by reducing known mixtures of I and II. The mixtures were placed in 0.1-mm. Irtran-2 cells and the infrared spectra from 11.0 to 12.4 μ were recorded. The difference between the absorbance value of the 11.9-μ maximum (due to VIII) and the value of the minimum at 11.7 μ was plotted *vs.* per cent of VIII (see Figure 1). The value obtained in the same way for the equilibration mixture gave, from the curve, 76.5% *exo-* and 23.5% *endo*-2-acetylbicyclo[2.2.1]heptane.

A New Diene-Addition Reaction of Steroids. The Synthesis of Steroidal Analogs Containing a Substituted Bicyclo[2.2.1]heptene System[1]

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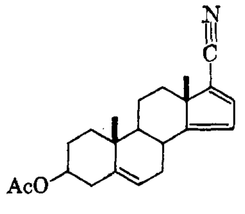
Received November 5, 1964

The D-ring diene system of 3β-acetoxy-17-cyano-5,14,16-androstatriene (I) has been found to undergo the Diels–Alder reaction. Maleic anhydride, acrolein, methyl acrylate, and 4-phenyl-1,2,4-triazoline-3,5-dione (IV) have been added to I. The scope of the reaction and the stereochemistry of the adducts are discussed.

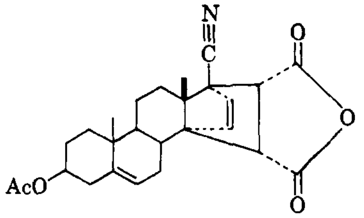
A number of steroids having double bonds at the 14- and 16-positions have been reported.[3] These ring-D conjugated dienes are considered to be highly reactive,[4] a conclusion which has thus far been based on the ease with which such systems undergo catalytic hydrogenation,[4,5] on analogy, and on the reported difficulty of introducing two units of unsaturation into the D-ring of steroids.[6] However, to our knowledge, the Diels–Alder reactivity of these systems has not been determined.

The product of such a diene addition would constitute a novel system in which the bridged D-ring may be viewed as a bicyclo[2.2.1]heptene-2 with a nitrile substituted at position 1, and with ring C of the steroid bridging positions 4 and 7. Moreover, the stereochemistry of the D-ring of such a system would correspond closely with that of one of the rotomers of 17α-alkyl or 17α-O-acyl steroids. Since 17α-substituted progesterone and testosterone derivatives are known to possess high biological activity,[7] the ring-D bridged analogs of these hormones might also be expected to be active.

3β-Acetoxy-17-cyano-5,14,16-androstatriene[5] (I) was chosen as starting material since, of the known 14,16-dienes, it appeared relatively to be both readily available and capable of being converted to the desired hormone analogs. Initial attempts to effect reaction of I with maleic anhydride in refluxing benzene or xylene failed. However, heating I overnight at 95–100° in an excess of molten maleic anhydride resulted in formation of adduct II in 69% yield. The reaction could most conveniently be followed by n.m.r. spectroscopy. The starting material (I) has peaks at δ 5.96 and 7.07 arising from the 15- and 16-vinyl hydrogens, respectively. These peaks are replaced in adduct II by a pair of doublets at δ 6.22 and 6.47.



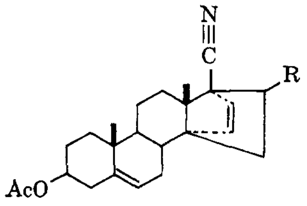
I



II

Heating I in acrolein at 105–107° for 64 hr. afforded adduct IIIa in 27% yield. The ring-D vinyl hydrogens of this substance appeared in the n.m.r. spectrum at δ 5.97 and 6.28.

Similarly, heating I in an excess of methyl acrylate at 115° for 7 days resulted in the formation of adduct IIIb in 69% yield. The n.m.r. spectrum of this substance has peaks at δ 5.88 and 6.20 corresponding to the ring-D vinyl hydrogens.



IIIa, R = CHO

b, R = $\underset{\underset{\displaystyle O}{\|}}{C}$—OMe

Substitution of electron-withdrawing substituents on a conjugated diene is known to lower the reactivity of the diene toward normal dienophiles.[8] In a recent study, 1-cyanocyclohexa-1,3-diene was reported to be so deactivated toward Diels–Alder reaction that it underwent rearrangement prior to addition.[9] The above addition reactions, therefore, demonstrate high Diels–Alder reactivity for steroidal 14,16-dienes.

