Preparation and Unusual Mass Spectra of 3,4,4-Trimethyl-5-oxo-*trans*-2-hexenoic Acid and Related Compounds

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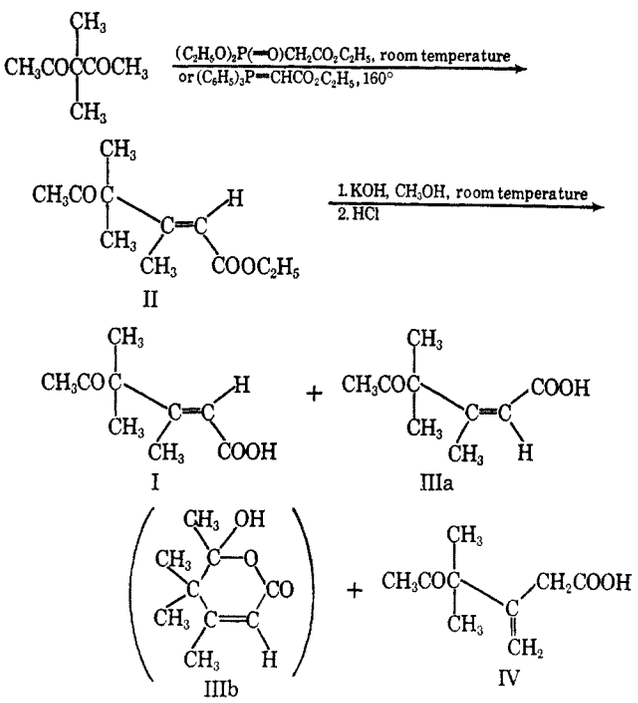
Ethyl 3,4,4-trimethyl-5-oxo-*trans*-2-hexenoate (II) has been prepared by the Wittig procedure and saponified to the corresponding acid (I) and its *cis* (III) and unconjugated (IV) isomers. Mass spectra of the three isomers differ strikingly from one another.

Synthesis.—In a recent preliminary report 3,4,4-trimethyl-5-oxo-*trans*-2-hexenoic acid (I) was identified as a product of the metabolism of (+)-camphor by a soil diphtheroid, strain Tl (*Mycobacterium rhodochrous*), and its metabolic precursor was suggested to be isoketocamphoric acid.[1] The structure of the metabolite was assigned from consideration of its spectral properties and confirmed by synthesis.[1a] The present paper presents details of the synthetic route employed and of the mass spectra of I and related compounds.

Commercially available acetylacetone was methylated to give 3,3-dimethyl-2,4-pentanedione, which was purified of incompletely methylated material by extraction with sodium hydroxide, then converted by two routes involving alternative modifications of the Wittig reagent[2] to ethyl 3,4,4-trimethyl-5-oxo-*trans*-2-hexenoate (II). A somewhat better conversion (46%) and yield (71%, based on unrecovered diketone) was effected with the more reactive triethyl phosphonoacetate than with carbethoxymethylenetriphenylphosphorane (34% conversion, 51% yield).

The ester prepared by both procedures had the same spectral properties and was shown by glpc and its nmr spectrum (Table I) to be essentially pure. However, it was isomerized in part during saponification, and both the desired acid I and isomeric compounds, which could be separated from I by thin layer and column chromatography, were isolated after saponification. These were identified as the corresponding *cis* acid III and 4,4-dimethyl-3-methylene-5-oxohexanoic acid (IV).

The relative amounts of the three acids (I, III, IV) isolated were 175:10:140. While these probably do not represent equilibrium values, they indicate minimum equilibrium proportions of II and III. The instability of the *cis* acid II was expected, but the relative stability of the unconjugated acid III is somewhat surprising. Equilibrium values have not been reported for a comparable system, whose best model might be 3-*t*-pentylbutenoic acid, but values are available for β-methylcrotonic acid. Goldberg and Linstead studied its isomerization at 100° in 25% potassium hydroxide and reported the equilibrium to give entirely the conjugated isomer.[3] In the present system the steric bulk of the β-alkyl substituent apparently shifts the equilibrium toward the unconjugated isomer. This favoring of IV relative to I is a manifestation of the same phenomenon found in the preferential formation of 2,4,4-trimethyl-1-pentene over 2,4,4-trimethyl-2-pentene[4] and of the observed preference for the unconjugated isomer in tautomeric equilibria of other β-alkyl-substituted unsaturated acid systems.[3-5]



