The Base-catalyzed Condensation Reaction of Dimethyl Malonate with 5-Chloro-2-methoxytropone and 2,5-Dichlorotropone. On the Solvent Effect for the Sites of the Reaction[1)]

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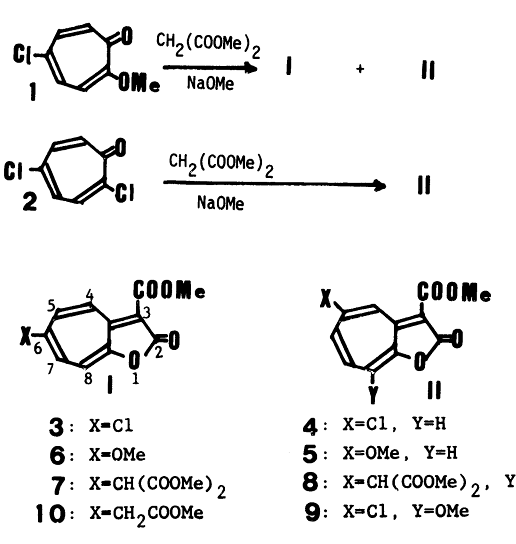
The sites of the nucleophilic attack of the base-catalyzed condensation of dimethyl malonate with 5-chloro-2-methoxytropone were solvent-dependent; the normal substitution product was predominant in benzene, but the *ciné*-substitution products were exclusive in methanol. With 2,5-dichlorotropone, the *ciné*-reaction products were exclusive in both solvents.

One of the most remarkable features on the nucleophilic substitution reaction of troponoid chemistry is a frequent occurrence of the abnormal substituion, or *ciné*-reaction,[2,3)] which means a reaction in which the leaving group on the aromatic ring is not located on the attacking site of the nucleophile. To date, many examples of such reactions have been recorded.[4)] This fundamental feature is important in order to understand the complicated mode of ring-closure in the azulene synthesis from the reactive troponoids.[5,6)] The condensation of troponoids with dimethyl malonate or ethyl acetoacetate is known to give, in the *ciné*- and/or normal mode, oxazulanones, 2*H*-cyclohepta[*b*]furan-2-ones,[7)] while, the methyl cyanoacetate and malononitrile, cyano derivatives, are known to give the functionalized azulene derivatives as major products.[8)] Moreover, the syntheses of the azulene derivatives from oxazulanones have been developed; *i.e.*, the consecutive condensation of some oxazulanones with active methylene derivatives[9)] and heating with various enamines.[10)] In view of the capability of introducing various kinds of functional groups to both five- and seven-membered rings of azulenes, these make the oxazulanones important as the starting materials. This paper will describe the solvent dependency of the *ciné*-reaction encountered in the formation of 2*H*-cyclohepta[*b*]furan-2-ones from 5-chlorotropolone derivatives, 5-chloro-2-methoxytropone (**1**) and 2,5-dichlorotropone (**2**), with dimethyl malonate.



3: X=Cl
6: X=OMe
7: X=CH(COOMe)$_2$
10: X=CH$_2$COOMe

4: X=Cl, Y=H
5: X=OMe, Y=H
8: X=CH(COOMe)$_2$, Y=H
9: X=Cl, Y=OMe

Scheme 1.

First of all, when a methanol solution of **1** was allowed to react with dimethyl malonate in the presence of sodium methoxide, a somewhat complicated reaction with a time-dependent product distribution occurred at 30 °C. After separation of the product mixture by the silica-gel column or high-pressure liquid chromatography, **3**—**10** were isolated and characterized. A minor product, **3**, was shown to be 6-chloro-3-methoxycarbonyloxazulanone (I: X=Cl) on the basis of the ^{1}H-NMR spectroscopy, and **4** was also identified to be 5-chloro-3-methoxycarbonyloxazulanone (II: X=Cl, Y=H). On the other hand, the major product, **5** (47%), was halogen-free, and its ^{1}H-NMR spectrum revealed a signal of another methoxyl group, introduced by a nucleophilic attack; it was the major product when the reaction was continued for a prolonged period, up to 8 h. In fact, **5** could be prepared from **4** by sodium methoxide at room temperature.

