

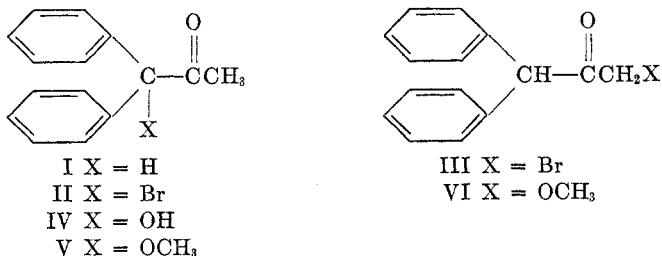
THE BROMINATION OF DIPHENYLACETONE AND SUBSEQUENT SOLVOLYSIS REACTIONS¹CALVIN L. STEVENS AND CARL T. LENK²*Received August 31, 1953*

In the work reported here an unsymmetrical ketone (I) was brominated in either *alpha* position in good yield depending upon the conditions of halogenation. Conditions for the rearrangement of one bromo ketone to the other are reported. The hydrolysis and methanolysis of one of the bromo ketones was shown to proceed with rearrangement of the functional group.

Alpha-halogenation of unsymmetrical ketones has been investigated extensively by Favorskii and co-workers (1) who formulated bromination rules for prediction of the position of the bromine in the product. Recently Jones, Catch, *et al.* (1a) have conducted a careful investigation of the bromination of methyl ethyl, methyl propyl, and methyl isopropyl ketones. The first two ketones gave mixtures of monobromo ketones but the last gave only bromo-methyl isopropyl ketone.

Hydrolysis of α -halo ketones has been used as a proof of structure (1, 2) although a carbon skeleton rearrangement has been reported during such a hydrolysis (2a). Recently Aston (2b) was led to question the structure of all α -bromo ketones that had been proved by hydrolysis and consequently also the rules for bromination formulated by Favorskii (1).

The rearrangement of a halogen atom in an unsymmetrical α -halo ketone is a known reaction. The rearrangement has been studied in the β -keto ester (3), β -diketone (3a), and steroid series (3b).



1,1-Diphenyl-2-propanone (I) was treated with bromine in carbon tetrachloride at -15° to give 87% of the crystalline 1-bromo-1,1-diphenyl-2-propanone (II). In acetic acid as a solvent, bromination of the diphenylacetone (I) at 70° gave 72% of the isomeric solid, 3-bromo-1,1-diphenyl-2-propanone (III). The structure of the 3-bromo ketone was proven by independent synthesis from the diazo ketone of diphenylacetyl chloride and dry hydrogen bromide.

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² Parke, Davis & Co. Fellow, 1951-1952.

In view of this synthesis the bromo ketone formed by bromination in carbon tetrachloride was assigned structure II.

The 1-bromo ketone (II) could be rearranged to the 3-bromo ketone (III) by treatment with dry hydrogen bromide in ether solution in a sealed bottle at 100°.

Hydrolysis of the 1-bromo ketone (II) proceeded in an aqueous dioxane solution at 100° to give 89 % of crystalline 1,1-diphenyl-1-hydroxy-2-propanone (IV). This α -hydroxy ketone was identical with the hydroxy ketone recently reported in this laboratory (4) and whose structure was proven by independent synthesis.

The hydrolysis of 3-bromo-1,1-diphenyl-2-propanone (III) proceeded with rearrangement of the functional group. After 24 hours in aqueous dioxane solution at 100°, the crystalline product, isolated in 50 % yield, proved to be the 1-hydroxy ketone (IV).

The results of methanolysis were similar to those of hydrolysis. Both the 1- and 3-bromo ketones (II and III), when dissolved in refluxing methyl alcohol, liberated halide ion and gave the same liquid methoxy ketone (V).

