Our results with **1g** do not preclude the possibility of the participation of an allylic cation in the Δ^{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).

3α-Hydroxy-4α,8,14-trimethyl-18-nor-5α,8α,14β-androstane-11,17-dione (4b). To a stirred, under nitrogen, solution of 3α-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 3α-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, 3β-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).

4α,8,14-Trimethyl-18-nor-5α,8α,14β-androst-3-ene-11,17-dione (5). To a stirred solution of 3α-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 Δ^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-3α,11α-dihydroxy[$^{14}C_6$,$^3H_4$]-16-deacetoxy-Δ^{15}-fusidate (3). A stirred solution of 16β-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 Δ^{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 (ϵ 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

(1) The very generous support of this work by the National Institutes of Health (Grants AM12156, CA13369, GM16928, and GM19882) and the National Science Foundation (Grants GB36201 and GB23801-A1) is gratefully acknowledged.

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

Chemical Shifts (τ) and Coupling Constants (J) for the 16α-H

Compd	τ	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 15β and 16α protons. Thus the dihedral angle between the 15α and 16α protons must approach zero. (b) W. von Daehne, H. Lorch, and W. O. Godtfredsen, *Tetrahedron Lett.*, 4843 (1968).

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Aromatization of Cyclic Ketones. I. Alkylcyclohexanone

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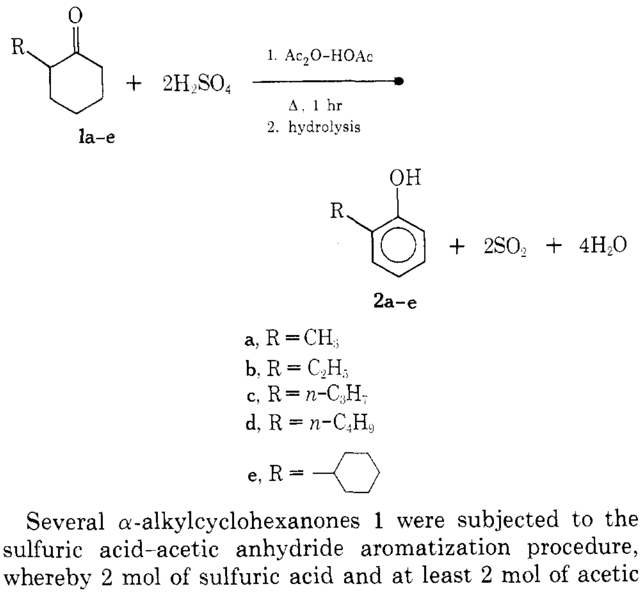
Several methods are reported in the literature for the aromatization of substituted cyclohexanones. In general, either high-temperature catalytic aromatizations[1] or a two-step process, halogenation–dehydrohalogenation,[2] were employed. Treatment of 3,3,5-trimethylcyclohexanone with 30% oleum for 7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



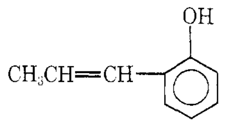
Several α-alkylcyclohexanones **1** were subjected to the sulfuric acid–acetic anhydride aromatization procedure, whereby 2 mol of sulfuric acid and at least 2 mol of acetic

Table I
Aromatization of α-Alkylcyclohexanones

Compd	Solvent	Moles of H_2SO_4 per mole of ketone	Yield, %	Product(s)[a]
1a	Ac_2O–HOAc	2.0	90	**2a**
1a	Ac_2O	2.0	80	**2a** (64%), 3-methylcatechol (36%)[c]
1b	Ac_2O–HOAc	2.0	50	**2b**
1c	Ac_2O–HOAc	2.0	60	**2c**
1c[b]	Ac_2O–HOAc	1.8	65	**1c** (10%), **2c** (40%), **3** (22%)
1d	Ac_2O–HOAc	2.0	65	**2d**
1d[b]	Ac_2O–HOAc	1.8	70	**1d** (22%), **2d** (30%), 4 (20%)
1e	Ac_2O–HOAc	2.0	90	**2e**

