Trichloroacetic Acid-induced Rearrangement of Steroids. Aromatisation of 17-Methyltestosterone into 1,2,10,15,16,17-Hexahydro-10,17,17-trimethylcyclopenta[*a*]phenanthren-3-one

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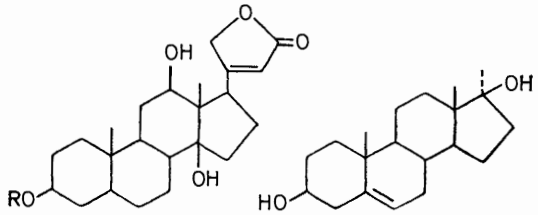
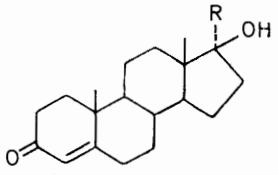
1,2,10,15,16,17-Hexahydro-10,17,17-trimethylcyclopenta[*a*]phenanthren-3-one has been isolated from the action of trichloroacetic acid on methyltestosterone, and identified from its physical properties and comparison with synthetic phenanthrenones. A new route to 4,4a-dihydro-4a-methylphenanthren-2(3*H*)-one is described. Some aspects of the mechanism of the steroid rearrangement have been investigated.

In the course of the development of a new method for the quantitative estimation of digoxin (1), the effect of acetic acid and of mono-, di-, and tri-chloroacetic acids on a number of cardiac glycosides and steroids was investigated. It was found [1] that trichloroacetic acid was the most effective in locating the greatest number of steroidal materials as fluorescent and strongly u.v.-absorbing products on t.l.c. plates. Of twenty steroids subjected to this reagent, digoxin (1), the aglycone digoxigenin (2), 17α-methylandrost-5-ene-3β,17β-diol (3), and 17-methyltestosterone (4), reacted most readily.



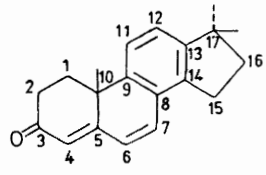
(1) R = $C_{18}H_{31}O_9$
(2) R = H

(3)

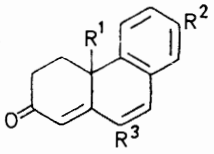


(4) R = Me
(11) R = H

The reaction with 17-methyltestosterone was examined in detail. A solution of the steroid in trichloroacetic acid in aqueous ethanol, heated under reflux, gave a product with a strong fluorescence and u.v. absorption at 366 nm. When the intensity of absorption had reached a maximum the reaction was terminated and a mixture was isolated which on column chromatography was separated into six fractions. Only one fraction had the intense u.v. absorption at 366 nm. This was rechromatographed to give a yellow compound, $C_{20}H_{22}O$. The u.v. absorption (Table) indicated the presence of an extended conjugated chromophore. The presence of a carbonyl group in conjugation with this chromophore was suspected from an intense 1 655 cm^{-1} i.r. band. This was established, as well as the identity of the chromophore, by reduction of the product with borohydride. The u.v. absorption of the product solution closely resembled that of *trans*-1-phenylbutadiene.[2] The presence of alkene and aryl systems in the product was indicated by intense i.r. absorption in the C=C stretching and C–H out-of-plane deformation regions. The benzene ring could be seen to be either 1,2,4,5- or 1,2,3,4-tetrasubstituted from an



(5)

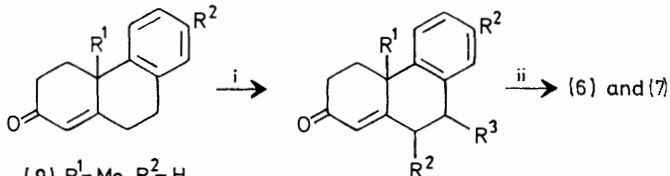


(6) R^1=Me, R^2=R^3=H
(7) R^1=Me, R^2=H, R^3=Br
(8) R^1=Et, R^2=Me, R^3=H

intense absorption [3] at 830 cm^{-1}. The ^1H n.m.r. spectrum (solvent $CDCl_3$) showed a clear AB quartet with the doublets centred at τ 2.80 and 2.95 (J_{AB} 9.0 Hz), establishing the presence of a 1,2,3,4-tetrasubstituted benzene ring.[3] The product was thus identified as the cyclopentaphenanthrenone (5).

The ^1H n.m.r. spectrum showed a further AB quartet with the two doublets centred at τ 3.10 and 3.65 (J_{AB} 9.0 Hz). This can be assigned to the *cis*-CH=CH system, and a singlet at τ 4.15 is due to C=CH–CO. The cyclopentene methylene absorptions are seen as triplets at τ 7.05 and 8.0 (J 7.0 Hz), a singlet at τ 8.56 is due to the 10-methyl group, and the 17-methyl signals occur as singlets at τ 8.61 and 8.66.

