Recrystallization of a 0.5-g sample from DMF–H_2O gave 0.35 g: mp 332° dec; uv (pH 1) 437 nm (ε 5780), 336 (7300), 268 (15,600), (pH 7) 328 (22,800), 268 (8900), (pH 11) 328 (22,900), 268 (9670); nmr (DMSO-d_6) δ 10.80 (s, 1, OCHNCO), 9.64, 9.37 (2 s, 2, NH_2), 3.70 (s, 3, OCH_3), 3.07 (s, 3, NCH_3).

Anal. Calcd for $C_{10}H_9N_3O_5 \cdot {}^1/_2H_2O$: C, 46.15; H, 3.85; N, 16.15. Found: C, 46.21; H, 3.64; N, 16.23.

1,3-Dibenzyl-6-amino-5-(3-carbomethoxy-2-propynoyl)uracil (3c).—To a suspension of 1,3-dibenzyl-6-aminouracil (3.07 g, 10 mmol) in 20 ml of DMF was added dimethyl acetylenedicarboxylate (1.56 g, 11 mmol) and the mixture was heated at 110° for 2 hr. To the dark red solution was added 150 ml of ether. The resulting precipitate was filtered and washed with 40 ml of ether to yield 1.62 g (39%), mp 235°. Recrystallization of a 1.1-g sample from DMF–H_2O gave 0.9 g: mp 239–240° uv (pH 1) 438 nm (ε 5500), 336 (6850), 270 (15,830), (pH 7) 330 (22,400), 273 (7930), (pH 11) 330 (22,100), 273 (7930); nmr (DMSO-d_6) δ 9.93, 9.63 (2 s, 2, NH_2), 7.20 (s, 10, 2 C_6H_5), 4.97 (s, 2, CH_2), 4.87 (s, 2, CH_2), 3.68 (s, 3, OCH_3).

Anal. Calcd for $C_{23}H_{19}N_3O_5$: C, 66.18; H, 4.59; N, 10.07. Found: C, 66.32; H, 4.55; N, 10.12.

1,3-Dimethyl-6-amino-5-(*cis*-3-carbomethoxypropenoyl)uracil (8).—1,3-Dimethyl-6-amino-5-(3-carbomethoxy-2-propynoyl)-uracil (**3a**) (500 mg, 1.9 mmol) was dissolved in a dimethoxyethane–water (1:1) mixture with warming and hydrogenated at 46 psi using PtO_2 (200 mg) as catalyst overnight.

The reaction mixture was filtered through Celite and washed thoroughly with hot dimethoxyethane. The filtrate was evaporated to dryness, and the residue was triturated with MeOH and filtered to give 340 mg (68%): mp 310° dec; uv (pH 1) 346 nm (ε 18,400), 276 (18,330), 230 (9950), (pH 7) 347 (18,850), 277 (18, 450), 230 (9950), (pH 11) 345 (18,700), 277 (18,800), 231 (9350); nmr (DMSO-d_6) δ 8,48, 7.87 (2 s, 2, NH_2), 6.77, 5.80 (2 d, 2, CH, J = 9 Hz), 3.58 (s, 3, OCH_3), 3.05, 2.97 (2 s, 6, NCH_3).

Anal. Calcd for $C_{11}H_{13}N_3O_5$: C, 49.44; H, 4.87; N, 15.73. Found: C, 49.63; H, 4.88; N, 15.61.

1,3-Dimethyl-6-amino-5-(*trans*-3-carbomethoxypropenoyl)-uracil (9).—1,3-Dimethyl-6-aminouracil (0.8 g, 5 mmol) and methyl 3-chloroformyl-*trans*-acrylate (1 g) were stirred in 30 ml of DMF at room temperature overnight. The reaction mixture was filtered, the filtrate was evaporated, and the oily residue was allowed to stand overnight at room temperature. The product was filtered and recrystallized from methanol, giving 300 mg of pure product (22%): mp 220–223°; uv (pH 1) 314 nm (ε 9100), 223 (20,800), (pH 7) 314 (8280), 223 (21,600), (pH 11) 307 (6360), 245 (sh), 229 (25,600); nmr (DMSO-d_6) δ 11.07 (s, 1, NH), 8.60 (s, 1, NH overlaps with CH), 8.37, 6.47 (2 d, 2, CH, J = 16 Hz), 3.77 (s, 3, OCH_3), 3.35, 3.17 (2 s, 6, NCH_3).

Anal. Calcd for $C_{11}H_{13}N_3O_5$: C, 49.44; H, 4.87; N, 15.73. Found: C, 49.59; H, 5.10; N, 15.79.

Registry No.—**3a**, 32970-29-9; **3b**, 32970-30-2; **3c**, 32970-31-3; **4a**, 32970-32-4; **4b**, 32970-33-5; **6a**, 32970-34-6; **6b**, 32970-35-7; **8**, 33016-10-3; **9**, 33016-11-4.

The Synthesis of 2-Methyl-7-ketoundecanolide, 8-Ketoundecanolide, and 2,4,6-Trimethyl-7-ketodecanolide[1]

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The Michael addition of acrylate esters to cyclic enamines has been extended to synthesize 2,4,6-trimethyl-7-ketodecanolide and 2-(3′-hydroxypropyl)cyclooctanone. The latter is converted to 8-ketoundecanolide by previously described procedures. The pyrrolidine enamines of 2-methylcycloheptanone (**3**) or *cis,trans*-2,*cis*-4,6-trimethylcycloheptanone (**4**) failed to give C-alkylation with 4-bromobutyl acetate (**12**). Attempted alkylation of the anions of the corresponding cyclohexylamine or aniline imines gave complex product mixtures. The 7-carbethoxy derivatives of **3** or **4** were alkylated with either **12** or 4-bromobut-1-ene to give intermediates which were converted to the desired 7-(4′-hydroxybutyl)cycloheptanones. These hydroxy ketones were cyclized, with difficulty, to give isomeric mixtures of the corresponding "7-7" enol ethers which could be oxidized with *m*-chloroperbenzoic acid (MCPBA) to 2-methyl-7-ketoundecanolide but not to 2,4,6-trimethyl-7-ketoundecanolide. A new synthesis of 7-carbethoxy-*cis,cis*-2,4,6-trimethylcycloheptanone from *cis,cis*-2,4,6-trimethylcyclohexanone is described. Extensions of aromatic solvent-induced nmr shifts to some of the intermediates are discussed.

We have previously reported the synthesis of bicyclic enol ethers *via* (a) the lithium–amine reduction of chromans[3] and (b) the acid-catalyzed closure of 2-(ω-hydroxyalkyl)cycloalkanones derived from enamine alkylations.[4] The enol ethers have been oxidized by a variety of reagents[3-6] to 10–12-membered ring ketolactones, including 7-ketoundecanolide, which represents the structural system of the methymycin group of macrolide antibiotics.

We now report extensions of these synthetic methods as well as new approaches involving β-keto esters which lead to 2,4,6-trimethyl-7-ketodecanolide and undecanolides. The substituents are located at some of the positions where methyl groups are found in methymycin.

We had originally planned on extending the synthesis of 2-(ω-hydroxyalkyl)cycloalkanones to methyl-substituted 7-ketoundecanolides *via* the alkylation of the pyrrolidine enamines **1** and **2** of 2-methylcycloheptanone (**3**) and 2,4,6-trimethylcycloheptanone (**4**) with 4-bromobutyl acetate (**12**). The cycloheptanones **3** and **4** were prepared by the diazoethane ring expansion of cyclohexanone (**5**) and 3,5-dimethylcyclohexanone (**6**) in 46 and 52% yields, respectively.[7] Commercial

(1) This investigation was supported by Public Health Service Research Grants AI 06303 and 07455 from the National Institute of Allergy and Infectious Diseases and by the Eli Lilly Co. This is part VII of the series, Medium Ring Compounds.

(2) To whom correspondence should be addressed at the Belfer Graduate School of Science, Yeshiva University, New York, N. Y. 10033.

(3) (a) I. J. Borowitz, G. Gonis, R. Kelsey, R. Rapp, and G. J. Williams, *J. Org. Chem.*, **31**, 3032 (1966); (b) I. J. Borowitz and G. Gonis, *Tetrahedron Lett.*, 1151 (1964).

(4) I. J. Borowitz, G. J. Williams, L. Gross, and R. Rapp, *J. Org. Chem.*, **33**, 2013 (1968).

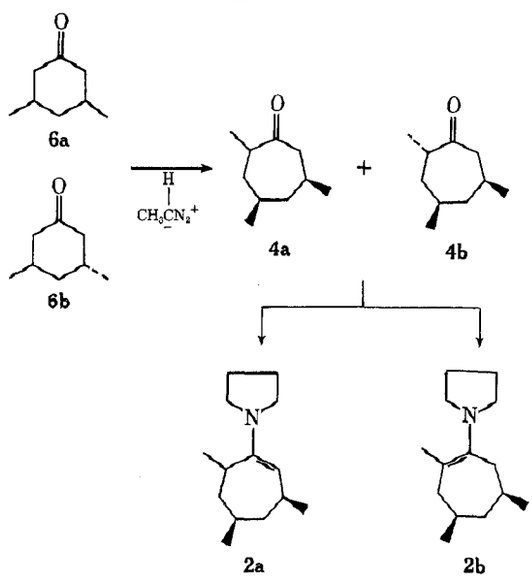
(5) I. J. Borowitz and R. Rapp, *ibid.*, **34**, 1370 (1969).