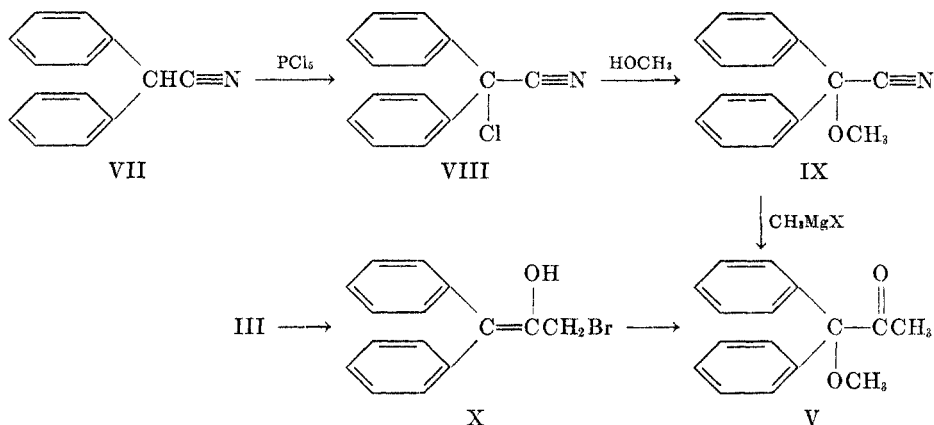
To prove the structure of the methoxy ketone from the methanolysis reactions both α -methoxy diphenylacetones (V and VI) were synthesized by unequivocal methods.

1,1-Diphenyl-3-methoxy-2-propanone (VI) was prepared by the method of Newman and Beal (5) from the diazo ketone of diphenylacetyl chloride, methyl alcohol, and boron trifluoride etherate. VI proved to be a low-melting solid. 1,1-Diphenyl-1-methoxy-2-propanone (V) was prepared from diphenylacetone nitrile (VII) by the sequence of reactions VII \rightarrow VIII \rightarrow IX \rightarrow V. The chlorodiphenylacetone nitrile (VIII) could be prepared in 86 % yield from VII and phosphorus pentachloride. Methanolysis of the chloro nitrile (VIII) gave diphenylmethoxyacetone nitrile (IX) in 66 % yield. Treatment of IX with excess methylmagnesium bromide gave 59 % of V. The infrared spectrum of this liquid methoxy ketone was significantly different from the spectrum of VI but identical with the spectra of the methoxy ketones from the alcoholysis reactions. Further, the semicarbazone derivatives were identical as shown by mixture melting point determinations.

These results prove that the methanolysis of the 3-bromo ketone (III) proceeded with rearrangement of the functional group.

Bromination of ketones is known to proceed by an acid-catalyzed mechanism through the enol (6) or by a peroxide catalyzed mechanism (3). Bromination and debromination of a ketone by a polar mechanism has been shown to be a reversible equilibrium by Bartlett (7), and Newman (8) has proposed a common cyclic intermediate. The exact nature of the mechanisms, rates, and equilibria that allow the directed bromination recorded here are unknown. However, in this connection the 3-bromo ketone (III), when placed under the conditions (chloroform solution with dry hydrogen bromide at -15°) of the formation of 1-bromo ketone (II), did not rearrange. The 1-bromo ketone (II) in acetic acid for 10 minutes in the presence of dry hydrogen bromide did not give ap-

preciable amounts of the 3-bromo ketone (III) although bromination of diphenylacetone (I) under these conditions gave a 72% yield of III. These results indicate that one bromo ketone is not an intermediate in the formation of the other.



The 1-bromo ketone was rearranged to the 3-bromo ketone in one hour in ether solution containing dry hydrogen bromide at 100°. That this reaction proceeded by reduction to diphenylacetone and bromine followed by rebromination could be shown by introduction of cyclohexene into the reaction with the bromine and actual isolation of I.

