Registry No.—**1**, 6719-21-7; **2** (R = H), 37842-62-9; **3** (R = CH_3), 34407-36-8; **3** (R = H), 51932-94-6; **4** (R = CH_3), 16115-53-0; *anti*-**4** (R = H), 52019-90-6; *syn*-**4** (R = H), 52019-91-7; **7**, 51932-95-7; **8**, 51932-96-8; **9**, 51932-97-9; **10**, 51932-98-0; **11**, 51932-99-1; **12**, 51933-00-7; **13**, 51933-01-8; **14**, 51933-02-9; **15**, 51933-03-0; benzyloxyamine, 622-33-3; triethyl orthoacetate, 78-39-7; triethyl orthoformate, 122-51-0; benzyloxyamine hydrochloride, 2687-43-6; ethyl formate, 109-94-4; benzoyl isothiocyanate, 532-55-8.

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(21) Although they are eluted close together from the column, the low absorption of 9-hydroxyxanthine and the very high absorption of 8-methylmercaptoxanthine at 290 nm permit a recognition of as little as 1% of the latter.

1,3-Bridged Aromatic Systems. XI. Stereochemistry of Reactions of Heterocyclic *N*-Oxides with Acetic Anhydride, Acetyl Chloride, and *p*-Toluenesulfonyl Chloride[1,2]

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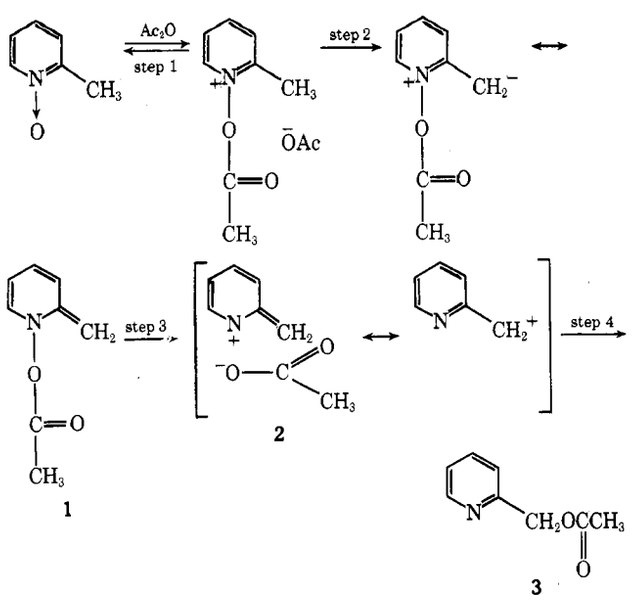
Reaction of the deuterium-labeled *N*-oxide **4** with acetic anhydride and acetyl chloride is highly stereospecific in that abstraction of syn deuterium leads to syn acetate **5**, while abstraction of anti hydrogen leads to anti acetate **6**; anhydro base **8**, in which the acetate function can rotate about the N–O axis, cannot, therefore, be an intermediate in these reactions. In reactions with acetyl chloride a bimolecular component of reaction diverts significant quantities of intermediate normally leading to anti acetate **6** to anti chloride **10**; the latter retains 95% of syn-deuterium label. Reaction of the unlabeled *N*-oxide of **4** with acetic anhydride-^{18}O shows that both syn and anti acetates are formed both by intramolecular transfer of *N*-acetate to the benzylic carbon atom (78.8 and 73.9%, respectively) and by a process involving return of external acetate (21.2 and 26.1%, respectively). Distribution of ^{18}O label in both the CO and C=O functions of derived acetates has been determined.

