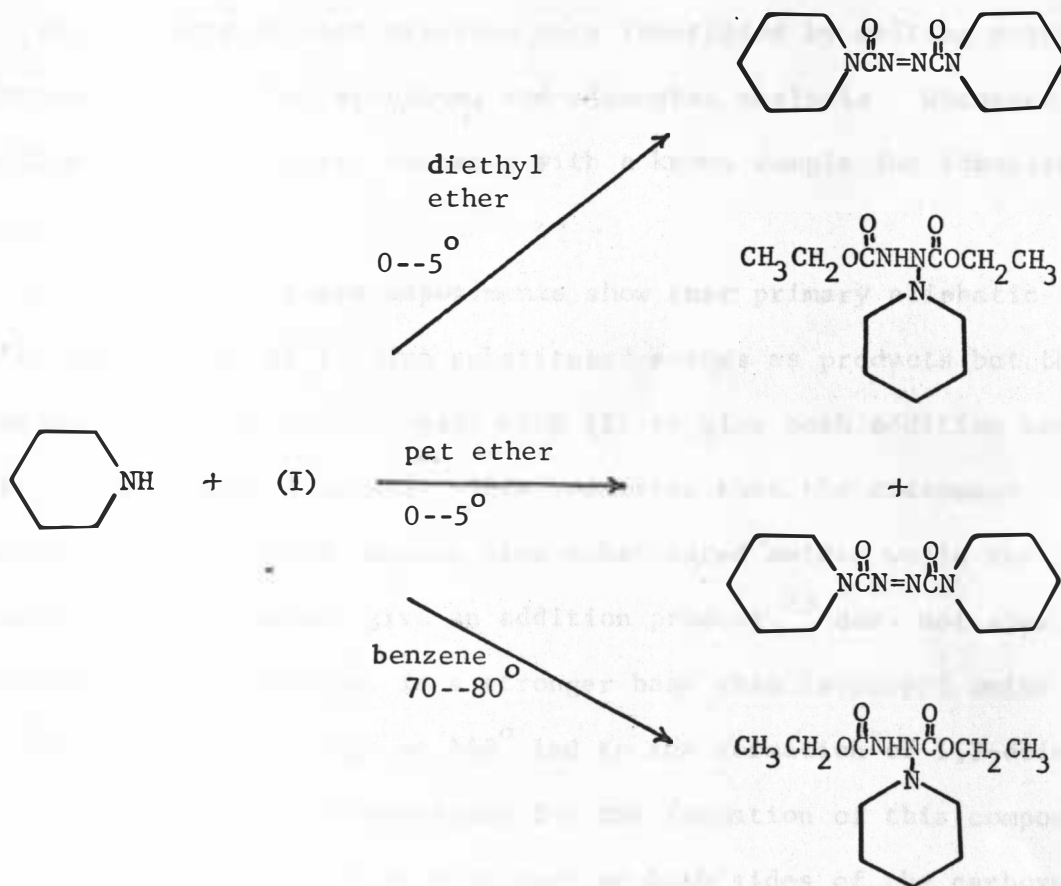
When isopropyl amine was reacted with (I) in refluxing benzene, the product was 1,6-diisopropyl biurea which resulted from the oxidation of isopropyl amine by (II). The imine produced was hydrolysed to acetone by addition of water and identified as the 2,4-dinitrophenyl hydrazone.



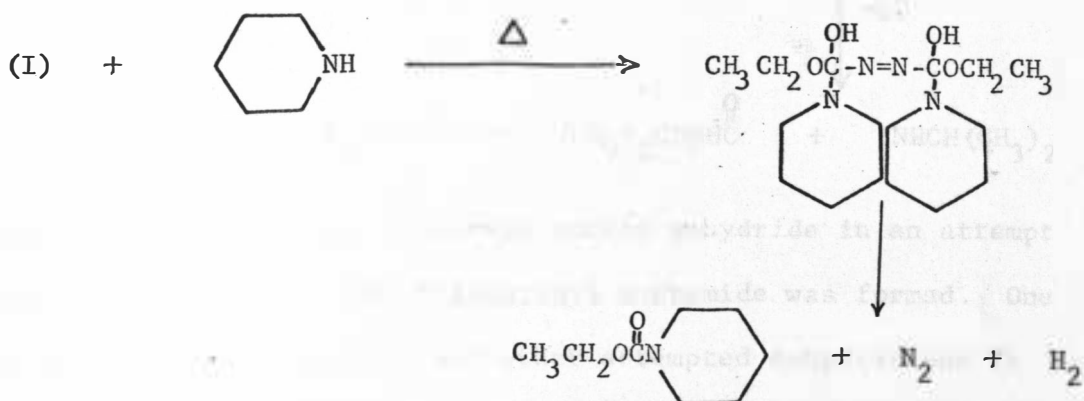
Secondary aliphatic amines such as piperidine were found to react with (I) to give both a substituted amide and an addition product.



