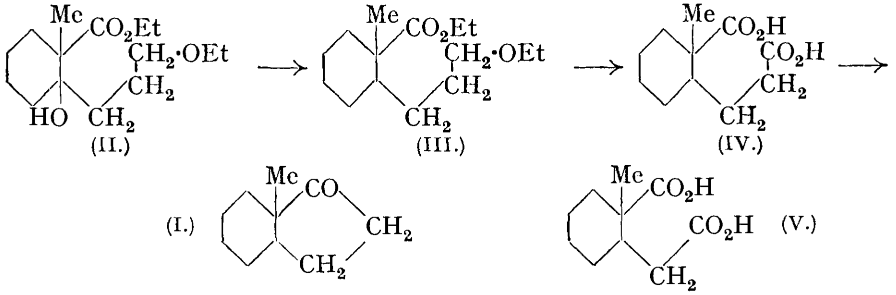
167. *The Synthesis of Dicyclic α-Ketones with an Angular Methyl Group.*

By G. A. R. Kon, R. P. Linstead, and C. Simons.

8-*Methyl*-1-*hydrindanone* (I) contains the essential structure of half the molecule of equilenin, œstrone, and other sex hormones. Its synthesis thus serves as a useful model for those of the natural compounds.

The work which we now describe is part of a general investigation, still in progress, of methods of synthesising α-ketones of this type. We have been led to publish an account of the synthesis of 8-methyl-1-hydrindanone and the corresponding decalone by the appearance of a paper by Chuang, Tien, and Ma (*Ber.*, 1936, **69**, 1494), which describes the preparation of the same compounds by a different method. Our methylhydrindanone, which we believe to be stereochemically homogeneous, differs in some respects from that of the Chinese workers.

The new synthetic method consists in the condensation of ethyl 2-methyl*cyclo*hexanone-2-carboxylate with the Grignard reagent prepared from γ-ethoxypropyl bromide, to the *hydroxy-ester* (II),* which by dehydration and reduction yields the saturated *ester* (III).


(II.) (III.) (IV.) (I.) (V.)

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* Since this paper was written, Robinson and Walker (this vol., p. 61) have described a condensation essentially similar to the above, but did not carry the preparation beyond the first two steps.

This compound showed the expected resistance to hydrolysis and the corresponding ethoxy-acid could only be obtained by repeated treatment with alcoholic potash. The acid on oxidation with chromic acid yielded an acid containing 2-methyl*cyclo*hexane-2-carboxylic-1-β-propionic acid (IV); an indirect method, involving the conversion of the ethoxy-acid into the corresponding iodo-acid and subsequent oxidation, was less successful. The dibasic acid has not so far been isolated in a pure condition, but the crude acid gave, on heating with a little baryta, 8-methyl-1-hydrindanone (I), which could readily be purified by regeneration from the semicarbazone.

Chuang, Tien, and Ma (*loc. cit.*) describe this ketone as a liquid yielding a semicarbazone melting in the crude state at 205—210° and after purification at 213°. Our *semicarbazone* melted in the crude state at 220—222° and after exhaustive crystallisation at 224·5°; the initial material, therefore, was nearly homogeneous. The regenerated *ketone* was a solid, closely resembling camphor (with which it is isomeric) in odour and appearance and melting at 34°. Oxidation of the pure ketone with nitric acid led to 2-methyl*cyclo*hexane-2-carboxylic-1-acetic acid (V), m. p. 163°, identical with that synthesised by Linstead and Millidge (J., 1936, 478, following Chuang, Tien, and Huang, *Ber.*, 1935, **68**, 864). As Chuang, Tien, and Ma's ketone also yielded this acid on oxidation, it is clear that it must have contained a large amount of the same stereoisomeric form; the fact that it was liquid and gave a lower-melting semicarbazone is probably due to the presence of stereoisomeric impurity.

The *trans*-configuration had been provisionally assigned to the acid of m. p. 163° (Linstead and Millidge, *loc. cit.*), but further work by one of us (R. P. L.) and Mr. Walpole casts doubt on this, and for the moment we prefer to leave the question of the configuration of these substances open.

