326. *Tetrahydrocitrylidene- and Citronellylidene-acetic Acids. Syntheses of* sec.-iso*Octyl*cyclo*pentane Derivatives.*

By H. N. Rydon.

Tetrahydrocitrylidene- and citronellylidene-acetic acids are starting materials for possible syntheses of 2-methyl-3-*sec.*-*iso*octyl*cyclo*pentanone. They have both been shown to be mixtures of Δ^{α}- and Δ^{β}-*isomerides*, which have been separated in a pure condition in each case. The Δ^{β}-*isomeride* (I) from tetrahydrocitrylideneacetic acid has been converted into a *bromo-ester*, both directly and through the *lactone* (IV), but this

bromo-ester did not react smoothly with ethyl sodiocyanoacetate. 1-*Methyl*-2-sec.-iso*octyl*cyclo*pentene* (IX), a possible intermediate in the synthesis of methyl-*sec.-iso*-octyl*cyclo*pentanone, has also been prepared. A study has been made of some possible methods for the conversion of *cyclo*pentanones into *sec.-iso*octyl*cyclo*pentanes; in this connexion α-*methyl*-α-cyclo*pentylacetone* has been synthesised.

MOST of the work described in this paper had as its object the synthesis of 2-methyl-3-*sec.-iso*octyl*cyclo*pentanone, which is the necessary starting material for the synthesis of cholesterol by the Mannich base method (Du Feu, McQuillin, and Robinson, J., 1937, 53; McQuillin and Robinson, J., 1938, 1097). A previous attempt to synthesise this material from dihydrocitronellylideneacetic acid had failed (Peak and Robinson, J., 1937, 1590). These authors prepared their unsaturated acid by the condensation of dihydrocitronellal with malonic acid in pyridine containing piperidine. The experience of the South Kensington school would lead one to suppose the acid so prepared to be a mixture of the desired Δ^{β}-isomeride with more or less of the Δ^{α}-isomeride. Accordingly, the method was investigated further; the optically inactive tetrahydrocitral was used in preference to the optically active dihydrocitronellal in order to avoid stereochemical complications.

Condensation of tetrahydrocitral with malonic acid in pyridine or triethanolamine gave the expected mixture of acids; this "tetrahydrocitrylideneacetic acid" was submitted to partial esterification (Kon, Linstead, and Maclennan, J., 1932, 2458; cf. Sudborough and Thomas, J., 1911, **99**, 2307; Eccott and Linstead, J., 1929, 2161). Hydrolysis of the *ester* so produced yielded 5 : 9-*dimethyl*-Δ^{3}-*decenoic acid* (I), the unesterified material being 5 : 9-*dimethyl*-Δ^{2}-*decenoic acid* (II). The structure of the Δ^{β}-acid (I) was confirmed by its oxidation to 2 : 6-dimethylheptoic acid (III), which was identified as its amide. In

$CHMe_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CO_2H$ (I.)

(II.) $CHMe_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CO_2H$

$CHMe_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CO_2H$ (III.)

$CHMe_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH{\cdot}CH_2{\cdot}CH_2$ (IV.)
$O\text{———}CO$

agreement with the findings of Linstead, Noble, and Boorman (J., 1933, 557) triethanolamine favoured the formation of the Δ^{β}-acid; with this catalyst the proportion of this acid in the mixture, as estimated by partial esterification, was 66%, whereas the product obtained with pyridine contained only 25% of the Δ^{β}-isomeride. Nevertheless, it was found most convenient to use the pyridine method and convert the Δ^{α}-acid so formed into the equilibrium mixture of tautomerides by the action of hot alkali; this mixture, which contained 47% of the Δ^{β}-acid, was separated into its components by partial esterification. By repeating this process several times it was possible to obtain the Δ^{β}-acid (I) in satisfactory yield.

The action of cold concentrated sulphuric acid on the Δ^{β}-acid (I) gave a good yield of γ-sec.-iso*octyl*-γ-*butyrolactone* (IV), but the *bromo-ester* obtained from this by the action of hydrogen bromide in alcohol gave no useful product on condensation with ethyl sodiocyanoacetate; this was also the case with the ester of the bromo-acid obtained by the addition of hydrogen bromide to the acid (I) and the projected synthesis was abandoned.

