[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN]

# Diels–Alder Reaction of Cinnamic Acid Derivatives with Cyclopentadiene

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*p*-Substituted *trans*-cinnamic acids, esters, amides and acid chlorides form adducts with cyclopentadiene. The reaction rates increase as electron-withdrawing substituents are introduced into the dienophile. The percentage of *endo*-carboxy isomer increases in the order amide < ester < acid < acid chloride. The percentage of *endo*-aryl isomer increases as the *para*-substituent is varied in the order methoxy < hydrogen < chloro < nitro. These stereochemical data are interpreted in terms of electron interactions across space in the transition state. Iodolactonization is shown to be a mild, selective method for analyzing and separating *endo–exo* mixtures of acids. The *exo*-acid is unaffected; the *endo*-acid forms an insoluble iodolactone which may be reconverted to the *endo*-acid in high yield with zinc and acetic acid.

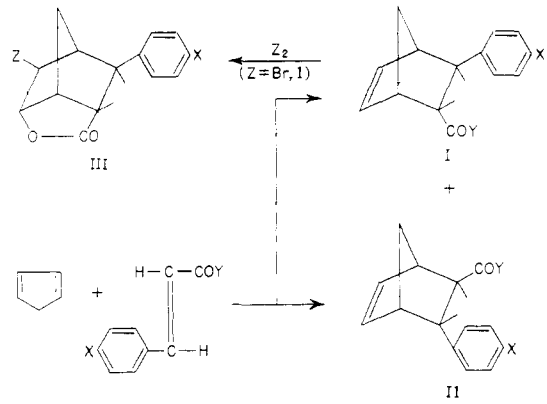
A cyclic diene reacts with a dienophile to form two stereoisomeric adducts. Alder showed that the *endo* isomer predominates over the *exo* in most cases, and explained this observation by the principle of "Maximum Accumulation of Double Bonds."[2] Theoretical interpretations of this rule have been given by Woodward and by Wassermann.[3]

The problem of the relative efficiencies of groups in causing *endo* orientation was approached by a study of *trans*-dienophiles.[4] In the present paper, this work is extended to *trans*-cinnamic acid derivatives, in which *para*-substituents of different electronegativities and various derivatives of the carboxyl function were introduced into the parent molecule. Scattered examples of Diels–Alder reactions of cinnamic acid derivatives have appeared in the literature,[5] but since none of these authors employed cyclopentadiene, *endo–exo* isomerism was not considered.

## Results

Adducts formed slowly in most cases when the dienophile was stored at 55° with excess cyclopentadiene in acetone or toluene for several weeks. However, *p*-dimethylamino- and *p*-methoxycinnamic acids and their methyl esters did not react under these conditions. Adducts formed much faster at 110° in toluene solution, and *p*-methoxycinnamic acid did react at this higher temperature. A few runs were performed at still higher temperatures.

Since most of the reactions did not go to completion under the conditions employed, the yields of adducts were determined analytically. With acids, the neutral equivalent of the acidic product permitted calculation of the extent of adduct formation. The acid chloride and ester adducts were hydrolyzed and analyzed similarly. With amide adducts, the amount of unreacted starting material was determined by ultraviolet or infrared spectrometry. In some cases, it was possible to remove most of the unreacted dienophile by distillation, extraction or crystallization procedures. Care was taken to ensure against loss of adduct, since otherwise the isomer ratios to be determined would have been meaningless.




**Stereoisomer Analysis.**—An attempt was made to determine the *endo–exo*[6] ratio in the acid adducts by bromolactonization, analogous to previous work.[4] Though bromination of the *endo*-acids (I, Y = OH) proceeded in the expected manner to III (Z = Br), the *exo*-acids (II, Y = OH) formed not only acidic bromination products but also nortricyclene derivatives and rearranged bromolactones.[7]

Iodolactonization[7,8] proceeded without complication and the *endo*-acids were converted quantitatively into the insoluble iodolactones (III, Z = I). The *endo–exo* ratio calculated from the weight of iodolactone was checked in one instance by infrared spectrometry, with good agreement. The *exo*-acids proved to be completely inert to aqueous iodine solutions and they could be recovered readily in pure form. The cinnamic acids were inert toward iodine in aqueous bicarbonate, as expected. The iodolactones were cleaved reductively with zinc and acetic acid[9] to the pure *endo*-acids in high yield.

(1) Abstracted from the Ph.D. Dissertation of C.D.V., February, 1955; Eastman Kodak Fellow, 1953–1954.

(2) The stereochemistry of the Diels–Alder reaction is discussed, with references, by M. C. Kloetzel in "Organic Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, pp. 10–12.

(3) (a) R. B. Woodward, THIS JOURNAL, **64**, 3058 (1942); (b) R. B. Woodward and H. Baer, *ibid.*, **66**, 645 (1944); (c) A. Wassermann, *J. Chem. Soc.*, 1511 (1935); (d) see also the discussion in C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 711–721, and in ref. 2, pp. 8-9.

(4) C. S. Rondestvedt, Jr., and J. C. Wygant, THIS JOURNAL, **73**, 5785 (1951); *J. Org. Chem.*, **17**, 975 (1952).

