Tetrahedron Letters No. 37, pp 3235 - 3238, 1975. Pergamon Press. Printed in Great Britain.

HIGH PRESSURE INDUCED 1,3-CYCLOADDITION OF NITRONIC ESTERS TO THE STEROIDAL DIPOLAROPHILES

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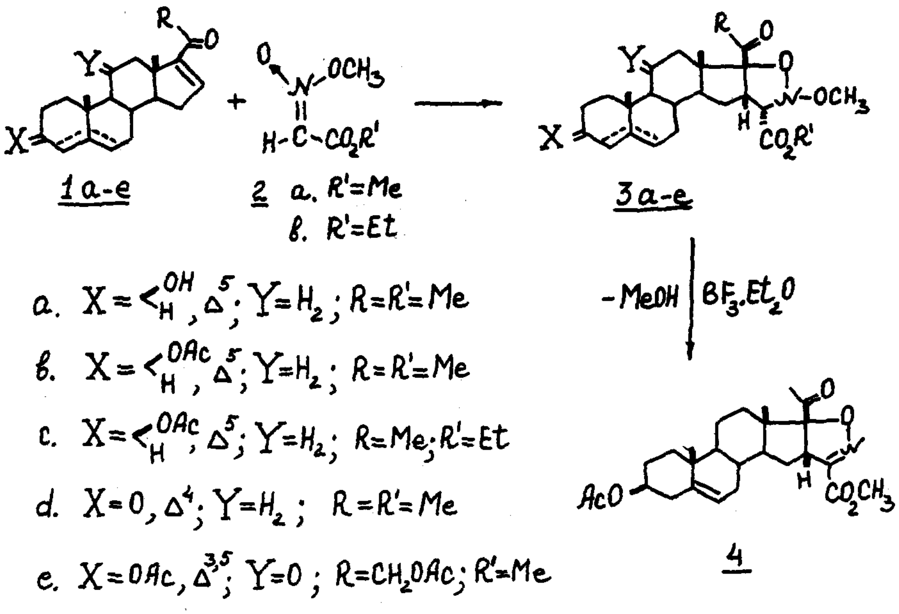
(Received in UK 21 July 1975; accepted for publication 7 August 1975)

It is known that nitronic esters undergo 1,3-dipolar cycloaddition to a wide variety of mono-and disubstituted olefines.[1] Being applied to the steroidal dipolarophiles 1 containing trisubstituted C=C bond this reaction should provide the entry to the new type of pentacyclic steroids with an additional isoxazolidine ring at 16,17 position.

We have found, however, that under usual conditions this reaction produces the desired cycloadducts with the yields no more than 2%. In this case thermal forcing of the cycloaddition is excluded because of thermolability of the starting 1,3-dipoles 2; the attempt to use Lewis acid catalyzed condensation of 1 with nitronic esters 2 gave only 4'H-steroido [16,17-d] - 1',2'-oxazoles similar to 4[2].

Recently it has been shown[3,4] that the several bimolecular reactions (and some cycloadditions among them) having an activation volume of about - 20-30cm^3/mole rather sensitive to high pressures and can be performed with good yields at 5000-15000 atm (instead of $\backsim$1% yield obtained at atmospheric pressure).

Now we wish to report the results of regio- and stereospecific synthesis of previously unknown N-methoxy [16,17-d] - tetrahydro-1',2'-oxazole derivatives of pregnanes 3 by cycloaddition of nitronic esters 2 to 16-dehydro-20-oxosteroids 1 at pressure 14000 atm (Scheme).



a. $X = <^{OH}_{H}, \Delta^5; Y = H_2; R = R' = Me$

b. $X = <^{OAc}_{H}, \Delta^5; Y = H_2; R = R' = Me$

c. $X = <^{OAc}_{H}, \Delta^5; Y = H_2; R = Me; R' = Et$

d. $X = O, \Delta^4; Y = H_2; R = R' = Me$

e. $X = OAc, \Delta^{3,5}; Y = O; R = CH_2OAc; R' = Me$

Scheme

General procedure is as follows. A solution of steroidal dipolarophile 1 (1 mmol) and nitronic ester 2 (4.5 mmol) in dry dichloromethane (3 ml) was kept at 20–40°C in ampoule at 14000 atm for 15–17 hours. Subsequent removal of the solvent and unreacted nitronic ester in vacuo followed by column chromatography on silica gel (gradient elution from hexane to ether) yielded (65–80%) the crystalline cycloadducts 3.