The mechanism of reaction of alkylpyridine *N*-oxides with acid anhydrides (Scheme I) and acid halides has been studied in great detail, and reviewed.[3] In reactions leading to substitution at the α-carbon atom it is generally thought that (1) step 1 is reversible,[4] (2) step 2 is generally rate determining,[4] (3) anhydro base (1) is an intermediate,[5] (4) step 3 involves heterolytic cleavage of the N–O bond (**2**),[6] and (5) step 4 is intramolecular in that it does not involve capture of external acetate.[4b,c,7]

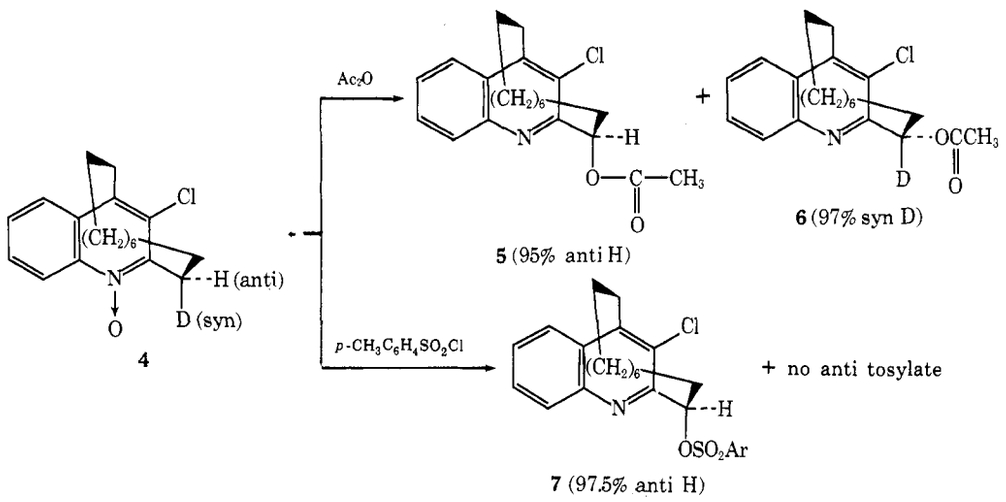
The recent availability of syn-deuterium labeled **4**[2] has provided an opportunity to consider the stereochemical aspects of such reaction for the first time. The reaction of **4** with acetic anhydride is summarized in Scheme II.

Reaction of **4** with acetic anhydride gives syn and anti-acetates **5** and **6** in the ratio of 1:4 as compared to a ratio of 1:1.1 when unlabeled[8] **4** is employed. This isotope effect is consistent with previous observations that proton removal (step 2, Scheme I) is rate determining.[4] What was not anticipated was the stereospecificity observed; syn acetate **5** was formed almost exclusively (95%) by removal of deuterium, while anti acetate **6** was formed almost exclusively by removal of anti hydrogen (97%). Reaction of **4** with *p*-toluenesulfonyl chloride led exclusively to syn tosylate, as pre-

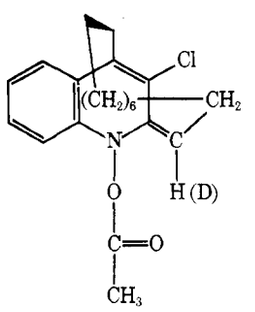
Scheme I



Scheme II



viously reported,[9] and the product was formed almost exclusively (97.5%) by removal of syn deuterium. These results clearly preclude a common intermediate in these reactions such as the anhydro base **8** in which the acetate function can rotate about the N–O bond.



8

Results of our study of the reaction of **4**[2] with acetyl chloride are summarized in Scheme III. Since syn and anti acetates **5** and **6** are not converted to chlorides by prolonged treatment with hot acetyl chloride,[10] formation of chlorides **9** and **10** established an intermolecular component of reaction in collapse of intermediates (type **1** and/or **2**) to products.