(5) (a) Ch. Weizmann, E. Bergmann and T. Berlin, THIS JOURNAL, **60**, 1331 (1938); (b) F. Bergmann and H. E. Eschinazi, *ibid.*, **65**, 1405 (1943); (c) R. Adams, W. D. McPhee, R. B. Carlin and Z. W. Wicks, *ibid.*, **65**, 356 (1943); (d) R. Adams and R. B. Carlin, *ibid.*, **65**, 360 (1943); (e) S. Fujise, Y. Horiuchi and T. Takahashi, *Ber.*, **69**, 2102 (1936); (f) S. Sugasawa, K. Kodama and S. Hara, *J. Pharm. Soc. Japan*, **60**, 138 (1940); *C. A.*, **34**, 7291 (1940).

(6) Throughout this paper, the unqualified words *endo* and *exo* refer to the configuration of the carboxyl group (or derivative); *endo* = I, *exo* = II. The aryl group lies *trans* to the carboxyl.

(7) C. D. Ver Nooy and C. S. Rondestvedt, Jr., THIS JOURNAL, **77**, 3583 (1955).

(8) E. E. van Tamelen and M. Shamma, *ibid.*, **76**, 2315 (1954).

(9) J. Bougault, *Ann. chim. phys.*, **14**, 145 (1908); K. Alder and F. Brochhagen, *Ber.*, **87**, 167 (1954).

The isomer ratios in acid chloride adducts were determined on the acids obtained after hydrolysis with aqueous sodium bicarbonate. The ester adducts were hydrolyzed with alcoholic alkali at room temperature and analyzed as acids. It was verified in one case that alkaline hydrolysis did not cause isomerization, since the mixed acids could be re-esterified with diazomethane to the original mixture of esters (infrared and melting point). The amide adducts could not be hydrolyzed quantitatively by mild methods (alkali or nitrous acid), so these *endo–exo* ratios were established by infrared comparison with artificial mixtures of known composition. The stereochemical results of this study are presented in Table I.

TABLE I

PERCENTAGE OF *endo* ISOMER I IN ADDUCTS OF *trans*-CINNAMIC ACID DERIVATIVES WITH CYCLOPENTADIENE[a,b]

| X | Y Cl | OH | $OCH_3$ | $NH_2$ |
|---|---|---|---|---|
| $NO_2$ | 64(3, ±0.3) | 30(2. ±1); 40[c] | 28 | 25; 15–20[d] |
| Cl | 67 | 40(2, ±3); 42[d](7, ±1) | .. | ..... |
| H | 67(2, ±0) | 43(5, ±3); 42[d](3, ±2); 23[e](2, ±2) | 44 | 34[d] |
| $CH_3O$ | 66 | 47[d](4, ±1) | .. | ..... |

[a] At 55° unless otherwise indicated. [b] Parenthetical figures are number of runs (if more than one) and average deviation. [c] Run in boiling acetic acid. [d] Run in boiling toluene. [e] Run in boiling bromobenzene.

**Isomerization of Adducts.**—Our interest lay in the relative rates of formation of *endo* and *exo* isomers. It therefore was important to establish that the observed isomer ratios actually reflected this difference in rates. It was possible that the adduct formed more rapidly actually might be thermodynamically less stable than the adduct formed more slowly; Woodward,[4b,10] Craig,[11] Berson,[12] Alder[13] and Kwart[14] have reported examples of this phenomenon, in which the first-formed adduct is completely or partially isomerized on long-continued heating. Accordingly, the isomer ratios for the formation of adducts between cyclopentadiene and cinnamic acid or *p*-chlorocinnamic acid were determined as a function of time in refluxing toluene. The results in Table II show clearly that this difficulty was absent. As a further check, and to investigate the possibility that the *trans* adducts might be isomerized slowly to *cis-endo* or *exo* isomers, the pure *endo* and *exo* adducts from cinnamic acid were refluxed in toluene for 100 hours. From the *endo* isomer, 85% of the starting material was recovered as iodolactone; the remaining 15% was not acidic. From the *exo* isomer, 4–5% was isolated as iodolactone, indicating that only slight isomerization had occurred.

TABLE II

PERCENTAGE *endo*-ISOMER I AS A FUNCTION OF TIME AT 110°

| Time, hr. | Yield of adducts,[a] % | Adducts as *endo* I, % |
|---|---|---|
| | Cinnamic acid | |
| 24 | 13 | 42 |
| 96 | 49 | 44 |
| 288 | 76 | 40 |
| | *p*-Chlorocinnamic acid | |
| 3 | 5 | 34[b] |
| 6 | 9 | 39 |
| 12 | 19 | 41 |
| 20 | 20 | 42 |
| 48 | 47 | 43 |
| 96 | 79 | 44, 42 |
| 216 | 62[c] | 41 |

[a] Ten moles of cyclopentadiene per mole of dienophile. [b] In samples of low adduct percentage, the experimental error in determining the iodolactone is larger than in other runs. [c] Material balance was poor in this run.

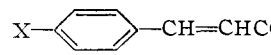
(10) R. B. Woodward and H. Baer, THIS JOURNAL, **70**, 1161 (1948).
(11) D. Craig, *ibid.*, **73**, 4889 (1951).
(12) J. A. Berson and R. Swidler, *ibid.*, **75**, 1721 (1953).
(13) K. Alder, *et al.*, *Ann.*, **504**, 219 (1933).
(14) H. Kwart and I. Burchuk, THIS JOURNAL, **74**, 3094 (1952).

