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STEREOSPECIFIC REACTIONS OF THE DIPHENACYL HALIDES

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In an earlier paper (1) it was shown that the diphenacyl halides, formed by the action of sodium ethoxide on phenacyl chloride or bromide, were *cis*- and *trans*-epoxy ketones of structures I and II. Definite stereochemical assignments were not made



although it was pointed out that both of the α -diphenacyl halides absorbed at longer wave lengths with greater intensity in the ultraviolet than did the corresponding β -isomers, and, by analogy with Cromwell's structure-spectra correlations in the ethylenimine ketone series (2), the lower melting, α -isomers might therefore be assigned *trans*- structures (II). In the present work we have shown that stereospecific reactions of the diphenacyl halides with aniline and with hydrazine now permit definite assignments of configuration.

Widman (3) originally reported that when α -diphenacyl chloride was heated with aniline at the reflux temperature, it was converted to 3-chloro-1,2,4-triphenylpyrrole, whereas the β -chloride, under similar conditions yielded 3-hydroxy-1,2,4-triphenylpyrrole. We have repeated this work and have found that both the chloro and the bromo compounds in the α -series yielded 3-halotriphenylpyrroles, while in the β -series, both diphenacyl halides were converted to the same 3-hydroxytriphenyl pyrrole. Although this reaction with aniline thus appears to be stereospecific, assignment of configuration to the parent epoxy ketones on the basis of the products formed is not unequivocal, since one can visualize a logical reaction sequence for the formation of both pyrrole derivatives from either the *cis*- or the *trans*-isomer. Under milder conditions of reaction with aniline, we have now found that the α - and β -diphenacyl halides also show a marked difference in behavior, and, as will be shown in the following discussion, such differences can clearly serve as a basis for distinguishing between the *cis*-(I) and *trans*- (II) isomers.

When refluxed in a mixture of aniline and water (1:8) for three hours, α -diphenacyl bromide was converted, in 41% yield, to 3-bromo-1,2,4-triphenylpyrrole identical with the product obtained from the high temperature reaction with aniline. Under the same conditions of reflux with an aniline-water mixture however, the β -diphenacyl bromide was converted to a stable monoanilino derivative, C₂₂H₁₉NO₂, in which a bromine atom had been replaced by an anilino residue. This compound was unchanged by heating above its melting point in the dry state, but on standing in glacial acetic acid saturated with dry hydrogen chloride, it was readily converted to a mixture of 3-hydroxy-1,2,4-triphenylpyrrole and 3-chloro-1,2,4-triphenylpyrrole. These experimental findings indicate clearly that the steric arrangement of bromomethyl and carbonyl groups in the α -bromide must be favorable for direct conversion to the pyrrole with aniline, whereas, in the β -bromide, further treatment of the initially formed anilino derivative is required to permit the interaction of the anilino and carbonyl groupings necessary for pyrrole formation. The anilino derivative must therefore contain a structural feature which restricts the interaction of these groupings, this restriction being removed on treatment with hydrogen chloride. The structure for the anilino derivative which best meets the above requirements is the epoxy ketone III bearing the carbonyl and anilino groupings in a *trans*relationship. Opening of the epoxide ring, as shown below, would permit the intramolecular condensation necessary to form the hydroxypyrrole, which, as Widman has shown (3) can readily be converted to the halopyrrole.¹



The physical and chemical properties of the anilino derivative are consistent with the arrangement of functional groups in III. The oxidation of iodide to iodine by this product, carbonyl absorption at 5.88 μ in the infrared (Fig. 1) and ultraviolet absorption at λ_{max} 246 m μ are in accord with the α,β -epoxy ketone structure, (4) and the presence of N—H is shown by the characteristic band in the infrared at 2.93 μ . Structure IV contains the correct carbon-nitrogen skeleton for pyrrole formation in acid² but its formation from the β -diphenacyl halides, which would involve an initial opening of the epoxide ring, does not explain the striking difference in behavior between the reactions in the α - and β - series.

¹^SAn alternate explanation for the formation of the 3-chloropyrrole would involve the opening of the epoxide ring to form the α -chloro- β -hydroxy ketone, followed by cyclization. ² In acid solution, III and IV could be readily interconvertible.





