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THALLIUM IN ORGANIC SYNTHESIS

PREPARATION OF STEROIDAL 1,4-DIEN-3-ONES

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Abstract— Steroidal 1.4-dien-3-ones are obtained as major products of the reaction between thallium (III) acetate and Δ^1 or Δ^4-3-keto steroids in acetic acid. 5α-cholestan-3-one. similarly treated. followed by esterification, gives mainly 2α-carbomethoxy-A-nor-5α-cholestane.

THE USEFULNESS of thallium salts in organic synthesis has been recently put in evidence. Their employment concerns both aromatic and aliphatic compounds with carbonyl, olefinic, and cyclopropanic functions.

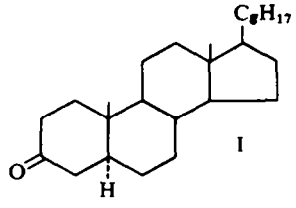
The reactivity of thallium (III) shows points of similarity with that of mercury (II) and lead (IV). The products of the reactions between olefins and Hg (II), Tl (III), and Pb (IV) acetates are thought to result from an addition adduct which can be isolated or is decomposed to give organic compounds and metal species of lower valences.

Some time ago we started an investigation on thallium salts and their reactivity with respect to carbonyl functions of steroidal compounds.

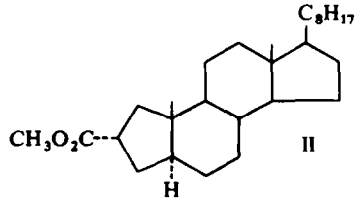
The action of thallium salts on carbonyl functions has been studied in detail by Wiberg and Koch[1] for cyclohexanone. Their results show that the main reaction is a cyclo-contraction giving cyclopentanecarboxylic acid; the proposed mechanism involves the formation of an adduct starting from the enol.

In this paper the results obtained on 3-keto-5α-steroids and on Δ^1 and Δ^4-3-keto steroids are described.

We have found that reaction of 5α-cholestan-3-one (I) with thallium triacetate in acetic acid (95%), followed by esterification with diazomethane, gives 2α-carbomethoxy-A-nor-5α-cholestane (II) as major product. Its identity was shown by comparison with the analogous product obtained from the Favorskii rearrangement on 2α-bromocholestan-3-one.[2,3]



I

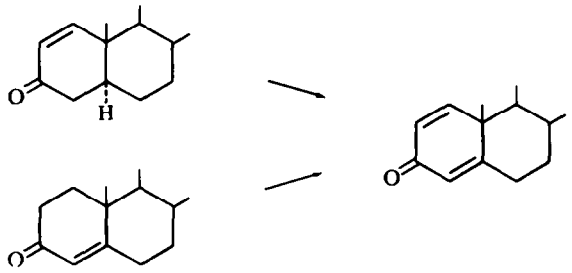


II

The thallium adduct with 5α-cholestan-3-one (and probably with 3-keto-5α-steroids in general) is likely to be formed by attack on the α portion of the molecule,

thus giving an intermediate in which, since the leaving group is bound in 2α, a ring contraction is favoured, the four centres involved being co-planar.

Reaction between Δ^1 or Δ^4-3-keto steroids and thallium triacetate in acetic acid (95%) gives 1,4-dien-3-ones with yields of 43–78%. The so formed 1,4-dien-3-ones do not undergo further modification by thallium acetate under the conditions described below. The reaction has been carried out using 7 steroids (Table 1).



The compounds obtained have been compared with authentic samples. The results allow us to enlarge on the number of reagents able to produce 1,4-dien-3-ones using Δ^1 or Δ^4-3-keto-steroids as starting material.

The reaction procedure can be explained by the following considerations; with Δ^1 and Δ^4-3-keto-steroids the adduct with thallium gives no ring-contraction because of strain due to the unsaturated centre which would be included in the contracted cyclic system. Thus, elimination occurs and it is certainly favoured in the case of the adduct with thallium eventually formed on the β side of the molecule (*trans* diaxial elimination).

TABLE 1. REACTION OF Δ^1 OR Δ^4-3-KETO STEROIDS WITH $Tl(OAc)_3$

Starting Δ^1 or Δ^4-3-keto steroid	Product (major)	Yield (%)
17β-acetoxy 3-oxo androsta-4-ene	17β-acetoxy 3-oxo androsta-1,4-diene[a]	78
17β-hydroxy-3-oxo 17α-methyl androsta-4-ene	17β-hydroxy 3-oxo 17α-methyl androsta-1,4-diene[a]	43
3-oxo cholesta-4-ene	3-oxo cholesta-1,4-diene[a]	76
3,17-dioxo androsta-4-ene	3,17-dioxo androsta-1,4-diene[b]	55
11β-hydroxy 17α:20, 20:21-bis-methylenedioxy 3-oxo pregna-4-ene	11β-hydroxy 17α:20, 20:21-bis-methylenedioxy 3-oxo pregna-4-diene[b]	57
17β-acetoxy 3-oxo androstan-1-ene	17β-acetoxy 3-oxo androstan-1,4-diene[a]	65
17β-acetoxy 3-oxo 1-methyl androsta-1-ene	17β-acetoxy 3-oxo 1-methyl androsta-1,4-diene[a]	74

[a] Ether extracted.
[b] CH_2Cl_2 extracted.

EXPERIMENTAL

Thallium triacetate has been prepared according to Meyer and Goldschmidt[4] and dried over P_2O_5 at 40° under high vacuum. M.ps were measured by a Kofler hot-stage apparatus. Optical rotations were taken at 20° by a Schmidt–Haensch polarimeter with a 1 dm cell. Identity of compounds was confirmed by com-

parison of IR spectra recorded on a Perkin–Elmer Grating Infrared spectrophotometer 521 (KBr disks).

Column chromatography was carried out with deactivated (grade II) Woelm neutral alumina.

Reaction of 5α-cholestan-3-one and thallium triacetate. 10 mmoles of 5α-cholestan-3-one and 30 mmoles of thallium triacetate in 71·5 ml of AcOH (95%) were heated at 80° for 2 hr. The mixture was cooled, diluted with water and ether extracted three times, the ether layers were washed with water to neutrality, collected and dried (Na_2SO_4). The residue from ether evaporation was esterified with ethereal CH_2N_2 to give 4·15 g of yellow oil. Cromatography on 107 g of Al_2O_3 and elution with 1·7 l of n. hexane gave 3·46 g (83%) of crude product, which crystallized (MeOH) to yield 2·75 g of 2α-carbomethoxy-A-nor-5α-cholestane (II) m.p. 98–99°, $[\alpha]_D^{20}$ + 24° (*c*, 2·0, $CHCl_3$).

General procedure for the preparation of steroidal 1,4-dien-3-ones. 1 mmole of Δ^1 or Δ^4-3-keto steroid and 3 mmoles of thallium triacetate were heated in 7·5 ml of AcOH (95%) at 80° for 8 hr.* The mixture was cooled, diluted with water, and extracted with ether or dichloromethane (Table 1). The organic extracts were washed with $NaHCO_3$ aq, then water to neutrality, collected and dried (Na_2SO_4). The residue obtained from solvent evaporation was chromatographed on deactivated neutral alumina. The main reaction product fractions were collected and the crude product crystallized.

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* A preliminary investigation made on testosterone acetate with thallium trifluoroacetate in acetic acid showed that the reaction time can be considerably shortened.