Summary

1. 4-Hydroxycoumarin exists completely as the enol.

2. Bromination, nitration, sulfonation and coupling with diazotized amines have been carried out with 4-hydroxycoumarin. These reactions yield 3-substituted-4-hydroxycoumarin.

3. 3-Nitro-4-hydroxycoumarin has been converted to 3-amino-4-hydroxycoumarin, β-amino-*o*-hydroxyacetophenone and β-nitro-*o*-hydroxyacetophenone.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF WISCONSIN]

Studies on 4-Hydroxycoumarin. VIII. Phenylhydrazine Degradation of 3,3′-Methylenebis-(4-hydroxycoumarin)[1]

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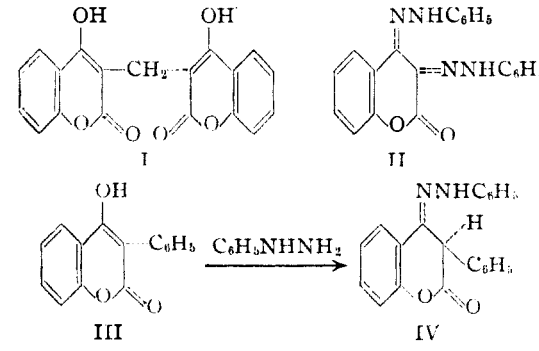
A reaction of great importance in the identification of 3,3′-methylenebis-(4-hydroxycoumarin) (I), the anticoagulant in spoiled sweet clover hay,[2] was the cleavage induced by heating with phenylhydrazine at 135°. A red-colored compound (V), $C_{21}H_{16}O_2N_4$, melting at 189–189.5°[3] was obtained. The composition of V suggested that two 4-hydroxycoumarin units were produced by a cleavage of I ($C_{19}H_{12}O_6$) with the loss of the methylene bridge and that by reaction of the nine carbon unit with phenylhydrazine V was produced. This paper deals with the structure of V and offers a rationalization on its formation.

Anschütz[4] reported a red-colored product obtained by heating 4-hydroxycoumarin with phenylhydrazine which melted at 186°. The empirical formula was given as $C_{15}H_{10}O_2N_2$, with a nitrogen content of 11.1%. The nitrogen content of V is 15.8%. Repeating Anschütz's directions, the compound obtained by us was red in color, melted at 189–189.5° and was identical with V as determined by a melting point of a mixture of the two products.

It appears that the Anschütz product and V are identical but that an error was made by Anschütz in the composition and empirical formula of the product. Product V is 1-phenyl-3-(*o*-hydroxyphenyl)-4-benzeneazo-5-pyrazolone or a tautomer thereof. Thus one of the phenylhydrazine residues is enjoined as part of the pyrazolone ring and the other as a benzeneazo group substituted on the pyrazolone ring. Evidence that V is a pyrazolone is indicated by the following.

The aromatic ring in the 4-hydroxycoumarin residue can be excluded as a possible position for the attachment of the phenylhydrazine residues because V gave salicylic acid on fusion with potassium hydroxide. Furthermore, two lines of proof showed that one of the phenylhydrazine residues occupied the 3-position of the 4-hydroxycoumarin residue. When 3-phenyl-4-hydroxycoumarin (III), a compound in which the 3-position is already substituted, was heated with phenylhydrazine at 135° a colorless product containing only one phenylhydrazine residue (IV) was obtained. When 2,3,4-triketochromane-3-phenylhydrazone (II), a compound having a 3-phenylhydrazino substituent, was heated with phenylhydrazine at 135°, V was obtained. When II was refluxed in ethanol with phenylhydrazine acetate (typical conditions for hydrazone formation) V was also formed but in smaller yields. In addition to V an orange product (XI) isomeric with it was produced. XI for reasons given below is assigned the structure 1-phenyl-4-benzeneazo - 5 - (*o* - hydroxyphenyl) - 3 - pyrazolone. To exclude the possibility that the 3-phenylhydrazino group of II might be removed under the conditions of this reaction and give a 4-hydroxycoumarin fragment which would then react with phenylhydrazine to yield V and XI, a 2,3,4-triketochromane-3-(*p*-substituted phenylhydrazone) was treated with phenylhydrazine to yield analogs of V and XI which still retained the *p*-substituent. The *p*-substituents used were methyl and nitro groups.[5]