Structures of I, III, and IV were assigned from their nmr, infrared, and ultraviolet spectra (Table I). These properties (and the mass spectrum, Figure 1, discussed below) for the synthetic *trans* acid I agreed perfectly with those for the acid derived microbiologically from camphor.[1]

Ultraviolet absorption spectra, with strong maxima near 220 mμ, show that ester II and acids I and III contain conjugated carboxyl functions, while the electronic spectrum of IV with its unconjugated carboxyl group contains only end absorption. These conclusions are confirmed by the infrared spectra of I–IV which contain appropriately conjugated or unconjugated carbonyl stretching bands. The infrared spectrum of IV contains the expected olefinic

(1) (a) P. J. Chapman, G. Meerman, I. C. Gunsalus, R. Srinivasan, and K. L. Rinehart, Jr., *J. Am. Chem. Soc.*, **88**, 618 (1966); (b) P. J. Chapman, I. C. Gunsalus, H. Uda, and E. J. Corey, *Biochemistry*, in press.

(2) S. Trippett, *Quart. Rev.* (London), **17**, 406 (1963).

(3) A. A. Goldberg and R. P. Linstead, *J. Chem. Soc.*, 2343 (1928).

(4) H. C. Brown and E. L. Berneis, *J. Am. Chem. Soc.*, **75**, 10 (1953).

(5) G. A. R. Kon, R. P. Linstead, and J. M. Wright, *J. Chem. Soc.*, 599 (1934).