Figure 1. Infrared Spectrum of the Anilino Derivative of the β -Diphenacyl Halides.



The corresponding reactions in an aniline-water mixture with the diphenacyl chlorides in the α - and β - series also showed significant differences. The β -chloride was converted in poorer yield to the same anilino derivative as obtained from the β -bromide, while the α -chloride was almost completely unreactive under these conditions. In the latter case, bimolecular displacement of chloride by aniline would be inhibited by the bulky *cis*-benzoyl group. There would be relatively less hindrance in the β -case where the benzoyl group is *trans*-, as pictured in Figure 2.

On the basis of the above reactions one may conclude that the α -diphenacyl halides have a *trans*- arrangement of phenyl and benzoyl groups (II) while the β -halides have a *cis*- arrangement (I).³ Additional evidence supporting these stereochemical assignments can be derived from the stereospecific reactions of the diphenacyl halides with hydrazine. Widman (3) reported that α -diphenacyl chloride could be converted to 3,5-diphenylpyridazine by vigorous refluxing with an excess of hydrazine hydrate, whereas no product could be isolated from the β -derivative under the same conditions. In repeating this work under milder reaction conditions we have found that both α -diphenacyl chloride and bromide could be converted to the pyridazine, reaction with the α -bromide taking place readily on standing overnight with hydrazine hydrate in a chloroform-ethanol solution. The same reaction in the β -series, however, appeared to be more complex and in no case led to pyridazine formation. Instead, it was found that

³ These results are in accord with recent findings (8) correlating the stereochemical configurations of *cis*- and *trans*-chalcone oxides with their ultraviolet absorption spectra.



FIGURE 2. β -DIPHENACYL BROMIDE showing the path for the displacement of bromide by aniline. The molecular model of the epoxide ring, outlined in heavy black lines, was constructed (1) to fit the Fischer-Taylor-Hirschfelder set, using bond angles and interatomic distances based on the data of G. L. Cunningham and co-workers (7).

refluxing both β -diphenacyl chloride and bromide in ethanol with excess hydrazine hydrate led to a product C₁₆H₁₈N which was identified as 2,4-diphenylpyrrole. The latter was synthesized by reduction of α -phenyl- β -benzoylpropionitrile (5) followed by selenium dehydrogenation, and the identity established by a mixture melting point determination and comparison of infrared spectra.

The ready conversion of the α -halides to the pyridazine derivative is consistent with a *cis*- arrangement of halomethyl and benzoyl groupings permitting interaction as pictured below.



Opening of the epoxide ring followed by aromatization would lead to the observed product.

The formation of 2,4-diphenylpyrrole in the reaction of hydrazine with the halides in the β -series appears to be a more unusual reaction, but may be analogous to the reactions with aniline at high temperature (3). A possible explanation for this result may be that in this case, two moles of diphenacyl halide react with one mole of hydrazine as pictured below, leading to a 3,3'-dihydroxydipyrrole.

Cleavage of the dipyrrole (6) and reduction to the 2,4-diphenylpyrrole could take place in the presence of the reducing agent, hydrazine.



In all of the reactions with aniline and hydrazine previously described, no simple carbonyl derivatives of the diphenacyl halides could be isolated. We have been able however to prepare 2,4-dinitrophenylhydrazones of the ketones in both the α - and β - series.

EXPERIMENTAL

Melting points. All melting points are corrected unless otherwise stated.

Infrared absorption spectra. All spectra were determined in chloroform solution with a Perkin-Elmer spectrophotometer, Model 21.

Ultraviolet absorption spectra. The ultraviolet absorption spectrum was determined with a Cary recording spectrophotometer, Model 11S. The solvent was 95% ethanol.

3-Bromo-1,2,4-triphenylpyrrole. (a) From α -diphenacyl bromide and aniline at high temperature. A mixture of 500 mg. of α -diphenacyl bromide (m.p. 136-137.5°) and 1 g. of aniline was heated until effervescence took place, and then refluxed for 15 minutes. The product was then worked up in the manner described by Widman for the reaction of α -diphenacyl chloride with aniline (3). The yield of crude material, m.p. 135.5-141° was 450 mg. (77%). Two recrystallizations from ethanol gave crystals which melted at 140-141° uncorr.