## Discussion

**Reaction Rates.**—Dienophilic properties are conferred upon an olefinic double bond by electron-withdrawing substituents; in general, the magnitude of the effect parallels the intensity of the electron withdrawal. It is apparent from Tables II and III that the reactivity of cinnamic acid derivatives increases in the order *p*-methoxy < unsubstituted < *p*-chloro < *p*-nitro, and amides < esters < acids < acid chlorides, as judged from the relative yields obtained in various times. These observations agree with predictions made from the ionic mechanism[3] for the Diels–Alder reaction. Although the yield of adduct from *p*-chlorocinnamoyl chloride does not fall in this sequence, the discrepancy is probably not real, since no unreacted dienophile could be detected. Adams and Carlin[5c,d] found, on the other hand, that several *o*-methoxycinnamic acids reacted without undue difficulty with isoprene and 2,3-dimethylbutadiene. Although they did not utilize cyclopentadiene, it probably also would react readily, since it is more reactive than acyclic dienes. Their results, therefore, are not in the predicted sequence. A possible explanation may be found in the steric interaction of the *o*-methoxyl with the side chain. Electron release by a resonance mechanism is ineffective unless the methoxyl group and the side chain can assume a planar quinonoid configuration, and scale models demonstrate some interference in the *ortho* orientation.[15] Alternatively, the difference may reflect merely the -I inductive effect of the methoxyl group acting more strongly from the *ortho* than from the *para* position.

TABLE III

PERCENTAGE YIELDS OF ADDUCTS AT 55° FROM VARIOUS DIENOPHILES



| X | Y Cl | OH | $OCH_3$ | $NH_2$ |
|---|---|---|---|---|
| $NO_2$ | 93[a](1.5)[b] | 76(5) | 89(5) | 67(5) |
| Cl | 30[a,c](1) | 40(5); 42(5) | ... | 11(5) |
| H | 99[d](1, 1.5) | 22(4); 28(6) | 10(4) | 4(5) |
| $CH_3O$ | 27[a](1) | 1.6(5) | 0 | ... |
| $(CH_3)_2N$ | ..... | 0 | 0 | ... |

[a] By hydrolysis to the acid. [b] Time given in weeks in parentheses. [c] The low yield is believed to result from experimental difficulties, since no unreacted dienophile was detected. [d] By conversion to amide.

(15) This explanation was suggested in private conversation by Dr. Hans Schmid, Zürich.

*endo–exo* **Ratios.**—Table I gives the average values obtained for the isomer ratios with various dienophiles. As the electron-withdrawing power of the substituent in the aromatic ring increases, the ability of the aryl group to interact with the electrons of the diene increases, and this is reflected in the increasing percentage of *endo*-aryl (*exo*-carboxyl) isomer formed. The change in isomer ratio is much more gradual than the change in over-all rate, suggesting that the intramolecular resonance which imparts dienophilic properties to a double bond is much stronger than the relatively feeble electronic interactions across space. The opposite trend (increasing *endo*-carboxyl) is noted as the electronegativity of the carboxy substituent increases from amide to ester, acid and acid chloride. Only a gradual trend is evident in the first three cases, but an abrupt change occurs with acid chloride functions. All the acid chlorides gave about 65% *endo*, with *para* substituents having almost no effect. From the previous work[4] it appears that a sulfonyl function is much more effective than carboxyl derivatives (except acid chloride) in causing *endo* orientation.

A discrepancy is noted between the present results and the previous report[4] that somewhat *less endo*-aryl isomer was produced with *p*-nitrophenyl than with phenyl. Analysis had been done by bromination, the *endo*-sulfo isomer forming an insoluble bromosultone. Since at that time it had not been recognized that the *exo*-sulfo isomers also might form insoluble material, the Diels–Alder reaction of 2-*p*-nitrophenylethenesulfonyl chloride with cyclopentadiene was reinvestigated briefly. It was found that the *crude* bromosultone prepared from the hydrolyzed adduct exhibited an infrared spectrum somewhat different from that of *purified* bromosultone. Since nortricyclene absorption at 12.0–12.5 $\mu$ was absent, the probable contaminant is rearranged bromosultone derived from the *exo*-sulfo isomer.[7] Were this actually the case, adjustment of the previously reported values probably would bring those results into line with the present trend; the necessary data are not now available, since iodosultonization gave somewhat erratic results.

A slight temperature effect on the isomer ratio is apparent in Table I. Sufficient data are not available to permit generalization, but it seems that isomer ratios in adducts from *p*-nitrocinnamic acid and amide are most sensitive to temperatures in the range 55–116°. Cinnamic acid adducts show no difference in isomer ratio between 55° and 110° but a pronounced change appeared in the two runs at 155°.

Since the relative rates of *endo* and *exo* isomer formation depend upon the energies of activation, some temperature coefficient would be expected. With a 40:60 ratio at 55°, the difference in Arrhenius energies would be approximately 270 cal./mole. Assuming these energies to be constant over the range 55–110°, the isomer ratio would change only to 38:62. This difference would not have been detectable with our experimental method. A similar calculation would predict an isomer ratio at 155° of 59:41. Since the observed value (77:23) is much lower in the *endo* isomer, it is probable that the *endo* isomer is being consumed by some side reaction, possibly thermal lactonization. Support for this idea is found in the data for the individual runs; the percentage *endo* decreases from 25% (24 hr.) to 21% (48 hr.). In any case, the data at 155° should be regarded with some suspicion.

It is also possible that a small difference in the entropies of activation would mask the temperature coefficient, since the electronegativity differences among the compounds studied should be reflected chiefly in the enthalpies of activation.

