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Rearrangements in Dihydroresorcinol Derivatives.IV.[1] Claisen Rearrangement of 3-Allyloxy-2-cyclohexen-1-ones[2]

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Heating of 3-allyloxy-2-cyclohexen-1-ones (IIa,b,c) caused a Claisen rearrangement and simultaneous cyclization to give 2-methyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofurans (IIIa,b,c) in 75, 70 and 78% yields, respectively. Under similar conditions, 3-allyloxy-2-methyl-2-cyclohexen-1-one (VI) gave 2-allyl-2-methylcyclohexane-1,3-dione (VII) in 81% yield, and 3-prenyloxy-2-cyclohexen-1-one (VIII) gave 2,2,3-trimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran (IX) in 95% yield. The reaction mechanisms were also discussed.

Although the Claisen rearrangement of allyl ethers of acyclic 1,3-diketones to 2-allyl-1,3-diketones[4] has been reported, there has been no investigation on that of cyclic 1,3-diketones. Recently, Dolby, *et al.*[5] have postulated that the reaction of 5,5-dimethylcyclohexane-1,3-dione and 2-methoxybutadiene giving 2-(3′-methoxy-2′-butenyl)-5,5-dimethylcyclohexane-1,3-dione would proceed *via* Claisen rearrangement of an allylic enol ether of 5,5-dimethylcyclohexane-1,3-dione. However, no positive proof for the formation and rearrangement of the allyl ether has been provided. Therefore, Claisen rearrangement of allylic enol ethers of cyclohexane-1,3-diones has now been investigated. We found that heating of 3-allyloxy-2-cyclohexen-1-one (IIa) brought about a Claisen rearrangement and simultaneous ring formation to afford 2-methyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran (IIIa) in 75% yield. Under the same conditions, 3-allyloxy-5-metyl-2-cyclohexen-1-one (IIb) and 3-allyloxy-5,5-dimethyl-2-cyclohexen-1-one (IIc) gave similarly 2,6-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran (IIIb) and 2,6,6-trimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran (IIIc), in 70 and 78% yields, respectively, while 3-allyloxy-2-methyl-2-cyclohexen-1-one (VI) and 3-prenyloxy-2-cyclohexen-1-one (VIII) gave 2-allyl-2-methylcyclohexane-1,3-dione (VII) and 2,2,3-trimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran (IX) in 81 and 95% yields, respectively. The present paper describes this.

The following three methods for preparing 3-allyloxy-2-cyclohexen-1-one (IIa) were investigated: (method A) refluxing a benzene solution of cyclohexane-1,3-dione (Ia) and allyl alcohol in the presence of *p*-toluenesulfonic acid for 10 hr using a Dean–Stark water–separator, (method B) reaction of 3-chloro-2-cyclohexen-1-one[6] with sodium allyloxide, and (method C) reaction of sodium salt of Ia[7] with allyl bromide. Method A and B gave IIa in 69 and 32% yields from Ia, respectively, and method C gave a mixture of IIa and two other unidentified products. Therefore, method A was employed for preparation of IIa and also of IIb and IIc, whose yields from Ib and Ic were 72 and 78%, respectively. For preparation of 3-allyloxy-2-methyl-2-cyclohexen-1-one (VI), however, method B afforded better result (66% yield).

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[1] Part III: Y. Tamura, Y. Kita and M. Terashima, *Chem. Pharm. Bull.* (Tokyo), **19**, 529 (1971).

[2] This work was presented at Meeting of Kinki Branch, Pharmaceutical Society of Japan, Kyoto, November 1968.

[3] Location: *6-5, Toneyama, Toyonaka, Osaka.*

[4] M. Bertrand and J. Le Gras, *Compt. Rend.*, **260**, 6926 (1965).

[5] L.J. Dolby, C.A. Elliger, S. Esfandiari and K.S. Marshall, *J. Org. Chem.*, **33**, 4508 (1968).

[6] A.R. Crossley and P. Haas, *J. Chem. Soc.*, **83**, 498 (1903).

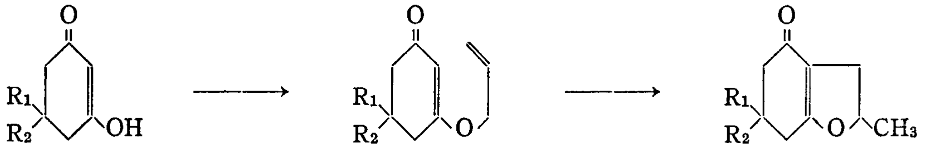
[7] C.A. Grob and H.R. Kiefer, *Helv. Chim. Acta*, **48**, 799 (1965).

