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THE ADDITION OF ARYL AZIDES TO THE STEROIDAL 16,17-DOUBLE BOND

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The 1,3-dipolar addition of azides to olefins has received careful study because of the interesting regiochemical results. It has been stated that "in the absence of steric effects, the product distribution will be determined by electronic effects occurring in the rate-determining step".[1] Houk[2] has predicted on the basis of a perturbation model for the concerted mechanism that for electron-withdrawing substituents on the olefin, 4-substituted 2-triazolines should predominate, whereas for electron-donating substituents on the olefin 5-substituted 2-triazolines should be the exclusive products.

These theoretical predictions have been borne out in the cases of vinyl ethers[3], enamines[4], esters[5] and nitriles[6]. Non-regiospecific addition of phenyl azide to methyl methacrylate was reported by Huisgen[7] and L'Abbé[8] obtained similar results for isopropenyl ketone, methacrylonitrile and methacrylamide. The results were in accord with the predictions of Bastide[9].

In order to probe the interplay of electronic and steric effects in the addition of phenyl azides to olefins we chose the 17-substituted 16,17-androstene nucleus as a platform. Addition of excess phenyl azide to 3β-acetoxypregna-5,16-dien-20-one (1a, 3g.) in the dark at 60° for 5 days gave the [17α,16α-d]-triazoline, 3a, 1.7g, as the major product together with the [16α,17α-b]-aziridine, 2a, 1.0g. The 20-keto group of 2a appeared at 1690 cm^{-1} due to interaction with the aziridine ring. The 16α,17α stereochemistry of 2a was established by examination of the width of the 16β-H signal (2Hz), which compares well with that of the same proton in 16α,17α-epoxides[10].

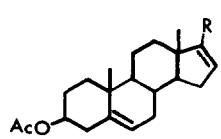
In confirmation of the regiochemical assignment the same dipolarophile gave with o-chlorophenyl azide the corresponding triazoline, 3c, and aziridine, 2c. In the pmr spectrum of the former the signal of the 16β-H appeared at lower field by 0.3 ppm than that of the same proton in the unsubstituted compound, 3a. This through-space deshielding effect of a halogen atom has been used by us[11] in proving the orientation of [16α,17α-d]-1',3'-diphenyl-2'-pyrazolino steroids and has ample precedent[12]. Such an effect can only be operative in the [17α,16α-d] isomer 3c.

In like manner were synthesized the p-tolyl derivatives 2b and 3b.

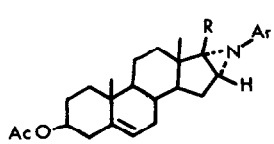
Although the 20-ketopyrazolines are stable alone at 65° they decompose to the aziridines at this temperature in the presence of phenyl azide. The rate of formation of aziridine under these conditions is however much lower than its rate of formation in the original addition reaction. This suggests that the chief source of aziridine in the addition is either the unobserved [16α,17α-d]-triazoline or a dipolar intermediate, which cyclizes with loss of nitrogen[13]. If indeed the [16α,17α-d]-triazoline is involved its lower stability relative to its regioisomer[14] would be contrary to electronic factors[8] but could possibly be explained in terms of acceleration of decomposition due to steric compression.

Addition of excess phenyl azide to 3β-acetoxy-17-cyanoandrost-5,16-diene, 1b (2.0g), occurred in the dark at 65° for 7 days to give a mixture of the expected triazoline, 3d (0.3g), and aziridine, 2d (1.3g). In comparable fashion were synthesized the p-tolyl analogs 3e, 2e and the o-chlorophenyl analogs 3f, 2f. The triazolines 3e, 3f could not be obtained completely pure but an even larger ortho-halogen effect was observed in the pmr spectrum (Table I) of 3f. It is interesting to note that in the case of a 17-cyano substituent the predominant product (ratio 4/1) is now the aziridine. This either reflects the higher radical-stabilizing character of the cyano group relative to an acetyl group, thus allowing the decomposition of the triazoline to proceed at a higher rate, under the same conditions, or a lower steric hindrance to formation of the regioisomeric [16α,17α-d]-triazoline.

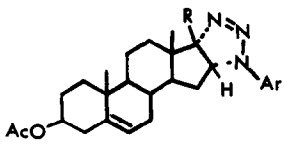
In the case of addition of phenyl azide to 3β-acetoxy-17-methoxyandrosta-5,16-diene, 1c (2.0g), at 70° for 7 days only one product, the [16α,17α-d]-triazoline, 4a (1.5g), was isolated (Table III). The regiochemistry of the addition was proved by the addition of o-chlorophenyl azide to the same olefin to yield the corresponding triazoline, 4b, in which the 16β-H appeared at exactly the same field position (4.63 ppm) as in the phenyl analog, 4a.