NOTE ADDED IN PROOF.—Very recently Winternitz, Mousseron and Rouzier[15a] examined the reaction of cyclopentadiene with cinnamic acid at 150–170°. Their crude adduct consisted of 15% *endo*:85% *exo*, in fair agreement with our result of 23%:77% at 155°. Their method of analysis was bromination in chloroform, but they did not examine this reaction mixture for nortricyclene derivatives or rearranged bromolactones.[7] The physical properties of their products do not agree with ours. They report for the *exo* acid, its S-benzylthiuronium salt, and the bromolactone from the *endo* acid m.p. 102–104°, 131–131.5°, and 114–115°, respectively. Our data for the same compounds are 115–116°, 137–138°,[15b] and 123–124°, respectively. It is probable that their bromolactone was contaminated by a rearranged bromolactone derived from the *exo* acid.

## Experimental[16]

The *trans*-cinnamic acid derivatives were prepared by conventional methods. *p*-Nitrocinnamic acid was prepared most conveniently by the method of Rai and Mathur[17a]; their alternate method[17b] did not give the reported yields, and the direct nitration of cinnamic acid required a tedious separation of isomers. The physical properties of the known compounds we prepared agreed with the literature values.

***p*-Chlorocinnamoyl chloride** was prepared from the acid using thionyl chloride; after two crystallizations from petroleum ether, the pale yellow needles melted at 79.0–79.5°.

*Anal.* Calcd. for $C_9H_6Cl_2O$: C, 53.76; H, 3.01. Found: C, 53.81; H, 3.15.

***p*-Chlorocinnamamide** was obtained in 96% yield by treatment of the chloride with cold concd. aqueous ammonia; colorless plates were obtained by two crystallizations from ethanol–water; m.p. 209–210°.

*Anal.* Calcd. for $C_9H_8ClNO$: C, 59.51; H, 4.44. Found: C, 59.71; H, 4.50.

**Methyl *p*-chlorocinnamate** was prepared from the chloride and absolute methanol in nearly quantitative yield; it crystallized from methanol–water as colorless needles, m.p. 76.0–76.5°.

*Anal.* Calcd. for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61. Found: C, 61.01; H, 4.61.

**Diels–Alder Reaction Conditions.**—A mixture of 0.025 mole of the cinnamic acid derivative and 0.1 mole of freshly distilled cyclopentadiene in 300 ml. of acetone or toluene was stored in a citrate bottle at 55°. The volatile materials were evaporated under an air jet. Reactions at 110 and 155° were conducted in refluxing toluene or bromobenzene. Freshly distilled dicyclopentadiene usually was employed instead of the monomer, since the monomer reaches equilibrium with the dimer very rapidly at these temperatures. On cooling the reaction mixtures, unreacted starting material often crystallized and it was removed by filtration. The

(15a) F. Winternitz, W. Mousseron and G. Rouzier, *Bull. soc. chim. France*, 170 (1955).

(15b) This derivative was prepared after receipt of their article.

(16) Microanalyses were performed by Anna Griffin in these laboratories, by Spang Microanalytical Laboratories, Plymouth, Mich., and by Micro-Tech Laboratories, Skokie, Ill. Melting points are uncorrected. The infrared spectra used in this work are reproduced in the Dissertation of C.D.V., obtainable from the University of Michigan Library; some of the spectra were obtained by Harry S. Blanchard and Masao Yoshimine.

(17) (a) J. Rai and K. B. L. Mathur, *J. Ind. Chem. Soc.*, **24**, 413 (1947); (b) **24**, 383 (1947).

