δ 7.90 (m, 4), 7.30 (m, 6), 3.30 (s, 4); mass spectrum (70 eV) *m/e* 238 (68, molecular ion), 105 (100).

When the mixture of olefin **2** and epoxide **4** was worked up under acidic conditions, new absorptions in the nmr (CCl_4) at δ 1.50–1.30 (m) and the ir (CCl_4) at 1674 cm^{-1} were observed. These were presumably due to the rearrangement[2a] of epoxide **4** to 1-benzoyl-1-phenylcyclopropane [lit.[18] ir (CCl_4) 1675 cm^{-1}; nmr (CCl_4) 7.4 (m, 10), 1.40 (apparent A_2B_2 m, 4)].

1,2-Diphenylcyclopentene (3) with *m*-Chloroperbenzoic Acid. A solution of 220 mg (1.00 mmol) of cyclopentene **3** in 3.0 ml of CCl_4 was treated with 180 mg (*ca.* 1.00 mmol) of *m*-chloroperbenzoic acid for 36 hr at 0°. The resulting mixture was filtered, washed with 10% aqueous $NaHCO_3$, dried over anhydrous K_2CO_3, and concentrated on a rotary evaporator. The crude product thus obtained was analyzed: ir (CCl_4) 1600–1750 cm^{-1} (transparent); nmr (CCl_4) δ 6.88 (s, 10) 2.10 (apparent broad d, J = 6.0 Hz, 4), 1.65 (apparent broad q, J = 5.0 Hz, 2); mass spectrum (70 eV) *m/e* 236 (molecular ion).

Nmr Method of Determining Rate Constants. A stock solution was prepared of cyclopropene **1** (*ca.* 0.08 *M*) and cyclobutene **2** (*ca.* 0.04 *M*) with CH_2Cl_2 and $PhCH_3$ as internal standards. The solution was analyzed to determine the initial (olefin/internal standard) integration ratios. The nmr tube was then cooled to 0° and an equal volume of *ca.* 0.075 *M* peracid stock solution was added. The tube was stored at 0° for 12–20 hr and then analyzed by nmr to determine the final (olefin/internal standard) integration ratios.

Each peak was integrated 8–12 times with the average integration value used in subsequent calculations. The relative rates were determined from the following equation[13]

$$\frac{k(1)}{k(2)} = \frac{\ln (\text{fraction 1 remaining})}{\ln (\text{fraction 2 remaining})}$$

where $k(1)/k(2)$ is the ratio of the second-order rate constants for olefins **1** and **2**, respectively, and the fraction **1** (or **2**) remaining at time t is the final time ratio (olefin$_t$/internal standard) divided by the initial ratio (olefin$_0$/internal standard).

Iodometric Method of Determining Rate Constants. A magnetically stirred solution containing known amounts of olefin and peracid was prepared at 0° in a 10-ml volumetric flask. A short time thereafter (1–2 min to allow mixing and thermal equilibration), a 1-ml aliquot was withdrawn with a calibrated (at 0°) syringe which was cooled to 0°. The aliquot was added to a solution of 1 ml of acetic acid and 1 ml of 10% aqueous KI. The liberated iodine was titrated with $Na_2S_2O_3$ (*ca.* 1×10^{-3}–1×10^{-4} *M*) which had been previously normalized with KIO_3. A stopwatch was started during the addition of the reaction solution to the acetic acid–KI solution. The peracid loss during the initial 1–2-min period from the prepared concentration was calculated and an appropriate correction was made in the time zero olefin concentration used in subsequent calculations.

The reaction solution was subsequently monitored at recorded times by withdrawing 0.5- or 1.0-ml aliquots with a chilled (0°), calibrated syringe. Ice was replaced in the cooling bath to maintain a temperature of 0°. The reaction solution was analyzed repeatedly until 20–60% peracid loss was noted. Usually, several (5–12) samples were analyzed at various times for each run.

