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TRANSFORMED STEROIDS—PART 95

HIGH PRESSURE INDUCED 1,3-DIPOLAR CYCLOADDITION OF NITRONIC ESTERS TO 16-DEHYDRO-20-OXO STEROIDS

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Abstract—High pressure induced cycloaddition of Z and E nitronic esters (2) to 16-dehydro-20-oxo steroids (1) leads to regiospecific formation of steroido [16α,17α-d] tetrahydro-1',2'-oxazoles (3 and 4). It is shown that both modes ("*exo-endo*") of dipolarophile approach to the dipole are realized for most steroids examined. All four possible isomers are isolated and their preferred conformations are established. It is shown that conversion of unstable stereomers to stable ones (3'→4; 4'→3) proceeds as a simultaneous nitrogen inversion and isoxazolidine cycle conformational change ($_SE \rightarrow E^S$).

In the course of our studies[1,2] on 16-dehydro-20-oxo steroidal reactivity in the cycloaddition process, we have investigated their reaction with nitronic esters. It is known that nitronic esters undergo 1,3-dipolar cycloaddition to a variety of mono- and disubstituted olefins.[3] Applied to the steroidal dipolarophiles (1) containing a trisubstituted C=C bond, this reaction should provide an entry to a new type of pentacyclic steroid with an additional isoxazolidine ring at the 16,17 position.

We have found, however, that under normal conditions, this reaction produced the desired cycloadducts in yields of no more than 2%. In this case thermal forcing of the cycloaddition is excluded because of thermolability of the starting 1,3-dipole 2; the use of Lewis acids as the reaction catalyst produces only steroido [16,17-d]-1,2'-oxazoles similar to 5.[2]

Recently, it has been shown[4,5] that the several bimolecular reactions, (and some cycloadditions among them) having an an activation volume of *ca.* −20 to −30 cm³/mole, are rather sensitive to high pressure and can be performed with good yields at 5000–15,000 atm (instead of ~1% yield obtained at atmoshperic pressure). It was tempting to try this approach for the reaction under study.

We now report the successful regiospecific synthesis of N - methoxy[16α,17α - d]tetrahydro - 1',2' - oxazole derivatives of pregnanes (3 and 4) by cycloaddition of Z and E nitronic esters 2, respectively, to 16-dehydro-20-oxo steroids(1) at a pressure of 14,000 atm† (Scheme 1).

Nitronic esters are known[7] to be a mixture of two geometric isomers in a ratio Z:E = 60:40; it is also known that the Z form is more reactive than the E isomer and isomerization does not occur in the course of cycloaddition. One might anticipate therefore that the reaction of a large excess of nitronic ester (2) should give the cycloadducts (3), arising from addition of the Z isomer only. This was confirmed by PMR analysis of the mixture which demonstrated the presence of the same quantity of E 2 isomer as was present in the starting mixture. Using the difference in reactivity of Z and E isomers towards a dipolarophile, we were able to isolate the E isomer 2 in pure form. The reaction of E 2 with 1 proceeded rather slowly (the reaction time is ~40 hr), the result being the formation of cycloadducts (4) which differed from the products (3) obtained for the reaction with the Z 2 isomer.

The cycloadduct structures as [16,17-d] tetrahydro-1',2'-oxazole derivatives of pregnanes 3 and 4 were assigned on the basis of the spectral data and confirmed by their transformation to the known 5[2] in the presence of trace amounts of ethereal BF_3.