TABLE IV

PROPERTIES OF ADDUCTS AND DERIVATIVES

| X | Compound Y | Z | M.p.,[a] °C. | Crystn. solvents[b] | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|
| | | | | *endo*-Acids I | | | | | |
| H | OH | .. | 107–108 | M–W | $C_{14}H_{14}O_2$ | 78.48 | 78.31 | 6.59 | 6.56 |
| Cl | OH | .. | 140.5–141.5 | EA–P2; M–W | $C_{14}H_{13}ClO_2$ | 67.61 | 67.59 | 5.27 | 5.39 |
| $CH_3O$ | OH | .. | 104–105 | EA–P2 | $C_{15}H_{16}O_3$ | 73.75 | 73.83 | 6.60 | 6.51 |
| | | | | *exo*-Adducts II | | | | | |
| H | OH | .. | 115.5–116 | M–W | $C_{14}H_{14}O_2$ | 78.48 | 78.27 | 6.59 | 6.55 |
| H | $NH_2$ | .. | 135.5–136 | M–W | $C_{14}H_{15}NO$ | 78.84 | 78.93 | 7.09 | 7.20 |
| H | $OCH_3$ | .. | 32–33 | P1 | $C_{15}H_{16}O_2$ | 78.91 | 78.89 | 7.07 | 7.07 |
| $NO_2$ | OH | .. | 176–176.5 | M | $C_{14}H_{13}NO_4$ | 64.86 | 64.84 | 5.05 | 5.05 |
| $NO_2$ | $NH_2$ | .. | 180.5–181.5 | E–W | $C_{14}H_{14}N_2O_3$ | 64.85 | 65.08 | 5.83 | 5.42 |
| $NO_2$ | $OCH_3$ | .. | 62–63 | M–W; P2 | $C_{15}H_{15}NO_4$ | 65.92 | 65.80 | 5.53 | 5.45 |
| Cl | OH | .. | 129–129.5 | E–W | $C_{14}H_{13}ClO_2$ | 67.61 | 67.52 | 5.27 | 5.46 |
| Cl | $NH_2$ | .. | 146–147 | E–W | $C_{14}H_{14}ClNO$ | 67.88 | 67.73 | 5.70 | 5.62 |
| $OCH_3$ | OH | .. | 124.5–125 | E–W | $C_{15}H_{16}O_3$ | 73.75 | 73.48 | 6.60 | 6.59 |
| | | | | Lactones III | | | | | |
| H | ... | I | 126.0–126.5 | Abs. E | $C_{14}H_{13}IO_2$ | 49.43 | 49.40 | 3.85 | 3.99 |
| H | ... | H | 86–87 | M | $C_{14}H_{14}O_2$ | 78.48 | 78.62 | 6.59 | 6.57 |
| H | ... | Br | 123–124 | M–W | $C_{14}H_{13}BrO_2$ | 57.35 | 57.24 | 4.47[c] | 4.74[c] |
| $NO_2$ | ... | I | 134–135 | A-E | $C_{14}H_{12}INO_4$ | 43.66 | 43.76 | 3.14 | 3.22 |
| $NO_2$ | ... | Br | 146.5–147 | M | $C_{14}H_{12}BrNO_4$ | 49.72 | 49.66 | 3.58[d] | 3.69[d] |
| Cl | ... | I | 139.5–140 | A–M; A–E | $C_{14}H_{12}ClIO_2$ | 44.89 | 44.69 | 3.23 | 3.45 |
| Cl | ... | Br | 136–137 | M–W | $C_{14}H_{12}BrClO_2$ | 51.32 | 51.22 | 3.69 | 3.69 |
| $OCH_3$ | ... | I | 152–153 | A–W | $C_{15}H_{15}IO_3$ | 48.67 | 48.37 | 4.08 | 4.13 |

[a] Reported values are for analytical samples crystallized to constant m.p. [b] E = ethanol (95%), M = methanol, W = water, A = acetone, EA = ethyl acetate, P1 = petroleum ether (30–40°), P2 = petroleum ether (60–75°). [c] Calcd.: Br, 27.26. Found: Br, 27.48. [d] Calcd.: Br, 23.53; N, 4.14. Found: Br, 23.80; N, 4.12.

toluene was removed in an air jet, the bromobenzene at reduced pressure (10–20 mm.).

With acid and acid chloride dienophiles, the residue was shaken with 5% sodium bicarbonate solution at room temperature until reaction was complete. The aqueous solution of sodium salts was extracted with ether, treated with Norit, and acidified with hydrochloric acid. The precipitated acids were collected, washed and dried. Ester and amide adducts were dissolved in ethanol, treated with Norit and recovered by evaporation of the ethanol.

**Determination of Unreacted Starting Material.**—In some cases, a portion of the unreacted dienophile could be separated conveniently. For determination of the isomer ratio this was unnecessary, and the amount of dienophile in the crude adduct was determined analytically. With the adducts from acids and acid chlorides, this was done by calculation from the neutral equivalent of the crude adduct. Ester adducts were treated similarly, after alkaline saponification at room temperature.

The amounts of cinnamamide and *p*-chlorocinnamamide in crude adducts derived from these dienophiles were determined from the ultraviolet spectra (obtained on a Cary recording ultraviolet spectrophotometer); their maxima in 95% ethanol fall at 2720 and 2770 Å., respectively, and the intensities obey Beer's law. The pure adducts were clear in this region. Since the adduct of *p*-nitrocinnamamide absorbs in this region, the amount of dienophile in the crude adduct was determined by an empirical matching of the infrared spectrum of the adduct mixture with those of artificial mixtures of dienophile and pure adducts.

**Determination of Isomer Ratios. Iodolactonization.**[8]—The failure of the bromolactonization method already has been discussed.[7] For identification of the pure *endo* adducts, they were brominated in aqueous bicarbonate,[7] and the bromolactones were purified by crystallization. Details are given below and in Table IV.

A sample (0.5–1.0 g.) of the mixed acid adducts from acid, acid chloride or ester dienophiles (the last two were hydrolyzed) was dissolved in 5 ml. of methanol in a centrifuge tube. The solution was almost neutralized with 20% sodium hydroxide solution, and 10 ml. of 5% sodium bicarbonate solution and water were added to make a volume of about 30 ml. The clear solution was treated with 1–2 ml. (an excess) of iodine stock solution[8] (5 g. of iodine, 10 g. of potassium iodide and 30 ml. of water) and allowed to stand for 15 min. The precipitated iodolactone was collected by centrifugation and washed with a little water, then kneaded with 10 ml. of 1% sodium thiosulfate solution. The iodolactone solidified as light tan granules which were washed with two 15-ml. portions of water, dried, and weighed. The loss by solubility of the unsubstituted iodolactone was determined to be 7 mg.; the loss for the substituted iodolactones could scarcely exceed this figure.

The supernatant liquid was treated with sodium thiosulfate to reduce the excess iodine, then acidified. The *exo*-carboxy isomer precipitated, contaminated by any unreacted cinnamic acid. Description of the purification is given in subsequent sections.

**Determination of Isomer Ratios. Infrared.**—As a check on the iodolactonization, the infrared spectrum of a cinnamic acid adduct free from starting material was compared to the spectra of several artificial mixtures of pure *endo* and *exo* adducts. The intensities of the peaks of the unknown lay between 35 and 40% *endo*, comparing very favorably to the value of 37% obtained by iodolactonization.