The presence of enolic hydroxyl groups in V and XI was shown by their solubility in alkali (0.5%). On acidification the parent products were regenerated. V dissolved slowly in the alkali and only by heating the solution. In contrast XI

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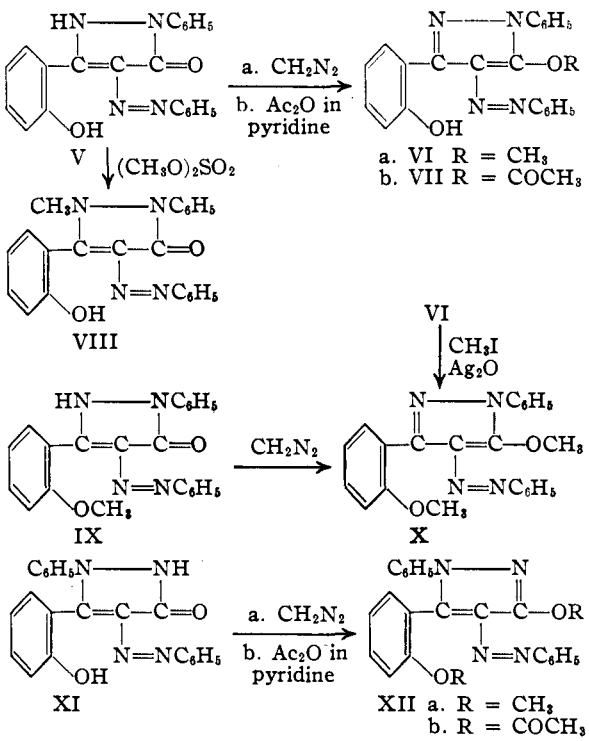
(2) Campbell and Link, *J. Biol. Chem.*, **138**, 21 (1941).

(3) Stahmann, Huebner and Link, *ibid.*, **138**, 513 (1941).

(4) Anschütz, *Ann.*, **367**, 169 (1909).

(5) Huebner and Link, THIS JOURNAL, **67**, 99 (1945).

dissolved immediately. V on treatment with an excess of diazomethane was transformed to a monomethyl ether (VI) while XI yielded a dimethyl ether XII, (a). Since VI differs from IX, a product of known constitution where the methyl substituent appears on the *o*-hydroxyphenyl group, the diazomethane methylation of V has occurred on the pyrazolone ring. The synthesis of IX by an unequivocal method is described below. On treatment of IX with diazomethane, a dimethyl ether (X) was obtained. To convert VI to X it was necessary to resort to the use of methyl iodide and silver oxide. A third monomethylated derivative of V, product VIII, was produced by treatment with dimethyl sulfate.



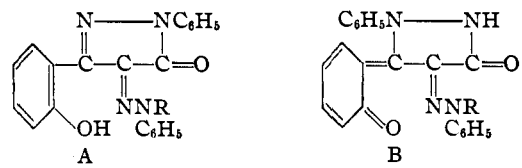
Paralleling the methylation reactions, V gave a monoacetate (VII) and XI gave a diacetate (XII, b) on reaction with acetic anhydride in pyridine. That the acetyl residue of VII is not on the *o*-hydroxyphenyl group is shown by the fact that it cannot be methylated by diazomethane as would be expected if the pyrazolone ring were unsubstituted by the acetyl group.