3-Prenyloxy-2-cyclohexen-1-one (VIII) was prepared by method C using silver salt of Ia.[8] Spectral data of IIa,b,c, VI and VIII are summarized in Table I.

TABLE I. Spectral Data of IIa,b,c, VI, VIII and IIIa,b,c

	IR $\nu_{max}^{CHCl_3}$ cm^{-1}		NMR (CDCl$_3$)τ	UVλ_{max}^{EtOH}mμ
IIa	1640	1600	3.98 (-C$\underline{H}$=CH$_2$) 4.65(-COCH=)	247
	995	940	4.67 (-CH=C$\underline{H}_2$) 5.60(-OCH$_2$-)	
IIb	1640	1600	3.97 4.63 4.65	249
	1000	940	5.58 8.88(-CH$_3$)	
IIc	1640	1600	3.97 4.63 4.65	250
	995	940	5.58 8.91	
VI	1637	1610	4.00 4.69 5.43 (-OCH$_2$-)	
	990	925	8.25 (-CH$_3$)	
VIII	1640	1600	4.66 (-CH=C<) 4.67(-COCH=)	
			5.67 (-OCH$_2$-) 8.28(-CH$_3$)	
IIIa	1619		5.06 (-OC$\underline{H}$(CH$_3$)-)	271
			8.58 (-OCH(C$\underline{H}_3$)-)	
IIIb	1618		5.05 8.58	270
			8.88 (-CH(C$\underline{H}_3$)-)	
IIIc	1621		5.03 8.58	272
			8.99 (-C(CH$_3$)$_2$-)	

Heating of IIa,b,c at 190—200° for 3 hr under nitrogen atmosphere caused a Claisen rearrangement and simultaneous cyclization to give 2-methyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofurans (IIIa,b,c) in 75, 70 and 78% yields, respectively. Structures of IIIa,b,c were deduced from spectral data indicated in Table I. The strong band at 1621—1619 cm^{-1} in infrared (IR) spectra suggests a presence of -CO-C=C-O- grouping. The nuclear magnetic resonance (NMR) signal of C-2 methyl protons appears at τ 8.58, doublet and that of C-2 proton at τ 5.03—5.06, multiplet.



Ia—c IIa—c IIIa—c

a: R$_1$=R$_2$=H; b: R$_1$=H, R$_2$=CH$_3$; c: R$_1$=R$_2$=CH$_3$

Chart 1

Following attempts were made to get an insight into the reaction. When the above reaction of IIa was carried out at 140° for 7 hr, 2-allylcyclohexane-1,3-dione (IV)[9] was obtained along with the cyclized derivative (IIIa). And, as the reaction temperature was raised, amount of IV decreased and that of IIIa increased (checked by IR and thin-layer chromatography (TLC)). Heating of IV at 190—200° for 3 hr under nitrogen atmosphere gave 65% of the cyclization product (IIIa). It was also shown that refluxing of IIa in acetic anhydride afforded 3-acetoxy-2-allyl-2-cyclohexen-1-one (V) in 84% yield, which was hydrolyzed with 10% HCl solution to IV in 70% yield. From these chemical evidences, IV was confirmed to be an intermediate of the transformation from IIa to IIIa.

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8) G.F. Woods and I.W. Tucker, *J. Am. Chem. Soc.*, **70**, 2174 (1948).

9) *a*) H. Stetter and W. Dierichs, *Chem. Ber.*, **85**, 1061 (1952); *b*) K.W. Rosenmund and H. Bach, *ibid.*, **94**, 2394 (1961).

