

γ -PYRONE DERIVATIVESIX. Preparing α -Phenylhydrazones of Derivatives of 3-Hydroxy- γ -pyrone*

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Coupling of the appropriate 3-hydroxy- γ -pyrone derivatives with labile diazonium compounds (phenyldiazonium oxide hydrate or in particular phenyldiazohydrate) gives 3,4-dioxo-2,3-dihydropyran-2-phenylhydrazone (V), 3,4-dioxo-6-carboxy-2,3-dihydropyran-2-phenylhydrazone (VI), 3,4-dioxo-6-ethoxy-carbonyl-2,3-dihydropyran-2-phenylhydrazone (VII), 5-(benzenazo)-3,4-dioxo-6-carboxy-2,3-dihydropyran-2-phenylhydrazone (VIII), 4-oxo-3,3-dihydroxy-6-hydroxymethyl-2,3-dihydropyran-2-phenylhydrazone (IX). The hydrazone VI is also formed by coupling phenyldiazohydrate with meconic acid or with the ferric chelate of comenic acid. Compounds VI-VIII are characterized as their quinoxaline derivatives. Isomerization of the appropriate phenylhydrazones gives 2-(benzenazo)-3-hydroxy- γ -pyrone, 6-(benzenazo)kojic acid, and the hitherto undescribed in the literature 6-(benzenazo)comenic and 3,6-bis(benzenazo)kojic acids.

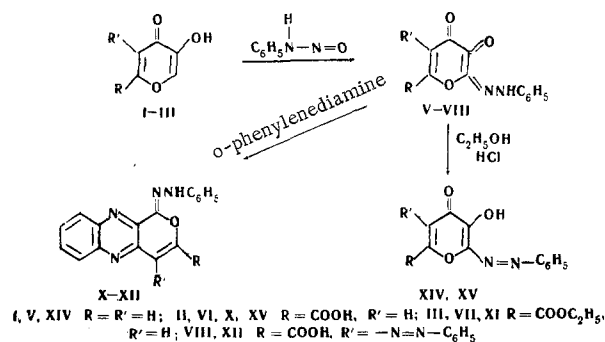
Some derivatives of 3-hydroxy- γ -pyrone in the tautomeric keto form are known to react with bromine, ethyl nitrite, and diazonium salts. Thus diazo coupling of phenyldiazonium acetate with 3-hydroxy- γ -pyrone (I) gave 3,4-dioxo-2,3-dihydropyran-2-phenylhydrazone (V) [2], while diazo coupling of phenyldiazonium acetate or chloride in alkaline solution with kojic acid (IV) gave 4-oxo-3,3-dihydroxy-6-hydroxymethyl-2,3-dihydropyran-2-phenylhydrazone (IX) [3, 4]. However, when kojic acid is coupled in alkaline solution with *o*-, *m*-, or *p*-tolyl diazonium chloride, the corresponding azo compounds are formed.

Our confirmation of information in the literature [2], and preparation of 3,4-dioxo-6-carboxy-2,3-dihydropyran-2-phenylhydrazone (VI), 3,4-dioxo-6-ethoxycarbonyl-2,3-dihydropyran-2-(*p*-sulfamido)phenylhydrazone and 3,4-dioxo-2,3-dihydropyran-2-(*p*-sulfamido)phenylhydrazone [5], contradict the findings of a number of authors [6-10], that reaction of 3-hydroxy- γ -pyrone derivatives with diazonium salts gives azo compounds.

The present work confirms that comenic acid (II), its ethyl ester (III), and meconic acid do not, either in acid or neutral solution, couple with phenyldiazonium chloride or acetate, and that under those conditions, pyrones I and IV give low yields of the corresponding hydrazones. However all these pyrones undergo smooth reaction with such labile diazo compounds as phenyldiazonium oxide hydrate, and in particular phenyldiazonium hydrate** (according to [11]

the hydrate of phenyldiazonium oxide), to give the phenylhydrazones V-IX.

The condition necessary for formation of phenylhydrazones V-IX is the presence of the labile diazo compounds indicated above, formed at the instant of mixing of the azo components.



Diazo coupling with salts of acid II can serve as confirmation of this. Thus the maximum yield of hydrazone VI (80%) is obtained by diazo coupling of the neutral sodium salt of acid II with a solution of phenyldiazohydrate alkaline to bromothymol blue (pH = 7.6). Coupling of the acid salt of II under those conditions cuts the yield of VI to 36%. On the other hand VI is not formed when a solution of the neutral salt of II containing excess sodium hydroxide (1 mole on II) is coupled with the phenyldiazohydrate (reaction mixture alkaline to phenolphthalein). Apparently the reaction product is an azo compound with properties differing markedly from those of the phenylhydrazones V-IX.

