in Table I. The results for hafnium dioxide were corrected for the zirconium dioxide content by means of data of Kelley,[4] and those for hafnium tetrachloride were corrected for the zirconium tetrachloride content by means of data of the author.[5] The corrections ranged from 0.09 to 0.99% for the dioxide and from 1.11 to 1.23% for the tetrachloride, depending upon the temperature.

The substances exhibit normal types of heat capacity curves over the temperature range 51–298°K., analogous in shape to those of the corresponding zirconium compounds.

TABLE I

HEAT CAPACITIES

T, °K.	C_p, cal./deg. mole	T, °K.	C_p, cal./deg. mole	T, °K.	C_p, cal./deg. mole
		HfO_2 (mol. wt., 210.60)			
52.47	2.216	114.60	6.507	216.37	11.82
56.55	2.499	124.63	7.153	226.34	12.21
60.70	2.818	136.02	7.843	236.13	12.53
65.29	3.177	146.13	8.435	245.94	12.89
70.13	3.525	156.02	9.000	256.36	13.21
74.90	3.853	166.07	9.523	266.38	13.51
80.36	4.237	176.11	10.04	276.25	13.81
85.12	4.562	187.91	10.61	286.50	14.11
94.99	5.220	196.35	10.98	296.34	14.33
104.57	5.845	206.35	11.42	(298.16)	(14.40)
		$HfCl_4$ (mol. wt., 320.43)			
52.26	11.48	114.45	20.54	216.53	26.81
56.24	12.17	124.48	21.54	226.22	27.18
60.51	13.00	135.90	22.55	236.15	27.47
64.93	13.85	146.16	23.34	245.86	27.71
69.42	14.63	155.96	23.98	256.37	27.93
73.99	15.34	166.15	24.60	266.41	28.16
79.91	16.25	176.19	25.15	276.27	28.40
84.01	16.86	186.15	25.64	286.53	28.62
94.88	18.30	196.10	26.07	296.55	28.73
104.44	19.42	206.33	26.42	(298.16)	28.80

Entropies.—The entropy increments between 51 and 298.16°K. (the measured range) were obtained by Simpson-rule integrations of C_p against log T plots. Extrapolations from 51 to 0°K. were made by means of the empirical Debye and Einstein function sums given below. The function sum for hafnium dioxide fits the measured data to within 1.0% up to 200°K. and to within 3.2% up to 298.16°K. Similarly, that for hafnium tetrachloride fits the measured data to within 1.0% up to 167°K. and to within 3.3% up to 298.16°K.

$$HfO_2\text{:}\ D(266/T) + E(479/T) + E(794/T)$$

$$HfCl_4\text{:}\ D(69.0/T) + 2E(161/T) + 2E(402/T)$$

The entropy results appear in Table II. They may be compared with values for zirconium dioxide and zirconium tetrachloride, which are, respectively, $S°_{298.16} = 12.12 \pm 0.08$[4b] and $S°_{298.16} = 44.5 \pm 0.5$.[5]

TABLE II

ENTROPIES AT 298.16°K. (CAL./DEG. MOLE)

	HfO_2	$HfCl_4$
0–51°K. (extrap.)	0.89	8.64
51–298.16°K (meas.)	13.29	36.93
$S°_{298.16}$	14.18 ± 0.10	45.6 ± 0.6

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[4] K. K. Kelley, (a) *Ind. Eng. Chem.*, **36**, 377 (1944); (b) U. S. Bur. Mines Bulletin 477 (1950).

[5] S. S. Todd, THIS JOURNAL, **72**, 2914 (1950).

Dehydration Products of 1,1,4,4-Tetraphenyl-1,4-butanediol[1]

BY WILLIAM J. WASSERMAN AND MILTON C. KLOETZEL

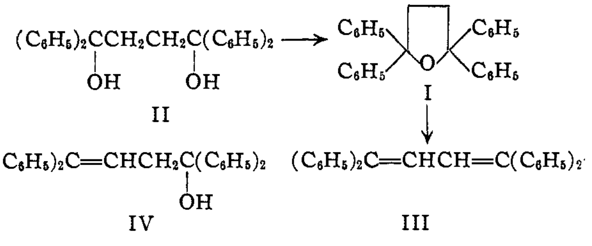
RECEIVED JANUARY 17, 1953

A compound melting at 182° and described as 2,2,5,5-tetraphenyltetrahydrofuran (I) was reported by Valeur[2] and again by Salkind and Teterin[3] to result from the dehydration of 1,1,4,4-tetraphenyl-1,4-butanediol (II) with boiling acetic acid. However, Acree[4] designated I as one of three possible structures for a substance, m.p. 163–165°, isolated from the reaction of phenylmagnesium bromide with diethyl succinate and also from the dehydration of the aforementioned diol.