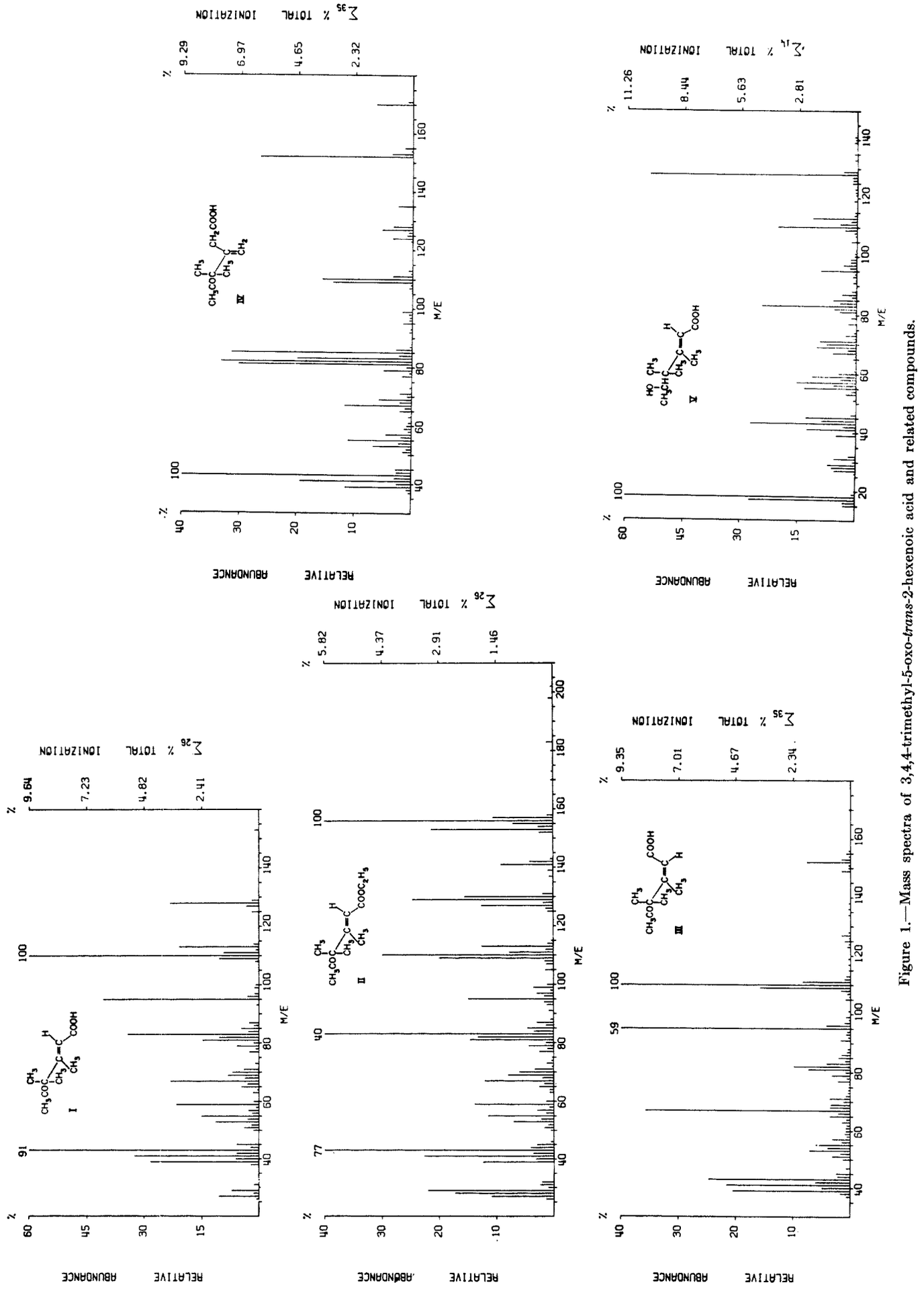


Figure 1.—Mass spectra of 3,4,4-trimethyl-5-oxo-*trans*-2-hexenoic acid and related compounds.

TABLE I
SPECTRAL PROPERTIES OF UNSATURATED ACIDS AND DERIVATIVES

	Uv[a]		Ir,[a,b] cm^{-1}			Nmr,[a,b] τ (J, cps)					
	λ_{max}, mμ	ϵ_{max}	C=O stretch	C=C stretch	C=C H bend	$C(CH_3)_2$	OCH_3	$C=CCH_3$	C=CH	COOH	Other protons
I	218	10,800	1705, 1685	1634 S[c]	960, 873	8.70 s	7.92 s	7.91 d (1)	4.04 q	−1.75	
II[c]	222	12,400	1715, 1708	1638 S	952, 868	8.76 s	8.01 s	7.97 d (1.5)	4.19 q		OCH_2CH_3, 5.87 q, 8.72 t (7)
IIIa, acid[d]						8.62 s	7.93 s	[8.04][e]			
IIIb, lactol	222	10,400	1708		960	8.82 s	8.40 s	8.04 sb	4.20 sb		OH, 5.88 b
IV		460[f]	1706	1638 W	918	8.72 s	7.80 s		4.70 s[g]	−1.22	$C=CCH_2COO$, 6.99 sb
									4.74 sb		

[a] Ultraviolet spectra were determined in 95% ethanol, infrared spectra in chloroform, and nmr spectra in deuteriochloroform except as noted. [b] Abbreviations: S = strong, W = weak, s = singlet, d = doublet, t = triplet, q = quartet, b = broad. [c] Infrared and nmr spectra in carbon tetrachloride. [d] The acid exists predominantly in the lactol form; only the values noted can be clearly assigned to the acid form. [e] Unresolved from a lactol peak. [f] End absorption only: ϵ_{220} 460. [g] Tentatively assigned *trans* to CH_2COO.

methylene absorption, at 918 cm^{-1}. Of the two conjugated acids that formed in preponderant yield, the *trans* structure is assigned to I.