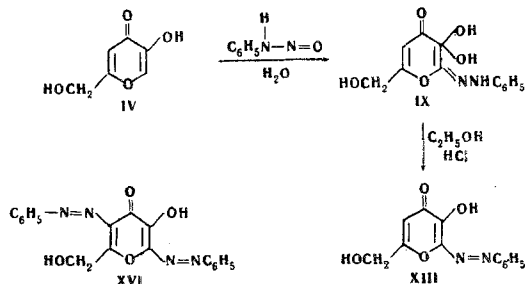
We also obtained VI by diazo coupling of phenyldiazohydrate with meconic acid, or with the ferric complex of comenic acid. Diazo coupling of pyrones I and III with phenyldiazohydrate gives, respectively, hydrazone V, and the hitherto undescribed 3,4-dioxo-6-ethoxycarbonyl-2,3-dihydropyran-2-phenylhydrazone (VII) and 5-(benzenazo)-3,4-dioxo-6-carboxy-2,3-dihydropyran-2-phenylhydrazone (VIII) (coupling with 2 moles of phenyldiazohydrate). The presence of an α -diketo group in hydrazones VI-VIII is confirmed by their undergoing condensation with *o*-phenylenediamine, to give hitherto unknown quinoxaline derivatives X-XII.

Optimum conditions for formation of hydrazone IX are diazo coupling of the sodium salt of acid IV with a solution of phenyldiazonium oxide hydrate, obtained by neutralizing phenyldiazonium chloride.

*For part VIII see [1].

**It is known that within a narrow pH range diazo solutions of phenyldiazohydrate readily isomerize to the nitrosamine acid.

The solution of the sodium salt of IV must be alkaline to bromothymol blue. Unlike the other phenylhydrazones, the hydrazone IX actually contains a molecule of water [3, 4], but the literature melting point of 147° or 150° C was found to be too high. When rapidly heated IX melts at 127°–129° C but when heated slowly it decomposes, and the melting point continually rises.



A possible isomerization of hydrazone IX to azo compound takes place with loss of water. Actually, treatment of IX with water, made alkaline, at 60° C, or better with boiling ethanol, acidified with hydrochloric acid, gives 6-(benzenazo)kojic acid (XIII). In a similar way hydrazones V and VI were converted to the corresponding azo compounds 2-(benzenazo)-3-hydroxy- γ -pyrone (XIV) and 6-(benzenazo)comenic acid (XV).

Acid XV was obtained by saponifying ester VII in alkaline solution.

Coupling acid IV with 3 molecules of phenyldiazohydrate, followed by isomerization without isolating the intermediate product, gives the hitherto undescribed 3, 6-bis(benzenazo)kojic acid.

Formation of α -phenylhydrazones by diazo coupling of I derivatives can take place by two routes. There is first formation of an azo compound which subsequently isomerizes to hydrazone, or the action of the labile diazo compound first leads to I being converted into the more reactive keto form, which then reacts with the nitrosamine acid. The latter variant of the reaction mechanism is more probable for the following reasons. Azo compounds XIII–XV which we prepared proved to be substances which were rather stable not only to oxidation, but also towards mineral acids and reduction, while α -phenylhydrazones I are readily isomerized to the corresponding azo compounds. In conclusion we assume that there is no reaction at all in acid solution between phenyldiazonium chloride, and free derivatives of I, and that reaction takes place with very great difficulty in neutral solution, while reaction with phenyldiazonium acetate takes place only in alkaline solution (i. e. in the presence of labile diazo compounds). These conclusions correspond precisely to the second variant of the sequential nature of the reaction.

EXPERIMENTAL

3, 4-Dioxo-6-carboxy-2, 3-dihydropyran-2-phenylhydrazone (VI). a) A solution of the acid sodium salt of II [3.12 g (0.02 mole) II, 90 ml water, and about

14 ml 10% NaOH (bromothymol blue)] was added to phenyldiazohydrate [1.86 g (0.02 mole) aniline, 18 ml dilute HCl (1:2), 1.5 g (0.02 mole) NaNO₂, in 6 ml water, and 11 ml 10% NaOH (bromothymol blue)] at 0° C. Excess dilute HCl (1:1) was added at –5° C (tested on filter paper: a black precipitate, and a stable pale-crimson spot). After salting out, the product was isolated as described in [5]. Yield 1.9 g or 36%, mp 195°–198° C (sealed capillary, decomp). The literature gives [5] mp 195°–198°. Found: C 55.00; H 3.30; N 11.50%; equiv 264. Calculated for C₁₂H₈N₂O₅: C 55.38; H 3.08; N 10.76%; equiv 260.

