Ketenes. IX. Reactions of Ketenes with Various Substituted Enamines[1]

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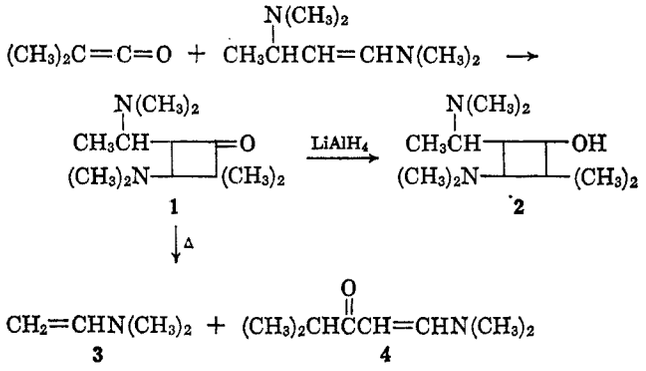
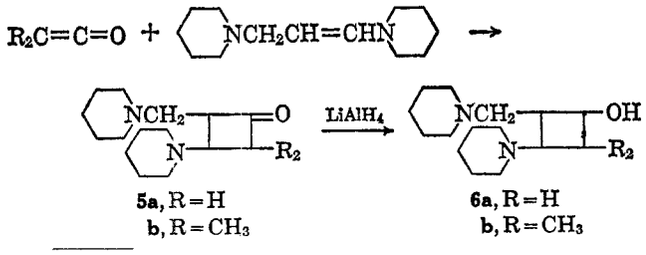
Dimethylketene and N,N,N′,N′-tetramethyl-1-butene-1,3-diamine underwent a 1,2-cycloaddition to give 3-(dimethylamino)-4-(1-dimethylaminoethyl)-2,2-dimethylcyclobutanone (1). This compound had limited stability but could be trapped as 3-(dimethylamino)-4-(1-dimethylaminoethyl)-2,2-dimethylcyclobutanol by reduction with lithium aluminum hydride. On warming, 1 rearranged to 1-dimethylamino-4-methyl-1-penten-3-one. Allylamines formed cyclobutanones with butylethylketene at elevated temperatures. N-Vinylamides and N-vinylsulfonamides also formed cyclobutanones with dimethyl-, butylethyl- and diphenylketenes.

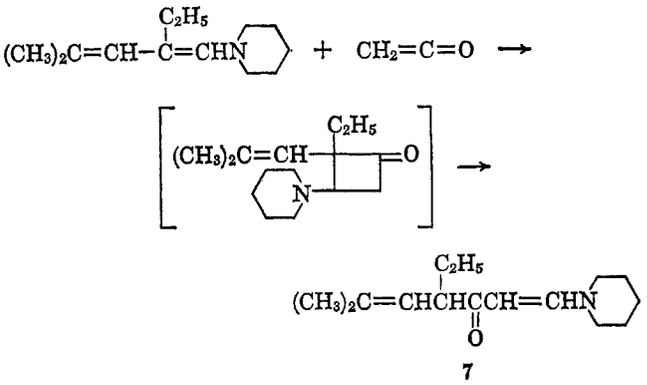
In an earlier paper[3] we described 1,2-cycloaddition reactions of ketenes and enamines. The present paper extends this reaction to include certain substituted enamines. Dialkylamino-substituted enamines are readily prepared from acrolein or crotonaldehyde and secondary amines. Dimethylketene and N,N,-N′,N′-tetramethyl-1-butene-1,3-diamine reacted vigorously at 10–20° to give 3-(dimethylamino)-4-(1-dimethylaminoethyl)-2,2-dimethylcyclobutanone (**1**). This compound was thermally unstable but could be trapped by reduction with lithium aluminum hydride to give the stable cyclobutanol **2**. Distillation of **1** resulted in a novel rearrangement to 1-(dimethylamino)-4-methyl-1-penten-3-one (**4**) and what was probably N,N-dimethylvinylamine (**3**). The presence of **3** was assumed because dimethylamine and a large amount of high-boiling tars were formed, probably by self-condensation of **3**, followed by elimination of dimethylamine.[4]