In the course of certain investigations of the hydrogenated furan nucleus we had occasion to prepare I and therefore found it necessary to establish the identities of the materials melting at 182° and at 163–165°.

The reaction of phenylmagnesium bromide with methyl β-benzoylpropionate was found to yield diol II in 54% yield when effected at room temperature,[5] 49% at the temperature of refluxing ether, and 41% at 0°. In the latter instance there was also produced a 10% yield of 1,4-diphenyl-1,4-butanedione.

Dehydration of diol II with boiling acetic acid or with bromine yielded a compound melting at 180.5–181.5° as reported by Valeur[2] and by Salkind and Teterin.[3] This substance showed the proper analysis for a monodehydration product of diol II and did not react with cold permanganate solution. Zerewitinoff analysis indicated that the compound contained no active hydrogen. With anhydrous formic acid the compound was dehydrated to 1,1,-4,4-tetraphenyl-1,3-butadiene (III). This compound is therefore 2,2,5,5-tetraphenyltetrahydrofuran (I) as originally designated by Valeur.[2]



Valeur[6] and Dilthey and Last[7] have reported excellent yields of diol II from the slow addition of diethyl succinate to phenylmagnesium bromide at

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[1] Abstracted from the M.S. thesis of William J. Wasserman. Presented at the 123rd National Meeting of the American Chemical Society, Los Angeles, March, 1953.

[2] A. Valeur, *Compt. rend.*, **136**, 694 (1903).

[3] J. Salkind and V. Teterin, *Ber.*, **62**, 1746 (1929).

[4] S. F. Acree, *Am. Chem. J.*, **33**, 180 (1905).

[5] M. C. Kloetzel, THIS JOURNAL, **62**, 3405 (1940).

[6] A. Valeur, *Bull. soc. chim. France*, **29**, 683 (1903).

[7] W. Dilthey and E. Last, *Ber.*, **37**, 2639 (1904).

room temperature. In our hands this reaction, effected in gently refluxing ether, yielded 64% of diol II and 11% of 1,4-diphenyl-1,4-butanedione when the reaction mixture was hydrolyzed with ammonium chloride solution. When dilute hydrochloric acid was employed for hydrolysis the yield of diol was reduced to 54% and a small quantity (6%) of 1,1,4,4-tetraphenyl-3-buten-1-ol (IV), m.p. 122.5–123.5°, was isolated.

Zerewitinoff analysis of the unsaturated alcohol showed the presence of one hydroxyl group. The compound rapidly decolorized cold permanganate solution. Structure IV was confirmed when ozonolysis yielded benzophenone and 3-hydroxy-3,3-diphenylpropanoic acid.

It is obvious that the substance reported by Acree[4] to melt at 163–165° is neither I nor IV. In an effort to obtain a sample of the material reported by Acree, diethyl succinate was added rapidly to phenylmagnesium bromide so that the reaction was effected in vigorously refluxing ether, and sulfuric acid was employed for hydrolysis. Under these conditions, which approximate as closely as possible those described by Acree, the products were obtained in the form of a mixture which was difficult to separate and which had a relatively narrow m. p. range in the vicinity of 160°. Upon careful fractional crystallization from carbon disulfide and nitromethane, this mixture finally yielded 2,2,5,5-tetraphenyltetrahydrofuran (I) and 1,1,4,4-tetraphenyl-1,3-butadiene (III).

It appears likely that the substance reported by Acree to melt at 163–165° was actually a mixture of I and III.

Experimental[8]

The reaction of methyl β-benzoylpropionate with phenylmagnesium bromide was effected as previously described[5] except that the ester was added to the mechanically stirred Grignard reagent, kept at ice-bath temperature, over a period of 35 minutes, and the temperature of the reaction mixture was subsequently allowed to rise to 20° during the course of one hour. Fractional crystallization of the product from acetone yielded 4.9 g. (41%) of **1,1,4,4-tetraphenyl-1,4-butanediol** (II), m.p. 203.5–204.5°, and 0.73 g. (10%) of **1,4-diphenyl-1,4-butanedione**, m.p. 145–146°. The latter showed no m.p. depression when mixed with an authentic sample of the diketone prepared by the method of Fritz.[9]

When the ethereal solution of methyl β-benzoylpropionate was added over a period of one hour to the Grignard reagent kept at constant reflux, the yield of diol II was 49%.