To confirm our conclusions two phenanthrenones were synthesised as model compounds. The route to compound (6) is shown in the Scheme. The phenanthrenone



(9) R^1=Me, R^2=H
(10) R^1=Et, R^2=Me

R^1=Me or Et, R^2=H or Me
R^3, R^4=H or Br

Scheme Reagents: i, *N*-bromosuccinimide; ii, Li_2CO_3–LiBr

(9) [4] was brominated and the mixed mono- and di-bromoderivatives, without separation, were dehydrobrominated. The major product (6) was accompanied by a

[1] A. Z. Britten and E. Njau, *Analyt. Chim. Acta*, 1975, **76**, 409.
[2] H. H. Jaffé and M. Orchin, 'Theory and Applications of Ultraviolet Spectroscopy,' Wiley, London, 1970, p. 232.
[3] 'An Introduction to Spectroscopic Methods for the Identification of Organic Compounds,' ed. F. Scheinmann, Pergamon, Oxford 1970, vol. I.
[4] F. H. Howell and D. A. H. Taylor, *J. Chem. Soc.*, 1958, 1248.

small amount of the bromo-derivative (7). The low yield of (7) prevented a full examination of its properties. Its u.v. absorption (Table) showed it to have the same chromophore as (5) and (6) and its molecular formula was confirmed by an accurate mass measurement. Structure (7) is assigned on the basis that a monobromo-product could only arise from a 9,10-dibromo-intermediate by monodehydrobromination, and that the 9-(benzylic)bromine atom would be eliminated in preference to the 10-bromo-substituent.

Attempts to prepare compound (6) by direct dehydrogenation [5] of (9) with dichlorodicyanobenzoquinone resulted in intractable mixtures and were abandoned. On the other hand, compound (8) was obtained in this way from the corresponding ketone † (10) in satisfactory yield.

U.v. data for phenanthrenones

Compound	$\lambda_{max.}$(EtOH)/nm (log ε)
(5)	243 (4.18), 357 (4.18)
(6)	240 (4.22), 350 (4.18)
(7)	250, 365
(8)	238 (4.23), 350 (4.22)

The Table shows that the u.v. absorptions of compounds (5)—(8) are almost identical, in agreement with the presence of a common chromophore. The ^{1}H n.m.r. spectra of (6) and (8) possess the alkene AB quartet and the C=CH–CO singlet as found for (5). Likewise both compounds show the intense 1 660 cm^{-1} i.r. absorption due to the conjugated carbonyl system and the 880—900 cm^{-1} band due to alkene C–H out-of-plane deformation.

The rearrangement was found to be structure- and reagent specific. Thus testosterone (11), under the same conditions, did not yield any product analogous to (5). 6,7-Didehydro-17α-methyltestosterone gave the same product (5) as 17α-methyltestosterone (4). The presence of a 17-methyl as well as a 17-hydroxy-group is clearly required for the aromatisation of ring c. This can only proceed after the 1,2-shift of the angular 13-methyl group to C-17 has occurred. This is an example of a well documented acid-catalysed 1,2-alkyl migration in steroids.[6] The aromatisation, however, is not a case of general acid catalysis. Use of acetic or hydrochloric instead of trichloroacetic acid did not give any of the product (5) from either (4) or its 6,7-didehydro-derivative. If the reaction of trichloroacetic acid with either (4) or the didehydro-compound was carried out in nitrogen then no (5) was formed. Therefore both trichloroacetic acid and oxygen are required for the aromatisation in either case. It may be also true that these are requirements for the 6,7-dehydrogenation of (4) prior to ring c aromatisation. A further requirement in the trichloroacetic acid reaction is a hydroxylic solvent. Use of dry dimethoxyethane and trichloroacetic acid did not produce the product (5). This last condition may be necessary to produce the acidic conditions required for the 1,2-alkyl migration.

† Provided by W. Nagata, Shionogi and Co. Ltd., Fukushima-ku, Osaka, Japan.

[5] W. Nagata, B.P. 1 204 075/1970.

EXPERIMENTAL

M.p.s. were determined with an Electrothermal apparatus. I.r. spectra were recorded with a Unicam SP 200 and u.v. spectra with a Beckmann Acta V spectrophotometer. The mass spectra were obtained with an A.E.I. MS9 spectrometer by direct insertion (ion source temperature 200—250 °C; ionising potential 70 eV). ^{1}H N.m.r. spectra were run with Perkin-Elmer R14 and Varian HA 100D instruments at 33 and 37 °C, respectively. All solvents and materials were laboratory grade unless stated otherwise.