The data were analyzed first by a least-squares program on a Hewlett-Packard Model 9820-A advanced programming calculator. The normal second-order rate equation was rearranged into terms of observables, for conditions of initial olefin concentration greater than initial peracid concentration

$$(1/A_\infty) \ln (2V_aA_\infty/M\text{ml}_t + 1) = (1/A_\infty) \ln (2V_aA_\infty/M\text{ml}_0 + 1) + k_2t$$

where A_∞ is the difference in the time zero concentration of olefins and peracid, respectively, V_a is the volume in milliliters of the reaction aliquot analyzed, M is the molarity of the thiosulfate stock solution, and ml$_t$ and ml$_0$ are the volumes of thiosulfate solution at time t and t_0 required to titrate the liberated iodine for the respective samples.

Subsequently, the data were analyzed with a nonlinear iterative least-squares computer program[19] on an IBM 360/65 computer. This program accounts for random errors present in all observables. In all cases, the data gave linear plots with the second-order rate equation and the rate constants were invariant over a varying range of initial reactant concentrations.

Acknowledgments. We thank the National Science Foundation and the Merck Co. Foundation for financial support of this work. We also thank the University of Rochester Computing Center for computer time.

Registry No.—**1**, 24168-52-3; **2**, 3306-02-3; **3**, 1485-98-9; **4**, 43187-63-9; **5**, 495-71-6; **6**, 43187-64-0; *m*-chloroperbenzoic acid, 937-14-4; 1,2-diphenyl-2-propen-1-one, 4452-11-3.

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Synthesis of *cis*- and *trans*-1-(3,4-Dimethoxybenzyl)-3,7-dimethyl-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline. Observations on the Mechanism of the Bischler–Napieralski Reaction

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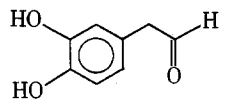
Considerable interest has been expressed recently in the possible contribution that tetrahydroisoquinolines derived endogenously from dopamine and related phenylethylamines and aldehydes such as 3,4-dihydroxyphenylacetaldehyde and acetaldehyde may make to central and peripheral adrenergic mechanisms.[1] As part of our investigations into the metabolism of the hallucinogenic compound 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (**1**),[2] we wish to examine the possible endogenous formation of tetrahydroisoquinolines derived from amine **1** and aldehyde **3**. Such condensation reactions presumably proceed by a Pictet–Spengler cyclization.[3] As has been reported for several drugs containing aromatic OCH_3 groups,[4] we have detected both the 2-O- and 5-O-demethylated compounds **2a** and **2b**, respectively, in the urine of rabbits administered amine **1** intraperitoneally.[5] Since Pictet–Spengler cyclizations readily occur with phenylethylamines ac-

tivated by a 3-hydroxy substituent,[3] tetrahydroisoquinoline formation involving an aminophenol derived metabolically from compound 1 appears possible.



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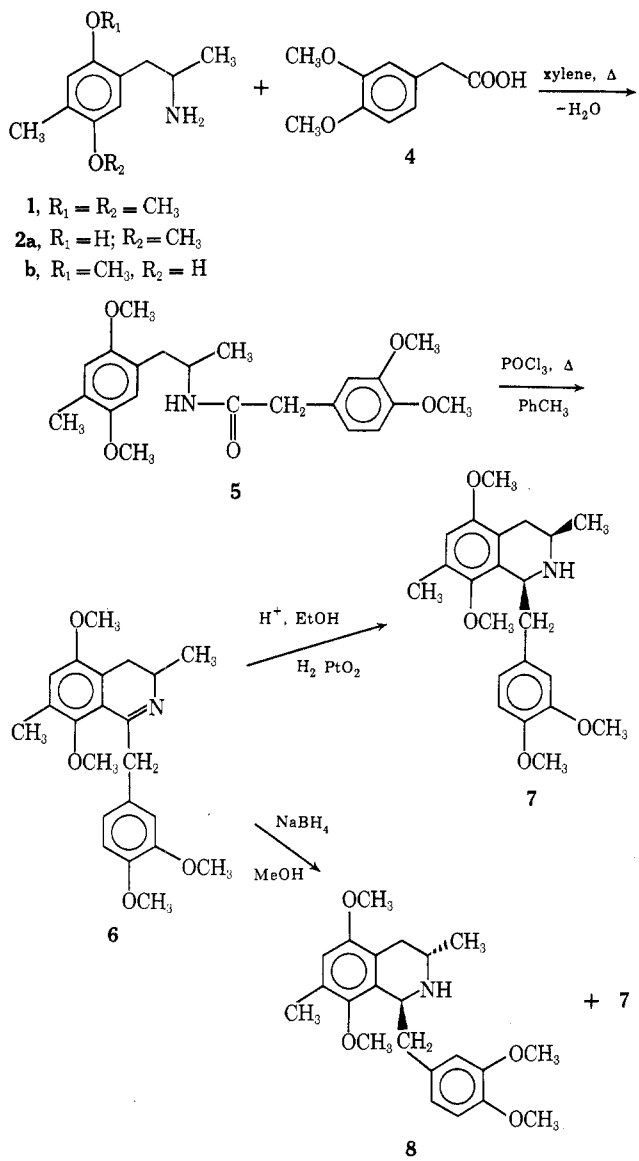
As an aid in our efforts to characterize possible tetrahydroisoquinoline formation, we have undertaken the synthesis of the title compounds 7 and 8 according to the sequence shown in Scheme I (relative configurations implied only). In our metabolism work-up, we plan to submit the aminophenol fractions to diazomethane methylation to convert phenolic tetrahydroisoquinolines to 7 and/or 8.