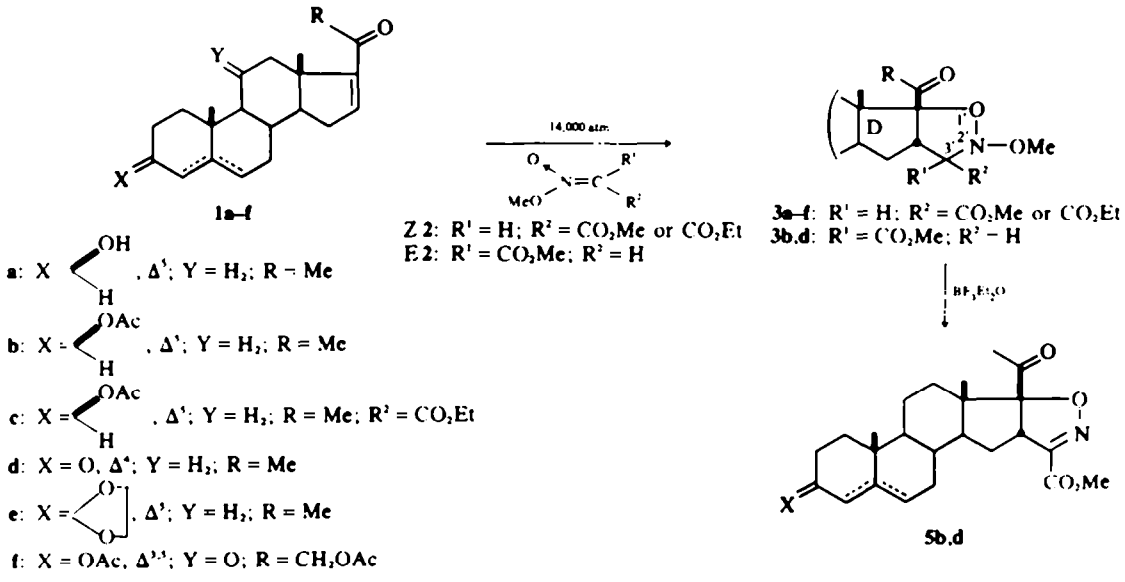
The 16α,17α-configuration of the heterocycle formed, presumably arising from the preferential rear side attack on the steroidal dipolarophile by the dipolar species, was confirmed by CD studies. Both compounds 3 and 4 exhibit a positive Cotton effect attributable to the $n \rightarrow \pi^*$ transition of the 20-oxo group. This positive effect is known[8] to be characteristic of pregnanes with a β acetyl side chain at C-17.

The reaction of 16-dehydropregnenolone (**1a**) or its acetate (**1b**) with a Z 2 isomer gave the corresponding N-methoxypregnano[16α,17α-d]tetrahydro - 1',2' - oxazoles (**3a–c**) as the sole stable products. On the other hand, in the case of cycloadducts (**3d–f**), two stereomeric products were isolated and separated by rapid chromatography under N_2. Thus the reaction of 16-dehydroprogesterone (**1d**) with Z 2, afforded the mixture of stereomers in a ratio **3d**:**3'd** ≃ 4:3. Similarly, 16-dehydroprogesterone 3-monoketal (**1e**) gave the mixture of stereomers in a ratio **3e**:**3'e** ≃ 2:1. As in the case of Z nitronic ester 2, the reaction of the dipolarophiles (**1b** and **1d**) with E 2 isomer also produced a mixture of two stereomeric adducts. Thus the reaction of **1b** with excess E 2 gave a mixture of stereomers in a ratio **4b**:**4'b** ≃ 1:2 with 40% yield‡ and in the case of **1d** a mixture of cycloadducts in a ratio **4d**:**4'd** ≃ 1:2 was obtained.

Both in the series of cycloadducts 3 and 4 these isomeric pairs have a difference in R_f values (TLC) and m.ps and very similar properties in their IR, PMR, mass spectra and CD curves (see Table 1 and Experimental). In each of the pairs, namely 3 and 3'; 4 and 4', one isomer

†Preliminary communication see Ref. 6.

‡The cycloadducts yield increase in the reaction mixture being kept for a long time does not occur but the demethoxy products 5 appear.



Scheme 1.