(6) I. J. Borowitz and R. Rapp, *Chem. Commun.*, 1202 (1969).

(7) (a) By a modification of the procedure of D. W. Adamson and J. Kenner, *J. Chem. Soc.*, 181 (1939), suggested by Dr. Adnan Sayigh. (b) For related cycloheptanone syntheses *via* a higher yield procedure and for stereochemical relationships see J. Marshall and J. J. Partridge, *J. Org. Chem.*, **33**, 4090 (1968).

6 (*ca.* 85% cis and 15% trans) was utilized. It was deemed unnecessary, at least in this initial phase of the work, to utilize pure *cis*-6 [available by the hydrogenation of 3,5-dimethylphenol[8] or from 3,5-dimethylcyclohexenone (7)]. This was because we found that diazoethane reacted much more rapidly with *cis*-6 than with *trans*-6. Indeed, most of the *trans*-6 of the original 85:15 mixture could be recovered unreacted. This observation is reasonable considering the generally slow addition of nucleophiles to cyclohexanones with axial substituents at C_3 (as in *trans*-6). Thus *cis*-6 is reduced 25 times faster than is *trans*-6 with sodium borohydride.[8] The ring expansion of 6 led to a 58:42 mixture of what is most likely *cis,cis*-2,4,6-trimethylcycloheptanone (4a) and the trans,cis isomer 4b (Scheme I).[7b] Equilibration of 4a and 4b gave a

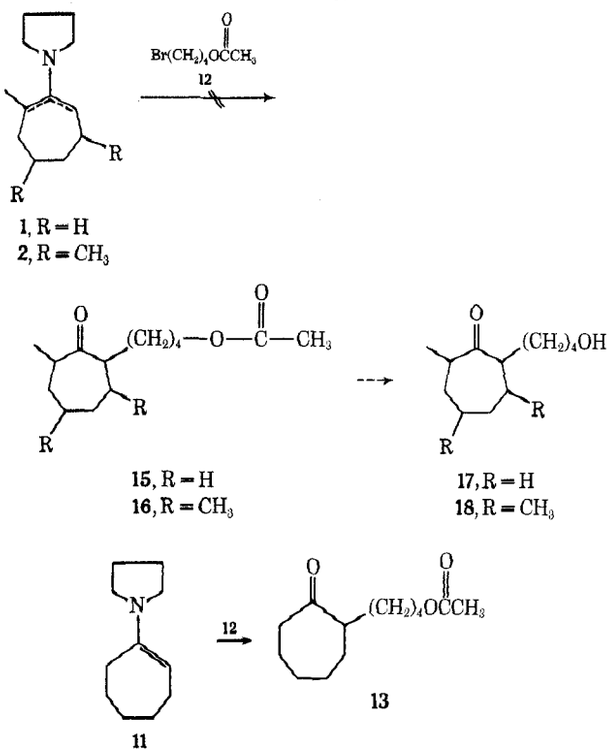
SCHEME I



change in composition to 88:12. The major isomer might be 4b if 2,4,6-trisubstituted cycloheptanones have energy profiles related to those of 2,5-disubstituted cycloheptanones.[7b]

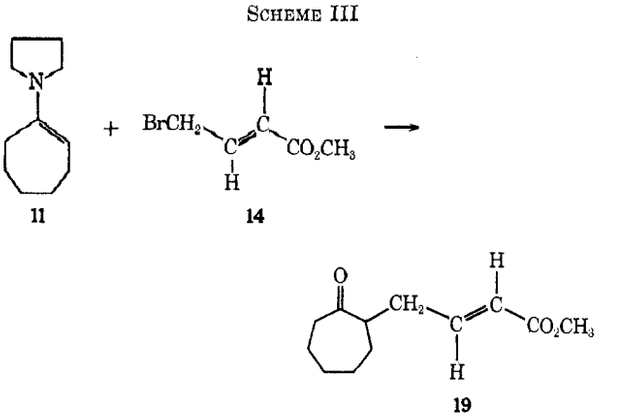
The pyrrolidine and morpholine enamines (1, 8) of 3 and the morpholine enamine (9) of 4 could not be consistently prepared by the usual azeotropic method. The pyrrolidine enamine (2) of 4 could not be made at all this way. The best method for the synthesis of 1, 2, and other pyrrolidine enamines of ketones which react sluggishly with pyrrolidine involves the use of trispyrrolidinylboron–pyrrolidine mixtures.[9] Enamines 1 and 2 were thus reproducibly prepared (52 and 89%, respectively). Other enamine syntheses involving trispyrrolidinylarsine[10] and the conversion of immonium perchlorates[11] are mentioned in the Experimental Section. The enamines 1 and 2 were found to consist of mixtures of the less substituted (1a, 2a) and the more substituted (1b, 2b) isomers in 68:32 and 46:54 ratios, respectively, by their nmr spectra. How this ground-state isomer distribution would influence the site of reaction of 1 and 2 was of concern since we wanted alkylation to occur on the less substituted side.[12] Both 1 and 2 gave no alkylation with 12.[13] These results are in contrast to our previously described reaction of pyrrolidinocycloheptene (11) with 12 to give 2-(4′-acetoxybutyl)cycloheptanone (13) in 48% yield (Scheme II).[4]

SCHEME II



It had been hoped that allylic halides such as methyl 4-bromocrotonate (14) would show reasonable reactivity with cycloheptanone enamines. The alkylation of 11 with 14 to give the desired 19 occurred in only 13% yield, however. This rather cumbersome pathway for the synthesis of 2-(4′-hydroxybutyl)cycloheptanones was therefore abandoned since it was anticipated that the alkylation of 1 or 2 with 14 would give even lower yields (Scheme III).

SCHEME III



(8) B. Rickborn and M. T. Wuesterhoff, *J. Amer. Chem. Soc.*, **92**, 6894 (1970).

(9) P. Nelson and A. Pelter, *J. Chem. Soc.*, 5142 (1965).

(10) H. V. Hirsch, *Chem. Ber.*, **100**, 1289 (1967).

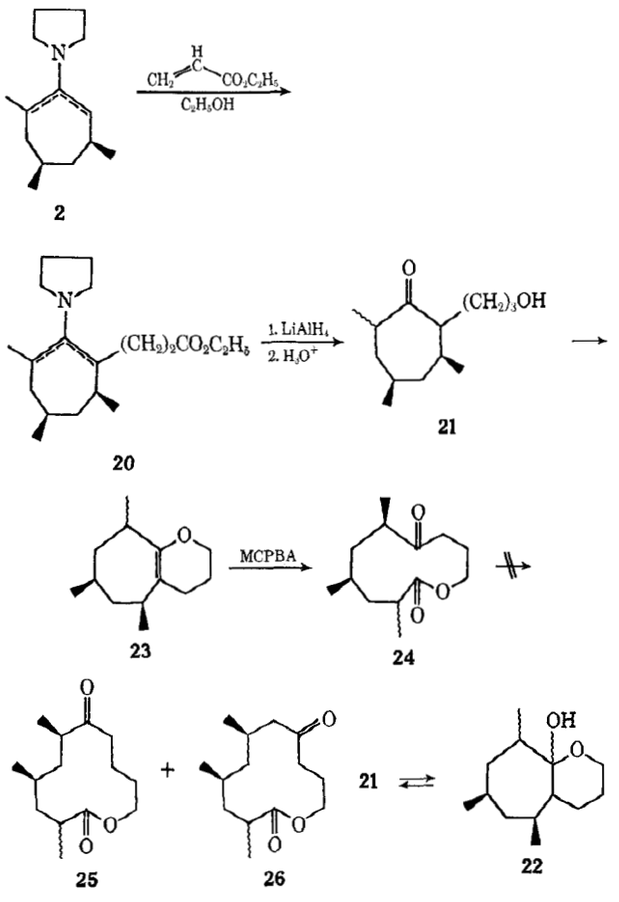
(11) S. Etheredge, Ph.D. Thesis, Columbia University, 1965; *Diss. Abstr.*, **26**, 4232 (1966).

(12) (a) W. D. Gurowitz and M. A. Joseph, *Tetrahedron Lett.*, 4433 (1965); (b) W. D. Gurowitz and M. A. Joseph, *J. Org. Chem.*, **32**, 3289 (1967); (c) F. Johnson, *Chem. Rev.*, **68**, 375 (1968).

(13) Cycloheptyl enamines are known to give 1:1 C to N alkylation: G. Opitz and H. Mildenberger, *Justus Liebigs Ann. Chem.*, **649**, 47 (1961).

