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REGENERATION OF KETONES FROM SEMICARBAZONES BY LEAD TETRA-ACETATE. A NOVEL PREPARATION OF 18-HYDROXYCORTICOSTERONE

David N. Kirk* and Christopher J. Slade

Medical Research Council Steroid Reference Collection, Chemistry Department, Westfield College, Hampstead, London, NW3 7ST, U.K.

Abstract. Lead tetra-acetate in acetic acid has been used to cleave a 3-semicarbazone in a novel preparation of 18-hydroxycorticosterone, designed to avoid strongly acidic conditions.

During a study[1] of possible synthetic routes to 18-hydroxycorticosterone (3) it became necessary to reduce the 11-oxo group selectively in 18-hydroxy-11-oxo-progesterone (1), to obtain the required 11β-hydroxy function. Other workers,[2] faced with a similar problem in the conversion of cortisone into cortisol, had found that the 3- and 20-oxo groups could be protected as their semicarbazones, permitting a borohydride reduction of the 11-oxo group before removal of the semicarbazone protecting groups by any of several acidic reagents.

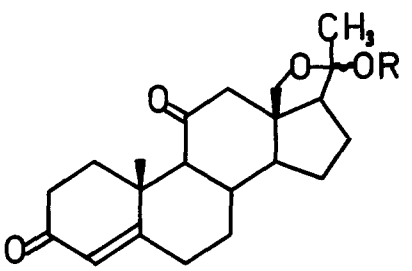
18-Hydroxy-20-oxo-corticosteroids, which exist as 18,20-hemiacetals, are intolerant of strongly acidic conditions,[3] so the use of a semicarbazone for our purpose demanded a milder method of cleavage. Model experiments on the semicarbazone of cholest-4-en-3-one showed that two methods used recently for cleavage of oximes and dinitrophenylhydrazones, namely boiling in slightly acidic acetone[4] or shaking with hypochlorite ('bleach') solution,[5] had no effect on the semicarbazone Methanolic thallium(III) nitrate[6] rapidly cleaved the semicarbazone but liberates nitric acid, whereas a similar mixture buffered with sodium acetate caused incomplete cleavage of the semicarbazone. Ceric ammonium nitrate[7] in aqueous ethanol also generates nitric acid during its reaction with semicarbazones.

We now report that lead tetra-acetate (LTA) in acetic acid cleaves the semicarbazones of cholest-4-en-3-one and other 4-en-3-ones rapidly and efficiently at room temperature. The immediate product is generally a mixture of the Δ^4-3-oxo steroid and its $\Delta^{3,5}$-dienol 3-acetate (5), in proportions depending upon the relative amounts of LTA and semicarbazone (excess LTA favours the Δ^4-3-oxo product). Any dienol acetate is readily hydrolyzed by mild alkaline treatment to give the Δ^4-3-oxo compound, so presents no problem in a situation where the critical feature is the avoidance of strong acids.

Previous reports have shown that LTA reacts with the semicarbazones of some aryl aldehydes to give 2-amino-5-aryl-1,3,4-oxadiazoles,[8] and that

semicarbazones of simple ketones (with LTA in CH_2Cl_2, followed by HClaq.) give 5-substituted-Δ^3-1,3,4-oxadiazolin-2-ones.[9] We find that cyclohexanone semicarbazone with LTA-acetic acid gives directly the known[9] spiro-Δ^3-1,3,4-oxadiazolin-2-one (6), accompanied by some cyclohexanone, the latter particularly when LTA is used in large excess. The 17-semicarbazone of 3β-hydroxyandrost-5-en-17-one similarly gave a mixture of the 17-ketone and the 17-spiro-($\Delta^{3'}$-1',3',4'-oxadiazolin-2'-one) derivative (7), as was evident from the i.r. spectrum [ν_{max} 1825 and 1540 cm^{-1} (cf. ref. 9), in addition to peaks characteristic of 3β-hydroxyandrost-5-en-17-one]. The ketone is readily regenerated, however from any such oxadiazolin-2-one derivative by brief treatment with methanolic alkali at room temperature. LTA-acetic acid is known to cleave oximes under vigorous conditions,[10] although giving iminoxy radicals and α-acetoxy-nitroso derivatives at low temperatures.[11]

