The Base-induced Reactions of 2-Halogeno-1,3-diketones in a Variety of Solvents

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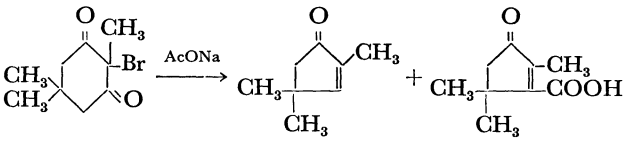
The reactions of 2-bromo-2-methyldimedone (**1**), 2,2-dibromodimedone (**6**), 2-bromo- and 2-chloro-2-methylcyclohexane-1,3-dione (**10a** and **10b**) and 2-acetyl-2,6-dibromocyclohexanone (**14**) with an equivalent of sodium acetate in a variety of solvents were studied. The constitutions and proportions of the products obtained by these reactions depended strongly on the structure of 2-halogeno-1,3-diketones and the solvents employed. The results were discussed in terms of the mechanisms proposed.

In a previous paper,[1] we have reported that 2-alkyl-2-bromodimedones undergo various types of reactions upon treatment with bases in aprotic solvents such as benzene and THF, and the mode of reactions strongly depends on the bases employed. This paper deals with the reactions of various 2-halogeno-1,3-diketones including 2-bromo-2-methyldimedone with a weak nucleophilic base such as sodium acetate in a variety of solvents. In this investigation, we found that the proportions of the products depended remarkably on the solvents used and also the structure of the 1,3-diketones.

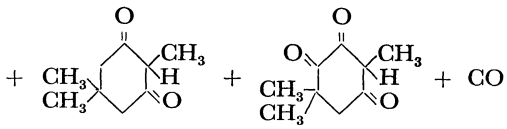
Results

Effects of Solvents. The reactions of 2-bromo-2-methyldimedone (**1**) with an equivalent of sodium acetate were conducted in a variety of solvents. In these reactions, 2,4,4-trimethyl-2-cyclopenten-1-one (**2**), 2,5,5-trimethyl-3-oxo-1-cyclopentenecarboxylic acid (**3**), 2-methyldimedone (**4**), 2,5,5-trimethylcyclohexane-1,3,4-trione (**5**) and carbon monoxide were isolated, proportions of these products being strongly dependent on the solvents employed. The reactions of 2,2-dibromodimedone (**6**) with an equivalent of sodium acetate in various solvents were then examined. These reactions afforded 2,3-dibromo-4,4-dimethyl-2-cyclopenten-1-one (**7**), 2-bromo-5,5-dimethylcyclohexane-1,3,4-trione (**8**), 2-bromodimedone (**9**) and carbon monoxide, proportions of the products again depending on the solvents used.

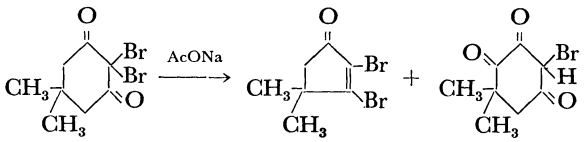
The structures of the products **2**—**4** and **7**—**9** were assigned as previously reported,[1] and the evolution of carbon monoxide was confirmed by vpc analysis of the evolved gas collected during the reaction. The structure of **5** was established from its elemental analysis and spectral data. The IR spectrum (KBr) showed a hydrogen-bonded hydroxyl absorption at 3200 cm^{-1}, three carbonyl absorptions at 1705, 1685, and 1650 cm^{-1}, and an absorption due to the C=C bond at 1640 cm^{-1}. The NMR spectrum ($CDCl_3$) exhibited a singlet (6H, two CH_3's attached at the 5-position) at δ 1.27, a singlet (3H, CH_3 attached at the 2-position) at δ 1.92, a singlet (2H, $-CH_2-$ at the 4-position) at δ 2.73, and a broad singlet (1H, an enol proton) at δ 7.0. The mass spectrum showed a parent peak at *m/e* 168. These spectral data indicate that **5** exists essentially in the form of **5a** under the conditions where the spectra were measured. The yields of the products **2**—**9** obtained by the above reactions are summarized in Table 1.



