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On the Reaction of the Half Ester of 2-Methylpropylidene Malonic Acid with *N*-Bromosuccinimide. Preparation of Ethyl Methyl (*E*)-2-Bromo-2-methylpropylidenemalonate

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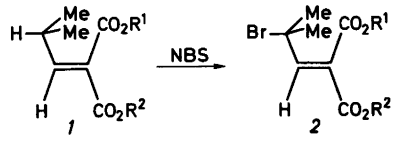
In addition to normal allylic bromination, a secondary reaction, bromodecarboxylation, takes place when the half esters of 2-methylpropylidene malonic acid react with *N*-bromosuccinimide (NBS). Of the two isomeric half esters the one having the carboxyl group on the same side as the bromoisopropyl group (*E*-isomer) undergoes this secondary reaction most easily, while there are strong indications that the *Z* isomer rearranges to the *E* isomer before reaction. The preparation of the isomerically pure ethyl methyl (*E*)-2-bromo-2-methylpropylidenemalonate is described.

In connection with a study of the stereochemistry of cyclopropane formation from allylic halides carrying electronegative γ-substituents,[1,2] we wanted to synthesize one of the two stereoisomers of the mixed diester *2a* (*E*) or *2b* (*Z*). Knoevenagel condensation of ethyl methyl malonate with isobutyraldehyde led to nonseparable mixtures of *1a* and *1b*. Allylic bromination of the isomer mixture to give *2a* and *2b* did not give any improved separation possibilities. Even use of *t*-butyl methyl malonate as the ester component did not lead to separation. However, we succeeded in synthesizing pure *2a* (*E* isomer) in the following way. Hydrogen



Scheme 1. a: R^1=Me, R^2=Et (*E*); b: R^1=Et, R^2=Me (*Z*); c: R^1=R^2=Me; d: R^1=Me, R^2=H (*Z*); e: R^1=H, R^2=Me (*E*).

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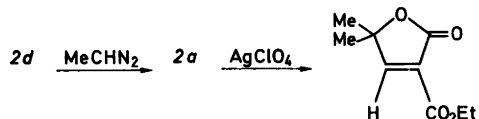
methyl malonate was condensed with isobutyraldehyde to give fair yields of mixtures of half esters *1d* and *1e*. Far better yields of *1d* and *1e* (≈50:50 mixture) were obtained by partial hydrolysis of *1c*. The isomer mixture could not be separated chromatographically. Therefore, the mixture was treated with one molar equivalent of *N*-bromosuccinimide (NBS). A substantial amount (about 30 %) of unreacted half ester indicated that secondary reactions of either *2d* or *2e* (or both) with NBS had taken place at a rate comparable with the primary reaction of *1d* or *1e* with NBS. When 1.5 molar equivalent of NBS was used essentially all the starting material was consumed and ^{1}H NMR indicated the presence of three compounds, *viz.* *2d*, *2e* and a new compound, *3*. Column chromatography yielded *3* in a pure state, while *2d* and *2e* could not be separated by this method. However, fractional crystallization gave one of the isomers in a pure crystalline state. Subsequent esterification of this compound with diazoethane gave *2a*. Its configuration as the *E* isomer was proven in the following way: As dimethyl γ-bromoalkylidene malonates could be converted to α-methoxycarbonyl-$\Delta^{\alpha,\beta}$-butenolides upon treatment with silver perchlorate,[3] the formation of α-ethoxycarbonyl-$\Delta^{\alpha,\beta}$-butenolide *4*[4] as the only product from the analogous reaction with *2a* strongly supported the stereochemical assignment (Scheme 2).



Scheme 2.

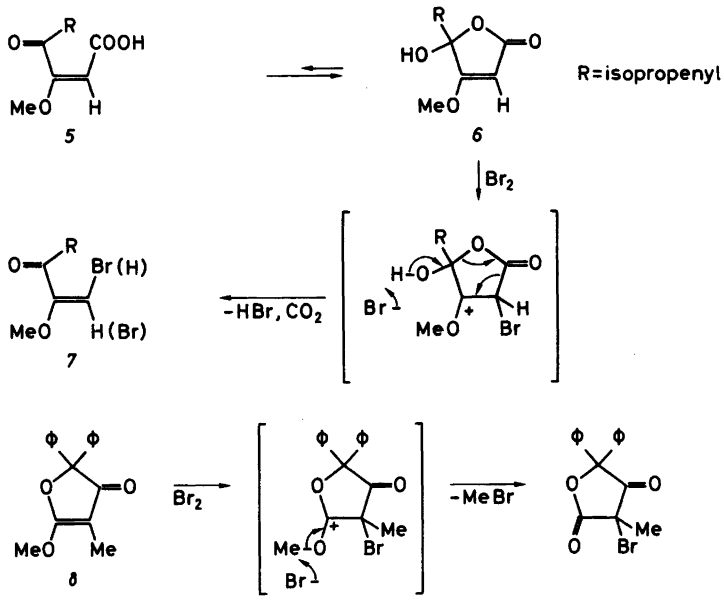
Compound *3* was neutral and had a composition of $C_7H_{10}Br_2O_2$, indicating that decarboxylation had taken place. ^1H and ^{13}C NMR spectroscopy revealed that a bromine atom had replaced the carboxyl group.

