Polycyclic Analogues of *trans*-Decalones. Part 4.[1] Synthesis, Optical Resolution, and Circular Dichroism of *trans-anti-trans*-Perhydrophenanthren-4-one

By **Benito Alcaide**, Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, Madrid-3, Spain
Franco Fernández,* Departamento de Química Orgánica, Facultad de Farmacia, Santiago de Compostela, Spain

Racemic perhydrophenanthren-4-one has been synthesised from the tricyclic enone (±)-(2). The derived saturated axial hydroxy-compound (5), resolved as its 3β-acetoxyandrost-5-ene-17β-carboxylate afforded the (−)-(4a*R*,4b*R*,8a*S*,10a*S*)-perhydrophenanthren-4-one (1) of high optical purity. C.d. data of (−)-(1), which represents the simplest rigid ketone with a ' front-octant ' six-membered ring hitherto studied, have been measured and the results are discussed.

OPTICALLY pure samples of extended ' all-*trans* '-decalones, *i.e.* the parent cyclic ketones with no substituents, are required for the investigation of the c.d. of carbonyl compounds, in order to provide reliable answers to specific questions concerning the contribution of key structural features to chiroptical properties.[2,3] Some of them, belonging to the perhydronaphthalene,[4] perhydroanthracene,[1,4] perhydronaphthacene,[5] and perhydrophenanthrene [6] series have already been studied.

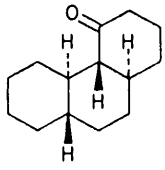
One of the aspects which most needed a direct determination on a simplified structure was the contribution of atoms or rings lying in a front octant. Analyses of data for the very limited number of well known steroidal structures where such features are present are complicated by the additional assumptions which have to be brought in to allow for angular methyl groups and other such structural features as the contribution of a fourth ring (in 1-oxosteroids) or the additivity of independent ' decalone systems ' at both sides of the carbonyl chromophore in ' middle ring ' ketones (7-oxo- and 11-oxo-steroids). In addition, in normal 7-oxosteroids the front octant ring is a five-membered one, so considerations of strain or deviations from perfect geometry of systems based on six-membered rings may interfere with attempts to evaluate ' front-octant behaviour '.

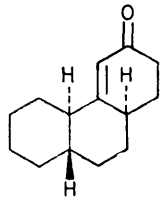
In this paper we report novel c.d. data for the hitherto unknown *trans-anti-trans*-perhydrophenanthren-4-one (1), the simplest rigid model with a ' front-octant ' six-membered ring.

RESULTS AND DISCUSSION

The saturated ketone (1) (racemic) was synthesized from the tricyclic enone (±)-(2). This known enone was prepared by condensation of the 2-hydroxymethylene derivative of (±)-*trans*-1-decalone with but-3-en-2-one in methanol using triethylamine as the basic catalyst. In this way the yield was improved in comparison with previous procedures [6,7] and by-products are avoided.

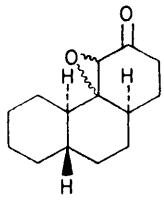
Compound (±)-(2) was treated with H_2O_2 under alkaline conditions to give only one of the two possible stereoisomers of the αβ-epoxyketone (3) (racemic). No attempt was made to determine its relative configuration. Transformation to the ketone (1) (racemic) was carried out by opening the epoxide ring of (±)-(3) with concentrated sulphuric acid in acetic acid followed, without isolation of the intermediate, by reduction with

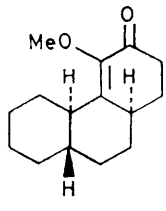

(1)


(2)

aqueous 57% HI in acetic acid. Treatment of compound (±)-(3) with refluxing methanolic sodium hydroxide should yield, according to the results of Reusch and Le Mahieu [8] for steroidal structures, the enol ether (4) (racemic). The crude product so obtained, which gave i.r. and n.m.r. spectra compatible with the enol ether structure, was reduced with HI as above, giving (±)-(1) in a yield similar to that of the first procedure.

