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Reactions of Cyclic 2,2-Dibromo-1,3-dicarbonyl Compounds with Nucleophiles

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The reactions of 2,2-dibromodimedone (1), 2,2-dibromo-cyclohexane-1,3-dione (2) and 2,2-dibromoindan-1,3-dione (3) with a variety of nucleophiles were studied. The reaction of 1, 2 and 3 with sodium ethoxide gave as main products diethyl 3,3-dimethylglutarate (4), diethyl glutarate (6) and diethyl phthalate (8), respectively. However, the reaction of 1 and 2 with disodium *meso*-1,2-diphenylethane-1,2-diolate gave 1,2-diphenylethane-1,2-dione (9) and benzoic acid (10) which are the oxidation products of the 1,2-diolate, and 2-bromodimedone (5) and 2-bromocyclohexane-1,3-dione (7) which are the debrominated products of 1 and 2, as main products. Treatment of 1 and 2 with nucleophiles such as phenylmethanethiol and sodium salt of diethyl malonate afforded the products produced by an oxidation or bromination of nucleophiles along with 5 and 7.

1. Introduction

In a previous paper¹⁾, we have reported that in the reaction of open-chain aliphatic 2,2-dibromo-1,3-dicarbonyl compounds with sodium alkoxides including disodium 1,2-diolates, a main path of the reaction is the splitting of the COCBr₂-CO bond caused by an attack of alkoxide ions to a carbonyl carbon of the 1,3-dicarbonyl compounds.

This paper deals with the reactions of cyclic 2,2-dibromo-1,3-dicarbonyl compounds with a variety of nucleophiles. The results of this study suggest that cyclic 2,2-dibromo-1,3-dicarbonyl compounds react with nucleophiles in somewhat different ways from open-chain 2,2-dibromo-1,3-dicarbonyl compounds.

2. Results and Discussion

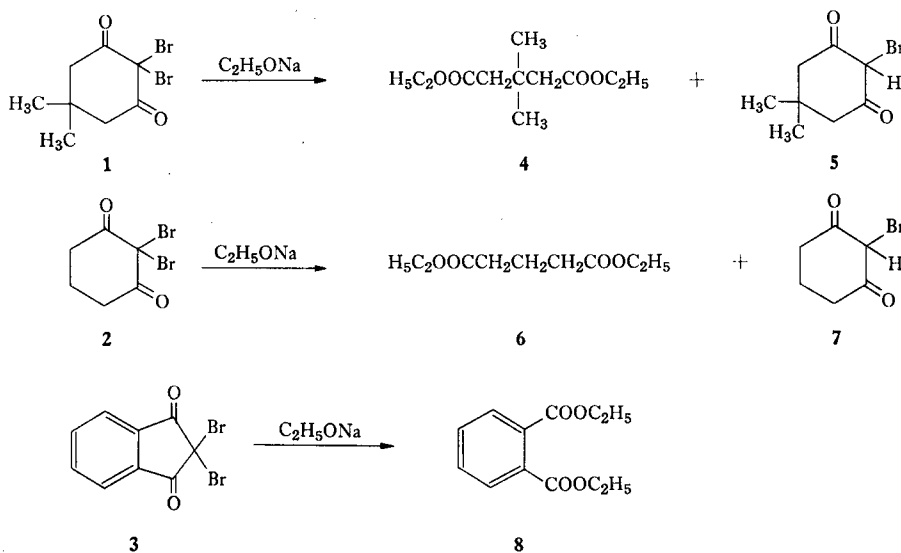
2,2-Dibromodimedone (1), 2,2-dibromocyclohexane-1,3-dione (2) and 2,2-dibromoindan-1,3-dione (3) were chosen as cyclic 2,2-dibromo-1,3-dicarbonyl compounds, and the reaction of these three compounds with two sodium alkoxides, phenylmethanethiol and sodium diethyl malonate, were studied.

Reaction with Sodium Alkoxides. The reaction of 1 with two equivalents of sodium ethoxide in dry ether gave diethyl 3,3-dimethylglutarate (4) and 2-bromodimedone (5). The reaction of 2 with two equivalents of sodium ethoxide afforded diethyl glutarate (6) and 2-bromocyclohexane-1,3-dione (7). In the reaction of 3 with two equivalents of sodium ethoxide, diethyl phthalate (8) was isolated as a main product. The results are summarized in Table 1.