Although the relatively small amount of the *cis* acid isolated precluded extensive study, it clearly exists predominantly as its δ-lactol, IIIb. This is apparent from its infrared spectrum, which contains hydroxylic –OH absorption (unbonded and hydrogen bonded, 3590 and 3350 cm^{-1}) rather than the characteristically broad carboxylic –OH absorption extending nearly to 2500 cm^{-1}, as found in the infrared spectra of II and IV. The lactol form is confirmed by the relatively high field positions of the geminal dimethyl (τ 8.82) and hemiketal methyl (τ 8.40) groups. Relative intensities of the *gem*-dimethyl absorption at τ 8.82 (lactol) and τ 8.62 (keto acid) indicate an approximate 3:1 ratio of lactol to keto acid.

It is of some interest that the position of the *gem*-dimethyl absorption is, as expected, somewhat lower when the group is *cis* to the carboxyl (τ 8.62 in IIIa) than when it is *trans* (τ 8.70 in I); similarly the olefinic methyl appears at lower field when *cis* (τ 7.91 in I) than when *trans* (τ 8.04 in IIIa) to the carboxyl.

Mass Spectra.—The mass spectrum of I (Figure 1) was initially an obstacle to the identification of I as a metabolite of camphor in that no molecular ion is found at m/e 170. A very weak peak (1% of base peak) is observed at m/e 153 (M − OH), but the intense peak (23%) of highest mass is that at m/e 128 (M − C_2H_2O). This peak is due to ion aI, formed by the exceedingly facile loss of ketene from the molecular ion and probably involving a six-membered cyclic transition state in a novel example of the McLafferty rearrangement[6] (Figure 2). Most of the remaining intense ions above m/e 80 can then be explained as resulting from ion aI (or its cyclic form, the protonated lactone bI), through loss of methyl (cI, m/e 113), water (d, m/e 110), methyl and water (e, m/e 95), or carboxyl (f, m/e 83), as shown.

Most of these fragmentations are attested by metastable ion peaks (Table II).[7] Other fragmentations indicated by metastable ion peaks are loss of carbon monoxide from e to give g (m/e 67), loss of acetyl from

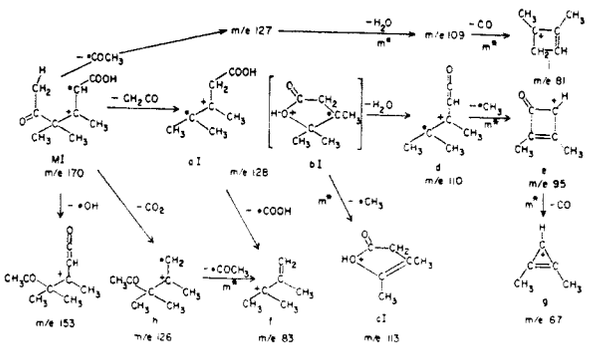


Figure 2.—Mass spectral fragmentations of keto unsaturated acids and derivatives.

decarboxylated I (h, m/e 126) to give f, and successive losses of water and carbon monoxide from a peak at m/e 127 (aI less a proton) to give, respectively, peaks at m/e 109 (d less a proton) and m/e 81 (i) (see Figure 2).

The general appearance of the mass spectrum of the ester II (Figure 1) is very similar to that of I, although a very weak (0.8%) molecular ion is observed and the ion at m/e 153 is much stronger (21%). Here the base peak is due to ion aII (M − 42 at m/e 156, m^* in Table II). Ion aII (or bII) undergoes the same

TABLE II
METASTABLE IONS

		m^* found				
	m^* calcd	I	II	III	IV	V
aI → c	99.7	99.7				99.7
aI → d	94.5				94.7	94.7
aI → f	53.8		53.7			53.8
d → e	81.9	82.0		82.0		
e → g	47.3	47.5	47.5	47.5		47.5
127 → 109	93.8	94.0	93.7	94.0	94.0	
109 → 81	60.2	60.5	60.5	60.5	60.3	
h → f	54.7	54.7	54.7	54.7	54.7	
aII → aI	105.0		105.0			
aII → f	44.1		44.3			
k → d	79.6			79.7		
170 → 152	135.9				136.0	
152 → 124	101.2				101.5	
170 → 127	94.9				94.7	
127 → 110	95.3				95.7	
110 → 82	61.1				61.3	
85 → 67	52.8				52.7	

(6) F. W. McLafferty, in "Mass Spectrometry of Organic Ions," F. W. McLafferty, Ed., Academic Press Inc., New York, N. Y., 1963, p 336.

