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Novel Enone–Benzene Rearrangement of 4,4-Dialkylcholest-5-en-3-ones to Ring-*B* Aromatic Steroidal Hydrocarbons Catalysed by *p*-Toluenesulfonic acid†

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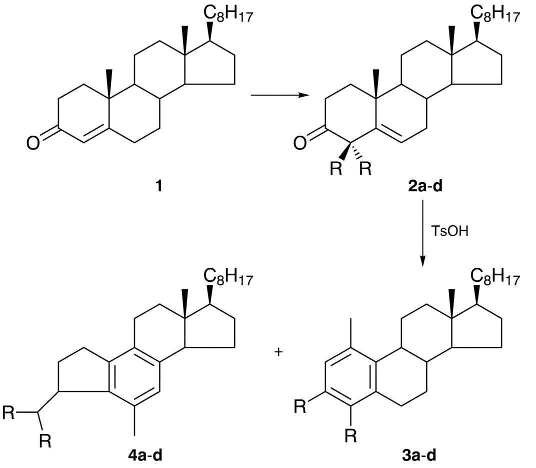
A new by-product, 6-methyl-3-isopropyl-*A*,19-dinorcholesta-6,8,10(5)-triene has been identified from the reaction of 4,4-dimethylcholest-5-en-3-one catalysed by *p*-toluenesulfonic acid in refluxing toluene, revealing a novel enone–benzene rearrangement.

Under acidic conditions, α,α-dimethyl-β,γ-unsaturated cyclohexanones, such as 4,4-dimethylcholest-5-en-3-one **2a**, undergo an enone–benzene rearrangement leading to aromatic, derivatives, such as 1,3,4-trimethyl-19-norcholesta-1,3,5(10)-triene **3a**.[1–4] Some aromatic steroidal hydrocarbons have been discovered in immature sediments[5,6] where they are presumably formed by rearrangement of natural steroids catalysed by acidic clay minerals. We recently run an enone–benzene rearrangement of **2a** catalysed by montmorillonite K-10 to give **3a** in moderate yield accompanying an intractable mixture of hydrocarbons as by-products.[7] Repetition of this reaction by employing TsOH as a catalyst gave **3a** in 65% yield and a new product, 6-methyl-3-isopropyl-*A*,19-dinorcholesta-6,8,10(5)-triene **4a**, was also isolated and identified. Herein we report the novel enone–benzene rearrangement of 4,4-dialkylcholest-5-en-3-ones **2a**–**d** leading to ring-*B* aromatic steroidal hydrocarbons **4a**–**d** catalysed by TsOH (Scheme 1).

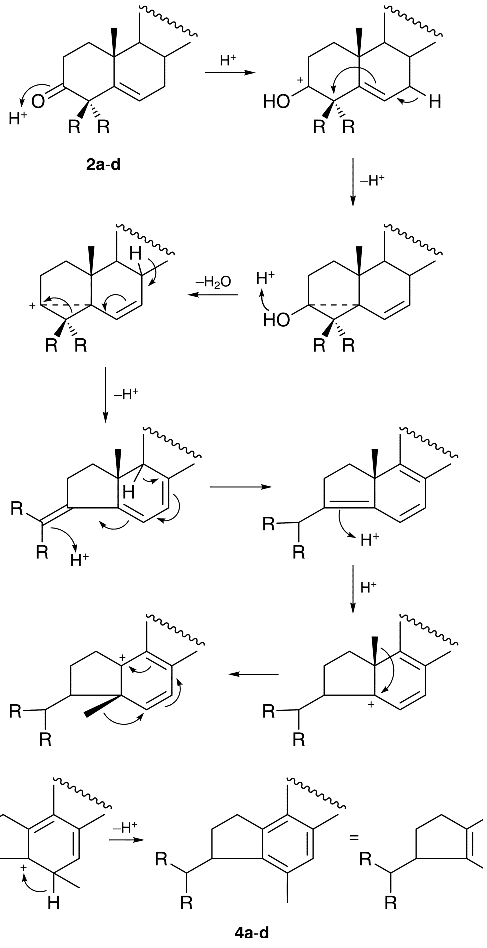


Scheme 1 **a** = Me, **b** = Et, **c** = Pr^n, **d** = Bu^n

According to the procedure described by Atwater,[8] 4,4-dialkylcholest-5-en-3-ones **2a**–**d** were prepared from cholest-4-en-3-one **1** and excess of the corresponding alkyl halides respectively. In the presence of TsOH, 4,4-dimethylcholest-5-en-3-one **2a** was heated in refluxing toluene for 13 h to provide 1,3,4-trimethyl-19-norcholesta-1,3,5(10)-triene **3a** in 65% yield and a by-product, 6-methyl-3-isopropyl-*A*,19-dinorcholesta-6,8,10(5)-triene **4a** in 25% yield which has not been reported in earlier studies.[1–4,7]

