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RING-D-BRIDGED STEROID ANALOGS—VII[1]

HOMOCONJUGATE DIELS-ALDER ADDITION OF METHYL PROPIOLATE TO SUBSTITUTED BICYCLO[2.2.1]HEPTADIENES

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Abstract—3β-Acetoxy-20-keto-5,14,16-pregnatriene (I) reacts with hexafluorobutyne or with dimethyl acetylenedicarboxylate to form normal Diels–Alder adducts. However, reaction of I with methyl propiolate leads to the stereospecific formation both of normal Diels–Alder adduct and of a diadduct derived from homoconjugate addition of a second mole of dienophile to the monoadduct. The stereochemistry of the monoadduct was established by a correlation with 14α, 17α-ethano-16α-carbomethoxypregn-5-ene-3β-ol-20-one acetate. The homoconjugate addition of methyl propiolate to methyl bicyclo[2.2.1]hepta-diene-2-carboxylate is also described.

THE 2,6-cycloaddition of dienophiles to bicyclo[2.2.1]heptadiene has been extensively studied.[2-11] However, to our knowledge, this reaction has rarely been looked for[9] and has not previously been observed in substituted bicyclo[2.2.1]heptadiene systems. We report here examples of homoconjugate Diels–Alder addition to the 3-monosubstituted and to 1,3,4,7,7-tetrasubstituted bicyclo[2.2.1]heptadiene systems.

We recently reported the reaction of 3β-acetoxy-20-keto-5,14,16-pregnatriene (I) with hexafluorobutyne at 130° to form the Diels–Alder adduct II.[12] We have now found that dimethyl acetylenedicarboxylate reacts with I, under similar conditions, to form an adduct to which we assign the structure III on the basis of spectroscopic evidence and of analogy to the demonstrated structure[12] of the product derived from the reaction of I with methyl acrylate.

In contrast to the above reactions, heating I in methyl propiolate at temperatures between 103 and 120° results in mixtures containing varying amounts of starting material, a product analysing as monoadduct, and a compound analysing for one part of I to two parts of methyl propiolate. As the monoadduct had spectroscopic properties in accord with those expected for the normal Diels–Alder adduct, it is assigned structure IV.

Selective catalytic hydrogenation of IV afforded two isomers in yields of 20% and 63%. The minor isomer proved to be identical with the known 14α, 17α-ethano-16α-carbomethoxypregn-5-ene-3β-ol-20-one acetate[1] (V); thus, the structure assigned to IV was confirmed. The major isomer proved to be the previously unknown 14α, 17α-ethano-16β-carbomethoxypregn-5-ene-3β-ol-20-one acetate (VI) since, on refluxing with methoxide in methanol, the acetate was hydrolysed and the carbomethoxy group was equilibrated to the more stable *endo* position to give 14α, 17α-ethano-16α-

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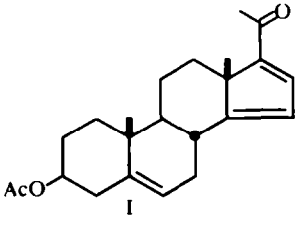
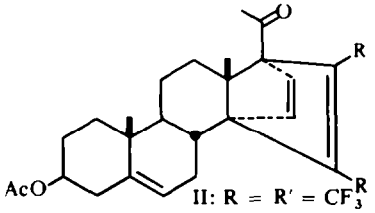
carbomethoxypregn-5-ene-3β-ol-20-one (VII). The latter compound was also prepared by selective hydrolysis of 14α, 17α-ethano-16α-carbomethoxypregn-5-ene-3β-ol-20-one acetate[1] (V).

Heating monoadduct IV with methyl propiolate at 107° for 162 hr afforded the diadduct in a yield of 65·5%, suggesting that the monoadduct is an intermediate in the formation of the diadduct. Assuming that the substituted bicycloheptadiene moiety of IV had undergone a 2,6-cycloaddition reaction, the diadduct could have any one of four structures. Structure VIII was assigned on the basis of NMR spin decoupling experiments which showed a doublet for Ha at 7·02 δ (J_{ab} = 3 Hz), a quartet for Hb at 3·13 δ (J_{ab} = 3, J_{bc} = 1 Hz), a multiplet for Hc at 3·45 δ, and a doublet for Hd at 2·62 δ (J_{CD} = 1·5 Hz).