Table 1. PMR chemical shifts and coupling constants of N-methoxyisoxazolidines obtained

Compound	Chemical shifts (δ, ppm) 18-CH_3	19-CH_3	21-CH_3	N-OCH_3	CO_2CH_3	3'-H	$J_{H_3,H_{16}}$
3a	a) 0.67	0.98	2.13	3.54	3.71	c)	
3b	a) 0.68	1.01	2.15	3.57	3.74	c)	
	b) 0.52	0.76	2.12	3.35	3.35	3.62 d	7.5 Hz
3c	a) 0.66	1.00	2.13	3.56		c)	
3d	a) 0.70	1.16	2.13	3.53	3.71	c)	
	b) 0.49	0.60	2.01	3.31	3.31	3.61d	7.6 Hz
3'd	a) 0.75	1.17	2.15	3.61	3.72	3.95d	6.6 Hz
3e	a) 0.68	1.01	2.15	3.55	3.75	c)	
	b) 0.53	0.80	2.18	3.31	3.33	c)	
3'e	a) 0.72	1.01	2.15	3.61	3.75	c)	
3f	a) 0.69	1.10	d) 4.80	3.61	3.75	c)	
3'f	a) 0.73	1.10	d) 4.79	3.69	3.76	c)	
4b	a) 0.70	1.00	2.20	3.61	3.76	4.43d	9.8 Hz
	b) 0.49	0.75	2.00	3.23	3.31	4.40d	9.8 Hz
4'b	a) 0.66	1.02	2.25	3.69	3.75	c)	
	b) 0.51	0.79	2.17	3.30	3.56	3.66d	1.5 Hz
4d	a) 0.72	1.16	2.19	3.61	3.74	4.43d	9.8 Hz
	b) 0.48	0.60	1.97	3.20	3.30	4.40d	9.8 Hz
4'd	a) 0.68	1.16	2.23	3.69	3.73	c)	
	b) 0.48	0.65	2.01	3.26	3.54	3.60d	2.0 Hz

a) measured in $CDCl_3$ solution

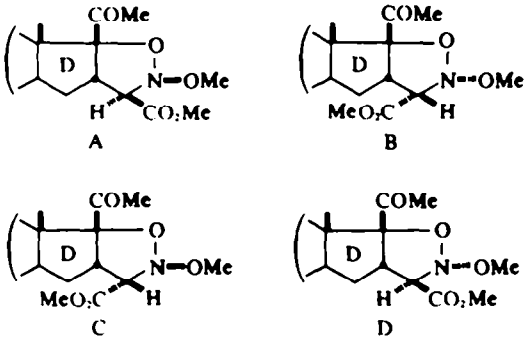
b) measured in C_6D_6 solution

c) the signal overlapped with other protons

d) quartet, OCH_2CH_3

having a larger R_f value and a lower m.p. is less stable and transforms without catalyst into a stable one of the other pair (*vide infra*). In the presence of trace amounts of $BF_3{\cdot}Et_2O$ each of the four isomers (3 and 3'; 4 and 4') afforded the same demethoxy derivative of the 5 series.

Thus most dipolarophiles (1) react with Z and E nitronic esters (2) to form two stereomeric pairs 3,3' and 4,4', respectively. Taking into account the regiospecifity of cycloaddition discussed and preferential rear side attack of the dipole, the compounds obtained can be expected to be the stereoisomers only at C-3' and N-atoms. Hence four partial structures A-D can be suggested for the cycloadducts (Scheme 2).



Scheme 2.

As one can see these structures represent all possible isomers at C-3' and N-atoms and are related as follows: A,B and C,D are diastereomeric pairs, A,C and B,D are C-3' epimeric pairs, A,D and B,C are nitrogen invertomers.