1,1′-(Propenylene)dipiperidine reacted with ketene and dimethylketene to give the cyclobutanones **5a** and **b**, as demonstrated by a strong infrared absorption 5.62 μ in the reaction solution. Reduction with lithium aluminum hydride yielded the corresponding cyclobutanols **6a** (84%) and **b** (89%) as a mixture of isomers. Four different *cis–trans* combinations each are possible for **6a** and **b**. Recrystallization of **6a** afforded one pure isomer in 42% yield. A similar recrystallization of **6b** gave 41% of one isomer and 6% of another lower-melting isomer. No conformational assignments were made for these materials.

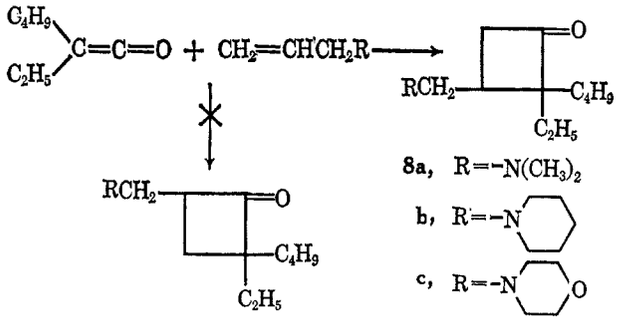


The reaction of ketene with the dienamine, 1-(2-ethyl-4-methyl-1,3-pentadien-1-yl)piperidine, gave 4-ethyl-6-methyl-1-piperidino-1,5-heptadien-3-one (**7**) in 21% yield and a large amount of undistillable residue.



The electron density at the double bond of allylamines is sharply reduced from that of enamines, and the competing dimerization of dimethylketene precluded efforts to obtain cycloadducts with such compounds. Higher dialkylketenes, because of their much lower rates of dimerization,[5] could be forced into cycloadditions with allylamines at elevated temperatures.

Butylethylketene when heated at 180° gave with N,N-dimethylallylamine a 32% yield of the cyclobutanone **8a**, with N-allylpiperidine a 22% yield of **8b**, and with N-allylmorpholine a 28% yield of **8c**. The structure of the N,N-dimethylallylamine and butylethylketene adduct was established by the nmr spectrum of the product as **8a** rather than the structure of the hypothetical alternate closure. The spectrum showed the methylene group next to the nitrogen as a



(1) Paper VIII in this series: J. C. Martin, K. R. Barton, P. G. Gott, and R. H. Meen, *J. Org. Chem.*, **31**, 943 (1966).

(2) To whom inquiries should be sent.

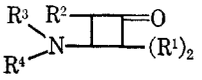
(3) R. H. Hasek and J. C. Martin, *ibid.*, **28**, 1468 (1963).

(4) C. Mannich and E. Kniss, *Ber.*, **74B**, 1629 (1941).

(5) R. H. Hasek, P. G. Gott, and J. C. Martin, *J. Org. Chem.*, **29**, 1239 (1964).

