New Synthetic Routes to Δ^2-Pyrazolin-5-ones[1]

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Three new synthetic routes to Δ^2-pyrazolin-5-ones involving base-catalyzed molecular rearrangements are reported.

Trois nouvelles méthodes de synthèse des Δ^2-pyrazolidones-5 sont rapportées; elles impliquent toutes des réarrangements catalysés par les bases. [Traduit par le journal]

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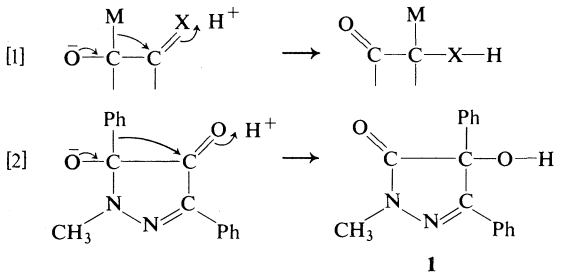
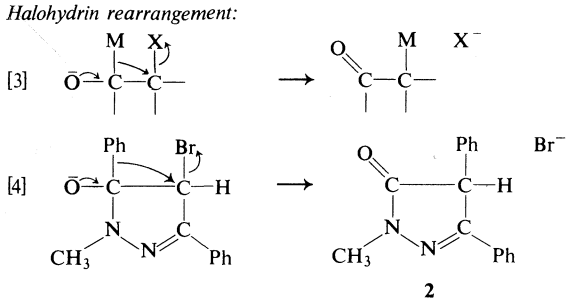
Introduction

Two related base-catalyzed rearrangement reactions are the acyloin and halohydrin rearrangements (eqs. 1 and 3). Both involve push–pull mechanisms, where an oxide ion is the electron source and an electronegative atom (X) is the electron sink. In the acyloin case, X is doubly bonded, whereas in the halohydrin case it is singly bonded. Although these reactions embody an easy way of placing a migrating group on the α carbon atom of a carbonyl functional group, they have been applied only sparingly to organic synthesis. This paper shows how appropriate substitution of the archetypes leads to two new convenient syntheses of Δ^2-pyrazolin-5-ones, exemplified by eqs. 2 and 4.

Acyloin rearrangement:



Halohydrin rearrangement:



Results and Discussion

Acyloin Rearrangement:

Treatment of 5-hydroxy-3,5-diphenyl-Δ^2-pyrazolin-4-one (**3***a*) or its methyl derivative **3***b* with methanolic potassium hydroxide gave respectively 4-hydroxy-3,4-diphenyl-Δ^2-pyrazolin-5-one (**4***a*) or **4***b* in 76–80% yields. The simplest possible mechanism of this reaction involves first the removal of the OH proton from **3** followed by an acyloin rearrangement of the anion (eq. 2). It is of interest that the Δ^2-pyrazolin-5-one appears to be thermodynamically more stable than the Δ^2-pyrazolin-4-one, which can be crudely rationalized as arising from the high inherent stability of amide-like structures (3).

Chemical evidence for the structures **4***a* and *b* was provided by the alternative synthesis of **4***b* by the oxidation of 1-methyl-3,4-diphenyl-Δ^2-pyrazolin-5-one (**2**) using hydrogen peroxide. This route has been shown by Veibel (4) to be a general method for hydroxylation of the 4-position of Δ^2-pyrazolin-5-ones.[3]

The structural assignments are also supported by the similarity of the i.r. and u.v. spectra between **4***a*, **4***b*, and the model compound **5** (5) (Table 1).

4-Hydroxy-3,4-diphenyl-Δ^2-pyrazolin-5-one (**4***a*) could alternatively be obtained by boiling 4-hydroxy-3,5-diphenylpyrazole (**6**) in methanolic

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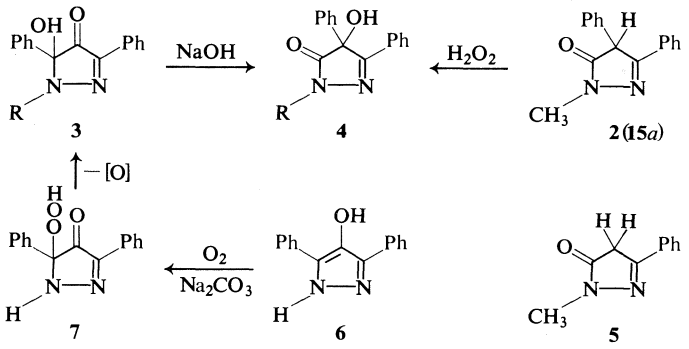
[3]Δ^2-Pyrazolin-5-ones might exist as at least two other tautomeric structures; however in this paper this name and structure have been arbitrarily chosen to represent the equilibrium mixture.

