Anal. Calcd. for $C_{21}H_{24}N_4O_8$: C, 54.78; H, 5.25. Found: C, 54.86; H, 5.03.

The base was recovered from a cold petroleum ether solution after decomposing the picrate with lithium hydroxide solution, m.p. 76–82°; n.m.r. showed ($CDCl_3$ solvent) τ 8.9 singlet (*t*-CH_3) 3H, 4.87 and 5.10 singlets (=CH_2) 2H; (DMSO solvent) 5.54 singlet vanished with D_2O (*t*-OH).

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.87; H, 9.15. Found: C, 77.72; H, 8.90.

2-Benzyl-3-hydroxy-1,3,4-trimethyl-1,2,3,6-tetrahydropyridine Hydrobromide.—The hydrobromide of IX was made and was found to melt at 167–169°, but was not further characterized. A solution of 0.40 g. of this salt in 2 ml. of 8.8 *N* hydrobromic acid was refluxed for 20 min. The solvent was removed under reduced pressure, and the crystalline product was recovered from acetone in 76% yield. Recrystallized by adding ethyl acetate to a solution in alcohol it melted at 209–211°; n.m.r. showed (base in $CDCl_3$) τ 8.9 singlet (*t*-CH_3) 3H, 9.12 doublet (CH=C—CH_3) 3H, 4.33 singlet (=CH) 1H; (DMSO) 5.72 singlet disappeared with D_2O (*t*-OH).

Anal. Calcd. for $C_{15}H_{22}BrNO$: C, 57.69; H, 7.10. Found: C, 57.97; H, 6.90.

2-Benzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine was isolated as the picrate[7] in the stated yields following catalytic (palladium–barium sulfate) reductions in alcohol solutions of the following: IV (81%), V (82%), VI (77%). By the action of 1 ml. of 1 *N* benzyl Grignard reagent on 0.3 g. of V the picrate of I was isolated in a 58% yield. All identifications were made by mixture melting points and by infrared spectra.

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[7] E. M. Fry and E. L. May, *J. Org. Chem.*, **26**, 2592 (1961).

Formation of Desoxybenzoin in the Borohydride Reduction of the Reaction Mixture of Benzoin with Thionyl Chloride and Pyridine*

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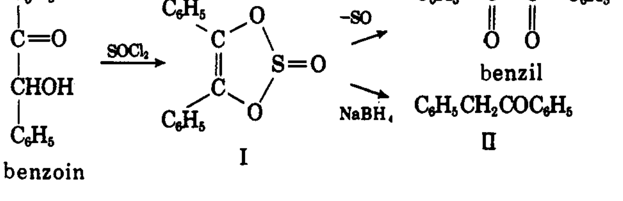
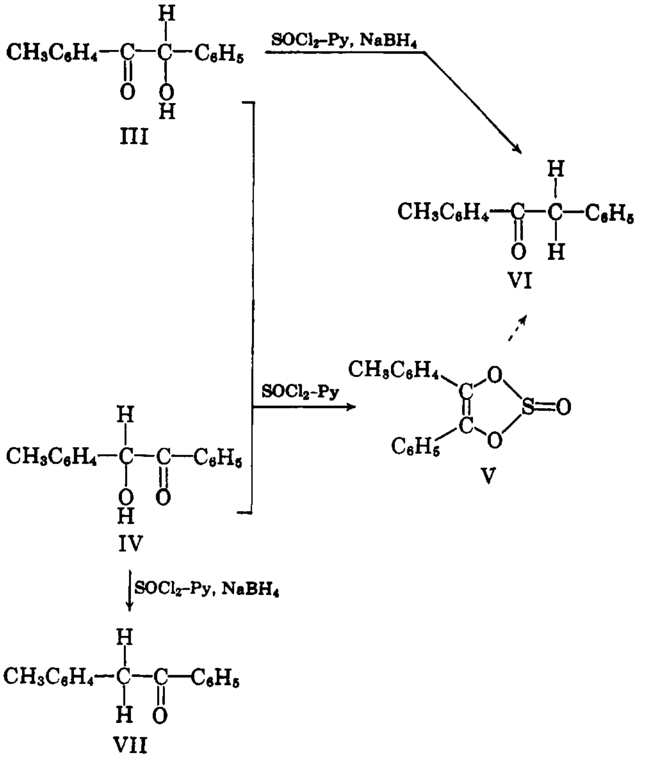
It was suggested in the previous reports[1a,b] that borohydride reduction of *cis*-stilbene-α,α'-diol sulfite (I) to desoxybenzoin (II) would account for the formation of II which had been encountered in the preparation of *trans*-stilbene[1a] and observed in the reaction of benzoin with thionyl chloride and pyridine in methylene chloride followed by treatment with sodium borohydride in 95% ethanol.[1b] This suggestion was derived only from the fact that borohydride reduction of desyl chloride gives only a mixture of 2-chloro-1,2-diphenylethanols rich in the *erythro* isomer,[1a] and thionyl chloride converts benzoin into benzil at room temperature *via* the enediol sulfite (I).[1a,b]



