[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

THE HALODIPHENACYLS. II. STEREOCHEMISTRY[1]

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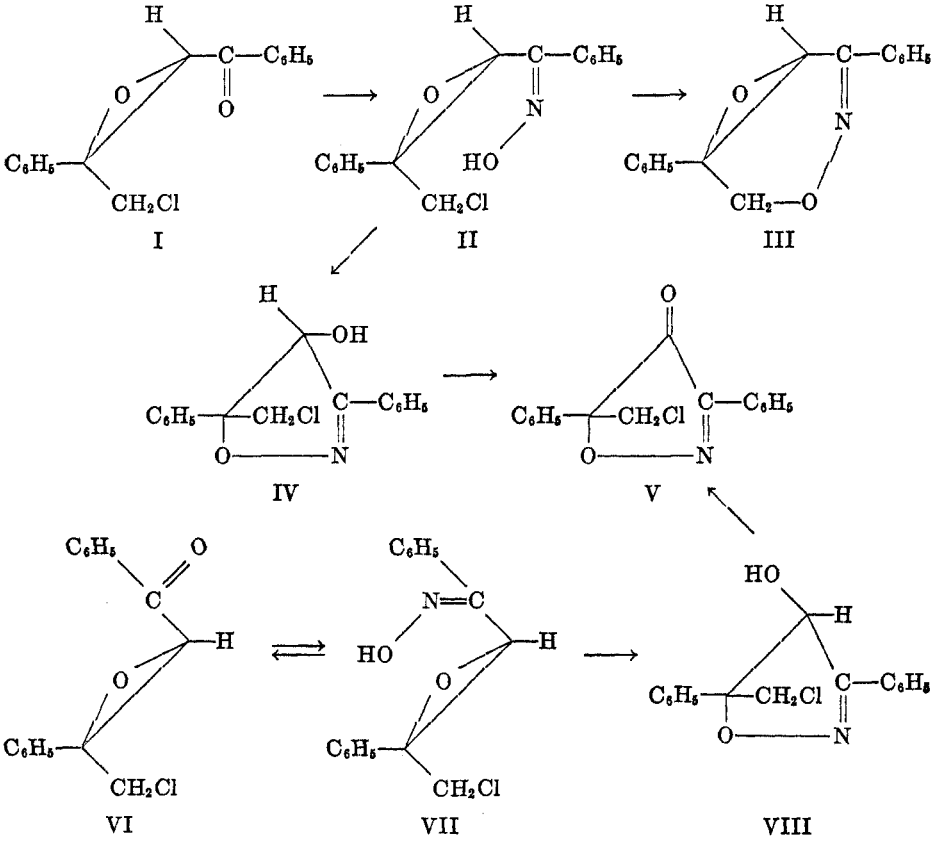
Received August 18, 1953

In the present investigation the low-melting α-chlorodiphenacyl was shown to be the *trans*-isomer (I) and the high-melting β-chlorodiphenacyl was shown to be the *cis*-isomer (VI). The structure of I was proven by preparation of the oxime (II) and ring closure of this oxime to the epoxyoxazine (III). The fact that the oximes of the α- and β-chlorodiphenacyls could be converted into the isomeric hydroxyisoxazolines (IV and VIII respectively) and that these hydroxyisoxazolines gave the same isoxazolone (V) proved that the β-chlorodiphenacyl was the *cis*-isomer.



[1] Abstracted from the thesis of Mr. Vincent Traynelis submitted in April 1953 to the Graduate School in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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Recently Berson (1) proposed the presently accepted gross structures for the bromodiphenacyls and Wasserman (2) discussed the stereochemistry of the two isomers. In this laboratory (3) the structures of the α-chloro-, α-bromo-, and α-iododiphenacyls and the structure of the β-chloro-, β-bromo-, and β-iododiphenacyls were correlated by chemical and physical means.

Although carbonyl derivatives of the halodiphenacyls were hitherto unknown, the oxime (II) of the α-chlorodiphenacyl could be prepared smoothly in 53% yield. By the same procedure the oxime of the β-chlorodiphenacyl was prepared in 66% yield. The oximes had the correct carbon and hydrogen content, both contained chlorine and nitrogen, and the infrared spectra showed the presence of an —OH group in each oxime. Further, the β-chlorodiphenacyl could be regenerated from the β-oxime in 42% yield.

