Table I. Oxygen Exchange during Benzamide Hydrolysis in 5.9% H_2SO_4 at 85.0°

Run 1			Run 2		
Time, min[a]	121/123[b]	% ^{18}O[c]	Time, min[a]	121/123[b]	% ^{18}O[c]
0	0.1005	90.87	0	0.1013	90.80
153	0.1030	90.66	150	0.1033	90.64
304	0.1049	90.51	312	0.1057	90.44
470	0.1071	90.33	478	0.1082	90.24
k_E[d] = 1.25×10^{-5} min^{-1}			k_E[d] = 1.30×10^{-5} min^{-1}		

[a] For hydrolysis, $k_H = 4.09 \times 10^{-3}$ min^{-1}, $t_{1/2}$ = 169 min (C. R. Smith and K. Yates, *J. Am. Chem. Soc.*, 93, 6578 (1971). [b] Ratio of peak intensities at *m/e* 121 and 123, measured on an AEI MS-902, equipped with a Vacuumetrics ratiometer. These values are the average of 30–40 determinations; standard deviations range from 0.00025 to 0.00035. [c] $(1/r)/(1 + (1/r))$,[8] r = 121/123. [d] Slope of the plot of ln (% ^{18}O − 0.2) *vs.* time.

Table II. Control Experiment Demonstrating Reproducibility of Mass Spectral Analysis

% labeled benzamide[a]	121/123[b]	% ^{18}O[c]	% labeled benzamide, calcd
100	0.1010	90.83	(100)
99.86	0.1030	90.66	99.81
99.73	0.1041	90.57	99.71
99.45	0.1069	90.34	99.46

[a] Samples of ^{18}O enriched benzamide diluted with small amounts of unlabeled material. [b,c] See footnotes *b* and *c* in Table I.

dominantly in an N-protonated form, so that the best leaving group will be amine and not water. In addition an analogy exists with the hydrolysis of imidate esters where a similar tetrahedral intermediate is formed and also decomposes in acid mainly by expulsion of amine.[10]

In conclusion the results obtained here provide compelling evidence for the intermediacy of tetrahedral species in the acid-catalyzed hydrolysis of benzamide, and there appears to be no reason to assign this reaction to a mechanistic category different from that of other hydrolysis reactions of carboxylic acid derivatives.

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(7) By extraction with methylene chloride, followed by washing with Na_2CO_3, evaporation of the solvent and recrystallization (chloroform–petroleum ether).
(8) The formula employed neglects contributions from the isotopes of the other elements. Although this means that the ^{18}O values are slightly in error, their trend remains the same and the error introduced in k_E is very small.
(9) In this experiment, unlabeled benzoic acid (1.0 g) and ammonium sulfate (0.5 g) were dissolved in 5.9% H_2SO_4, and the solution was heated at 85° overnight. Upon cooling, labeled benzamide (0.02 g) was added and a sample of benzamide recovered by the usual procedure.[7] This showed no difference in the 121/123 ratio from that of the original benzamide (0.1011 and 0.1010).
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The Pyridine Route to Optically Active Estrone and 19-Norsteroids

Sir:

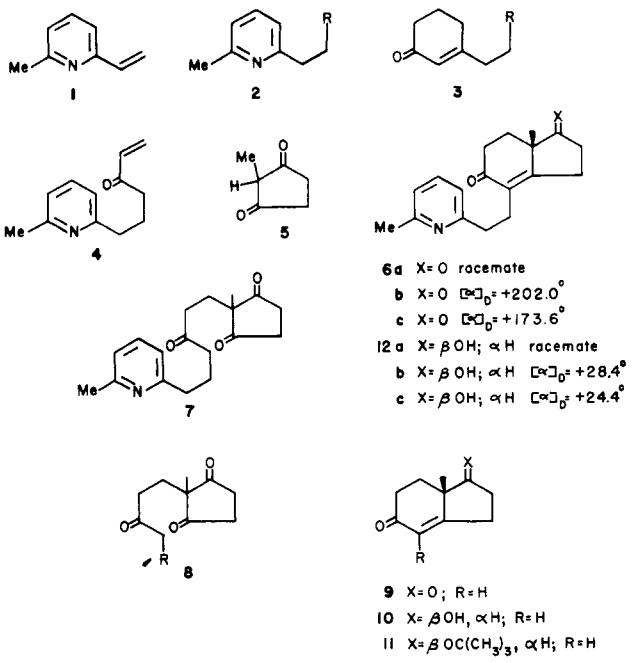
The use of the bis annelating agent **1** has been previously described.[1-3] System **2** may be elaborated after reaction of **1** with a nucleophilic equivalent of R. Such systems are convertable by reductive hydrolytic cyclization into cyclohexenones such as **3**. Alternatively, compound **4** may be employed as a tris annelating agent.[4a] For instance, reaction of **4** with **5**[5a] under acidic catalysis gives racemic hydrindenedione (**6a**). Of course, the use of **6a** in a total synthesis of estrone would require recourse to resolution if optically active product is to be produced.[5b]

