sodium bicarbonate solution, then with water, and the benzene distilled off without previous drying (the small amount of water still being present distils azeotropically with the benzene). The residue was recrystallized or distilled, respectively, as indicated in Table I.

Example: α-[*o-hydroxybenzylidene*]-γ-*butyrolactone* (IV). The apparatus consisted of a 500-cc. three-neck flask fitted with a stirrer, a reflux condenser, a thermometer, and a nitrogen-inlet tube. 12.2 g (0.1 mole) of salicylaldehyde and 17.2 g. (0.2 moles) of butyrolactone were dissolved in 100 cc. of benzene. The mixture was cooled down to +3° by means of an ice salt bath. During the whole reaction the mixture was well stirred. A slow stream of nitrogen was passed over the mixture. Within 15 min., 13.5 g. (0.25 mole) of sodium methoxide were added in portions. The temperature rose to 27° and the mixture turned to a brownish jelly which was then diluted with 100 cc. of benzene. Stirring was continued for 3 more hr., then the mixture was heated on a water bath for 45 min. (temperature 60–65°).

After standing over night, sufficient 10% sulfuric acid was added under stirring to make the mixture acidic; stirring was continued for 1 hr. and the precipitate which had been formed was filtered by suction and washed thoroughly with water. Yield: 12.0 g. (63%), m.p. 184–185°. The analytical sample, after 3 recrystallizations from methanol, had the same melting point.

The filtrate was separated, the benzene layer was washed with dilute sodium bicarbonate solution, then with water and distilled. A brown oil remained which furnished, on distillation, 4.0 g. of salicylaldehyde, b.p. 195–200°. Yield based upon consumed aldehyde: 93%.

Tetrabromide of XXIV. 2 g. of XXIV were dissolved in 10 cc. of chloroform. By means of a buret, a solution of 6.2 g. bromine in 20 cc. of chloroform was added dropwise and the solution left over night in an open porcelain dish. White crystals (5.0 g., 96%), m.p. 182–183.5°, were formed after evaporation of the solvent. After 3 recrystallizations from methanol, the m.p. was 192.5–193° (dec.).

Anal. Calcd. for $C_{13}H_{12}Br_4O_2$: Br, 61.49. Found: Br, 61.86.

An attempt to prepare a bromide of XXVII by similar means resulted only in dark viscous oils.

α-[*3-Methoxy-4-hydroxybenzylidene*]-γ-*butyrolactone* (XVII) *from* XIV. 15.5 g. of XIV, 100 cc. of concd. hydrochloric acid, and 250 cc. of glacial acetic acid were heated under reflux for 1.5 hr. After standing over night the solvents were distilled off. The residue solidified and was recrystallized by dissolving in 100 cc. of methanol and adding 100 cc. of water. Yield 10.5 g. (95%), m.p. 151–152°.

α-[*p-Hydroxybenzylidene*]-γ-*butyrolactone* (VI) *from* XIII. 38.1 g. of XIII, 266 cc. of concd. hydrochloric acid, and 762 cc. of glacial acetic acid were boiled for 1.5 hr., then the solvents were removed. The residue was recrystallized from 1.5 liter of water furnishing 16.2 g. of product, m.p. 179–180°. By concentrating the mother liquors, an additional 1.5 g. (m.p. 173–176°) were obtained. Total yield: 17.7 g. (69%).

Hydrogenations (Table II). The hydrogenations were performed by dissolving or suspending 2–20 g. (mostly 5 g.) of the condensation products in 250 cc. of methanol (or tetrahydrofuran), adding 5–10% by weight of platinum oxide (by American Platinum Works) and shaking under 45–50 lbs. of hydrogen in a Parr apparatus until the pressure remained constant. Application of heat apparently had no influence on the yields. After 15 min. to 24 hr. (depending on the amount of starting material rather than on the particular compound), the pressure remained constant.

The catalyst was removed by filtration, the solvent distilled off and the residue worked up by crystallization or distillation.

Acknowledgment. The authors are indebted to National Aniline Division for a gift of *p*-acetamidobenzaldehyde. They appreciate gratefully the skillful assistance of Mr. Horst Schmank and Mr. Ronald Hemingway.

CINCINNATI 21, OHIO

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF WAYNE STATE UNIVERSITY]

The Halodiphenacyls. III. The Structure and Reactions of the Hydrogen Bromide Adduct[1]

CALVIN L. STEVENS AND RICHARD G. HISKEY[2]

Received July 8, 1958

The adduct formed from the reaction of β-bromodiphenacyl with hydrogen bromide was shown to be the α-hydroxy-β-bromoketone III and is interpreted in this work to involve *cis* addition to the epoxide. The reaction of III with sodium iodide gave the α-hydroxy-β-methylene ketone IV, which was stable in neutral solution but which rearranged to the diketone VI in acid solution. The two acetates, XIV and IIIa, which had previously been prepared from the reaction of acetyl bromide with I and II, respectively, proved to be diastereoisomers and showed that the opening of the α,β-epoxyketones with acetyl bromide in this instance is stereospecific and involved the same stereochemistry as the opening with hydrogen bromide.