TABLE I

CYCLOADDUCTS FROM KETENES WITH N-ALKENYLAMIDES AND N-ALKENYLSULFONAMIDES

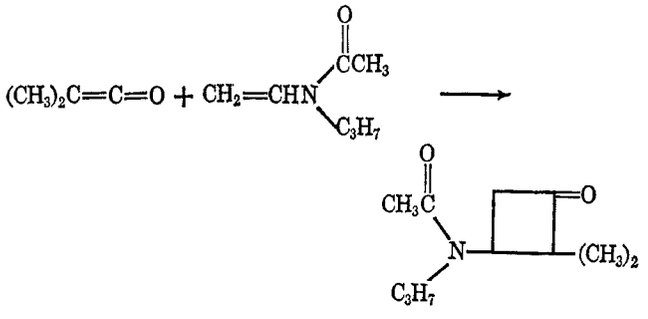


R¹	R²	R³	R⁴	Bp, °C (mp)	Pressure	Yield, %	$n^{20}D$	Formula	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found
CH_3	H	$CH_3C(=O)$	C_3H_7	126–128	1.5 mm	48	1.4758	$C_{11}H_{19}NO_2$	67.0	66.8	9.7	10.0	7.1	7.0
CH_3	H	$CH_2(CH_2CH_2)C(=O)$		140 (44–44.5[a])	0.5 mm	30	1.4951	$C_{11}H_{19}NO_2$	66.3	66.1	8.3	8.5	7.7	7.7
CH_3	H	$C_6H_5C(=O)$	C_3H_7	(65–66.5[b])		61		$C_{16}H_{21}NO_2$	74.1	74.4	8.2	8.0	5.4	5.5
C_6H_5	CH_3	$CH_3C(=O)$	C_3H_7	(161–162[c])		~90		$C_{22}H_{25}NO_2$	78.8	79.0	7.5	7.1	4.2	4.0
CH_3	H	$C_6H_5SO_2$	CH_3	102 (58–60[a])	2.5 μ	24	1.5429	$C_{13}H_{17}NO_3S$[d]	58.4	58.4	6.4	6.4	5.2	5.2
C_2H_5 $(CH_3)_2CHCH_2$	H	$C_6H_5SO_2$	CH_3	103–109	1 μ	85	1.5290	$C_{17}H_{25}NO_3S$[e]	63.1	63.1	7.8	7.9	4.3	4.4

[a] Recrystallized from ethyl alcohol. [b] Recrystallized from hexane. [c] Recrystallized from benzene. [d] Calcd.: S, 12.0. Found: 12.2. [e] Calcd.: S, 9.9. Found: 10.0.

multiplet at 2.41 ppm and the ring methylene group as a multiplet at 2.75 ppm. When **8a** was treated with sodium in deuterium oxide, the multiplet at 2.75 ppm was removed from the spectrum. This confirmed **8a** as the correct structure because the ring methylene group of the hypothetical alternate structure would not exchange with deuterium.

The electron-rich double bonds of N-vinylcarboxamides and N-vinylsulfonamides also underwent 1,2-cycloadditions with ketoketenes to give cyclobutanones. Dimethylketene reacted with N-propyl-N-vinylacetamide to give 2,2-dimethyl-3-(N-acetylpropylamino)-cyclobutanone (**9**) in 48% yield. Diphenylketene added readily to N-propenyl-N-propylacetamide to give the cyclobutanone **10** in high yield.



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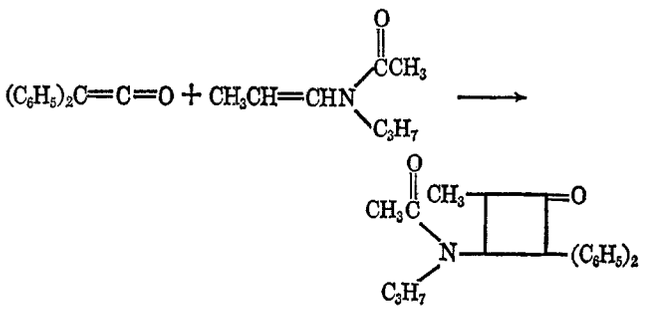

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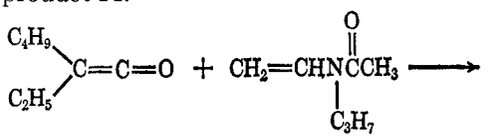
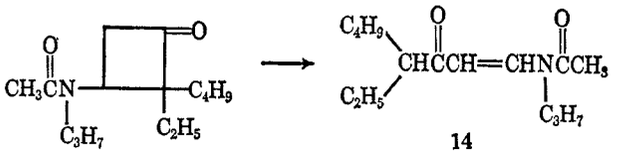
A list of the reaction products from ketenes and N-unsaturated amides prepared during this work is given in Table I. The structural assignments for these new types of cyclobutanones were based on elemental analysis, infrared and nmr spectra, and analogy to previous work.