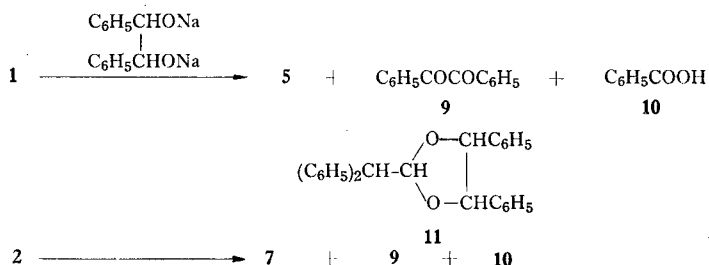
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Table 1. Reactions of 2,2-Dibromo-1,3-diones with Sodium Alkoxides

Compd.	Nucleophile	Solvent	Products (Yield, %)
1	C ₂ H ₅ ONa	Ether	4(38), 5(35)
2	C ₂ H ₅ ONa	Ether	6(71), 7(5)
3	C ₂ H ₅ ONa	Ether	8(73)
1	C ₆ H ₅ CHONa C ₆ H ₅ COHNa	THF	9(10), 10(27), 11(17), 5(40)
2	C ₆ H ₅ CHONa C ₆ H ₅ COHNa	THF	9(14), 10(21), 7(63)

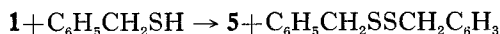


However, treatment of **1** with an equivalent of disodium *meso*-1,2-diphenylethane-1,2-diolate in dry THF yielded **5**, 1,2-diphenylethane-1,2-dione (**9**) and benzoic acid (**10**), accompanied with a small amount of 1,2-(diphenylmethylenedioxy)-1,2-diphenylethane (**11**) which was identified from the spectral data and also by the comparison with an authentic sample²⁾. Similar treatment of **2** with disodium *meso*-1,2-diphenylethane-1,2-diolate gave **7**, **9** and **10**, but no **11** was obtained. In both of these reactions, the products which would be produced by the ring-opening reaction of **1** and **2** were not isolated. These results are included in Table 1.



A striking feature in the reaction of **1** and **2** with the disodium 1,2-diolate is that the oxidation of the 1,2-diolate by **1** and **2** takes place as a main path of the reaction. This result is in contrast with the results obtained for the reaction of open-chain 2,2-dibromo-1,3-dicarbonyl compounds with a disodium 1,2-diolate. For example, in the reaction of dibromodibenzoylmethane (**12**) with disodium *meso*-1,2-diphenylethane-1,2-diolate, the carbonyl carbon of **12** was attacked by the 1,2-diolate to produce mono- and dibenzoyl esters of the 1,2-diol and mandelic acid which seemed to be derived from α,α -dibromoacetophenone¹⁾ with the splitting of the COCBr₂-CO bond. However, no such bond-splitting reaction took place in the case of the reaction of **1** and **2**. The difference in behavior between the open-chain substrate such as **12** and the cyclic substrates such as **1** and **2** in the reaction with the 1,2-diolate may be attributed to the difference in a steric interaction between the substrate and the reagent.

Reaction with Phenylmethanethiol. Treatment of **1** with an equivalent of phenylmethanethiol in dry THF gave **5** in 90% yield and dibenzyl disulfide in 81% yield.



Reaction with Sodium Salt of Diethyl Malonate. The reactions of **1**, **2** and **3** with sodium salt of diethyl malonate were conducted in THF, and various products derived from the salt as well as **5** and **7** were isolated. The products derived from the salt include diethyl bromomalonate (**13**), 1,1,2,2-tetraethoxycarbonylethane (**14**), 1,1,2,2-tetraethoxycarbonylethylene (**15**) and diethyl dibromomalonate (**16**). The results are summarized in Table 2.