To establish the suitability of LTA for our purpose, the 3,20-bis-semicarbazone was prepared from pregn-4-ene-3,11,20-trione. The bis-semicarbazone (200 mg) was subjected to sodium borohydride (100 mg) in ethanol-THF (10 ml, 1.1, with 0.1 ml of 1M-NaOH) under reflux for 8 h to reduce the 11-oxo group. Water was added to precipitate the product, which was dried and treated with LTA (400 mg) in acetic acid (5 ml) at room temperature for 5 min, followed by pouring into $NaHCO_3$aq. and extraction with ether, to give 11β-hydroxypregn-4-ene-3,20-dione (94 mg) in 60% over-all yield from the trione, after t.l.c. purification. Separate experiments confirmed that only traces of oxadiazolinone derivatives are formed from 20-semicarbazones.



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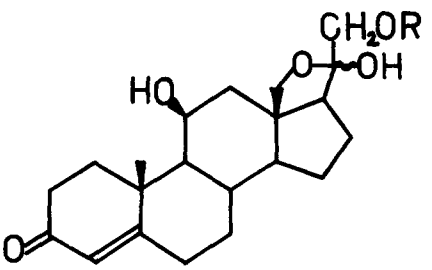
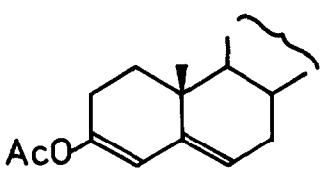
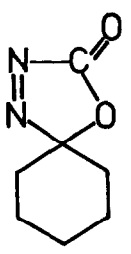
(2) R=Me



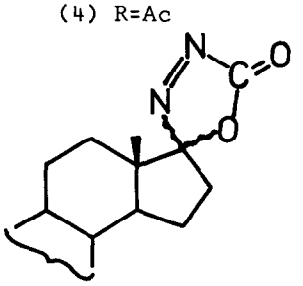
(3) R=H
(4) R=Ac



(5)



(6)



(7)

For the preparation of 18-hydroxycorticosterone (3), 18-hydroxy-11-oxoprogesterone (1) was first converted into the 20-methoxy derivative (2) of its hemiacetal by dissolution in slightly acidic methanol.[1,3b] The 3-semicarbazone was then formed under basic conditions (semicarbazide hydrochloride-pyridine-methanol) and reduced as above with sodium borohydride in ethanol-THF (1.1, under reflux for 12 h). Cleavage of the 3-semicarbazone was conveniently accomplished together with the required de-protection at C-20 and acetoxylation at C-21 by brief treatment (10 m, room temperature) of the crude reduced material with an excess of LTA in acetic acid. The product, after extraction *via* ether, was a mixture containing the required 21-acetoxy-11β,20-dihydroxy-18,20-epoxypregn-4-en-3-one (4) and also its 3-enol acetate (5), in the approximate ratio 1.2. The enolic and 21-acetoxy groups were readily hydrolysed by aqueous methanolic potassium hydroxide to give 18-hydroxycorticosterone, identified by comparison with an authentic sample. The yield of purified (t.l.c.) product over five steps from 18-hydroxy-11-oxoprogesterone (100 mg), without isolation of intermediates, was 26%

It was fortunate, for present purposes, that oxadiazolinones do not form in the reaction of semicarbazones of 4-en-3-ones. A control experiment with the semicarbazone of the saturated 5α-cholestan-3-one, however, led to the 3-spiro-oxadiazolinone derivative and the free ketone in *ca.* 1 1 ratio. Conjugation in the 4-en-3-one probably favours its formation.

