CYCLIZATION OF ACETYLENE-d_2 TO BENZENE-d_6

Sir:

Benzene-d_6 may be prepared directly from acetylene-d_2 at room temperature by use of a modified silica–alumina catalyst. Previously described methods of preparation of benzene-d_6 required either high-temperature (650°) pyrolysis[1] of acetylene-d_2 or the exchange[2] of benzene with D_2SO_4. Both of these methods are inherently wasteful of deuterium in that the pyrolysis reaction results in a number of undesirable deuterium-containing products while the exchange reaction requires a number of exchanges. Also, the subsequent separation and purification procedures are laborious and time-consuming. On the other hand, the preparation described here is relatively easy and efficient. No products other than benzene-d_6 are formed in the reaction.

The deuterium content of the benzene-d_6 depends only on the purity of the deuterium oxide[3] used to form acetylene-d_2 from calcium carbide. Prior to reaction with deuterium oxide, the calcium carbide is heated to 600° to remove all traces of hydrogen or acetylene from the solid. By this means acetylene-d_2, analyzed mass spectrometrically to contain 99.5% D, is prepared.

The modified catalyst is prepared by repeatedly exposing Houdry Type M-46 silica–alumina cracking catalyst (previously dried at 275°) to diborane.[4] The drying temperature is not critical but does determine the amount of bound water[5] retained by the catalyst and, consequently, the amount of diborane that will react with the hydroxyl groups on the surface.[6]

In a typical preparation approximately 300 cc. of acetylene-d_2 was circulated through a 3-cm.-thick bed of the modified catalyst (10 g.) in a closed system whose total capacity was 600 cc. As it was formed, the product was collected in a trap cooled by Dry Ice. After circulation for forty-five minutes the Dry Ice was replaced by liquid nitrogen to condense the unused acetylene-d_2. The catalyst was then heated to 150° *in vacuo* to recover any adsorbed benzene-d_6. The benzene-d_6 was separated from the acetylene-d_2 by high-vacuum fractionation. Under these conditions approximately 50% of the acetylene-d_2 had been converted to benzene-d_6. By mass spectral analysis the benzene-d_6 was found to contain 2.7% of the C_6D_5H species (equivalent to 0.45%H). The mass spectrum of the product compared favorably with that of the API[7]; however, the product prepared here had a slightly higher deuterium content.

When the acetylene-d_2 was first exposed to the catalyst bed, an appreciable amount of heat was evolved; consequently, for larger scale preparations it may be advisable to cool the catalyst.

Significantly, there was no exchange of deuterium or hydrogen between the modified catalyst and the acetylene or benzene. It was possible to prepare, alternately, benzene and benzene-d_6 on the same catalyst bed without forming partially-deuterated products. However, when a mixture of acetylene and acetylene-d_2 was passed through the modified catalyst, the product consisted of both even and odd numbered deuteriated benzenes with deuterium and hydrogen statistically distributed among these species. A detailed study of the cyclization reaction, directed toward shedding light both on the mechanism of cyclization of acetylene and the catalytic nature of silica–alumina gels, is being carried out and will be reported later.

RESEARCH LABORATORY I. SHAPIRO
OLIN MATHIESON CHEMICAL CORPORATION
PASADENA, CALIFORNIA H. G. WEISS

RECEIVED MAY 13, 1957

(1) G. R. Clemo and A. McQuillen, *J. Chem. Soc.*, 851 (1935).
(2) C. K. Ingold, C. G. Raisin and C. L. Wilson, *ibid.*, 915 (1936).
(3) Obtained from Stuart Oxygen Co., 99.5% D_2O.
(4) I. Shapiro, H. G. Weiss, M. Schmich, S. Skolnik and G. B. L. Smith, THIS JOURNAL, **74**, 901 (1952).
(5) I. Shapiro and I. M. Kolthoff, *ibid.*, **72**, 776 (1950).
(6) I. Shapiro and H. G. Weiss, *J. Phys. Chem.*, **57**, 219 (1953).
(7) American Petroleum Institute Research Project No. 44, Carnegie Inst. of Tech., Serial No. 609.