Previous studies have resulted in the elucidation of the structure and stereochemistry of the halodiphenacyls.[3–6] Thus α-, and β-bromodiphenacyl were shown to be I and II, respectively, and the facile isomerization of the α-isomer (I) to the β-isomer (II) with base has been discussed.[4,6]

The conversion of II to I by reaction with hydrogen bromide followed by treatment of the adduct with ammonia has been reported.[6] The present re-

(1) Abstracted from the thesis of Mr. Richard G. Hiskey submitted in June 1955 to the Graduate School at Wayne State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Wyandotte Chemical Corporation Fellow, 1953–1955.

(3) J. Berson, *J. Am. Chem. Soc.*, **74**, 5175 (1952).

(4) H. H. Wasserman, N. E. Aubrey, and H. E. Zimmerman, *J. Am. Chem. Soc.*, **75**, 96 (1953).

(5) C. L. Stevens, R. J. Church, and V. T. Traynelis, *J. Org. Chem.*, **19**, 522 (1954).

(6) C. L. Stevens and V. T. Traynelis, *J. Org. Chem.*, **19**, 522 (1954).

port describes the characterization and further chemical reactions of the adduct III.

The adduct III was obtained in 85% yield as previously reported.[5] An infrared spectrum of the adduct showed a hydroxyl stretching band and the ultraviolet spectrum showed the carbonyl group still in conjugation with the phenyl group. To establish the location of the hydroxyl group, the adduct was treated with sodium periodate in aqueous dioxane. The bromohydrin reacted slowly, consuming 1 equivalent of periodate in 49 hours. However, under the same conditions benzoin was completely oxidized in 45 minutes.

Acylation of the bromohydrin at 0° afforded an acetoxy derivative, m.p. 103°, in 86% yield. The same derivative has been previously prepared by heating β-bromodiphenacyl and acetyl bromide in a sealed tube at 100°.[7] Similarly the benzoate and tosylate derivatives could be prepared in 50–60% yield.

Confirmation of the α-hydroxyketone nature of the bromohydrin was obtained by oxidation with *N*-bromosuccinimide.[8] During the reaction, hydrogen bromide was evolved and succinimide was isolated in 99% yield. An infrared spectrum of the yellow reaction product showed the twin carbonyl absorption at 5.82 μ and 5.95 μ, indicative of an α-diketone.[9,10] The diketone proved to be thermally unstable even during molecular distillation, however bromine analysis on the crude reaction product indicated two bromine atoms to be present. Treatment of the dibromodiketone with sodium periodate yielded benzoic acid. All of these results are consistent with α-hydroxy-β-bromoketone III as the structure of the hydrogen bromide adduct. The assignment of III is in accord with the halohydrin resulting from the similar treatment of other α-ketooxides.[9,10]

Previously Church[11] reported the reaction of III with zinc in ethanol yielded a bromine free crystalline compound. The infrared spectrum of the debrominated product showed a hydroxyl stretching band and carbonyl absorption but no absorption in the 6.1 μ or 11.0 μ region. The same material IV could be prepared by treating the bromohydrin with sodium iodide in acetone at room temperature or by reaction with chromous chloride in acetone.

Treatment of the bromohydrin acetate (IIIa) with sodium iodide under similar conditions yielded the acetate derivative (IVa) of the debrominated material. The acetate prepared in this manner was identical in all respects to the derivative obtained directly from the debrominated alcohol IV.

That IVa did, in fact, contain a terminal methylene grouping was indicated by treatment with ozone, which afforded 1,3-diphenyl-2-acetoxypropane-1,3-dione (VII). These results were further substantiated by reduction experiments on IV. The compound readily adsorbed 2 moles of hydrogen and the product showed no carbonyl adsorption in the infrared spectrum. When the hydrogenation was stopped at 1 mole uptake, a clear liquid (V), presumably a mixture of diastereoisomers, was isolated. The infrared spectrum showed hydroxyl and carbonyl absorption and the ultraviolet spectrum indicated the carbonyl group to be in conjugation with a benzene ring.

Oxidation of V with sodium dichromate at 0° afforded the α-diketone VI. The material was assigned the structure of an α-diketone by the characteristic infrared spectrum and the conversion to 2-phenyl-3(1-phenylethyl)quinoxaline (VIII) with *o*-phenylenediamine.

When an ether solution of IV was saturated with dry hydrogen bromide at 0°, the same α-diketone VI resulted, as evidenced by a comparison of the infrared spectra and the quinoxaline derivatives VIII. The rearrangement product VI also resulted when an attempt was made to purify IV on alumina. Rearrangements of this nature (IV → VI) have been reported with other allylic alcohols containing a terminal methylene grouping.[12] When IVa was treated under the same conditions only unchanged acetoxyketone was recovered.

The structure of the α-hydroxyketone V, the α-diketone VI, obtained from oxidation of V and rearrangement of IV, and the quinoxaline derivative VIII of the α-diketone, were confirmed by two independent syntheses. In the first synthetic approach, dypnone (IX) was converted into 1,3-diphenylbutan-1-one (X). The ketone could be brominated in glacial acetic acid yielding a mixture of diastereomeric α-bromoketones XI which were separated by fractional crystallization into 59.4% of needles, m.p. 82–83°, and 23.5% of clusters, m.p., 120–121°. That the two compounds were α-brominated ketones and diastereoisomers, was demonstrated by the base catalyzed isomerization of the 82° isomer to the 120° isomer. Hydrolysis of either isomer of XI with refluxing alkali provided an impure liquid, similar in infrared and ultraviolet spectrum to Va. Oxidation of the hydrolysis product, followed by treatment with *o*-phenylenediamine, yielded 39% of VIII. The yield of VIII from V was 76.5%.

