2,5-cyclohexadienone[15] in 250 ml. of dry ether was added during 15 minutes to a stirred excess of phenylmagnesium bromide in ether. The mixture was refluxed for 45 minutes and then worked up in a conventional way to yield 47.0 g. (86%) of crude I, m.p. 116–120°. Recrystallization from benzene yielded 45.8 g. of colorless I, m.p.[16] 120.0–121.0°. Attempts to isolate another solid from the remaining reaction products were in vain.

Reaction of I with Formic Acid.—A mixture of 29.9 g. of I and 300 ml. of 90% formic acid was stirred at 0–5° for 8 hours. During this time the solid particles of I gradually disappeared and a pale yellow oil was formed. The reaction mixture was poured on 1 kg. of ice and this mixture extracted thrice with ether. The ethereal extract, after washing with 10% aqueous potassium hydroxide solution (extracts saved, see below), water, and saturated sodium chloride solution, was dried over anhydrous magnesium sulfate. Removal of the ether left 15.5 g. of a yellow oil which on distillation was separated into 4.4 g. of a fraction, b.p. 100–130° at 5 mm., which partly solidified, and 3.7 g. of a fraction, b.p. 150–190° at 5 mm. At this point, distillation was stopped as the residue was decomposing with the evolution of hydrogen chloride. Recrystallization of the lower boiling fraction from alcohol afforded 4.3 g. (25%) of *p*-methylbiphenyl (II), m.p. 45.5–47.0°, undepressed by mixing with an authentic sample of *p*-methylbiphenyl, m.p. 46.5–47.0°, prepared as described below. The infrared spectra of the two substances were identical.

From the above higher boiling fraction, a small amount of a solid, m.p. 88.5–90.0°, was obtained. Since this solid, on hydrolysis in concentrated sulfuric acid, yielded 2-methyl-4-phenylbenzoic acid[3] (IV), m.p. 169.0–171.0°, it was undoubtedly 3-methyl-4-trichloromethylbiphenyl (III).

Anal. Calcd. for $C_{14}H_{11}Cl_3$: C, 58.9; H, 3.9; Cl, 37.3. Found: C, 59.0; H, 4.0; Cl, 36.9.

From the aqueous potassium hydroxide solutions mentioned above was obtained 6.4 g. (30%) of IV on acidification. This had undoubtedly come from hydrolysis of II in the 90% formic acid solvent. To check this, a sample of benzotrichloride was stirred in 90% formic acid for 12 hours at 20–25°. An almost quantitative yield of benzoic acid was obtained.

***p*-Methylbiphenyl (II).**—Reduction of 38.7 g. of *p*-phenylbenzoic acid, m.p. 223–225°, in 500 ml. of ether by addition to a stirred solution of 7.5 g. of lithium aluminum hydride in 300 ml. of ether during 1 hour afforded *p*-phenylbenzyl alcohol,[17] b.p. 170–175° at 8 mm., m.p. 105.0–107.0°, in 90% yield.

A mixture of 18.4 g. of *p*-phenylbenzyl alcohol, 0.6 g. of palladium chloride, 3.0 g. of activated charcoal (Darco G-60) and 75 ml. of alcohol was shaken under 50 p.s.i. of hydrogen. After 1 hour the theoretical amount of hydrogen had been absorbed and a conventional work-up afforded 14.0 g. (84%) of *p*-methylbiphenyl. A recrystallized and sublimed sample melted at 46.5–47.0°.

p-Ethylbiphenyl, m.p. 36–37°, prepared by a Clemmensen reduction of *p*-phenylacetophenone,[18] m.p. 118–120°, had an infrared spectrum which differed significantly from that of II, whereas the infrared absorption spectra of 4-methylbiphenyl was identical to that of II.

2,6-Dichloro-4-methyl-4-trichloromethyl-2,5-cyclohexadienol (VIII).—Reduction of 2,6-dichloro-4-methyl-4-trichloromethyl-2,5-cyclohexadienone by treatment with sodium borohydride as described[6] yielded VIII, m.p. 125.5–127.5°, in 74% yield.

Rearrangement of VIII.—A solution of 2.2 g. of VIII in 30 ml. of acetic acid and 15 ml. of concentrated sulfuric acid[19] was heated on a steam-bath for 2 hours. The mixture was diluted with water and the solid collected. Recrystallization from Skellysolve B (petroleum ether, b.p. 65–70°) yielded 1.0 g. of an acid, m.p. 183.5–184.5°. On refluxing with methanolic sulfuric acid, this acid was converted in high yield into the corresponding methyl ester, m.p. 45.5–46.5°, after recrystallization from Skellysolve B and sublimation.

