114. *Hydrogenation of 4′-Hydroxydiphenylylacetic Acid.*

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A possible synthesis of certain analogues of steroidal hormones required 4-4′-hydroxy*cyclo*hexyl*cyclo*hexylacetic acid. This was obtained by hydrogenation of 4′-hydroxy-4-diphenylylacetic acid.

KINDLER (WILLGERODT) reaction of 4′-methoxy-4-diphenylyl methyl ketone gave 4′-methoxy-4-diphenylylacetic acid. This was demethylated and the dipotassium salt of the phenolic acid obtained was hydrogenated in aqueous solution at high temperature and pressure, Raney nickel being used as catalyst. The mixture of acids obtained was esterified and separated into phenolic and non-phenolic fractions. The non-phenolic fraction was a mixture of perhydro-compounds and yielded two stereoisomers of 4-4′-hydroxy*cyclo*hexyl*cyclo*hexylacetic acid (m. p.s 214° and 215·5—216°). These isomers were assigned a *trans*-configuration in the *cyclo*hexylacetic acid ring since each upon oxidation gave the same keto-acid which by Clemmensen reduction gave the known [1] *trans*-4-*cyclo*hexyl*cyclo*hexylacetic acid.

Hydrogenation of 4′-hydroxy-4-diphenylylacetic acid with shorter time and reduced pressure of hydrogen and Raney nickel : substrate ratio led to the recovery of partially hydrogenated material. The non-phenolic fraction yielded a stereoisomer of 4-4′-hydroxy*cyclo*hexylphenylacetic acid (m. p. 219—220°). The mother liquors from the acidified mixture, after removal of reduced material and catalyst, slowly gave the other stereoisomer of this acid (m. p. 174·5—175°).

The isolation of *p*-4′-hydroxy*cyclo*hexylphenylacetic acid on partial hydrogenation of 4′-hydroxy-4-diphenylylacetic acid agrees with the findings of other workers [2] where preferential reduction of the phenolic ring in a 4-hydroxydiphenyl system occurs when Raney nickel is used as catalyst under basic conditions.

EXPERIMENTAL

4′-Methoxy-4-diphenylylacetic Acid.—4′-Methoxy-4-diphenylyl methyl ketone (52 g.), morpholine (36 ml.), and sulphur (9·2 g.) were refluxed with stirring for 10 hr. and then poured into sodium hydroxide solution (13%; 750 ml.). The mixture was stirred and refluxed for 12 hr., and then cooled and filtered. The residue was extracted with portions of boiling water and the combined filtrates were acidified. The precipitate was filtered off (crude yield 63%) and recrystallised (from benzene and then aqueous alcohol), giving white plates of *4′-methoxy-4-diphenylylacetic acid*, m. p. 188—188·5° (Found: C, 74·4; H, 6·0; MeO, 12·8%; equiv., 239. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8; MeO, 12·8%; equiv., 242). The p-*bromophenacyl ester* was obtained as white micro-needles (from benzene), m. p. 180° (Found: C, 62·9; H, 4·5; Br, 18·0. $C_{24}H_{21}O_4Br$ requires C, 62·9; H, 4·4; Br, 18·2%). The *amide* formed white micro-needles (from ethanol), m. p. 258—259° (Found: C, 74·3; H, 6·1; N, 5·6. $C_{15}H_{15}O_2N$ requires C, 74·7; H, 6·3; N, 5·8%).

4′-Hydroxy-4-diphenylylacetic Acid.—4-Methoxy-4′-diphenylylacetic acid (30 g.) was refluxed with acetic acid (400 ml.) and hydrobromic acid (48%; 50 ml.) for 16 hr. The acetic acid was then removed and the residue diluted with water to give a crystalline mass (27·2 g.; 96%). Recrystallisation (from acetic acid) gave plates of *4′-hydroxy-4-diphenylylacetic acid*, m. p. 244—245° (Found: C, 73·9; H, 5·4. $C_{14}H_{12}O_3$ requires C, 73·7; H, 5·3%). The *acetate* was obtained (from aqueous alcohol) as white micro-crystals, m. p. 187·5—188·5° (Found: C, 71·2; H, 5·4; Ac, 16·3%; equiv., 269. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2; Ac, 15·9%; equiv., 270).