b) A solution of the neutral sodium salt of II, prepared as described in a) above, but with the addition of 32 ml 10% NaOH (phenolphthalein) was added to the phenyldiazohydrate*, and VI was isolated as described above. Yield 4.2 g (80%). Undepressed mixed mp with the compound prepared as described in a).

c) A solution of the neutral sodium salt of I (prepared as described in a) with, however, addition of 35 ml 10% NaOH, i. e., with excess of alkali sufficient to neutralize the HCl] was added at 0° C to a phenyldiazonium chloride solution [prepared as described in a), but not made alkaline], and the compound isolated and purified as described in a). Yield 4.2 g (80%).

d) A solution of the di-Na salt of meconic acid [4 g (0.02 mole) acid and 32 ml 5% NaOH (phenolphthalein)] was added to phenyldiazohydrate, yield of VI 4.16 g (80%).

e) A solution of the acid Na salt of meconic acid [4 g (0.02 mole) acid and 16 ml 5% NaOH] was added to phenyldiazohydrate; yield of VI 2.6 g (50%).

f) A solution of the di-Na salt of meconic acid was added to a solution of phenyldiazonium chloride, and then, altogether, 24 ml 10% NaOH, till the mixture was slightly alkaline to bromothymol blue. Yield of VI 3.4 g (65%).

g) Diazo coupling was effected between phenyldiazohydrate [ex 0.28 g (0.003 mole) aniline], and an acid solution of the ammonium salt of the ferric-comenic acid complex [12] [0.52 g (0.001 mole) acid, 15 ml water, and 4 ml 10% ammonia solution]. Yield 0.25 g (30%). VI.

3-Carboxy-1H-pyrano[3, 4-b]quinoxaline-1-phenylhydrazone (X). A mixture of 5.2 g (0.02 mole) VI, 250 ml dioxane, and a solution of 4.4 g (0.04 mole) o-phenylenediamine in 20 ml AcOH were heated together for 1 hr at 80° C, then the solvent almost completely vacuum-distilled off at 50° C. Water was added to the cooled residue until precipitation was complete, the precipitate filtered off and washed with water. It was purified by dissolving in boiling ethanolic alkali, filtering, and acidifying the filtrate with dilute HCl (1:1). Yield 6.0 g (89%). Mp 350° (decomp,

*Unless specially mentioned, here and subsequently the phenyldiazohydrate solution was prepared by the method described previously.

sealed capillary). The compound was bright-orange, insoluble in ether, CHCl_3 , and benzene, slightly soluble in EtOH. Found: C 65.59; H 4.53; N 16.50%. Calculated for $\text{C}_{18}\text{H}_{12}\text{N}_4\text{O}_3$: C 65.06; H 4.61; N 16.86%.

3, 4-Dioxo-6-ethoxycarbonyl-2, 3-dihydropyran-2-phenylhydrazone (VII). A solution of the Na salt of pyrone III [3.6 g (0.02 mole) III, about 22 ml 5% NaOH (bromthymol blue)] was added at 0° to a solution of diazonium oxide hydrate, prepared as described under a) (see IX) [1.86 g (0.02 mole) aniline, but bromthymol blue yellow, and Congo Red]. The product, which was black with a dark-violet hue, was isolated as described under a) (see VI). Mass 4.3 g 75% yield. Mp 190°C (ex dioxane-ether-petrol ether). The compound was slightly soluble in water, CHCl_3 (crimson solution), benzene, ether (orange-red solution), more soluble in EtOH and AcOH (red solution). Found: C 56.90; H 4.80; N 10.88%. Calculated for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_5$: C 57.39; H 4.16; N 9.72%.

3-Ethoxycarbonyl-1H-pyrano[3, 4-b]quinoxaline-1-phenylhydrazone (XI) was prepared similarly to X, from 1.4 g (0.0005 mole) hydrazone VII, 50 ml dioxane, and a solution of 1.1 g (0.1 mole) o-phenylenediamine in 5 ml glacial AcOH. Yield 1.3 g. The compound was bright-orange, insoluble in water, ether, benzene, slightly soluble in EtOH and boiling AcOH. Mp $335^\circ\text{--}340^\circ\text{C}$ (decomp, sealed tube). Found: C 66.02; H 5.20; N 16.25%. Calculated for $\text{C}_{20}\text{H}_{16}\text{N}_4\text{O}_3$: C 66.66; H 4.44; N 15.55%.

