[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Ethylene Imine Ketones. VI.[1] Reactions with Phenylhydrazine[2]

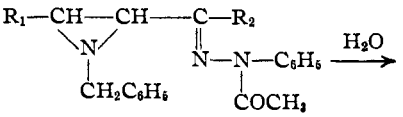
BY NORMAN H. CROMWELL AND HERMAN HOEKSEMA[3]

Continuing our comparative studies of the reactions of ethylene imine ketones with known reactions of epoxy ketones it was of interest to investigate the behavior of the former with phenylhydrazine. A similar study of the reaction of hydrazine with an epoxy ketone[4] has shown that the epoxide ring is opened to give an intermediate 4-hydroxypyrazoline which on heating loses water to yield the corresponding pyrazole.

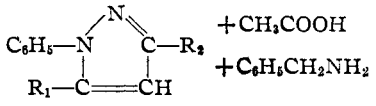
It was of considerable interest to compare the phenylhydrazine reactions of the *cis* and *trans* isomeric 1-benzyl-2-phenyl-3-*p*-toluylethylenimines, reported in a previous communication.[5]

With what may be presumed to be the *trans* forms in each case[1,5] 1-benzyl-2-phenyl-3-benzoylethylenimine,[6] 1-benzyl-2-*p*-tolyl-3-benzoylethylenimine,[7] and 1-benzyl-2-phenyl-3-*p*-toluylethylenimine,[5] each reacted with phenylhydrazine in glacial acetic acid to give the corresponding pyrazoles (I), (II) and (III) and the N-acetylphenylhydrazones of the ethylene imine ketones, (IV), (V) and (VI). The identities of the former were established by comparison with authentic samples synthesized by known methods.

The N-acetylphenylhydrazones (IV), (V) and (VI) have been assigned these structures because on hydrolysis they give the expected pyrazoles, and because they have absorption spectra, see Fig. 1, that are similar only to that of an N-acetylphenylhydrazone.[8]



(IV) R_1 and R_2 = C_6H_5
(V) R_1 = *p*-$CH_3C_6H_4$; R_2 = C_6H_5
(VI) R_1 = C_6H_5; R_2 = *p*-$CH_3C_6H_4$



(I) and (III)

Since it was possible that the general absorption spectra shown by these compounds (V) and (VI) were the result of pyrazole impurities in an acetylated pyrazoline of type (IX), study of the spectrum of a mixture of the pyrazole (III) and of the acetylated product (IX) was undertaken. As is indicated by Fig. 2, such an explanation of the general absorption shown by (VI) is unlikely.

Even with the mildest conditions the pyrazole resulted from the phenylhydrazine reactions with the *trans* form of 1-benzyl-2-phenyl-3-*p*-toluylethylenimine. The mechanism of its formation probably involves the intermediate formation of the phenylhydrazone (A) which then undergoes an intramolecular ring opening and closure to form the 4-benzylaminopyrazoline (B). The configuration of (B) may be such that the benzylamino group on carbon atom-4 and the hydrogen on carbon-5 are on the same side of the pyrazoline ring. Compound (B) might then lose benzylamine readily by an intramolecular reaction as indicated to form the pyrazole.

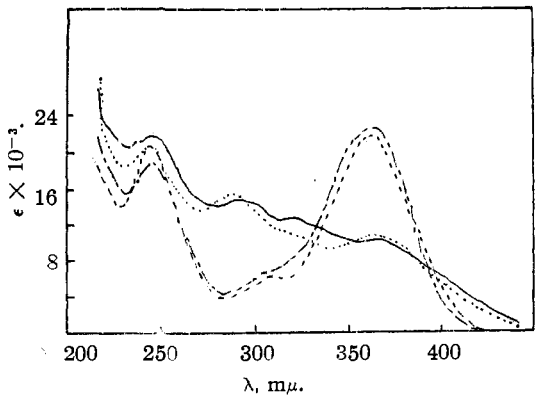


Fig. 1.—V, . . .; VI, —; VII, — —; IX, – – –.

