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MICHAEL ADDITIONS TO STEROIDAL 1-ENE-3-ONES

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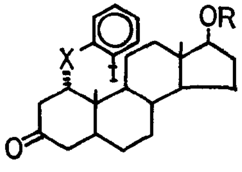
Abstract

A reactivity pattern was established for Michael addition of aryl thiolates to 17-acetoxy 5α-androst-1-en-3-one. An abnormal bicyclic bridged adduct was obtained in the reaction of thiourea.

In the course of a programme concerned with remote group functionalisation at C-9 in steroids via adducts of general structure (1) it became necessary to establish reactivity parameters for Michael additions at C-1 of steroidal 1-ene-3-ones and 1,4-diene-3-ones.[1] We report our exploratory studies in this area.



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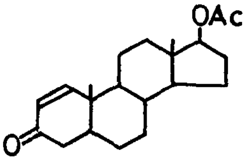

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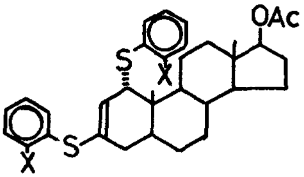

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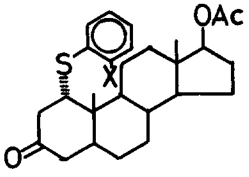
17-Acetoxy 5α-androst-1-en-3-one (2) was reacted under acid catalysis ($HClO_4$) with excess of o-nitrothiophenol, thiophenol and o-iodothiophenol, to give in high yield the adducts (3, $X=NO_2$,H,I), in which Michael addition has been followed by thioenol ether formation. This latter reaction was relatively rapid and could not be suppressed under a range of conditions. Adducts (3) were obtained together with small quantities of the chromatographically inseparable Δ^1 isomers, and were characterised spectroscopically and by elemental analysis as isomeric mixtures. The retro-Diels Alder fragmentation of ring A in the mass spectra of (3) was particularly pronounced. No corresponding adducts of phenols or of anilines were obtained under these conditions.

Base catalysed reactions (NaOEt) with o-nitrobenzenethiol under a range of conditions gave no Michael adduct, the equilibrium lying almost completely towards the reactant side. Neither two-phase systems nor other bases resulted in isolable adducts. Sodium benzenethiolate, however, gave in 75% yield the α-adduct (4) and sodium o-iodobenzenethiolate gave, in 90% yield, (5).[2] Neither phenols nor anilines gave comparable adducts. Only sodium benzenethiolate reacted with the dienone (6) to give adduct (7) (20% yield).

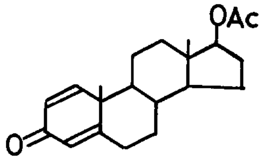
A novel reaction was uncovered when thiourea reacted with (2) under base catalysis to give in 95% yield the 1-hydroxy-3-thioxo-2,4-diazabicyclo[3,3,1]nonane (8),[3] m.p. 268-270°, $\nu_{max.}$(KBr) 3420, 3380 and 3250 cm^{-1} (OH and NH); δ 0.62 and 0.66 (13- and 10- Me), 4.35 (1H,d,*J* 5Hz,1-H), 5.9, 7.6 and 8.15 (each 1H, exch., OH and NH). This reaction could not be reversed by aqueous base or by treatment with toluene-*p*-sulphonic acid, illustrating the stability of the bicyclic system. This reaction is unique to thiourea (urea, O-methylisothiourea and O-methylisourea did not give adducts). The 3-thioxo structure, rather than an alternative 5-hydroxy-3-imino-4-aza-2-thiabicyclo[3.3.1.] nonane structure was assigned, following transformation of (8) to its methylthio derivative by methyl iodide-sodium bicarbonate.

All new compounds gave correct elemental analyses and/or high resolution mass measurement.



4, X=H

5, X=I



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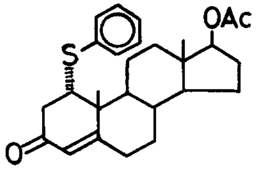

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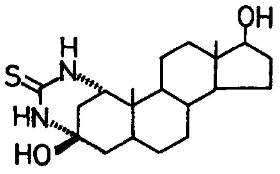

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1. Examples of Michael additions to C-1 are rare. See, for example, M. Kocor, M. Gumulka and C. Cynkowski, *Tetrahedron Letters*, 1972, 4625. In a particularly relevant study a series of thiols were added to steroidal dienones to give estrogen biosynthesis inhibitors; R.W. Brueggemeier, E.E. Floyd and R.E. Counsell, *J. Med. Chem.*, 1978, *21*, 1007.

2. It was of interest that attempted transformation of (4) or (5) to the sulphoxides by ozonolysis or peracid reaction led to (2) due to facile β-elimination of arylsulphenic acid at room temperature.

3. The closest precedents for the addition of thiourea to enones lie in two possibly contradictory studies; (a) acyclic enones give 2-thioxo 1,2,3,4-tetrahydropyrimidines; R. Onoda, S. Tanaka and T. Narita, *Akita Daigaku Kyoiku Gakuba Kenkyu Kiyo, Shizen Kagaku*, 1976, *26*, 62 (Chem. Abs. 1977, *86*, 54015); (b) α-Ylidenecycloalkanones give 2-imino 2,3-dihydro[1,3]thiazines; T. Lorand, D. Szabo and A. Neszmelyi, *Acta Chim. Acad. Sci. Hung.*, 1977, 93, 51.

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