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Syntheses of Isomeric Methylpseudoionones and Isomeric Pseudoionones by Means of the Wittig Reaction

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Four isomeric methylpseudoionones and two isomeric pseudoionones were separately synthesized by the Wittig reaction of citral a or citral b with the corresponding phosphonates. Two isomeric pseudoionones were also synthesized by the Wittig reaction of citral a or citral b with 2-oxopropylidenetriphenylphosphorane. The configurations and the conformations of the dienone systems in four methylpseudoionones and two pseudoionones were discussed on the basis of the infrared and ultraviolet absorption data.

Since butanone has an active methyl and an active methylene group, the condensation of citral (I) with butanone results in the formation of two pairs of methylpseudoionones, i. e., *n*-methylpseudoionones (II) and isomethylpseudoionones (III). The four isomers have been isolated as their semicarbazones or phenylsemicarbazones.[1,2] The direct synthesis of each isomer, however, has never been reported.

Recently, II, III, and pseudoionone (IV) were synthesized by the reaction of citral (an isomeric mixture) with the corresponding 2-oxoalkylidenetriphenylphosphoranes,[3] but the configurations and the conformations of the dienone systems were not described.

In the present experiment, the syntheses of each isomeric methylpseudoionone and pseudoionone were attempted by the use of the corresponding phosphonates, according to the modified Wittig reaction.[4] The phosphonates employed in the present investigation were prepared by the Michaelis-Arbuzov reaction.[5]

Diethyl 2-oxopropylphosphonate (V) was treated successively with sodium amide and with a 96 : 4 mixture of citral a (Ia) and citral b (Ib) (Ia-rich I) to afford a 95 : 5 isomeric mixture of *trans*-3, *trans*-5-pseudoionone (IVa) and its 5-*cis* isomer (IVb). The treatment of V with a 2 : 98 mixture of Ia and Ib (Ib-rich I) in the same way gave a 2 : 98 mixture of isomers, IVa and IVb. These products were confirmed by gas chromatographic identification with authentic samples obtained by the aldol condensation of Ia-rich I or Ib-rich I with acetone, by a study of the infrared spectra[*1] of the products (Table I)[*2], and by elementary analyses of the semicarbazones.[*3] IVa and IVb were also prepared by the reaction of 2-oxopropylidenetriphenylphosphorane (VI) with Ia-rich I or Ib-rich I for the sake of comparison. The results (Table II) show that the phosphonate method gave better yields than the phosphorane method, and that the reaction proceeded substantially stereospecifically (only *trans* isomers were produced).

TABLE I. SOME CHARACTERISTIC ABSORPTION BANDS IN THE INFRARED SPECTRA OF THE MODIFIED WITTIG REACTION PRODUCTS (liquid film)

	ν(C=O) cm^{-1}	ν(C=C) cm^{-1}	δ(C–H) cm^{-1}
IVa	1668 vs, 1688 vs*	1633 vs, 1590 vs	975 s
IVb	1668 vs, 1687 vs*	1631 vs, 1588 vs	973 s
IIa	1667 vs, 1688 vs*	1631 vs, 1593 vs	977 s
IIb	1667 vs, 1687 vs*	1630 vs, 1593 vs	973 s
IIIa	1662 vs	1632 vs, 1596 m	
IIIb	1662 vs	1630 vs, 1592 m	

* Splitting carbonyl bands.

Each isomeric mixture rich in *trans*-4,*trans*-6-*n*-methylpseudoionone (IIa), its 6-*cis* isomer (IIb), *trans*-3, *trans*-5-isomethylpseudoionone (IIIa), or its

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1) H. Barbier, Y. R. Naves and P. Ardizio, *Bull. soc. chim. France,* **1951**, 254.

2) Y. R. Naves, H. Barbier and P. Ardizio, ibid., **1951**, 639.

3) K. Fujiwara, H. Takahashi and M. Ohta, This Bulletin, **35**, 2042 (1962).

4) Cf. W. S. Wadsworth and W. D. Emmons, *J. Am. Chem. Soc.,* **83**, 1733 (1961).