Anal. Calcd. for $C_9H_8O_2Cl_2$: C, 49.6; H, 3.7. Found: C, 49.4; H, 3.7.

The above acid was shown to be 3,5-dichloro-2-methylbenzoic acid (X) as follows.

Proof of Structure of X.—The above acid (0.52 g.) was dissolved in 5 ml. of concentrated sulfuric acid and the solution was treated with several portions of sodium azide at 40° during two hours.[20] Dilution with water yielded an amine sulfate which was converted to the free amine by alkali. This amine was reductively deaminated[21] to a dichlorotoluene, which, on oxidation by refluxing with an excess of dilute potassium permanganate for 15 hours yielded 0.11 g. of an acid, after the customary workup and recrystallization from benzene–Skellysolve B, which melted at 161.0–162.0°, alone and mixed with an authentic sample of 2,4-dichlorobenzoic acid,[22] m.p. 161.0–162.0°.

(15) Prepared as described in M. S. Newman and A. G. Pinkus, *J. Org. Chem.*, **19**, 978 (1954).

(16) In ref. 3, a m.p. of 120.8–121.0° is given.

(17) J. von Braun, *Ann.*, **436**, 299 (1924).

(18) In ref. 7, a m.p. of 120.0–121.0° was reported.

(19) In ref. 6, a solution of 15 ml. of 20% sulfuric acid in 50 ml. of acetic acid was used. When we repeated this, no rearranged acid was obtained.

(20) See H. Wolff, ref. 11.

(21) According to N. Kornblum, ref. 12.

(22) M. Gomberg and L. H. Cone, *Ann.*, **370**, 183 (1909), give a m.p. of 164°. Our authentic sample was prepared by the oxidation of 2,4-dichlorobenzyl chloride.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

Asymmetric Induction Studies with Optically Active Biphenyls. V. On the Unreliability of Absolute Configurational Assignments Based on Hydride Reductions of Phenylglyoxylates[1]

BY JEROME A. BERSON AND MICHAEL A. GREENBAUM

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Reduction of phenyldihydrothebaine phenylglyoxylate with lithium aluminum hydride produces phenylethylene glycol with an absolute configuration enantiomeric with that of the atrolactic acid produced by addition of methylmagnesium iodide to the phenylglyoxylate. An abnormal reactivity order of the carbonyl groups of ethyl phenylglyoxylate is observed, the *ester* carbonyl group being reduced *faster* than the keto carbonyl group with sodium borohydride. This result demonstrates the need for extreme caution in assignments of absolute configuration based on hydride reductions of phenylglyoxylates.

Prelog's elegant "atrolactic acid method" of establishing absolute configurations of optically active alcohols[2] involves the reaction of methylmagnesium iodide with an optically active phenylglyoxylate, followed by saponification (1). In a formally analogous reaction (2), reduction of an

$$C_6H_5COCO_2R^* \xrightarrow[2,\ H_2O]{1,\ CH_3MgI} C_6H_5\underset{\displaystyle CH_3}{\overset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}}CO_2H + R^*OH \quad (1)$$

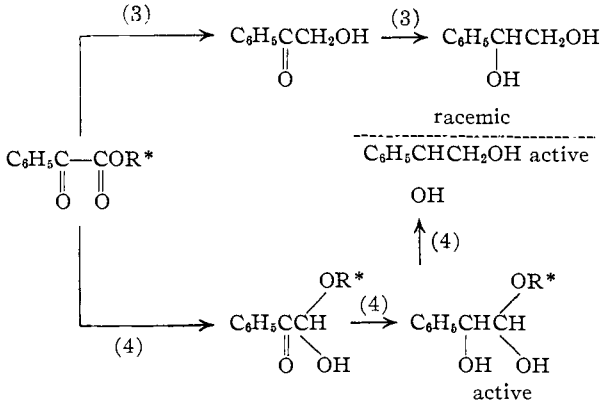
$$C_6H_5COCO_2R^* \xrightarrow{LiAlH_4} C_6H_5\underset{\displaystyle OH}{\overset{|}{\underset{|}{C}}}HCH_2OH + R^*OH \quad (2)$$

(1) This work was supported in part by a grant, NSF-G 4375, from the National Science Foundation.