Halodecarboxylation takes place in the well-known Hunsdiecker reaction where silver carboxylates react with halogen.[5] In protic solvents (water, methanol or acetic acid) bromodecarboxylation products are formed in the reaction of bromine with some thiophene carboxylic acids.[6] Chlorodecarboxylation of carboxylic acids with lead tetraacetate and lithium chloride in refluxing benzene has been described,[7] and the use of *N*-chlorosuccinimide as chloride source in such halodecarboxylation is demonstrated.[8] In the latter procedure, however, mixtures of polar nonprotic and protic solvents were used. Only one report of bromodecarboxylation using NBS is found in the literature, *viz.* with penicillic acid (*5*⇄*6*) and analogues.[9] Neither the reaction mechanism nor the stereochemistry of the products (*7*) were discussed in this report. However, it seems clear that the analogy to our results is rather weak since the substrate penicillic acid is found to exist predominantly in the lactol form *6* (Scheme 3).[10]

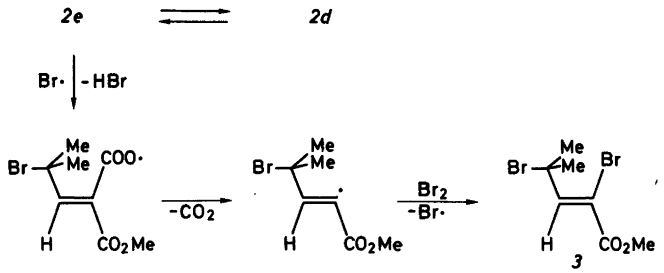
It is not unlikely that lactol *6* reacts with bromine (formed in small amounts in NBS reactions) in a manner analogous to the reaction of 2,2-diphenyl-5-methoxy-4-methylfuranone *8* (Scheme 3).[11]

Thus, there are no reports of bromodecarboxylation in the reaction of NBS with α,β-unsaturated acids. For reasons discussed below, substrates where allylic bromination could take place *cis* to the carboxylic acid are of special interest to us. *cis*-Alkyl-α,β-unsaturated acids were isomerized to the *trans* compounds before being brominated.[12a] 3-Methyl-2-butenoic acid (β,β-dimethyl acrylic acid), however, gave a mixture of the isomeric monobromo acids with no sign of bromodecarboxylated products.[13]

A straightforward decision on the stereochemistry of *3* could not be made. It appeared from ^1H NMR monitoring of the reaction of NBS with the mixture of *1d* and *1e* that the two isomers were brominated in the allylic position at comparable rates. Bromodecarboxylation, however, seemed to take place faster with *2a* (*E* isomer) where the carboxyl group is *cis* to the bromoisopropyl group. In view of the complicated reaction picture involved by having at least four compounds present, *viz.* *1d*, *1e*, *2d* and *2e*, all able to react with NBS, it was decided to simplify the reaction. α-Bromoisobutyraldehyde was condensed with methyl hydrogen malonate[14] to give a nonseparable mixture of *2d* and *2e*. Unfortunately, during this reaction considerable



Scheme 3.



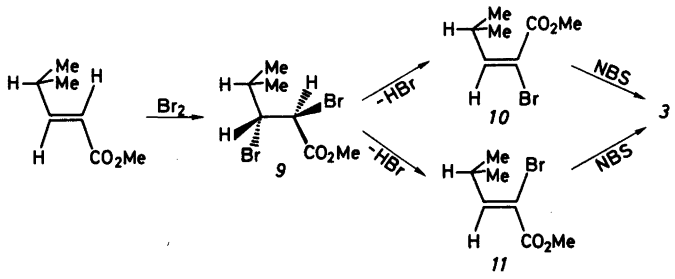
Scheme 4.