The products of the reaction of (I) with piperidine depended greatly on the solvent used and the temperature at which the reaction was carried out. When diethyl ether was used as the solvent and the temperature was held between 0° and 5°, di-N,N-pentamethylene azodicarboxamide was the only product. In petroleum ether at 0--5°, a mixture of amide and addition product were formed. In petroleum ether at 35--45°, the addition product, 1,2-dicarboethoxy-N-piperidylhydrazine, was the major product with some amide formed also. In benzene at 0--5°, the addition product was the major product, but again some of the amide was formed. In benzene at 70--80°, the addition product was the only product formed.



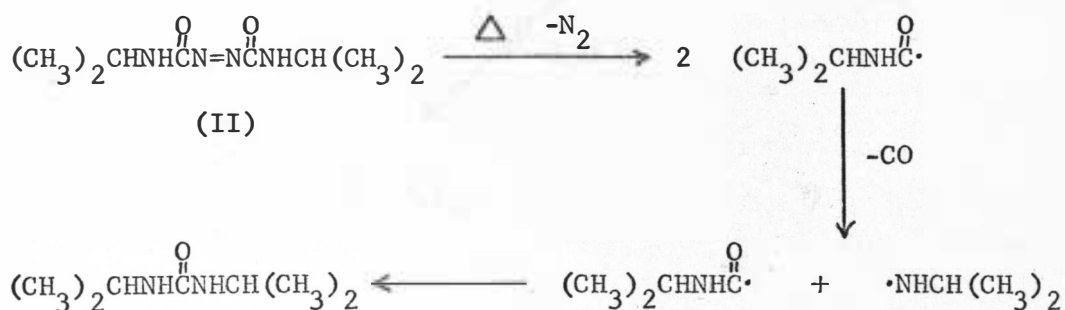
When piperidine was reacted with (I) with no solvent at 70--120°, the major product was ethyl N,N-pentamethylene urethane, which probably comes from a free radical decomposition.



The products of each reaction were identified by melting point, infrared spectrum, nmr spectrum, and elemental analysis. Whenever possible, the product was compared with a known sample for identification.