The fact that V obtained by hydrolysis of XI was impure was evident by the lower extinction coefficient in the ultraviolet spectrum and the low yield of quinozaline derivative and made another syntheses of V desirable. When phenylglyoxal

(7) C. Paal and H. Schultze, *Ber.*, **36**, 2386 (1903).

(8) M. Z. Barakat, M. F. Abd El-Wahab, and M. M. El-Sadr, *J. Am. Chem. Soc.*, **77**, 1670 (1955).

(9) H. O. House, *J. Am. Chem. Soc.*, **76**, 1235 (1954).

(10) H. H. Wasserman and N. E. Aubrey, *J. Am. Chem. Soc.*, **78**, 1726 (1956).

(11) R. J. Church, Thesis, Wayne University, 1952.

(12) (a) A. S. Dreiding and J. A. Hartman, *J. Am. Chem. Soc.*, **78**, 1216 (1956). (b) C. Djerassi, C. R. Smith, A. E. Lippman, S. Figdor, and J. Herran, *J. Am. Chem. Soc.*, **77**, 4801 (1955).

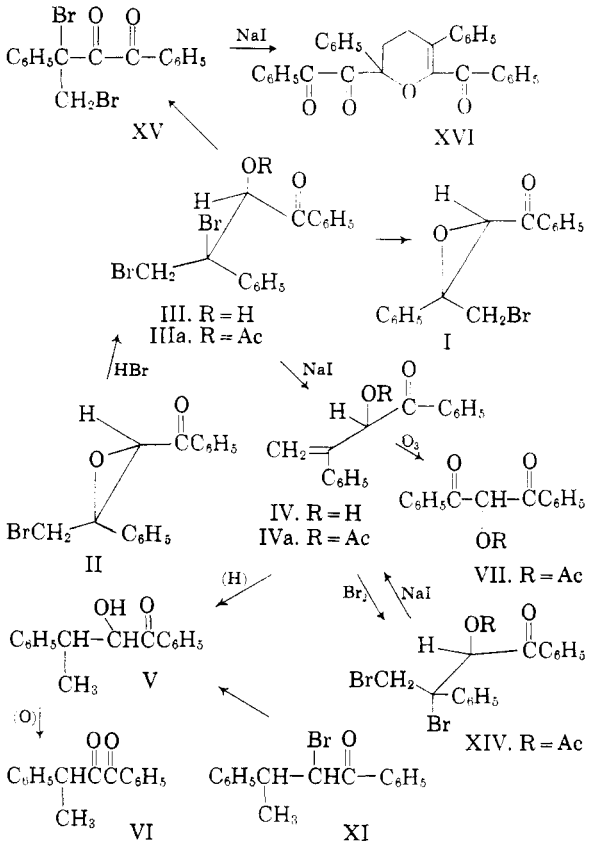
(XIII) was treated with α-phenylethylmagnesium chloride (XII), a 13.2% yield of clear liquid was obtained by molecular distillation. The Grignard product was identical in all respects to V and provided, on oxidation and quinoxaline formation, a 52.7% yield of VIII. The properties of V, VI, and VIII obtained by the second method were identical to those of the products arising from IV.

Bromination of IVa at 60° yielded a diastereometric dibromacetate XIV, m.p. 120–121°, in 81.4% yield. The same acetate was previously prepared by heating acetyl bromide and α-bromodiphenacyl in a sealed tube.[7] That the 103° acetate and the 120° acetate were diastereoisomers was demonstrated by their conversion to IVa with sodium iodide in acetone. Similar bromination of IV yielded only VI and not the expected β-bromohydrin.

A consideration of these data in view of the recent work from other laboratories cited below indicates that the stereochemical structure of the bromohydrin corresponds to that given in formula III. The *cis* nature of β-bromodiphenacyl (II) has been previously assigned[6] and the conversion of the bromohydrin III to the *trans*-α-bromodiphenacyl is also known.[5] Thus the reaction sequence II → III → I must involve one inversion or an odd number of inversions during the course of the two reactions. The *cis* acid catalyzed opening of epoxides has been discussed in some detail by Wasserman,[10] Brewster[13a] and Curtin,[13b] who provide certain well documented examples that clearly involve acid catalyzed *cis* opening of epoxides. The obvious structural similarity of the halodiphenacyls and the dypnone oxides of Wasserman,[10] together with the stereochemical requirement of the sequence II → III → I provides the basis for the stereochemical assignment of III, resulting from *cis* opening of the oxide II.

In this work I was treated with hydrogen bromide under the same conditions described for the β-isomer II, but no tractable product could be isolated. However, acetyl bromide is known to open each of the halodiphenacyls I and II to give different products. These products were shown to be diastereoisomers and not structural isomers and thus the reaction of acetyl bromide with the epoxides is stereospecific. Further, the acetate IIIa, which is formed from II, is related to III and indicates that this opening is a *cis*-opening of the epoxides.

