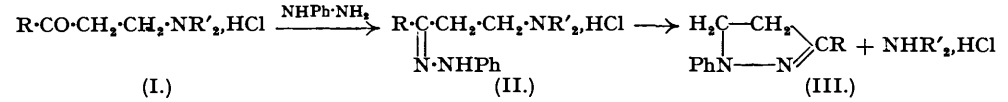
33. *Pyrazoline Ring Formation. Part I. The Action of Phenylhydrazine on Some Saturated and Unsaturated β-Amino-ketones.*

By Hugh B. Nisbet.

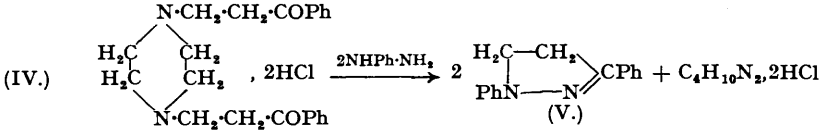
Phenylhydrazine, acting on *β-sec.*-aminoethyl ketones in the form of their hydrochlorides, gives first the phenylhydrazone, which by extrusion of a *sec.*-base residue yields a pyrazoline derivative. Examination of the possible reaction mechanisms suggests the intermediate formation of a vinyl derivative which undergoes prototropic rearrangement to the pyrazoline.

The phenylhydrazones of α-unsaturated *β-sec.*-aminoethyl ketone hydrochlorides on treatment with acid yield in the main 3-*β-sec.*-aminoethylpyrazolines. In addition, however, by extrusion of a *sec.*-base residue certain styryl and substituted styryl ketone phenylhydrazones of this type have been shown to yield minute quantities of 1 : 5-diphenyl-3-vinylpyrazoline derivatives. The formation of the phenylhydrazones of styryl vinyl ketones as intermediates is postulated.

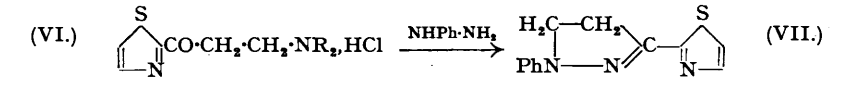
Many β-amino-ketone hydrochlorides of type (I), when acted upon by phenylhydrazine, give the pyrazoline (III) instead of the expected phenylhydrazone (II). For example, Jacob and Madinaveitia (J., 1937, 1929) showed that, warmed with phenylhydrazine in a solution of sodium acetate in 50% acetic acid, the hydrochlorides of β-dimethylaminopropiophenone (I; R = Ph, R′ = Me) and methyl β-dimethylaminoethyl ketone



(I; R and R′ = Me) gave 1 : 3-diphenyl- and 1-phenyl-3-methyl-pyrazoline respectively. Although the intermediate phenylhydrazones were not prepared by these workers, that such compounds are formed has now been proved by the isolation of the *phenylhydrazones* of β-dimethylaminopropiophenone hydrochloride and of β-piperidylpropiophenone hydrochloride (II; R = Ph, R′ = NC_5H_{10}) by the method of Auwers and Voss (*Ber.*, 1909, **42**, 4411) and it has been shown that both are converted into 1 : 3-diphenylpyrazoline by warming with a solution of sodium acetate in 50% acetic acid. Moreover, 1 : 4-bis-β-benzoylethylpiperazine dihydrochloride (IV) with phenylhydrazine under the same conditions gives a mixture from which 1 : 3-diphenylpyrazoline (V) can be isolated.

