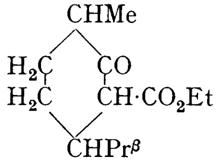
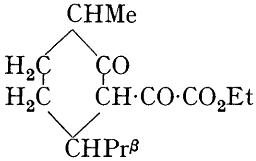
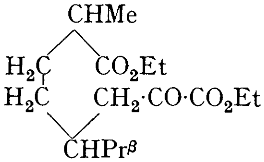
# **66.** *Syntheses in the Sesquiterpene Series. Part II. The Condensation of Ethyl Oxalate and Tetrahydrocarvone.*

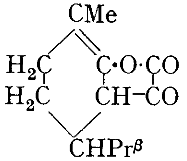
By A. E. Bradfield, E. R. Jones, and J. L. Simonsen.

For the synthesis of sesquiterpenes derived from eudalene, cyclic β-ketonic esters appeared likely to be of value, since they would permit of the introduction of the angular methyl group. Kötz and his collaborators (for a summary, see Kötz and Meyer, *J. pr. Chem.*, 1913, **88**, 261) have shown that these esters are conveniently prepared by the condensation of cyclic ketones with ethyl oxalate; and, as a preliminary to the use of less readily accessible ketones, the condensation of *l*-tetrahydrocarvone and ethyl oxalate has been studied. Under the conditions described on p. 316 we were unable to isolate the ketonic ester (I), the main product being *ethyl* α-*keto*-ζ-*methyl*-γ-iso*propylsuberate* (III), the primary condensation product (II) evidently undergoing ring fission in the presence of the sodium ethoxide. The ring fission of cyclic ketonic esters by sodium ethoxide has been observed frequently (*inter al.*, Kötz and Schüler, *Annalen*, 1906, **350**, 217; Kötz, *ibid.*, 1907, **357**, 192), the facility with which it proceeds showing considerable variation, but so far as we are aware this reaction does not as a rule proceed at low temperatures.


(I.)


(II.)


(III.)


(IV.)

Ethyl α-keto-ζ-methyl-γ-*iso*propylsuberate is a mixture of the ketonic and the enolic form, and derivatives of both have been prepared. Its high molecular refraction, $[R_L]_D$ 81·16, compared with 79·44 and 80·49 calculated for the ketonic and the enolic form respectively, suggests that it exists mainly as the enol.

Oxidation of the keto-acid with hydrogen peroxide in alkaline solution gave *d*-α-methyl-δ-*iso*propylpimelic acid (compare Ruzicka and Trebler, *Helv. Chim. Acta*, 1920, **3**, 762), which was characterised by its *diamide*, m. p. 181—182°, and *di*-p-*toluidide*, m. p. 156—157°. When the keto-acid was warmed with concentrated sulphuric acid, ring closure occurred with the formation of the *lactone* of $\Delta^1$-*menthen*-2-*ol*-3-*glyoxylic acid* (IV), m. p. 115°. Like other lactones of this type, it decomposed readily on exposure to the air and it was hydrolysed by alkali to the parent ketone (*l*-tetrahydrocarvone) and oxalic acid.

Kötz and Meyer (*loc. cit.*, p. 271) found that the condensation of *l*-menthone with ethyl oxalate by sodium ethoxide in ligroin solution gave as the main product the lactone of

$\Delta^3$-menthen-3-ol-2-glyoxylic acid. Repetition of this condensation under conditions similar to those used for *l*-tetrahydrocarvone has shown that, though this lactone is formed in small quantity, the normal condensation product, ethyl menthone-2-carboxylate (Gardner, Perkin, and Watson, J., 1910, **97**, 1770), can be readily isolated. We obtained no evidence of the occurrence of ring fission.

## EXPERIMENTAL.

*Condensation of* l-*Tetrahydrocarvone and Ethyl Oxalate.*—To sodium ethoxide (alcohol, 100 c.c.; sodium 7·7 g.) cooled in ice–salt, a cooled mixture of *l*-tetrahydrocarvone ($[\alpha]_{5461}$ $-$ 20·3°; 51 g.) and ethyl oxalate (49 g.) was added gradually. After 36 hours at 0° the deep red solution was poured on a mixture of ether, dilute sulphuric acid, and ice, the ethereal layer separated, and the aqueous solution extracted twice with ether. The combined extracts were dried, the solvent removed, and the residual oil heated under diminished pressure (20 mm.) at 130—180° (bath-temperature); vigorous evolution of gas occurred and a distillate (10·5 g.) of ethyl oxalate and *l*-tetrahydrocarvone was collected; the residue distilled at 155—160°/2 mm. (yield, 63·5 g.). When a portion of the crude ester (30 g.) was digested with methyl-alcoholic potash (400 c.c.; potassium hydroxide, 30 g.), potassium oxalate (2 g.) separated. The filtrate was distilled in steam and the oil (4 g.) obtained, b. p. 99—100°/16 mm., was shown to be *l*-tetrahydrocarvone by the preparation of the 2 : 4-*dinitrophenylhydrazone*, m. p. 133°, crystallising from alcohol in orange-red plates (Found : N, 16·4. $C_{16}H_{22}O_4N_4$ requires N, 16·8%). The alkaline solution from the steam distillation was concentrated, acidified, and extracted with ether; $\alpha$-keto-$\xi$-methyl-$\gamma$-*iso*propylsuberic acid (23 g.) remained as a gum on removal of the solvent. The *silver* salt was an amorphous solid (Found : Ag, 47·6. $C_{12}H_{18}O_5Ag_2$ requires Ag, 47·2%). The *ethyl* ester (alcohol–sulphuric acid) was a faintly yellow oil, b. p. 148·5/1·4 mm., $d_{25°}^{25°}$ 1·003, $n_D^{25°}$ 1·4548, $[\alpha]_{5461}$ + 7·7 (Found : C, 64·3; H, 9·6. $C_{16}H_{28}O_5$ requires C, 64·0; H, 9·3%); it gave an intense purple coloration with alcoholic ferric chloride, was readily soluble in sodium hydroxide, but insoluble in sodium carbonate solution, and its 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in fine yellow needles, m. p. 50° (Found : C, 54·7; H, 6·8. $C_{22}H_{32}O_8N_4$ requires C, 55·0; H, 6·7%). The *acetyl* derivative, prepared by digesting the ester with acetic anhydride and a drop of pyridine for 2 hours, was a colourless oil, b. p. 163°/2 mm.; it gave no colour with ferric chloride (Found : C, 63·2; H, 8·7. $C_{18}H_{30}O_6$ requires C, 63·2; H, 8·8%). The *methyl* ester was an almost colourless oil, b. p. 153°/2·5 mm., which gave a violet coloration with ferric chloride (Found : C, 61·4; H, 9·1. $C_{14}H_{24}O_5$ requires C, 61·7; H, 8·8%).