Reduction of these cyclobutanones to the corresponding cyclobutanols was achieved by using sodium borohydride or by catalytic hydrogenation over a ruthenium catalyst. The cyclobutanone **9** was hydrogenated to 2,2-dimethyl-3-(N-acetylpropylamino)cyclobutanol (**11**) in 81% yield by using a ruthenium-on-carbon catalyst at 100° and 3000 psi. 2,2-Dimethyl-3-(N-benzoylpropylamino)cyclobutanone gave 2,2-dimethyl-3-(N-benzoylpropylamino)cyclobutanone (**12**) in 80% yield upon treatment with sodium borohydride.

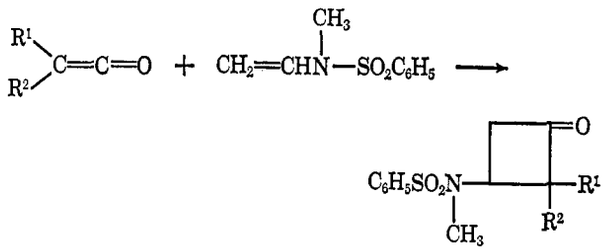
A mixture of butylethylketene and N-propyl-N-vinylacetamide after refluxing for several hours in hexane showed a characteristic cyclobutanone absorption in the infrared at 5.63 μ. There was no absorption peak for the distilled product; instead, it had infrared maxima at 5.9, 6.18 and 6.3 μ. The distillate was not the expected cyclobutanone **13**, but the acrylic product **14**.





13 **14**

Ketenes also undergo cycloaddition reactions with N-vinylsulfonamides as indicated by the reactions of N-methyl-N-vinylbenzenesulfonamide with dimethylketene and ethylisobutylketene.



15a, $R^1 = R^2 = CH_3$

b, $R^1 = C_2H_5$; $R^2 = iso\text{-}C_4H_9$

The reaction with dimethylketene was carried out at room temperature to give the cyclobutanone **15a** in 24% yield, whereas the ethylisobutylketene experiment was run at 180° to give the cyclobutanone **15b** in 85% yield. The structural assignments for these cyclobutanones were based on elemental analysis, infrared and nmr spectra, and analogy to other cycloaddition work.

N-Vinylphthalimide and N-vinylcarbazole did not react with dimethylketene in benzene at room temperature. Tetrakis(dimethylamino)ethylene did not react with dimethylketene but converted it to the lactone dimer, 2,2,4-trimethyl-3-hydroxy-3-pentenoic acid β-lactone.

Experimental Section

Ketene was obtained from an industrial production unit; dialkylketenes were prepared by pyrolysis of the corresponding anhydrides;[6] and diphenylketene was prepared by dehydrohalogenation of diphenylacetyl chloride. N-Methyl-N-vinylbenzenesulfonamide,[7] 3-dimethylamino-N,N-dimethyl-1-butenylamine,[8] 1,1′-(propenylene)dipiperidine,[8] tetrakis(dimethylamino)ethylene,[9] and the N-unsaturated carboxamides[10] were prepared according to published procedures. 2-Ethyl-4-methyl-1-piperidino-1,3-pentadiene [bp 94° (5 mm), $n^{20}D$ 1.5001] was prepared according to the method of Mannich.[8] N-Vinylpyrrolidone was obtained from General Aniline and Film Corp.; N-vinylcarbazole and N-vinylphthalimide were obtained from Monomer-Polymer Laboratories; and the allylamines were obtained from Peninsular Chemresearch, Inc.

Infrared spectra were determined on a Baird AB-2 instrument. Nmr spectra were recorded on a Varian A-60 instrument at 60 Mc with field position values referred to tetramethylsilane as an internal standard.