When the dibromodiketone XV, from IIIa, was treated with sodium iodide the expected α,β-unsaturated diketone was not obtained, but rather a dimeric material was isolated. In analogy with other reported dimers from similar compounds[14] it is suggested that the structure is that of a substituted tetrahydropyran derivative such as XVI.



EXPERIMENTAL

α-3,4-Dibromo-1,3-diphenyl-2-hydroxybutan-1-one. β-Bromodiphenacyl II (m.p. 160–161°) was prepared in 54.7% yield according to the procedure of Wasserman *et al.*[4] A cold slurry of 15.8 g. (0.05 mole) of β-bromodiphenacyl in 150 ml. of dry ether was saturated with anhydrous hydrogen bromide for 4 hr. The white fluffy solid which formed was filtered and recrystallized twice from a petroleum ether–benzene mixture to yield 16.84 g. (85%) of α-3,4-dibromo-1,3-diphenyl-2-hydroxybutan-1- one (III), m.p. 144–145° (dec.).

Periodic oxidation of α-3,4-dibromo-1,3-diphenyl-2-hydroxybutan-1-one. To 1.1523 g. (2.89 millimoles) of bromohydrin III in 96 ml. of pure dioxane was added 50 ml. of a solution containing 10.5105 g. of sodium metaperiodate in 250 ml. of water. The mixture was diluted to 250 ml. and at intervals 10 ml aliquots were withdrawn and titrated with 0.1*M* sodium arsenite and 0.05*M* iodine solutions. After 49 hr. a sample containing 10 ml. standard arsenite solution consumed 2.90 ml. of standard iodine solution indicating 1.06 molar equivalents of periodate had reacted with 1.0 equivalent of sample. An aliquot withdrawn after 90 hr. indicated no further oxidation. Under the same conditions a 0.6153 g. (2.90 millimoles) sample of benzoin consumed 1.07 moles of periodate in approximately 45 min.

Reaction of III *with N-bromosuccinimide.* Following the procedure of Barakat *et al.*[8] a mixture of 4.0 g. (0.01 mole) of bromohydrin III and 1.78 g. (0.01 mole) of *N*-bromosuccinimide in 50 ml. of dry carbon tetrachloride was refluxed on a steam bath for 5 hr. After the evolution of hydrogen bromide ceased, 0.940 g. (94.9%) of succinimide, m.p. 123–124°, was removed by filtration. The solvent was removed *in vacuo* and the yellow liquid was taken up in 10 ml. of benzene, diluted with petroleum ether and 170 mg.

(13) (a) J. Brewster, *J. Am. Chem. Soc.*, **78**, 4061 (1956). And references cited. (b) D. Y. Curtin, A. Bradley, and Y. G. Hendrickson, *J. Am. Chem. Soc.*, **78**, 4064 (1956).

(14) (a) K. Alder and E. Ruden, *Ber.*, **74**, 920 (1941). (b) C. Mannich, *Ber.*, **74**, 557 (1941).

of white solid, probably unreacted bromohydrin, m.p. 120.5–122.5° (dec.) was removed by filtration. The benzene filtrate was concentrated *in vacuo* to yield 3.53 g. of the dibromodiketone as a viscous yellow liquid. The diketone could not be distilled without extensive decomposition even at low pressure. Bromine analysis on the crude liquid from oxidation indicated an impure dibromide. Although the analysis for bromine was not satisfactory for complete characterization, the ultraviolet spectrum exhibited an absorption peak at 261 mμ (ϵ_{max} = 11,200) and the infrared spectrum showed absorption at 5.82 μ and 5.95 μ indicating an α-diketone conjugated to a benzene nucleus.

α-3,4-Dibromo-1,3-diphenyl-2-acetoxybutan-1-one (IIIa). A solution prepared from 50 ml. of cold acetic anhydride containing 2 drops of perchloric acid and 10.0 g. (0.025 mole) of bromohydrin (IIIa) was stored at 0° for 40 hr. and then poured on ice. The mixture was neutralized in the cold with solid sodium carbonate and the solid which formed filtered, washed well with water and dried *in vacuo*. Two recrystallizations from petroleum ether–benzene afforded 9.5 g. (86.3%) of the bromohydrin acetate as white prisms m.p. 102–103°.[7] The acetate derivative proved quite unstable when exposed to light but could be stored several months in the dark at 10°.

Anal. Calcd. for $C_{18}H_{16}Br_2O_3$: C, 49.15; H, 3.67. Found: C, 48.85; H, 3.87.

The acetate could also be prepared in 86.3% yield using acetyl chloride and pyridine at 0°. A mixture melting point with samples from each method of preparation was not depressed.

The benzoate derivative could be prepared in 59.3% yield using benzoyl chloride and pyridine at 0°, m.p. 123–124°.

Anal. Calcd. for $C_{23}H_{18}Br_2O_3$: C, 55.00; H, 3.61. Found: C, 55.12; H, 3.42.

