

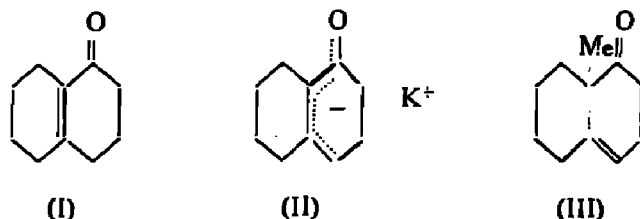
## ANGULAR METHYLATION STUDIES ON $\Delta^{4(10)}$ -OCTALONE-1

BY J. A. K. QUARTEY

$\Delta^{4(10)}$ -Octalone-1 (VI) has been obtained by the Birch reduction of 5:6:7:8-tetrahydro-1-naphthyl hydroxyethyl ether (VII: R=CH<sub>2</sub>CH<sub>2</sub>OH), followed by mild acid hydrolysis. The octalone (VI) cannot be methylated in the angular position under the usual conditions. On catalytic hydrogenation in a neutral medium it affords almost quantitatively *trans*-1-decalone (IX).

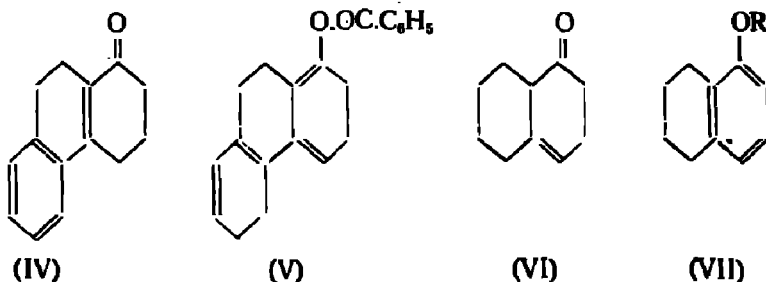
Abundant evidence has been obtained that the angular methyl groups can be omitted in steroid analogues with retention of considerable hormonal activity. Thus, as has been established, 19-nortestosterone (Birch, *J. Chem. Soc.*, 1950, 367) and 19-norprogesterone (Djerassi *et al.*, *J. Amer. Chem. Soc.*, 1953, 75, 4440) possess a high order of activity (see also Djerassi *et al.*, *ibid.*, 1953, 75, 4117; 1954, 76, 4092; 1955, 77, 148). Johnson *et al.* (*ibid.*, 1953, 75, 4866) found 18-nor-D-homoandrostan-3:17a-dione to be as active as the natural androstan-3:17-dione. Earlier, Birch and Quartey (*Chem. & Ind.*, 1953, 489) had produced evidence that an 18:19-*bis*-nor-D-homosteroid possessed some activity, and had advanced the view that *bis*-nor-D-homo analogues of steroid hormones might in general be expected to show considerable activity, provided that the *trans* configuration was present at the C.D ring-junction. Johnson *et al.* (*J. Org. Chem.*, 1954, 19, 670), however, found that 18:19-*bis*-nor-D-homotestosterone had little activity. Thus the question of the structural requirements for hormonal activity needs further investigation.

In the general case it is desirable, however, to have the angular methyl groups present, and methods have been examined for their introduction into the preformed nucleus (Birch, Quartey, and Smith, *J. Chem. Soc.*, 1952, 1768). These methods depend on the supposition that if compounds of type (I) can be converted into the salts of the mesomeric anion (II), addition of a methyl cation may be expected to yield predominantly the desired product (III).