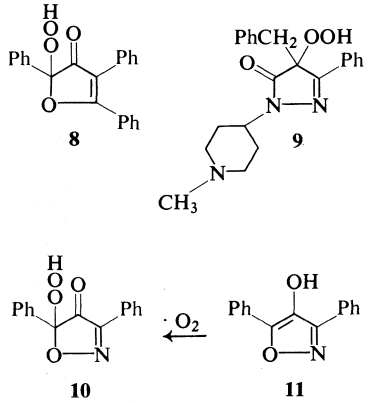


SCHEME 1

TABLE 1. Spectral data

Compound	I.r. (Nujol mull) (cm^{-1})	U.v. (95% ethanol) λ_{max} (nm)	ε
4*a*	1704	297	13 800
4*b*	1691	310	13 000
5 (5)	1698	301	12 190

sodium carbonate in the presence of air. The rationalization of this reaction (Scheme 1: **6** → **7** → **3***a* → **4***a*) is based on the established occurrence of hydroperoxide intermediates such as **8** (6) and **9** (7) in the aerial oxidation of related



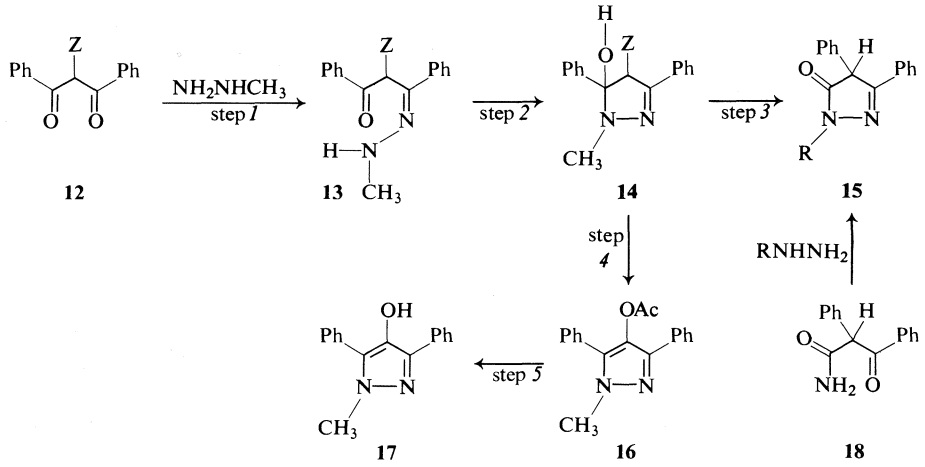
heterocycles, and on their known conversion to parent alcohols (8). The most closely related hydroperoxide in the literature is **10** which was recently proposed as an intermediate arising from aerial oxidation of **11** (9).

Halohydrin Rearrangement

Treatment of 2-bromo-1,3-diphenyl-1,3-propanedione (**12***a*) with methylhydrazine in ethanol at room temperature gave 1-methyl-3,4-diphenyl-Δ²-pyrazolin-5-one (**15***a*) in a 56% yield.

The probable reaction sequence is shown in Scheme 2 (**12***a* → **13***a* → **14***a* → **15***a*). The first two steps which are standard ketone reactions are followed by a base-catalyzed halohydrin rearrangement in step *3*. Of the several reasonable alternative mechanisms, most of which differ only in the order of occurrence of the dozen or so minor steps, the given mechanism was favored for the following reasons. (*a*) Stable analogs of the intermediate **14** have been isolated by other workers (10). (*b*) The intermediate **14** can be diverted to an alternative product, 4-hydroxy-1-methyl-3,5-diphenylpyrazole (**17**), if Z^- is a poorer leaving group than Br^-. Treatment of **12***b* with methylhydrazine gives **17** in 92% yield (3). It is seen that when the two competing reactions proceed by loss of groups of similar leaving capability (OH^- and OAc^-), then the product-controlling factor is the fact that the next step gives rise to the more stable aromatic (6π-electron system) in the observed reaction but not in the competing one (step *4 vs.* step *3*). (*c*) Steps *2* and *3* are actually a manifestation of the well-authenticated Favorskii reaction proceeding via the semibenzilic mechanism.