Both **3a** and **4a** show exactly the same R_f value on silica gel TLC and they could not be separated by usual silica gel column chromatography. However, **4a** was spotted above **3a** on silica gel impregnated with 10% $AgNO_3$ and they could be separated by 10% $AgNO_3$ silica gel column chromatography.[9]

The TLC behaviour of compound **4a** indicated it to be a hydrocarbon. The mass spectra of both **4a** and **3a** show the molecular ion at *m*/*z* 394 as the base peak, *i.e.* **4a** and **3a** are isomers. The ^{1}H NMR spectrum of **4a** exhibited two doublets at δ 1.036 (3 H, *J* 6.5) and 1.300 (3 H, *J* 6.9 Hz) and two singlets at δ 2.134 (3 H) and 6.935 (1 H). These imply the presence of an extra isopropyl in **4a** since the 26,27-dimethyl group was assigned at 0.881 (6 H, d, *J* 6.5 Hz). There should be also a benzene ring in **4a** and a methyl (δ 2.134) and a hydrogen (δ 6.935) bound to it. The



Scheme 2

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Table 1 Enone–benzene rearrangement of 4,4-dialkylcholest-5-en-3-ones

Compound	Time (h)	Yield **3** (%)	Yield **4** (%)
2a	13	65	25
2b	7.5	75	20
2c	6	60	15
2d	7	75	15

^{13}C DEPT NMR spectrum of **4a** displayed five quaternary carbons at δ 138.70, 138.46, 133.08, 132.07 and 131.64 and one tertiary carbon at δ 127.12. This unambiguously indicates a pentasubstituted benzene ring in **4a**. From all these results the structure of **4a** can be assigned as 6-methyl-3-isopropyl-*A*,19-dinorcholesta-5,7,9-triene, although the stereochemistry at C-3 cannot be addressed from our data.

Similarly, 4,4-diethylcholest-5-en-3-one **2b**, 4,4-dipropylcholest-5-en-3-one **2c** and 4,4-dibutylcholest-5-en-3-one **2d** gave 1-methyl-3,4-diethyl-19-norcholesta-1,3,5(10)-triene **3b** and 6-methyl-3-(1′-ethylpropyl)-*A*,19-dinorcholesta-6,8,10(5)-triene **4b**, 1-methyl-3,4-dipropyl-19-norcholesta-1,3,5(10)-triene **3c** and 6-methyl-3-(1′-propylbutyl)-*A*,19-dinorcholesta-6,8,10(5)-triene **4c** and 1-methyl-3,4-dibutyl-19-norcholesta-1,3,5(10)-triene **3d** and 6-methyl-3-(1′-butylpentyl)-*A*,19-dinorcholesta-6,8,10(5)-triene (**4d**) respectively. The results are listed in Table 1. The mass spectra of **4a**–**4d** all show a fragment at *m*/*z* 351 which is attributed to loss of the branched alkyl groups from C-3.

The formation of compound **4** from **2** reveals a novel enone–benzene rearrangement. A plausible mechanism is shown in Scheme 2.

It is worth noting that the migrating groups, propyl in **2c** and butyl in **2d**, are not isomerised during the enone–benzene rearrangement to **3c** and **3d**, since there was no extra isopropyl and isobutyl observed from the ^{1}H NMR and mass spectra of **3c** and **3d**.

Experimental

Melting points were uncorrected. IR spectra were recorded on a FTS-40 spectrometer as liquid films, ^{1}H and ^{13}C NMR spectra on Varian INOVA-500, Bruker AM-400 and AC-80 spectrometers by using tetramethylsilane (TMS) as internal standard and CDCl$_3$ as solvent and mass spectra on a VG-7070E spectrometer (EI, 70 eV).