6-(Benzenazo)comenic [6-(benzenazo)-5-hydroxy- γ -pyrene-2-carboxylic] acid (XV). a) 3.0 g dry acid VI was dissolved in 80 ml acetone + dry MeOH (1:1) in the cold, and after filtering, using charcoal, the solvent was vacuum-distilled off. The dry residue was dissolved in EtOH, acidified (Congo Red) with HCl, boiled for 1/2 hr until the reddish orange color vanished, then filtered hot, using charcoal, and the product precipitated with water. It was recrystallized from boiling EtOH, using precipitation with water. Yield 1.6 g (30%). Mp 220°C . It was insoluble in water, very slightly soluble in ether, benzene and CHCl_3 (cold), soluble in EtOH (brown solution), dioxane (reddish-brown solution), AcOH (chestnut-brown solution), and Me_2CO (yellowish-brown solution). Color reaction with FeCl_3 [12]: water layer greenish-gray; CHCl_3 layer orange. Found: C 54.90; H 3.60; N 11.30%. Calculated for $\text{C}_{12}\text{H}_8\text{N}_2\text{O}_5$: C 55.38; H 3.08; N 10.76%.

b) About 10.0 g impure ester VII was dissolved in 150 ml boiling EtOH, acidified with HCl (to Congo Red), and the solution filtered hot, using charcoal; excess EtOH was vacuum-distilled off, concentrating to 1/5th volume, and after making alkaline with 10% NaOH (phenolphthalein), the whole was heated at 50°C for 1/2 hr. The mixture was acidified with dilute HCl (1:1) (Congo Red), and all the solvent vacuum distilled. After washing with ether the residue was dissolved in EtOH, filtered hot using charcoal, and after removing excess EtOH, the compound was precipitated with water and NaCl. Yield 2.0 g, 23%. Undepressed mixed mp with the compound prepared as described above.

5-(Benzenazo)-3, 4-dioxo-6-carboxy-2, 3-dihydropyran-2-phenylhydrazone (VIII). A solution of the neutral Na salt of acid VI [from 1.86 g (0.01 mole) VI, 30 ml water, and about 8 ml 10% NaOH (phenolphthalein)] was added to phenyldiazohydrate [from 1.86 g (0.02 mole) aniline] held at 0°C . The compound was isolated after acidifying as described in a) (see IX). The black precipitate was purified by dissolving in water made alkaline with Et_2NH (yellow color of bromthymol blue), and at 0° , and then acidifying with dilute HCl (Congo Red). Weight of the air-dried precipitate 2.0 g, yield 55%. Mp 290°C (after precipitating from $\text{MeOH}\text{--}\text{Me}_2\text{CO}$ solution with water). The compound was soluble in water, Me_2CO , EtOH, AcOH, and dioxane (red solution), very slightly soluble in CHCl_3 , benzene, and ether. Found: C 59.11; H 3.81; N 15.11%; equiv 360. Calculated for $\text{C}_{18}\text{H}_{12}\text{N}_4\text{O}_5$: C 59.41; H 3.31; N 15.31%; equiv 364.

b) A phenyldiazohydrate solution was prepared from 3.6 g (0.04 mole) aniline, held at 0°C , and over a period of 1/2 hr a solution of 4.0 g (0.02 mole) meconic acid in 40 ml water plus 16 ml 10% NaOH (phenolphthalein) added. The product was isolated as described above. Mass 4.0 g, yield 55%. Undepressed mixed mp with the compound prepared as described in a) above.

4-(Benzenazo)-3-carboxy-1H-pyrano [3, 4-b]quinoxaline-1-phenylhydrazone (XII). A hot solution of 0.5 g (0.005 mole) o-phenylenediamine in 2 ml AcOH was added to a warm filtered solution (60°C) of 1.0 g (0.0025 mole) crude hydrazone VIII in 50 ml glacial AcOH, and at the same temperature the solution was concentrated to 1/10th of its original volume by vacuum distilling off the solvent. Precipitation with water then gave a brown precipitate which was filtered off and washed with water; it was then recrystallized from boiling EtOH acidified with HCl, precipitating with water. Yield 0.53 g (40%). Mp 290°C (decomp). The compound was insoluble in water, slightly soluble in EtOH, dioxane, Me_2CO , ether, and benzene. Found: C 67.00; H 4.35; N 18.80. Calculated for $\text{C}_{24}\text{H}_{16}\text{N}_6\text{O}_3$: C 66.55; H 4.11; N 19.26%.

