Steroids and Arynes. Part II.[1] Some reactions of Arynes with Steroidal Dienes and Trienes

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Steroid 5,7-dienes undergo the ene-reaction with benzyne and tetrachloro- and tetrafluoro-benzyne. Tetrafluorobenzyne also forms a 5,8-adduct with a 5,7-diene and with a 5,7,9(11)-triene. Cholesta-2,4-diene gives 1,4-adducts with benzyne and tetrafluorobenzyne. The pyrolyses of some adducts are discussed.

THE reaction of conjugated steroidal dienes in Diels–Alder addition reactions is well known.[2] Recently, it has been shown that 5,7-dienes undergo an ene-reaction with a variety of dienophiles in addition to giving, in certain cases, the normal Diels–Alder products.[2b,c,e,f] Although the reactions of carbene and dihalogenocarbenes with steroidal olefins and dienes are well known,[3] until recently [1] no similar reactions of arynes had been described. We now report, in full, the reactions described in our preliminary communication,[1] together with some further results in this area.

7-Dehydrocholesteryl methyl ether (1; R^1 = Me) [4] is best prepared by the reaction of 7-dehydrocholesterol

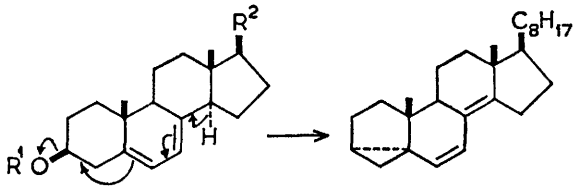
[1] Part I, I. F. Eckhard, H. Heaney, and B. A. Marples, *Tetrahedron Letters*, 1967, 4001. Part II is Aryne Chemistry Part XX.

[2] (*a*) L. F. Fieser and M. Fieser, 'Steroids,' Reinhold, New York, 1959, pp. 109, 265; (*b*) D. Neville Jones, P. F. Greenhalgh, and I. Thomas, *Tetrahedron*, 1968, **24**, 297; (*c*) J. Lakeman, W. N. Speckamp, and H. O. Huisman, *Tetrahedron*, 1968, **24**, 5151, and references cited therein; (*d*) T. L. Popper, F. E. Carlon, H. M. Marigliano, and M. D. Yudis, *Chem. Comm.*, 1968, 1434; (*e*) A. M. Lautzenheiser and P. W. Le Quesne, *Tetrahedron Letters*, 1969, 207; (*f*) K. D. Bingham, G. D. Meakins, and J. Wicha, *J. Chem. Soc.* (*C*), 1969, 671.

[3] (*a*) L. H. Knox, E. Valarde, S. Berger, D. Cuadriello, P. W. Landis, and A. D. Cross, *J. Amer. Chem. Soc.*, 1963, **85**, 1851; (*b*) A. J. Birch and G. S. Subba Rao, *Tetrahedron*, 1966, supp. 7, 391; (*c*) M. S. Nazer, *J. Org. Chem.*, 1965, **30**, 1737; (*d*) F. T. Bond and R. H. Cornelia, *Chem. Comm.*, 1968, 1189.

[4] S. Bernstein and K. J. Sax, *J. Amer. Chem. Soc.*, 1951, **73**, 846.

with n-butyl-lithium and methyl iodide in dimethyl sulphoxide. Attempts to prepare (1; R^1 = Me) by using trimethylorthoformate and perchloric acid [5] gave largely the 3α,5α-cyclo-steroid (3). This product

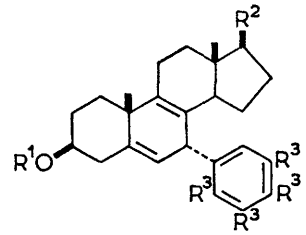


(1) $R^2 = C_8H_{17}$
(2) $R^2 = C_9H_{17}$

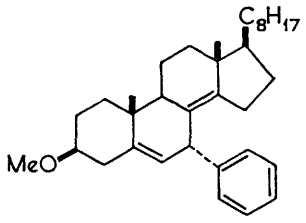
(3)

is analogous to that obtained by solvolysis of ergosteryl tosylate,[6] and undoubtedly is formed by way of a mixed orthoester and a 3-homoallylic carbonium ion.[5] Benzyne, generated from *o*-fluorophenylmagnesium bromide in tetrahydrofuran, reacted with (1; R^1 = Me) to give compounds (4) and (7) which were separated by t.l.c. on silica impregnated with silver nitrate, after initial removal of aromatic by-products by chromatography on alumina. The dienes (4) and (7) are formed by two ene-reactions involving, respectively, the hydrogen atoms at C-9 and C-14. They are analogous to products obtained by reaction of other dienophiles with 5,7-dienes.[2b,c,e,f] The structures of (4) and (7) are supported by analytical and spectroscopic data. The ^{1}H n.m.r. spectrum of (4) shows peaks at τ 2·8—3·1 (5H, m, Ar), 4·7—4·9 (m, =CH), 6·1—6·4 (m, PhCH), 6·82 (s, OMe), 6·8—7·4 (m, OCH), 8·74 (s, 19-Me), 9·0—9·2 (m, side-chain), and 9·30 (18-Me). The anisotropic shielding of the 18-methyl group and deshielding of the 19-methyl group are consistent with the 8,9-double bond.[2b,c,7] In the ^{1}H n.m.r. spectrum of compound (7), the signals due to the 18- and 19-methyl groups are superimposed on the side-chain signals (τ 9·0—9·3). This anisotropic deshielding of the 18-methyl group and shielding of the 19-methyl group would be expected for for an 8,14-olefin.[2b,c,7] Benzyne has a singlet ground-state [8] and the ene-reaction is a symmetry-allowed concerted process.[9] The 7-phenyl group in compounds (4) and (7) thus has the α-configuration since the 9α- and 14α-hydrogen atoms are involved in the reaction. The absence of typical Diels–Alder adducts in this reaction may be, in part, ascribed to steric crowding in the transition state. If it is assumed that the transition state is product-like, it is clear from models that benzyne-attack at the α-face of the diene would result in interaction between the *ortho*-hydrogen atoms and the 3α-, 4α-, and 15α-hydrogen atoms and also between the 7-hydrogen atom and the 18-methyl group. Attack at the β-face of the diene would result in considerable interaction between the *ortho*-hydrogen atom and the 18-methyl group. Such steric crowding would not be present in the ene-reaction transition state.

