to reflux. The reflux temperature gradually rose to 220° over a period of 5–6 hours. The heating was continued an additional 8 hours. The mixture was cooled, and the product was extracted with benzene. The benzene solution was filtered and dried. The benzene was removed, and the crude product was distilled at 10 mm. to yield 6 g. (41.5%) of the biphenyl, b.p. 103–105°. On standing the product crystallized. After three crystallizations from methanol, the m.p. was 95.5–96.5°.

*Anal.* Calcd. for $C_{16}H_6F_{12}$: C, 45.09; H, 1.42; F, 53.50. Found: C, 45.13, 45.17; H, 1.57, 1.51; F, 53.76, 53.92.

**5-Nitro-1,3-bis-(trifluoromethyl)-benzene.**—The procedure was identical to that used to prepare 2-nitro-1,4-bis-(trifluoromethyl)-benzene. The starting material was 1,3-bis-(trifluoromethyl)-benzene.[15] The reaction gave 66.5% of product of b.p. 75–77° at 10 mm. A sample redistilled for analysis had b.p. 75.5° at 11 mm. and $n^{25}$D 1.4250.

*Anal.* Calcd. for $C_8H_3O_2NF_6$: C, 37.05; H, 1.17. Found: C, 37.08, 36.88; H, 1.02, 1.18.

**5-Amino-1,3-bis-(trifluoromethyl)-benzene.**—Reduction of 5-nitro-1,3-bis-(trifluoromethyl)-benzene with stannous chloride by the procedure previously described gave an 80% yield of the amine; b.p. 75–78° at 10 mm. A sample redistilled for analysis had b.p. 75.5–76° at 10 mm. and $n^{24.5}$D 1.4318.

*Anal.* Calcd. for $C_8H_5F_6N$: C, 41.94; H, 2.20. Found: C, 41.07, 41.20; H, 2.09, 2.17.

The acetyl derivative prepared in the usual way and recrystallized from benzene melted from 152.5–154°.[16]

*Anal.* Calcd. for $C_{10}H_7ONF_6$: C, 44.29; H, 2.62. Found: C, 43.56, 43.78; H, 2.51, 2.71.

**5-Iodo-1,3-bis-(trifluoromethyl)-benzene.**—The procedure previously described applied to 5-amino-1,3-bis-(trifluoromethyl)-benzene resulted in a 66.5% yield of the iodide, b.p. 59–61° at 10 mm., $n^{25}$D 1.4592.

*Anal.* Calcd. for $C_8H_3F_6I$: C, 28.26; H, 0.89. Found: C, 28.30, 28.04; H, 1.05, 0.89.

**3,3′-5,5′-Tetrakis-(trifluoromethyl)-benzene.**—With the above iodide the previously described Ullmann procedure gave a 30% yield of the biphenyl of b.p. 120–124° at 10 mm. After three crystallizations from methanol the product had a m.p. of 85–86°.

*Anal.* Calcd. for $C_{16}H_6F_{12}$: C, 45.09; H, 1.42; F, 53.50. Found: C, 44.99, 44.84; H, 1.17, 1.28; F, 53.96; 53.01.

**Ultraviolet Absorption Spectra.**—A Beckman model DU quartz spectrophotometer was employed for the determinations. The solvent employed was, in all cases, Spectro Grade isoöctane (2,2,4-trimethylpentane) from the Phillips Petroleum Company.

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[15] We are indebted to the Hooker Electrochemical Company for samples of pure 1,3- and 1,4-bis-(trifluoromethyl)-benzene.

[16] N. L. Drake, *et al.*, *ibid.*, **68**, 1602 (1946). These workers nitrated a mixture of 1,3- and 1,4-bis-(trifluoromethyl)-benzene, reduced the mixed nitro compounds to the mixed amines, acetylated and finally separated the 5-acetamino-1,3-bis-(trifluoromethyl)-benzene, for which they report a melting point of 156.2–157.2°.

NORTH ADAMS, MASS.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

# The Hydrogenation of 4-Hydroxybiphenylcarboxylic Acids

BY WILLIAM G. DAUBEN AND MASATO TANABE

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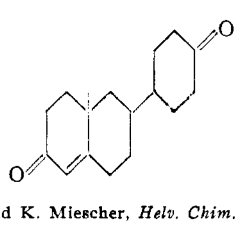
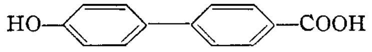
When 4-hydroxybiphenyl-4′-carboxylic acid was hexahydrogenated over Raney nickel in alkali, reaction occurred only in the hydroxyl substituted ring and both a *cis* and a *trans* isomer was isolated. Perhydrogenation yielded only one pure product which was shown to possess the *trans* configuration in the carboxyl substituted ring. When 4-hydroxybiphenyl-3′-carboxylic acid was hexahydrogenated, again reaction occurred only in the hydroxyl substituted ring but only one isomer was isolated.