Table 2. Reactions of 2,2-Dibromo-1,3-diones with Sodium Salt of Diethyl Malonate

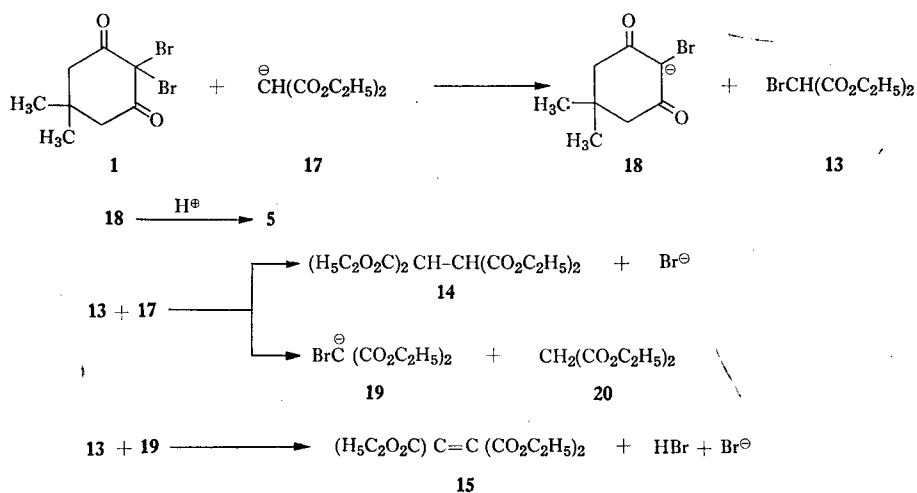
Compd.	Molar ratio of compd. to nucleophile	Solvent	Products (Yield, %)
1	1 : 1	THF	13 (70), 14 (8), 15 (3), 5 (85)
1	1 : 2	THF	13 (5), 14 (3), 15 (65), 5 (70)
2	1 : 1	THF	13 (62), 14 (10), 15 (2), 7 (66)
3	1 : 1	THF	14 (75), 16 (13)

The proportion of the compounds **13**–**16** in the isolated products varied with the structure of 2,2-dibromo-1,3-dicarbonyl compounds. In addition, when **1** was used as a substrate, the yield of **15** was found to increase with a concomitant decrease in the yield of **13** with increasing the amount of sodium salt of diethyl malonate employed.

These results suggest that the reactions proceed through the pathway illustrated in Scheme 1 (the pathway for the reaction of **1** with sodium salt of diethyl malonate is shown as an example). A key step for the reactions is a transfer of bromine from **1** to the malonate carbanion **17** as a bromine cation to produce the carbanion of **1** and **13**.

In conclusion, the results presented in this paper suggest that cyclic 2,2-dibromo-1,3-dicarbonyl compounds are inhibited to a larger extent from the COCBr₂-CO bond cleavage reaction by an attack of nucleophiles to the carbonyl carbon. Instead, the com-

Scheme 1.



pounds have the capability of supplying a bromine cation to nucleophiles.

3. Experimental

2,2-Dibromodimedone (1). This compound was prepared as described previously³⁾, mp 144–145°C.

2,2-Dibromocyclohexane-1,3-dione (2). A 16.0 g (0.1 mol) of bromine was added dropwise at room temperature to a stirred suspension of 11.5 g (0.1 mol) of cyclohexane-1,3-dione and 11.8 g (0.1 mol) of sodium acetate in 50 ml of the CHCl_3 -water (1:1) mixture. After consumption of bromine, a suspension of 11.8 g (0.1 mol) of sodium acetate in 50 ml of CHCl_3 and then 16.0 g (0.1 mol) of bromine were added successively to the reaction mixture. The mixture was further stirred at room temperature for 2 hr, and the CHCl_3 solution was separated. The aqueous solution was extracted with 50 ml of CHCl_3 . Two CHCl_3 solutions were combined, washed with water, dried, and evaporated to give a solid. Recrystallization of the solid from CCl_4 - CHCl_3 (3:1) gave 20.2 g (73%) of **2**, mp 90–91°C. IR (KBr): 1720 cm^{-1} ($\text{C}=\text{O}$).

Found: C, 26.88; H, 2.13%. Calcd for $\text{C}_6\text{H}_6\text{O}_2\text{Br}_2$: C, 26.70; H, 2.24%.