The recent report of Sauer and Wiest[10] indicates that while substitution of electron-withdrawing groups on a double bond normally increases the activity of the olefin as a dienophile, the inverse effect is observed if the diene is heavily substituted with electron-with-

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[1] This work was supported, in part, by Grants AM-06900-01 and AM-06900-02 (National Institute of Arthritis and Metabolic Diseases), and 2 G-555-R 1 (Division of General Medical Sciences) from the National Institutes of Health, U. S. Public Health Service.

[2] To whom inquiries regarding this work should be addressed.

[3] L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 567, 753–755, 761, 791.

[4] See ref. 3, p. 567.

[5] P. A. Plattner, H. Heusser, and A. Segre, *Helv. Chim. Acta*, **31**, 249 (1948).

[6] (a) E. R. Glazier, *J. Org. Chem.*, **27**, 4397 (1962); (b) J. Fajkos, *Collection Czech. Chem. Commun.*, **23**, 1559 (1958).

[7] N. Applezweig "Steroid Drugs," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp. 313–320 and 337–344.

[8] J. Sauer, D. Lang, and A. Mielert, *Angew. Chem., Intern. Ed. Engl.*, **1**, 268 (1962).

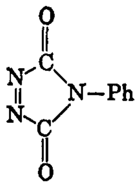
[9] G. Smith, C. L. Warren, and W. R. Vaughan, *J. Org. Chem.*, **28**, 3323 (1963), and references cited therein.

[10] J. Sauer and H. Wiest, *Angew. Chem., Intern. Ed. Engl.*, **1**, 269 (1962).

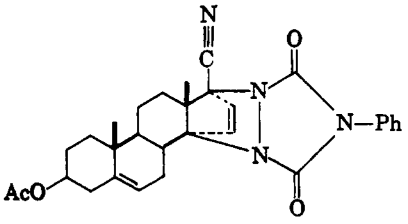
drawing substituents. Since our diene component, I, which is substituted with the strongly electron-withdrawing cyano group reacted readily with normal dienophiles, we hoped that it might also react with normally less reactive dienephiles. However, in exploratory runs the compound failed to add to vinyl acetate, to methyl vinyl ether, or to *cis*-dichloroethylene.

The 3β-acetoxy-17-cyano-5,14,16-androstatriene also failed to give a Diels–Alder adduct when heated with α-chloroacrylonitrile or ethyl azodicarboxylate. Since both of these dienophiles bear substituents on either side of the double bond, it seemed likely that their failure to react was caused by steric hindrance. Cookson[11] has shown that, in cases where transoid azodicarboxylic esters failed to react, the *cis*-azo compound, 4-phenyl-1,2,4-triazolin-3,5 dione (IV), may react.

That 4-phenyl-1,2,4-triazoline-3,5-dione (IV) reacted rapidly with the diene system of I, even at room temperature, was shown by the disappearance of the red color of a solution of III in acetone within 5 min. following addition of an equivalent quantity of I. The adduct V was isolated and characterized; its n.m.r. spectrum has peaks, at δ 6.37 and 6.59, typical of the D-ring vinyl hydrogen peaks of the adducts.



IV



V

The adduct V was found to decompose into starting materials, rapidly, at room temperature in acetonitrile, chloroform, and methylene chloride. Decomposition of the adduct was very much slower, at room temperature, in solutions of acetone, methanol, or pyridine, but became rapid if the solutions were heated to reflux. In anhydrous, nonhydroxylic solvents, the decomposition could be followed by observing the development of the red color characteristic of solutions of 4-phenyl-1,2,4-triazoline-3,5-dione (IV). In several instances such solutions were worked up to afford spectrally pure I.

In contrast to the instability which was characteristic of V, the maleic anhydride adduct II was recovered unchanged when heated to 180° (0.009 mm.). Repeated melting of II at atmospheric pressure, however, quantitatively effected reverse Diels–Alder reaction, as shown by n.m.r. examination of the residue.

Stereochemistry.—Dreiding stereomodels of I indicate that the β-face of ring D is less hindered than the α-face, and catalytic hydrogenation of steroidal 14,16-dienes is known to occur by attack from the β-side.[5] The Diels–Alder reactions of I are therefore presumed to proceed by approach of the dienophile from the β-side. Thus, the 4-phenyl-1,2,4-triazoline-3,5-dione adduct should have the stereochemistry depicted in V.