2,2,5,5-Tetraphenyltetrahydrofuran (I).—When 2.03 g. of diol II was added to 50 cc. of boiling glacial acetic acid and the solution was boiled for 5 minutes, 1.32 g. (68%) of I separated from the solution upon cooling; m.p. 180.5–181.5° after two recrystallizations from acetone.

The tetrahydrofuran was also obtained when 4.7 g. of a 13% solution of bromine in chloroform was added dropwise to a solution of 1.00 g. of the diol in 100 cc. of chloroform. After standing at 20° for 6.5 hours the solution was evaporated under reduced pressure. The residue was crystallized once from acetone to yield 0.58 g. (61%) of I.

Anal. Calcd. for $C_{28}H_{24}O$: C, 89.32; H, 6.42. Found: C, 89.30; H, 6.19.

The tetrahydrofuran did not decolorize a 2% aqueous solution of potassium permanganate at 20°. A Zerewitinoff determination[10] showed the absence of active hydrogen.

A mixture of 180 mg. of 2,2,5,5-tetraphenyltetrahydrofuran and 5 cc. of anhydrous formic acid was refluxed for 3 hours. After dilution with 5 cc. of water the mixture was extracted with 30 cc. of benzene and the extract was washed with 5% potassium hydroxide solution. Evaporation of the dried benzene extract yielded 0.13 g. (76%) of crude 1,1,4,4-tetraphenyl-1,3-butadiene (III) which melted at 202.5–203.5° after two recrystallizations from acetone and one from benzene. Valeur[2] reported a m.p. of 202°.

Reaction of Diethyl Succinate with Phenylmagnesium Bromide. (a) Slow Addition of Ester.—A solution of 17.6 g. of diethyl succinate in 70 cc. of ether was added, over a period of 2.5 hours, to the gently refluxing Grignard reagent prepared from 13.7 g. of magnesium, 82.2 g. of bromobenzene, 110 cc. of ether and a small crystal of iodine. The mixture was then refluxed for an additional period of 0.5 hour and allowed to stand at 20° for 3 hours.

Sixty per cent. of the reaction solution was poured over a mixture of ice and ammonium chloride solution and the resulting suspension was filtered. The crystalline solid was combined with an additional quantity obtained by evaporation of the ether layer. Fractional crystallization from acetone yielded 15.2 g. (64%) of **1,1,4,4-tetraphenyl-1,4-butanediol** (II) and 1.6 g. (11%) of **1,4-diphenyl-1,4-butanedione**. No 1,1,4,4-tetraphenyl-3-buten-1-ol (IV) was found.

The remaining 40% of the original Grignard reaction solution was hydrolyzed by pouring onto a mixture of 300 g. of ice and 5 cc. of concentrated hydrochloric acid. Filtration yielded some solid which was added to that obtained by evaporation of the ether layer. Fractional crystallization from acetone yielded 8.5 g. (54%) of **1,1,4,4-tetraphenyl-1,4-butanediol**, 1.0 g. (11%) of **1,4-diphenyl-1,4-butanedione**, and 0.9 g. (6%) of **1,1,4,4-tetraphenyl-3-buten-1-ol** (IV), m.p. 117–118°. Two recrystallizations from acetone raised the m.p. of IV to 122.5–123.5°.

The unsaturated alcohol decolorized cold 2% permanganate solution practically instantaneously. Reaction with methylmagnesium iodide at 90° in a Zerewitinoff analysis yielded 0.89 mole of methane per mole of IV.

Anal. Calcd. for $C_{28}H_{24}O$: C, 89.32; H, 6.42. Found: C, 89.37; H, 6.56.

A 200-mg. sample of 1,1,4,4-tetraphenyl-3-buten-1-ol dissolved in 70 cc. of reagent ethyl acetate was treated with a stream of oxygen containing 2% ozone for 0.5 hour at 20°. The ozonide solution was then allowed to stand for 3 days in contact with a solution of 5 cc. of 3% hydrogen peroxide in 70 cc. of water. The ethyl acetate layer was then extracted with 50 cc. of 10% aqueous sodium bicarbonate and evaporated to dryness. When the residue was heated with 10 cc. of ethanol and 150 mg. of 2,4-dinitrophenylhydrazine, and 0.2 cc. of concentrated hydrochloric acid was added, a clear solution resulted. Continued refluxing for 5 minutes resulted in the separation of an orange crystalline precipitate. This was washed with cold ethanol and upon crystallization from 25 cc. of acetic acid yielded 50 mg. of **benzophenone 2,4-dinitrophenylhydrazone**, m.p. 234–235°. This material produced no m.p. depression when mixed with authentic benzophenone 2,4-dinitrophenylhydrazone.