Borohydride reduction of I to II is understandable as an SN1 reaction by analogy to borohydride reduction of an alkyl tosylate.[2] In the ring-substituted derivative of I derived from the asymmetric benzoin bearing an electron-releasing group in the *para* position on one phenyl ring, the electron-releasing group would facilitate the ionization of the C–O bond α to the unsubstituted phenyl ring, and, therefore, borohydride reduction would yield the 4-substituted desoxybenzoin. Thus, both 4-methylbenzoin[3] (III) and 4'-methylbenzoin[4] (IV) are postulated to yield 4-methyldesoxybenzoin[5] (VI) *via* *cis*-4-methylstilbene-α,α'-diol sulfite (V) in the reaction with thionyl chloride–pyridine followed by treatment with sodium borohydride. However, III and IV gave the corresponding desoxybenzoins, VI in 74.6% yield and 4'-methyldesoxybenzoin[5] (VII) in 71.7% yield, respectively. This fact eliminates the possibility of borohydride reduction of I to desoxybenzoin.



Although Goto and Kishi had reported debromination in borohydride reduction of α'-bromo ketones by the catalytic action of metal salts,[6] desyl chloride gave no appreciable amount of desoxybenzoin under the same conditions as in the formation of desoxybenzoin from benzoin.

There remains another possibility, the borohydride reduction of desyl chlorosulfite (VIII) to desoxybenzoin. The reaction mixture of benzoin with thionyl chloride–pyridine in methylene chloride at −20° shows two absorption bands at 1698 and 1214 cm.$^{-1}$ due to carbonyl group and S=O group, respectively. On borohydride reduction, the reaction mixture gave desoxybenzoin in 46.4% yield when the molar ratio of benzoin to thionyl chloride was 1, but the reaction mixture with the molar ratio 2 gave desoxybenzoin in 20.5% yield. When the reaction mixture in methylene chlo-

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* To Professor Louis F. Fieser.

[1] (a) L. F. Fieser and Y. Okumura, *J. Org. Chem.*, **27**, 2247 (1962); (b) Y. Okumura, *ibid.*, **28**, 1075 (1963).

[2] H. C. Brown and H. M. Bell, *ibid.*, **27**, 1928 (1962).

[3] A. Weissberger, *et al.*, *Ann.*, **478**, 112 (1930).

[4] R. T. Arnold and R. C. Fuson, *J. Am. Chem. Soc.*, **58**, 1295 (1936).

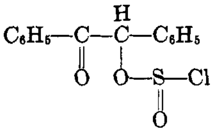
[5] M. Tiffeneau and J. Lévy, *Bull. soc. chim. France*, **49**, 1738 (1931).

[6] T. Goto and Y. Kishi, *Tetrahedron Letters*, No. **15**, 513 (1961).

ride is allowed to stand in an ice bath for a long time, the infrared spectrum shows the presence of about 30% of benzil besides desyl chloride. Thin layer chromatography of the reaction mixture on silica gel in a solvent system of 1:1 petroleum ether–benzene showed the presence of desyl chloride in small amount besides a substance of R_f 0.12 and showed an increase in the amount of desyl chloride on warming. The reaction mixture in methylene chloride, after being shaken with water and dried by passing through a cone of anhydrous sodium sulfate, gave a thin sirup on evaporation of the solvent at reduced pressure. This thin sirup turned into benzoin with liberation of sulfur dioxide at room temperature. The reaction mixture of benzoin with thionyl chloride–pyridine in methylene chloride, after being treated with p-toluidine and removal of excess reagents, showed the presence of a substance of R_f 0.17 in the thin layer chromatogram and gave desoxybenzoin in 63.6% yield by borohydride reduction in 95% ethanol. The relationship between the yield of desoxybenzoin and the molar ratio of benzoin to thionyl chloride eliminates the intermediacy of didesyl sulfite, and the experimental results described above would indicate the intermediacy of desyl chlorosulfite.

