William Anderson, and Mr. Harold Smith of the Oregon Graduate Center for mass spectra. The National Science Foundation (Grant No. GB-12278), Research Corporation, and The Alfred P. Sloan Foundation generously provided funds which facilitated purchase of the 220-MHz nmr spectrometer. The nmr (^{13}C) spectrum was determined through the generous cooperation of Bruker Scientific, Inc., Elmsford, N. Y.

Some Aspects of the Photochemical and Mass Spectral Behavior of Bridgehead Acetone Derivatives

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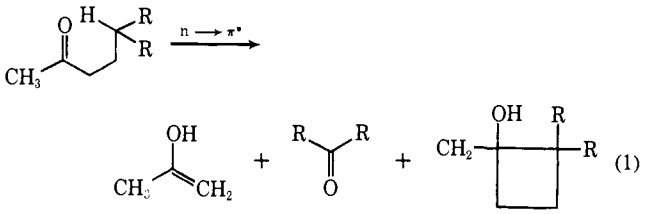
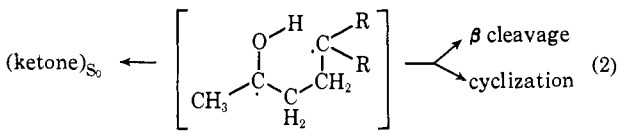
Abstract: The behavior of the following ketones was examined under conditions of irradiation with ultraviolet light ($\lambda > 260$ nm) and under electron impact in a mass spectrometer: 1-norbornylacetone (**2**), 1-bicyclo[2.2.2]-octenylacetone (**7**), 1-bicyclo[2.2.2]octylacetone (**12**), 1-bicyclo[3.3.1]nonylacetone (**17**), and 1-adamantylacetone (**18**). The principal irradiation products were the cyclobutanols derived from intramolecular hydrogen abstractions followed by cyclization. The most significant fragmentations in the mass spectrometer led to the formation of $M^+ - 58$ ions in contrast to the usual behavior of acetone derivatives. The differences between these systems and acyclic analogs are attributed to the strain associated with introduction of double bonds at bridgeheads.

The mechanism of the type II photoelimination reaction of aliphatic ketones has received considerable attention over the past few years.[1,2] It has been found that ketones having γ-hydrogen atoms undergo cleavage at the β bond with formation of an olefin and an enol, and, to a lesser extent, cyclobutanols (eq 1). These reactions are believed to involve biradical



(1)

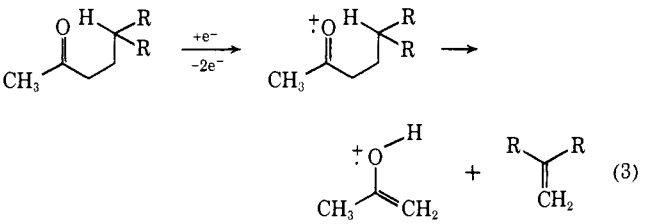
intermediates which may be formed by hydrogen abstraction by either singlet or triplet excited states of the carbonyl groups. The quantum efficiencies of these reactions have been rationalized in terms of the partitioning of these biradicals[2] (eq 2).



(2)

The objective of this research was directed toward enlarging our understanding of the scope of this reaction. Specifically, we sought to determine the structural factors which affect the relative efficiencies of the product-forming steps in eq 2. For this purpose, we chose to examine the photochemical behavior of the following ketones: 1-norbornylacetone (**2**), 1-bicyclo[2.2.2]octenylacetone (**7**), 1-bicyclo[2.2.2]octylacetone (**12**), 1-bicyclo[3.3.1]nonylacetone (**17**), and 1-adamantylacetone (**18**). The choice of these compounds was dictated by the expected gradation[3] in ease of formation of the different bridgehead olefins which could be formed as a result of type II eliminations. Cyclobutanol formation, on the other hand, was expected to be considerably less sensitive to the changes in the carbon skeletons.

As a sequel, a comparison of the photochemical results was to be made with the fragmentation processes induced by electron impact. In simple systems it has been noted that ketones having γ-hydrogen atoms undergo McLafferty cleavages (eq 3) in the mass spectrometer. Several investigators have commented[4] on these similarities and an approximate correlation between quantum yields of photoeliminations and efficiency of McLafferty cleavages has been noted. It was anticipated that information bearing on the generality of this correlation would be available from these studies. Furthermore, the scope of the McLafferty



(3)

(1) P. J. Wagner and G. S. Hammond, *J. Amer. Chem. Soc.*, **88**, 1245 (1966); J. N. Pitts, Jr., D. R. Burley, J. C. Mani, and A. D. Broadbent, *ibid.*, **90**, 5902 (1968); N. C. Yang, S. P. Elliott, and B. Kim, *ibid.*, **91**, 7551 (1969); R. A. Caldwell and P. M. Fink, *Tetrahedron Lett.*, 2987 (1969); P. J. Wagner and P. A. Kelso, *ibid.*, 4151 (1969); F. D. Lewis and N. J. Turro, *J. Amer. Chem. Soc.*, **92**, 311 (1970).

(2) P. J. Wagner and H. N. Schott, *ibid.*, **91**, 5383 (1969); P. J. Wagner, *ibid.*, **89**, 5898 (1967); P. J. Wagner and A. E. Kemppainen, *ibid.*, **91**, 3085 (1969).

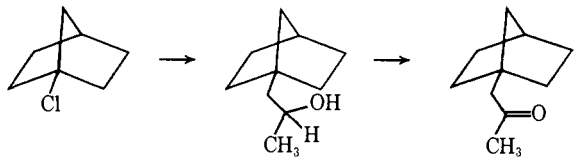
(3) For a recent discussion see J. A. Marshall and H. Faubl, *ibid.*, **92**, 948 (1970); J. R. Wiseman and W. A. Pletcher, *ibid.*, **92**, 956 (1970).

(4) J. N. Pitts, Jr., J. K. Foote, and J. K. S. Wan, *Photochem. Photobiol.*, **4**, 323 (1965); T. W. Martin and J. N. Pitts, Jr., *J. Amer. Chem. Soc.*, 77, 5465 (1955); A. J. C. Nicholson, *Trans. Faraday Soc.*, **50**, 1067 (1954); F. W. McLafferty, *Anal. Chem.*, **31**, 82 (1959); for a critical discussion, see T. W. Bentley and R. A. W. Johnstone, *Advan. Phys. Org. Chem.*, **8**, 152 (1970).

rearrangement itself would be extended significantly by a study of these ketones since the generality of this rearrangement has not been tested in situations in which olefin strain might play a role in the efficiency of the cleavage.