2,2-Dibromoindan-1,3-dione (3). This compound was prepared by the bromination of indan-1,3-dione in a manner similar to that described above in 85% yield, mp 174–175°C (lit.⁴⁾, mp 175–176°C). IR (KBr): 1750 and 1730 cm^{-1} ($\text{C}=\text{O}$).

Found: C, 35.51; H, 1.18%. Calcd for $\text{C}_9\text{H}_4\text{O}_2\text{Br}_2$: C, 35.57; H, 1.33%.

Reaction of 1 with Sodium Ethoxide. A stirred mixture of 1.5 g (5.0 mmol) of **1** and 0.68 g (10 mmol) of sodium ethoxide in 60 ml of dry ether was refluxed for 5 hr. The mixture was poured into 50 ml of water, neutralized with 1N HCl, and the ether solution was separated. The aqueous solution was extracted with two 40 ml portions of ether. All of the ether solutions were combined, washed with 5% Na_2CO_3 , dried over

Na_2SO_4 , and then evaporated. The residue was distilled to give 0.41 g (38%) of diethyl 3,3-dimethylglutarate (**4**), bp 82–84°C/3 mmHg. IR (film): 1735 cm^{-1} (C=O). NMR (CCl_4): δ 1.08 (s, 6H, $(\text{CH}_3)_2\text{C}<$), 1.24 (t, $J=7.0$ Hz, 6H, two of $-\text{CO}_2\text{CH}_2\text{CH}_3$), 2.35 (s, 4H, $-\text{CH}_2\overset{\text{C}}{\underset{\text{C}}{\text{C}}}\text{CH}_2-$), and 4.12 ppm (q, $J=7.0$ Hz, 4H, $-\text{CO}_2\text{CH}_2\text{CH}_3$).

Found: C, 61.37; H, 9.06%. Calcd for $\text{C}_{11}\text{H}_{20}\text{O}_4$: C, 61.11; H, 9.32%.

The Na_2CO_3 solution was neutralized with 1N HCl, and then extracted with ether. The ether solution was dried over Na_2SO_4 and evaporated to give a solid which upon recrystallization from CCl_4 - CHCl_3 (2:1) afforded 0.38 g (35%) of 2-bromodimedone (**5**), mp 169–172°C (lit.³), mp 175–176°C. IR (KBr): 1620 cm^{-1} (C=O).

Found: C, 43.62; H, 5.13%. Calcd for $\text{C}_8\text{H}_{11}\text{O}_2\text{Br}$: C, 43.86; H, 5.06%.

Reaction of 2 with Sodium Ethoxide. A stirred mixture of 1.0 g (3.7 mmol) of **2** and 0.52 g (7.6 mmol) of sodium ethoxide in 50 ml of dry ether was refluxed for 4 hr. The reaction mixture was worked up as described above, and separated into two parts consisting of neutral and Na_2CO_3 soluble components.

From the neutral components, 0.49 g (71%) of diethyl glutarate (**6**) was obtained, bp 70–72°C/1 mmHg. IR (film): 1735 cm^{-1} (C=O). NMR (CDCl_3): δ 1.25 (t, $J=7.0$ Hz, 6H, two of $-\text{CO}_2\text{CH}_2\text{CH}_3$), 1.70–2.40 (m, 6H, $-\text{CH}_2\text{CH}_2\text{CH}_2-$), and 4.10 ppm (q, $J=7.0$ Hz, 4H, two of $-\text{CO}_2\text{CH}_2\text{CH}_3$). MS: m/e 188 (M^+).

Found: C, 57.18; H, 8.76%. Calcd for $\text{C}_9\text{H}_{16}\text{O}_4$: C, 57.43; H, 8.57%.

From the Na_2CO_3 soluble components, a solid was obtained. Recrystallization of the solid from CHCl_3 - CCl_4 (1:1) afforded 0.04 g (5.6%) of 2-bromocyclohexane-1,3-dione (**7**), mp 167–169°C (lit.⁵), mp 171°C. IR (KBr): 1580 cm^{-1} (C=O).

Found: C, 37.52; H, 3.88%. Calcd for $\text{C}_6\text{H}_7\text{O}_2\text{Br}_2$: C, 37.73; H, 3.69%.