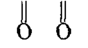
From the reaction mixtures of benzoins with thionyl chloride–pyridine followed by borohydride reduction, the corresponding benzils were isolated: benzil (26.3%) from benzoin, 4-methylbenzil[7] (IX, 5.6%) from III, IX (6.9%) from IV. Formation of desoxybenzoin in better yield in borohydride reduction of p-toluidine-treated reaction mixture could be explained by the assumption that desyl chlorosulfite is trapped in the form of desyl p-tolylsulfiminate and prevented from changing into benzil or desyl chloride. The fact that 4- and 4′-methylbenzoins give the corresponding desoxybenzoins in better yields than benzoin itself, indicates that the methyl group on the ring would facilitate the ionization of C–O bond of the chlorosulfites and, therefore, the borohydride reduction would proceed through an SN1 mechanism. Borohydride reduction of desyl chlorosulfite would account also for the fact that borohydride reduction of a preparation of desyl chloride from benzoin and thionyl chloride by gentle heating gave a small amount of desoxybenzoin.

Formation of the benzil IX from the benzoins III and IV in lower yield would indicate that the resonance of methyl group with benzoyl group or phenyl group and the inductive effect of the methyl group decrease the acidity of hydrogen atom on α-carbon atom, and the formation of the methyl derivative of I is retarded.



$$\mathrm{C_6H_5{-}\underset{\underset{O}{\|}}{C}{-}\overset{H}{\underset{O{-}\underset{\underset{O}{\|}}{S}{-}Cl}{\underset{|}{C}}}{-}C_6H_5}$$

VIII



$$\mathrm{CH_3C_6H_4{-}\underset{\underset{O}{\|}}{C}{-}\underset{\underset{O}{\|}}{C}{-}C_6H_5}$$

IX

Experimental

4-Methylbenzoin (**III**) was prepared from p-bromotoluene and mandelamide by the method described by Weissberger, *et al.*,[3] m.p. 109–110°, ν_{max} in CCl$_4$ 3540 (O–H) and 1677 cm.$^{-1}$ (C=O).

Borohydride Reduction of the Reaction Mixture of III with Thionyl Chloride–Pyridine.—To a solution of 2.1 g. (0.0093 mole) of III in 40 ml. of methylene chloride containing 1.49 ml. (0.0186 mole) of pyridine, cooled in an ice bath, was added 0.74 ml. (0.0102 mole) of thionyl chloride in 5 ml. of methylene chloride with stirring. After being stirred for 30 min., the solvent and excess thionyl chloride were removed by evacuation at low temperature, and the residue was dissolved in 30 ml. of 95% ethanol and treated with 180 mg. (0.00476 mole) of sodium borohydride for 10 min. The reaction mixture was diluted with 70 ml. of water, acidified with 1 N HCl, and extracted with ether. The ether layer was washed with 5% sodium bicarbonate solution and saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of ether gave 2.0 g. of residue, which was chromatographed on 40 g. of alumina and gave 1.46 g. (74.6%) of 4-methyldesoxybenzoin (VI) (eluted with petroleum ether, b.p. 30–70°), m.p. 107° (lit.[5] m.p. 106–107.5°), ν_{max} in CCl$_4$ 1679 cm.$^{-1}$ (C=O), 0.12 g. (5.6%) of 4-methylbenzil[7] (IX) (eluted with 1:1 petroleum ether–benzene), ν_{max} in CHCl$_3$ 1672 cm.$^{-1}$ (C=O), and 0.37 g. of III.

4′-Methylbenzoin (**IV**) was prepared from phenylglyoxal and toluene by the method described by Arnold and Fuson,[4] m.p. 115–116°, ν_{max} in CCl$_4$ 3570 (O–H) and 1682 cm.$^{-1}$ (C=O).

Borohydride Reduction of the Reaction Mixture of IV with Thionyl Chloride–Pyridine.—Compound IV, 2.1 g., was treated in the same manner as III and gave 1.40 g. (71.7%) of 4′-methyldesoxybenzoin (VII) (eluted with petroleum ether), m.p. 95° (lit.[5] m.p. 94–95°), ν_{max} in CCl$_4$ 1683 cm.$^{-1}$ (C=O), 0.14 g. (6.9%) of IX (eluted with 1:1 petroleum ether–benzene), and 0.39 g. of IV (eluted with 1:4 ether–benzene).

Borohydride Reduction of the Reaction Mixture of Benzoin with Thionyl Chloride–Pyridine. A. Benzoin–Thionyl Chloride–Pyridine, 1:1:1:2.—Benzoin, 2.0 g. (0.00942 mole), was treated with 0.75 ml. (0.0103 mole) of thionyl chloride, 1.51 ml. (0.0188 mole) of pyridine, and 180 mg. (0.00476 mole) of sodium borohydride in the same manner as III and gave 0.86 g. (46.7%) of desoxybenzoin, m.p. 55–56° (eluted with benzene), 0.52 g. (26.3%) of benzil (eluted with ether), and 0.11 g. of benzoin (eluted with methanol). In one case, 1.05 g. (56.5%) of desoxybenzoin and 0.34 g. (16.9%) of benzil were isolated.