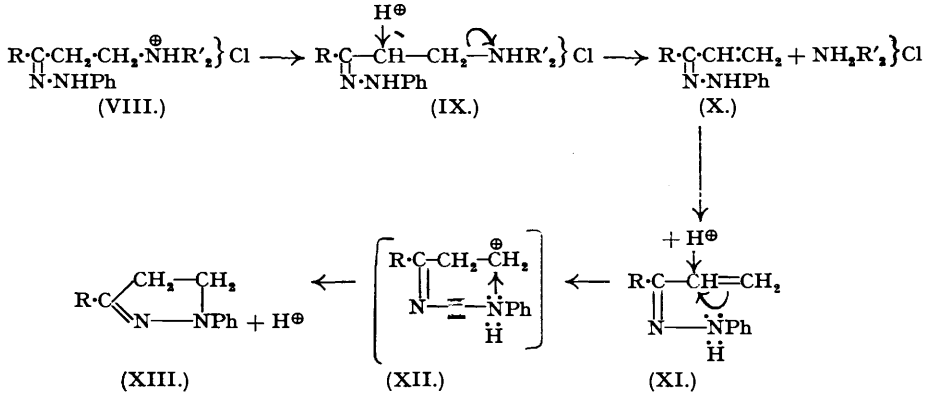


Levvy and Nisbet (J., 1938, 1053) record the formation of 1-phenyl-3-thiazylpyrazoline (VII) in attempts to prepare the phenylhydrazones of similar β-aminoketone hydrochlorides (VI) derived from 2-acetyl-4-phenylthiazole by the Mannich reaction :

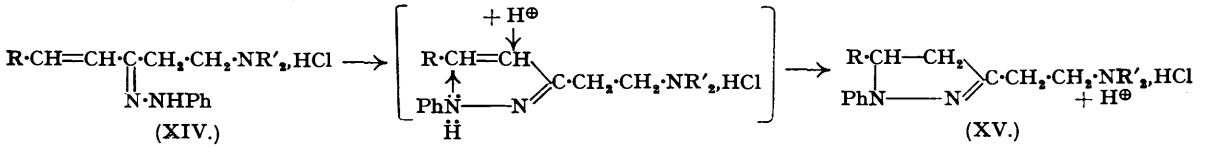


and Harradence and Lions (*J. Proc. Roy. Soc. N.S. Wales*, 1939, **72**, 233) observed the formation of pyrazolines from phenylhydrazine and several aryl β-morpholinoethyl ketones and β-morpholinoethyl 2-thienyl ketone.

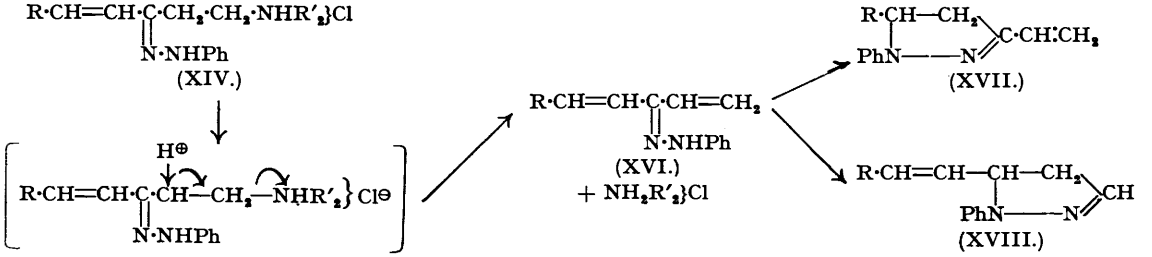
All the pyrazolines, so formed, are obtained by the extrusion of a secondary base residue, followed by ring closure. Among the mechanisms which can be suggested for this reaction the most probable is one which postulates initiation of the change by propagation of the instability originating in the ammonium group (VIII) to a hydrogen atom attached to the β-carbon atom (IX). This hydrogen extruded as a proton would initiate a series of changes which result in the production of an unsaturated linkage in the αβ-position (X). An intramolecular protropic change initiated by semi-polar activation of the double bond (XI) and completed by electron donation from the nitrogen atom and extrusion of a proton (XII and XIII) would bring about the pyrazoline ring formation thus :



The isomerisation in acid solution of the phenylhydrazones of αβ-unsaturated β′-dialkylaminoethyl ketone hydrochlorides of type (XIV) has been used extensively in the formation of 3-β-substituted aminoethylpyrazolines (XV) (Nisbet, J., 1938, 1237, 1568, 1572), the salts of which have been shown to have considerable efficacy as surface local anæsthetics (Sinha, *J. Pharm. Exp. Ther.*, 1936, **57**, 199; 1939, **66**, 54; Levvy and Nisbet, *ibid.*, 1939, **65**, 129).



