[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

IDENTIFICATION OF PHENYLHYDRAZONES AND ISOMERIC PYRAZOLINES OBTAINED FROM CHALCONES

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Received November 11, 1936; revised December 4, 1936

In their study of the behavior of aldehydes toward phenylhydrazine Fischer and Knoevenagel¹ found that when acrolein is used the product is 1-phenylpyrazoline instead of the expected hydrazone. Much later



Auwers and Müller² studied this reaction further, and reached the conclusion that the pyrazoline in this and other instances is formed through the rearrangement of an unstable hydrazone and noted that in those cases where the latter can be isolated, treatment of it with hot acetic acid causes rearrangement. This view was supported by the work of Auwers and Voss³ who isolated the hydrazones of cinnamic aldehyde and benzalacetone, and showed that heating them with acetic acid causes their rearrangement to the corresponding pyrazolines. But some hydrazones of this group failed to respond to this test, for the authors just quoted were unable to rearrange the product obtained from cinnamic aldehyde and p-nitrophenylhydrazine, although the compound was subsequently shown by reduction to be a hydrazone.

In extension of their study Auwers and co-workers specified the characters of the radicals in an α,β -unsaturated ketone of the type R—CH=CH—CO—R' which they thought would permit the formation of a stable hydrazone, and Straus⁴ studied the behavior of a few such ketones in which R and R' contained a halogen atom or the nitro radical as substituents. He found that the closing of the pyrazoline ring occurs readily when the substituent is in either ketone or hydrazine residue, and that when both are substituted the hydrazone is quite stable and requires

¹ FISCHER AND KNOEVENAGEL, Ann., 239, 194 (1887).

² AUWERS AND MÜLLER, Ber., 41, 4230 (1908).

³ Auwers and Voss, *ibid.*, 42, 4412 (1909).

⁴ STRAUS, *ibid.*, **51**, 1458 (1918).

energetic treatment for rearrangement. Raiford and Davis⁵ studied the behavior of five ketones the structures of which, according to the above view, seemed most favorable to the formation of stable hydrazones. They were unable to confirm Straus' prediction with regard to the stability conferred by substituents. In no case was a hydrazone isolated but in each instance the required pyrazoline was obtained.

With respect to the unsubstituted ketone chalcone, Auwers and Voss reached the conclusion that the "hydrazone of benzalacetophenone is so labile that it cannot be isolated, even at low temperature, but that it rearranges at once to give 1,3,5-triphenylpyrazoline." Although Raiford and Davis succeeded in isolating and characterizing this hydrazone, the



need was felt, in this and other work published from this Laboratory,⁶ for more satisfactory tests to distinguish between these hydrazones and their rearrangement products.

In previous work it has been found that the Knorr⁷ color test for pyrazoline bases, in which a drop of solution of ferric chloride, chromic acid, nitrous acid or similar oxidizing agent is added to a concentrated sulfuric acid solution of the suspected compound, to give a blue-violet color, is so sensitive that a hydrazone containing only a trace of pyrazoline will give a positive reaction.⁸ But the fact that acids are the reagents which most readily bring about the rearrangement of these hydrazones raises the question whether some pyrazoline is formed when these reagents are applied. Auwers and co-workers also noted that the Knorr test is often given by the mother liquors from which the hydrazones have been crystallized, and that such solutions frequently show a blue fluorescence if pyrazoline is present.

In the present work an attempt was made to find a qualitative test for distinguishing between these isomers by utilizing an observation made by Knorr and Laubmann.⁹ These workers found that, in the bromination of 1,3,5-triphenylpyrazoline, a bluish-green color was developed at the beginning of the reaction. In our experiments it was found that when a very small portion of a hydrazone of this group, spread on a filter paper, is brought in contact with bromine vapor the color changes from yellow

⁵ RAIFORD AND DAVIS, J. Am. Chem. Soc., 50, 159 (1928).

⁶ RAIFORD AND CO-WORKERS, J. Am. Chem. Soc., 55, 1125 (1933); 56, 174 (1934).

⁷ KNORR, Ann., 238, 200 (1887).

⁸ AUWERS AND VOSS, Ber., 42, 4417 (1909).