*Oxidation of $\alpha$-Keto-$\xi$-methyl-$\gamma$-*iso*propylsuberic Acid with Hydrogen Peroxide.*—To a solution of the keto-acid (6 g.) in sodium hydroxide (15 c.c.; sodium hydroxide, 2·5 g.) (ice) hydrogen peroxide (100-vol., 3·5 c.c.) was gradually added. After the vigorous reaction had ceased, the mixture was warmed on the water-bath, cooled, acidified, and extracted with ether; $\alpha$-methyl-$\delta$-*iso*propylpimelic acid (5·4 g.), b. p. 186—188°/1·5 mm., $[\alpha]_{5461}$ + 12° (in ethyl alcohol; $c$ = 6·2), was obtained as a faintly yellow oil. The *diamide* crystallised from water in needles, m. p. 181—182° (Found : C, 61·5; H, 10·5. $C_{11}H_{22}O_2N_2$ requires C, 61·7; H, 10·3%), and the *di*-p-*toluidide* from dilute alcohol in lustrous plates, m. p. 156—157° (Found : C, 75·8; H, 8·8. $C_{25}H_{34}O_2N_2$ requires C, 76·1; H, 8·6%).

*Lactone of $\Delta^1$-Menthen-2-ol-3-glyoxylic Acid.*—The keto-acid mixed with ten times its weight of concentrated sulphuric acid was heated at 80—85° for 10 minutes, and the cooled solution poured on ice. The brownish-green solid that separated was collected and dissolved in warm aqueous ammonia (*d* 0·880); on cooling, the ammonium salt crystallised in long prisms which decomposed on exposure to the air. After two recrystallisations from aqueous ammonia, the salt was decomposed with hydrochloric acid and the *lactone* was collected and thrice crystallised from dilute alcohol (charcoal), being obtained in long prisms, m. p. 115°, $[\alpha]_{5461}$ + 104° (in alcohol; $c$ = 1·25). The lactone decomposed somewhat rapidly on exposure to the air, but could be kept for weeks in an evacuated desiccator [Found : C, 69·5, 69·3; H, 7·7, 7·9; *M* (Rast), 212. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%; *M*, 208]. The 2 : 4-*dinitrophenylhydrazone* crystallised from dilute alcohol in small orange-red prisms, decomp. 95° (Found : C, 53·5; H, 5·7. $C_{18}H_{20}O_6N_4,H_2O$ requires C, 53·2; H, 5·4%). When digested with aqueous sodium hydroxide, the lactone decomposed with formation of *l*-tetrahydrocarvone (2 : 4-dinitrophenylhydrazone) and oxalic acid.

*Condensation of* l-*Menthone and Ethyl Oxalate.*—*l*-Menthone ($\alpha_{5461}$ $-$ 23°; 15·4 g.) was condensed with ethyl oxalate under conditions similar to those used for the condensation of *l*-tetrahydrocarvone. Fractional distillation of the product readily resolved it into two fractions, (i) — 130°/3 mm. and (ii) 165—195°/3 mm. From the lower-boiling fraction, ethyl menthone-2-carboxylate, b. p. 136—137°/9 mm., $d_{25^\circ}^{25^\circ}$ 0·996, $n_D^{25^\circ}$ 1·4660, $[\alpha]_{5461}$ + 44·2°, was isolated (Found : C, 69·1; H, 9·5. Calc. : C, 69·0; H, 9·7%). The higher-boiling fraction partly crystallised on keeping; the solid, after being washed with ligroin (b. p. 40—60°), crystallised from ligroin (b. p. 60—80°) in needles, m. p. 138° (softening at 100°) (Kötz and Meyer give m. p. 142·5°), $[\alpha]_{5461}$ + 12° (in alcohol; *c* = 1·8) (Found : C, 69·2; H, 7·9. Calc. : C, 69·2; H, 7·7%). As observed by Kötz and Meyer, the lactone decomposed on exposure to the air, but it was stable in a low vacuum. With alcoholic ferric chloride it gave a green colour, which changed through brown to red on keeping. When digested with alkali it gave menthone (2 : 4-dinitrophenylhydrazone, m. p. 144° alone and in admixture) and oxalic acid. It differed from the isomeric lactone derived from *l*-tetrahydrocarvone in being readily soluble in sodium carbonate solution.

The authors are indebted to the Government Grants Committee of the Royal Society and to Imperial Chemical Industries, Ltd., for grants, and one of them to the University of Wales for a Studentship.

UNIVERSITY COLLEGE OF NORTH WALES, BANGOR.

[*Received, January 8th,* 1935.]