The Reaction of Dimethylketene with N,N,N′,N′-Tetramethyl-1-butene-1,3-diamine.—Dimethylketene (105 g, 1.5 moles) was added to a stirred solution of 146 g (1.03 moles) of N,N,N′,N′-tetramethyl-1-butene-1,3-diamine in 200 ml of hexane. The temperature of the exothermic reaction was kept at 25–65° by an ice bath. The reaction solution was stirred at room temperature for 3 hr after the addition was complete. Distillation through a 12-in. packed column gave 106.3 g (76%) of the ketone **4**, bp 111–113° (4 mm). The infrared spectrum of **4** was identical with that of **4** prepared from ketene and N,N-dimethylisobutenylamine.[3]

Anal. Calcd for $C_8H_{15}NO$: C, 68.0; H, 10.6; N, 9.9. Found: C, 68.0; H, 10.6; N, 9.6.

During the distillation of **4**, continuous decomposition took place. The gas that was evolved was trapped and found to be dimethylamine. The dimethylamine was probably eliminated from the dimerization of N,N-dimethylvinylamine (**3**).

3-Dimethylamino-4-(1-dimethylaminoethyl)-2,2-dimethylcyclobutanol (2).—Under a nitrogen atmosphere, 48.3 g (0.69 mole) of dimethylketene was added over a period of 15 min to a stirred solution of 97 g (0.69 mole) of N,N,N′,N′-tetramethyl-1-butene-1,3-diamine in 250 ml of ether. The exothermic reaction was kept at 10–20° by an ice bath. The reaction solution was stirred at room temperature for 2 hr after the addition was complete and was added slowly to a stirred slurry of 19 g (0.5 mole) of lithium aluminum hydride in 200 ml of ether. The reaction temperature was kept at 10–15° during the addition, and later the mixture was stirred at room temperature for 6 hr. Ethyl acetate was added to destroy excess lithium aluminum hydride, followed by successive additions of 20 ml of water, 15 ml of 20% sodium hydroxide solution, and 70 ml of water. The resulting mixture was filtered, and the filtrate was distilled through a 10-in. packed column to give 60.1 g (40%) of **2**, bp 83–91° (0.5 mm). This material solidified on standing. A sample recrystallized from hexane had mp 85–87°; infrared absorption (Nujol), 3.20 μ; nmr spectrum (CCl_4), singlets at 1.01 and 1.27 (methyl groups), 2.12 and 2.37 (dimethylamino groups), and at 4.42 (hydroxy group), and multiplets at 2.63 (methylidyne protons) and 3.60 ppm (–C(H)–O–).

Anal. Calcd for $C_{12}H_{26}N_2O$: C, 67.2; H, 12.2; N, 13.1. Found: C, 67.3; H, 12.1; N, 13.2.

3-Piperidino-2-(piperidinomethyl)cyclobutanol (6a).—Under the same conditions used for **2**, 4.2 g (0.1 mole) of 1,1′-(propenylene)dipiperidine and ketene in 200 ml of ether gave 21 g (84%) of crude **6a** as a waxy solid. Recrystallization from benzene gave 10 g (42%) of **6a**: mp 107–108°; infrared absorptions (KBr), 3.20 and 3.61 μ.

Anal. Calcd for $C_{15}H_{28}N_2O$: C, 71.4; H, 11.1; N, 11.1. Found: C, 71.3; H, 11.2; N, 11.1.

2,2-Dimethyl-3-piperidino-4-(piperidinomethyl)cyclobutanol (6b).—Under the same conditions used for **2**, 21 g (0.3 mole) of dimethylketene and 62.5 g (0.3 mole) of 1,1′-(propenylene)dipiperidine in 300 ml of ether gave 74 g (89%) of **6b** as a mixture of isomers. Recrystallization from hexane gave 35 g (41%) of **6b** (major isomer): mp 135–138°; infrared absorptions (KBr), 3.18 and 3.62 μ; nmr spectrum (CH_2Cl_2), two single peaks at 0.92 and 1.08 (methyl groups), broad singlet at 1.47 ($-CH_2-CH_2CH_2-$ in piperidino rings), broad multiplet at 2.26 (methylene groups adjacent to nitrogen and methylidyne protons of positions 2 and 3 of cyclobutane ring), singlet at 2.95 (–OH), and doublet at 3.22 ppm (methylidyne proton at position 1 of cyclobutane ring).