Citronellylideneacetic acid [a mixture of the isomerides (V) and (VI)] was prepared by Rupe and Lotz (*Ber.*, 1903, **36**, 2796) by the condensation of citronellal with malonic acid in pyridine solution. Despite the fact that Rupe, Pfeiffer, and Splittgerber (*Ber.*, 1907, **40**, 2813) recognised the product to be a mixture of isomerides, it has been used in synthetic work (Ruzicka and Steiger, *Helv. Chim. Acta*, 1927, **10**, 680; von Braun and Rudolph, *Ber.*, 1934, **67**, 1735). Application of the methods used with tetrahydrocitrylideneacetic acid led to the separation of the components, 5 : 9-*dimethyl*-$\Delta^{2:8}$-*decadienic*

$CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CO_2H$ (V.)

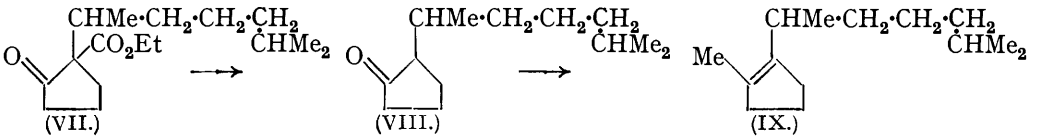
$CMe_2{:}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CO_2H$ (VI.)

acid (V) and 5 : 9-*dimethyl*-$\Delta^{3:3}$-*decadienic acid* (VI), in a state of purity.* The crude

* Both of these acids may of course be mixtures of *iso*propylidene and *iso*propenyl isomerides.

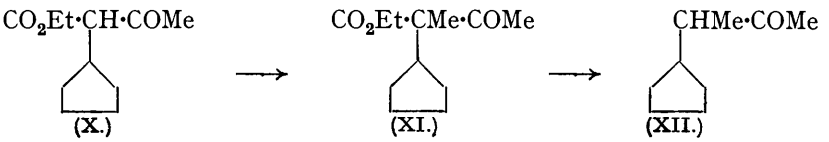
citronellylideneacetic acid contains 30% of the Δ^{β}-isomeride (VI), and this is present to the extent of 75% in the mixture obtained by alkali equilibration.

The following series of reactions seemed to offer another possible synthetic approach to the desired ketone :



Condensation of *sec.-iso*octyl iodide with the potassio-derivative of ethyl *cyclo*pentanone-2-carboxylate yielded *ethyl* 2-sec.-iso*octyl*cyclo*pentanone-2-carboxylate* (VII). On hydrolysis with baryta this yielded both α-sec.-iso*octyladipic acid* and 2-sec.-iso*octyl*cyclo*pentanone* (VIII); more ketone was obtained by ketonisation of the adipic acid with baryta. The ketone (VIII) reacted readily with methylmagnesium iodide; dehydration of the product yielded 1-*methyl*-2-sec.-iso*octyl*-Δ^{1}(?)-cyclo*pentene* (IX). This unsaturated hydrocarbon reacted readily with selenious acid in boiling butyl alcohol; the product was a complex mixture and has not been fully investigated.

The development of the furfural synthesis of 3'-keto-1 : 2-*cyclo*pentenophenanthrenes (Robinson, J., 1938, 1390) rendered it desirable to work out a satisfactory synthesis of *sec.-iso*octyl*cyclo*pentanes from *cyclo*pentanones. Some model experiments on these lines have been carried out. The Grignard reaction with *sec.-iso*octyl iodide and *cyclo*pentanone failed (cf. *iso*propyl iodide; Meerwein, *Annalen*, 1914, **405**, 155) and recourse was made



to a less direct method. *Ethyl* cyclo*pentylacetoacetate* (X), synthesised in the usual way from *cyclo*pentanol, was methylated to *ethyl* cyclo*pentylmethylacetoacetate* (XI). Alkaline hydrolysis yielded α-*methyl*-α-cyclo*pentylacetone* (XIII); the product obtained by condensing this ketone with *iso*butaldehyde was a complex mixture which has not been fully investigated.

