

Synthesis, Stereochemistry, and Isomerisation of α -Phenylethylidene-succinic Esters and Related Compounds

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The lack of stereoselectivity in the Stobbe condensation involving acetophenone or diethyl α -phenylethylidene-succinate can be attributed to *E2* elimination through both diastereoisomeric lactone intermediates, base catalysed isomerisation of ester reactant or product(s), or a combination of these reactions.

THE Stobbe condensation of unsymmetrical aryl ketones with succinic esters does not show the stereoselectivity usually found with aromatic aldehydes.¹⁻³ Condensation of acetophenone with diethyl succinate gives a 1 : 1 mixture of ethyl (*E*)- and (*Z*)- α -phenylethylidenesuccinates (1a) and (1b),^{1,4,5} while with benzaldehyde, only ethyl (*E*)-benzylidenesuccinate is obtained.⁶ The base catalysed isomerisation of (*E*)-benzylidenesuccinic acid, reported by Stobbe,⁷ could not be substantiated.⁸

The lack of stereoselectivity in the case of aryl ketones can be explained by base catalysed isomerisation of succinic ester reactant and product(s), and by eclipsing effects in the *E2* reaction of the intermediate lactones (or the *E1cB* reaction of the lactone anions) leading to the arylmethylidenesuccinic half esters.

E2 and *E1cB* Reactions show a strong preference for *trans*-elimination⁹ and are influenced markedly by steric interactions in the transition state.¹⁰ For example, the 1-bromo-1,2-diphenylpropanes (4) and (5) undergo

E2 elimination to yield (*Z*)- and (*E*)-1,2-diphenylprop-1-enes (6) and (7), in 93 and 94% yield, respectively. The latter reaction is five times faster than the former. Since the diastereoisomeric diphenylbromopropanes (4) and (5) have similar thermodynamic stability, the difference in rate of elimination relates to the difference in stability of their transition states leading to elimination. The transition state from conformer (4) of the *threo*-isomer is destabilised by interaction between the two phenyl groups to a greater extent than is the transition state from conformer (5) of the *erythro*-isomer having interactions between phenyl and methyl groups.¹⁰

Following from Johnson's mechanism¹¹ for the Stobbe reaction, we suggest that the condensation of aromatic aldehydes with succinic esters yields two diastereoisomeric lactones (8; R = H) and (9; R = H) but that only one can adopt the antiperiplanar conformation (8; R = H) favoured for *E2* elimination, giving a

¹ W. S. Johnson and G. H. Daub, *Org. Reactions*, 1951, **6**, ch. 1.

² H. G. Heller and B. Swinney, *J. Chem. Soc. (C)*, 1967, 2452.

³ R. J. Hart and H. G. Heller, *J. Chem. Soc. (C)*, 1972, 1321.

⁴ H. Stobbe, *Annalen*, 1899, **308**, 114; 1911, **380**, 36.

⁵ G. H. Daub and W. S. Johnson, *J. Amer. Chem. Soc.*, 1948, **70**, 418; 1950, **72**, 501.

⁶ H. Stobbe and E. Koepfel, *Ber.*, 1894, **27**, 2405.

⁷ H. Stobbe, *Ber.*, 1908, **41**, 4350.

⁸ R. J. Hart, Ph.D. Thesis, Aberystwyth, 1970.