Reaction of 3 with Sodium Ethoxide. A stirred mixture of 1.0 g (3.3 mmol) of **3** and 0.46 g (6.6 mmol) of sodium ethoxide in 50 ml of dry ether was refluxed for 5 hr. The reaction mixture was poured into water, neutralized with 1N HCl, and the ether layer was separated. The ether solution was washed with 5% Na_2CO_3 , dried, and then evaporated. The residue was distilled to give 0.53 g (72%) of diethyl phthalate (**8**), bp 153–155°C/20 mmHg, which was identified by the comparison of IR spectrum and retention time in VPC with those of an authentic sample.

Reaction of 1 with Disodium meso-1,2-Diphenylethane-1,2-diolate. A solution of 1.1 g (5.2 mmol) of meso-1,2-diphenylethane-1,2-diol in 30 ml of THF was added to a suspension of 0.48 g (10 mmol) of sodium hydride in 20 ml of THF, and the mixture was refluxed with stirring for 1 hr. A solution of 1.5 g (5 mmol) of **1** in 20 ml of THF was then added to the above mixture at room temperature, and the resulting mixture was refluxed for 5 hr. The reaction mixture was poured into 50 ml of water, neutralized with 1N HCl, and extracted with two 100 ml portions of ether. The combined ether extracts were washed with 5% Na_2CO_3 , dried over Na_2SO_4 and evaporated to leave an oil. The oil was partly solidified on rubbing with a spatula. The solid was separated

by filtration to give 0.3 g (27%) of *meso*-1,2-diphenylethane-1,2-diol. The filtrate was separated into two portions by passing through an alumina column using CHCl_3 - CCl_4 (3:1) as an eluent. From the first portion of the eluates, 0.11 g (10%) of 1,2-diphenylethane-1,2-dione (**9**) was obtained, mp 94–95°C (lit.⁶), mp 95°C). The compound **9** thus obtained was identical with an authentic sample in every respect. From the second portion of the eluates, 0.17 g (17%) of 1,2-(diphenylmethylmethylenedioxy)-1,2-diphenylethane (**11**), mp 130–131°C (lit.⁷), mp 132°C) after recrystallization from *n*-hexane, was obtained. IR (KBr): 3040, 1600 and 1130 cm^{-1} . NMR (CDCl_3): δ 4.65 (d, $J=5$ Hz, 1H), 5.30 (s, 2H), 5.76 (d, $J=5$ Hz, 1H), and 6.55–7.60 ppm (m, 20H, aromatic H). MS: m/e 225 ($\text{M}^+ - 167$), 197 180 and 167.

Found: C, 85.62; H, 6.07%. Calcd for $\text{C}_{28}\text{H}_{24}\text{O}_2$: C, 85.68; H, 6.16%.

The compound (**11**) thus obtained was identical with an authentic sample prepared from *meso*-1,2-diphenylethane-1,2-diol by the method of Daniloff²⁾ in every respect.

The Na_2CO_3 solution was neutralized with 1N HCl and extracted with ether. The ether extract was dried over Na_2SO_4 and evaporated to leave a solid. Sublimation of the solid under reduced pressure gave 0.17 g (27%) of benzoic acid (**10**) and left a residue which upon recrystallization from CCl_4 - CHCl_3 (2:1) gave 0.44 g (40%) of **5**.

Reaction of 2 with Disodium meso-1,2-Diphenylethane-1,2-diolate. A mixture of 1.35 g (5 mmol) of **2** and 1.6 g (5.2 mmol) of disodium *meso*-1,2-diphenylethane-1,2-diolate in 60 ml of dry THF was refluxed for 5 hr. The resulting reaction mixture was worked up by a manner similar to that described in the reaction of **1** with disodium *meso*-1,2-diphenylethane-1,2-diolate. From neutral components, 80 mg (14%) of **9** was obtained and a starting material was recovered as 0.52 g (47%) of *meso*-1,2-diphenylethane-1,2-diol. In this case, **11** was not isolated. From the Na_2CO_3 soluble components, 70 mg (21%) of **10** and 0.6 g (63%) of **7** were obtained.