Experimental.

Tetrahydrocitral (cf. Paal, D.R.-P. 298,193) was prepared by the hydrogenation of citral at 2—4 atms. in alcohol in the presence of palladised strontium carbonate. Yield, 80%; b. p. 99—101°/22 mm.

Tetrahydrocitrylideneacetic Acid.—(i) 41 G. of tetrahydrocitral were mixed with 39 g. of triethanolamine, and 28 g. of powdered malonic acid added with shaking; the mixture became hot and set to a pasty mass. This was heated on the water-bath until evolution of carbon dioxide ceased (21 hours). It was then acidified with 50% (weight) sulphuric acid, extracted with ether, washed, dried, and distilled. The product (22 g.), b. p. 160—170°/17 mm., was purified by means of sodium bicarbonate and redistilled, yielding 15 g. (29%) of tetrahydrocitrylideneacetic acid, b. p. 164—166°/15 mm. $n_{D}^{16^{\circ}}$ 1·4450 (Found : equiv., by titration, 194. Calc. for $C_{12}H_{22}O_2$, 198); partial esterification (see below) showed this material to contain 66% of the Δ^{β}-isomeride. The method was useless for large-scale working owing to the formation of troublesome emulsions.

(ii) 285 G. of malonic acid were added to a mixture of 250 g. of tetrahydrocitral and 500 c.c. of pyridine. After being kept at room temperature for 6 hours, the mixture was heated overnight on the water-bath. The pyridine was removed by steam-distillation and the residue was acidified and extracted with ether. Distillation of the dried extract yielded 240 g. (75%) of a tetrahydrocitrylideneacetic acid, b. p. 170—175°/16 mm. (Found : equiv., by titration, 195), shown by partial esterification to contain 25% of the Δ^{β}-isomeride.

Partial esterification. 1 G.-mol. of the above acid was kept at room temperature overnight with 100 c.c. of N-ethyl alcoholic hydrogen chloride and 230 c.c. of absolute alcohol. The product was poured into an excess of 10% sodium carbonate solution. The Δ^{β}-ester thrown

out was extracted with ether, dried, and distilled; *ethyl* 5 : 9-*dimethyl*-Δ^3-*decenoate* was thus obtained as a colourless oil, b. p. 134—135°/15 mm., with a rose-like odour (Found : C, 73·7; H, 11·5. $C_{14}H_{26}O_2$ requires C, 74·2; H, 11·5%).

The residual sodium carbonate solution was acidified; the Δ^α-acid liberated was extracted with ether, dried, and distilled. 5 : 9-*Dimethyl*-Δ^2-*decenoic acid* (II) was obtained in this way as a colourless oil, b. p. 158—160°/7 mm., $n_D^{19°}$ 1·4580, with a waxy odour (Found : C, 72·6; H, 11·0; equiv., by titration, 195. $C_{12}H_{22}O_2$ requires C, 72·65; H, 11·1%; equiv., 198). The p-*bromophenacyl* ester formed leaflets, m. p. 47°, from methyl alcohol (Found : C, 60·6; H, 6·7. $C_{20}H_{27}O_3Br$ requires C, 60·8; H, 6·8%).

The Δ^β-ester was added to a cold 20% aqueous solution of 2 equivs. of potassium hydroxide, rendered homogeneous with alcohol (about 50 c.c. for 10 g. of ester), and kept at room temperature overnight. After dilution, neutral matter was removed by extraction with ether and the residual solution was then acidified and extracted with ether. Distillation of the dried extract yielded 5 : 9-*dimethyl*-Δ^3-*decenoic acid* (I) as a viscous colourless oil, b. p. 162°/13 mm., $n_D^{19°}$ 1·4540, with a waxy colour (Found : C, 72·5; H, 11·2. $C_{12}H_{22}O_2$ requires C, 72·65; H, 11·1%). The p-*bromophenacyl* ester crystallised from methyl alcohol in leaflets, m. p. 39° (Found : C, 60·7; H, 6·8. $C_{20}H_{27}O_3Br$ requires C, 60·8; H, 6·8%).

