

# HYDROXY KETONES—PART XII : FRIES REARRANGEMENT OF THE ESTERS OF CYCLOHEXANE BUTYRIC ACID

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Six esters of phenol, o-, m- and p-cresols, 1- and 2-naphthols with cyclohexane butyric acid were prepared by condensing cyclohexane butyryl chloride with the respective phenols and subjected to Fries rearrangement at 120° and 160° in the absence of a solvent. Two isomeric hydroxy ketones, wherever demanded by theory, were isolated by employing chemical methods although the yields of these were low ranging between 2 and 16.6%; these have been characterised through their 2 : 4-dinitrophenylhydrazones.

Adams *et al*<sup>1-5</sup> prepared and tested a variety of fatty acids for their antileprosy effect and observed that disubstituted acetic acids having molecular weights between 250 and 280 possessed strong physiological properties and that the effect was more marked if the  $\omega$ -cyclohexyl group is present as one of the alkyl groups.

Cyclohexane aliphatic acids and their amides were also reported to possess mosquito repellent properties<sup>6</sup> and the effectiveness of the homologous series increased with the number of the carbon atoms in the side chain upto a certain length and then decreased. Thus, increasing the length by insertion of 1, 2 or 3 carbon atoms increased the initial effectiveness of the repellent progressively whereas the addition of 4 and 5 carbon atoms decreased its effectiveness; cyclohexane butyric acid with a minimum dose of 0.10 gm was found to be the most effective mosquito repellent.

Some hydroxy chlorodiphenylmethanes were synthesised in these laboratories and tested for their physiological properties; a few of these were found to be effective larvicides, especially against DDT resistant larvae<sup>7</sup>.

Prompted by these observations and in continuation of our earlier work<sup>7</sup>, we reported the preparation, by the Fries rearrangement of the esters of cyclohexane carboxylic acid, of some hydroxy ketones<sup>8</sup>.

The present investigation was taken up with two objects : (i) to study the effect of the chain length attached to the alicyclic ring in the acyl part of the ester in this migration and compare it with the observations already reported in the earlier paper and (ii) to synthesise substituted diphenylmethanes, having a cyclohexane butyryl side chain, obtainable by the reduction of the hydroxy ketones recorded in this paper, which may be physiologically active.

It may be mentioned that while the work presented in this communication and the one already published<sup>8</sup> was almost complete, a paper<sup>9</sup> describing the migration of some esters of cyclohexane butyric acid appeared and as our results were at variance with those reported, we repeated the entire work and now record below our results thereby confirming our earlier observations.

We have isolated the isomeric ortho- and para-hydroxy ketones, wherever demanded by theory, by employing chemical methods for their separation but these authors have reported the isolation of only one ketone in all the cases studied. The yields of these ketones were poor and ranged between 2 and 16.6 per cent. No mention has been made by these authors of about 50 per cent of the unchanged ester which is obtained in every migration.

Further, 3-methylphenyl cyclohexane butyrate on Fries migration gave us only the ortho-hydroxy ketone characterised by Pyman's test but these authors report the isolation of the p-hydroxy ketone, which we never obtained. It might be mentioned here that similar migration of 3-methylphenylcyclohexane carboxylate had furnished the ortho-hydroxy ketone<sup>8</sup>.

As the yields of the hydroxy ketones were poor, none of these could be reduced to the desired diphenylmethanes.

#### EXPERIMENTAL PROCEDURE

##### *Cyclohexane butyryl chloride*

To cyclohexane butyric acid (17 g; 1 mole) contained in a round bottomed flask (500 ml.) fitted with a reflux condenser, phosphorus pentachloride (23 g; 1.1 mole) was added and the contents heated until the evolution of hydrogen chloride ceased (3 hrs). The reaction product was distilled when pure *cyclohexane butyryl chloride* had b.p. 94°/3.5 mm. (yield : 12.6 g ; 61.1 %).