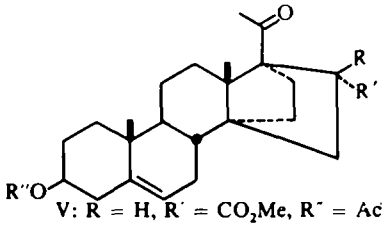
While all available evidence supports the assignment of structure VIII to the diadduct, we were disturbed both by the lack of a previous example of a homoconjugate Diels–Alder addition proving competitive in rate with a mormal Diels–Alder reaction and by the lack of a previous example of a homoconjugate Diels–Alder addition to a substituted bicyclo[2.2.1]heptadiene. Moreover, since the addition of methyl propiolate to I is very much slower than the corresponding addition to cyclopentadiene,[13] the further question was raised as to whether the competitive formation of IV and of VIII was caused by slow formation of IV or by fast formation of VIII.



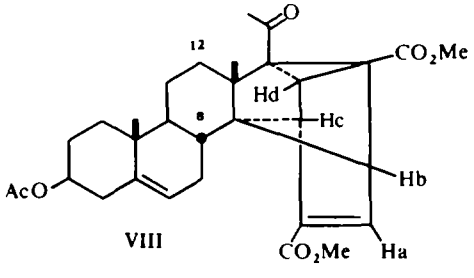
I



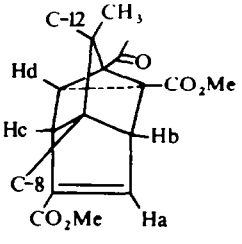
II: R = R′ = CF_3
III: R = R′ = CO_2Me
IV: R = CO_2Me, R′ = H



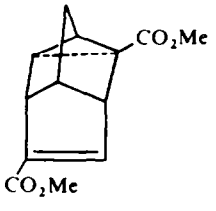
V: R = H, R′ = CO_2Me, R″ = Ac
VI: R = CO_2Me, R′ = H, R″ = Ac
VII: R = R″ = H, R′ = CO_2Me



VIII



Enlarged detail of VIII



IX

Reaction of methyl bicyclo[2.2.1]heptadiene-2-carboxylate[13] with methyl propiolate, under conditions similar to those employed to convert IV to VIII resulted in the formation of IX in over 30% yield. This result provides the desired example of a simple substituted bicyclo [2.2.1]heptadiene undergoing homoconjugate addition, and it shows that the competitive formation of IV and of VIII is caused primarily by slow formation of IV.

EXPERIMENTAL

M.ps. were determined in capillary tubes on a mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tennessee. The IR spectra were determined on a Perkin-Elmer Infracord Model 137 or on a Beckman IR-8 spectrophotometer. NMR spectra were determined in $CDCl_3$ on a Varian A-60 spectrometer and are reported in parts per million downfield from a TMS internal standard.

14α, 17α-*Etheno*-15,16-*dicarbomethoxypregna*-5,15-*diene*-3β-*ol*-20-*one acetate* (III). A mixture of I (1·05 g), dimethyl acetylenedicarboxylate (1·5 ml) and hydroquinone (10 mg) was sealed in a glass tube under reduced press and heated at 130° for 148 hr. After the tube had cooled, it was opened, and the volatile material was distilled under reduced press. The residue was dissolved in benzene and filtered through a column of 25 g of Woelm neutral alumina. Final elution by 100 ml benzene containing 5% EtOAc gave a total of 795 mg crude product which crystallized from acetone–hexane to afford III, in a yield of 658 mg (47%) as white rectangular plates, m.p. 150–152°; ν^{Nujol} 1740 (sh), 1728, 1715, 1685, 1620 cm^{-1}. The NMR spectrum had singlets at δ 2·02 (acetate), 2·25 (21-Me), 3·78 (Me of ester), 3·72 (Me of ester) and peaks in the vinyl hydrogen region at δ 5·39 (m), 6·91 (d, J = 5·6 Hz) and 7·02 (d, J = 5·6 Hz). (Found: C, 70·35; H, 7·56. Calc. for $C_{29}H_{36}O_7$: C, 70·14; H, 7·31%).

Diels–Alder reaction of methyl propiolate with 3β-*acetoxy*-20-*keto*-5,14,16-*pregnatriene* (I). A mixture of I (1·096 g) hydroquinone (20 mg) and methyl propiolate (1·2 ml) was sealed in a glass tube under reduced press and heated at 107–108° for 160 hr. After the tube had cooled, it was opened and the volatile material was distilled under reduced press. The residue was chromatographed on a column of 35 g of Merck acid-washed alumina. The column was first developed by 250 ml of n-hexane containing up to 80% benzene. Elution with 50 ml of benzene then yielded 135 mg of impure I. Passage of 100 ml of 5% EtOAc in benzene eluted IV in a yield of 624 mg (45%), as a pale yellow foam: ν^{Nujol} 1745, 1732, 1695 cm^{-1}; λ_{max}^{MeOH} 234 mμ (ε 3980). The NMR spectrum had singlets at δ 2·03 (acetate), 2·24 (21-Me), 3·71 (0-Me) and peaks in the vinyl hydrogen region at 5·43 (m), 6·76 (d, J = 5·5 Hz), 6·96 (d, J = 5·5 Hz), and 7·44 (s). (Found: C, 73·74; H, 7·81. Calc. for $C_{27}H_{34}O_5$: C, 73·95; H, 7·81%).