Conversion of the β-oxime (VII) to the starting ketone indicated no rearrangement in the formation of the oxime. An improbable alternate explanation would involve two rearrangements in the preparation and reconversion of the oxime. The structure assigned to the α-oxime (II) was supported by the fact that the preparation from α-chlorodiphenacyl utilized the same experimental conditions as for the β-oxime. The intensity of the ultraviolet absorption maximum of the α-oxime (II, λ_{max} 251.5 mμ, ε 12,300) was significantly higher than the maximum of the β-oxime (VII, λ_{max} 250 mμ, ε 10,800). This relationship is similar to that exhibited by the halodiphenacyls, the α-isomers of which have significantly greater absorption intensities than the β-isomers (*cf.* ref 3). Although all of the β-halodiphenacyls (*cis* isomers) melt at a higher temperature than the corresponding α-isomers (*trans* isomers), the oxime of the α-chlorodiphenacyl melted at a higher temperature than the oxime of the β-isomer.

When α-chlorodiphenacyl oxime (II) was dissolved in liquid ammonia, a product which had lost the elements of hydrogen chloride was isolated in 98% yield. The infrared spectrum of the product, which lacked an absorption band below 3μ, indicated the hydroxyl group had participated in the reaction. The product still contained the epoxide linkage since the addition of hydrogen chloride gave a new isomer of the oxime which showed an hydroxyl band in the infrared spectrum. These facts indicate that the initial reaction was a ring closure reaction between the chloromethyl group and the oxime group with the formation of 3,5-diphenyl-4,5-epoxy-1,2,6*H*-oxazine (III). The β-chlorodiphenacyl oxime under the original reaction conditions with liquid ammonia gave a 90% yield of starting material.

The ring closure indicated that the oxime group and chloromethyl group must have a *cis* arrangement about the ethylene oxide ring in II. Since no rearrangement occurred in the preparation of the oxime from the chloro ketone, α-chlorodiphenacyl must have the phenyl group *trans* to the benzoyl group.

In an attempt to convert the α-chlorodiphenacyl oxime to the starting ketone under the conditions used for the reconversion of the β-oxime, a new isomer was isolated in 90% yield. The same isomer was obtained from the reactions of the α-oxime in acetic acid with hydrobromic acid, sulfuric acid, and hydrochloric acid in 92%, 95% and 97% yield respectively. When the α-oxime was heated above its melting point, an isomer identical with the above isomer was

TABLE I

ULTRAVIOLET SPECTRA[a] OF THE HALODIPHENACYLS AND DERIVATIVES

COMPOUND	λ_{max}	ϵ
α-Chlorodiphenacyl oxime (II)	246.5	13,300
β-Chlorodiphenacyl oxime (VII)	245	10,800
3,5-Diphenyl-4,5-epoxy-1,2,6*H*-oxazine (III)	242	9,900
	278	5,200
III·HCl	250	11,000
trans-3,5-Diphenyl-5-chloromethyl-4-hydroxy-2-isoxazoline (IV)	262	15,600
cis-3,5-Diphenyl-5-chloromethyl-4-hydroxy-2-isoxazoline (VIII)	262	15,000
3,5-Diphenyl-5-chloromethyl-2-isoxazol-4-one (V)	228	15,800
	306	5,600

[a] All the spectra were determined in ethanol solution with the exception of the two oximes which were determined in cyclohexane.

formed in 86% yield. The observed double melting point of the α-oxime is a result of the above rearrangement.

The fact that the various mineral acids rearranged the α-oxime to the same isomer indicated that the chloromethyl group did not participate in the reaction. One interpretation of the rearrangement involves the intramolecular addition of the oxime group to the oxide with the formation of the secondary alcohol (IV). This interpretation was confirmed by the oxidation with chromium trioxide of the secondary alcohol to the corresponding ketone (V) in 92% yield. The infrared spectrum confirmed the presence of the carbonyl group.

Since the α-oxime was shown above to have the phenyl and hydrogen *cis* to the ethylene oxide ring, a *trans*-intramolecular epoxide opening by the oxime group can only give compound IV (*trans*-3,5-diphenyl-5-chloromethyl-4-hydroxy-2-isoxazoline; the *trans* term refers to the arrangement of the 4-hydroxyl and 5-phenyl groups about the isoxazoline ring).

The β-chlorodiphenacyl oxime (VII) when heated in acetic acid solution containing sulfuric acid, rearranged to give a fifth isomer (VIII) in 88% yield. The similarity of the infrared spectrum of this product with that of IV and the virtual identity of the ultraviolet spectra (*cf.* Table I) from these compounds (VIII and IV) indicated that they were diastereoisomers. Oxidation of the isomer (VIII) from the β-oxime gave *the same ketone* as oxidation of the isomer from the α-oxime. This oxidation experiment proved that both secondary alcohols (VIII and IV) differed only in the arrangement of the groups around the two asymmetric carbon atoms. The fact that the oximes gave diasteromeric *secondary alcohols* by intramolecular ring opening of the epoxide groups proved that the oximes and consequently the chlorodiphenacyls also had a diastereomeric relation. Thus, VIII is *cis*-3,5-diphenyl-5-chloromethyl-4-hydroxy-2-isoxazoline and β-chlorodiphenacyl (VI) and the β-oxime (VII) are the *cis*-isomers.

