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 α,β-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.

(3) R. Lyle and G. Lyle, THIS JOURNAL, **74**, 4059 (1952).

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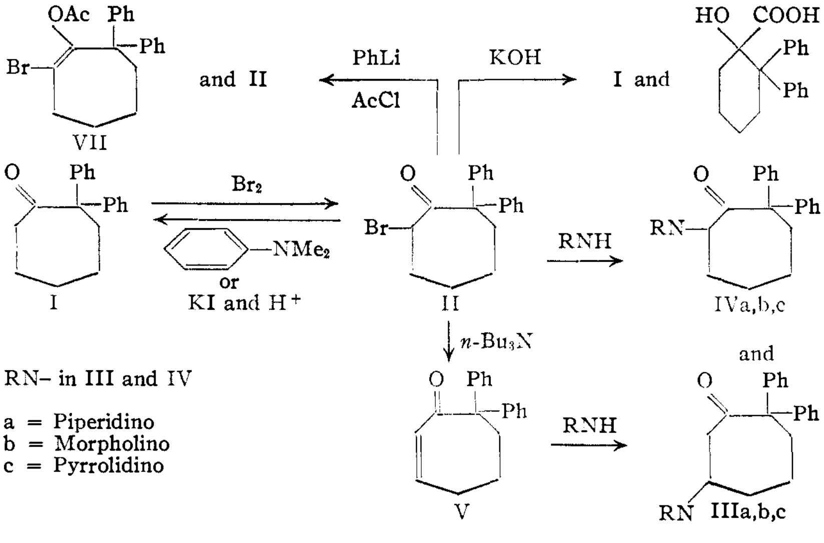

picoline even using the high reaction temperature of refluxing tetralin. The low yield was partly explained by the isolation of an 87% yield of 2,2-diphenylcycloheptanone (I) from the reaction of II with dimethylaniline. Apparently the use of tertiary amines such as α- or γ-picoline and dimethylaniline, containing an easily substituted hydrogen, causes reduction of the bromoketone II to the ketone I. This type of reduction has been noted in the case of certain halo steroids.[8] A consideration of these results and the ease of formation of 6-dialkylamino-2,2-diphenylcycloheptanones (III) suggested the use of a trialkyl amine to effect the dehydrohalogenation. Thus refluxing II with tri-*n*-butylamine in tetralin produced a 34% yield of 7,7-diphenyl-2-cycloheptenone (V).

Additional indication of the positive nature of the halogen of II was obtained from the attempted Favorski rearrangement of this compound in aqueous alcoholic alkali. From this reaction there was obtained a small amount of 2,2-diphenylcycloheptanone (I) and 1-hydroxy-2,2-diphenylcyclohexanecarboxylic acid (VI) rather than the expected 2,2-diphenylcyclohexanecarboxylic acid. VI was shown to be identical with the product of the reaction of alkali with 7,7-dibromo-2,2-diphenylcycloheptanone.[3] In the presence of base, II probably undergoes disproportionation into 2,2-diphenylcycloheptanone (I) and 7,7-dibromo-2,2-diphenylcycloheptanone. The latter compound is then converted into VI as indicated in our earlier communication.[3] Although no reaction was observed on treatment of II with resorcinol in alkaline medium, an immediate formation of iodine resulted on mixing an aqueous solution of potassium iodide with II dissolved in alcoholic hydrogen chloride. Thus the bromine of II under certain conditions definitely exhibits a positive nature.

Since the carbonyl of 2,2-diphenylcycloheptanone (I) has been shown to resist reaction with organomagnesium and lithium reagents,[9] it was thought that either coupling or metal halogen interchange might result on treatment of II with phenyllithium. Treatment of the reaction mixture with water gave a 40% recovery of the starting material II and 10% of 2,2-diphenylcycloheptanone (I). On the other hand, addition of acetyl chloride produced a complex mixture from which a small amount of starting material and a new compound, VII, could be isolated. This new substance VII contained a double bond, as indicated by addition of bromine, contained halogen (Beilstein test), but did not possess a methyl ketone group (negative iodoform test). On attempting to prepare a ketone derivative of VII only the bromoketone (II) was recovered. The results of these tests and the carbon and hydrogen analyses indicate that the compound VII is the enol acetate of 7-bromo-2,2-diphenylcycloheptanone.

Experimental

7-Bromo-2,2-diphenylcycloheptanone (II).—To a refluxing solution of 10 g. of 2,2-diphenylcycloheptanone (I)[3] in 15 ml. of carbon tetrachloride was added dropwise a solution of 2 ml. of bromine in 10 ml. of carbon tetrachloride. After the addition was complete, the solution was refluxed for 1 hr. and the solvent removed by distillation under reduced pressure. The solid residue was recrystallized from benzene and petroleum ether yielding 11.7 g. (90%) of 7-bromo-2,2-diphenylcycloheptanone (II), m.p. 125.7–126.0°.