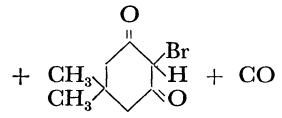
1 **2** **3**



4 **5**

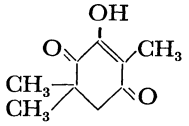


6 **7** **8**

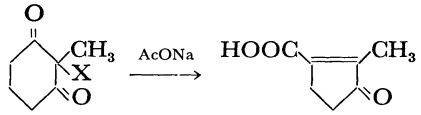


9

Effects of the Structure of 1,3-Diketones. Treatment of 2-bromo-2-methylcyclohexane-1,3-dione (**10a**) with an equivalent of sodium acetate in THF under reflux afforded 2-methyl-3-oxo-1-cyclopentenecarboxylic acid (**11**), its mixed anhydride (**12**) and 2-methylcyclohexane-1,3-dione (**13**). Similar treatment of 2-chloro-2-methylcyclohexane-1,3-dione (**10b**) with an equivalent of sodium acetate in THF gave the same products. However, the reaction of 2-acetyl-2,6-dibromocyclohexanone (**14**) with an equivalent of sodium acetate in THF afforded a mixture of 2-acetyl-1-cyclopentenecarboxylic acid (**15**) and its mixed anhydride (**16**). The yields of the products obtained by the above reactions are summarized Table 2.



5a

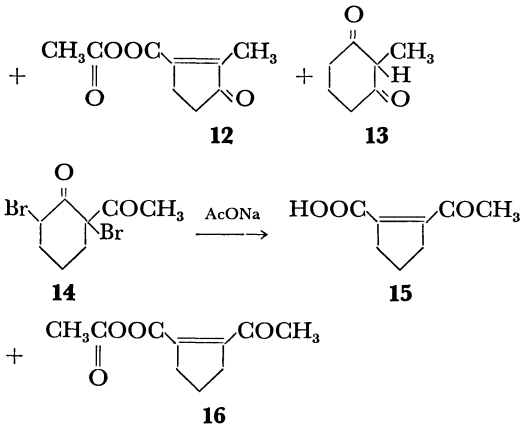


10a; X=Br
b; X=Cl

11

Table 1. Reactions of **1** and **7** with sodium acetate

Compd	Solvent	Reaction temp., °C	Time hr	Products			(%) Recovered starting material
1	Benzene	80	5	**2**(4)	**3**(3)	**4**(Trace)	**1**(57)
1	Ether	35	5	**2**(4)		**4**(5)	**1**(42)
1	THF	65	5	**2**(20)	**3**(37)	**4**(20)	**1**(6)
1	*t*-BuOH	83	5	**2**(20)	**3**(13)	**4**(20)	
1	CH_3CN	80	5	**2**(28)	**3**(18)	**4**(8)	
1	EtOH	78	5	**2**(50)	**5**(22)	**4**(2)	
1	MeOH	65	5	**2**(58)	**5**(20)		
1	MeOH	0—5	5	**2**(20)			
1	THF-water (3 : 2)	70	5	**2**(22)	**3**(15)	**4**(15)	
1	Benzene-water (6 : 1)	80	5				**1**(88)
6	THF	65	5	**7**(25)	**8**(16)	**9**(32)	
6	THF-water (6 : 1)	70	5	**7**(12)	**8**(25)	**9**(33)	
6	DMF	80	5	**7**(3)	**8**(75)		



