200 mg, m.p. 186–187°. *Anal.* Found: C, 59.26; H, 5.44. Calcd. for $C_9H_{10}O_4$: C, 59.33; H, 5.53.

C) Synthesis of 2,6-Dimethoxybenzoic Acid (IX). *m*-Dinitrobenzene (83 g.) was treated with potassium cyanide in methanol to yield 2,6-dimethoxybenzonitrile (13.5 g.). The nitrile was refluxed in concentrated potassium hydroxide solution and the resulting potassium salt treated with concentrated hydrochloric acid to yield 2,6-dimethoxybenzoic acid, yield 14 g., m.p. 186°. *Anal.* Found: C, 59.28; H, 5.39. Calcd. for $C_9H_{10}O_4$: C, 59.33; H, 5.53.

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Relationship between Stereoisomerism and Biological Activity of Pyrethroids

Part IV. The Oxidative Degradation of ($\pm$)-Allethrolone-methylether*

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($\pm$)-Allethrolone-methylether (II), when first oxidized by ozone and then by potassium hypobromite, affords ($\pm$)- α -methoxysuccinic acid (V) through the intermediate keto acids (III) and (IV).

In connection with the elucidation of the absolute configuration of naturally derived pyrethrolone and cinerolone, a preliminary study was made with readily accessible ($\pm$)-allethrolone in order to gain information whether it affords some potential key intermediate of the well-established configuration by chemical conversions. The oxidative degradation of free allethrolone which would lead to malic acid in the sequel was rejected because

of the experimental difficulty to be predicted by the feeble rotatory power of malic acid*** which would result from the analogous oxidations of optically active pyrethrolone and cinerolone. Thence, the authors' attention was directed to allethrolone-methylether which in the sequel of appropriate oxidations would

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*** Stereochemical correlations between malic acid, α -methoxysuccinic acid and glyceraldehyde will be detailed in the next paper which deals with the oxidations of naturally derived pyrethrolone and cinerolone.

* Part III: This Bulletin, 22, 393 (1958)

1) H. Staudinger and L. Ruzicka, *Helv.*, **7**, 212 (1924).

Infra-red spectra of a) (±)- α -methoxysuccinic acid dimethylester (liquid),
b) synthetic specimen (liquid)

hydrazone m.p. 105° and consumed 3 mols of potassium hypobromite to give (V) together with bromoform.

The well-demonstrated *cyclopentenolone* structure of allethrolone and consequently of its methylether necessitates that the carbon skeleton of the resulting α -methoxysuccinic acid represents the fragmental $C_{(3)}-C_{(4)}-C_{(5)}-C_{(1)}$ chain in this order in the parent compound.

This chemical conversion of allethrolone-methylether to α -methoxysuccinic acid should render it feasible to establish, by analogous oxidations of (+)-pyrethrolone- and (+)-cinerolone methylethers, the chemical correlation of naturally derived pyrethrolone and cinerolone with glyceraldehyde *via* the key intermediate α -methoxysuccinic acid.

EXPERIMENTAL

Melting and boiling points were uncorrected. Microanalyses were carried out by the Microanalytical Division of Mitsui Laboratory of Kyoto University, to whom the authors' thanks are due. Infrared spectra were recorded with a Parkin-Elmer double beam spectrophotometer Model 21.

Allethrolone-methylether

Allethrolone semicarbazone (25g. m.p. 211–213°, La Forge et al.²⁾ recorded m.p. 213–4°) was boiled with

250ml. of methanol containing 15g. of concentrated sulfuric acid under reflux for two hours and a half. The solution was poured into 500ml. of water, and the separated oil was extracted with petroleum ether. Washing and distillation of the organic layer gave allethrolone-methylether (10g.), b.p. 72–3°/2 mm., n_D^{20} 1.4880. By the standard method, the semicarbazone was prepared. m.p. 174–5° (*Anal.* Found: C, 66.59; H, 8.99; N, 15.62. Calcd. for $C_{10}H_{16}ON_3$: C, 66.63; H, 8.95; N, 15.54.).