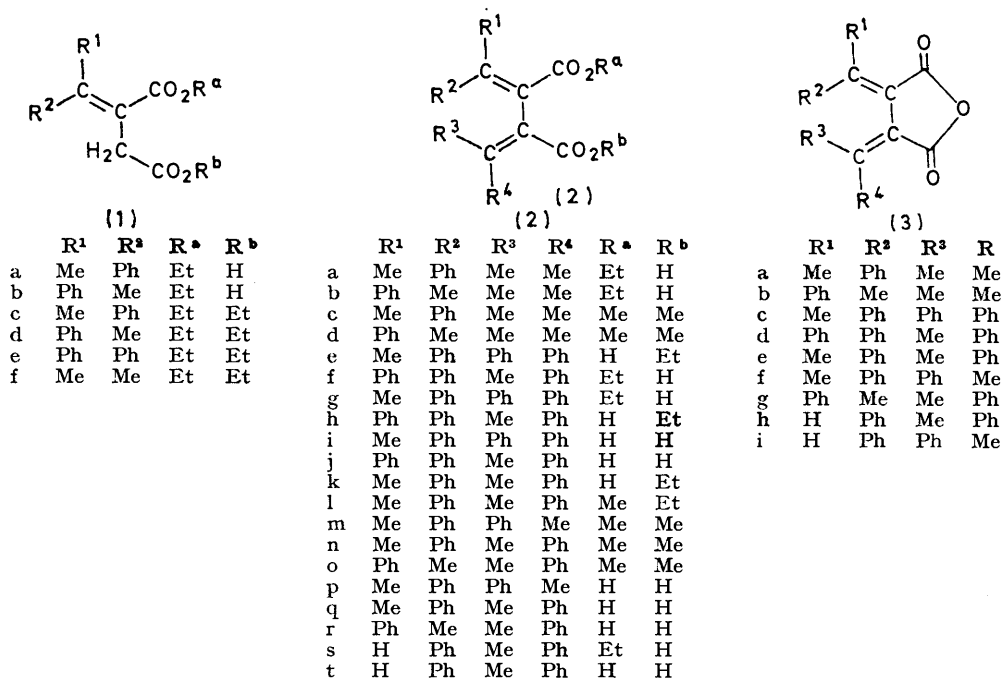
⁹ E. D. Hughes, C. K. Ingold, and R. Pasternak, *J. Chem. Soc.*, 1953, 382.

¹⁰ D. J. Cram, F. D. Greene, and C. H. Depuy, *J. Amer. Chem. Soc.*, 1956, **78**, 790.

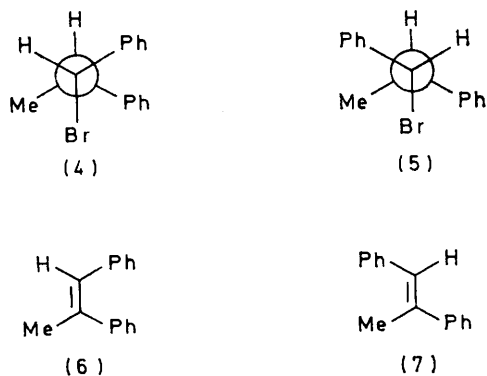
¹¹ D. A. Dunnigan, W. S. Johnson, and A. L. McCloskey, *J. Amer. Chem. Soc.*, 1950, **72**, 514.

transition state with no eclipsing effects between phenyl and ester groups, and allowing maximum overlap of the developing *p*-orbitals.³ The analogous conformer (9A; R = H) from the other lactone gives rise to an unfavourable transition state, having severe steric interactions between eclipsed phenyl and ester groups, preventing coplanarity and overlap of the forming *p*-orbitals. Conformer (9B; R = H) lacks the necessary *transoid* arrangement between the parts of the eliminant.

part, why mixtures of ethyl (*E*)- and (*Z*)- α -phenylethylidenesuccinates (1a) and (1b) are obtained. Condensations involving mesitaldehyde and 2,6-dichlorobenzaldehyde give (*Z*)-arylmethylenesuccinic esters in good yield.¹² In these cases, the steric interactions of the *ortho*-substituents with the lactone ring in conformer (8) must disturb the fine balance between steric and electronic effects controlling the relative stability of the two transition states for elimination.

