Preparation of Substituted 5,6-Dihydro-4H-1,3-Oxazines from Olefins[1]

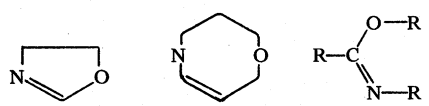
3769

ABSTRACT

The 5,6-dihydro-4H-1,3-oxazine derivatives of methyl oleate and related compounds have been prepared. These novel six-membered heterocyclic compounds were obtained by the condensation of N-hydroxymethyl or N-chloromethylbenzamide with methyl oleate or its derivatives. These reactions can be regarded as 1,4-dipolar addition reactions.

INTRODUCTION

Δ^2-Oxazolines [1] and 5,6-dihydro-4H-1,3-oxazines [2] are heterocyclic compounds characterized by the bonding sequence of an oxygen-carbon-double bond-nitrogen within their cyclic framework. As such, they can be more generally classified, in comparison with the acyclic analogs [3] as cyclic imidic esters. These heterocyclic compounds have been known for some time (1,2), and in recent years considerable interest has been shown in their chemistry (3-6).



[1] [2] [3]

In previous publications from our laboratory, we have described the preparation and characterization of several oxazoline derivatives of fatty acids (7,8). The present paper describes the preparation of the six-membered analogs of cyclic imidic esters (namely, the oxazine derivatives of fatty acids and related compounds) and establishes the geometry of the isomeric oxazines so prepared.

[1]Presented at the AOCS-ISF World Congress in Chicago, October 1970.

[2]ARS, USDA.

EXPERIMENTAL PROCEDURES

Materials

cis-9-Octadecene and *trans*-9-octadecene were prepared by the lithium aluminum hydride reduction of the tosylates of oleyl and elaidyl alcohols (9). Purity as determined by gas liquid chromatography and thin layer chromatography, was 98-99%.

cis-3-Hexene (96%), *trans*-3-hexene (99%), oleyl alcohol (98%) and methyl oleate (98%) were purchased and used as received. N-Hydroxymethylbenzamide and N-chloromethylbenzamide were prepared as described in the literature (10,11).

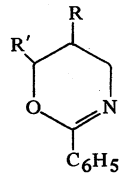
Preparation of Substituted 5,6-Dihydro-4H-1,3-Oxazines

Procedure A: To a cold (15 C), stirred solution of the olefin (10 mmol) and N-hydroxymethylbenzamide (10 mmol) in acetic acid (20 ml) was added concentrated sulfuric acid (1 ml). The mixture was kept at 10 C for 2.5 hr and poured onto ice water (100 ml). The solution was filtered to remove the precipitated solids, and the filtrate was made basic with potassium hydroxide pellets and extracted with ether. The combined organic layers were washed with water, dried over $MgSO_4$, and the solvent was removed in vacuo. The oxazine was purified by distillation or chromatography on Florisil. Yield data are listed in Table I. The IR spectra of the 5,6-dihydrooxazines are characterized by the following absorption bands: 2980 (C-H), 1660 (C=N), 1560, 1350, 1280, 1125 (C-O), 1075 and 700 cm^{-1}.

Procedure B: To a cold (0 C), stirred solution of stannic chloride (25 mmol) in $CHCl_3$ (25 ml) was added a solution of the olefin (25 mmol) and N-chloromethylbenzamide (25 mmol) in $CHCl_3$ (75 ml) over a period of 0.5 hr. The reaction mixture was stirred for 2 hr and then poured onto 75 ml of 2 *N* NaOH solution. The $CHCl_3$ layer was separated, washed with H_2O, dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo. The crude oxazine was purified either by distillation under reduced pressure or by column chromatography on Florisil. Yield data are given

TABLE I

Substituted 5,6-Dihydro-4H-1,3-Oxazines[a]



Compound	Stereo chemistry	R	R′	% Yield[b] Method A	% Yield[b] Method B	Boiling point, C (mm)
4a	*cis*	C_2H_5	C_2H_5	53	85	112 (.15)
4b	*trans*	C_2H_5	C_2H_5	49	87	118 (.10)
4c	*cis*	C_8H_{17}	C_8H_{17}	46	77	196 (.10)
4d	*trans*	C_8H_{17}	C_8H_{17}	41	---	208 (.10)
4e[c]	*cis*	C_8H_{17}	$C_7H_{14}CH_2OH$	---	57	---[d]
4f[c]	*cis*	C_8H_{17}	$C_7H_{14}CO_2CH_3$	42	80	---[d]

[a]All new compounds gave acceptable elemental analyses.

[b]Based on starting olefin.