Therefore, **5** is 5-methoxy-3-methoxycarbonyloxazulanone (II: X=MeO, Y=H). Similarly, **6** was shown to be 6-methoxy-3-methoxycarbonyloxazulanone (I: X=MeO) by chemical correlation with **3**, and **7** and **8** correspond to the malonic ester derivatives from **3** and **4** (I and II: X=CH(COOMe)$_2$, Y=H).

The structure of **9** was determined to be 5-chloro-8-methoxy-3-methoxycarbonyloxazulanone (II: X=Cl, Y=OMe) by its mass spectrum [*m*/*e*, 268, 270 (M$^+$, $C_{12}H_9O_5Cl$)] and the ^{1}H-NMR analysis: A low-field signal at δ 9.09 indicated the presence of a chlorine atom at C-5, and its broadened shape due to a long-range coupling indicated the presence of a hydrogen atom at C-6. This was further confirmed by comparison of the chemical shifts of C-7 proton with **6** [δ=6.79 (dd, *J*=11, 2.5 Hz)]; therefore, another methoxyl group of **9** is at the C-8.

The remaining product, **10**, is the monodecarboxylated derivative of **7** (I: X=CH$_2$COOMe).

The base-catalyzed condensation reaction of **1** with dimethyl malonate in benzene solution was slower than that in methanol, and the product distribution was considerably different. The major product in this case was the normal condensate, **3** (64%), which was

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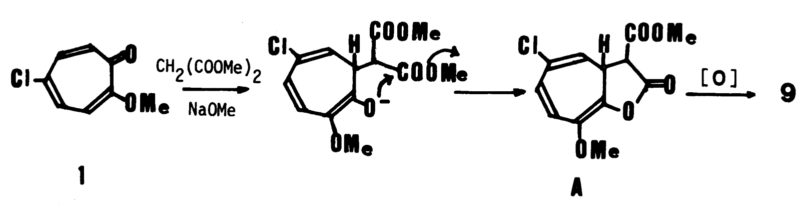

Scheme 2.

Table 1. The product distributions (yield/%) of the condensation reaction of 1 and 2 to dimethyl malonate in various solvents

Products	Normal condensates (I)				*ciné*-Condensates (II)				Recovered
	Cl (3)	OMe (6)	CH(COOMe)$_2$ (7)	CH$_2$COOMe (10)	Cl (4)	OMe (5)	CH(COOMe)$_2$ (8)	Cl, Y=OMe (9)	(1)
1 in Methanol	3	7	2	1	7	47	3	5	18
1 in Benzene	64		7		11			3	24
1 in Benzene-Ether	47		1		11	3			24
2 in Methanol					62	16			17
2 in Benzene					65		3		8
2 in Benzene-Ether					65	2			5

Table 2. The ^{1}H NMR spectra of cyclohepta [*b*] furanones

Compd δ_n	3	4	5	6	7	8	9	10
δ_4	8.68	8.87	8.40	8.80	8.77	8.83	9.09	8.87
δ_5	7.58	(Cl)	(OMe)	7.39	7.63	(Malonyl)	(Cl)	7.53
δ_6	(Cl)	7.33	7.2	(OMe)	(Malonyl)	7.41	7.29	(CH$_2$COOMe)
δ_7	7.55	7.33	7.2	6.74	7.49	7.41	6.79	7.37
δ_8	7.23	7.33	7.2	7.42	7.36	7.41	(OMe)	7.37
δ_{Me}	3.93	3.91	3.90 4.00	3.92(6H)	3.80(6H) 3.93	3.80(6H) 3.93	3.92 4.17	3.74 3.93
$\delta_{R\text{-}H}$					4.61(1H)	4.76(1H)		3.70(2H)
$J_{4\text{-}5}$	12.5	—	—	12.5	12.5	—	—	12.0
$J_{6\text{-}7}$	—	a)	a)	—	—	a)	11.0	—
$J_{7\text{-}8}$	10.5	a)	a)	11.0	10.0	a)	—	—
$J_{4\text{-}6}$	—	1.0	2.5	—	—	a)	—	—
$J_{5\text{-}7}$	2.0	—	—	3.0	1.5	—	2.5	a)

a) By first-order analysis the coupling constants could not be determined, due to overlapping of signals.