4-Oxo-3, 3-dihydroxy-6-hydroxymethyl-2, 3-dihydropyran-2-phenylhydrazone (IX). a) A solution of 1.42 g (0.01 mole) kojic acid in 42 ml water plus about 8 ml 5% NaOH (not over 0.01 mole; blue to bromthymol blue) was held at 0°C , and to it added a solution of phenyldiazonium oxide hydrate, prepared from phenyldiazonium chloride [0.95 g (0.01 mole) aniline, 10 ml dilute HCl (1:2), 0.75 g NaNO_2 in 3 ml water, and about 4 ml 10% NaOH (red to Congo Red, yellowish-green to bromthymol blue)]. Then excess dilute HCl (1:1) was added at 5°C (a test drop on filter paper showed a scarlet precipitate, with a spot of stable orange color), and the product was salted out, filtered off, and stirred with ice-water. Then it was immediately separated and washed three times with a minimum amount of water. Yield 2.0 g (75%). After drying on a porous plate and in a vacuum-oven (50°), it was dissolved in cold EtOH-ether for purification and immediately precipitated with petrol

ether (bp 90°). Mp 127°–129° C (decomp). When slowly heated it had mp 150°–170°, or else did not melt below 300°. In the cold it was very slightly soluble in EtOH, dioxane, Me₂CO, and AcOH (red color); when dissolved in boiling EtOH, the color changed to chestnut, and this was also observed when ethanol solutions were kept for about 24 hr. A solution of the compound in mixed AcOH–dioxane gave a violet color with phenylhydrazine. Found: C 55.15; H 4.68; N 10.30%. Calculated for C₁₂H₁₂N₂O₅: C 54.75; H 4.18; N 10.64%.

b) Diazo coupling of phenyldiazonium acetate [ex 0.9 g (0.01 mole) aniline] with 1.42 g (0.01 mole) IV in 5% NaOH (blue to bromothymol blue) gave a scarlet compound, yield 1.0 g (38%). Mp 150°–160° C (decomp).

6-(Benzenazo)kojic acid [2-hydroxymethyl-5-hydroxy-6-(benzenazo)-γ-pyrone (XIII)]. A solution of 1.0 g crude hydrazone IX in 10 ml EtOH was made acid with HCl (to Congo Red) refluxed for 15 min, twice filtered hot using charcoal, excess EtOH evaporated off, and the product precipitated with water, filtered off next day, and washed with water. Yield 0.5 g mp 220° C (ex EtOH). The compound was insoluble in water, benzene, ether, and CHCl₃ (leaving them practically uncolored), but was soluble in EtOH; Me₂CO (orange color), dioxane, and AcOH (yellow). Found: C 55.03; H 4.50; N 11.12%. Calculated for C₁₂H₁₀N₂O₄: C 58.53; H 4.06; N 11.38%.

3, 6-Bis(benzenazo)kojic acid [3, 6-bis(benzenazo)-2-hydroxymethyl-5-hydroxy-γ-pyrone (XVI)]. A solution of phenyldiazohydrate [from 2.8 g (0.03 mole) aniline] was coupled with a solution of 1.42 g (0.01 mole) kojic acid in 14 ml water and 32 ml 5% NaOH. The product was isolated as described for XIII, recrystallized from EtOH, acidified with HCl. Yield 1.6 g (45%). Mp 135° C. It was insoluble in water, slightly soluble in ether and benzene, soluble in EtOH, Me₂CO, and dioxane. Found: C 60.70; H 4.40; N 15.60%. Calculated for C₁₈H₁₄N₄O₄: C 61.08; H 4.11; N 16.00%.

3, 4-Dioxo-2, 3-dihydropyran-2-phenylhydrazone (V). A solution of phenyldiazohydrate was coupled at 0° with a solution of 1.12 g (0.01 mole) pyrone I in 18 ml water plus about 4 ml 10% NaOH (blue to bromothymol blue). The product was isolated as de-

scribed for the hydrazone IX. Yield 1.8 g (80%), mp 170°–176° C. It was scarlet. The literature [2] gives mp 170°–176° C. No color with 1% FeCl₃ solution in EtOH.

2-(Benzenazo)-3-hydroxy-γ-pyrone (XIV). A solution of 1.1 g (0.005 mole) hydrazone V in 33 ml EtOH was acidified with HCl (Congo Red) and boiled for 15 min, filtered hot using charcoal, and the product precipitated with water. It was recrystallized from EtOH, by precipitating with water. Yield 0.22 g (20%). Mp 190° C. The compound was dark-brown, soluble in AcOH, Me₂CO, dioxane (orange red), and ether (yellow). Found: C 61.50; H 4.11; N 13.41%. Calculated for C₁₁H₈N₂O₃: C 61.11; H 3.70; N 12.97%.

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