

A SIMPLE METHOD FOR THE PREPARATION OF BICYCLO[2.2.2]-
OCTANE SYSTEMS FROM METHYL VINYL KETONE DERIVATIVES

Ken-ichi Morita and Zennosuke Suzuki

Basic Research Laboratories, Toyo Rayon Co., Ltd.

Kamakura, Japan

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In a recent communication¹, we noted that the treatment of 16-dehydropregnenolone acetate with trimethyl orthoformate in the presence of an acid catalyst furnished bicyclo[2.2.2]octane systems. It is now found that some methyl vinyl ketone derivatives also react with trimethyl orthoformate in the presence of an acid catalyst to yield bicyclo[2.2.2]octane systems.

A stirred mixture of 3-methyl-3-buten-2-one (I_a) (0.5 M), trimethyl orthoformate (0.5 M) and orthophosphoric acid² (0.02 M) was distilled slowly. Methyl formate was first distilled out during a period of seven hours, followed by methanol. The residue was hydrolyzed with dilute hydrochloric acid at room temperature for

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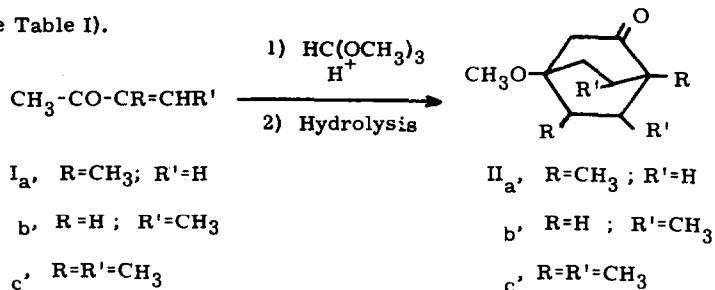
K. Morita, G. Slomp and E. V. Jensen, J. Am. Chem. Soc., 84, 3779 (1962).

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The use of sulfuric acid, boron trifluoride etherate or p-toluene-sulfonic acid gave lower yields of the desired product.

five minutes. Distillation of the product gave 4-methoxy-1,5-dimethylbicyclo[2.2.2]octan-2-one (II_a) in 72 per cent yield. Analogous reactions of 3-penten-2-one (I_b) and of trans-3-methyl-3-penten-2-one (I_c) with trimethyl orthoformate gave 4-methoxy-6,7-dimethylbicyclo[2.2.2]octan-2-one (II_b) (10% yield) and 4-methoxy-1,5,6,7-tetramethylbicyclo[2.2.2]octan-2-one (II_c), (54% yield), respectively. The low yield observed in the case of I_b presumably suggests that the main reaction proceeded to form 4-methoxy-1,3-pentadiene. The observed polymeric material could be derived from it. Only a polymeric material was obtained from the reaction of methyl vinyl ketone with trimethyl orthoformate under the similar condition described above, although a quantitative formation of methyl formate and methanol was observed. Reaction of a methanol solution of mesityl oxide with trimethyl orthoformate in the presence of sulfuric acid gave a complex mixture and no bicyclooctane derivative could be isolated.

The assignment of the structures for II_a, II_b and II_c is based on n.m.r. and infrared spectra that show the presence of a tertiary methoxyl group and a six-membered ring ketone, respectively (see Table I).



When a methanol solution of I_c was treated with trimethyl orthoformate in the presence of sulfuric acid for 5 hours at room temperature, II_c (50%) and a mixture, b. p. 40-43°C at 5 mmHg, (24%) were obtained. The latter was separated by vapor phase chromatography to 4,4-dimethoxy-3-methyl-2-pentene, n_D^{20} 1.4400 (Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.19 Found: C, 66.81; H, 10.69) and 2,4,4-trimethoxy-3-methylpentane, n_D^{20} 1.4222 (Calcd. for $C_9H_{20}O_3$: C, 61.33; H, 11.44 Found: C, 61.58; H, 11.26). Ansell et al.³ reported that trimethyl orthoformate, in methanol with a trace of hydrochloric acid, and ethyl vinyl ketone gave 1,3,3-trimethoxypentane and an analogous reaction of 2-methyl-1-pentene-3-one gave 3,3-dimethoxy-2-methyl-1-pentene.