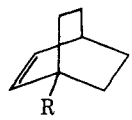
Syntheses

1-Norbornylacetone (**2**) was prepared by a two-step sequence from 1-chloronorbornane. Reaction of the lithium derivative of the latter compound with propylene oxide produced alcohol **1** which could readily be oxidized to form ketone **2**.

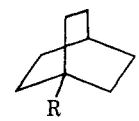


1 **2**

The starting material for the synthesis of the bicyclooctyl derivatives was ester **3**[5] which was converted to the carbinol **4** upon treatment with lithium aluminum hydride. The corresponding tosylate **5** gave the nitrile **6** on treatment with sodium cyanide in dimethyl sulfoxide. Reaction of nitrile **6** with methyllithium gave an imine which on hydrolysis yielded ketone **7**.

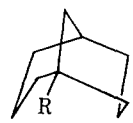


3, R = CO_2Et
4, R = CH_2OH
5, R = CH_2OTs
6, R = CH_2CN
7, R = $CH_2C(=O)CH_3$

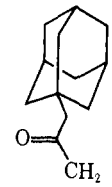


8, R = CO_2Et
9, R = CH_2OH
10, R = CH_2OTs
11, R = CH_2CN
12, R = $CH_2C(=O)CH_3$

Both the saturated analog, 1-bicyclo[2.2.2]octylacetone (**12**) and 1-bicyclo[3.3.1]nonylacetone (**17**) were synthesized by similar sequences starting with the corresponding esters **8** and **13**, respectively. The 1-adamantylacetone (**18**) used was obtained from the Lilly



13, R = CO_2Et
14, R = CH_2OH
15, R = CH_2OTs
16, R = CH_2CN
17, R = CH_2COCH_3



18

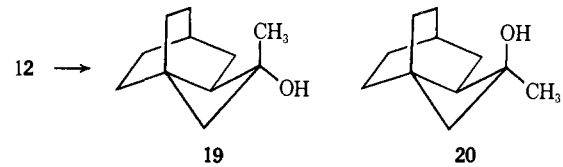
Research Center, Ltd.[6]

The structures of the ketones were confirmed by infrared, nuclear magnetic resonance, and mass spectral data. For example, all of these systems displayed carbonyl absorptions in the infrared at *ca.* 5.8 μ. In the nmr spectra, singlets which could be attributed to methylene and methyl groups adjacent to carbonyl functions were observed near δ 2.0. Finally, the mass spectra of these systems uniformly displayed the expected molecular ions and intense fragmentation ions at *m/e* 43 ($CH_3C{\equiv}O^+$).[7]

Results and Discussion of Irradiations

Dilute solutions of the ketones in *tert*-butyl alcohol were irradiated until most of the starting material had disappeared. The photoproducts were detected and isolated by gas chromatography and characterized by elemental analyses, mass spectrometry, and infrared and nmr spectroscopy. In all cases the products were found to be tertiary alcohols, and it is assumed that these materials correspond to the various cyclobutanols expected for ketones having γ-hydrogen. With the exception of **17**, highly volatile components were conspicuously absent from the gas chromatograms of the photosylates. Irradiation of **17** did lead to the appearance of acetone and some low molecular weight products, but the latter did not accumulate to an appreciable extent. In addition, attempts to trap bridgehead olefins by addition of acetic acid[8] did not prove successful.

Tentative stereochemical assignments were made to some of the alcohols on the basis of nmr data. The arguments can be illustrated by a consideration of the spectra of the two products formed on irradiation of 1-bicyclo[2.2.2]octylacetone (**12**). The difference in chemical shifts of the methyl resonances was used to assign structure **19**[8] to the major product (59%) and structure **20** to the minor product (24%). The methyl



19 **20**

resonance for the major product appeared at δ 1.45 and that for the minor alcohol appeared at δ 1.32. These assignments are consistent with the analogy to 1-methylcyclobutanol (δ_{CH_3} 1.30) and with the expected effect of steric crowding on the chemical shift of the methyl group of **19**.[9] These assignments were strengthened by a similar analysis of the products formed from 1-bicyclo[2.2.2]octenylacetone. Of the three photoproducts isolated, one isomer showed a methyl resonance at δ 1.25. Since this compound gave compound **20** upon catalytic reduction of the double bond it is assigned structure **21**. The nmr spectrum of the mixture of the other two photoproducts showed methyl resonances at δ 1.47 and 1.13. In this case, reduction produced only compound **19**. These data can be reasonably interpreted only in terms of structures **22** and **23**, *i.e.*, in one isomer, **22**, the methyl resonance is *deshielded* by steric crowding, whereas in the other, **23**, the methyl resonance is *shielded* by the anisotropic effect[10] of the double bond.

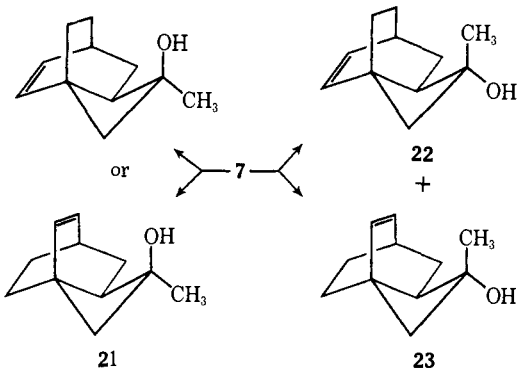
(5) J. C. Kauer, R. E. Benson, and G. W. Parshall, *J. Org. Chem.*, 30, 533 (1965). We are deeply indebted to Dr. Kauer for samples of this ester and for assistance with the synthesis.

(6) We are grateful to Dr. S. S. Szinai and the Lilly Research Center, Ltd. for this sample; see W. H. W. Lunn, W. D. Podmore, and S. S. Szinai, *J. Chem. Soc. C*, 1657 (1968).

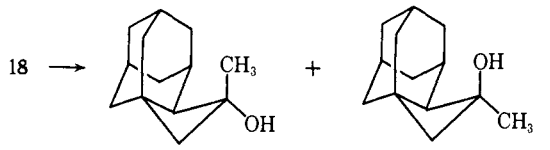
(7) A. G. Sharkey, Jr., J. L. Shultz, and R. A. Friedel, *Anal. Chem.*, 28, 934 (1956).