At the moderate temperatures employed for the condensation reactions, the isomer in which the acyl substituents derived from the dienophile are *endo* should predominate.[12] Since only a single product was isolated for each of the addition reactions, the adducts are assumed to be the *endo* isomers, and the maleic anhydride adduct should have the structure II. The acrolein and methyl acrylate adducts are tentatively assigned the structures IIIa and IIIb, respectively, for the reasons advanced above and by analogy to the reported predominance of "head-to-head" addition in the Diels–Alder reactions of ethyl acrylate with 1-cyanobutadiene[13] and with 1-carboethoxy-1,3-cyclohexadiene.[14,15]

Efforts are currently in progress to confirm the stereochemical assignment made above and to synthesize the ring-D bridged adducts of progesterone and testosterone.

Experimental[16]

3β-Acetoxy-17-cyano-5,14,16-androstatriene (I).—The procedure of Plattner, Heusser, and Segre[5] was followed for the preparation of I from 5-androsten-3β-ol-17-one 3-acetate. The product crystallized from ethanol as fine rods: m.p. 178–179°, λ_{max}^{EtOH} 287 mμ (log ε 3.99), ν^{Nujol} 2220 (conjugated nitrile) and 1735 cm.$^{-1}$ (acetate carbonyl); lit.,[5] plates from methanol, m.p. 172–173.5°, λ_{max} 286 mμ (log ε 4.05). The n.m.r. spectrum ($CDCl_3$) contained a doublet at δ 7.07 (J = 2 c.p.s.) and a multiplet at 5.96 attributed to the 16- and 15-vinyl protons, respectively.

Anal. Calcd. for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.07; N, 4.15. Found: C, 78.12; H, 8.16; N, 4.34.

Attempted Diels–Alder Reaction of Maleic Anhydride with I in Aromatic Solvents. A.—A solution of 113 mg. of 3β-acetoxy-17-cyano-5,14,16-androstatriene (I) and 33 mg. of freshly sublimed maleic anhydride in 15 ml. of benzene was heated under reflux for 6 hr. The solvent was then distilled under reduced pressure. The residue crystallized from benzene–petroleum ether (b.p. 30–60°) to afford 85 mg. of I. The mother liquors appeared to consist mainly of I as determined by thin layer chromatography.

B.—The same quantities of reactants as in A were heated under reflux for 18 hr. in 2 ml. of xylene. On work-up, 90 mg. of I was recovered.

Adduct II of I with Maleic Anhydride.—A mixture of 1.017 g. of I and 1.176 g. of freshly distilled maleic anhydride was heated at 95–100° for 26 hr. Excess anhydride was then removed by heating to 100° under reduced pressure. The residue was crystallized from acetone–petroleum ether to afford 900 mg. of the adduct II (68% yield) as colorless plates, m.p. 206°. Recrystallization from actone–petroleum ether gave an analytical sample: m.p. 208–209°; ν^{Nujol} 2240 (nitrile), 1860, 1775 (anhydride), 1735, 1250 cm.$^{-1}$ (acetate). The n.m.r. spectrum ($CDCl_3$) showed doublets in the vinyl hydrogen region at δ 6.22 (J = 6 c.p.s.) and 6.47 (J = 6 c.p.s.).

Anal. Calcd. for $C_{26}H_{29}NO_5$: C, 71.70; H, 6.71; N, 3.22. Found: C, 71.53; H, 6.50; N, 3.16.

Adduct IIIa of I with Acrolein.—A mixture of 150 mg. of I, 1.5 ml. of freshly distilled acrolein, and a trace of hydroquinone was heated in a sealed evacuated tube at 105–107° for 64 hr. The mixture was then heated for 1 hr. at 100° (20 mm.). The residue was slurried in 25 ml. of ethyl acetate and then filtered. The filtrate, after being concentrated, crystallized to

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[11] R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *Tetrahedron Letters*, **No. 14**, 615 (1962).

[12] (a) M. C. Kloetzel, *Org. Reactions*, **4**, 10 (1948); (b) J. C. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961).

[13] H. R. Snyder and G. I. Poos, *J. Am. Chem. Soc.*, **72**, 4106 (1950).

