Mechanisms of Cleavage of Heteroaromatic Ethers. III. The Acid-Catalyzed Cleavage of (S)-(+)-2-(1′-Methylheptoxy)pyrimidine[1,2]

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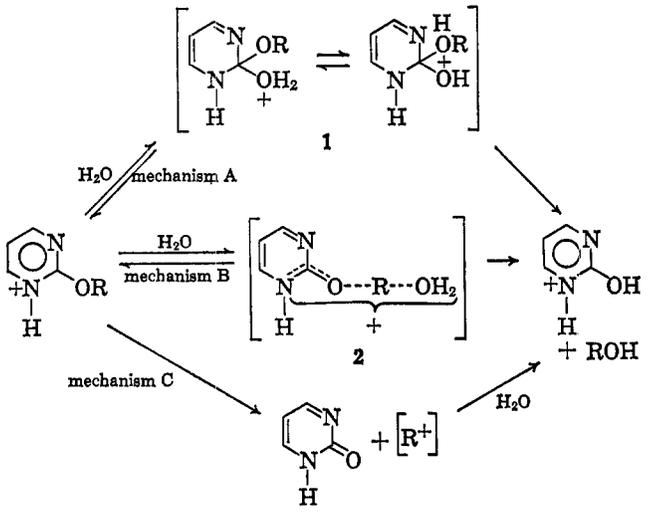
Cleavage of (*S*)-(+)-2-(1′-methylheptoxy)pyrimidine in hydroalcoholic phosphoric acid medium has been shown to proceed *via* an SN1 mechanism involving a 2-octylcarbonium ion.

In the preceding paper of this series[2] three general mechanisms were advanced for the cleavage of 2-alkoxypyrimidines in aqueous acid. These are mechanism A, the typical aromatic nucleophilic displacement, SNAr, which proceeds *via* the bimolecular addition complex, **1**; mechanism B, the synchronous bimolecular nucleophilic displacement reaction, SN2, in which the transition state, **2**, represents the midpoint of the reaction; and mechanism C, the SN1 mechanism in which the substrate achieves carbonium ion character in the transition state. These three mechanisms are depicted in Chart I.

CHART I



It is well known that the cleavage of many aryl alkyl ethers proceeds with difficulty and requires either a strong Lewis acid or a concentrated mineral acid.[4,5] While mechanisms analogous to B and C may be operating in the cleavage reactions of these refractory ethers,[6] no evidence has yet been presented to support these mechanisms for the facile cleavage of α- or γ-alkoxy heteroaromatic compounds. This situation obtains because for a considerable time it had been assumed that these heterocyclic ethers undergo their hydrolyses in dilute aqueous acid *via* mechanism A.[7-9]

In the previous paper of this series[2] data were presented for the hydrolytic cleavage of 2-methoxypyrimidine[^{18}O] in aqueous sulfuric acid which supported the assignment of an SNAr mechanism as the major cleavage pathway. In addition, evidence was obtained for the cleavage of 2-methoxypyrimidine in aqueous hydrochloric acid which indicated that the reaction proceeded in part through an SN2 mechanism. It is worth noting that these hydrolyses were effected in dilute acid media.

In a continuing effort to examine the relationship between structure and mechanism, experiments were conducted on a 2-alkoxypyrimidine in which the aliphatic carbon atom directly bonded to the ethereal oxygen atom was secondary and asymmetric. A system of this type could serve to distinguish among the three mechanisms shown in Chart I.

When such an optically active 2-alkoxypyrimidinium cation undergoes hydrolytic cleavage according to the SNAr mechanism, the asymmetric carbon atom of the product alcohol will *retain* the configuration extant in the cationic starting material, mechanism A. By contrast, SN2 attack by a water molecule at the asymmetric carbon atom would yield an alcohol whose configuration is *inverted* compared with that in the starting material, mechanism B. Finally, since mechanism C involves an SN1 process proceeding through a carbonium ion with planar symmetry, the alcohol formed by subsequent attack of solvent, would be *racemic*.[10]

Results and Discussion

It was found that 2-(1′-methylheptoxy)pyrimidine was cleaved completely after 24 hr at reflux in 40 vol % aqueous ethanol which was 0.5 *M* in phosphoric acid. Alkaline cleavage proved difficult; facile cleavage appears to be a property of the protonated substrate.