Enamine 2 was allowed to react with ethyl acrylate to give the enamine ester **20** (80%) which was reduced with lithium aluminum hydride and acid hydrolyzed by described procedures[4] to give 7-(3′-hydroxypropyl)-2,4,6-trimethylcycloheptanone (**21**, Scheme IV). In

SCHEME IV



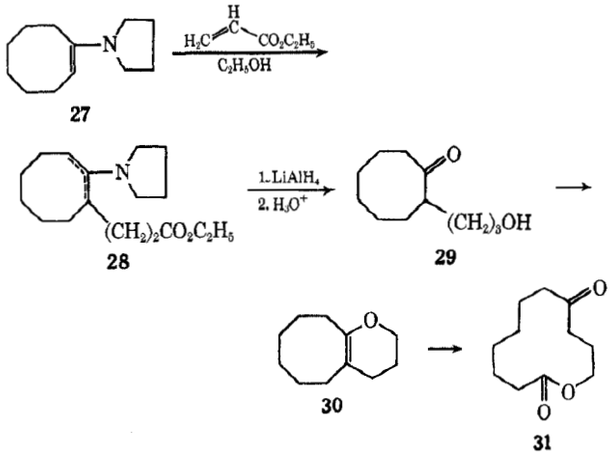
comparing the lack of alkylation of **1** or **2** with **12** to the facile Michael addition of **2**, several points can be made. The extent to which **1** or **2** are N-alkylated by **12** is not known but it is presumably not exclusive since some **12** is recovered.[13] Both N and C alkylation of enamines with alkyl halides are irreversible while Michael addition on nitrogen, if it occurs, is reversible.[14] The C-alkylated Michael adduct is thus thermodynamically favored. The hydroxy ketone **21** exists mainly in the hydroxy ether form **22**, a harbinger of its facile conversion to the enol ether **23**, which was done with acid catalysis. The overall yield of 23 from 2 was 48%. The stereochemistry of the indicated methyl group in **23** remains undefined.

As previously found for other bicyclic enol ethers, only the endocyclic isomer (**23**) was formed. Oxidation of **23** with *m*-chloroperbenzoic acid (MCPBA) gave 2,4,6-trimethyl-7-ketodecanolide (**24**, 66%) as essentially one stereoisomer.

Keto lactone **24** is a possible precursor of 2,4,6-trimethyl-7-ketoundecanolide (**25**) which has three of the five alkyl substituents present in methymycin. An attempt at the ring expansion of **24** with diazomethane–aluminum chloride to give **25** and/or **26** was unsuccessful.[15,16]

2-(3′-Hydroxypropyl)cycloalkanones close fairly readily to the corresponding bicyclic hydroxy ethers when the cycloalkanones are six or seven membered.[4] We now demonstrate this closure for the eight-membered ring case as well. Pyrrolidinocyclooctene (**27**) was converted to 2-(3′-hydroxypropyl)cyclooctanone (**29**) *via* the enamine ester **28** (Scheme V). Dehydra-

SCHEME V



tive closure of **29** to the "8-6" enol ether **30** and MCPBA oxidation gave 8-ketoundecanolide (**31**). The overall yield of **31** from **27** was only 4%, considerably lower than those obtained in our previously described cases.[4]

Our second pathway toward the synthesis of 2-(4′-hydroxybutyl)cycloheptanones involved the Stork alkylation of Schiff base anions.[17] Unfortunately, the magnesium anion of the cyclohexylimine of cyclohexanone (**32**) reacted with both the acetate and bromo groups of **12** so that this readily obtained[4] precursor of the hydroxybutyl moiety could not be used directly. Preliminary reactions of the magnesium anion of the anil of 2-methylcycloheptanone (**33**) with 1-bromo-4-trimethylsilyloxybutane or 1-chloro-4-pyranyloxybutane gave little of the desired products. We then turned to the use of 4-bromobut-1-ene (**34**) which is convertible to ω-hydroxybutyl at a later stage. Alkylation of the anion of **32** with **34** gave **36** (63%). Similar reaction of the cyclohexylimine of cycloheptanone (**35**) with **34** gave a complex mixture. Compounds **36** and **37** (the latter obtained in 72% yield from **44**) were converted to their respective ketals **38** and **39** and hydroborated to give the desired hydroxybutyl ketones **40** and **41** (Scheme VI).

Our third and best route for the synthesis of 2-(4′-hydroxybutyl)cycloheptanones involved the alkylation of β-keto esters. 2-Methylcycloheptanone (**3**) readily gave the 7-carbethoxy derivative **45**, upon reaction with diethyl carbonate.[18] The formation of **45**, whose structure was established by nmr, is related to the α′

(14) (a) G. Stork, A. Brizzolara, H. Landesman, and J. Szmuszkovicz, *J. Amer. Chem. Soc.*, **85**, 207 (1963); (b) M. E. Kuehne in "Enamines", A. G. Cook, Ed., Marcel Dekker, New York, N. Y., 1969, Chapter 8.

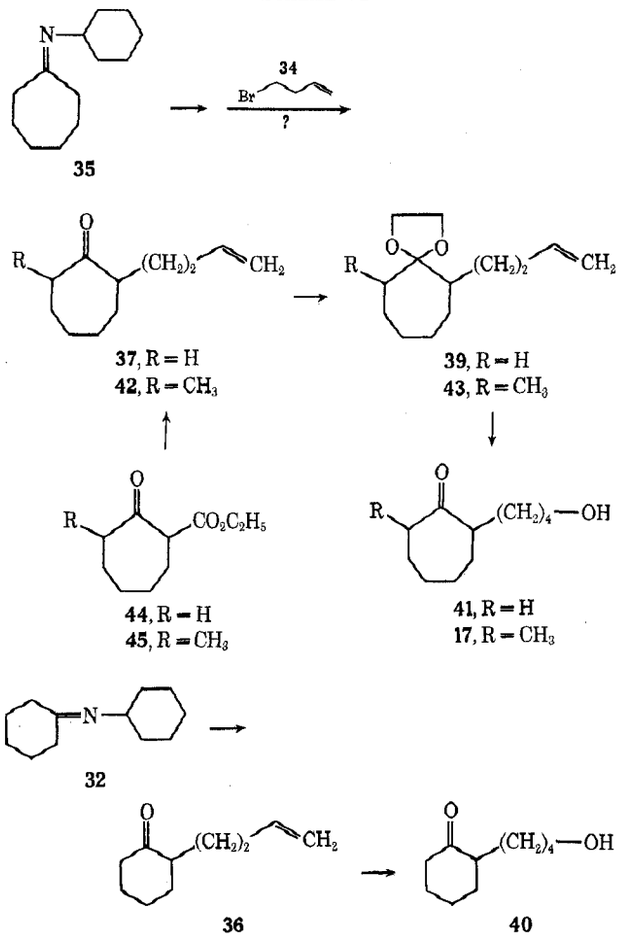
(15) Cycloundecanones have been ring expanded in 15% yield: E. Mueller and M. Bauer, *Justus Liebigs Ann. Chem.*, **654**, 92 (1962).

(16) R. Mayer, *Chem. Ber.*, **96**, 3096 (1963).

(17) G. Stork and S. R. Dowd, *J. Amer. Chem. Soc.*, **85**, 2178 (1963).

(18) S. J. Rhoads, J. C. Gilbert, A. W. Decora, T. R. Garland, R. J. Spangler, and M. J. Urbigkit, *Tetrahedron*, **19**, 1625 (1963).

SCHEME VI



carbethoxylation of 2-methylcyclopentanone[19a] or 2-methylcyclohexanone.[19b] Attempts to carbethoxylate **4** gave low yields of 2,4,6-trimethyl-7-carbethoxycycloheptanone (**46**) and led to ring opening to give diethyl 2,4,6-trimethylsuberate (**47**). Attempts at the base-catalyzed reclosure of **47** to **46** failed. In view of this result and because of the known nonstereohomogeneity of **4**, a stereospecific route of reasonable yield for **46** was sought. It was developed *via* a higher temperature (35°) modification of the boron trifluoride etherate catalyzed ring expansion of *cis,cis*-2,4,6-trimethylcyclohexanone (**51**) with ethyl diazoacetate.[20] Ketone **51** was synthesized by the hydrogenation of 2,4,6-trimethylphenol (**49**) to give a mixture of stereoisomeric alcohols **50** and ketone **51** which was oxidized with chromic acid.[21] Ketone **51** was shown to be mainly one isomer, *i.e.*, the all-equatorial cis,cis configuration, by nmr and vpc examination. Furthermore the β-keto ester **46** also appeared to be essentially one isomer upon examination of its nmr spectrum (Scheme VII, Table I).

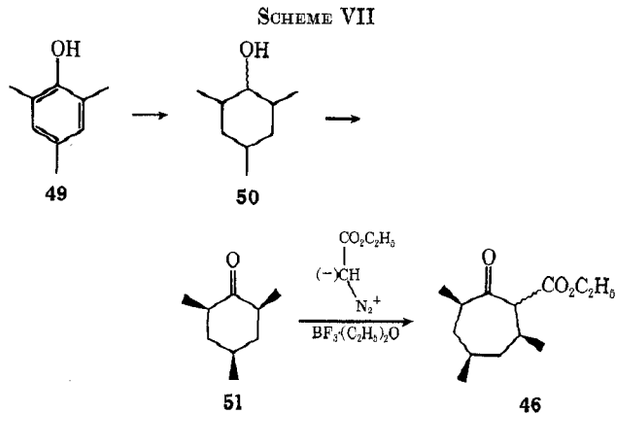
While **44** was readily converted to its enolate with sodium ethoxide and then gave **52** (72%, Scheme VIII), **45** reacted much more slowly and gave only 24% of **53** upon alkylation with **34**. The stronger base, potassium triphenylmethide, afforded the conversion of **45**

(19) (a) K. Sisido, K. Utimoto, and T. Isida, *J. Org. Chem.*, **29**, 2781 (1964); (b) E. J. Corey, T. H. Topie, and W. A. Wozniak, *J. Amer. Chem. Soc.*, **77**, 5415 (1955).