[14] J. Kagan and F. D. Greene, *J. Org. Chem.*, **28**, 2965 (1963).

[15] For related examples, see K. Alder, M. Schumacher, and O. Wolff, *Ann. Chem.*, **564**, 79 (1949).

[16] Melting points were determined in capillary tubes on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. The infrared spectra were determined on a Perkin-Elmer Infracord Model 137 (and in the case of adduct IIIa on a Perkin-Elmer Model 237). N.m.r. spectra were determined on a Varian A-60 spectrometer and are reported in parts per million downfield from a tetramethylsilane internal standard.

give 48 mg. (27%) of IIIa, m.p. 198°. The analytical sample, m.p. 202° (sharp), was obtained by recrystallization from ethyl acetate. The infrared spectrum (KBr) had bands at 2750, 1712 (aldehyde), 2237 (nitrile), and 1728, 1236 cm.$^{-1}$ (acetate). The n.m.r. spectrum ($CDCl_3$) had doublets in the vinyl proton region at δ 5.97 (J = 6 c.p.s.) and 6.28 (J = 6 c.p.s.). The aldehyde proton appeared as a singlet at δ 9.70.

Anal. Calcd. for $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56. Found: C, 75.75; H, 7.98; N, 3.68.

A semicarbazone was prepared, m.p. 230–231°.

Anal. Calcd. for $C_{26}H_{34}N_4O_3$: C, 69.30; H, 7.61; N, 12.44. Found: C, 69.39; H, 7.80; N, 12.27.

Adduct IIIb of I with Methyl Acrylate.—A mixture of 200 mg. of I, 0.5 ml. of freshly distilled methyl acrylate, and a trace of hydroquinone was heated in a sealed evacuated tube to 115° for 7 days. The mixture was then transferred to a round-bottom flask and heated on a steam bath at 25 mm. for 1 hr. The residue, in benzene solution, was chromatographed over 30 g. of Merck alumina. Passage of 250 ml. of a 1:1 mixture of benzene–chloroform through the column eluted a fraction which crystallized from methanol to yield 174 mg. (69%) of IIIb, m.p. 160–163°. The analytical sample was prepared by repeated recrystallizations from methanol followed by two recrystallizations from 2-propanol: m.p. 169–170°; ν^{Nujol} 2250 (nitrile), 1735, 1740 cm.$^{-1}$ (ester C=O). The n.m.r. spectrum (CCl_4) had peaks in the vinyl proton region at δ 5.88 (J = 6 c.p.s.) and 6.20 (J = 6 c.p.s.).

Anal. Calcd. for $C_{26}H_{33}NO_4$: C, 73.73; H, 7.85; N, 3.31. Found: C, 73.69; H, 7.80; N, 3.05.

Attempted Diels–Alder Reaction of I with Vinyl Acetate.—A mixture of I, vinyl acetate, and a trace of hydroquinone was heated in a sealed evacuated tube at 110° for 95 hr. Work-up of the reaction mixture resulted only in recovery of I. In a second run conducted at 185° for 47 hr., the product appeared to be largely polymeric. No adduct could be isolated.

Attempted Diels–Alder Reaction of I with Methyl Vinyl Ether.—A mixture of I, methyl vinyl ether, and a trace of N-phenyl-2-naphthylamine were sealed under nitrogen in a stainless steel bomb fitted with a glass liner and heated to 200–208° for 24 hr. The product appeared to be polymeric. Similarly, heating I with methyl vinyl ether and a trace of hydroquinone at 185° for 48 hr. resulted, after work-up, in the recovery of a large amount of polymer and a trace amount of I.

Attempted Diels–Alder Reaction of I with *cis*-Dichloroethylene.—A mixture of I, *cis*-dichloroethylene, and a trace of hydroquinone was heated in a sealed evacuated tube at 185° for 24 hr. The diene component I was recovered quantitatively. When the reaction was run at 195° for 80 hr., polymer and I were isolated from the reaction mixture.

Attempted Diels–Alder Reaction of I with α-Chloroacrylonitrile.—Mixtures of I, α-chloroacrylonitrile, and trace amounts of hydroquinone were heated under nitrogen in one case at 110° for 22 hr., in other cases under reflux for 4 or 6 hr. In all cases at least 80% of the I employed was recovered.