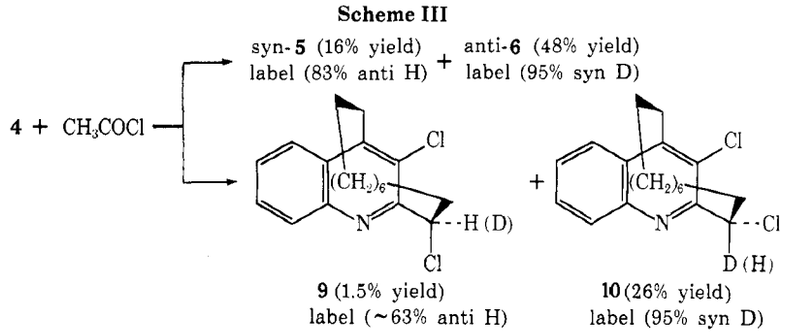
When reaction of unlabeled **4** was carried out in acetic anhydride saturated with tetramethylammonium chloride, no syn or anti chlorides (**9** and **10**) were formed. It was concluded, therefore, that the intermolecular component of reaction probably occurs rapidly from intermediates derived from the ion pair **11** without appreciable intervention by external nucleophile.

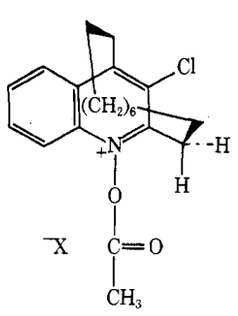
The results summarized in Scheme III are consistent with those observed with acetic anhydride in that syn acetate **6** is formed largely by removal of syn deuterium while anti acetate **7** is formed almost exclusively by removal of anti hydrogen. The total amounts of syn products (**5** + **9**) and anti products (**6** + **10**) are comparable with those formed with acetic anhydride; however, it is apparent that the intermediate(s) leading to labeled anti acetate is significantly diverted to anti chloride **10**.

Examination of the reaction of unlabeled **4** with symmetrically labeled acetic anhydride-^{18}O (95.5% ^{18}O) furnished additional information[7] relative to this reaction. The products are summarized in Scheme IV. The syn and anti acetates were separated by liquid chromatography; the ^{18}O label was determined by mass spectrometry. Distribution of label in products was simplified since, in addition to the parent ion (which gave total ^{18}O label), these acetates fragmented as illustrated in Scheme V (ketene formation is common for aromatic acetates[11]), which permitted definition of label in the alcohol oxygen as well as the carbonyl oxygen.