[a] Ratio of products based on glc analysis. [b] Several higher boiling materials detected by glc (28%) were not identified. [c] M. S. Kablaoui and H. Chafetz, unpublished results.

anhydride (Ac_2O) to 1 mol of ketone were employed. The major product isolated was the corresponding *o*-alkylphenyl acetate. Hydrolysis of the product yields the *o*-alkylphenols. Best yields were obtained when sulfuric acid was added, preferably at room temperature, to a solution of the ketone, Ac_2O, and acetic acid (HOAc)[4] in a dry nitrogen atmosphere. The use of 1.8 mol of H_2SO_4 for **1c** and **1d** gave appreciable amounts of the 2-(1-alkenyl)phenols (**3, 4**)[5] as by-products. Results are shown in Table I.



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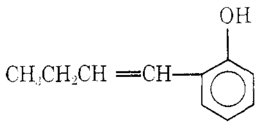

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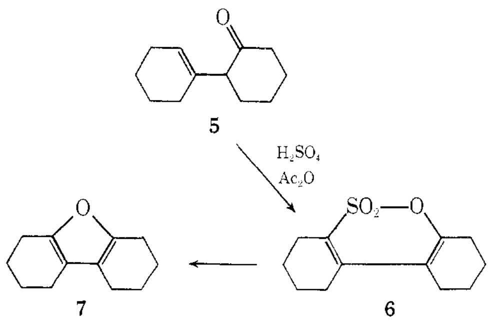
No aromatization occurred when sodium bisulfate, *p*-toluenesulfonic acid, or sulfoacetic acid was substituted for H_2SO_4, or when phthalic or succinic anhydride replaced Ac_2O.

Non-α-alkylated cyclohexanones exhibited different behavior. Thus cyclohexanone and 3-methyl- and 4-methylcyclohexanone as well as 2-(1-cyclohexenyl)cyclohexanone (**5**, aldol condensation product[6] of cyclohexanone), when subjected to the above aromatization procedure, gave high-boiling, nonphenolic materials. Such materials are believed[7] to be the sultone **6** and octahydrobenzofuran **7**. The literature[8] reported the formation of **6** by the reaction of **5** with cold concentrated H_2SO_4 and Ac_2O. Pyrolysis[8] of **6** gave **7**.



It seems that non-α-alkylated cyclohexanones give aldol condensation products when subjected to the above aromatization procedure. In the case of α-alkylated cyclohexanones, the corresponding *o*-alkylphenols are usually isolated. It is reasonable to assume that under the above conditions, non-α-alkylated cyclohexanones undergo aldol condensation faster than aromatization while α-alkylated cyclohexanones aromatize (or form the enol acetate) faster than forming aldol condensation products. The fact that non-α-alkylated cyclohexanones undergo aldol condensations faster than the α-alkylated is known in the literature.[9] To further verify this, cyclohexanone and 2-methyl- and 4-methylcyclohexanone were treated at room temperature with hydrogen chloride; cyclohexanone and 4-methylcyclohexanone formed the aldol dimer while 2-methylcyclohexanone was recovered unreacted.

Acetylation of the enol form of α-alkylcyclohexanone appears to be the first step of the aromatization. Thus, analysis of the products formed when refluxing began indicated the presence of only the enol acetate[10] (90%) and *o*-alkylphenyl acetate (10%). After 10 min of reflux, over 50% of the aromatized product was isolated. No enol acetate remained after 1 hr.

It is proposed that the aromatization of 2-alkylcyclohexanones involves O-acetylation of the enol form followed by two hydride abstractions giving first the diene followed by the product **2** and SO_2. Several mechanisms can be postulated for the hydride abstraction and formation of SO_2. One possibility could involve the sulfonation of the ketone or its enol acetate with concentrated H_2SO_4 or acetyl sulfate (the product of the reaction of H_2SO_4 with Ac_2O) followed by desulfonation[3,12] to give SO_2 and H_2O. Another alternative mechanism could involve hydride abstraction as in the formation of adamantanones from adamantane[13] or the action of *tert*-butyl chloride–aluminum bromide complex on isopentene.[14]

Experimental Section

The ir spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer; the nmr spectra were obtained on a Varian Associates Model V-4311 spectrometer operating at 60 MHz. All glc analyses were run on a SE-30 column programmed from 100 to 250°.