Two samples of (*S*)-(+)-2-(1′-methylheptoxy)pyrimidine (**3**) were prepared from the sodium alkoxide of (*S*)-(+)-2-octanol and 2-chloropyrimidine. Each sample was cleaved during 20 hr at reflux in 0.5 *M* phosphoric acid in a 40 vol % aqueous ethanol medium. The 2-octanol produced during the cleavage was isolated from each reaction mixture; neither sample exhibited a measurable optical reaction.

(1) This research was supported by a National Science Foundation Cooperative Graduate Fellowship, Oct 1, 1959–Sept 30, 1961, and by the Research Board of the Graduate College of the University of Illinois, Grant No. 56-92-62. Their assistance is hereby gratefully acknowledged.

(2) Paper II: R. Daniels, L. T. Grady, and L. Bauer, *J. Am. Chem. Soc.*, **87**, 1531 (1965).

(3) This paper is abstracted from the thesis submitted by L. T. Grady to the Graduate College of the University of Illinois at the Medical Center, 1963, in partial fulfillment of the requirements for the Ph.D. degree.

(4) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1953, p 171.

(5) By contrast, aryl alkyl ethers substituted in the *ortho* or *para* positions by nitro groups or other electron attracting groups undergo facile cleavage. In these cases the reactions are facilitated by effects similar to those operating in the case of α- or γ-alkoxyheteraromatic compounds. See J. Sauer and R. Huisgen [*Angew. Chem.*, **72**, 294 (1960)] for a review of this subject.

(6) E. R. Alexander, "Principles of Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, p 214 ff.

(7) B. Lythgoe, *Quart. Rev.* (London), **3**, 181 (1949).

(8) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951).

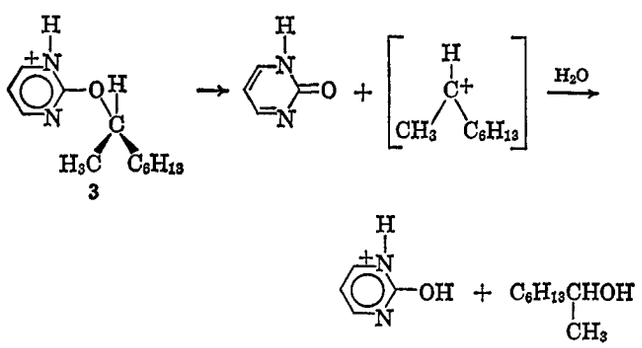
(9) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 384 ff.

(10) In this presentation it is assumed that the carbonium ion is a symmetrical moiety and has no dissymmetry associated with it by the leaving group.

When a control sample of (*S*)-(+)-2-octanol was treated in an identical fashion, the recovered 2-octanol retained 90.6 ± 0.4% of its optical activity. This result is in agreement with studies involving the equilibration of other optically active secondary alcohols in dilute aqueous phosphoric acid.[11,12] Therefore, it is apparent that the racemic 2-octanol isolated from the cleavage mixture could not be the result of a secondary racemization of optically active 2-octanol produced by that cleavage.

In another experiment, a small quantity of impure ether was recovered from a reaction mixture undergoing incomplete cleavage. Although the size of the sample precluded maximal purification, it did exhibit $[\alpha]^{26}D$ + 23.3 ± 0.1° compared to +25.56 ± 0.02° for the original sample of ether. This indicates that the cationic substrate does not racemize prior to the cleavage of the alkyl–oxygen bond. Consequently, the racemic 2-octanol isolated from each cleavage mixture must have resulted only from the intimate mechanism by which the ether was cleaved.

The formation of racemic 2-octanol is consistent with an SN1 mechanism which produces a symmetrical planar carbonium ion having sufficient stability to allow attack by a water molecule on either side of its plane.[13]



Experimentally, solvolyses involving the optically active 2-octyl system usually proceed with considerable inversion of configuration along with some racemization.[14,15] Generally, these systems involve a neutral substrate where the leaving group is a negative ion so that heterolysis gives rise to an ion pair. In the present case, the substrate is positively charged and heterolytic cleavage affords a neutral molecule. The 2-pyrimidone formed is an unusually good leaving group so that, within the spectrum of SN1–SN2 reactions, the course of this nucleophilic displacement is close to the limiting SN1 mechanism.