Further elution of the above column by 150 ml 5% EtOAc in benzene gave 310 mg residue which crystallized from acetone to afford VIII, in a yield of 228 mg (18%) as white rectangular plates: m.p. 228–229°; ν^{Nujol} 1735, 1717, 1712 and 1695 cm−1; λ_{max}^{MeOH} 245 mμ (ε 6310). The NMR spectrum had peaks at δ 2·00 (acetate), 2·26 (21-Me), 3·60 (0-Me), 3·76 (0-Me) and 5·32 (vinyl H) as well as the peaks mentioned in the Discussion. (Found: C, 71·48; H, 7·46. Calc. for $C_{31}H_{38}O_7$: C, 71·24; H, 7·33%).

Formation of diadduct VIII *from* 14α, 17α-*etheno*-16-*carbomethoxypregna*-5,15-*diene*-3β-*ol*-20-*one acetate* (IV) *and methyl propiolate*. A mixture of IV (160 mg) methyl propiolate (1·0 ml) and hydroquinone (7 ml) was sealed in a glass tube, under reduced press, and then heated at 107° for 162 hrs. After the usual work-up, the product was crystallized from acetone to afford VIII, in a yield of 125 mg (65%), as rectangular plates; m.p. 227–228°. Mixed m.p. NMR spectroscopy, and TLC indicated that this substance was identical with VIII, as reported above.

Catalytic hydrogenation of 14α, 17α-*etheno*-16-*carbomethoxypregna*-5,15-*diene*-3β-*ol*-20-*one acetate* (IV). A soln of IV (165 mg) in 150 ml of EtOH was hydrogenated over 50 mg of 10% Pd–C at room temp under 3·64 Kg/cm^2 for 10 hr. After the catalyst had been removed by filtration, the EtOH was distilled under reduced press. The residue was chromatographed over 15 g of Merck acid-washed alumina. After the column had been developed by hexane and hexane–benzene mixtures, a 150 ml benzene eluted 50 mg of a mixture predominant in one component (TLC). This fraction crystallized from hexane to afford V in a yield of 33 mg, as white needles. The substance was identical with V, as prevously prepared, by m.p. mixed m.p. and NMR criteria.

Elution by a further 200 ml benzene, containing up to 10% EtOAc afforded 112 mg of the other isomer. This substance was combined with the mother liquor from the first fraction and crystallized from

MeOH to afford VI, in a yield of 104 mg of fine white crystals: m.p. 176–177°; ν Nujol 1730, 1695 cm^{-1}. The NMR spectrum had singlets at δ 0·91 (18-Me), 2·04 (acetate), 2·12 (21-Me), 3·66 (0-Me) and a multiplet at 5·39 (6-vinyl hydrogen). (Found: C, 73·31; H, 8·58. Calc. for $C_{27}H_{38}O_5$: C, 73·27; H, 8·65%).

Epimerization of 14α, 17α-*ethano*-16β-*carbomethoxypregn*-5-*ene*-3β-*ol*-20-*one acetate* (VI). A soln of VI (95 mg and NaOMe (30 mg) in 20 ml MeOH was refluxed for 52 hrs. The soln was then concentrated under reduced press. The residue was partitioned between ether and water. The organic phase was dried and then evaporated to dryness. The residue crystallized from EtOH to give (VII), in a yield of 63 mg (73%), as thin needles: m.p. 193–195°; ν^{Nujol} 3420–3300, 1730, 1693 CM^{-1}. The NMR spectrum had singlets at δ 0·97 (18-Me), 2·19 (21-Me), and 3·66 (OMe) and a multiplet at 5·39 (6-vinyl H). (Found: C, 74·86; H, 9·09. Calc. for $C_{25}H_{36}O_4$: C, 74·96; H, 9·00%).