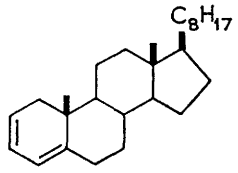
It was anticipated that reaction of benzyne with cholesta-2,4-diene (8) would involve less steric crowding and should give the normal Diels–Alder adducts.



(4) R^1 = Me; $R^2 = C_8H_{17}$; R^3 = H
(5) R^1 = Me; $R^2 = C_8H_{17}$; R^3 = F
(6) R^1 = Ac; $R^2 = C_9H_{17}$; R^3 = Cl



(7)



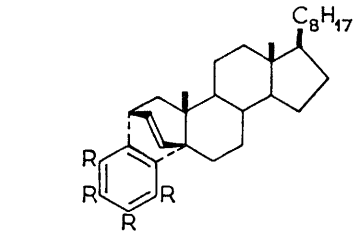
(8)

Cholesta-2,4-diene [10] is most conveniently prepared by dehydration of cholesterol with alumina in boiling *p*-cymene. The co-product, cholesta-3,5-diene, was removed by preparative t.l.c. on silver nitrate-impregnated silica. Benzyne, generated as described above and from anthranilic acid and 3-methylbutyl nitrite [11] in methylene chloride, reacted with cholesta-2,4-diene (8) to give a small yield (8%) of adducts (9) (11) in the approximate ratio 4 : 1. Aromatic by-products were removed from the crude product by steam distillation and compounds (9) and (11) were separated by t.l.c. on silver nitrate-impregnated silica. No other products were identified. Hydrogenation of compounds (9) and (11) gave compounds (12) and (14) respectively. The ^{1}H n.m.r. spectra of the dihydro-compounds (12) and (14) confirm the stereochemistry of the adducts (9) and (11). As expected, the 19-methyl signal moves downfield on hydrogenation of compound (9) (τ 8·99—8·85) due to the removal of the anisotropic shielding by the β-bridging double-bond. Similarly, it moves upfield on hydrogenation of compound (11) (τ 9·62—9·69) due to the removal of the anisotropic deshielding by the α-bridging double-bond. The very high-field position of the 19-methyl signal in the ^{1}H n.m.r. spectrum of compound (11) is due to the anisotropic shielding by the benzene ring.

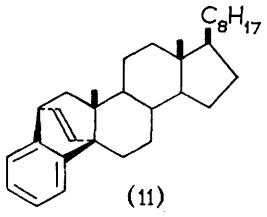
We have previously reported that tetrahalogenobenzynes have greater dienophilic properties than

[5] J. P. Dusza, J. P. Joseph, and S. Bernstein, *Steroids*, 1966, **8**, 495.
[6] N. L. Wendler, in 'Molecular Rearrangements,' ed. P. de Mayo, Interscience, New York, 1964, p. 1077.
[7] N. S. Bhacca and D. H. Williams, 'Applications of N.M.R. Spectroscopy in Organic Chemistry,' Holden-Day, San Francisco, 1964, ch. 2.
[8] R. Hoffmann, A. Imamura, and W. J. Hehre, *J. Amer. Chem. Soc.*, 1968, **90**, 1499.
[9] R. B. Woodward, *Chem. Soc. Special Publ.* 1967, no. 21, p. 248.
[10] Ref. 2 (*a*), p. 264.
[11] L. Friedman and F. M. Logullo, *J. Amer. Chem. Soc.*, 1963, **85**, 1549.

benzyne.[12a,b] To test this hypothesis, we investigated the reaction of tetrafluorobenzyne with the dienes (1; R^1 = Me) and (8) and, similarly, the reaction of tetrachlorobenzyne with ergosteryl acetate (2; R^1 = Ac). Preparatory to carrying out these reactions, we investigated the reaction of cyclohexa-1,3-diene [13] with tetrafluorobenzyne, generated from pentafluorophenylmagnesium chloride in ether–cyclohexane, and from pentafluorophenyl-lithium in light petroleum–ether.



(9) R = H
(10) R = F



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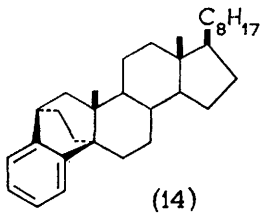

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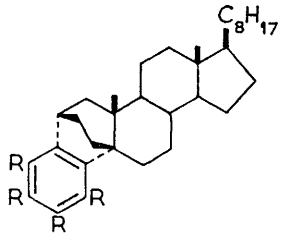
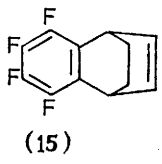


(12) R = H
(13) R = F

The major product, the adduct (15) (77%), was separated from an isomeric mixture of dihydro-2′,3′,4′,5′-tetrafluorobiphenyls (11%) by preparative g.l.c. These latter products, which are formed by the ene-reaction, slowly dehydrogenate during chromatography to give 2,3,4,5-tetrafluorobiphenyl.[12a] The ratio of Diels–Alder product (15) to ene-product is much higher than that reported for the reaction of benzyne with cyclohexa-1,3-diene,[14] thus confirming the anticipated, enhanced dienophilic properties of tetrafluorobenzyne. Reduction of compound (15) gave the dihydro-compound (16) [12a] and pyrolysis of compound (15) at 300° gave 1,2,3,4-tetrafluoronaphthalene.[15]

Reaction of tetrafluorobenzyne, generated from pentafluorophenyl-lithium, with 7-dehydrocholesteryl methyl ether (1; R^1 = Me) gave the Diels–Alder adduct (17) (22%) and the ene-product (5) (51%) which were separated by t.l.c. on silver nitrate-impregnated silica. A third impure fraction, containing at least one ene-product, was isolated but could not be purified. The adduct (17) was readily hydrogenated to give the dihydro-compound (18). The 19-methyl signal in the ^{1}H n.m.r.