(7) No metastable ions are found for the transitions aI → d and aI → f in the spectra of I, but metastable ions for these fragmentations are found in the spectra of other compounds (II, IV, and V, see below).

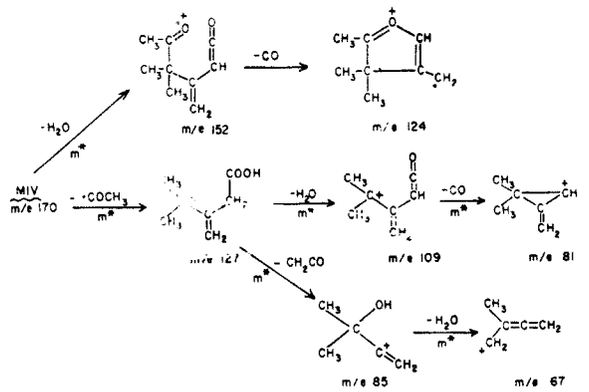
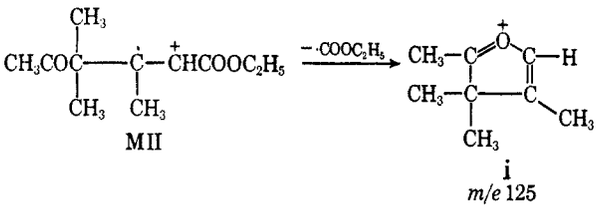
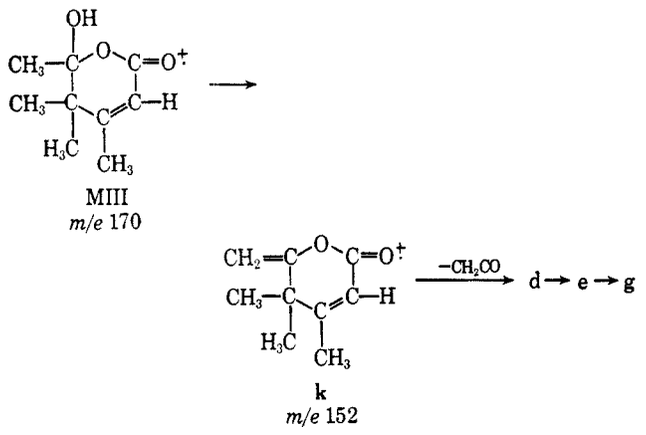


Figure 3.—Mass spectral fragmentation of 3-methylene-4,4-dimethyl-3-oxo-hexanoic acid.

further decompositions as aI (or bI) to give cII (*m/e* 141), d (*m/e* 110), e (*m/e* 95), and f (*m/e* 183).[8,9] In addition, aII can lose ethylene to give ion aI (*m/e* 128) and its successors, cI (*m/e* 113), d, and e. Loss of carbethoxy from the molecular ion gives ion j at *m/e* 125.



The mass spectrum of the *cis* unsaturated acid III is quite different from that of I and II, as might be expected for the cyclic lactol IIIb. A weak molecular ion (MIII, *m/e* 170) is found and this loses water, rather than ketene or a hydroxyl (ethoxyl) radical like MI (MII), to give ion k. Ion k is then the source of further fragmentation, losing ketene to yield d (*m/e* 110), which gives (Table II), as usual, e (*m/e* 95) and g (*m/e* 67). Since ion aI (*m/e* 128) is missing, ion cI is also absent.



(8) The spectrum of the sodium borohydride reduction product V of the keto acid I (prepared by Dr. P. J. Chapman) is very similar to those of the acid I and the ester II. The base peak is at *m/e* 128 (aI) and the usual fragmentations to cI, d, e, and f provide the other observed strong peaks. Moreover, the molecular ion is missing, indicating that the principal feature triggering cleavage between C-4 and C-5 is the Δ^2 olefinic bond rather than the C-5 carbonyl group. On the other hand, the two γ-alkyl substituents probably also contribute to the fragmentation to a, since simple α,β-unsaturated esters do not undergo this type of McLafferty rearrangement as a major fragmentation process.[9]

(9) R. Ryhage, S. Ställberg-Stenhagen, and E. Stenhagen, *Arkiv Kemi*, **18**, 179 (1961).