Two conclusions are apparent from the ^{18}O-labeling

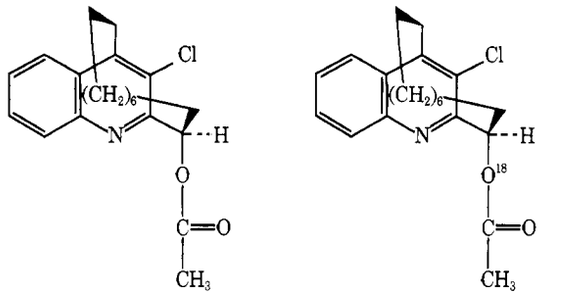
Scheme III



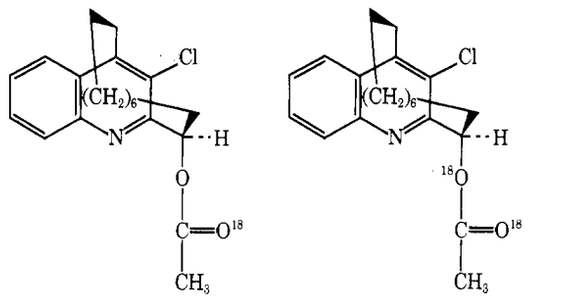


11

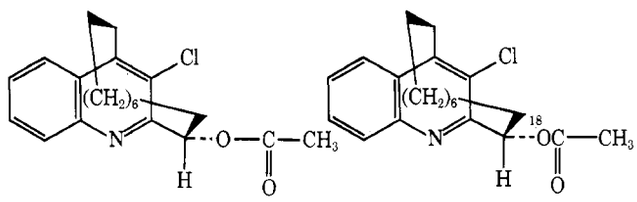
Scheme IV



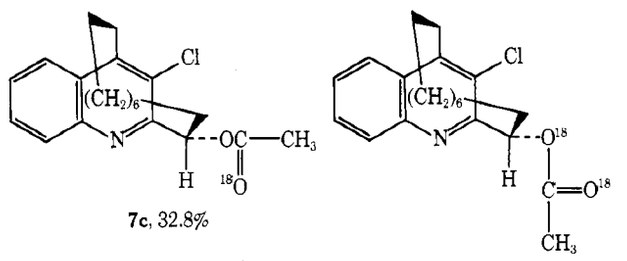
6a, 4.3% **6b**, 24.3%



6c, 51.3% **6d**, 20.1%

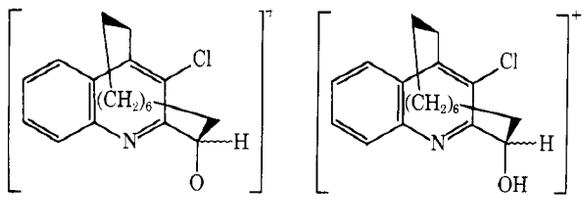


7a, 4.1% **7b**, 38.5%



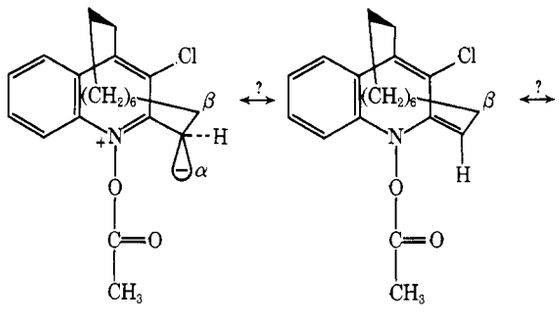
7c, 32.8% **7d**, 24.6%

Scheme V

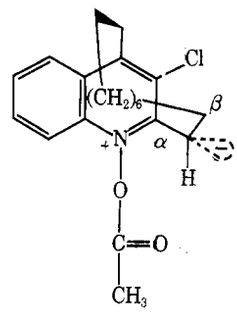


12, *m/e* 316 **13**, *m/e* 317 + $CH_2{=}C{=}O$

studies: (1) Unlike reaction of 2-picoline *N*-oxide with labeled acetic anhydride which involves only intramolecular transfer[7] of acetate (from 1), formation of **6d** and **7d** implies that the reaction of **4** with acetic anhydride involves only ~78.8% intramolecular transfer in formation of the syn acetate **6** and ~73.9 intramolecular transfer[12] in formation of anti acetate **7** from intermediates such as **14a** and **14c.** In addition there is a competing reaction leading to acetates (21.2 and 26.1%, respectively) which involves return of ^{18}O doubly labeled acetate.[12,13] When a sample of a mixture of unlabeled **5a** and **6a** was heated (7.5 hr) with symmetrically labeled acetic anhydride-^{18}O, there was no



14a **14b**

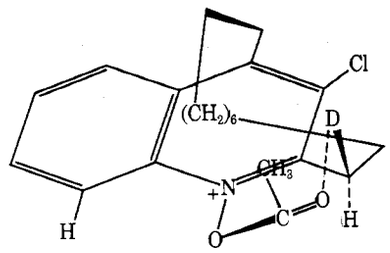


14c

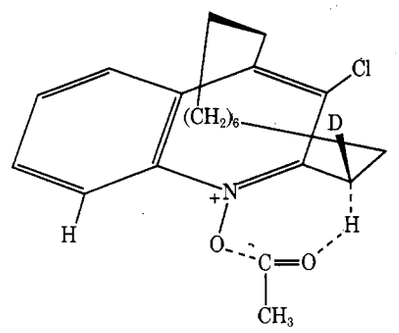
incorporation of ^{18}O in recovered **5a** or **6a.** Thus, it would appear that dilabeled acetates **6d** and **7d** are primary reaction products, which supports the intermolecular return of external acetate (~25%) with acetic anhydride. This result is consistent with the intermolecular component with acetyl chloride leading to halides.[14]