In recent years, a great deal of interest has been centered about the preparation of compounds related to biologically active steroids and noticeable success has been achieved in certain series in which part of the steroid ring system has been omitted. For example, the work of Miescher and his group[1] on the bisdehydrodoisynolic acids and Horeau and Jacques[2] on the allenoic acids has indicated the extent to which the basic tetracyclic ring system can be varied and still retain biological activity. Another interesting study has been reported by Wilds[3] where it was found that compound I, lacking ring C but otherwise closely related to a homoandrosterone, possessed definite androgenic activity.

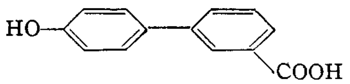


I

It is evident that the synthesis of other related steroidal model compounds could be accomplished if partially or fully hydrogenated derivatives of substituted biphenyls were available. The most useful starting materials for such a study would be the hydrogenated derivatives of 4-hydroxybiphenyl-4′-carboxylic acid (II) and its 3′-carboxylic acid isomer III. The preparation of reduced derivatives of acid II has been previously investigated. Johnson[4] has reported the preparation of one isomer, 4-(4-hydroxyphenyl)-cyclohexylcarboxylic acid (IV), by nitration of 4-phenylcyclohexylcarboxylic acid followed by reduction and diazotization or by the sodium and alcohol reduction of the methyl ether of II.[5] The isomeric hexahydro isomer V has been prepared by



II



III

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[1] G. Anner and K. Miescher, *Helv. Chim. Acta*, **30**, 1422 (1947), and earlier papers.

[2] A. Horeau and J. Jacques, *Bull. soc. chim. France*, 707 (1948), and earlier papers.

[3] A. L. Wilds and C. H. Shunk, THIS JOURNAL, **72**, 2388 (1950).

[4] W. S. Johnson and R. D. Offenhauer, *ibid.*, **67**, 1045 (1945).

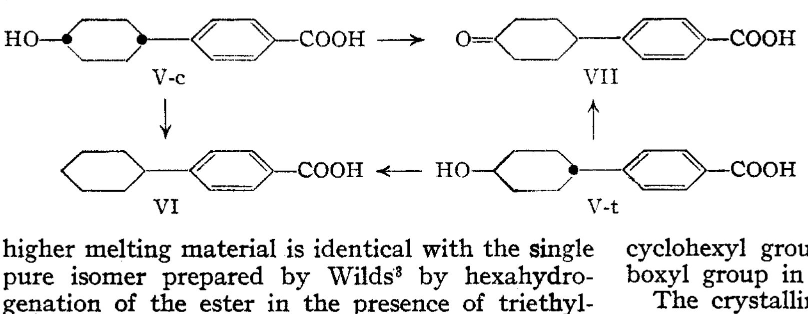
[5] W. S. Johnson, G. D. Gutsche and R. D. Offenhauer, *ibid.*, **68**, 1648 (1946).

Wilds[3] by controlled hydrogenation over Raney nickel W-6 of the ester of the aromatic acid II. By utilizing more forcing conditions, this latter worker also found perhydrogenation occurred and one isomer of 4-(4-hydroxycyclohexyl)-cyclohexanecarboxylic acid (VIII) was isolated. In the related series, 6-hydroxy-1(or 2)-naphthoic acid, Dauben, Hiskey and Markhart[6] have reported that selective hydrogenation to either a tetrahydro or perhydro derivative can be achieved in aqueous alkali in the presence of W-2 Raney nickel. This method has now been extended to the two hydroxybiphenylcarboxylic acids II and III.

The starting acid II was prepared according to the procedure of Johnson, Gutsche and Offenhauer[5] except for minor modifications. The unsymmetrical acid III was best made by allowing *p*-methoxyphenylmagnesium bromide to react with 3-methylcyclohexanone, dehydration and dehydrogenation of the product and oxidation of the resulting 3-methyl-4′-methoxybiphenyl with potassium permanganate to 4-methoxybiphenyl-3′-carboxylic acid. The methoxy acid was demethylated with 48% hydrobromic acid in acetic acid to yield the hydroxy acid III and the over-all yield in this preparation was 42%.

The hydrogenation of 4-hydroxybiphenyl-4′-carboxylic acid (II) was first conducted utilizing an aqueous solution of one equivalent of sodium carbonate and acid over W-2 Raney nickel. For hexahydrogenation approximately 5 hours were required and the product obtained was a crystalline solid, m.p. 170–225°. It was separated into phenolic and non-phenolic fractions by esterification with methanol and sulfuric acid followed by extraction with cold alkali.