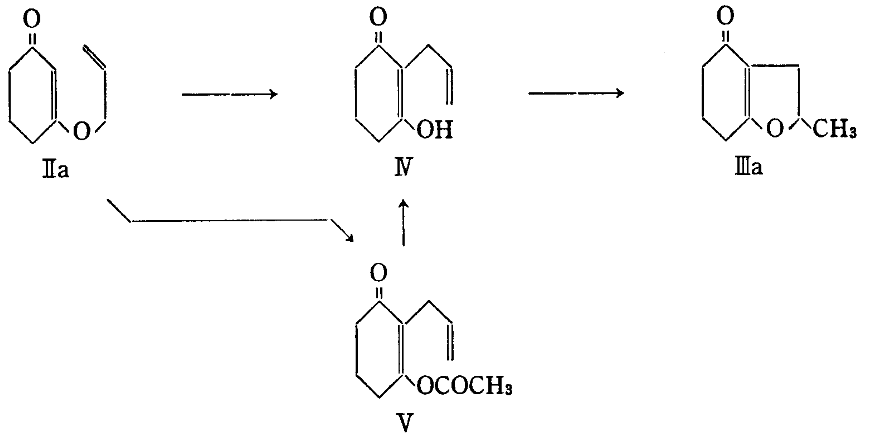

Chart 2

The Claisen rearrangement of 3-allyloxy-2-methyl-2-cyclohexen-1-one (VI) under similar conditions to those employed for II gave 2-allyl-2-methylcyclohexane-1,3-dione (VII) in 81% yield. The structural assignment of VII was assumed from its NMR spectral data ($CDCl_3$) τ 4.38 (multiplet, $-C\underline{H}=CH_2$), 5.00 (multiplet, $-CH=C\underline{H}_2$), 7.29 (doublet, $-C\underline{H}_2CH=$) and 8.77 (singlet, $-CH_3$), and finally confirmed by identification with a sample prepared by treatment of potassium salt of Ia and allyl bromide in aqueous solution. No cyclization was realized by further thermal treatment of VII.

Heating of 3-prenyloxy-2-cyclohexen-1-one (VIII) in the same manner as described above gave 2,2,3-trimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran (IX) in 95% yield. The structure of IX was based on its NMR spectral data. In the NMR spectra of IX, the signal of *gem*-dimethyl protons (τ 8.68, singlet, 6H) appears at lower field than that of methyl protons (τ 8.90, doublet, 3H). Hence the former dimethyl groups should be placed at C–2 (neighboring to O-atom) and the latter methyl group at C–3.

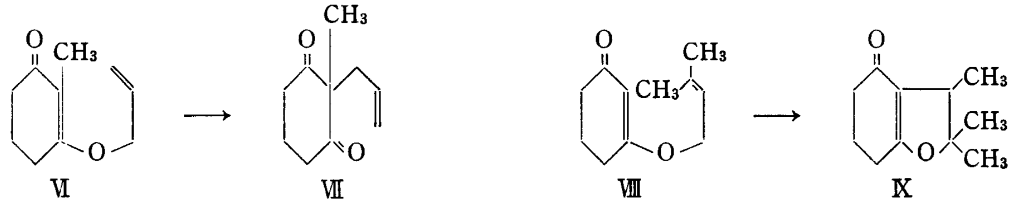

Chart 3

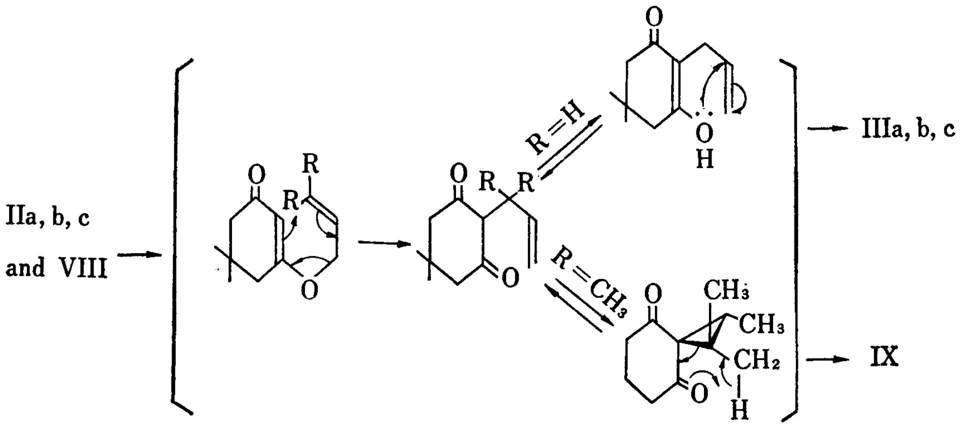

Chart 4

An intramolecular mechanism is proposed for the present Claisen rearrangement from the following cross-over studies, which were carried out in tributylamine solution. Heating of a mixture of IIc and Ia in tributylamine gave IIIc as a sole cyclization product. Similar treatment of a mixture of IIa and Ic gave only IIIa, and that of a mixture of IIa and VIII gave a mixture of IIIa and IX. Thus, the transformation from II to III is supposed to proceed through a normal Claisen rearrangement and successive cyclization, and the transformation from VIII to IX through a spirocyclopropyl intermediate[10] as shown in Chart 4.

