

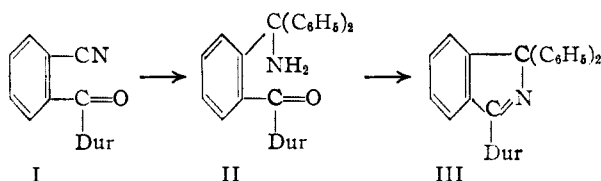
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Ring Closures Involving Highly Hindered Ketone Groups

BY REYNOLD C. FUSON AND WILLIAM C. HAMMANN¹

Duryl phenyl ketone does not form hydrazones. Suitably constituted hydrazine derivatives, however, undergo intramolecular reactions analogous to hydrazone formation.

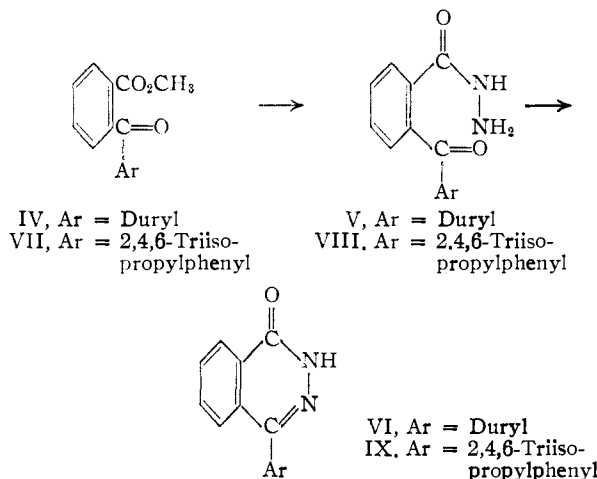
Quinoxaline formation in the reaction between *o*-phenylenediamine and certain derivatives of mesityl glyoxal or mesityl phenyl diketone² is remarkable because the ring closure step is the formation of an internal Schiff base of a highly hindered ketone. The carbonyl group of such a ketone is prevented by the adjacent methyl groups from taking part in typical carbonyl reactions; for example, it does not react with hydroxylamine, hydrazine or phenylhydrazine.³ More surprising is the production of 1,1-diphenyl-3-durylpseudoisindole (III) by the action of phenylmagnesium bromide on *o*-cyanophenyl duryl ketone (I). This reaction is believed to involve the formation of a primary amine (II) which undergoes ring closure to yield the pseudoisindole—a cyclic Schiff base.⁴



The distinctive feature of these carbonyl reactions with amino compounds is that they are *intramolecular*. It suggests that other reactions of a similar nature which fail to proceed intermolecularly might be realized as intramolecular processes. That the influence of the *o*-methyl groups is significant even in intramolecular reactions, however, is indicated by the observation that not all mesityl glyoxals react intramolecularly with *o*-phenylenediamine to give quinoxalines.²

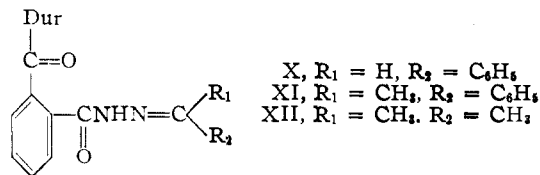
The study of several compounds especially designed to favor intramolecular reactions has given further insight into these anomalous reactions of the hindered ketone group. When methyl 2-duroylbenzoate (IV) was treated with hydrazine hydrate in boiling ethanol, the product was 1-duryl-4-phthalazone (VI). Treatment of methyl *o*-2,4,6-triisopropylbenzoylbenzoate (VII) under identical conditions gave 1-(2,4,6-triisopropylphenyl)-4-phthalazone (IX).

The duryl phthalazone (VI) was also produced by pyrolyzing the hydrazine salt of *o*-duroylbenzoic acid; in either case, the hydrazide must be formed as an intermediate. In unhindered keto acids such as *o*-benzoylbenzoic acid formation of phthalazones occurs readily and undoubtedly involves initial formation of the hydrazones.⁵ Under the condi-



tions used in these reactions *o*-duroylbenzoic and *o*-mesitoylbenzoic acids do not form phthalazones. Success with such keto acids and their derivatives has been achieved only when hydrazine formation could take place.

