COMMUNICATIONS TO THE EDITOR

REDUCTION OF KETONES WITH DIPHENYLTIN DIHYDRIDE. A NEW TYPE OF HYDRIDE REDUCTION

Sir:

Recently van der Kerk, Luijten and Noltes have reported that organotin hydrides of the type R_3SnH (R = phenyl, n-propyl, *n*-butyl) add readily at 70–90°, via an apparently non-radical mechanism, to olefins substituted with groups such as alkyl, aryl, cyano, carbomethoxy, carboxamido, and aryloxy.[1] We attempted to bring about a similar reaction between diphenyltin dihydride and methyl vinyl ketone, reaction (1). However, in wet ether at room temperature in 15 hours, reaction (2) occurred instead.

$$(C_6H_5)_2SnH_2 + CH_2{=}CHCOCH_3 \longrightarrow \begin{cases} (C_6H_5)_2Sn(CH_2CH_2COCH_3)_2 & (1) \\ (C_6H_5)_2Sn + CH_2{=}CHCHOHCH_3 & (2) \end{cases}$$

The products were separated easily by virtue of the fact that the yellow diphenyltin which was formed is insoluble in ether. A 59% yield of pure methyl vinyl carbinol was isolated.

In the usual reductions of carbonyl compounds by metal hydrides a metal salt of the alcohol is formed by the addition $M - H + R_2C{=}O \rightarrow R_2CHOM$. A hydrolysis step is thus necessary in the isolation of the alcohol. The distinctive characteristic of the present reaction is that *two hydrogens* undergo uncatalyzed[2] transfer from tin to the carbonyl group leading directly to the alcohol—no hydrolysis step is required.

Diphenyltin dihydride selectively reduces the carbonyl group of α,β-unsaturated aldehydes and ketones as suggested by the above and the following examples. In each case the α,β-unsaturated alcohol was the only product isolated. The yield of pure product is indicated in parentheses: cinnamaldehyde (75%), mesityl oxide (60%), chalcone (75%), and crotonaldehyde (59%).

Simple carbonyl compounds which have been reduced include cyclohexanone (82%), benzophenone (59%), and benzaldehyde (62%). Camphor and 2-acetylcyclohexanone, on the other hand, are unaffected by diphenyltin dihydride under the same conditions in two days.

A substantial degree of stereoselectivity in this reduction is revealed by the following results: benzil yields 84% of pure *meso*-hydrobenzoin; *d*-carvone, 83% of carveols containing 97% *d-cis*-carveol (based on optical rotation); 4-*t*-butylcyclohexanone, 85% of 4-*t*-butylcyclohexanols containing about 90% *trans* isomer; 2-methylcyclohexanone, 83% of 2-methylcyclohexanols containing 78% *trans* isomer.

Further details on this and other reductions by organotin hydrides will be submitted later.

(1) G. J. M. van der Kerk, J. G. Noltes and J. G. A. Luijten, *J. Applied Chem.*, **7**, 356 (1957).

(2) Uncatalyzed in the sense that a solid hydrogenation catalyst is not needed.

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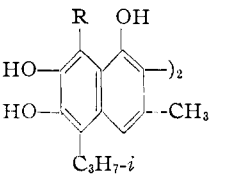
RECEIVED JUNE 10, 1958

TOTAL SYNTHESIS OF GOSSYPOL

Sir:

Reaction of freshly prepared apogossypol[1,2] (I), 2,2′ - bi - 1,6,7 - trihydroxy - 5 - isopropyl - 3-methylnaphthyl, the very unstable degradation product of gossypol[2] (II), with N,N′-diphenylformamidine[3,4] ($C_6H_5NHCH{=}NC_6H_5$) gave a compound identical with dianilinogossypol[2,5] (III) prepared from gossypol by the action of aniline, m.p. and