Equilibration. The large amounts of the Δ^α-acid obtained by the pyridine method were converted into the Δ^β-acid by the following procedure : 118 G. of the Δ^α-acid (II) were heated for 24 hours in a boiling water-bath with 50 g. of sodium hydroxide in 100 c.c. of water and 100 c.c. of ethyl alcohol. The product was poured into water and acidified, and the recovered acid extracted with ether, dried, and distilled. It was submitted to partial esterification, and the recovered Δ^α-acid again equilibrated. By repeating the process several times the bulk of the Δ^α-acid was converted into the required Δ^β-isomeride (I). The equilibrated acid was found, by the partial esterification method, to contain 53% of the Δ^α-isomeride.

Oxidation of the Δ^β-*Acid.*—2 G. of the pure Δ^β-acid (I) were dissolved in 20 c.c. of 10% sodium bicarbonate solution and stirred at 0° while a solution of 5 g. of potassium permanganate in 200 c.c. of water was added dropwise during 30 minutes; after being stirred for a further 2½ hours, the solution was filtered and evaporated, and the residue acidified and extracted with ether. Distillation of the dried extract gave 0·6 g. of an acid, b. p. 123—128°/18 mm. (Found : equiv., by titration, 161·3. Calc. for $C_9H_{18}O_2$: equiv., 158. Calc. for $C_{10}H_{20}O_2$: equiv., 172). This was heated for a short time with a little phosphorus trichloride, and the crude chloride decanted dropwise with shaking into 3 c.c. of aqueous ammonia (*d* 0·880) cooled in ice. The precipitated amide was filtered off, washed, and twice recrystallised from dilute acetone. 2 : 6-Dimethylheptoamide formed leaflets, m. p. 95—96° (Found : N, 8·5. Calc. for $C_9H_{19}ON$: N, 8·9%); Kögl and Boer (*Rec. Trav. chim.*, 1935, **54**, 779) record m. p. 99—100°. The m. p. was depressed to 80—85° on admixture with a specimen of tetrahydrogeranamide kindly provided by Prof. J. L. Simonsen, F.R.S.

Lactonisation of the Δ^β-*Acid.*—92 G. of the pure acid (I) were mixed carefully during 10 minutes with 92 g. of concentrated sulphuric acid, rise of temperature being minimised by cooling in running water. After being kept at room temperature for 24 hours, the product was poured into an excess of 10% sodium carbonate solution and extracted with ether. Distillation of the dried extract afforded 52 g. (57%) of γ-sec.-iso*octyl*-γ-*butyrolactone* (IV) as a colourless oil, b. p. 158—162°/13 mm., $n_D^{23°}$ 1·4619, having a strong odour of apricots (Found : C, 73·1; H, 10·85. $C_{12}H_{22}O_2$ requires C, 72·65; H, 11·1%). Experiments in which more dilute sulphuric acid was used or in which the reaction time was shorter gave lower yields.

Bromodimethyldecoic ester. (i) 52 G. of the Δ^β-acid (I) were kept overnight at room temperature in a closed vessel with 100 c.c. of a 50% (weight-volume) solution of hydrogen bromide in acetic acid. The acetic acid was then removed under reduced pressure, and the residue treated, in ice, with 75 c.c. of ethyl alcohol and 10 c.c. of concentrated sulphuric acid and kept at room temperature for 24 hours. The product was poured into water and extracted with ether. Distillation of the dried extract yielded much low-boiling material and 30 g. of *ethyl* 4(?)-*bromo*-5 : 9-*dimethyldecoate*, b. p. 145—150°/1·5 mm. (Found : Br, 25·1. $C_{14}H_{27}O_2Br$ requires Br, 26·0%).

(ii) 66 G. of the lactone (IV) were dissolved in 150 c.c. of absolute alcohol and saturated with hydrogen bromide at 0°. After being kept overnight at room temperature, the product was poured into water and extracted with ether. Distillation of the washed and dried extract yielded 66 g. (65%) of the above bromo-ester, b. p. 143—148°/0·6 mm.

