The Stereochemical Effect of a Carboxyl Function on the Reduction of Ketones with Sodium Borohydride[1a]

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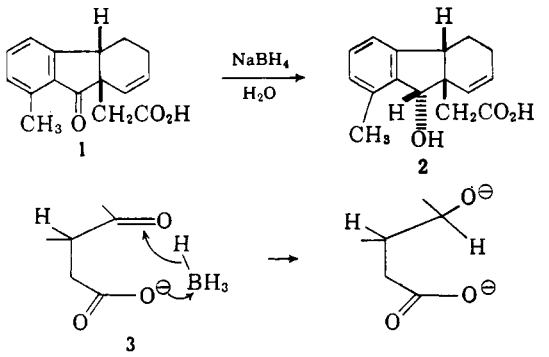
The reduction with sodium borohydride in water and in methanol of the following keto acids and the corresponding methyl esters has been studied: 1-keto-2-indanylacetic acid (**4**), 4-ketocyclohexanecarboxylic acid (**10**), 3-ketocyclohexanecarboxylic acid (**14**), and 2-ketocyclohexylacetic acid (**18**). The stereochemical outcome of these reductions is in accord with the postulate that the major product is the more stable isomer and offers little or no support for the possibilities that the carboxylate anion directs the stereochemical course of the reduction either by assisting hydride ion transfer (as in **3**) or by electrostatic shielding.

Our earlier observation[2a] that reduction of the sodium salt of the acid **1** with sodium borohydride produced predominantly the hydroxy acid **2**, a result requiring attack of the borohydride anion from the more hindered side of the ketone group, prompted us to explore the possible use of the carboxyl function to direct the stereochemical course of other ketone reductions. This directive effect could be envisioned as an intramolecular solvation of the borohydride ion by the carboxylate ion (as in **3**, an ester function could serve in a similar capacity), assisting the transfer of the hydride ion.[3] Although it is not in keeping with the



transformation **1** → **2** and an analogous transformation,[2b] the suggestion has been made[4] that electrostatic shielding is an important factor in causing attack by the borohydride anion to occur from the side of the molecule opposite to the carboxylate anion.

In order to assess the importance of these factors in simple systems wherein the carboxyl function is not constrained to a conformation in which it must lie immediately over a carbonyl function to be reduced, the reductions summarized in Chart I and Table I were performed. The preparative route to 1-keto-2-indanylacetic acid (**4**) is worthy of note since this process is not only simpler than previously described procedures[5] but also offers an unambigous route to 7-substituted 1-indanone derivatives. Our efforts to study the stereochemistry of the reduction of the keto acid **21a** were complicated by the formation of a mixture of lactones **22** and **23**. Although the n.m.r. spectrum of the lactone mixture indicated that the *trans* lactone was the predominant product, we were unsuccessful in resolving the mixture and, consequently, could not establish that the mixture obtained represented the products of a kinetically controlled process. In reductions of the keto ester **21b**, we were surprised to find that a substantial amount of a stereoisomeric mixture of diols **24** was produced. This diol mixture **24**, also obtained by reaction of the keto ester with lithium aluminum hydride, could be reoxidized to the keto acid **21a**. Since the other reductions

TABLE I

REDUCTION OF KETO ACID DERIVATIVES WITH SODIUM BOROHYDRIDE

Keto acid derivative	Solvent	% *trans* Isomer in product[a]
4a	H_2O	79
10a	H_2O	89
	MeOH	72
10b	MeOH	68
14a	H_2O	10
	MeOH	17
14b	MeOH	11
18a	H_2O	66
	MeOH	64
18b	MeOH	53

[a] In all cases save for the first entry, the product composition was determined by gas chromatography.

(1)(a) This research has been supported by Grant No. RG-8761 from the National Institutes of Health; (b) National Research Council Postdoctoral Fellow, 1960–1961.

(2)(a) H. O. House, R. G. Carlson, H. Müller, A. W. Noltes, and C. D. Slater, *J. Am. Chem. Soc.*, **84**, 2614 (1962); (b) a comparable result has been reported by L. J. Chinn, E. A. Brown, R. A. Mikulec, and R. B. Garland, *J. Org. Chem.*, **27**, 1733 (1962).

(3)(a) A comparable suggestion has been made by T. Matsumato, T. Nishida and H. Shirahma, *ibid.*, **27**, 79 (1962); (b) Both the previously mentioned authors (ref. 3a) and J. D. Connolly and K. H. Overton [*J. Chem. Soc.*, 3366 (1961)] have suggested the alternative possibility that a complex is first formed between borane and a nucleophilic functional group after which an intramolecular hydride transfer occurs. To us this alternative seems improbable for reactions carried out in solvents which can serve as good nucleophiles.

(4) D. M. S. Wheeler and M. Wheeler, *Chem. Ind.* (London), 463 (1961).

(5) (a) L. H. Groves and G. A. Swan, *J. Chem. Soc.*, 867 (1951); (b) B. P. Sen, A. Chatterjee, S. K. Gupta, and B. K. Bhattacharyya, *J. Indian Chem. Soc.*, **35**, 751 (1958).

(6) For references to other reductions of lactones with borohydrides see E. Schenker, *Angew. Chem.*, **73**, 81 (1961).