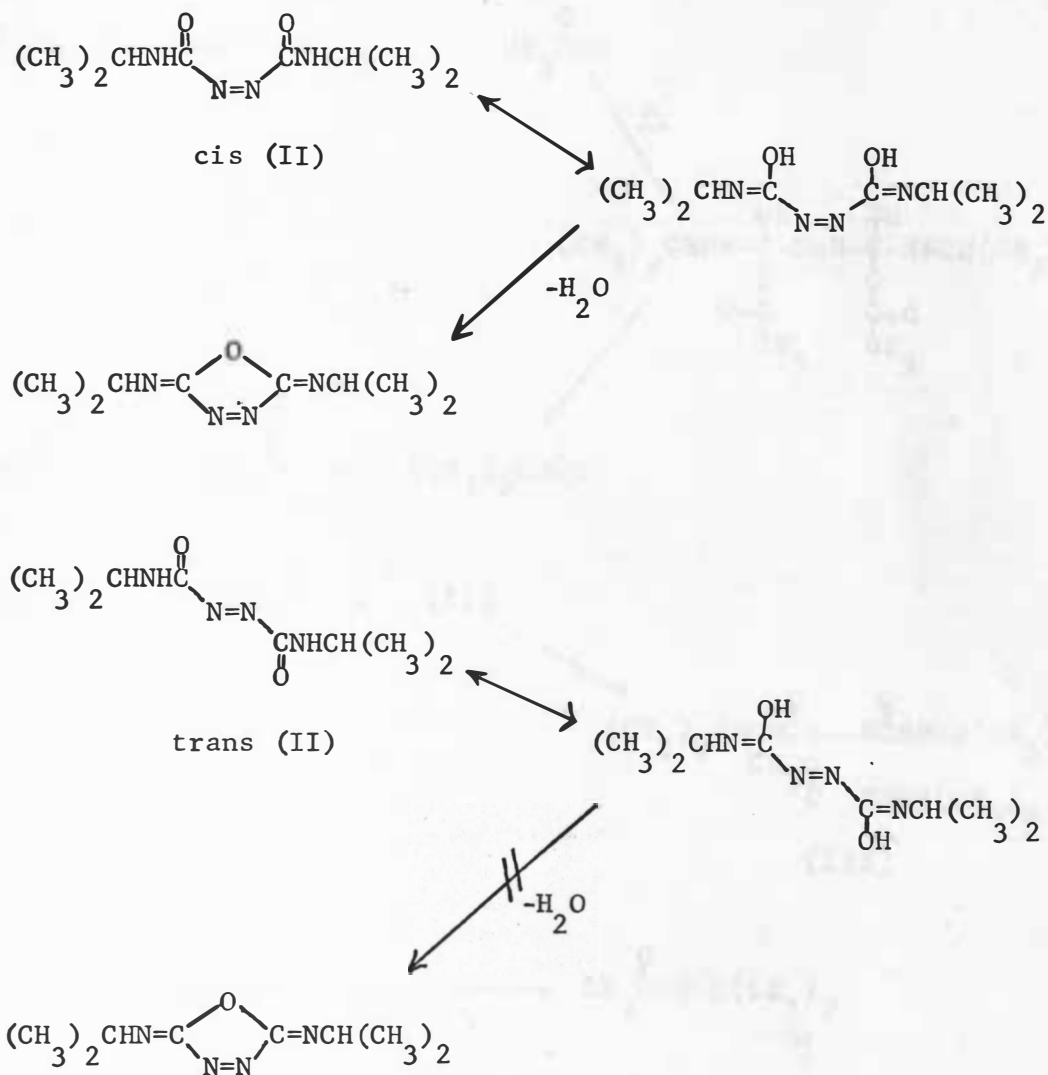
The results of these experiments show that primary aliphatic amines react with (I) to give substituted amides as products but that secondary aliphatic amines react with (I) to give both addition products and substituted amides. This indicates that the statement, strongly basic aliphatic amines give substituted amides while the majority of other amines give an addition product,²³ does not always hold true since piperidine is a stronger base than isopropyl amine.

The pyrolysis of (II) at 140° led to the formation of 1,3-diisopropyl urea. A proposed mechanism for the formation of this compound is the free radical cleavage on either or both sides of the carboxyl groups.