The sodium bicarbonate extract of the ethyl acetate solution was acidified with hydrochloric acid and then extracted with five 20-cc. portions of ether. Evaporation of the ether and crystallization of the residue from Skellysolve F yielded 50 mg. of **3-hydroxy-3,3-diphenylpropanoic acid** in colorless needles, m.p. 211–212°, which gave no depression of m.p. when mixed with authentic acid prepared by the method of Rupe and Busolt.[11]

(b) Rapid Addition of Ester.—A solution of 35.2 g. of diethyl succinate in 140 cc. of ether was added, over a period of 70 minutes, to the vigorously refluxing Grignard reagent prepared from 27.4 g. of magnesium, 164.4 g. of bromobenzene, 220 cc. of ether, and a small crystal of iodine. After being allowed to stand at 20° for 3.5 hours the reaction mixture was poured onto a large quantity of ice and then treated with 10 cc. of 5% sulfuric acid. When the ether had evaporated the suspended solid was filtered and recrystallized from ethanol or acetone. Separation of pure compounds could not be effected by successive recrystallizations from these solvents, but mixtures melting over such ranges as 147–158°, 156–163°, 157–161° and 159.5–163.5° were obtained easily.

Separation of a typical mixture finally was effected in the

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[8] All melting points are uncorrected. Analyses are by Dr. Adalbert Elek, Elek Microanalytical Laboratory, Los Angeles, California.

[9] V. Fritz, *Ber.*, **28**, 3028 (1895); *ibid.*, **29**, 1750 (1896).

[10] H. E. Zaugg and W. M. Lauer, *Anal. Chem.*, **20**, 1022 (1948).

[11] H. Rupe and E. Busolt, *Ber.*, **40**, 4537 (1907).

following manner. A 5.3-g. sample, m.p. 156–163°, was treated with a mixture of 15 cc. of carbon disulfide and 5 cc. of nitromethane, whereupon all but 1.92 g. of solid dissolved. The insoluble portion was crystallized twice from acetone to yield 0.70 g. of **2,2,5,5-tetraphenyltetrahydrofuran** (I). Recrystallizations of the soluble portion of the original mixture eventually yielded 0.12 g. of **1,1,4,4-tetraphenyl-1,3-butadiene** (III) as the only other compound which could be isolated in pure condition.

DEPARTMENT OF CHEMISTRY
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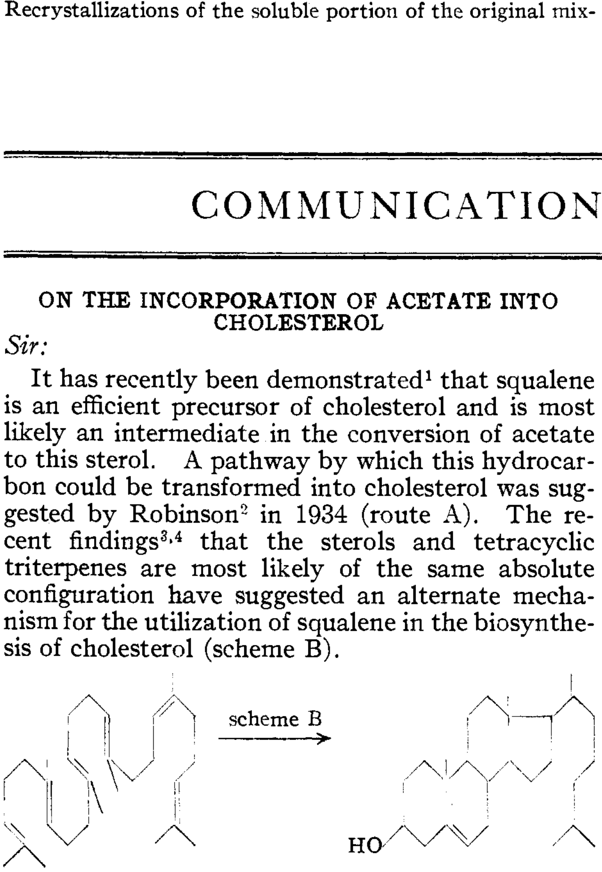
COMMUNICATIONS TO THE EDITOR

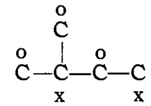
ON THE INCORPORATION OF ACETATE INTO CHOLESTEROL

Sir:

It has recently been demonstrated[1] that squalene is an efficient precursor of cholesterol and is most likely an intermediate in the conversion of acetate to this sterol. A pathway by which this hydrocarbon could be transformed into cholesterol was suggested by Robinson[2] in 1934 (route A). The recent findings[3,4] that the sterols and tetracyclic triterpenes are most likely of the same absolute configuration have suggested an alternate mechanism for the utilization of squalene in the biosynthesis of cholesterol (scheme B).