Summary

The data presented herein on the acid-catalyzed hydrolytic cleavage of (*S*)-(+)-2-(1′-methylheptoxy)-pyrimidinium cation are consistent with an SN1 mechanism involving the inactive 2-octyl carbonium ion intermediate. Earlier findings of SNAr and SN2 mechanisms for the case of the 2-methoxypyrimidinium cation[2] taken in conjunction with the results reported in this paper demonstrate that the hydrolytic cleavage of 2-alkoxypyrimidines can proceed by any of the three general mechanisms outlined in these reports. By analogy, these mechanistic considerations may be extended to other α- or γ-alkoxy-substituted nitrogen heteroaromatic compounds. In light of these results, it will be of interest to examine the mechanism of cleavage of alkoxybenzenes possessing electron withdrawing groups, *e.g.*, picryl ethers.

Experimental Section

Materials.—2-Chloropyrimidine was prepared as described in the preceding paper of this series.[2] Sodium dispersion (50%; 7-μ average particle size) in toluene was obtained from the U. S. Industrial Chemical Co. Anhydrous tetrahydrofuran was prepared by distillation from lithium aluminum hydride. (*S*)-(+)-2-Octanol was purchased from the Aldrich Chemical Co. Polarimetric determinations were performed using an O. C. Rudolph and Sons, Model No. 70 polarimeter; all solutions were in 95% ethanol in 1-dm tubes.

(*S*)-(+)-2-(1′-Methylheptoxy)pyrimidine.—A solution of (*S*)-(+)-2-octanol (13.02 g, 0.100 mole, $[\alpha]^{19}D$ + 9.77 ± 0.02°), in anhydrous tetrahydrofuran (20 ml) was added dropwise with vigorous stirring and occasional cooling, to a mixture of sodium dispersion in toluene (50%, 5.06 g, 0.110 mole) and anhydrous tetrahydrofuran (30 ml). The mixture was refluxed for 3 hr and cooled; the undissolved sodium was removed manually. A solution of 2-chloropyrimidine (11.45 g, 0.100 mole) in tetrahydrofuran (40 ml) was added dropwise with continuous stirring and cooling over a period of 30 min. The mixture was refluxed for 5.5 hr, cooled, and poured into 300 ml of 10% aqueous potassium carbonate. The mixture was extracted thrice with 20-ml portions of ether and the combined extracts was washed with 30 ml of saturated aqueous sodium chloride and dried with anhydrous potassium carbonate. The dried extract was concentrated by distillation through a 16 × 2 cm column packed with multiple-turn glass helices. The residual material was distilled and a fraction boiling between 85 and 95°, at 0.07 torr, was collected, 16.00 g (76.8%). This distillate was redistilled and two fractions were collected bp 88–96° at 0.07 torr, $n^{22}D$ 1.4801, $[\alpha]^{20}D$ + 26.57 ± 0.02°.

This preparation was repeated using (*S*)-(+)-2-octanol of lesser optical purity ($[\alpha]^{26}D$ 8.73 ± 0.02°) and a 72.5% yield of (*S*)-(+)-2-(1′-methylheptoxy)pyrimidine was obtained, bp 90–97° at 0.07 torr; redistilled, bp 93–100° at 0.07 torr, $n^{23}D$ 1.4801, $[\alpha]^{26}D$ + 25.56 ± 0.02°.

By employing racemic 2-octanol, samples of racemic 2-(1′-methylheptoxy)pyrimidine were prepared by this method in yields of 70–77%, bp 92–96° at 0.06 torr, $n^{24}D$ 1.4796.

The infrared absorption spectrum was consistent with that expected for 2-substituted pyrimidines.[16] Ultraviolet absorption maxima appeared at 278.8 mμ (log a_{max} 3.71) and 209.5 mμ (log a_{max} 3.94) in 4 *N* hydrochloric acid.