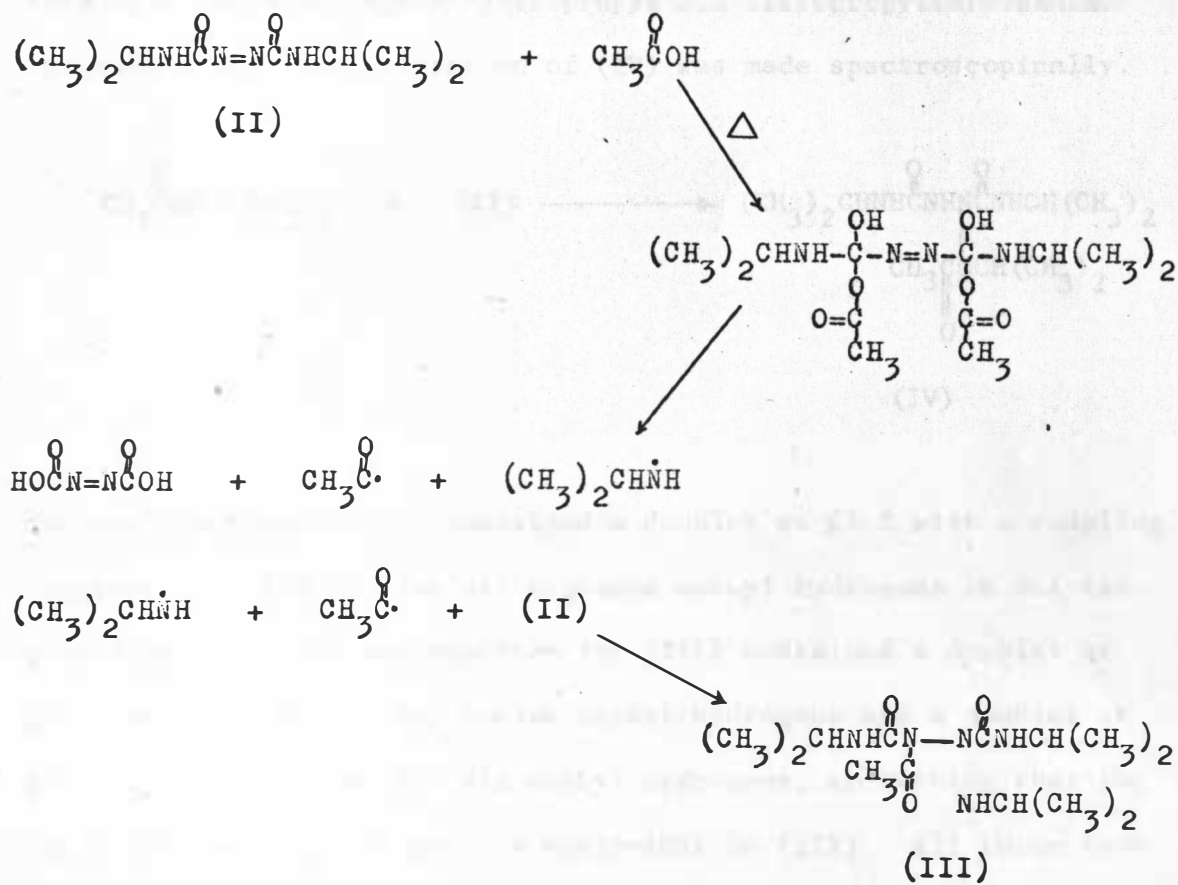
When (II) was refluxed in excess acetic anhydride in an attempt to cyclize it by dehydration, N-isopropyl acetamide was formed. One reason for the failure of this and other attempted dehydrations is that (II) probably exists in the thermodynamically more stable trans

configuration. It is known that ethyl azodicarboxylate (I) exists predominantly in the trans configuration.³²

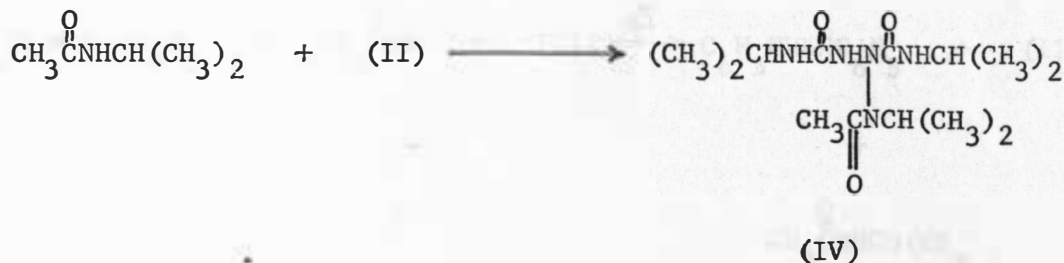


To investigate the mechanism for the formation of N-isopropyl acetamide, (II) was refluxed in glacial acetic acid. Three products were isolated from this reaction: 1,6-diisopropyl biurea, N-isopropyl acetamide, and 1-acetyl-1,2-diisopropylcarboxamido-3-isopropyl

triazane (III). These products indicate that a possible mechanism might be:



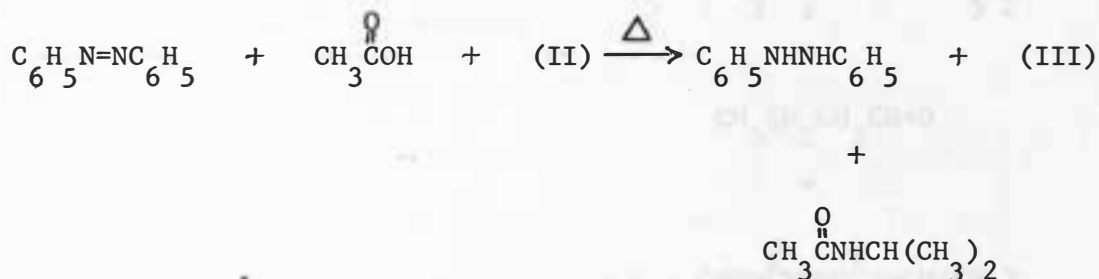
In an attempt to determine the structure of (III), (II) was reacted with N-isopropyl acetamide. The structure of the product of this reaction was 1-acetyl-1-isopropyl-2,3-diisopropylcarboxamido-triazane (IV). Identification of (IV) was made spectroscopically.



