# CIV.—*Syntheses of Cyclic Compounds. Part VI. 3- and 4-Methyl*cyclo*hexanones.*

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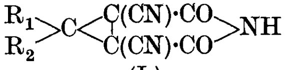
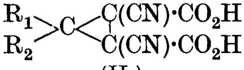
The principal object of the present investigation was to determine the influence of the substitution of a methyl group for hydrogen in the 3- and 4-positions upon the character and the configuration of the *cyclo*hexane ring. The only previous work on this subject appears to be that of Birch and Thorpe (J., 1922, **121**, 1821), who found that the bridged *spiro*-compounds (I), where $R_1R_2C$ is 3- and 4-methyl*cyclo*hexane, decomposed completely into the open-chain compound (III) on treatment with alkali under standard conditions, a result in contrast with that obtained with the unsubstituted *cyclo*hexane ring ($R_1R_2C$ = *cyclo*hexane), where the *spiro*-compound (II) was produced (Birch, Gough, and Kon, J., 1921, **119**, 1315). It is doubtful whether this method of comparing stabilities of ring systems, in its present state, is of any great value, since all the compounds (I) with substituents, $R_1R_2C$, other than *cyclo*hexane are converted into the open-chain compounds (III) under the conditions employed and no means have yet been found for distinguishing between the rates of fission of individual members of the series. The method adopted in the present research is that described by one of us (Vogel, J., 1928, 2010) for the comparison of substituent groups and ring systems. The cyano-esters (IV) were prepared by the condensation of the ketones with ethyl cyanoacetate in the presence of piperidine and reduced in ethereal solution with moist aluminium amalgam; the relative yields of the unimolecular (V) and the bimolecular products (VI) are shown in Table I, the values for the *cyclo*pentane and *cyclo*hexane compounds being included for purposes of comparison : in so far as the yields of the



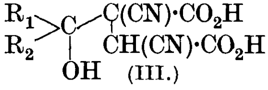
$$\begin{array}{l}R_1\\R_2\end{array}\!\!>C<\!\!\begin{array}{l}C(CN)\cdot CO\\C(CN)\cdot CO\end{array}\!\!>NH$$

(I.)



$$\begin{array}{l}R_1\\R_2\end{array}\!\!>C<\!\!\begin{array}{l}C(CN)\cdot CO_2H\\C(CN)\cdot CO_2H\end{array}$$

(II.)

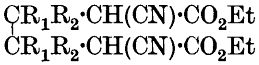


$$\begin{array}{l}R_1\\R_2\end{array}\!\!>\!\!\begin{array}{c}C\\|\\OH\end{array}\!\!\!\begin{array}{l}C(CN)\cdot CO_2H\\CH(CN)\cdot CO_2H\\ \end{array}$$

(III.)

(IV.) $CR_1R_2{:}C(CN)\cdot CO_2Et$

(V.) $CHR_1R_2\cdot CH(CN)\cdot CO_2Et$



$$\begin{array}{l}CR_1R_2\cdot CH(CN)\cdot CO_2Et\\ |\\ CR_1R_2\cdot CH(CN)\cdot CO_2Et\end{array}$$

(VI.)

TABLE I.

| | $CR_1R_2{:}C(CN)\cdot CO_2Et$. | Yield % (V). | Yield % (VI). |
|---|---|---|---|
| $CR_1R_2$ | = *cyclo*pentane | 79 | 13 |
| | = *cyclo*hexane | 84 | 6 |
| | = 3-methyl*cyclo*hexane | 83 | 6 |
| | = 4-methyl*cyclo*hexane | 87 | 4 |

bimolecular compounds—which owing to their relatively slight volatility are employed for comparative purposes—are concerned, there seems to be no essential difference in behaviour between the unsubstituted and the methyl-substituted *cyclo*hexane rings.

The unsaturated cyano-esters have the $\alpha\beta$-structure: the $\beta\gamma$-isomeride is present, if at all, in very small quantity. The $\beta\gamma$-structures assigned to the cyano-esters derived from 3- and 4-methyl*cyclo*hexanones by Harding, Haworth, and Perkin (J., 1908, **93**, 1943) and by Harding and Haworth (J., 1910, **97**, 486) require correction: the esters are completely reduced by moist aluminium amalgam and no definite evidence has been obtained of the presence of any appreciable quantity of unsaturated isomerides in the reduction products.

Prolonged hydrolysis of the reduced cyano-esters (V) with alcoholic potassium hydroxide afforded the corresponding malonic acids, the constitution and saturated character of which were proved by their synthesis from the iodides and ethyl sodiomalonate (compare Zelinski and Alexandrow, *Ber.*, 1901, **34**, 3885).