By an entirely similar method we have obtained 9-*methyl*-1-*decalone*, starting with ethyl methyl*cyclo*hexanonecarboxylate and δ-ethoxybutyl bromide. The *semicarbazone* of this compound had the same melting point as that described by Chuang, Tien, and Ma (*loc. cit.*); the ketone regenerated from it was a liquid but otherwise very similar to the ketone (I).

EXPERIMENTAL.

Ethyl 1-*Hydroxy*-2-*methyl*-1-(*γ-ethoxypropyl*)cyclo*hexane*-2-*carboxylate* (II).—60 G. of γ-ethoxypropyl bromide (Noyes, *Amer. Chem. J.*, 1897, **19**, 767), 30 c.c. of ether, and a crystal of iodine were added to 9 g. of magnesium. As the reaction proceeded, 300 c.c. of ether were gradually added; when no further action took place, the solution was decanted from unchanged metal and gradually dropped into an ice-cold ethereal solution of 48 g. of ethyl 2-methyl*cyclo*hexanone-2-carboxylate; a white solid was precipitated. The mixture was boiled under reflux for 2 hours, cooled, and decomposed with ice and dilute hydrochloric acid. The ethereal solution of the products was washed with sodium bicarbonate solution and water and dried over sodium sulphate, the ether distilled off, and the residue fractionated. The desired fraction (50 g.) boiled at 144°/4 mm. (Found: C, 66·0; H, 10·3. $C_{15}H_{28}O_4$ requires C, 66·1; H, 10·4%). A solid acid was not obtained on alkaline hydrolysis.

Ethyl 2-*Methyl*-1-(*γ-ethoxypropyl*)-$\Delta^{6(?)}$-cyclo*hexene*-2-*carboxylate*.—50 G. of the hydroxy-ester were boiled under reflux for 16 hours with 50 g. of oxalic acid and 50 c.c. of water. The acid was then neutralised with caustic soda, the ester extracted with ether, and the extract washed, dried over sodium sulphate, and evaporated, yielding the unsaturated *ester* (40 g.), b. p. 122°/2 mm. (Found: C, 70·4; H, 10·4. $C_{15}H_{26}O_3$ requires C, 70·8; H, 10·3%). The ester was unsaturated to bromine and to tetranitromethane and did not give a solid acid on hydrolysis.

Ethyl 2-*Methyl*-1-(*γ-ethoxypropyl*)cyclo*hexane*-2-*carboxylate* (III).—The unsaturated ester (35 g.) in 40 c.c. of acetic acid (distilled over chromic acid) was shaken with hydrogen and 0·75 g. of Adams's catalyst, 3100 c.c. of hydrogen being taken up. The solution was filtered from the catalyst, and the *ester* isolated by addition of water and extraction with ether, the extract being washed with alkali and water, dried, and evaporated; 33 g. of b. p. 123°/3 mm. were thus obtained and found to be saturated to tetranitromethane (Found: C, 70·8; H, 11·0. $C_{15}H_{28}O_3$ requires C, 70·3; H, 11·0%). The ester was not hydrolysed by boiling with dilute hydrochloric acid (2 : 1) for 6 hours, with 15% aqueous-alcoholic potassium hydroxide for 21 hours, or with a mixture of 3 parts of hydrochloric acid, 4 parts of acetic acid, and 1 part of water for 24 hours. Finally, 49 g. of the ester were boiled under reflux with 20 g. of potassium hydroxide in 70 c.c. of methyl alcohol for 5 hours, the solvent distilled off, and the unchanged ester extracted with ether and re-hydrolysed. After three such treatments 44 g. of crude acid together with 1·5 g. of neutral material were obtained; the acid did not solidify.

2-*Methyl*cyclo*hexane*-2-*carboxylic*-1-β-*propionic Acid* (IV).—(1) An ice-cold suspension of 7 g. of the ester (III) in 20 c.c. of hydriodic acid (saturated at 0°) was saturated with hydrogen iodide, kept for an hour, and then boiled under reflux until no more ethyl iodide was given off. The mixture was extracted with ether, and the iodo-acid (6 g.) recovered from the extract by shaking with alkali and re-acidification. It did not solidify; it was dissolved in 13 c.c. of acetic acid and treated with a solution of 6·5 g. of chromic acid in 6 c.c. of water and 14 c.c. of acetic acid. Much heat was evolved and iodine was liberated; the solution was then boiled for 40 minutes. The cold solution was diluted and extracted with ether, and the acid converted into the silver salt. This decomposed on boiling; the acid was recovered from it by means of nitric acid and isolated in the usual way, but the yield was poor (0·5 g.). The acid was a pasty solid with an equivalent of 134 (Calc. for the acid IV, 107).