Some spectral data and melting points of the products obtained are given in Table.x) Their structures as [16,17-d]tetrahydro-1',2'-oxazoles derivatives of pregnanes 3 were assigned on the basis of the spectral data and confirmed by transformation of N-methoxy-3b to the known 4[2] in the presence of trace amounts of ethereal BF_3 in dichloromethane solution at ambient temperature. Thus the regiospecificity of the investigated cycloaddition was established.

The 16α, 17α-configuration of the formed heterocycle, presumably arising from the preferential rear side attack on the steroidal dipolarophile by

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x) Satisfactory elemental analyses data were obtained for all products.

the dipolar species, was confirmed by CD studies. The compounds 3 exhibit positive Cotton effect (λ_{max} 293 nm with $\Delta\varepsilon$2.8) attributable to the $n \rightarrow \pi^*$ transition of the 20-oxo group. This positive effect is known[5] to be characteristic of pregnanes with a β acetyl side chain at C-17.

One might anticipate that the cycloaddition discussed may give rise to a pair of stereoisomers arising from the slow nitrogen inversion in the heterocycle formed.[6] In fact, the reaction of 3β-hydroxy-20-oxopregna-5,16-diene 1a or its acetate 1b with nitronic ester 2a and 2b gave respective N-methoxypregnano [16α, 17α-d] tetrahydro-1',2'-oxazoles 3a, 3b and 3c as the sole stable products. On the other hand, in the case of cycloadducts 3d and 3e two products were isolated and separated by rapid chromatography in N_2 atmosphere on silica gel (gradient elution from hexane to ether) (see Table). Thus the reaction of 3,20-dioxopregna-4,16-diene 1d with nitronic ester 2a afforded the mixture of stereoisomers 3d in ratio A:B ≃ 3:4.

Table

Compound		M.p. (hexane-ether)	$\nu^{CHCl_3}_{C=O}$ cm^{-1}	Chemical shifts (δ,p.p.m)[a]				
				18-CH_3	19-CH_3	21-CH_3	N-OCH_3	CO_2CH_3
3a		213-216°	1715,1750	0.67	0.98	2.13	3.54	3.71
3b		219-222°	1715,1730,1745	0.68	1.01	2.15	3.57	3.74
3c		176-180°	1715,1730,1750	0.66	1.00	2.13	3.56	
3d	A	131-135°	1685,1720,1755	0.75	1,17	2.15	3.61	3.72
	B	226-230°	1670,1707,1755	0.70	1.16	2.13	3.53	3.71
3e	A	102-106°	1710,1735,1755	0.73	1.10	4.79[b]	3.69	3.76
	B	181-185°	1710,1750 - 60	0.69	1.10	4.80[b]	3.61	3.75

a) measured on a Varian DA-60-IL spectrometer in $CDCl_3$ solutions with TMS as internal standard

b) quartet, OCH_2CH_3.

Similarly 3,21-diacetate 1e produced the mixture of stereoisomers 3e in ratio A:B $\simeq$ 1:2. In both cases low melting products are unstable and readily transformed without catalyst into their isomers. Both A and B isomers when treated with trace amounts of ethereal BF_3 afford the same demethoxy compound of type 4. The two pairs A,B have very similar properties in their IR, ^{1}H-NMR, mass spectra and CD curves. Some observed differences in their chemical shift values for the N-methoxy- and 18-methyl proton signals (see Table) taken together with the coupling pattern of the 3'-proton resonance signal at 3.8 - 3.9 ppm (d; $J \simeq$ 6.5 Hz and 7.5 Hz for A and B isomers, respectively) suggested that the isomers produced might be nitrogen invertomers.

This part of investigation will be a subject of forthcoming report.

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