The mass spectrum of the unconjugated acid IV is also quite distinct from those of its isomers (I and III). It alone contains a reasonably intense molecular ion (6%) and the spectrum is richer in fragmentation pathways. The acetylium ion provides the base peak, a strong ion at *m/e* 152 (l, M − 18) loses carbon monoxide to give a weak peak at *m/e* 124, a sequence of increasingly intense pairs of peaks at *m/e* 128–127, 110–109, and 82–81 corresponds to the sequence 127 → 109 → 81 in the spectrum of I, and the h → f transition of I is also found. It is of interest that some ions at the same masses as those in the spectra of I have different structures or origins. The ion at *m/e* 128 is not aI, since neither ion cI (*m/e* 113) nor ion e (*m/e* 95) is found. Also, the ion at *m/e* 67 is formed here by a different route: 170 → 127 → 85 → 67. Possible structures of some of the above ions are suggested in Figure 3.

Experimental Section[10]

3,3-Dimethyl-2,4-pentanedione.—A solution of 10.8 g of sodium methoxide, 20.0 g of 2,4-pentanedione, and 30.0 g of methyl iodide in 150 ml of dimethylformamide stood at room temperature for 21 hr, then was worked up to give 15.5 g (68%) of crude, oily 3-methyl-2,4-pentanedione, bp 165–172° (lit.[11] 60–65° (13 mm)). The product was combined with material from a second experiment (total, 35.0 g) and added slowly, with stirring under nitrogen, to a cooled suspension of 7.2 g of sodium hydride (from 12.7 g of sodium hydride in mineral oil) in 350 ml of freshly distilled dry dimethylformamide. Methyl iodide (47.0 g) in 50 ml of dimethylformamide was added over 30 min to the resulting suspension, which was then stirred at room temperature overnight. The reaction mixture was diluted with water, saturated with salt, and extracted with ether. The ether layer was concentrated, washed with aqueous 10% sodium hydroxide solution to remove any unreacted enolizable diketone, then with saturated salt solution, and dried over anhydrous sodium sulfate. Removal of solvent gave an oil, which on distillation afforded 25.5 g (67%) of 3,3-dimethyl-2,4-pentanedione, bp 173° (lit.[12] 173°), pure by glpc.[10]

Ethyl 3,4,4-Trimethyl-5-oxo-*trans*-2-hexenoate (II). A. From Triethyl Phosphonoacetate.—A suspension of 1.2 g of sodium hydride (washed free of mineral oil with petroleum ether (bp 60–68°)) in 10 ml of dimethylformamide was stirred in a three-necked flask (nitrogen inlet, drying tube, dropping funnel, ice bath) while 11.2 g of triethyl phosphonoacetate (prepared from triethyl phosphite and ethyl bromoacetate)[13] in 10 ml of dimethylformamide was added during 15 min. Next, 6.2 g of 3,3-dimethyl-2,4-pentanedione in 10 ml of dimethylformamide was added, then the solution was stirred for 24 hr at room temperature and worked up in the usual fashion. Fractional distillation yielded 2.2 g of unreacted ketone, bp 75–80° (15 mm), 3.7 g of the desired ester II, bp 76–80° (0.4 mm), and 2.0 g of a mixture, from which 0.7 g of the desired ester was obtained by chromatography on silica gel, eluting with 5% ethyl acetate in benzene. The total conversion was thus 46%, yield 71%. Ultraviolet, infrared, and nmr spectra are summarized in Table I; the mass spectrum is found in Figure 1.