The reason for competitive reactions leading to the 4-en-3-one and its $\Delta^{3,5}$-dienol acetate is less clear. The common intermediate is assumed to be of type (10), formed through the mechanism illustrated (cf. tosylhydrazones[12]). We postulate that a complex (11), from (10) and a second molecule of LTA, can break down in unimolecular manner to give the 4-en-3-one (12). An excess of LTA would favour this process. When LTA is deficient, however, expulsion of the nitrogenous residue may require assistance in the form of proton abstraction from C-6, leading to the dienol acetate (5). Gas evolution (presumably N_2) was generally observed.

To establish that product formation is complete in the reaction mixture, and does not occur during aqueous work-up, the 3,20-bis-semicarbazone of 11β-hydroxyprogesterone (see above) was allowed to react with LTA in CD_3CO_2D in the n.m.r. spectrometer. The ^{1}H-n.m.r. spectrum showed all the features characteristic of a mixture (in the same solvent) of 11β-hydroxyprogesterone and its 3,5-dien-3-ol 3-acetate, in *ca.* 3 2 ratio. There were no signals to suggest the presence of a significant amount of any other steroidal species.

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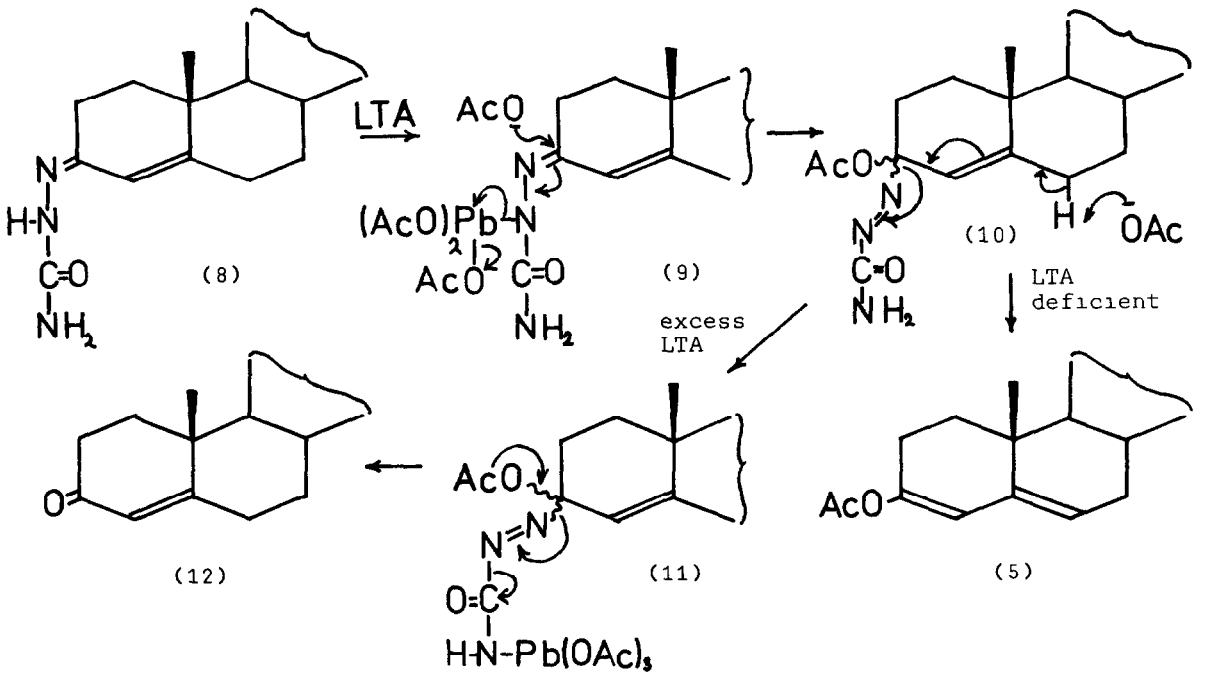

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