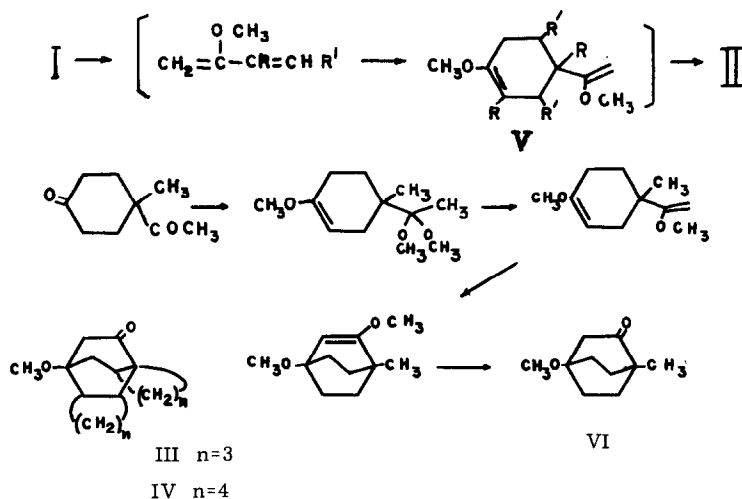
Compound II_a , II_b and II_c each appear to consist of one stereochemical modification, whereas 4-methoxy-5,6:1,7-bispropanobicyclo[2.2.2]octan-2-one (III)⁴ and 4-methoxy-5,6:1,7-bisbutanobicyclo[2.2.2]octan-2-one (IV)¹ derived from 1-acetyl-1-cyclopentene and 1-acetyl-1-cyclohexene, respectively, were each found to consist of two stereoisomers.

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M. F. Ansell, J. W. Lown, D. W. Turner and D. A. Wilson, *J. Chem. Soc.*, 3036 (1963).

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I. A. Favorskaya and L. V. Fedorova [*Zhur. Obshch. Khim.*; **24**, 242 (1954); *Chem. Abstr.*, **49**, 45396 (1955)] apparently obtained this substance by an acid-catalyzed dimerization of 1-(1-methoxyvinyl)-1-cyclopentene, but assigned an incorrect structure.



The positive evidence that the intermediate of this unique reaction is V is provided by the following experiments. Reaction of a methanol solution of 4-acetyl-4-methyl-1-cyclohexanone with trimethyl orthoformate at 25°C (20 hr.) gave a 73% yield of 4-(1,1-dimethoxyethyl)-4-methyl-1-methoxy-1-cyclohexene, b. p. 121-122.5°C at 14 mmHg, n_D^{20} 1.4751 (Calcd. for $\text{C}_{12}\text{H}_{22}\text{O}_3$: C, 67.25; H, 10.35. Found: C, 67.44; H, 10.26) which was further transformed into 4-(1-methoxyvinyl)-4-methyl-1-methoxy-1-cyclohexene in 80% yield, b. p. 121-122°C at 14 mmHg, n_D^{20} 1.4825 (Calcd. for $\text{C}_{11}\text{H}_{18}\text{O}_2$: C, 72.48; H, 9.95. Found: C, 71.64; H, 9.82, contaminated with little keto compound) by boiling it in acetic anhydride-pyridine (5 hr.). Treatment of this substance with boron trifluoride etherate in benzene solution at reflux (3 hr.) afforded, after hydrolysis, in 80% yield 4-methoxy-1-methylbicyclo[2.2.2]octan-2-one (VI).

TABLE I
Physical Constants of Substituted 4-Methoxybicyclo[2.2.2]octan-2-ones

Compound	b. p. °C (mmHg)	n_D^{20}	infra red C = O	OCH ₃	n. m. r. OCH ₃ bridge-head methyl	Carbon % (calculated)	hydrogen % (calculated)
II _a 1,5-dimethyl- ^a	114-116(12)	1.4799	1723	1109	3.13 (ppm) (in CCl ₄)	72.25 (72.49)	9.96 (9.95)
II _b 6,7-dimethyl-	94-95(5)	1.4792	1723	1109	3.10 (in CCl ₄)	72.71 (72.49)	9.69 (9.95)
II _c 1,5,6,7- ^b tetramethyl-	113-116(3)	1.4859	1723	{ 1105 1127	3.13 (in CCl ₄)	74.36 (74.24)	10.56 (10.55)
VI 1-methyl ^c	117-119(17)	1.4802	1725	1110	3.15 (in CCl ₄)	71.32 (71.39)	9.59 (9.58)
III 5,6:1,7- ^d bispropano-	142-143(2.5)	1.5215 (26°C)	1723		{ 3.21 (in CDCl ₃) 3.23	76.81 (76.88)	9.25 (9.47)
IV 5,6:1,7- bisbutano-	{ major isomer minor isomer (m. p. 79-79.5°C)	{ 1.5290 (23°C)	1723		{ 3.20 (in CDCl ₃) 3.22		

a) oxime, m. p., 128-129°C, Found: C, 67.15; H, 9.72; N, 6.99.

b) oxime, m. p., 150-151°C, Found: C, 69.62; H, 10.30; N, 6.24.

c) oxime, m. p., 127-128°C, Found: C, 65.42; H, 9.35; N, 7.59.

d) a mixture of two diastereomers.