It was found that the phenolic fraction, after saponification of the ester, consisted exclusively of the starting phenolic acid II. The non-phenolic fraction, after saponification, yielded a solid which could easily be separated into two compounds. The separation was accomplished by saturation of an aqueous solution of the sodium salt of the mixture with sodium nitrate; the salt of one isomer was insoluble under these conditions. The two isomeric acids so obtained melt at 235–237° (V-t) and 194–195.5° (V-c), respectively. The yield of V-t was 10% and of V-c was 45%. The higher melting material is identical with the single pure isomer prepared by Wilds[3] by hexahydrogenation of the ester in the presence of triethylamine. That the acids V-c and V-t were the two geometric isomers, *i.e.*, *cis*- and *trans*-4-(4-hydroxycyclohexyl)-benzoic acids, was proved in the following manner. Both acids on treatment with acetic acid saturated with hydrogen bromide were converted into bromo acids which, when subjected to hydrogenolysis in the presence of sodium methoxide,[6] yielded the known acid, 4-cyclohexylbenzoic acid (VI).[7] Furthermore, when acids V-c and V-t were oxidized with chromic acid, the same keto acid, 4-(4-ketocyclohexyl)-benzoic acid (VII),[3] was obtained. The ultraviolet spectra of these two acids show a maximum of high intensity (log $\epsilon$ 4.0) at 236 m$\mu$, a characteristic of aromatic acids.[6,8] The assignment of configuration of these isomers is purely arbitrary, the *trans* configuration V-t being given to the higher melting isomer and the *cis* configuration to the lower melting V-c. It is of passing interest to note that when 4-hydroxybiphenyl itself is hydrogenated[9] in base over Raney nickel, hydrogenation of the hydroxylated ring is preferred.



In the hexahydrogenation of acid II, it appeared possible that the slow rate of reaction was due to the insolubility of the mono-sodium salt in aqueous solution. It was found that by performing the hydrogenation on the di-potassium salt which is soluble in water, the reaction rate was not markedly increased. However, the ratio of V-c to V-t formed in this homogeneous reaction was quite different, the isomer V-t being formed in 39% yield and the isomer V-c in 19%. When W-5 Raney nickel was utilized under these same conditions, a marked increase in rate was observed, the reaction being complete in one hour, but the isomer ratio remained about constant (43% V-t and 29% V-c). The change of the "*trans*"/"*cis*" ratio from 0.23 in the heterogeneous reaction conducted at a *p*H of about 8 to a value of 1.6–1.9 for the homogeneous reaction at *p*H 11–12, is interesting.

The perhydrogenation of acid II was accomplished using the di-potassium salt in aqueous solution. After 10 hr., the theoretical amount of hydrogen for complete saturation of both rings had been absorbed. The crystalline product VIII, obtained in a yield of 55%, was apparently one pure isomer (of the four possible) and melts from 174–175°. The stereochemistry of this material was partially determined by conversion to the known *trans*-4-cyclohexylcyclohexanecarboxylic acid (IX).[10] The method employed was to convert the perhydro acid VIII to the bromo acid and the halogen was removed by hydrogenolysis as described above. It has previously been shown that such a procedure does not affect the configuration of the carbonyl group.[6] The product obtained was identical with the known *trans*- acid IX. Thus the acid VIII contains the 4-hydroxycyclohexyl group in a position *trans* to the carboxyl group in the cyclohexane ring.

The crystalline perhydrohydroxy acid also was oxidized with chromic acid to a crystalline keto-acid X, m.p. 174–175°, which was identical with one of

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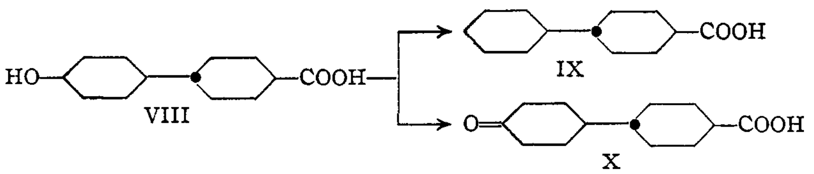
(6) W. G. Dauben, C. F. Hiskey and A. H. Markhart, Jr., *ibid.*, **73**, 1393 (1951).

(7) H. A. Mayes and E. E. Turner, *J. Chem. Soc.*, 500 (1929).

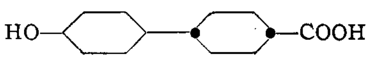
(8) C. M. Moser and A. I. Kohlenberg, *ibid.*, 804 (1951).

(9) H. E. Ungnade and A. D. McLaren, THIS JOURNAL, **66**, 118 (1944).