Aromatization of 2-Methylcyclohexanone. Into a 300-ml, three-neck flask equipped with a magnetic stirrer, a gas sparger, a condenser, and a thermometer were charged 5.0 g (0.044 mol) of 2-methylcyclohexanone (2-MCH), 50 ml of acetic anhydride, and 50 ml of HOAc. Concentrated sulfuric acid (9.0 g, 0.09 mol) was slowly added at room temperature to the mixture. The reaction mixture was then heated to reflux for 1 hr while dry nitrogen was passed through at the rate of 140 ml/min. The work-up of the reaction mixture was done by quenching in 150 ml of ice-water and stirring for 30 min to decompose all the acetic anhydride followed by extraction with ether (4 × 50 ml). The combined ether extracts were washed once with 50 ml of saturated $NaHCO_3$ solution and once with saturated NaCl solution, dried, and stripped on a rotary evaporator to give a residue (6.5 g) whose glc analysis indicated the presence of one compound. Upon distillation of the residue, 6.0 g (90% yield) of *o*-cresyl acetate was isolated. The product was identified by comparison of its ir and nmr spectra with those of an authentic sample. When air was substituted for dry nitrogen in the above run, low yields (~50%) of *o*-cresyl acetate were isolated.

Isolation of Intermediates in the Aromatization of 2-Methylcyclohexanone. The aromatization of 2-MCH was repeated whereby samples were taken during the course of the aromatization. After work-up, the residue was analyzed. When the temperature of the reaction reached 50°, *o*-cresyl acetate (traces), the enol acetate of 2-MCH, and 2-MCH were isolated. At reflux, the enol acetate of 2-MCH (about 90%) and *o*-cresyl acetate (10%) were isolated. After 15 min of reflux, 58% of *o*-cresyl acetate was isolated.

Aromatization of α-Substituted Cyclohexanones. The aromatizations were carried out by the same procedure used for the aromatization of 2-MCH. Variations in solvent and amount of H_2SO_4 used are shown in Table I.

Aromatization of 2-Propylcyclohexanone (1c). The title compound (5.0 g, 0.35 mol), 6.6 g (0.066 mol) of H_2SO_4, 75 ml of Ac_2O, and 75 ml of HOAc were refluxed for 1 hr as in the case of 2-methylcyclohexanone. After work-up of the reaction mixture, a glc analysis indicated the presence of four compounds. The first (10%) and second (40%) were identified as the enol acetate of the starting material and 2-propylphenyl acetate, respectively, by comparison of the ir and nmr spectra with those of authentic samples. The fourth compound (18%) was not identified. The third compound (22%) was identified as 2-(1-propenyl)phenyl acetate (3): ir (neat) 5.75 (-OAc), 6.1 μ (C=C); nmr ($CDCl_3$) δ 1.89 (d, 3 H, CH_3C=C-), 2.32 (s, 3 H, CH_3COO-), 6.3 (m, 2 H, -CH=CH-), and 7.25 (m, 4 H, aromatic).

When the above run was repeated using 7.7 g (0.077 mol) of concentrated H_2SO_4, only 2-propylphenyl acetate (70%) was isolated.

Aromatization of 2-butylcyclohexanone gave similar results (Table I).

Reaction of Hydrogen Chloride with Methylcyclohexanones. Into three separate test tubes were charged 5 ml each of cyclohexanone and 2-methyl- and 4-methylcyclohexanone. Hydrogen chloride was bubbled at room temperature into each of the test tubes for 15 min. Analysis of the products by ir and nmr indicated that cyclohexanone and 4-methylcyclohexanone gave different products than the starting material whereas 2-methylcyclohexanone was recovered unreacted.

Registry No.—**1a**, 583-60-8; **1b**, 4423-94-3; **1c**, 94-65-5; **1d**, 1126-18-7; **1e**, 90-42-6; 3 acetate, 35922-87-3; cyclohexanone, 108-94-1; 4-methylcyclohexanone, 589-92-4; hydrogen chloride, 7647-01-0.