Anal. Calcd. for $C_{19}H_{19}BrO$: C, 66.48; H, 5.58. Found: C, 66.43; H, 5.35.

Preparation of 6- and 7-Dialkylamino-2,2-diphenylcycloheptanones (III, IV).—A solution of 5 g. (0.015 mole) of 7-bromo-2,2-diphenylcycloheptanone (II) and 0.073 mole of the secondary amine in 25 ml. of tetralin was refluxed for 5 hr. The secondary amine hydrobromide which precipitated was removed by filtration and washed with ether. The organic filtrate was extracted with water until the washings were neutral to litmus and was then extracted with 10% hydrochloric acid solution. This extract from the various reaction mixtures was worked up as follows.

(a) 6- and 7-Piperidino-2,2-diphenylcycloheptanones (IIIa, IVa).—6 - Piperidino - 2,2 - diphenylcycloheptanone (IIIa) hydrochloride precipitated from the hydrochloric acid solution on standing overnight. On conversion to the free base and recrystallization from isopropyl alcohol, this hydrochloride gave 1.8 g. (35%) of IIIa as a white solid, m.p. 115.9–116.1°.

Anal. Calcd. for $C_{24}H_{29}NO$: C, 82.95; H, 8.41. Found: C, 82.85; H, 8.59.

The acid solution remaining after the removal of IIIa was neutralized yielding 1.0 g. (20%) of 7-piperidino-2,2-diphenylcycloheptanone (IVa), m.p. 143.4–144.4° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{24}H_{29}NO$: C, 82.95; H, 8.41. Found: C, 82.62; H, 8.57.

(b) 6- and 7-Morpholino-2,2-diphenylcycloheptanones (IIIb, IVb).—The hydrochloric acid extract was neutralized and extracted with ether. Evaporation of the ether yielded a mixture of the 6- and 7-morpholino-2,2-diphenylcycloheptanones (IIIb, IVb). Separation of the mixture was accomplished by precipitating IIIb from a methanol solution of the free bases after seeding with a pure sample. This procedure gave 0.4 g. (8%) of IIIb, m.p. 112.8–113.3° after further recrystallization from methanol.

Anal. Calcd. for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79. Found: C, 78.96; H, 7.82.

Evaporation of the methanol solution, after removal of IIIb, gave 1.6 g. (31%) of 7-morpholino-2,2-diphenylcycloheptanone (IVb). On recrystallization from methanol IVb was obtained as a white solid, m.p. 134.9–135.2°.

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[8] G. Rosenkranz, O. Mancera, J. Gatica and C. Djerassi, *ibid.*, **72**, 4077 (1950).

[9] N. Martin, Thesis, University of New Hampshire, 1952.

Anal. Calcd. for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79. Found: C, 78.86; H, 7.99.

(c) **6- and 7-Pyrrolidino-2,2-diphenylcycloheptanones (IIIc, IVc) Hydrochlorides.**—The hydrochloric acid extracts of this reaction mixture on standing deposited a mixture of the hydrochlorides of IIIc and IVc. This mixture was separated by fractional crystallization from ethanol, 1.9 g. (35%) of 6-pyrrolidino-2,2-diphenylcycloheptanone (IIIc) hydrochloride precipitating in the first crops. Further recrystallization of IIIc hydrochloride from ethanol gave the pure material, m.p. 200.0–200.2°.

Anal. Calcd. for $C_{23}H_{28}ClNO$: C, 74.67; H, 7.63. Found: C, 74.39; H, 7.84.

7-Pyrrolidino-2,2-diphenylcycloheptanone (IVc) hydrochloride was obtained from the mother liquor and from the original hydrochloric acid filtrate. The combined solids were recrystallized from methanol–ether giving 0.7 g. (13% of IVc, m.p. 254–259°.

Anal. Calcd. for $C_{23}H_{28}ClNO$: C, 74.67; H, 7.63. Found: C, 74.62; H, 7.82.

Reactions of 7-Bromo-2,2-diphenylcycloheptanone (II) with Tertiary Amines. (a) **Picoline.**—A solution of 5 g. of II in 10 ml. of a commercial mixture of β- and γ-picolines and 40 ml. of redistilled tetralin was refluxed 5 hr. The reaction mixture was steam distilled after the addition of a small amount of sodium hydroxide solution. The nonvolatile portion was dissolved in ether and the solution decolorized by treatment with Norite. After evaporation of the ether the residue was recrystallized from ethanol yielding 0.4 g. (10%) of **7,7-diphenyl-2-cycloheptenone** (V), m.p. 135.8–136.5°.

Anal. Calcd. for $C_{19}H_{18}O$: C, 86.99; H, 6.92. Found: C, 86.96; H, 6.84.

A comparable yield was obtained by using 50 ml. of the picoline mixture without tetralin as solvent.

(b) **Pyridine.**—A solution of 5 g. of II in 25 ml. of pyridine was refluxed for 22 hr. The reaction mixture was poured into hydrochloric acid solution and the product taken up in ether. After removal of the ether, 1.1 g. of unreacted II and 0.2 g. of 7,7-diphenyl-2-cycloheptenone (V) was obtained.