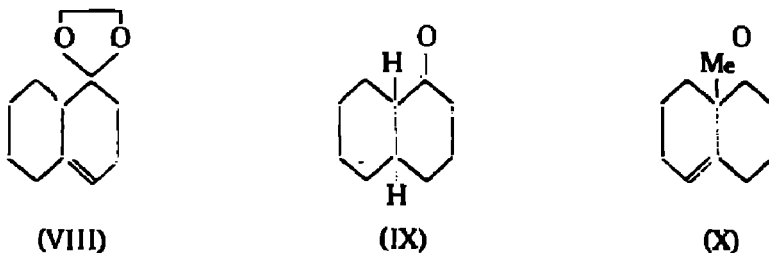
The double bond in (I) is extremely stable, the equilibrium between simple  $\alpha$ : $\beta$ - and  $\beta$ : $\gamma$ -unsaturated ketones in the presence of acid or basic catalysts being generally largely in favour of the  $\alpha$ : $\beta$ -isomer. Hence indirect methods are required for the formation of the salt of the mesomeric anion (II); though in some cases the requisite salts may be directly produced by the

action of the correct enolising agent. An attempt to obtain such a salt from (IV) by conversion first to the enol-acetate failed, though the enol-benzoate (V) could be obtained (in poor yield). The acid hydrolysis of this enol-benzoate is as facile as that of enol-ethers.



The usual Birch (metal-alcohol/liquid ammonia) reduction of aromatic compounds of type (VII), followed by vigorous acid hydrolysis of the dihydrobenzene "acids", results in the conjugated ketone of type (I). Birch (*J. Chem. Soc.*, 1944, 430) reported that the reduction and subsequent hydrolysis of (VII: R=Me) gave only a trace of (I). This has been confirmed, the yield of (I) being 3% calculated on the isolated 2:4-dinitrophenylhydrazone. It has been found, however, that the ether (VII: R=CH<sub>2</sub>.CH<sub>2</sub>OH), is reduced smoothly and affords a good yield of the ketone on hydrolysis (64%). Milder conditions of hydrolysis have been found to yield 34% of  $\beta$ : $\gamma$ -unsaturated ketone (VI). This unconjugated isomer has been examined for angular methylation.

An angular methyl group could not be introduced into (VI) to furnish (III) under the usual conditions with potassium amide in liquid ammonia, or even in boiling toluene, followed by methyl iodide. The ketone (VI) was recovered unchanged from these experiments. It has not been possible to obtain satisfactory analyses for the ketones (I) and (VI) even after purification through the semicarbazones.



Any possibility of the formation of a spiroketal, such as (VIII), which corresponds more closely to the analysis, can, however, not be sustained since the ketones were obtained by acid hydrolysis (cf. Birch, Murray, and Smith, *J. Chem. Soc.*, 1951, 1945). Furthermore, the ketone (VI) was isolated as the sodium bisulphite addition compound, and the other (I) not furnishing such an adduct; the derivatives of (I) and (VI) gave the correct analyses.

The ketone (VI) on treatment with acid is converted into (I), which can itself be directly obtained by more vigorous hydrolysis of the reduction product of (VII: R=CH<sub>2</sub>.CH<sub>2</sub>OH). The ultraviolet characteristics of (I),  $\lambda_{\max}$  244 m $\mu$ ,  $\epsilon_{\max}$  8,800;  $\lambda_{\min}$  286 m $\mu$ ,  $\epsilon_{\min}$  67.6;  $\lambda_{\max}$  301-304 m $\mu$ ,  $\epsilon_{\max}$  74.7, are in agreement with those reported for  $\Delta^{9(10)}$ -octalone-1 by Campbell and Harris (*J. Amer. Chem. Soc.*, 1941, 63, 2721) who record  $\lambda_{\max}$  243 m $\mu$ ,  $\epsilon_{\max}$  10,000;  $\lambda_{\max}$  305 m $\mu$ ,  $\epsilon_{\max}$  63.1.

The ketone (VI) is hydrogenated almost quantitatively, with palladium-charcoal in ether, to a ketone, which has been characterised as *trans*-1-decalone (IX), the production of the more stable *trans* configuration being in accordance with the expectation (cf. the hydrogenation of unsaturated steroids). It is thus clear that the starting material was substantially the pure ketone (VI), and the conclusion then is that it cannot be methylated in the angular position by the usual procedure, i.e., the energy required to form the resonant ion (II) is not reached though a positive result would have been helpful in deciding between the isomeric ketones (III) and (X), obtained by various earlier workers, e.g. Plentl and Bogert (*J. Org. Chem.*, 1941, 6, 669).