1,3-Diphenyl-2-hydroxybut-3-en-1-one (IV). To 5.0 g. (0.0125 mole) of bromohydrin (III) dissolved in 100 ml. of dry acetone was added a solution of 13 g. (0.086 mole) of dry sodium iodide in 120 ml. of dry acetone. The mixture was kept at room temperature for 14 hr. The precipitated sodium bromide was filtered, washed with dry acetone, and amounted to 2.55 g. (100%). The filtrate was decolorized with cold saturated sodium bisulfite solution, diluted to 1 l. with water and extracted four times with 50-ml. portions of ether. The combined ether extracts were washed once with water and dried over magnesium sulfate. After removal of the solvent *in vacuo*, a white crystalline solid was obtained, which after two recrystallizations from dilute methanol yielded 2.62 g. (87.9%) of 1,3-diphenyl-2-hydroxybut-3-ene-1-one, m.p. 80–82°.

An analytical sample recrystallized from methanol melted at 82–83°.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.78; H, 6.09.

The debromination could also be accomplished in 80.3% yield when the bromohydrin was refluxed with zinc in ethanol or in 83.1% yield using chromous chloride[15] in acetone.

Rearrangement of 1,3-diphenyl-2-hydroxybut-3-en-1-one (IV) *to 1,3-diphenylbutane-1,2-dione* (VI). A solution containing 270 mg. (1.13 millimoles) of the unsaturated keto-alcohol (IVa), 10 ml. of 10% hydrochloric acid and 10 ml. of ethanol was heated at reflux for 3 hr. and then neutralized with *N* sodium hydroxide. The solution was extracted four times with 20-ml. portions of ether and the combined ether extracts washed with water and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded 260 mg. of 1,3-diphenylbutane-1,2-dione as a yellow liquid which was distilled through a small Hickman molecular still, b.p. 30°/0.001 mm.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92 Found: C, 79.85; H, 6.02.

Recently this compound has been reported by Wasserman (ref. 10) from the isomerization of dypnone oxide and was characterized as the mono-2,4-dinitrophenylhydrazone, m.p. 196–197°.

The quinoxaline derivative (VIII) was prepared by refluxing 100 mg. (0.42 millimole) of the diketone (VI) and 55 mg. (0.5 millimole) of *o*-phenylenediamine in 3 ml. of glacial acetic acid for 45 min. The solution was diluted with 3 ml. of water and the solid recrystallized three times from dilute ethanol to yield 70 mg. (53.8%) of white needles m.p. 116–116.5°.

Anal. Calcd. for $C_{22}H_{18}N_2$: C, 85.12; H, 5.84. Found: C, 85.51; H, 5.52.

The ultraviolet spectrum exhibited absorption peaks at 323.5 mμ (ϵ_{max} = 10,300) and 239 mμ (ϵ_{max} = 34,300). Recently VIII has been prepared by treating the crude diketone (VI), obtained by the method of ref. 10, with *o*-phenylenediamine dihydrochloride in ethanol, and melted at 117.5–118.5°. The ultraviolet spectrum of this material exhibited absorption peaks at 239 mμ (ϵ_{max} = 35,400) and 323 mμ (ϵ_{max} = 10,300).[16]

Treatment of the diketone (VI) with sodium *meta*periodate in aqueous dioxane afforded a 50.2% yield of benzoic acid.

1,3-Diphenyl-2-hydroxybutan-1-one (V) A solution of 1.0 g. (4.2 millimoles) of 1,3-diphenyl-2-hydroxybut-3-en-1-one (IVa) in 20 ml. of ethyl acetate was hydrogenated in the presence of 100 mg. of 5% palladium on charcoal catalyst at room temperature and atmospheric pressure. The hydrogen uptake was stopped after 102 ml. (1 mole) of hydrogen was absorbed. Removal of the solvent *in vacuo* and distillation of the residue through a small Hickman molecular still yielded 0.87 g. (86.8%) of 1,3-diphenyl-2-hydroxybutan-1-one, b.p. 81° (0.5μ); n_D^{24} 1.5799.

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 79.79; H, 6.70. Found: C, 79.90; H, 6.97.

The ultraviolet spectrum exhibited an absorption peak at 245 mμ (ϵ_{max} = 12,550).

1,3-Diphenylbutane-1,2-dione (VI) *from 1,3-diphenyl-2-hydroxy-butan-1-ene* (V). To 100 mg. (0.412 millimole) of the keto alcohol (V), obtained by reduction of 1,3-diphenyl-2-hydroxybut-3-ene-1-one (IV), in 5 ml. of glacial acetic acid was added a solution of 97.2 mg. (0.49 millimole) of sodium dichromate dihydrate in 10 ml. of glacial acetic acid. The solution was kept at room temperature for 20 hr. and the excess dichromate decomposed with 3 drops of methanol. The reaction mixture was poured into 300 ml. of water, extracted with ether and the combined ether extract washed with cold 5% sodium bicarbonate, water, and dried over magnesium sulfate. Removal of the solvent yielded 95 mg. of a yellow liquid whose infrared spectrum was identical with that of the α-diketone obtained by acid rearrangement of the unsaturated keto alcohol.

A quinoxaline derivative, prepared in the same manner, was obtained in 76.5% yield and melted at 115–116°. A mixture melting point with the quinoxaline obtained by acid rearrangement melted at 116.5–117°.