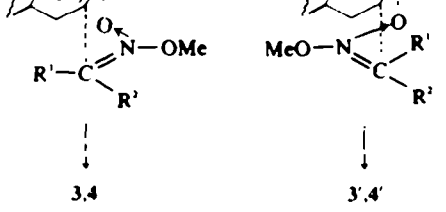
The final structural assignments could be deduced from detailed examination of ^{1}H NMR spectra of stereomeric cycloadducts.†

To determine the preferred conformation for each stereomeric steroido[16α,17α-d] - N - Methoxy - isoxazolidines, we used the dependence of the vicinal proton–proton ($J_{H_{17}H_{16}}$) and nitrogen–proton ($J_{^{15}N,H_{17}}$) coupling constants upon the mutual spatial arrangement of the interacting nuclei. The PMR data are summarized in Tables 1 and 2. The assignment of the 3'-proton signal was made by means of spin decoupling and INDOR experiments and by preparation of the corresponding C-3'-(d) deutero stereomeric adducts (3 and 4). The isomeric adducts containing ^{15}N were prepared by cycloaddition of $CH(CO_2Me)=^{15}N(O)OMe$ (2)[16] to 16-dehydroprogesterone (1d).

The relationships between stereomers were established also by isomerization data. As mentioned, stereomeric isoxazolines 3,3' and 4,4' differ in stability within each pair. Therefore, on standing, or melting, or refluxing in benzene, toluene or methanol solutions, less stable isomers (4') easily transformed into the high melting stable ones (3; obtained by cycloaddition of the Z form of the dipole 2).

This transformation was confirmed by PMR data: the 3'-H signal at δ3.60 ppm and J 7.5 Hz, characteristic of isoxazolidine (3), appears in the spectrum of isomerization products of 4' (instead of δ4.40 ppm and J 9.8 Hz for 4). A similar isomerization process was observed for unstable isomers (3') produced from Z 2. The PMR spectrum of 3' isomerization products contains a 3'-H doublet at δ4.40 ppm and J 9.7 Hz identical to that for isomers 4. In the conditions of the above isomerization both stable isomers 3 and 4 do not undergo any changes. It should be noted that the compounds 3 and 4 have identical R_f values in various elution systems and very close m.ps.

These isomerization results lead us to the conclusion that stereomeric pairs 3,3' and 4,4' are not epimeric at C-3' (i.e. A,C and B,D)‡ or nitrogen invertomeric (i.e. A,D and B,C), but diastereomeric ones, arising from the two modes ("*exo-endo*" type) of the dipolarophile 1 approach to the Z and E dipoles 2, i.e. these are A,B pairs for 3,3' and C,D pairs for 4,4' (Scheme 3).



Scheme 3.

This conclusion was finally confirmed by consideration of $J_{^{15}N,H_3}$ values (Table 2). In ^{15}N containing cycloadducts 3d and 3'd these coupling constants are equal to 5.4 and 6.2 Hz, respectively, and for 4d the one is <0.1 Hz. In accordance with the recently established dependence of N,H coupling constants on orientation of the nitrogen

†In choosing preferred conformation for isoxazolidine adducts we took into account the following factors. In accordance with previous studies,[9-11] we assumed the heterocycle exists in the conformation close to envelope type (N^E), the N atom being out of the plane of the four remaining atoms and the nitrogen lone pair is quasi equatorial. These assumptions are based on X-ray analysis data.[14] Such a preferred conformation for N-alkoxy isoxazolidines was recently accounted for by anomeric effect.[15]

‡There was no 3'H-d-exchange during the isomerization of 3' and 4' in CD_3OD–CD_3ONa.

Table 2. The nitrogen-proton coupling constants values of ^{15}N containing N-methoxyisoxatolidines

Compound	$^2J_{^{15}N,H_3}$
3d	5.4 Hz
3'd	6.2 Hz
4d	<0.1 Hz
4'd■	

■ $^3J_{^{15}N,H_3}$ impossible to determine because of overlapping H-16 signal with steroidal ring protons

■■ was not obtained labelled ^{15}N.

lone pair[16,17] these data (i) indicate quasi equatorial orientation of nitrogen long pair and (ii) point to the possibility of the stereomeric pairs 3,3' and 4,4' to be isomers arising from "*exo*" and "*endo*" approach of steroid molecule to the dipole. In fact, a large $^2J_{15N,H_3}$ value both for 3 and 3' indicate *cis* orientation of the N atom and 3'-proton that may be realized only for the A,B-pair (Scheme 4). The choice of conformation within the pair can be made by consideration of J_{H_{16},H_3}. Anomalously, a low J_{H_{16},H_3} value for isomer 4' proves *trans* orientation of H-3' and H-16 and consequently the same orientation of H-16 and the N atom.[13,18] Since 3 can be produced by 4'-isomerization, we can assign *cis* orientation of H-16 and nitrogen for 3 (correspondingly in 3' these atoms are *trans* oriented).