Optical resolution was achieved by fractional crystallisation of the mixture of diastereoisomeric esters

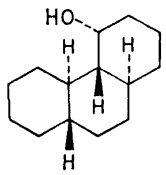

(3)


(4)

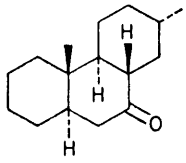
obtained from the HO-axial tricyclic alcohol (5) (racemic) and 3β-acetoxyandrost-5-ene-17β-carboxylic acid chloride. Compound (±)-(5) was formed in the reduction of the ketone (±)-(1) with lithium aluminium hydride as the main product (*ax* : *eq* 80 : 20, by n.m.r.) and was isolated chromatographically from the crude mixture of epimers. The less soluble diastereoisomer of the androstenecarboxylate derivatives was obtained after multiple

fractional crystallisations to constant m.p. Reductive cleavage of this ester with lithium aluminium hydride gave the (—)-alcohol (5) which was oxidised to the corresponding (—)-ketone (1).

The positive ($n \longrightarrow \pi^*$) Cotton effect showed this ketone to have the absolute configuration shown in



(5)



(6)

structure (1) (see the Figure for a representation of its rear- and front-octant projections). From a structural point of view, (1) can be considered as a *trans*-1-decalone on which a third ring has been built with all significant new C–C bonds lying in a front octant.

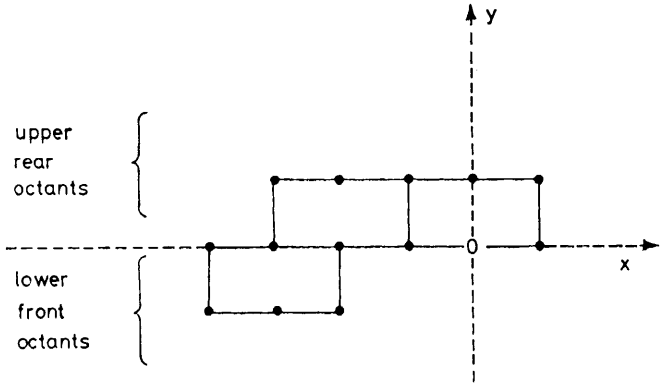


FIGURE Rear- and front-octant projections of (1)

The first empirically estimated values for the contribution of a ' front-octant ' ring to the ($n \longrightarrow \pi^*$) Cotton effect were derived [9] from a direct comparison between $\Delta\varepsilon$ data for a des-D-7-oxo-5α-steroid (6) and those for D-homo-5α-androstan-7-one. This led Klyne and Kirk [2] to predict $\Delta\varepsilon$ values for the parent tricyclic ketone (1), which can now be properly tested.

Table 1 gives the values of $\Delta\varepsilon$ determined experimentally for (4a*R*,4b*R*,8a*S*,10a*S*)-*trans-anti-trans*-perhydrophenanthren-4-one (1) in a variety of solvents. For the ($n \longrightarrow \pi^*$) transition, these values agree reasonably well with those previously predicted,[2] although the two series of data show slightly greater divergence in more polar solvents.

Thus, contributions of a third ' front-octant ' ring, expressed as $\delta\Delta\varepsilon$, can now be obtained as the differences between experimental values of $\Delta\varepsilon$ (smoothed to the nearest 0.05 unit) for (4a*R*,8a*S*)- *trans*-1-decalone [2] and for ketone (1), and are shown in Table 2. As these new $\lambda\Delta\varepsilon$ values are established with a minimum of previous hypotheses (namely with only that of simple additivity), we consider them as essentially confirming, and only slightly amending, those previously estimated by Klyne and Kirk, which are also included in Table 2 for comparison.