In the absence of evidence to the contrary, the positions in the pyrazolone ring of the methyl and acetyl groups in these compounds are assigned provisionally by analogy to the known compounds in the pyrazolone class. When 1-phenyl-3-methyl-5-pyrazolone is treated with diazomethane the O-methyl compound[6] is formed. Reaction with benzoyl chloride in pyridine produces the O-benzoate.[7]

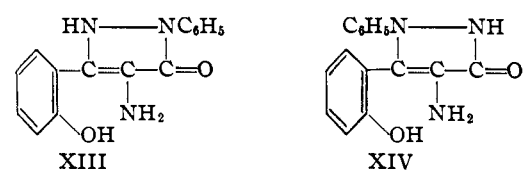
(6) von Pechmann, *Ber.*, **28**, 1626 (1895).

(7) Stolz, *J. prakt. Chem.*, (2) **55**, 146 (1897).

Product VI is similarly designated as an O-methyl compound and VII as an O-acetyl compound. VIII then must be a N-methylated product. The possibility that the methyl and acetyl compounds are derivatives of the hydrazone tautomers of V and XI, products A and B, is ruled out by the fact that VI, VII, X and XII (a and b) on hydrogenation yielded aniline rather than N-methylaniline or acetanilide.



In the hydrogenation of V and XI at one atmosphere pressure over palladium, two molar equivalents of hydrogen were consumed. The color of V and XI disappears. One of the reduction products resulting from both V and XI was aniline. The methyl homologs of V and XI prepared from 2,3,4-triketochromane-3-(*p*-methylphenylhydrazone) gave *p*-toluidine on reduction. This indicates that the phenylhydrazine residue affected by the reduction was the one originally on the 3-position of the 4-hydroxycoumarin residue.



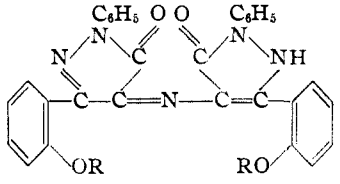
In addition to aniline, V yielded 1-phenyl-3-(*o*-hydroxyphenyl)-4-amino-5-pyrazolone (XIII). Product XI gave 1-phenyl-4-amino-5-(*o*-hydroxyphenyl)-3-pyrazolone (XIV) on reduction. Both of these amines are stable to the most drastic reduction procedures. This was suggestive of a pyrazolone structure in which one of the phenylhydrazine molecules reacting with the 4-hydroxycoumarin fragment was incorporated into V and XI in such a way that it resisted reduction. Due to the insolubility of V in the hydrogenation reaction medium, a better preparative method for XIII was to carry out the reduction with hydriodic acid. It is of interest to note that XI was reduced to XIV by heating in phenylhydrazine.

The two amines, XIII and XIV, differ widely in their properties. XIII, like 1-phenyl-3-methyl-4-amino-5-pyrazolone,[8] is unstable to oxygen and is converted by air to the rubazonic acid type compound (XV). This change can be brought about by merely allowing the amine hydrochloride to remain in contact with air or more conveniently by either boiling an aqueous solution of the hydrochloride in an open flask or by oxidizing with the requisite amount of potassium permanganate. XIII was converted to a mono-

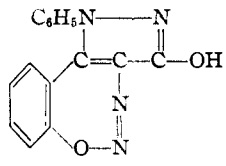
(8) Knorr, *Ann.*, **238**, 189 (1887).

acetate (probably an N-acetate) by treating an ice-water suspension of the hydrochloride with acetic anhydride and sodium acetate; to a tribenzoate by the Schotten–Baumann technique; and to a tetraacetate by refluxing with sodium acetate in acetic anhydride. XIII liberates nitrogen when treated with nitrous acid.

XIV in contrast to XIII is stable toward oxygen. This is in agreement with the properties of 1 - phenyl - 4 - amino - 5 - methyl - 3 - pyrazolone.[9] XIV yields a tetraacetate as a characteristic derivative. On treatment with nitrous acid, a diazo oxide (XVII) is formed. The diazo oxide ring may either involve the benzene ring hydroxyl or the pyrazole ring hydroxyl. The former structure is indicated since XXI, on which the benzene ring hydroxyl is methylated, does not form a diazo oxide on diazotization but liberates nitrogen. The possibility that XVII is a nitroso compound is ruled out because of a negative Liebermann reaction.