(10) L. F. Fieser, *et al.*, *ibid.*, **70**, 3191 (1948).



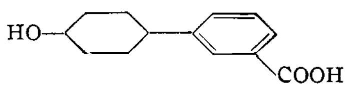
the keto-acids previously described by Wilds.[3] This latter worker has reported that when the ester of acid II was perhydrogenated under his conditions only one pure crystalline isomer could be isolated (m.p. 196°) and when this acid was oxidized, a ketone (m.p. 95–96°) was obtained. When his crude perhydrogenated mixture was oxidized directly, two keto-acids (m.p. 96° and 174°) were obtained. Since the perhydrohydroxy acid obtained in the present work has been related to the *trans*-4-cyclohexylcyclohexane carboxylic acid (IX), the higher melting ketone X, m.p. 174°, also must have the *trans* configuration. Thus the pure hydroxy acid and corresponding ketone obtained by Wilds must be of the *cis* structure XI.



XI

Of the four possible perhydrohydroxy acids (XII, XIII, XIV, XV), the isomer prepared in this work must be either the *trans–trans* XII or the *trans–cis* XIII while the product reported by Wilds must be either the *cis–trans* (XIV) or the *cis–cis* (XV).

The hexahydrogenation of 4-hydroxybiphenyl-3′-carboxylic acid (III) was conducted in potassium hydroxide solution over W-5 Raney nickel. The rate of hydrogenation, however, was much more rapid than with the 4′-isomer, three mole equivalents of hydrogen being absorbed in one hour. The mixture of solid acids so obtained was separated into phenolic and non-phenolic components by esterification followed by alkaline extraction. The phenolic fraction yielded only starting acid while the non-phenolic material gave a pure single isomer of 3-(4-hydroxycyclohexyl)-benzoic acid (XVI) in 60% yield.



XVI

Such a result is in contrast to the formation of two isomeric non-phenolic acids from 4-hydroxybiphenyl-4′-carboxylic acid (II). The structure assignment of XVI was made on the basis of its chemical reactivity and the observance of a maximum at 231 mμ (log ε 4.0) in its ultraviolet absorption spectrum. When the hydrogenation was conducted in sodium carbonate solution, identical results were obtained as with the dipotassium salt. The configuration of the hexahydro acid XVI is not known at present.

**Acknowledgment.**—The authors wish to express their appreciation to Professor Donald S. Noyce for his coöperation in connection with this work and to the Office of Naval Research for support under contract N7 onr 29520.

## Experimental[11]

**4-Hydroxybiphenyl-4′-carboxylic Acid (II).**—The corresponding methoxy acid, prepared following the procedure of Johnson,[5] was demethylated by heating 40 g. (0.175 mole) with 525 ml. of acetic acid and 105 ml. of 48% hydrobromic acid for 15 hr. under a nitrogen atmosphere. After the heating period, 300 ml. of solvent was removed by distillation at reduced pressure and 300 ml. of water added. Upon cooling the mixture, 35 g. of crude hydroxy acid was obtained. Recrystallization from dioxane and cyclohexane and then from dilute acetic acid yielded 30 g. (80%) of pure acid, m.p. 288–290° (uncor.). The reported melting point is 293–294°.[12]

**Hexahydrogenation of 4-Hydroxybiphenyl-4′-carboxylic Acid. (a) As Monosodium Salt.**—4-Hydroxybiphenyl-4′-carboxylic acid (4.0 g., 18.8 mmoles), 1.0 g. (9.4 mmoles) of sodium carbonate and 2 ml. of W-2 Raney nickel was suspended in a total volume of 31 ml. of water. The mixture was hydrogenated at an initial pressure of 2500 p.s.i. (25°) and temperature of 125°. After 6 hr. a hydrogen uptake of 2 mole equivalents had been absorbed. The temperature was then raised to 150° over a period of 30 min. and one additional mole equivalent of hydrogen was rapidly absorbed. Continued shaking of the bomb for an additional 15 min. resulted in no discernible hydrogen consumption. After the bomb had cooled, the catalyst was filtered and the bomb and catalyst washed with water. The filtrate (150 ml.) was acidified with excess concentrated hydrochloric acid to yield 2.9 g. of a colorless solid, m.p. 220–232°. The mixture of acids was esterified by heating under reflux for 8 hr. with 100 ml. of methanol and 2 ml. of concentrated sulfuric acid. The solution was concentrated to 25 ml., water added and the liquid esters dissolved in ether. The ethereal solution, after washing twice with 5% sodium carbonate, was separated into phenolic and non-phenolic fractions by extracting with two 20-ml. portions of cold 10% potassium hydroxide. The combined alkaline extracts were refluxed for 2 hr. and then acidified to yield 1.2 g. (30%) of starting aromatic acid, m.p. 265–285°. Recrystallization from dilute acetic acid gave a pure acid, m.p. 290–291°.