Alternatively compound **7**[4a] can be produced in high yield[4b] from the reaction of **4** and **5** in ethyl acetate containing triethylamine. The prochiral nature of **7** lends itself to the possibility of asymmetrically induced aldolization under the influence of L-amino acids. This highly original concept had been demonstrated and used with great success by Hajos[6a,b] and Eder[7] in the synthesis of the parent hydrindenedione **9** (R = H) from the oxobutyl system **8** (R = H). In pursuing this approach, we were not unmindful of previous reports,[7] which indicated a sharp deterioration of asymmetric specificity in the transformation of **8** → **9**, as R becomes alkyl.

We report the total synthesis of optically active estrone and the commercially important 19-norsteroids involving, as a key step, the conversion of prochiral **7** → *optically active* **6** *with high asymmetric specificity via an aromatic amino acid.*

The sign and value of $[\alpha]_D$ for the pure 13*S* antipode, **6b**, were obtained as follows. Reduction of the pure 13*S* enantiomer, **9**,[6,7] with sodium borohydride gave **10**. The latter was converted to **11** $[\alpha]_D$ +94.6° (benzene, *c* 1%) according to Hajos.[8] Picolyethylation of **11** (1 equiv of enone **1**; 1 equiv of potassium *tert*-amyl oxide–*tert*-amyl alcohol; 2 equiv of **1**; reflux 12 hr) followed by cleavage of the *tert*-butyl ether (HCl–EtOH–H_2O; reflux 45 min) gave **12b** $[\alpha]_D$ +28.4° (benzene, *c* 1%), in 36% yield. Jones oxidation of **12b** gave optically pure **6b** $[\alpha]_D$ +202.0° (benzene, *c* 1%).

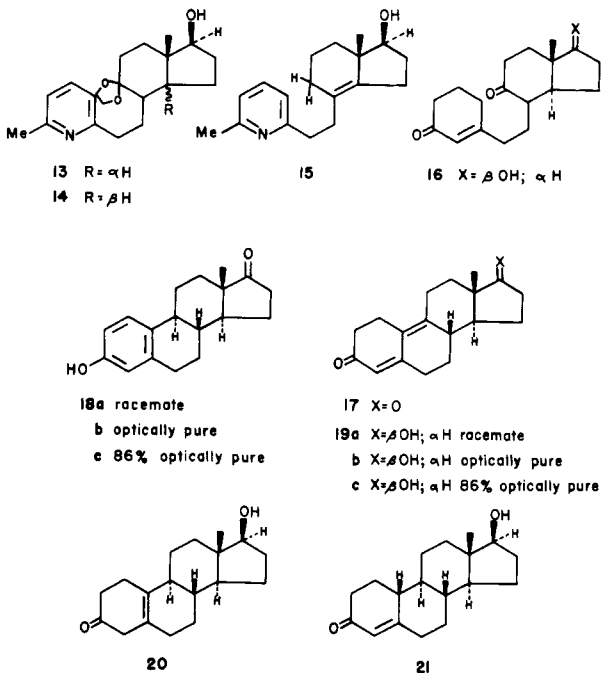
Attempted cyclization of **7** under the influence of L-proline using the conditions of either Hajos[6] or Eder[7] gave disappointing results in terms of optical specificity. Fortunately, it was found that reaction of **7** with L-phenylalanine under conditions similar to those of Eder[7] (1 equiv of trione; 1.2 equiv of amino acid; 0.5 equiv of $HClO_4$ in acetonitrile 2.7 ml/mmol of trione; reflux 40 hr) gave **6c** $[\alpha]_D$ +173.6° (i.e., 86% optical purity) in 82% chemical yield from **4**.[9] We now describe the conversion of **6c** into estrone and 19-norsteroids. Separations of the c series (86% optically pure) into the optically pure (b compounds) and largely racemic (a compounds) was achieved with nearly perfect efficiency in one recrystallization at the tetracyclic stages (vide infra).



