Diels–Alder Addition to Steroidal 14,16-Dien-20-ones: Formation of 14α,17α,- and 14β,17β-Adducts

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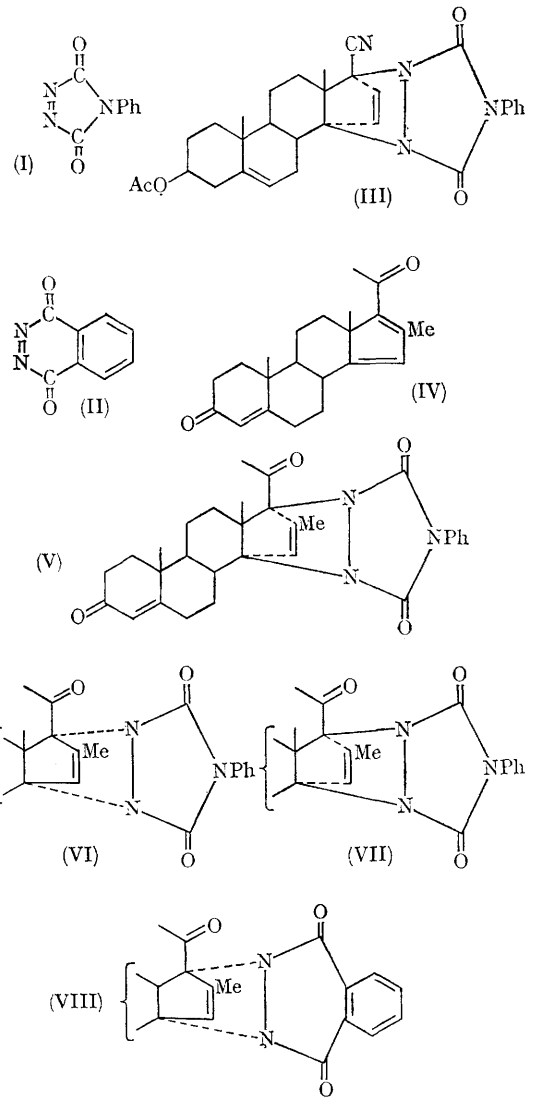
DIELS–ALDER additions to steroidal 14,16-dienes have been studied extensively by Solo and his co-workers.[1,2] Irrespective of the dienophile used, however, only one addition product was isolated from each reaction, to which the 14β,17β-stereochemistry was assigned. We now report the formation of both the 14α,17α- and the 14β,17β-adducts by the reaction of a 14,16-diene with reactive cyclic azo-compounds. The *cis*-azo-dienophiles, 4-phenyl-1,2,4-triazoline-3,5-dione (I),[3] and phthalazine-1,4-dione (II)[4] have been described as exceedingly reactive. Solo[1] observed that the reaction of (I) with 3β-acetoxy-17-cyanoandrosta-5,14,16-triene proceeded readily; however, the unstable adduct (III) decomposed rapidly to starting materials.



Reaction of 16-methylpregna-4,14,16-triene-3,20-dione (IV)[5] (1·15 equiv.) in methylene chloride with (I), generated from 4-phenyl-1,2,4-triazole-3,5-dione[6] *cf.* method of Gillis and Hagarty,[7] proceeded readily at 5°. After fractional crystallization, two isomeric compounds were isolated, the 14β,17β-adduct (V), (47%):† {m.p. 192—193°; $[\alpha]_D$ −13° (dioxan); λ_{max} 238 mμ (ε 25,000); n.m.r. δ 1·23 (10-CH_3), 1·37 (13-CH_3), 1·89 (16-CH_3, d, $J_{MeC=CH}$ 2 c./sec.), 2·67 (20-CH_3), 5·79 (4-H), 5·90 p.p.m. (15-H, d, $J_{MeC=CH}$ 2 c./sec.)}, and the 14α,17α-adduct (VI), (8%): {m.p. 184—187°; $[\alpha]_D$ + 111° (dioxan); λ_{max} 239 mμ (ε 22,220); n.m.r. δ 0·99 (13-CH_3), 1·22 (10-CH_3), 1·94 (16-CH_3, d, $J_{MeC=CH}$ 2 c./sec.), 2·57 (20-CH_3), 5·79 (4-H), 5·92 (15-H, d, $J_{MeC=CH}$ 2 c./sec.)].