(2) V. Prelog, *Bull. soc. chim. France*, 987 (1956), and references therein cited.

optically active phenylglyoxylate with lithium aluminum hydride produces optically active phenylethylene glycol.[3] Lithium aluminum hydride reduction of (+)-mandelic acid gives (+)-phenylethylene glycol,[3] and since (+)-mandelic acid and (+)-atrolactic acid have corresponding configurations,[4] the configurations of (+)-phenylethylene glycol and (+)-atrolactic acid are correlated. In the three cases where comparisons are available (phenylglyoxylates of borneol, menthol and α-amyrin),[3] reactions (1) and (2) give self-consistent results; a given phenylglyoxylate affords acid and glycol with identical signs of rotation and hence with corresponding configurations.

The present paper reports an attempt to extend the hydride reduction method to the case of phenylglyoxylates of optically active 2-hydroxybiphenyls. Since previous work[5] had shown that phenyldihydrothebaine phenylglyoxylate (I) gave (−)-atrolactic acid, we anticipated that compound I would give (−)-phenylethylene glycol upon lithium aluminum hydride reduction. In fact, however, (+)-phenylethylene glycol is obtained. A possible source of this anomaly lies in the fact that *both* carbonyl groups of the phenylglyoxylate are attacked by the reagent. If the normal reactivity order (ketone > ester) were reversed, and the ester function were completely reduced to a salt of primary alcohol, totally racemic glycol



would result (path 3). However, reduction to a salt of a hemiacetal followed by reduction of the keto function would in general lead to active glycol (path 4). Asymmetric induction in the creation of the asymmetric center of the glycol by path (4) would then be controlled by the geometry of *two* already existing centers, namely that in R*, which was originally asymmetric, and that in the hemiacetal carbon, which is formed in the first step of path (4). The over-all stereochemical result reflected in the sign of rotation of the glycol produced would be difficult to predict and therefore would bear no readily discernible relationship to the configuration of R*.

In an effort to circumvent this difficulty, we have examined the sodium borohydride reduction of phenyldihydrothebaine phenylglyoxylate, anticipating that only the keto group would be reduced. In methanol, dioxane or *t*-butyl alcohol, reduction gives good yields of phenyldihydrothebaine as the only isolable basic product. No evidence for the presence of phenyldihydrothebaine mandelate is obtained. Further, the crude neutral products of these reductions are free of absorption in the carbonyl region. From a reduction in diethylene glycol diethyl ether at room temperature, there is obtained 58% of phenylethylene glycol and 66% of phenyldihydrothebaine; at 100°, the same two products are obtained in yields of 71 and 70%, respectively.

It is not unreasonable that in a phenylglyoxylate, the juxtaposition of a phenyl and two contiguous carbonyl groups might produce an abnormal reactivity order. In agreement with this, we find that sodium borohydride in dioxane at 100° converts ethyl phenylglyoxylate to phenylethylene glycol in good yield (64% isolated); virtually no carbonyl-containing product is produced. The ester function is apparently reduced *first* in this process, since ethyl mandelate, the expected product of prior reduction of the keto function, is recovered in 90% yield under the reduction conditions that produce phenylethylene glycol from ethyl phenylglyoxylate. That the phenyl group plays an important role in deactivating the keto function is indicated by the fact that a normal reactivity order is observed with a model aliphatic α-ketoester. Ethyl pyruvate is smoothly reduced under the above conditions to ethyl lactate in 71% yield.

Although we have not proved that there is an abnormal reactivity order in lithium aluminum hydride reductions of phenylglyoxylates, the suspicion that the order observed with sodium borohydride also may obtain with lithium aluminum hydride is strong enough to dictate extreme caution in the assignment of absolute configurations on the basis of hydride reductions of phenylglyoxylates unless independent corroboration is available.

The optical yields of the asymmetric reductions reported in the Experimental are maximum values calculated on the basis of $[\alpha]_D$ 58.7° (95% ethanol) as the rotation of optically pure phenylethylene glycol. This value is obtained on the arbitrary assumption that no racemization occurs in the lithium aluminum hydride reduction of methyl mandelate $[\alpha]_D$ +41.0°($CHCl_3$) (23.3% optically pure on the basis of $[\alpha]_D$ 176° for optically pure material[6]) to phenylethylene glycol $[\alpha]_D$ +13.7° (95% ethanol). Partial racemization (at least 31%) apparently accompanies the lithium aluminum hydride reduction[3] of optically pure (+)-mandelic acid, since the glycol obtained[3] had $[\alpha]_D$ +40.6° (95% ethanol). The previously reported[3] optical yields now must be multiplied by a factor no greater than 0.69.