Attempted synthesis of the methylether by boiling the free allethrolone with methanol and sulfuric acid under the same conditions resulted in a very poor yield (below 4%) of the desired ether.

Ozonolysis and potassium hypobromite oxidation

Allethrolone-methylether (5g.) dissolved in chloroform (30ml.) was treated with excess of ozone at 0°. The solvent was evaporated under reduced pressure and the residual ozonide was decomposed with 5% sodium hydroxide. After being freed from neutral products by extraction with ether, it gave the crude acid product (3g.). This acid was positive against carbonyl reagents. The crude acid (3g.) was dropped into 10% potassium hypobromite solution (150ml.) at 10° with stirring, and stirring was continued at 70° for half an hour. After decomposing the excessive hypobromite by the addition of sodium bisulfite, the reaction mixture was extracted with ether to remove bromoform formed, and the aqueous solution was acidified with dil. sulfuric acid and was continuously extracted with ether by percolation for twenty-four hours.

2) Milton S. Schechter, Nathan Green and F.B. LaForge, *J. Am. Chem. Soc.*, **71**, 3172 (1949).

Evaporation of the ether extract gave α -methoxy-succinic acid, m.p. 101–4°, (1.0 g.). Recrystallizations from ethyl acetate-chloroform gave pure acid in prisms, m.p. 104–5°, not depressed by the admixture of the authentic specimen prepared by Purdie's procedures³⁾, (*Anal.* Found: C, 40.77; H, 5.58; CH₃O, 20.1. Calcd. for C₅H₈O₅: C, 40.54; H, 5.44; CH₃O, 20.9), equivalent weight by titration Found: 73.88 Calcd. For C₅H₈O₅·(COOH)₂ 74.05. By the standard method with diazo-methane, the dimethylester was prepared. b.p. 67–9°/5 mm., n_D^{20} 1.4291. For IR-spectra, see the Fig. in the text.

Permanganate and potassium hypobromite oxidations.

Allethrolone-methylether (5 g.), suspended in water (200 ml.), was cooled in ice-water and, to this, 3% permanganate solution (700 ml.) was added dropwise

3) Purdie and W. Marshall, *J. Chem. Soc.*, **67**, 946.

with stirring during four hours, until the permanganate solution was no longer decolourized. The product was acidified with sulfuric acid and extracted with ether. Evaporation under high vacuum of the ether solution gave keto-acid (VI). Yield 2.3 g. 2,4-Dinitrophenylhydrazones m.p. 105° (*Anal.* Found: C, 44.29; H, 4.47; N, 17.13. Calcd. for C₁₂H₁₄O₇N₄: C, 44.17; H, 4.33; N, 17.17). By the same procedures as described above, the keto-acid (2.3 g.) was oxidized with potassium hypobromite (10 w/v %, 70 ml.) and also gave α -methoxy-succinic acid (V), m.p. and mixed m.p. 104–5°, (1.0 g.), together with bromoform.

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Relationship between Stereoisomerism and Biological Activity of Pyrethroids

Part V. The Absolute Configuration of (+)-Pyrethrolone and (+)-Cineralone*

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The oxidative degradations of the methyl-ethers of naturally derived pyrethrolone and cineralone eventually afford (–)- α -methoxysuccinic acid. This chemical conversion without disturbance of the asymmetric centre concerned, establishes, beyond doubt, the absolute configuration of the asymmetric C₄, involved in (+)-pyrethrolone and (+)-cineralone in the ultimate correlation between these alcohols and (–)-glyceraldehyde *via* the key intermediate, (–)- α -methoxysuccinic acid.

Remarkable advances have been made in the field of pyrethrum chemistry during the last decade and almost all important problems, i.e. structural and synthetic, have successively

been dissolved by many workers. However, the sole pending important problem is the elucidation of the absolute configuration of naturally derived pyrethrolone and cineralone. These two cyclopentenolones constitute the alcohol-moieties of the pyrethrins and their

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