In the previous report from this laboratory (3) the correlation of structures of the α-halodiphenacyls as well as the β-halodiphenacyls was presented. In view of this correlation and the present work, the α-chloro-, α-bromo-, and

α-iododiphenacyls are the *trans*-isomers while the β-halodiphenacyls are the *cis*-isomers.

EXPERIMENTAL

β-Chlorodiphenacyl oxime. A mixture of 5.0 g. (0.018 mole) of β-chlorodiphenacyl, 5.0 g. of hydroxylamine hydrochloride, 40 ml. of methanol, and 25 ml. of pyridine was heated at gentle reflux for five minutes. The solvents were removed, and the residue was triturated with water and acidified with acetic acid. The resulting solid was filtered and recrystallized from an ethanol-water (6–5 ratio) solution. The yield of β-chlorodiphenacyl oxime was 3.5 g. (66%), m.p. 137–138°.

Anal. Calc'd for $C_{16}H_{14}ClNO_2$: C, 66.81; H, 4.90.
Found: C, 66.57; H, 5.13.

α-Chlorodiphenacyl oxime. The procedure used was identical to the one above. From 5.0 g. (0.018 mole) of α-chlorodiphenacyl, 5.0 g. of hydroxylamine hydrochloride, 50 ml. of ethanol, and 50 ml. of pyridine there was isolated 2.8 g. (53%) of pure α-chlorodiphenacyl oxime. The white needles melted at 155° when inserted at 150° into a melting point bath, which was heated at the rate of 4° per minute. At 157° the clear liquid solidified and melted at 198–200°.

Anal. Calc'd for $C_{16}H_{14}ClNO_2$: C, 66.81; H, 4.90.
Found: C, 67.13; H, 4.95.

α-Chlorodiphenacyl oxime with liquid ammonia. A solution of 1.0 g. (3.4 millimoles) of α-chlorodiphenacyl oxime in 30 ml. of liquid ammonia was allowed to stand in an acetone-Dry Ice bath for three hours. The ammonia was allowed to evaporate and 30 ml. of water was added. The solid was filtered, washed with water, dried *in vacuo* and weighed, 830 mg., m.p. 99–102°. Recrystallization from ethanol gave 735 mg. (87%) of pure 3,5-diphenyl-4,5-epoxy-1,2,6*H*-oxazine, m.p. 105–106°.

Anal. Calc'd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21.
Found: C, 76.39; H, 4.96.

β-Chlorodiphenacyl oxime with liquid ammonia. Using the same procedure as above 200 mg. (0.70 millimole) of β-chlorodiphenacyl oxime, after standing in liquid ammonia solution for three hours, gave 195 mg. (97%) of starting material. The product was identified by melting point and mixture melting point, 134–136°.

Addition of hydrogen chloride to 3,5-diphenyl-4,5-epoxy-1,2,6H-oxazine. To a solution of 250 mg. (1.0 millimole) of the oxazine in 15 ml. of glacial acetic acid was added 3 ml. of concentrated hydrochloric acid (*sp. gr.* 1.19). After two hours at room temperature, the green solution was poured into 100 ml. of water. The solid that formed was filtered and washed with water. Recrystallization from ethanol gave 50 mg. (17%) of the hydrogen chloride adduct, m.p. 143° (dec.). An analytical sample melted at 147–148° (dec.).

Anal. Calc'd for $C_{16}H_{14}ClNO_2$: C, 66.81; H, 4.90.
Found: C, 67.08; H, 5.18.

trans-3,5-Diphenyl-5-chloromethyl-4-hydroxy-2-isoxazoline. The *trans* term refers to the arrangement of the 5-phenyl and 4-hydroxy groups about the isoxazoline ring. When 500 mg. (1.7 millimole) of α-chlorodiphenacyl oxime was placed in an oil-bath at 165°, the solid melted with some decomposition and then solidified. After recrystallization from ethanol, the yield of *trans*-3,5-diphenyl-5-chloromethyl-4-hydroxy-2-isoxazoline was 430 mg. (86%), m.p. 210–211°. The pale violet needles were converted to white needles, after treatment with charcoal, with no change in melting point.

Anal. Calc'd for $C_{16}H_{14}ClNO_2$: C, 66.83; H, 4.90.
Found: C, 66.84; H, 5.17.