The non-phenolic esters remaining after evaporation of the ether were saponified by heating under reflux for 6 hr. with 40 ml. of 10% alcoholic potassium hydroxide. The precipitated acids obtained upon acidification (m.p. 167–173°) were a mixture of the *cis*- and *trans*-4-(4-hydroxycyclohexyl)-benzoic acids. The isomers were separated by dissolving the solid mixture in 15 ml. of warm 1 *N* sodium hydroxide and a solution of 6 g. of sodium nitrate in 10 ml. of water added. Upon cooling, an insoluble sodium salt precipitated which was filtered, washed with a small amount of cold water and then dissolved in 10 ml. of hot water. Acidification gave 0.29 g. (10% based upon recovered starting acid) of the "*trans*"-isomer, m.p. 228.5–234.5°. This material was recrystallized from acetone, m.p. 235–237°. Wilds[3] reports a value of 236° for his hexahydro material.

*Anal.* Calcd. for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32; neut. equiv., 220. Found: C, 70.79; H, 7.17; neut. equiv., 221.

The filtrate from the above separation of the insoluble sodium salt was acidified to yield 1.31 g. (45.5%) of the "*cis*"-isomer, m.p. 175–187°; it was recrystallized from acetone, m.p. 194.0–195.7°.

*Anal.* Found: C, 70.67; H, 7.60; neut. equiv., 225.

**(b) As Dipotassium Salt.**—To a solution of 4-hydroxybiphenyl-4′-carboxylic acid (2.14 g., 10 mmoles) in 1.5 g. (27 mmoles) of potassium hydroxide and water, 3 ml. of W-5 Raney nickel catalyst was added and the total volume brought up to 31 ml. with water. The mixture was hydrogenated at an initial pressure of 2500 p.s.i. (25°). The bomb was heated to 125° and after one hr., 3 mole equivalents of hydrogen had been absorbed. The catalyst was filtered from the cooled reaction mixture and the filtrate acidified, yield 1.9 g., m.p. 175–200°. The acids were dissolved in 15 ml. of warm 1 *N* sodium hydroxide and 5 g. of

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[11] All melting points are corrected. Analyses by the Microanalytical Laboratory of the Department of Chemistry, University of California.

[12] L. F. Fieser and C. K. Bradsher, THIS JOURNAL, **58**, 1738 (1936).

sodium nitrate was added. After cooling, the insoluble sodium salt was filtered and redissolved in hot water. Acidification gave 0.65 g. (42.5% based upon recovered starting acid) of "*trans*"-4-(4-hydroxycyclohexyl)-benzoic acid, m.p. 230–235°.

Acidification of the filtrate yielded 1.15 g. of a mixture of starting acid and the lower melting "*cis*"-isomer. The precipitate was fractionally crystallized from acetone and afforded in 2 crops a total of 0.45 g. (29.4% based upon recovered starting acid) of the "*cis*"-isomer, m.p. 187–193°. The mother liquor was evaporated to dryness and the residue recrystallized from dilute acetic acid to yield 0.65 g. of starting aromatic acid, m.p. 285–291°.

Starting with 4.0 g. of acid and using 3 month old W-2 Raney nickel under the same conditions, 4 hr. were required for hexahydrogenation and 1.27 g. (37.5%) of the "*trans*"-isomer, 0.63 g. (18.6%) of the "*cis*"-isomer and 0.7 g. of the starting acid was obtained.

**4-Cyclohexylbenzoic Acid from "*cis*" and "*trans*"-4-(4-Hydroxycyclohexyl)-benzoic Acids.**—The "*cis*"-acid V-c (0.22 g., 1 mmole, m.p. 194–195°) was mixed with 3 ml. of glacial acetic acid saturated with hydrogen bromide and the mixture warmed on a steam-bath for 6 hr. The solution was poured into 30 ml. of cold water and the precipitated bromo acid was extracted with a total volume of 20 ml. of chloroform. The chloroform extract was washed with water and dried over magnesium sulfate. After removal of the solvent, the residue was dissolved in 30 ml. of methanol containing 0.06 g. of sodium; 3 ml. of Raney nickel was added and the mixture hydrogenated at an initial pressure of 40 p.s.i. After 3 hr., the hydrogenation was stopped, the catalyst filtered, washed with methanol and the filtrate evaporated to dryness. The residue was dissolved in water, acidified with excess concentrated hydrochloric acid and the mixture heated on the steam-bath to ensure complete conversion to the acid. The 4-cyclohexylbenzoic acid was filtered and recrystallized once from petroleum ether (b.p. 30–60°) and once from dilute ethanol, m.p. 195–196° (lit.[7] m.p. 199°). Upon mixing with the starting "*cis*"-hydroxy acid (m.p. 195°), the mixture melts from 145–160°.