Anal. Calcd for $C_{17}H_{32}N_2O$ (135–138° isomer): C, 72.9; H, 11.4; N, 10.0. Found: C, 73.1; H, 11.5; N, 10.1.

The filtrate from the recrystallization of the above isomer was evaporated to give a solid residue. Repeated recrystallizations of this material from hexane gave 5.1 g of another isomer of **6b**: mp 80–82.5°; nmr spectrum (CCl_4), two single peaks at 0.97 and 1.02 (methyl groups), broad singlet at 1.51 ($-CH_2CH_2CH_2-$ in piperidino rings), broad multiplet at 2.25 (methylene groups adjacent to nitrogen and methylidyne proton at position 1 of cyclobutane ring), and singlet at 4.32 ppm (–OH).

4-Ethyl-6-methyl-1-piperidino-1,5-heptadien-3-one (7).—Ketene (25 g, 0.59 mole) was added to a solution of 100 g (0.52 mole) of 1-(2-ethyl-4-methyl-1,3-pentadien-1-yl)piperidine in 275 ml of benzene. The reaction was quite exothermic, and the temperature was kept at 15–30° by use of an ice bath. After being stirred for 2 hr, the solution was distilled through a 6-in. Vigreux column to give some unchanged starting enamine, a large amount of dark, high-boiling residue, and 26 g (21%) of **7**: bp 155° (0.3 mm); $n^{20}D$ 1.5421; infrared absorptions (smear), 6.0, 6.15, and 6.35 μ; nmr spectrum (benzene), triplet at 1.00 and quartet at 1.67 (ethyl group), broad peaks at 1.12 and 2.70 (piperidino group), singlet at 1.69 (methyl groups attached to double bond), multiplet at 3.02 (methylidyne proton), doublet at 5.04 (olefinic proton), and pair of doublets at 5.10 and 7.75 ppm (—CH=CH—N<).

Anal. Calcd for $C_{15}H_{25}NO$: C, 76.6; H, 10.6; N, 6.0. Found: C, 76.7; H, 10.5; N, 5.4.

2-Butyl-3-(dimethylaminomethyl)-2-ethylcyclobutanone (8a).—A mixture of 63 g (0.5 mole) of butylethylketene and 60 g (0.7 mole) of N,N-dimethylallylamine was heated in an autoclave at 180° for 8 hr. The reaction mixture was distilled through an 18-in. Vigreux column to give 34 g of unchanged N,N-dimethylallylamine and 64 g of crude **8a**, bp 80.5–84° (0.5 mm). The crude product was treated with a 10% hydrochloric acid solution and extracted with ether to remove the by-product, 2,4-dibutyl-2,4-diethyl-1,3-cyclobutanedione. The aqueous layer was neu-

(6) R. H. Hasek and E. U. Elam (to Eastman Kodak Co.), Canadian Patent 618,772 (1961).

(7) T. L. Cairns and J. C. Sauer, *J. Org. Chem.*, **20**, 627 (1955).

(8) C. Mannich, K. Handke, and K. Roth, *Ber.*, **69**, 2112 (1936).

(9) R. L. Pruett, J. T. Barr, K. E. Rapp, C. T. Bahner, J. D. Gibson, and R. H. Lafferty, Jr., *J. Am. Chem. Soc.*, **72**, 3646 (1950).

(10) H. Breederveld, *Rec. Trav. Chim.*, **79**, 1197 (1960).

tralized with a 20% sodium hydroxide solution, extracted with ether, and dried over anhydrous magnesium sulfate. Distillation of this solution through a 6-in. Vigreux column gave 34 g (32%) of **8a**: bp 80–82° (0.6 mm); infrared absorption (smear), 5.63 μ; nmr spectrum (neat), multiplet at 0.90 (methyl groups), multiplet at 1.36 (four methylene groups), singlet at 2.20 (dimethylamino group), multiplet at 2.32 (methylidyne proton), multiplet at 2.75 (methylene group in ring), and multiplet at 2.41 ppm (methylene group adjacent to nitrogen).

Anal. Calcd for $C_{13}H_{25}NO$: C, 74.0; H, 11.8; N, 6.6. Found: C, 73.9; H, 12.2; N, 6.9.