1,2,10,15,16,17-Hexahydro-10,17,17-trimethylcyclopenta[a]*phenanthren-3-one* (5).—A solution of 17β-hydroxy-17α-methylandrost-4-en-3-one (4) (1.0 g) in trichloracetic acid–80% aqueous ethanol (1 : 1 v/v; 5.0 ml) was heated on an oil-bath at 130 °C for 3 h (air condenser). The oily residue was taken up in ether and the solution was washed with 2.5% sodium hydroxide solution and water, dried (Na_2SO_4), and evaporated at 60 °C under reduced pressure to give a clear glass (600 mg). This was taken up in the minimum of ether and chromatographed on neutral alumina (activity I; 300 g; 4.0 cm i.d. column), eluted with petroleum (b.p. 60—80 °C), petroleum–diethyl ether (3 : 1), petroleum–ether (1 : 1), and ether, in that order. Fractions (50 ml) were examined by u.v. and t.l.c. [silica; C_6H_6–$CHCl_3$(9 : 1)]. Six substances, R_F 0.13, 0.24, 0.34, 0.45, 0.66, and 0.75, were detected. The major component, R_F 0.45, was the only one with intense u.v. absorption at 240 and 350 nm. The absorptions of the other components did not differ substantially from that of the starting material. The fractions with the 350 nm absorption were pooled and evaporated and the product was chromatographed under the same conditions to give the *phenanthrenone* (5) as pale yellow needles (65 mg), m.p. 154—155° (from petroleum) (Found: C, 86.1; H, 8.05%; M^+, 278.1670. $C_{20}H_{22}O$ requires C, 86.35; H, 7.95%; M, 278.1668); $\nu_{max.}$(KBr) 1 655, 1 615, 1 600, 1 575, 880, and 830 cm^{-1}.

4,4a-Dihydro-4a-methylphenanthren-2(3H)-one (6).—The ketone (9) [4] (1.0 g) was heated under nitrogen with stirring under reflux in carbon tetrachloride (25.0 ml) containing *N*-bromosuccinimide (0.67 g) and benzoyl peroxide (0.010 g). After 40 min the mixture was cooled and the succinimide filtered off and washed with carbon tetrachloride. The filtrate and washings were combined and taken to dryness under reduced pressure. The residual oil (1.10 g) on t.l.c. [silica; C_6H_6–$CHCl_3$(9 : 1)] was separated into four components, of which one was starting material. The mixture was passed down a column of neutral alumina in petroleum–ether (9 : 1) and used in the next stage.

The products were boiled under reflux, under nitrogen in dry dimethylformamide (25.0 ml) containing lithium carbonate (0.118 g) and lithium bromide (0.139 g). After 3 h the mixture was cooled, filtered, poured into water, and extracted with ether. The extract was dried (Na_2SO_4) and evaporated to yield an oil (300 mg). Column chromatography on neutral alumina gave a product containing two components (t.l.c.), separated by preparative t.l.c. [silica; C_6H_6–$CHCl_3$ (9 : 1)] into the phenanthrenone (6) [200 mg, 20% based on (9)], pale yellow needles, m.p. 98—99° (from petroleum) (lit.,[7] 97—98°); $\nu_{max.}$(KBr) 1 650, 1 610, 1 580, 1 560, 880, and 755 cm^{-1}; τ($CDCl_3$) 8.61 (3 H, s, 4a-Me), 4.19 (1 H, s, H-1), 3.7 and 3.3 (ABq, J 10 Hz,

[6] D. N. Kirk and M. P. Hartshorn, ' Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, p. 270.

[7] E. Wenkert and T. E. Stevens, *J. Amer. Chem. Soc.*, 1955, **78**, 2318.

9- and 10-H), and 2.90—2.65 (4 H, m, aromatic), and its *10-bromo-derivative* (7) (4.0 mg), m.p. 123—125° (Found: M^+, 288.015. $C_{15}H_{13}BrO$ requires M, 288.014); $\nu_{max.}$(KBr) 1 665, 1 640, 1 610, 815, and 765 cm^{-1}.

4a-*Ethyl*-4,4a-*dihydro*-7-*methylphenanthren*-2(3H)-*one* (8). —A solution of the ketone (10) in dry benzene (10.0 ml) containing ethanol (1.0 ml), ethyl orthoformate (1.0 ml), and pyridine hydrochloride (10.0 mg) was heated under reflux under nitrogen for 10 h. The solution was poured onto ice-cooled aqueous 2N-sodium carbonate and extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated to yield the enol ether of (10) (100 mg). The crude ether in aqueous 95% acetone (13.0 ml) was treated with dichlorodicyanobenzoquinone (96 mg) in aqueous 95% acetone (7 ml) and stirred for 10 min. The mixture was poured onto ice–water and the product extracted with ether. The extract was washed with 2N-sodium carbonate and water, dried (Na_2SO_4), and evaporated. The resulting oil was chromatographed [preparative t.l.c.; silica; C_6H_6–$CHCl_3$ (9 : 1)] to afford the *phenanthrenone* (8) (20 mg), m.p. 69—70° (from petroleum) (Found: M^+, 238.135. $C_{17}H_{18}O$ requires M, 238.135); $\nu_{max.}$(KBr) 1 650, 1 603, 1 570, 1 565, 905, and 815 cm^{-1}; τ($CDCl_3$) 9.30 (3 H, t, J 8.0 Hz., Me of angular Et), 7.68 (3 H, s, 7-Me), 4.14 (1 H, s, H-1), 3.65 and 3.32 (ABq, J 10.0 Hz, 9- and 10-H), and 2.98—2.72 (3 H, m, 5-, 6-, and 8-H).

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