Examination of the formula for these phenylhydrazones (XIV), however, indicates the possibility that pyrazoline formation may be achieved by another route, for if the styryl group is regarded as the group R in compounds of type (I), formation of the pyrazoline of type (III) by extrusion of the secondary base residue cannot be excluded. If the mechanism postulated for the extrusion of this residue be accepted, the intermediate (XVI), which is the phenylhydrazone of a styryl vinyl ketone, will be formed. This, by intramolecular prototropic change, would give rise to either or both the isomeric pyrazolines (XVII) and (XVIII).



Nothing appears to be known regarding the rearrangement of phenylhydrazones of styryl vinyl ketones, but Raiford and his collaborators (*J. Amer. Chem. Soc.*, 1933, **55**, 1125; 1934, **56**, 174) have shown that, in the phenylhydrazones of unsymmetrically substituted dibenzylideneacetones, where one of the benzene nuclei

carries an electron-attracting group, such as nitro, ring closure involves the unsaturation further away from that nucleus. Conversely, also, they show that where a nucleus carries an electron-donating group, such as *p*-methoxy, the unsaturation nearer this nucleus is involved in ring closure. If the same conditions apply to the rearrangement of the phenylhydrazones of styryl vinyl ketones, the resulting pyrazoline formed by the extrusion of the secondary base residue from compounds of type (XIV) in the cases studied is more likely to be the vinylpyrazoline (XVII) than the isomeric styryl compound (XVIII), for the presence of an electron-donating group such as phenyl, *p*-methoxyphenyl or methylenedioxyphenyl, as a constituent of the styryl radical is more likely to have the styryl unsaturation activated for intramolecular prototropic change than the vinyl group.

Although it has not been possible to investigate the whole range of reactions utilised in the earlier work on the formation of 3-β-dialkylaminoethylpyrazoline salts, certain selected cases have been examined and sufficient evidence accumulated to show that extrusion of a secondary base residue, followed by ring closure, does occur to a minute extent in many cases simultaneously with the normal isomerisation of phenylhydrazones of type (XIV).

For the reasons stated above, the new compounds are tentatively assigned the constitution of 3-vinylpyrazolines. Their exact constitution is amenable to determination by oxidation and reduction processes combined with alternative synthesis, and it is hoped to report on these at a later date when conditions are favourable for continuance of this work. Meantime, it has been found that isomerisation of the phenylhydrazones of 1-piperidino-5-(3′ : 4′-methylenedioxyphenyl)-Δ^4-penten-3-one hydrochloride and of the corresponding 5-*p*-anisyl derivative give predominating yields of 1-phenyl-5-(3′ : 4′-methylenedioxyphenyl)-3-β-piperidinoethylpyrazoline hydrochloride and the 5-*p*-anisyl derivative, but that minute traces are formed of compounds at present assigned the constitutions of 5-(3′ : 4′-*methylenedioxyphenyl*)- and 5-p-*anisyl*-1-*phenyl*-3-*vinylpyrazoline* respectively.

Phenylhydrazine, acting on 1-(*di*-β-*hydroxyethyl*)*amino*-5-*phenyl*-Δ^4-*penten*-3-*one hydrochloride* and on *dicinnamylethylpiperazine hydrochloride*, gives mixtures from which by isomerisation with dilute acetic acid the same compound 1 : 5-*diphenyl*-3-*vinylpyrazoline* is obtained in minute quantities by extrusion of the secondary base residues. This compound has not been isolated, as one might expect it should be, in the isomerisation of the phenylhydrazone of 1-piperidino-5-phenyl-Δ^4-penten-3-one hydrochloride.