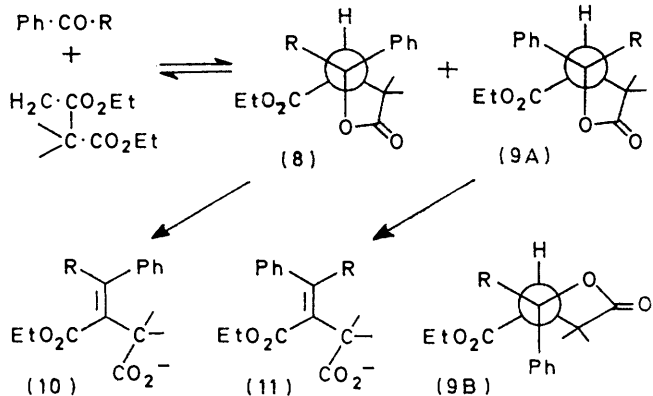


Thus lactone (9) does not undergo elimination to yield the (*Z*)-arylmethylenesuccinic ester anion (11), but



gives back the reactants, which can recombine to give lactone (8) which undergoes elimination to yield the (*E*)-arylmethylenesuccinic half ester anion (10). When aryl ketones such as acetophenone are involved, the stability of the transition state from the conformer (8; R = Me) for one lactone is reduced by the steric interactions between methyl and ester groups, and the transition state from conformer (9B; R = Me) of the other lactone becomes of similar stability, explaining, in

Stobbe reported that *E-Z*-isomerisation occurred in the condensation of diethyl (*E*)- α -phenylethylidenesuccinate (1c) with acetone, as subsequent hydrolysis gave a mixture of (*E*)- and (*Z*)-isopropylidene-(α -phenylethylidene)succinic acids.¹³ On repeating this reaction, a 40 : 60



mixture of (*E*)- and (*Z*)-half esters (2a) and (2b) were obtained, but on hydrolysis, each half ester gave a mixture of (*E*)- and (*Z*)-isopropylidene(α -phenylethylidene)succinic acids. The diacids were converted into

¹² H. G. Heller and R. M. Megit, *J.C.S. Perkin I*, 1974, 923.

¹³ H. Stobbe and F. Gademann, *Annalen*, 1911, **380**, 39.

was determined by measuring the relative intensity by integration of characteristic absorptions of each component.

EXPERIMENTAL

U.v. spectra were measured with a Unicam SP 1800A spectrometer: n.m.r. spectra were obtained for solutions in deuteriochloroform with a Perkin-Elmer R12 (60 MHz) or a Varian HA100 (100 MHz) spectrometer (tetramethylsilane as internal standard). Condensations were carried out under nitrogen using freshly distilled or recrystallised reactants, and solvents which had been dried by distillation from sodium hydride. Petrol refers to light petroleum, b.p. 60–80°. Reactants were added dropwise to a stirred boiling solution of potassium *t*-butoxide in *t*-butyl alcohol.^{1,15} After heating for the period stated, the reaction mixture was cooled, acidified with 5*M*-hydrochloric acid and the solvent removed under reduced pressure. The residue was dissolved in ether, extracted with 4*M*-sodium carbonate solution, and the aqueous extracts acidified. The liberated half esters were extracted with ether, and the ethereal solution was dried (MgSO₄), filtered, and evaporated. The residual half esters were hydrolysed by boiling with 7% aqueous potassium hydroxide solution (3 h) and the diacids were liberated by addition of 5*M*-hydrochloric acid. Diacids were converted into their corresponding anhydrides by boiling (1 h) with acetyl chloride (20 ml per g of acid). Acetyl chloride was removed and the anhydride purified as described.