The structure of **13** was confirmed by the comparisons of IR and NMR spectral data with those of the authentic sample and also by the mixture melting-point test. The structure of **11** was assigned by its spectral data. The IR spectrum (KBr) showed multiple absorptions characteristic of a carboxyl group at 3200—2800 cm^{-1}, carbonyl absorptions at 1720 and 1670 cm^{-1}, and an absorption due to the C=C bond at 1630 cm^{-1}. The NMR spectrum ($CDCl_3$) exhibited a singlet (3H, $-CH_3$ attached at the 2-position) at δ 1.76, a multiplet (4H, $-CH_2-CH_2-$ at the 4- and 5-positions) at δ 2.1—3.0, and a singlet(1H, –COOH at the 3-position) at δ 8.37. The UV spectrum (95% ethanol) had a maximum absorption at 243 nm (ε 13000). This spectrum was similar in shape to that of 3-oxo-1-cyclopentenecarboxylic acid (λ_{max}^{EtOH} 243 nm(ε1 5000)).[2] The mass spectrum showed a parent peak at *m/e* 140. The structure of **12** was confirmed by its spectral data (see Experimental) and chemical modification; the mild treatment of **12** with sodium hydroxide solution gave **11**. The structure of **15** was also established by its spectral data. The IR spectrum showed a carbonyl absorption at 1700 cm^{-1}, a carboxyl absorption at 1690 cm^{-1}, and an absorption due to the C=C bond at 1630 cm^{-1}. The NMR spectrum ($CDCl_3$) exhibited a singlet (3H, $-COCH_3$) at δ 2.45, a multiplet (6H, $-CH_2-CH_2-CH_2-$ at the 3-, 4- and 5-positions) at δ 2.0—2.91, and a singlet (1H, –COOH) at δ 12.4. The mass spectrum showed a parent peak at *m/e* 154. The structure of **16** was deduced by its spectral data (see Experimental) and by the fact that the mild treatment of **16** with NaOH solution gave **15**.

Table 2. Reactions of various 2-halogeno-1,3-diones with sodium acetate in THF under reflux

1,3-Dione	Reaction time, hr	Products (%)		
10a	5	**11**(25)	**12**(12)	**13**(18)[a]
10b	4	**11**(18)	**12**(4)	**13**(20)[b]
14	5	**15**(40)	**16**(17)	

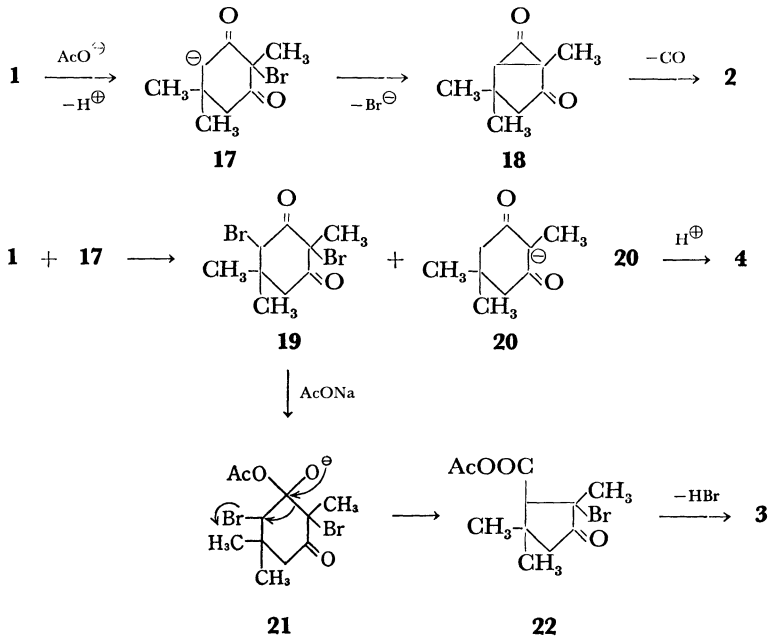
a) The starting material, **10a**, was recovered in 11% yield. b) The starting material, **10b**, was recovered in 15% yield.