(2) 8 G. of the ester (III) in 25 c.c. of acetic acid were treated with 17·5 g. of chromic acid in 60 c.c. of acetic acid. Much heat was evolved; the green solution was freed from acetic acid under reduced pressure and extracted with ether. The residue obtained after removal of the ether was converted into the potassium salt, and the solution filtered from chromium hydroxide and acidified. The acid obtained by extraction with ether had, after removal of traces of acetic acid, an equivalent of 211 and was therefore monobasic; it was presumably the half-ester of the required acid.

(3) The crude ethoxy-acid (44 g.) in 90 c.c. of acetic acid was gradually treated with 65 g. of chromic acid in 130 c.c. of acetic acid and 10 c.c. of water, causing the evolution of much heat. The reaction was completed by warming on the steam-bath for 75 minutes. After addition of 800 c.c. of water the solution was extracted eight times with ether, and the extract evaporated; the residue was distilled under reduced pressure to remove acetic acid and then purified as described under (2) above; 15 g. of crude acid with an equivalent of 130 were obtained. It did not solidify in an evacuated desiccator after a month and a pure silver salt could not be obtained; an attempt to purify it through the ester was also unsuccessful.

8-*Methyl*-1-*hydrindanone* (I).—1·2 G. of crystalline baryta and 15 g. of the crude dibasic acid, freed from the last traces of acetic acid by warming in a high vacuum, were slowly distilled from a Claisen flask kept at 275—320°. The distillate was taken up in ether, washed with dilute caustic soda solution, then water, dried, and distilled, yielding 4 g., b. p. 84°/5 mm., together with 1 g. of a higher fraction. The latter gave but little semicarbazone, whereas the main fraction gave a copious precipitate of a *semicarbazone*, m. p. 224·5° after three crystallisations from methyl alcohol (Found: C, 63·3; H, 9·2. $C_{11}H_{19}ON_3$ requires C, 63·1; H, 9·2%). The *ketone* regenerated from it by means of oxalic acid distilled at 84°/5 mm. as a colourless liquid, which rapidly solidified to a camphor-like mass, m. p. 33—34° (Found: C, 78·1; H, 10·8. $C_{10}H_{16}O$ requires C, 78·9; H, 10·6%).

2-*Methyl*cyclo*hexane*-1-*carboxylic*-2-*acetic Acid* (V).—1·2 G. of the ketone were warmed under reflux for 45 minutes with 6 c.c. of concentrated nitric acid, then for 2 hours longer with the addition of 5 c.c. of water, an all-glass apparatus being used. The solid acid obtained on cooling was recrystallised from very dilute acetic acid, forming a microcrystalline powder, m. p. 162—163°, mixed m. p. with a genuine specimen of the acid 163° (Found: C, 60·2; H, 8·4. Calc. for $C_{10}H_{16}O_4$: C, 60·0; H, 8·1%).

δ-*Ethoxybutyl Bromide*.—The corresponding alcohol was obtained from γ-ethoxypropyl bromide by the method of Palomaa and Jansson (*Ber.*, 1931, **64**, 1606), who used the chloride. The *bromide*, prepared from it by the method used by Noyes (*loc. cit.*) for the preparation of the lower homologue, boiled at 169°, the yield being 35 g. from 47 g. of the alcohol (Found: Br, 43·6. $C_6H_{11}OBr$ requires Br, 44·2%). This preparation and the analysis were first carried out in these laboratories by Dr. P. A. Winsor.

Ethyl 1-*Hydroxy*-2-*methyl*-1-(δ-*ethoxybutyl*)cyclo*hexane*-2-*carboxylate*.—A Grignard reagent, prepared from 21 g. of δ-ethoxybutyl bromide, was treated with ethyl 2-methyl*cyclo*hexanone-2-carboxylate exactly as described on p. 815; no precipitate was produced. The product gave 14 g. of the *ester*, b. p. 165°/0·5 mm. (Found: C, 66·9; H, 10·5. $C_{16}H_{30}O_4$ requires C, 67·1; H, 10·6%).

