39% exchange of the methyl protons,[2] whereas a single pass of this compound through our g.l.c. column resulted in *95% exchange*. In addition, the superiority of the g.l.c. approach is further emphasized upon comparison of results showing 16% incorporation of deuterium in di-*n*-hexyl ketone after two passes through the deuterated alumina column[2] with those obtained on 2,11-dodecanedione by our method. Even though the number of exchangeable hydrogens in this diketone is ten, compared with four in the di-*n*-hexyl ketone, a single pass of the former through the g.l.c. column resulted in a 93% uptake of deuterium.

The ease and rapidity with which exchange of enolizable hydrogens can be quantitatively achieved should make this method attractive for the high quality preparation of pure deuterated samples of synthetic and natural products available in only minute amounts (microgram range). Experiments are in progress on the application of the technique in a micro (capillary column gas chromatography) as well as a preparative scale.

Of course, introduction of tritium could be accomplished in an analogous fashion, with subsequent reduction of the functionality to obtain nonexchangeable tritium-labeled compounds for tracer experiments.

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A New Method of Dihalocarbene Generation Based on Trihalomethylmetal Compounds

Sir:

It has been reported that trimethyl(trifluoromethyl)-tin releases difluorocarbene at 150°.[1] We report here a procedure that allows utilization of this compound in CF_2 generation at 80° in a nonbasic medium to give, in the presence of olefins, *gem*-difluorocyclopropanes in very good yield. This procedure also can be used to generate CCl_2 from $C_6H_5HgCCl_2X$ (X = Cl and Br) at room temperature. Several examples serve to illustrate the utility of our method.

A mixture of 11.8 mmoles of $(CH_3)_3SnCF_3$, 15 mmoles of sodium iodide, and 100 mmoles of cyclohexene in 1,2-dimethoxyethane (DME) was heated under nitrogen at 80° for 12 hr. Gas chromatographic analysis of the filtered reaction mixture showed the presence of trimethyltin iodide[2] (90%) and 7,7-difluorobicyclo[4.1.0]heptane[3] (73%). A similar reaction with tetramethylethylene gave 1,1-difluorotetramethylcyclopropane[5] in 77% yield. This new procedure appears to generate CF_2 under the mildest conditions reported thus far and gives the best yields of *gem*-difluorocyclopropanes reported to date. We expect that trifluoromethylmercury compounds also would serve well in these reactions.

$$(CH_3)_3SnCF_3 + NaI + \text{>C=C<} \longrightarrow (CH_3)_3SnI + \text{>C(CF}_2\text{)C<} + NaF$$

The application of these procedures to (trihalomethyl)-mercurials was equally satisfactory. For example, to 7 mmoles of $C_6H_5HgCCl_3$ and 70 mmoles of cyclohexene in 25 ml. of benzene was added 7 mmoles of dry NaI in 5.5 ml. of DME. The mixture was stirred at 30° under nitrogen for 48 hr., then was filtered to remove C_6H_5HgI. G.l.c. analysis (G.E. SE-30 on Chromosorb W) of the filtrate after one high vacuum trap-to-trap distillation showed that 7,7-dichlorobicyclo-[4.1.0]heptane[2] had been formed in 72% yield; chloroform[2] also was present (14%). These products were not formed under these conditions in the absence of sodium iodide. When this reaction was carried out at 80° during 4 hr., the dichloronorcarane and the chloroform yields were 72.4 and 7.2%, respectively. Dichloronorcarane was produced in 16% yield under these conditions when no sodium iodide was added. A similar reaction of the 1:1 $C_6H_5HgCCl_2Br$–NaI reagent system with cyclohexene at room temperature (4 hr.) gave 7,7-dichlorobicyclo[4.1.0]heptane (75%) and 7-bromo-7-chlorobicyclo[4.1.0]heptane (~1%). In the absence of sodium iodide, this reaction carried out under these conditions gave the dichloronorcarane in 1.5% yield.