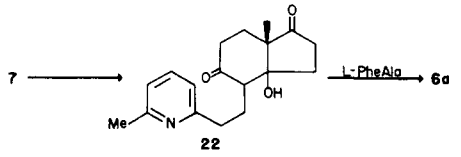
Selective reduction of **6c** with sodium borohydride–ethanol gave **12c**[10a] $[\alpha]_D$ 24.4° (*c* 1% benzene; i.e., 86% optically pure) in 88% yield. Compound **12c** was reduced under conditions (90% EtOH; 0.1 equiv of $HClO_4$; 3 atm of Pd–C) similar to those of McKenzie,[11,12] and the resultant product was treated with ethylene glycol–toluene–*p*-TsOH, under reflux for 36 hr. Chromatography on silica gel[13] gave compounds **13**[10] and **14**[10] in yields of 45 and 17%, respectively. Unfortunately, the hydrogenolysis product, **15**[10a] was also obtained in 21% yield. While the level of stereoselectivity (trans:cis = 2.6:1) is in keeping with expectations for catalytic reduction of this type of system,[11,14-16] the serious competition from hydrogenolysis does not have precedent.

Reductive hydrolysis and cyclization ((i) 1.1 equiv of Na–NH_3–EtOH–Et_2O); (ii) NaOH–EtOH–H_2O, room temperature, 2,5 hr) of compound **13** followed by deketalization during acid work-up, gave crude **16**[10a] which served as a common intermediate for estrone (**18b**) and 19-nor-steroids (**19b, 20,** and **21**). Jones oxidation of **16** was followed by cyclodehydration (*p*-TsOH; glacial HOAc, 100°, 1.5 hr). The crude, dienedione **17**[10] was isomerized with acetyl bromide–acetic acid anhydride[2,17] and the phenolic (estrone) acetate hydrolyzed (potassium carbonate–aqueous methanol). Chromatography gave a 48% yield (from **13**) of crystalline estrone (**18c**): $[\alpha]_D$ +138.4 (*c* 1% dioxane); authentic sample of **18b**, $[\alpha]_D$ +161.0° (same conditions). A single recrystallization (Et_2O–MeOH) gave a 39% yield (from **12**) of totally synthetic estrone (**18b**): $[\alpha]_D$ +160.0°, mp 254–255°, authentic sample 255–256° (undepressed). From the mother liquors there was obtained a 9% yield of virtually racemic estrone (**18a**) $[\alpha]_D$ +7.25°. *The yield of optically pure estrone from monocyclic* ***5*** *is 13%.*

In a separate series, compound **16** was directly cyclized (*p*-TsOH, glacial HOAc) and the tetracyclic acetate thus produced was cleaved (KOH–MeOH). Chromatography afforded a 68% yield (from **12**) of crystalline hydroxydienone (**19c**):[10a] $[\alpha]_D$ −249.5° (*c* 1%, $CHCl_3$) lit.[18] $[\alpha]_D$ for **19b** −290.2° (same conditions). One recrystallization (Et_2O–MeOH) separated **19c**[10] into a 56% yield (from **12**) of optically pure **19b** $[\alpha]_D$ −290.0°; mp 188–190°, lit.[18] 187–189°) and a 12% yield of virtually racemic **19a** ($[\alpha]_D$ −10.7°). *The yield of optically pure* ***19b*** *which has itself been reported*[18] *to possess powerful antifertility activity, is 18% from* ***5.*** Compound **18b** was converted[19] (83%) by the action of sodium ammonia–ethanol into **20,** the well-known $\Delta^{5,10}$ tautomer of 19-nortestosterone[20] (**21**). The conversion of **20** → **21** has been achieved[21] (MeOH–HCl) in virtually quantitative yield.