(8) The gross structure of **19** was confirmed by conversion (CrO_3, followed by NaOBr) to bicyclo[2.2.2]octane-1,2-dicarboxylic acid (see Experimental Section).

(9) For references and examples see S. Winstein, P. Carter, F. A. L. Anet, and A. J. R. Bourn, *J. Amer. Chem. Soc.*, 87, 5247 (1965). The datum for 1-methylcyclobutanol was taken from J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press, London, 1966, p 1126.



The results with 1-adamantylacetone followed a similar pattern; the methyl resonance for the major (61%) product appeared at δ 1.58 and that for the minor (24%) product appeared at δ 1.35. Consequently, structures **24** and **25**, respectively, were assigned to these products.[11] The ratio of **24** to **25** did not



change appreciably when the solvent was changed from *tert*-butyl alcohol to benzene although the quantum yield yields were about twofold greater in the former solvent. This behavior is typical of aliphatic ketones and has been ascribed to solvation of the biradical (eq 2) by *tert*-butyl alcohol.[1,2] It was of interest to determine the extent to which hydrogen–deuterium exchange between the biradical and a deuterated solvent would compete with the back reaction. For this purpose, ketone **18** was irradiated in *tert*-butyl alcohol-*O-d* until 50% of the ketone had been consumed. The recovered ketone was analyzed by mass spectroscopy[12] and shown to contain about 2% deuterium incorporation at the ring carbons. The significance of this result will be discussed below.

Irradiation of 1-norbornylacetone resulted in the production of two major products both of which showed the properties expected for cyclobutanols. In contrast to the results with **12** and **18**, both isomers displayed methyl resonances at δ 1.30. If these data are interpreted to indicate that both of these isomers have structures in which the methyl groups are found in the less-hindered positions, it becomes difficult to rationalize the absence of the corresponding epimers since the latter were the predominant products from **12** and **18**. Perhaps small geometrical differences in the norbornyl system sufficiently change the magnetic environment of the methyl groups such that the analogies cannot be applied.[13]

The irradiation of **17** in several different solvents produces a broad spectrum of products. At least six products were formed whose retention times were compatible with cyclobutanol structures. A material isolated in 13% yield showed infrared and nmr spectra which were consistent with the presence of two cyclobutanols (δ_{CH_3} 1.40 and 1.21). The quantum yield for the formation of these isomers was 0.009 based on the efficiency of disappearance of the starting material (Φ = 0.07). The efficiency of acetone production was 0.045, but since none of the other products was produced in a comparable yield, it seems likely that type II elimination may not be the only source of acetone.

The tendency of these cyclic acetone derivatives to produce cyclobutanols in preference to type II elimination products stands in marked contrast with the behavior of acyclic ketones. It is significant that the quantum efficiencies for cyclobutanol formations for **17** and **18**[11] are of the same order of magnitude as those reported for simple aliphatic ketones.[1,2] The low quantum efficiencies for ketone disappearance can, therefore, be attributed to inefficient β cleavages of the biradical intermediates (eq 2). The increased barriers to cleavage[14] are undoubtedly a manifestation of the high strain energy which would be required to insert double bonds at the bridgeheads.

Since it was possible to detect at least a small amount of deuterium exchange at the ring positions of **18** during photolysis, in *tert*-butyl alcohol-*O-d* it can be said that at least some hydroxy biradicals (eq 2) survive long enough to undergo hydrogen–deuterium exchange before undergoing reversion to the ground state.[15] The low efficiency of the exchange process[16] may be an indication that other pathways for radiationless decay are operative. Heller[17] has suggested that quantum efficiencies of photochemical hydrogen abstraction reactions may be controlled by the rates of relaxation of vibrationally excited stretching modes formed *via* conversion of electronic energy into vibrational energy. This mode of deactivation does not require back transfer of hydrogen atoms, and would, therefore, not lead to exchange in deuterated media. In between these extremes lies a highly ordered complex in which the migrating hydrogen is weakly bonded to both carbon and oxygen.

Mass Spectra. The mass spectra of these ketones were determined at 70 eV and some of the data obtained are summarized in Table I. Examination of the data in Table I reveals some interesting anomalies. For example, the fragmentation pattern observed for 1-bicyclo[2.2.2]octenylacetone (**7**) at first glance appears

(10) J. W. ApSimon, W. G. Craig, P. V. Demarco, D. W. Mathieson, L. Saunders, and W. B. Whalley, *Tetrahedron*, 23, 2357 (1967).

(11) During the preparation of this manuscript two other groups reported similar results: S. L. Murov, *14th Annu. Rep. Res. (Petrol. Res. Fund)*, 14, 110 (1970); R. B. Gagosian, J. C. Dalton, and N. J. Turro, *J. Amer. Chem. Soc.*, 92, 4752 (1970). The structural assignments by the latter authors were also based on analysis of nmr spectral data. The sum of the quantum yields for cyclobutanol formation was 0.043 (benzene).

(12) Z. Dolejšek, S. Hála, V. Hanuš, and S. Landa, *Collect. Czech. Chem. Commun.*, 31, 435 (1966). The analysis involves comparison of the relative intensities of the peaks at *m/e* 135 ($M^+ - 57$) and 136. See K. Bieman, "Mass Spectroscopy, Organic Chemistry Applications," McGraw-Hill, New York, N. Y., 1962, p 223.

(13) It is not unlikely that both of the products isolated have the cyclobutyl ring fused exo in view of the expected relative stability of this ring system [*cf.* E. J. Corey and R. S. Glass, *J. Amer. Chem. Soc.*, 89, 2600 (1967)] and the known unreactivity of the C-7 position toward radical abstraction [*cf.* C. Kooyman and G. C. Vegter, *Tetrahedron*, 4, 382 (1958)].

(14) E. D. Feit (*Tetrahedron Lett.*, 1475 (1970)) has estimated a barrier of 8 kcal/mol for cyclization of a 1,4-hydroxy biradical. The barrier for cleavage must be >2 kcal/mol higher in these systems.

(15) A related result was recently reported by F. D. Lewis, *J. Amer. Chem. Soc.*, 92, 5602 (1970).

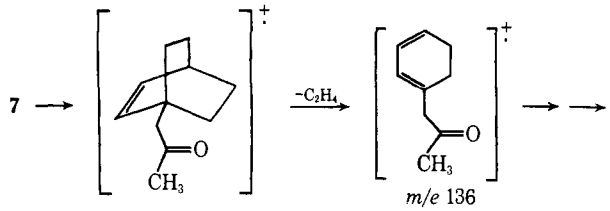
(16) The quantum efficiency of exchange is estimated to be 0.005. This value is based on our estimate of ϕ_{cyc} in *tert*-butyl alcohol (see Experimental Section) and on the measured deuterium incorporation.