### EXPERIMENTAL

1 : 2 : 3 : 4 : 9 : 10-Hexahydro-1-ketophenanthrene (IV).—Resorcinol dimethyl ether (20 g.) was dissolved in ethanol (150 c.c.) and added to liquid ammonia (1.5 litres). Sodium (9 g.) in thin slices was added; after the reaction water (1 litre) was slowly added. The mixture was extracted with ether (4×100 c.c.), the ether extract washed once with water (150 c.c.), and dried ( $K_2CO_3$ ). It was then evaporated under nitrogen under reduced pressure and the product distilled to afford 1 : 4-dihydro-2 : 6-dimethoxybenzene, b.p. 86°/12 mm, yield 16.8 g. (83%).

To a solution of potassium amide (from the metal, 2.25 g., 1.1 mole) in liquid ammonia (ca. 200 c.c.) was added the above dihydro ether (14.0 g.), the solution changing to a deep red colour with the formation of the potassium salt. The solution was left for 10 minutes and then phenethyl bromide was slowly added with swirling until the red colour was discharged (9.3 g. of the bromide). Water (100 c.c.) was cautiously added, and the product extracted with ether. The ether extract was washed once with water, and evaporated. 1 : 3-Dimethoxy-2-phenethylcyclohexa-3 : 6-diene, so obtained, was hydrolysed with 2*N*-HCl (10 c.c.) for 10 minutes on the steam bath. The solution was cooled, extracted with ether, and the ether extract shaken with small portions of sodium hydroxide solution (10%) until acidification gave no further precipitate. The crystalline solid so obtained was removed by filtration and crystallised from ethyl acetate-petrol ether (60-80°) (1 : 1) to furnish colorless prisms of 2-phenethylcyclohexane-1 : 3-dione, m.p. 147°, in 85% yield, based on the dihydro ether. The above diketone (3.0 g.) was added as a fine powder to a stirred solution of phosphoric anhydride (12 g.) in phosphoric acid (1.75 c.c.). The solution was kept under nitrogen at 150° for 45 minutes, after which it was cooled. Water was added, the product extracted with ether, the ether extract dried ( $Na_2SO_4$ ), and evaporated. Purification was achieved by chromatography on activated alumina (30 g.) when the 1 : 2 : 3 : 4 : 9 : 10-hexahydro-1-ketophenanthrene was eluted with ether-petrol ether (40-60°) (2 : 1) and crystallised from petrol ether (b.p. 40-60°) to provide colorless prisms, m.p. 48-49°, yield 1.5 g., 55% based on the dione. (Found: C, 84.8; H, 7.15. Calc. for  $C_{14}H_{14}O$ : C, 84.8; H, 7.1%). Johnson, Johnson, and Petersen (*J. Amer. Chem. Soc.*, 1946, 68, 1928) record m.p. 49-49.5° for the material purified through the semicarbazone.

The oxime was crystallised from ethanol, m.p. 140°. (Found: N, 6.4. Calc. for  $C_{14}H_{15}ON$ : N, 6.6%). Johnson, Johnson, and Petersen (*loc. cit.*) record m.p. 141-42°.

The above ketone, when heated with acetic anhydride together with a trace of *p*-toluenesulphonyl chloride on the steam bath for 1.5 hours under nitrogen, was recovered unchanged, m.p. 48-49°, undepressed by the starting material.

2 : 3 : 9 : 10-Tetrahydrophenanthrene-1-benzoate (V).—The above ketone (1.0 g.) was heated with benzoyl chloride (5 c.c.) at 120-30° under nitrogen for 3 hours. The solution was cooled, poured into dilute 5% NaOH solution, and left overnight. It was extracted with ether, the ether

extract washed, dried ( $K_2CO_3$ ), and evaporated. The product was taken up in little of ether and put on a column of activated alumina (ca. 30 g.). The chromatogram was developed and after a preliminary first fraction of petrol ether (40-60°), the product was eluted with ether—petrol ether (40-60°) (1 : 1).