amounts of *2e* was transformed to α-methoxycarbonyl-γ,γ-dimethyl-$\Delta^{\alpha,\beta}$-butenolide *13*.[3] However, as shown in the Experimental section, it was possible to obtain an approximately equimolar mixture of *2d* and *2e*. ^{1}H NMR monitoring of the reaction of this mixture with NBS demonstrated that the *E* isomer (*2e*) reacted faster to give *3*. Pure *Z* isomer *2d* reacted very slowly with NBS to give *3*, and, again using ^{1}H NMR monitoring, it was shown that *2d* isomerized to *2e before* bromodecarboxylation took place. Small peaks in the ^{1}H NMR spectra indicating the presence of the *E* isomer of *3* was observed, but the compound could not be isolated by column chromatography. Thus the following reaction route to *3* may be envisaged (Scheme 4).

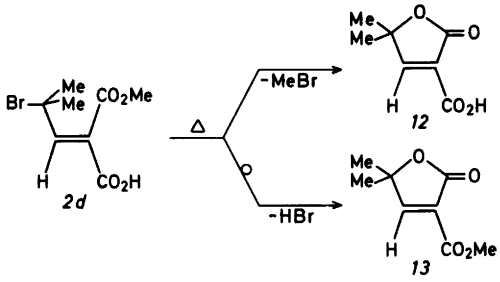
A chemical confirmation of the suggested structure of *3* was obtained by bromination of methyl 4-methyl-2-pentenoate and subsequent dehydrobromination of the isomerically pure dibromo ester *9*. Interestingly both the *E* and *Z* isomers (*10* and *11*) were formed (45 % *E* and 55 % *Z* isomer), probably through carbanion inversion in the first step in an ElcB-reaction. When the isomer mixture was reacted with NBS, only *3* was formed (Scheme 5).

Reaction of the isomer mixture with 0.1 molar equivalent NBS showed that the *E* isomer was transformed into the *Z* isomer before bromination took place.[12,15] Additional indications of the correct choice of stereochemistry for *3* were obtained from ^{1}H NMR spectroscopy. The olefinic protons in *10* and *11* appeared at 6.4 and 7.0 ppm and the low field value was assigned to *Z* isomer *11* as this proton will experience a deshielding due to the ester carbonyl group.[16] Allylic bromination of *1c*→*2c* lead to a downfield shift of the olefinic proton of ≈ 0.4 ppm.[3] Thus one should expect a chemical shift of about 7.4 ppm for the olefinic proton of *3*, observed value 7.57 ppm. Moreover, the aforementioned supposed *E* isomer of *3* exhibited an absorption at 7.25 ppm, most likely the olefin proton signal. Additionally, the olefinic signal from *Z*-2-bromo-2-butenoic acid appeared at 7.60 while the analogous signal from the *E* form appeared at 7.10 ppm.[12a]

As mentioned before, *Z* isomer *2d* rearranged to the *E* isomer *2e* during the reaction with NBS. On heating at 78 °C (boiling tetrachloromethane) in the absence of NBS and radical initiator *2d* slowly isomerized to *2e*. Prolonged heating (~30 h) gave lactone *13* as the only product. Heating at 140 °C for 1 h (tetrachloroethane) *2d* gave mixtures of lactones *12* and *13*.[3] The relative yield showed an interesting variation with concentration, ranging from *13*:*12* = 45:55 using 0.09 M concentration to 70:30 in 0.7 M solution (Scheme 6).



Scheme 5.



Scheme 6.

EXPERIMENTAL

General. Melting points (uncorrected) were determined on a micro hot-stage. IR spectra were recorded on a Perkin-Elmer 457 Grating Infrared Spectrophotometer, ^{1}H NMR spectra on a Varian HA 100-15 D spectrometer operating at 98 MHz, ^{13}C NMR spectra on a JEOL FX-60 FT NMR spectrometer. Elemental analyses were performed by I. Beetz, West Germany.

Partial hydrolysis of dimethyl 2-methylpropylidenemalonate (1c). *1c* (111.6 g, 0.6 mol) was dissolved in MeOH (85 ml) and KOH (35.3 g, 0.63 mol) dissolved in MeOH (150 ml) was added and the solution was left overnight in the refrigerator. MeOH was evaporated, water added and the aqueous solution extracted with ether to remove 7.7 g of a mixture containing starting material, *dimethyl 2-methyl-1-propenylmalonate* and *methyl 4-methyl-3-pentenoate* (GLC). The aqueous solution was acidified and extracted with ether to give 55.3 g crude product which was distilled twice to give 28.8 g of a somewhat impure 50:50 (approx.) mixture of the *Z* and *E* isomer of *methyl hydrogen 2-methylpropylidenemalonate* (*1d* and *ie*). Using column chromatography (SiO_2, tetrachloromethane – ether, 98:2) the impurities were removed but the isomers could not be separated.