One interpretation of the solvolysis reaction of the 3-bromo ketone to yield the 1-substituted keto derivatives evolves an enol intermediate (X) which could undergo solvolysis accompanied by allylic rearrangement to give the 1-substituted derivatives. An alternate interpretation involves rearrangement of the 3-bromo ketone to the 1-bromo ketone followed by solvolysis. The 3-bromo ketone could not be made to rearrange to the 1-bromo ketone in this investigation. Further, the rearrangement does not proceed first by solvolysis of the 3-bromo ketone to give 3-substituted derivatives and then rearrangement of the 3-substituted derivatives to the 1-substituted derivatives, since the 3-methoxy ketone (VI) under the conditions of the reaction could be recovered unchanged.

EXPERIMENTAL

1-Bromo-1,1-diphenyl-2-propanone (II). 1,1-Diphenyl-2-propanone was prepared according to the directions in Organic Syntheses (9). A solution was prepared from 4.9 g. (0.023 mole) of this diphenylacetone (I) and 35 ml. of carbon tetrachloride and the solution was cooled to -15° . Bromine (3.8 g., 0.023 mole) was added dropwise with vigorous stirring. After the addition, the mixture was stirred an additional hour and then the solvent was removed under reduced pressure. The product was dissolved in low-boiling petroleum ether and the solution was allowed to crystallize at -5° . From the solution 5.65 g. (87%) of 1-bromo-1,1-diphenyl-2-propanone (II) could be obtained, m.p. $55-56^\circ$ (10). An analytically pure sample melted at $56.5-57.5^\circ$.

Anal. Calc'd for $\text{C}_{15}\text{H}_{13}\text{BrO}$: C, 62.29; H, 4.53.

Found: C, 62.28; H, 4.55.

3-Bromo-1,1-diphenyl-2-propanone (III). Bromine (32 g., 0.2 mole) in 25 ml. of acetic

acid was added dropwise to a stirred solution of 42.0 g. (0.2 mole) of the diphenylacetone (I) in 150 ml. of acetic acid at a temperature of 60–70°. After an additional hour of stirring at this temperature, the mixture was poured onto cracked ice. The solid which slowly crystallized was washed with cold isopropyl alcohol and dried to give 42 g. (72%) of 3-bromo-1,1-diphenyl-2-propanol, m.p. 62–64° (11). Recrystallization from petroleum ether gave an analytically pure sample, m.p. 68.5–69.5°.

Anal. Calc'd for $C_{15}H_{13}BrO$: C, 62.29; H, 4.53; Br, 27.7.

Found: C, 62.46; H, 4.64; Br, 27.4.

With 0.1-mole quantities and a short reaction time of 10 minutes, the same yield (72%) of 3-bromo ketone (III) was obtained.

The 3-bromo ketone was made independently according to the method of Lutz and Wilson (12) except that dry hydrogen bromide was used instead of concentrated hydrobromic acid to decompose the diazo ketone. The 3-bromo ketone made in this manner melted at 68–69° and was identical by mixture melting point determination with the compound from bromination.

Methanolysis of 1- and 3-bromo-1,1-diphenyl-2-propanone. The 1-bromo-1,1-diphenyl ketone (II; 2.0 g.) was dissolved in 20 ml. of absolute methanol and heated to reflux for 6 hours. Distillation of the reaction mixture gave 78% of 1,1-diphenyl-1-methoxy-2-propanone, b.p. 112–113° (0.2 mm.); n_D^{25} 1.5670.

Anal. Calc'd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71; CH_3O , 12.9.

Found: C, 80.08; H, 6.81; CH_3O , 12.5.

The semicarbazone of this methoxy ketone was prepared, m.p. 193–194°.

Anal. Calc'd for $C_{17}H_{18}N_2O_2$: C, 68.66; H, 6.44.

Found: C, 68.19; H, 6.74.