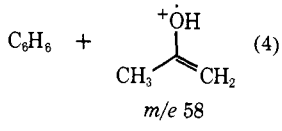
(17) A. Heller, *Mol. Photochem.*, 1, 257 (1969).

Table I. Relative Intensities of Selected Mass Spectral Peaks

	Relative intensity of selected ions					
Ketone	M^+	$M^+ - 58$	$M^+ - 57$	*m/e* 58	*m/e* 43	$M^+ - 18$
2	6.5	39	14	4	100	1
12	17	29	15	4.3	100	8
17	5	92	26	5.5	100	4
18	8.5	2	122	1.6	100	0.5
7	1	2.5	1	32	100	

normal[7] in that an intense peak was observed at *m/e* 58, presumably the ionized form of acetone enol.[4,7] If ketone **7** is able to undergo a simple McLafferty cleavage, it would be surprising if the saturated systems did not also produce intense ions at *m/e* 58. A more likely explanation of the discrepancy would be that **7** undergoes a retro-Diels–Alder reaction prior to McLafferty rearrangement (eq 4). The observation of a peak at *m/e* 136 further supports this mechanism.





(4)

In contrast, the saturated ketones examined show relatively low intensity ions at *m/e* 58, and it can be stated that the McLafferty rearrangement does not contribute appreciably to the fragmentation of the molecular ions of these systems. On the other hand, relatively intense ions are observed at $M^+ - 58$ which, in a formal sense, may be attributed to McLafferty processes in which the charge is retained by the olefinic fragment. Furthermore, there is a rough trend in the relative intensities of these ions which parallels the expected ease of formation of double bonds at the various bridgeheads;[3] *i.e.*, **17** > **2**–**12** > **18**. There is reason to believe that this analysis may be oversimplified, however. Although McLafferty cleavages which result in charged olefins are precedented, the charge distribution is apparently controlled mainly by the relative magnitudes of the ionization potentials of the olefin *vs.* that of acetone enol.[18] As most simple olefins have higher ionization potentials than acetone enol, the most commonly observed fragmentation possesses yield-ionized acetone enol and uncharged olefins. Unfortunately, the available literature data on ionization potentials of strained *vs.* simple olefins are contradictory. Relative values obtained from electron-impact measurements suggest that strained olefins have unusually high values,[19a] but values obtained from photoelectron spectra[19b] are in the opposite direction. To make matters worse, there is no general agreement on the best value of the ionization potential for acetone enol. As the literature values range from 8.2[20] to 9.1 eV,[4,18] a definitive analysis of the fragmentations in question cannot be made at this time. For the moment, these fragmentations may be considered as formal "McLafferty" rearrangements although the structures of the $M^+ - 58$ ions remain an open question.

The behavior of 1-adamantylacetone under electron impact contrasts markedly with that of the other bridgehead acetone derivatives in that no appreciable $M^+ - 58$ fragment was observed. Instead, the predominent cleavage led to loss of acetonyl radicals and the appearance of an intense peak at *m/e* 135 ($C_{10}H_{15}^+$).[12] Although this kind of cleavage contributes significantly to the overall fragmentations of all of the saturated ketones, its relative importance is clearly enhanced in the breakdown of the molecular ion from **18**. While one of the controlling factors which regulates the importance of this process must be the stability of the incipient $C_{10}H_{15}^+$ ion, other considerations must also be important. For example, there is a poor correlation between the relative amount of this kind of fragmentation and the stabilities of the unrearranged bridgehead cations derived from these systems.[21] This being the case, and the additional probability that some or all of the $M^+ - 57$ ions may have rearranged structures,[12] make it appear likely that the enhancement of the $M^+ - 57$ process in **18** is only apparent. It may be that the molecular ion of **18** is unable to undergo the "McLafferty" rearrangement for purely structural reasons; thus, competitive processes become more significant.

Another interesting aspect of the mass spectral behavior of these ketones is the appearance of significant fragmentation peaks at $M^+ - 18$.[22] Ordinarily, aliphatic ketones do not give rise to this kind of fragmentation. For example, Yeo and Williams[22,23] found no significant $M^+ - 18$ peaks in the mass spectra of 3-octanone and several other aliphatic ketones with fewer carbon atoms. Fragmentation with loss of water did become significant with ketones which contained at least seven carbon atoms in a side chain. The ten-membered ring transition state postulated by these authors would be geometrically unattainable in the polycyclic systems in question. As an alternative mechanistic pathway for dehydration, we propose that cyclobutanol formation precedes elimination of water. Although it has been shown that fragmentation of a simple aliphatic analog, 3-methylhexanone, does not involve cyclobutanol formation,[24] this process has been implicated[25] in the interpretations of the cracking patterns

(18) S. Meyerson and J. D. McCollum, *Advan. Anal. Chem. Instrum.*, 2, 179 (1963); H. E. Audier, *Org. Mass Spectrosc.*, 2, 283 (1969).

(19) (a) The ionization potential of cyclopropene has been found to be 0.77 eV higher than that for cyclohexene (9.18 eV); see J. Collin and F. P. Lossing, *J. Amer. Chem. Soc.*, **81**, 2064 (1959). Similarly, norbornene (9.05 eV) was found to have a fairly high ionization potential by T. McAllister, Z. Dolesek, F. P. Lossing, R. Gleiter, and P. von R. Schleyer, *ibid.*, **89**, 5982 (1967). (b) For example, the first ionization potential for cyclohexene (9.12 eV) lies above that for norbornene (8.97 eV); see P. Bischof, J. A. Hashmall, E. Heilbronner, and V. Hornung, *Helv. Chim. Acta*, **52**, 1745 (1969).

(20) E. Murad and M. G. Inghram, *J. Chem. Phys.*, 40, 3263 (1964).

(21) W. G. Dauben and C. D. Poulter, *J. Org. Chem.*, **33**, 1237 (1968); P. von R. Schleyer, P. Isele, and R. C. Bingham, *ibid.*, **33**, 1239 (1968).

(22) A. N. H. Yeo and D. H. Williams, *Org. Mass Spectrosc.*, 2, 331 (1969).

(23) In the cases of **12** and **17**, metastable ions were observed which correspond to the process $M^+ \rightarrow M^+ - H_2O + 18$; see the Experimental Section for data.