In the treatment of **12***b* with methylhydrazine, the stage at which the acetoxyl group is hydro-



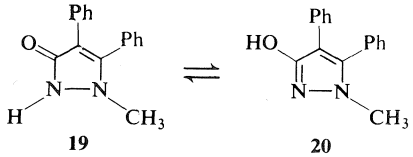
12 13 14 15 16 17 18

a, Z = Br, R = CH_3; *b*, Z = OAc, R = H; *c*, R = Ph

SCHEME 2

lyzed has not been established, but we represent this step as being the final one, since **16**, a phenolic-type ester should be hydrolyzed the fastest of all the compounds involved. If acetic acid is the solvent used in the above reaction the acetylated product **16** can be isolated.

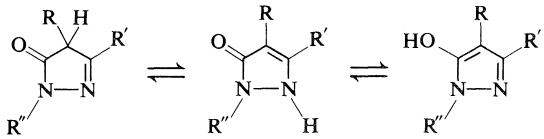
The structure of **15***a* was established chemically by a variation of the well-known route to Δ^2-pyrazolin-5-ones from β-oxocarboxylic acid derivatives. α-Phenyl-α-benzoylacetamide (**18**) was heated with methylhydrazine dihydrochloride in refluxing ethanol for 4 h to give a 50% yield of **15***a*. When **18** was treated with hydrazine and phenylhydrazine, the expected products **15***b* and *c* were obtained and their melting points agreed with literature values (11, 12). The α-phenyl-α-benzoylacetamide was prepared by acid hydrolysis of α-phenyl-α-benzoylacetonitrile which had been made by condensing ethyl benzoate with benzyl cyanide in the presence of sodium ethoxide. Since this method of synthesis of **15** does not completely rule out the possibility of one of the tautomeric pair **19** and **20** being the actual structures, extra evidence concerning the position of the methyl group on the ring was necessary. This was afforded by the conversion of **15***a* to the alcohol **4** using hydrogen peroxide (reported earlier in paper). No alcoholic product is conceivable for a similar oxidation of **19** or **20**.



19 20

Before this final piece of evidence was obtained, there was skepticism over the structure of **15***a*, since Grünanger and Vita-Finzi had reported (11) that this compound has m.p. 272–274 °C compared with m.p. (double) 216–219, 235–237 °C obtained by us. This difference could arise through polymorphism, but we suggest that the compound obtained by those workers had, in fact, structure **19** or **20**, since their synthesis involving methylation of 5-ethoxy-3,4-diphenylpyrazole followed by hydrolytic removal of the ethyl group was ambiguous and no additional evidence was offered.

With the skeletal structure of **15***a* established, it remains to determine the position of the labile hydrogen. The three most probable tautomeric structures are **21***a*, **22***a*, and **23***a*. Katritzky and Maine (5) have studied the i.r. spectra of a number



21 22 23

a, R = R′ = Ph; R″ = CH_3

of pyrazolin-5-ones and alkylated examples of the three types of tautomers and report that in chloroform solution the Δ^2-pyrazolin-5-ones (**21**) show a strong band around 1700 cm^{-1}, the Δ^3-pyrazolin-5-ones (**22**) show a strong band around 1630–1660

cm^{-1}, and the 5-hydroxypyrazoles (**23**) show no strong band between 1600 and 2000 cm^{-1}. However in the solid state (Nujol mull), whereas **21** still shows a distinctive band, **22** and **23** cannot be distinguished with certainty because both absorb in the low 1600's. In this work we obtained only solid state i.r. spectra, and no band appeared between 1620 and 2000 cm^{-1} indicating the absence of **21***a*, but not distinguishing between **22***a* and **23***a*. The tautomer **21***a* was also ruled out by the u.v. spectrum which was somewhat different from the spectra of model compounds **4***a* and *b*, and by the n.m.r. spectrum which did not show the ring CH proton but instead possessed a labile proton which only became visible by proton exchange in DMSO containing a trace of D_2O. U.v. and n.m.r. data were of no help in distinguishing between **22***a* and **23***a*.