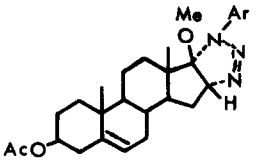
1a, R=$COCH_3$
b, R=CN
c, R=OCH_3



2a, R=$COCH_3$, Ar=C_6H_5
b, R=$COCH_3$, Ar=p-$CH_3C_6H_4$
c, R=$COCH_3$, Ar=o-ClC_6H_4
d, R=CN, Ar=C_6H_5
e, R=CN, Ar=p-$CH_3C_6H_4$
f, R=CN, Ar=o-ClC_6H_4



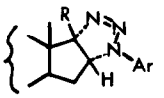
3a, R=$COCH_3$, Ar=C_6H_5
b, R=$COCH_3$, Ar=p-CH_3-C_6H_4
c, R=$COCH_3$, Ar=o-Cl-C_6H_4
d, R=CN, Ar=C_6H_5
e, R=CN, Ar=p-CH_3-C_6H_4
f, R=CN, Ar=o-Cl-C_6H_4



4a, Ar=C_6H_5
b, Ar=o-Cl-C_6H_4

In the transition state for addition of a 1,3-dipole to the α-face of a 16,17-double bond there is considerable steric interaction between a terminal aryl group on the 1,3-dipole and the 12-methylene group. Steric factors would thus be expected to direct addition to give [17α,16α-d]-1'-phenyltriazolines e.g. 3a-f. Despite this the electronic factors prevail in the case of electron-donating 17-alkoxy derivatives leading to [16α,17α-d]-1'-phenyltriazolines, 4a, b.

Table I



Compound	R	Ar	m.p.	nmr 18-CH_3	nmr 16β-H	Other	Mass Spectrum
3a	$COCH_3$	C_6H_5	185°.d.	0.83	4.85	2.41(21-CH_3)	447(13,M^+-28), 141(100)
3b	$COCH_3$	p-$CH_3C_6H_4$	187°.d.	0.82	4.75	2.38(21-CH_3)	
3c	$COCH_3$	o-ClC_6H_4	161°.d.	0.80	5.18	2.41(21-CH_3)	481(47,M^+-28), 43(100)
3d	CN	C_6H_5	168°.d.	1.20	4.70	-	-
3e	CN	p-$CH_3C_6H_4$	-	1.20	4.60	-	-
3f	CN	o-ClC_6H_4	-	1.19	5.25	-	-

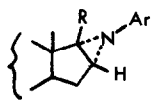
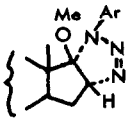


Table II

Compound	R	Ar	m.p.	nmr 18-CH_3	nmr 16β-H	Other	Mass Spectrum	
2a	$COCH_3$	C_6H_5	173-4°	0.88	3.29	1.59(21-CH_3)	447(74)	43 (100)
2b	$COCH_3$	p-$CH_3C_6H_4$	166-7°	0.86	3.25	1.58(21-CH_3)	461(69)	43(100)
2c	$COCH_3$	o-ClC_6H_4	213°	0.95	3.22	1.89(21-CH_3)	481(46)	43(100)
2d	CN	C_6H_5	194-5°	1.00	3.16	-	430(22)	414(100)
2e	CN	p-$CH_3C_6H_4$	201°	1.01	3.15	-	444(20)	428(100)
2f	CN	o-ClC_6H_4	254°	1.04	3.26	-	464(20)	449(100)

Table III



Compound	Ar	m.p.	nmr 18,CH_3	nmr 16β-H	Other	Mass Spectrum
4a	C_6H_5	105°d.	0.95	4.63	2.96(17-OCH_3)	435(15,M^+-28), 77(100)
4b	o-ClC_6H_4	128°d.	0.96	4.63	3.08(17-OCH_3)	469(12,M^+-28), 141(100)

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11) B. Green, B. L. Jensen, and P. L. Lalan, unpublished work.

12) See for example G. W. Gribble and J. R. Douglas, Jr., J. Amer. Chem. Soc., 92, 5764 (1970).

13) This seems unlikely on first sight, see M. K. Meilahn, B. Cox, and M. E. Munk, J. Org. Chem., 40, 819 (1975), but might be explicable in terms of steric hindrance to direct cycloaddition.

14) The [16α,17α-d]-triazoline could not be detected during a long term addition at 40°.