accompanied by **4**, **7**, and **9**. Formation of a chloro methoxy derivative, **9**, in this inert solvent can be explained only in terms of the *ciné*-reaction *via* intermediary adduct **A** which was followed by an autooxidative dehydrogenation. An alternative explanation, *i.e.*, a nucleophilic introduction of methoxyl group on the C-8 position of **4** followed by a dehydrogenation, is not true since, as mentioned above, **4** was exclusively converted to **5**. Such a behavior has precedence in the condensation of 2-(*p*-tolylsulfonyloxy)tropone with some active methylene reagents.[11]

Furthermore, the product distribution in the reaction of **2** in a mixed solution of benzene–ether (1 : 1)[12] revealed an intermediary figure to those in methanol and in benzene. Occurrence of **3**—**5**, and **7** was directly confirmed by isolations.

Subsequently, the same reaction was carried out with **2** and dimethyl malonate. In methanol, the major product was **4** (62%) which was accompanied by a minor product, **5** (16%). No other compound was detected other than the recovered tropone, **1** (17%); the condensation thus occurred exclusively with the *ciné* mode. The reaction in benzene also produced the *ciné*-reaction products, **4** (65%) and **8**, together with the recovered **1** (8%). As expected, the reaction in a mixed solution of benzene–ether disclosed similar features to the results obtained from the reaction in methanol; it gave **4** (65%) and **5**.

Therefore, the results disclosed a solvent dependence in the reaction of **1** and dimethyl malonate, where the *ciné*-reaction was favored in the protic solvent, but in nonpolar aprotic solvent the normal substitution reaction was predominant. On the other hand, the reaction of **2** and dimethyl malonate exclusively gave the *ciné*-reaction products in every case.

Consequently, the reaction of **1** and dimethyl malonate is solvent-dependent; in methanol, the predominant process was the *ciné*-reaction, but in benzene, the reverse was true. It is known that in many cases encountered in the troponoid field, thoroughly different product distributions have arisen from slightly different reaction conditions; therefore, one must be careful in drawing conclusions based on a single fact. However, in the present case, it is certain that the nature of solvents decided the course of the reaction. In methanol, the nucleophile, dimethyl sodiomalonate, should be tightly solvated, while, in benzene the reagent is rather naked. As results, nucleophilic attack by the solvated bulky reagent to C-2 position, the substituted site, might become unfavorable due to a steric hindrance.

The reaction of **2** with dimethyl malonate always proceeded in the exclusive *ciné*-mode.

The case-catalyzed condensation of **1** and **2** with other active methylene compounds, methyl acetoacetate and methyl *p*-nitrophenylacetate, gave other interesting features; these results will be presented in an independent paper.

Experimental

Throughout the study, the NMR spectra were measured by a JEOL FX-100 Model spectrometer in $CDCl_3$ solutions unless otherwise mentioned, and the chemical shifts were expressed in the δ unit from the internal standard, TMS. The UV spectra were measured in methanol solutions using a Hitachi Model 124 spectrometer. The IR spectra were measured with a JASCO Model A-102 spectrometer in either CCl_4 solutions or with KBr disks. High-resolution mass spectra were taken by JEOL OlSG Model spectrometer, and the figures were obtained by visual reading on the photographic plates.