1,3-Diphenylbutan-1-one (X). A solution of 22.29 (0.1 mole) of dypnone (IX), prepared by the method of Muller and Spinose-Stockel[17] in 32% yield, was hydrogenated with 1.0 g. of platinum oxide in 250 ml. of ethyl acetate at 25° in a Parr apparatus. The hydrogen uptake was stopped at one mole. Removal of the solvent, followed by two recrystallizations from methanol yielded 13.5 g. (60.2%) of white plates, m.p. 73–74°.[18,19]

1,3-Diphenyl-2-bromobutan-1-one (XI). To 7.5 g. (0.033 mole) of 1,3-diphenylbutan-1-one (X) in 60 ml. of glacial

(15) G. Rosenkranz, O. Macera, J. Gatica, and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 4077 (1950).

(16) H. O. House and D. J. Reif, *J. Am. Chem. Soc.*, **77**, 6525 (1955).

(17) A. Muller and G. Spinose-Stockel, *Osterr. Chem. Ztg.*, **49**, 130 (1948).

(18) E. P. Kohler and G. Heritage, *Am. Chem. J.*, **31**, 655 (1904).

(19) E. P. Kohler, *Am. Chem. J.*, **42**, 394 (1909).

acetic acid was added dropwise with stirring 5.34 g. (0.033 mole) of bromine in 10 ml. of glacial acetic acid. The solution was stirred for 20 min. and then poured on ice. The crude solid, 10.1 g., was filtered and fractionally crystallized from hexane. Two solids were obtained, one, 6.0 g. (59.4%), crystallized in needles, m.p. 82–83°, the other, 2.37 g. (23.5%), in clusters, m.p. 120–121°.[20]

Anal. Calcd. for $C_{16}H_{15}BrO$: C, 63.38; H, 4.99. Low melting isomer, found: C, 63.34; H, 5.01. High melting isomer, found: C, 63.22; H, 5.15.

Isomerization of the 1,3-diphenyl-2-bromobutanones. To 5.0 g. (0.016 mole) of the low-melting bromoketone was added a solution containing 1.28 g. (0.032 mole) of sodium hydroxide in 20 ml. of dioxane and 20 ml. of water. The solution was refluxed for 20 min., poured on ice, and extracted with ether. Removal of the solvent yielded 3.70 g. of a yellow oil which solidified to afford 0.500 g. (10%) of high melting isomer, m.p. 119–120°, and 2.92 g. (58.4%) of the low melting isomer.

1,3-Diphenyl-2-hydroxybutan-1-one from 1,3-diphenyl-2-bromobutan-1-one. A solution containing 2.09 g. (6.89 millimoles) of low-melting bromoketone, 0.50 g. (12.5 millimoles) of sodium hydroxide, 22 ml. of dioxane, and 10 ml. of water was refluxed for 1.5 hr., poured on ice, and extracted with ether. Removal of the solvent yielded 1.18 g. of yellow liquid which was distilled through a small Hickman molecular still, b.p., 80–90° at 0.001 mm. The infrared spectrum was similar but not completely identical with the keto-alcohol obtained by reduction of IV. Oxidation of the product from the bromoketone using the conditions previously described, followed by treatment with *o*-phenylenediamine in glacial acetic acid afforded a 38.4% yield of the quinoxaline derivative, m.p. 116.5–118°. A mixture melting point with the quinoxaline from reduction of oxidation of 1,3-diphenyl-2-hydroxybut-3-en-1-one (IV) was not depressed.

1,3-Diphenyl-2-hydroxybutan-1-one from phenylglyoxal. To 1.73 g. (0.071 g. atom) of magnesium turnings in 50 ml. of dry ether, under a nitrogen atmosphere, was added 10.0 g. (0.071 mole) of α-chloroethylbenzene in 100 ml. of dry ether, dropwise, with stirring, in 5 hr. The Grignard reagent was added, in 3 hr., with vigorous stirring, to a cold solution of 9.7 g. (0.07 mole) of phenylglyoxal in 200 ml. of dry ether in a nitrogen atmosphere. Hydrolysis with ammonium chloride solution, followed by ether extraction and removal of the solvent yielded 0.780 g. of solid, m.p. 152–153° (dec.) and 12.4 g. of yellow liquid. Trituration of the liquid with methanol, afforded 0.80 g. of *meso*-2,3-diphenylbutane, m.p. 122–124°. Distillation of 5.4 g. of the remaining liquid through a Hickman still yielded 1.07 g. of 1,3-diphenyl-2-hydroxybutan-1-one, b.p. 80° at 0.0005 mm., n_D^{25} 1.5694. The infrared spectrum was identical with the product from reduction and the ultraviolet spectrum exhibited an absorption peak at 246.5 mμ (ϵ_{max} = 12,400).

Oxidation of the keto alcohol prepared in this manner, followed by treatment with *o*-phenylenediamine gave the quinoxaline derivative (VIII), m.p. 116–117°, in 52.7% yield. The material was identical in all respects to the quinoxaline from the reduction and oxidation of IVa.