The 3-bromo-1,1-diphenyl ketone (III; 15 g.) was dissolved in 100 ml. of absolute methanol and refluxed for 16 hours. The alcohol was evaporated and the resulting oil was distilled to give 10 g. (77%) of 1,1-diphenyl-1-methoxy-2-propanone (V), b.p. 114–115° (0.1 mm.); n_D^{25} 1.5687. The infrared spectrum of this compound when compared to the methanolysis product from the bromo ketone (II) indicated they were identical. Further, the semicarbazone derivative melted at 192–193° and the melting point was not depressed when mixed with a sample prepared above.

Independent synthesis of 1,1-diphenyl-1-methoxy-2-propanone (V). (a). *Diphenylmethoxyacetoneitrile (IX).* Diphenylacetoneitrile (40.0 g., 0.21 mole) was heated for three hours at 100° with 40.3 g. (0.23 mole) of phosphorus pentachloride. The volatile products were evaporated under reduced pressure and the residue was dissolved in 100 ml. of benzene and poured onto ice. The organic layer was washed with a suspension of calcium carbonate and water and then the benzene was evaporated. Distillation gave 40.8 g. (86%) of chlorodiphenylacetoneitrile, b.p. 112–114° (1.5 mm.). The chlorine content was 16.5% (Calc'd 15.6%).

The chloronitrile (VIII, 13.3 g., 0.06 mole) was dissolved in 50 ml. of dry methanol and 5.4 g. (0.064 mole) of sodium bicarbonate was added. The mixture was stirred for 30 hours at 35°, after which time the salt was filtered and the solvent was removed by evaporation. The weight of the salt indicated 98% reaction. The residue after evaporation was distilled to give 9.2 g. of a pale yellow oil, b.p. 121–122° (0.8 mm.). The oil solidified and was recrystallized from methyleyclohexane to give 8.6 g. (66%) of diphenylmethoxyacetoneitrile, m.p. 50–52°. An analytically pure sample was white and melted at 53–53.5°.

Anal. Calc'd for $C_{15}H_{13}NO$: C, 80.72; H, 5.84.

Found: C, 80.85; H, 5.90.

(b) *1,1-Diphenyl-1-methoxy-2-propanone.* An ethereal solution of the Grignard reagent was prepared from 12.8 g. (0.09 mole) of methyl iodide and 2.2 g. (0.09 g.-atom) of magnesium. An ether solution of 9.85 g. (0.044 mole) of diphenylmethoxyacetoneitrile (IX) was added and the solution was heated to reflux for seven hours. Within the first half-hour a granular white solid precipitated. The ether was removed, benzene was added, and the mixture was stirred and heated for 1½ hours at 70°. After the reaction had been cooled to 0°, 70 ml. of 20% hydrochloric acid was added. After ten minutes at 0°, the mixture was

cooled, 25 ml. of water was added, and the water layer was separated. The benzene layer was evaporated and the residue was dissolved in dioxane and again treated with 20% hydrochloric acid at 60° for 11 hours. After addition of water and benzene, the benzene layer was evaporated and the residue was distilled to give 6.1 g. (59%) of the 1,1-diphenyl-1-methoxy-2-propanone (V), b.p. 110° (0.3 mm.), n_D^{24} 1.5700.

A semicarbazone derivative was prepared in 75% yield, m.p. 191.5–193°. A mixture melting point with the sample prepared above was not depressed.

1,1-Diphenyl-3-methoxy-2-propanone (VI). The compound was prepared by the method of Newman and Beal (5). The diazoketone (5 g., 0.02 mole), m.p. 66–67.5°, from diphenylacetylchloride and diazomethane (13) was dissolved in 100 ml. of absolute methanol and 1 ml. of boron trifluoride etherate was added. In 2½ hours at room temperature the theoretical amount of nitrogen was evolved. The methanol was evaporated under reduced pressure and the residue was dissolved in ether. The ether solution was washed with bicarbonate solution and then water. After the ether was evaporated, the residue was distilled under reduced pressure to give (66%) of 1,1-diphenyl-3-methoxy-2-propanone (VI) which solidified, m.p. 35–35.5°.