Some physical properties of the pure ketones * are recorded in Table II (compare Schoorl, *Rec. trav. chim.*, 1929, **48**, 935). The refractive indices were measured at about 20°; the exact temperatures are given in the Experimental section. The surface tensions and the densities were determined over a range of temperatures and have been reduced to 20°, a linear variation with temperature being assumed. The parachors, $[P]$ (obs.), were calculated by the usual formula. The parachors, $[P_1]$, for the corresponding cyclic hydrocarbons can be evaluated from the observed values for the cyclic ketones by substituting Sugden's values of 2H for $:O$. If, now, from these the parachor for the simple *cyclo*hexane ring be found by replacing the value for $CH_3$ by that for H, the contribution per

TABLE II.

*cyclo*Hexanones.

| | 2-Methyl. | 3-Methyl. | 4-Methyl. |
|---|---|---|---|
| B. p. (mm.) | 165°/757 | 169°/748 | 171°/747 |
| $n_D^{20°}$ | 1·4484 | 1·4463 | 1·4455 |
| $d_{4°}^{20°}$ | 0·9261 | 0·9141 | 0·9151 |
| $[R_L]_D$ (obs.) | 32·45 | 32·69 | 32·61 |
| $[R_L]_D$ (calc.) | 32·34 | 32·34 | 32·34 |
| $\gamma^{20°}$ | 31·99 | 31·23 | 31·04 |
| $[P]$ (obs.) | 288·2 | 290·0 | 289·6 |
| $[P]$ (calc.) | 288·1 | 288·1 | 288·1 |

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* The results for 2-methyl*cyclo*hexanone have been included for the sake of completeness.

$CH_2$ group, $[P'_1/n]$, which is an important criterion of the configuration of the ring (Vogel, J., 1928, 2018), can be calculated: the results (Table III, which includes the previous results for the unsubstituted 6-ring) are in close agreement with that obtained from the observed parachor for the simple *cyclo*hexane ring and thus provide further support for the view that there is no essential difference in configuration between the unsubstituted *cyclo*hexane ring and that present in 3- and 4-methyl*cyclo*hexanones.

TABLE III.

| | 6-Ring. | 2-Methyl. | 3-Methyl. | 4-Methyl. |
|---|---|---|---|---|
| $[P_1]$.............. | 242·4 | 279·2 | 281·0 | 280·6 |
| $[P'_1/n]$ ......... | 40·4 | 40·0 | 40·3 | 40·3 |

## EXPERIMENTAL.

The 3- and 4-methyl*cyclo*hexanones used were the pure products supplied by the Deutsche Hydrierwerke Aktiengesellschaft.

### 4-*Methyl*cyclo*hexane Series.*

Ethyl 4-methyl*cyclo*hexylidene-1-cyanoacetate was prepared by the condensation of 4-methyl*cyclo*hexanone and ethyl cyanoacetate in the presence of piperidine (Harding, Haworth, and Perkin, *loc. cit.*) in *ca.* 60% yield. It had b. p. 172°/21 mm. (Harding, Haworth, and Perkin give b. p. 165—168°/14 mm.), $d_{4^\circ}^{21\cdot2^\circ}$ 1·0227, $n_D^{21\cdot2^\circ}$ 1·4882, $[R_L]_D$ 58·38 (calc., 56·42).

*Ethyl* r-4-*Methyl*cyclo*hexyl*-1-*cyanoacetate* (as V).—The preceding ester (100 g.) was reduced with 150 g. of moist aluminium amalgam in ether (Vogel, J., 1927, 594; 1928, 2010): there was a period of induction of about 1·5 hours and the reaction was complete after 7 hours. The product was worked up in the usual manner and distilled, *ethyl* r-4-*methyl*cyclo*hexyl*-1-*cyanoacetate* (87 g.) passing over at 160—169°/21 mm. (more than 90% at 163°/21 mm.). The viscid residue, having been washed several times with light petroleum (b. p. 40—60°), crystallised when left over-night in a vacuum over concentrated sulphuric acid (yield, 4 g.); it melted at 75° (softening at 65°) and was the bimolecular *cyano-ester* (Found: *M*, in camphor, 421. $C_{24}H_{36}O_4N_2$ requires *M*, 418). The liquid reduction product after redistillation had b. p. 162°/20 mm., $d_{4^\circ}^{22\cdot2^\circ}$ 1·0018, $n_D^{22\cdot2^\circ}$ 1·4585, whence $[R_L]_D$ 57·03 (calc., 56·89) (Found: C, 68·6; H, 9·1. $C_{12}H_{19}O_2N$ requires C, 68·8; H, 9·2%).