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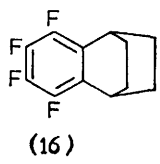

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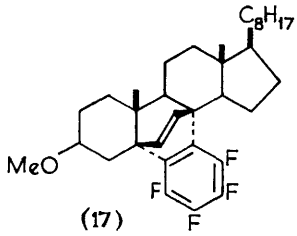
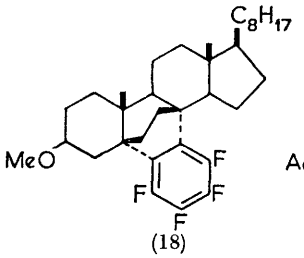


(17)



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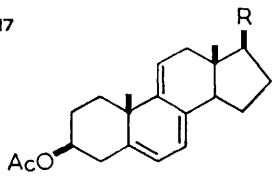


(19) R = C_9H_{17}
(20) R = C_8H_{17}

spectrum of compound (17) moves downfield on hydrogenation (τ 9·01—8·89) as does the 18-methyl signal (τ 9·16—9·10). These shifts are only compatible with a β-bridging double-bond. Apart from the signals due to aromatic protons, the ^{1}H n.m.r. spectrum of the ene-product (5) is almost identical to that of compound (4) thus confirming the presence of an 8,9-double bond. Production of the adduct (17) confirms the greater electrophilic properties of the tetrafluorobenzyne compared to benzyne. The steric crowding in the transition state is clearly insufficient to completely nullify the dienophilic properties of tetrafluorobenzyne.

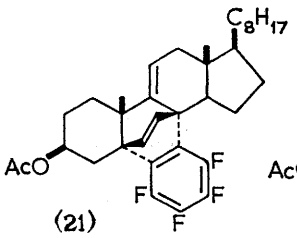
Reaction of cholesta-2,4-diene (8) with tetrafluorobenzyne, generated from pentafluorophenyl-lithium, gave the α-adduct (10) (15%) which was separated from the reaction mixture by t.l.c. on silver nitrate-impregnated silica. Hydrogenation of compound (10) gave compound (13) and the downfield shift of the 19-methyl signal in the ^{1}H n.m.r. spectrum (τ 9·02 to 8·90) confirmed the shown stereochemistry. Small quantities of unidentified poly-adducts were isolated from the reaction mixture. As expected, the yield of adduct compound (10) was greater than the combined yield of compounds (9) and (11) but both are disappointingly low.

Tetrachlorobenzyne, generated from tetrachloroanthranilic acid [16] and 3-methylbutyl nitrite in methylene chloride,[12b] reacted with ergosteryl acetate (2; R^1 = Ac) to give the ene-product (6) which was separated from the reaction mixture by chromatography. A singlet in the ^{1}H n.m.r. spectrum at τ 2·92 (C_6Cl_4H) confirms that compound (6) is an ene-product, and the chemical shift of the 19-methyl signal (τ 8·69) confirms

[12] (*a*) J. P. N. Brewer, I. F. Eckhard, H. Heaney, and B. A. Marples, *J. Chem. Soc.* (*C*), 1968, 664; (*b*) H. Heaney and J. M. Jablonski, *J. Chem. Soc.* (*C*), 1968, 1895.
[13] K. Ziegler, A. Späth, E. Schaaf, W. Schumann, and E. Winkelmann, *Annalen*, 1942, **551**, 109.
[14] (*a*) G. Wittig, *Angew. Chem. Internat. Edn.*, 1965, **4**, 731; (*b*) H. E. Simmons, *J. Amer. Chem. Soc.*, 1961, **83**, 1657.
[15] E. Nield, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 1959, 166.
[16] R. Howe, *J. Chem. Soc.* (*C*), 1966, 478.

the presence of the 8,9-double-bond. The absence of any Diels–Alder adduct in the product may be ascribed to the large steric interactions between the *ortho*-chlorine atoms and the α-hydrogen atoms at C-3, C-4, and C-15.

It has been reported that 9(11)-dehydroergosteryl acetate (19) [17] and 5,7,9(11)-cholestatrienyl acetate (20) [18] have greater reactivity towards dienophiles than the corresponding 5,7-dienes. Accordingly, we have investigated the reaction of 5,7,9(11)-cholestatrienyl acetate (20) [18] with tetrafluoro- and tetrachloro-benzyne. The former gave, after reacetylation and t.l.c., the α-adduct (21) (3%) and the β-adduct (22) (9%), whilst the latter gave no isolable 1,4-adducts or ene-products. A decreased reactivity of the 5,7-diene system is thus apparent. This implies that steric interactions in the Diels–Alder reaction transition-state are increased. Inspection of models however suggests that the converse is true and thus other factors are operating. The configurations of the adducts are apparent from a comparison of their ^{1}H n.m.r. spectra with those of the reduced compounds (23) and (24). The 18- and



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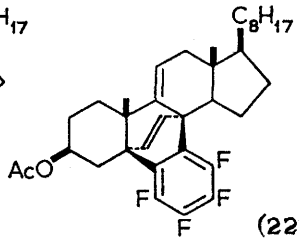
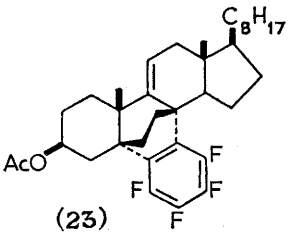