Condensation of this bromo-ester with ethyl sodiocyanoacetate gave only a poor yield of material of doubtful homogeneity.

Citronellylideneacetic Acid.—This was prepared by the method of Ruzicka and Steiger (*Helv. Chim. Acta*, 1927, **10**, 684).

Partial esterification. 31 G. of the acid were kept at room temperature overnight with 37 c.c. of absolute ethyl alcohol and 16 c.c. of N-ethyl-alcoholic hydrogen chloride. The product was poured into 250 c.c. of 10% sodium carbonate solution and the Δ^{β}-ester thrown out was extracted with ether, dried, and distilled, yielding 10 g. (28%) of *ethyl* 5 : 9-*dimethyl*-$\Delta^{3:8}$-*decadienate* as a colourless oil, b. p. 139—141°/13 mm., having a pleasant sweet smell (Found : C, 74·8; H, 10·6. $C_{14}H_{24}O_2$ requires C, 75·0; H, 10·7%).

The residual sodium carbonate solution was acidified and the precipitated Δ^{α}-acid was extracted with ether. Distillation of the dried extract afforded 19 g. (60%) of 5 : 9-*dimethyl*-$\Delta^{2:8}$-*decadienic acid* (V) as a viscous colourless oil, b. p. 173—175°/13 mm., with a waxy odour (Found : C, 73·5; H, 10·3; equiv., by titration, 193·5. $C_{12}H_{20}O_2$ requires C, 73·5; H, 10·2%; equiv., 196).

16 G. of the pure Δ^{β}-ester were hydrolysed by keeping overnight with 8 g. of potassium hydroxide in 40 c.c. of water and 100 c.c. of alcohol. The solution was poured into water and, after removal of neutral material by extraction with ether, the Δ^{β}-acid was thrown out by acidification, extracted with ether, dried, and distilled. 5 : 9-*Dimethyl*-$\Delta^{3:8}$-*decadienic acid* (VI) (10 g.; 72%) was a colourless viscous oil, b. p. 163—165°/1 mm., with a waxy odour (Found : C, 73·6; H, 10·0; equiv., by titration, 197·8. $C_{12}H_{20}O_2$ requires C, 73·5; H, 10·2%; equiv., 196).

Equilibration. This was carried out by the method described for dimethyldecenoic acid (p. 1547). The equilibrated acid contained of the Δ^{β}-isomeride.

Methyl-sec.-iso*octyl*cyclo*pentene*.—37 G. yl *cyclo*pentanone-2-carboxylate were converted into the potassio-derivative by heating under reflux in an oil-bath at 110—140° with 9 g. of powdered potassium in 250 c.c. of xylene. After addition of 57 g. of *sec.-iso*octyl iodide the mixture was refluxed in an oil-bath at 140—150° for 33 hours. The product was cooled and diluted with water; the xylene layer was separated, washed, dried, and distilled, yielding 36·5 g. (59%) of *ethyl* 2-sec.-iso*octyl*cyclo*pentanone*-2-*carboxylate* (VII), b. p. 165—175°/14 mm., $n_D^{18°}$ 1·4588 (Found : C, 70·8; H, 10·5. $C_{16}H_{28}O_3$ requires C, 71·6; H, 10·45%).

36·5 G. of the keto-ester (VII) were refluxed for 72 hours with a solution of 70 g. of baryta in 210 c.c. of water. The cooled solution was acidified and extracted with ether. The residue obtained on evaporation of the ethereal extract was purified by means of sodium carbonate. On distillation the neutral portion gave 3·5 g. (13%) of 2-*sec.-iso*octyl*cyclo*pentanone, b. p. 134—136°/16 mm. (see below). The acidic product was a gum which slowly crystallised. After draining on porous earthenware, two crystallisations from light petroleum (b. p. 40—60°) yielded α-sec.-iso*octyladipic acid* in leaflets, m. p. 54° (Found : C, 65·1; H, 10·25. $C_{14}H_{26}O_4$ requires C, 65·1; H, 10·1%).