α-Phenylethylidenesuccinic Acid Derivatives.—A mixture of diethyl succinate (180 g, 1.1 mol) and acetophenone (120 g, 1 mol) was added dropwise to a cooled stirred suspension of sodium hydride (50 g; 60% dispersion in oil; 1.4 mol) in benzene (250 ml) containing a few drops of ethanol to initiate the exothermic reaction. After 1.5 h at 12–25°, ethanol was added to decompose any unchanged sodium hydride and the solvent was removed under reduced pressure. Work-up by the general procedure described gave a 50 : 50 mixture of ethyl (*E*)- and (*Z*)-*α*-phenylethylidenesuccinate (1a) and (1b) as a pale yellow oil (187 g, 84% yield). Trituration of the oil with benzene and petrol gave the (*Z*)-half ester (1b) (64 g), cubes from ether–petrol, m.p. 111–112° (lit.,⁵ 111–112°). Esterification with hydrogen chloride in ethanol gave only the (*Z*)-diethyl ester (1d) (64 g, 90% yield), b.p. 138–140° at 0.5 mmHg. Diethyl (*Z*)-*α*-phenylethylidenesuccinate (1d) (2.7 g) was boiled (40 min) with a solution of potassium *t*-butoxide (1.14 g) in *t*-butyl alcohol (60 ml). Work-up by the general procedure gave a neutral fraction containing a 66 : 34 mixture of diethyl (*E*)- and (*Z*)-*α*-phenylethylidenesuccinates (1c) and (1d).

Isopropylidene-(α-phenylethylidene)succinic Acid Derivatives.—Diethyl isopropylidenesuccinate (1f)¹⁶ (10.7 g, 0.05 mol), acetophenone (6 g, 0.05 mol), and potassium *t*-butoxide (6 g, 0.06 mol) in *t*-butyl alcohol (250 ml), heated for 10 min, gave a pale yellow oil (11.5 g, 80% yield) consisting of a 40 : 60 mixture of ethyl (*E*)- and (*Z*)-isopropylidene-(*α*-phenylethylidene)succinate (2a) and (2b). Fractional crystallisation of the oil from ether–petrol gave the (*Z*)-half ester (2b), (4.5 g, 25% yield), cubes, m.p. 120–121°. A second crop of crystals gave the (*E*)-half ester (2a) (1.2 g, 11% yield), plates, m.p. 121–122°. A mixed m.p. determination showed a marked depression. Hydrolysis of the (*E*)- and of the (*Z*)-half esters (2a) and (2b) gave an

¹⁵ W. S. Johnson, J. W. Petersen, and W. P. Schneider, *J. Amer. Chem. Soc.*, 1947, **69**, 74.

80 : 20 and a 30 : 70 mixture of (*E*)- and (*Z*)-isopropylidene-(*α*-phenylethylidene)succinic acids [from the composition of the mixture of dimethyl esters (2c) and (2d) obtained by the action of diazomethane on the mixture of diacids]. The diacids (10 g), gave a mixture of anhydrides as an oil which solidified on trituration with ethanol. Fractional crystallisation from petrol gave (*Z*)-isopropylidene-(*α*-phenylethylidene)succinic anhydride (3b) (3 g), needles, m.p. 112° (lit.,¹³ 112°), λ_{\max} (hexane) 297 nm (log ϵ 4.03). A second crop of crystals gave (*E*)-isopropylidene-(*α*-phenylethylidene)succinic anhydride (3a), yellow needles, m.p. 132–133° (lit.,¹⁷ 132–133°), λ_{\max} (hexane) 226 and 301 nm (log ϵ 4.13 and 4.50).

Diphenylmethylene-(α-phenylethylidene)succinic Acid Derivatives.—Diethyl (*Z*)-*α*-phenylethylidenesuccinate (1d) (9.2 g, 0.3 mol), benzophenone (6.1 g, 0.3 mol), and potassium *t*-butoxide (4 g, 0.4 mol) in *t*-butyl alcohol (200 ml), heated for 10 min, gave a yellow oil (7.5 g, 56%) consisting of a 55 : 45 mixture of ethyl (*E*)- and (*Z*)-diphenylmethylene-(*α*-phenylethylidene)succinate (2e) and (2f) respectively. The oil, on treatment with ether–petrol, gave ethyl (*E*)-diphenylmethylene-(*α*-phenylethylidene)succinate (2e) (0.6 g), plates, m.p. 185–186°.