(22)



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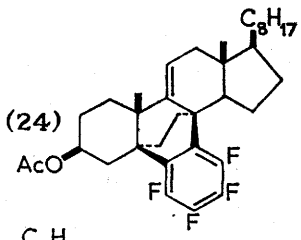

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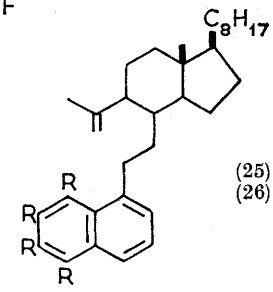
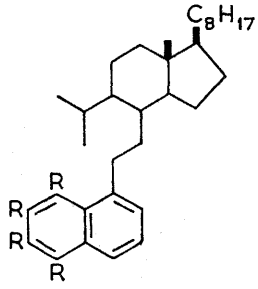


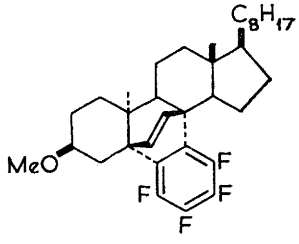
(25) R = H
(26) R = F

19-methyl-group signals are downfield (τ 9·18 and 8·70 respectively) in compound (23) compared to their chemical shifts (τ 9·30 and 8·81 respectively) in compound (21). Similarly, the 18- and 19-methyl-group signals are upfield (τ 9·14) in compound (24) compared to their chemical shifts (τ 9·08) in compound (22). Formation of a β-adduct across positions-5 and -8 has not previously been reported. It is apparent that the 9,11-double-bond opens up the β-face of the 5,7-diene and then there is much less interaction between the *ortho*-substituent on the benzyne and the 18-methyl group. Attempts to hydrogenate the 9,11-double-bond of the α-adduct (21), with platinum in acetic acid and perchloric acid, failed.

Pyrolysis of adducts (9) and (10) at 250° gave the naphthalene derivatives (25) and (26) respectively. At higher temperatures, the retro-Diels–Alder reaction is accompanied by others and several products were detected by t.l.c. These were not investigated further. The ^{1}H n.m.r. spectrum of (25) shows the presence of 7-aromatic protons (m, τ 1·8—2·8), 2 olefinic protons (br,s, τ 5·13), and a vinyl methyl group (br,s, τ 8·34); further, it has a u.v. spectrum typical of naphthalene $\lambda_{max.}$ 226 (ε, 72,500), 263 (3500), 273 (6000), 283 (7300), and 294 nm. (4800). Hydrogenation of compound (25) gave the dihydro-compound (27). The ^{1}H n.m.r. spectrum compound (26) is very similar to that of compound (25) apart from the signals of the aromatic protons. Irradiation of the vinyl methyl-group sharpened the olefinic protons signal ($W_{\frac{1}{2}}$ 7 to 4 Hz), and similarly irradiation of the latter signal sharpened the vinyl methyl-group signal ($W_{\frac{1}{2}}$ 4·5 to 2 Hz). The sum of the coupling constants for spin-spin coupling between the olefinic protons and the vinyl methyl-group is thus 2·5—3 Hz. The u.v. spectrum of compound (26) is similar to that of compound (25), and on hydrogenation, compound (26) gave compound (28).



(27) R = H
(28) R = F



(29)

The adduct (17) was virtually unchanged after prolonged pyrolysis at 250—300°. The only pure product isolated is formulated as the isomer (29). The mass spectrum of compound (29) is very similar to that of the adduct (17) and shows that they are isomeric (molecular weight 546) and very similar in structure. The ^{1}H n.m.r. spectrum of compound (29) shows a high-field methyl-group signal (τ 9·56) and indicates that the 3-methine proton is in an equatorial conformaton ($W_{\frac{1}{2}}$ 8—9 Hz). These data are consistent with the 10α-configuration, the high-field position of the 19-methyl group due to the anisotropic shielding by the benzene ring. The mechanism of the reaction leading to compound (29) is not known but it may involve homolysis of and reformation of the 9,10-bond.

[17] A. Windaus and R. Langer, *Annalen*, 1933, **508**, 105.
[18] A. van der Gen., W. A. Zunnebeld, U. K. Pandit, and H. O. Huisman, *Tetrahedron*, 1965, **21**, 3651.

EXPERIMENTAL

All reactions with organolithium and Grignard reagents were carried out under dry nitrogen in apparatus dried overnight at 120°. Solvents were dried over sodium wire. Tetrahydrofuran was, in addition, freshly distilled from lithium aluminium hydride, and dimethyl sulphoxide was dried by distillation from calcium hydride. Solutions of products were dried with anhydrous sodium sulphate and solvents were removed under reduced pressure in a rotary evaporator. Light petroleum refers to that fraction having a boiling range of 60—80°. Column chromatography was carried out with deactivated (grade III) Camag or Woelm alumina. Merck–Kieselgel PF_{254} silica gel was used for preparative t.l.c.

I.r. spectra were determined with Perkin-Elmer 237 and 257 spectrophotometers. U.v. spectra were determined (for hexane solutions unless specified otherwise) with a Unicam SP 800 spectrophotometer. ^1H n.m.r. (60 MHz) and ^{19}F n.m.r. (56·4 MHz) spectra were determined (for carbon tetrachloride solutions unless specified otherwise) with a Perkin-Elmer R10 spectrometer. Mass spectra were determined with A.E.I. MS/9 and MS/12 mass spectrometers.