Scheme I

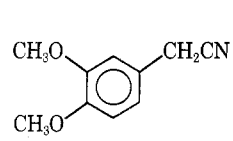


1, $R_1 = R_2 = CH_3$
2a, $R_1 = H$; $R_2 = CH_3$
b, $R_1 = CH_3$, $R_2 = H$

Amide 5 was prepared directly from amine 1 and 3,4-dimethoxyphenylacetic acid (4) in xylene, with azeotropic removal of water.[6] Cyclization of 5 to the 3,4-dihydroisoquinoline 6 in the Bischler-Napieralski fashion[7] was achieved in 56.6% yield in refluxing toluene with phosphorus oxychloride following a modified literature procedure.[8] Dihydroisoquinoline 6 was isolated as the crude base and was not further purified. Attempts to prepare its hydrochloride failed and therefore it was characterized as its picrate derivative. The structure of 6 was confirmed by its electron impact mass spectrum (eims), which showed an appreciable molecular ion m/e 369 (65%). Other abundant ions in the spectrum were at m/e 368 (74%, M − H), 354, (68%), M − CH_3), 338 (41%), 218 (65%, M − benzyl − substituent), and 180 (100%). Furthermore, the chemical ionization mass spectrum (cims)[9] of 6 showed a parent ion at m/e 370 (100%, MH^+).

The products of the Bischler-Napieralski cyclization included a number of neutral compounds in addition to the base 6. The neutral compounds were divided into a hexane-soluble and a hexane-insoluble fraction. The hexane-insoluble material was shown to be 3,4-dimethoxyphenylacetonitrile (9, 26% yield) by comparison of its melting point and ir, nmr, and mass spectra to those of an authentic sample. The hexane-soluble fraction was distilled to give a small amount of material boiling at 65–76° (0.075 mm), followed by a fraction boiling at 76–84°. Glpc analysis showed that the first fraction contained three major compounds, A, B, and C, and a very small amount of a fourth compound, D. The second fraction contained mostly C, with small amounts of A, B, and D. Redistillation of the second fraction gave pure C (16%) which was identified as 1-(2,5-dimethoxy-4-methylphenyl)-2-chloropropane (10) by elemental analysis and nmr and mass spectra.

Gc-eims of the first fraction gave a spectrum with major ions at m/e 178 (78%) and 163 (100%) for compound A. High-resolution cims of A gave an ion of mass 179 (MH^+) corresponding to $C_{11}H_{15}O_2$. These results suggested that A was 2,6-dimethyl-5-methoxy-2,3-dihydrobenzofuran (11). This assignment was supported by the nmr spectrum of the first fraction containing A as the major component. The spectrum showed the following bands assigned to the dihydrobenzofuran 11: a doublet centered at δ 1.43 ppm (J = 6 Hz, $CHCH_3$); a singlet at δ 2.18 ppm ($ArCH_3$); a multiplet at δ 2.61–3.52 ppm (CH_3CHCH_2); and a multiplet at *ca.* δ 4.6–5.1 ppm ($OCHCH_3$). The aromatic and methoxy protons of A overlapped with those of B and C. The yield of A was *ca.* 2%.