The second observation is that in the intramolecular transfer of acetate leading to syn acetate **6,** the oxygen atom attached to the original *N*-oxide becomes preferentially attached to the benzylic carbon atom in product (ratio of **6c/6b** 2.1). In the intramolecular transfer reaction leading to anti acetate **7** there is more nearly complete scrambling of the oxygen atoms (ratio of **7b/6c** 1.1). The distribution of ^{18}O label in anti acetate is nearly identical with that observed by Oae[7b] for reaction of quinaldine *N*-oxide with labeled aceetic anhydride. By similar studies of ^{18}O-label distribution in products derived from 2-picoline *N*-oxide and 2,6-lutidine *N*-oxide, Oae[4c] has provided strong support for the importance of conformational preference of rotation about the N–O bond in the intermediate **1** (Scheme I) on distribution of ^{18}O label in products.

While we are not able at this time to conclusively explain these results, we have no reason to question intermediates of type **14a** and **14c** and the conclusion that such intermediates collapse to products with retention of configuration at the α-carbon atom. Whether there is any contribution from an anhydro base structure (**14b**) may, in fact, be irrelevant to the stereochemistry of products. Inspection of models (Stuart–Briebgleb) shows that there may be two conformational isomers, **14a** (acetate up relative to the aromatic ring) and **14c** (acetate down relative to the aromatic ring), which are derived from two conformational stereomers of the assumed salts **15u** and **15d.** Presumably **15u** and **15d** could interconvert chemically by reversibility to *N*-oxide and CH_3COX. Inspection of such models show, however, that **15u** and **15d** probably cannot eequilibrate by simple rotation about the N–O bond. Furthermore, if the β-carbon atom (labeled β in **14** and **15**) is conformationally as near to coplanarity as possible with the aromatic ring (a requisite for maximum interaction of the type **14a** ↔ **14b**), these models show that the syn proton in **15u** can be in close proximity to the *N*-oxide carbonyl function while in **15d** the *N*-oxide carbonyl group has access to the anti proton. Anchimeric assistance by the *N*-acetate group during



15u



15d

proton abstraction may, therefore, provide rational for the observation that removal of syn proton leads to syn acetate while removal of anti proton leads to anti acetate. The observation that reaction of unlabeled 4 with acetic anhydride saturated with sodium acetate causes no change in the ratio of syn to anti acetate is consistent with such anchimeric assistance. The importance of N-acetate conformational isomers and their effect on label product distribution has already been noted.[4b,c,7b]

In this model the zwitterion intermediate corresponding to 14a (whether ultimately going to cationic, radical, or anhydro base intermediates) leading to syn acetate has the N-acetate function (and presumably the acetic acid being formed) up relative to the α carbon. Preferential migration of ^{16}O to carbon would be indicative of steric constraint of the migrating acetyl group, caused by bridge methylene, which prevents the two oxygen atoms from being totally equivalent during the rapid collapse to products. Similarly, the intermediate zwitterion 14c may have the nucleophile(s) down relative to the α-carbon atom, and thus lead to anti products. Lack of preference for migration of N oxygen to the benzylic carbon leading to anti acetate suggests that, in this case, the oxygen atoms of the mmigrating N-acetate group are less constrained by the bridge methylene groups. This is consistent with Oae's[7b] interpretation for results with quinaldine N-oxide which is a limiting case since there is no bridge for interaction. In this regard, attention should also be called to the work of Koenig[8] who has suggested a two-electron transfer process for decomposition of the zwitterion through σ overlap of the α and 3-carbon atoms; symmetry considerations make it clear that a planar transition state for the heterocyclic cleavage of the N–OAc bond is unlikely. Our stereochemical results are not inconsistent with this interpretation.

Attempts to confirm the presence of two salts of type **15d** and **15u** by isolation of isomeric acetyl perchlorates, acetyl fluoroborates, and/or acetyl picrates were unsuccessful. Reaction of unlabeled 4 under conditions which readily give such salts[4a,d,e] with 2-picoline lead only to the corresponding protonated salts of unlabeled N-oxide 4.