To a solution of 300 mg. (1.05 millimoles) of α-chlorodiphenacyl oxime in 25 ml. of glacial acetic acid was added 1 ml. of concentrated hydrochloric acid (*sp. gr.* 1.19). After 15 minutes the reaction mixture, containing a white solid, was poured into 50 ml. of water. The solid was filtered, washed with water, and dried *in vacuo*. The yield of *trans*-3,5-diphenyl-5-chloromethyl-4-hydroxy-2-isoxazoline was 290 mg. (96.5%) and melted alone and when mixed with the above isoxazoline at 208–209°. Hydrobromic acid in acetic acid, sulfuric acid

in acetic acid, and hydrochloric acid in ethanol gave the same isoxazoline in 92%, 95%, and 90% yield, respectively.

cis-3,5-Diphenyl-5-chloromethyl-4-hydroxy-2-isoxazoline. To a solution of 650 mg. (2.3 millimoles) of β-chlorodiphenacyl oxime in 30 ml. of acetic acid was added 7 ml. of 30% sulfuric acid. After heating on a steam-bath for five minutes, the reaction mixture was poured into 150 ml. of water. When crystallization was complete, the solid was filtered, washed with water, and dried *in vacuo*. The yield of *cis*-3,5-diphenyl-5-chloromethyl-4-hydroxy-2-isoxazoline was 575 mg. (88%), m.p. 113–115°. Recrystallization of 375 mg. from an ethanol-water (3–2 ratio) solution gave 335 mg. of white needles, m.p. 116–117°.

Anal. Calc'd for $C_{16}H_{14}ClNO_2$: C, 66.81; H, 4.90.

Found: C, 66.88; H, 5.24.

3,5-Diphenyl-5-chloromethyl-2-isoxazol-4-one. To a suspension of 390 mg. (1.4 milliequivalents) of *trans*-3,5-diphenyl-5-chloromethyl-4-hydroxy-2-isoxazoline in 60 ml. of acetic acid was added a solution of 90 mg. (1.4 milliequivalents) of chromium trioxide in 80% acetic acid-water. A trace of sulfuric acid was added and the mixture was heated on a steam-bath for 30 minutes. The reaction solution was poured into 150 ml. of water and the solid that formed was filtered, washed with water, and dried *in vacuo*. The yield of 3,5-diphenyl-5-chloromethyl-2-isoxazol-4-one was 355 mg. (92%), m.p. 79–80°. Recrystallization from ethanol gave 255 mg. (76%) of pure isoxazolone, m.p. 80–81°.

Anal. Calc'd for $C_{16}H_{12}ClNO_2$: C, 67.23; H, 4.24.

Found: C, 67.29; H, 4.24.

Using the same procedure as above 200 mg. (0.70 milliequivalent) of *cis*-3,5-diphenyl-5-chloromethyl-4-hydroxy-2-isoxazoline was oxidized by 50 mg. (0.70 milliequivalent) of chromium trioxide to 180 mg. (91%) of 3,5-diphenyl-5-chloromethyl-2-isoxazol-4-one, m.p. 79–80°. A mixture melting point with the above isoxazolone was not depressed. Also the ultraviolet and infrared spectra of the two compounds were identical.

Hydrolysis of β-chlorodiphenacyl oxime to β-chlorodiphenacyl. To a solution of 300 mg. (1.1 millimoles) of β-chlorodiphenacyl oxime in 15 ml. of ethanol was added 5 ml. of water and 1 ml. of concentrated hydrochloric acid. After three days at room temperature, the crystals that formed were filtered and were recrystallized from ethanol. The β-chlorodiphenacyl, 75 mg. yield, melted alone and when mixed with an authentic sample at 147–148°.

The reaction solution was allowed to stand 14 additional days at room temperature and then was diluted with 100 ml. of water. The resulting solid was filtered and fractional crystallization from an ethanol-water solution gave 45 mg. of β-chlorodiphenacyl, m.p. 147–148°. The total yield of β-chlorodiphenacyl was 120 mg. (42%). Also isolated was 100 mg. of impure starting material. Recrystallization could not remove the contaminant which was probably the *cis*-isoxazoline (VIII).

Spectra. The infrared spectra were determined with a Beckman IR2T infrared spectrophotometer and the ultraviolet spectra were determined with a Beckman D. U. spectrophotometer.

Acknowledgment. The authors wish to thank Mr. Michael Pappo and Miss Phylis Tocco for microanalyses, Dr. J. M. Vandenbelt, Parke, Davis and Company, for the ultraviolet spectra, and Mr. R. Bruce Scott, Parke, Davis and Company for the infrared spectra.

SUMMARY

The structures of the α- and β-chlorodiphenacyls were proven to be the *trans*- and *cis*-isomers respectively.

DETROIT 1, MICHIGAN

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