7-Dehydrocholesteryl Methyl Ether (1; R = Me) [4] *and* 3α,5α-*Cyclocholesta*-6,8(14)-*diene* (3).—A suspension of 7-dehydrocholesterol (3 g.) in trimethyl orthoformate (20 ml.) and perchloric acid (60% aqueous solution, 0·35 ml.) [5] was stirred at room temperature for 20 min. and then poured into a cold, saturated solution of sodium hydrogen carbonate. The mixture was extracted with ether and the product was chromatographed on alumina. Elution with benzene–light petroleum (1 : 9) gave 3α,5α-*cyclocholesta*-6,8(14)-*diene* (3) (1·85 g.), m.p. 48—49° (from ethanol), τ 4·43 (q, CH=CH, $J_{AB} \simeq 9·7$ Hz, 9·14 (d, side chain), 9·11 (s, 19-Me), 9·24 (s, 18-Me), and 9·4—9·7 (m, cyclopropane), $\lambda_{max.}$ 262 nm. (ε 24,400). Elution with benzene–light petroleum (1 : 1) gave 7-dehydrocholesteryl methyl ether (1; R^1 = Me) (1·2 g.), m.p. 120—121° (from aqueous acetone), $[\alpha]_D$ −106° (*c*, 1·4, $CHCl_3$) (lit.,[4] m.p. 123—125°, $[\alpha]_D$ −104°). A quantitative yield of (1; R^1 = Me) was obtained by treatment of (1; R^1 = H) with *n*-butyllithium (1 mol.) and methyl iodide (1·5 mol.) in dry dimethyl sulphoxide at room temperature for 2 hr. The resultant mixture was poured into water and the precipitated methyl ether was filtered off.

Reaction of Benzyne with the Methyl Ether (1; R^1 = Me).—A suspension of magnesium (0·9 g.) in a solution of (1; R^1 = Me) (2·6 g.) in tetrahydrofuran (50 ml.) and dibromoethane (2 drops) was gently warmed and stirred. A solution of *o*-bromofluorobenzene (5·8 g.) in tetrahydrofuran was added dropwise at a rate sufficient to keep the solution boiling under reflux. The mixture was then heated under reflux for 1 hr. and finally poured into an ammonium chloride–ice mixture. Extraction with ether gave a crude product which was chromatographed on alumina. Elution with benzene removed aromatic by-products and elution with ether–benzene (1 : 3) gave a mixture of compounds (4) and (7) (1·8 g.). Preparative t.l.c. on silica impregnated with silver nitrate (10%) [elution (×3) with benzene–light petroleum (1 : 1)] gave 3β-*methoxy*-7α-*phenylcholesta*-5,8(9)-*diene* (4) (675 mg.), m.p. 133—134° (from aqueous acetone), $\nu_{max.}$ (mull) 665, 702, 760, 1105, and 1602 $cm.^{-1}$, $\lambda_{max.}$ 219 nm., molecular weight (mass spectrum) 474, ^1H n.m.r. see Discussion (Found: C, 85·7; H, 10·85. $C_{34}H_{50}O$ requires C, 86·0; H, 10·6), and 3β-*methoxy*-7α-*phenylcholesta*-5,8(14)-*diene* (7) (1·1 g.), m.p. 102—104° (from aqueous acetone), $\nu_{max.}$ (mull) 667, 702, 772, 1102, and 1602 $cm.^{-1}$ $\lambda_{max.}$ 217 nm., molecular weight (mass spectrum) 474, τ 2·86 (m, phenyl), 4·6—4·8 (m, =CH), 6·1—6·3 (m, PhCH), 6·77 (s, OMe), 6·8—7·2 (m, OCH), and 9·0—9·2 (m, side-chain, 18- and 19-Me) (Found: C, 85·85; H, 10·5. $C_{34}H_{50}O$ requires C, 86·0; H, 10·6%)

Cholesta-2,4-*diene* (8) (ref. 10).—A stirred mixture of cholesterol (20 g.), freshly activated alumina (40 g., heated for 24 hr. at 600°), and *p*-cymene (300 ml.) was heated under reflux in a Dean and Stark apparatus for 16 hr. The mixture was filtered and the crude product was crystallised from acetone. T.l.c. on silica impregnated with silver nitrate [elution (×2) with benzene–light petroleum (1 : 9)] gave *cholesta*-2,4-*diene* (8), (10 g.), m.p. 66—68° (from acetone) $\lambda_{max.}$ 266, 275 nm. ($\varepsilon_{max.}$ 6100) [lit.,[10] m.p. 68·5°, $\lambda_{max.}$ 267, 275 nm. ($\varepsilon_{max.}$ 6300].

Reaction of Benzyne with Cholesta-2,4-*diene* (8). (*a*) Benzyne was generated as above from *o*-fluoromagnesium bromide (33 mmoles) in a solution of cholesta-2,4-diene (8) (1·9 g.) in tetrahydrofuran. The crude product was chromatographed on alumina and elution with light petroleum gave a fraction (300 mg.) from which aromatic by-products were removed by steam distillation. The residue (215 mg.), after t.l.c. on silver nitrate-impregnated silica (10%) [elution (×3) with benzene–light petroleum (1 : 1)], gave the α-*adduct* (9) (60 mg.), m.p. 99—100·5° (from acetone–methanol), $\nu_{max.}$ (KBr) 700, 750, 1620, and 3050 $cm.^{-1}$, $\lambda_{max.}$ 216 (ε 5000), and 232infl. nm. (1600), τ 2·55—3·1 (m, Ar), 3·5—4·05 [eight lines, CH=CH, $J_{AB} \simeq 7·5$, J_{AX} (apparent) $\simeq 5·6$, and J_{BX} (apparent) $\simeq 1·3$ Hz], 6·2—6·5 (m, PhCH), 8·99 (s, 19-Me), 9·15 (d, side-chain), and 9·36 (s, 18-Me) (Found: C, 88·9; H, 10·75. $C_{33}H_{48}$ requires C, 89·1; H, 10·9%), and the β-*adduct* (11) (20 mg.), 125—126° (from acetone), τ 2·7—3·1 (m, Ar), 3·25—3·9 [eight lines, CH=CH, $J_{AB} \simeq 7·7$, J_{AX} (apparent) $\simeq 5·8$, and J_{BX} (apparent) $\simeq 1·3$ Hz], 6·1—6·5 (m, PhCH), 9·13 (d, side-chain), 9·34 (s, 18-Me), and 9·62 (s, 19-Me).