5) G. M. Kosolapoff, "Organophosphorus Compounds," 1st Ed., J. Wiley & Sons Inc., New York, N. Y. (1950), Chap. 7.

6) H. Köster, *Chem. Ber.,* **80**, 248 (1947).

[*1] The infrared spectra were measured through the courtesy of Dr. Yoshitaka Matsuoka and Mr. Kenya Sakaguchi of the Eisai Research Laboratories.

[*2] The infrared and ultraviolet absorption spectra of the products (as mixtures) were measured without further purification.

[*3] This conclusion might be supported by the following reports: Surber and his co-workers observed that the preparation of the α, β-*cis* form of methyl ketones unsaturated in the α, β- and γ, δ-positions with respect to the carbonyl group proves practically impossible (W. Surber, V. Theus, L. Colombi and H. Schinz, *Helv. Chim. Acta,* **39**, 1299 (1956)). Naves and his co-workers reported that the most probable configuration for III and IV is *trans*-3, *trans*-5 or *trans*-3, *cis*-5, while that for II is *trans*-4, *trans*-6 or *trans*-4, *cis*-6 (Ref. 2).

TABLE II. PSEUDOIONONES OBTAINED BY MEANS OF THE WITTIG REACTIONS

Reagent		Reaction conditions	B. p. of product °C/mmHg	Yield, %	Composition of product*4 (IVa : IVb)	d_4^{20}	n_D^{20}	Semicarbazone $C_{14}H_{23}N_3O$*5 M. p.*6 °C	Anal. Calcd., %	Anal. Found, %
Ia-rich I	VI	4 hr. at 100—110°C	95—100/0.5	26	95 : 5					
Ib-rich I	VI	4 hr. at 100—110°C	95—96/0.8	19	7 : 93					
Ib-rich I	VI	4 hr. at 100—110°C 1/2 hr. at 142°C	98—100/0.9	37	11 : 89					
Ia-rich I	V	See Experimental	100—105/0.6	49	95 : 5	0.9073	1.4891	139.5—141	C : 67.43 H : 9.30 N : 16.85	67.25 9.38 17.03
Ib-rich I	V	See Experimental	92—98/0.8	48	2 : 98	0.9086	1.4862	139—140	C : 67.43 H : 9.30 N : 16.85	67.08 9.33 17.05

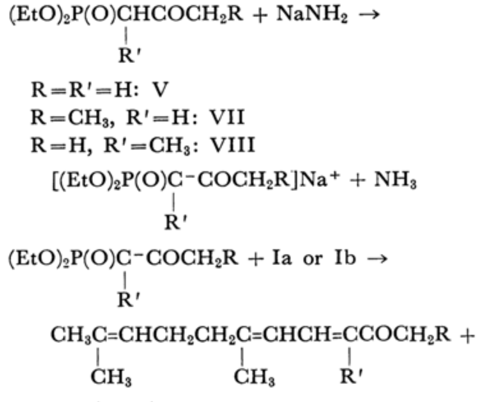
TABLE IV. METHYLPSEUDOIONONES PREPARED BY MEANS OF THE MODIFIED WITTIG REACTION

Reagent		B. p. of product °C/mmHg	Yield, %	Composition of product*4				d_4^{20}	n_D^{20}	Crystalline derivatives*5,*7 M. p. °C	Anal. Semicarbazone $C_{15}H_{25}N_3O$		Anal. 4-Phenylsemicarbazone $C_{21}H_{29}N_3O$	
				IIa	IIb	IIIa	IIIb				Calcd., %	Found, %	Calcd., %	Found, %
Ia-rich I	VII	111—114/0.55	75	93.1	5.2	0.8	0.8	0.8959	1.5264	153—154			C : 74.30 H : 8.61 N : 12.38	74.39 8.75 12.46
Ib-rich I	VII	107—111/0.75	67	2.8	95.5		1.7	0.9015	1.5227	138.5—140			C : 74.30 H : 8.61 N : 12.38	74·15 8.66 12.60
Ia-rich I	VIII	94—98/0.2	63	1.4		94.1	4.5	0.9117	1.5299	184—186	C : 68.40 H : 9.57 N : 15.96	68.15 9.78 16.20		
Ib-rich I	VIII	88—92/0.07	62		3.0	3.2	93.8	0.9110	1.5250	169—171	C : 68.40 H : 9.57 N : 15.96	68.68 9.59 16.21		