2-Butyl-2-ethyl-3-(piperidinomethyl)cyclobutanone (8b).—Under the same conditions used for **8a**, butylethylketene and N-allylpiperidine gave **8b** in 22% yield: bp 98–101° (0.15 mm); infrared absorption (smear), 5.62 μ.

Anal. Calcd for $C_{16}H_{29}NO$: C, 76.4; H, 11.6; N, 5.6. Found: C, 75.8; H, 11.6; N, 5.8.

2-Butyl-2-ethyl-3-(morpholinomethyl)cyclobutanone (8c).—Under the same conditions used for **8a**, butylethylketene and N-allylmorpholine gave 28% of **8c**: bp 108–110° (0.1 mm); infrared absorption (smear), 5.64 μ.

Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.1; H, 10.7; N, 5.5. Found: C, 70.8; H, 10.8; N, 5.7.

2,2-Dimethyl-3-(N-acetylpropylamino)cyclobutanone (9).—To a stirred solution of 55.9 g (0.44 mole) of N-propyl-N-vinylacetamide in 200 ml of benzene was added 35 g (0.5 mole) of dimethylketene under nitrogen. The reaction temperature slowly rose to 35°. After being stirred for 5 hr, the solution was distilled through a 12-in. Vigreux column to obtain some unchanged N-propyl-N-vinylacetamide, tetramethyl-1,3-cyclobutanedione, and 42.0 g (48%) of **9**: bp 126–128° (1.5 mm); $n^{20}D$ 1.4758; infrared absorptions (smear), 5.65 and 6.13 μ; nmr spectrum (neat), triplet at 0.93 (methyl of propyl group), two peaks at 0.94 and 1.26 (*gem*-dimethyl group), a singlet at 2.05 (methyl of acetyl group), multiple peaks at 1.25 and 1.93 (middle methyl of propyl group), multiple peaks from 3.11 to 3.52 (methylene of ring and methylene in propyl group adjacent to nitrogen), and triplet at 4.03 ppm (methylidyne proton).

Anal. Calcd for $C_{11}H_{19}NO_2$: C, 67.0; H, 9.7; N, 7.1. Found: C, 66.8; H, 10.0; N, 7.1.

2,2-Dimethyl-3-(N-acetylpropylamino)cyclobutanol (11).—A solution of 30 g of the cyclobutanone **9** in 70 ml of ethyl alcohol was hydrogenated in a rocking autoclave at 100° and 3000 psi over 5 g of a 5% ruthenium-on-carbon (powdered) catalyst. This reaction solution was filtered to remove the catalyst, and the filtrate was distilled through a 10-in. packed column to give 25.2 g (81%) of **11**: bp 143° (0.8 mm); $n^{20}D$ 1.4845; infrared absorptions (smear), 2.95 and 6.15 μ.

Anal. Calcd for $C_{11}H_{21}NO_2$: C, 66.4; H, 10.5; N, 7.0. Found: C, 66.2; H, 10.7; N, 6.9.

2,2-Dimethyl-3-(N-benzoylpropylamino)cyclobutanol (12).—To a solution of 12.3 g (0.05 mole) of 2,2-dimethyl-3-(N-benzoylpropylamino)cyclobutanone in 30 ml of ethyl alcohol was added slowly with stirring a solution of 0.76 g (0.02 mole) of sodium borohydride in 5 ml of water. The reaction solution was stirred for 1 hr at room temperature and then evaporated on a steam bath. The residue was taken up in ether, washed with water, and dried over anhydrous sodium sulfate. Distillation of this solution gave 9.8 g (80%) of **12** as a clear, very viscous distillate: bp 192–196° (1 mm); infrared absorptions (smear), 3.0 and 6.2 μ.

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.6; H, 8.8; N, 5.4. Found: C, 73.4; H, 8.8; N, 5.3.