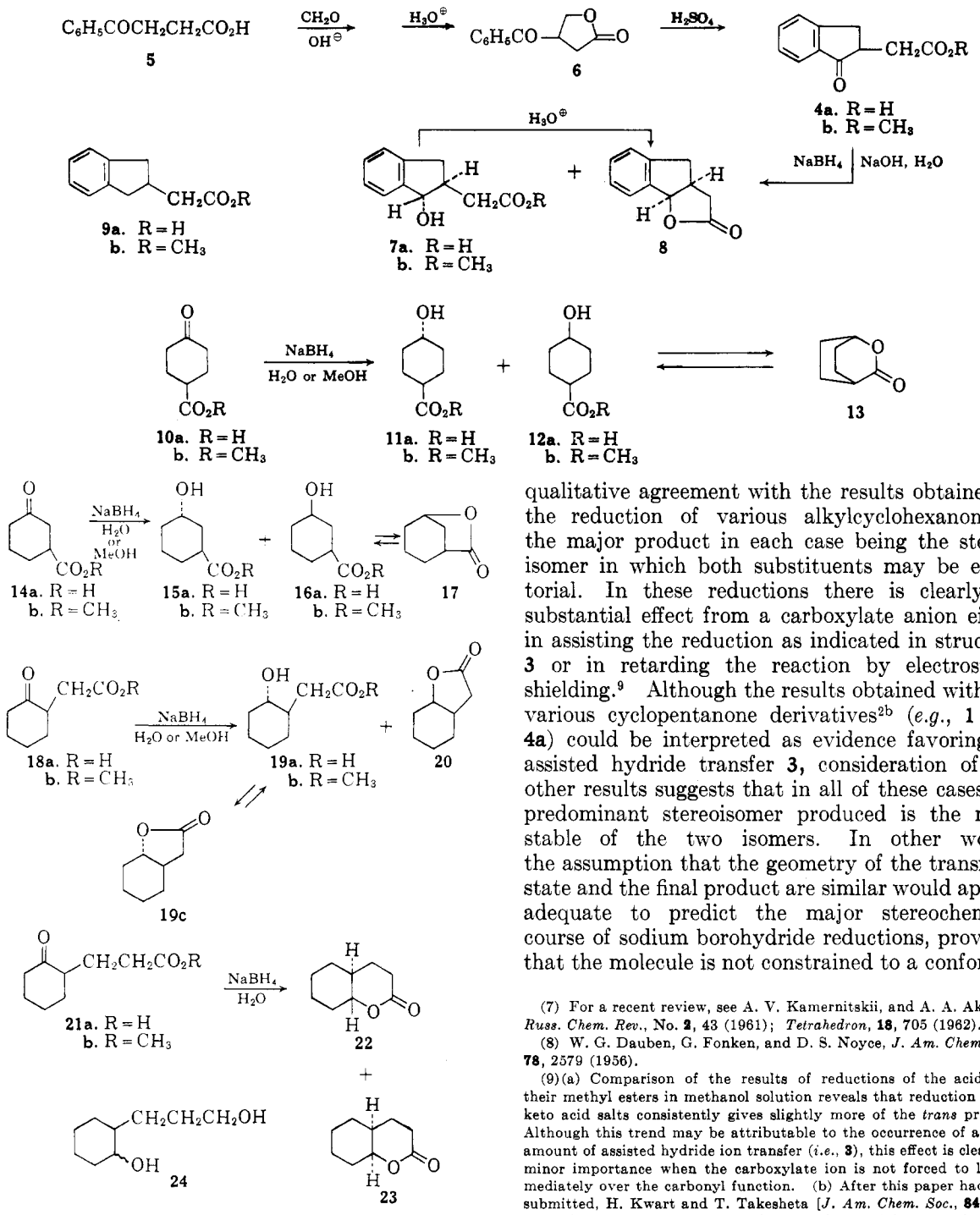


Chart I

studied clearly indicated that an ester function was not reduced under the reaction conditions employed, we were led to believe that the initial hydroxy esters formed on reduction of the keto ester **21b** were converted to the lactones **22** and **23** in the reaction mixture and underwent further reduction. In accord with this idea, reduction of the lactone mixture **23** and **24** produced the diol mixture **24**.[6]

The stereochemical results (Table I) obtained with the various cyclohexane derivatives are in qualitative agreement with the results obtained in the reduction of various alkylcyclohexanones,[7,8] the major product in each case being the stereoisomer in which both substituents may be equatorial. In these reductions there is clearly no substantial effect from a carboxylate anion either in assisting the reduction as indicated in structure **3** or in retarding the reaction by electrostatic shielding.[9] Although the results obtained with the various cyclopentanone derivatives[2b] (*e.g.*, **1** and **4a**) could be interpreted as evidence favoring an assisted hydride transfer **3**, consideration of the other results suggests that in all of these cases the predominant stereoisomer produced is the more stable of the two isomers. In other words, the assumption that the geometry of the transition state and the final product are similar would appear adequate to predict the major stereochemical course of sodium borohydride reductions, provided that the molecule is not constrained to a conforma-

(7) For a recent review, see A. V. Kamernitskii, and A. A. Akhrem, *Russ. Chem. Rev.*, No. **2**, 43 (1961); *Tetrahedron*, **18**, 705 (1962).

(8) W. G. Dauben, G. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).