B. 1:0.5:1.—Benzoin (2.0 g.) was treated with 0.34 ml. of thionyl chloride, 0.76 ml. of pyridine, and 180 mg. of sodium borohydride as described above and gave 0.38 g. (20.5%) of desoxybenzoin, 0.24 g. (12.2%) of benzil, and 0.48 g. of benzoin.

Reaction Mixture of Benzoin with Thionyl Chloride–Pyridine in Methylene Chloride.—The reaction mixture with the molar ratio 1:1.1:2 was prepared in the same manner as III. Thin layer chromatography of this mixture on silica gel with solvent system of 1:1 benzene–petroleum ether showed the presence of small amounts of benzil (R_f 0.39), desyl chloride (R_f 0.34), and a trace of benzoin (R_f 0.02) besides a substance of R_f 0.06, and showed an increase in the amount of desyl chloride on warming. The reaction mixture, immediately after the preparation in methylene chloride, was shaken with water and dried by passing through a cone of anhydrous sodium sulfate. Evaporation of the solvent at 0° *in vacuo* gave a colorless thin sirup. This thin sirup turned into a white powder liberating sulfur dioxide on standing at room temperature, m.p. 125–130°; thin layer chromatography (silica gel, 2:1 benzene–petroleum ether) showed the presence of desyl chloride (R_f 0.45) besides benzoin (R_f 0.08).

Treatment with p-Toluidine.—To the reaction mixture of benzoin (2 g.) with thionyl chloride–pyridine (1:1:2) in methylene chloride at 0°, was added 1.07 g. (1 mole equiv.) of p-toluidine in 20 ml. of methylene chloride with stirring. After being stirred for 30 min., the reaction mixture was transferred to a separatory

Table I

Chromatography of Reaction Mixtures on a Silica Gel Layer

Compd.	R_f values[a] Mixture A[b]	Mixture B[c,d]	Mixture C[d,e]
Benzoin	0.02	0.08	0.08
Intermediate	0.06	. .	0.17
Desyl chloride	0.34	0.45	0.45
Benzil	0.39	. .	. .

[a] Detected by spraying with 50% sulfuric acid and under ultraviolet light. [b] The reaction mixture of benzoin with thionyl chloride–pyridine (1:1.1:2); solvent: 1:1 petroleum ether–benzene. [c] Reaction mixture A in methylene chloride shaken with water. [d] Solvent: 2:1 benzene–petroleum ether. [e] Reaction mixture A treated with p-toluidine.

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(7) H. H. Hatt, A. Pilgrim, and W. J. Hurran, *J. Chem. Soc.*, 93 (1936).

funnel and washed with 0.1 N HCl, 5% sodium bicarbonate solution, and water, then dried over anhydrous sodium sulfate and evaporated to an orange-red sirup. Thin layer chromatography (silica gel, 2:1 benzene–petroleum ether) showed the presence of a substance of R_f 0.17 as major product besides desyl chloride (R_f 0.45) and benzoin (R_f 0.08) (see Table I). Treatment of this sirup with 180 mg. of sodium borohydride in 95% ethanol gave 1.18 g. (63.6%) of desoxybenzoin. Details of the substance of R_f 0.17 will be reported elsewhere.

The Clemmensen Reduction of 1,3-Diketones*[1]

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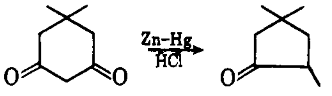
Received November 16, 1964

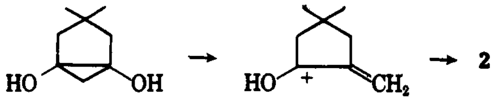
The use of amalgamated zinc in concentrated hydrochloric acid to reduce a ketone or aldehyde carbonyl to methylene is well known, and since the introduction of the method by Clemmensen[2] it has found wide use in organic chemistry.[3] The reaction has been used mainly to reduce monocarbonyl compounds, but the reduction of some diketones has also been reported. In 1933, Khuda[4] subjected 5,5-dimethylcyclohexane-1,3-dione (**1**) to this procedure and obtained, as one product, a monoketone different from the expected 3,3-dimethylcyclohexanone. Dey and Linstead[5] repeated this work and showed that the anomalous product was a ring-contracted ketone, 2,4,4-trimethylcyclopentanone (**2**).