1,3-Diphenyl-2-acetoxybut-3-en-1-one (IVa). Following the procedure described for the preparation of IV, 9.0 g. (0.02 mole) of α-3,4-dibromo-1,3-diphenyl-2-acetoxybutan-1-one (IIIa) yielded 5.05 g. (90.1%) of 1,3-diphenyl-2-acetoxybut-3-ene-1-one, m.p. 80–84°, when treated with 20 g. of sodium iodide in acetone for 24 hr. Two recrystallizations from dilute ethanol raised the melting point to 85–86°. A mixture melting point with the acetate prepared from 1,3-diphenyl-2-hydroxybut-3-en-1-one with acetic anhydride and acetyl chloride[11] melted at 84–85°.

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.15; H, 5.76. Found: C, 77.25; H, 5.87.

1,3-Diphenyl-2-acetoxybutan-1-one (Va). Using the same conditions described for the reduction of IVa 1.0 g. (3.5 millimoles) of the unsaturated ketoacetate yielded 0.740 g. (74%) of clear liquid, b.p. 70–80° (0.5μ), n_D^{24} 1.5571.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.52. Found: C, 76.63; H, 6.64.

Ozonization of 1,3-diphenyl-2-acetoxybut-3-en-1-one (IVa). A solution of 0.636 g. (2.27 millimoles) of unsaturated acetoxyketone (IVb) in 30 ml. of ethyl acetate was cooled to −70° and saturated with ozone. After about 1 hr. the excess ozone was decomposed with 10% ferrous sulfate solution and the sample and trap solutions combined and distilled into 2,4-dinitrophenylhydrazine solution but no formaldehyde was detected. The aqueous distillation residue was extracted with ether and the extracts washed, dried, and evaporated to yield 0.100 g. (15.6%) of 1,3-diphenyl-2-acetoxypropane-1,3-dione, (VII), m.p. 92–94°.[21] A mixture melting point with an authentic sample was not depressed and the infrared spectra of the two materials were identical.

β-3,4-Dibromo-1,3-diphenyl-2-acetoxybutan-1-one (XIV). To 3.0 g. (10.8 millimoles) of 1,3-diphenyl-2-acetoxybut-3-ene-1-one (IVa) dissolved in 40 ml. of dry carbon tetrachloride, 1.8 g. (10.8 millimoles) of bromine was added dropwise, with stirring. The flask was illuminated with an infrared lamp during the bromination. Removal of the solvent yielded 4.65 g. of a white solid, which after two recrystallizations from petroleum ether afforded 3.87 g. (81.4%) of the β-bromohydrin acetate as white needles, m.p. 120–121°.

Anal. Calcd. for $C_{18}H_{16}Br_2O_3$: C, 49.15; H, 3.67. Found: C, 49.10; H, 4.05.

Regeneration of 1,3-diphenyl-2-acetoxybut-3-en-1-one (IVa) could be accomplished in 53.9% yield by treating the β-bromohydrin acetate with sodium iodide in acetone at room temperature for 26 hr. A mixture melting point with the unsaturated acetoxyketone from the α-bromohydrin acetate was not depressed and the infrared spectra were identical.

Bromination of 1,3-diphenyl-2-hydroxybut-3-ene-1-one under the same conditions gave only 1,3-diphenyl-butane-1,2-dione (VI) identical in all respects to the previous preparation.

Reaction of 3,4-dibromo-1,3-diphenylbutane-1,2-dione with sodium iodide. To 5.0 g. (12.6 millimoles) of dibromo diketone (XV) in 20 ml. of dry acetone was added a solution of 9.6 g. (6.40 millimoles) of dry sodium iodide in 40 ml. of dry acetone. After 2 hr. the solvent was removed *in vacuo* and the residue extracted with hexane until the extracts were no longer yellow. During the extraction several drops of acetone were added to prevent extraction of iodine. Removal of the solvent by vacuum afforded 3.0 g. of a yellow liquid which was titrated with methanol to yield 1.56 g. of dimer as dense yellow prisms, m.p. 132–134°.

Anal. Calcd. for $C_{32}H_{24}O_4$: C, 81.33; H, 5.12; mol. wt. 472. Found: C, 81.46; H, 5.15; mol. wt. (Rast) 524.

The ultraviolet spectrum exhibited an absorption peak at 250.5 mμ (ϵ_{max} = 26,200).

A quinoxaline derivative could be prepared in the manner previously described, m.p. 190.5–192.5°.

Anal. Calcd. for $C_{38}H_{28}N_2O_2$: C, 83.80; H, 5.18. Found: C, 83.60; H, 5.50.

The ultraviolet spectra exhibited absorption peaks at 322 mμ (ϵ_{max} = 10,900) and 239 mμ (ϵ_{max} = 56,300).

Bromination product of the dimer. To 200 mg. (0.42 millimoles) of the dimer (XVI) in 10 ml. of dry carbon tetrachloride was added 135 mg. (0.85 millimoles) of bromine in

(20) The bromoketone has been reported by T. S. Stevens, *J. Chem. Soc.*, 2114 (1930), m.p. 76°, by bromination of the ketone in carbon tetrachloride. When the reaction conditions were repeated a 68.2% yield of the low melting isomer was obtained, m.p. 77–80°.

(21) E. P. Kohler and J. L. E. Erickson, *J. Am. Chem. Soc.*, **53**, 2308 (1931).