The Reaction of Butylethylketene with N-Propyl-N-vinylacetamide.—A solution of 51 g (0.4 mole) of N-propyl-N-vinylacetamide and 50 g (0.4 mole) of butylethylketene in 100 ml of hexane was refluxed for 8 hr. The infrared spectrum of this solution had a strong band at 5.63 μ (cyclobutanone). The solution was distilled through a 12-in. packed column to recover about 20 g of unchanged butylethylketene dimer and 45 g of a mixture of unchanged N-propyl-N-vinylacetamide and butylethylketene dimer, bp 64–107° (0.15 mm). The product (26 g) was taken at 107–133° (0.15 mm). This material was redistilled through a spinning-band column to give 5.1 g of N-(4-ethyl-3-oxo-1-octen-1-yl)-N-propylacetamide (**14**): bp 126° (0.2 mm); $n^{20}D$ 1.5022; infrared absorptions (smear), 5.9, 6.18, and 6.3 μ; nmr spectrum (CCl_4), a pair of doublets at 5.75 and 8.04 ppm

$$\begin{matrix} & & O & & \\ & & \| & & \\ R & C & C & H{=}CHNR_2 & \end{matrix}$$

(the protons of the RCCH=CHNR$_2$ grouping).

Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.1; H, 10.7; N, 5.5. Found: C, 71.0; H, 10.7; N, 5.5.

N-Methyl-N-(2,2-dimethyl-3-oxocyclobutyl)benzenesulfonamide (15a).—To a stirred solution of 197 g (1.0 mole) of N-methyl-N-vinylbenzenesulfonamide in 500 ml of acetonitrile under nitrogen was added 70 g (1.0 mole) of dimethylketene. The reaction temperature was held at 25–35° by a cooling bath. After being stirred for several hours, the reaction solution was distilled through a 12-in. Vigreux column to recover some tetramethyl-1,3-cyclobutanedione and 127 g of unchanged N-methyl-N-vinylbenzenesulfonamide, bp 113–114° (0.8 mm). The distillation was continued in a molecular still to give 65 g (24%) of **15a**, bp 93–102° (2–3 μ), $n^{20}D$ 1.5429. This distillate slowly crystallized on cooling. A sample recrystallized from ethyl alcohol had mp 58–60°; infrared absorption (KBr), 5.62 μ; nmr spectrum (CCl_4), doublet at 1.18 (*gem*-dimethyl group), singlet at 2.70 (methyl group on nitrogen), multiple peaks between 2.81 and 3.92 (methylene and methylidyne groups of cyclobutane ring), and multiplet at 7.52 ppm (aromatic protons).

Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.4; H, 6.4; N, 5.2; S, 12.0. Found: C, 58.4; H, 6.4; N, 5.2; S, 12.2.

Synthesis and Hydrolysis of α- and ϵ-Peptides of Lysine[1]

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In order to compare ϵ-peptide bonds with α-peptide bonds, dipeptides of L-lysine were synthesized by coupling glycine, L-alanine, L-phenylalanine, L-leucine, or L-aspartic acid to the α- or ϵ-amino group of lysine by the mixed carboxylic–carbonic acid anhydride method. The first-order rate constants of hydrolysis of these peptides were studied in 3 *N* and 6 *N* HCl and NaOH at 55, 75, and 97°. Except for the aspartyllysines, there were only slight differences in the rates of acid-catalyzed hydrolysis of the corresponding α- and ϵ-peptides under various experimental conditions. In base-catalyzed hydrolysis, ϵ-peptides were hydrolyzed 4–9.5 times faster than α-peptides showing that the position of the peptide bond as well as the side chain of the amino acid coupled to lysine determine the rate of hydrolysis.

In proteins the amino group on the side chain of lysine residues offers the possibility of an alternate structure involving the ϵ-amino group in addition to or instead of the α-amino group in chemical linkage to the adjacent amino acid. In the former case a branched chain protein is formed as observed in bovine growth hormone[3] and collagen.[4] Polypeptidyl proteins in which branched chains are built onto a protein mole-

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(2) Based on a dissertation presented by J. D. P. to the Graduate School of St. Louis University in partial fulfillment of the requirements for the Ph.D. in biochemistry.

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