1.8 g of 2-amino-2-methylpropan-1-ol in xylene solution (50 ml). After 7 days, the mixture was extracted to give 0.73 g of product: mp 79°; ir (Nujol) $\nu_{OH}$ 3500, $\nu_{NH}$ 3200 $cm^{-1}$; nmr ($CDCl_3$) $CH_3(4',4')$ 1.23, $CH_2(5')$ 3.55 ppm.

**17β-Hydroxy-4',4'-dimethylspiro(5α-androstane-3,2'-oxazolidine)-3'-oxyl (3)** was prepared as described above, using 0.73 g of crude amine and 0.53 g of *m*-chloroperbenzoic acid (oxidation time 5 hr). Thin layer chromatography gave 0.48 g of yellow product (yield 63%): mp 175–176° (methanol-water) (lit.[2] mp 172–174°); uv (cyclohexane) λ 450 mμ (ε ~13); esr ($CHCl_3$, $M/1000$) $a_N$ = 14.9 G.

**Spiro(5α-cholestane-3,5'-hydantoin) (7a).** According to Maki,[13] a mixture of 5α-cholestan-3-one (3.86 g), ammonium carbonate (5.7 g), and potassium cyanide (2 g) in 80% ethanol (150 ml) was heated at 57–58° for 10 days. The precipitate was filtered, washed with water, and dried to give 4 g of white powder (yield 87%): mp 274°; ir (KBr) $\nu_{NH}$ 3200, $\nu_{CO}$ 1780 and 1730 $cm^{-1}$.

The crude product (0.200 g) was extracted repeatedly with ethyl acetate to give 0.125 g of white powder **7a**, mp 276° (lit.[13] mp 273–274°), ir (KBr) identical with that of crude product.

**3α-Amino-5α-cholestane-3β-carboxylic Acid (8a).** According to Maki,[13] **7a** (0.125 g, mp 276°), sodium hydroxyde (5 g), and water (5 ml) were heated for 1 hr with occasional addition of water. At the end of this time, a large amount of water was added and the mixture was filtered. The precipitate was dissolved by addition of 70% sulfuric acid. The sulfate obtained was treated with concentrated ammonia to give 0.100 g (yield 87%) of white product **8a**, mp 264° (lit.[13] mp 262–264°).

**Methyl 3α-Amino-5α-cholestane-3β-carboxylate (9a).** According to Maki,[13] a solution of **8a** sulfate in methanol (20 ml) and concentrated sulfuric acid (4 ml) was refluxed for 8 hr. The methanol was evaporated and the residue was extracted with ether after neutralization with sodium carbonate solution. A 0.100-g yield (95%) of white product **9a** was obtained: mp 141° (methanol) (lit.[13] mp 141–141.5°); ir (Nujol) $\nu_{NH_2}$ 3300, $\nu_{CO}$ 1725 $cm^{-1}$; nmr ($C_6D_6$) $CH_3$ carboxylate 3.44 ppm.

**3α-Amino-5α-cholestane-3β-hydroxymethyl (10a).** **9a** (0.1 g, mp 141°) in ether solution was added to a suspension of lithium aluminum hydride (0.25 g) in ether solution (100 ml). The mixture was refluxed for 12 hr. The excess of hydride was decomposed,[16] the ether layer was filtered, and the solvent was removed. **10a** (0.084 g, yield 90%) was obtained: mp 155–158°; ir (Nujol) $\nu_{OH}$ ~3500 $cm^{-1}$; nmr ($C_6D_6$) $CH_2$ hydroxymethyl 3.12 ppm; nmr ($CDCl_3$) $CH_2$ 3.25 ppm.

**2',2'-Dimethylspiro(5α-cholestane-3,4'-oxazolidine) (11a).** Azeotropic distillation of **10a** (0.08 g) with an excess of acetone and a trace of *p*-toluenesulfonic acid gave 0.082 g (yield 95%) of viscous oil **11a**: ir (Nujol) $\nu_{NH}$ 3200 $cm^{-1}$; nmr ($C_6D_6$) $CH_3(2',2')$ 1.4, $CH_2(5')$ 3.53 ppm; nmr ($CDCl_3$) $CH_3(2',2')$ 1.45, $CH_2(5')$ 3.58 ppm.