XV R = H
XVI R = CH_3

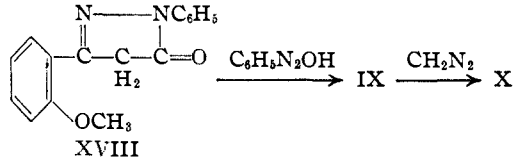


XVII

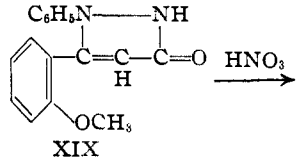
The final proof of structure of V and XI came as a result of their synthesis from compounds containing the pyrazolone nucleus.

The phenylpyrazolone (XVIII) prepared from *o*-methoxybenzoylacetic ester[10,11] was coupled with diazotized aniline yielding IX. On further treatment with diazomethane, a dimethyl ether (X) was obtained which is identical with the one obtained by the successive actions of diazomethane and methyl iodide–silver oxide on V. After treatment of IX with hydriodic acid in acetic acid, followed by acetylation, an acetate identical with the tetraacetate of XIII was obtained. When the reaction with hydriodic acid was continued for only thirty minutes, the resulting amine still retained the methoxyl group and was oxidized by air to the rubazonic acid dimethyl ether (XVI). Since this product is insoluble in alkali, the potential enolic hydroxyl in the pyrazolone ring does not confer acid properties to the compound.

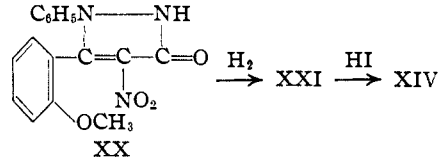
A derivative of XI was synthesized by the following independent method. *o*-Methoxybenzoylacetic ester on condensation with β-acetylphenylhydrazine in the presence of phosphorus trichloride yielded 1-phenyl-5-(*o*-methoxyphenyl)-3-pyrazolone (XIX), an isomer of XV. This method of synthesis was used for 1-phenyl-5-methyl-3-pyrazolone by Mayer.[12] Nitration to produce XX followed by hydrogenation and demethylation yielded an amine identical to XIV.



XVIII



XIX



XX

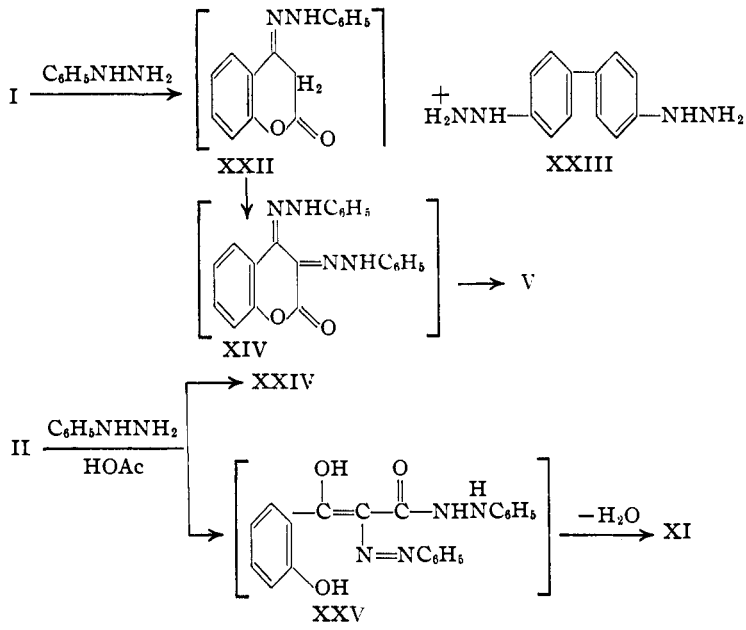
In the reaction that produces V by a cleavage of 3,3′-methylenebis-(4-hydroxycoumarin) (I), it is of interest to determine the chemical fate of the methylene bridge. A possible answer to this question is obtained from the study of the similar cleavage of 3,3′-benzylidenebis-(4-hydroxycoumarin) by aniline. These analogs were chosen because the product containing the bridge fragment had properties which made chemical isolation possible. 3,3′-Benzylidenebis-(4-hydroxycoumarin) was cleaved by boiling aniline to produce two moles of the 4-anilidocoumarin[4] and 4,4′-diaminotriphenylmethane. It is reasonable to believe that the analogous reaction occurs in the cleavage of I by phenylhydrazine. A 4-phenylhydrazino coumarin derivative (XXII) and 4,4′-dihydrazinodiphenylmethane (XXIII) would be the first products. Carbon 3 of XXII is oxidized as the second phenylhydrazine residue enters the molecule to produce the osazone type intermediate (XXIV). This product (XXIV) then rearranges to produce the stable V which is isolated. This oxidation of carbon 3 also occurs in the transformation of 4-hydroxycoumarin to V. The oxidizing agent is probably phenylhydrazine since V is also formed when the reaction is carried out under nitrogen with freshly distilled phenylhydrazine.

