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

FORMATION OF PYRAZOLINES FROM UNSYMMETRICALLY SUBSTITUTED DIBENZALACETONES

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The purpose of this work was to extend our study of the action of phenylhydrazine on α,β-unsaturated ketones. In previous experiments (1) it was found possible in some instances to isolate the phenylhydrazones assumed by Auwers and co-workers (2) to be the first products in this reaction, but in many cases these compounds rearranged immediately to the isomeric pyrazolines. Straus (3) claimed that the ease of rearrangement will depend on the presence of substituents in the ketone and hydrazine residues. He stated that if one of the latter contains halogen or the nitro radical, closure of the pyrazoline ring will occur readily, while if both are substituted the hydrazone will be stable. It was desired to test these possibilities further.

To decide whether this rearrangement had occurred, in previous work a number of methods have been studied. Auwers and Voss (4) found that the color test for pyrazolines proposed by Knorr (5), 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 not satisfactory. A trace of pyrazoline will give a positive reaction, and the fact that acids are the reagents which most readily bring about the rearrangement of these hydrazones[1] raises the question whether some pyrazoline is formed when the reagent is applied. When the compound in question can be reduced by sodium amalgam (6) to give aniline as one product, it is regarded as a hydrazone.[2] This can usually be rearranged by boiling acetic acid.[3] Products

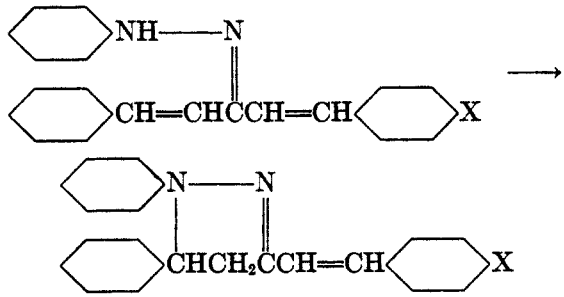
[1] Auwers and co-workers noted that the mother liquors from which the phenylhydrazones have been crystallized often respond to the Knorr test.

[2] This test does not cover all cases, for Auwers and Kreuder [*Ber.*, **58**, 1983 (1925)] could not reduce the compound obtained from benzalacetone and *p*-tolylhydrazine, although this product was reported as a hydrazone because boiling it with acetic acid changed it to an oil that responded to the Knorr test.

[3] Auwers and Voss failed by this method to rearrange the product obtained from cinnamic aldehyde and *p*-nitrophenylhydrazine, although the compound was shown by reduction to be a hydrazone. Bauer and Dieterle [*Ber.*, **44**, 2701 (1911)] had similar experiences.

that cannot be reduced or rearranged are generally regarded as pyrazolines.[4]

Besides the stability of these phenylhydrazones another consideration is of interest here, *viz.*, the direction of ring closure in the rearrangement. If the hydrazone is derived from a ketone containing but one α,β-unsaturation it can rearrange in but one direction to give a pyrazoline. If it is obtained from a symmetrical diunsaturated ketone it must give the same pyrazoline regardless of the radical engaged in closing the ring. When the ketone contains two α,β-unsaturations and is, in addition, unsymmetrical, two products are theoretically possible, depending on the direction in which ring closure takes place, and it is to be expected that this change will depend to some extent on the characters of the substituents in the ketones used.



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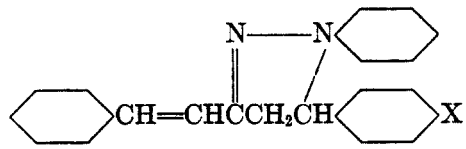


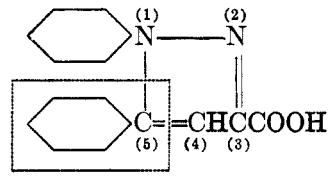
II

To identify the pyrazolines, Straus (3) suggested that if they have been derived from dibenzalacetone or one of its substitution-products they may be oxidized by potassium permanganate solution to give 1,5-diphenylpyrazole-3-carboxylic acid (7) and benzoic acid. He oxidized but two compounds in this way, both of which were derived from symmetrical ketones which contained no substituents. From the first one he obtained benzoic acid and the required pyrazole acid, and from the second benzoic acid only. Bauer and Dieterle (8), also, oxidized two pyrazolines by this

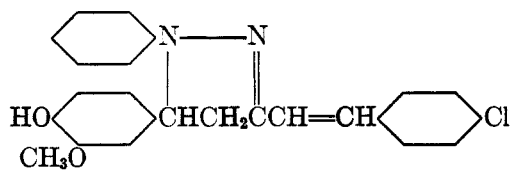
[4] It is of interest here to note that Raiford and Peterson [*J. Org. Chem.*, **1**, 548 (1937)] were able to distinguish between the phenylhydrazones and isomeric pyrazolines obtained from certain chalcones by microscopic examination of their crystals.

method and were able to isolate the required pyrazole acids. Oxidation of the products obtained in the present study should distinguish between structures I and II.