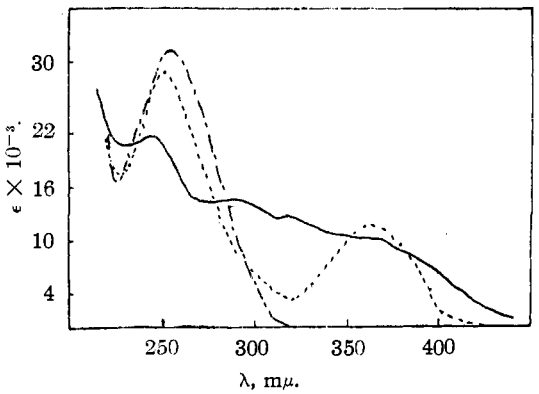


Fig. 2.—VI, —; III, — —; mixture of III and IX, – – –.

(1) For the previous paper in this series see Cromwell and Wankel, THIS JOURNAL, **71**, 711 (1949).

(2) Presented before a session of the Division of Organic Chemistry, 114th Meeting of the American Chemical Society, St. Louis, Mo., September 8, 1948.

(3) Abstracted from the thesis of Herman Hoeksema submitted to the Graduate College of the University of Nebraska in partial fulfillment of the requirements for the Ph.D. degree, June, 1948. American Chemical Society predoctoral research fellow, 1947–1948.

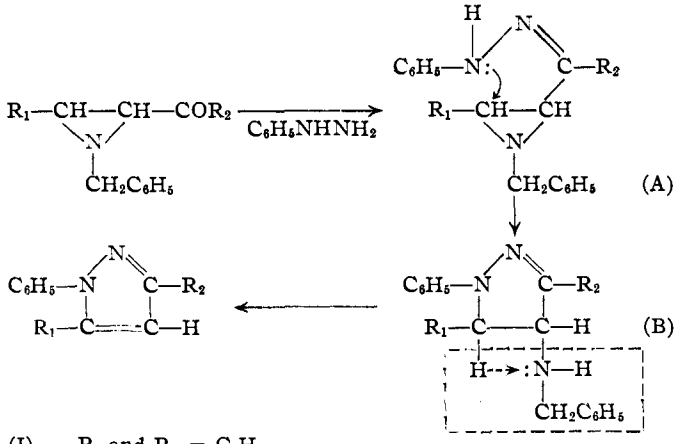
(4) Jorlander, *Ber.*, **49**, 2782 (1916).

(5) Cromwell and Hoeksema, THIS JOURNAL, **71**, 708 (1949).

(6) Cromwell, Babson and Harris, *ibid.*, **65**, 312 (1943).

(7) Cromwell, *ibid.*, **69**, 258 (1947).

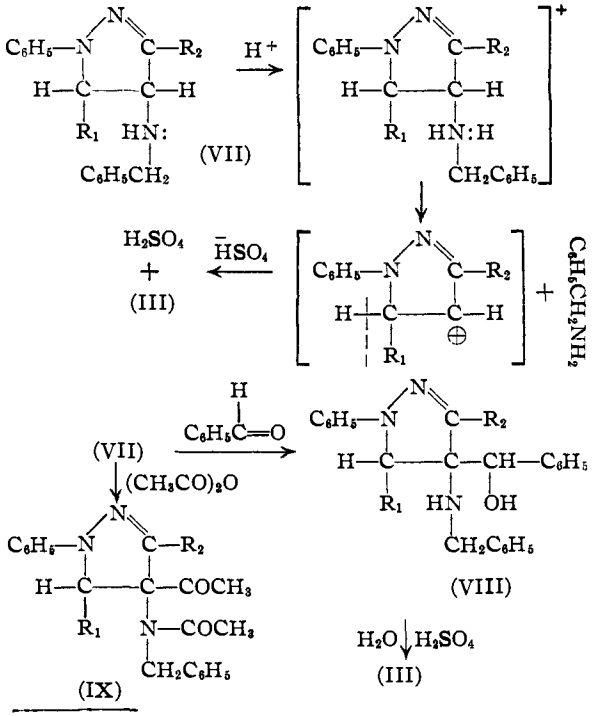
(8) Grammaticakis, *Bull. soc. chim.*, [5] **7**, 527 (1940).