The spectrum of a sample of cinnamamide adduct which had been largely freed of starting material was compared to those of artificial mixtures of pure *exo*-amide and *endo*-rich samples of known composition (see below); spectrograde acetone was used as solvent. The *p*-nitrocinnamamide adduct could not be freed from starting material, so that various amounts of this dienophile were incorporated in the mixture of pure *exo*- and *endo*-rich amides; dimethylformamide was used as solvent.[18]

**Cinnamic Acid and Cyclopentadiene.**—Isomer ratios were determined from the mixed adduct containing unreacted cinnamic acid. When necessary for preparative work, the bulk of the cinnamic acid was removed by extraction of the crude adduct with petroleum ether (30–40°) or cyclohexane, in which solvents cinnamic acid is almost insoluble.

The pure *endo* adduct was obtained by the following procedure. A sample, 18.0 g., of crude adduct, neut. equiv. 198, was iodinated as described above, giving 11.5 g. of crude iodolactone. This crystallized (Norit) as colorless plates, recovery 9.5 g.

(18) The quantitative infrared spectroscopy was performed on a Perkin-Elmer model 21 recording spectrometer.

In one experiment, an (apparently) polymorphic form of the iodolactone, m.p. 118–119°, was obtained; its analysis agreed well with the calculated value. The infrared spectra of the two samples in carbon disulfide were congruent, and a mixture of the two melted at the higher figure.

A sample (3.4 g., 0.01 mole) of the iodolactone was dehalogenated by shaking it in 100 ml. of absolute ethanol, 8 g. of Raney nickel catalyst and 2 ml. of pyridine under hydrogen for four hours. The mixture was filtered and evaporated, the residue in ether was washed successively with dilute acid, water and 5% sodium bicarbonate solution. The ether was evaporated and the residual lactone was crystallized; yield 66%, m.p. 84.5–85.5°.

The pure *endo* adduct was obtained by adding 8 g. of zinc dust slowly to a solution of 6.8 g. (0.02 mole) of iodolactone in 20 ml. of glacial acetic acid. Heat developed. After three hours, the mixture was filtered, the solid was washed with 75 ml. of hot water, and the combined filtrates were further diluted with water and extracted with ether. The ether was extracted with 5% sodium bicarbonate solution, which on acidification yielded 3.7 g. (87%) of white solid, m.p. 105–106.8°. It depressed the m.p. of the *exo* isomer (see below) to 92°.

The bromolactone was prepared in 90% yield from the pure *endo* isomer.

Bromination of a sample of mixed adducts (neut. equiv. 212) gave a small amount of the same bromolactone. In addition, a few drops of yellow oil were isolated, b.p. 107° (20 mm.), $n^{22.5}D$ 1.6057, analyzing for C, 52.76; H, 3.87. It was not investigated further. A higher-boiling fraction was obtained, b.p. 98–100° (0.25 mm.), $n^{24}D$ 1.6212. This pale yellow oil was analyzed immediately after distillation, giving results indicating a tetrabromo structure. It lost hydrogen bromide after standing for an hour or more. It was not studied further.

*Anal.* Calcd. for $C_{13}H_{12}Br_4$: C, 32.00; H, 2.48. Found: C, 32.10, 32.11; H, 2.63, 2.55 (on separate samples).

An attempt to prepare the amide from the pure *endo*-acid by the action of boiling thionyl chloride and cold aqueous ammonia led to a product of wide melting range which could not be purified. Evidently cyclization or isomerization had taken place.

The *exo* isomer was isolated from the filtrate from the iodolactonization. The white solid, 9.95 g., was boiled with cyclohexane and cooled, giving 2.0 g. of cinnamic acid. The filtrate was evaporated and the residue was dissolved in methanol and treated with Norit. Addition of a little water and cooling gave 4.81 g. of colorless blades. Additional material could be obtained from the filtrate, which also contained more cinnamic acid.

The same *exo* isomer was isolated in another run by removal of the cinnamic acid (cyclohexane) and crystallization of the residue eighteen times from petroleum ether (60–75°) and aqueous methanol. It melted at 113–113.5°, analyzed correctly, and did not depress the melting point of the material described above.

The *exo*-amide was prepared by boiling 1.00 g. of the acid with 5 ml. of thionyl chloride for 30 min., evaporating the excess thionyl chloride, and adding 10 ml. of ice-cold concd. ammonium hydroxide. The solid was filtered, washed and crystallized; 0.70 g. (71%).

The *exo*-methyl ester was prepared from the acid with ethereal diazomethane. It was crystallized twice in a Skau tube, then sublimed at 25° (0.1–0.5 mm.) as a white solid.

**Methyl Cinnamate and Cyclopentadiene.**—The residue after evaporation of the solvent was distilled; the unreacted methyl cinnamate was collected at 70–80° (0.1 mm.). The residue was shaken for 1 hr. at room temperature with methanolic potassium hydroxide, diluted with water, treated with Norit, and acidified. The neutral equivalent of the acidic solid was used to calculate the additional amount of methyl cinnamate not removed by distillation.

**Cinnamoyl Chloride and Cyclopentadiene.**—The residue after removal of the solvent was shaken with 5% sodium bicarbonate solution, and the acids thus obtained were analyzed as described for the acid adducts. In one experiment, the residue was divided into two equal parts. One was hydrolyzed as above and analyzed by neutral equivalent and iodolactonization. The other half was shaken with excess liquid ammonia in dry ether and the resulting amide mixture was washed with water and dried at 0.1 mm. This amide mixture was assumed to have the same *endo–exo* ratio as that determined for the acids obtained from the other half.