5 ml. of carbon tetrachloride. Light was applied from an infrared lamp and hydrogen bromide was copiously evolved. The solvent was removed *in vacuo* to yield a yellow oil which solidified on trituration with petroleum ether. Two recrystallizations from petroleum ether–benzene yielded 135 mg. (67.5%) of yellow needles, m.p. 162–163°. A test for bromine was negative.

Anal. Calcd. for $C_{32}H_{22}O_4$: C, 81.68; H, 4.71. Found: C, 81.35; H, 4.89.

The ultraviolet spectra exhibited absorption peaks at 250 mμ (ϵ_{max} = 30,550) and 357 mμ (ϵ_{max} = 16,500).

Acknowledgement. The authors wish to thank Mr. Robert French for the microanalyses and Dr. J. M. Vandenbelt, Parke, Davis and Company, for ultraviolet spectra.

DETROIT 2, MICH.

[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

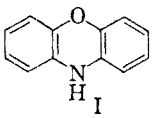
Preparation and Some Reactions of Phenoxazine and Phenoselenazine

PAULETTE MÜLLER, N. P. BUU-HOÏ, AND R. RIPS

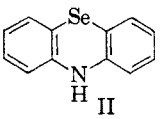
Received July 25, 1958

Improved methods for the preparation of phenoxazine and phenoselenazines have been elaborated, and some reactions of these heterocycles have been investigated. Phenoselenazine and 2-chlorophenoselenazine readily underwent β-cyanoethylation; β-(10-phenoselenazyl)- and β-(2-chloro-10-phenoselenazyl)propionic acid, obtained on hydrolysis of the corresponding nitriles, were successfully cyclized to ketones derived from a new four-ringed nitrogen heterocycle.

Phenoxazine (I) and phenoselenazine (II) are two rarely investigated heterocycles, although they are isologs of phenothiazine, the nucleus of numerous dye-stuffs and pharmaceutical molecules. Recently, however, several phenoxazine derivatives have recaptured interest for their antitubercular activity,[1] and phenoselenazine itself is not devoid of pharmacological interest, since the selenium analogs of promethazine and chlorpromazine have shown antihistamine activity similar to that of their sulfur-containing analogs.[2] These observations prompted an investigation of the methods of



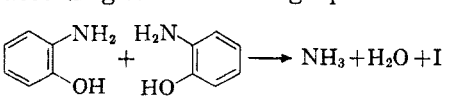
I



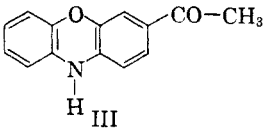
II

preparation of phenoxazine and phenoselenazine, and also of certain aspects of their chemical reactivity.

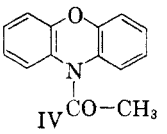
The classic method for preparing phenoxazine, involving the condensation of catechol with *o*-aminophenol,[3] necessitated the use of sealed tubes, and yields were very erratic. A far more convenient method has now been found to consist of the autocondensation of *o*-aminophenol in the presence of iodine according to the following equation:



This preparation of phenoxazine, which can be performed in open vessels and gives reliable yields, recalls the Knoevenagel method for synthesizing secondary diarylamines by iodine-catalyzed condensation of naphthols with primary arylamines.[4] Friedel-Crafts condensation of phenoxazine with acetyl chloride in the presence of aluminum chloride was found to give a monoketone, possibly 3-acetylphenoxazine (III), along with larger quantities of 10-acetylphenoxazine (IV). Position 3 is more probable than position 2, in view of the



III



IV

stronger orienting influence of the imino group.

The procedure described in the literature by Cornelius,[5] and later by Karrer,[6] for the preparation of phenoselenazine, which consisted of the condensation of diphenylamine with selenious chloride in benzene, has now been considerably improved by performing the reaction in chloroform, the use of this solvent allowing a better control of the reaction and enhancing the yield. The same method was also applied for preparing 2-chlorophenoselenazine; in both cases, the purity of the reaction products is greatly enhanced by vacuum-distillation prior to recrystallization.

Both phenoselenazine and 2-chlorophenoselenazine readily underwent β-cyanoethylation with acrylonitrile in the presence of benzyltrimethylammonium methoxide to give β-(10-phenoselenazyl)propionitrile (V) and β-(2-chloro-10-phenoselenazyl)propionitrile (VI). Thus, phenoselenazine

(1) *Cf.* B. Boothroyd and E. R. Clark, *J. Chem. Soc.*, 1499, 1504 (1953); these papers also give earlier relevant references.

(2) P. Müller, N. P. Buu-Hoï, and R. Rips, unpublished results.

(3) A. Bernthsen, *Ber.*, **20**, 943 (1887); F. Kehrmann, *Ann.*, **322**, 9 (1902); phenoxazine was also prepared by heating *o*-aminophenol with its hydrochloride, by F. Kehrmann and A. A. Neil, *Ber.*, **47**, 3102 (1914).

(4) E. Knoevenagel, *J. prakt. Chem.*, [2] **89**, 17 (1914).

(5) W. Cornelius, *J. prakt. Chem.*, [2] **88**, 398 (1913).

(6) P. Karrer, *Ber.*, **49**, 603 (1916).