5-*cis* isomer (IIIb) was prepared by the reaction of Ia-rich I or Ib-rich I with diethyl 2-oxobutylphosphonate (VII) or diethyl 1-methyl-2-oxopropylphosphonate (VIII). All these products were identified by a comparison of their retention times with those of authentic samples rich in II and rich in III, which were prepared in the manner described by Köster.[6] The identifications were supported by the infrared[*1] and ultraviolet absorption spectra of the products (Tables I and III)[*2] and by elementary analyses of the carbonyl derivatives[*3]. The results are summarized in Table IV.

TABLE III. UV ABSORPTION DATA (in EtOH)

	λ_{max} (mμ)		ε_{max}	
IIa	293		24500	
		(292)[7]		(22500)[7]
IIb	293.5		23100	
IIIa	294		24500	
		(293.5)[7]		(25000)[7]
IIIb	295		23500	
IV		(291)[8]		(21000)[8]



$$(EtO)_2P(O)\underset{\displaystyle R'}{C}HCOCH_2R + NaNH_2 \rightarrow$$

R=R′=H: V
R=CH$_3$, R′=H: VII
R=H, R′=CH$_3$: VIII

$$[(EtO)_2P(O)\underset{\displaystyle R'}{C^-}COCH_2R]Na^+ + NH_3$$

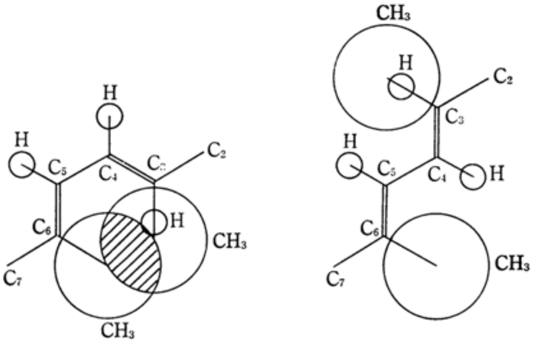
$$(EtO)_2P(O)\underset{\displaystyle R'}{C^-}COCH_2R + \text{Ia or Ib} \rightarrow$$

$$CH_3\underset{\displaystyle CH_3}{C}{=}CHCH_2CH_2\underset{\displaystyle CH_3}{C}{=}CHCH{=}\underset{\displaystyle R'}{C}COCH_2R + (EtO)_2P(O)O^-$$

R=R′=H: IVa or IVb
R=CH$_3$, R′=H: IIa or IIb
R=H, R′=CH$_3$: IIIa or IIIb

It can be noted that each isomeric methylpseudoionone is synthesized in an excellent yield by the use of the phosphonate method.

The presence and the intensity of an absorption maximum at 294 or 295 mμ in the ultraviolet absorption spectra of isomethylpseudoionones (IIIa, IIIb) appeared to show that the diene systems of IIIa and IIIb have the *s-trans* conformation; if they had the *s-cis* conformation, a strong steric hindrance between the C-3 and the C-6 methyl groups would break the co-planarity of the conjugated dienone systems and an additional absorption maximum would appear near 220 mμ, a maximum which may be associated with the partial enone chromophore (Fig. 1).[9-11] In the ultraviolet absorption spectra of *n*-methylpseudoionones (IIa, IIb) and pseudoionones (IVa, IVb), the orders of λ_{max}- and ε_{max}-values were essentially identical with those of isomethylpseudoionones (IIIa, IIIb). This fact may be reasonably explained by the *s-trans* conformation in the diene systems of these compounds.



s-cis *s-trans*

Fig. 1. Two conformations of the diene systems in IIIa and IVa.
Dimentions used: C–C bond length 1.54 Å, C=C bond length 1.33 Å, C–H bond length 1.08 Å, H covalent-bond radius 0.31 Å, Me covalent-bond radius 1.39 Å, bond angle at doubly bonded carbon 120° (Cf. Ref. 9).