Experimental

Boiling and melting points were uncorrected. The NMR spectra were measured on a Hitachi Perkin-Elmer H-60 type (60 Mc) spectrometer with tetramethyl silane as internal reference, IR spectra on a Hitachi EPI-G2 spectrophotometer and UV spectra on a Hitachi EPS-3T spectrophotometer.

3-Allyloxy-2-cyclohexen-1-one (IIa)——Method A: A solution of cyclohexane-1,3-dione (Ia) (11.1 g, 0.100 mole), allyl alcohol (29.0 g, 0.500 mole) and *p*-TsOH (0.35 g) in C_6H_6 (30.0 ml) was refluxed for 10 hr using a Dean-Stark water-separator. The reaction mixture was diluted with C_6H_6, washed with 5% Na_2CO_3 and sat. NaCl solution and dried over $MgSO_4$. After removal of the solvent the residue was distilled under reduced pressure to give 10.5 g (69%) of IIa as a colorless liquid, bp 79.5—81° (0.05 mmHg). *Anal.* Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.94; H, 7.92. Oxime, mp 120—121° (from ligroin). *Anal.* Calcd. for $C_9H_{13}O_2N$: C, 64.65; H, 7.84; N, 8.34. Found: C, 64.66; H, 7.73; N, 8.36.

Method B: A solution of 3-chloro-2-cyclohexen-1-one[6] (1.56 g, 0.0120 mole), prepared[6] from Ia with PCl_3 in 70% yield, and sodium allyloxide (1.20 g, 0.0150 mole) in allyl alcohol (20.0 ml) was allowed to stand at room temperature for 5 days. The reaction mixture was evaporated and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with sat. NaCl solution and dried over $MgSO_4$. After removal of the solvent, the residue was distilled under reduced pressure to give 0.830 g (45% from 3-chloro-2-cyclohexen-1-one; 32% from Ia) of IIa.

Method C: Allyl bromide was added to a solution of Na salt of Ia[7] in allyl alcohol and the mixture was refluxed for 8 hr. The solution was diluted with ether, washed with 5% Na_2CO_3 and sat. NaCl solution and dried over $MgSO_4$. The solvent was removed and the residue was distilled under reduced pressure to give a mixture of IIa and two other products (checked by TLC), which were not further investigated.

3-Allyloxy-5-methyl-2-cyclohexen-1-one (IIb)——Prepared from 5-methylcyclohexane-1,3-dione (Ib) (10.0 g) according to method A in preparation of IIa. Yield of IIb was 9.54 g (72%), a colorless liquid, bp 74—76° (0.01 mmHg). *Anal.* Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.93; H, 8.27.

3-Allyloxy-5,5-dimethyl-2-cyclohexen-1-one (IIc)——Prepared from 5,5-dimethylcyclohexane-1,3-dione (Ic) (10.0 g) according to method A in preparation of IIa. Yield of IIc was 10.0 g (78%), a colorless liquid, bp 82° (0.10 mmHg) (lit. bp 155° (20 mmHg)[11]). *Anal.* Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 72.96; H, 9.07.

2-Methyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran (IIIa)——a) Compound IIa (8.00 g) was heated at 190—200° for 3 hr under N_2 atmosphere. Distillation under reduced pressure gave 5.99 g (75%) of IIIa as a colorless liquid, bp 83—84° (0.88 mmHg). Semicarbazone, 84% yield, mp 216° (from EtOH–H_2O). *Anal.* Calcd. for $C_{10}H_{15}O_2N_3$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.34; H, 7.42; N, 19.86.

b) 2-Allylcyclohexane-1,3-dione (IV)[9] (0.500 g) was heated at 190—200° for 3 hr under N_2 atmosphere. The produced dark liquid was dissolved in ether, washed with 5% Na_2CO_3 and sat. NaCl solution and dried over $MgSO_4$. The solvent was evaporated and the residue was distilled under reduced pressure to give 0.325 g (65%) of IIIa, bp 85° (bath temp., 0.4 mmHg).