(24) A. F. Gerrard, R. L. Hale, R. Liedtke, W. H. Faul, and C. A. Brown, *Org. Mass Spectrosc.*, 3, 683 (1970).

(25) S. Meyerson, C. Fenselau, J. L. Young, W. R. Landis, E. Selke, and L. C. Leitch, *ibid.*, 3, 689 (1970); R. J. Liedtke and C. Djerassi, *J. Amer. Chem. Soc.*, **91**, 6814 (1969); J. Kossanyi and J. K. Mogto, *Org. Mass Spectrosc.*, 3, 721 (1970).

of aliphatic aldehydes and diketones. It is apparent that more than one mechanism can be operable in these dehydration processes; the predominant pathway in a given case will ultimately be determined by the structure of the molecule in question.

Summary and Conclusions

The chemically efficient production of highly strained cyclobutanols represents a powerful synthetic method for the preparation of several novel ring systems. On the other hand, generation of bridgehead double bonds, and, presumably, other strained olefins by photoelimination, does not appear to be a useful transformation. Although the molecular ions of all of the ketones except **18** underwent formal McLafferty cleavages, it was concluded that skeletal rearrangements may have attended these processes. The inability of 1-adamantylacetone to undergo McLafferty rearrangement is attributed to purely structural limitations on this process. Therefore, this ketone, at least, shows rather different behavior in photolytic and mass spectral processes. To the extent that the other ketones undergo fragmentations *via* cyclobutanol intermediates, the mass spectral results parallel the photochemical behavior.

Experimental Section

Infrared spectra were determined as liquid films or as noted on a Perkin-Elmer Model 21 or Model 137 spectrophotometer. Nuclear magnetic resonance spectra were obtained from Varian spectrometers (A-60 or HA-100) in carbon tetrachloride (except where otherwise stated) solutions with tetramethylsilane as an internal standard. Relative intensities were usually within ±10% of the expected values. Mass spectra were obtained at 70 eV on a Hitachi RMU 7 mass spectrometer. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Gas chromatograms were obtained from an Aerograph Model A90P on the following columns: A, 5–18% Carbowax 20M (5–15 ft × 0.25 in.); B, 10% DCQF1 (5 ft × 0.25 in.); C, 1% DCQF1–4% Carbowax 20M (15 ft × 0.19 in.). Relative retention times (t_r) refer to the ratios of retention times of the cyclobutanols to the corresponding ketones. Yields were calculated on the assumption that all detector responses were equal. This assumption was experimentally verified in the case of **18** and **22**.

1-Norbornylacetone (2). A slurry of lithium was prepared in 100 ml of dry, freshly distilled cyclohexane by the following procedure. A 60-g piece of paraffin rod which contained 30% lithium dispersion, 1% sodium dispersion, and 2% oleic acid[26] was placed in a flask which contained 100 ml of dry benzene. The benzene was removed by suction through a fritted disk after the wax had dissolved. After two more rinses with dry benzene and three rinses with dry cyclohexane, 100 ml of dry cyclohexane was added and the slurry was heated to reflux. A solution of 23.09 g (0.18 mol) of 1-chloronorbornane[27] in 100 ml of cyclohexane was added over a period of 1 hr in a nitrogen atmosphere. After an additional 3 hr of reflux, 10 g of freshly distilled propylene oxide was added over a 3-hr period. After an additional 3-hr reflux a second quantity (3 g) of oxide was added followed by a 30-min reflux period. The excess lithium was destroyed by addition of methanol. The solution was acidified with dilute sulfuric acid and extracted with chloroform. The extracts were dried and evaporated and the residue was distilled at 75° (0.1 mm) to yield 3.53 g (13%) of 1-(1-norbornyl)propan-2-ol (**1**): nmr δ 3.86 (sex, J = 6 Hz, HCO), 2.27 (s, OH), 2.16 (s, HC), 1.8–1.0 (m); ir 3.0 (OH), 8.90, 9.20, 10.67, 11.57, and 12.05 μ.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.57; H, 11.22.

A solution of 3.33 g (0.022 mol) of **1** in 60 ml of acetone was cooled to 0° and treated with 5.5 ml of Jones reagent[28] over a 1-hr period. The reaction was quenched by addition of 1 ml of isopropyl alcohol. After dilution with water, the mixture was extracted with chloroform. The extracts were washed with water, sodium bicarbonate solution, and water. After drying and evaporation, there was obtained 2.5 g (76%) of 1-norbornylacetone (**2**): bp 54–60° (1 mm); nmr 2.04 (s, CH_3), 2.56 (s, $CH_2C{=}O$), 2.17 (s, HC), 2.0–0.9 (m); ir 5.83 μ (s, C=O).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 79.02; H, 10.56.

1-Bicyclo[2.2.2]octenylacetone (7). 1-Bicyclo[2.2.2]octenylcarbinol was prepared by reduction of ester **3** with lithium aluminum hydride in ether. From 6.5 g of ester there was obtained 4.4 g (90%) of alcohol **4**: bp 60° (0.2 mm) [lit.[29] bp 95–96° (11 mm)]. The tosylate ester **5** had mp 94–95° [lit.[29] mp 96.5–97.5°].

A solution of 6 g of the tosylate **5** and 1.5 g of sodium cyanide in 60 ml of dimethyl sulfoxide was heated at 90–100° under nitrogen for 5 hr.[30] The cooled reaction mixture was poured into water and extracted with methylene chloride. The extracts were washed with water, dried, and distilled (bp 70–75° (0.2 mm)) to yield 2.8 g (93%) of nitrile **6**: mp 32–33°; nmr δ 6.21 (m, HC=), 2.57 (m, HC), 2.40 (s, CH_2CN), 1.0–2.0 (m).

Anal. Calcd for $C_{10}H_{13}N$: C, 81.59; H, 8.90. Found: C, 81.80; H, 8.73.

A solution of 1.23 g (8.4 mmol) of nitrile **6** in 10 ml of anhydrous ether was added dropwise over 1.5 hr to 15 ml of 1.67 *M* methyllithium solution (25 mmol) in a nitrogen atmosphere. The reaction mixture was stirred and cooled during the addition period. The resulting mixture was stirred at 25° for 20 hr after which time the hydrolysis was commenced by addition of 6 *N* sulfuric acid and a small amount of dioxane. After all of the precipitate had dissolved (0.5 hr at 70°), the product was extracted into ether. The combined extracts were dried and evaporated. The residue was preparatively gas chromatographed (A, 170°) to yield 0.4 g (29%) of ketone **6**: nmr δ 6.1 (m, HC=), 2.50 (s, $CH_2C{=}O$), 2.11 (s, CH_3), 1.8–1.0 (m); ir 3.29 (w, HC=), 5.83 (s, C=O), 6.20 (w, C=C), 14.44 (s) μ; molecular ion *m/e* 164 (calcd 164); selected peaks *m/e* (rel intensity) 164 (1), 136 (5), 106 (2.5), 58 (32), 43 (100).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.48; H, 10.16.

