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IMPROVED SYNTHESIS OF 1,2,4-TRIAZOLINE-3,5-DIONE DERIVATIVES OF ERGOSTEROL AND A NEW METHOD FOR THEIR RECONVERSION TO ERGOSTEROL

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Abstract: The ergosterol diene system reacts in excellent yield with a series of 4-substituted 1,2,4-triazoline-3,5-diones generated by *in situ* oxidation of the appropriate hydrazides with phenylseleninic anhydride or phenylseleninic acid. Diaryltelluroxide and diphenylselenoxide are also efficient oxidants. The diene system can be smoothly regenerated by alkaline hydrolysis.

The 4-phenyl-1,2,4-triazoline-3,5-dione (Cookson reagent) derivatives of ergosterol esters have played an important role in the manipulation of the side chain. The method generally used to remove the protecting group has been reduction by lithium aluminium hydride[1].

We have developed a superior method for the preparation of 1,2,4-triazoline-3,5-dione derivatives and have examined various alternatives to phenyl at position 4. In the past hydrazides of type (**1**) have been oxidised to triazalinones of type (**2**), before reaction with an ergosterol ester or other diene. In general the oxidants used are incompatible with the sensitive double bond system of ergosterol (**3**, R' = H). Recently it was shown that phenylseleninic anhydride $(PhSeO)_2O$ is an efficient oxidant for hydrazine derivatives[2,3]. In fact phenylseleninic anhydride reacts nearly quantitatively at

room temperature in tetrahydrofuran with hydrazides of type (**1**) in the presence of ergosterol and its esters to give derivatives of type (**4**). Only 1/3 of a mole of the anhydride is needed and the sole selenated product is diphenyl diselenide. Phenylseleninic acid[3], which is in equilibrium with the anhydride at room temperature, gives equally good yields.

Table I gives a comparison between t-butyl hypochlorite, the best oxidant hitherto available[4], phenylseleninic anhydride and phenylseleninic acid. The anhydride can also be used on the hydrazide (**1**, R = Ph) in presence of ergosterol in pyridine. Without isolation benzoyl chloride was added and the benzoate (**4**, R = Ph, R' = PhCO) was obtained in 96% yield. We also prepared (**4**, R = Ph, R' = PhCO) by oxidation with dianisyl telluroxide and with diphenylselenoxide in yields of 98% and 81% respectively.

Regeneration of the diene system from adducts of type (**4**) has also been effected by heating with strong organic bases[5] and by heating in dimethylsulphoxide[6]. With new 1,2,4-triazoline-3,5-diones available we decided to examine again[7] the possibility of regenerating the diene system by simple alkaline hydrolysis. We find that treatment of the adducts with 2·1 N KOH in 95% ethanol (14 ml for 0.3 mmol) under nitrogen gives back ergosterol in excellent yield. For example the adduct (**4**, R = Ph, R' = PhCO) gave ergosterol (98%) after 1.5 hours reflux or after 36 hours at room temperature. Some comparative data are given in Table II. The derivative (**4**, R = p-NO_2-C_6H_4-, R' = PhCO) was particularly easily hydrolysed and, indeed, the same result was obtained after 20 hours at room temperature. In conclusion, the reagent (**1**, R = p-NO_2-C_6H_4) has the advantage over the others in the efficiency of its addition to ergosterol derivatives and its subsequent removal.

Table I

Adduct (4)	$(PhSeO)_2O$[a]	$PhSeO_2H$[a]	t-BuOCl[b]		
	Yield isolated (%)		Yield (%)	Temp. (°C)	Time (mins.)
(R = H, R' = PhCO)	87	89	0	0	–
(R = Ph, R' = PhCO)	96	98	90	0	30
(R = Ph-CH=N-, R' = PhCO)	92	–	48	0	40
(R = p-MeO-C_6H_4-C=N-, R' = PhCO)	96	93	81	0	30
(R = p-NO_2-C_6H_4-CH=N-, R' = PhCO)	90	–	62	20	50
(R = p-$NO_2C_6H_4$-, R' = PhCO)	97	97	80	20	75
(R = Ph, R' = H)	96	–	–	–	–
(R = p-$NO_2C_6H_4$-, R' = H)	97	–	–	–	–

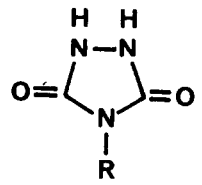
a) Typically to the anhydride (0.024 g, 0.066 mmol) [or the acid 0.132 mmol] in tetrahydrofuran (2.5 ml) was added in one portion the hydrazide (**1**, R = Ph) (0.040 g, 0.22 mmol) and ergosterol benzoate (**3**, R = PhCO) (0.1 g, 0.2 mmol). After 2 hours at room temperature under nitrogen the solution was chromatographed (p.l.c., toluene/EtOAc 4:1) to give $(PhSe)_2$ (0.021 g) and the adduct (**4**, R = Ph, R' = PhCO) (0.130 g) (96%) [98%].

b) To the triazolinedione (1 mmol) suspended in CH_2Cl_2 (12 ml) was added t-BuOCl (1 mmol) in CH_2Cl_2 (1 ml) at the temperature indicated in Table I and left for the time also given in Table I. This solution was then treated with ergosterol benzoate (added as solid) until the red colour disappeared. The yields are corrected for the urazole not oxidised.

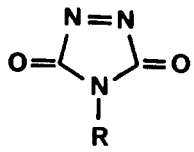
Table II[a]

Adduct (4)	Conversion to ergosterol (%)
(R = H, R' = PhCO)	10
(R = Ph, R' = PhCO)	37
(R = Ph-CH=N-, R' = PhCO)	53
(R = p-MeO-C_6H_4-CH=N-, R' = PhCO)	29
(R = p-NO_2-C_6H_4-CH=N-, R' = PhCO	67
(R = p-NO_2-C_6H_4-, R' = PhCO)	98

a) The adduct (0.1 mmol) in 0.8 N 95% ethanolic KOH (2.9 ml) was heated under flux under nitrogen for 2 hours. The ergosterol was separated by chromatography.



(1)



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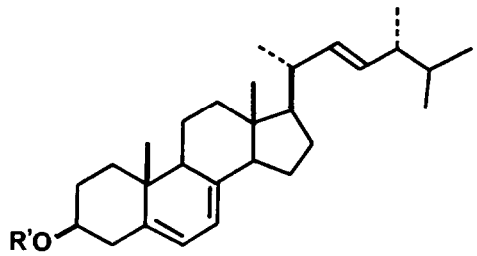

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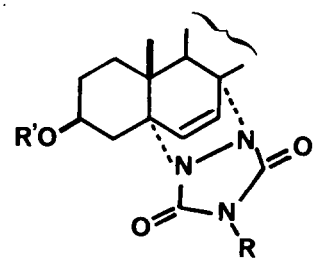

(4)

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