1-Methyl-3,4-diphenyl-Δ²-pyrazolin-5-one (**15***a*) may also be prepared by treatment of 2,2-dibromo-1,3-diphenyl-1,3-propanedione with a fourfold excess of methylhydrazine in ethanol. Although this reaction must involve an extra reduction step compared with the conversion of **12***a* to **15***a*, both reactions give yields of about 55%.

Conclusion

Three new synthetic routes to Δ²-pyrazolin-5-ones have been reported in this paper. One of the advantages of each of the routes is that phenyl groups can easily be incorporated into the system. The difficulty of introducing phenyl groups using traditional syntheses is supported by the fact that neither of the two key products (**2** and **4**) reported in this paper had been prepared previously, in spite of the abundance of Δ²-pyrazolin-5-ones in the literature. It is suggested that the acyloin and halohydrin rearrangements deserve much more attention than they receive at present, especially in the synthesis of compounds bearing aryl substituents and when dealing with compounds sensitive to acid.

It is of interest that an analog of the aerial oxidation of 4-hydroxy-1-methyl-3,5-diphenylpyrazole (**6**) followed by acyloin rearrangement to 4-hydroxy-1-methyl-3,4-diphenyl-Δ²-pyrazolin-5-one (**4***a*) exists in nature in the conversion of ibogaine to iboluteine (13).

Experimental

M.p.'s were determined on a Meltemp apparatus and are uncorrected. I.r. spectra were obtained on a Beckman IR 5A spectrophotometer in Nujol mulls unless otherwise indicated, and strong bands between 1000 and 4000 cm^{-1} are quoted. U.v. spectra were measured on a Unicam SP 800 spectrophotometer in 95% EtOH at 25°. N.m.r. spectra were recorded on a Varian A60A spectrometer using an internal TMS standard. Microanalyses were performed by C. Daesslé, Organic Microanalyses, Montreal, Quebec.

*4-Hydroxy-3,4-diphenyl-Δ²-pyrazolin-5-one (**4***a*)

*(a) From 5-Hydroxy-3,5-diphenyl-Δ²-pyrazolin-4-one (**3***a*)*

A solution of **3***a* (14) (111 mg) in 1 ml 5% methanolic potassium hydroxide was refluxed for ½ h, 5 ml of water was added, and the solution refrigerated at 5° for 15 h. The solid product (85 mg, 76%) was filtered and crystallized twice from aqueous ethanol to give pure **4***a*, m.p. 210–212.5°; ν_{max} 3190, 2550 br, 1704, 1590, 1276, and 1142 cm^{-1}; λ_{max} 216 (ε 14 800) and 297 nm (13 800); δ (acetone-d_6) 6.10 (1H, s, OH), 7.25–7.60 (8H, m, aromatic), 7.78–7.94 (2H, m, aromatic), and 10.53 p.p.m. (1H, s, NH); *m/e* (70 eV): 252 (74%, M^+), 105 (100%), 77 (85%).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.44; H, 4.80; N, 11.11. Found: C, 71.93; H, 4.87; N, 11.22.

*(b) From 4-Hydroxy-3,5-diphenylpyrazole (**6**)*

A mixture of **6** (14) (0.236 g, 0.001 mol), sodium carbonate (0.117 g, 0.0011 mol), and 90% methanol (20 ml) was refluxed for 2 h. The solids were filtered and washed with a small amount of methanol. Evaporation of the filtrate left solids which melted at 370–415°. Fractional recrystallization from ethanol gave a 32% yield of the starting material and a 31% yield of **4***a*, identified by mixture m.p. and i.r. spectrum.