The simultaneous production of V and XI when II is refluxed in ethanol with phenylhydrazine acetate probably proceeds as follows: II reacting with phenylhydrazine leads to the osazone type intermediate XXIV, and a phenylhydrazide type intermediate, XXV. These then yield V and XI.

Experimental

3-Phenyl-4-phenylhydrazinocoumarin (IV).—3-Phenyl-4-hydroxycoumarin (III) (2 g.) was heated with 5 ml. of phenylhydrazine at 135° for one hour. The crystals that separated on cooling were filtered and washed with benzene. After two recrystallizations from ethanol and one from acetone–water, the yield was 2.0 g., m. p. 184–185°.

(9) Michaelis and Kotelmann, *Ann.*, **350**, 296 (1906).
(10) Tahara, *Ber.*, **25**, 1306 (1892).
(11) Huebner and Link, *J. Biol. Chem.*, **138**, 532 (1941).
(12) Mayer, *Ber.*, **36**, 717 (1903).



Anal. Calcd. for $C_{21}H_{16}O_2N_2$: C, 76.8; H, 4.9; N, 8.5. Found: C, 76.6; H, 5.0; N, 8.7.

Formation of 1-Phenyl-3-(*o*-hydroxyphenyl)-4-benzeneazo-5-pyrazolone (V) from 2,3,4-Triketochromane-3-phenylhydrazone (II).—One gram of II was heated with 3 ml. of phenylhydrazine at 135° for two hours. The mixture was poured into ice water containing an excess of hydrochloric acid and the crude V that separated was recrystallized from ethanol, yield 0.85 g., m. p. 189–189.5°.

Formation of V and 1-Phenyl-4-benzeneazo-5-(*o*-hydroxyphenyl)-3-pyrazolone (XI) from II.—A mixture of 16 g. of II, 20 ml. of acetic acid and 20 ml. of phenylhydrazine in 500 ml. of ethanol was refluxed for twelve hours. The red needles of V produced during the reaction were filtered and the mother liquor concentrated to 100 ml., cooled and a second crop of V collected. The combined crops were recrystallized from ethanol, yield 10 g., m. p. 189–189.5°.

The ethanol filtrate from which the two crops of V had been taken was poured into a large volume of ice-water acidified with hydrochloric acid. The black gum thrown out of solution was filtered, dried and dissolved in 100 ml. of ether. Skellysolve B was added in small portions until no further crystallization of the deep red platelets of XI occurred. The yield of XI was 11 g., m. p. 189–190°. The melting point of a mixture with V was 170–177°. When the red product was recrystallized from ethanol, a partial conversion to an orange polymorphic form occurred. After three recrystallizations this conversion was complete. Irradiation with ultraviolet light, prolonged heating of a melt of the orange modification and treatment with iodine failed to bring about the reverse transformation. The melting point of the orange needles is 184–185°; the melting point of the mixture with V is 160–165°; with the red polymorph 184–185°. In all subsequent preparations of XI, the orange modification was obtained.