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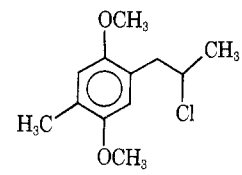

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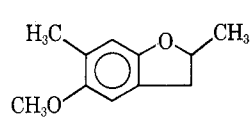

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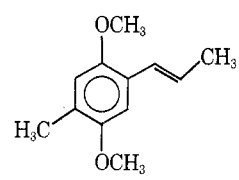
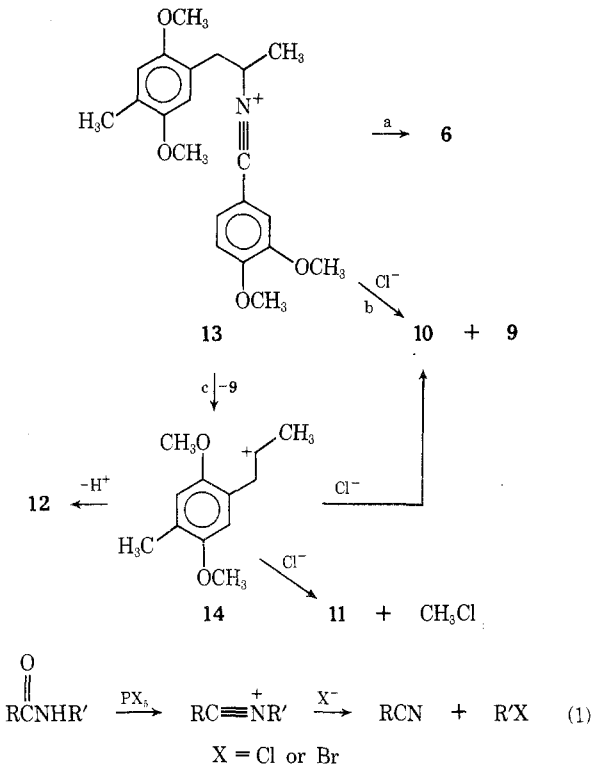


12

Gc-eims of B showed major ions at m/e 192 (100%), 177 (73%), and 146 (31%). High-resolution cims gave an ion at m/e 193 (MH^+) corresponding to $C_{12}H_{17}O_2$. Compound B was tentatively identified at 1-(2,5-dimethoxy-4-methylphenyl)-1-propene (12). The identity of D was not established.

In a recent study on the mechanism of the Bischler-Napieralski reaction, Fodor and coworkers showed[10] that the intermediate preceding the cyclization is a nitrilium ion, species 13 in Scheme II. Furthermore, they proposed that the von Braun degradation of amides[11] also proceeds *via* a nitrilium ion (eq 1).

Scheme II



Several groups have observed the formation of a nitrile (a von Braun product) in Bischler–Napieralski reactions.[12] However, the isolation of chloride **10** represents the first instance of the characterization of an alkyl halide among the products of a Bischler–Napieralski reaction. This finding suggests that the two reactions may indeed converge as proposed by Fodor's group. The von Braun reaction (eq 1) is usually carried out with a phosphorus pentahalide,[11] although thionyl chloride has been used occasionally.[13] Our results suggest that phosphorus oxyhalides may also be used in the degradation of amides. This possibility merits further investigation, since the use of a phosphorus pentahalide results in α-halogenation[14] when the carbon α to the carbonyl bears hydrogen(s). Our isolation of **9** suggests that the use of phosphorus oxyhalides may avoid this complication.

Intermediate **13** may undergo several reactions, as shown in Scheme II. Route a is the Bischler–Napieralski cyclization. Route b yields the nitrile **9** and chloride **10**, *i.e.*, the products of the von Braun degradation[11] of amides. Route c leads to the carbonium ion **14**, which may lose a proton to give **12**, or may cyclize to **11** *via* chloride attack on the 2-methoxy group. Formation of **12** by dehydrohalogenation of **10** cannot be ruled out. The relative importance of routes a, b, and c is influenced by the "nucleophilicity" of the ring and the stability of carbonium ion **14**.