These reactions involve intermediate formation of trihalomethide ion. This was shown when the $C_6H_5HgCX_3$ + NaI (1:1) reaction was carried out in anhydrous acetone. The major products obtained with $C_6H_5HgCCl_3$ at room temperature were chloroform[2] (34%), dimethyl(trichloromethyl)carbinol[2] (26%), and phenylmercuric iodide (93%); in a reaction carried out at reflux, these products were formed in yields of 59, 12, and 84%, respectively. The action of sodium iodide in acetone on $C_6H_5HgCCl_2Br$ at room temperature gave bromodichloromethane (43%) and dimethyl-(bromodichloromethyl)carbinol[6] (15%) as major products. The formation of haloform, presumably by proton abstraction from acetone by CX_3^-, is essentially irreversible in the absence of strong base, hence $(CH_3)_2(CX_3)COH$ yields are low.

Further evidence for a CX_3^- intermediate is given by reactions in which acrylonitrile, an efficient trap for nucleophiles, was used as substrate. In one such reaction $C_6H_5HgCCl_2Br$, NaI, and acrylonitrile were used in 1:1.1:3 molar ratio; the reaction was carried out as described for the cyclohexene case in benzene–DME at room temperature during 4 hr. A similar work-up of the brown reaction mixture showed bromodichloromethane[2] (28.5%), 1,1-dichloro-2-cyanocyclopropane[2,7] (16%), and 4-bromo-4,4-dichlorobutyroni-

(1) H. C. Clark and C. J. Willis, *J. Am. Chem. Soc.*, 82, 1888 (1960).
(2) Identified by comparison of its infrared spectrum and g.l.c. retention time with those of an authentic sample.
(3) Refractive index and infrared spectrum agreed with literature data.[4] The yield of the difluoronorcarane under these conditions in the absence of NaI was *ca.* 1%.
(4) J. M. Birchall, G. W. Cross, and R. N. Haszeldine, *Proc. Chem. Soc.*, 81 (1960).
(5) N.m.r.: triplet (J = 2.0 c.p.s.) at 1.08 p.p.m. downfield from TMS (Varian A60, in CCl_4); $n^{25}D$ 1.3772; microanalysis satisfactory.
(6) M.p. 119–120°; identified by microanalysis and infrared and n.m.r. spectra.
(7) Prepared in 76% yield by the reaction of $C_6H_5HgCCl_2Br$ with acrylonitrile in benzene at 80°: D. Seyferth and R. J. Minasz, manuscript in preparation.

trile[8] (2%) to be present. When this reaction was carried out using acrylonitrile as solvent, the bromodichloromethane and the $CCl_2BrCH_2CH_2CN$ yields rose to 40 and 13.4%, respectively; no 1,1-dichloro-2-cyanocyclopropane was present, and some polyacrylonitrile was formed.

Thus the mechanism of the $C_6H_5HgCX_3$–NaI–olefin reaction appears to be

$$C_6H_5HgCX_3 + I^- \longrightarrow C_6H_5HgI + CX_3^-$$

$$CX_3^- \longrightarrow CX_2 + X^-$$

$$CX_2 + \text{C=C} \longrightarrow \text{C(CX}_2\text{)C}$$

The sodium iodide procedure is a useful variation of the mercurial route[9] to dihalocarbenes. It allows use of $C_6H_5HgCCl_2Br$ and $C_6H_5HgCCl_3$ at room temperature in dihalocyclopropane synthesis, as well as use of $C_6H_5HgCCl_3$ at 80° in much shorter reaction times. The presence of iodide ion and the intermediacy of CX_3^- in these reactions, however, can introduce complications, as the reactions with acrylonitrile show. This general procedure could find useful application in the dihalomethylenation of olefins of limited thermal stability and especially in the preparation of *gem*-difluorocyclopropanes. Our investigations in this general area are continuing.

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(8) M.p. 53–54.5°; identified by microanalysis and infrared and n.m.r. spectra.

(9) D. Seyferth, J. M. Burlitch, and J. K. Heeren, *J. Org. Chem.*, 27, 1491 (1962), and subsequent papers.

(10) Alfred P. Sloan Foundation Fellow, 1962–1966.

(11) National Institutes of Health Predoctoral Fellow.