I, R = H
II, R = CHO
III, R = $C_6H_5N{=}C-$

mixed m.p. 302° (dec.); infrared spectra (KBr) identical. Hydrolysis[6,7,8] of dianilinogossypol yields gossypol. Apogossypol hexamethyl ether has now been demethylated to apogossypol by the use of boron bromide.[9] Identification was established by infrared ($CHCl_3$) comparison and acetylation of the demethylated product. The latter was identical (infrared and mixed m.p.) with apogossypol hexacetate.[1] Since (a) reaction of N,N′-diphenylformamidine with phenols is reported always to introduce the entering group ($C_6H_5N{=}CH-$) ortho to a hydroxyl group[3] and (b) the structure of apogossypol and its hexamethyl ether[10] has been established by an unambiguous synthesis, the results described comprise a total synthesis of gossypol. The structure of gossypol (II), 2,2′-bi-8-formyl-1,6,7-trihydroxy-5-isopropyl-3-methylnaphthyl, formulated by Adams[2] as a

(1) E. P. Clark, *J. Biol. Chem.*, **78**, 159 (1928).

(2) R. Adams, R. C. Morris, T. A. Geissman, D. J. Butterbaugh and E. C. Kirkpatrick, THIS JOURNAL, **60**, 2193 (1938).

(3) J. B. Shoesmith and J. Haldane, *J. Chem. Soc.*, 2704 (1923); 2405 (1924).

(4) R. Kuhn and H. A. Staab, *Ber.*, **87**, 274 (1954).

(5) Kindly supplied by Drs. A. M. Altschul and V. L. Frampton, Southern Regional Laboratory, U. S. D. A.

(6) F. E. Carruth, THIS JOURNAL, **40**, 647 (1918).

(7) E. P. Clark, *J. Biol. Chem.*, **76**, 229 (1928).

(8) V. K. Murty, K. S. Murty and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **A16**, 54 (1942).

(9) F. L. Benton and T. E. Dillon, THIS JOURNAL, **64**, 1128 (1942).

(10) J. D. Edwards, Jr., and J. L. Cashaw, *ibid.*, **79**, 2283 (1957).

result of his extensive studies is now conclusively authenticated.

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THE FORMATION OF α-IMINO ACIDS IN THE ENZYMATIC OXIDATION OF AMINO ACIDS[1]

Sir:

Kinetic application of the borate-tautomerase system[2] to the oxidation of L-tyrosine with ophio L-amino acid oxidase[3] (Fig. 1) confirmed earlier demonstrations[4,5,6] that the oxidase produced the keto tautomer of the α-keto acid. However, in phosphate or tris-(hydroxymethyl)-aminomethane buffers tautomerase addition resulted in formation of a transient absorbing intermediate whose accumulation depended both on the tautomerase and oxidase concentrations (Fig. 2, curves 2, 3, 4). Without tautomerase a smooth rise in optical density from formation of the weakly absorbing keto-enol equilibrium mixture was observed (Fig. 2, curve 1). Tautomerase does not alter the keto-enol equilibrium and could produce only a steeper rise in optical density to the final equilibrium value.

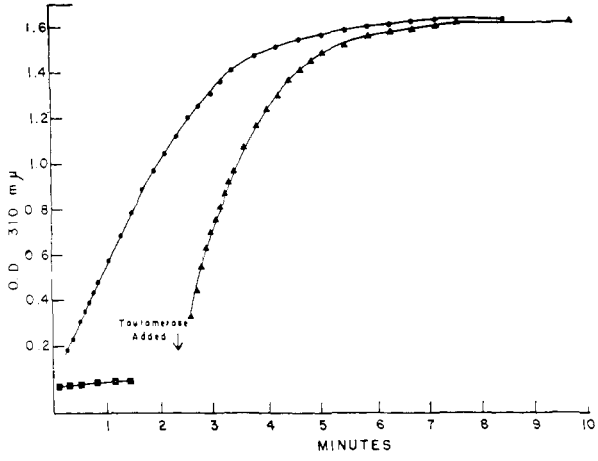


Fig. 1.—Oxidation of 0.4 μmoles L-tyrosine in 3.5 ml. 0.57 *M* borate, *p*H 7.2, with ophio L-amino acid oxidase at 25°: ■, formation of non-absorbing keto-*p*-hydroxyphenylpyruvate. Addition of 0.2 ml. tautomerase at ↓ (▲) or at zero time (●) catalyzed equilibration with the strongly absorbing enol borate. All experiments contained 1 mg. catalase and 4 mg. crude venom of *Agkistrodon piscivorus piscivorus*.[3]