In conclusion we have the following preferred conformations for stereomeric cycloadducts 3,3' and 4,4' (Scheme 4).

Thus, the transformation of unstable isomers into stable ones (3'→4; 4'→3) proceeds as a simultaneous nitrogen inversion and isoxazolidine cycle conformational change ($_NE \rightarrow E^N$). The sharp differences in thermodynamic stability of the diastereomeric N-methoxyisoxazolidines allow the assumption that the cycloaddition is largely a kinetically controlled process.

EXPERIMENTAL

All m.ps are uncorrected. The IR spectra were recorded with a UR-10 spectrometer (VEB Carl Zeiss, Jena). CD spectra were taken on a recording Cary 60 spectropolarimeter with CD-6002 model attachment at +25° in dioxane solns. The PMR spectra were measured using a Varian DA-60-IL and WP-60 spectrometers with TMS as internal standard. The mass spectra were taken on a Varian MAT CH-6 spectrometer.

Determinations of purity were provided using of TLC on silica gel Woelm plates, with ether–hexane system: 2:1 (I); 4:1 (II); 5:1 (III). All column chromatography separations were carried out on silica gel (200–250 mesh) in N_2 atmosphere.

[16α,17α-d] - 2'α - *Methoxy* - 3'β - *methoxycarbonyl* - *tetrahydro* - 1',2' - *oxazole derivative of* 3β - *Hydroxy* - 20 - *oxopregn* - 5 - *ene*, **3a**. A soln of **1a** (0.3 g; 0.95 mmol) and a mixture of Z,E **2** (0.9 g; 6.7 mmol) in dry CH_2Cl_2 (2 ml) was kept at 30° in an ampoule at 14,000 atm for 18 hr. Subsequent removal of the solvent and unreacted nitronic ester *in vacuo* followed by column chromatography (elution with hexane–ether 3:2) yielded 0.34 g (80%) of **3a**; m.p. 213–216° (CH_2Cl_2); IR spectrum (ν cm^{-1}; KBr): 1707, 1750, 3615. (Found: C, 66.83; H, 8.52; N, 3.22. $C_{25}H_{37}NO_6$ requires: C, 67.09; H, 8.33; N, 3.13%).

[16α,17α-d] - 2'β - *Methoxy* - 3'β - *methoxycarbonyl* - *tetrahydro* - 1',2' - *oxazole derivative of* 3β - *hydroxy* - 20 - *oxopregn* - 5 - *ene acetate*, **3b**. A soln of **1b** (0.5 g; 1.4 mmol) and a mixture of Z,E **2** (0.9 g; 6.7 mmol) in dry CH_2Cl_2 (2 ml) was kept at 22° in ampoule at 14,000 atm for 17 hr and then worked up as described. Chromatography (elution with hexane–ether 4:1) afforded **3b**, yield: 0.5 g (73%); m.p. 219–222° (ether–hexane); R_f 0.56 (system I). IR spectrum (ν cm^{-1}, $CHCl_3$): 1245, 1255, 1715, 1730, 1750. CD: λ_{max} 293 nm ($\Delta\epsilon$ + 2.8). (Found: C, 66.04; H, 7.82; N, 2.95. $C_{27}H_{39}NO_7$ requires: C, 66.22; H, 8.05; N, 2.86%).