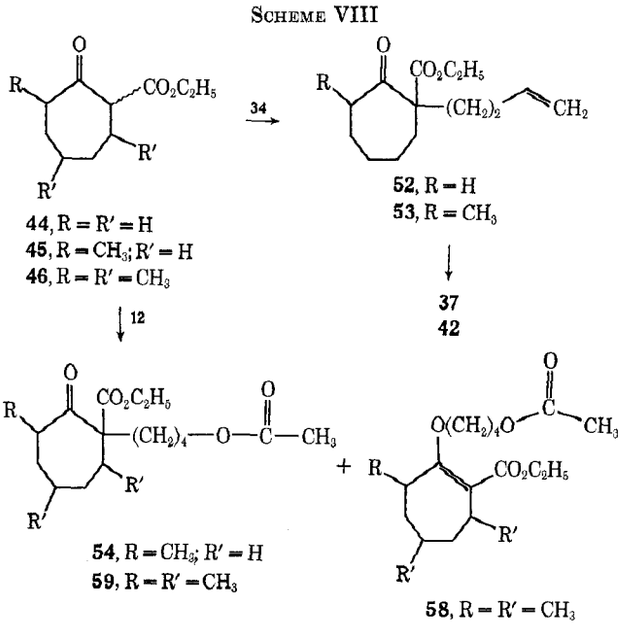
(20) W. T. Tai and E. W. Warnhoff, *Can. J. Chem.*, **42**, 1333 (1964).

(21) A previous synthesis of **51** from **49** gave no physical constants: J. Seibl and T. Gäumann, *Helv. Chim. Acta*, **46**, 2857 (1963).

SCHEME VII



SCHEME VIII



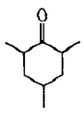
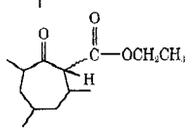
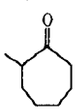
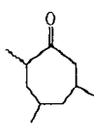
to **53** in 76% yield. Decarboxylation of **52** or **53** gave **37** or **42** (Scheme VI). Alkylation of **45** with **12** using sodium hydride–glyme gave **54** in 56% yield without the complication of reaction of the acetate group noted for Schiff base anions.

Hydrolysis of **54** with alcoholic potassium hydroxide gave 2-methyl-7-(4′-hydroxybutyl)cycloheptanone (**17**). The acid-catalyzed cyclization and dehydration of **17** to **56** (Scheme IX) proved to be much more difficult than were similar conversions on **21**, **41**, or other ω-hydroxyalkylcycloalkanones. The azeotropic removal of water with acid in toluene failed. In the various possible transition states leading to ring closure, the carbonyl group must become tetrahedral, thereby going through an eclipsing interaction with the adjacent methyl group. This interaction is presumably the cause for the unfavorable closure encountered. The effect of an α′ methyl group is evidently more pronounced in the formation of a seven-membered ether ring than for the corresponding six-membered ring. Thus **21** closed to **22** normally (Scheme IV) but 2-methyl-7-(4′-hydroxybutyl)cyclohexanone closed to its hydroxy ether with much more difficulty than did 2-(4′-hydroxybutyl)cyclohexanone (**40**).

The conversion of **17** to a mixture of the "7-7" enol ethers **56a** and **56b** was accomplished by utilizing *p*-

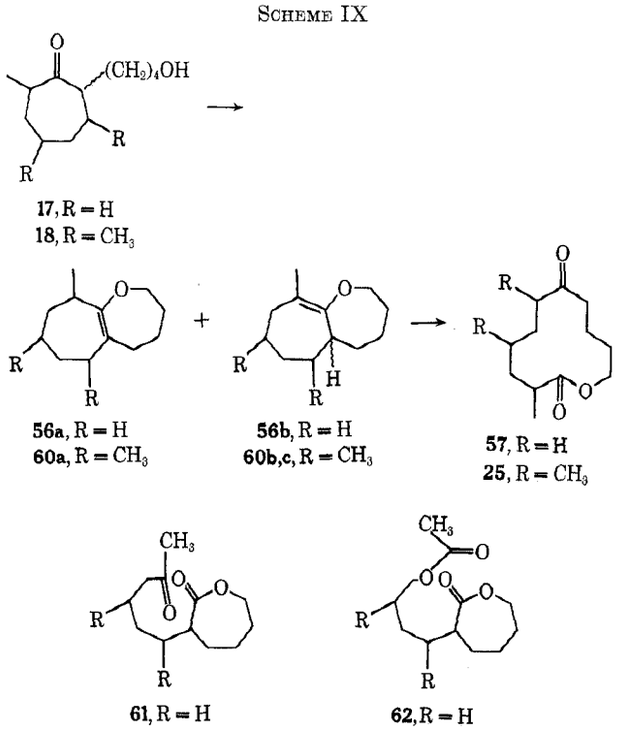
TABLE I

AROMATIC SOLVENT-INDUCED SHIFTS FOR VARIOUS KETONES

Compd	No.	Group	$\Delta = \delta_{CCl_4} - \delta_{C_6H_6}$, Hz	$\Delta = \delta_{CCl_4} - \delta_{1\text{-methylnaphthalene}}$, Hz
	65	C_2 Methyl[a]	−1.3[c]	+4.8
	66	$C_{2,6}$ Dimethyl[b]	−1.5[c]	+2.7
	51	$C_{2,6}$ Dimethyl[a]	−2.4	+3.6
		C_4 Methyl[d]	+15.6	+33
		C_2 Methyl[e]	+5.1	+14.7
	46	C_4 Methyl[f]	+13.2	+31
		C_6 Methyl[g]	+12.6	+13
		C_7 H[h]	−13.2	
		OCH_2[i]	+13.8	
		OCH_2CH_3[j]		
	3	C_2 Methyl[k]	+1.5	+6.5
	4a,b (3:1)	C_2 Methyl[l] (minor)	−2.6	+1.8
		(major)	+0.3	+6.4
		C_4 Methyl[m]	+11.5	+26
		C_6 Methyl[n]	+11.8	+23.8

[a] d, J = 5.7 in all solvents. [b] J = 5.9 (CCl_4), 5.8 (C_6H_6), 5.6 Hz (1-methylnaphthalene). [c] Reference 23. [d] J = 5.4 (C_6H_6), 5.2 Hz (1-methylnaphthalene). [e] J = 6.8, 6.1, 6.4 Hz. [f] J = 5.4, 5.3, 4.8 Hz. [g] J = 6.4, 5.2, 6.8 Hz. [h] J = 10.2 (CCl_4), 10.5 Hz (C_6H_6). [i] q, J = 7.2 (CCl_4), 7.0 Hz (C_6H_6). [j] t, J = 7.2, 6.5, 5.9 Hz. [k] d, J = 7 Hz (all solvents). [l] C_2 methyl resolved into two doublets on 100-Hz full scale; J = 6.6, 5.7 Hz (CCl_4). [m] d, J = 6.7 (CCl_4), 6.0 Hz (1-methylnaphthalene). [n] d, J = 5.8, 6.0 Hz.

SCHEME IX



toluenesulfonic acid catalysis and the solvent system toluene–dimethylformamide.[22]

Oxidation of **56** with excess MCPBA gave 2-methyl-7-ketoundecanolide (**57**, 27%). None of the anticipated **61** or **62** was isolated, although these products may have been formed (see Experimental Section).

The alkylation of **46** with **12** utilizing sodium hydride in glyme or toluene gave poor yields of **59** (*ca.* 9%, Scheme VIII). Reaction of **46** with **12** using potassium triphenylmethide in glyme was also poor. The use of sodium hydride in toluene–dimethylformamide (in ratios varying from 4:1 to 2:1) gave a mixture of O- and C-alkylated products (**58**, **59**) in total yield of *ca.* 40% in each case. The mixture of **58** and **59** was hydrolyzed with base and then with dilute aqueous acid to remove **58** and to give the desired hydroxy ketone **18**. The closure and dehydration of **18** occurred to a minor extent to give a mixture of three enol ethers, **60a**, **60b**, and **60c** (Scheme IX). Attempts to improve the conversion of **18** to **60** failed. Oxidation of a mixture of **60** and some **18** gave a mixture of products which may have contained **25** (see Experimental Section). The difficulties encountered in the closure of **18** made necessary the finding of another route to **60** and yet more substituted "7-7" enol ethers. Research toward this goal is in progress.

ASIS Measurements.—The assignment of cis,cis stereochemistry to 2,4,6-trimethylcyclohexanone (**51**) is based partially upon nmr solvent shift data (Table I). The magnitude of ASIS (aromatic solvent induced shifts)[23] for the C_2 and C_6 methyl groups when compared to the model compounds 2-methylcyclohexanone (**65**) and *cis*-2,6-dimethylcyclohexanone (**66**) suggests that **51** is the all-equatorial isomer as shown (Scheme VII). The C_4 methyl group becomes relatively more

(22) This solvent system may enhance the proton transfers needed for the dehydrative cyclizations. See C. D. Hurd and W. H. Saunders, *J. Amer. Chem. Soc.*, **74**, 5324 (1952), for similar effects in acetal formation.