4-*Methyl*cyclo*hexyl*-1-*malonic Acid.*—Solutions of ethyl 4-methyl*cyclo*hexyl-1-cyanoacetate (30 g.) in rectified spirit (160 g.) and of potassium hydroxide (100 g.) in water (100 g.) were mixed, heated on the steam-bath for 24 hours (the evolution of ammonia had then ceased), and evaporated to dryness. The residue was triturated several times with ether to remove any unchanged ester and acidified with dilute sulphuric acid; 4-methyl*cyclo*hexyl-1-malonic acid, m. p. 172°, precipitated in almost quantitative yield, had m. p. 182—183° after several crystallisations from formic acid (*d* 1·2) (Hope and Perkin, J., 1909, **95**, 1367, give m. p. 177—178°) (Found: equiv., by titration with baryta, 101. Calc., 100). An additional small quantity was extracted by ether from the filtrate after saturation with ammonium sulphate.

*Synthesis of* 4-*Methyl*cyclo*hexyl*-1-*malonic Acid from* 4-*Methyl*cyclo*hexyl Iodide and Ethyl Sodiomalonate.*—4-Methyl*cyclo*hexanone was reduced with sodium and moist ether (compare Bentley, J., 1895, **67**, 264) to the alcohol, b. p. 174°/760 mm. This (116 g.) was treated with red phosphorus (9·5 g.) and iodine (90 g.), rise of temperature being prevented, and after 12 hours the whole was heated on the steam-bath for 2 hours, and 4-*methyl*cyclo*hexyl iodide* isolated in the usual manner (compare Bentley, *loc. cit.*). It had b. p. 63°/3·5 mm., $d_{4^\circ}^{20\cdot9^\circ}$ 1·5086, $n_{\mathrm{D}}^{20\cdot9^\circ}$ 1·5325, whence $[R_L]_{\mathrm{D}}$ 46·04 (calc., 45·13) (Found: I, 56·6. $C_7H_{13}I$ requires I, 56·7%). When freshly distilled, the iodide is a colourless mobile liquid with a characteristic odour.

The reaction between 4-methyl*cyclo*hexyl iodide (127 g.; 1 mol.) and ethyl sodiomalonate (2 mols.: * compare Zelinski and Alexandrow, *loc. cit.*; prepared from 90·7 g. of ethyl malonate, 13·05 g. of sodium, and 200 c.c. of dry alcohol) was carried out in the way described by Hope and Perkin (J., 1909, **95**, 1363). The product on distillation gave first ethyl malonate and 4-methyl*cyclo*hexyl iodide; ethyl 4-methyl*cyclo*hexyl-1-malonate then passed over at 164—168°/29 mm. On redistillation, it boiled at 161—163°/18 mm. (Hope and Perkin give b. p. 163—165°/20 mm.); yield, 75 g. or 55%.

The acid obtained by the hydrolysis of the ester with alcoholic potassium hydroxide on the steam-bath melted, after three crystallisations from formic acid, at 182—183° (decomp.) (Found: equiv., by titration, 100·5) and was identical (mixed m. p.) with 4-methyl*cyclo*hexyl-1-malonic acid prepared as described above. From the filtrate from the precipitated acid, saturated with ammonium sulphate, ether extracted about 2 g. of an acid, m. p. 100—110°, and 110° after recrystallisation from benzene: this was probably impure *r*-3-methyl*cyclo*hexyl-1-malonic acid (m. p. 120—121°; mixed m. p. 116—117°) (Found: equiv., 101), but the quantity was too small for identification.

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* A slightly smaller yield was obtained with equimolecular quantities.

### 3-*Methyl*cyclo*hexane Series.*

Ethyl 3-methyl*cyclo*hexylidene-1-cyanoacetate was prepared in *ca.* 60% yield by the condensation of the ketone with ethyl cyanoacetate in the presence of piperidine (Harding and Haworth, *loc. cit.*) and had b. p. 160—163°/15 mm. A middle fraction prepared for analysis had b. p. 163°/16 mm., $d_{4^\circ}^{19\cdot1^\circ}$ 1·0288, $n_{D}^{19\cdot1^\circ}$ 1·4914, whence $[R_L]_D$ 58·36 (calc., 56·42) (Found : C, 69·2; H, 8·2. Calc. : C, 69·5; H, 8·3%).