(*b*) A solution of anthranilic acid (5·5 g.) in methylene chloride (200 ml.) was added during ½ hr. to a stirred solution of the diene (8) (3·7 g.) and isopentyl nitrite (14 g.) which was heated under reflux. After 4 hr., the solvent was removed and the crude product was extracted repeatedly with light petroleum. The resultant solution was filtered through alumina and gave a pale yellow syrup (1·0 g.). T.l.c. [elution with benzene–light petroleum (1 : 19)] gave a mixture of α-*adduct* (9) and β-*adduct* (11) (4α : 1β; 300 mg.), which was separated as in (*a*).

Reactions of Tetrafluorobenzyne.—(*a*) *Generated from pentafluorophenylmagnesium chloride.* A suspension of magnesium turnings (4·86 g.) in a solution of chloropentafluorobenzene (20·2 g.) in ether (100 ml.) was maintained at 30° in an ice-bath during the slow addition of dibromoethane (18·7 g.). A solution of cyclohexa-1,3-diene [13] (50 g.) in cyclohexane (200 ml.) was added and ether was distilled off until the liquid temperature was 78°. The mixture was heated under reflux for 6 hr. and after being cooled was hydrolysed with dilute hydrochloric acid. Extraction with ether gave the crude product which was filtered in light petroleum–ether through a short column of alumina. The resultant pale yellow solid (17 g.) was shown by g.l.c. to consist of the *adduct* (15) (77%), mixed 2′,3′,4′,5′-*tetrafluorodihydrobiphenyls* (11%) and *brominated products* (12%). Preparative g.l.c. (5 ft. 30% SE 30 on firebrick

at 200°) gave the *adduct* (15), m.p. 84—85° (from ethanol), $\nu_{max.}$ (KBr) 720, 1040, 1630, and 3070 cm.$^{-1}$, τ 3·35—3·70 (m, CH=CH), 5·45—5·85 (m, 2CH), and 8·1—8·9 (m, $2CH_2$) (Found: C, 63·1; H, 3·55; F, 33·5. $C_{12}H_8F_4$ requires C, 63·15; H, 3·55; F, 33·35%), the mixed 2′,3′,4′,5′-*tetrafluoro-dihydrobiphenyls*, $\nu_{max.}$ (film) 1040, 1630, and 3030 cm.$^{-1}$, $\lambda_{max.}$ 213 (ε 3,060), and 259 (390) nm., and some 2,3,4,5-tetrafluorobiphenyl.[12a]

(*b*) *Generated from pentafluorophenyl-lithium.* A solution of n-butyl-lithium (2·5—2·7M in hexane) (1 equiv.) was added to a stirred solution of the diene and bromopentafluorobenzene (1 equiv.) in light petroleum–ether at −30°. After 2 hr. the solution was allowed to slowly warm to room temperature and was then set aside overnight. The mixture was acidified with dilute hydrochloric acid and then extracted with ether.

Cyclohexa-1,3-diene. Cyclohexa-1,3-diene (40 g.),[13] bromopentafluorobenzene (12·4 g.), and n-butyl-lithium in hexane (19·5 ml., 2·57M) gave a crude product (11 g.) (see above for analysis).

7-*Dehydrocholesteryl methyl ether* (1; R^1 = Me). The ether (1; R^1 = Me) (2·55 g.), bromopentafluorobenzene (3·16 g.), and n-butyl-lithium in hexane (5 ml.; 2·57M) gave a crude product (4·7 g.) shown by g.l.c. (5 ft. 2% QFI on Chromosorb W at 240°) to be composed of the *adduct* (17) (17%), *ene-product* (5) (43%), an unidentified mixed fraction (19%), and starting material (1; R^1 = Me) (21%). Preparative t.l.c. on silver nitrate-impregnated silica (or urea) (10%) and elution with benzene–light petroleum (3 : 7), gave 3β-*methoxy*-7α-(2,3,4,5-*tetrafluorophenyl*)*cholesta*-5,8(9)-*diene* (5), m.p. 119—120° (from ethanol), $\nu_{max.}$ (KBr) 700, 1100, 1620, and 3040 cm.$^{-1}$, $\lambda_{max.}$ 217 and 263infl. nm., τ 3·1—3·7 (m, C_6F_4H), 4·75—4·9 (m, =CH), 5·7—5·9 (m, C_6F_4H·CH), 6·78 (s, OMe), 6·85—7·35 (m, OCH), 8·74 (s, 19-Me), 9·14 (d, side-chain), and 9·30 (s, 18-Me), ϕ 139·8 (m), 147·6 (m), 157·0 (t), and 160·3 (m) (Found: C, 74·55; H, 8·45; F, 14·1. $C_{34}H_{46}F_4O$ requires C, 74·65; H, 8·5; F, 14·2%), the *adduct* (17) m.p. 172—173° (from ethanol), $\nu_{max.}$ (KBr) 710, 765, 1095, 1630, and 3060 cm.$^{-1}$, $\lambda_{max.}$ 217 (ε 6,800) and 270 (550)) nm., τ 3·78 (q, CH=CH, $J_{AB} \simeq 8{\cdot}6$ Hz), 6·1—6·6 (m, OCH), 6·63 (s, OMe), 6·8—7·3 (m, 4αH), 9·01 (s, 19-Me), 9·14 (d, side-chain), and 9·16 (18-Me), ϕ 144·4 (m), 146·6 (m), 160·1 (m), and 161·3 (m) (Found: C, 74·8; H, 8·45; F, 13·9. $C_{34}H_{46}F_4O$ requires C, 74·65; H, 8·5; F, 14·2%).