*5-Hydroxy-1-methyl-3,5-diphenyl-Δ²-pyrazolin-4-one (**3***b*)

Compound **3***b* was prepared according to the method for 5-hydroxy-3,5-diphenyl-Δ²-pyrazolin-4-one (**3***a*) (14) with slight modification. A cooled (ice-bath), stirred solution of diphenylpropanetrione hydrate (15) (1.28 g, 0.005 mol) in methanol (10 ml) was treated with a solution of methylhydrazine (0.43 ml, *ca.* 0.008 mol) in methanol (1 ml). After 1 h, water (40 ml) was added to cause precipitation. Compound **3***b* was isolated in bright orange prisms, m.p. 140–141° (dec.) (from cold dilute methanol or warm benzene–petroleum) (65–75% yield); ν_{max} 3236, 1696, 1674 strong, 1204, and 1177 cm^{-1}; λ_{max} 215 (infl) (ε 13 400), 271 (15 800), and 420 nm (4660); δ ($CHCl_3$-*d*) 3.25 (3H, s, Me), 7.25–7.47 (9H, m, 8H aromatic, 1H hydroxyl exchangeable with D_2O), and 7.93–8.09 p.p.m. (2H, m, aromatic).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.10; H, 5.18; N, 10.65.

*4-Hydroxy-1-methyl-3,5-diphenyl-Δ²-pyrazolin-5-one (**4***b*)

*(a) From 5-Hydroxy-1-methyl-3,5-diphenyl-Δ²-pyrazolin-4-one (**3***b*)*

A mixture of **3***b* (95 mg) and 1 ml 5% methanolic potassium hydroxide was refluxed for 1/2 h, 5 ml of water was added, and the solution kept at 5° for 15 h. The solid product (76 mg, 80%) was filtered and recrystallized twice from aqueous ethanol to give pure **4***b*, m.p. 179–181°; ν_{max} 3155, 2721, 2667, 1691, 1603, 1198, 1183, and 1173 cm^{-1}; λ_{max} 217 (ε 14 700) and 310 nm (13 000); δ (acetone-d_6) 3.35 (3H, s, Me), 6.08 (1H, s, OH), 7.27–7.60

(8H, m, aromatic), and 7.78–7.95 p.p.m. (2H, m, aromatic).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.19; H, 5.21; N, 10.32.

*(b) From 1-Methyl-3,4-diphenyl-Δ²-pyrazolin-5-one (**2** or **15a**)*

The method was according to Jucker and Lindenmann (7). Hydrogen peroxide (40%) (0.87 ml) was added to a cooled (0–5°) solution of **2** (0.5 g, 0.002 mol) in 1.5% sodium hydroxide (8.5 ml). The mixture was stoppered, stirred for 1 h, and allowed to stand in a refrigerator for 24 h. The mixture was then neutralized with 5% hydrochloric acid, and the volume was reduced to one-fifth of the initial volume. A small amount of ethanol was added to dissolve the solids. On cooling crystals formed and recrystallization yielded 0.22 g (44%) of **4***b*, m.p. 178–180° identified by i.r. spectrum and mixture m.p.

Structure **2** may be converted to **4***b* by aerial oxidation, simply by heating it at its m.p. (~237°) in a m.p. tube for ½ h. The product was isolated and identified by its i.r. spectrum and mixture m.p.

*1-Methyl-3,4-diphenyl-Δ²-pyrazolin-5-one (**2** or **15a**)*

*(a) From 2-Bromo-1,3-diphenyl-1,3-propanedione (**12a**)*

Methylhydrazine (1.4 g, 0.03 mol) was added dropwise in 3 min to a warm suspension of **12***a* (16) (3.03 g, 0.01 mol) in ethanol (100 ml) under stirring. After addition, the mixture was stirred at room temperature for 1.5 h. The bulk of solvent was removed at reduced pressure and then 70% aqueous acetone (10 ml) was added. On cooling in an ice-bath, crystals formed and were collected. Recrystallization from 70% aqueous acetone gave 1.41 g (56%) of **15***a*, double m.p. 216–219° (then 235–237°); ν_{max} (KBr) 2550 br, 1601 s, 1427, 1392, 1292, 1069, and 1026 cm^{-1}; λ_{max} 240 (infl) (ε 14 700), 265 (infl) (11 200), and 300 (infl) nm (6310); δ ($CDCl_3$) 6.35 (3H, s, NMe), 7.20–7.40 (10H, m, aromatic) and deuterium exchange revealed 1 exchangeable H; *m/e* (70 eV): 250 (100%, M^+), 179 (35%), 178 (30%).