With regard to the short-wavelength Cotton effect, predictions [3a] about the contribution of the third ' front-octant ' ring of (1) in n-hexane, represented by $(\delta\Delta\varepsilon)_H$, were less clear cut, as they ranged from *ca.* —0.5, for

TABLE 1

Cotton effects for (4a*R*,4b*R*,8a*S*,10a*S*)-*trans-anti-trans*-perhydrophenanthren-4-one (1) (wavelength in parentheses)

	$\Delta\epsilon(n \longrightarrow \pi^*)$		$\Delta\epsilon$ (Short wavelength)	
Solvent	Found	Calc.[a]	Found	Calc.[b]
n-Hexane	+1.46 (295)	+1.45	⩽0 (195 [c])	?
Dioxan	+1.59 (297)	+1.6		
Acetonitrile	+1.78 (297)	+1.7	−1.6 (195 [c])	
Methanol	+2.14 (293)	+1.95	−2.2 (196 [c])	
2,2,2-Trifluoroethanol	+2.34 (288)		−4.1 (195)	−5

[a] From ref. 2. [b] From ref. 3. [c] Limit of measurement. The exact wavelength of the c.d. maximum could not be determined from the experimental curves.

systems in which the carbonyl group belongs to a terminal ring (as it would be for *ent*-1-oxo-5α-steroids) to —6.0, attributed to those with the carbonyl group placed in a middle ring (as in 7-oxo-D-homo-steroids or *ent*-11-oxo-5α-steroids).

Unfortunately, instrumental ' noise ', in both the solvent and solution c.d. curves in the short-wavelength region, precluded a clear-cut determination of the c.d. maxima of (—)-(1) in all solvents except 2,2,2-trifluoroethanol (TFE). Nevertheless, for n-hexane the solution curve, although deviating only a little from the curve for the solvent alone, was unambiguously on the negative side, with $-0.4 < \Delta\varepsilon < 0$ at 195 nm. Despite this uncertainty, a comparison of the result with that for (4a*R*,8a*S*)-*trans*-1-decalone,[3a] allows us to evaluate $(\delta\Delta\varepsilon)_H$ for the ' front-octant 'ring in (1) as near to —4.0, which seems to contradict the proposed distinction [3] between ' terminal-ring ' and ' middle-ring ' ketones.

TABLE 2

Contribution of the third ' front-octant ' ring in (1), $\delta\Delta\varepsilon$ ($n \longrightarrow \pi^*$)

	n-Hexane	Dioxan	Acetonitrile	Methanol
This work	+0.65	+0.75	+0.95	+1.20
Previous estimate *	+0.65	+0.75	+0.85	+1.0

* From ref. 2.

Moreover, the persistence of negative values of ($\Delta\varepsilon$) at short wavelength for (1) in all solvents clearly indicates that the contribution of its front-octant ring is fairly strongly negative, *i.e.* octant-dissignate, or rather obeying a quadrant rule.[9] The result in TFE agrees better with the previous estimate.[3b] The contribution of the third ' front-octant ' ring of (1) in this solvent, $(\delta\Delta\varepsilon)_T$, may now be evaluated as —2.2 (previous estimate —3.0).

C.d. measurements on the alcohol (−)-(5) confirms that it has the hydroxy-group in a position corresponding to the enantiomer of an 11β-hydroxy-5α-steroid.[10]

EXPERIMENTAL

Alumina was Merck grade I (Brockman); 'deactivated alumina' refers to grade I treated with 2% of water. I.r. spectra were obtained for KBr discs and n.m.r. spectra for solutions in carbon tetrachloride. C.d. spectra were provided by Dr. P. M. Scopes and Professor D. N. Kirk, Westfield College, London.