1-Bicyclo[2.2.2]octylacetone (12). Tosylate **10** was prepared from 1-carbethoxybicyclo[2.2.2]octane[29] by lithium aluminum hydride reduction and tosylation: mp 75–76° [lit.[29] mp 79–80°]. The tosylate (15 g) was converted to the nitrile **11** (5.8 g, 76%) by the above procedure: bp 66° (0.1 mm); nmr δ 2.02 (s, CH_2CN) and 1.58 (s); ir 4.45 (w, C≡N) μ.

Anal. Calcd for $C_{10}H_{15}N$: C, 80.48; H, 10.13. Found: C, 80.91; H, 9.91.

The nitrile (5.0 g) was converted with methyllithium to ketone **12** (1.3 g, 23%): bp 65–70° (0.2 mm); nmr δ 1.52 (s), 1.97 (s, CH_3), and 2.07 (s, $CH_2C{=}O$), 5.84 (C=O) μ; metastable ion *m/e* 132 (calcd for $166^+ \rightarrow 18 + 148^+$, 132.0).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.24; H, 11.03.

1-Adamantylacetone (18) was used as received and had the following properties: bp 86–88° (0.5 mm) [lit.[6] bp 76–78° (0.15 mm)]; nmr δ 2.08 (s, $CH_2C{=}O$), 2.02 (s, CH_3), 2.1–1.5 (m); ir 5.85 (s, C=O) μ.

Photolyses. Irradiations were carried out in cylindrical flasks equipped with a water-cooled immersion well equipped with a Corex filter and a 450-W medium-pressure mercury arc (Hanovia, type L). Before and during the irradiations a stream of dry, oxygen-free nitrogen was bubbled through the solutions. At the end of the irradiation period the solvent was removed by evaporative sublimation at 25° and *ca.* 0.2 mm into a receiver cooled in liquid nitrogen.

Irradiation of 2. A solution of 1.0 g of **2** in 120 ml of *tert*-butyl alcohol was irradiated for 32 hr. Analysis of the photostolyate by gc (A, 150°) revealed the presence of two products in 15 and 30% yields. The short retention time product (t_{rel} = 1.1) had the following properties: nmr δ 1.95 (s), 1.30 (s, CH_3), 2.25–1.0 (m); ir (CCl_4) 2.83 (sh) and 2.95 (br) (OH), 8.35, 10.87 μ; mass spectrum *m/e* (rel intensity) 152 (1.6), 134 (3.2), 94 (31.6), and 43 (100).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.67; H, 10.33.

(26) Obtained from Lithium Corporation of America; the particle size was <30 μ.

(27) R. L. Bixler and C. Niemann, *J. Org. Chem.*, 23, 742 (1958).

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(29) H. D. Holtz and L. M. Stock, *J. Amer. Chem. Soc.*, 87, 2404 (1965).

(30) R. A. Smiley and C. Arnold, *J. Org. Chem.*, 25, 257 (1960), and L. Friedman and H. Shechter, *ibid.*, 25, 877 (1960).

The long retention time product (t_{rel} 1.8) had the following properties: nmr δ 2.08 (s),1.30 (s, CH_3), 3.42 (OH), 2.2–1.0 (m); ir (CCl_4) 2.81 (sh) and 3.03 (br) (OH), 8.40, 10.58, 10.73, and 11.60 μ; mass spectrum *m/e* (rel intensity) 152 (1.1), 134 (5.6), 94 (47), and 43 (100).

Anal. Found: C, 78.78; H, 10.80.

Irradiation of 18. A solution of **18** (1.02 g) in 105 ml of *tert*-butyl alcohol was irradiated for 16 hr. About 5% of the starting material remained and two photoproducts were detected by gc (C, 125°) in yields of 24 (t_{rel} 0.87) and 61% (t_{rel} 1.8). The two products were isolated by preparative gc and characterized. The long retention time product (**24**) was a viscous oil: nmr ($CDCl_3$) δ 1.58 (s, CH_3), 1.93 (s), 2.27 (s, OH), 1.3–2.3 (m); ir ($CHCl_3$) 2.73 (sh) and 2.87 (br) (OH), 8.50, 9.00, 10.73, 11.00 μ; mass spectrum *m/e* (rel intensities) 192 (1.8), 174 (53), 159 (31), and 131 (100).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.95; H, 10.12.

The short retention time peak (**25**) was a solid: mp 101–104°; nmr ($CDCl_3$) δ 1.35 (s, CH_3), 1.55 (s, OH), 1.75 (s) 1.3–2.2 (m), 2.7 (d, J = 12 Hz); ir ($CHCl_3$) 2.73 (sh) and 2.85 (br) (OH), 8.41, 8.64, 10.99, 11.18 μ; mass spectrum *m/e* (rel intensities) 192 (4), 174 (16), 149 (76), 135 (66), 43 (100).

Anal. Found: C, 80.95; H, 10.12.

Irradiation of 18 in *tert*-Butyl Alcohol-*O*-*d*. a. A solution of 200 mg of **18** in 11 ml of *tert*-butyl alcohol-*O*-*d* (98% d_1)[31] was irradiated in a Pyrex test tube in a Rayonet reactor with the 3100-Å sources until two-thirds of the ketone had disappeared. The ketone was then recovered by preparative gc and subjected to mass spectral analysis.

b. The experiment was repeated but the extent of reaction was limited to 50%.

c. A blank was run in which the ketone and the *tert*-butyl alcohol-*O*-*d* were in contact for the same length of time as in a, but in the dark.

Mass Spectral Data. The averaged relative intensities for peaks with *m/e* 135 and 136 are given for each of the above cases and for pure **18**: (a) 135 (100), 136 (14.7); (b) 135 (100), 136 (14.7); (c) 135 (100), 136 (12.6); **18**, 135 (100), 136 (12.2). From these data, it may be calculated that the ring carbons of the recovered **18** from case a had the following isotopic analysis: case a, 97.8% d_0, 2.2% d_1; case b, 97.6% d_0, 2.4% d_1; case c, >99.6% d_0.