The pure "*trans*"-acid V-t (0.22 g., 1 mmole, m.p. 235–237°) when carried through the same procedure as described above, gave 130 mg. (64%) of 4-cyclohexylbenzoic acid, m.p. 195–196°, mixed melting point with acid obtained from degradation of "*cis*"-isomer, 194–195.5°.

**4-(4-Ketocyclohexyl)-benzoic Acid from "*cis*" and "*trans*" 4-(4-Hydroxycyclohexyl)-benzoic Acids.**—The "*trans*"-acid V-t (0.22 g., 1 mmole) m.p. 235–237°) was dissolved in 5 ml. of glacial acetic acid. A solution of chromic anhydride (0.138 g., 1.37 mmoles) dissolved in 14 ml. of water and 0.7 ml. of acetic acid was added dropwise over the period of one hour with stirring to the solution of the alcohol. After the addition was complete, the solution was stirred for an additional 2 hr. Methanol (2 ml.) was added to destroy the excess chromic anhydride and the solution poured into 150 ml. of water containing 5 ml. of concentrated hydrochloric acid. The colorless material which precipitated was extracted with 30 ml. of chloroform, the chloroform extract washed with water and dried. Evaporation of the solvent left an oily residue which was recrystallized from acetone affording totally 180 mg. (82.5%) of ketoacid, m.p. 227.5–230.5° (lit.[3] 228–230°).

The "*cis*"-acid V-c (0.275 g., 1.25 mmoles, m.p. 193–195°) was oxidized and processed as above to yield 204 mg. (74%) of ketoacid, m.p. 228–231°, mixed melting point with keto-acid prepared by oxidation of "*trans*"-isomer, 228–230°.

**Perhydrogenation of 4-Hydroxybiphenyl-4′-carboxylic Acid.**—To a solution of 4-hydroxybiphenyl-4′-carboxylic acid (4.0 g., 18.8 mmoles) and 2.1 g. (36.5 mmoles) of potassium hydroxide in water, 4 ml. of W-5 Raney nickel catalyst was added and the total volume brought up to 31 ml. with water. The hydrogenation was conducted at an initial pressure of 2500 p.s.i. (25°) and 150°; 10 hr. were required for a hydrogen uptake of 6 mole equivalents. The catalyst was filtered, washed with water and the filtrate (200 ml.) acidified with excess hydrochloric acid. The solid was separated and recrystallized from acetone, yield 2.3 g. (54.5%), m.p. 173.7–174.7°.

*Anal.* Calcd. for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80; neut. equiv., 226. Found: C, 68.75; H, 9.55; neut. equiv., 227.

***trans*-4-Cyclohexylcyclohexanecarboxylic Acid from 4-(4-Hydroxycyclohexyl)-cyclohexanecarboxylic Acid.**—The perhydrohydroxy acid VIII (0.5 g., 2.2 mmoles, m.p. 173.7–174.7°) was warmed on a steam-bath for 7 hr. with 5 ml. of glacial acetic acid saturated with hydrogen bromide. The acid was insoluble in the cold but upon warming a solution was obtained. After the heating period, the solution was poured into water, the oily solid extracted with 100 ml. of chloroform and the extract washed with water and dried. After removal of the solvent, the residual oil was dissolved in 50 ml. of methanol containing 0.2 g. of sodium and 3 ml. of Raney nickel added. The mixture was hydrogenated at an initial pressure of 40 p.s.i. for 6 hr. The catalyst was filtered and the filtrate evaporated to dryness. The residue was dissolved in water, the solution acidified and the precipitate extracted with two 50-ml. portions of ether. After washing and drying the ethereal solution, the solvent was evaporated and the residue recrystallized once from petroleum ether (b.p. 30–60°) to yield 350 g. (76.9%) of *trans*-4-cyclohexylcyclohexanecarboxylic acid, m.p. 155–158°. After recrystallization from the same solvent, the melting point is 159–160° (lit.[10] 161–162°).

The amide was prepared and melts 199–200° (lit.[10] 202–203°).