(23) M. Fétizon, J. Goré, P. Laszlo, and B. Waegell, *J. Org. Chem.*, **31**, 4047 (1966).

shielded in benzene (as compared to carbon tetrachloride) while the C_2 and C_6 methyls become deshielded. This is in agreement with previous measurements on substituted cyclohexanones, which indicate that groups furthest away from the carbonyl oxygen become most shielded in benzene.[23] The larger shifts obtained with 1-methylnaphthalene suggest that it may prove to be more useful than is benzene. In the case of **46**, the largest ASIS is again found for the C_4 methyl. The doublet for this methyl is broadened, as compared to the other methyls, in all solvents because of "virtual coupling" with the C_3 and C_5 methylene groups.[24] The observed coupling of the $C_{6,7}$ protons (10.2 Hz) is equally compatible with dihedral angles of 0 or 140°. The former suggests a cis $C_{6,7}$ stereochemistry, while the latter is compatible with a trans stereochemistry.[25] Inspection of Drieding models indicates that both are reasonable; so a choice between them is not yet possible. Our limited data suggests that cycloheptanone ASIS may be quite different from those found for cyclohexanones, although larger shifts can be expected for methyl groups further away from the carbonyl in both ring systems.

Experimental Section[26]

Ring Expansion of Cyclohexanones.—2-Methylcycloheptanone (**3**) was synthesized in 46–49% yield (1 peak by vpc on 20% SE-30 at 120°) by the reaction of cyclohexanone with diazoethane generated *in situ* from the reaction of *N*-nitroso-*N*-ethylcarbamate with potassium carbonate and methanol.[27] Similar reaction of 82:18 *cis*/*trans*-3,5-dimethylcyclohexanone (**6a**, **6b**)[28a] (62 g, 0.5 mol) gave (1) material with a boiling point up to 105°, discarded; (2) 24.5 g, bp 105–200° (mostly 175–185°) [vpc[28b] unknown peak (6%), **6a** (30%), **6b** (47%), unknown peak (17%)]; and (3) 38 g, bp 200–210°, pure 2,4,6-trimethylcycloheptanone (**4**).

This represents a yield of 52% of **4** and a recovery of *ca.* 11.5 g of **6b**. Since the original **6** contained *ca.* 11 g of **6b**, only **6a** was ring expanded; *i.e.*, **4** is composed of *cis*-4,6-dimethyl isomers. Redistillation of fraction 3 gave **4**: bp 96° (16 mm); ir (CCl_4) 1704 cm^{-1}; nmr (CCl_4) τ 7.4–7.8 (m, 3, $C_{2,7}H$), 8.4 (m, 6), 8.96 (d, 3, C_2CH_3), 9.00 (d, 3, C_6CH_3), 9.05 (broad d, virtually coupled,[24] 3, C_4CH_3); (CCl_4, after treatment with Na–CH_3OD) τ 8.4 (m, 6), 8.98 (s, 3, C_2CH_3), 9.00 (d, 3, C_6CH_3), 9.05 (broad d, 3, C_4CH_3); vpc (20% SE-30 at 129–163° or 20% XF-1150 at 115–135°) one peak but two peaks (58:42) on 20% DEGS at 117°; 88:12 after treatment with $NaOCH_3$–CH_3OH or CH_3OD; 2,4-DNP of original mixture of isomers had mp 88–90° (C_2H_5OH). *Anal.* Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.97; H, 11.92.

Attempted separation of 38:62 **6a**:**6b** by the anticipated faster reaction of **6a** with sodium bisulfite failed to change the isomeric ratio. The mixture (5.1:1) of **6a**:**6b** was converted to the semicarbazone, mp 194–197°. Four recrystallizations from C_2H_5OH–H_2O gave mp 200–200.5° (lit.[29] mp semicarbazone of **6a** 200.5–201.5°, mp semicarbazone of **6b** 178.4–179.3°). Acid hydrolysis gave 7:1 **6a**:**6b** (vpc on 5% FFAP at 113°). Reduction of 3,5-dimethylcyclohexenone (**7**) in C_2H_5OH with Pd/C, H_2, and 3 *N* HCl gave 8:1 **6a**:**6b**.[29] Similar reduction under neutral or basic conditions gave 4:1 **6a**:**6b** (vpc, 15% Carbowax at 110°).

Formation of Enamines. A. Acid-Catalyzed Treatment with Pyrrolidine or Morpholine.—Treatment of **3** with pyrrolidine (2 equiv) under azeotropic conditions in benzene gave the enamine **1** (71%), bp 136–137° (15 mm), ir (film) 1630 cm^{-1}. Later repetition or reaction in toluene gave poorer yields. Similar treatment of **4** gave no enamine. Treatment of **3** or **4** with morpholine in benzene gave the enamines **8** (72%), bp 137–139° (15 mm), ir (film) 1640 cm^{-1}, and **9** (27%), bp 143–145° (9 mm), ir (film) 1637 cm^{-1}.

B. Trispyrrolidinylboron (67) Method. Trispyrrolidinylboron (67).—To a solution of pyrrolidine (42.7 g, 0.600 mol) in *n*-hexane (100 ml) in an ice–salt bath was added boron trichloride (11.7 g, 0.100 mol) with stirring. A two-phase system resulted and stirring was continued as the reaction mixture was brought to room temperature. Upon slight warming an exothermic reaction began so that cooling was again needed. During this reaction the lower layer solidified. After the reaction subsided, stirring was briefly continued, the hexane layer was combined with benzene washings of the solid layer, and the combined organic solution was distilled to give **67** (10.68 g, 0.0483 mol, 48%), bp 130–140° (0.15 mm), low-melting solid. Exposure to the atmosphere during work-up should be kept to a minimum, since **67** is readily hydrolyzed.[9] Reaction of **3** (12.4 g, 0.056 mol) with **67** (1 equiv), pyrrolidine (2 equiv), and *p*-toluenesulfonic acid (0.2 g) in benzene (60 ml) at reflux for 65 hr gave **1** (5.1 g, 0.029 mol, 52%), bp 119–120° (6 mm), ir (CH_2Cl_2) 1630 cm^{-1}, and recovered **3** (0.9 g, 0.0079 mol, 14%). Similar reaction of **4** for 6 days gave **2** in 89% yield: bp 92–94° (0.05 mm); ir (CH_2Cl_2) 1630 cm^{-1}; nmr (CCl_4) τ 6.0 (m, 0.46, vinyl H), 7.1–7.45 (m, 4, CH_2N), 8.2 (m, 12.54), 8.85 (d, 3, CH_3), 9.0 (d, 3, CH_3), 9.12 (d, 3, CH_3).

C. Conversion of Immonium Perchlorates.[11]—Treatment of **3** with pyrrolidinium perchlorate (1 equiv) and triethylamine (1 drop) in benzene gave the immonium perchlorate **68** (83%). Treatment of **68** with potassium *tert*-butoxide (2 equiv) in benzene gave **2** (40%), bp 112–116° (6 mm), and recovered **3** (29%), bp 69–70° (6 mm).

D. Trispyrrolidinylarsine Method.—A solution of trispyrrolidinylarsine[10] (**69**, 75.9 g, 0.263 mol) and cycloheptanone (**10**, 45.1 g, 0.403 mol) was stirred at room temperature. After 7 min a white precipitate of As_2O_3 formed. The mixture was stirred for a total of 1 hr and diethyl ether (100 ml) was added. The filtrate, after removal of As_2O_3, was combined with one from **69** (12.5 g, 0.043 mol) and **10** (7.4 g, 0.066 mol), dried, and distilled to give a forerun (3.3 g, mostly **10**) and **11** (62.6 g, 0.38 mol, 81%), bp 115–117° (2.3 mm), ir identical with that of genuine **11**. Treatment of **69** with **3** (1.5 equiv) gave no reaction at room temperature after 1 hr. Pyrrolidine (7 drops, *ca.* 0.5 ml) was added and the mixture was heated for 15 hr at 150–160°. Work-up as above gave recovered **3** and examine **1** (*ca.* 1:1 by ir). Similar treatment of **69** with **4** gave very slow formation of a white precipitate and little conversion to the enamine.

Attempted C Alkylation of Enamines.—Treatment of 4-bromobutyl acetate (**12**) with **1** in xylene at reflux for 24 hr or with **2** in toluene (40 hr) or in acetonitrile (60 hr) gave no C alkylation and partial recovery of starting compounds. Reaction of pyrrolidinocycloheptene (**11**, 13.2 g, 0.080 mol) and methyl ω-bromocrotonate (**14**, 18 g, 0.10 mol) in dry methanol (125 ml) at reflux (24 hr) gave **19** (2.2 g, 0.010 mol, 13%): bp 113° (0.1 mm); ir (film) 1730, 1710 cm^{-1}; nmr (CCl_4) τ 7.2–9.0 (m, 13), 4.3 (d, 1, vinyl H), 3.2 (m, 1, vinyl H), and 6.35 (s, 3, OCH_3). Reaction of pyrrolidinocyclohexene with **14** gave 35% of C-alkylated ketone instead of the reported[30] 54% yield.

Synthesis of 2,4,6-Trimethyl-7-ketodecanolide (24).—Reaction of **2** with ethyl acrylate (2 equiv) in ethanol[4,11] gave the pyrrolidine enamine of 7-(2′-carbethoxyethyl)-2,4,6-trimethylcycloheptanone (**20**, 80%), bp 144–146° (0.2 mm), ir (film) 1740, 1640 cm^{-1}. Reduction of **20** with lithium aluminum hydride gave **7-(3′-hydroxypropyl)-2,4,6-trimethylcycloheptanone (21)**, which existed mostly as the hydroxy ether tautomer, ir (CH_2Cl_2) 3600 (sharp), 3400 (broad), 1680 cm^{-1} (w). Crude **21** was treated with *p*-TSA in benzene under azeotropic conditions for 90 hr to give enol ether **23** (60% from **20**): bp 70–71.5° (0.35 mm); ir (CH_2Cl_2) 1665 cm^{-1}; nmr (neat) τ 6.25 (t, 2, CH_2O), 7.52 (d of t, 2, allylic methine H), 8.0–8.8 (m, 9), 9.02 (d, 6, allylic CH_3, J =

(24) E. D. Becker, "High Resolution Nuclear Magnetic Resonance," Academic Press, New York, N. Y., 1969, pp 163–166.