General Procedure for the Enone–Benzene Rearrangement of 4,4-*Dialkylcholest*-5-*en*-3-*ones*.—A mixture of compound **2** (0.20 mmol), TsOH (100 mg, 0.57 mmol) and toluene (15 ml) was heated at refluxing temperature for 6–13 h (Table 1) using a Dean–Stark apparatus for water removal. The progress of the reaction was monitored by TLC. After cooling, the mixture was neutralised with a saturated solution of sodium bicarbonate, diluted with water (30 ml), extracted with light petroleum (3 × 30 ml) and dried (MgSO$_4$). The solvent was evaporated under reduced pressure and the residue separated by column chromatography on 10% AgNO$_3$–silica gel, eluted with light petroleum (b.p. 60–90 °C)–toluene (100:1, v/v), to give **4** and **3** successively.

3a: R_f 0.54 (light petroleum–toluene, 20:1 v/v, as eluent); mp 82–84 °C (colourless needles from acetone, lit.,[2] 83–86 °C); $\tilde{\nu}_{max}$/cm^{-1} 3054, 2998, 2875, 1469, 1377; δ_H (400 MHz) 0.757 (3 H, s, 18-Me), 0.909, 0.914 (6 H, 2d, *J* 6.6, 26,27-Me$_2$), 0.963 (3 H, d, *J* 6.5 Hz, 21-Me), 2.142 (3 H, s, C-4-Me), 2.259 (3 H, s, C-3-Me), 2.333 (3 H, s, C-1-Me), 6.862 (1 H, s, 2-H); δ_C (100 MHz, number of carbon) 12.74 (18), 14.87 (Ar-Me), 18.56 (21), 20.00 (Ar-Me), 21.70 (Ar-Me), 22.56 (26), 22.80 (27), 23.86 (11), 23.86 (23), 26.17 (15), 28.02 (25), 28.32 (16), 28.47 (6), 30.26 (7), 35.88 (20), 36.20 (22), 39.55 (24), 40.69 (8), 40.88 (12), 43.52 (13), 47.01 (9), 55.84 (14), 56.62 (17), 130.38 (2), 132.14, 133.00, 133.82, 136.99 (1, 3, 4, 5 and 10); *m*/*z* 394 (100%, M$^+$), 379 (20), 365 (8), 239 (18), 211 (20), 198 (27), 185 (40), 171 (35), 159 (38), 145 (20), 133 (12).

4a: R_f 0.60; colourless oil; $\tilde{\nu}_{max}$/cm^{-1} 3034, 2956, 2863, 1459, 1394, 1383; δ_H (400 MHz) 0.881 (6 H, d, *J* 6.5, 26,27-Me$_2$), 0.978 (3 H, *J* 6.3, 21-Me), 0.982 (3 H, s, 18-Me), 1.036 (3 H, d, *J* 6.5, C-1′-Me), 1.300 (3 H, d, *J* 6.9 Hz, C-1′-Me), 2.134 (3 H, s, C-6-Me), 6.935 (1 H, s, 7-H); δ_C (125 MHz) 14.66 (18), 19.70 (21), 20.23 and 22.41 (2 × C-1′-Me), 22.58 (26), 22.58 (C-6-Me), 22.82 (27), 23.83 (23), 24.49 (12), 25.62 (15), 28.02 (25), 28.63 (16), 28.81 (11), 33.90 (20), 34.00 (1), 34.69 (4), 35.55 (2), 35.94 (22), 39.53 (24), 40.19 (3), 40.73 (13), 52.39 (14), 53.57 (17), 127.12 (7), 131.64, 132.07, 133.08, 138.46, 138.70 (5, 6, 8, 9 and 10); *m*/*z* 394 (100%, M$^+$), 379 (40), 365 (30), 351 (3), 281 (10), 254 (14), 239 (30), 211 (10), 171 (20), 143 (10), 84 (28).

3b: R_f 0.60; colourless oil; $\tilde{\nu}_{max}$/cm^{-1} 3068, 2954, 2868, 2733, 1471, 1375; δ_H (80 MHz) 0.75 (3 H, s, 18-Me), 0.89 (6 H, d, *J* 6.0, 26,27-Me$_2$), 0.94 (3 H, d, *J* 6.4, 21-Me), 1.14 (3 H, t, *J* 7.5, C*H*$_3$CH$_2$), 1.23 (3 H, t, *J* 7.5, C*H*$_3$CH$_2$), 2.32 (3 H, s, C-1-Me), 2.62 (2 H, q, *J* 7.5, CH$_3$C*H*$_2$), 2.64 (2 H, q, *J* 7.5 Hz, CH$_3$C*H*$_2$), 6.85 (1 H, s, 2-H); δ_C (100 MHz) 12.80 (18), 14.30 (C-1-Me), 15.60 (2′), 18.55 (21), 21.34 (1′), 21.95 (1″), 22.57 (26), 22.82 (27), 23.83 (11), 23.83 (23), 25.26 (2″), 26.23 (15), 28.03 (25), 28.27 (16), 28.47 (6), 29.08 (7), 35.87 (20), 36.18 (22), 39.54 (24), 40.80 (8), 40.89 (12), 43.54 (13), 47.24 (9), 55.92 (14), 56.56 (17), 129.10 (2), 134.28, 136.41, 137.13, 137.34, 138.47 (1, 3, 4, 5, 10); *m*/*z* 422 (100%, M$^+$), 407 (10), 393 (15), 267 (10), 241 (18), 227 (24), 213 (25), 185 (27), 159 (35).