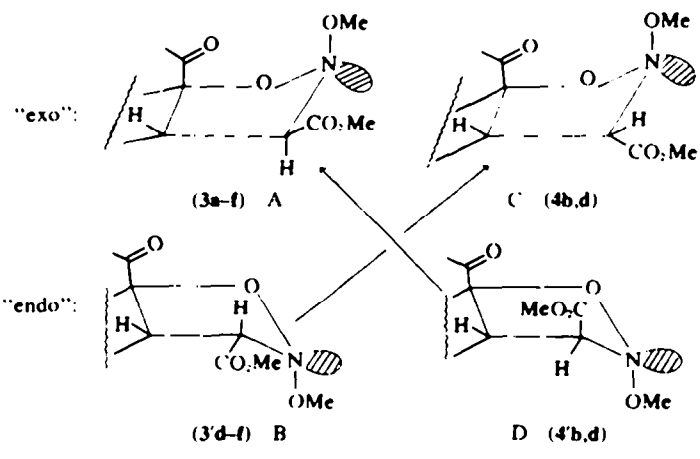
[16α,17α-d] - 2'β - *methoxy* - 3'β - *ethoxycarbonyl* - *tetrahydro* - 1',2' - *oxazole derivative of* 3β - *hydroxy* - 20 - *oxopregn* - 5 - *ene acetate*, **3c**. This compound was prepared as above starting from **1b** and a mixture of Z,E **2** (R^2=CO_2Et); yield: 65%; m.p. 176–180° (ether–hexane). IR spectrum (ν cm^{-1}, KBr): 1250, 1715, 1735, 1745. (Found: C, 66.87; H, 7.93; N, 3.04. $C_{28}H_{47}NO_7$ requires: C, 66.77; H, 8.21; N, 278%). Similarly, 3'α-d **3b** was prepared starting from **1b** and mixture of 2-d Z,E **2** (deuterium content >85%).

Cycloaddition of 16-*dehydroprogesterone* **1d** *to Z nitronic ester* **2**. A soln of **1d** (0.5 g; 1.5 mmol) and a mixture of Z,E **2** (0.9 g; 6.7 mmol) in dry CH_2Cl_2 (2 ml) was kept at 22° in an ampoule at 14,000 atm for 17 hr and worked up as described. Rapid chromatography of the oily residue (1.25 g) using gradient elution from hexane to ether afforded **3'd** (0.23 g; 32%); m.p. 131–135° (ether–hexane); R_f 0.46 (system I). IR spectrum (ν cm^{-1}; $CHCl_3$): 1630, 1685, 1720, 1750. CD: λ_{max} 292 nm ($\Delta\epsilon$ + 1.9). (Found: C, 67.40; H, 7.94; N, 3.29. $C_{25}H_{35}NO_6$ requires: C, 67.39; H, 7.92; N, 3.14%). Further gradient elution from hexane to ether gave **3d** (0.29 g; 41%); m.p. 226–230° (ether–hexane); R_f 0.40 (system I). IR spectrum (ν cm^{-1}; $CHCl_3$): 1625, 1670, 1707; 1750. CD: λ_{max} 292 nm ($\Delta\epsilon$ + 2.7). (Found: C, 67.33; H, 8.09; N, 3.38. $C_{25}H_{35}NO_6$ requires: C, 67.39; H, 7.92; N, 3.14%).

Similarly, 3'α-d **3d**, 3'β-d **3'd** and ^{15}N-**3d**, ^{15}N-**3'd** were prepared starting from **1d** and the mixture of 2-d Z,E **2**, **1d** and ^{15}N-Z,E **2**, respectively.

Cycloaddition of 16-*dehydroprogresterone* 3-*monoethyleneketal* **1e** *to Z nitronic ester* **2**. A soln of **1e** (0.5 g; 1.4 mmol) and a mixture of Z,E **2** (0.9 g; 6.7 mmol) in dry CH_2Cl_2 (2 ml) was kept at 22° in an ampoule at 14,000 atm for 20 hr and worked up as described. Rapid chromatography using gradient elution from hexane to ether afforded the [16α,17α-d] - 2'α - methoxy - 3'α - methoxycarbonyl - tetrahydro - 1',2' - oxazole derivative **3'e** (0.12 g; 17%); m.p. 128–130°; 211–217° (ether–hexane); R_f 0.41 (system I). IR spectrum (ν cm^{-1}; KBr): 1710, 1750. *m/e* 489 (M^+, $C_{27}H_{39}NO_7$ requires 489.57). By continued elution, **3'e** (0.21 g; 32%) was isolated, m.p. 218–221.5° (ether–hexane); R_f 0.30 (system I). IR spectrum (ν cm^{-1}, KBr): 1715, 1755. (Found: C, 66.54; H, 8.18; N, 2.69. $C_{27}H_{39}NO_7$ requires; C, 66.23; H, 8.03; N, 2.86%).