Attempted Diels–Alder Reaction of I with Ethyl Azodicarboxylate.—A mixture of I, ethyl azodicarboxylate, and a trace of hydroquinone was heated at 100° for 6 hr. Routine work-up led to the recovery of unchanged I.

Heating I, ethyl azodicarboxylate, and a trace of N-phenyl-2-naphthylamine, under nitrogen, at 148° for 21 hr. led to the formation of a complex mixture (demonstrated by thin layer chromatography), but none of the desired adduct could be isolated.

Adduct V of I with 4-Phenyl-1,2,4-triazoline-3,5-dione (IV). A.—Equivalent quantities of I and IV[11] were mixed in acetone at room temperature. The red color characteristic of IV was completely discharged within 5 min.

B.—To a solution of 120 mg. (calculated) of 4-phenyl-1,2,4-triazoline-3,5-dione (IV), prepared *in situ*[11] in 30 ml. of dioxane, was added 110 mg. of I. The red solution was left at room temperature overnight, the color fading to a pale yellow. The solution was then evaporated to dryness under reduced pressure at room temperature. The resulting foam on trituration with methanol, at room temperature, gave adduct V as an off-white powder, m.p. 162.5–163.5° dec., yield 113 mg. Recrystallization from aqueous acetone gave an analytical sample: m.p. 164–165° dec.; ν^{Nujol} 1789 and 1739 (carbonyl), 1600 and 1501 cm.$^{-1}$ (phenyl). The n.m.r. spectrum ($CDCl_3$) showed a singlet at δ 7.38 (phenyl) and doublets in the vinyl proton region at δ 6.37 (J = 6 c.p.s.) and 6.59 (J = 6 c.p.s.).

Anal. Calcd. for $C_{30}H_{32}N_4O_4$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.28; H, 6.10, N, 10.58.

Acknowledgment.—We wish to express our appreciation to Syntex, S. A., for a generous gift of starting material.

Reactive Intermediates in the Bicyclo[3.1.0]hexyl and Bicyclo[3.1.0]hexylidene Systems. I. The Acid-Catalyzed Addition of Methanol and Acetic Acid to Bicyclo[3.1.0]hexene-2[1]

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Thermodynamically controlled acid-catalyzed addition of acetic acid or methanol to bicyclo[3.1.0]hexene-2 results in 4-acetoxycyclohexene or 4-methoxycyclohexene, respectively. Kinetically controlled addition of methanol results in predominantly *cis*- and *trans*-2-methoxybicyclo[3.1.0]hexane, with formation of small amounts of 4-methoxycyclohexene. Acid-catalyzed addition of methanol-*d* to bicyclo[3.1.0]hexene-2 proceeds stereospecifically *cis* to yield *trans*-3-deuterio-*trans*-2-methoxybicyclo[3.1.0]hexane.

The recent work of Winstein and Sonnenberg[3] on the trishomocyclopropenyl carbonium ion and the research of Roberts and co-workers[4] on bicyclobutonium ion intermediates stimulated our interest in electrophilic additions to bicyclo[3.1.0]hexene-2 (**1**). Two main alternative reaction pathways for electrophilic addition of HY to **1** appear to be available. For example, addition of HY to **1** might be expected to proceed through a trishomocyclopropenyl intermediate **2**, while addition in the reverse manner could conceivably produce intermediates analogous to bicyclobutonium ion intermediates such as **3** and **4**. Generation of **3** and **4** could result in the formation of five different structures (not including *cis–trans* isomers).[5] Thus it seemed to us that electrophilic additions to **1** would provide an opportu-

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[1] Presented at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Aug. 1964; Abstracts, p. 59S.

[2] National Defense Education Act Fellow, 1961–1964.

[3] S. Winstein and J. Sonnenberg, *J. Am. Chem. Soc.*, **83**, 3235 (1961); **83**, 3244 (1961).

[4] M. S. Silver, M. C. Caserio, H. E. Rice, and J. D. Roberts, *ibid.*, **83**, 3671 (1961).

[5] Formal analogy to the carbon scrambling found by R. H. Mazur, W. N. White, D. A. Semenov, C. C. Lee, M. S. Silver, and J. D. Roberts [*ibid.*, **81**, 4390 (1959)] would suggest that four bicyclobutonium ion intermediates in addition to **3** and **4** are possible, although they could not be formed directly from **1**.