The Condensation Reaction of 5-Chloro-2-methoxytropone (1) and Dimethyl Malonate in Methanol. Anhydrous methanol (25 cm^3) containing dimethyl malonate (775 mg), NaOMe (285 mg) and **1** (500 mg) was warmed to 30 °C with stirring. The reaction was monitored by an occasional check of high-pressure liquid chromatogram (polasil T/ethyl acetate–hexane). After 8 h, the solvent was removed by evaporation, and the residue was neutralized with dil HCl and chromatographed on a silica-gel column to give three fractions of product mixture: From benzene–ether (80 : 20), a mixture of **3** and **4** (**a**, yellow solid, 59 mg), was at first eluted, and subsequently, a mixture of **5**, **8**, and **7** (**b**, yellow solid, 307 mg), was obtained; from the latest fractions, a mixture of **6**, **9**, and **10** (**c**, yellow solid, 77 mg), was obtained together with recovered **1** (89 mg).

Further fractionation of these products was performed by high-pressure liquid chromatography (micropolasil/ethyl acetatehexane): Thus, from the fraction **a**, analytical samples of **3**, 6-chloro-3-methoxycarbonyloxazulanone (yellow needles; mp 250—251 °C [Found: C, 55.18; H, 2.94%. Calcd for $C_{11}H_7O_4Cl$: C, 55.37; H, 2.96%. δ(C)=51.9, 116.5, 129.3, 134.4, 140.7, 145.8, 153.0, 157.3, 163.5, and 164.4], 20 mg (3%)), and **4**, 5-chloro-3-methoxycarbonyloxazulanone (yellow needles; mp 172—173 °C [Found: C, 54.95; H, 2.98%. δ(C)= 51.8, 97.0, 117.4, 129.0, 135.1, 135.3, 147.8, 151.5, 158.5, 163.3, and 169.3], 38 mg (7%)) were isolated.

Similarly, analytical samples of **5**, **8**, and **7** were isolated from the fraction **b**, and showed the following properties: **5**, 5-methoxy-3-methoxycarbonyloxazulanone (yellow needles; mp 200—201 °C [Found: C, 61.47; H, 4.05%. Calcd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.03%. δ(C)=51.5, 56.6, 94.1, 108.1, 115.1, 129.3, 134.3, 153.7, 157.3, 164.8, 165.2, and 168.4], 265 mg (47%)), **8**, 3-methoxycarbonyl-5-[bis(methoxycarbonyl)methyl]oxazulanone (yellow needles; mp 181.5—182 °C [Found: C, 57.44; H, 4.18%; M.W., 334.0647. Calcd for $C_{16}H_{14}O_8$: C, 57.49; H, 4.22%; M. W., 334.0689], 27 mg (3%)), and **7**, 3-methoxycarbonyl-6-[bis(methoxycarbonyl)-methyl]oxazulanone (yellow crystals; mp 170—171 °C[Found: C, 57.35; H, 4.28%; M. W., 334.0652], 14 mg (2%)).

Preparative thin-layer chromatography (PTLC) of the fraction **c** gave **9**, 5-chloro-8-methoxy-3-methoxycarbonyloxazulanone (yellow needles; mp 231—232 °C [Found: C, 53.54; H, 3.37%; M. W., 268.0148. Calcd for $C_{12}H_9O_5Cl$: C, 53.65; H, 3.38%; M. W., 268.0139], 30 mg (5%)), **10**, 3-methoxycarbonyl-6-(methoxycarbonylmethyl)oxazulanone (yellow needles; mp 170—171 °C [Found: C, 60.80; H, 4.28%; M. W., 276.0615. Calcd for $C_{14}H_{12}O_6$: C, 60.87; H, 4.38%; M. W., 276.0634], 7 mg (1%), and **6**, 6-methoxy-3-methoxycarbonyloxazulanone (yellow crystals; mp 250—251 °C [Found: C, 61.44; H, 4.09%. Calcd for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30%], 38 mg (7%)).

The Condensation Reaction of 1 and Dimethyl Malonate in Benzene. An anhydrous benzene (25 cm^3) solution of dimethyl malonate (775 mg), NaOMe (285 mg), and **1** (500 mg) was warmed at 30 °C with stirring. After 8 h, the solvent was removed *in vacuo* at room temperature, and the residue was extracted with chloroform and dil HCl. The organic extracts were chromatographed on a silica-gel column to give a mixture of **3** and **4** (417 mg), **7** (48 mg; 7%), **9** (20 mg; 3%), and the unreacted **1** (120 mg; 24%). Separation of **3** and **4** was made by repeated silica-gel column chromatography; the yields were 340 mg (64%) for **3**, and 65 mg (11%) for **4**.