Anal. Calcd for $C_{12}H_{20}N_2O$ (208.30): C, 69.19; H, 9.68; N, 13.45. Found: C, 69.38; H, 9.42; N, 13.66.

Hydrolysis of (*S*)-(+)-2-(1′-Methylheptoxy)pyrimidine.—A solution of this ether (5.25 g, 0.0252 mole, $[\alpha]^{20}D$ +26.57°) in 500 ml of a 0.5 *M* solution of phosphoric acid in 40 vol % aqueous ethanol was refluxed for 20 hr and then treated according to the 2-octanol isolation procedure described below. The sample of 2-octanol (1.90 g, 59%), bp 72–80° at 10 torr, was isolated and redistilled, bp 78–85° at 20 torr, $n^{22}D$ 1.4272, $[\alpha]^{20}D$ 0.00 ± 0.03°, lit.[17] $n^{20}D$ 1.4264, for either optically active or racemic 2-octanol.

The experiment was repeated using ether of lesser optical purity ($[\alpha]^{26}D$ +25.56) and a 57% yield of 2-octanol was isolated ($[\alpha]^{28}D$ 0.00 ± 0.03°), along with unchanged ether (1.17 g, 19.5% recovery), bp 80–143° at 12 torr. Redistillation provided a 0.78-g sample, bp 120–145° at 12 torr, $[\alpha]^{26}D$ + 23.3 ± 0.1°.

Control Experiment.—(*S*)-(+)-2-Octanol (3.75 g, 0.0288 mole, $[\alpha]^{19}D$ +9.77°) and 2-pyrimidinol were dissolved in 500 ml of 0.5 *M* phosphoric acid in 40 vol % aqueous ethanol and the solu-

(11) J. M. O'Gorman and H. J. Lucas, *J. Am. Chem. Soc.*, **72**, 5489 (1950).

(12) E. R. Alexander, H. M. Busch, and G. L. Webster, *ibid.*, **74**, 3173 (1952).

(13) The alternate possibility of equal rate SNAr and SN2 mechanisms would also give rise to racemic 2-octanol. This eventuality is considered highly unlikely.

(14) H. Weiner and R. A. Sneen, *J. Am. Chem. Soc.*, **87**, 287 (1965).

(15) H. Weiner and R. A. Sneen, *ibid.*, **87**, 292 (1965).

(16) A. R. Katritzky, *Quart. Rev.* (London), **13**, 353 (1959).

(17) J. B. M. Koppock and F. R. Goss, *J. Chem. Soc.*, 1789 (1939).

tion was refluxed for 20 hr. A sample of 2-octanol was isolated as described in the 2-octanol isolation procedure (3.70 g, 99% recovery), bp 81–84° at 15 torr. The sample was redistilled to provide 2-octanol, bp 73–74° at 10 torr, $[\alpha]^{19}D$ + 8.85 ± 0.03°, $n^{23}D$ 1.4259.

2-Octanol Isolation Procedure.—The hydrolysis mixture or the control (*ca.* 500 ml) was distilled through a 32 × 1.6 cm vacuum-jacketed column packed with single-turn glass helices and fitted with a total reflux, partial take-off head. Ethanol (160 ml) was removed at an 8:1 reflux ratio over a period of 3 hr. The residue was cooled, the column was washed with three 5-ml portions of the distillate, and 20 ml of saturated aqueous sodium hydroxide was added to the combined material. This alkaline mixture was treated with 100 g of anhydrous potassium carbonate, extracted with four 30-ml portions of *n*-pentane, and the combined organic extracts were washed with 30 ml of saturated aqueous sodium chloride and dried with anhydrous potassium carbonate. The *n*-pentane was removed by distillation through a 16 × 2 cm column packed with multiple-turn glass helices; the residue was distilled.

Samples of 2-octanol isolated by this procedure were found to be pure by gas–liquid chromatographic analysis (20% diethylene glycol succinate on Chromosorb-P; 160°, 35 psi of helium).