The infrared spectra of *n*-methylpseudoionones (IIa, IIb) and pseudoionones (IVa, IVb) showed two absorption bands in the C=O stretching region, while such doublet carbonyl bands were absent in the spectra of isomethylpseudoionones (IIIa,

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[*4] These isomer ratios were calculated from the peak-areas of the respective gas chromatograms by assuming identical ionization characteristics for all the isomers. The conditions for gas chromatography were as follows. For IV: Stationary phase, polydiethyleneglycol succinate. Carrier gas, helium (63 ml./min.). Column temperature, 193°C. For II and III: Stationary phase, SE-30(1 m.)+polyneopentylglycol succinate (2 ml.). Carrier gas, helium (24 ml./min.). Column temperature, 180°C.

[*5] These values were of derivatives obtained by the treatment of the products (mixtures) with the corresponding carbonyl reagents, followed by recrystallization from ethanol.

[*6] Tiemann reported earlier that the two semicarbazones of IV both melted at 142°C (F. Tiemann, *Ber.*, **32**, 115 (1899)).

[*7] Naves and his co-workers reported that the 4-phenylsemicarbazones with the m. p. of 157—157.5°C and 141—141.5°C correspond to IIa and IIb respectively (Ref. 2). They also reported that the two semicarbazones of III melt at 191—191.5°C and 157—158°C, but there was no description of the configuration of III (Ref 1).

7) R. M. Lusskin and L. Winston, *J. Am. Chem. Soc.*, **71**, 2412 (1949).

8) A. Burawoy, *J. Chem. Soc.*, **1941**, 20.

9) E. A. Braude, E. R. H. Jones, H. P. Koch, R. W. Richardson, F. Sondheimer and J. B. Toogood, ibid., **1949**, 1890.

10) E. A. Braude and E. R. H. Jones, *J. Am. Chem. Soc.*, **72**, 1041 (1950).

11) E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, **1955**, 3773.

IIIb). Many authors have reported such a carbonyl splitting in the infrared spectra of *trans*-3-penten-2-one and its 5-alkyl homologs; they have ascribed the effect to an equilibrium between the *s-cis* and *s-trans* conformations.[12-15] On the other hand, it has been reported that no such carbonyl splitting is observed in the infrared spectra of 3-methyl-*trans*-3-penten-2-one and its 3-ethyl homolog, which have the same partial enone structure as that of isomethylpseudoionones (IIIa, IIIb); it has also been reported that the spectral properties of 3-methyl-*trans*-3-penten-2-one and its 3-ethyl homolog are very close to those of the ketones with a fixed *s-trans* conformation.[14] Although no definite evidence can be offered except the infrared spectral data, the conjugated enone systems of *n*-methylpseudoionones (IIa, IIb) and pseudoionones (IVa, IVb) seem to exist in an equilibrium between *s-cis* and *s-trans* conformations, while the systems of isomethylpseudoionones (IIIa, IIIb) may exist predominantly or exclusively in the *s-trans* conformation.

The infrared spectra of *n*-methylpseudoionones (IIa, IIb), isomethylpseudoionones (IIIa, IIIb), and pseudoionones (IVa, IVb) showed two absorption bands due to C=C stretching vibrations at 1630—1633 and 1588—1596 cm^{-1}. The intensities of both bands in the spectra of *n*-methylpseudoionones (IIa, IIb) and pseudoionones (IVa, IVb) were nearly equal, while the intensity of the band at 1592 or 1596 cm^{-1} in the spectra of isomethylpseudoionones (IIIa, IIIb) was weakened. This weakened intensity could be ascribed to an effect of the C-3 methyl group, which should polarize the C-3 double bond in the direction opposite to the effect of the carbonyl group.[14]