Perhydrogenation of 4′-Hydroxy-4-diphenylylacetic Acid.—4′-Hydroxy-4-diphenylylacetic acid (10 g.), in water (400 ml.) containing potassium hydroxide (4·92 g.) and W5 Raney nickel (12 g.), was hydrogenated at 240° and 200 atm. for 20 hr. The catalyst was then removed and the filtrate acidified. The precipitate (9·01 g.) was refluxed with methanol (100 ml.) and sulphuric acid (2 ml.) for 9 hr., and the solution then diluted with water and extracted with ether.

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[1] Fieser *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 3186.

[2] Dauben and Tanabe, *ibid.*, 1953, **75**, 4969.

The ethereal extract was washed with sodium hydrogen carbonate solution (5%) and then with potassium hydroxide solution (10%; 3 × 30 ml.). The aqueous layer remaining was refluxed for 7½ hr., filtered, and acidified to give phenolic material (0·06 g.). The ethereal liquors were evaporated and refluxed for 10 hr. with alcoholic potassium hydroxide (10%), and then diluted with water and acidified to give acidic material (7·8 g.; m. p. 163—173°). This material did not absorb at 265 mμ. (*a*) The acidic material (1 g.) was twice recrystallised (from acetic acid) to give material (0·06 g.), m. p. 207·5—209°; two more crystallisations yielded white micro-crystals of *4-4′-hydroxy*cyclo*hexyl*cyclo*hexylacetic acid*, m. p. 214° (Found: C, 70·8; H, 10·2. $C_{14}H_{24}O_3$ requires C, 70·0; H, 10·1%). The *acetate* was obtained [from light petroleum (b. p. 60—80°)] as white micro-needles, m. p. 96·5—98° (Found: C, 68·6; H, 9·3. $C_{16}H_{26}O_4$ requires C, 68·1; H, 9·3%). (*b*) The acidic material (3 g.) was dissolved in N-sodium hydroxide solution (20 ml.) and water (80 ml.). The solution was filtered and sodium nitrate (10 g.) dissolved in it by boiling, and the solution then set aside at room temperature for some hours. The acid was recovered from the precipitated sodium salt (1·074 g.; m. p. 189—200°). This procedure was then repeated with half the quantities of reagents given above. The recovered material, (0·55 g.; m. p. 200—206°) was twice recrystallised (from aqueous acetic acid), giving white micro-crystals of *4-4′-hydroxy*cyclo*hexyl*cyclo*hexylacetic acid*, m. p. 215·5—216°, which depressed the melting point of the isomeric acid described above (*a*) (Found: C, 69·9; H, 10·2%; equiv., 244. $C_{14}H_{24}O_3$ requires C, 70·0; H, 10·1%; equiv., 240). The *acetate* was obtained [from light petroleum (b. p. 60—80°)] as white micro-crystals, m. p. 140—141·5° (Found: C, 68·3; H, 9·4. $C_{16}H_{26}O_4$ requires C, 68·1; H, 9·3%), which depressed the melting point of the isomeric acetate described above (*a*).

Oxidation of 4-4′-*Hydroxy*cyclo*hexyl*cyclo*hexylacetic Acid.*—The stereoisomer (0·25 g.), m. p. 214°, of 4-4′-hydroxy*cyclo*hexyl*cyclo*hexylacetic acid was dissolved in acetic acid and oxidised with chromium trioxide in aqueous acetic acid. The solution was worked up in the usual manner to give a glass (0·17 g.). The ketonic fraction was separated by preparation of the semicarbazone which upon subsequent hydrolysis and recrystallisation (from carbon tetrachloride) gave micro-needles of *4-4′-oxo*cyclo*hexyl*cyclo*hexylacetic acid*, m. p. 138·5° (Found: C, 70·3; H, 9·2%; equiv., 243. $C_{14}H_{22}O_3$ requires C, 70·5; H, 9·3%; equiv., 238). The *semicarbazone* (from aqueous acetic acid) had m. p. 205·5—206·5° (decomp.) (Found: C, 60·4; H, 8·2; N, 13·7. $C_{15}H_{25}O_3N_3$ requires C, 61·0; H, 8·5; N, 14·2%). The *ethyl ester* 2 : 4-*dinitrophenylhydrazone* was obtained (from ethanol) as long, orange needles, m. p. 141° (Found: C, 59·2; H, 6·9; N, 12·5. $C_{22}H_{30}O_6N_4$ requires C, 59·2; H, 6·8; N, 12·6%).