(9)(a) Comparison of the results of reductions of the acids and their methyl esters in methanol solution reveals that reduction of the keto acid salts consistently gives slightly more of the *trans* product. Although this trend may be attributable to the occurrence of a small amount of assisted hydride ion transfer (*i.e.*, **3**), this effect is clearly of minor importance when the carboxylate ion is not forced to lie immediately over the carbonyl function. (b) After this paper had been submitted, H. Kwart and T. Takesheta [*J. Am. Chem. Soc.*, **84**, 2833 (1962)] reported the reduction of ethyl 4-ketocyclohexanecarboxylate (**10**, R = Et) with sodium borohydride in isopropyl alcohol to produce a mixture of hydroxy esters containing, after acetylation, 73.8% of the *cis* isomer corresponding to structure **12**. Since this result was clearly at variance with our work, Mr. C. J. Wright in our laboratories reduced a sample of the keto ester **10b** following the procedure described in the Experimental section except that methanol was replaced by isopropyl alcohol. The product contained 69% of the *trans* isomer **11b** and 31% of the *cis* isomer **12b**. Although this difference in results seems too large to be the result of a change from an ethyl to a methyl ester, the lack of detail in the preliminary report of Kwart and Takesheta precludes any evaluation of the analytical method used by these authors. In any case, none of our results, except possibly the formation of the lactone **23** and the corresponding diol **24**, can be construed as evidence favoring a transition state of the type designated as III by Kwart and Takesteta.

tion in which addition from one side of a carbonyl group is excessively hindered.

Experimental[10]

The Lactone 6 of 3-Benzoyl-4-hydroxybutyric Acid.[11]—To a solution prepared from 13.8 g. (0.1 mole) of potassium carbonate, 17.8 g. (0.1 mole) of β-benzoylpropionic acid and 50 ml. of water was added 10 ml. (0.11 mole) of 37% aqueous formaldehyde. After the solution had been allowed to stand for 20 hr. at room temperature, it was acidified and extracted with ether. The extract was dried, concentrated, diluted with benzene and again concentrated. Distillation of the residue separated 12.6 g. (72%) of the lactone **6**, b.p. 168–182° (0.5 mm.), [lit.,[11] 176–176.5° (4.5 mm.)] which crystallized from ether as 12.0 g. (71%) of white plates, m.p. 64–65° (lit.,[11] 65–66°), with infrared absorption[12] at 1775 cm.$^{-1}$ (γ-lactone C=O) and 1685 cm.$^{-1}$ (conj. C=O) and ultraviolet maxima[13] at 245.5 mμ (ε 12,900) and 281 mμ (ε 1,150).

1-Keto-2-indanylacetic Acid (4a).—A solution of 50.2 g. (0.264 mole) of the lactone **6** in 200 ml. of concentrated sulfuric acid was heated to 99° (steam bath) for 9 min. and then poured onto ice. The crude keto acid **4a**, collected on a filter, amounted to 46.1 g. (91%), m.p. 145–147°. Succes sive recrystallizations from benzene and from methanol afforded 30.2 g. (60%) of the pure acid as pale yellow prisms, m.p. 149–150° (lit.,[5a] 147–148°), with infrared absorption[14] at 1740 cm.$^{-1}$ (carboxyl C=O intramolecularly hydrogen-bonded to ketone) and 1670 cm.$^{-1}$ (conj. cyclopentenone lowered by hydrogen bonding) and ultraviolet maxima[13] at 244.5 mμ (ε 12,700) and 293 mμ (ε 2,620).

Reaction of an 8.0-g. (0.042 mole) sample of the keto acid **4a** with excess ethereal diazomethane followed by extraction with aqueous sodium bicarbonate, drying, concentration and distillation afforded 5.59 g. (65%) of the crude ester **4b**, b.p. 108–111° (0.45 mm.). Crystallization from a benzene–petroleum ether mixture separated 4.21 g. (49%) of the pure *keto ester* **4b** as white needles, m.p. 41–42°, with infrared absorption[15] at 1738 cm.$^{-1}$ (ester C=O) and 1717 cm.$^{-1}$ (conj. cyclopentenone C=O) and ultraviolet maxima[13] at 245 mμ (ε 13,200) and 290 mμ (ε 2,700).

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.57; H, 5.99.

Reduction of 1 Keto-2-indanylacetic Acid. A. With Sodium Borohydride.—To a solution of 1.0 g. (0.027 mole) of sodium borohydride in 9 ml. of 0.2 *N* aqueous sodium hydroxide was added, dropwise and with stirring, a solution of 10 g. (0.053 mole) of the keto acid **4a** in 67 ml. of water containing 0.1 mole of sodium hydroxide. After the solution had been stirred at room temperature for 20 hr., it was cooled to 0°, cautiously acidified with dilute hydrochloric acid, and immediately extracted with ether.[16] After the ethereal solution had been extracted with aqueous sodium bicarbonate, acidification of the aqueous bicarbonate extract as previously described followed by appropriate manipulations afforded 9.14 g. of crude product which partially crystallized from benzene to separate 7.59 g. (75.9%) of the hydroxy acid **7a** as white needles, m.p. 139–140°, whose melting point was raised to 140.5–141°[17] by recrystallization. The product has infrared absorption[18] at 3360 cm.$^{-1}$ (assoc. O—H) and 1695 cm.$^{-1}$ (carboxyl C=O) with a series of low intensity (ε 966–1070) ultraviolet maxima in the region 258 to 272 mμ.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.47; H, 6.34.

Reaction of a 2.00-g. (10.4 mmoles) sample of the hydroxy acid **7a** with ethereal diazomethane as previously described afforded 1.57 g. (74%) of the *hydroxy ester* **7b** as white prisms, m.p. 102–103°, from an ether–petroleum ether mixture. The product has infrared absorption[12] at 3620 cm.$^{-1}$ (unassoc. O—H), 3520 cm.$^{-1}$ (assoc. O—H) and 1730 cm.$^{-1}$ (ester C=O) with a series of low intensity (ε 946–1050) ultraviolet maxima in the region 258–272 mμ.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.75; H, 7.14.