4b: R_f 0.66; colourless oil; $\tilde{\nu}_{max}$/cm^{-1} 3068, 1459, 1372, 874; δ_H (400 MHz) 0.873 (6 H, d, *J* 6.6, 26,27-Me$_2$), 0.918 (3 H, t, *J* 7.6, 3′-Me), 0.958 (3 H, t, *J* 7.6, 2″-Me), 0.966 (3 H, d, *J* 6.3 Hz, 21-Me), 0.985 (3 H, s, 18-Me), 2.103 (3 H, s, C-6-Me), 6.793 (1 H, s, 7-H); *m*/*z* 422 (20%, M$^+$), 393 (100), 351 (8), 186 (22).

3c: R_f 0.65; colourless oil; $\tilde{\nu}_{max}$/cm^{-1} 3068, 2733, 1464, 1375, 967, 857, 734; δ_H (80 MHz) 0.74 (3 H, s, 18-Me), 0.88 (6 H, d, *J* 6.0, 26,27-Me$_2$), 0.94 (3 H, d, *J* 6.2, 21-Me), 1.00 (6 H, t, *J* 7.0, 2 × CH$_3$), 2.30 (3 H, s, C-1-Me), 2.43 (2 H, t, *J* 7.0, C*H*$_2$CH$_2$CH$_3$), 2.54 (2 H, t, *J* 7.0, C*H*$_2$CH$_2$CH$_3$), 6.81 (1 H, s, 2-H); *m*/*z* 450 (100%, M$^+$), 435 (6), 421 (18), 408 (20), 295 (8), 269 (15), 241 (18), 199 (20), 173 (25), 95 (12).

4c: R_f 0.72; colourless oil; $\tilde{\nu}_{max}$/cm^{-1} 3030, 1461, 1376, 872; δ_H (400 MHz) 0.871 (6 H, d, *J* 6.1, 26,27-Me$_2$), 0.920 (6 H, t, *J* 7.4, 4′,3″-Me$_2$), 0.963 (3 H, d, *J* 6.4 Hz, 21-Me), 0.984 (3 H, s, 18-Me), 2.104 (3 H, s, C-6-Me), 6.771 (1 H, s, 7-H); *m*/*z* 450 (20%, M$^+$), 407 (100), 351 (10), 199 (20), 143 (8).

3d: R_f 0.69; colourless oil; $\tilde{\nu}_{max}$/cm^{-1} 3068, 2731, 1462, 1377, 946, 864, 726; δ_H (80 MHz) 0.74 (3 H, s, 18-Me), 0.88 (6 H, d, *J* 6.0, 26,27-Me$_2$), 0.95 (3 H, d, *J* 6.1, 21-Me), 0.97 [6 H, t, *J* 6, 2 × CH$_3$(CH$_2$)$_3$], 2.30 (3 H, s, C-1-Me), 6.81 (1 H, s, 2-H); *m*/*z* 478 (100%, M$^+$), 393 (8), 269 (14), 243 (14), 213 (14), 187 (18), 159 (10), 133 (10), 95 (10), 57 (22).

4d: R_f 0.77; colourless oil; δ_H (400 MHz) 0.871 (6 H, d, *J* 6.1, 26,27-Me$_2$), 0.878 (6 H, t, *J* 7, 5′,4″-Me$_2$), 0.962 (3 H, d, *J* 6.1 Hz, 21-Me), 0.984 (3 H, s, 18-Me), 2.103 (3 H, s, C-6-Me), 6.776 (1 H, s, 7-H); *m*/*z* 478 (20%, M$^+$), 421 (100), 351 (15), 213 (20), 143 (10).

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