(I) R_1 and R_2 = C_6H_5
(II) R_2 = C_6H_5, R_1 = p-$CH_3C_6H_4$
(III) R_1 = C_6H_5, R_2 = p-$CH_3C_6H_4$

The *cis* form (low melting) of 1-benzyl-2-phenyl-3-*p*-toluylethylenimine[5] gave excellent yields of 1,5-diphenyl-3-*p*-tolyl-4-benzylaminopyrazoline (VII). Even in warm glacial acetic acid this *cis* isomer gave only (VII). The structure assigned to (VII) is consistent with the fact that it gives the standard tests for pyrazolines, that it shows the same blue fluorescence as the known parent 1,5-diphenyl-3-*p*-tolylpyrazoline,[9] and that it cannot be hydrogenated to yield aniline as would be expected with a phenylhydrazone. Moreover, in strong acid solution (VII) loses benzylamine to give the corresponding pyrazole (III).

The aminopyrazoline (VII) condensed with benzaldehyde to give a product whose properties indicate it probably has structure (VIII), and with acetic anhydride to give the diacetylated product which has been assigned the structure (IX). These are expected reactions, for the pyrazolines have active hydrogen in the 4-position.[10] Compound (VIII) was converted to pyrazole (III) on heating with dilute sulfuric acid. The properties of compounds of types (VIII) and (IX) are being studied further in an extended investigation. Studies of the absorption spectra of the diacetylated aminopyrazoline (IX) and of the benzaldehyde condensation product (VIII) indicated them to be similar to those of both the parent 1,5-diphenyl-3-*p*-tolylpyrazoline and the 4-benzylamino-1,5-diphenyl-3-*p*-tolylpyrazoline (VII) (see Figs. 1 and 3). It is to be observed that pyrazolines and phenylhydrazones have similar but not identical spectra, see Fig. 3.



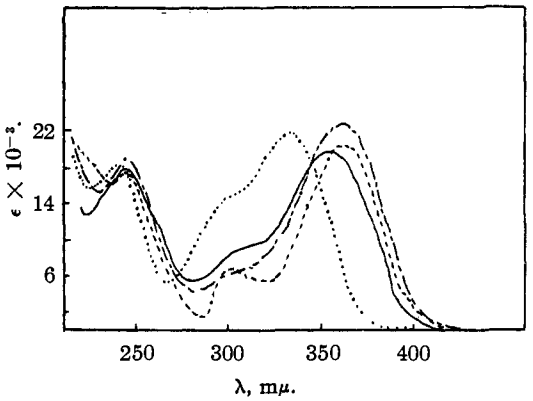


Fig. 3.—1,5-Diphenyl-3-*p*-tolylpyrazoline,—; VII, — –; VIII, – – –; X, ...

The formation of the aminopyrazoline (VII) from the *cis* isomer may be explained by the same mechanism as given above for the formation of (A) and (B) from the *trans* ethylene imine ketone. In the former case, however, the benzylamino group on carbon-4 and the hydrogen on carbon-5 might now be expected to turn up on opposite sides of the pyrazoline ring and intramolecular loss of benzylamine becomes less probable. Thus in neutral or basic media (VIII) is quite stable, but in acid solution, where solvolytic protons are available, (VII) can lose benzylamine to give the pyrazole by the mechanism shown later.

These considerations may suggest why 4-amino derivatives of 1,3,5-triarylpyrazolines have heretofore been unknown.

Acknowledgment.—The senior author appreciates a grant from the Research Council of the University of Nebraska which aided in the completion of this investigation.

(9) Raiford and Peterson, *J. Org. Chem.*, 1,544 (1937).

(10) Curtius and Wirsing, *J. prakt. Chem.*, [2] 50, 531 (1894).