Anal. Calc'd for C₂₂H₁₆BrN: N, 3.72; Br, 21.38.

Found: N, 3.91; Br, 20.32.

(b) From α -diphenacyl bromide and aniline-water mixture. A mixture of 500 mg. of α -diphenacyl bromide (m.p. 136-137.5°), 1 g. of aniline, and 15 cc. of water was refluxed for three hours and then worked up in the manner described above for formation of the anilino derivative (III). The yield of crude pyrrole, m.p. 122-134° (uncorr.) was 240 mg. (41%). The infrared spectrum of this product was identical in every respect with that of the 3-bromo-1,2,4-triphenyl pyrrole described above in (a).

Conversion of β -diphenacyl bromide to the anilino derivative (III). A mixture of 5 g. of β -diphenacyl bromide (m.p. 161-162.5°), 13.5 g. of aniline (b.p. 85°/25 mm.), and 100 cc. of water was heated with stirring. The mixture was refluxed for 3 hours and then cooled. The red oil which remained was triturated with dilute acetic acid until a light yellow solid resulted. This was filtered, washed with water, and then recrystallized from ethanol to yield 3.1 g. of white needles, m.p. 119-120°. From the mother liquor there was obtained another 1 g. of product, m.p. 116-118°; yield 80%.

The anilino derivative liberated iodine when treated with sodium iodide and acetic acid. The infrared spectrum showed an absorption at 2.93 μ and at 5.88 μ .

Anal. Calc'd for C22H19NO2: C, 80.22; H, 5.81; N, 4.45.

Found: C, 80.32; H, 5.94; N, 4.29.

Conversion of β -diphenacyl chloride to the anilino derivative, III. A mixture of 4 g. of β diphenacyl chloride (m.p. 151-153°), 10 g. of aniline, and 80 cc. of water was allowed to react under the same conditions as the above reaction using β -diphenacyl bromide. From the reaction mixture there was isolated 1.7 g. of anilino derivative identical with the 119-120° melting product obtained from the reaction with β -diphenacyl bromide; yield 41%. Starting material (1.42 g.), was also recovered; yield 36%.

The action of hydrogen chloride on the anilino derivative III. (a) Formation of chlorotriphenylpyrrole. The anilino derivative III (3 g., m.p. 119-120°) was covered with 10 cc. of glacial acetic acid which had been saturated with hydrogen chloride. The yellow reaction mixture was allowed to stand for 13 hours during which time it turned deep green and deposited fine yellow needles (590 mg.) of m.p. 144.5-146° (uncorr.). The infrared spectrum of this compound was identical with the 3-chloro-1,2,4-triphenylpyrrole obtained from the high temperature reaction of α -diphenacyl chloride with aniline. This product was purified from chloroform-ethanol.

Anal. Calc'd for C₂₂H₁₆ClN: N, 4.25; Cl, 10.75.

Found: N, 4.04; Cl, 10.31.

(b) Formation of hydroxytriphenylpyrrole. To the mother liquor from the reaction mixture described in (a) above was added 5 cc. of ethanol and the solution was kept at 0° overnight, whereupon 140 mg. of fine yellow-green needles m.p. 114-132° (uncorr.) separated. This product was characterized as 3-hydroxy-1,2,4-triphenylpyrrole by conversion to the known acetyl derivative. The latter product, m.p. 133.5-134°, was identical with the acetyl derivative of the hydroxytriphenylpyrrole prepared by the method of Widman (3).

Anal. Calc'd for C24H19NO2: C, 81.56; H, 5.42; N, 3.96.

Found: C, 81.52; H, 5.36; N, 4.03.

The action of aniline on α -diphenacyl chloride in the presence of water. A mixture of 3 g. of α -diphenacyl chloride (m.p. 116-118°), 7.5 g. of aniline, and 60 cc. of water was stirred and heated at the reflux temperature for 3 hours. From the reaction mixture, which was worked up in the usual way, 370 mg. of unidentified product of m.p. 124-128° was isolated. The remaining crude reaction product was identified (by comparison of infrared spectra) as unreacted starting material. After repeated recrystallization, (five or six times) the yield of pure recovered α -chloride was 1.8 g. (60%).