Cholesta-2,4-diene (8). The diene (8) (1·85 g.), bromopentafluorobenzene (4·6 g.), and n-butyl-lithium in hexane (5·85 ml.; 2·57M) gave a crude product (3·5 g.) which after t.l.c. on silver nitrate-impregnated silica (10%) and elution (×2) with benzene–light petroleum (1 : 19), gave the *adduct* (10) (400 mg.), a gum, $\nu_{max.}$ (CCl_4) 735, 1070, 1625, 3060 cm.$^{-1}$, $\lambda_{max.}$ 217 (ε 6,800) and 265infl. (770) nm., τ 3·5—4·0 (m, CH=CH), 5·7—6·05 (m, RC_6F_4CH), 9·02 (s, 19-Me), 9·15 (d, side-chain), and 9·34 (s, 18-Me), ϕ 143·6 (m), 145·5 (m) 147·6 (m) and 147·9 (m) (Found: C, 76·4; H, 8·55; F, 15·0. $C_{33}H_{44}F_4$ requires C, 76·7; H, 8·6; F, 14·7).

3β-*Acetoxycholesta*-5,7,9(11)-*triene* (20) (ref. 17). The triene (20) (1·3 g.), bromopentafluorobenzene (2·47 g.), and n-butyl-lithium in hexane (3·9 ml.; 2·5M) gave, after acetylation with acetic anhydride in pyridine, a crude product (2·0 g.) which was filtered through alumina as a light petroleum solution. The resultant pale yellow oil (1·1 g.) gave, after t.l.c. on silver nitrate-impregnated silica (10%) and elution (×3) with benzene–light petroleum (1 : 1), the α-*adduct* (21) (50 mg.), m.p. 109—110° (from ethanol), τ 3·70 (q, CH=CH, $J_{AB} \simeq 7{\cdot}4$ Hz), 4·45—5·1 (m, =CH and AcOCH), 6·8—7·3 (m, 4αH), 8·01 (s, AcO), 8·81 (s, 19-Me), 9·11 (d, side-chain), and 9·30 (s, 18-Me), molecular weight (mass spectrum) 572, and the β-*adduct* (22) (150 mg.), m.p. 164—165° (from ethanol), $\nu_{max.}$ (KBr) 780, 1040, 1640, 1740, and 3060 cm.,$^{-1}$ $\lambda_{max.}$ 220 (ε 9500), and 268 nm. (500), τ 3·71 (q, CH=CH, $J_{AB} \simeq 7{\cdot}4$ Hz), 4·5—4·8 (m, =CH), 4·8—5·4 (m, AcOCH), 7·98 (s, AcO), 9·07 (s, 18- and 19-Me), and 9·12 (d, side-chain), molecular weight (mass spectrum) 572 (Found: C, 73·1; H, 7·65. $C_{35}H_{44}F_4O_2$ requires C, 73·4; H, 7·75%).

Reaction of Tetrachlorobenzyne with Ergosteryl Acetate (2; R^1 = Ac).—A solution of tetrachloroanthranilic acid (2·8 g.) in acetone (50 ml.) was added during 15 min. to a stirred solution of ergosteryl acetate (4·4 g.) and 3-methylbutyl nitrite (3 ml.) in methylene chloride (100 ml.) which was heated under reflux. After 1 hr. tetrachloroacridone was filtered off and the filtrate gave a yellow solid which was chromatographed on alumina. Elution with light petroleum gave a small fraction which was not investigated further and elution with benzene–light petroleum (1 : 19) gave a white solid which crystallised from alcohol to give 3β-*acetoxy*-7α-(2,3,4,5-*tetrachlorophenyl*)*cholesta*-5,8(9)-*diene* (7) (1·35 g.), m.p. 202—204°, $\nu_{max.}$ (KBr) 750, 1030, 1240, 1740, and 3050 cm.$^{-1}$, $\lambda_{max.}$ 217 nm., τ 2·92 (s, C_6Cl_4H), 4·5—5·0 (m, 3=CH), 5·2—5·9 (m, AcOCH and C_6H·Cl_4CH), 8·08 (s, AcO), 8·69 (s, 19-Me), and 9·0—9·4 (m, side-chain and 18-Me) (Found: C, 66·6; H, 7·05; Cl, 21·8. $C_{35}H_{46}O_2Cl_4$ requires C, 66·3; H, 7·1; Cl, 21·75). Ergosteryl acetate (1·05 g.) was recovered from the mother liquors.

Hydrogenation of Adducts.—A solution of the adduct in ethyl acetate was shaken with 10% palladium on charcoal catalyst in an atmosphere of hydrogen until uptake of gas ceased. The solution was filtered and removal of the solvent gave the dihydro-compound.

α-*Adduct* (9). The adduct (9) (48 mg.) gave the *dihydro*-α-*adduct* (12) (47 mg.) as a gum, $\nu_{max.}$ (mull) 665 and 752 cm.$^{-1}$, τ 2·6—3·2 (m, Ar), 7·0—7·3 (m, Ph·CH), 8·85 (s, 19-Me), 9·15 (d, side-chain), and 9·36 (s, 18-Me) (Found: C, 88·65; H, 11·2. $C_{33}H_{50}$ requires C, 88·7; H, 11·3).

β-*Adduct* (11). The adduct (11) (5 mg.) gave the *dihydro*-β-*adduct* (14) (5 mg.), m.p. 116—117° (from ethanol), τ 2·6—3·2 (m, Ar), 7·0—7·2 (m, PhCH), 9·14 (d, side-chain), 9·32 (s, 18-Me), and 9·69 (s, 19-Me), molecular weight (mass spectrum) 446.