RESOLUTION OF DL-MEVALONIC ACID AND THE SYNTHESIS AND BIOLOGICAL ACTIVITIES OF DL-3-HYDROXY-3-METHYLGLUTARALDEHYDIC ACID

Sir:

The discovery of mevalonic acid, a new acetate-replacing and growth factor for lactobacilli, was reported recently,[1,2] and its structure was proven to be 3,5-dihydroxy-3-methylpentanoic acid (I).[3,4] The synthesis of DL-mevalonic acid has been reported,[3,4,5] and it was found to have one-half the microbiological activity of the natural compound.[3,4]

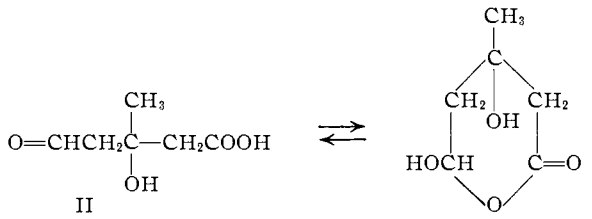
Fractional crystallization of the amides obtained by reaction of DL-mevalonic acid lactone with (+)-α-phenyl-1-naphthalenemethylamine yielded an amide melting at 151–152° (*Anal.* Calcd. for $C_{23}H_{25}NO_3$: C, 76.00; H, 6.93; N, 3.85. Found: C, 76.28; H, 6.90; N, 3.81) $[\alpha]^{25}D$ + 29° (*c*, 1.1 in chloroform). Alkaline hydrolysis of this amide yielded mevalonic acid (isolated as the crystalline N,N′-dibenzylethylenediammonium salt, m.p. 125–126°; *Anal.* Calcd. for $C_{28}H_{44}N_2O_8$: C, 62.66; H, 8.26. Found: C, 62.60; H, 8.28) which had microbiological activity for *Lactobacillus acidophilus*, ATCC 4963,[1] equal to that of the natural isomer.

When it became known[6] that mevalonic acid is a precursor in the formation of cholesterol, consideration of alternative biosynthetic reactions led to an evident interest in the closely related aldehyde, 3-hydroxy-3-methylglutaraldehydic acid (mevaldic acid, II). This new aldehyde has now been synthesized for study in "isoprenoid" biosynthetic systems.

A Reformatsky reaction involving the dimethylacetal of acetoacetaldehyde and ethyl bromoacetate

(1) H. R. Skeggs, L. D. Wright, E. L. Cresson, G. D. E. Macrae, C. H. Hoffman, D. E. Wolf and K. Folkers, *J. Bact.*, **72**, 519 (1956).
(2) L. D. Wright, E. L. Cresson, H. R. Skeggs, G. D. E. Macrae, C. H. Hoffman, D. E. Wolf and K. Folkers, THIS JOURNAL, **78**, 5273 (1956).
(3) D. E. Wolf, C. H. Hoffman, P. E. Aldrich, H. R. Skeggs, L. D. Wright and K. Folkers, *ibid.*, **78**, 4499 (1956).
(4) D. E. Wolf, C. H. Hoffman, P. E. Aldrich, H. R. Skeggs, L. D. Wright and K. Folkers, *ibid.*, **79**, 1486 (1957).
(5) C. H. Hoffman, A. F. Wagner, A. N. Wilson, E. Walton, C. H. Shunk, D. E. Wolf, F. W. Holly and K. Folkers, *ibid.*, **79**, 2316 (1957).
(6) P. A. Tavormina, M. H. Gibbs and J. W. Huff, *ibid.*, **78**, 4498 (1956).

yielded ethyl DL-3-hydroxy-3-methyl-5,5-dimethoxypentanoate (III), b.p. 61–63° (0.1 mm.), $n^{25}D$ 1.4353. (*Anal.* Calcd. for $C_{10}H_{20}O_5$: C, 54.53; H, 9.15. Found: C, 54.79; H, 8.95.) Hydrolysis of III with sodium hydroxide yielded DL-3-hydroxy-3-methyl-5,5-dimethoxypentanoic acid (IV) which was isolated as the crystalline N,N′-dibenzylethylenediammonium salt, m.p. 107–107.5°. (*Anal.* Calcd. for $C_{32}H_{52}N_2O_{10}$: C, 61.52; H, 8.39; N, 4.48. Found: C, 61.32; H, 8.73; N, 4.60.) Hydrolysis of IV at 25° with 0.1*N* hydrochloric acid yielded DL-3-hydroxy-3-methylglutaraldehydic acid (II) in solution. The presence of the unstable and reactive aldehyde II was proven by reduction of it with either hydrogen over a platinum catalyst or with sodium borohydride in alkaline solution to give DL-mevalonic acid (I) in apparently quantitative yield as based on microbiological assay. Varying the time of acid hydrolysis of IV from 15 minutes to 5 hours did not appreciably reduce the high yield of DL-mevalonic acid, although dehydration and decarboxylation of II to 3-methylcrotonaldehyde was observed when more vigorous hydrolysis conditions were employed. After either reduction step, the DL-mevalonic acid was isolated as its crystalline N,N′-dibenzylethylenediammonium salt in *ca.* 30% yield. This product was shown to be identical with an authentic sample of N,N′-dibenzylethylenediammonium bis-(DL-mevalonate) by comparison of the infrared spectra, by a mixed melting point determination and by microbiological assay with *Lactobacillus acidophilus*, ATCC 4963.