Concentration of the various remaining organic mother liquors and extracts from the sodium borohyride reduction followed by crystallization from aqueous ethanol afforded 1.82 g. (19.8%) of the lactone **8** as white plates, m.p. 65–66°,[17] with infrared absorption[15] at 1785 cm.$^{-1}$ (γ-lactone C=O) and a series of low intensity (ε 950–1080) ultraviolet maxima in the region 258–273 mμ.

Anal. Calcd. for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.92; H, 5.95.

After a solution of 1.00 g. (5.3 mmoles) of the hydroxy acid **7a** and 30.3 mg. of *p*-toluenesulfonic acid in 90 ml. of benzene had been refluxed for 24 hr., the mixture was concentrated, diluted with ether, washed with aqueous sodium bicarbonate, dried, and concentrated. The residual lactone **8** (0.78 g. or 85%, m.p. 62–63.5°) was recrystallized from aqueous ethanol to separate the pure lactone **8**, m.p. 65–66°, identified with the previously described sample by a mixed melting point determination and comparison of infrared spectra.

B. Catalytic Hydrogenation.—A solution of 4.9919 g. (26.3 mmoles) of the keto acid **7a** in 75 ml. of ethanol was hydrogenated at room temperature and atmospheric pressure over the catalyst obtained from 250.4 mg. of platinum oxide. The reaction was stopped after the absorption of 651 ml. (1.0 equiv.) of hydrogen and then filtered and concentrated. Application of the previously described isolation procedure followed by fractional crystallization of the crude acidic fraction from benzene separated 810.1 mg. (17.5%) of the lactone **8**, m.p. 64.5–65.5°, 985.4 mg. (19.7%) of the hydroxy acid **7a**, m.p. 139.5–140.5°, 836.5 mg. (16.7%) of the starting keto acid **4a**, m.p. 147–148°, and 362.4 mg. (7.2%) of 2-indanylacetic acid (**9a**), m.p. 90–91°.

From a comparable hydrogenation of 4.9969 g. (26.3 mmoles) of the keto acid **4a** in 75 ml. of ethanol over 249.3 mg. of a 10% palladium-on-carbon catalyst which was interrupted after the absorption of 645 ml. (1.0 equiv.) of hydrogen, the products, isolated as in the previous case, were 571.3 mg. (11.4%) of the lactone **8**, m.p. 64–65°, 2.6081 g. (52.2%) of the hydroxy acid **7a**, m.p. 140–140.5°, 145.1 mg. (2.9%) of the unchanged keto acid **4a**, m.p. 147.5–148.5°, and 129.4 mg. (2.6%) of the acetic acid **9a**, m.p. 90–91°.

A solution of 3.9915 g. (21 mmoles) of the keto acid **4a** in 50 ml. of acetic acid was hydrogenated at room temperature and atmospheric pressure over 0.8 g. of a 10% palladium-on-carbon catalyst until the hydrogen uptake (1070 ml. or 2.08 equiv.) ceased. After the mixture had been filtered and

(10) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated, magnesium sulfate was employed as a drying agent. The infrared spectra were determined with either a Baird, Model B, or a Perkin–Elmer, Model 21, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 14. The n.m.r. spectra were determined at 60 mc. with a Varian, Model A-60, n.m.r. spectrometer. The mass spectra were obtained with a CEC, Model 21-130, mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

(11) The procedure of J. Rothe and H. Zimmer [*J. Org. Chem.*, **24**, 586 (1959)], has been modified with a substantial increase in yield.

(12) Determined in chloroform solution.

(13) Determined in 95% ethanol solution.

(14) Determined as a suspension in a potassium bromide pellet.

(15) Determined as a solution in carbon tetrachloride.

(16) If these precautions were not taken in the isolation, an appreciable fraction of the initially formed hydroxy acid **7a** was converted to the lactone **8**. (*Cf.* ref. 2b.)

(17) D. H. Peacock and B. K. Menon [*J. Chem. Soc.*, 1296 (1934)] report melting points of 131–132° and 72–73° for the acid **7a** and the lactone **8**, respectively. The reason for these discrepancies is not apparent.

(18) Determined as a Nujol mull.

concentrated, an ethereal solution of the crude residue was washed with water, dried, and concentrated. Recrystallization of the residue from the petroleum ether separated 3.33 g. (83.2%) of *2-indanylacetic acid* **9a** as white plates, m.p. 90–91° (lit.,[5a] 91–92°), with infrared absorption[15] at 1710 cm.$^{-1}$ (carboxyl C=O) and a series of low intensity (ϵ 1200–1370) ultraviolet maxima in the region 258–274 mμ.

Reaction of 1.45 g. (7.6 mmoles) of the acetic acid **9a** with ethereal diazomethane as previously described followed by crystallization of the crude product from petroleum ether afforded 1.30 g. (85%) of the *ester* **9b** as white needles, m.p. 29–33°. Recrystallization afforded the pure ester, m.p. 33–34°, with infrared absorption[15] at 1740 cm.$^{-1}$ (ester C=O) and a series of low intensity (ϵ 1,230–1,410) ultraviolet maxima in the region 258–273 mμ.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.78; H, 7.56.