Anal. Calcd. for $C_{21}H_{16}O_2N_4$: C, 70.8; H, 4.5; N, 15.8; mol. wt., 356. Found: C, 70.7; H, 4.6; N, 15.8; mol. wt., 336 (Rast).

1-Phenyl-3-(*o*-hydroxyphenyl)-4-(*p*-methylbenzeneazo) - 5 - pyrazolone.—2,3,4 - Triketochromane - 3 - (*p*-methylphenylhydrazone)[5] (27 g.) was refluxed with 35 ml. of acetic acid and 35 ml. of phenylhydrazine in 250 ml. of ethanol. Soon after refluxing was begun, the red product separated in a flaky form. After two hours the mixture was cooled, the product collected and recrystallized from ethyl acetate, yield 12 g., m. p. 215–216°.

Anal. Calcd. for $C_{22}H_{18}O_2N_4$: N, 15.2. Found: N, 15.4.

1-Phenyl-4-(*p*-methylbenzeneazo)-5-(*o* - hydroxyphenyl) - 3 - pyrazolone.—The mother liquor from the above preparation was concentrated to about 50 ml., cooled and 10 g. of a mixture of products obtained. The desired product was separated by chromatographic analysis on aluminum oxide. The mixture dissolved in benzene (2% solution) was adsorbed on the column. Elution with benzene–ethanol (50:1) developed a dark band of the 3-pyrazolone at the top of the column. The isomeric 5-pyrazolone was removed from the column. By using benzene–ethanol (1:1) the red band of the desired isomer was eluted. One gram of the original mixture yielded 0.7 g. of the 3-pyrazolone which was further purified by recrystallizing from ethyl acetate, m. p. 205–206°.

Anal. Calcd. for $C_{22}H_{18}O_2N_4$: N, 15.2. Found: N, 15.2.

1-Phenyl-3-(*o*-hydroxyphenyl)-4-(*p*-nitrobenzeneazo)-5-pyrazolone.—One gram of 2,3,4-triketochromane-3-(*p*-nitrophenylhydrazone)[5] was refluxed with 2 ml. of acetic acid and 2 ml. of phenylhydrazine in 100 ml. of ethanol. The red needles that separated on cooling were recrystallized from nitrobenzene, yield 0.3 g., m. p. 284–285°.

Anal. Calcd. for $C_{21}H_{15}O_4N_5$: N, 17.5. Found: N, 17.4.

Conversion of V to the O-Monomethyl Ether (VI).—V (3.8 g.) was dissolved in 850 ml. of boiling ethyl acetate, the solution cooled to 0° and an excess of diazomethane distilled into the mixture. After four hours, the ethyl acetate was removed and the resulting sirup dissolved in 25 ml. of benzene and chromatographed on an aluminum oxide column. The desired product was eluted with benzene, leaving a dark greenish band of an impurity on the column. The benzene was distilled off and the product recrystallized from ethanol. Three grams of the orange-red needles of VI, m. p. 121–123°, was obtained.

Anal. Calcd. for $C_{22}H_{18}O_2N_4$: N, 15.1. Found: N, 15.3.

Conversion of V to the N-Monomethyl Ether (VIII).—One gram of V was dissolved in 6 ml. of 1.5 *N* sodium methoxide, water was added and the methanol removed *in vacuo*. Dimethyl sulfate (1.5 g.) was added and the mixture shaken until the dimethyl sulfate had disappeared. The mixture was acidified and the precipitate filtered and recrystallized three times from ethanol, m. p. 135–137°.

Anal. Calcd. for $C_{22}H_{18}O_2N_4$: C, 71.4; H, 4.9; N, 15.1. Found: C, 71.3; H, 5.1; N, 15.3.

Conversion of VI and IX to the Dimethyl Ether (X).—VI (0.50 g.) and 5 ml. of methyl iodide were refluxed for six hours in 25 ml. of dry benzene with 2 g. of silver oxide. The silver salts were centrifuged, and the centrifugate concentrated to dryness. The residue was recrystallized twice from ethanol to yield 0.40 g. of orange-yellow platelets, m. p. 122–123°.