⁹ KNORR AND LAUBMANN, *ibid.*, **21**, 1210 (1888).

to orange, and frequently to brick-red. Under the same treatment a pyrazoline turns green almost instantaneously.

Another test which has been used to distinguish between these isomers is their behavior toward reducing agents. Reduction of the hydrazones by sodium amalgam in presence of alcohol and acetic acid, as directed by Tafel,¹⁰ to give aniline and the corresponding aliphatic amine, was found by Auwers and Kreuder¹¹ to be unsatisfactory because too large an amount of hydrazone is required to give a suitable quantity of aniline, and for the further reason that in some cases the test fails to give any aniline regardless of the amount of hydrazone used.

In the present work when the phenylhydrazone of benzalacetone, m.p., $138-139^{\circ}$,* which may here be called the β form, was reduced by sodium and alcohol at about the boiling point of the latter, and the reaction mixture was worked up in the manner described by Raiford and Davis,⁵ 50 per cent. of the aniline required by the expected reaction was obtained, about 30 per cent. of unchanged starting material was recovered, and there remained a small portion of oil which should have been α -phenyl- γ -aminobutane, but which could not be identified.

This hydrazone was also reduced by Schlenk's¹² method modified to the extent that the reaction was carried through at about 55° rather than at the boiling point of the alcohol used as a solvent. In this case there was obtained a 76 per cent. yield of a product that turned out to be the phenylhydrazone of benzylacetone. To identify this compound it was prepared in a different way. First, separate portions of benzalacetone were reduced to benzylacetone. With the method of Harries and Eschenbach¹³ the yield was low, while with that described by Adams, Kern and Shriner¹⁴ it was much better. This product was identified by conversion of one portion of it into the semicarbazone, and another into the phenylhydrazone. These changes are indicated below.

¹⁰ TAFEL, *ibid.*, **22**, 1854 (1889).

¹¹ AUWERS AND KREUDER, *ibid.*, **58**, 1976 (1925).

* The first lot of this material prepared melted at $156-157.5^{\circ}$, which agrees with the observations of FISCHER [Ber., 17, 576 (1884)] who found 157°. When this product was allowed to stand in a glass container for about six months and was then recrystallized from alcohol it melted at $138-139^{\circ}$. All subsequent attempts to prepare this hydrazone by the method which in the first instance gave the higher-melting product, gave material that melted at $138-139^{\circ}$. The yields were comparable. Analysis of the product indicated that it was pure, and rearrangement of it gave the expected pyrazoline.

¹² SCHLENK, J. prakt. Chem., [2], 78, 50 (1908).

¹³ HARRIES AND ESCHENBACH, Ber., 29, 383 (1896).

¹⁴ ADAMS, KERN, AND SHRINER, "Organic Syntheses," Wiley, New York, 1932, Coll. Vol., p. 95.





Reduction of the phenylhydrazone of chalcone was carried out with sodium amalgam in alkaline solution as directed by Schlenk. In this case 20 per cent. of the required aniline was obtained, 5 per cent. of the hydrazone was rearranged to 1,3,5-triphenylpyrazoline, while 20 per cent. was reduced to give the hydrazone of β -phenylpropiophenone. The identity of this product was established by subjecting chalcone to the series of reactions specified above for benzalacetone. With the phenylhydrazone of 4'-chlorochalcone, reduction gave 12 per cent. of the required aniline, and 21 per cent. of a heavy brown oil that gave a good analysis for the phenylhydrazone of β -phenylethyl 4-chlorophenyl ketone. The same product was obtained by catalytic reduction of 4'-chlorochalcone to the saturated ketone, and treatment of the latter with phenylhydrazine. Although a small amount of aniline was obtained in the reduction of each of these hydrazones, the aliphatic amines which might have been expected, in terms of Tafel's observations, were not obtained.