Reduction of 4-Ketocyclohexanecarboxylic Acid Derivatives 10.—A mixture of the methyl 4-hydroxycyclohexanecarboxylates [**11b** and **12b**, b.p. 96–98 (0.35 mm.)] was obtained by the hydrogenation of methyl *p*-hydroxybenzoate as previously described.[19] Saponification of this mixture followed by treatment with acetic anhydride as previously described[20] afforded the lactone **13** as white needles from a cyclohexane–benzene mixture, m.p. 126–127° (lit.,[20] 126–128°) with infrared absorption[15] at 1755 cm.$^{-1}$ (δ-lactone C=O). Oxidation of the mixture of hydroxy esters **11b** and **12b** with chromic acid in aqueous acetic acid yielded the keto ester **10b**[21] b.p. 80–81° (0.4 mm.), n^{25}D 1.4649 which was also obtained by reaction of the keto acid **10a**, m.p. 69–70° (lit.,[22] 68–70°), with excess ethereal diazomethane. An authentic sample of the *cis* hydroxy acid **12a** was obtained as white needles, m.p. 151–152.4° (lit. 152.5°,[20a] 149.4–150.2°[20b]), by saponification of the lactone **13** followed by recrystallization from an ethyl acetate–cyclohexane mixture. Reaction of this *cis* hydroxy acid **12a** with excess ethereal diazomethane yielded the pure[23,24] *cis* hydroxy ester **12b** which was distilled in a short path still (125° at 0.3 mm.), n^{25}D 1.4694.[25] An authentic sample of the *trans* hydroxy acid **11a** was obtained as white needles from ethyl acetate, m.p. 146.5–147.5° (lit. 148°,[20a] 146.5–147.5°[20b]), from the mixture produced on reduction of the keto acid **10a** with sodium borohydride in aqueous sodium hydroxide. The pure acid **11a** was separated after an involved procedure including fractional crystallization from ethyl acetate, reesterification, distillation and saponification followed by further fractional crystallization from ethyl acetate. Reaction of the acid **11a** with excess ethereal diazomethane produced the pure[23] *trans* hydroxy ester **11b**, distilled in a short path still (125° at 0.3 mm.), n^{25}D 1.4633.[21,25] Mixtures of the esters **10b**, **11b**, and **12b** (including any lactone **13**) could be analyzed by use of two gas chromatographic columns[23,26] and appropriate calibration curves were prepared.

For the reduction of the keto acid **10a** in water, a solution of 1.44 g. (10 mmoles) of the acid **10a** and 0.40 g. (10 mmoles) of sodium hydroxide in 25 ml. of water was treated with 189.7 mg. (5 mmoles) of sodium borohydride and the resulting solution was stirred for 4 hr. at room temperature. The reaction mixture was acidified with dilute hydrochloric acid, saturated with ammonium sulfate, and continuously extracted with ether. After the ethereal extract had been dried and concentrated, it was treated with excess ethereal diazomethane and then washed with aqueous sodium bicarbonate, dried, concentrated, and distilled in a short-path still (125° at 0.2 mm.).

The ester mixture **11b** and **12b** was analyzed[23] both before and after distillation to establish the lack of unintentional fractionation. The absence of the keto ester **10b** in the mixtures was established.[26] For reduction of the keto acid **10a** in methanol the same procedure was employed except that the 25 ml. of water in the reduction mixture was replaced by 25 ml. of methanol and the reaction mixture was stirred for 4 hr. at 0° rather than at room temperature. As a control experiment, a mixture of 147 mg. of the *trans* acid **11a**, 1.293 g. (91% of the mixture) of the *cis* acid **12a**, 580.8 mg. of acetone, 0.4 g. of sodium hydroxide and 189.7 mg. of sodium borohydride in 25 ml. of water was stirred for 4 hr. and then subjected to the previously described isolation procedure. The recovered ester mixture **11b** and **12b** (1.36 g. or 87%) contained 93–96% of the *cis* ester **12b**.

For the reductions of the keto ester **10b**, a solution of 1.560 g. (0.01 mole) of the ester and 189.7 mg. (5 mmoles) of sodium borohydride in 25 ml. of methanol was stirred for 4 hr. at 0° and then acidified to pH 4–6 by the addition of dilute hydrochloric acid. After the resulting mixture had been concentrated, the residue was extracted with ether and the ethereal extract was dried, concentrated, and distilled in a short path still (125° at 0.2 mm.). The hydroxy ester mixture **11b** and **12b** was analyzed as in previous cases. As a control experiment 1.6236 g. (0.0103 mole) of the ester mixture **11b** and **12b** containing 90% of the *cis* isomer **12b**, 581 mg. of acetone, and 189.7 mg. of sodium borohydride in 25 ml. of methanol was stirred at 0° for 4 hr. The ester mixture (1.3 g. or 82%), isolated as previously described, contained 86 to 88% of the *cis* isomer. The product compositions summarized in Table I are averages of two or more runs. The yields of distilled ester mixtures isolated from the various runs were 68–77% for **10a** reduced in water, 46–89% for **10a** reduced in methanol, and 73–87% for **10b** reduced in methanol.

Reduction of 3-Ketocyclohexanecarboxylic Acid Derivatives 14.—Δ^3-Cyclohexenecarboxylic acid was converted to the keto acid **14a** [white prisms from a cyclohexane–ethyl acetate mixture, m.p. 72–73° (lit.,[27] 73°)] by bromination and subsequent reaction with sodium hydroxide as previously described.[27] Reaction of the acid **14a** either with excess ethereal diazomethane or with methanol and sulfuric acid afforded the keto ester **14b**, b.p. 136–137° (20 mm.), n^{25}D 1.4628 [lit.,[28] 121–123° (16 mm.), n^{24}D 1.4590]. Hydrogenolysis of the bromo lactone derived from Δ^3-cyclohexenecarboxylic acid as previously described[27] yielded the lactone **17** as white needles from hexane, m.p. 120–121.5° (lit.,[20a,29] 119–120°), with infrared absorption[15] at 1780 cm.$^{-1}$ (γ-lactone C=O). Saponification of the lactone **17** followed by recrystallization from ethyl acetate afforded the *cis* hydroxy acid **16a** as white needles, m.p. 131–132° (lit.,[20a,39] 131–132°). Reaction of the *cis* hydroxy acid **16a** with ethereal diazomethane produced the pure[26,30] *cis* hydroxy ester as a colorless liquid from short-path distillation (100° at 0.3 mm.),

(19) R. H. Martin and R. Robinson, *J. Chem. Soc.*, 491 (1943).

