A Convenient Process for the Synthesis of Organic Compounds of High Deuterium Content

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Numerous methods for synthesis of organic compounds containing heavy isotopes of hydrogen have been described [1] but none of them allows the production of miscellaneous organic substances with a high isotope content. Recently we have found a general process through which a complete replacement of light hydrogen can be carried out in a wide range of organic compounds including compounds of high molecular weight.[2]

The present process consists of a direct exchange reaction between an organic compound containing light hydrogen and a source of heavy hydrogen in the presence of alkali, a metal catalyst of the type used for hydrogenation, and a promoter in the form of a suitable peroxide. It has been used for the production of perdeuterated fatty acids, dicarboxylic acids, ketones, alcohols and hydrocarbons of diverse types. The isotopic purity (over 99 %) of deuterium-containing compounds thus prepared is limited only by the purity of the deuterium source.

In this note we show the mass spectrum (Fig. 1) and infrared spectrum (Fig. 2) of a sample of methyl perdeuterio-n-docosanoate prepared from behenic acid by the new process. The isotopic purity of this ester is

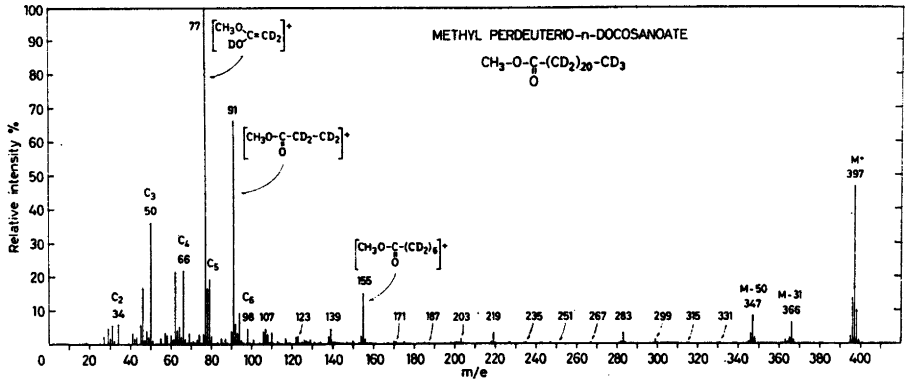

Fig. 1. Mass spectrum of methyl perdeuterio-n-docosanoate.

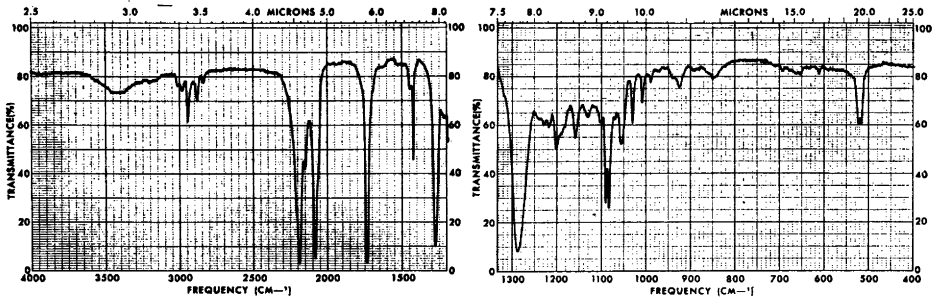

Fig. 2. Infrared spectrum of methyl perdeuterio-n-docosanoate in KBr-phase (conc. 1.8/300 mg; Perkin-Elmer model 337).

over 99 %; it is much higher than that of the same ester synthesized through stepwise coupling of small deuterated units.[3]

Full details of this work will be published later.

This work was supported by *Statens Medicinska Forskningsråd.*

1. See reviews on isotopic hydrogen compounds in Murray III, A. and Williams, D. L. *Organic Syntheses with Isotopes*, Interscience, New York & London 1958, Part 2, chap. 16.
2. Dinh-Nguyên, Ng. and Stenhagen, E. *Swedish patent appl.* No. 1280 (1965).
3. Dinh-Nguyên, Ng. *Acta Chem. Scand.* **16** (1962) 2301.

Received May 11, 1966.

1,2-Diarylcyclopropane Derivatives

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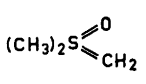
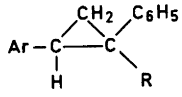
Recently, Corey and Chaykovsky [1] observed that dimethyloxosulfonium methylide (I) generated from the readily accessible trimethylsulfoxonium iodide [2] by proton transfer to a strong base reacted with a conjugated carbonyl compound receptive to Michael addition to give a cyclopropane derivative. The application of this reagent was extended to alpha-substituted stilbenes with a view to obtain 1,2-diarylcyclopropane derivatives (II) which might possess useful pharmacological properties.



I



II

R = COOH, $CONH_2$, NH_2

Ethyl α-phenylcinnamate obtained by esterification of *trans* α-phenylcinnamic acid reacted with the ylide I to form ethyl 1,2-diphenylcyclopropanecarboxylate in 78.6 % yield; hydrolysis of the ester with ethanolic KOH yielded a mixture of two isomeric acids which were separated by fractional crystallization from ethanol. The two isomeric acids were subjected to modified Curtius reaction [3] to obtain crude isocyanates which were hydrolysed by suspending in 15 % aq. KOH and letting the mixture stand at room temperature for 4—7 days with occasional shaking. The amines were isolated as the hydrochlorides.

In the case of 1-phenyl-2-(*p*-anisyl)- and 1-phenyl-2-(*p*-chlorophenyl)-cyclopropanecarboxylic acids it was found advantageous to convert the crude azides into benzylurethans which smoothly underwent catalytic hydrogenation to give the amines.

In order to study the effect of chain length, α-phenylcinnamonitrile was reacted with the ylide I to obtain 1,2-diphenylcyclopropylcyanide; $LiAlH_4$ reduction of the nitrile gave 1,2-diphenylcyclopropylmethylamine isolated as the hydrochloride. Jaz and Weiler [4] have recently reported the formation of cyclopropane derivatives by the addition of diazomethane to α-cyanostilbenes.

Preliminary pharmacological testing of the compounds listed in Table 1 indicated that they were quite toxic and did not exhibit significant pharmacological effects.**

Experimental. Microanalyses were carried out by W. Egger and G. Cornali of these laboratories.

The procedure used for the preparation of 1,2-diarylcyclopropanecarboxylic acids is illustrated by the following example.

1,2-Diphenylcyclopropanecarboxylic acid. To a stirred solution of trimethylsulfoxonium iodide (0.15 mole) in 225 ml of dimethylsulfoxide in nitrogen atmosphere sodium hydride (0.15 mole, 46 % suspension in mineral oil) was added in small portions. When hydrogen evolution was complete, a solution of ethyl α-phenylcinnamate (0.12 mole) in 75 ml of dimethylsulfoxide was added dropwise. The reaction mixture was stirred for 1 h after the addition was over and was then placed in a water bath maintained at 55—60° for 1.5 h. It was poured into ice water and the mixture

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** The author is grateful to Dr. H.-H. Frey of these laboratories for carrying out pharmacological tests.