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Book Reviews

Experimental Chemotherapy. Volume II. Chemotherapy of Bacterial Infections. Part I. Edited by R. J. SCHNITZER, formerly Chemotherapy Department, Hoffmann-LaRoche, Inc., Nutley, N. J., and FRANK HAWKING, Division of Chemotherapy and Parasitology, National Institute for Medical Research, London, England. Academic Press, Inc., 111 Fifth Ave., New York 3, N. Y. 1964. xvii + 614 pp. 16 × 24 cm. Price, $23.00.

"Experimental Chemotherapy" is an ambitious, four-volume undertaking, the purpose of which is to present a comprehensive coverage of the entire field of chemotherapy. Volume II of this treatise is Part I of two volumes subtitled "Chemotherapy of Bacterial Infections." This section is devoted to a series of discussions of the broad field of antibacterial chemotherapy, emphasizing the biochemistry of antimicrobial therapy as well as the pharmacology and toxicology of a few specific agents such as the sulfonamides and nitrofurans. Volume III will be concerned with specific antibacterial agents and their modes of action as well as the chemotherapy of fungal, rickettsial, and viral infections.

As with most treatises of this type, a compilation of chapters written by experts in the field under discussion, the results are variable although the individual contributions in this work are generally of quite high caliber. Viewed as a whole, however, this volume is not up to the uniformly high level of the first member of this series [for review, see A. Burger, *J. Med. Chem.*, **6**, 825 (1963)]. Particularly noteworthy are the chapters on nitrofurans by Henry E. and Mary F. Paul and on sulfonamides by L. Neipp. Both are models of clarity in setting forth the pharmacological aspects of these drugs. The excellent chapter by H. J. Rogers might have been entitled "The Mode of Action of Sulfonamides and Some Antibiotics Which Affect Cell Wall Synthesis," rather than the broader title it has since this discussion has been limited to these subjects. It appears from the contents of this volume and the published table of contents for Volume III that much published work on the mechanisms of action of several antibacterial agents will be omitted from this series. This chapter also contains a very clear exposition of structure and function in bacterial and mammalian cells. Finally, Robert Knox has written a stimulating introduction to "Strategy and Tactics in Antibacterial Chemotherapy."

The decision to include the introductory chapter on antibacterial dyestuffs by C. H. Browning is difficult to defend since some important aspects of antibacterial chemotherapy (*e.g.*, steroidal antibiotics or phenols and other disinfectants such as heavy metal compounds) will apparently not be included in this series. The chapter does not do justice to the chosen topic since many antibacterial dyes are not included, and the physical basis for the interaction of dyes with bacterial cells is not fully explored. The chapter by D. J. Kushner, "Microbial Resistance to Harsh and Destructive Environmental Conditions," while informative, seems unrelated to the remainder of the book and could have been omitted without appreciably detracting from the value of the volume as a text on antibacterial chemotherapy.

The editors have intended "to present a reference work useful to investigators . . . concerned with experimental work on new chemotherapeutically active substances," and it is in this respect that the medicinal chemist reading this volume will be most disappointed. There is no attempt to present the chemistry of these substances and too little emphasis on the correlation of structure or physical properties with biological activity. Only clinically useful drugs are discussed, and the data presented on analogs is minimal. Nevertheless, because of the wealth of information collected in this text, it will still be required reading for the medicinal chemist, as well as biologists and physicians or veterinarians, engaged in research in this field.

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The Chemistry and Biochemistry of Fungi and Yeasts. Proceedings of the Symposium on the Chemistry and Biochemistry of Fungi and Yeasts held in Dublin, Ireland, 18–20 July, 1963. Edited by The International Union of Pure and Applied Chemistry. Butterworth Inc., 7235 Wisconsin Ave., Washington 14, D. C. 1963. v + 181 pp. 16.5 × 25.5 cm. Price, $8.50.

The symposium recorded in this volume consisted of fourteen lectures contributed by various international authorities and arranged in three sections under the respective headings of fungal metabolites, the biochemistry of fungi, and the chemistry and biochemistry of yeasts.

The first section contains material that will be generally most familiar to the organic chemist. In it, V. Prelog described the elegant and detailed work carried out by him and his colleagues on