**Cinnamamide and Cyclopentadiene.**—In runs with toluene as solvent, the unreacted cinnamamide crystallized on cooling and was removed. In the acetone runs, the solvent was evaporated, and the residue was dissolved in a small amount of hot toluene and cooled to remove the starting material. The toluene solutions were evaporated and the residues were dissolved in ethanol, treated with Norit, evaporated, and dried at 0.1 mm. Traces of cyclopentadiene polymers were not removed by this treatment.

An attempt to hydrolyze the amide adducts to acids by the action of butyl nitrite and dry hydrogen chloride in acetic acid[19] gave only about 10% hydrolysis, although cinnamamide itself was hydrolyzed in 80% yield by this method.

***p*-Nitrocinnamic Acid and Cyclopentadiene.**—*p*-Nitrocinnamic acid was removed readily from the crude adduct by virtue of its insolubility in methanol. The adduct from the methanol filtrate, m.p. 169–171° dec., was recrystallized eight times from methanol, giving a light green solid, m.p. 176–176.5°, unchanged by further crystallization. This pure *exo* isomer formed no iodolactone.

Iodination of a bicarbonate solution of 3.00 g. of a crude adduct, neut. equiv. 243, precipitated 1.1 g. of crude iodolactone. It was dissolved in acetone, treated with Norit, diluted with an equal volume of 95% ethanol, and cooled; 0.6 g. of a light green solid crystallized.

No attempt was made to prepare the pure *endo*-acid, since the zinc–acetic acid treatment would surely reduce the nitro group.

The solid acid, 2.2 g., from the iodolactonization filtrate was dissolved in warm absolute methanol, diluted with water, and cooled to give 1.3 g. of light greenish-yellow solid *exo*-acid, m.p. 175–176°. Two more crystallizations gave pale green needles, m.p. 176–176.5°. Its melting point was not depressed when it was mixed with the sample of *exo* adduct obtained by direct crystallization.

The *exo*-amide was prepared in 62% yield.

The *exo*-methyl ester, prepared with diazomethane, was a pale green solid.

A sample of adduct was prepared from 4.83 g. (0.025 mole) of *p*-nitrocinnamic acid and 6.6 g. (0.1 mole) of freshly distilled cyclopentadiene at 55° for 4.5 weeks. The bicarbonate solution of the crude product was treated with 1.5 ml. of bromine. The mixture was extracted with ether, which upon evaporation deposited 3.25 g. of solid, m.p. 105–116°. It was crystallized four times from methanol, giving 0.65 g. of pale green solid, m.p. 119.5–120°, identical with 3-bromo-5-*p*-nitrophenylnortricyclene prepared from the pure *exo*-acid. From the mother liquors, by evaporation and five crystallizations from methanol, there was isolated 0.2 g. of light green solid, the bromolactone derived from the *endo* isomer. The pure *exo* isomer does not form a rearranged bromolactone.[7]

**Methyl *p*-Nitrocinnamate and Cyclopentadiene.**—The residue, after removal of the solvent, was crystallized from methanol (Norit) to give 89% of mixed adduct as light green crystals, m.p. 67–70°. The stereoisomers could not be separated by chromatography on alumina or Magnesol–Celite.

*Anal.* Calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53. Found: C, 65.71; H, 5.49.

A sample of the mixed adducts, 2.0 g., was shaken with 1 g. of potassium hydroxide in 20 ml. of ethanol for 1 hr. at room temperature. The somewhat dark solution was diluted with 100 ml. of water, treated with Norit, and acidified to give 1.6 g. (84%) of mixed acids, m.p. 159–164°. This mixture was shown to be 28% *endo* by iodolactonization. A sample was re-esterified with diazomethane to give mixed esters of m.p. 66–69°, and the infrared spectra (carbon disulfide) of the original and regenerated esters were practically identical. Thus alkaline hydrolysis had not caused isomerization.

***p*-Nitrocinnamamide and Cyclopentadiene.**—It was not possible to remove unreacted starting material from the crude adduct without risk of loss of the latter. The mixed amide was very resistant to butyl nitrite–hydrogen chloride or alkaline hydrolysis. The *endo*-rich sample of amide

(19) N. Sperber, D. Papa and E. Schwenk, THIS JOURNAL, **70**, 3091 (1948).

for infrared analysis was prepared from the *p*-nitrocinnamoyl chloride–cyclopentadiene adduct as described above under the cinnamamide adduct.

***p*-Chlorocinnamic Acid and Cyclopentadiene.**—Most of the unreacted *p*-chlorocinnamic acid crystallized on cooling the toluene solutions. The iodolactone, prepared in the usual way, was reductively cleaved by zinc as described above. The *endo*-acid was obtained as a white solid in 81% yield, m.p. 138–139.5°.

The bromolactone was prepared from the pure *endo*-acid.

The filtrate from the iodolactonization produced a mixture of *p*-chlorocinnamic acid and the *exo* adduct. When treated with methanol, most of the remaining *p*-chlorocinnamic acid remained undissolved. The adduct was isolated from the filtrate by crystallization.