*Ethyl* r-3-*Methyl*cyclo*hexyl*-1-*cyanoacetate.*—The preceding ester (100 g.) was reduced with 150 g. of moist aluminium amalgam in ether (7 hours). The product gave on distillation *ethyl* r-3-*methyl*cyclo*hexyl*-1-*cyanoacetate* (83 g.), which passed over at 150—153°/15 mm., mainly at 152°/15 mm. The residue crystallised after being treated with light petroleum (b. p. 40—60°) in the manner detailed for the 4-methyl compound; yield, 6 g. It had m. p. 76° (softening at 65°) and was probably a mixture of isomeric bimolecular cyano-esters (Found : *M*, in camphor, 416. $C_{24}H_{36}O_4N_2$ requires *M*, 418). The liquid reduction product after redistillation had b. p. 152°/15 mm., $d_{4^\circ}^{22\cdot4^\circ}$ 1·0022, $n_{D}^{22\cdot4^\circ}$ 1·4586, whence $[R_L]_D$ 57·02 (calc., 56·89) (Found : C, 68·4; H, 9·1. $C_{12}H_{19}O_2N$ requires C, 68·8; H, 9·2%).

r-3-*Methyl*cyclo*hexyl*-1-*malonic Acid.*—The hydrolysis of ethyl 3-methyl*cyclo*hexyl-1-cyanoacetate was effected (36 hours) as described under the 4-methyl compound. The resultant oily acid, crystallised twice from benzene, formed needles, m. p. 115—116° (rapidly heated), 120—121° (slowly heated) (Found : C, 60·3; H, 8·1; equiv., 99. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·1%; equiv., 100). r-3-*Methyl*cyclo*hexyl*-1-*malonic acid* is soluble in water, chloroform, ether, and formic acid; it is sparingly soluble in dilute hydrochloric acid and in benzene when cold but dissolves readily on warming (the corresponding 4-methyl compound is very soluble in ether, but dissolves readily in water, chloroform, and formic acid only when warm). The presence of an isomeric acid could not be detected.

*Synthesis of* r-3-*Methyl*cyclo*hexyl*-1-*malonic Acid from* 3-*Methyl*cyclo*hexyl Iodide and Ethyl Sodiomalonate.*—In the ways already indicated, 3-methyl*cyclo*hexanone was converted through the alcohol, b. p. 174°/760 mm., into 3-methyl*cyclo*hexyl iodide,* b. p. 61—63°/3 mm. (Knoevenagel, *Annalen*, 1897, **297**, 154, gives b. p. 82—83°/10 mm.) (yield, almost quantitative), a colourless mobile liquid with a characteristic odour when freshly distilled.

The condensation with ethyl sodiomalonate was carried out, in

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* This probably contained some of the 4-methyl iodide (see p. 773).

the manner already described, with 97 g. of the iodide, 10 g. of sodium, 200 c.c. of dry alcohol, and 138 g. of ethyl malonate. The product, b. p. 159—163°/19 mm. (45 g.), hydrolysed with twice the calculated quantity of alcoholic potassium hydroxide, gave an almost quantitative yield of oily acids, which solidified on trituration with benzene. The acids were treated with cold formic acid : the insoluble portion, recrystallised three times from hot formic acid, melted at 182—183° and its identity with 4-methyl*cyclo*hexyl-1-malonic acid was confirmed by direct comparison and by a mixed m. p. determination (Found : equiv., 99); the soluble portion was evaporated to dryness on the steam-bath, the resultant oil triturated with a small quantity of benzene, and the solid thus obtained treated with cold formic acid. The residue obtained on evaporation of the filtrate melted at 110—111° after several crystallisations from benzene (Found : C, 60·1; H, 8·1%; equiv., 99·5). This acid resembles *r*-3-methyl*cyclo*hexyl-1-malonic acid, prepared from the cyano-ester, very closely in properties (solubility, crystalline form, etc.) and is probably identical with it; a mixture of the two melted at 117—118°. There appeared to be a very small quantity of an isomeric acid present which could not be removed by fractional crystallisation from common organic solvents.

In order to put the surprising nature of the above result, *viz.*, the formation of approximately equal quantities of 3- and 4-methyl*cyclo*hexylmalonic acids in the condensation of 3-methyl*cyclo*hexyl iodide and ethyl sodiomalonate, beyond all question, the whole experiment was repeated with pure 3-methyl*cyclo*hexanone prepared from the semicarbazone, m. p. 189—190°. (The ketone employed for the above experiments gave a quantitative yield of a semicarbazone, m. p. 186°, and 189—190° after two crystallisations from dilute methyl alcohol.) The pure ketone was successively converted into the alcohol, b. p. 173°/760 mm., the iodide, b. p. 61—62°/3 mm., and ethyl methyl*cyclo*hexylmalonate, b. p. 158—162°/22 mm., mainly 160°/22 mm. (47 g. of the iodide furnished 23 g. of the malonic ester). The ester on hydrolysis gave the same mixture of acids as before. This remarkable reaction will be more fully investigated : possibly, during the conversion of 3-methyl*cyclo*hexanol into the iodide and under the influence of the phosphorus iodides present, dehydration occurs, followed by addition of hydrogen iodide in the two positions leading to the formation of 3- and 4-methyl*cyclo*hexyl iodides.

