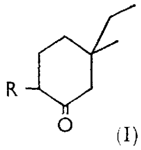
The Chemistry of Fungi. Part LIV.[1] The Synthesis of (±)-5-Ethyl-2,5-dimethylcyclohexanone and of (±)-3-Ethyl-3-methyl-6-oxoheptanoic Acid

By J. N. T. Gilbert, A. J. Hannaford, K. Minami, and W. B. Whalley

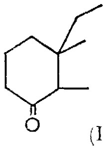
The substances named in the title have been synthesised. They are the racemates of the corresponding optically active compounds derived from ring C of rosenonolactone.

ALKALINE degradation of rosoic acid,[2] derived from the fungal diterpene rosenonolactone, furnishes, *inter alia*, (—)-5-ethyl-2,5-dimethylcyclohexanone (I; R = Me). We now report the synthesis of the racemate of this ketone and of several derivatives.

Thus, in accord with general principles, methylation of 3-ethyl-3-methylcyclohexanone[3] (I; R = H), by way of the pyrrolidine enamine[4] gave a mixture (which was separated by gas–liquid chromatography) of (±)-5-ethyl-2,5-dimethylcyclohexanone (I; R = Me), together with lesser amounts of the isomeric (±)-3-ethyl-2,3-dimethylcyclohexanone (II).



(I)



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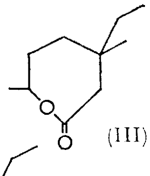
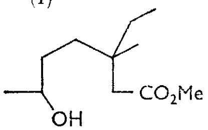
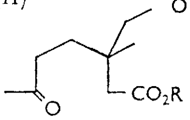


(III)



(IV)



(V)

The infrared spectrum (film and in $CHCl_3$) of (±)-(I; R = Me) and of the natural ketone, were identical. The semicarbazone and the 2,4-dinitrophenylhydrazone of (±)- (I; R = Me) had infrared spectra identical with the corresponding spectra of the derivatives[5] obtained from the optically active ketone (I; R = Me). Reduction of (±)- (I; R = H) gave rise to (±)-3-ethyl-3-methylcyclohexanol. Repeated attempts to resolve the hydrogen phthalate of this alcohol, with, *e.g.*, strychnine, brucine, and dehydroabietylamine, were unsuccessful. We also failed to resolve (±)-3-ethyl-3-methylcyclohexanone by way of the (—)-menthylhydrazone.[6]

Oxidation of (±)-5-ethyl-2,5-dimethylcyclohexanone (I; R = Me) with trifluoroperacetic acid furnished the lactone (III) which was converted by way of the hydroxy-ester (IV) and the keto-ester (V; R = Me) into (±)-3-ethyl-3-methyl-6-oxoheptanoic acid (V; R = H). The semicarbazone of this acid had an infrared spectrum (in $CHCl_3$ and in Nujol) identical with that of the corresponding optically active acid derived by ozonolysis[5] of (—)-5-ethyl-2,5-dimethylcyclohexanone.

EXPERIMENTAL

(±)-5-*Ethyl*-2,5-*dimethylcyclohexanone*.—A mixture of (±)-3-ethyl-3-methylcyclohexanone[3] (40 g.), pyrrolidine (40 g.), and benzene (150 ml.) was heated under reflux with azeotropic removal of water until reaction was complete (2 hr.). All solvent was removed *in vacuo* and benzene (100 ml.) and methyl iodide (50 ml.) were added to the residue: the mixture was then heated under reflux for 24 hr. After addition of water (50 ml.) the mixture was refluxed for a further hour, cooled, acidified with 2N-sulphuric acid, and extracted with ether. The product was purified by distillation followed by gas–liquid chromatography using a 7 ft. column packed with Apiezon L at 150° and a hydrogen

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[2] A. Harris, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 1958, 1799.

[3] R. Pummerer, F. Aldebert, and H. Sperber, *Annalen*, 1953, **583**, 191.