(25) (a) Reference 24, pp 103–105; (b) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); (c) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

(26) Instrumental techniques have been described elsewhere: I. J. Borowitz, K. C. Kirby, Jr., P. E. Rusek, and E. W. R. Casper, *J. Org. Chem.*, **36**, 88 (1971). Mass spectra were done on Hitachi RMU-6 mass spectrometers at Einstein Medical School, N. Y., and Columbia University, unless otherwise noted. Solvents used were dried by distillation from phosphorus pentoxide, calcium hydride, or lithium aluminum hydride. Reactions involving carbanions were conducted under an atmosphere of prepurified nitrogen. All vpc columns employed Chromosorb W and were 5 ft × 1/4 in. unless otherwise noted.

(27) D. W. Anderson and J. Kenner, *J. Chem. Soc.*, 181 (1939).

(28) (a) A commercial sample from Aldrich Chemical Co. was used; (b) a 20% XF-1150 column at 140° was used.

(29) R. L. Augustine and A. D. Broom, *J. Org. Chem.*, **25**, 802 (1960).

(30) A. Chatterjee, *Tetrahedron Lett.*, 959 (1965).

7.5 Hz), and 9.16 (d, 3, CH_3, J = 7.5 Hz). Addition of **23** (4.0 g, 0.021 mol) to MCPBA (85% purity, 12.2 g, 0.060 mol) in CH_2Cl_2 (80 ml) over 15 min was followed by a reflux period of 20 min. After 1 hr at 25° work-up gave **24** (3.1 g, 0.0136 mol, 65%): mp 68.5–69.5° [recrystallized from petroleum ether (bp 30–60°)]; ir (CCl_4) 1740, 1720 cm^{-1}; nmr (CCl_4) τ 5.90 (m, 2, CH_2O), 7.4–8.8 (m, 11), 8.93 (d, 3, CH_3), 8.95 (d, 3, CH_3), 9.00 (br d, 3, C_4 CH_3); mass spectrum (70 eV) m/e 226 ($M\cdot^+$), 211, 198, 183, 155, 140, 125, 111, 98, 87, 82, 69, 55. *Anal.* Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.81; H, 9.80.

Treatment of **24** with diazomethane and aluminum chloride in diethyl ether[16] gave only **24** and no **25**.

8-Ketoundecanolide (31).—Treatment of pyrrolidinocyclooctene with ethyl acrylate (1.5 equiv) in C_2H_5OH for 22 hr at reflux gave **1-pyrrolidino-2-(2′-carbethoxyethyl)cyclooctene (28,** 35%): bp 124–136° (0.1 mm); ir (film) 1730, 1630 cm^{-1}; nmr (CCl_4) τ 5.47 (t, 0.67, vinyl H), 5.98 (q, 2, CH_2CH_3), 7.28 (m, 4, CH_2N), 8.16 (m, 19.3), 8.80 (t, 3, CH_3CH_2). Reduction of **28** with $LiAlH_4$ gave **2-(3′-hydroxypropyl)cyclooctanone (29),** ir (film) 3380, 1705 cm^{-1}. The 2,4-DNP of **29** had mp 136–137° (C_2H_5OH–H_2O). *Anal.* Calcd for $C_{17}H_{24}N_4O_5$: C, 56.03; H, 6.64; N, 15.38. Found: C, 56.23; H, 6.51; N, 15.50.

Crude **29** gave **2-oxabicyclo[4.6.0]dodec-1(6)-ene (30)** in 38% yield upon reflux in benzene, *p*-TSA with azeotropic removal of water (40 hr): bp 106–108° (14 mm); ir (film) 1685 cm^{-1}; nmr (CCl_4) τ 6.20 (2 t, 2, CH_2O), 7.95, 8.15, 8.5 (m, 16). Addition of **30** to MCPBA (3 equiv) in CH_2Cl_2 at a slow rate (to allow solution to gently reflux), followed by 30 min at room temperature, gave, after work-up,[4] **8-ketoundecanolide (31,** 51%): mp 35–37°; ir (CH_2Cl_2) 1730, 1710 cm^{-1}; nmr (CCl_4) τ 5.99 (t, 2, CH_2O), 7.4–8.0, 8.0–8.8 (m, 16). *Anal.* Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.52; H, 9.07.

Conversion of Schiff Base Anions to 2-Alkylated Ketones. A. Schiff Bases.—*N*-Cycloheptylidenecyclohexylamine (**35,** 61% from cycloheptanone and cyclohexylamine) gave bp 91–95° (0.10 mm) [lit.[17] bp 83–88° (0.05 mm)]; ir (film) 1645 cm^{-1}. 2-Methylcycloheptanone gave the cyclohexylimine in 90% yield, bp 107° (1.6 mm), ir (CH_2Cl_2) 1645 cm^{-1}, and the anil **33** (90%), bp 107–112° (1.2 mm), ir (film) 1645 cm^{-1}. 2,4,6-Trimethylcycloheptanone gave no cyclohexylimine but gave the anil (70%), bp 114–116° (0.65 mm), ir (film) 1650 cm^{-1}. *Anal.* Calcd for $C_{16}H_{29}N$: C, 83.76; H, 10.10. Found: C, 83.53; H, 10.31.

B. Alkylations.—*N*-Cyclohexylidenecylohexylamine (**32,** 35.8 g, 0.20 mol)[17] was added to butylmagnesium chloride (66 ml of a 3 *N* solution, 0.2 mol) in THF (400 ml), and the mixture was heated at reflux for 2 hr and cooled. 4-Bromobut-1-ene (**34,** 27 g, 0.20 mol) was added slowly, and the resultant mixture was heated at reflux for 15 hr and cooled. After hydrolysis with aqueous hydrochloric acid (10%, 100 ml) at reflux for 20 hr, the mixture was extracted with ether. The organic layer was washed with 5% $NaHCO_3$ (five 150-ml portions) and H_2O (100 ml), dried, and distilled to give **2(3′-butenyl)cyclohexanone (36,** 19.1 g, 0.126 mol, 63%): bp 82–86° (2.5 mm); ir (film) 1730, 1640 cm^{-1}; nmr (CCl_4) τ 4.17 (m, 1, $CH{=}CH_2$), 5.01 (m, 2, $CH{=}CH_2$), 6.43 (m, 1, CHC=O) and 7.51-8.85 (m, 12).

Similar treatment of **35** with butylmagnesium chloride gave little product. Formation of the Schiff base anion of **35** with methylmagnesium bromide in dibutyl ether followed by alkylation with **34** gave a mixture (many peaks by vpc on 20% SE-30).

Attempted alkylations of the anion of **32,** formed with butylmagnesium chloride or ethylmagnesium bromide, with 4-bromobutyl acetate (**12**) or 3-bromopropyl acetate (reflux *ca.* 18 hr) gave complex mixtures (by tlc and vpc on 20% SE-30).

C. Formation of 2-(3′-Butenyl)cycloalkanone Ketals.—The dioxolane **38** (75% from **36** and ethylene glycol, *p*-TSA, benzene azeotrope, 12 hr) had bp 60–66° (0.05 mm); ir (film) 1640 cm^{-1}; nmr (neat) τ 4.21, 5.12 (vinyl H), 6.16 (s, 4, $-OCH_2CH_2O-$), and 7.82–8.92 (m, 13). The dioxolane **39** (78% from **37**) had bp 91–93° (0.5 mm); ir film) 1640 cm^{-1}; nmr (neat) τ 4.22, 5.02, 6.21 (assigned as for **38**), and 8.33 (m, 15). 2-Methyl-7-(3′-butenyl)cycloheptanone (**42**) slowly gave the dioxolane **43** (19%) after treatment with ethylene glycol in toluene azeotrope for 5 days: bp 148–149° (14 mm); nmr (neat) τ 3.9–4.55, 4.98, 5.22 (vinyl H), 6.12, 6.14 ($-OCH_2CH_2O-$), 7.8–8.8 (m, 14), 9.12 (d, 3, CH_3, J = 7 Hz).

D. Hydroboration of Butenyl Ketals.—Hydroboration[31] of **38** gave the dioxolane of 2-(4′-hydroxybutyl)cyclohexanone, ir (film) 3320 cm^{-1}. The ketal was hydrolyzed with concentrated HCl (5 ml) in C_2H_5OH (50 ml) to give **2-(4′-hydroxybutyl)cyclohexanone (40),**[4] which was treated with *p*-TSA in benzene under azeotropic conditions as previously reported[4] to give **2-oxabicyclo[5.4.0]undec-1(7)-ene** (3.76 g, 0.024 mol, 28% from the butenyl ketal **38**), bp 68–72° (2.0 mm), spectral data identical with that of a genuine sample.[4]

Similar hydroboration of **42** gave **2-methyl-7-(4′-hydroxybutyl)cycloheptanone (17)** in 42% yield; spectral data are as given below.