1 **2**

Confirmation of this result was obtained by Khuda and Mukherji[6] who carried out an unambiguous synthesis of this five-membered ring ketone. Subsequently it was shown that another 1,3-diketone underwent rearrangement on Clemmensen reduction, 2,2,4,4-tetramethylcyclobutane-1,3-dione giving some 2,5-dimethylhexan-3-one.[7] A number of cases have been reported where 1,3-diketones have been reduced by the Clemmensen method to hydrocarbons, but unequivocal evidence for the structures of the latter is lacking.[3]

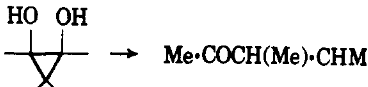
In a review of the Clemmensen reaction, Staschewski[8] proposed a mechanism for the rearrangement observed with 5,5-dimethylcyclohexane-1,3-dione. He postulated that the diketone adds two electrons and two protons to give a diradical which then, intramolecularly, forms a new carbon–carbon bond (**1** → **3**). In the acidic medium this intermediate undergoes a pinacol-type rearrangement (**3** → **4**), further reduction leading to the observed product **2**. It appears that this reaction is faster than the subsequent reduction of the monoketone, enabling the latter to be isolated in up to 50% yield.



3 **4**

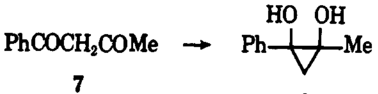
We now present evidence to show that this rearrangement is a general one for the Clemmensen reduction of 1,3-diketones.

Pentane-2,4-dione gave 3-methylbutan-2-one as the sole ketonic product, gas chromatography demonstrating the absence of unrearranged pentan-2-one. On the mechanism developed above, it is not possible to distinguish between C-1 and C-3 of the starting material in the final product. However, by using 3,3-dimethylpentane-2,4-dione, the intermediate cyclopropanediol (**5**) may rearrange either by migration of the C-1 methyl group to give, finally, 2,4-dimethylpentan-3-one or by migration of the C-3 CMe$_2$ group to give, finally, 3,4-dimethylpentan-2-one (**6**). In fact **6** was shown to be the only monoketone present in the products.



5 **6**

1-Phenylbutane-1,3-dione (**7**) would form an unsymmetrical cyclopropanediol (**8**), and, if it rearranged by loss of the hydroxyl group on the carbon α to the phenyl group to form a benzylic carbonium ion, then the final product would be 3-phenylbutan-2-one. Loss of the other hydroxyl group would lead to 2-methyl-1-phenylpropan-1-one. In fact, only the former ketone was obtained and the isomeric one was shown to be absent. 2-Phenylbutane, the product of complete reduction of the rearranged ketone, was shown to be a minor product of this reaction.



7 **8**

The present results, taken with those obtained previously, offer strong support for the mechanism proposed[8] for the Clemmensen reduction of 1,3-diketones.

Experimental

Pentane-2,4-dione.—Pentane-2,4-dione (30 g., 0.30 mole) was added to zinc (200 g., 3.06 g.-atoms), previously amalgamated by the procedure of Martin[3] in 8 M hydrochloric acid (350 ml.), and the mixture was heated under reflux in a flask fitted with a short distillation column. Slow distillation was begun after a few minutes and continued until no more oily droplets passed over. Ether extraction of the distillate yielded a liquid which on distillation gave a forerun (b.p. up to 40°), probably hydrocarbons; a fraction, b.p. 93–96°, 9.1 g. (35%); and a fraction b.p. 130–145°, 0.27 g., chiefly pentane-2,4-dione, leaving a residue of 0.82 g. The second fraction was pure 3-methylbutan-2-one and showed identical boiling point, infrared and n.m.r. spectra, and gas chromatographic retention volume with those of an authentic sample.[9] The semicarbazone had m.p. and m.m.p.

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* To Professor Louis F. Fieser.

(1) A preliminary report has been published: N. J. Cusack and B. R. Davis, *Chem. Ind.* (London), 1426 (1964).

(2) E. Clemmensen, *Ber.*, **46**, 1837 (1913); **47**, 51 (1914); **47**, 681 (1914).

(3) E. L. Martin, *Org. Reactions*, **1**, 155 (1942).

(4) M. Qudrati-Khuda, *Nature*, **132**, 210 (1933).

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(6) M. Qudrati-Khuda and A. Mukherji, *J. Indian Chem. Soc.*, **23**, 435 (1946).

(7) H. L. Herzog and E. R. Buchman, *J. Org. Chem.*, **16**, 99 (1951).

(8) D. Staschewski, *Angew. Chem.*, **71**, 726 (1959).

(9) F. C. Whitmore, W. L. Evers, and H. S. Rothrock, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 408.