The Condensation of 1 and Dimethyl Malonate in a Mixture of Benzene and Ether. NaOMe (120 mg) and dimethyl malonate (375 mg) were dissolved in anhydrous ether (20 cm^3) and mixed with benzene solution (20 cm^3) of **1** (350 mg) and kept at 30 °C for 8 h. The mixture was then treated with dil HCl, and extracted with ethyl acetate. The organic extracts were chromatographed on a silica-gel column to give a yellow solid, **3** (175 mg; 47%), **4** (40 mg; 11%), **5** (9.5 mg; 3%), **7** (4.5 mg; 1%), and the recovered **1** (85 mg; 24%).

The Condensation of 2,5-Dichlorotropone (2) with Dimethyl Malonate in Methanol. A methanol solution (50 cm^3) of **2** (505 mg, NaOMe (280 mg), and dimethyl malonate (450 mg) was kept at 30 °C for 8 h, although disappearance of **2** was already recognized after 1.5 h on a high-pressure liquid chromatogram. After evaporation of the solvent *in vacuo* at room temperature, the residue was treated with dil HCl, and extracted with ethyl acetate. Silica-gel column chromatography of the mixture afforded **4** (245 mg; 62%), **5** (90 mg; 16%), and the recovered **1** (60 mg; 17%).

The Condensation of 2 with Dimethyl Malonate in Benzene. Anhydrous benzene (50 cm^3) containing dimethyl malonate (300 mg), NaOMe (110 mg), and **2** (200 mg) was kept at 30 °C for 8 h. The reaction was somewhat slower than in methanol; it took 4 h to consume **2**. The mixture was washed with dil HCl and extracted with ethyl acetate. Silica-gel column chromatography of the mixture afforded **4** (165 mg; 65%) and **8** (10 mg; 3%), along with **1** (15 mg; 8%).

The Condensation of 2 and Dimethyl Malonate in a Mixture of Benzene and Ether. To an anhydrous ether solution (20 cm^3) of dimethyl malonate (375 mg) and NaOMe (110 mg), a benzene solution (20 cm^3) of **2** (230 mg) was added at once, and kept at 30 °C for 8 h. The mixture was then acidified by dil HCl, and extracted with ether. The silica-gel column chromatography of the mixture gave **4** (280 mg; 65%), and **5** (8 mg; 2%), together with **1** (15 mg; 4.5%).

The Further Conversion of 4 into 5. A Methanol solution (10 cm^3) containing **4** (10 mg) and NaOMe (2 mg) was kept at room temperature for 24 h. The mixture was diluted with aqueous HCl and extracted with ether. The NMR analysis of the organic fractions confirmed the presence of **5**, but of no other product.

The Conversion of 3 to 6. A methanol solution (10 cm^3) of **3** (15 mg) was similarly treated with NaOMe (2 mg) for 24 h. The NMR analysis of the product confirmed the exclusive formation of **6**.

*Formation of **8** from **4**.* A benzene solution (5 cm^3) of **4** (20 mg) was treated with **2** (50 mg) and NaOMe (1 mg) at 30 °C for 8 h. From the mixture, only **8**, 6 mg, was separated by PTLC.

*Formation of **7** from **3**.* A benzene solution (5 cm^3) of **3** (10 mg) and **2** (20 mg) with NaOMe (1 mg) was heated at 30 °C for 8 h. The mixture was fractionated by means of PTLC to afford **7** (4 mg). No other compound was detectable.

References

1) The major part of the study was carried out more than two decades ago, but it has not been published yet. We wish to report the results of the repeated experiments at Kyushu University with newly determined physicochemical data.