(10) Gas–liquid partition chromatograms were carried out on an Aerograph A90P-2 chromatograph, using a column (1/4 in. × 6 ft) of 8% EGSS-X on Gaschrom P at column temperature 155°, helium pressure 22 psi. Melting points were taken on a Kofler micro hot stage and are uncorrected. Mass spectra were determined by Mr. J. A. Wrona on an Atlas CH4 mass spectrometer with TO4 ion source, employing the vacuum lock technique. All spectra were determined both at 70 ev and at reduced ionizing voltage, usually 12 to 15 ev. Samples were not heated. Infrared spectra were determined on Perkin-Elmer spectrophotometers, Models 237 and 221, ultraviolet spectra on a Beckman spectrophotometer, Model DB, and nmr spectra on a Varian A-60 spectrometer. Microanalyses were performed by Mr. J. Nemeth and his associates.

(11) K. Von Auwers and H. Jacobsen, *Ann.*, **426**, 161 (1922).

(12) M. F. Ansell, W. J. Hickinbottom, and A. A. Hyatt, *J. Chem. Soc.*, 1592 (1955).

(13) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, Chapter 7.

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.67; H, 9.09. Found: C, 66.33; H, 9.00.

B. From Carbethyoxymethylenetriphenylphosphorane.—A mixture of 7.1 g of 3,3-dimethyl-2,4-pentanedione and 19.0 g of carbethoxymethylenetriphenylphosphorane[14] was stirred at 155–160° for 24 hr, then cooled, extracted with petroleum ether (bp 60–68°), and worked up. Distillation yielded 2.4 g of unreacted ketone and 3.7 g (34% conversion, 51% yield) of the desired ester. The ester was found by infrared and nmr spectra to be identical with that obtained by procedure A. Although the presence of the *cis* isomer could not be detected in the nmr spectrum, glpc[10] showed the presence of a very small amount of another compound with a slightly shorter retention time.

Saponification of Ethyl 3,4,4-Trimethyl-5-oxo-*trans*-2-hexenoate (II).—A solution containing 0.5 g of the ester (II), 25 ml of methanol, 1.25 g of potassium hydroxide, and 2 ml of water stood at room temperature for 18 hr, then was diluted with water, acidified with 5 ml of concentrated hydrochloric acid, and concentrated under vacuum. Crystalline 3,4,4-trimethyl-5-oxo-*trans*-2-hexenoic acid (I), 100 mg, mp 128–219°, precipitated and was filtered. A mixture melting point of synthetic I and the camphor metabolite[1] was undepressed. Ultraviolet, infrared, and nmr spectra are summarized in Table I; its mass spectrum is found in Figure 1.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.53; H, 8.24; Mol wt, 170. Found: C, 63.72; H, 8.30.

The mother liquor from filtration of I was saturated with salt and extracted with ether. The ether layer was dried over anhydrous sodium sulfate; removal of solvent gave a semisolid residue which was shown by tlc (silica gel G; 9:1 benzene–acetic acid) to contain three compounds: R_f 0.65, 0.53, and 0.18 (trace). The most mobile component was identified as 3,4,4-trimethyl-5-oxo-*trans*-2-hexenoic acid (I), R_f 0.65. Chromatography over a column of silica gel using benzene containing 3% acetic acid as eluant gave 75 mg of I (total yield, 41% from saponification) and 140 mg (33%) of 4,4-dimethyl-3-methylene-5-oxohexanoic acid (II), R_f 0.53. Both compounds crystallized from benzene–pentane; compound II had mp 53°. Ultraviolet, infrared, and nmr spectra of III are summarized in Table I; its mass spectrum is found in Figure 1.

Anal. Found: C, 63.52; H, 8.26; mol wt, 170 (mass spectrometry).

Eluting the column with benzene–acetic acid (4:1) gave 10 mg of the third isomer, **3,4,4-trimethyl-5-oxo-*cis*-2-hexenoic acid,** existing predominantly as the δ-lactol (IIIb). Crystallization from benzene–pentane gave aggregates, mp 110–131°.[15] Although the small amount of compound available precluded further purification, it was found to be pure by tlc on silica gel. Ultraviolet, infrared, and nmr spectra are summarized in Table I; the mass spectrum is found in Figure 1.

Anal. Found: mol wt, 170 (mass spectrometry).