TABLE I

##### PHENYL ESTERS

Ester	b.p. or m.p. °C	Yield %	Mol. formula	Found C	% H	Requires C	% H
Phenylcyclohexyl butyrate.	175/1.5 mm	55	C <sub>16</sub> H <sub>22</sub> O <sub>2</sub>	77.9	8.8	78.0	8.9
2-Methylphenyl cyclohexyl butyrate.	220.3°/3.5 mm	50	C <sub>17</sub> H <sub>24</sub> O <sub>2</sub>	78.3	9.0	78.4	9.2
3-Methylphenyl cyclohexyl butyrate.	210°/4.0 mm	50	C <sub>17</sub> H <sub>24</sub> O <sub>2</sub>	78.2	9.1	78.4	9.2
4-Methylphenyl cyclohexyl butyrate.	202.3°/2.0 mm	50	C <sub>17</sub> H <sub>24</sub> O <sub>2</sub>	78.3	9.2	78.4	9.2
1-Naphthyl cyclohexyl butyrate.	71	40	C <sub>20</sub> H <sub>24</sub> O <sub>2</sub>	81.1	8.2	81.0	8.1
2-Naphthyl cyclohexyl butyrate.	51	45	C <sub>20</sub> H <sub>24</sub> O <sub>2</sub>	81.2	8.0	81.0	8.1

*Preparation of the esters*

Cyclohexane butyryl chloride (1 mole) was heated on water bath under reflux with the appropriate phenol (1.1 mole) until the evolution of hydrogen chloride ceased. The reaction mixture was cooled, poured into water and extracted with ether. The ethereal solution was washed free of phenol, dried and ether recovered; the esters were purified by distillation under reduced pressure or by crystallisation from dilute ethanol and the yields of the esters ranged between 40–55 per cent. The analytical and other data for the esters prepared are given in Table 1.

*Fries migration of the esters*

The ester (1 mole) was intimately mixed with powdered anhydrous aluminium chloride (1.3 mole) and the contents heated under anhydrous conditions in an oil bath at 120° and 160° for 2 hours. The reaction product was hydrolysed with ice-cold hydrochloric acid and extracted with ether. The ethereal extract was washed successively with sodium bicarbonate (5 per cent), sodium carbonate (5 per cent) and sodium hydroxide (2 per cent) and finally with water. The residual ethereal solution was dried and on recovering ether unreacted ester was isolated in all the cases. The sodium bicarbonate extracts gave no deposits of the acid on acidification, while sodium carbonate and sodium hydroxide extracts gave the ortho- and para-hydroxy ketones respectively on acidification.

*Hydroxy-ketones*

1. *Phenyl cyclohexyl butyrate* (1.87 g) at 120° gave :

(a) 2-Hydroxyphenyl cyclohexane butyryl ketone, b.p. 158°/1.5 mm.

(Yield : 0.15 g ; 8.5%).

(Found : C, 77.9 ; H, 8.7.  $C_{16}H_{22}O_2$  requires C, 78.0 ; H, 8.9%).

It gave a violet colour with aqueous ferric chloride and a 2 : 4-dinitrophenylhydrazone, m.p. 237°.

(b) 4-Hydroxyphenyl cyclohexane butyryl ketone, m.p. 136–37°.

(Yield : 0.21 g ; 11.2%).

(Found : C, 77.8 ; H, 8.8.  $C_{16}H_{22}O_2$  requires C, 78.0 ; H, 8.9%).

It gave no coloration with aqueous ferric chloride ; its 2 : 4-dinitrophenylhydrazone, had m.p. 127°.

(c) Unchanged ester recovered was 1.0 g (53.4%).

Reaction at 160° with the same amount of the above ester gave

(i) o-hydroxy ketone (0.24 g ; 12.8%),

(ii) p-hydroxy ketone (0.07 g ; 3.7%), and

(iii) unreacted ester (0.36 g ; 19.2%),

2. *2-Methylphenyl cyclohexane butyrate* (2.5 g) at 120° furnished only :

(a) 4-Hydroxy 3-methylphenyl cyclohexane butyryl ketone, b.p. 146°/1 mm.

(Yield : 0.21 g ; 8.4%).

(Found : C, 78.2 ; H, 9.0.  $C_{17}H_{24}O_2$  requires C, 78.4 ; H, 9.2%).

It gave no coloration with aqueous ferric chloride ; its 2 : 4-dinitrophenylhydrazone had m.p. 241°.

(b) Unchanged ester recovered was 1.4 g (56%).

The above ester (2.5 g) on migration at 160° gave the p-hydroxy ketone (0.12 g ; 4.8%) and the unchanged ester recovered was 0.44 g (17.6%).

3. *3-Methylphenyl cyclohexane butyrate* (2.5 g) at 120° gave only :

(a) 2-Hydroxy 4-methyl or 2-hydroxy 6-methylphenyl cyclohexane butyryl ketone, b.p. 218-20°/6 mm.