In previous work in this laboratory the oxidation of pyrazolines was done in aqueous mixtures, as suggested by Straus. This involved two difficulties. These compounds are but slightly soluble in water, and under the conditions, heating was required to complete the oxidation. Elevated temperatures favor further reaction which involves degradation of the pyrazole acid. Thus, oxidation of 1,5-diphenyl-3-styrylpyrazoline in this way, by G. V. Gundy formerly of this laboratory, gave but 39% of the required pyrazole acid, and 137% of benzoic acid. Treatment of a purified sample of the pyrazole acid there obtained with permanganate gave benzoic acid, which indicates that the pyrazole ring must be ruptured between atoms 1 and 5 and also between 4 and 5. Degradation was more pronounced when the nitro group was present as a substituent.



In the work now reported an effort was made to avoid oxidative degradation of the pyrazole acid (a) by conducting the reaction in pyridine solution, (b) by working at room temperature or but slightly above, and (c) by choosing for position 5 a residue that would probably resist oxidation. It was thought that the last could be achieved by taking into account the following facts. Our previous studies in this field seemed to show that the closing of the pyrazoline ring takes place in such a way as to involve that radical of the original ketone which contains the less "acidic" substituent (9), which requires the more "acidic" radical to be attached at position 3 in the pyrazoline. The use of vanillal-4-chlorobenzalacetone as the starting ketone would, under such a requirement, bring the vanillyl radical into position 5. The pyrazole acid obtained from such a pyrazoline



might be expected to resist further oxidation under the conditions, for Tiemann (10) found that all attempts to oxidize vanillin to vanillic acid left the material unchanged or degraded it to amorphous products that

could not be identified, according to conditions of the experiment. In a similar way Brady and Dunn (11) failed to oxidize 5-bromovanillin into the corresponding acid by chromic acid and by alkaline permanganate. In simpler cases Bücking (12), and Fittig and Remsen (13) found that 4-hydroxybenzaldehyde and protocatechuic aldehyde, respectively, are not easily oxidized by potassium permanganate solution but require fusion with caustic potash to give the corresponding acids. The resistance to oxidation in these cases appears to be due to the exposed hydroxyl group, for Tiemann (14) found that ethylvanillin can be oxidized smoothly into the corresponding vanillic acid. He did not record the yield of his product, but Perry (15) obtained a 90% yield of acid by oxidation of methylvanillin, and high yields from eleven of its substitution-products.

TABLE I

VANILLAL-4-CHLOROBENZALACETONE AND SUBSTITUTION-PRODUCTS

SUBSTITUENT IN VANILLAL RESIDUE	YIELD, %	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES, HALOGEN	
						Calc'd	Found
Vanillal (unsubs.)...	93	Alcohol (80%)	Yellow prisms	137–138	$C_{18}H_{15}ClO_3$	11.28	11.17
5-Bromo-.....	96	Acetic acid	Yellow needles	191–192	$C_{18}H_{14}BrClO_3$	29.35	29.51
6-Bromo-.....	74	Alcohol	Orange needles	179–180	$C_{18}H_{14}BrClO_3$	29.35	29.12
5-Nitro-.....	67	Alcohol	Orange plates	186–187	$C_{18}H_{14}ClNO_5$	9.87	9.84

EXPERIMENTAL

Preparation of ketones. Vanillalacetone and its substitution-products were prepared as directed by Glaser and Tramer (16) with the exception that a larger proportion of acetone was used. These products were carefully purified before being used in the next condensation. It might be supposed that the desired ketone containing the 4-chlorostyryl radical could be made with equal ease by condensation of the required vanillalacetone with 4-chlorobenzaldehyde or by the interaction of 4-chlorobenzalacetone with vanillin or the required substitution-product. As a matter of experiment, the first method only gave satisfactory results. When the second was attempted, tarry matter was formed and the product was difficult to purify. Similar results were found in closely related cases by Raiford and Cooper (17). Recrystallized vanillalacetone or its substitution-product was mixed with an alcoholic solution of 4-chlorobenzaldehyde, the liquid was made strongly alkaline with sodium hydroxide solution, and the mixture was allowed to stand in the ice chest for several hours. The sodium salt that separated was collected, dissolved in hot water, the ketone was freed by treatment with acetic acid, and was purified by crystallization from a suitable solvent. Analytical data for the new ketones are given in Table I.