These results represent the first direct indication of Knoop's[7] imino acid intermediate in the oxidation of amino acids. The humps in Fig. 2 result from the formation of the enamine tautomer of the α-imino acid, and represent up to 5% of the initial tyrosine concentration estimated from the extinction coefficients of enol *p*-hydroxyphenylpyruvate and α-N-acetylamino-*p*-hydroxycinnamate. In the presence of tautomerase the reaction takes the course:

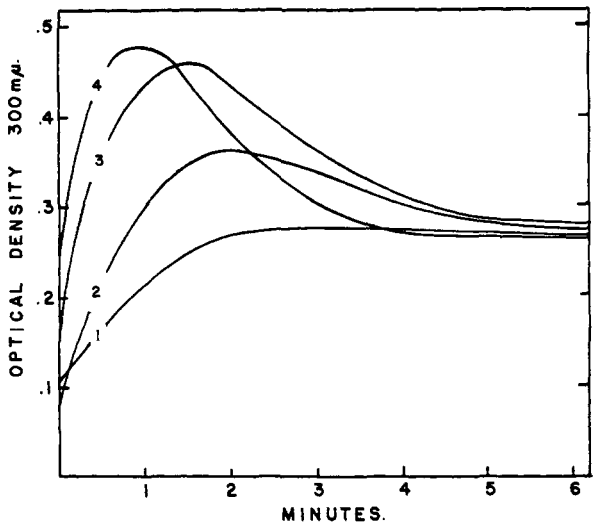
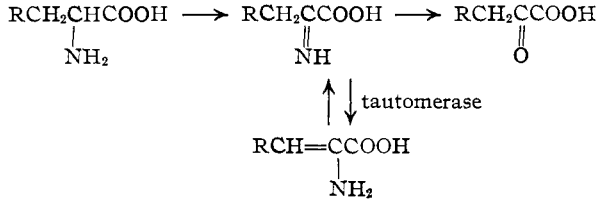


Fig. 2.—Oxidation of 1.2 μmoles of L-tyrosine in 3.2 ml. of 0.0375 *M* phosphate, 0.045 *M* KCl, *p*H 7.2, other conditions as in Fig. 1: curve 1, 8 mg. oxidase, no tautomerase; curve 2, 8 mg oxidase, 0.025 ml. tautomerase; curve 3, 8 mg. oxidase, 0.2 ml. tautomerase; curve 4, 12 mg. oxidase 0.2 ml. tautomerase.



It is assumed that tautomerase, which catalyzes the keto-enol tautomerization of the α-keto acids, also catalyzes the imine-enamine tautomerization of the α-imino acids. The relatively slow spontaneous rate of the latter tautomerization and the rapid imino acid hydrolysis preclude observation of this effect without tautomerase.

Similar enamine accumulations were observed during oxidation of L-phenylalanine and L-tryptophan. The accumulation of the tryptophan intermediate required the presence of a new rat liver indolylpyruvate tautomerase and did not occur with pig kidney tautomerase which is inactive with indolylpyruvate.[2] The interpretation of the humping effect as a transient enamine accumulation is thus supported by the specificity of indolylpyruvate tautomerase.

It should be emphasized that the keto tautomer of the α-keto acid is the ultimate product of the L-amino acid oxidase reaction. Added tautomerase is essential for formation of the enamine, and from the formation of this intermediate it follows that the imine tautomer is the initial amino acid

(1) This investigation was supported by Atomic Energy Commission Contract No. AT(30-1)-901.

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(3) Obtained from Ross Allen's Reptile Institute, Silver Springs, Fla.

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(6) C. Frieden and S. F. Velick, *Biochem. Biophys. Acta*, **23**, 439 (1957).

(7) F. Knoop, *Z. physiol. Chem.*, **67**, 482 (1910); F. Knoop and H. Oesterlin, *ibid.*, **148**, 294 (1925).