(20)(a) M. Kilpatrick and J. G. Morse, *J. Am. Chem. Soc.*, **75**, 1846 (1953); (b) D. S. Noyce and H. I. Weingarten, *ibid.*, **79**, 3098 (1957).

(21) This ester has been described by S. Siegel and J. M. Komarmy [*ibid.*, **82**, 2547 (1960)], who report n^{25}D 1.4589 for the keto ester **10b** and n^{25}D 1.4687 for the *trans*-hydroxy ester **11b**,

(22) E. Hardegger, P. A. Plattner, and T. Blank, *Helv. Chim. Acta.*, **27**, 793 (1944).

(23) A gas chromatography column packed with Dow-Corning Silicone Fluid, no. 550, suspended on ground firebrick was employed for this analysis.

(24) Collection of the eluent from the gas chromatographic column established that the *cis* ester was converted to the lactone on the column.

(25) The *cis* ester **12b** is reported (ref. 22) to boil at 150° (water aspirator pressure), n^{21}D 1.4705, and the *trans* ester **11b** is reported to boil at 119–120° (water aspirator pressure), n^{23}D 1.4693. There is question as to the purity of the *trans* acid derivatives **11** (see ref. 20) reported in this work.

(26) A gas chromatographic column packed with 20 M Carbowax suspended on ground firebrick was employed for this analysis.

(27) R. Grewe, A. Heinke, and C. Sommer, *Chem. Ber.*, **89**, 1978 (1956).

(28) D. Banerjee, J. Dutta, and G. Bagavant, *Proc. Indian Acad. Sci.*, **46A**, 80 (1957).

(29) W. H. Perkin, Jr., *J. Chem. Soc.*, **85**, 431 (1904); W. H. Perkin, Jr., and G. Tattersall, *ibid.*, **91**, 490 (1907).

(30) A gas chromatography column packed with Dow-Corning Silicone Fluid, no. 710, on ground firebrick was employed for this analysis.

$n^{25}D$ 1.4650.[31] After a mixture of the hydroxy acids **15a** and **16a** from reduction of the keto acid with sodium borohydride had been heated in refluxing benzene containing a small amount of *p*-toluenesulfonic acid for 24 hr. with continuous separation of water, the resulting acidic fraction (remaining after removal of the lactone **17**) was repeatedly recrystallized from ethyl acetate to separate the *trans* hydroxy acid **15a** as white needles, m.p. 115–117° (lit.,[20] 120°), whose purity (>98%) was assessed by conversion to the *trans* ester **15b** with diazomethane. A sample of the *trans* ester **15b** was obtained by collecting a mixture of the *trans* ester **15b** and the lactone **17**[24] from a gas chromatography column[30] and then removing the lactone by selective saponification with aqueous potassium carbonate. Subsequent short-path distillation (110° at 0.3 mm.) afforded the pure[26,30] *trans* ester **15b**, $n^{25}D$ 1.4662.[31]

The reductions of the keto acid **14a** and ester **14b** and the product analyses[26,30] were carried out as previously described. From a control experiment, performed as previously described with a mixture of hydroxy esters **15b** and **16b** containing 78% of the *trans* isomer **15b**, the recovered ester mixture (90% recovery) contained 76–80% of the *trans* isomer **15b**. The yields of distilled ester mixtures isolated from the various runs summarized in Table I were 75–78% for **14a** reduced in water, 75–95% for **14a** reduced in methanol and 82–96% for **14b** reduced in methanol.

Reduction of 2-Ketocyclohexylacetic Acid Derivatives 18.—Samples of the keto acid **18a** and ester **18b** were obtained as previously described.[2a] Reduction of the keto ester **18b** with sodium borohydride in methanol followed by saponification, acidification and short-path distillation (150° at 0.2 mm.) afforded 78% of a mixture[30] of lactones **19c** and **20**, $n^{25}D$ 1.4765. Selective saponification of this mixture with cold (0°) aqueous potassium hydroxide preferentially saponified the *trans* lactone **19c**. The *trans* acid **19a**, recovered from the alkaline solution by acidification and subsequent extraction, crystallized from a cyclohexane–ethyl acetate mixture as white needles, m.p. 106.5–107° (lit.,[32] 105.8–106.6°). After a solution of the *trans* hydroxy acid **19a** and a small amount of *p*-toluenesulfonic acid in benzene had been refluxed for 24 hr., appropriate manipulations separated the pure[30] *trans* lactone **19c** as a colorless liquid after short-path distillation (125° at 0.2 mm.), $n^{25}D$ 1.4762 [lit. b.p. 126° (8 mm.),[32] $n^{20}D$ 1.4777[33]], yield 74%, with infrared absorption[15] at 1780 cm.$^{-1}$ (γ-lactone C=O) and n.m.r. absorption[15] centered at 6.28 τ (half-band width *ca.* 20 c.p.s.) attributable to an axial proton[34] adjacent to a C—O bond. Reaction of the *trans* acid **19a** with excess ethereal diazomethane afforded the ester **19b** with infrared absorption[15] at 3440 cm.$^{-1}$ (assoc. O—H and 1730 cm.$^{-1}$ (ester C=O). Several attempts to purify this material by short-path distillation resulted in partial conversion to the lactone **19c** and collection from a gas chromatograph converted the ester **19b** completely to the lactone **19c**. When a solution of the potassium salts of the *cis* and *trans* hydroxy acids was acidified with hydrochloric acid at 0° and then immediately extracted with ether, the ethereal extract, after having been washed with sodium bicarbonate, was enriched[30] in the *cis* lactone **20**. Repetition of this process separated a sample of the pure[30] *cis* lactone **20** as a colorless liquid from short-path distillation (125° at 0.3 mm.) [lit.,[32] b.p. 112° (6 mm.), $n^{20}D$ 1.4773], with infrared absorption[15] at 1775 cm.$^{-1}$ (γ-lactone C=O) and n.m.r. absorption[15] centered at 5.55 τ (half-band width *ca.* 7 c.p.s.) attributable to an equatorial proton[34] adjacent to a C—O bond.