### *Determination of Surface Tensions and of Densities over a Range of Temperatures. Calculation of the Parachor.*

The apparatus and procedure employed in these determinations were those already described (Vogel, J., 1928, 2027). The correction for the meniscus was 0·24 mm., and the mean constant $K$ 1·8746. The symbols in the tables have already been defined (Vogel, *loc. cit.*).

All the ketones were regenerated, by means of oxalic acid, from the semicarbazones, which had been recrystallised from rectified spirit until the m. p.'s were constant.

2-*Methyl*cyclo*hexanone*, $M = 112{\cdot}10$, b. p. 165°/757 mm., $n_{\mathrm{D}}^{19\cdot4^\circ}$ 1·4484, $d_{4^\circ}^{19\cdot4^\circ}$ 0·9255, whence $[R_L]_{\mathrm{D}}$ 32·45 (calc., 32·34). Semicarbazone, m. p. 195—196°.

Densities determined : $d_{4^\circ}^{18\cdot9^\circ}$ 0·9270 ; $d_{4^\circ}^{61\cdot4^\circ}$ 0·8927 ; $d_{4^\circ}^{83\cdot4^\circ}$ 0·8756.

| $t$. | $h$. | $H$. | $d_{4^\circ}^{t^\circ}$. | $\gamma$. | Parachor. |
|---|---|---|---|---|---|
| 22·3° | 18·55 | 18·31 | 0·9253 | 31·76 | 287·6 |
| 61·4 | 16·84 | 16·60 | 0·8927 | 27·78 | 288·3 |
| 81·6 | 16·04 | 15·80 | 0·8770 | 25·98 | 288·6 |
| | | | | | Mean 288·2 |

3-*Methyl*cyclo*hexanone*, $M = 112{\cdot}10$, b. p. 169°/747·5 mm., $d_{4^\circ}^{18\cdot7^\circ}$ 0·9151, $n_{\mathrm{D}}^{18\cdot7^\circ}$ 1·4463, whence $[R_L]_{\mathrm{D}}$ 32·69. Semicarbazone (also recrystallised twice from methyl alcohol), m. p. 191°.

Densities determined : $d_{4^\circ}^{18\cdot2^\circ}$ 0·9155 ; $d_{4^\circ}^{61\cdot8^\circ}$ 0·8816 ; $d_{4^\circ}^{85\cdot1^\circ}$ 0·8636.

| $t$. | $h$. | $H$. | $d_{4^\circ}^{t^\circ}$. | $\gamma$. | Parachor. |
|---|---|---|---|---|---|
| 21·5° | 18·40 | 18·16 | 0·9129 | 31·08 | 289·9 |
| 63·1 | 16·62 | 16·38 | 0·8806 | 27·04 | 290·3 |
| 83·5 | 15·62 | 15·38 | 0·8648 | 24·93 | 289·7 |
| | | | | | Mean 290·0 |

4-*Methyl*cyclo*hexanone*, $M = 112{\cdot}10$, b. p. 171°/747 mm., $d_{4^\circ}^{19\cdot3^\circ}$ 0·9159, $n_{\mathrm{D}}^{19\cdot3^\circ}$ 1·4455, whence $[R_L]_{\mathrm{D}}$ 32·61. Semicarbazone, m. p. 197°.

Densities determined : $d_{4^\circ}^{18\cdot2^\circ}$ 0·9164 ; $d_{4^\circ}^{62\cdot6^\circ}$ 0·8831 ; $d_{4^\circ}^{85\cdot6^\circ}$ 0·8648.

| $t$. | $h$. | $H$. | $d_{4^\circ}^{t^\circ}$. | $\gamma$. | Parachor. |
|---|---|---|---|---|---|
| 20·2° | 18·33 | 18·09 | 0·9148 | 31·02 | 289·2 |
| 62·6 | 16·62 | 16·38 | 0·8831 | 27·05 | 289·6 |
| 84·3 | 15·76 | 15·52 | 0·8658 | 25·19 | 290·0 |
| | | | | | Mean 289·6 |

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