Adduct (10). The adduct (10) (80 mg.) gave the *dihydro-compound* (13) (79 mg.), as a gum, $\nu_{max.}$ (CCl_4) 1080 and 2960 cm.$^{-1}$, τ 6·5—6·8 (m, RC_6F_4CH), 8·90 (s, 19-Me), 9·15 (d, side-chain), and 9·35 (s, 18-Me) (Found: C, 76·2; H, 8·15. $C_{33}H_{46}F_4$ requires C, 76·4; H, 8·95).

Adduct (15). The adduct (15) (100 mg.) gave the di-dihydro-compound (16) (100 mg.), m.p. 113—114° (from ethanol) (lit.,[12a] m.p. 113—114°).

Adduct (17). The adduct (17) (80 mg.) gave the *dihydro-compound* (18) (80 mg.), m.p. 169—170° (from acetone), $\nu_{max.}$ (KBr) 880, 1100, 2930 cm.$^{-1}$, τ 6·2—6·6 (m, OCH), 6·68 (s, OMe), 8·89 (s, 19-Me), 9·10 (s, 18-Me), and 9·12 (d, side-chain) (Found: C, 74·2; H, 8·65; F, 13·7. $C_{34}H_{48}F_4O$ requires C, 74·4; H, 8·85; F, 13·6).

Adduct (21). The adduct (21) (10 mg.) gave the *dihydro-compound* (23) (10 mg.), a gum, τ 4·4—5·2 (m, =CH and AcOCH), 8·02 (s, AcO), 8·70 (s, 19-Me), 9·12 (d, side-chain), and 9·18 (s, 18-Me), molecular weight (mass spectrum) 574.

Adduct (22). The adduct (22) (80 mg.) gave the *dihydro-compound* (24) (79 mg.), m.p. 162—162·5° (from ethanol),

$\nu_{max.}$ (KBr) 880, 1040, 1630, 1750, 2970 cm.$^{-1}$, τ 4·5—4·75 (m, =CH), 4·75—5·2 (m, AcOCH), 8·02 (s, AcO), 9·14 (s, 18- and 19-Me), and 9·14 (d, side-chain), molecular weight (mass spectrum) 574.

Pyrolysis of Adducts.—The adduct was heated in an evacuated Carius tube (*ca.* 500-ml. capacity) at the temperature and for the period of time specified below.

Adduct (9). Adduct (9) (60 mg.) after 12 hr. at 250° gave *the naphthalene* (25) (58 mg.), m.p. 88—89° (from ethanol), $\nu_{max.}$ (KBr) 780, 800, 890, 1650, and 3080 cm.$^{-1}$, u.v. (see Discussion) τ 1·8—2·8 (m, Ar), 5·13br (s $=CH_2$), 6·8—7·4 (m, $ArCH_2$), 8·34 (s, Me–C=), 9·12 (d, side-chain), and 9·25 (18-Me) (Found: C, 89·2; H, 10·85. $C_{33}H_{48}$ requires C, 89·1; H, 10·9%).

Adduct (10). Adduct (10) (150 mg.) after 12 hr. at 250° gave the *naphthalene* (26) (96 mg.), m.p. 112—113° (from ethanol), $\nu_{max.}$ (KBr) 760, 890, 1060, 1645, 1670, and 3080 cm.$^{-1}$, $\lambda_{max.}$ 220 (ε 78,800), 262 (3260), 274 (5990), 283 (7040), and 293 (3050) nm., τ 1·9—2·2 (m, Ar), 2·35—2·8 (m, Ar), 5·22br (s, $=CH_2$), 8·35 (s, Me–C=), 9·12 (d, side-chain), and 9·25 (18-Me) (Found: C, 76·3; H, 8·4; F, 14·9. $C_{33}H_{44}F_4$ requires C, 76·7; H, 8·6; F, 14·7%).

Adduct (15). Adduct (15) (100 mg.) after 12 hr. at 300° gave 1,2,3,4-tetrafluoronaphthalene (88 mg.), m.p. 106—107° (from ethanol) (lit.[12a] m.p. 110—111°).

Adduct (17). Adduct (17) (80 mg.) after 24 hr. at 250° gave, after t.l.c. on silver nitrate-impregnated silica (10%) [elution (× 2) with benzene–light petroleum (3 : 7)], the *adduct* (29) (8 mg.) as a gum, τ 3·40 (q, CH=CH, $J_{AB} \simeq 7·9$ Hz), 6·2—6·5 (m, OCH), 6·64 (s, MeO), 9·06 (s, 18-Me), 9·11 (d, side-chain), and 9·62 (s, 19-Me), molecular weight (mass spectrum) 546, and starting material (67 mg.).

Hydrogenation of Compounds (25) *and* (26).—This was carried out as described for the adducts. The naphthalene (25) (25 mg.) gave the *dihydro-compound* (27) (25 mg.) as a gum, τ 1·9—2·8 (m, Ar), 6·9—7·4 (m, $ArCH_2$), 8·9—9·3 [m, side-chain and 9-$(Me)_2CH$] and 9·32 (s, 18-Me).

The naphthalene (26) (44 mg.) gave the *dihydro-compound* (28) (42 mg.), m.p. 96—97° (from ethanol), $\nu_{max.}$ (KBr) 760, 1060, and 3050 cm.$^{-1}$, τ 1·9—2·8 (m, Ar), 6·7—7·2 (m, $ArCH_2$), 8·9—9·3 [m, side-chain and 9-$(Me)_2CH$], and 9·32 (s, 18-Me) (Found: C, 76·35; H, 8·6; F, 14·8. $C_{33}H_{46}F_4$ requires C, 76·4; H, 8·95; F, 14·65%).

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