2 : 3 : 9 : 10-*Tetrahydrophenanthrene-1-benzoate*, obtained in poor yield, was crystallised from ether, m.p. 134°. (Found : C, 83.1 ; H, 5.8.  $C_{21}H_{18}O_2$  requires C, 83.4 ; H, 6.0%). The infrared absorption spectrum in nujol mull showed bands at the following wave lengths ( $\mu$ ) : (3.95N), 5.77s, 6.05m, 6.25m, 6.31m, 6.40m, (6.90N), (7.27N), 7.64w, 7.90s, 7.97s, 8.35m, 8.57s, 8.90s, 9.20s, 9.37m, 9.75m, 10.00w, 11.15w, 11.36w, 11.60w, 12.45w, 12.70w, 13.24s, 13.70m, 14.06s, 14.63w. (s = strong, m = medium, w = weak).

With Brady's reagent it gave 1 : 2 : 3 : 4 : 9 : 10-hexahydro-1-ketophenanthrene-2 : 4-dinitrophenylhydrazone.

5 : 6 : 7 : 8-*Tetrahydro-1-naphthylhydroxyethyl Ether* (VII : R =  $CH_2CH_2OH$ ).—Commercial  $\alpha$ -naphthol (50 g.) was reduced with sodium (40 g.) in boiling amyl alcohol (600 g.) over a period of 2 hours. The solution was cooled, poured into water, and the amyl alcohol steam-distilled. After cooling, the sodium salt was acidified with HCl (dil.), the solution extracted with ether, the ether extract washed, dried ( $Na_2SO_4$ ), evaporated, and distilled under nitrogen. Unless the distillation was under nitrogen, appreciable decomposition of the product occurred, this being presumably due to aromatisation. 5 : 6 : 7 : 8-Tetrahydro-1-naphthol boiled at 144°/14 mm (41 g.) and it was crystallised from petrol ether (40-60°), m.p. 74-75°. (Found : C, 81.1 ; H, 7.85. Calc. for  $C_{10}H_{12}O$  : C, 81.1 ; H, 8.1%). Bamberger and Bordt (*Ber.*, 1890, 23, 215) record m.p. 68.5-69°. The methyl ether (VII : R = Me) (29 g. from 34 g. of the phenol) boiled at 124°/10mm,  $n_D^{20}$  1.566.

To the above 5 : 6 : 7 : 8-tetrahydro-1-naphthol (30 g.), dissolved in 10% NaOH solution (160 c.c.) and heated on the steam bath, was slowly added with stirring ethylene chlorhydrin (80 g., 5 moles) in small portions, 10% NaOH solution being added to keep the mixture alkaline. At the end of the addition of the ethylene chlorhydrin, a further 150 c.c. of 10% NaOH solution was added, the mixture stirred for a further  $\frac{1}{2}$  hour, cooled and extracted with ether. The ether extract was washed, dried ( $Na_2SO_4$ ), evaporated, and distilled under nitrogen. The product distilled almost quantitatively (35 g., 90% of the theoretical) as a viscous yellow oil, b.p. 135-37°/0.1 mm.

5 : 6 : 7 : 8-*Tetrahydro-1-naphthylhydroxyethyl ether* (VII : R =  $CH_2CH_2OH$ ) was crystallised from petrol ether (40-60°) in dimorphic white needles, m.p. 41-42°, which on repeated recrystallisation gave white plates, m.p. 51°. (Found : C, 75.2 ; H, 8.2.  $C_{12}H_{16}O_2$  requires C, 75.0 ; H, 8.3%).