FIG. 1.—PHENYLHYDRAZONE OF 4'-CHLOROCHALCONE FIG. 2.—1,5-DIPHENYL-3-(4-CHLOROPHENYL)PYRAZOLINE

An additional aid used to distinguish between these isomers was microscopic examination of the forms in which they separate when they are crystallized from certain solvents. In almost every case when the hydrazones here under consideration separated from the acetic acid solution, in which they were usually prepared, they were deposited as flat plates. From methyl or ethyl alcohol needles were obtained. The crystal shapes of the pyrazolines varied but little when different solvents were used. With acetic acid the needles formed were long and characteristic in appearance. Frequently, in carrying through a preparation of these hydrazones or an attempt to reduce or rearrange them, it was found possible to follow the change by removal of a few drops of the reaction mixture, evaporation to crystallization, and examination of the residue with a microscope. The appearance of these crystals is shown in Figs. 1 and 2 for a typical hydrazone-pyrazoline pair crystallized from acetic acid.

EXPERIMENTAL

Ketones containing saturated hydrocarbon residues.—Benzylacetone was obtained in 34% yield as an oil that boiled at 235–236° under 748 mm. pressure, by reduction of benzalacetone by the method of Harries Eschenbach.¹³ When reduction was carried through as directed by Adams, Kern, and Shriner¹⁴ the same oil was obtained, but the yield was 67%. The product was further characterized by conversion into a semicarbazone which crystallized from alcohol in colorless plates that melted at 142°.

Anal. Calc'd for C₁₁H₁₅N₃O: N, 20.48. Found: N, 20.51.

 β -Phenylpropiophenone was prepared in 87% yield by reduction of chalcone by the method of Adams, Kern and Shriner. The product was identified by conversion

| SUBSTITUENT IN PHENYL' | YIELD, | м.р., °С. | FORMULA | ANALYSES | | | |
|---|----------------|--------------------------------|--|------------|-------|--------------|--------------|
| | | | | Halogen, % | | Nitrogen, % | |
| | | | | Calc'd | Found | Cale'd | Found |
| 4'-Bromo- 4'-Methyl- ^b 4'-Methoxy- | 69 53 37 | 116-118ª 101-102 106-107 | $\begin{array}{c} C_{21}H_{17}BrN_2\\ C_{22}H_{20}N_2\\ C_{22}H_{20}N_2O\end{array}$ | 21.22 | 21.30 | 8.97 8.53 | 9.04 8.60 |

TABLE I PHENYLHYDRAZONES FROM SUBSTITUTED CHALCONES

^a Though this compound gave a satisfactory analysis for halogen there is some uncertainty concerning its purity. In repeated preparations of the compound crystallization from acetic acid gave material that showed a melting range of 110-120°. After one recrystallization from alcohol the product melted at 100-101°, but repeated crystallizations from the same solvent raised this to 116-118°. The pyrazoline obtained from it by rearrangement was readily purified and melted satisfactorily.

^b According to Weygand and Matthes [Ann., **449**, 31, 59 (1926)], 4'-methylchalcone used in the preparation of this hydrazone can exist in alpha and beta forms that melt at 74.8-75.4° and 55-56°, respectively. When either of these is heated to about 220° and quickly cooled the gamma form melting at 44° is obtained. The product used here melted at 77° and was regarded as the alpha form.

into the oxime, which melted at 82° as previously recorded.¹⁵ A portion of the ketone was dissolved in a mixture of alcohol and acetic acid, and was refluxed for an hour with phenylhydrazine. The alcohol was evaporated, the oily residue was extracted with dilute hydrochloric acid, then with ether; the ether solution was dried with anhydrous sodium sulfate, and the solvent was distilled off. The residue was a yellowish-brown oil which did not crystallize. A yield of 56% was obtained. The same product was obtained in part by reduction of the phenylhydrazone of benzalacetophenone by Schlenk's method. Each was analyzed for nitrogen.

Anal. Calc'd for C₂₁H₂₀N₂: N, 9.33. Found: N, 9.24 and 9.26.

 β -Phenylethyl 4-chlorophenyl ketone was prepared by reduction of 4'-chlorochalcone as described above. The yield was 93%. Crystallization from alcohol gave color-

¹⁵ PERKIN AND STENHOUSE, J. Chem. Soc., 59, 1008 (1891).

less needles that melted at 73° . The product was further identified by conversion into an oxime, which separated from dilute alcohol in colorless needles that melted at $91-92^{\circ}$.

Anal. Cale'd for C₁₅H₁₄ClNO: Cl, 13.67. Found: Cl, 13.40.