16·5 G. of the gummy acid were slowly distilled with 0·5 g. of baryta at 350—360° under somewhat diminished pressure. The distillate was taken up in ether, washed with sodium carbonate solution, dried, and distilled, yielding 7 g. (52%) of 2-sec.-iso*octyl*cyclo*pentanone* (VIII) as a colourless oil, b. p. 135—137°/17 mm., $n_D^{18°}$ 1·4548, having a waxy ketonic odour (Found : C, 79·4; H, 12·3. $C_{13}H_{24}O$ requires C, 79·6; H, 12·25%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl alcohol in yellow prisms, m. p. 86—87° (Found : N, 15·15. $C_{19}H_{28}O_4N_4$ requires N, 14·9%).

10·5 G. of the ketone (VIII) were added dropwise, with shaking, at 0° to a Grignard reagent prepared from 7·6 g. of methyl iodide, 1·3 g. of magnesium, and 20 c.c. of anhydrous ether. After being kept at room temperature for an hour, the mixture was refluxed on the water-bath for 45 minutes, cooled, decomposed with ice and dilute sulphuric acid, and extracted with ether. The residue obtained by evaporation of the dried extract was refluxed overnight with 10 g. of hydrated oxalic acid in 10 c.c. of water. The cooled product was diluted with water and extracted with ether; the extract was washed with sodium carbonate solution, dried, and distilled. 1-*Methyl*-2-sec.-iso*octyl*-Δ^{1}(?)-cyclo*pentene* (IX) (6 g.; 60%) was thus obtained as a colourless, almost odourless oil, b. p. 112—115°/18 mm., $n_D^{18°}$ 1·4572 (Found : C, 86·4; H, 13·4. $C_{14}H_{26}$ requires C, 86·6; H, 13·4%).

*Methyl*cyclo*pentylacetone*.—111 G. of *cyclo*pentyl bromide (Noller and Adams, *J. Amer. Chem. Soc.*, 1926, **48**, 1084) were added to a cooled mixture of 97·5 g. of ethyl acetoacetate and sodium ethoxide (from sodium, 17 g., and absolute alcohol, 225 c.c.). After refluxing on the water-bath for 4 days, the product was poured into water, extracted with ether, dried, and distilled. Ethyl *cyclo*pentylacetoacetate (X) so obtained (94 g.; 63%) had b. p. 125—130°/18 mm., $n_D^{18°}$ 1·4527. With phenylhydrazine in acetic acid it yielded 1-*phenyl*-3-*methyl*-4-cyclo-

pentyl-5-pyrazolone, which crystallised from dilute alcohol in pale yellow needles, m. p. 133—134° (Found : N, 11·1. $C_{15}H_{18}ON_2$ required N, 11·6%).

94 G. of the above keto-ester (X) were added to a solution of 11 g. of sodium in 150 c.c. of absolute alcohol. 85 G. of methyl iodide were added to the cooled product and, after the vigorous reaction had abated, the mixture was refluxed on the water-bath overnight. On working up in the usual way *ethyl* cyclo*pentylmethylacetoacetate* (XI) (66 g.; 66%) was obtained as a colourless oil, b. p. 128—131°/13 mm., $n_D^{15°}$ 1·4607 (Found : C, 67·8; H, 9·3. $C_{12}H_{20}O_3$ requires C, 67·9; H, 9·4%).

66 G. of the keto-ester (XI) were freed from unmethylated material by washing with 5% sodium hydroxide solution and then refluxed for 18 hours with 40 g. of potassium hydroxide in 400 c.c. of water. The product was distilled in steam, and the distillate extracted with ether. Distillation of the dried extract gave 30 g. (69%) of *α-methyl-α*-cyclo*pentylacetone* (XII) as a colourless oil, b. p. 76—79°/17 mm., $n_D^{20°}$ 1·4470, having a strong camphor-like odour (Found : C, 76·9; H, 11·4. $C_9H_{16}O$ requires C, 77·2; H, 11·4%). The *semicarbazone* crystallised from dilute alcohol in rhombic leaflets, m. p. 98° (Found : N, 21·0. $C_{10}H_{19}ON_3$ requires N, 21·3%).

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