Conversion of the α -diphenacyl halides to 3,5-diphenylpyridazine with hydrazine. (a) α -Diphenacyl bromide. A mixture of 650 mg. of α -diphenacyl bromide, 5 ml. of hydrazine hydrate (85%), and 50 ml. of ethanol was refluxed for $\frac{1}{2}$ hour. The yellow solution was cooled, and then poured into 300 ml. of cold water. The precipitate which formed was recrystallized from ethanol, yielding white needles, m.p. 144-145°.

Anal. Cale'd for C₁₆H₁₂N₂: C, 82.73; H, 5.21; N, 12.06.

Found: C, 82.73; H, 4.96; N, 12.17.

(b) α -Diphenacyl chloride. The reaction was carried out as in (a) above using 1 g. of α -diphenacyl chloride, 6 ml. of hydrazine hydrate, and 50 ml. of ethanol. From the reaction mixture there was isolated 550 mg. (65%) of crude product. After one recrystallization, the melting point was 139-141°. A mixture melting point determination and comparison of infrared spectra showed this product to be identical with the 3,5-diphenylpyridazine obtained in (a) above.

Anal. Calc'd for C₁₆H₁₂N₂: C, 82.73; H, 5.21; N, 12.06.

Found: C, 82.57; H, 5.21; N, 12.02.

Conversion of the β -diphenacyl halides to 2,4-diphenylpyrrole with hydrazine. (a) β -Diphenacyl bromide. A mixture of 3.5 g. of β -diphenacyl bromide, 18 ml. of hydrazine hydrate (85%), and 200 ml. of ethanol was refluxed for $\frac{1}{2}$ hour. The solution was cooled, poured into water, and the precipitate was collected. The crude product, (785 mg.) (33%) was recrystallized from ethanol, yielding white crystals m.p. 179-180°.

Anal. Cale'd for $C_{16}H_{13}N$: C, 87.64; H, 5.98; N, 6.39.

Found: C, 87.40; H, 5.74; N, 6.34.

This product was shown to be 2,4-diphenylpyrrole by a mixture melting point determination and comparison of infrared spectra with an authentic sample prepared by the method of Allen and Wilson (5).

(b) β -Diphenacyl chloride. A mixture of 3 g. of β -diphenacyl chloride, 18 ml. of hydrazine hydrate, and 150 ml. of ethanol was allowed to react as in (a) above and worked up to give 770 mg. (31%) of 2,4-diphenylpyrrole. The melting point of the twice-recrystallized product was 177-179°. The infrared spectrum and a mixture melting point with an authentic sample established its identity

Formation of the 2,4-dinitrophenylhydrazones of the diphenacyl halides. (a) β -Diphenacyl chloride. A mixture of 1 g. of β -diphenacyl chloride, 1.45 g. of 2,4-dinitrophenylhydrazine, and 50 cc. of ethanol was heated to reflux. The heat was removed, 20 drops of conc'd hydrochloric acid was added, and the reaction mixture was again refluxed for 3 minutes. The orange precipitate which formed melted at 181–182°, (dec.) Recrystallization from an ethanol-chloroform mixture yielded orange needles melting 183° (dec.)

Anal. Calc'd for C₂₂H₁₇ClN₄O₅: C, 58.35; H, 3.78; N, 12.37.

Found: C, 58.58; H, 4.05; N, 12.14.

(b) β -Diphenacyl bromide. The 2,4-dinitrophenylhydrazone, prepared as in (a) above, formed orange needles from ethanol-chloroform, m.p. 178° (dec.)

Anal. Calc'd for C₂₂H₁₇BrN₄O₅: C, 53.13; H, 3.45.

Found: C, 52.69; H, 3.48.

(c) α -Diphenacyl chloride. The 2,4-dinitrophenylhydrazone prepared as in (a) above formed orange needles from ethanol, m.p. 203° (dec.)

Anal. Calc'd for C₂₂H₁₇ClN₄O₅: C, 58.35; H, 3.78; N, 12.37.

Found: C, 58.62; H, 4.34; N, 12.39.

SUMMARY

The reactions of the diphenacyl halides with aniline and hydrazine have been found to be stereospecific. Based on the products obtained from these reactions, assignment of *cis*- and *trans*- configurations to the parent β - and α -epoxy ketones, respectively, has been made.

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