Reaction of the isomer mixtures of 1d *and* 1e *with* N-*bromosuccinimide* (NBS). The isomer mixture (*ca.* 50:50 – 17.2 g, 0.1 mol) NBS (26.7 g, 0.15 mol), dibenzoyl peroxide (100 mg) and tetrachloromethane (100 ml) was refluxed for 45 min. The usual work-up gave 27.4 g crude product. 6 g of this product were dissolved in tetrachloromethane and applicated on an SiO_2 column. Elution with tetrachloromethane gave 1.9 g of *methyl 2,4-dibromo-4-methyl-2-pentenoate* (3). B.p. 81 – 84 °C/0.4 mm Hg. Found: C 29.9, H 3.6, Br 55.6. Calc. for $C_7H_{10}Br_2O_2$: C 29.4, H 3.5, Br 55.9. ^{1}H NMR (CCl_4): δ 7.57 (1H,s), 3.80 (3H,s), 2.06 (6H,s). ^{13}C NMR (CCl_4): δ 161.9 (C1), 147.5 (C3), 115.0 (C2), 57.1 (C4), 53.1 (CH_3O), 33.8 2×CH_3). IR (film): 1745 (s), 1630 (s) cm^{-1}. The column was stripped with 100 ml tetrachloromethane – ether (1:1) giving 4.1 g of an oil which was crystallized from tetrachloromethane to give *methyl hydrogen* (Z)-*2-bromo-2-methylpropylidenemalonate* (2d). M.p. 103 – 104 °C. Found: C 38.1, H 4.4, Br 31.1. Calc. for $C_8H_{11}BrO_4$: C 38.3, H 4.4, Br 31.8. ^{1}H NMR (CCl_4): δ 12.16 (1H, s), 7.22 (1H, s), 3.86 (3H, s), 1.99 (6H, s). ^{13}C NMR (CCl_4): 169.0 and 165.4 (2×C=O), 150.4 (Cβ), 123.8 (Cγ), 57.5 (Cα), 32.8 (2×CH_3). Treatment of *2d* with equimolar amounts of etheral diazomethane gave *2c*.[3]

Reaction of ethyl methyl (E)-*2-bromo-2-methylpropylidenemalonate* (2a) *with silver perchlorate. 2a* was made by treatment of *2d* with etheral diazoethane. B.p. 86 – 88 °C/0.05 mm Hg. Anal. C, H, Br. ^{1}H NMR (CCl_4): δ 7.03 (1H, s), 4.26 (2H, q, J=7 Hz), 3.80 (3H, s), 1.94 (6H, s), 1.34 (3H, t, J=7 Hz). *2a* (0.84 g, 3 mmol) was dissolved in ethyl acetate (25 ml) and cooled to −45 °C. Silver perchlorate monohydrate (0.72 g, 3.2 mmol) was dissolved in ethyl acetate (25 ml) and cooled to −45 °C. After mixing precipitation of silver bromide occurred almost spontaneously and after standing for 2 h the solvent was evaporated. Chloroform was added to the residue, silver bromide filtered off, and the filtrate was carefully washed with water, dried ($MgSO_4$) and the solvent was evaporated to give 0.50 g of an oil identified as *α-ethoxycarbonyl-γ,γ-dimethyl* $\Delta^{\alpha,\beta}$*-butenolide* (4).[4]