Experimental.

1-*Di*-(β-*hydroxyethyl*)*amino*-5-*phenyl*-Δ^4-*penten*-3-*one Hydrochloride*.—Diethanolamine (10·5 g.) was dissolved in ethyl alcohol (20 ml.) and concentrated hydrochloric acid (8·9 ml.), benzylideneacetone (14·6 g.) added, the mixture heated to boiling, paraformaldehyde added in two portions (3 g. and 1·5 g.), and refluxing continued after each addition until the mixture was homogeneous. After about 10 mins., the reaction mixture was filtered hot and kept in a vacuum for 3 weeks. On scratching, a solid was obtained which, dissolved in alcohol and precipitated with ether, gave the *hydrochloride*. Crystallised from a very small quantity of alcohol, this formed slightly yellowish crystals (13 g.), m. p. 105° (Found : N, 4·45, 4·5. $C_{15}H_{21}O_3N$,HCl requires N, 4·7%).

1-*Di*-(β-*hydroxyethyl*)*amino*-5-(4′-*methoxyphenyl*)-Δ^4-*penten*-3-*one hydrochloride*, similarly prepared from diethanolamine hydrochloride, anisylideneacetone, and paraformaldehyde, formed squat, slightly yellow crystals, m. p. 84°, from *iso*propyl alcohol (Found : C, 58·3; H, 7·7. $C_{16}H_{23}O_4N$,HCl requires C, 58·3; H, 7·3%).

Di(*cinnamylethyl*)*piperazine Hydrochloride*.—Piperazine (4·3 g.) was dissolved in ethyl alcohol (20 ml.) and concentrated hydrochloric acid (8·9 ml.), and benzylideneacetone (14·6 g.) and paraformaldehyde (4·5 g. in 1·5 g. lots) added to the refluxing mixture. After 1½ hrs.' heating, the crystals that had separated were collected and washed with ethyl alcohol. They were soluble in hydrochloric acid (2N), slightly soluble in methyl alcohol containing some concentrated hydrochloric acid, and readily soluble in acetic acid, glacial or slightly diluted. Crystallised from aqueous acetic acid (1 : 1), the *compound* formed white needles which decomposed above 200° (Found : N, 5·8. $C_{26}H_{30}O_2N_2$,2HCl requires N, 5·9%).

The following new phenylhydrazones have been prepared by the method of Auwers and Voss (*loc. cit.*) : *Phenylhydrazone of β-dimethylaminopropiophenone hydrochloride*, yellow needles from ethyl alcohol, m. p. 172° (Found : C, 67·2; H, 7·25; N, 13·45. $C_{17}H_{21}N_3$,HCl requires C, 67·2; H, 7·25; N, 13·8%). *Phenylhydrazone of β-piperidylpropiophenone hydrochloride*, yellow plates from ethyl alcohol, m. p. 162° (Found : C, 69·5; H, 7·3; N, 12·1. $C_{20}H_{25}N_3$,HCl requires C, 69·9; H, 7·6; N, 12·2%). The *base*, precipitated by dilute alkali, crystallised from aqueous alcohol in pale yellow needles, m. p. 84° (Found : N, 13·7. $C_{20}H_{25}N_3$ requires N, 13·7%).