In an attempt to obtain analytically pure trione **7**, virtually pure material was submitted to silica gel chromatography. Rather than pure **7**, there was obtained a 48% yield of the racemic β-aldol **22,** mp 132–134°.[10] It is interesting to note that reaction of **22** with L-phenylalanine (under the same conditions used for conversion of **7** → **6c**) gave **6a.** It can be concluded that β-aldol **22** is not in equilibrium with trione **7** since, to the extent that trione **7** were produced under the reaction conditions, it would be diverted by the L-phenylalanine to give **6c.**



The above reactions constitute a simple route to the optically active, versatile, dienone **19** and to a variety of biologically important steroids.[20] Were the inefficiency of the conversion of **12** → **13** to be overcome, this steroid synthesis could well compete with any of the existing processes[22,23] in terms of availability of starting materials, simplicity of reagents, ease of operations and optical specificity.[24]

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Siloxene as a Unique Catalyst for Structural Isomerization of *n*-Butene

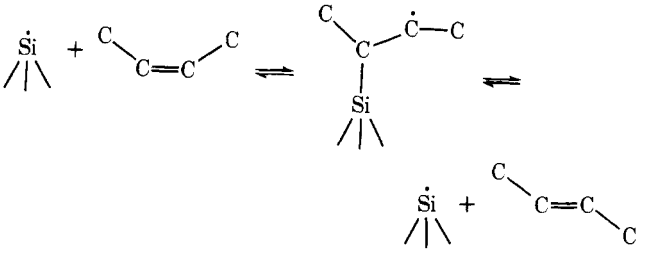
Sir:

Siloxene $(Si_6O_3H_6)_n$ is a unique solid with high surface area and contains reactive Si–H groups.[1-4] The reactivity of the Si–H groups of siloxene toward various substances has been studied in some detail,[2-4] but its potentiality as a heterogeneous catalyst has never been explored. We have used siloxene as the catalyst for isomerization of *n*-butenes and found it has a unique characteristic for the reaction. It catalyzes the cis–trans isomerization of butene-2, but it has no activity for double bond migration, i.e., 1-butene to 2-butene or vice versa.

Siloxene was prepared by the reaction of calcium silicide with hydrochloric acid and water in 1-propanol essentially according to the method described by Kautsky and Pfleger.[2] Calcium silicide (2.5 g) was added to the mixture of 300 ml of 1-propanol, 55 ml of water, and 10 ml of concentrated hydrochloric acid at 0°, and the system was continuously agitated in the dark under a nitrogen atmosphere. After 50–70 hr, the product was filtered under nitrogen and washed with 1-propanol and then with ethyl ether at 0°. The solid thus shows infrared bands due to Si–H stretching at 2120 and 2250 cm^{-1} and has a surface area of 560 m^2/g. Siloxene was then transferred to a reaction vessel of 44 ml and evacuated at 200° for 5 hr. This treatment caused a slight loss in the intensity of the 2120-cm^{-1} band. Then, the system was maintained at the reaction temperature and butene was introduced. After 1 hr, the product distribution was analyzed by gas chromatography. The results are summarized in Table I. It is clearly seen that siloxene has a catalytic activity for cis–trans isomerization, but no activity for double bond migration of butenes. The presence of hydrogen in the system does not alter the situation.

In the case of catalysis by metals or metal oxides, it is the usual observation that structural isomerization of butene-2 accompanies double bond migration. The unusual nature of the catalysis by siloxene seems to be explained by a free radical mechanism. Actually, in gas phase catalysis, free radicals such as I,[5,6] RS,[7] NO_2,[8] or NO[9] are known to promote structural isomerization without enhancing double bond migration.

We propose the following mechanism for the structural isomerization of butene-2, assuming the presence of hydrogen deficient silicon sites.



Though the presence of the hydrogen deficient sites could not be confirmed easily, the following information was obtained concerning the free radical character of the siloxene. The solid exhibits an ESR signal at $g = 2.004$ with the spin number of $1.3 \times 10^{15}/g$. Adsorption of *cis*-butene-2 does not alter the ESR spectrum, indicating that the above equilibrium much favors the side of the dissociated form at room temperature. However, after 50 $mmHg$ of sulfur dioxide, which has much higher electron affinity than butene,

Table I. Product Distribution of Butene over Siloxene

Starting butene	Temp (°C)	Weight of catalyst (mg)	Butene pressure (mmHg)	Hydrogen pressure (mmHg)	Product distribution (%)			
					cis-C_4H_8-2	*trans*-C_4H_8-2	C_4H_8-1	C_4H_{10}
cis-Butene-2	80	88	203	0	83	17	0	0
cis-Butene-2	80	184	146	60	88	12	0	0
cis-Butene-2	100	17	253	128	71	28	1	0
cis-Butene-2	150	35	106	52	63	36	0	1
Butene-1	100	77	388	0	0	0	100	0
Butene-1	100	90	257	106	0	0	100	0