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Effect of Dichloromethane on the Reaction of Carbethoxynitrene with *trans*-1,2-Dimethylcyclohexane

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There is ample experimental evidence to support the statement that nitrenes, generated from a variety of precursors, can be made to cross from an initially formed singlet state to a lower energy triplet state by collisional deactivation with inert solvent molecules.[1-3] Collisional deactivation or destabilization of singlet states by inert solvents can mean the actual promotion of intersystem crossing by electronic interactions as with heavy-atom solvents or, as is more probably the case with dichloromethane, simply that the solvent by being inert allows intramolecular intersystem crossing to compete favorably with reactive collision, or both.

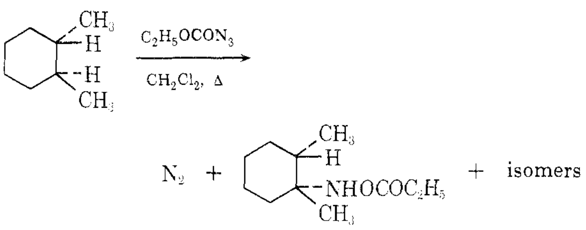
Table I
Thermal Decomposition of Ethyl Azidoformate in Dichloromethane-*trans*-1,2-Dimethylcyclohexane (TDCH) Solutions[a]

Mol % TDCH	Stereospecificity (% trans insertion product)	Proportion of tertiary product[b]	Absolute yield %[c]
100	96.5	38.7	26.2
89.9	98.5	39.6	37.3
79.9	97.8	35.6	34.4
66.7	96.2	38.1	30.0
51.0	94.5	35.4	38.0
39.5	95.6	33.7	37.5
19.2	96.4	28.2	35.2
8.1	92.0	22.6	37.7

[a] Reaction mixtures were carefully degassed and azide decomposition was carried out in evacuated, sealed tubes at 120° for 90 hr; analysis by vpc. [b] Proportion of tertiary C–H insertion product to other isomers; tertiary/(tertiary + secondary + primary). [c] Total absolute yield of all insertion products.

However, Breslow has recently reported that yields of insertion (singlet) products of carbalkoxynitrenes, ROCON, with cyclohexane are increased upon dilution with hexafluorobenzene.[4] Furthermore, in an accompanying communication, Lwowski demonstrates that dichloromethane acts to stabilize the singlet-state character of a number of alkanoylnitrenes, RCON, without removing their C–H insertion reactivity,[5] although it was noted that no such effect of dichloromethane on yields and product ratios had been observed from previous studies with carbethoxynitrene, ROCON, R = Et.[6]

As part of a long-range study of the factors which influence the singlet–triplet character of nitrenes, we now present evidence that dichloromethane has a noticeable effect on the reactions of a carbalkoxynitrene (ROCON) as well as alkanoylnitrenes (RCON). Table I summarizes results from a study of the reaction of thermally generated carbethoxynitrene with *trans*-1,2-dimethylcyclohexane (TDCH) at various dilutions with dichloromethane (eq 1).



(1)

The results given for each concentation of hydrocarbon are based on triplicate runs with an error of ±2% for the stereospecificity, ±2% for the proportion tertiary product, and ±5% for the absolute yields. From the data in Table I it is evident that changing the concentration of the hydrocarbon by dilution with dichloromethane does not affect the stereospecificity of the insertion; *i.e.*, little *cis*-1,2-dimethyl-1-cyclohexylurethane is formed from the trans hydrocarbon. This result supports the conclusion, based on a wealth of other experiments, that only singlet carbethoxynitrene inserts into unactivated C–H bonds.[7] Competition experiments established that the tertiary C–H bonds of *cis*-1,2-dimethylcyclohexane react 1.2 times faster than the corresponding bonds in the trans isomer; a factor of 1.7 was found for these hydrocarbons using cyanonitrene, NCN.[2] Otherwise, the cis and trans isomers gave similar product patterns on vpc analysis and the trans isomer was chosen for study. With pure (>99%)