**2',2'-Dimethylspiro(5α-cholestane-3,4'-oxazolidine)-3'-oxyl (6a).** **11a** (0.08 g) was oxidized using 0.045 g of *m*-chloroperbenzoic acid. Thin layer chromatography (silica gel, 90% pentane–10% ether) gave 0.040 g (yield 47%) of yellow crystals of **6a**: mp 188° (ethanol); uv (cyclohexane) λ 450 mμ (ε ~9.5); esr ($CHCl_3$, $M/1000$) $a_N$ = 15.2 G, no hyperfine structure (Figure 1c).

*Anal.* Calcd for $C_{31}H_{54}NO_2$: C, 78.75; H, 11.51; O, 6.77; N, 2.96. Found: C, 78.76; H, 11.56; O, 6.98; N, 2.85.

**2',2'-Dimethylspiro(5α-cholestane-3,4'-oxazolidine)-3'-oxyl (6a and 6b).** The same method as above was used on the crude hydantoin **7**, mp 274° (mixture of two epimeric hydantoins **7a** and **7b**), without purification of intermediate products. Hydrolysis of crude hydantoins (0.5 g, mp 274°) with sodium hydroxide gave 0.41 g of white product, mp 263° (mixture of two epimeric amino acids).

This crude mixture (0.41 g) in *ethanol* solution (100 ml) containing anhydrous hydrochloric acid was allowed to stand at room temperature overnight. The residue, obtained after evaporation of the ethanol, was extracted with ether to give 0.45 g of white product, mp 105° (mixture of epimeric amino esters): ir (KBr) $\nu_{CO}$ 1720 $cm^{-1}$; nmr ($CDCl_3$) $CH_3$ carboxylate 1.3 (triplet, $J$ = 6 Hz), $CH_2$ carboxylate 4.2 ppm (quadruplet, $J$ = 6 Hz).

This crude amino ester (0.12 g) was reduced with lithium aluminum hydride (0.25 g) to give 0.10 g of white solid, mp 155–157° (mixture of epimeric amino alcohols): ir (Nujol) $\nu_{OH}$ 3500 $cm^{-1}$; nmr ($CDCl_3$) $CH_2$ hydroxymethyl 3.25 ppm.

An azeotropic distillation of crude amino alcohols (0.1 g) with an excess of acetone gave 0.105 g of viscous product (mixture of two epimeric oxazolidines): ir (Nujol) $\nu_{NH}$ 3300 $cm^{-1}$; nmr ($CDCl_3$) $CH_3(2',2')$ 1.45, $CH_2(5')$ 3.57 ppm.

This mixture of oxazolidine (0.105 g) was oxidized with *m*-chloroperbenzoic acid (0.06 g). Thin layer chromatography (silica gel, 90% pentane–10% ether) gave two products in 86.5:13.5 ratio: 0.044 g of yellow crystals, mp 188° (ethanol), identical with **6a**, and 0.007 g of yellow crystals **6b**, mp 150–155°, esr ($CHCl_3$, $M/1000$) $a_N$ = 15.1 G, hyperfine structure (Figure 1b).

**Registry No.**—**3**, 39665-50-4; **4**, 51820-19-0; **5**, 51820-20-3; **6a**, 51231-13-1; **6b**, 51231-14-2; **7a**, 5119-47-1; **7b**, 5167-92-0; **8a**, 5071-18-1; **8b**, 5119-44-8; **9a**, 5071-19-2; **9b**, 5071-15-8; **10a**, 51231-15-3; **10b**, 51231-16-4; **11a**, 51231-17-5; **11b**, 51540-03-5; 4',4'-dimethylspiro(5α-cholestane-3,2'-oxazolidine), 51231-18-6; 5α-cholestan-3-one, 566-88-1; 2-amino-2-methylpropan-1-ol, 124-68-5; 4',4'-dimethylspiro-5β-chlolestane-3,2'-oxazolidine), 51231-19-7; 17β-hydroxy-4',4'-dimethylspiro(5α-androstane-3,2'-oxazolidine), 51231-20-0.