Catalytic hydrogenation of dihydroisoquinoline **6** in acidic ethanol gave a tetrahydroisoquinoline isolated as the hydrochloride in good yield. The eims of this product was dominated by an intense ion at m/e 220, resulting from loss of the 1 substituent, as expected for a 1-benzyl-1,2,3,4-tetrahydroisoquinoline.[15] The molecular ion was not discernible, and all other ions were weak in intensity. The eims gave a strong parent ion at m/e 372 (MH^+, 100%), an ion at m/e 220 (46%), and a fragment at m/e 153 (10%).

The product of the catalytic hydrogenation of **6** behaved as a single compound on four different glpc columns (SE-30, OV-1, OV-17, and OV-25). On the other hand, reduction of **6** with sodium borohydride in methanol gave two bands when chromatographed on OV-1, OV-17, or OV-25. The ratio of the areas under the curves was *ca.* 25:1. Lithium aluminum hydride gave similar results. The retention time of the major product was identical with that of the catalytic hydrogenation product, while the minor product had a longer retention time. The minor product, collected from an OV-17 column, gave, on cims analysis, an MH^+ ion at m/e 372 and fragment ions at m/e 220 (80%) and 153 (30%). Gc–eims analysis of the sodium borohydride products gave identical spectra for the two compounds. It is thus concluded that these two products are the *cis*- and *trans*-tetrahydroisoquinolines **7** and **8**. In view of the mechanism[16] of catalytic hydrogenation, it is felt that the product of the catalytic hydrogenation of **6** is the cis isomer **7**. Clemo and Turnbull prepared[17] several 1,3-disubstituted 1,2,3,4-tetrahydroisoquinolines by catalytic hydrogenation of the corresponding 3,4-dihydro compounds, but did not indicate the stereochemistry. Dyke[18] and his coworkers reduced several 1,3-disubstituted 3,4-dihydroisoquinolinium salts with sodium borohydride, but they too did not comment on the steric course of the reaction. Bailey and DeGrazia recently described[19] the synthesis of *cis*- and *trans*-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline *via* catalytic hydrogenation of the corresponding dihydro compound. The cis:trans ratio obtained was 9:1.

Experimental Section

Boiling points and melting points are uncorrected. Ir spectra were determined using a Perkin-Elmer Model 337 grating spectrophotometer. Nmr spectra were taken on a Varian Associates A-60A spectrometer and chemical shifts are reported in parts per million (δ) downfield relative to TMS as internal standard. Eims were obtained on an AEI MS 12 spectrometer at 50 eV. Gc–eims analyses were performed with the same mass spectrometer interphased with an Infotronics Model 2400 gas chromatograph using glass columns. Cims analyses were obtained using an AEI MS 902 instrument modified for cims and using isobutane (0.7 Torr) as reactant gas. All glpc analyses were performed on a Varian Aerograph 2100 Life Sciences gas chromatograph equipped with a hydrogen flame ionization detector, and using glass columns packed with acid-washed DMCS-treated Chromosorb W coated with a stationary phase as indicated. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz., or the Microanalytical Laboratory of the University of California, Berkeley.

***N*-2-[1-(2,5-Dimethoxy-4-methylphenyl)propyl]-3,4-dimethoxyphenylacetamide (5).** Freshly sublimed homoveratric acid (**4**, 16.7 g, 85 mmol), amine **1**[20] (18.2 g, 87 mmol), and xylene (300 ml) were heated under reflux for 18 hr with azeotropic removal of water using a Dean–Stark trap. The solution was then allowed to cool to room temperature. Hexane (100 ml) was added, and the precipitated product was filtered and washed with hexane. The filtrate and washings were combined and evaporated. The solids thus obtained were combined and recrystallized from isopropyl alcohol–hexane to yield 32.1 g (97%) of **5**: mp 152–153°; nmr ($CDCl_3$) δ 1.16 (d, J = 6 Hz, 3, $CHCH_3$), 2.21 (s, 3, $ArCH_3$), 2.72 d, br, 2, $CHCH_2$), 3.42 (s, 2, $COCH_2$), 3.63 (s, 3, OCH_3), 3.75 (s, 3, OCH_3), 3.80 (s, 3, OCH_3), 3.88 (s, 3, OCH_3), *ca.* 3.8–4.5 (m, 1, CH_2CH), 5.60–6.05 (br, 1, NH), *ca.* 6.50–7.00 (m, 5, aromatic H's); eims (50 eV) m/e (rel intensity) 387 (10.4), 192 (84.2), 177 (6.6), 166 (8.4), 165 (12.3), 151 (24.5), 135 (6.2), 44 (100).

Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.61. Found: C, 68.10; H, 7.30; N, 3.60.

1-(3,4-Dimethoxybenzyl)-3,7-dimethyl-5,8-dimethoxy-3,4-dihydroisoquinoline (6). Amide **5** (25.0 g, 64.5 mmol), toluene (225 ml), and freshly distilled $POCl_3$ (100 ml) were heated at 100° under a nitrogen atmosphere for 2 hr. The solvent and most of the excess $POCl_3$ were then evaporated on a rotary evaporator using water aspiration. The residue was treated with 1 *N* HCl (200 ml) with ice cooling and stirring. The acidic solution was extracted with Et_2O (4 × 100 ml), and the extracts were combined, washed with water (100 ml) and with concentrated $KHCO_3$ solution (100 ml), and dried (Na_2SO_4). This ether solution contained the neutral products. The acidic, aqueous layer was cooled in ice and stirred magnetically under nitrogen while 15% NaOH solution was added dropwise until pH 13. The alkaline solution was extracted with ether (4 × 100 ml), and the combined ether extracts

were dried (K_2CO_3) and evaporated. The resulting thick oil slowly crystallized in the cold to give 13.44 g (56.5%) of crude **6**. The picrate was prepared according to Pasto and Johnson,[21] mp 149–152°.

Anal. Calcd for $C_{28}H_{30}N_4O_{11}$: C, 56.18; H, 5.05; N, 9.36. Found: C, 56.13; H, 5.24; H, 9.18.

The Et_2O solution containing the neutral products was evaporated and the residual oil was triturated with hexane (20 ml). The precipitated solid was filtered and recrystallized from ether–hexane to give 3.0 g (26%) of 3,4-dimethoxyphenyltonitrile (**9**), melting point, ir, nmr, and eims identical with those of an authentic sample. The above hexane filtrate was concentrated and the residue was vacuum distilled to give two fractions as described in the text. Compounds A, B, C and D (fraction 1) were analyzed by glpc on an SE-30 (3%) column at 100° and had retention times of 2.4, 2.8, 7.0, and 4.6 min, respectively. Redistillation of fraction 2 gave pure 1-(2,5-dimethoxy-4-methylphenyl)-2-chloropropane: bp 90° (0.06 mm); nmr ($CDCl_3$) δ 1.47 (d, 3, $CHCH_3$), 2.22 (s, 3, $ArCH_3$), 3.18 (d, 2, $CHCH_2$), 3.74 (s, 3, OCH_3), 3.75 (s, 3, OCH_3), 4.35 (sextet, 1, CH_3CH), 6.68 (s, 2, aromatic H's); mass spectrum (50 eV) *m/3* (rel intensity) 230 (15), 228 (44), 165 (100), 135 (34), 119 (24).

Anal. Calcd for $C_{12}H_{17}ClO_2$: C, 62.99; H, 7.50. Found: C, 63.24; H, 7.52.

***cis*-1-(3,4-Dimethoxybenzyl)-3,7-dimethyl-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (7) Hydrochloride.** Following a published procedure[22] the dihydroisoquinoline (**6**, 1.0 g, 2.7 mmol) was dissolved in EtOH (125 ml), and concentrated HCl (0.22 ml) was added, followed by 0.10 g of PtO_2. The mixture was shaken with hydrogen gas at 27 psi for 17 hr. The catalyst was filtered off and the solvent was removed at reduced pressure. The solid residue was recrystallized from EtOH–Et_2O to give a first crop, 0.76 g, and a second crop, 0.07 g. A sample from the first crop had mp 233° dec; nmr (DMSO-d_6) δ 1.48 (d, 3, $CHCH_3$), 2.30 (s, 3, $ArCH_3$), *ca.* 2.67–3.85 (m, 5, CH_3CHCH_2, $CH_3CHNCHCH_2$), 3.78 [s, 6 $(OCH_3)_2$], 3.80 [s, 6, $(OCH_3)_2$], *ca.* 4.3–4.9 (br, 1, ArCHN), 6.8–7.3 (m, 4, aromatic H's).