TABLE I

PHYSICAL AND ANALYTICAL PROPERTIES

Pyrazoles	No.	M. p., °C.	Yield, %	Formula	Percentage composition Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1,3,5-Triphenyl-	(I)	135	37	$C_{21}H_{16}N_2$	85.10	5.44	9.46	85.32	5.57	9.51
1,3-Diphenyl-5-*p*-tolyl-	(II)	119	46	$C_{22}H_{18}N_2$	85.14	5.84	9.03	85.18	5.70	9.22
1,5-Diphenyl-3-*p*-tolyl-	(III)	130	32	$C_{22}H_{18}N_2$	85.14	5.84	9.03	85.40	5.75	9.02
Acetylphenylhydrazones of										
1-Benzyl-2-phenyl-3-benzoylethylenimine	(IV)	135–140	33	$C_{30}H_{27}N_3O$	80.86	6.33	9.43	80.95	6.24	9.42
1-Benzyl-2-*p*-tolyl-3-benzoylethylenimine	(V)	148	30	$C_{31}H_{29}N_3O$	...	..	9.14	...	..	9.04
1-Benzyl-2-phenyl-3-*p*-toluylethylenimine	(VI)	149	30	$C_{31}H_{29}N_3O$	81.01	6.36	9.14	81.41	6.41	9.10
1,5-Diphenyl-3-*p*-tolylpyrazoline										
4-Benzylamino-	(VII)	124	75	$C_{29}H_{27}N_3$	83.41	6.52	10.07	83.60	6.60	10.14
4-Benzylamino-4-(phenylhydroxymethyl)-	(VIII)	165–170	67	$C_{36}H_{33}N_3O$	82.57	6.35	8.03	82.62	6.67	7.78
4-Acetobenzylamino-4-aceto-	(IX)	91–96	75	$C_{33}H_{31}N_3O_2$	79.01	6.23	8.38	78.87	6.55	8.26

Experimental

Reaction of Ethylene Imine Ketones (*trans* Isomers) with Phenylhydrazine in: (a) Glacial Acetic Acid.—The ethylene imine ketone (2.1 g., 0.006 mole) was dissolved in 10 ml. of glacial acetic acid. One gram (0.009 mole) of phenylhydrazine was added and the solution warmed to 50° for a few minutes and then cooled to room temperature. After standing at room temperature for twenty-four hours the solution was cooled to 0° and the precipitated product removed by filtration and purified by recrystallization from benzene–alcohol mixtures to give the colorless pyrazole. The acetic acid filtrate was treated with an equal volume of water to give a yellow gummy precipitate which was recrystallized several times from benzene–absolute alcohol and benzene–petroleum ether mixtures to give the yellow N-acetylphenylhydrazones of the ethylene imine ketones.

In this way the pyrazole (I) and N-acetylphenylhydrazone (IV) were obtained from 1-benzyl-2-phenyl-3-benzoylethylenimine[6]; pyrazole (II) and N-acetylphenylhydrazone (V) from 1-benzyl-2-*p*-tolyl-3-benzoylethylenimine[7]; and pyrazole (III) and N-acetylphenylhydrazone (VI) from 1-benzyl-2-phenyl-3-*p*-toluylethylenimine (high m.p.)[5] (see Table I). A mixture of (V) and (VI) melted at 125–135°.

(b) Pyridine Solution.—A 35% yield of the pyrazole (III) resulted when the corresponding ethylene imine ketone (high melting) was mixed with one equivalent of glacial acetic acid and 2.5 equivalents of phenylhydrazine in pyridine solution at room temperature. No other products were isolated from this experiment.

(c) Alcohol Solution.—To a solution of 3.0 g. (0.009 mole) of 1-benzyl-2-phenyl-3-*p*-toluylethylenimine (high m.p.) in 150 ml. of ethyl alcohol was added 1.0 g. (0.009 mole) of phenylhydrazine and 1.0 g. (0.017 mole) of glacial acetic acid. The solution stood at room temperature for four hours and in the ice chest for three days. The precipitated product was removed by filtration and recrystallized from alcohol, 1.1 g. (38% yield), m.p. 129.5°, mixed with (III), m.p. 129–130°. From the residual reaction mixture was recovered 0.1 g. of the unchanged starting ethylene imine ketone.

Synthesis of Pyrazoles (I), (II) and (III).—The pyrazoles (II) and (III) were prepared for the first time from the corresponding benzalacetophenone dibromides by the method outlined by Barnes[11] in 20–35% yields. These products melted the same as (II) and (III), respectively, and mixtures showed no depression of melting point. A mixture of (II) with (III), however, melted at 98–105°.

(11) Barnes and Dodson, THIS JOURNAL, **65**, 1585 (1943).

The pyrazole (I), a known compound, was prepared according to the method of Wislicenus[12] in 50% yields and was identical with (I).