Experimental

Lithium Aluminum Hydride Reduction of (+)-Methyl Mandelate.—To a vigorously stirred solution of 5.0 g. of lithium aluminum hydride in 400 ml. of anhydrous ether was added during 30 minutes a solution of 12.0 g. of methyl mandelate, $[\alpha]^{30}_D$ +41.0° ($CHCl_3$, *c* 5.31, *l* 2), in 200 ml. of anhydrous ether. After one hour at room temperature,

(3) V. Prelog, M. Wilhelm and D. B. Bright, *Helv. Chim. Acta*, **37**, 221 (1954).

(4) J. H. Brewster, THIS JOURNAL, **78**, 4061 (1956), and references therein cited.

(5) J. A. Berson and M. A. Greenbaum, *ibid.* **80**, 445 (1958).

(6) Average of 177 and 174°, the highest rotations reported for methyl mandelate in chloroform. *Cf.* L. Arpesella, A. La Manna and M. Grassi, *Gazz. chim. ital.*, **85**, 1354 (1955), and W. A. Bonner, THIS JOURNAL, **73**, 3126 (1951).

saturated ammonium chloride solution was added, the layers were separated, the aqueous layer was extracted twice with 100-ml. portions of chloroform, and the combined organic layers were dried over magnesium sulfate. Evaporation of the solvents left 9.5 g. (94%) of phenylethylene glycol, m.p. 60.0–64.5°, $[\alpha]^{30}D$ +13.7° (95% ethanol, *c* 3.91, *l* 2). The infrared spectrum was identical with that of an authentic sample of the racemate.

Reduction of Phenyldihydrothebaine Phenylglyoxylate. A. With Lithium Aluminum Hydride.—A solution of the free base was prepared by shaking 17.5 g. of phenyldihydrothebaine phenylglyoxylate perchlorate[5] with ether and concentrated ammonia water. The ether solution was dried over calcium sulfate in the dark in a nitrogen atmosphere, filtered, and added during 40 minutes to a stirred solution of 2.0 g. of lithium aluminum hydride in 250 ml. of anhydrous ether. After an additional hour, saturated ammonium chloride solution and then 50 ml. of 15% hydrochloric acid were added. The layers were separated, the aqueous layer was extracted with chloroform, and the combined organic layers were extracted with 15% hydrochloric acid, washed with water and dried over calcium sulfate. Evaporation of the neutral fraction gave an oil the infrared spectrum of which indicated it to be essentially pure phenylethylene glycol. This material was chromatographed on alumina in chloroform. After a trace of yellow impurity had been washed off the column with chloroform, elution with methanol gave 1.7 g. (45%) of colorless phenylethylene glycol, m.p. 53–57°, $[\alpha]D$ +28.0° (95% ethanol, *c* 2.02, *l* 2), 48% optically pure, infrared spectrum identical with that of the racemate.

The basic fraction (hydrochloric acid extracts and washings) was neutralized with bicarbonate and extracted with ether. After having been dried over calcium sulfate, the ether solution was evaporated to give an oil which was taken up in 95% ethanol and treated with 72% perchloric acid until no further precipitation was noted. The colorless, crystalline product was dried to give 7.1 g. (50%) of phenyldihydrothebaine perchlorate, m.p. 241–244°.

B. With Sodium Borohydride.—A solution of 2.5 g. of sodium borohydride in 200 ml. of dry diethylene glycol diethyl ether was prepared at 100° and cooled to room temperature, whereupon only a slight turbidity developed. It was treated with a solution of phenyldihydrothebaine phenylglyoxylate (from 3.0 g. of perchlorate) in 50 ml. of diethylene glycol diethyl ether. After 5 minutes, the solution was poured into 500 ml. of 10% hydrochloric acid, extracted with chloroform, dried, and evaporated to give 0.45 g. of phenylethylene glycol, m.p. 62–65°, $[\alpha]^{30}D$ +5.8° (95% ethanol, *c* 2.55, *l* 2), 10% optically pure, infrared spectrum identical with that of the racemate.

From the acid-soluble fraction, there were obtained 1.55 g. (66%) of phenyldihydrothebaine perchlorate, m.p. 244–246° (dec.), $[\alpha]D$ +33.8° (95% ethanol).