$\Delta^{4(10)}$ -*Octalone-1* (VI).—5 : 6 : 7 : 8-Tetrahydro-1-naphthylhydroxyethyl ether (30 g.), dissolved in ethanol (600 c.c.), was added to liquid ammonia (ca. 1.5 litres). Sodium (86 g., 6 moles) in thin slices was added with shaking. After the reaction, water (1 litre) was gradually added and the solution extracted with ether. The ether extract was washed, dried ( $K_2CO_3$ ), evaporated, and the product distilled almost quantitatively under nitrogen. After two preliminary fractions, b.p. 34°/0.05 mm and 70°/0.05 mm, 3 : 5 : 6 : 7 : 8 : 9-hexahydro-1-naphthylhydroxyethyl ether (20 g.) was collected at 123-25°/0.05 mm (66% yield). The above hexahydro-1-naphthylhydroxyethyl ether was dissolved in ether (ca. 50 c.c.), 0.5 N-HCl (ca. 25 c.c.) added, and the whole shaken for 3.5 hours at room temperature (ca. 20°). The ether layer was separated,

the aqueous solution extracted with ether, and the combined ether extract reduced to ca. 15 c.c. This was left shaking with freshly prepared saturated sodium bisulphite solution (ca. 25 c.c.) overnight. The sodium bisulphite adduct (19 g.) was filtered and thoroughly washed with ether.

The combined ether filtrate and washings were concentrated and shaken again for ca. 4 hours with saturated sodium bisulphite solution, when a further 6 g. of the bisulphite adduct was recovered. The sodium bisulphite adduct (25 g.) so obtained was decomposed with *N* sodium carbonate (300 c.c.) and ether (150 c.c.), and the aqueous solution again extracted with ether. The combined ether extract was washed once with water, dried ( $K_2CO_3$ ), evaporated, and distilled under nitrogen. The  $\Delta^4(10)$ -octalone-1 (8 g.) distilled almost quantitatively as a colorless liquid at  $112^\circ/14$  mm,  $n_D^{25}$  1.507. (Found: C, 77.8; H, 9.4.  $C_{10}H_{14}O$  requires C, 80.0; H, 9.3%).  $\lambda_{\min}$  270  $m\mu$ ,  $\epsilon_{\min}$  25;  $\lambda_{\max}$  289-290  $m\mu$ ,  $\epsilon_{\max}$  30.

With Brady's reagent in the cold the orange 2:4-dinitrophenylhydrazone was obtained. If the product was quickly filtered and washed with ethanol, it could be crystallised from the latter, m.p.  $157^\circ$ . Treatment with Brady's reagent in the hot furnished the deep red derivative of  $\Delta^9(10)$ -octalone-1. Its semicarbazone was crystallised from ethanol; m.p. varied from  $218^\circ$  (decomp.) to  $228^\circ$  (decomp.) with the rate of heating. (Found: C, 63.3; H, 8.4; N, 20.8.  $C_{11}H_{17}ON_3$  requires C, 63.2; H, 8.2; N, 20.3%).

$\Delta^9(10)$ -Octalone-1 (I).—5:6:7:8-Tetrahydro-1-naphthylhydroxyethyl ether (20 g.) in ethanol (500 c.c.) was reduced with sodium (50 g.) in liquid ammonia (ca. 1.5 litre) as above. The product was worked up as above and the resulting oil hydrolysed with 2*N*-HCl (25 c.c.) on the steam bath for  $\frac{1}{2}$  hour, extracted with ether and the ether extract washed, dried ( $Na_2SO_4$ ), and distilled under nitrogen. After a preliminary fraction (1.5 g.), b.p.,  $110-20^\circ/14$  mm, the bulk of the product (7.7 g.) distilled at  $120-40^\circ/14$  mm and boiled at  $131-33^\circ/14$  mm on redistillation. (Found: C, 77.7; H, 9.5. Calc. for  $C_{10}H_{14}O$ : C, 80.0; H, 9.3%). From the distillation residue 4.5 g. of the starting material was recovered by crystallisation from petrol ether (b.p.  $40-60^\circ$ ). Yield of  $\Delta^9(10)$ -octalone-1, based on reacting material, was therefore 64%. For the material purified via the semicarbazone, the analysis was still incorrect. (Found: C, 76.2; H, 9.2%),  $n_D^{21.5}$  1.517, but the ultraviolet absorption spectrum was in accordance with expectation:  $\lambda_{\max}$  244  $m\mu$ ,  $\epsilon_{\max}$  8,800;  $\lambda_{\min}$  286  $m\mu$ ,  $\epsilon_{\min}$  67.6;  $\lambda_{\max}$  301-304  $m\mu$ ,  $\epsilon_{\max}$  74.7 (cf. Campbell and Harris, *loc. cit.*). The  $\Delta^9(10)$ -octalone-1 semicarbazone was crystallised from ethanol, m.p.  $242-44^\circ$  (decomp.). (Found: C, 62.7; H, 8.2; N, 20.2. Calc. for  $C_{11}H_{17}ON_3$ : C, 63.2; H, 8.2; N, 20.3%). Cook and Lawrence (*J. Chem. Soc.*, 1937, 817) report semicarbazone m.p.  $242-43^\circ$ ; Hüchel and Naab (*Annalen*, 1933, 502, 136) report m.p.  $244^\circ$  (decomp.).