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## Trans Dehydration of Alcohols with Methyl(carboxysulfamoyl) Triethylammonium Hydroxide Inner Salt[1]


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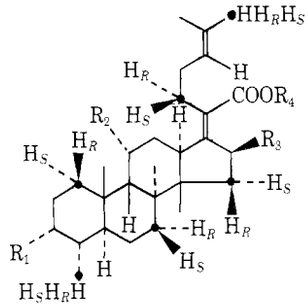
During the course of our investigations into the mode of incorporation of hydrogen atoms of biosynthetic precursors into polyprenoids, we required a procedure applicable to microscale operations allowing the introduction of a double bond *via* a cis elimination of an hydroxyl function. A novel and convenient procedure for the dehydration of secondary and tertiary alcohols utilizing methyl(carboxysulfamoyl) triethylammonium hydroxide inner salt (**6**) claimed to proceed *via* cis elimination has been reported by Burgess, *et al.*[3] Indeed, these authors have shown that the dehydration of *threo*- and *erythro*-2-deuterio-1,2-diphenylethanol is a cis-elimination process. Based on this observation, the generality of the cis elimination was suggested.[3,4]

Dehydration of steroidal alcohols with the reagent **6** has been accomplished without affecting other functional groups of the molecule, such as ketones, unsaturated ketones, acetylenes, and acetates.[4] Because of the potential utility of this reagent, we undertook an exploration of the stereochemistry of the process.

Treatment of 3α-acetoxymethyl fusidate (**1b**)[5,6] with the reagent **6** for 1.5 hr in refluxing benzene afforded the $\Delta^{9(11)}$ olefin (**2**)[5] in 90% yield. The crude reaction product was scrutinized for the $\Delta^{11}$ olefin but none could be isolated. In fusidic acid (**1a**) the 11α-hydroxyl and the

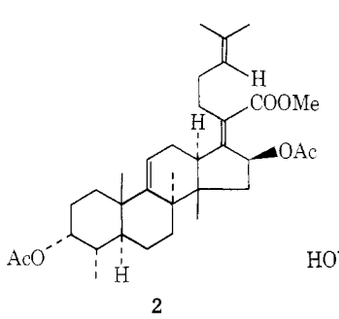


· carbon derived from C-2 of MVA

$H_R$ derived from 2-pro-*R* of MVA

$H_S$ derived from 2-pro-*S* of MVA

**1a**, $R_1 = R_2 = OH$; $R_3 = OAc$; $R_4 = H$
**b**, $R_1 = OAc$; $R_2 = OH$; $R_3 = OAc$; $R_4 = CH_3$
**c**, no $\Delta^{24}$; $R_1 = R_2 = OH$; $R_3 = OAc$; $R_4 = H$
**d**, no $\Delta^{24}$; $R_1 = R_2 =$ THPO (tetrahydropyranyloxy); $R_3 = OAc$; $R_4 = H$
**e**, $R_1 = R_2 = OH$; $R_3 = OAc$; $R_4 = CH_3$
**f**, no $\Delta^{24}$; $R_1 = R_2 = OH$; $R_3 = OAc$; $R_4 = CH_3$
**g**, no $\Delta^{24}$; $R_1 = R_2 =$ THPO; $R_3 = OH$; $R_4 = CH_3O$
**h**, no $\Delta^{24}$; $R_1 = R_2 =$ THPO; $R_3 = OAc$; $R_4 = CH_3O$



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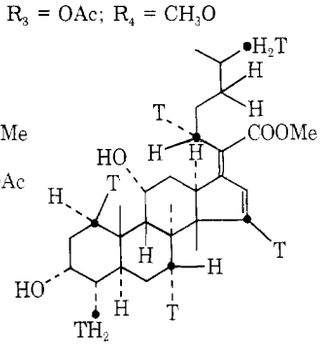


3

9β-hydrogen are trans diaxial,[5,6] and hence the isolated olefin is the product of a trans elimination.

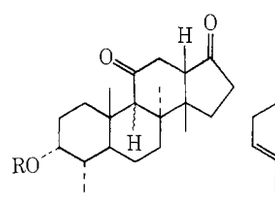
Elimination of 11-hydroxyl functions in pregnane derivatives with the reagent **6** had been reported.[4] The 11β-hydroxyl derivative gave the $\Delta^{9(11)}$ olefin in 96% yield, while the 11α-hydroxyl derivative gave the $\Delta^{9(11)}$ olefin in only 9% yield. The results are contrary to those expected if one maintains the cis-elimination mechanism. The 11α-hydroxyl, being cis to the 9α-hydrogen, should be more readily eliminated than the 11β-hydroxyl. Crabbé, *et al.*,[4] could not satisfactorily explain the lack of reactivity of the 11α-hydroxyl; however the result with the 11β-hydroxyl was rationalized by assuming that a C-11 cation is formed first, and this is followed by an intramolecular hydrogen transfer from C-9 to C-11. Stabilization of the resulting C-9 cation was then postulated to occur *via* the loss of a C-11 hydrogen and $\Delta^{9(11)}$ bond formation. A more reasonable explanation consistent with our observations is that a trans elimination is operating in the case of the 11β-hydroxyl. This explanation is supported by the results obtained in the elimination of the 3α-hydroxyl of **4b** described below.