Experimental Section

Reaction of 4 with Acetic Anhydride. A. Unlabeled 4. A mixture of unlabeled N-oxide 4[9] (500 mg, 1.57 mmol) and acetic anhydride was heated (100°) for 11 hr. Excess acetic anhydride was destroyed by treatment with water; the cooled mixture was extracted with chloroform which was subsequently washed with aqueous bicarbonate. The oil (690 mg) obtained from the chloroform gave a single spot by tlc[15] composed of syn and anti acetate.

The acetates were separated analytically by high pressure liquid chromatography [8 ft × 2.2 mm i.d., Porasil A, eluted with chloroform–petroleum ether[16] (1:1) at 0.75 ml/min; retention time of syn andd anti acetates are 16 min and 22.5 min, respectively], or preparatively [on ⅜ in. × 8 ft (or ¼ in. × 8 ft) columns at 3-ml/min flow rate].

Syn acetate **5**: mp 116–118° from petroleum ether;[17] pmr ($CDCl_3$) δ 8.3–7.3 (m, 4, aromatic H), 6.55 [q (X portion of ABX, $J_{AX} + J_{BX}$ = 14 Hz), 1, $CHOCOCH_3$], 3.80–3.00 (m, 2, benzylic CH_2), 2.7 to −0.3 (m, 16, CH_2), 2.10 (s, 3, CH_3CO_2).

Anal. Calcd for $C_{21}H_{26}ClNO_2$: C, 70.11; H, 7.23; N, 3.88. Found: C, 69.88; H, 7.36; N, 3.82.

Anti acetate 6 (unlabeled): mp 149–150° from petroleum ether[17]–chloroform; pmr ($CDCl_3$) δ 8.2–7.4 (m, 4, aromatic H), 6.08 [q (X portion of ABX, $J_{AX} + J_{BX}$ = 16 Hz, 1, $CHOCOCH_3$)], 3.8–3.3 (m, 2, benzylic CH), 2.7 to −0.3 (m, 16, CH_2), 2.08 (s, 3, CH_3CO_2).

Anal. Calcd for $C_{21}H_{26}ClNO_2$: C, 70.11; H, 7.23; N, 3.88. Found: C, 70.02; H, 7.22; N, 3.88.

The ratio of syn acetate to anti acetate was 1:1.1 as determined by the CH_3CO_2 pmr resonances and by hydrolysis and isolation of the corresponding syn and anti alcohols.[9]

B. Labeled 4.[2] This compound was treated as described above. The ratio of syn acetate to anti acetate was 1:4 (pmr resonances at δ 2.10 and 2.08). Deuterium analyses were concluded on the separated pure syn and anti alcohol obtained[9] from the mixed acetates by hydrolysis.

Syn alcohol: mass spectral analysis[18] showed 94.3% unlabeled alcohol and 5.7% d_1 species; the pmr spectrum ($CDCl_3$) integrated for 0.95 protons at δ 5.35[9] *vs.* 4 aromatic protons at 8.11–7.46 (sample was shaken with D_2O to eliminate hydroxyl proton which overlaps the methine absorption).

Anti alcohol: mass spectral analysis[18] showed 2.6% unlabeled species and 97.4% monodeuterated speciees; the pmr spectrum ($CDCl_3$) showed no methine resonance at δ 5.05.[9]

Reaction of Unlabeled 4 with Acetic Anhydride-^{18}O. The reaction of unlabeled 4 (75.1 mg) with acetic anhydride-^{18}O (250 mg, 95.52% ^{18}O, from Miles Laboratory, Elkhart, Ind.) was carried out (100°, 7.5 hr) essentially as described in A, above; however, labeled solvent (203.3 mg) was recovered by distillation. The mixture of syn and anti acetates (6 and 7) were separated by high pressure liquid chromatography to give pure syn acetate 6 (mp and mmp 115–117°) and pure anti acetate 7 (mp and mmp 152–153°).