***trans*-4-(4-ketocyclohexyl)-cyclohexanecarboxylic Acid from 4-(4-Hydroxycyclohexyl)-cyclohexanecarboxylic Acid.**—The hydroxy acid VIII (0.5 g., 2.2 mmoles, m.p. 174–175°), dissolved in 9 ml. of glacial acetic acid, was oxidized as described above for the hexahydro series with a solution of 0.41 g. of chromic anhydride dissolved in 0.4 ml. of water and 0.9 ml. of acetic acid. The crude reaction product was recrystallized from ether–petroleum ether (30–60°) to yield 350 g. (70.8%) of *trans*-4-(4-ketocyclohexyl)-cyclohexanecarboxylic acid, m.p. 167–176°. Recrystallization from acetone raised the melting point to 174–176.5°. Wilds[3] reports a value of 175–176.5° for one of his isomeric perhydro keto acids.

**4-Methoxy-3′-methylbiphenyl.**—*p*-Bromoanisole (200 g., 1.07 moles), dissolved in 350 ml. of dry ether was added dropwise to a mixture of 26 g. (1.07 moles) of magnesium turnings in 200 ml. of dry ether containing 1 ml. of purified ethyl iodide. The rate of addition was such as to keep the reaction mixture gently refluxing. The refluxing was continued for an additional hour after completed addition of the bromide. The *p*-methoxyphenylmagnesium bromide solution was thoroughly cooled in an ice-bath and 180 g. (1.6 moles) of 3-methylcyclohexanone dissolved in 200 ml. of dry ether was added rapidly with stirring. After stirring for one hour at ice temperature, the complex was decomposed with excess cold 1 *N* sulfuric acid. The ethereal layer was separated, washed with water and dried. The ether was removed by distillation and the residue dissolved in 200 ml. of glacial acetic acid and added to 10 ml. of acetic anhydride and 2 g. of 2-naphthalenesulfonic acid. The mixture was heated under reflux for one hour and then poured into water. The precipitated oil was extracted with a total volume of 500 ml. of ether and the extract dried. The ether was removed and the product fractionated through an 18-inch Podbielniak spiral wire type of column. A fore-run of 3-methylcyclohexanone and *p*-bromoanisole was received and impure 4-methoxy-3′-methyl-3′,4′,5′,6′-tetrahydrobiphenyl was obtained, b.p. 144–146° (6 mm.), yield 147 g. (65.5%). Analysis of a center fraction indicated that dehydration was incomplete.

The partially dehydrated product (145 g., 0.71 mole) was heated with 28.25 g. (1.5 moles) of sulfur at an initial temperature of 225°. At first there was a vigorous dehydration reaction followed by a copious evolution of hydrogen sulfide. The temperature was gradually raised to 240° over a period of 3.5 hr. at the end of which time the evolution of hydrogen sulfide had ceased. After cooling, the hard red solid was dissolved in ether, transferred to a distillation flask, the solvent removed and the product distilled, b.p. 139–141° (4 mm.), yield 116.7 g. (81% based on tetrahydro compound). The pale yellow distillate was recrystallized from dilute ethanol and the colorless plates melt 51–52°. The over-all yield based on *p*-bromoanisole was 53%.

*Anal.* Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.90; H, 6.87.

**4-Methoxybiphenyl-3′-carboxylic Acid.**—4-Methoxy-3′-methylbiphenyl (40 g., 0.202 mole) was dissolved in 800 ml. of pyridine and 800 ml. of water and heated on a steam-bath with stirring. A total of 127 g. (0.808 mole) of potassium permanganate was added portionwise over a period of 3.5 hr. The concentration of permanganate was never permitted to exceed 2–3% (3.2–4.8 g. per addition). Each successive addition was made after the characteristic permanganate color had disappeared. The oxidation mixture was filtered while still warm and the manganese dioxide then digested on a steam-bath with 300 ml. of 50% aqueous acetone and refiltered. The combined filtrates were concentrated to a volume of 600 ml., the concentrate extracted with a total of 500 ml. of ether and then cautiously acidified to congo red paper with concentrated hydrochloric acid. The white precipitated acid was separated and recrystallized from dilute acetic acid, yield 24 g. (97% based upon recovered starting material), m.p. 202–203°.

*Anal.* Calcd. for $C_{14}H_{12}O_3$: C, 73.66; H, 5.30; neut. equiv., 228. Found: C, 73.82; H, 5.40; neut. equiv., 228.

Evaporation of the ether from the extraction of the alkaline reaction mixture followed by removal of the pyridine yielded 18 g. of recovered starting material.

The methyl ester of the acid was prepared using excess diazomethane and the product recrystallized from petroleum ether (b.p. 30–60°), m.p. 70–71.5°.

*Anal.* Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.50; H, 5.64.

**4-Hydroxybiphenyl-3′-carboxylic Acid.**—The methoxy acid (20 g., 0.088 mole) was refluxed for 13 hr. under nitrogen atmosphere with 250 ml. of glacial acetic acid and 75 ml. of 48% hydrobromic acid. The solution was concentrated to half volume by distillation at reduced pressure, water added and the solution allowed to cool. The phenolic acid crystallized and was recrystallized from dilute acetic acid, yield 16.5 g. (88%), m.p. 241–242°.