Preparation of 1 : 3-*Diphenylpyrazoline*.—By heating the phenylhydrazones of β-dimethylamino- and β-piperidylpropiophenone (in 1 g. quantities) with 50% acetic acid (10 ml.) and sodium acetate (1 g.) on a water-bath for 2 hrs., solids separated which, crystallised from ethyl alcohol, proved to be in each case 1 : 3-diphenylpyrazoline, m. p. and mixed m. p. with an authentic specimen 151°. The same compound was also obtained on heating dibenzoylethylpiperazine hydrochloride (2·1 g.) in 50% acetic acid (20 ml.) with sodium acetate (2 g.) and phenylhydrazine (2·2 g.) on a water-bath for 1½ hrs. The oily solid which separated solidified on cooling. Collected and washed with ethyl alcohol, this solid was boiled with 95% alcohol (150 ml.); most of it then dissolved, leaving a minute quantity of an unidentified white *compound*, m. p. 195° (Found : C, 76·8; H, 7·0%). The alcoholic solution, poured into water, gave 1 : 3-diphenylpyrazoline (mixed m. p. 151°).

Isomerisation of the Phenylhydrazones of α-Unsaturated β′-Piperidinoethyl Ketone Hydrochlorides and Isolation of some 3-*Vinylpyrazolines*.—The phenylhydrazones were refluxed with aqueous acetic acid (1 acid : 5 water) or hydrochloric acid (2N) until the normal isomerisation was complete, which generally occurred in a few minutes. In the cases indicated below, the reaction mixture on filtration left minute quantities of yellow solids, at present assigned the constitution of 3-vinylpyrazolines. The filtrates in most cases examined yielded the normal isomerisation products.

1-*Phenyl*-5-(3′ : 4′-*methylenedioxyphenyl*)-3-*vinylpyrazoline*. The phenylhydrazone of 1-piperidino-5-(3′ : 4′-methylenedioxyphenyl)-Δ^4-penten-3-one hydrochloride (4·4 g.), treated as described with aqueous acetic acid (15 ml.), gave a residue which crystallised from methyl alcohol in yellow plates (0·07 g.), m. p. 155° (Found : C, 73·7; H, 5·6. $C_{18}H_{16}O_2N_2$ requires C, 73·9; H, 5·5%). The filtrate contained 1-phenyl-3-(β-piperidylethyl)-5-(3′ : 4′-methylenedioxyphenyl)-pyrazoline hydrochloride.

1-*Phenyl*-5-(4′-*methoxyphenyl*)-3-*vinylpyrazoline*, similarly obtained from the phenylhydrazone of 1-piperidino-5-(4′-methoxyphenyl)-Δ^4-penten-3-one hydrochloride (12 g.), crystallised from 95% alcohol in yellow microcrystalline plates (0·01 g.), m. p. 180° (Found : C, 77·1; H, 6·8; N, 10·7. $C_{18}H_{18}ON_2$ requires C, 77·7; H, 6·4; N, 10·1%). The filtrate yielded the normal isomerisation product, 1-phenyl-3-(β-piperidylethyl)-5-(4′-methoxyphenyl)pyrazoline hydrochloride.

1 : 5-*Diphenyl*-3-*vinylpyrazoline*. This could not be isolated in the treatment of 1-piperidino-5-phenyl-Δ^4-penten-3-one hydrochloride with dilute acid. The crude phenylhydrazone obtained from 1-di-(β-hydroxyethyl)amino-5-phenyl-Δ^4-penten-3-one hydrochloride (36 g.), when heated with 2N-hydrochloric acid (150 ml.), gave a residue of the *vinylpyrazoline*. Crystallised from 95% alcohol, this formed bright yellow plates (1·7 g.), m. p. 138° (Found : C, 81·7; H, 6·2; N, 11·8. $C_{17}H_{16}N_2$ requires C, 82·2; H, 6·5; N, 11·3%).

The crude phenylhydrazone of dicinnamylethylpiperazine hydrochloride (4 g.), boiled under reflux with glacial acetic acid for 2 mins., gave a bright yellow solid which crystallised from 95% alcohol in plates (0·47 g.), m. p. 138°. This was proved by mixed m. p. to be identical with the compound described above (Found : C, 81·9; H, 6·4; N, 11·8%).

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