Ethyl 2-*Methyl*-1-(δ-*ethoxybutyl*)-$\Delta^{6(?)}$-cyclo*hexene*-2-*carboxylate*.—The hydroxy-ester (24 g.) was dehydrated in the course of 19 hours as described on p. 815 and gave 20 g. of the unsaturated *ester*, b. p. 135°/0·4 mm. (Found: C, 71·2; H, 10·6. $C_{16}H_{28}O_3$ requires C, 71·6; H, 10·5%).

Ethyl 2-*Methyl*-1-(δ-*ethoxybutyl*)cyclo*hexane*-2-*carboxylate*.—The reduction of the unsaturated ester (19 g.) was carried out as described on p. 815; some 1800 c.c. of hydrogen were taken up and 17 g. of the saturated *ester* were obtained, b. p. 149°/0·8 mm. (Found: C, 70·7; H, 11·3. $C_{16}H_{30}O_3$ requires C, 71·1; H, 11·2%). The ester was hydrolysed by the method given on p. 816; the acid did not solidify and was used for the next step without purification.

9-*Methyl*-1-*decalone*.—The crude ethoxy-acid (13 g.) in 26 c.c. of acetic acid was treated with 18 g. of chromic acid in 36 c.c. of acetic acid and 4 c.c. of water in quantities of 2—3 c.c. at a time, and the mixture finally warmed on the steam-bath for an hour. The acetic acid was distilled off under reduced pressure, and the residue dissolved in 10% sodium hydroxide solution. The solution was boiled and filtered, and the precipitate washed with water. The filtrate was concentrated to 200 c.c., acidified, and extracted with ether. The extract was evaporated, finally in a high vacuum, and the residue of crude dibasic acid distilled with the addition of 0·4 g. of baryta at 310° (bath temperature). The distillate was taken up in ether and washed with caustic soda solution, the solvent removed, and the residue treated with semicarbazide acetate. The *semicarbazone*, which formed with some difficulty, had m. p. 223° after several crystallisations (yield, 0·8 g.) (Found: C, 64·7; H, 9·5. $C_{12}H_{21}ON_3$ requires C, 64·5; H, 9·5%). The ketone regenerated from it was a liquid which did not solidify in a freezing mixture.

Alternative Preparation of 9-*Methyl*-1-*decalone*.—21 G. of the crude iodo-acid prepared as described on p. 816 were treated with an ice-cold mixture of 10 c.c. of absolute alcohol and 1·4 c.c. of sulphuric acid. After being left in a freezing mixture for 3—4 hours and at room temperature for 2 days, the oily mass deposited crystals. It was taken up in ether, and the extract washed with sodium carbonate solution and water, dried, and evaporated; 13 g. of solid *ethyl* 2-*methyl*-1-(γ-*iodopropyl*)cyclo*hexane*-2-*carboxylate* were obtained, which formed plates from dilute alcohol, m. p. 94° (Found: I, 38·2. $C_{13}H_{23}O_2I$ requires I, 37·5%); 6 g. of the acid were recovered from the alkaline washings and were re-esterified.

16 G. of the iodo-ester were heated with 3·5 g. of potassium cyanide in 3·5 c.c. of alcohol and 1 c.c. of water for 24 hours. Without isolation of the nitrile formed, 15 g. of potassium hydroxide in 45 c.c. of 50% alcohol were added, and the mixture boiled for 7 hours. The liquid was then acidified and warmed for an hour to decompose the alkali cyanide, and the oil extracted with ether and re-hydrolysed with 65 c.c. of 15% aqueous potassium hydroxide to ensure that no acid ester remained (4 hours). On working up, 5·5 g. of a light brown acidic gum were obtained; this did not crystallise and on heating with a little baryta gave a poor yield of the dicyclic ketone, identified by the semicarbazone (m. p. 222°, mixed m. p. 223°).

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IMPERIAL COLLEGE, LONDON, S.W. 7.

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