The successful isolation of *o*-duroylbenzoylhydrazine (V) presented an opportunity to investigate the ease of the ring closure step. The conversion of the intermediate hydrazide (V) to the phthalazone (VI) takes place in about 30 minutes in boiling ethanol. At room temperature an ethanolic solution of the hydrazide is stable, and recrystallization from cold ethanol is successful. By contrast, the hydrazide reacts at room temperature with benzaldehyde in one minute to give 1-benzylidene-2-(*o*-duroylbenzoyl)-hydrazine (X), with acetophenone in five minutes to give 1-(*o*-duroylbenzoyl)-2-(α -phenylethylidene)-hydrazine (XI) and with acetone to give 1-(*o*-duroylbenzoyl)-2-isopropylidenehydrazine (XII).



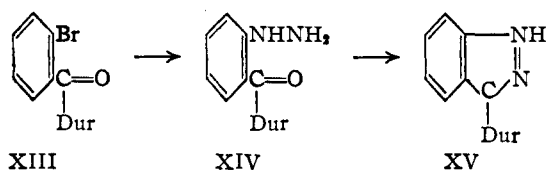
It is of interest that compound XII was hydrolyzed and converted to 1-duryl-4-phthalazone (VI) by treatment with dilute acetic acid.

The formation of a phenylhydrazone of a hindered ketone by an intramolecular reaction was realized in the reaction of *o*-bromophenyl duryl ketone (XIII) with hydrazine. The product of hydrazinolysis (XIV) evidently undergoes ring closure to yield 3-durylisindazole (XV).

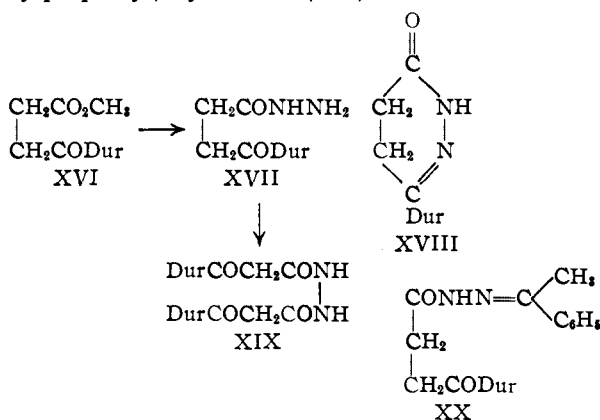
Molecules so constructed that intramolecular reaction of a hindered ketone and an amino group would result in a five- or six-membered ring do not always react in this way, however. For example,

(1) Rohm and Haas Fellow, 1950-1951.

(2) R. C. Fuson and Q. F. Soper, *J. Org. Chem.*, **9**, 193 (1944).(3) A. Hantzsch, *Ber.*, **23**, 2773 (1890); A. W. Smith, *ibid.*, **24**, 4052 (1891); F. Baum, *ibid.*, **28**, 3210 (1895); E. Feith and S. H. Davies, *ibid.*, **24**, 3546 (1891); E. Bouveault, *Compt. rend.*, **124**, 156 (1897).(4) R. C. Fuson, W. D. Emmons and R. Tull, *J. Org. Chem.*, **16**, 648 (1951).(5) R. von Rothenberg, *J. prakt. Chem.*, [2] **51**, 140 (1895).



when methyl β -duroylpropionate (XVI) was treated with hydrazine hydrate in boiling ethanol, the product was β -duroylpropionylhydrazine (XVII) rather than 3-duryl-6-pyridazinone (XVIII). Ring closure could not be effected even by heating β -duroylpropionylhydrazine (XVII) for four hours above its melting point, and the only product isolated from this reaction was 1,2-bis-(β -duroylpropionyl)-hydrazine (XIX). That the hydrazide group is capable of normal reaction is shown by the conversion of compound XVII by treatment with acetophenone to 1-(α -phenylethylidene)-2-(β -duroylpropionyl)-hydrazine (XX).