The ^{18}O label in the syn and anti acetates 6 and 7 was determined by mass spectral analysis:[18] the molecular ion region (M^+ 359) gave mono- and dilabeled ^{18}O acetate abundances; the molecular ion minus acetyl (**12**, *m/e* 316) and molecular ion minus ketene (**13**, *m/e* 317) gave alcohol oxygen ^{18}O abundances. Possible ^{18}O isotope effects leading to 12 and 13 was assumed to be negligible at high (70 eV) ionization voltages. The calculations were performed by the method of Biemann[18] and the results are shown in Scheme IV.

Reaction of 4 with Acetyl Chloride. A. With Unlabeled 4. Unlabeled N-oxide 4 (300 mg, 0.944 mmol) was heated (60°) with excess acetyl chloride (16 hr); the mixture was cooled; and excess acetyl chloride was destroyed by additions of water. The mixture was extracted with chloroform which was subsequently washed with water and dilute aqueous bicarbonate. The oil obtained from the dried chloroform extract was subjected to preparative tlc[19] to give the following listed in order of increasing R_f.

1. A mixture of pure syn and anti acetates 5 and 6 unlabeled: 220 mg, 65% yield; ratio of syn:anti 1:1.5 by pmr integration of resonance at δ 6.55 (methine H) and 6.08 (methine H) and a ratio of 1:1.45 by integration of resonances at 2.10 and 2.08, respectively, for CH_3CO_2).

2. Anti chloride (unlabeled 10): 70 mg, 22% yield; mp 140–140.5° from chloroform–petroleum ether;[17] pmr ($CDCl_3$) δ 8.25–7.55 (m, 4, aromatic H), 5.18 [q (X portion of ABX system, $J_{AX} + J_{BX}$ = 16 Hz), 1, methine H], 3.86–3.08 (m, 3, benzylic CH_2 plus 1 bridge proton), 2.55 to −0.16 (m, 15, CH_2); mass spectrum *m/e* (rel intensity), M^+ 335 (36), 300 (100), 265 (8.7), 241 (8.9) and 239 (13) (M^+ consistent for two chlorine atoms).

Anal. Calcd for $C_{19}H_{23}Cl_2N$: C, 67.92; H, 6.90; N, 4.17. Found: C, 67.66; H, 6.73; N, 4.20.

Confirmation of the anti configuration was made by noting the pmr shift (1.79 ppm) in methine resonance in going from the free base to the N-oxide by a procedure previously described.[10]

3. Syn chloride (unlabeled **9**): 30 mg, 9.5% yield; mp and mmp[10] 144–145°.

B. With Labeled 4.[2] The reaction was carried out as described in A, above, to give the following.

1. A mixture of pure syn and anti acetates **5** and **6**: 64.3% yield; ratio of syn:anti 1:3.3.

2. Pure anti chloride **10** (25.9% yield): the pmr spectrum showed no methine at δ 5.18 (anti chloride) which confirmed deuterium at the methine carbon; mass spectral analysis showed 95.2% monodeuterated species and 4.8% unlabeled species.

3. Pure syn chloride (1.5% yield): mass spectral analysis showed 63.2% nondeuterated, 32.7% monodeuterated, and 4.1% dideuterated species; the pmr spectrum (using a computer of average transients) gave an apparent triplet centered at δ 5.97 for anti H (**9**) which integrated for ~0.5H *vs.* aromatic H.

Analysis of the label in acetates **5** and **6** was conducted on the pure alcohols obtained by hydrolysis.[9] The syn alcohol (mp and mmp 158–159°)[9] showed by mass spectral analysis 82.7% unlabeled and 17.3% monodeuterated species; the pmr spectrum ($CDCl_3$) showed, subsequent to treatment of a sample with D_2O to eliminate overlapping signals due to OH, a quartet at δ 5.33 (methine H) which integrated to 0.85 H *vs.* the aromatic H. The anti alcohol (mp and mmp 205–206°)[9] showed by mass spectral analysis[18] 97.4% d_1 and 2.6% d_2 species; pmr showed no observable methine resonance.

