

Positional Orientation Effects in Quinone Dehydrogenation of 5 β ,14 α -Bufa-20(22)-enolide

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Summary The DDQ dehydrogenation of (IV) can be directed towards formation of either a 1:1-mixture of (VII) and (VIII), in the presence of anhydrous hydrogen chloride, or exclusively to an α -pyrone system (VI) under the influence of toluene-*p*-sulphonic acid.

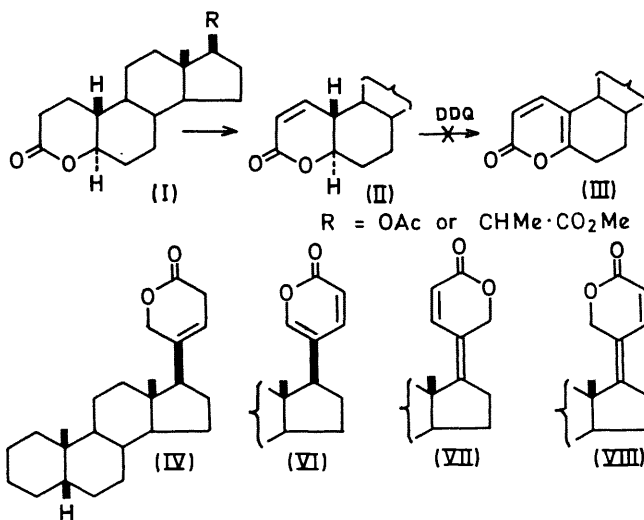
MUCH work has been published on the quinone-mediated dehydrogenation of steroid ketones,¹ though there are few examples of such reactions of steroid lactones. Saturated steroid δ -lactones of structure (I) have been converted into $\alpha\beta$ -unsaturated lactones (II) (*ca.* 50%) by prolonged (96–130 hr.) exposure to an excess of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in dioxan.² The unsaturated lactones (II) seemingly do not undergo DDQ dehydrogenation to yield the respective α -pyrones (III).

We report the behaviour of 5 β ,14 α -bufa-20(22)-enolide (IV), a new steroidal $\beta\gamma$ -unsaturated δ -lactone,³ toward chloranil (V) and DDQ under various reaction conditions.

This study was aimed at establishing whether the reaction of (IV) with quinone generates the α -pyrone system (VI),³ or possibly lends itself to abstraction of a hydride ion from C-17 to provide the isomeric bufadienolides, a semi-solid compound [M]_D –27° (*c* 1.3, CHCl₃) (A), and a crystalline product melting at 193–194°, [M]_D –95° (*c* 1.7, CHCl₃) (B), were obtained in a 1:1 ratio.

When (IV) (100 mg) was exposed to the action of (V) (2 equiv.) in boiling dioxan (50 ml) for 120 hr. and the product chromatographed on alumina (KGF₂₅₄), the two isomeric bufadienolides, a semi-solid compound [M]_D –27° (*c* 1.3, CHCl₃) (A), and a crystalline product melting at 193–194°, [M]_D –95° (*c* 1.7, CHCl₃) (B), were obtained in a 1:1 ratio.

Compound A is assigned the structure (VII) on the basis of (i) its elemental analysis; (ii) its i.r. peaks at 1720 (vs), 1625 (m), and 1520 (w) cm⁻¹; (iii) its u.v. spectrum (EtOH) exhibiting a peak at 290 nm (ϵ 9750); (iv) its n.m.r. spectrum



(CCl₄) indicating the appearance of new low-field signals assigned to structure (VII) as follows: τ 2.62 (1H, m, 22-H), 4.4 (1H, m, 23-H), 5.25 (2H, unresolved q, 21-H₂), 8.75 (3H, s, 18-H₃), and 9.07 (3H, s, 19-H₃); (v) its o.r.d. curve† showing negative Cotton effect as follows: (*c* 0.015, hexane),

† O.r.d. measurements were taken on a Cary 60 recording spectropolarimeter.

25–27°; $[\Phi]_{340} - 6350^\circ$; $[\Phi]_{315} - 11,730^\circ$; $[\Phi]_{290} - 21,500^\circ$ (trough); $[\Phi]_{282} 0^\circ$; $[\Phi]_{235} + 28,800^\circ$ (peak); $[\Phi]_{220} + 18,100^\circ$.

The assignment of structure (VIII) for product B is also inferred from: (i) its elemental analysis; (ii) the i.r. spectrum (CHCl_3): 1720 (vs), 1630 (s), and 1580 (w) cm^{-1} ; (iii) the u.v. spectrum (EtOH): 292–293 nm (ϵ 13,400); (iv) the n.m.r. spectrum (CCl_4): τ 3.0 (1H, d, 22-H; J 4.5 Hz), 4.85 (1H, d, 23-H; J 4.5 Hz), 4.95 (2H, unresolved q, 21- H_2), and 9.0 (6H, s, 19- H_3 + 18- H_3); (v) the rather intense negative Cotton effect provided by o.r.d. measurements, in agreement with formulation (VIII) as follows: (c 0.01, hexane), $[\Phi]_{340} - 7800^\circ$; $[\Phi]_{315} - 14,900^\circ$; $[\Phi]_{305} - 25,500^\circ$ (trough); $[\Phi]_{282} 0^\circ$; $[\Phi]_{245} + 46,000^\circ$ (peak); $[\Phi]_{220} + 35,450^\circ$.

Ruthenium tetroxide oxidation⁴ of either (VII) or (VIII) (in CCl_4) leads exclusively to 5 β -androstan-17-one, m.p. 100° (lit.⁵ m.p. 105°), thus substantiating isomeric structures for the two dienolides.

The differences in the spectroscopic properties and the o.r.d. curves between (VII) and (VIII) are most likely due to steric effects of conjugation. Models reveal that the 13-methyl group in (VII) exerts hindrance to coplanarity of the dienolide system, whereas in (VIII) it does not.

In boiling *t*-butyl alcohol or benzene (IV) seems to be inert to the action of (V) and also to that of the higher-potential DDQ. However, if (IV) is exposed to prolonged action of DDQ (2 equiv.) in boiling dioxan (130 hr.), only minor amounts of dehydrogenation product, consisting of

(VI), (VII), and (VIII) in a ratio of 1:1:1, are obtained. The addition of pyridine (7 equiv.) accelerated DDQ-dehydrogenation; the reaction is essentially complete after 12 hr. at 100°, exhibiting only minor change in the product ratio (4:3:3, respectively). Reaction in the presence of anhydrous hydrogen chloride was extremely rapid at room temperature with complete conversion in about 3 hr., and, apart from traces of (VI), the product consisted exclusively of (VII) and (VIII) in equal amounts. The DDQ-initiated reaction in the presence of toluene-*p*-sulphonic acid (0.5 equiv.) was also rapid in boiling dioxan with complete conversion in about 3 hr., but, in contrast to the HCl-catalysed reaction, the exclusive product was the bufa-20,22-dienolide (VI).³ Compounds (VII) and (VIII) could not be converted into (VI) upon prolonged exposure to the action of toluene-*p*-sulphonic acid in boiling dioxan.

By appropriate choice of the catalyst (acidic) the DDQ dehydrogenation of (IV) can be directed towards formation of either (VI) or to (VII) and (VIII).

The preferred abstraction of the less acidic C-17 hydrogen in the HCl-catalysed DDQ dehydrogenation of (IV), as contrasted to the specific elimination of the more acidic C-21 hydrogen in the presence of toluene-*p*-sulphonic acid, suggests that the transition state for the reaction may be regarded as an acid-base complex, the interactions in which affect the rates and the location of the double-bond formation.⁶

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