Comparative Irradiations of 18. Separate solutions of 64 mg of **18** were prepared in either 3 ml of benzene or 3 ml of *tert*-butyl alcohol, degassed to <0.1 mm, and sealed into 13 × 100 mm Pyrex test tubes. The test tubes were irradiated for 114 hr on a merry-go-round apparatus as described below. Comparison of the disappearance of **18** by gc (C, 125°) revealed that the rate of consumption of **18** and the rates of formation of the alcohols were doubled in *tert*-butyl alcohol as compared to benzene.

Irradiation of 12. A solution of 1.030 g of **12** in 110 ml of *tert*-butyl alcohol was irradiated for 25.5 hr. Two photoproducts were detected by gc analysis (B, 140°) in yields of 24 (t_r 1.0) and 59% (t_r 1.6). The minor product **20** showed nmr ($CDCl_3$) absorptions at δ 1.32 (CH_3) and 1.0–2.0 (m); ir ($CHCl_3$) 2.7 (sh) an d2.84 (b) (OH), 8.20, 9.83, 11.12 μ; mass spectrum (rel intensities) *m/e* 166 (3.3), 148 (28), 133 (25.5), 43 (100).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.43; H, 11.27.

The major alcohol **19** showed nmr ($CDCl_3$) absorptions at δ 1.45 (s, CH_3), 1.83 (s), 2.37 (s, OH), and 2.3–1.1 (m); ir ($CHCl_3$) 2.70 (sh) and 2.84 (br) (OH), 8.43, 10.06, 10.68, and 10.98 μ; mass spectrum (rel intensities) 166 (3.3), 148 (24), 133 (25), and 43 (100).

Anal. Found: C, 79.70; H, 10.91.

Bicyclo[2.2.2]octane-1,2-dicarboxylic Acid.[8] To a solution of 208 mg of **19** in 10 ml of glacial acetic acid was added 840 mg of chromium trioxide while maintaining the temperature at *ca.* 25°. The mixture was stirred for 1 hr after the addition. Water and salt were added followed by ether extraction. The extracts were washed with water and 5% sodium hydroxide solution. The basic extracts were acidified with dilute hydrochloric acid and the liberated acidic product was extracted into ether. Evaporation of the ether gave 40 mg of an oil: ir 5.83 μ; nmr δ 2.06 (s, CH_3). This material was assumed to be a keto acid and was further degraded by addition to 2 ml of a solution of sodium hypobromite[32] followed by stirring for 1 hr. The reaction was extracted with ether, acidified, and reextracted with ether. A small amount of crystals was obtained with mp 170–180° (lit.[33] mp 200–201°); mmp 185–195°; infrared and mass spectra were virtually identical with the reference spectra.

Irradiation of 7. A solution of 0.54 g of **7** in 107 ml of *tert*-butyl alcohol was irradiated for 25.5 hr. The gas chromatogram (A, 160°) at this point revealed a trace of starting ketone and very small amounts of three minor components and three major components in the yields 16 (t_r 0.64) and 36.5% ($t_r \sim 1.6$). The latter constituent was clearly a mixture as evidenced by the presence of a shoulder.

The short retention time peak, **21**, showed nmr ($CDCl_3$) absorptions at δ 6.3 (p, HC=), 2.0 (s), 1.25 (s, CH_3), and 2.7–1.0 (m); ir ($CHCl_3$) 2.74 (sh) and 2.83 (br) (OH), 8.50, 10.60, 10.95 μ; mass spectrum *m/e* (rel intensity) 164 (1.0), 146 (1.3), 106 (14), 71 (100), 43 (71).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.41; H, 9.94.

The mixture of alcohols **22** and **23** with long retention times showed nmr ($CDCl_3$) absorptions at δ 6.2 (m, HC=), 2.68 (s), 2.07 (s), 1.47 (s), 1.13 (s), 2.8–0.9 (m); ir ($CHCl_3$) 2.73 (sh) and 2.86 (br) (OH), 8.40, 8.89, 10.52, 10.98 μ.

Anal. Found: C, 80.16; H, 9.88.

Catalytic Reductions. A 7-mg sample of **21** in 2 ml of ethanol was reduced in the presence of 10% Pd/C. The retention time of the product on columns A and B was identical with that of **20**.

Similarly the mixture of **22** and **23** was reduced to **19** as shown by gc comparisons on columns A and B.

1-Bicyclo[3.3.1]nonylacetone (17). 1-Bicyclo[3.3.1]nonylmethanol (**14**) was prepared in 87% yield by reduction of 1-ethoxycarbonylbicyclo[3.3.1]nonane[3] with lithium aluminum hydride. The crude alcohol was converted to the tosylate **15**, mp 75°, after crystallization from methanol.

Anal. Calcd for $C_{17}H_{24}O_3S$: C, 66.20; H, 7.84. Found: C, 66.40; H, 8.18.

The nitrile **16** was prepared by reaction of 20 g of tosylate with 11 g of sodium cyanide in 400 ml of dimethyl sulfoxide (90°, 23 hr). There was obtained 9.3 g (88%) of the nitrile **16**: bp 96–116° (0.015 mm); nmr δ 2.08 (CH_2CN), 1.19–2.33 (m); ir 4.44 (C≡N) μ.

Anal. Calcd for $C_{11}H_{17}N$: C, 80.93; H, 10.50. Found: C, 80.69; H, 10.46.

The nitrile (3.57 g) was converted to ketone **17** by reaction with 70 ml of methyllithium solution (1.67 *N*): yield 2.80 g (72%); nmr δ 2.14 (s, CH_2C=O), 2.03 (s, CH_3), 2.2–1.15 (m); ir 5.85 μ (C=O); metastable ion at *m/e* 146 (calcd for $180^+ \rightarrow 18 + 162^+$, 145.8).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.65; H, 11.03.

Quantum Yield Determinations. Three milliliters of a 0.2 *M* solution of ketone **17** in *tert*-butyl alcohol was placed in a 13 × 100 mm Pyrex test tube, degassed three times at *ca.* 0.1 mm, and sealed *in vacuo*. Duplicate tubes were irradiated at 25 ± 1° with the 450-W Hanovia lamp using as a filter a 1-cm path of a 0.002 *M* potassium dichromate–1% potassium carbonate solution.[34] The light intensity was monitored by parallel irradiation of 0.1 *M* solutions of 5-*endo*-bicyclo[2.2.1]heptenyl methyl ketone for which a quantum yield of 0.14 has been determined by benzophenone–benzhydrol actinometry.[35] The ketone concentration was monitored by quantitative gas chromatography (A, 180°) using heptadecane as an internal standard and averaging six determinations. Acetone concentrations were determined by comparisons of peak areas of the photolysis solution with those of standard solutions and averaging six determinations for each run. The following values were obtained: ϕ_{-K} 0.070; ϕ_A 0.045. On the basis of the preparative experiments, the quantum yield of cyclobutanol formation is estimated to be 0.009.