[4] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, 1963, **85**, 207.

[5] A. Robertson, W. R. Smithies, and E. Tittensor, *J. Chem. Soc.*, 1949, 879.

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flow rate of 130 ml./min., to give (*a*), (±)-3-ethyl-3-methylcyclohexanone (*ca.* 10 g.) and (*b*), a mixture (*ca.* 15 g.) of (±)-5-ethyl-2,5-dimethylcyclohexanone and (±)-3-ethyl-2,3-dimethylcyclohexanone. This mixture was separated on an aluminium column (15 ft. × $\frac{5}{8}$ in.) packed with Embacel, 60—100 mesh, using a column temperature of 147°, a hydrogen flow rate of 200 ml./min., and an Autoprep A700 to give (±)-5-*ethyl*-2,5-*dimethylcyclohexanone* as the major component, retention time 39·5 min., with $\nu_{max.}$ (film) 1700 (ketone) cm.$^{-1}$ (Found: C, 77·5; H, 11·8. $C_{10}H_{18}O$ requires C, 77·8; H, 11·8%). The *semicarbazone* formed needles, m. p. 177—178° from methanol (Found: C, 63·5; H, 9·9; N, 19·0. $C_{11}H_{21}N_3O$ requires C, 62·5; H, 10·0; N, 19·9%). The 2,4-*dinitrophenylhydrazone* formed orange plates, from ethanol, m. p. 157° (Found: C, 57·7; H, 6·4; N, 16·7. $C_{16}H_{22}N_4O_4$ requires C, 57·5; H, 6·6; N, 16·8%).

The minor component of the mixture was (±)-3-*ethyl*-2,3-*dimethylcyclohexanone* (retention time 43 min.) with $\nu_{max.}$ (film) 1710 (ketone) cm.$^{-1}$ (Found: C, 78·2; H, 11·4. $C_{10}H_{18}O$ requires C, 77·9; H, 11·8%). The infrared spectrum (film and in $CHCl_3$) differed considerably from that of the isomeric ketone. The *semicarbazone* formed needles, m. p. 183—184°, from methanol (Found: C, 62·2; H, 10·3; N, 19·7. $C_{11}H_{21}N_3O$ requires C, 62·5; H, 10·0; N, 19·9%). The infrared spectrum differed considerably from that of the isomeric semicarbazone. The mixed m. p. of the semicarbazone was *ca.* 168—172°. The close proximity of the retention times of the two cyclohexanones made it very difficult, even by repeated cycling, to prepare them in quantity uncontaminated by the respective isomer.

Reduction of (±)-3-ethyl-3-methylcyclohexanone (10 g.) dissolved in ethanol (100 ml.) and water (5 ml.) containing sodium borohydride (2·7 g.) was complete in 24 hr. at room temperature. Purified by distillation, (±)-3-*ethyl*-3-*methylcyclohexanol* (7·3 g.) was a mobile liquid (Found: C, 76·2; H, 13·0. $C_9H_{18}O$ requires C, 76·0; H, 12·8%). Oxidation of this alcohol with Jones' reagent [7] regenerated (quantitatively) the parent cyclohexanone. Prepared from the cyclohexanol (5 g.), phthalic anhydride (6·4 g.), and pyridine (45 ml.) at 100° during 5 hr., the acid *phthalate* formed stout prisms (7·5 g.), m. p. 95—96°, from chloroform (Found: C, 70·4; H, 7·5. $C_{17}H_{22}O_4$ requires C, 70·3; H, 7·6%). The p-*nitrobenzoate* formed needles, m. p. 58°, from methanol (Found: C, 66·1; H, 7·5; N, 4·8. $C_{16}H_{21}NO_4$ requires C, 66·0; H, 7·3; N, 4·8%).