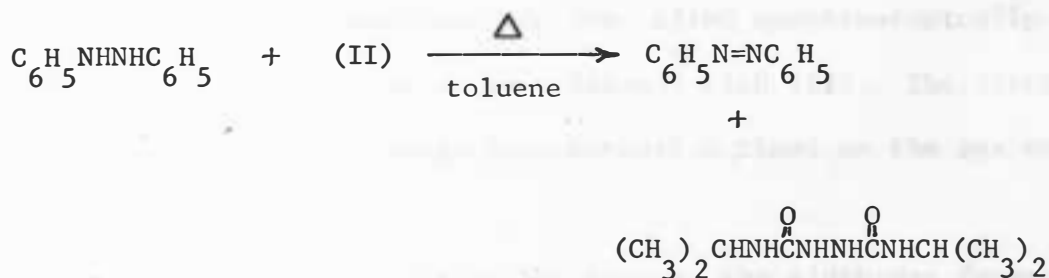
The nmr spectrum of (IV) contained a doublet at δ 1.2 with a coupling constant, $J = 6.5$ Hz, for all eighteen methyl hydrogens on the isopropyl groups. The nmr spectrum for (III) contained a doublet at δ 1.18 with $J = 6.5$ Hz for twelve methyl hydrogens and a doublet at δ 1.12 with $J = 6.0$ Hz for six methyl hydrogens, indicating that the three isopropyl groups are not equivalent in (III). All three isopropyl groups in (IV) are bonded to amide nitrogens, but one isopropyl group in (III) is bonded to an amine nitrogen. The amine group provides a greater shielding of the methyl hydrogens than does the amide group. Since N-isopropyl acetamide did not react with (II) to give (III), the formation of (III) must be by a mechanism which does not involve N-isopropyl acetamide except as one of the end products.

The proposed mechanism for the reaction of (II) with acetic acid involves the formation of the reducing intermediate, diimide. If

diimide was formed during the reaction, addition of azobenzene to the reaction mixture should result in the formation of hydrazobenzene. However, the absorption in the visible region ($\lambda_{\text{max}} = 440 \text{ m}\mu$) did not change appreciably during the reaction. It was also found that (II)

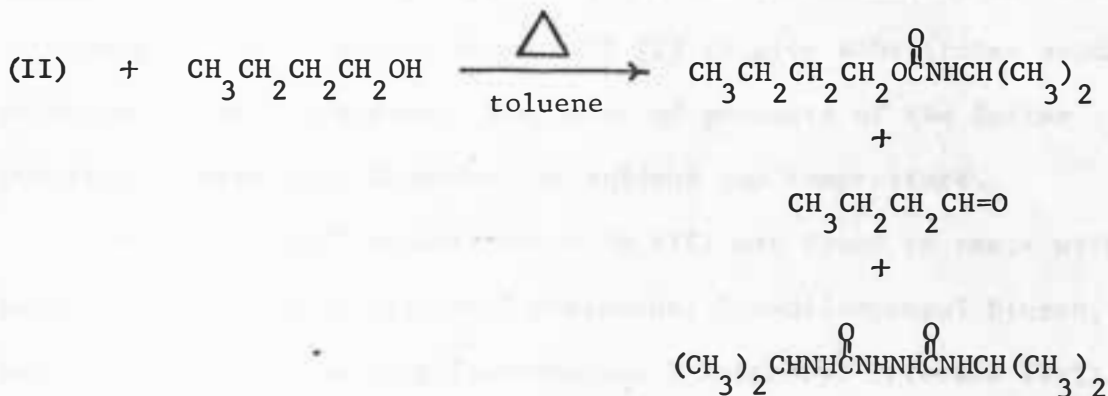
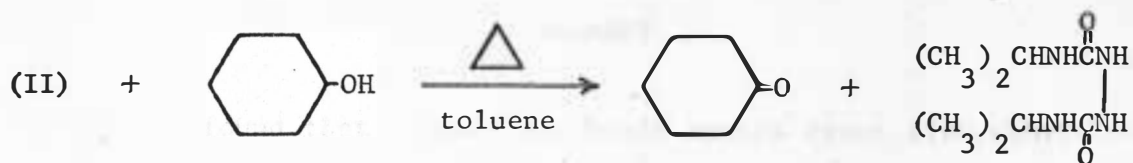