***p*-Methoxycinnamic Acid and Cyclopentadiene.**—No adduct could be detected in a reaction run at 55° for 5 weeks. Adducts were isolated from reactions in refluxing toluene, longer times giving higher yields. Unreacted *p*-methoxycinnamic acid crystallized on cooling.

The pure *endo* adduct was prepared by reductive cleavage of the iodolactone with zinc in 95% yield.

The *exo*-acid, obtained from the iodolactonization filtrate, was separated from the *p*-methoxycinnamic acid by two crystallizations.

**Miscellaneous Experiments.**—The adduct from methyl *p*-chlorocinnamate was an oil which did not crystallize and was heavily contaminated with cyclopentadiene polymers. No further investigation of it was made.

*p*-Dimethylaminocinnamic acid and its methyl ester did not form adducts at 55° for long times. The acid did not form an adduct at 110°, but the ester was not investigated.

ANN ARBOR, MICHIGAN

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

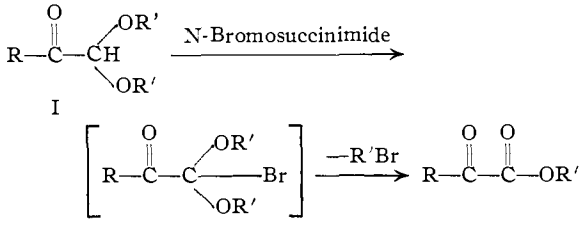
# Reaction of Dialkylacetals of α-Ketoaldehydes with N-Bromosuccinimide. A New Synthesis for α-Ketoesters

BY JOHN B. WRIGHT

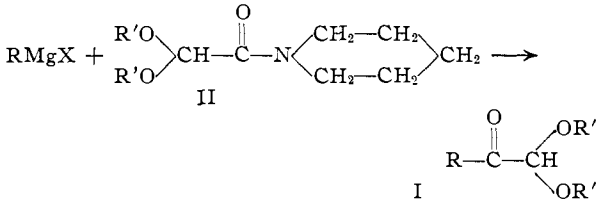
RECEIVED APRIL 27, 1955

Dialkylacetals of α-ketoaldehydes (I), on treatment with N-bromosuccinimide, were found to be converted to α-ketoesters in very good yield.

We have found that acetals of α-ketoaldehydes react with N-bromosuccinimide to give the corresponding α-ketoesters in very good yield. Since the requisite acetals (I) can be prepared readily in




excellent yield by the reaction of Grignard reagents with dialkoxyacetylpiperidines[1] (II), this represents a convenient two-step synthesis of α-ketoesters from Grignard reagents.

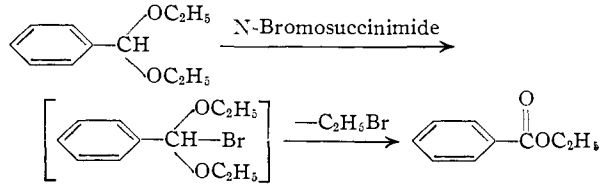


The reaction with N-bromosuccinimide was carried out with pyruvaldehyde diethylacetal (I, R = $CH_3$; R' = $C_2H_5$), pyruvaldehyde dibutylacetal (R = $CH_3$; R' = $n$-$C_4H_9$), *t*-butylglyoxal diethylacetal (R = $(CH_3)_3C$; R' = $C_2H_5$) and phenylglyoxal diethylacetal (R = $C_6H_5$; R' = $C_2H_5$). The yields varied from 72 to 78%. The reactions were carried out in the usual way using carbon tetrachloride as the solvent. When the reaction was complete, the solvent was removed and the residue distilled *in vacuo*.

(1) A. Wohl and M. Lange, *Ber.*, **41**, 3615 (1908); *cf.* also the Experimental part of paper.

In the case of the pyruvaldehyde acetals, bromination on the carbon not containing the alkoxy groups to give α-bromopyruvaldehyde dialkylacetals was possible. As a matter of fact, Mowat[2] has reported the preparation of α-bromopyruvaldehyde diethylacetal by the bromination of pyruvaldehyde diethylacetal with bromine. We have found, however, that when the bromination is carried out with N-bromosuccinimide in the presence of light the reaction proceeds in a different manner and essentially pure pyruvate esters are obtained.

Marvell and Joncich[3] have reported that benzaldehyde diethylacetal reacts with N-bromosuccinimide to give ethyl benzoate and they have postulated a somewhat analogous course for this reaction.




## Experimental[4,5]

**Bromination of Pyruvaldehyde Diethylacetal with N-Bromosuccinimide. Preparation of Ethyl Pyruvate.**—In a flask fitted with an efficient reflux condenser equipped with a calcium chloride tube was added 57.5 g. (0.394 mole) of freshly distilled pyruvaldehyde diethylacetal, 70.2 g. (0.394 mole) of N-bromosuccinimide[6] and 288 ml. of dry carbon tetrachloride. The mixture was heated by a 250-watt drying lamp placed about 12 inches below the flask. As soon as the mixture began to reflux the light was turned

(2) J. H. Mowat, U. S. Patent 2,436,073.

(3) E. N. Marvell and M. J. Joncich, THIS JOURNAL, **73**, 973 (1951).

(4) All boiling points reported are uncorrected.

(5) We wish to thank Mr. W. A. Struck and his associates of these laboratories for the microanalytic data reported herein, Dr. J. L. Johnson for the infrared data, and Mr. A. Barton for technical assistance.

(6) Purchased from Arapahoe Chemical Co., Boulder, Colo.