The phenylhydrazone, obtained as explained above for the non-halogenated compound, was a reddish-brown oil that could not be crystallized. Analysis indicated that it was nearly pure.

Anal. Calc'd for C₂₁H₁₉ClN₂: Cl, 10.61. Found: Cl, 10.70.

Phenylhydrazones of α,β -unsaturated ketones.—The ketones used here are on record, and were prepared by standard methods. To obtain the hydrazones the calculated quantity of phenylhydrazine was added with efficient stirring to a saturated acetic acid solution of the ketone at room temperature, and stirring was continued until the product crystallized out. The solid was immediately collected

| | | м.р., °С. | ANALYSES | | | | |
|-------------------------------|--|-----------|------------|-------|-------------|-------|--|
| substituent in position 3 | FORMULA | | Halogen, % | | Nitrogen, % | | |
| | | | Cale'd | Found | Calc'd | Found | |
| 4-Chlorophenyl- | $C_{21}H_{17}ClN_2$ | 150-0.5 | 10.67 | 10.68 | | | |
| 4-Bromophenyl- | $\mathrm{C}_{21}\mathrm{H}_{17}\mathrm{BrN}_{2}$ | 156-7 | 21.22 | 21.43 | | | |
| 4-Tolyl- | $C_{22}H_{20}N_2$ | 152-3 | | | 8.97 | 8.94 | |
| 3-Nitrophenyl- | $\mathrm{C}_{21}\mathrm{H}_{17}\mathrm{N}_{3}\mathrm{O}_{2}$ | 131 | | | 12.24 | 12.38 | |
| 4-Hydroxyphenyl- | $C_{21}H_{18}N_2O$ | 116-8 | | | 8.91 | 8.87 | |
| 4-Acetoxyphenyl- | $C_{23}H_{20}N_2O_2$ | 165-6 | | | 7.86 | 7.75° | |
| 4-Methoxyphenyl- ^b | $C_{22}H_{20}N_2O$ | 141-1.5 | | | 8.54 | 8.71 | |

| TABLE II | |
|----------|--|
|----------|--|

Substituted 1,5-Diphenylpyrazolines from α,β -Unsaturated Ketones

^a This compound was further identified by preparing it directly by acetylation of 1,5-diphenyl-3-(4-hydroxyphenyl)pyrazoline. A mixture of these products melted without depression.

^b This product crystallized in fine colorless needles from alcohol. All others were crystallized from alcohol or acetic acid in yellow needles.

on a gravity filter, and washed with several portions of warm methyl alcohol in order to remove adhering acetic acid which would slowly bring about rearrangement of a portion of the hydrazone during the drying of the material. In this way the hydrazones listed in Table I were obtained. When 4'-hydroxy-, 4'-acetoxy-, and 3'-nitrochalcone, respectively, were used no hydrazones could be isolated. In each case the required pyrazoline was obtained, which indicated that the hydrazones were too unstable to exist under the conditions of the experiment.

Preparation of pyrazolines.—When the hydrazones indicated above were mixed with acetic acid and heated under reflux for one hour they were rearranged to the isomeric pyrazolines. Also, the latter were obtained directly by boiling a mixture of the required ketone, phenylhydrazine, and acetic acid. Analytical data and other properties for products obtained by both methods are given in Table II.

SUMMARY

1. It has been found that several substituted chalcones can be reduced in the presence of platinum oxide as catalyst to give the corresponding β -phenylpropiophenones.

2. Phenylhydrazones were obtained from 4'-chloro-, 4'-bromo-, 4'methyl-, and 4'-methoxychalcone, while 3'-nitro-, 4'-hydroxy- and 4'acetoxy- derivatives gave pyrazolines directly.

3. Reduction of the phenylhydrazones of α , β -unsaturated ketones with sodium amalgam, with the continual passage of carbon dioxide into the reaction mixture gave the hydrazones of the corresponding saturated ketones. This indicated that only the ethylenic linkages had been affected. When attempts were made to reduce the isomeric pyrazolines the starting material was recovered quantitatively.

4. From acetic acid these hydrazones crystallize in flat plates, while the pyrazolines separate in needles. The colors developed by these compounds in the presence of bromine vapor are different, and may assist in distinguishing the isomers.