Diethyl diphenylmethylenesuccinate (1e) (34 g, 0.1 mol), acetophenone (12 g, 0.1 mol), and potassium *t*-butoxide (12 g, 0.11 mol) in *t*-butyl alcohol (600 ml), heated for 10 min, gave a pale yellow oil (38 g, 93% yield) consisting of a 35 : 65 mixture of ethyl (*E*)- and (*Z*)-diphenylmethylene-(*α*-phenylethylidene)succinate. Fractional crystallisation of the oil from ether–petrol gave the (*Z*)-half ester (2h) (12.5 g), needles, m.p. 115–116°. A second crop of crystals gave the (*E*)-half ester (2g) (3.5 g), plates, m.p. 172–173°, and a final crop of crystals (11.6 g) was a mixture of half esters. Hydrolysis of either (*E*)- or (*Z*)-half esters, or the mixture of (*E*)- and (*Z*)-half esters gave, in each case, an 80 : 20 mixture of the (*E*)- and (*Z*)-diphenylmethylene-(*α*-phenylethylidene)succinic acids, (2i) and (2j) respectively. The mixed (*E*)- and (*Z*)-diacids (10.5 g) gave an 80 : 20 mixture of the corresponding (*E*)- and (*Z*)-diphenylmethylene-(*α*-phenylethylidene)succinic anhydrides (3c) and (3d) respectively. Crystallisation of the mixed anhydrides from chloroform–petrol gave the (*E*)-anhydride (3c) (5.5 g), orange plates, m.p. 204–205° (Found: C, 81.7; H, 5.0. C₂₅H₁₈O₃ requires C, 81.9; H, 4.95%), λ_{\max} (CHCl₃) 303 and 381 nm (log ϵ 4.13 and 3.83). The (*Z*)-isomer (3d) was not isolated.

Bis-(α-phenylethylidene)succinic Acid Derivatives.—Diethyl (*Z*)-*α*-phenylethylidenesuccinate (1d) (15 g, 0.06 mol), acetophenone (6.8 g, 0.06 mol), and potassium *t*-butoxide (6.8 g, 0.07 mol) in *t*-butyl alcohol (200 ml), heated for 30 min, gave an orange oil (14.6 g, 81% yield) consisting of a 55 : 30 : 15 mixture of ethyl (*E,E*)-, (*E,Z*)-, and (*Z,Z*)-bis-(*α*-phenylethylidene)succinates, respectively. On trituration with ether–petrol, the oil gave the (*E,Z*)-half ester (2k) (3.6 g), prisms from ether–petrol, m.p. 158–160°. The (*E,Z*)-half ester (2k) (1 g) was esterified with methanol and hydrogen chloride, giving ethyl methyl (*E,Z*)-bis-(*α*-phenylethylidene)succinate (2l) (0.88 g, 84% yield), rods from petroleum (30–40°), m.p. 80–80.5° (Found: C, 75.8; H, 6.7. C₂₃H₂₄O₄ requires C, 75.8; H, 6.6%). The (*E,Z*)-ethyl methyl ester (2l) (0.2 g) was boiled (3 h) with a solution of sodium methoxide [from sodium (0.64 g)] in methanol (30 ml). Work-up gave a 55 : 30 : 15 mixture of dimethyl

¹⁶ C. G. Overberger and C. W. Roberts, *J. Amer. Chem. Soc.*, 1949, **71**, 3618.

¹⁷ H. Stobbe, *Ber.*, 1905, **38**, 3673.

(*E,E*)-, (*E,Z*)-, and (*Z,Z*)-bis-(α -phenylethylidene)succinates, (2m), (2n), and (2o) respectively. No isomerisation occurred when the (*E,Z*)-ethyl methyl ester (2l) was boiled in methanol.