2) T. Nozoe, S. Seto, and T. Sato, *Proc. Jpn. Acad.*, **30**, 473 (1954); R. D. Howorth and P. B. Tenker, *J. Chem. Soc.*, **1955**, 911; Y. Kitahara, *Sci. Repts. Tohoku Univ., Ser. I*, **39**, 250, 258 (1956); T. Sato, *Nippon Kagaku Zasshi*, **80**, 1056, 1058, 1067, and 1071 (1969).

3) The term "*ciné*"-substitution first appeared in a review article on nucleophilic substitution by J. F. Bunnett and R. E. Zahler (*Chem. Rev.*, **49**, 273 (1951)).

4) Y. Kitahara, *Sci. Repts. Tohoku Univ., Ser. I*, **40**, 74 (1956); T. Nozoe, S. Seto, S. Matsumura, and Y. Murase, *Bull. Chem. Soc. Jpn.*, **35**, 1179 (1962); S. Itô, J. Tsunetsugu, T. Kanno, H. Sugiyama, and H. Takeshita, *Tetrahedron Lett.*, **1965**, 3659; G. Biggi, F. D. Cima, and F. Pietra, *J. Am. Chem. Soc.*, **95**, 7101 (1973); F. Pietra, *J. Chem. Soc., Chem. Commun.*, **1974**, 501; H. Takeshita, A. Mori, T. Minami, and H. Kondo, *Heterocycles*, **14**, 793 (1980). See also reviews: T. Nozoe, K. Takase, and H. Matsumura, "Non-Benzenoid Aromatic Compounds" in "Dai Yuki Kagaku (Comprehensive Organic Chemistry)," ed by M. Kotake, Asakura, Publ., Tokyo (1955), Vol. 13, pp. 178—213; T. Nozoe, "Chemistry of Non-Benzenoid Aromatic Compounds," ed by D. Ginsberg, Interscience Publ., Amsterdam (1959), pp. 39—464.

5) T. Nozoe, S. Matsumura, Y. Murase, and S. Seto, *Chem. Ind. (London)*, **1955**, 1257; T. Nozoe, S. Seto, S. Matsumura, and T. Asano, *Proc. Jpn. Acad.*, **32**, 339 (1956); T. Nozoe, S. Seto, and S. Nozoe, *ibid.*, **32**, 472 (1956).

6) In general, 2-methoxytropone derivatives are known to give the normal reaction products, on the other hand, 2-halogenotropones and 2-(*p*-tolysulfonyloxy)tropones are known to give the *ciné*-reaction products. However, nucleophilicity and bulkiness of reagents as well as substitution patterns of the troponoid ring can not be neglected as controlling factors.

7) T. Nozoe, S. Seto, and S. Matsumura, *Proc. Jpn. Acad.*, **28**, 483 (1952); S. Seto, *Sci. Repts. Tohoku Univ., Ser. I*, **37**, 367 (1953); T. Sato, *Nippon Kagaku Zasshi*, **80**, 1342, 1345, 1347, and 1349 (1959).

8) T. Nozoe, S. Seto, K. Takase, S. Matsumura, and T. Nakazawa, *Nippon Kagaku Zasshi*, **86**, 346 (1965).

9) T. Nozoe, K. Takase, and N. Shimazaki, *Bull. Chem. Soc. Jpn.*, **37**, 1644 (1964); T. Nozoe, K. Takase, and S. Fukuda, *ibid.*, **44**, 2210 and 2215 (1971).

10) P. W. Yang, M. Yasunami, and K. Takase, *Tetrahedron Lett.*, **1971**, 4275; M. Yasunami, A. Chen, P. W. Yang, and K. Takase, *Chem. Lett.*, **1980**, 579; K. Takase and M. Yasumi, *Yuki Gosei Kagaku Kyokai Shi*, **39**, 1172 (1981).

11) T. Nozoe, K. Takase, M. Kato, and T. Nogi, *Tetrahedron*, **27**, 6023 (1971).

12) This rather odd solvent system was primarily employed in order to prevent the freezing of the reaction mixture in our refrigerator.