An important difference in the proximity of the carbonyl and hydrazide groups of *o*-duroylbenzoylhydrazine (V) and β -duroylpropionylhydrazine (XVII) is indicated by their infrared spectra. In the former compound, there is no absorption characteristic of the amino group, which indicates that this group is hydrogen bonded with the carbonyl group, while in the latter compound, the amino group absorbs strongly. Evidently, *o*-duroylbenzoylhydrazine exists chiefly in the chelated form while this conformation is of minor importance in β -duroylpropionylhydrazine. This result, probably arising from the more rigid structure of *o*-duroylbenzoylhydrazine, supports the view that statistically the opportunity for ring closure of this hydrazide would be substantially greater than for β -duroylpropionylhydrazine.

Experimental⁶

***o*-2,4,6-Triisopropylbenzoylbenzoic Acid.**—A mixture of 20.4 g. of 1,3,5-triisopropylbenzene, 16.3 g. of phthalic anhydride, 31.9 g. of aluminum chloride and 150 ml. of carbon disulfide was stirred at room temperature with occasional warming for 24 hours and poured over a mixture of 200 g. of ice and 30 ml. of concentrated hydrochloric acid. The carbon disulfide was removed by steam distillation and the solid product collected by filtration. A solution of the product in 700 ml. of hot 10% ammonium hydroxide was boiled for two minutes with 2 g. of Darco and filtered while hot. The solid obtained after acidification of the ammonium hydroxide solution was crystallized from 300 ml. of 60% ethanol. *o*-2,4,6-Triisopropylbenzoylbenzoic acid (m.p. 199–200°) was obtained in a yield of 23 g. (66%).

*Anal.*⁷ Calcd. for $\text{C}_{23}\text{H}_{28}\text{O}_2$: C, 78.37; H, 8.01. Found: C, 78.30; H, 8.26.

The product obtained by heating a mixture of 1.0 g. of the acid and 0.03 g. of powdered copper at 275° for one hour melted at 97–99°. The reported melting point of 2,4,6-triisopropylbenzophenone⁸ is 97–99°.

Methyl *o*-2,4,6-Triisopropylbenzoylbenzoate (VII).—A solution of 5 g. of *o*-2,4,6-triisopropylbenzoylbenzoic acid and 10 ml. of thionyl chloride was allowed to stand at room temperature for 30 minutes. After removal of the excess thionyl chloride under reduced pressure and at a temperature below 60°, the crude *o*-2,4,6-triisopropylbenzoylbenzoyl chloride was dissolved in 20 ml. of anhydrous methanol and the solution kept at room temperature for 2 hours. The ester, which had crystallized from the solution, was collected on a filter and recrystallized from methanol. Methyl *o*-2,4,6-triisopropylbenzoylbenzoate (m.p. 117–118°) was obtained in the form of large prisms in a yield of 4 g. (78%).

Anal. Calcd. for $\text{C}_{24}\text{H}_{30}\text{O}_2$: C, 78.64; H, 8.25. Found: C, 78.77; H, 8.34.

Methyl *o*-Duroylbenzoate (IV).⁹—*o*-Duroylbenzoyl chloride was prepared by the action of 100 ml. of thionyl chloride on 100 g. of *o*-duroylbenzoic acid. The mixture was boiled under reflux one hour and the excess thionyl chloride then distilled with the water-pump. The solid acid chloride was heated under reflux with 2.5 l. of methanol. The ester crystallized on cooling; yield 85 g. (81%); m.p. 155.0–156.5°.

Anal. Calcd. for $\text{C}_{19}\text{H}_{20}\text{O}_2$: C, 76.99; H, 6.80. Found: C, 76.78; H, 6.99.

1-Mesityl-4-phthalazone.—A solution of 5 g. of *o*-mesitylbenzoic acid, 2 ml. of 85% hydrazine hydrate and 15 ml. of ethanol was boiled under reflux for 8 hours. No precipitate formed. The ethanol was distilled, and near the end of the distillation a white solid separated, which fused to a yellow mass when it was strongly heated. After 5 minutes of heating the mass was allowed to cool and solidify. Crystallization of the solid from ethanol gave 2 g. (41%) of 1-mesityl-4-phthalazone in the form of bright yellow crystals melting at 262–263°.

Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}$: C, 77.24; H, 6.10; N, 10.60. Found: C, 77.11; H, 6.26; N, 10.63.

Several recrystallizations of the product from ethanol did not remove the color, but sublimation gave an almost white powder.

1-Mesityl-4-chlorophthalazine.—A solution of 1 g. of 1-mesityl-4-phthalazone in 3 ml. of phosphorus oxychloride was heated on a water-bath for 30 minutes, poured into 20 ml. of water and neutralized with 40% sodium hydroxide solution. The light yellow solid which precipitated was recrystallized from ether. 1-Mesityl-4-chlorophthalazine (m.p. 192–193°) was obtained as colorless crystals in a yield of 0.7 g. (64%).

Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{Cl}$: C, 72.20; H, 5.35; N, 9.91. Found: C, 71.97; H, 5.42; N, 9.95.

1-Duryl-4-phthalazone (VI). A. By the Reaction of Hydrazine Hydrate with *o*-Duroylbenzoic Acid.—A solution of 14 g. of *o*-duroylbenzoic acid, 5.0 ml. of 95% hydrazine hydrate and 80 ml. of ethanol was boiled under reflux for 2 hours. No precipitate formed. The reaction was continued by the procedure described for *o*-mesitylbenzoic acid. The product, 1-duryl-4-phthalazone, was obtained in a yield of 8 g. (60%), and after digestion with ethanol it melted with decomposition at approximately 320°. Two recrystallizations of the bright yellow product from ethanol did not discharge the color, but sublimation gave a white powder which decomposed near 320°.

B. By the Reaction of Hydrazine Hydrate with Methyl *o*-Duroylbenzoate.—A solution of 1.0 g. of methyl *o*-duroylbenzoate, 2 ml. of 85% hydrazine hydrate and 10 ml. of ethanol was boiled under reflux for 2 days. The solution was filtered while hot in order to isolate 0.6 g. of white crystals which had formed during the reflux period. An additional 0.2 g. of product crystallized from the cold filtrate so that the total yield of 1-duryl-4-phthalazone was

(7) The microanalyses were performed by Miss Emily Davis, Miss Rachel Kopel, Mrs. Jean Fortney and Mrs. Katherine Pih.

(8) R. C. Fuson, E. M. Bottorff, R. E. Foster and S. B. Speck. *THIS JOURNAL*, **64**, 2573 (1942).

(9) This experiment was performed by Dr. W. D. Emmons.

(6) All melting points are corrected.

0.8 g. (93%). The product was sublimed at 250° (0.3 mm.); the sublimate decomposed near 325°.

Anal. Calcd. for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.05. Found: C, 77.64; H, 6.54; N, 9.98.

C. From *o*-Duroylbenzoylhydrazine.—When a solution of 0.5 g. of *o*-duroylbenzoylhydrazine in 10 ml. of ethanol was boiled under reflux, a solid began to separate within 30 minutes. The product, which was collected after a total reflux time of 2 hours, melted with decomposition at 335°. A known sample of 1-duryl-4-phthalazone decomposed at 335° on the same melting point apparatus.

1-(*o*-2,4,6-Triisopropylphenyl)-4-phthalazone (IX).—A solution of 1 g. of methyl *o*-2,4,6-triisopropylbenzoylbenzoate, 3 ml. of 85% hydrazine hydrate and 5 ml. of ethanol was boiled under reflux for 24 hours. The white crystals (m.p. 239–240°), which separated from the cold reaction mixture, were collected on a filter in a yield of 0.8 g. (80%). Sublimation of the product, 1-(2,4,6-triisopropylphenyl)-4-phthalazone, at 180° (0.3 mm.) raised its melting point to 240–242°.