TABLE II
PYRAZOLINES

SUBSTITUTED PHENYL GROUPS			YIELD, %	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES, HALOGEN	
Pos. 1	Pos. 3	Pos. 5						Calc'd	Found
4-Chloro-	Phenyl- (unsubs.)	4-Chloro-	55	Acetic acid	Yellow needles	135[a,b] 136	$C_{21}H_{16}Cl_2N_2$	19.34	19.01
4-Chloro-	4-Chloro-	Phenyl- (unsubs.)	78	Alcohol	Yellow needles	135[a,b] 135.5	$C_{21}H_{16}Cl_2N_2$	19.34	18.99
Phenyl- (unsubs.)	4-Chlorostyryl-	3-Methoxy-4-hydroxy-	67	Alcohol	Yellow needles	174[b]	$C_{24}H_{21}ClN_2O_2$	8.77	8.84
Phenyl- (unsubs.)	4-Chlorostyryl-	3-Methoxy-4-hydroxy-5-bromo-	65	Ethyl acetate	Yellow needles	170[b] 171	$C_{24}H_{20}BrClN_2O_2$	23.88	24.28
Phenyl- (unsubs.)	4-Chlorostyryl-	3-Methoxy[c]-4-hydroxy-6-bromo-	94	Alcohol	Pale yellow needles	161[b] 162	$C_{24}H_{20}BrClN_2O_2$	23.88	23.34
Phenyl- (unsubs.)	4-Chlorostyryl-	3-Methoxy[c]-4-hydroxy-5-nitro-	35	Ethyl acetate	Red needles	208–209	$C_{24}H_{20}ClN_3O_4$	7.89	7.72

[a] A mixture of these melted at 114–116°.

[b] Boiling acetic acid caused no change.

[c] The reactants were mixed at about 70° and the liquid was allowed to stand at room temperature.

TABLE III

1,5-Diphenylpyrazole-3-carboxylic Acids

Substituents in phenyl in position 5	Yield, %	Solvent	Crystal form	M.P., °C.	Formula	Analyses			
						Halogen		Nitrogen	
						Calc'd	Found	Calc'd	Found
3-Methoxy-4-hydroxy-	31	Carbon tetrachloride	Yellow powder	165[a]	$C_{17}H_{14}N_2O_4$			9.03	9.23
3-Methoxy-4-hydroxy-5-bromo-	22	Benzene	Pale yellow cubes	161–163[b]	$C_{17}H_{13}BrN_2O_4$	20.56	20.56		
3-Methoxy-4-hydroxy-6-bromo-	25	Alcohol	Yellow powder	175	$C_{17}H_{13}BrN_2O_4$	20.56	20.60		
3-Methoxy-4-hydroxy-5-nitro-	25	Dilute alcohol	Brown powder	90[c] (about)	$C_{17}H_{13}N_3O_6$			11.83	8.23[d]

[a] This product softened a few degress below this temperature. Prolonged heating at 100° caused partial decomposition.

[b] A mixture of this and the pyrazoline, m.p., 166–167°, from which it was obtained melted over a range of 150–155°.

[c] This was not a sharp melting point, but seemed to involve some decomposition.

[d] Though the pyrazoline from which this compound was obtained gave a good analysis for halogen and seemed pure, analyses of the acid for nitrogen were irregular.

Condensation of ketones with phenylhydrazine. One and one-half to two molecular proportions of the required freshly distilled phenylhydrazine was added to a glacial acetic acid solution of the ketone that was about saturated at room temperature, and the mixture was allowed to stand for several days. Usually the product separated spontaneously; when this did not occur it was necessary to cool the mixture or distill off a portion of the solvent under reduced pressure. Attempts to precipitate the products by dilution of the reaction-mixtures with water gave amorphous masses that could not be crystallized. Analytical data and other properties are shown in Table II.

Oxidation of pyrazolines. The calculated amount of finely powdered potassium permanganate was slowly added at room temperature to a pyridine solution of the pyrazoline while the mixture was stirred vigorously. The precipitated manganese dioxide was removed by filtration, suspended in water, the mixture was saturated with sulfur dioxide, and the insoluble material (A) reserved. The pyridine filtrate was distilled, the residue was mixed with (A), and the mixture distilled with steam until 4-chlorobenzoic acid could no longer be detected in the distillate. The distillate was made alkaline with sodium hydroxide, the liquid was evaporated to a small volume, acidified with dilute hydrochloric acid, and extracted with ether. 4-Chlorobenzoic acid was isolated from the extract and identified by mixed melting point determination with a known sample. The average yield was 32%. The non-volatile pyrazole acid remaining after steam distillation was removed by extraction with chloroform, the solution was dried, the solvent was distilled, and the residue was crystallized from a suitable liquid. These acids are listed in Table III.

SUMMARY

Several α,β-diunsaturated unsymmetrical ketones containing the 4-chlorobenzal and the vanillal or substituted vanillal radicals have been condensed with phenylhydrazine. In no case was the phenylhydrazone isolated, but the isomeric pyrazoline was obtained in each instance.

Oxidation of these pyrazolines with potassium permanganate gave, in each case, 4-chlorobenzoic acid and the required pyrazole-3-carboxylic acid, which shows that the direction of rearrangement was away from the chlorobenzal radical.

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