Hydrolysis of the N-Acetylphenylhydrazones (IV) and (VI).—One-gram samples of compounds (IV) and (VI), respectively, were mixed with 5 ml. of hot alcohol. These suspensions were poured into 25 ml. of boiling 20% sulfuric acid and the resulting mixtures refluxed for ten hours. The solutions were cooled and the colorless products filtered and recrystallized from alcohol. In this way 90–100% yields of the pyrazole (I) resulted from (IV), and the pyrazole (III) from (VI).

Reaction of 1-Benzyl-2-phenyl-3-*p*-toluylethylenimine (*cis* Form) with Phenylhydrazine: (a) In Alcohol Solution.—Nine grams (0.027 mole) of the low m.p. ethylene imine ketone was dissolved in 150 ml. of ethyl alcohol. To this solution were added 3.0 g. (0.027 mole) of phenylhydrazine and 3.0 g. (0.05 mole) of glacial acetic acid. As the solution stood at room temperature slow crystal growth was observed. After four hours the mixture was cooled to yield a pale-yellow product which was recrystallized twice from absolute alcohol to give colorless crystals of (VII). All solutions of this product displayed a blue fluorescence. It also gave the Knorr[13] and the Raiford[9] tests for pyrazolines. On refluxing a benzene solution of (VII) for three hours no change took place.

(b) In Glacial Acetic Acid.—A 2.1-g. (0.006 mole) sample of the ethylene imine ketone (m.p. 72–74°) was dissolved in 10 ml. of glacial acetic acid and 1.0 g. (0.009 mole) of phenylhydrazine added. The solution was heated to 50° for a few minutes, allowed to stand at room temperature for three hours and finally cooled in the ice chest for several days. No precipitation took place. On adding water to the reaction mixture a gummy product was obtained which, after recrystallization from alcohol, gave a 48% yield of a product identical in all respects with the aminopyrazoline (VII).

Attempted Hydrogenations of the Aminopyrazoline (VII).—The aminopyrazoline (VII) resisted hydrogenation and was recovered unchanged from reaction mixtures employing palladium on charcoal and hydrogen at 50 lb./sq. in. at 100°, or platinum oxide under similar conditions. Boiling sodium and alcohol solutions likewise did not change this product.

Hydrolysis of the Aminopyrazoline (VII).—A 3.0-g. sample of (VII) was warmed on a steam-bath for three and one-half hours with 50 ml. of 20% sulfuric acid. From the cooled solution was isolated 2.1 g. of a pyrazole identical with (III).

(12) Wislicenus, *et al.*, *Ann.*, **308**, 253 (1899).

(13) Knorr, *Ann.*, **238**, 200 (1887).

Reaction of Benzaldehyde with the Aminopyrazoline (VII).—Two grams (0.0048 mole) of (VII) was mixed with 3.1 g. (0.29 mole) of benzaldehyde, 5 ml. of ethyl alcohol and 1 ml. of glacial acetic acid and heated under reflux for eight hours. Cooling the reaction mixture gave a product which, after recrystallization from absolute alcohol and then a benzene–absolute alcohol mixture, was a pale-yellow crystalline material (VIII). Calcd. for $C_{36}H_{32}N_3O$: mol. wt., 523.6. Found: mol. wt., 510. When a sample of (VIII) was heated for five hours with 20% sulfuric acid, pyrazole (III) resulted in a 60% yield.

TABLE II

ABSORPTION SPECTRA OF PHENYLHYDRAZINE DERIVATIVES IN 95% ALCOHOL

Derivative	Fig. no.	Molar concn. × 10^5	Maxima λ(mμ)	Maxima ε×10^{-3}	Minima λ(mμ)	Minima ε×10^{-3}
(V)	1	14.3	360	10.7	335	9.09
			288	15.4	272	13.4
			244	20.3	231	18.2
(VI)	1, 2	9.06	365	10.5	359	10.3
			324	12.8	313	12.5
			287	14.8	275	14.3
			245	21.8	230	20.5
(VII)	1, 3	4.77	361	22.9	282	4.27
			245	18.9	230	15.1
(IX)	1	4.95	365	22.4	317	5.50
			312	6.28	284	3.87
			245	20.4	228	14.0
(III)	2	6.19	255	31.4	227	16.9
Mixture of [a] (III) + (IX)	2	4.65	365	11.5	320	3.08
			253	28.8	227	17.5
(VIII)	3	5.03	365	20.2	320	5.80
			308	6.32	284	3.50
			245	17.7	235	16.3
1,5-Diphenyl-[b] 3-*p*-tolyl-pyrazoline	3	2.40	355	19.9	278	5.08
			242	17.9	223	12.7
(X)	3	5.93	333	21.9	267	5.32
			240	18.3	223	15.1