Anal. Calcd. for $C_{23}H_{28}N_2O$: C, 79.28; H, 8.10; N, 8.04. Found: C, 79.03; H, 8.39; N, 8.26.

***o*-Duroylbenzoylhydrazine (V).**—A solution of 20 g. of *o*-duroylbenzoic acid and 50 ml. of thionyl chloride was heated under reflux for one hour. The excess thionyl chloride was separated from the *o*-duroylbenzoyl chloride by distillation under a water pump. A 5-g. portion of the acid chloride was allowed to stand at room temperature with 15 ml. of 85% hydrazine hydrate for 24 hours. The solid was separated from the hydrazine solution by filtration and washed, in sequence, with 100 ml. of water, 100 ml. of 5% sodium bicarbonate solution and 100 ml. of water. A yield of 4.5 g. (90%) of *o*-duroylbenzoylhydrazine was obtained, and a small sample was crystallized from cold ethanol for analysis. When the pure hydrazide was dropped on a melting point block at temperatures above 205°, it fused at first, then solidified and decomposed near 320°.

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 72.94; H, 6.80; N, 9.46. Found: C, 73.25; H, 6.96; N, 8.95.

The infrared spectrum¹⁰ shows absorption characteristic of a carbonyl group at 1637 cm^{-1} , of another carbonyl group at 1671 cm^{-1} and of an imino group at 3327 cm^{-1} ; but there is no absorption characteristic of the amino group.

1-Benzylidene-2-(*o*-duroylbenzoyl)-hydrazine (X).—A mixture of 0.5 g. of *o*-duroylbenzoylhydrazine, 10 ml. of ethanol and 1.0 ml. of benzaldehyde was shaken in the cold. A heavy precipitate formed in less than 30 seconds, and the reaction was completed by boiling the mixture for one minute. The product, 1-benzylidene-2-(*o*-duroylbenzoyl)-hydrazine, which was isolated from the mixture by filtration, melted at 244–246°. After it had been recrystallized from ethanol, it melted at 248–249°.

Anal. Calcd. for $C_{23}H_{24}N_2O_2$: C, 78.10; H, 6.29; N, 7.29. Found: C, 77.83; H, 6.38; N, 7.37.

1-(*o*-Duroylbenzoyl)-2-(α -phenylethylidene)-hydrazine (XI).—Two minutes after the addition of 2 ml. of acetophenone to a solution of 0.5 g. of *o*-duroylbenzoylhydrazine in 20 ml. of ethanol a precipitate began to form. After 2 hours had been allowed for the completion of the reaction, 0.5 g. (75%) of solid (m.p. 212–214°) was collected on a filter. The product, 1-(*o*-duroylbenzoyl)-2-(α -phenylethylidene)-hydrazine, melted at 213–214° after it had been recrystallized from ethanol.

Anal. Calcd. for $C_{26}H_{26}N_2O_2$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.30; H, 6.35; N, 7.02.

1-(*o*-Duroylbenzoyl)-2-isopropylidenehydrazine (XII).—A small sample of *o*-duroylbenzoylhydrazine was recrystallized three times from acetone. The crystals obtained melted at 236–241° and had the composition calculated for 1-(*o*-duroylbenzoyl)-2-isopropylidenehydrazine.

Anal. Calcd. for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 75.01; H, 7.47; N, 8.10.

When a solution of 0.016 g. of the isopropylidenehydrazine, 1 ml. of ethanol and 0.10 ml. of glacial acetic acid was heated under reflux, a precipitate began to form in one hour.

(10) The infrared spectra were observed and interpreted by Miss Elizabeth Petersen.

After a total reflux time of 2 hours the reaction mixture was cooled, and the solid which separated was collected on a filter. 1-Duryl-4-phthalazone was obtained in a yield of 0.010 g. (75%). The product did not melt when dropped on a melting block at 265° and decomposed near 325°.

3-Durylisoindazole (XV).—A mixture of 2.0 g. of *o*-bromobenzoyldurene, 4 ml. of 85% hydrazine hydrate and 10 ml. of 1-butanol was heated at reflux for 38 hours. Crystals formed during the reflux period. Filtration of the cold reaction mixture yielded 1.5 g. (95%) of white crystals; m.p. 271–274°. The product, 3-durylisoindazole, melted at 271–272° after it had been recrystallized from ethanol.