(Yield : 0.4 g ; 16.1%).

(Found : C, 78.3 ; H, 9.1.  $C_{17}H_{24}O_2$  requires C, 78.4 ; H, 9.2%).

It gave a violet coloration with aqueous ferric chloride and a 2 : 4-dinitrophenylhydrazone, m.p. 195°.

(b) Unchanged ester recovered was 1.25 g ; 50%. Migration of this ester (2.5 g) at 160° gave the above hydroxy ketone (0.3 g ; 12%) characterised by its colour reaction and 2 : 4-dinitrophenylhydrazone m.p. and mixed m.p. 195°.

Unchanged ester weighed 1.3 g (52%).

4. *4-Methylphenyl cyclohexane butyrate* (2.5 g) at 120° yielded :

(a) 2-Hydroxy 5-methylphenyl cyclohexane butyryl ketone, b.p. 185°/3 mm.

(Yield : 0.33 g ; 13.2%).

(Found : C, 78.2 ; H, 9.0.  $C_{17}H_{24}O_2$  requires C, 78.4 ; H, 9.2%).

It gave a violet coloration with aqueous ferric chloride and a 2 : 4-dinitrophenylhydrazone, m.p. 174-5°.

(b) Unchanged ester recovered weighed 1.2 g.

Reaction at 160° with the same amount of ester gave the above o-hydroxy ketone (0.44 g ; 17.6%) characterised by the colour reaction ; the m.p. and mixed m.p. of the 2 : 4 dinitrophenylhydrazone (174-5°) was undepressed.

(c) Unchanged ester weighed 1.2 g (48%).

5. *1-Naphthyl cyclohexane butyrate* (3.0 g) at 120° furnished :

(a) 1-Hydroxy 2-naphthyl cyclohexane butyryl ketone, b.p. 129-130°/5 mm ; m.p. 91°

(Yield : 0.42 g ; 14.0%).

(Found : C, 81.1 ; H, 8.0.  $C_{20}H_{24}O_2$  requires C, 81.0 ; H, 8.1%).

It gave a violet coloration with aqueous ferric chloride and a 2 : 4-dinitrophenylhydrazone, m.p. 239°.

(b) 1-Hydroxy 4-naphthyl cyclohexane butyryl ketone, b.p. 195.6°/3 mm.

Yield : (0.06 g ; 2%).

(Found : C, 80.8 ; H, 8.0.  $C_{20}H_{24}O_2$  requires C, 81.0 ; H, 8.1%).

It gave no coloration with aqueous ferric chloride ; its 2 : 4-dinitrophenylhydrazone had m.p. 251°.

(c) Unchanged ester weighed 1.4 g (46.6%).

Reaction of the above ester (3.0 g) at 160° gave the above hydroxy ketone (0.17 g ; 5.6%) ; mixed m.p. of the 2 : 4-dinitrophenylhydrazone, 251° was undepressed.

Unchanged ester recovered weighed 1.8 g (60%).

6. 2-Naphthyl cyclohexane butyrate (3 g) at 120° gave :

(a) 2-Hydroxy 1-naphthyl cyclohexane butyryl ketone, b.p. 155.6°/6 mm.

(Yield : 0.5 g ; 16.6 %).

(Found : C, 80.9 ; H, 8.2.  $C_{20}H_{24}O_2$  requires C, 81.0 ; H, 8.1%).

It gave a red coloration with aqueous ferric chloride and a 2 : 4-dinitrophenylhydrazone, m.p. 241°.

(b) 6-Hydroxy 2-naphthyl cyclohexane butyryl ketone, b.p. 167.9°/4 mm.

(Yield : 0.4 g ; 13.3%).

(Found : C, 81.1 ; H, 8.0.  $C_{20}H_{24}O_2$  requires C, 81.0 ; H, 8.2%).

It gave no coloration with aqueous ferric chloride ; its 2 : 4-dinitrophenylhydrazone had m.p. 249°.

(c) Unchanged ester weighed 1.6 g (53.3%).

Migration of the above ester (3.0 g) at 160° furnished only 2-hydroxy 1-naphthyl cyclohexane butyryl ketone (0.3 g ; 10%).

Unchanged ester was 1.2 g (40%).

It gave red coloration with aqueous ferric chloride and 2 : 4-dinitrophenylhydrazone, m.p. 249° ; mixed m.p. with the 2 : 4-dinitrophenylhydrazone of the ketone obtained at 120° was undepressed.

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