The reductions of the keto acid **18a** and ester **18b** and the product analyses[30] were performed as previously described. Application of the previously described control experiment to a sample of the pure *trans* ester **19b** resulted in the recovery of 93% of material containing[30] only the *trans* ester **19b** and (or) the *trans* lactone **19c**. The yields of the distilled lactone–ester mixtures from the various runs summarized in Table I were 85–94% for **18a** in water, 72–86% for **18a** in methanol, and 81–90% for **18b** in methanol.

Reduction of 3-(2-Ketocyclohexyl)propionic Acid Derivatives 21.—Reaction of cyclohexanone with methyl acrylate in a Michael condensation afforded the pure[30] keto ester **21b**, b.p. 114–115° (1.5 mm.), $n^{25}D$ 1.4662 [lit.,[35] b.p. 135–137° (11 mm.), $n^{20}D$ 1.4640], from which the keto acid **21a** (white prisms from an ether–ethyl acetate–pentane mixture, m.p. 62–63°, lit.[35] 64–66°) was obtained by saponification. A solution of 17.85 g. (0.11 mole) of the keto acid **21a**, 4.50 g. (0.115 mole) of sodium hydroxide and 1.897 g. (0.05 mole) of sodium borohydride in 100 ml. of methanol was stirred under nitrogen for 4 hr. at 0° and then acidified, saturated with ammonium sulfate, and extracted with ether. After the ethereal extract had been washed with aqueous sodium bicarbonate, dried, and concentrated, distillation separated 11.5 g. (68%) of the mixture of lactones **22** and **23** as a colorless liquid, b.p. 93–94.5° (0.3 mm.), $n^{25}D$ 1.4902. Acidification of the bicarbonate washings followed by appropriate manipulations separated another 2.9 g. (total yield 14.4 g. or 85%) of the lactone mixture, $n^{25}D$ 1.4901. All of the gas chromatography columns at our disposal exhibited only a single peak for this product which has infrared absorption[15] at 1735 cm.$^{-1}$ (δ-lactone C=O) and weak end absorption in the ultraviolet.[13] The n.m.r. spectrum[15] of the material has complex absorption in the region 7.4 to 9.0 τ as well as two peaks (together attributable to one proton) centered at 5.57 τ (half-band width *ca.* 7 c.p.s.) and 6.18 τ (half-band width *ca.* 18 c.p.s.) attributable,[34] respectively to the equatorial proton adjacent to the C—O bond in the *cis* lactone **23** (*ca.* 33% of the mixture) and the axial proton adjacent to the C—O bond in the *trans* lactone **22** (*ca.* 67% of the mixture).

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15; mol. wt., 154. Found: C, 70.08; H, 9.16; mol. wt., 154 (mass spectrum).

A solution of 36.85 g. (0.20 mole) of the keto ester **21b** and 7.56 g. (0.20 mole) of sodium borohydride in 250 ml. of methanol was stirred for 8 hr. while the reaction mixture, originally at 0°, was allowed to warm to room temperature. After the resulting mixture had been acidified, 20 g. (0.31 mole) of potassium hydroxide was added and the resulting solution was refluxed overnight and then concentrated and partitioned between ether and water. After the ether solution had been dried and concentrated, distillation of the residue afforded 23.5 g. (74.5%) of the diol mixture **24** as a very viscous, colorless liquid, b.p. 119–120° (0.3 mm.), which was redistilled [b.p. 104–105° (0.15 mm)] for analysis. The diol mixture has infrared absorption[15] at 3620 cm.$^{-1}$ (unassoc. O—H) and 3320 cm.$^{-1}$ (assoc. O—H) but no absorption in the 6 μ region attributable to a carbonyl function.

Anal. Calcd. for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.10; H, 11.61.

After a cold (0°) solution of 1.54 g. (0.010 mole) of the lactones **22** and **23** and 3.795 g. (0.1 mole) of sodium borohydride in 25 ml. of methanol had been stirred for 4 hr., acidification of the mixture followed by extraction with ether and appropriate manipulations separated the crude diols **24** which were distilled in a short-path still (130° at 0.3 mm.) to afford 1.405 g. (90%) of the diols **24** identified with the previously described sample by comparison of infrared spectra. Reduction of 1.75 g. (0.01 mole) of the keto ester **21b** with 0.500 g. (0.013 mole) of lithium aluminum hydride in 25 ml. of ether for 1 hr. was followed by consumption of the excess hydride with acetone and precipitation of the aluminum salts by addition of saturated aqueous ammonium

(31) A mixture of the hydroxy esters **15b** and **16b**, prepared by hydrogenation of methyl *m*-hydroxybenzoate, was reported (ref. 20a) to boil at 143–144° (23 mm.).