Anal. Calcd. for $C_{17}H_{18}N_2$: N, 11.19. Found: N, 11.24.

The infrared spectrum shows no absorption characteristic of a carbonyl group, but an absorption band at 3470 cm^{-1} indicates an imino group.

β -Duroylpropionic Acid.—Sixty grams of aluminum chloride was slowly added with stirring to a solution of 27 g. of durene and 20 g. of succinic anhydride in 60 ml. of *sym*-tetrachloroethane. The reaction mixture was stirred at room temperature for 18 hours and poured over ice. The solvent was removed by steam distillation and the residue crystallized from a solution of 250 ml. of ethanol and 200 ml. of water. A yield of 20 g. (43%) of white crystals, m.p. 140–150°, was obtained. The β -duroylpropionic acid was recrystallized from 300 ml. of benzene; m.p. 160–161°.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 71.77; H, 7.74. Found: C, 71.89; H, 7.76.

Methyl β -Duroylpropionate (XVI).—A solution of 9 g. of β -duroylpropionic acid, 3 ml. of concentrated sulfuric acid and 30 ml. of methanol was boiled under reflux for 2 hours. The ester, which crystallized from the cold reaction mixture, was taken up in ether. The ethereal solution was washed in sequence with water, 10% sodium bicarbonate solution and water. Evaporation of the ether left 8.5 g. (95%) of methyl β -duroylpropionate, which after crystallization from methanol melted at 103–103.5°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 72.55; H, 8.12. Found: C, 72.51; H, 8.26.

β -Duroylpropionylhydrazine (XVII).—A solution of 1.1 g. of methyl β -duroylpropionate, 1.5 ml. of 85% hydrazine hydrate and 2 ml. of ethanol was boiled under reflux for 4 hours. A yield of 0.96 g. (85%) of β -duroylpropionylhydrazine crystallized from the cold reaction mixture. The white platelets, which were obtained by recrystallization of the solid from ethanol, melted at 157–158°.

Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.43; H, 8.30; N, 11.04.

The same results were obtained when the reaction mixture was boiled for 24 instead of 4 hours.

The infrared spectrum shows absorption characteristic of a carbonyl group at 1686 cm^{-1} , of an amide carbonyl group at 1624 cm^{-1} , of an imino group at 3339 cm^{-1} and of an amino group at 3238 and 3147 cm^{-1} .

1-(β -Duroylpropionyl)-2-(α -phenylethylidene)-hydrazine (XX).—Acetophenone (0.5 ml.) was added to a solution of 0.15 g. of β -duroylpropionylhydrazine in 5 ml. of ethanol. A solid began to precipitate from the solution 15 minutes after the time of mixing, and after 4 hours 0.19 g. (96%) of white needle-like crystals (m.p. 178–179°) was collected on a filter. The product, 1-(β -duroylpropionyl)-2-(α -phenylethylidene)-hydrazine, melted at 179–180° after recrystallization from ethanol.

Anal. Calcd. for $C_{27}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 8.00. Found: C, 75.67; H, 7.50; N, 7.86.

1,2-Bis-(β -duroylpropionyl)-hydrazine (XIX).—A small test-tube containing 0.26 g. of β -duroylpropionylhydrazine was held at 180–190° in a metal-bath for 4 hours. The product, which solidified when cooled, was isolated by crushing the tube in a beaker, dissolving all the organic matter in 10 ml. of hot ethanol, filtering the ethanolic solution and allowing it to cool. A brown solid (0.05 g., 22%), m.p. 217–218°, crystallized from the solution. After recrystallization from 6 ml. of ethanol, the 1,2-bis-(β -duroylpropionyl)-hydrazine melted at 219–220°.

Anal. Calcd. for $C_{28}H_{26}N_2O_4$: C, 72.38; H, 7.81; N, 6.03. Found: C, 72.50; H, 8.02; N, 5.85.