Discussion

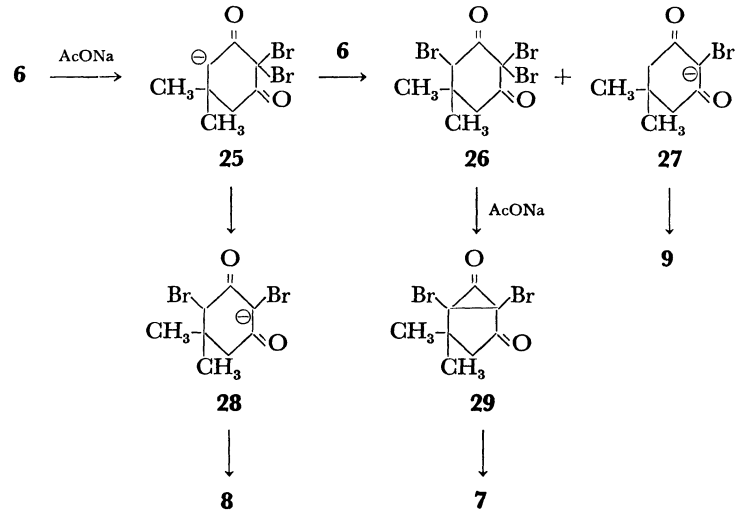
Effects of Solvents. A striking feature of the reaction of **1** with sodium acetate is that the proportion and constitution of the products are largely dependent on the solvents employed. The results of Table 1 indicate that the yields of the products increase with increase in the polarity of the solvents. Specifically, the use of alcohols caused pronounced effects on the constitution of the products; *i. e.*, (1) the yield of **2** increased remarkably with a marked decrease in the yields of **3** and **4**, and (2) the formation of the trione **5** was observed.

These results could be interpreted in terms of the mechanism proposed in the previous paper,[1] which is outlined in Scheme 1.

A key intermediate in the formation of **2** is the cyclopropanone **18** which is produced by an elimination of bromide ion from the carbanion **17**. The carbanion **17** reacts also with **1** to produce the dibromide **19** and the carbanion **20** which affords **4** on protonation. The dibromide **19** is converted by the semibenzylic type-rearrangement to **22** and then to **3** upon treatment with sodium acetate. The polar solvents may facilitate these ionic reactions, thus leading to an increase in the yields of the products. The use of alcohols may favor the formation of **18** by assisting the elimination of

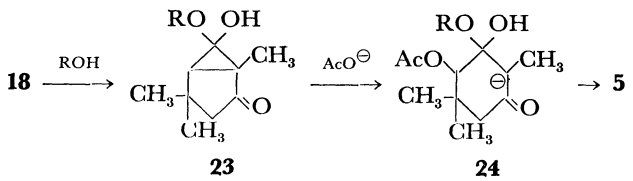


Scheme 1.



Scheme 2.

bromide ion from **17**, probably through a hydrogen bonding between the solvents and bromine, which is depicted as -Br···HOR. Thus, the reactions in alcohols result in the increase in the yield of **2**, accompanied by the decrease in the yields of other products which are produced from **17**. It is conceivable that in an alcohol **18** forms the alkyl acetal which is stable.[3] The reaction of **23** with sodium acetate may result in the formation of **5**.

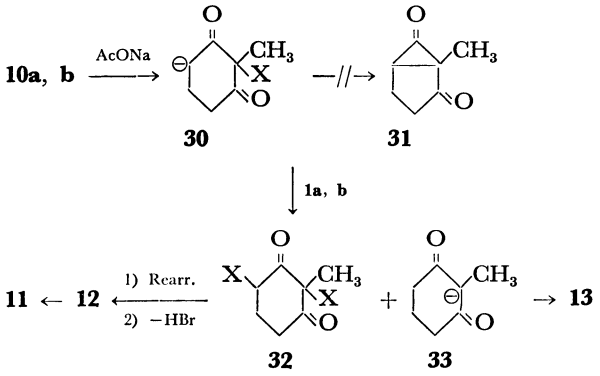


The behavior of **6** for the reaction with sodium acetate could also be explained by the mechanism proposed previously[1] (Scheme 2).