Hydrolysis of the (*E,Z*)-half ester (2k) (2 g) gave a 55 : 30 : 15 oily mixture of (*E,E*)-, (*E,Z*)-, and (*Z,Z*)-bis-(α -phenylethylidene)succinic acids (2p), (2q), and (2r) respectively, from which the (*E,Z*)-diacid (2q) (0.19 g) separated on trituration with ether-petrol. The (*E,Z*)-diacid (2q) (0.19 g) gave (*E,Z*)-bis-(α -phenylethylidene)succinic anhydride (3e) (0.15 g), yellow prisms from chloroform-petrol, m.p. 139° (Found: C, 78.55; H, 5.4. $C_{20}H_{16}O_3$ requires C, 78.9; H, 5.3%), λ_{max} (CHCl₃) 283 and 331 nm (log ϵ 3.97 and 3.99).

The mixture of diacids (1.8 g) gave a 55 : 30 : 15 mixture of the corresponding (*E,E*)-, (*E,Z*)-, and (*Z,Z*)-anhydrides (3f), (3e), and (3g), respectively, from which (*Z,Z*)-bis-(α -phenylethylidene)succinic anhydride (3g) (0.15 g) separated on trituration with ether, colourless cubes from chloroform, m.p. 215—216°, which give yellow solutions (Found: C, 79.0; H, 5.4. $C_{20}H_{16}O_3$ requires C, 78.9; H, 5.3%), λ_{max} (CHCl₃) 328 nm (log ϵ 4.14). The ether filtrate was evaporated and the residue crystallised from chloroform-petrol. The (*E,Z*)-anhydride (3e) (0.3 g) separated first. A second crop of crystals gave (*E,E*)-bis-(α -phenylethylidene)succinic anhydride (3f) (0.6 g), fine yellow needles from petrol, m.p. 175—176° (Found: C, 79.0; H, 5.2. $C_{20}H_{16}O_3$ requires C, 78.9; H, 5.3%), λ_{max} (CHCl₃) 289 nm (log ϵ 4.13).

Benzylidene-(α -phenylethylidene)succinic Acid Derivatives.
—Diethyl (*Z*)- α -phenylethylidenesuccinate (1d) (13.8 g,

0.05 mol), benzaldehyde (4.8 g, 0.05 mol), and potassium t-butoxide (6.4 g, 0.06 mol) in t-butyl alcohol (400 ml) were heated for 40 min to give ethyl (*E*)-benzylidene-(*Z*)- α -phenylethylidene succinate (2s) (14 g, 84% yield), plates from aqueous ethanol, m.p. 139—140°. Hydrolysis of the (*E,Z*)-half ester gave the corresponding (*E,Z*)-diacid (2t) (80% yield), prisms from benzene, m.p. 224—226°. The (*E,Z*)-diacid (2t) (12.5 g) yielded (*E*)-benzylidene-(*Z*)- α -phenylethylidenesuccinic anhydride (3h) (9.5 g, 77% yield), yellow needles from benzene-petrol, m.p. 120—121° (Found: C, 78.6; H, 4.7. $C_{19}H_{14}O_3$ requires C, 78.65; H, 4.9%), λ_{max} (hexane) 278 and 341 nm (log ϵ 4.02 and 4.07).

A 50 : 50 mixture of diethyl (*E*)- and (*Z*)- α -phenylethylidenesuccinates (1c) and (1d) (15 g, 0.05 mol), benzaldehyde (7.4 g, 0.07 mol), and sodium ethoxide [from sodium (5 g, 0.2 mol)] in ethanol (250 ml) gave the sodium salt of the succinic half ester, which was filtered off and hydrolysed, yielding (*E,E*)-benzylidene-(α -phenylethylidene)succinic acid (6.5 g, 48% yield), prisms from methanol, m.p. 212—214° (lit.,¹⁸ 212—214°). (*E,E*)-Benzylidene-(α -phenylethylidene)succinic anhydride (3i) was obtained from the (*E,E*)-diacid in 72% yield, yellow prisms from benzene-petrol, m.p. 148° (lit.,¹⁸ 148°), λ_{max} (hexane) 285 and 344 nm (log ϵ 4.23 and 3.89).

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¹⁸ H. Stobbe, *Annalen*, 1911, **380**, 55.