The 2:4-dinitrophenylhydrazone was found to be polymorphic. Crystallised from ethyl acetate it had m.p.  $224-25^\circ$ . (Found: C, 58.0; H, 5.7; N, 17.15. Calc. for  $C_{10}H_{18}O_4N_4$ : C, 58.2; H, 5.5; N, 17.0%) and from benzene it had m.p.  $266-67^\circ$  (Found: C, 58.0; H, 5.7; N, 17.25. Calc. for  $C_{10}H_{18}O_4N_4$ : C, 58.2; H, 5.5; N, 17.0%). Cook and Lawrence (*loc. cit.*) report m.p. (xylene)  $266-67^\circ$  (decomp.); Birch (*J. Chem. Soc.*, 1944 430) gives m.p.  $264^\circ$ . The  $\Delta^9(10)$ -octalone-1 oxime was crystallised from aqueous methanol, m.p.  $144-45^\circ$ . Cook and Lawrence (*loc. cit.*) report m.p.  $144-45^\circ$ ; Hüchel and Naab (*loc. cit.*) report m.p.  $148^\circ$ .

*trans*- $\alpha$ -Decalone (IX).— $\Delta^4(10)$ -Octalone-1 (5 g.) was dissolved in ether and hydrogenated with 5% Pd-C catalyst. The absorption of hydrogen was rather slow at first, but more rapid later, one molar proportion of hydrogen being absorbed in the course of a day.

The product was filtered from the catalyst, dried ( $\text{Na}_2\text{SO}_4$ ), and distilled under nitrogen to yield 5 g. of *trans*- $\alpha$ -decalone, b.p.  $107^\circ/15$  mm,  $n_D^{14}$  1.490. (Found: C, 78.8; H, 10.8. Calc. for  $\text{C}_{10}\text{H}_{18}\text{O}$ : C, 78.9; H, 10.5%). The product crystallised on standing overnight in the refrigerator.

The 2: 4-dinitrophenylhydrazone was crystallised from benzene, m.p.  $231^\circ$  (decomp.). (Found: C, 57.7; H, 5.6; N, 17.1. Calc. for  $\text{C}_{18}\text{H}_{20}\text{O}_4\text{N}_4$ : C, 57.8; H, 6.0; N, 16.7%).

The semicarbazone was crystallised from methanol, m.p.  $227-28^\circ$ . (Found: C, 63.1; H, 8.9; N, 19.9. Calc. for  $\text{C}_{11}\text{H}_{18}\text{ON}_3$ : C, 63.2; H, 9.1; N, 20.1%).

The oxime was crystallised from ethanol as needles, m.p.  $167-68^\circ$ , which sublimed at  $58^\circ/0.1$  mm. (Found: C, 72.4; H, 10.4; N, 8.0. Calc. for  $\text{C}_{10}\text{H}_{17}\text{ON}$ : C, 71.9; H, 10.2; N, 8.4%).

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