14α, 16α-*Ethano*-16α-*carbomethoxypregn*-5-*ene*-3β-*ol*-20-*one* (VII) *from* 14α, 17α-*ethano*-16α-*carbomethoxypregn*-5-*ene*-3β-*ol*-20-*one acetate* (v). A soln of V (245 mg) KOH (423 mg) and 2·0 ml water is 15·0 meOH was refluxed for 1 hr and afterwards cooled at room temp. It was then concentrated under vacuum and the residue was partitioned between ether and water. The ether extract was dried with anhyd $MgSO_4$ and removal of ether gave a white residue which was crystallized from MeOH to afford 210 mg of VII identical in mixed melting point IR, NMR that produced above.

Addition of methyl propiolate to methyl bicyclo [2.2.1]*heptadiene*-2-*carboxylate*. A mixture of methyl bicyclo [2.2.1]heptadiene-2-carboxylate[13] (1·9 g), methyl propiolate (3·5 ml) and hydroquinone (5 mg) was heated in a sealed tube at 106–107° for 169 hr. The mixture was then taken to dryness under reduced press. Chromatography of the residue on a column of 150 g of Woelm neutral alumina resulted in the isolation of IX in a yield of 0·875 g (30%), as an oil; ν^{CHCl_3} 1720 (sh) and 1710 cm^{-1}. The NMR spectrum had three proton singlets at 3·62 and 3·72 δ (OMe groups), a one proton doublet at 7·13 δ ($J \sim 3{\cdot}2$ Hz, vinyl H), two proton multiplets at δ = 1·71 (Ha's), 2·23 (Hb's) and 3·08 (Hc, Hd) and a one proton multiplet at 2·54 (He). (Found: C, 66·79; H, 6·08. Calc. for $C_{13}H_{14}O_4$: C, 66·66; H, 6·02%).

Direct formation of IX *from reaction of methyl propiolate with cyclopentadiene*. A mixture of freshly distilled cyclopentadiene, (3 ml), methyl propiolate (7 ml) and a trace of hydroquinone was heated at 106° in a sealed tube for 70 hrs. The NMR spectrum of the crude product indicated that it was a mixture consisting mainly of methyl bicyclo[2.2.1]heptadiene-2-carboxylate and IX, inequal proportions. Distillation under reduced press gave pure methyl bicyclo[2.2.1]heptadiene-2-carboxylate, in a yield of 1·5 g (27%). The NMR of the residue indicated that it consisted mainly of IX.

Dimethyl tetracyclo[4.3.0.0.^{2,7}0^{3,9}]*nonane*-1,4-*dicarboxylate*. The crude IX, obtained as residue in the distillation reported above, was dissolved in 35 ml THF and hydrogenated over 5% Pd-C at 3·66 Kg/cm^2. Distillation under reduced press, afforded dimethyl tetracyclo[4.3.0.0.^{2,7}0^{3,9}]nonane-1,4-dicarboxylate in a yield of 2·1 g, as a colorless oil: ν^{CHCl_3} 1720 cm^{-1}. The NMR spectrum had s singlet arising from the OMe protons at δ = 3·68 and a complex series of multiplets extending from δ = 1·23 to 3·15. (Found: C, 66·17; H, 7·03. Calc. for $C_{13}H_{16}O_4$: C, 66·09; H, 6·83%).

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REFERENCES

[1] Part VI: A. J. Solo, B. Singh, E. Shefter, and A. Cooper, *Steroids* **11**, 637 (1968).
[2] E. F. Ullman, *Chem. & Ind.* 1173 (1958).
[3] A. T. Blomquist and Y. C. Meinwald, *J. Am. Chem. Soc.* **81**, 667 (1959).
[4] H. K. Hall, *J. Org. Chem.* **25**, 42 (1960).
[5] C. G. Krespan, B. C. McKusick, and T. L. Cairns, *J. Am. Chem. Soc.* **83**, 3428 (1961).
[6] R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *Tetrahedron Letters* 615 (1962).
[7] S. J. Cristol, E. L. Alfred, and D. L. Wetzel, *J. Org. Chem.* **27**, 4058 (1962).
[8] C. D. Weis, *Ibid.* **28**, 74 (1963).
[9] R. C. Cookson, E. Crundwell, R. R. Hill, and J. Hudec, *J. Chem. Soc.* 5416 (1964).
[10] H. Heaney and J. M. Jablonski, *Tetrahedron Letters* 27733 (1967).
[11] R. C. Cookson, J. Damel, and M. Godfrey, *Tetrahedron* **24**, 1529 (1968).
[12] A. J. Solo and B. Singh, *J. Med. Chem.* **10**, 1048 (1967).
[13] K. Alder and H. Wirtz, *Leibys. Ann.* **601**, 138 (1956).