To evaluate the stereochemistry of the dehydration of the 3α-hydroxyl of **4b**, 3-acetoxymethyl fusidate (**1b**) was converted to **4a** as previously described.[7] The saponification of **4a** to **4b** was carried out under conditions which would ensure complete isomerization of the 9β-H to the more stable 9α-H.[8] Indeed, the physical properties (melting point, $[\alpha]D$) of the product agreed with those reported[8] for **4b**. Exposure of **4b** to the reagent **6** for 1 hr in refluxing benzene yielded the $\Delta^3$ olefin **5**. In alcohol **4b** the 3α-hydroxyl and the 4β-hydrogen are trans diaxial; hence the isolated product (**5**) is again the result of a trans elimination.

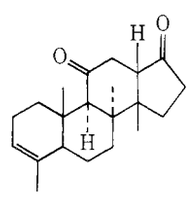
**Table I**

| Compd | $^3H:^{14}C$ isotopic ratio[a] | $^3H:^{14}C$ atomic ratio |
|---|---|---|
| **1e** | 5.04 | 6.00:6 |
| **1f** | 5.03 | 6.00:6 |
| **1d** | 4.98 | 5.92:6 |
| **1h** | 4.96 | 5.90:6 |
| **3** | 4.96 | 5.90:6 |

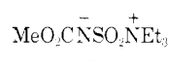
[a] Isotopic ratios were determined on samples first purified by tlc and then repeatedly crystallized from a suitable solvent. Reported values are the average of three crystallizations.



**4a**, R = Ac 9β
**b**, R = H 9α



5

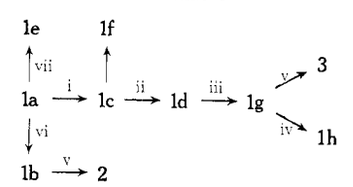


6

Considerations of the mode of formation of squalene and its oxidative cyclization to protosterols predict that the hydrogens derived from 2-pro-*R* and 2-pro-*S* protons of mevalonic acid (MVA) will be located in the derived fusidic acid[5,7] as shown in **1a**. Consequently, fusidic acid (**1a**) biosynthesized from (3*RS*,2*R*)[2-$^{14}$C,2-$^3$H]-MVA will have *inter alia* a $^3$H atom at the 15β position. In a previous study[9] we had indeed confirmed that [$^{14}C_6$,$^3H_6$]fusidic acid (**1a**) biosynthesized from (3*RS*,2*R*)[2-$^{14}$C,2-$^3$H]-MVA has a $^3$H atom at the 15β position. Proton magnetic resonance[10] and X-ray[11] studies of fusidane derivatives have indicated that the cis 16β-C–O and the 15β-C–H bonds have a rigid, nearly eclipsed orientation. It was felt that this stereochemistry should favor a cis elimination of the 16β-OH and 15β-$^3$H.

Consequently [$^{14}C_6$,$^3H_6$]fusidic acid[9] (**1a**; · -$^{14}$C; $H_R$-$^3$H) biosynthesized from (3*RS*,2*R*)[2-$^{14}$C,2-$^3$H]mevalonic acid was converted to 16β-hydroxydihydrofusidate (**1g**) as outlined[8] in Scheme I. Treatment of the [$^{14}C_6$,$^3H_6$]-16β-ol

**Scheme I**



i, $H_2$/Pd on $BaCO_3$[6b]
ii, dihydropyran-*p*-toluenesulfonic acid
iii, $LiAlH_4$–tetrahydrofuran, $CH_2N_2$
iv, $Ac_2O$–pyridine (50°)
v, $MeO_2\bar{C}N\overset{+}{S}O_2\overset{+}{N}Et_3$–benzene[3]
vi, $Ac_2O$–pyridine[6b]
vii, ethereal $CH_2N_2$[6b]

**1g** (counted as **1h**) with reagent **6** for 2 hr in refluxing benzene yielded the [$^{14}C_6$,$^3H_6$] olefin **3**.[9] The $^3H:^{14}C$ ratios of the olefin **3** and the 16β-ol **1g** were identical (see Table I), indicating that $^3$H was not lost. It can be concluded that the $\Delta^{15}$ product isolated was obtained *via* loss of the 16β-OH and the gauche 15α-H and again the overall process is equivalent to a trans elimination.