2,6-Dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran (IIIb)——Compound IIb (1.68 g) was heated at 190—200° for 3 hr under N_2 atmosphere. Distillation under reduced pressure gave 1.18 g (70%) of IIIb as a colorless liquid, bp 90—91° (0.92 mmHg). Semicarbazone, mp 183—184.5° (from EtOH–H_2O). *Anal.* Calcd. for $C_{11}H_{17}O_2N_3$: C, 59.17; H, 7.68; N, 18.82. Found: C, 59.31; H, 7.59; N, 18.92.

2,6,6-Trimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran (IIIc)[12]——Compound IIc (1.51 g) was heated at 190—200° for 3 hr under N_2 atmosphere. Distillation under reduced pressure gave 1.18 g (78%) of IIIc as a colorless liquid, bp 85—85.5° (0.75 mmHg). Semicarbazone, mp 175.5—176.5° (from EtOH–H_2O). *Anal.* Calcd. for $C_{12}H_{19}O_2N_3$: C, 60.73; H, 8.04; N, 17.71. Found: C, 60.96; H, 8.04; N, 17.48.

2-Allylcyclohexane-1,3-dione (IV)——a) Prepared according to the method of H. Stetter and W. Dierichs,[9a] mp 122—124° (lit. mp 126°,[9a] 128°[9b]).

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[10] *a*) E.N. Marvell, D.R. Anderson and J. Ong, *J. Org. Chem.*, **27**, 1109 (1962); *b*) A. Jefferson and F. Scheinmann, *Chem. Comm.*, **1966**, 239.

[11] R.D. Desai, *J. Chem. Soc.*, **1932**, 1079.

[12] *cf.* K. Ichikawa, O. Itoh and T. Kawamura, *Bull. Chem. Soc. Japan*, **41**, 1240 (1968).

b) A suspension of 3-acetoxy-2-allyl-2-cyclohexen-1-one (V) (0.368 g) in 10% HCl solution (8.0 ml) was stirred at 40° for 4 hr to give 0.310 g of IV.

3-Acetoxy-2-allyl-2-cyclohexen-1-one (V)——A solution of IIa (10.2 g, 0.0670 mole) in Ac_2O (13.6 g, 0.133 mole) was refluxed for 2.5 hr under N_2 atmosphere and then evaporated. The residue was distilled under reduced pressure to give 10.9 g (84%) of V as a colorless liquid, bp 86—89° (0.15 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760, 1670, 1015, 920. UV λ_{max}^{EtOH} mμ: 239. NMR ($CDCl_3$) τ: 4.28 ($-C\underline{H}=CH_2$), 5.02 ($-CH=C\underline{H}_2$), 7.02 ($-C\underline{H}_2-CH=$), 7.80 ($-COCH_3$). *Anal.* Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.33; H, 7.33.

3-Allyloxy-2-methyl-2-cyclohexen-1-one (VI)——A solution of sodium allyloxide (5.83 g, 0.0728 mole) and allyl alcohol (50.0 ml) was added slowly to a solution of 2-methylcyclohexane-1,3-dione (10.0 g, 0.0690 mole) in allyl alcohol (34.0 ml) with ice-cooling. The mixture was allowed to stand at room temperature for 5.5 days. Precipitated NaCl was filtered and washed with $CHCl_3$. The filtrate and the $CHCl_3$ washing were combined, washed with sat. NaCl solution and dried over $MgSO_4$. The solvent was evaporated and the residue was distilled under reduced pressure to give 7.53 g (66%) of VI as a colorless liquid, bp 85—87° (0.07 mmHg). *Anal.* Calcd. for $C_{10}H_{14}O_2$: C, 72.27; H, 8.49. Found: C, 71.92; H, 8.48.