Effects of the Structure of 2-Halogeno-1,3-diketones. Another striking feature of the results of this investigation is that the mode of the reaction of 2-halogeno-1,3-diketones with sodium acetate is strongly influenced by the structure of the 1,3-diketones. The reaction of **10a** and **10b** with sodium acetate led to the formation of **11**, **12**, and **13**. However, in these reactions the cyclopentenone corresponding to **2** could not be isolated.

These results suggest that two methyl substituents attached at the 5-position of cyclohexane-1,3-dione plays an important role for the formation of the cyclopropanone intermediate. In the case of the reaction of **1**, the reaction of the carbanion **17** with **1** is more or less interfered by a steric interference caused by two methyl substituents at the 5-position, thus **17** can partly be transformed to the cyclopropanone **18** (see Scheme 1). On the other hand, in the reactions of **10a** and **10b**, the carbanion **30** is readily converted to **32** and **33** upon

the reaction with **10a, b** without the formation of the cyclopropanone **31** (see Scheme 3).



Scheme 3.

Similarly, the reaction of **14** with sodium acetate in THF lead preferentially to the formation of the rearranged products **15** and **16** in accordance with the mechanism proposed.

Experimental

2-Bromo-2-methyldimedone (**1**) and 2,2-dibromodimedone (**6**) were prepared by the methods previously reported.[1]

*Reactions of **1** with Sodium Acetate in Benzene, Ether, THF, THF–Water (3 : 2), t-Butyl Alcohol, and Acetonitrile.* A mixture of 0.5 g (2.2 mmol) of **1** and 0.2 g (2.5 mmol) of AcONa in 30 ml of a solvent was refluxed for 5 hr. The reaction mixture was poured into water, neutralized with 1M HCl, and then extracted with ether. The ether extract was washed with a 5% aqueous Na_2CO_3 solution, dried over Na_2SO_4, and evaporated to leave an oil. Distillation of the oil gave 2,4,4-trimethyl-2-cyclopenten-1-one (**2**); bp 160—165 °C. The yield of **2** was determined by vpc analysis of the reaction mixture.

The Na_2CO_3 solution was neutralized with 1 M HCl and extracted with ether. The ether extract was dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel with benzene–CCl_4 (1 : 3). The earlier fraction gave 2,5,5-trimethyl-3-oxo-1-cyclopentenecarboxylic acid (**3**); mp 189—191 °C. The latter fraction afforded 2-methyldimedone (**4**); mp 160—162 °C. The yields of **2**, **3** and **4** are given in Table 1.

*Reaction of **1** with Sodium Acetate in Methanol.* A mixture of 0.5 g (2.2 mmol) of **1** and 0.2 g (2.5 mmol) of AcONa in 30 ml of MeOH was refluxed for 5 hr. The reaction mixture was worked up as described above and separated into two fractions (the neutral fraction and the Na_2CO_3 soluble fraction). From the neutral fraction, crude **2** was obtained as an oil. Vpc analysis of the reaction mixture indicated that the mixture contained 0.15 g (58%) of **2**.

From the Na_2CO_3 soluble fraction, a solid was obtained. Recrystallization of the solid from $CHCl_3$ gave 0.07 g (20%) of 2,5,5-trimethylcyclohexane-1,3,4-trione (**5**); mp 161—162 °C.

Found: C, 64.35; H, 7.33%. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19%.

*Reaction of **6** with Sodium Acetate.* A mixture of 1.0 g (3.4 mmol) of **6** and 0.3 g (3.7 mmol) of AcONa in 50 ml of DMF was heated at 70 °C for 5 hr. The reaction mixture was poured into 50 ml of water, neutralized with 1 M HCl, and then extracted with two 30 ml portions of ether. The ether extracts were washed with 5% aqueous Na_2CO_3 solution, dried over Na_2SO_4 and evaporated to leave an oil. The oil was chromatographed on a silica gel with *n*-hexane–CCl_4 (5 : 1) to give 27 mg (3%) of 2,3-dibromo-4,4-dimethyl-2-cyclopenten-1-one (**8**); mp 85—86 °C.