Anal. Calcd for $C_{22}H_{30}NO_4Cl$: C, 64.77; H, 7.41; N, 3.44. Found: C, 64.85; H, 7.37; N, 3.62.

Reduction of 6 with Sodium Borohydride. The dihydroisoquinoline **6** (1.0 g, 2.7 mmol) was dissolved in anhydrous MeOH (15 ml) and the solution was stirred under nitrogen. $NaBH_4$ (0.35 g, 7.8 mmol) dissolved in anhydrous MeOH (10 ml) was added in small portions over *ca.* 5 min to the solution of the dihydroisoquinoline. The resulting solution was stirred under a nitrogen atmosphere overnight. The solvent was then removed at water-aspirator pressure and the residual solid was treated with water (20 ml) and heated on a steam bath for 15 min. After cooling, the reaction mixture was extracted with Et_2O (4 × 10 ml) and the combined, dried (K_2CO_3) extracts were evaporated to give a yellow-brown oil. Gc–eims analysis was performed on this product as described in the text.

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Registry No. **1**, 15588-95-1; **4**, 93-40-3; **5**, 49558-61-4; **6**, 49558-62-5; **6** picrate, 49613-56-1; **7**, 49558-63-6; **7** hydrochloride, 49558-64-7; **8**, 49558-65-8; **10**, 49558-66-9; **11**, 49558-67-0; **12**, 49558-68-1.

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The Claisen Rearrangement of *N*-Allylketene *O,N*-Acetals[1a]

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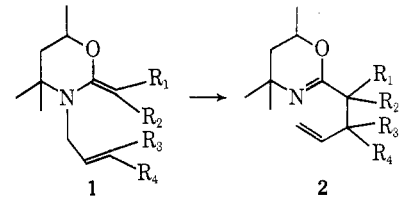
The early development of the vinyl ether–Claisen rearrangement and later modifications of this transformation in the form of the amide–Claisen of Eshenmoser and coworkers[2] and the ortho ester–Claisen of Johnson and coworkers[3] have made this rearrangement a valuable tool for the synthetic chemist. All of the above examples use one of the two required precursors to the 1,5-diene system in large excess. We wish to report a procedure which allows for the economical utilization of both precursors.

Earlier from these laboratories the ester enolate–Claisen was reported.[4] This transformation consisted of the efficient connection of an allylic alcohol and a carboxylic acid *via* ester formation. Subsequent generation and rearrangement of the derived enolate provides a useful route to γ,δ-unsaturated acids.

As a complementary procedure, we have investigated the generation of the ketene *O,N*-acetals **1** and their Claisen-type rearrangement to the dihydro-1,3-oxazines **2**.



Meyers[5] has reported the preparation of a similar ketone *O,N*-acetal **5** from the dihydrooxazine **3** through alkylation with methyl iodide and then treatment with sodium hydride. Our attempts to alkylate these dihydrooxazines in excess allyl bromide or chloride, either at room temperature or reflux, were unsuccessful. The presence of hexamethylphosphoramide (HMPA), dimethylsulfoxide (DMSO), or dimethylformamide (DMF) did not improve these results. It is possible that in a less sterically congested dihydrooxazine direct alkylation would be possible.

A more circuitous route to the ketene *O,N*-acetal **1** was required. This led to the discovery that the oxazinium salts **8** were readily formed from the γ-hydroxy amides **7** by treatment with thionyl chloride in tetrahydrofuran (THF). Neutralization by lithium diisopropylamide in THF led to the ketene *O,N*-acetals **1**. The desired dihydrooxazines **2** were then obtained by heating these ketene *O,N*-acetals **1** in refluxing decalin (190°) for 1 hr.