Reaction of 1 with Phenylmethanethiol. A stirred mixture of 1.0 g (3.4 mmol) of **1** and 0.44 g (3.4 mmol) of phenylmethanethiol in 50 ml of dry THF was refluxed for 4 hr. The solvent was evaporated to leave an oil which partly solidified upon standing. The solid was separated by filtration, and it was 0.67 g (90%) of **5**. Distillation of the filtrate under reduced pressure gave 0.35 g (81%) of dibenzyl disulfide as an oily material which upon standing solidified, mp 69–70°C (lit.⁷), mp 71–72°C). Dibenzyl disulfide thus obtained was identical with an authentic sample in every respect.

Sodium Salt of Diethyl Malonate. A solution of sodium ethoxide in ethanol was prepared by adding sodium into anhydrous ethanol. An equivalent of diethylmalonate was then added to the above solution. The mixture was heated at 60°C for 1 hr and evaporated to dryness.

Reaction of 1 with Sodium Salt of Diethyl Malonate. A stirred mixture of 1.5 g (5 mmol) of **1** and 0.95 g (5.2 mmol) of sodium salt of diethyl malonate in 50 ml of dry THF was refluxed for 5 hr, poured into 50 ml of water, neutralized with 1N HCl, and then extracted with ether. The ether extract was washed with 5% Na_2CO_3 , dried over Na_2SO_4

and evaporated. Distillation of the residue under reduced pressure gave 1.0 g (70%) of diethyl bromomalonate (**13**), bp 65–70°C/1 mmHg, which was identical in IR spectrum and the retention time in VPC with those of an authentic sample. Further distillation of the residue gave 0.07 g (8%) of 1,1,2,2-tetraethoxycarbonylethylene (**15**) which distilled out at 110–120°C/1 mmHg and solidified upon standing, mp 55–56°C (lit.⁸), mp 57–58°C). IR (KBr): 1750, 1740, and 1720 cm^{-1} (C=O).

Found: C, 53.32; H, 6.56%. Calcd for $\text{C}_{14}\text{H}_{20}\text{O}_8$: C, 53.17; H, 6.33%.

The residue of the distillation was chromatographed on alumina with CHCl_3 to give 25 mg (3%) of 1,1,2,2-tetraethoxycarbonylethane (**14**), mp 74–75°C (lit.⁹), mp 76°C). IR (KBr): 1730 cm^{-1} (C=O).

Found: C, 52.60; H, 6.73%. Calcd for $\text{C}_{14}\text{H}_{22}\text{O}_8$: C, 52.83; H, 6.92%.

The Na_2CO_3 solution was neutralized with 1N HCl and extracted with ether. The ether solution was dried over Na_2SO_4 and evaporated to give 0.95 g (85%) of **5**.

The reaction of **1** with two equivalents of sodium salt of diethyl malonate was carried out under the same conditions as above, and the products shown in Table 2 were isolated.

Reaction of 2 with Sodium Salt of Diethyl Malonate. A stirred mixture of 1.0 g (3.7 mmol) of **2** and 0.7 g (3.8 mmol) of sodium salt of diethyl malonate in 50 ml of dry THF was refluxed for 5 hr. The resulting reaction mixture was worked up as described above. From the neutral components, 0.55 g (62%) of **13**, 0.1 g (10%) of **14** and 0.02 g (2%) of **15** were isolated. From the Na_2CO_3 soluble portion, 0.48 g (66%) of **7** was obtained.

Reaction of 3 with Sodium Salt of Diethyl Malonate. A stirred mixture of 1.0 g (3.3 mmol) of **3** and 0.62 g (3.4 mmol) of sodium salt of diethyl malonate in 50 ml of dry THF was refluxed for 5 hr. The resulting reaction mixture was worked up as described above. The residue obtained after evaporation of the ether solution containing neutral components was distilled under reduced pressure to give 0.14 g (13.3%) of diethyl dibromomalonate (**16**), bp 110–151°C/3 mmHg, which was identical in IR spectrum and the retention time in VPC with those of an authentic sample.

The residue of the distillation was chromatographed on an alumina column with benzene to give 0.46 g (75%) of **14**.

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