Reaction of 4 with *p*-toluenesulfonyl chloride was carried out as previously described[10] to give only syn tosylate (m 122–123° from ether);[20] no anti tosylate[10] was detected. The mass spectrum of this product showed 97.5% d_1 and 2.5% d_2 species; pmr ($CDCl_3$) showed one proton (methine H) at δ 6.35.[9]

Registry No.—**4** (unlabeled), 25907-81-7; **4** (labeled), 51820-05-4; *syn*-**5** acetate, 51933-62-1; *syn*-**5** alcohol, 25866-36-8; *anti*-**6** acetate (unlabeled), 52078-88-3; *anti*-**6** acetate (labeled), 52151-91-4; *anti*-**6** alcohol (labeled), 52079-43-3; *syn*-**7** tosylate, 37781-25-2; *syn*-**9**, 37781-27-4; *anti*-**10** (unlabeled), 52019-95-1; *anti*-**10** (labeled), 52078-89-4; acetic anhydride, 108-24-7; acetyl chloride, 75-36-5; *p*-toluenesulfonyl chloride, 98-59-9.

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References and Notes

(1) Supported in part by the National Science Foundation Grant No. GP 35429.
(2) For the preceding article in this series, see W. E. Parham, P. E. Olson, and K. R. Reddy, *J. Org. Chem.*, 2432 (1974).
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(10) W. E. Parham, K. B. Sloan, K. R. Reddy, and P. E. Olson, *J. Org. Chem.*, **38**, 927 (1973).
(11) No chlorides were detected on prolonged (138.5 hr) treatment of syn and anti acetates with refluxing acetyl chloride.
(12) D. Rosenthal, private communication.
(13) Calculations were performed by modified method of S. Oae and coworkers; *cf.* ref 7.
(14) Return of an acetate ion pair associated with the activated complex may be analogous to results obtained with acetyl chloride.
(15) Silica gel, petroleum ether[16]–ether (3:2) as eluent.
(16) Bp 30–60°.
(17) Bp 60–90°.
(18) K. Biemann, "Mass Spectrometry; Organic Chemical Applications," McGraw-Hill, New York, N. Y., 1962, pp 204–250.
(19) Silica gel developed with petroleum ether[16]–ether (85:15).
(20) The syn tosylate melts at 104–107° when crystallized from chloroform–petroleum ether[16] and is analytically pure. When the material is crystallized from ether, the mp is 122–123°.

Hydrolysis of 2-Methoxyfuran[1]

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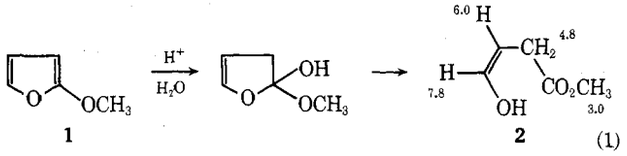
The acid-catalyzed hydrolysis of 2-methoxyfuran in aqueous dimethyl sulfoxide results in the formation of crotonolactone (**4**, 55–65%), methyl succinate semialdehyde (**5**, 16–23%), and methyl *cis*-4-hydroxycrotonate (**6**, 16%), as determined by nmr spectroscopy. These findings are not in agreement with an earlier report[2] and require revision of the proposed mechanism of hydrolysis of 2-methoxyfuran.

The acid-catalyzed hydrolysis of 2-methoxyfuran (**1**) has been reported[2] to yield the enol **2** of the methyl ester of succinic acid semialdehyde, presumably arising *via* a tetrahedral addition intermediate[3] (eq 1). The proposed intermediate is similar in structure to those believed to be formed in many acyl transfer reactions,[4] and in particular to those of ester hydrolysis[5] and formation.[6] It seemed of special interest to determine whether the direction of decomposition of the addition intermediate would be pH dependent, as had been found with the closely related intermediates generated during the lactonization of coumarinic acids,[6] and if so, to measure the partitioning ratio of the different ionic species of the intermediate. While attempting to obtain this information, we have found that the hy-



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