2,4,6-Trimethylcyclohexanone (51). A. Reduction of 2,4,6-Trimethylphenol.—A mixture of 2,4,6-trimethylphenol (**49,** 27.2 g, 0.20 mol) and 5% Rh–Al_2O_3 (2.5 g) in absolute C_2H_5OH (150 ml) and HOAc (5 ml) was hydrogenated at 25–50 psig and 25° in a Parr shaker until 48 lb of hydrogen (*ca.* 0.6 mol) was consumed. Filtration and evaporation *in vacuo* gave a residue which was dissolved in ether (250 ml), washed with $NaHCO_3$ (two 100-ml portions) and NaCl (100 ml), dried, and evaporated to give a mixture of **50** and **51** (22.18 g, 0.157 mol if pure **50,** 78%), ir (film) 3610, 1710 cm^{-1}. To crude **50, 51** (63.0 g, *ca.* 0.44 mol) in acetone (360 ml) in an ice bath was added CrO_3 (30 g, 0.30 mol) in water (84 ml) and H_2SO_4 (23.2 ml) at a rate sufficient to maintain a reaction temperature of 10–15° (2 hr). The mixture was stirred at 22° for 1 hr, and $NaHSO_3$ (18.2 g) was added with ice bath cooling (exothermic reaction) until the mixture became green. The organic layer, combined with ether and acetone washings of the inorganic layer, gave **51** (50.3 g, 0.36 mol, 81%): bp 72–79° (15 mm); ir (film) 1710 cm^{-1}; nmr (CCl_4) τ 7.3–8.3 (m, 7), 9.05 (d, 3, C_4CH_3, J = 5.6 Hz), 9.07 (d, 6, $C_{2,6}$ CH_3, J = 6.0 Hz); (C_6H_6) 9.03 (d, 6), 9.31 (d, 3); vpc (15% Carbowax 20M) one peak at 120°. *Anal.* Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.90; H, 11.67.

2,4,6-Trimethyl-7-carbethoxycycloheptanone (46).—Ethyl diazoacetate (18.7 g, 0.15 mol) in ether (20 ml) was added dropwise with stirring over 3 hr to a solution of $BF_3\cdot C_2H_5O$ (44.7 g, 0.31 mol, freshly distilled from CaH_2) and **51** (44.0 g, 0.31 mol) in ether (40 ml) under nitrogen. The reaction temperature did not exceed 35°. Lower yields of **46** were obtained at 0–5° or >35°. After 15 hr at 22°, the reaction mixture was poured over ice (110 g) and extracted with ether (five 120-ml portions) to give **46** (21.4 g, 0.095 mol, 60% based on 1 equiv of **51**): bp 100–105° (0.1 mm); ir (film) 1740, 1710 cm^{-1}; vpc one peak (5% SE-30, 145°); nmr (CCl_4) τ 5.89 (q, 2, CH_2CH_3), 7.5–8.5 (m, 7), 8.76 (t, 3, CH_2CH_3, J = 7.2 Hz), 9.01 (d, 3, C_2CH_3), 9.03 (d, 3, C_6CH_3), 9.11 (d, 3, C_4CH_3), 7.09 (d, 1, C_7 H, J = 10.2 Hz). The data (Table I) are consistent with the presence of one isomer of **46**. Reaction of **51** with 1 equiv of ethyl diazoacetate gave 18% of **46**. *Anal.* Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.70; H, 9.84.

Formation and Alkylation of β-Keto Esters.—2-Carbethoxycycloheptanone (**44,** 92%) had bp 118–124° (14 mm). Similar reaction of 2-methylcycloheptanone with diethyl carbonate and NaH gave **2-methyl-7-carbethoxycycloheptanone (45,** 89%): bp 113–136° (14 mm) [lit.[32] bp 113–116° (6 mm)]; ir (film) 3400 (w, enolic OH), 1745 (s, ester), 1710 (s, ketone), 1640, 1610 cm^{-1}; nmr (neat) τ 5.88 (q, 2, CH_2CH_3), 6.2–6.65 (m, 0.76 H ketonic isomer CH(C=O)O), 7.3, 8.4 (m, 9.3), 8.81 (t, 3, CH_2CH_3), 8.90 (d, 3, CH_3CH). The presence of **45** and not 2-methyl-2-carbethoxycycloheptanone is confirmed by the partial presence of the enolic form and a doublet at τ 8.90. Similar reaction of **4** gave **46** (19–25%), ir and nmr identical with those of **46** from ring expansion of **51**, and diester **47** (26%): bp 150–159° (14 mm); ir (film) 1730 cm^{-1}; nmr (CCl_4) τ 5.87 (q, 4, CH_2CH_3), 7.9 (br s, 2, α H), 8.6–9.15 (complex m, 22, CH, CH_2, CH_3). Reaction of **4** with ethyl chloroformate and potassium triphenylmethide in glyme gave only starting ketone. Hydrolysis of **46** with ethanolic KOH (reflux for 18 hr) gave 85:15 **4a**:**4b**.[33] Attempted closure of **47** with potassium *tert*-butoxide in ether gave no reaction.

Alkylation of the sodium enolate of **45** (from **45** and NaH in toluene at reflux for 3 hr) with **12** (10 equiv, at reflux overnight in toluene) gave **2-methyl-7-carbethoxy-7-(4′-acetoxybutyl)cycloheptanone (54,** 56%): bp 118–156° (0.3 mm); ir (film) 1735, 1705 cm^{-1}; nmr (CCl_4) τ 5.85 (q, 2, CH_2CH_3), 6.0 (t, 2, CH_2O),

(31) H. C. Brown, "Hydroboration," W. A Benjamin, New York, N. Y., 1962.

(32) J. R. Mahajan and P. C. Dutta, *J. Chem. Soc.*, 62 (1960).

(33) This mixture of **4a,b** is probably formed from one initially formed isomer during the prolonged exposure to base.

7.3 (m, 1, C_7 H), 8.05 (s, 3, $CH_3(C{=}O)O$), 8.2–8.8 (m, 14), 8.74 (t, 3, CH_2CH_3), 8.97 (d, 3, CH_3CH, J = 7 Hz).

2-Carbethoxy-2-(3′-butenyl)cycloheptanone (52), from the sodium enolate of carbethoxycycloheptanone (from **44** and $NaOC_2H_5$ in C_2H_5OH at reflux for 15 hr) with **34** (1.1 equiv, at reflux for 15 hr), 72%, had bp 103–109° (0.25 mm); ir (film) 1730, 1700, 1640 cm^{-1}; nmr (neat) τ 4.25 (m, 1, $CH{=}CH_2$), 5.01 (m, 2, $CH{=}CH_2$), 5.87 (q, 2, CH_2CH_3), 6.49 (m, 2, allylic H), 7.50–8.48 (m, 12), 8.80 (t, 3, CH_2CH_3).

2-Methyl-7-carbethoxy-7-(3′-butenyl)cycloheptanone (53), from the potassium enolate of **45** (from **45** and potassium triphenylmethide) with **34** (at reflux in DME for 15 hr), 85%, had bp 136–138° (0.75 mm); ir (neat) 1740, 1720, 908 cm^{-1} ($CH{=}CH_2$); nmr (neat) τ 3.85–4.55, 4.98, 5.2 (as above, vinyl H), 5.82 (q, 2, CH_2CH_3), 7.2, 8.0, 8.3 (m, 13), 8.74 (t, 3, CH_2CH_3), 8.91 (d, 3, C_7 CH_3); mass spectrum (70 eV) m/e (rel intensity) 252 ($M^{\cdot+}$, 4), 244 (8), 207 (12), 198 (100), 166 (26), 155 (75), 151 (50), 148 (70), 136 (28), 123 (32), 108 (92), 94 (35), 80 (48). The use of $NaOC_2H_5$–C_2H_5OH for enolate formation gave **53** in 24% yield. *Anal.* Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.51; H, 9.73.

2,4,6-Trimethyl-7-carbethoxy-7-(4′-acetoxybutyl)cycloheptanone (59).—Addition of **46** (26.0 g, 0.116 mol) to NaH (hexane washed, 5.7 g, 0.118 mol) in toluene (110 ml)–DMF (30 ml) gave a clear solution after a 30-min reflux period. Alkylation with **12** (23.0 g, 0.118 mol) at reflux for 18 hr (pH then *ca.* 7) gave NaBr (12 g, 0.116 mol) and a mixture of **59** and O-alkylated diester **58** (15.6 g, 0.046 mol, 40%): bp 150–155° (0.15 mm); (film) 1700 sh, 1730 cm^{-1}; nmr (CCl_4) τ 5.8–6.1 (m, OCH_2), 8.05 (s, 3, $OCOCH_3$), 8.15–8.55 (m, CH, CH_2), 8.58–8.92, 9.0–9.1 (m, 12, CH_3); vpc (10% SE-30 at 200°) three peaks in ratio of 23 (**58**): 25:52 (**59** isomers). The assignment of **58** is based on its disappearance (and appearance of **46**) after treatment of **58** and **59** with dilute aqueous HCl, *i.e.*, **58** was hydrolyzed to **46**. *Anal.* Calcd for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47. Found: C, 66.82; H, 9.43.