Studies in Mass Spectroscopy. VI.[1a] Mass Spectra of Substituted Diethyl Malonates

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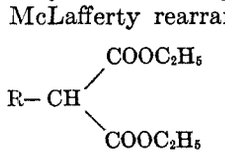
The mass spectra of representative mono- and dialkyl diethyl malonates have been investigated. These molecules break down mainly by loss of an alkyl substituent with hydrogen rearrangement (McLafferty rearrangement). The enolic nature of the resulting fragment is suggested by its subsequent decompositions. Enolic fragments are also apparently formed upon elimination of $COOC_2H_4$ (loss of ester group with hydrogen rearrangement) in the spectra of monoalkyl diethyl malonates.

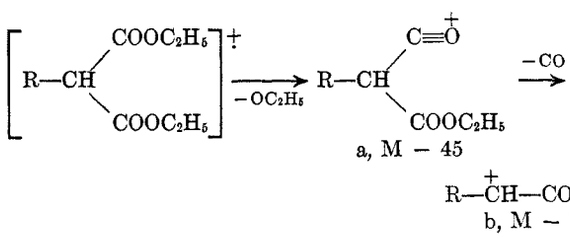
Although the mass spectra of a number of malonic acids have been determined,[2] a detailed study of the synthetically important malonate esters has not been reported. This paper deals with the interpretation of the mass spectra (Table 1 and Figures 1–6) of diethyl malonate and a number of the more important alkyl and aryl derivatives. The most important reactions occurring upon electron impact in many of these compounds appear to lead to enolic fragment ions (as deduced from the further decomposition of these fragment ions). The evidence upon which specific structures for such fragment ions are based comes from allylic cleavage reactions (which occur in a predictable manner); the specific structures aid interpretation of the spectra in a general and self-consistent manner. However, it is emphasized that this is the only evidence available for assigning fragment ion structures, which therefore must be regarded as speculative throughout this paper.

In the spectra of diethyl malonate (I) and the monosubstituted derivatives II–XI, a molecular ion is generally observed only for those cases in which the substituent does not carry a suitable hydrogen atom to participate in the McLafferty rearrangement[3] with a carbonyl group of the ester. Thus, diethyl malonate (I) and the methyl, allyl, phenyl, and benzyl derivatives (II, IV, X, and XI) exhibit molecular ions in their spectra.



I, R = H
II, R = CH_3
III, R = C_2H_5
IV, R = $CH_2CH{=}CH_2$
V, R = *n*-C_3H_7
VI, R = *i*-C_3H_7
VII, R = *n*-C_4H_9
VIII, R = *i*-C_4H_9
IX, R = *t*-C_4H_9
X, R = C_6H_5
XI, R = $C_6H_5CH_2$

In general, three important types of fragmentation are evident from the spectra (Table I and Figures 1–4) of these compounds. First, all the spectra contain pronounced (13–100% relative to the base peak) M − C_2H_5O ions (a) which correspond to the base peak when R = H (I) or when R is a small alkyl group [R = CH_3 (II) or C_2H_5 (III)]. Frequently ion a decomposes by elimination of carbon monoxide to an M − $COOC_2H_5$ species, b, as evidenced by appropriate metastable ions in the spectra of III, IV, and VI.



a, M − 45

b, M − 73

Second, loss of one ester group occurs with hydrogen rearrangement to give an M − $COOC_2H_4$ ion (M − 72), whose relative abundance decreases with increasing size of the alkyl substituent as indicated in Table II. The decrease in the relative abundance of the M − 72 fragment is due to the increasing importance of the McLafferty rearrangement as R becomes larger and also the additional tendency for the M − 72 ion to fragment further when R is larger. The further fragmentation of the M − 72 species strongly supports its representation as the enolic form c, perhaps formed *via* a cyclic transition state (see XII → c). Thus, if the alkyl substituent R is large enough to permit loss of an alkyl radical through allylic cleavage in c, then abundant fragment ions corresponding to the formation of d

(1) (a) Part V: J. H. Bowie, D. W. Cameron, R. G. F. Giles, and D. H. Williams, *J. Chem. Soc.*, in press. (b) To whom inquiries should be addressed.

(2) R. I. Reed and W. K. Reid, *ibid.*, 5933 (1963).

(3) F. W. McLafferty in "Determination of Organic Structure by Physical Methods," Vol. 2, Academic Press, Inc., New York, N. Y., 1962, pp 129–149.