Degradation of the side-chain[5] and of ring A[6] of cholesterol formed from C^{14}-labeled acetate in biological experiments has indicated that such a biosynthesis might proceed by condensation of isoprenoid units labeled as shown in (I).[7] Therefore, if route A was followed



$$\overset{o}{\mathrm{C}}-\underset{x}{\overset{\overset{\overset{o}{\mathrm{C}}}{|}}{\mathrm{C}}}-\overset{o}{\mathrm{C}}-\underset{x}{\mathrm{C}}$$

I

carbon atoms 10, 13, 20 and 25 of cholesterol would be derived from a carboxyl carbon of acetate and carbon atoms 18, 19, 21 and 26 from the methyl carbon. Such would not be the case if the tetracyclic triterpenoid type of scheme (B) was followed since a migration of a carbon atom would be involved. Thus in route B, carbon atoms 10, 20 and 25 would be from carboxyl carbons and carbon atoms 13, 18, 19, 21 and 26 from methyl carbons. Hence, the acetic acid derived from a Kuhn–Roth oxidation of cholesterol which had been formed biosynthetically from C^{14}-methyl-labeled acetic acid should contain C^{14} in the carboxyl group if route B was followed and not if route A was utilized.

Such an experiment was performed and the acetic acid so obtained was degraded by a Schmidt reaction. It was found that the acetic acid had a specific activity of 55,[8] the carboxyl carbon had 35 and the methyl carbon had 74. It is seen that the carboxyl carbon atom of acetic acid derived from cholesterol possessed C^{14} as would be predicted by route B and thus would rule against the Robinson postulate (route A).

If one assumes that the ratio of methyl carbons to carboxyl carbons in cholesterol derived from acetate[9] is 15/12 and that 5 of the 8 carbon atoms of the 4 molecules of acetic acid (from the angular positions as discussed above) obtained from the Kuhn–Roth oxidation of such a labeled cholesterol are, in turn, derived from the methyl carbons, then the specific activity of the carbon dioxide obtained by decarboxylation of acetic acid should have a value of only 22. The higher value, 35, can be reconciled by consideration of the involvement of the progenitor, methyl-labeled acetate, in the tricarboxylic acid cycle which would lead to some doubly-labeled acetate. This degree of randomization is of the same order of magnitude as recently reported by Cornforth, Hunter and Popják.[6]

These results strongly indicate that if squalene is directly utilized in the synthesis of cholesterol, a reaction scheme of type B is strongly suggested.[10]

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[1] R. G. Langdon and K. Bloch, *J. Biol. Chem.*, **200**, 135 (1953).

[2] R. Robinson, *J. Soc. Chem. Ind.*, **53**, 1062 (1934).

[3] W. Klyne, *J. Chem. Soc.*, 2916 (1952).

[4] W. G. Dauben, D. F. Dickel, O. Jeger and V. Prelog, *Helv. Chim. Acta*, **36**, 325 (1953).

[5] J. Wüersch, R. L. Huang and K. Bloch, *J. Biol. Chem.*, **195**, 439 (1952).

[6] J. W. Cornforth, G. D. Hunter and G. Popják, *Biochem. J.*, **53**, xxiv (1953).

[7] The methyl carbon of acetate is denoted by o and the carboxyl carbon by x.

[8] All specific activities are expressed as dis./min./mg. $BaCO_3$

[9] H. N. Little and K. Bloch, *J. Biol. Chem.*, **183**, 33 (1950).

[10] A recent report by Woodward and Bloch (THIS JOURNAL, **75**, 2023 (1953)) has suggested the same reaction scheme.

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RECEIVED MAY 1, 1953

POSSIBLE SIGNIFICANCE OF LACTONES AS INTERMEDIATES IN OXIDATION OF CARBONACEOUS MATERIALS

Sir:

Controlled oxidation of aqueous, alkaline suspensions of bituminous coals results in the conversion of about 50% of the carbon to a mixture of