The Na_2CO_3 solution was neutralized with 1M HCl and extracted with ether. The ether solution was dried over Na_2SO_4, and evaporated to give a solid. Recrystallization of the solid from CCl_4–$CHCl_3$ (1 : 3) gave 0.59 g (75%) of 2-bromo-5,5-dimethylcyclohexane-1,3,4-trione (**8**); mp 188—190 °C.

The reactions of **6** with AcONa in other solvents were carried out similarly, and the products shown in Table 1 were isolated.

*2-Bromo-2-methylcyclohexane-1,3-dione (**10a**).* To a stirred mixture of 4.5 g (36 mmol) of 2-methylcyclohexane-1,3-dione[5] and 4.2 g (36 mmol) of AcONa in 60 ml of $CHCl_3$–H_2O (6 : 1), 5.7 g (36 mmol) of bromine was added dropwise below 5 °C. After the addition, the mixture was further stirred for 1 hr, and then the $CHCl_3$ layer was separated. The aqueous layer was extracted with 30 ml of $CHCl_3$. The combined $CHCl_3$ solutions were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was chromatographed on a silica gel with CCl_4 to give 4.5 g (62%) of **10a**; bp 65—66 °C/2 mmHg. IR(film): 1735 and 1710 cm^{-1}. NMR(CCl_4): δ 1.75 (s, 3H, CH_3) and 1.90—3.60 ppm (m, 6H, $-CH_2CH_2CH_2-$).

Found: C, 41.33; H, 4.68%. Calcd for $C_7H_9O_2Br$: C, 41.00; H, 4.42%.

*Reaction of **10a** with Sodium Acetate.* A mixture of 1.5 g (7.3 mmol) of **10a** and 0.6 g (7.4 mmol) of AcONa in 50 ml of THF was refluxed for 5 hr. The reaction mixture was poured into water, neutralized with 1M HCl and then extracted with two 30 ml portions of ether. The combined ether extracts were washed with 5% aqueous Na_2CO_3 solution. The ether layer was separated, dried over Na_2SO_4 and evaporated to give an oil. The oil was separated into two fractions by chromatography on a silica gel with CCl_4. The earlier fraction gave 0.16 g (12%) of acetic 1-oxo-2-methyl-2-cyclopentene-3-carboxylic anhydride (**12**). IR(film): 1770, 1720, 1680 and 1630 cm^{-1}. NMR($CDCl_3$): δ 1.56 (s, 3H, $-CH_3$), 2.18 (*s*, 3H, $-OCOCH_3$), and 1.95—2.85 ppm (m, 4H, $-CH_2CH_2-$). Mass spectrum: *m/e* 182 (M^+).

Found: C, 59.72; H, 5.83%. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53%.

The mild treatment of **12** with an aqueous NaOH afforded 2-methyl-3-oxo-1-cyclopentenecarboxylic acid (**11**). The latter fraction of the chromatography gave 0.2 g (13%) of **10a**.

The aqueous Na_2CO_3 solution was neutralized with 1M HCl, and then extracted with ether. The ether extract was dried over Na_2SO_4, and evaporated. The solidified residue was subjected to fractional recrystallizations from CCl_4–$CHCl_3$ (4 : 1), which afforded 0.2 g (22%) of 2-methylcyclohexane-1,3-dione (**13**); mp 200—202 °C (lit,[5] mp 204 °C and 0.26 g (25%) of 2-methyl-3-oxo-1-cyclopentenecarboxylic acid (**11**). An analytical sample of **11** was obtained by recrystallization from $CHCl_3$; mp 168—170 °C.

Found: C, 59.82; H, 5.51%. Calcd for $C_7H_8O_3$: C, 59.99; H, 5.75%.