Decarboxylation of β-Keto Esters.—Basic hydrolysis (10% NaOH in 3:1 C_2H_5OH–H_2O) of **52** gave 2-(3′-butenyl)cycloheptanone (**37**, 31%): bp 105–134° (0.6 mm); ir (film) 1670, 1695 cm^{-1}; nmr (neat) τ 4.27, 5.00 (vinyl H), 7.25–8.84 (m, 15). *Anal.* Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.64; H, 11.00. Similar hydrolysis of **53** gave **2-methyl-7-(3′-butenyl)cycloheptanone (42)**, 84%: bp 93–97° (3.5 mm); ir (film) 1705, 905 cm^{-1}; nmr (neat), τ 3.9–4.5, 4.99, 5.22 (as above, vinyl H), 7.5, 7.9, 8.8 (m, 14), 9.02 (d, 3, CH_3, J = 7 Hz); vpc one peak; mass spectrum (70 eV) m/e (rel intensity) 180 ($M^{\cdot+}$, 15), 168 ($M - H_2O$, 14), 126 (72), 111 (23), 84 (100), 52 (52), 41 (95). *Anal.* Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.78; H, 11.25. Hydrolysis of **54** with KOH, C_2H_5OH–H_2O (8:1) at reflux for 20 hr gave **2-methyl-7-(4′-hydroxybutyl)cycloheptanone (17**, 47%): bp 113–117° (0.05 mm); ir (film) 3580, 1705 cm^{-1}; nmr (CCl_4) τ 6.1 (s, 1, OH), 6.48 (t, 2, CH_2O), 8.1–8.85 (m, 16), 9.02 (d, 3, CH_3). Hydrolysis of the mixture of **58** and **59** with aqueous alcoholic NaOH for 48 hr at reflux, followed by treatment with 1 *N* HCl at room temperature for 24 hr, gave **2,4,6-trimethyl-7-(4′-hydroxybutyl)cycloheptanone (18**, 43%): bp 140° (0.1 mm); ir (film) 3500, 1700 cm^{-1}; nmr (CCl_4) τ 5.95 (s, 1, OH), 6.45 (t, 3, CH_2O), 7.2 (m, 1, α H), 8.4 (m, 13), 8.98 (d, 3, C_2 CH_3), 9.05 (d 3, C_6 CH_3), 9.10 (d, 3, C_4 CH_3); vpc (5% SE-30 at 190°) one peak; mass spectrum (70 eV) m/e (rel intensity) 226 ($M^{\cdot+}$, 4), 208 ($M - H_2O$, 4), 154 (21), 139 (42), 112 (100), 109 (38), 95 (65), 83 (68), 70 (32). *Anal.* Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.07; H, 11.58.

Hydrolysis of **58** and **59** with aqueous alcoholic KOH at 22° for 8 hr gave crude **2,4,6-trimethyl-7-carbethoxy-7-(4′-hydroxybutyl)cycloheptanone (64)** which was decarboxylated with anhydrous LiI, collidine[34] at reflux for 48 hr to **18** (20–55% in several runs).

Cyclization of 4′-Hydroxybutyl Ketones to Bicyclic Enol Ethers.—No reaction occurred when **17** was treated with *p*-TSA in benzene under azeotropic conditions. Little conversion to the "7-7" enol ethers **56a,b** was observed upon distillation of **17** from *p*-TSA (at 0.1 or 14 mm), potassium pyrosulfate, or acid-washed alumina (at 260°). A solution of **17** (5.99 g, 0.030 mol) and *p*-TSA (10 mg) in toluene (125 ml)–DMF (25 ml) was heated at reflux through a Soxhlet extractor filled with CaH_2 for 7 days. Pyridine (3 ml) was added to the cooled mixture, which was distilled to give 12-methyl-2-oxabicyclo[5.5.0]-dodec-1(7)ene (**56a**) and an isomer **56b**, 22%: bp 105–125° (14 mm); ir (film) 1665 cm^{-1}; nmr (CCl_4) τ 6.25, 6.45 (m, 2, CH_2O), 7.7–8.8 (m, CH_2, vinyl CH_3 of **56b**), 8.95 (d, 1.7, CH_3-CH, 57% of **56a**); vpc–mass spectrum[35] (70 eV) m/e (rel intensity) component A 180 ($M^{\cdot+}$, 57), 165 (22), 151 (30), 137 (56), 126 (48), 121 (25), 109 (37), 95 (56), 81 (61), 67 (74), 55 (83), 41 (100); component B differing intensities for above peaks; M + 1 = 13.0, M + 2 = 1.12; calcd for $C_{12}H_{20}O$, M + 1 = 13.3, M + 2 = 1.02.

Similar treatment of **18** (or azeotropic removal of H_2O for up to 8 days) gave **8,10,12-trimethyl-2-oxabicyclo[5.5.0]dodec-1(7)-ene (60a)** and isomers **60b** and **60c** (three peaks by vpc on 10% SE-30 at 180°): ir (film) 1680 cm^{-1}; vpc–mass spectrum[36] (70 eV) m/e (rel intensity) peak A 208 (86), 193 (100), 179 (17), 166 (100), 165 (100), 151 (32), 139 (37), 137 (32), 126 (53), 123 (38), 112 (45), 111 (73), 109 (38), 97 (43), 95 (68), 81 (63), 67 (53), 55 (100); vpc peaks B and C gave very similar fragmentation; M + 1 = 16.2; calcd for $C_{14}H_{24}O$, M + 1 = 15.6. The isomers **60a–c** were generally formed in minor yield along with much starting material (**18**). Attempts to separate reasonable amounts of **60a–c** were not successful. Similar results were obtained upon treatment of **18** in toluene–DMF with methanesulfonic acid. Other attempted dehydrative cyclization of **18** with *p*-TSA in benzene, HMPA–toluene, etc., gave no reaction.

Oxidation of Bicyclic Enol Ethers to Keto Lactones.—Addition of **56a** and **56b** to MCPBA (3 equiv) in CH_2Cl_2 at a slow rate to maintain reflux (20 min), followed by 2 hr at room temperature, and work-up,[4] gave **2-methyl-7-ketoundecanolide (57**, 27%): mp 70–71.5°; ir (KBr) 1717, 1695 cm^{-1}; nmr (CCl_4) τ 5.9 (m, 2, CH_2O), 7.55 (m, 5, $C_{2,6,8}$ H), 8.4 (m, 10), and 8.90 (d, 3, CH_3, J = 7 Hz); vpc (10% SE-30 at 180°); one peak; mass spectrum[37] (70 eV) m/e (rel intensity) 212.1440 (M^+, 16), 156 (5), 139 (37), 126 (47), 112 (42), 111 (28), 101 (33), 98 (100), 84 (47), 69 (67), 68 (70), 56 (40), 55 (92); calcd for $C_{12}H_{20}O_2$, 212.1412. *Anal.* Calcd for $C_{12}H_{20}O_2$: C, 67.89; H, 9.50. Found C, 67.90; H, 9.56.

The crude oxidation mixture had an nmr peak at τ 7.8, suggestive of a methyl ketone such as **61** which would form from the endocyclic olefin **56b**.

Similar oxidation of the crude mixture of **60a–c** and **18** resultant from the attempted dehydrative closure of **18** gave oils: one main and several minor isomers by vpc (5% SE-30 at 160°); ir (film) 1728, 1700 cm^{-1}; nmr (CCl_4) τ 5.95 (t, CH_2O), 8.05, 8.1–8.8, 8.75, 8.9–9.1 (CH_3); mass spectrum (70 eV) m/e 254, 240 (weak); calcd for $C_{14}H_{24}O_3$, 240.

Registry No.—**1a**, 33015-68-8; **1b**, 33015-99-5; **2a**, 32971-08-7; **2b**, 33016-00-1; **3**, 932-56-9; **4a**, 32971-09-8; **4a** 2,4-DNP, 32971-10-1; **4b**, 32971-11-2; **4b** 2,4-DNP, 33021-04-4; **8**, 33068-10-9; **9**, 33015-70-2; **11**, 14092-11-6; **17**, 33015-72-4; **18**, 33015-73-5; **19**, 32971-12-3; **21**, 32971-13-4; **23**, 32971-14-5; **24**, 32971-15-6; **25**, 32971-19-0; **28**, 33015-74-6; **29**, 33015-75-7; **29** 2,4-DNP, 33016-01-2; **30**, 33015-76-8; **31**, 33015-77-9; **33**, 33015-78-0; **35**, 6114-69-8; **36**, 16178-83-9; **37**, 33015-80-4; **38**, 33015-81-5; **39**, 33068-12-1; **42**, 33015-82-6; **43**, 33015-83-7; **45**, 2206-76-0; **46**, 32971-16-7; **47**, 33015-85-9; **51**, 32971-17-8; **52**, 33015-86-0; **53**, 33068-13-2; **54**, 33015-87-1; **56a**, 33015-88-2; **56b**, 33015-89-3; **57**, 33015-90-6; **58**, 33015-91-7; **59**, 33015-92-8; **60a**, 33015-93-9; **60b**, 33015-94-0; **65**, 583-60-8; **66**, 766-42-7; **67**, 4426-24-8; 2-methylcycloheptylcyclohexylimine, 33015-97-3; 2,4,6-trimethylcycloheptanone anil, 33015-98-4.

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(34) F. Elsinger, *Org. Syn.*, **45**, 7 (1965).

(35) Performed on an LKB vpc-inlet mass spectrometer at the University of Pittsburgh by Dr. Gary Koppel.

(36) Performed on a Varian Atlas CH-5 vpc-inlet mass spectrometer by Mr. Jack Landis, City University of New York.

(37) High resolution mass spectral data were obtained on an MS-9 mass spectrometer by Dr. Rodger Foltz at the Battelle High Resolution Mass Spectrometry Center supported by the National Institutes of Health, Division of Research Resources, Contract No. NIH-69-2226.