Anal. Calc'd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71.

Found: C, 80.03; H, 6.64.

The semicarbazone of this methoxy ketone (VI) melted at 130–131°.

Anal. Calc'd for $C_{17}H_{19}N_3O_2$: C, 68.66; H, 6.45.

Found: C, 68.55; H, 6.48.

The oxime³ melted at 130–131°.

Anal. Calc'd for $C_{16}H_{17}NO_2$: C, 75.26; H, 6.71.

Found: C, 75.41; H, 6.82.

Hydrolysis of 1- and 3-bromo-1,1-diphenyl-2-propanone. The 1-bromo ketone (II, 0.7 g.) was dissolved in 10 ml. of dioxane and 2.5 ml. of water was added. After the solution had been refluxed for three hours, the solvents were evaporated and the residue was dissolved in petroleum ether from which 0.5 g. (89%) of 1,1-diphenyl-1-hydroxy-2-propanone (IV) crystallized, m.p. 63–65°. A mixture melting point with an authentic sample (4) was not depressed.

The 3-bromo ketone (III, 2.9 g.) was dissolved in 25 ml. of dioxane and 10 ml. of water was added. After 24 hours at the reflux temperature the solvents were evaporated. After evaporation, the residue solidified to give 1.4 g. (62%) of 1,1-diphenyl-1-hydroxy-2-propanone (IV) m.p. 63–65°. A mixture melting point with an authentic sample was not depressed.

Rearrangement of 1-bromo-1,1-diphenyl-2-propanone (II) *to the 3-bromo ketone* (III). Diphenylacetone (I, 21.0 g., 0.1 mole) was dissolved in 150 ml. of absolute ether and cooled to –15° and 16 g. (0.1 mole) of bromine was added. The solution was divided in half. Evaporation of the solvent from the first half at reduced pressure gave 83% of 1-bromo ketone, m.p. 47–51°. The mixture melting point with an authentic sample which melted at 52–53° was 47–52°.

The second half of the original solution containing the 1-bromo ketone was sealed in a bottle and heated to 100° for one hour. Evaporation of the solvent gave 7.7 g. (55% based on one-half of the starting material) of 3-bromo ketone, m.p. 63–65°. A mixture melting point with authentic 3-bromo ketone (m.p. 68–69°) was not depressed, 65–67°.

In a similar reaction 25 ml. of cyclohexene was added to half the reaction after bromination. After heating this mixture 16% crude diphenylacetone (I) could be isolated, m.p., 53–56°. Recrystallization from petroleum ether gave 10% of pure diphenylacetone, m.p. 60–61°; mixture m.p. 60–61°.

Attempted rearrangement of 1,1-diphenyl-3-methoxy-2-propanone (VI).³ A solution of 10.1 g. (0.042 mole) of VI in 140 ml. of dry methanol was heated to the reflux temperature and 100 ml. of alcohol containing 0.044 mole of dry hydrogen bromide gas was added slowly over

³ These experiments were performed by Mr. Ted Mills.

a period of nine hours. After this time, the solvent was evaporated under reduced pressure and the residue was distilled to give 7.6 g. (75%) of recovered VI. The infrared spectra of the product was identical with authentic VI and an oxime derivative did not depress the melting point when mixed with an authentic oxime.

SUMMARY

Bromination of diphenylacetone (I) at low temperatures in chloroform or ether gave 1-bromo-1,1-diphenyl-2-propanone (II) in high yield. At high temperatures in acetic acid the corresponding 3-bromo ketone (III) was produced in high yield. The 1-bromo ketone could be caused to rearrange to the 3-bromo ketone. Hydrolysis of either bromo ketone gave 1-hydroxy-1,1-diphenyl-2-propanone (IV) and alcoholysis of either bromo ketone gave 1-methoxy-1,1-diphenyl-2-propanone (V), the structure of which was proven by independent synthesis.

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