Experimental

Materials.—Citrals (Ia-rich I and Ib-rich I) were isolated from commercial lemongrass oil by the procedure described in a previous paper.[16] Ia-rich I: b. p. 66—68°C /0.7 mmHg, Ia : Ib=96 : 4. Ib-rich I: b. p. 61—63°C 10.7 mmHg, Ia : Ib=2 : 98. 2-Oxopropylidenetriphenylphosphorane (VI) was obtained by the reaction of chloroacetone and triphenylphosphine, followed by the treatment of the resultant 2-oxopropylidenetriphenylphosphonium chloride with 10% sodium carbonate.[17] Diethyl 2-oxopropylphosphonate (V) was prepared from triethyl phosphite and bromoacetone. B. p. 75—78°C/0.3 mmHg; yield 53%; $\nu_{C=O}$ 1714, $\nu_{P=O}$ 1259, ν_{P-O} 1165, ν_{C-O} 1025 cm^{-1}. Diethyl 2-oxobutylphosphonate (VII) was prepared from triethyl phosphite and bromomethyl ethyl ketone. B. p. 91—95°C/0.7 mmHg; yield 65%; $\nu_{C=O}$ 1713, $\nu_{P=O}$ 1256, ν_{P-O} 1167, ν_{C-O} 1026 cm^{-1}. Diethyl 1-methyl-2-oxopropylphosphonate (VIII) was prepared from triethyl phosphite and 1-bromoethyl methyl ketone. B. p. 70—73°C/0.25 mmHg; yield 11%; $\nu_{C=O}$1716, $\nu_{P=O}$1253, ν_{P-O}1167, ν_{C-O}1027 cm^{-1}.

The Reaction of a 96 : 4 Citral Mixture (Ia-rich I) or a 2 : 98 Citral Mixture (Ib-rich I) with 2-Oxopropylidenetriphenylphosphorane (VI).—A solution of 3.04 g. (0.02 mole) of Ia-rich I and 6.37 g. (0.0 2mole) of VI in 70 ml. of *n*-butyl ether was heated while being stirred on an oil bath. When the reaction has been completed the solvent was evaporated, a small amount of cold ether was added to the residue, and the crystallized triphenylphosphine oxide was filtered off and washed with ether. The combined filtrate and washings were then dried over anhydrous sodium sulfate. After the solvent had been removed, the residue was distilled off under reduced pressure to give 1.0 g. of a 95 : 5 mixture of IVa and IVb. The same procedure with Ib-rich I gave 0.8 g. of a 7 : 93 mixture of IVa and IVb. In the reaction with Ib-rich I, the prolongation of the reaction time by one half-hour at a refluxing temperature resulted in the formation of 1.4 g. of a 11 : 89 mixture of IVa and IVb.

The Modified Wittig Reaction with the Phosphonates.—To a suspension of 1.95 g. (0.05 mole) of sodium amide in 30 ml. of dry tetrahydrofuran (THF), there was added a solution of 9.71 g. (0.05 mole) of V in 20 ml. of dry THF with stirring and cooling. After the addition was complete, the temperature of the reaction mixture was gradually raised to -3—-1°C, after which the reaction was continued at that temperature until the evolution of ammonia had ceased. The reaction mixture was then again cooled below -10°C, and a solution of 7.61 g. (0.05 mole) of Ia-rich I or Ib-rich I in 20 ml. of dry THF was added. The reaction mixture was gradually warmed to room temperature and allowed to stand overnight. The solvent being evaporated under reduced pressure, the residue was poured into a large excess of water and extracted with ether. The ethereal extract was washed with water and dried over anhydrous sodium sulfate. After the solvent had been removed, the oily residue was distilled under reduced pressure to afford 4.7 g. of a 95 : 5 mixture, or 4.6 g. of a 2 : 98 mixture, of IVa and IVb.

The products rich in IIa, rich in IIb, rich in IIIa, and rich in IIIb, were prepared in a similar manner.

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[12] Cf. I. Bell, E. R. H. Jones and M. C. Whiting, ibid., **1958**, 1313.

[13] Cf. R. D. Campbell and N. H. Cromwell, *J. Am. Chem. Soc.*, **79**, 3456 (1959).

[14] R. Meck and K. Noack, *Chem. Ber.*, **93**, 210 (1960).

[15] K. Noack and R. N. Jones, *Can. J. Chem.*, **39**, 2225 (1961).

[16] K. Sasaki, *J. Chem. Soc. Japan, Pure Chem. Sect. (Nippon Kagaku Zasshi)*, **87**, 763 (1966).

[17] F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 41 (1957).