Our results with **1g** do not preclude the possibility of the participation of an allylic cation in the $\Delta^{15}$ formation. However, the complete stereospecificity of the reaction which proceeded with retention of all of the $^3H$ would mitigate against this argument.

Thus in the three cases studied by us, products of an overall trans rather than the expected cis dehydration were isolated. The unlikely possibility that cis elimination occurs first and is followed by a subsequent isomerization is not ruled out by our results. However, it is apparent that based on the structures of the *isolated* end products, the generalization of the mechanism of the reaction as a cis-elimination process is not tenable.

## Experimental Section[12]

**Methyl 3-Acetoxy-$\Delta^{9(11)}$-fusidate (2).** To a stirred solution of methyl 3-acetoxyfusidate (**1b**,[5,6] 100 mg) in benzene (20 ml) under an atmosphere of $N_2$ was added dropwise a solution of methyl(carboxysulfamoyl) triethylammonium hydroxide inner salt (**6**, 50 mg) in benzene (20 ml). The solution was stirred at room temperature for 0.5 hr and refluxed for 0.5 hr. Additional reagent **6** (50 mg) was added and the reaction was refluxed for 1 hr and then terminated with water. The benzene layer was washed with $H_2O$ and dried over $Na_2SO_4$ and the solvent was removed. The olefin (90 mg) was purified by preparative tlc [silica gel, hexane–acetone (8:2)]. The olefinic zone was eluted with $CHCl_3$–EtOAc (4:1) and further fractionated by argentation tlc [silica gel–silver nitrate 15%; hexane–acetone (7:3)] to yield homogenous olefin **2**[5] (70 mg): ir 3020 $cm^{-1}$ (C=C); nmr 4.52 ppm (1 H, t, $J$ = 3 Hz, 11-H); $m/e$ 494 ($M^+$ − HOAc).

**3$\alpha$-Hydroxy-4$\alpha$,8,14-trimethyl-18-nor-5$\alpha$,8$\alpha$,14$\beta$-androstane-11,17-dione (4b).** To a stirred, under nitrogen, solution of 3$\alpha$-acetoxydione **4a**[7] (725 mg) in MeOH (160 ml) was added KOH (40 g) in $H_2O$ (40 ml). The stirring was continued overnight at room temperature under $N_2$ and then the mixture was refluxed for 1 hr. Water (200 ml) was added, and the mixture was neutralized and extracted with EtOAc. The combined extract was washed with $H_2O$ and dried ($Na_2SO_4$) and the solvents were removed. The resulting residue was fractionated on tlc [silica gel, hexane–acetone (7:3)]. The recovered 3$\alpha$-hydroxydione **4b**[8] (446 mg) was crystallized (MeOH): mp 230–232° (lit.[8] mp 237–239° uncorrected); $[\alpha]^{24}_{589}$ − 172° (0.1225 g/100 ml) (lit.[8] −176°); ir 3470 (OH), 1733 and 1685 $cm^{-1}$ (C=O); nmr 6.28 (1 H, broad s, 3$\beta$-H), 8.33, 8.80, 8.98, and 9.07 ppm (12 H, s, 4-, 8-, 14-, and 19-$CH_3$); $m/e$ 332 ($M^+$), 314 ($M^+$ − 18).

**4$\alpha$,8,14-Trimethyl-18-nor-5$\alpha$,8$\alpha$,14$\beta$-androst-3-ene-11,17-dione (5).** To a stirred solution of 3$\alpha$-hydroxydione **4b** (177 mg) in benzene (3 ml) the reagent **6** (200 mg) in benzene (10 ml) was added. The mixture was refluxed for 1 hr and processed as above. The recovered olefin (75 mg) was fractionated first by preparative tlc [silica gel, hexane–acetone (7:3)] and then by argentation preparative tlc (silica gel–silver nitrate 15%). The recovered $\Delta^3$ olefin **5** was crystallized (EtOAc–hexane): mp 145–149°; ir 1733 and 1693 $cm^{-1}$ (C=O); nmr 4.69 (1 H, broad s, 3-H), 8.14 (3 H, d, $J$ = 2 Hz, 4-$CH_3$), 8.80, 8.89, and 9.10 ppm (9 H, s, 8-, 14-, 19-$CH_3$); $m/e$ 314 ($M^+$), 299 ($M^+$ − 15).