From a reaction run at 100° for 5 minutes in diethylene glycol diethyl ether, there were obtained 0.57 g. (71%) of phenylethylene glycol, m.p. 64–67°, $[\alpha]D$ +2.1° (95% ethanol), and 1.65 g. (70%) of phenyldihydrothebaine perchlorate, m.p. 244–246° dec.

Reductions run in methanol, dioxane and *t*-butyl alcohol gave phenyldihydrothebaine perchlorate and carbonyl-free neutral material.

Borohydride Reduction of Ethyl Phenylglyoxylate.—A solution of 2.28 g. of sodium borohydride in 150 ml. of dioxane was heated at 100°, stirred and treated with a solution of 5.34 g. of ethyl phenylglyoxylate in 50 ml. of dioxane during 5 minutes. After an additional 10 minutes, dilute hydrochloric acid was added, the mixture was concentrated to a small volume, diluted with chloroform, dried over calcium sulfate and filtered. This solution showed only weak carbonyl absorption and gave a faint positive Brady test. Cooling deposited 2.65 g. (64%) of phenylethylene glycol, m.p. 65–67°, infrared spectrum identical with that of the racemate.

Application of the above reduction conditions to 5.40 g. of ethyl mandelate, extraction with chloroform, and distillation gave 4.85 g. (90%) of ethyl mandelate, b.p. 155–156° (35 mm.), $n^{26}D$ 1.5101, infrared spectrum identical with that of the starting material, which had b.p. 156–157° (35 mm.), $n^{26}D$ 1.5106.

Borohydride Reduction of Ethyl Pyruvate.—A sample of 5.8 g. of ethyl pyruvate was reduced with 5.56 g. of sodium borohydride according to the above procedure. Extraction with chloroform and distillation gave 4.2 g. (71%) of ethyl lactate, b.p. 152–153°, $n^{26}D$ 1.4136, infrared spectrum identical with that of an authentic sample.

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[CONTRIBUTION FROM THE MCPHERSON CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Condensed Cyclobutane Aromatic Compounds. VIII. The Mechanism of Formation of 1,2-Dibromobenzocyclobutene; A New Diels–Alder Synthesis

BY M. P. CAVA, A. A. DEANA AND K. MUTH

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The conversion of $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene to 1,2-dibromobenzocyclobutene by iodide ion proceeds *via* a transient *o*-quinodimethane derivative. The *o*-quinodimethane intermediate can be trapped by maleic anhydride or N-phenylmaleimide to give the expected 2,3-disubstituted naphthalenes. *p*-Benzoquinone and 1,4-naphthoquinone can be employed also as dienophiles, giving simple syntheses of 1,4-anthraquinone and 5,12-naphthacenequinone, respectively.

Two mechanisms have been suggested for the conversion of $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene (I) to 1,2-dibromobenzocyclobutene (II). The first of these[1] involves a concerted elimination reaction giving rise to a highly reactive *o*-quinodimethane derivative (III) which then cyclizes spontaneously to the observed dibromide II. Reactions analogous to each of the two steps of this proposed mechanism have already been reported. Formation of a polymer of *o*-quinodimethane (IV) occurs readily[2] when attempts are made to convert the chloroether V into a Grignard reagent, but cyclization of IV to benzocyclobutene can be observed under different conditions, particularly in the gas phase.[3] The second mechanism suggested for the formation of 1,2-dibromobenzocyclobutene[4] assumes the generation of the intermediate carbanion VI, which displaces a bromide ion from the opposite and very close carbon atom.[5]

Since it was possible to trap *o*-quinodimethane itself as a Diels–Alder adduct with N-phenylmaleimide,[3] it appeared that this dienophile should be capable also of trapping the dibromo-*o*-quinodimethane III, if this molecule actually is an intermediate in the conversion of tetrabromide I to dibromide II. This expectation was indeed realized. When $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene (I) and sodium iodide are warmed in dimethylformamide at 60–70° for twenty-four hours in the pres-

(1) M. P. Cava and D. R. Napier, THIS JOURNAL, **79**, 1701 (1957).
(2) F. G. Mann and F. H. C. Stewart, *J. Chem. Soc.*, 2826 (1954).
(3) M. P. Cava and A. A. Deana, THIS JOURNAL, **81**, 4266 (1959).
(4) F. R. Jensen and W. E. Coleman, *J. Org. Chem.*, **23**, 869 (1958).
(5) The conversion of I to II *via* VI would seem to be an almost concerted process: otherwise, a considerable amount of VI would be lost by proton abstraction from the solvent (ethanol).