Preparation of (±)-4,4a-*Epoxyperhydrophenanthren*-3-*one* (3).—To a cooled (0 °C) solution of the enone (2) (10 g; racemic) in methanol (300 ml) containing sufficient aqueous 1M NaOH to bring the pH to 10—11, was added dropwise while stirring aqueous 30% H_2O_2 (25 ml). The reaction mixture was then kept below 5 °C and stirred for 2 h. Dilution with water precipitated the product which was filtered off, giving of (±)-(3) as white needles (10.2 g, 96%), m.p. 86—87 °C (methanol); $\nu_{max.}$ 1 710 cm^{-1}; δ 3.18 (O–CH) (Found: C, 76.5; H, 8.95. $C_{14}H_{20}O_2$ requires C, 76.32; H, 9.15%).

Preparation of (±)-*Perhydrophenanthren*-4-*one* (1).—(*a*) To a stirred solution of the racemic epoxyketone (3) (2 g) in acetic acid (30 ml) at 20 °C was added dropwise during 1 h a solution of concentrated H_2SO_4 (2 ml) in acetic acid (250 ml). The resulting dark solution was stirred for 2 h, then diluted with water, cooled to 0 °C, extracted with ether, and the solvent removed under reduced pressure. The crude oily product (2 g) was dissolved in acetic acid (150 ml), mixed with aqueous 57% HI (7 ml) and refluxed under N_2 for 30 min. Extraction with ether and removal of the solvent afforded a crude oil (1.6 g), which was chromatographed on deactivated alumina (80 g). Elution with benzene gave the racemic ketone (±)-(1) (0.7 g) as an oil that solidified on standing; m.p. 43—44 °C after sublimation (100 °C at 15 mmHg); $\nu_{max.}$ 1 700 cm^{-1}; *m/e* 206 (M^+, 81%) and 110 (M^+-96, 100) (Found: C, 81.6; H, 10.8. $C_{14}H_{22}O$ requires C, 81.50; H, 10.75%). The 2,4-dinitrophenylhydrazone, yellow needles from methanol, had m.p. 188—189 °C (Found: C, 62.2; H, 6.75; N, 14.25. $C_{20}H_{26}N_4O_4$ requires C, 62.15; H, 6.78; N, 14.49%).

(*b*) To (±)-(3) (1 g) in methanol (200 ml) was added aqueous 4M NaOH (18 ml) and the solution was refluxed for 24 h. Dilution with water and extraction with ether yielded a pale yellow viscous oil (1 g); $\nu_{max.}$ 1 670, 1 600, and 1 200 cm^{-1}; δ 3.55 (MeO), no vinyl proton. This crude oil was dissolved in acetic acid (80 ml), mixed with aqueous 57% HI (4 ml) and refluxed under N_2 for 30 min. Work-up as before gave 360 mg of the purified ketone (±)-(1).

Preparation of (±)-trans-anti-trans-*Perhydrophenanthren*-4ax-*ol* (5).—The racemic ketone (±)-(1) (2.5 g) in dry ether (250 ml) was refluxed for 6 h with $LiAlH_4$ (0.55 g). Hydrolysis with cold diluted HCl (150 ml), extraction with ether, and removal of the solvent gave the crude racemic alcohol (5) (2.5 g) containing some 20% of the *equatorial*-OH epimer (n.m.r.) Chromatography of this crude product on deactivated alumina (100 g) and elution with benzene gave racemic axial alcohol (±)-(5) (1.6 g). Crystallisation from light petroleum at −15 °C afforded the pure alcohol (±)-(5), m.p. 64—65 °C; $\nu_{max.}$ 3 340, 1 055, 1 000, and 950 cm^{-1}; δ 3.93 ($W_{\frac{1}{2}}$ 7 Hz, CHOH); *m/e* 208 (M^+, 13 %), 190 (M^+ −18, 100) (Found: C, 80.75; H, 11.55. $C_{14}H_{24}O$ requires C, 80.70; H, 11.61%).