(c) **Dimethylaniline.**—A solution of 5 g. of II in 25 ml. of dimethylaniline was refluxed for 10 hr. The reaction mixture was worked up as in (b) above yielding 3.3 g. (87%) of 2,2-diphenylcycloheptanone (I), m.p. 92–93°. A mixture melting point with an authentic sample showed no depression.

(d) **Tri-*n*-butylamine.**—A solution of 5 g. of II in 8.6 ml. of tri-*n*-butylamine and 25 ml. of tetralin was refluxed for 12 hr. After cooling, the tri-*n*-butylamine hydrobromide was filtered off and washed with ether. The combined organic layers were steam distilled, and the residual oil was dissolved in ether. After distillation of the ether, the remaining solid was recrystallized from isopropyl alcohol yielding 1.3 g. (34%) of 7,7-diphenyl-2-cycloheptenone (V), m.p. 131–135°.

Preparation of 6-Dialkylamino-2,2-diphenylcycloheptanones (III) from 7,7-Diphenyl-2-cycloheptenone (V).—A solution of 0.5 g. of V and 1 ml. of the amine in 5 ml. of tetralin was refluxed for 5 hr. The product was worked up as in the preparation of 6- and 7-dialkylamino-2,2-diphenylcycloheptanones (III, IV). The melting points of the products of these reactions were identical with those of III formed in the above reactions of II with secondary amines.

Reaction of 7-Bromo-2,2-diphenylcycloheptanone (II) with Aqueous Alcoholic Potassium Hydroxide.—To a solution of 8 g. of potassium hydroxide in 11 ml. of water and 94 ml. of ethanol was added 5 g. of II. The mixture was refluxed for 4 hr. and poured into 150 ml. of water. The precipitated product was extracted into ether and was found to be 2,2-diphenylcycloheptanone (I), (0.5 g., m.p. 87–90°). The aqueous solution was neutralized with acid and the solid which separated was taken up in ether. On evaporation of the ether there remained a gummy residue which was crystallized by treatment with low-boiling petroleum ether. Recrystallization from benzene and petroleum ether gave 1.1 g. of a white solid, m.p. 165.3–165.8°. This compound was shown to be **1-hydroxy-2,2-diphenylcyclohexanecarboxylic acid** (VI) by analyses and comparison with an authentic sample.[3]

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80; neut. equiv., 296. Found: C, 77.07, 76.68; H, 6.68, 6.83; neut. equiv., 294.

Reaction of 7-Bromo-2,2-diphenylcycloheptanone (II) with Potassium Iodide.—To 15 ml. of a saturated solution of hydrogen chloride in ethanol was added 0.1 g. of II. After the solid dissolved, an aqueous solution of potassium iodide was added. The solution immediately turned dark red. Extraction of the solution with carbon tetrachloride gave the characteristic violet color of iodine, and evaporation of the solvent produced a small amount of 2,2-diphenylcycloheptanone (I).

Reaction of 7-Bromo-2,2-diphenylcycloheptanone (II) with Phenyllithium. (a) **Addition of Water.**—To a solution of phenyllithium prepared from 4.0 ml. of bromobenzene and 0.54 g. of lithium in ether was added 5.0 g. of II in 25 ml. of benzene. The solution was refluxed for 4 hr., treated with water and extracted with ether. After removal of the solvent, the solid residue was fractionally crystallized from methanol yielding 2.1 g. (40% recovery) of II and 0.4 g. (10%) of 2,2-diphenylcycloheptanone (I).

(b) **Addition of Acetyl Chloride.**—In the manner described above 10 g. of II was treated with phenyllithium. After the addition was complete, the reaction was refluxed for 2.5 hr. An excess of acetyl chloride was added to the reaction and, after all reaction subsided, water was added. The solution was made basic with sodium hydroxide and the layers separated. The ether layer was dried over calcium chloride and the solvent removed by distillation. A solution of the residue in petroleum ether was cooled in a Dry Ice–acetone-bath and 0.6 g. of recovered II precipitated. The remaining residue partially crystallized on standing giving 1.1 g. of a solid VII, m.p. 108–109° after recrystallization from ethanol. This material, as well as the noncrystalline residue, gave 7-bromo-2,2-diphenylcycloheptanone (II) on attempting the preparation of an oxime,[10] gave a positive Beilstein test for halogen, gave a negative iodoform test for methyl ketone, decolorized bromine in carbon tetrachloride, and gave a negative ferric chloride test for enols. These tests, as well as the analytical data, indicate the solid VII to be the enol **acetate** of 7-bromo-2,2-diphenylcycloheptanone (VII).

Anal. Calcd. for $C_{21}H_{21}BrO_2$: C, 65.46; H, 5.49. Found: C, 65.75; H, 5.67.

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[10] R. Shriner and R. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 138.