Synthesis of 3. Methyl 4-methyl-2-pentenoate (12.8 g, 0.1 mol) was dissolved in tetrachloromethane (100 ml) and bromine (16.8 g, 0.105 mol) dissolved in tetrachloromethane (100 ml) was added slowly keeping the reaction temperature below 5 °C (protected from light). The solution was placed in the refrigerator overnight, then the solvent was evaporated and the residue distilled. B.p. 112 °C/12 mm Hg. Yield 19.0 g. *Methyl 2,3-dibromo-4-methylpentanoate* (9). Anal. C, H, Br. ^{1}H NMR ($CDCl_3$): δ 4.46 (2H, broad singlet, assigned to protons at C2 and C3), 3.82 (3H, s), 2.40 (1H, sept., J=6.5 Hz), 1.11 (3H, d, J=6.5 Hz), 0.93 (3H, d, J=6.3 Hz). ^{13}C NMR ($CDCl_3$): δ 168.4 (C1), 61.3 (C2), 53.1 (OCH_3), 46.0 (C3), 29.4 (C4), 21.9 and 15.1 (2×Me). *9* (9.7 g – 33.6 mmol) was dissolved in methanol (30 ml) and dry potassium acetate (3.6 g – 37 mmol) was added and the solution was refluxed for 24 h. After dilution with ice-water, extraction with ether followed by washing the ether solution with sodium bicarbonate solution and finally drying ($MgSO_4$), gave 6.4 g product, b.p. 59 – 62 °C/0.5 mm Hg. ^{1}H NMR showed that both the *E* and *Z* isomer (*10* and *11*) of *methyl 2-bromo-4-methyl-2-pentenoate* were formed. The mixture contained approximately 45 % *E* and 55 % *Z* isomer. ^{1}H NMR (CCl_4): *Z* isomer: δ 6.99 (1H, d, J=9 Hz), 3.76 (3H, s), ~2.9 (m, 1H), 1.09

(6H, d, $J=6.5$ Hz); *E* isomer 6.36 (1H, d, $J=10$ Hz), 3.76 (3H, s), ~3.3 (m, 1H), 1.05 (6H, d, $J=6.5$ Hz).

Mixture of *10* and *11* (4.6 g, 22 mmol) was dissolved in tetrachloromethane (35 ml), *N*-bromosuccinimide (4.35 g, 24.4 mmol) and dibenzoylperoxide (50 mg) was added and the solution refluxed for 4 h. Usual work-up gave 6.0 g of crude product shown by ^{1}H NMR to be identical to *3*.

Hydrolysis of α-methoxycarbonyl-γ-γ-dimethyl-$\Delta^{\alpha,\beta}$-butenolide (13). *13* (2.0 g) was heated in 6 N HCl (20 ml) for 3 h and the mixture was evaporated to dryness to give 1.8 g of a white residue, *α-carboxy-γ,γ-dimethyl-$\Delta^{\alpha,\beta}$-butenolide* (12), m.p. 136–137 °C ($CHCl_3$). Anal. C, H. ^{1}H NMR ($CDCl_3$): δ 10.7 (1H, s), 8.49 (1H, s), 1.76 (6H, s). IR ($CHCl_3$): 2500–3500 (s), 1770 (s), 1725 (s) cm^{-1}.

Thermal decomposition of 2d. *A. At 140 °C.* Four solutions of *2d* in tetrachloroethane (molarity 0.09, 0.28, 0.47 and 0.70, respectively) were heated in NMR-tubes at 140 °C for 1 h. Integration of the ^{1}H NMR spectra (olefinic protons) gave concentration ratios of approx. 45:55, 60:40, 70:30 and 70:30 of the products *13* and *12*.

B. At 78 °C. 2d (100 mg) was dissolved in tetrachloromethane and heated at reflux temperature. ^{1}H NMR monitoring indicated a slow isomerization to *2e*. After about 30 h only absorbtion signals from lactone *13* were observed.

Condensation of 2-bromo-2-methylpropanal with methyl hydrogen malonate Tetrahydrofuran (500 ml) was cooled in an icebath and $TiCl_4$ (55 ml, 0.5 mol) dissolved in tetrachloromethane (125 ml) was added slowly with vigorous stirring. The bromoaldehyde (37.8 g, 0.25 mol, made by reaction of bromine with the 2-methylpropanal in the presence of calcium carbonate[17]) and the half-ester (29.5 g, 0.25 mol) dissolved in tetrahydrofuran (80 ml) was then added dropwise. Finally pyridine (80 ml, 1 mol) dissolved in tetrahydrofuran (150 ml) was added very slowly. After 20 h at room temperature water (250 ml) and ether (250 ml) was added and the phases separated. The organic phase was washed with water, dried and the solvents evaporated. 49.7 g light brown oil was obtained, shown by ^{1}H NMR to contain approx. 40 % *2d*, 20 % *2e* and 40 % *13*. Ether (25 ml) was added to the oil and the solution left overnight at −35 °C. Crystals (14.7 g) were filtered off and identified as the $\Delta^{\alpha,\beta}$-butenolide *13*.[4] Pentane (10 ml) was added and the solution was again left overnight at −35 °C. Crystals (10.7 g) were filtered off and identified as *2d*. The filtrate was evaporated and the residue subjected to column chromatography (SiO_2, tetrachloromethane–ether). Fractions containing approx. equal proportions of *2d* and *2e* were collected.

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