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19; O, 6.39. Found: C, 77.22; H, 5.51; N, 11.06; O, 6.07.

(b) From 2,2-Dibromo-1,3-diphenyl-1,3-propanedione

The reaction was performed in a similar manner as in section *a*. The molar ratio of the dibromopropanedione to methylhydrazine was 1:4. Compound **15***a* was obtained in 57% yield.

*(c) From α-Phenyl-α-benzoylacetamide (**18**)*

1 ml of an aqueous solution containing methylhydrazine dihydrochloride (0.0024 mol) was added to a solution of **18** (see below) (0.48 g, 0.002 mol) in absolute ethanol (20 ml). The mixture was refluxed for 4 h. The mixture was neutralized (about p*H* 7) with 10% sodium hydroxide. The solution was reduced to half its volume, followed by cooling in an ice-bath. The crystals that formed were collected and purified giving a yield of 0.25 g (50%).

Compound **15***a* obtained from the three methods had identical spectral and physical properties.

Δ²-Pyrazolin-5-ones

α-Phenyl-α-benzoylacetamide (**18**) was prepared according to the method for the corresponding ethyl ester (17) with slight modification: α-phenyl-α-benzoylacetonitrile, obtained by condensing ethyl benzoate with benzyl cyanide in the presence of sodium ethoxide (17), was hydrolyzed in ethanol (with *ca.* 70% saturation of hydrogen chloride gas); m.p. 178.5–180° (lit. m.p. 178° (18)). The amide **18** was condensed with hydrazines to yield the Δ²-pyrazolin-5-ones.[4]

*3,4-Diphenyl-Δ²-pyrazolin-5-one (**15b**)*

This compound was obtained under conditions similar to those used for **15***a*. The refluxing time was 5 h. The yield was 68%; m.p. 234–236° (lit. m.p. 234–235° (11)); ν_{max} 3285, 3190, 1700, 1601, 1226, and 1016 cm^{-1}; λ_{max} 241 (infl) (ε 12 400) and 265 (infl) nm (10 700); δ (DMSO-d_6) 7.13 and 7.23 (10H, s, aromatic) and 10.77 p.p.m. (>1H, broad, NH; deuterium exchange revealed 2 exchangeable H).

*1,3,4-Triphenyl-Δ²-pyrazolin-5-one (**15c**)*

This compound was obtained by refluxing a mixture of the amide (**18**) (0.24 g, 0.001 mol), phenylhydrazine hydrochloride (0.18 g, 0.0012 mol), and ethanol (5 ml) for 1 h. The crystals that separated on cooling were recrystallized from ethanol, m.p. 191.5–193.5° (lit. m.p. 193–194° (12)) (64% yield); ν_{max} 1597, 1300, 1125, and 968 cm^{-1}; δ ($CHCl_3$-*d*) 7.30–8.10 (16H, m, 15H aromatic, 1H hydroxyl exchangeable with D_2O).

*4-Hydroxy-1-methyl-3,5-diphenylpyrazole (**17**) and 4-Acetoxy-1-methyl-3,5-diphenylpyrazole (**16**)*

Compound **17** was prepared (3) by refluxing a mixture of 2-acetoxy-1,3-diphenyl-1,3-propanedione (**12***b*) (16) and methylhydrazine in ethanol. The 4-acetoxypyrazole (**16**) was obtained when acetic acid was used as a solvent.

A solution of methylhydrazine (0.23 g, 0.005 mol) in acetic acid (1 ml) was added to a solution of **12***b* (1.13 g, 0.004 mol) in acetic acid (6 ml). The mixture was stirred at room temperature for 1 h. After most of the solvent was removed at reduced pressure, water (10 ml) was added. The oily product crystallized on prolonged cooling and agitation, m.p. 109–111° (from benzene–petroleum) (0.99 g, 85%). This product is identical with the one prepared by acetylation of the 4-hydroxypyrazole **17** (3).

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[4]Condensation of ethyl α-phenyl-α-benzoylacetate with hydrazine and phenylhydrazine gave the Δ²-pyrazolin-5-ones, **15***b* (11) and *c* (12), respectively.

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