The stereoisomer, m. p. 215·5—216°, of 4-4′-hydroxy*cyclo*hexyl*cyclo*hexylacetic acid was similarly oxidised to give material, m. p. and mixed m. p. 138·5° with the aforementioned sample of 4-4′-oxo*cyclo*hexyl*cyclo*hexylacetic acid. The ethyl ester 2 : 4-dinitrophenylhydrazone was obtained as long orange needles, m. p. and mixed m. p. 141° with the corresponding derivative of the aforementioned sample of 4-4′-oxo*cyclo*hexyl*cyclo*hexylacetic acid.

Clemmensen Reduction of 4-4′-*Oxo*cyclo*hexyl*cyclo*hexylacetic Acid.*—4-4′-Oxo*cyclo*hexyl*cyclo*hexylacetic acid (0·45 g.) was refluxed with amalgamated zinc (10 g.), water (20 ml.) concentrated hydrochloric acid (25 ml.), and acetic acid (25 ml.) for 11½ hr. The supernatant liquid was decanted off and cooled to give a flocculent precipitate (0·35 g.; m. p. 131—132°). Recrystallisation (from aqueous acetic acid) gave white micro-crystals of *trans*-4-*cyclo*hexyl*cyclo*hexylacetic acid, m. p. and mixed m. p. 136—137° with an authentic sample (Found: C, 75·2; H, 10·5%; equiv., 224. Calc. for $C_{14}H_{24}O_2$: C, 75·0; H, 10·8%; equiv., 224). The p-*bromophenacyl ester* was obtained (from aqueous ethanol) as felted micro-needles, m. p. 142·5—143·5° (Found: C, 62·2; H, 7·0; Br, 18·6. $C_{22}H_{29}O_3Br$ requires C, 62·7; H, 6·9; Br, 19·0%).

Partial Hydrogenation of 4′-Hydroxy-4-diphenylylacetic Acid.—4′-Hydroxy-4-diphenylylacetic acid (5 g.), in water (400 ml.) containing potassium hydroxide (2·46 g.) and W5 Raney nickel (3 g.), was hydrogenated at 240° and 170 atm. for 10 hr. The suspension was then filtered and acidified to give a mixture of acids (3·75 g.; m. p. 179—190°). This material was separated into phenolic and non-phenolic fractions as previously described. The phenolic fraction gave a white solid (0·51 g.; m. p. 235—239°) which on crystallisation (from aqueous acetic acid) gave plates, m. p. and mixed m. p. 244° with authentic 4′-hydroxy-4-diphenylylacetic acid. The non-phenolic fraction gave a mixture of acids (1·79 g.; m. p. 199—203°) which upon repeated crystallisation (from aqueous acetic acid) gave micro-needles of p-*4′-hydroxy*cyclo*hexylphenylacetic acid*, m. p. 219—220° (Found: C, 71·2; H, 7·7. $C_{14}H_{18}O_3$

requires C, 71·8; H, 7·7%); $\lambda_{max.}$ (in 95% ethanol) 263 mμ (log ε 2·60) [cf.[3] toluene, $\lambda_{max.}$ 262 (log ε 2·45); *p-cyclo*hexylphenol, $\lambda_{max.}$ 278 (log ε 3·35)]. The *acetate* was obtained as white micro-needles [from light petroleum (b. p. 60—80°)], m. p. 115·5° (Found: C, 69·7; H, 7·3. $C_{16}H_{20}O_4$ requires C, 69·6; H, 7·3%).

After removal of nickel and precipitated acids from the reaction solution, the mother liquors slowly deposited (3 days) an amorphous solid (0·24 g.; m. p. 166—168°). Repeated crystallisation (from aqueous acetic acid) gave white micro-crystals of p-*4'-hydroxy*cyclo*hexylacetic acid*, m. p. 174·5—175° depressed on admixture with the stereoisomer, m. p. 219—220° (Found: C, 71·5; H, 7·9. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). The *acetate* was obtained [from light petroleum (b. p. 60—80°)] as long white needles, m. p. 121° (depressed on admixture with the acetate of the stereoisomer, m. p. 219—220°); $\lambda_{max.}$ (95% ethanol) 262·5 (log ε 2·54) (Found: C, 70·0; H, 7·2. $C_{16}H_{20}O_4$ requires C, 69·6; H, 7·3%).

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[3] Friedel and Orchin, " Ultra-violet Spectra of Aromatic Compounds," John Wiley and Sons, New York, 1951.