*2-Chloro-2-methylcyclohexane-1,3-dione (**10b**).* To a stirred suspension of 3.0 g (24 mmol) of **13** in 100 ml of $CHCl_3$, 2.7 g (25 mmol) of *t*-butyl hypochlorite was added gradually under nitrogen atmosphere at −10 °C. After the addition was completed, the reaction mixture was further stirred for 2 hr at −10 °C, and washed with 20 ml of 5% aqueous Na_2CO_3 solution, then with water. The $CHCl_3$ solution was dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel with CCl_4 to give 2.2 g (58%)

of **10b**; bp 70—71 °C/4 mmHg. IR(film): 1740 and 1715 cm^{-1}. NMR (CCl_4): δ 1.60 (s, 3H, CH_3) and 2.00—3.60 ppm (m, 6H, $-CH_2CH_2CH_2-$).

Found: C, 52.58; H, 5.33%. Calcd for $C_7H_9O_2Cl$: C, 52.35; H, 5.65%.

*Reaction of **10b** with Sodium Acetate.* A mixture of 1.5 g (9.3 mmol) of **10b** and 0.78 g (9.5 mmol) of AcONa in 50 ml of THF was refluxed for 4 hr. The reaction mixture was worked up according to the procedures similar to those described for the reaction of **10a** with AcONa, and separated into the neutral fraction and the Na_2CO_3 soluble fraction. The oil obtained from the neutral fraction was chromatographed on a silica gel with CCl_4. The earlier fraction gave 0.07 g (4%) of **12**. The latter fraction afforded 0.23 g (15%) of the recovered starting material (**10b**). The solid obtained from the Na_2CO_3 soluble fraction was subjected to fractional recrystallizations from CCl_4–$CHCl_3$ (4 : 1), which afforded 0.24 g (18%) of **11** and 0.24 g (20%) of **13**.

*2-Acetyl-2,6-dibromocyclohexanone (**14**).* To a stirred mixture of 5.0 g (36 mmol) of 2-acetylcyclohexanone[6] in 80 ml of $CHCl_3$, 5.7 g (36 mmol) of bromine was added gradually below 5 °C. A solution of 4.9 g (36 mmol) of AcONa, and then 5.7 g (36 mmol) of bromine were added successively to the above mixture below 5 °C. After the addition was completed, the reaction mixture was stirred further for 2 hr at 5 °C, and then the $CHCl_3$ layer was separated. The $CHCl_3$ solution was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The residual oil decomposed upon distillation, but could be chromatographed on a silica gel with CCl_4 to give (7.2 g (68%) of **14**. IR(film): 1720 and 1730 cm^{-1}. NMR (CCl_4): δ 24.2 (s, 3H. $-COCH_3$) and 1.2—4.0 (m, 7H, $-BrCH-CH_2-CH_2-CH_2-$).

Found: C, 32.56; H, 3.67%. Calcd for $C_8H_{10}O_2Br_2$: C, 32.25; H, 3.38%.

*Reaction of **14** with Sodium Acetate.* A mixture of 1.0 g (3.3 mmol) of **14** and 0.3 g (3.6 mmol) of AcONa in THF was refluxed with stirring for 5 hr. The reaction mixture was worked up as described above and separated into two fractions. An oil obtained from the neutral fraction was chromatographed on a silica gel with *n*-hexane–benzene (1 : 1) to give 82 mg (12%) of acetic 2-acetyl-1-cyclopentene-1-carboxylic anhydride (**16**); bp 85—90 °C/1 mmHg. IR(film): 1770, 1730, 1700 and 1630 cm^{-1}. Mass spectrum: *m/e* 196 (M^+).

Found: C, 61.58; H, 6.42%. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.17%.

The mild treatment of **16** with an aqueous NaOH solution afforded 2-acetyl-1-carboxy-1-cyclopentene (**15**). The chromatography gave also 0.15 g of a tarry material which could not be purified.

An oily material, which was obtained from the Na_2CO_3 soluble fraction, was triturated with ice-water. A solid thus obtained was recrystallized from $CHCl_3$ to give 0.2 g (40%) of **15**; mp 75—76 °C.

Found: C, 62.31; H, 6.48%. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54%.

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3) It is well established that cyclopropanone is readily converted to the alkyl acetal upon dissolving it in alcohol.[4]

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