[a] A 1.93-mg. sample of (III) and 2.72 mg. of (IX) were dissolved in 200 ml. of 95% alcohol. The molar concn. of this solution was calculated assuming a molecular weight of 501.6 (value for (IX)). [b] Prepared according to the directions of Raiford and Peterson, ref. 9.

Acetylation of Aminopyrazoline (VII).—A 1.0-g. sample of (VII) was refluxed for two hours with 15 ml. of acetic anhydride. Most of the acetic anhydride was distilled under vacuum and the residue treated with sodium bicarbonate solution. The solid residue was recrystallized from benzene and petroleum ether and finally from 90% alcohol. The pale-yellow product was dried under vacuum at 80° for three hours to give (IX).

Benzyl-*p*-methylacetophenone Phenylhydrazone (X).—This phenylhydrazone (X) was prepared from benzyl-*p*-methylacetophenone in the usual way in 90% yields and recrystallized from ethyl alcohol, m.p. 77–79°. This compound decomposed to a tar after exposure to light and air for a few days.

Anal. Calcd. for $C_{22}H_{22}N_2$: N, 8.91. Found: N, 9.10, 8.94.

Absorption Spectra Measurements.—These measurements were made using a Beckman Model DU Photoelectric Quartz Spectrophotometer. At the sensitivity used, the maximum band width was one millimicron, with a rated accuracy of 0.1%. Pure 95% alcohol was used as a solvent medium since most of these compounds were not sufficiently soluble in a non-polar solvent such as heptane (see Figs. 1, 2 and 3, and Table II).

Summary

1. *trans* Ethylene imine ketones react with phenylhydrazine to give the corresponding pyrazoles and N-acetylphenylhydrazones of the ethylene imine ketones.

2. *cis* Ethylene imine ketones give the intermediate 4-aminopyrazolines which are stable in neutral or basic solutions but lose benzylamine to give the pyrazole when a solvolytic proton becomes available in acid solutions.

3. The absorption spectra of these compounds have been compared to aid in the elucidation of their structures. The pyrazolines have similar but not identical spectra with those of related phenylhydrazones.

LINCOLN, NEBRASKA RECEIVED AUGUST 2, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, SOUTHWESTERN MEDICAL COLLEGE]

16-Substituted Steroids. VI. The Steric Structure of Steroidal 16,17-Ketols and 16,17-Glycols[1]

BY MAX N. HUFFMAN AND MARY HARRIET LOTT

Stodola, Kendall and McKenzie[2,3] have shown that the zinc–acetic acid reduction of 16-oximino-17-ketosteroids followed by acetylation results in the formation of 16-keto-17-acetoxysteroids. The Stodola reduction of 16-oximinodehydroisoandrosterone, for instance, was found to give, after acetylation with acetic anhydride in pyridine, an androstenediolone diacetate in which the ketone group clearly occupied the C_{16} position. We have confirmed this finding of Stodola and co-workers and furthermore shown that the acetoxyl at C_{17} has the α spatial configuration. If the 3(β),17-diacetoxy-16-keto-Δ^5-androstene (I) of Stodola is treated with ethyl mercaptan in the presence of fused zinc chloride and anhydrous sodium sulfate[4] a crystalline diethyl thioacetal (II) is readily obtained in good yield. This thioacetal loses its mercaptyl residues on hydrogenolysis with modified Raney nickel, and there is obtained the known 3(β),17(α)-diacetoxy-Δ^5-androstene (III). Since in these reactions there can be no question of

(1) The announcement of the findings described in this publication was presented as a Communication by Huffman and Lott, THIS JOURNAL, 69, 1835 (1947).

(2) Stodola, Kendall and McKenzie, *J. Org. Chem.*, 6, 841 (1941).

(3) Stodola and Kendall, *ibid.*, 7, 336 (1942).

(4) Bernstein and Dorfman, THIS JOURNAL, 68, 1152 (1946).