Registry No.—I, 14919-54-1; II, 6994-98-5; IIIa, 14919-56-3; IIIb, 14919-57-4; IV, 6994-96-3; V, 14919-59-6.

Acknowledgment.—This investigation was supported by a grant (No. AI 04769) from the U. S. Public Health Service, National Institute of Allergy and Infectious Diseases.

(14) D. B. Denney and S. T. Ross., *J. Org. Chem.* **27**, 998 (1962).

(15) The compound is apparently polymorphic, since further recrystallization from ether–pentane sometimes gave mp 152–154°, sometimes mp 110–131°.

The Synthesis of Some 3,7-Dialkyl-3,7-diazabicyclo[3.3.1]nonanes and a Study of Their Conformations

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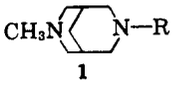
A series of 3-methyl-7-alkyl-3,7-diazabicyclo[3.3.1]nonanes (N-methyl-N′-alkylbispidines) have been prepared by Mannich cyclocondensations on 1-methyl-4-piperidone followed by Wolff–Kischner reduction of the intermediate ketones. Dipole moment and nmr studies indicate that their preferred conformation is a flattened chair–chair. All of these diamines titrate as monoamines; the formation of very stable hydrogen-bonded adamantanelike cations is proposed to account for this behavior. The reaction of N,N′-dimethylbispidine with diiodomethane is also discussed.

Of the numerous methods which have been reported for the synthesis of the 3,7-diazabicyclo[3.3.1]nonane system,[1] those which are related to the classical Robinson–Schöpf reaction[2] are among the most versatile. Without exception, however, these heterocycles are substituted on both bridgehead carbon atoms.[3] The parent diamine itself has been prepared only by multistep, relatively low yield syntheses.[4]

In the course of other investigations, we found a need for several 3-methyl-7-alkyl-3,7-diazabicyclo-[3.3.1]nonanes (hereafter referred to as N-methyl-N′-alkylbispidines (1)), and it is our studies concerning the synthesis and properties of these compounds which we now wish to report.

Results and Discussion

It occurred to us that a two-step approach to the synthesis of 1 starting with a double Mannich con-



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densation of commercially available 1-methyl-4-piperidone with formaldehyde and alkylamine to give the diazabicyclic ketone 2 would be worthy of investigation. The success of House and coworkers[5] in

(1) For a review, see H. Stetter, *Angew. Chem., Intern. Ed. Engl.*, **1**, 286 (1962).

(2) For a discussion of the stereochemistry of this reaction, see L. A. Paquette and J. W. Heimaster, *J. Am. Chem. Soc.*, **88**, 763 (1966).

(3) (a) S. Chiavarelli, F. Toeffer, R. L. Vittori, and P. Mazzeo, *Gazz. Chim. Ital.*, **94**, 1021 (1964); (b) K. Hohenlohe-Oehringen, *Monatsh.*, **94**, 1208 (1963); (c) S. Chiavarelli and L. V. Fennoy, *J. Org. Chem.*, **26**, 4895 (1961); (d) S. Chiavarelli, G. Settimj, and H. M. Alves, *Gazz. Chim. Ital.*, **87**, 109 (1957); (e) Z.-Y. Kyi and W. Wilson, *J. Chem. Soc.*, 1706 (1951); (f) E. F. L. J. Anet, G. K. Hughes, D. Marmion, and E. Ritchie, *Australian J. Sci. Res.*, **3A**, 330 (1950); (g) C. Mannich and F. Veit, *Ber.*, **68B**, 506 (1935); (h) C. Mannich and P. Mohs, *ibid.*, **63B**, 608 (1930).

(4) (a) F. Bohlmann, N. Ottawa, and R. Keller, *Ann.*, **587**, 162 (1954); (b) H. Stetter and H. Hennig, *Ber.*, **88**, 789 (1955); (c) F. Galinowsky, F. Sparatore, and H. Langer, *Monatsh.*, **87**, 100 (1956).

(5) H. O. House, P. P. Wickham, and H. C. Müller, *J. Am. Chem. Soc.*, **84**, 3139 (1962).