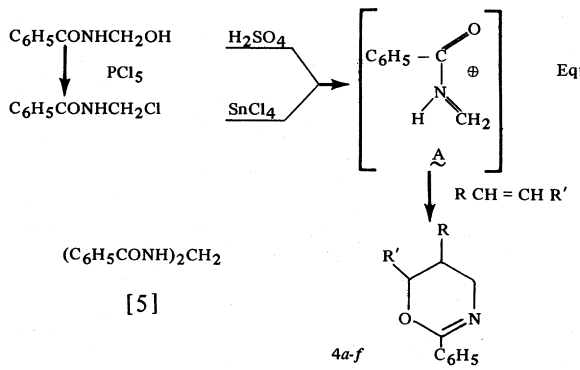
[c]Obtained as a mixture of 9,10 positional isomers.

[d]Purified by column chromatography.

in Table I.

RESULTS AND DISCUSSION

Syntheses of 5,6-dihydro-4H-1,3-oxazines from olefins were accomplished by two procedures, both of which are acid-catalyzed condensation reactions. In one procedure (method A) the olefin was condensed with N-hydroxymethylbenzamide with sulfuric acid as the condensation catalyst eq. [1]. The second procedure (method B) utilized was the reaction of the unsaturated compound with N-chloromethylbenzamide in the presence of stannic chloride eq. [1]. The oxazines were obtained as liquids and were purified by either distillation or column chromatography.



Equation 1

As noted previously (12), a major side reaction in the sulfuric acid-catalyzed reactions is the self condensation of N-hydroxymethylbenzamide to the methylene bis-amide derivative [5]. This reaction is not observed with stannic chloride and probably accounts for the low oxazine yields when the sulfuric acid method is employed (Table I). Of the two procedures studied the N-chloromethylbenzamide method is preferred, even though the reagent is obtained from N-hydroxymethylbenzamide and requires the use of equimolar quantities of stannic chloride. Larger overall yields of oxazines and the ease of isolation of the reaction products favor this choice.

The addition reactions can be formally regarded as synchronous 1,4-dipolar addition reactions to the olefin, and Schmidt (13) has demonstrated that they probably occur via the addition of a protonated methylidenebenzamide ion (A, equation [1]) to the olefin. Also with model olefins, both additions occur in a stereospecific fashion (13). Accordingly the reaction of a *cis* olefin, e.g., methyl oleate with either reagent yields a 4H-1,3-oxazine derivative, wherein the 5,6-alkyl ring substituents have a *cis* relationship. In like manner, when a *trans* olefin is the starting material, the substituents of the product have the *trans* geometry. Besides elemental analyses and strong IR absorptions at 1660 cm^{-1}, specific proof of structure for the oxazine derivatives was obtained by NMR spectroscopy. In our oxazines with *cis* substituents located at the 5,6 positions, the observed methine-methine proton coupling constant is ca. 9.0 Hz, while for *trans*-substituted oxazines it is 3.5 Hz; these values agree with previous reports (13).

In contrast to the oxazoline ring structure, the oxazine ring is more resistant to hydrolysis. The latter can be cleaved by aqueous acid or base to the respective γ-hydroxyamide. Also when the imidic ester function is contained within the oxazine ring, the imidic nitrogen atom becomes less basic than when it is found in the oxazoline ring, since the oxazines do not readily form isolable salts while the oxazolines yield crystalline salts with a variety of nonnucleophilic acids (7,14).

REFERENCES

1. Wiley, R.H., and L.L. Bennett, Jr., Chem. Rev. 44:447 (1949).
2. McKee, R.L., in "The Chemistry of Heterocyclic Compounds," Vol. 17, New York, John Wiley and Sons, 1962, p. 341.
3. Frump, J.A., Chem. Rev. 71:483 (1971).
4. Seeliger, W., E. Aufderhaar, W. Diepers, R. Feinauer, R. Nehring, W. Thier and H. Hellmann, Angew. Chem. Int. Ed. Engl. 5:875 (1966).
5. Giordano, C., G. Ribaldone and G. Borsotti, Synthesis 1971:92.
6. Meyers, A.I., and E.M. Smith, J. Amer. Chem. Soc. 92:1084 (1970); Meyers, A.I., and A.C. Kovelesky, Ibid. 91:5887 (1969); Meyers, A.I., I.R. Politzer, B.K. Bandlish and G.R. Malone, Ibid. 91:5886 (1969).
7. Foglia, T.A., L.M. Gregory and G. Maerker, J. Org. Chem. 35:3779 (1970).
8. Maerker, G., E.T. Haeberer, E.T. Donahue and T.A. Foglia, J. Heterocycl. Chem. 7:563 (1970).
9. Dyen, M.E., H.C. Hamann and D. Swern, JAOCS 43:431 (1966).
10. Hellmann, H., angew. Chem. 69:463 (1957).
11. Böhme, H., R. Broese, A. Dick. F. Eiden and D. Schünemann, Chem. Ber. 92:1599 (1959).
12. Seeliger, W., and W. Diepers, Justus Liebigs Ann. Chem. 697:171 (1966).
13. Schmidt, R.R., Angew. Chem. Int. Ed. Engl. 8:602 (1969).
14. Tomalia, D.A., N.D. Ojha and B.P. Thill, J. Org. Chem. 34:1400 (1969).