Irradiations of 17. Several small scale irradiations of **17** were carried out in Pyrex test tubes under a nitrogen atmosphere. The following solvents were evaluated in these experiments: *tert*-butyl alcohol, hexane, cyclohexane, benzene, *tert*-amyl alcohol, acetonitrile, *tert*-butyl alcohol–acetic acid. In all cases, complex

(31) Purchased from Isotopes, Westwood, N. J.

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(34) P. J. Wagner, *J. Amer. Chem. Soc.*, 89, 5898 (1967).

(35) Unpublished results with A. Rousseau; see R. R. Sauers, W. Schinski, and M. M. Mason, *Tetrahedron Lett.*, 79 (1969).

product mixtures were formed on irradiation. Small amounts of products with short retention times were observed, but these materials did not accumulate sufficiently to allow isolation. Addition of acetic acid after irradiation did not lead to any new product peaks.

A preparative scale photolysis was carried out on 0.76 g of **17** in 100 ml of nitrogen-purged *tert*-butyl alcohol. After irradiation for 24 hr, the solvent was removed *in vacuo* and the residue was subjected to preparative gc (B, 180°). The major product (0.10 g) appeared to be a mixture of cyclobutanols as evidenced by the presence of hydroxyl absorptions in the infrared spectrum at 2.90 μ: nmr δ 1.21 (s) and 1.40 (s); mass spectrum *m/e* (rel intensities) 180 (11), 162 (38), 122 (100), 43 (81).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.70; H, 11.03.

Several minor products were detected in quantities too small to isolate and characterize.

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Studies on Polypeptides. XLIX. Fragment Condensations with Peptide Derivatives Related to the Primary Structure of Ribonuclease T_1[1-4]

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Abstract: Syntheses are described of three *N*-benzyloxycarbonylpeptide *tert*-butoxycarbonylhydrazides which correspond to positions 12–23, 24–34, and 35–47, respectively, of the proposed primary structure of the enzyme ribonuclease T_1. Evidence is presented to indicate that these materials are sequentially homogeneous. These fragments were condensed to form an *N*-benzyloxycarbonylhexatricontapeptide *tert*-butoxycarbonylhydrazide corresponding to positions 12–47 of the primary sequence of the enzyme. Available techniques to evaluate homogeneity of complex peptides are critically discussed and the concept of "diagnostic" amino acid residues is introduced.

Ribonuclease T_1 [ribonucleate guanine nucleotido-2′-transferase (cyclizing), 2.7.7.26] is an acidic single-chain protein, 104 amino acid residues in length, cross-linked by two disulfide bridges.[5] The enzyme can be unfolded by reduction,[6,7] and such unfolding is accompanied by a complete loss of activity. Essentially complete reactivation occurs when the reduced enzyme is allowed to reoxidize.[6,7] Thus, assembly of the correct peptide chain will constitute synthesis of the enzyme.

Ribonuclease T_1 contains one residue each of lysine, arginine, and tryptophan, and no methionine; moreover, three of the four half-cystines are located in the N-terminal region of the peptide chain. From the point of view of synthesis these structural characteristics simplify the problem of side-chain protection and it was for this reason that this particular enzyme was selected for exploratory synthetic studies. The peptide chain was subdivided into a number of *N*-benzyloxycarbonylpeptide *tert*-butoxycarbonylhydrazide fragments B to F (Figure 1) which provide potential building blocks for the synthesis of larger sections of the polypeptide chain.

The present article describes syntheses of fragments B, C, and D and their assembly into the protected hexatricontapeptide hydrazide BCD (Figure 2, shaded section). This peptide derivative corresponds to positions 12–47 of the amino acid sequence of the enzyme.

Preparation of Fragments B, C, and D

Doubly protected peptide hydrazides, such as fragments B, C, and D, are desirable intermediates for con-

(1) See K. Hofmann, R. Andreatta, F. M. Finn, J. Montibeller, G. Porcelli, and A. J. Quattrone, *Bioorg. Chem.*, 7, 66 (1971), for paper XLVIII in this series.

(2) Supported by grants from the U. S. Public Health Service and the Hoffmann-La Roche Foundation. The early phases of this investigation were supported by the Research Laboratories, Edgewood Arsenal, Contract DA-18-035-AMC-307 (A). The opinions expressed are those of the authors and do not reflect endorsement by the contractor.

(3) Preliminary communications of some of the results presented in this communication have appeared: (a) N. Yanaihara, C. Yanaihara, G. Dupuis, J. Beacham, R. Camble, and K. Hofmann, *J. Amer. Chem. Soc.*, **91**, 2184 (1969); (b) K. Hofmann in "Peptides 1969," E. Scoffone, Ed., North Holland Publishing Co., Amsterdam, 1971, p 130.

(4) The amino acid residues except glycine are of the L configuration. The following abbreviations are used: AP-M = aminopeptidase M; DCC = *N,N′*-dicyclohexylcarbodiimide; DMSO = dimethyl sulfoxide; DMF = dimethylformamide; EC = ethylcarbamyl; F = formyl; OCP = 2,4,5-trichlorophenyl ester; ONHS = *N*-hydroxysuccinimido ester; O-*t*-Bu = *tert*-butyl ester; TEA = triethylamine; TFA = trifluoroacetic acid; THF = tetrahydrofuran; tlc = thin-layer chromatography; X = *tert*-butoxycarbonylhydrazide; Y = benzyloxycarbonylhydrazide; Z = benzyloxycarbonyl. In order to simplify the designation of the complex products the following nomenclature is used: fragments B, C, D, CD, and BCD = the *N*-benzyloxycarbonyl *tert*-butoxycarbonylhydrazides: fragments B, C, D, CD, and BCD *tert*-butoxycarbonylhydrazides = the amino-deprotected *tert*-butoxycarbonylhydrazides; fragment B, C, D, CD, and BCD hydrazides = the free hydrazides of the *N*-benzyloxycarbonyl fragments.

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