Preparation of (−)-(4R,4aR,4bR,8aS,10aS)-trans-anti-trans-*Perhydrophenanthren*-4-*ol* (5).—Crude diastereoisomeric esters (1.3 g) were obtained from 3β-acetoxyandrost-5-ene-17β-carboxylic acid [11] (3.5 g), as its acid chloride and the racemic axial alcohol (±)-(5) (1.5 g) in pyridine (30 ml) in the usual way.[4] Chromatography on deactivated alumina (elution with benzene) afforded the pure esters, as a mixture of both diastereoisomers, giving no separation between them. This material was crystallised eight times from ethyl acetate to give the ester of the alcohol (5) (135 mg). The two final crystallisations did not change the m.p. of the product, m.p. 189—190 °C; $\nu_{max.}$ 1 725, 1 710, and 1 240 cm^{-1} (Found: C, 78.35; H, 9.75. $C_{36}H_{54}O_4$ requires C, 78.5; H, 9.9%).

The foregoing pure ester * (115 mg) was reductively cleaved with $LiAlH_4$ (110 mg) in dry ether (40 ml) under reflux for 9 h. Hydrolysis with cold dilute HCl, extraction with ether, and removal of the solvent gave a mixture of the tricyclic alcohol (5) and 21-norpregn-5-ene-3β,20-diol, which was chromatographed on deactivated alumina (15 g). Elution with benzene and benzene-ether (95 : 5) gave the (−)-alcohol (5) (37 mg); m.p. 87—88 °C after sublimation (100 °C at 15 mmHg); $[\alpha]_D^{23}$ −44° (*c* 0.25 in $CHCl_3$); Δε −0.84 (208 nm, in n-hexane).

Preparation of (−)-(4aR,4bR,8aS,10aS)-trans-anti-trans-*Perhydrophenanthren*-4-*one* (1).—The (−)-alcohol (5) (25 mg) was oxidised in acetic acid (4 ml) with CrO_3 (20 mg) for 15 h at room temperature. The usual work-up, followed by chromatography on alumina (5 g; elution with benzene) and sublimation (100 °C at 15 mmHg) gave (−)-ketone (1) (21 mg) m.p. 72—73 °C; $[\alpha]_D^{23}$ −98.5° (*c* 0.2 in $CHCl_3$).

We thank Prof. D. N. Kirk for the facilities for the measurement of the c.d. spectra, as well as for some comments about their interpretation.

[0/1478 *Received*, 29*th September*, 1980]

* Optical purity of all the present products rests upon the criterion of constancy of m.p. of the 3β-acetoxyandrostenecarboxylate of the alcohol, which has given good results in other cases.[1,4,5,6] Neither $[\alpha]_D$ nor the ^1H n.m.r. spectra of mixtures of diastereoisomeric esters varied significantly, while m.p.s approached asymptotically the final value of the pure ester.

REFERENCES

[1] Part 3; B. Alcaide and F. Fernández, *An. Quim.*, 1980, **76***C*, 41.
[2] D. N. Kirk and W. Klyne, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1076.
[3] D. N. Kirk, *J. Chem. Soc., Perkin Trans. 1*, (*a*) 1980, **787**; (*b*) 1980, 1810.
[4] F. Fernández, D. N. Kirk, and M. Scopes, *J. Chem. Soc., Perkin Trans. 1*, 1974, 18.
[5] B. Alcaide and F. Fernández, *Ann. Quim.*, 1979, **75**, 952.
[6] B. Alcaide, F. Fernández, and M. P. Tarazona, to be published.
[7] R. D. Haworth and A. F. Turner, *J. Chem. Soc.*, 1958, 1240.
[8] W. Reusch and R. Le Mahieu, *J. Am. Chem. Soc.*, 1963, **85**, 1669.
[9] D. N. Kirk, W. Klyne, and W. P. Mose, *Tetrahedron Lett.*, 1972, 1315.
[10] D. N. Kirk, W. P. Mose, and D. M. Scopes, *J. Chem. Soc., Chem. Commun.*, 1972, 81.
[11] J. Staunton and E. J. Eisenbraun, *Org. Synth.*, 1962, **42**, 4.