Cycloaddition of **1f** *to Z nitronic ester* **2**. A soln of **1f** (0.5 g;



Scheme 4.

1.1 mmol) and a mixture of Z,E 2 (0.9 g; 6.7 mmol) in dry CH_2Cl_2 (2 ml) was kept at 22° in an ampoule at 14,000 atm for 19 hr and worked up as described. Gradient elution from hexane to ether gave the [16α,17α-d] - 2'α - methoxy - 3'α - methoxycarbonyl - tetrahydro - 1',2' - oxazole derivative **3'f** (0.18 g; 27%); m.p. 102–106° (ether-hexane); R_f 0.64 (system II). IR spectrum (ν cm $^{-1}$; KBr): 1640, 1675, 1705, 1735, 1755. *m/e* 559 (M$^+$, $C_{29}H_{37}NO_{10}$ requires 559.59). Further elution gave **3f** (0.33 r; 50%); m.p. 181–185° (ether–hexane); R_f 0.54 (system II). IR spectrum (ν cm^{-1}; KBr): 1655, 1675, 1705, 1750–1755. *m/e* 559 (M$^+$, $C_{29}H_{37}NO_{10}$ requires: 559.59).

Cycloaddition of 16-*dehydropregnenolone acetate* **1b** *to E nitronic ester* **2**. A soln of **1b** (0.6 g, 1.7 mmol) and E **2** (0.4 g; 3 mmol) (obtained by the method,[19] m.p. 35°, δ_{CH} 6.7 ppm) in dry CH_2Cl_2 (2 ml) was kept at 22° in an ampoule at 14,000 atm for 40 hr. Rapid chromatography of an oily residue (1.2 g) using hexane–ether (5:1) afforded 0.2 g of strating **1b** and 0.22 g of the [16α,17α-d] - 2'α - methoxy - 3'β - methoxycarbonyl - tetrahydro - 1',2' - oxazole derivative **4'b**; m.p. 138–140°; 209–214° (ether-hexane); R_f 0.62 (system I). IR spectrum (ν cm $^{-1}$; KBr): 1250, 1710, 1735, 1750. (Found: C, 65.70; H, 7.73; N, 2.83. $C_{27}H_{39}NO_7$ requires: C, 66.22; H, 8.05; N, 2.86%). Further eluation with hexane–ether (2:3) gave **4b** (0.11 g); m.p. 185–189° (ether–hexane); R_f 0.56 (system I). IR spectrum (ν cm^{-1}; KBr): 1250, 1710, 1735–1755. *m/e* 489 (M$^+$, $C_{27}H_{39}NO_7$ requires: 489.59).

Similarly, 3'α-d **4'b** and 3'β-d **4b** were prepared from **1b** and 2-d E **2**.

Cycloaddition of 16-*dehydroprogesterone* **1d** *to E nitronic ester* **2**. The cycloaddition of **1d** (0.6 g; 1.9 mmol) to E **2** (0.4 g; 3 mmol) was carried out similarly. Chromatography gave the following three compounds: (1) 0.27 g of starting **1d**; (2) 0.22 g (26%) of the [16α,17-d] - 2'α - methoxy - 3'β - methoxycarbonyl - tetrahydro - 1',2' - oxazole derivative **4'd**; m.p. 135–137.5°; 207–218° (ether–hexane); R_f 0.55 (system III). IR spectrum (ν cm^{-1}; KBr): 1615, 1670, 1710, 1750. (Found: C, 67.59; H, 8.18; N, 3.08. $C_{25}H_{35}NO_6$ requires: C, 67.39; H, 7.92; N, 3.14%); (3) 0.09 g (10%) of **4d**; m.p. 181–185° (ether–hexane); R_f 0.44 (system III). IR spectrum (ν cm $^{-1}$; KBr); 1620, 1680, 1715. *m/e* 445 (M$^+$, $C_{25}H_{35}NO_6$ requires: 445.54).