2-Allyl-2-methylcyclohexane-1,3-dione (VII)——a) Compound VI (1.01 g) was heated at 190—200° for 3 hr under N_2 atmospehre. The resulted stuff was dissolved in ether and the solution was washed with 5% Na_2CO_3 and sat. NaCl solution and dried over $MgSO_4$. After removal of the solvent the residue was distilled under reduced pressure to afford 0.820 g (81%) of VII as a colorless liquid, bp 63° (0.23 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725, 1693, 1000, 930. NMR ($CDCl_3$) τ: 4.38 ($-C\underline{H}=CH_2$), 5.00 ($-CH=C\underline{H}_2$), 7.29 ($-C\underline{H}_2CH=$), 8.77 ($-CH_3$). *Anal.* Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.00; H, 8.60. When VII was heated at 190—200° for 3 hr under N_2 atmosphere, most part of VII was recovered unchanged.

b) 2-Methylcyclohexane-1,3-dione (6.31 g, 0.05 mole) was added to 20% KOH solution (14.0 ml, 0.05 mole) with ice-cooling. The mixture was heated at 90° until most part of material was dissolved, and then cooled under the tap. Allyl bromide (6.50 g, 0.054 mole) and Cu powder (0.12 g) were added to the above cooled solution and the mixture was stirred at room temperature for 10 hr. The reaction mixture was made alkaline with ice-cooled 5% Na_2CO_3 solution to pH 9 and extracted with ether. The ethereal extract was washed with 5% Na_2CO_3 and sat. NaCl solution and dried over $MgSO_4$. The solvent was removed and the residue was distilled under reduced pressure to give 3.72 g (45%) of VII as a colorless liquid, bp 69.5—72° (0.5 mmHg). In another run, this reaction was carried out employing 14.7 g (0.117 mole) of 2-methylcyclohexane-1,3-dione, 70.0 ml (0.250 mole) of 20% KOH solution, 14.5 g (0.120 mole) of allyl bromide and 0.28 g of Cu powder, and the reaction mixture was treated by the same manner as described above. The ethereal extract gave nothing of VII, while acidification of the alkaline solution with conc. HCl solution to pH 2 gave 11.8 g (55%) of 6-methyl-5-oxo-8-nonenoic acid as a deep yellow viscous liquid, bp 119.5° (0.17 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1708, 1000, 920. NMR ($CDCl_3$) τ: 4.19 ($-C\underline{H}=CH_2$), 4.98 ($-CH=C\underline{H}_2$), 8.92 ($-CH_3$). Semicarbazone, mp 114.5—115.5° (from EtOH–H_2O). *Anal.* Calcd. for $C_{11}H_{19}O_3N_3$: C, 54.75; H, 7.94; N, 17.42. Found: C, 54.59; H, 7.91; N, 17.52.

3-Prenyloxy-2-cyclohexen-1-one (VIII)——A suspension of Ag salt[8] (12.0 g, 0.0548 mole) of Ia and prenyl bromide (7.50 g, 0.0503 mole) in abs. C_6H_6 (40.0 ml) was refluxed for 20 min with vigorous stirring. The reaction mixture was filtered to remove separated AgBr and remained Ag salt. The filtrate was washed with 10% NaOH and sat. NaCl solution and dried over $MgSO_4$. The solvent was evaporated and the residue was distilled under reduced pressure to give 2.37 g of VIII as a colorless liquid, bp 98—101° (0.08 mmHg). The structure of VIII was confirmed by the spectral data given in Table I.

2,2,3-Trimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran (IX)——Compound VIII (1.62 g) was heated at 190—200° for 3 hr under N_2 atmosphere. The resulted stuff was distilled under reduced pressure to give IX (1.53 g, 95%) as a colorless liquid, bp 92° (0.07 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1615. NMR ($CDCl_3$) τ: 7.13 ($-C\underline{H}(CH_3)-$), 8.68 ($-C(CH_3)_2-$), 8.90 ($-CH(C\underline{H}_3)-$). Semicarbazone, mp 184—185° (from EtOH–H_2O). *Anal* Calcd. for $C_{12}H_{19}O_2N_3$: C, 60.73; H, 8.07; N, 17.71. Found: C, 61.06; H, 8.13; N, 18.12.

Cross-over Study——a) A 1:1 mixture of IIa and Ic was added to 5 eq. moles of Bu_3N and heated at 190—200° for 3 hr under N_2 atmosphere. The solution was evaporated to give a crude liquid, a mixture of IIIa and Ic (checked by IR).

b) A 1:1 mixture of IIc and Ia was added to 5 eq moles of Bu_3N and heated at 190—200° for 3 hr under N_2 atmosphere. The solution was evaporated to give a crude liquid, a mixture of IIIc and Ia (checked by IR).

c) A 1:1 mixture of IIc and VIII was added to 5 eq moles of Bu_3N and heated at 190—200° for 3 hr under N_2 atmosphere. The solution was evaporated to give a crude liquid, a mixture of IIIc and IX (checked by IR).