(32) M. S. Newman and C. A. Vanderwerf, *J. Am. Chem. Soc.*, **67**, 233 (1945).

(33) J. H. Brewster and C. H. Kucera, *ibid.*, **77**, 4564 (1955).

(34) J. I. Musher, *ibid.*, **83**, 1146 (1961).

(35) M. Haring and T. Wagner-Jauregg, *Helv. Chim. Acta*, **40**, 852 1957).

chloride. After the precipitate had been washed with ether, the combined ethereal solutions were dried, concentrated, and distilled in a short-path still (130° at 0.25 mm.) to separate 1.314 g. (83%) of the diols **24** identified by comparison of infrared spectra.

A 1.58-g. (0.01 mole) sample of the diols **24** (obtained by reduction of the keto ester **21b** with sodium borohydride) was oxidized with a solution of 2.0 g. (0.02 mole) of chromic acid and 2 ml. of concentrated sulfuric acid in 50 ml. of water. After the mixture had been stirred at room temperature for 3 hr., it was saturated with ammonium sulfate and extracted with ether. Extraction of the ethereal solution with aqueous sodium bicarbonate followed by acidification of the aqueous extract, saturation with ammonium sulfate, and extraction with ether separated 1.5 g. of crude acidic product. Fractional crystallization from cyclohexane–ether mixtures separated 0.843 g. (50%) of the crude keto acid **21a**, m.p. 50–53°, whose melting point was raised to 62–63° by recrystallization. The identity of this oxidation product with the keto acid **21a** was established by a mixed melting point determination and comparison of infrared spectra.

The Chemistry of Carbanions. I. The Reaction of Triphenylmethane with Potassium[1]

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The reaction of triphenylmethane with potassium in 1,2-dimethoxyethane produced solutions of triphenylmethyl potassium containing various cleavage and reduction products derived from triphenylmethane. The addition of butadiene to the reaction mixture prevented the formation of the by-products from triphenylmethane, the diene being converted to *trans*-2-butene and mixtures of octadienes and dodecatrienes.

For a study of the relative stabilities of enolate anions derived from unsymmetrical ketones, we desired a base–solvent system which could be conveniently prepared and would permit rapid and quantitative conversion of a ketone to a solution of its enolate anions. Since distinct advantages, both in terms of the solubility and reactivity of carbanions, are derived from use of the solvents 1,2-dimethoxyethane,[2] dimethylformamide,[2c,3] and dimethyl sulfoxide,[2c,4] we considered use of only these solvents in our study. Of these solvents, we consider 1,2-dimethoxyethane by far the most convenient in preparative work because of its stability and relatively low boiling point facilitating its removal from reaction mixtures. In addition dilute solutions of potassium metal may be obtained[5] in 1,2-dimethoxyethane. Since the most suitable base appeared to be the deeply colored triphenylmethyl anion, we focused our attention on possible methods for the preparation of solutions of metal derivatives of the triphenylmethyl anion in 1,2-dimethoxyethane, preferably in the absence of other contaminants.[6]

In an effort to obtain this base–solvent combination, solutions of triphenylmethane in 1,2-dimethoxyethane were treated with sodium hydride, metallic sodium, and metallic potassium. Although little if any reaction was achieved in the first two cases, reaction of potassium with excess triphenylmethane (**1**) in 1,2-dimethoxyethane effected complete conversion of the potassium to triphenylmethylpotassium (**2**) in approximately eighteen hours. However, it was apparent that this reaction was not to be free from by-products since no hydrogen was evolved in the course of the preparation. The various by-products formed are summarized in Chart I.

The nature of these by-products suggests strongly that the initial reaction of triphenylmethane with potassium forms the ion radical **7**[7] which then dimerizes and cleaves as in **8**.[8,9]

Alternatively the original ion radical **8** may react

(1) This research has been supported by Grant No. 594A from the Petroleum Research Fund.

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(6) The following references summarize the methods which have been used to prepare triphenylmethylsodium and triphenylmethylpotassium. (a) K. Ziegler and F. Thielmann, *Ber.*, **56**, 1740 (1923); (b) C. A. Kraus and T. Kawamura, *J. Am. Chem. Soc.*, **45**, 2756 (1923); (c) R. Levine, E. Baumgarten, and C. R. Hauser, *ibid.*, **66**, 1230 (1944); (d) W. B. Renfrow, Jr., and C. R. Hauser, "Organic Synthesis," Coll. Vol. 2, John Wiley & Sons, Inc., New York, N. Y., 1943, p. 607; (e) J. Eisch and W. C. Kaska, 138th National Meeting of the American Chemical Society, New York, N. Y., September 11–16, 1960, Abstracts of Papers, p. 52-P; see also H. Normant and B. Angelo, *Bull. soc. chim. France*, 354 (1960); (f) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 866 (1962); (g) G. W. H. Scherf and R. K. Brown [*Can. J. Chem.* **38**, 2450 (1960)] have reported the formation of triphenylpotassium from triphenylmethane and potassium in 1,2-dimethoxyethane. However, these authors apparently did not examine the reaction mixture to learn what other materials were present.

(7) The ion radicals derived from biphenyl and naphthalene (ref. 6a) have served as strong bases which were used to prepare the triphenylmethyl anion.