will oxidize hydrazobenzene to azobenzene, so that any azobenzene reduced by diimide will be oxidized back to azobenzene by (II).



It was found that (II) will oxidize secondary alcohols to ketones and primary alcohols to aldehydes. The preparation of the 2,4-dinitrophenylhydrazones and vapor phase chromatography were used to identify the reaction products.

With low molecular weight primary alcohols, the main product was the corresponding urethane.



N-isopropyl-n-butyl urethane was identified spectroscopically as the main product of the reaction of n-butanol with (II). The other urethanes were detected by their long retention times on the gas chromatograph at 190°.

Since no oxygen is present in the system, the aldehydes formed cannot be oxidized further. The reactions were carried out in toluene and the insoluble biurea removed by filtration to aid in the purification of the products. The fact that the formation of urethanes from low molecular weight alcohols prevents the formation of very much aldehyde limits the preparative value of this procedure to the use of alcohols with high molecular weights.

Amines can also be oxidized to imines using (II). The procedure was very similar to that for oxidation of alcohols.

SUMMARY

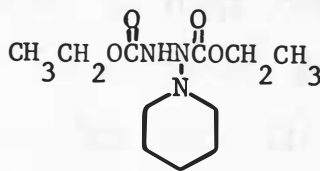
It was found that primary aliphatic amines react with ethyl azodicarboxylate (I) to give substituted azodicarboxamides but that secondary aliphatic amines react with (I) to give substituted azodicarboxamides and triazanes. The ratio of products of the latter reaction is very much dependent on solvent and temperature.

N,N'-diisopropyl azodicarboxamide (II) was found to react with acetic acid to give N-isopropyl acetamide, 1,6-diisopropyl biurea, and 1-acetyl-1,2-diisopropylcarboxamido-3-isopropyl triazane (III).

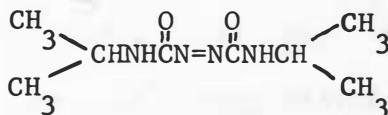
The oxidation of primary alcohols by (II) to aldehydes seems to be a function of the molecular weight of the alcohols. The oxidation of n-octanol yielded n-octanal and some n-octyl-N-isopropyl urethane, but oxidation of n-propanol and n-butanol gave only the corresponding urethanes. It would seem reasonable to speculate that the oxidation of primary alcohols by (II) may be useful as a preparative method for the preparation of aldehydes of high molecular weights. The oxidation of cyclohexanol gave cyclohexanone.

The oxidation of isopropyl amine to isopropylidene amine by (II) seems to indicate that this procedure may have preparative value for the preparation of more complex imines.

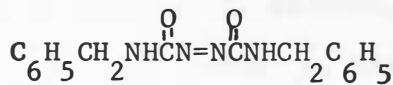
LIST OF NEW COMPOUNDS



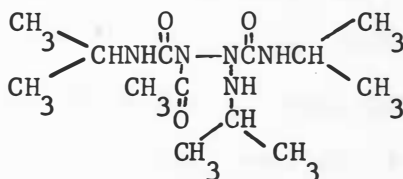
1,2-dicarboethoxy-N-piperidylhydrazine



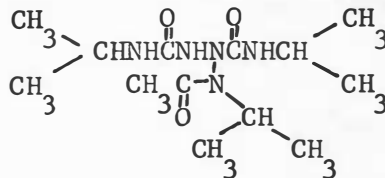
N,N'-diisopropyl azodicarboxamide



N,N'-dibenzyl azodicarboxamide



1-acetyl-1,2-diisopropylcarboxamido-3-isopropyl triazane (III)



1-acetyl-1-isopropyl-2,3-diisopropylcarboxamidotriazane (IV)

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