Reaction of (IV) with (II) under identical conditions afforded, after chromatography and fractional crystallization, the adducts (VII) (47%): {m.p. 248—252° (decomp.); $[\alpha]_D$ − 177° ($CHCl_3$); λ_{max} 239 mμ (ε 33,600), 318 mμ (ε 5200); n.m.r. δ 1·29 (10- and 13-CH_3), 2·09 (16-CH_3, d, $J_{MeC=CH}$ 2 c./sec.), 2·33 (20-CH_3), 5·80 (4-H), 5·94 p.p.m. (15-H, d, $J_{MeC=CH}$ 2 c./sec.), and (VIII) (9%): {m.p. 235—240°; $[\alpha]_D$ + 168° ($CHCl_3$); λ_{max} 239 mμ (ε 29,800), 317 mμ (ε 5000); n.m.r. δ 1·08 (13-CH_3), 1·27 (10-CH_3), 2·10 (16-CH_3, d, $J_{MeC=CH}$ 2 c./sec.), 2·27 (20-CH_3), 5·89 (4-H), 5·90 p.p.m. (15-H, d, $J_{MeC=CH}$ 2 c./sec.)}, as well as some of the unchanged trienone (IV). An additional quantity of (VIII) was detected in the mother liquors.

† Satisfactory elementary analyses have been obtained for all new compounds. Melting points are uncorrected. N.m.r. spectra were measured on a Varian A-60-A spectrometer in $CDCl_3$ solutions using Me_4Si as internal standard. U.v. spectra were determined in methanol. Mass spectra were determined on a CEC 21-103 spectrometer using a direct-inlet system at a temperature of 200—230°.

	14α,17β $[\alpha]_D$	14β,17α $[\alpha]_D$	$\Delta[\alpha]_D$
Progesterone	+201° ($CHCl_3$)[10]	+139° ($CHCl_3$)[8a]	− 62°
Pregnenolone	+ 25° ($CHCl_3$)[10]	− 14° ($CHCl_3$)[8a]	− 39°
Pregnenolone acetate ..	+ 14° ($CHCl_3$)[10]	− 18° ($CHCl_3$)[8a]	− 32°
(V)		− 13° (dioxan)	−124°
(VI)	+111° (dioxan)		
(VII)		−177° ($CHCl_3$)	−345°
(VIII)	+168° ($CHCl_3$)		

The assignment of structures (V) and (VII) to the 14β,17β-adducts and (VI) and (VIII) to the 14α,17α-adducts, respectively, rest on the following observations. Elemental analysis, u.v., and i.r. spectra are in agreement with the structures proposed for each pair of adducts. Mass spectra indicated that the adducts were formed without molecular rearrangement; (V) and (VI) had the highest *m/e* at 324 [molecular ion of (IV)]. Also the overall spectra were virtually identical to the spectrum of (IV). The 14β,17β-configuration was suggested initially for the adducts (V) and (VII) which were isolated as the predominant component in each reaction. This follows the earlier assignment of Solo[1] who ascribed the β-configuration to each of the single products obtained, based on the argument that catalytic hydrogenation of steroidal 14,16-dien-20-ones afford 14β,17α-pregnane derivatives.[8] Recently, a derivative of the single Diels–Alder product formed in the reaction of 3β-acetoxypregna-5,14,16-trien-20-one and methyl acrylate was shown to be the β-adduct by *X*-ray crystallographic analysis.[9]

Our stereochemical assignments for (VI) and (VIII) as the 14α,17α-adducts are further supported by the differences in specific rotation observed for each of the two pairs of adducts. It is known[10] that the change from 14α,17β- to 14β,17α-stereochemistry results in a negative shift in rotation. Since (V) and (VII) have been assigned the same configuration at C-14 and C-17 as 14β,17α-progesterone and (VI) and (VIII) are sterically related to progesterone, it is expected that the direction of change in the specific rotation from (VI) to (V) and from (VIII) to (VII) will parallel the change of rotation from a 14α,17β-steroid to a 14β,17α-steroid.

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