Similarly, 3'α-d **4'd** and 3'β-d **4d** were prepared starting from **1d** and 2-d E **2**.

[16α,17α-d] - 3' - *Methoxycarbonyl* - 4'H - 1',2' - *oxazole derivative of* 3β - *hydroxy* - 20 - *oxo* - *pregn* - 5 - *ene acetate* **5d**. To a soln of **3b** (0.06 g; 0.12 mmol) in dry CH_2Cl_2 (4 ml) $BF_3{\cdot}Et_2O$ (0.01 ml) was added. The mixture was kept at 20° for 24 hr, then diluted with ether (5 ml) and while stirring vigorously water (5 ml) was added. The organic layer was separated, washed with water and dried. The solvent was removed *in vacuo* and residue was purified by chromatography (elution with hexane–ether) and crystallized from ether–hexane to give **5d** as colourless needles; yield: 0.04 g, m.p. 205–208°, identical (IR, PMR, m.m.p.) with the authentic[2] sample of **5d**.

Similarly, isoxazolidines **4d** and **4'd** were transformed to the same isoxazolidine **5d**.

[16α,17α-d] - 3' - *Methoxycarbonyl* - 4'H - 1',2' - *oxazole derivative of* 3,20 - *dioxopregn* - 4 - *ene* **5d**. A soln of **3d** (1.3 g; 2.7 mmol) and $BF_3{\cdot}Et_2O$ (0.03 ml) in dry CH_2CL_2 (30 ml) was kept at 20° for 2 days, then the mixture was worked up as above. The residue was purified by column chromatography using hexane–ether (1:1) followed by recrystallization from ether–hexane to give **5d** (1.02 g); m.p. 177–178.5°. IR spectrum (ν cm $^{-1}$; KBr): 1600, 1625, 1675, 1725. PMR spectrum (δ ppm; $CDCl_3$): 0.75 (s, 18-CH_3), 1.16 (s, 19-CH_3), 2.23 (s, 21-CH_3), 3.81 (s, CO_2CH_3), 4.18 (dd, 16-H), 5.68 (broad s, 4-H). (Found: C, 69.77; H, 7.45; N, 3.94. $C_{24}H_{31}NO_5$ requires: C, 69.71; H, 7.56; N, 3.93%).

Similarly, isoxazolidines **3'd**, **4'd** and **4d** were transformed to the same demethoxy compound **5d**.

[16α,17α-d] - 2'β - *Methoxy* - 3'α - *methoxycarbonyl* - *tetrahydro* - 1',2' - *oxazole derivative of* 3,20 - *dioxopregn* - 4 - *ene* 3 - *monethyleneketal* **4e**. A soln of **3'e** (0.04 g; 0.08 mmol) in dry C_6H_6 (2 ml) was refluxed for 1 hr. The solvent was removed *in vacuo* and the crystalline residue was recrystallized from ether–hexane to give 0.038 g of **4e**; m.p. 205–210°. PMR spectrum (δ ppm; C_6H_6): 0.50 (s, 18-CH_3), 0.76 (s, 19-CH_3), 1.94 (s, 21-CH_3), 3.11 (s, N–OCH_3), 3.25 (s, CO_2CH_3), 4.38 (d, 3'-H, J = 10 Hz), 5.01 (m, 6-H).

Similarly, isoxazolidine **4d** and ^{15}N-**4d** were obtained starting from **3'd** and ^{15}N-**3'd**, respectively. The isoxazolidine **3d** was obtained starting from **4'd** in above described manner.

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