II

Solutions of the aldehyde were prepared from the acetal immediately before biological testing. The microbiological activity of DL-3-hydroxy-3-methylglutaraldehydic acid for *Lactobacillus acidophilus* was found to be about 1/200 that of DL-mevalonic acid. The corresponding dimethylacetal (IV) was essentially inactive in this test. The effect of the aldehyde II on the incorporation of acetate into cholesterol was studied. Experiments (Table I) show that DL-3-hydroxy-3-methylglutaraldehydic acid suppresses the incorporation of 1-C^{14}-labelled acetate into cholesterol by rat liver homogenate to about the same degree as mevalonic acid. The corresponding acetal was inactive in this system. Work is in progress to prepare the labelled aldehyde so that it can be studied in this and other biosynthetic systems.

TABLE I

INHIBITION OF THE INCORPORATION OF 1-C^{14}-LABELLED ACETATE INTO CHOLESTEROL

Each flask contained 5 ml. of rat liver homogenate, 1 mg. each of ATP and DPN, and 0.2 mg. 1-C^{14}-acetate (2.44 μcurie). Compounds were added as indicated. Final volume was 10 ml. Gas phase was 95% O_2–5% CO_2. Incubation with agitation was carried out at 37° for 4.5 hr. Cholesterol was isolated and counted as the digitonide.

Compound added	Level, mg.	Experiment 1 Recovered cholesterol c.p.m./mg. C	Experiment 1 % Inhibition	Experiment 2 Recovered cholesterol c.p.m./mg. C	Experiment 2 % Inhibition
None	...	5,294	..	16,519	..
DL-Mevalonic acid	1.0	...	..	9,288	44
	1.5	1,808	66	6,340	62
	3.0	212	96	305	96
DL-Mevaldic acid	1.0	4,294	19	11,919	28
	1.5	1,349	75	11,007	33
	3.0	184	97	2,221	87
DL-3-Hydroxy-3-methyl-5,5-dimethoxypentanoic acid	1.5	5,574	0	17,030	0
	3.0	...	..	16,828	0

CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES DIVISION OF MERCK & CO., INC. RAHWAY, NEW JERSEY

CLIFFORD H. SHUNK
BRUCE O. LINN
JESSE W. HUFF
JAMES L. GILFILLAN
HELEN R. SKEGGS
KARL FOLKERS

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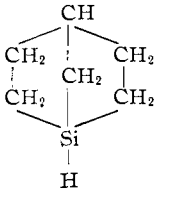
STEREOCHEMISTRY OF HYDRIDE ION DISPLACEMENT FROM SILICON. ENHANCED RATES AT BRIDGEHEAD AND 4-RING SILICON ATOMS[1]

Sir:

The reactions of triorganosilanes, R_3SiH, with hydroxide ion in 95% ethanol have received much study and proceed $R_3SiH + OH^- + SH \rightarrow R_3SiOH + H_2 + S^-$, where SH represents solvent. Hydroxide is not consumed and hydrogen formation (which is quantitative) follows a pseudo first order rate law. These reactions are first order with respect to both silane and hydroxide, $-d[\text{silane}]/dt = k_2[\text{silane}][OH^-]$,[2] and are thus formally similar to SN2 displacements on carbon from the standpoint of kinetics.

In this communication we wish to record data on the reactivities of bridgehead (I) and 4-ring (II)



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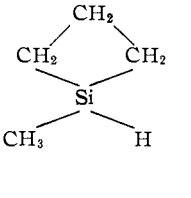

II

silicon hydrides relative to the reactivities of acyclic and other previously known cyclic silicon hydrides.[3,4]

(1) Paper 53 in a series on organosilicon chemistry; for 52 see L. H. Sommer, O. W. Steward and P. G. Campbell, THIS JOURNAL, **79**, in press (1957).

(2) For a recent paper on hydrogen isotope effects and pertinent references to earlier work on these reactions see L. Kaplan and K. E. Wilzbach, *ibid.*, **77**, 1297 (1955).

(3) The bridgehead silane, I, has been reported, L. H. Sommer and O. F. Bennett, *ibid.*, **79**, 1008 (1957).

(4) The 4-ring silane, II, 1-methyl-1-silacyclobutane, b.p. 63° (733 mm.), $n^{20}D$ 1.4313 was prepared by a conventional 3-step procedure from allyl chloride and methyldichlorosilane as starting materials. *Anal.* Calcd. for $C_4H_{10}Si$: Si, 32.6; H (attached to Si), 1.16. Found: Si, 32.2; H (attached to Si), 1.11. The infrared spectrum of II had the sharp maximum at 8.9 μ characteristic of four other silacyclobutane compounds prepared in This Laboratory.