Prepared by the interaction of (−)-menthylhydrazide [6] (7·3 g.) and (±)-3-ethyl-3-methylcyclohexanone (5 g.) in boiling ethanol (30 ml.) and acetic acid (0·5 ml.) during 2 hr., the (−)-*menthylhydrazone* (10 g.) formed needles, m. p. 163—164°, from ethanol $[\alpha]_D^{25}$ −38·4° (*c*, 1·04 in ethanol) (Found: C, 71·5; H, 11·2; N, 8·5. $C_{20}H_{36}N_2O_2$ requires C, 71·4; H, 10·8; N, 8·3%).

(±)-3-*Ethyl*-3-*methyl*-6-*oxoheptanoic Acid*.—A mixture of trifluoracetic anhydride (11·2 ml.), methylene chloride (25 ml.), and 85% hydrogen peroxide (1·7 ml.) was stirred at 0° for 1 hr., and then added during 30 min. to a solution of (±)-5-ethyl-2,5-dimethylcyclohexanone (4·6 g.) in methylene chloride (30 ml.) containing disodium hydrogen phosphate (21·3 g.) at 0°. After attaining room temperature the mixture was heated under reflux for 1 hr. The inorganic salts were then collected and washed with methylene chloride, and the combined methylene chloride solution washed with 2N-sodium carbonate. Distillation gave the *lactone* of 3-ethyl-3-methyl-6-hydroxyheptanoic acid as a liquid (4·6 g.) (Found: C, 69·8; H, 10·6. $C_{10}H_{18}O_2$ requires C, 70·5; H, 10·7%), with $\nu_{max.}$ (film) 1725 (ε lactone carbonyl) cm.$^{-1}$.

A solution of this lactone (1 g.) in methanol (150 ml.) containing sodium (0·25 g.) was heated under reflux for 1 hr., cooled, acidified with 2N-hydrochloric acid, concentrated *in vacuo*, and extracted with ether. Distillation of the product gave (±)-*methyl* 3-*ethyl*-3-*methyl*-6-*hydroxyheptanoate* as an oil (1 g.) (Found: C, 64·6; H, 10·9; OMe, 17·0. $C_{10}H_{19}O_2OMe$ requires C, 65·3; H, 11·0; OMe, 15·4%), with $\nu_{max.}$ (film) 3800 (hydroxyl) and 1725 (ester carbonyl) cm.$^{-1}$. Analysis by g.l.c., using a 2 m. column packed with Apiezon L at 193° with a hydrogen flow rate of 200 ml./min., showed the presence of only one component with a retention time of 27·1 min.

Oxidation of this alcohol with Jones' reagent [7] gave (almost quantitatively) (±)-*methyl* 3-*ethyl*-3-*methyl*-6-*oxoheptanoate* as an oil with $\nu_{max.}$ (film) 1722 (ester carbonyl) and 1705 (aliphatic ketone) cm.$^{-1}$ (Found: C, 66·4; H, 10·0. $C_{11}H_{20}O_3$ requires C, 66·0; H, 10·1%). Analysis by g.l.c., using a 2 m. column packed with Apiezon L at 188° and a hydrogen flow rate of 190 ml./min., showed the presence of only one component, with a retention time of 30·8 min. The *semicarbazone* formed plates, m. p. 103°, from aqueous methanol (Found: C, 55·9; H, 9·1; OMe, 11·5. $C_{12}H_{23}N_3O_3$ requires C, 56·0; H, 9·0; OMe, 12·1%).

Hydrolysis of this ester with 10% methanolic sodium hydroxide readily formed (±)-3-ethyl-3-methyl-6-oxoheptanoic acid (an oil) with $\nu_{max.}$ (film) 1720 (acid carbonyl) and 1710 (aliphatic ketone) cm.$^{-1}$, which was characterised as the *semicarbazone*, which formed needles, m. p. 162° from ethanol (Found: C, 54·0; H, 8·6; N, 18·0. $C_{11}H_{21}N_3O_3$ requires C, 54·3; H, 8·7; N, 17·3%).

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