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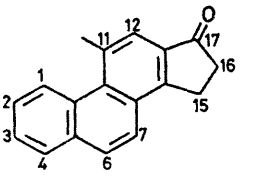
A Carcinogen with a Bridged Bay Region:† Synthesis, *X*-Ray Structure, and Biological Activity of 15,16-Dihydro-1,11-methanocyclopenta[*a*]-phenanthren-17-one

By TARLOCHAN S. BHATT, MAURICE M. COOMBS,* and ANNA-MAIJA KISSONERGHIS
(*Chemistry Laboratory, The Imperial Cancer Research Fund, Lincolns Inn Fields, London* WC2A 3PX)
and ALEXANDRA F. D. CLAYTON* and MARY MCPARTLIN
(*Department of Chemistry, The Polytechnic of North London, London* N7 8DB)

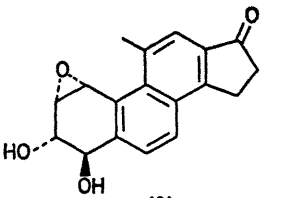
Summary 15,16-Dihydro-1,11-methanocyclopenta[*a*]phenanthren-17-one has been synthesised and its *X*-ray structure determined; although it has a bridged bay region, it is a carcinogen.

ALTHOUGH many phenanthrene derivatives are known to be carcinogenic the corresponding anthracenes are inactive. This appears to be related to the recent observations that the biologically active metabolites of many of these carcinogens are bay region diol epoxides.[1] The strong carcinogen 15,16-dihydro-11-methylcyclopenta[*a*]phenanthren-17-one[2] (**1**) for example gives (**2**) as its ultimate carcinogenic form.[3] The 11-ethyl homologue of (**1**) is less carcinogenic and the 11-butyl ketone is inactive[2] suggesting that bulky substituents progressively inhibit attack in the bay region. This is consistent with evidence that the mechanism of the action of bay region diol epoxides proceeds with the nucleophilic opening of the epoxide and subsequent covalent binding at the benzylic position [C(1) in (**1**)] to DNA, through the exocyclic amino group of a guanine residue.[4] Unexpectedly the analogous bridged compound (**3**) in which the bay region is completely blocked is carcinogenic.

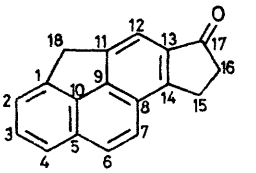
15,16-Dihydro-1,11-methanocyclopenta[*a*]phenanthren-17-one (**3**) was synthesised‡ by established methods.[5]



(1)



(2)



(3)

Condensation of 1,10-methano-1,2,3,4-tetrahydrophenanthren-4-one[6] with diethyl succinate in a Stobbe reaction followed by cyclisation and decarboxylation of the resulting

† A 'bay region' is a concave exterior region of a polycyclic aromatic hydrocarbon bordered by 3 phenyl rings, at least one of which is a terminal ring.

‡ Satisfactory analytical and spectral data were obtained for all new compounds.

half-ester yielded 11,12,15,16-tetrahydro-1,11-methanocyclopenta[*a*]phenanthren-17-one. Dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in boiling benzene readily gave (**3**), m.p. 195 °C, δ (220 MHz, CD_2Cl_2), 7·72—7·98 (m, 6H, ArH), 4·37 (s, 2H, Ar-CH_2-Ar), 3·42—3·54 (t, 2H, CH_2), and 2·82—2·90 (m, 2H, O=C-CH_2); λ_{max} 266·5 (log ε 4·77), 277 (4·76), 303 (3·34), 348 (3·03), and 365·5 nm (2·86).

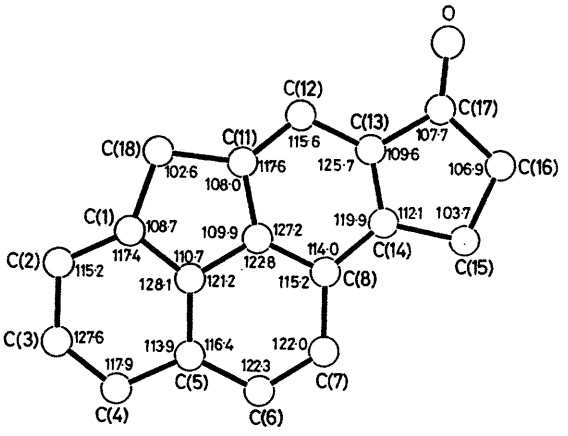


FIGURE. The structure of 15,16-dihydro-1,11-methanocyclopenta[*a*]phenanthren-17-one showing angles (°). The numbering is as shown in formula (**3**) and important bond lengths are: C(1)–C(2), 1·403; C(2)–C(3), 1·408; C(1)–C(10), 1·396; C(10)–C(9), 1·418; C(9)–C(11), 1·413; C(11)–C(12), 1·370; C(12)–C(13), 1·422; C(1)–C(18), 1·527; C(11)–C(18), 1·541; and C(6)–C(7), 1·371 Å; with e.s.d.s averaging C–C, 0·008 Å, and C–C–C, 0·7°.

Crystal data: (**3**), $C_{18}H_{12}O$, orthorhombic, space group *Pbca*, $a = 7·504(2)$, $b = 15·009(2)$, $c = 18·450(3)$ Å, $U = 2464·3$ Å^3, $Z = 8$. Intensity data were collected with a Philips PW1100 four-circle diffractometer using Mo-K_α radiation from a graphite monochromator. The structure was solved by direct methods (SHELX '76) and refined to an *R*-value of 0·0807 using 764 reflections with $I/\sigma(I) > 2·5$.§

The *X*-ray structure of (**3**) is shown in the Figure. The structure of a compound with a bridged bay region has not been reported previously, but considerable distortion of the phenanthrene ring system would be expected in order to accommodate the fused five-membered ring. The structure of (**3**) is planar to within 0·08 Å but there are marked angular distortions, particularly near the bay region (Figure).

The methano-ketone (**3**) was found to be mutagenic in the Ames' test with *Salmonella typhimurium* TA100.[6] In ongoing mouse skin painting tests for carcinogenicity tumour incidence at 8 months is 45% compared with 75%, under identical conditions, for the strongly carcinogenic 11-methyl-ketone (**1**), which has an Iball Index of 46.[6]

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§ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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