*Anal.* Calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.76; neut. equiv., 214. Found: C, 72.68; H, 4.63; neut. equiv., 215.

**Hexahydrogenation of 4-Hydroxybiphenyl-3′-carboxylic Acid.**—4-Hydroxybiphenyl-3′-carboxylic acid (2.46 g., 15 mmoles), 0.85 g. (15 mmoles) of potassium hydroxide and 3 ml. of W-5 Raney nickel catalyst were placed in a total volume of 31 ml. of water and hydrogenated at an initial pressure of 2500 p.s.i. (25°) and 75°. The theoretical amount of hydrogen for saturation of one ring was absorbed in one hour. The catalyst was filtered and the filtrate acidified. The oil was extracted with ether, the solvent removed and the material esterified with 100 ml. of methanol and 2 ml. of concentrated sulfuric acid. The phenolic and non-phenolic fractions were separated and processed as described for the 4′-isomer. The phenolic fraction yielded 1 g. of 4-hydroxybiphenyl-3′-carboxylic acid. The hexahydro isomer yielded a single pure compound upon recrystallization from ether–hexane, m.p. 150–151.8°, yield 1.6 g. (63.5%).

*Anal.* Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32; neut. equiv., 220. Found: C, 70.57; H, 7.35; neut. equiv., 224.

The hydrogenation in one equivalent of sodium carbonate gave the same yield of the non-phenolic isomer.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF NEW HAMPSHIRE]

# The Reactions of 7-Bromo-2,2-diphenylcycloheptanone[1]

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The preparation and several reactions of 7-bromo-2,2-diphenylcycloheptanone (II) are reported. The reaction of II with secondary amines yields both 6- and 7-dialkylamino-2,2-diphenylcycloheptanones. An attempted Favorski rearrangement of II gave 1-hydroxy-2,2-diphenylcyclohexanecarboxylic acid rather than the expected 2,2-diphenylcyclohexanecarboxylic acid. Dehydrobromination of II produced 7,7-diphenyl-2-cycloheptenone. From these reactions evidence is obtained indicating that the halogen of II shows a definite positive nature.

The ease of preparation of 2,2-diphenylcycloheptanone (I)[3] has suggested its use as an intermediate in the preparation of various cyclic products difficultly obtainable by other methods. This report includes the study of 7-bromo-2,2-diphenylcycloheptanone (II) as a starting material for such further syntheses. It is of interest to compare certain of these results with reported reactions of 6-bromo-2,2-diphenylcyclohexanone[4,5] and the more recently described 5-bromo-2,2-diphenylcyclopentanone.[6]

2,2-Diphenylcycloheptanone (I) was brominated in boiling carbon tetrachloride giving an excellent yield of 7-bromo-2,2-diphenylcycloheptanone (II). This bromination is more difficult than that recorded for 2,2-diphenylcyclohexanone[4] but does not give the complications noted with 2,2-diphenylcyclopentanone.[6]

Attempted reactions of the haloketone II with silver acetate or sodium acetate failed giving only recovered starting material. However, a slight reaction was observed on treatment of II with secondary heterocyclic amines in refluxing toluene or xylene for long periods of time. This reaction could be more successfully effected, however, at the higher temperature of refluxing tetralin. The solid isolated was identified as a mixture of the 6- and 7-dialkylamino-2,2-diphenylcycloheptanones (III, IV). The 6-dialkylamino-2,2-diphenylcycloheptanones (III) probably resulted from the dehydrohalogenation of II with subsequent 1,4-addition of the secondary amine to the $\alpha,\beta$-double bond produced. This structure was confirmed by isolation of III from the reaction of the heterocyclic amine with 7,7-diphenyl-2-cycloheptenone (V). The 6- and 7-piperidino- (IIIa, IVa), morpholino- (IIIb, IVb) and pyrrolidino- (IIIc, IVc) 2,2-diphenylcycloheptanones were prepared by these methods. The open chain secondary amine, diethylamine, due to its larger steric requirement (F strain[7]), gave only negligible yields of diethylamino-2,2-diphenylcycloheptanone.

The dehydrobromination of 7-bromo-2,2-diphenylcycloheptanone (II) to 7,7-diphenyl-2-cycloheptenone (V) was unexpectedly complicated as compared to the cyclohexyl analog.[4] Very low yields of V were obtained on refluxing II with pyridine or

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[2] These results were abstracted from the M.S. thesis of R. A. Covey submitted to the faculty of the University of New Hampshire.

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