**Methyl 24,25-Dihydro-3$\alpha$,11$\alpha$-dihydroxy[$^{14}C_6$,$^3H_4$]-16-deacetoxy-$\Delta^{15}$-fusidate (3).** A stirred solution of 16$\beta$-hydroxy dihydrofusidate **1g**[9] (93 mg) in benzene (10 ml) was treated with reagent **6** (50 mg) in benzene (10 ml). After stirring at room temperature for 0.5 hr, the mixture was refluxed for 2 hr and worked up as above. Preparative tlc [silica gel, hexane–acetone (4:1)] gave the $\Delta^{15}$ olefin **3**[9] (30 mg), which was crystallized (EtOAc): mp 160–161°; ir 1665 and 1610 (conjugated C=O), 980 $cm^{-1}$ (C=CH); nmr 3.62 (1 H, d, $J$ = 6 Hz, 16-H), 3.10 ppm (1 H, d, $J$ = 6 Hz, 15-H); uv (EtOH) 274 nm ($\epsilon$ 17,200); $m/e$ 472 ($M^+$).

**Registry No.** —**1b**, 51424-41-0; **1g**, 51373-34-3; **2**, 51373-35-4; **3**, 51373-36-5; **4a**, 13263-12-2; **4b**, 51424-42-1; **5**, 51381-68-1; **6**, 51373-37-6.

## References and Notes

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(10) (a) The nmr spectra of fusidic acid derivates (see data below) reveals vicinal coupling between the 15$\alpha$ and 16$\alpha$ protons of 8 Hz

Chemical Shifts ($\tau$) and Coupling Constants ($J$) for the 16$\alpha$-H

| Compd | $\tau$ | $J$, Hz |
|---|---|---|
| **1a** | 4.14 (d) | 8 |
| **1b** | 4.08 (d) | 8 |
| **1d** | 4.22 (d) | 7 |
| **1h** | 4.21 (d) | 8 |
| **1e** | 4.18 (d) | 8 |

and *ca.* 1 Hz between the 15$\beta$ and 16$\alpha$ protons. Thus the dihedral angle between the 15$\alpha$ and 16$\alpha$ protons must approach zero. (b) W. von Daehne, H. Lorch, and W. O. Godtfredsen, *Tetrahedron Lett.*, 4843 (1968).

(11) A. Cooper and D. C. Hodgkin, *Tetrahedron*, **24**, 909 (1968).

(12) Melting points were taken on a hot stage and are corrected. Infrared spectra were recorded on KBr microdisks on a Perkin-Elmer Model 237 spectrometer. Mass spectra were obtained on a Du Pont 21-491 instrument. Nmr spectra were recorded on a Varian DA-60 spectrometer at 60 MHz with samples dissolved in $CDCl_3$. Glc analyses were performed on a Hewlett-Packard Model 7620A glc equipped with a flame ionization detector. A 6 ft silanized glass column of 1% SE-30 on Gas-Chrom Q was used for all analyses. Specific activities and $^3H$:$^{14}C$ ratios were determined on samples which were purified by tlc and crystallized to constant specific activity of $^{14}C$ and constant $^3H$:$^{14}C$ ratio.

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# Aromatization of Cyclic Ketones. I. Alkylcyclohexanone

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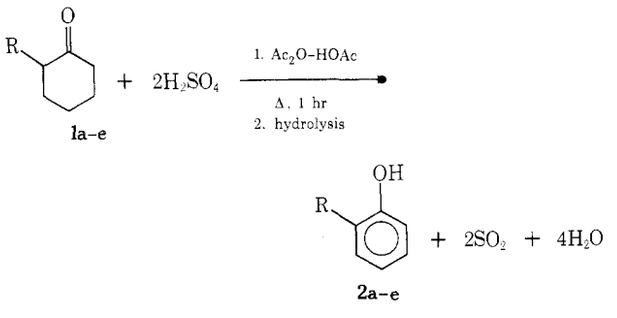
Several methods are reported in the literature for the aromatization of substituted cyclohexanones. In general, either high-temperature catalytic aromatizations[1] or a two-step process, halogenation–dehydrohalogenation,[2] were employed. Treatment of 3,3,5-trimethylcyclohexanone with 30% oleum for 7 days at room temperature followed by steam distillation gives about a 10% yield of trimethylphenol.[3]




a, R = $CH_3$
b, R = $C_2H_5$
c, R = $n$-$C_3H_7$
d, R = $n$-$C_4H_9$
e, R = 

Several $\alpha$-alkylcyclohexanones **1** were subjected to the sulfuric acid–acetic anhydride aromatization procedure, whereby 2 mol of sulfuric acid and at least 2 mol of acetic