One gram of IX in ethyl acetate was treated in the usual manner with diazomethane, yield 0.7 g., m. p. 122–123°.

Anal. Calcd. for $C_{23}H_{20}O_2N_4$: N, 14.6. Found: N, 14.7.

Conversion of XI to the Dimethyl Ether (XII, a).—Five grams of XI in 200 ml. of ethanol was treated with an excess of diazomethane. The ethanol was removed by concentration. The residue was dissolved in chloroform and acidic impurities extracted with alkali. The chloroform was removed and the residue recrystallized three times from ethanol, yield 3 g., m. p. 170–173°.

Anal. Calcd. for $C_{23}H_{20}O_2N_4$: C, 72.0; H, 5.2; N, 14.6. Found: C, 71.7; H, 5.6; N, 14.7.

Conversion of V to the Monoacetate (VII).—V (1 g.) was suspended in 5 ml. of pyridine; 5 ml. of acetic anhydride was added and the mixture was warmed on the steam-bath until solution occurred. After one hour at room temperature, the solution was poured into ice water. The resulting red-orange product was recrystallized three times from ethanol; m. p. 154–155°; yield 1 g. Deacetylation yielded V.

Anal. Calcd. for $C_{23}H_{18}O_3N_4$: C, 69.3; H, 4.5; N, 14.1. Found: C, 69.2; H, 4.5; N, 14.1.

Conversion of XI to the Diacetate (XII, b).—XI (7.7 g.) was acetylated by the method described in the preceding experiment. The product was recrystallized from ethanol, yield 6.0 g., m. p. 134–136°. Deacetylation yielded XI.

Anal. Calcd. for $C_{25}H_{20}O_4N_4$: N, 12.7. Found: N, 12.7.

Aniline as a Hydrogenation Product of VI, VII, X and XII (a and b).—The reduction of all five of these compounds was carried out in essentially the same manner. One gram of the substance and 4 molar equivalents of a 10% methanolic hydrogen chloride solution were dissolved in 200 ml. of ethyl acetate. The hydrogenation was carried out over palladium at one atmosphere. Within thirty minutes two molar equivalents of hydrogen had reacted. The catalyst was collected and the filtrate concentrated to dryness *in vacuo*. The residue was suspended in about 25 ml. of water and made alkaline. An ether extract was made, the ether removed on the steam-bath and the residue steam distilled. From the distillate, aniline, micro b. p. 184°, was obtained in about 50% yields. The aniline was identified as acetanilide, m. p. 114°.

Reduction of 1-Phenyl-3-(*o*-hydroxyphenyl)-4-benzeneazo-5-pyrazolone (V).—Nine grams of V was refluxed for one hour in 100 ml. of acetic acid and 25 ml. of 58% hydriodic acid, the iodine produced being reduced with hypophosphorous acid. The colorless solution was concentrated *in vacuo* and the sirup dissolved in a minimum of hot concentrated hydrochloric acid. On cooling 5 g. of **1-phenyl-3-(*o*-hydroxyphenyl)-4-amino-5-pyrazolone hydrochloride (XIII)**, was collected. The mother liquor was made alkaline and steam distilled. The aniline liberated was identified as described above.

The **monoacetate of XIII** was prepared by suspending 3 g. of the amine hydrochloride and 3 ml. of acetic anhydride in 20 ml. of ice-water and slowly adding sodium acetate until the excess acetic anhydride was destroyed. After six recrystallizations from ethanol a constant melting point of 172–175° was obtained, yield, 0.9 g.

Anal. Calcd. for $C_{17}H_{15}O_3N_3$: N, 13.7. Found: N, 13.6.

The **tribenzoate of XIII** was prepared by the Schotten–Baumann method, m. p. 150–152°. The product was recrystallized from benzene–Skellysolve B.

Anal. Calcd. for $C_{36}H_{25}O_6N_3$: C, 74.6; H, 4.3; N, 7.3. Found: C, 74.6; H, 4.5; N, 7.3.

The **tetraacetate of XIII** was prepared by refluxing the amine hydrochloride with acetic anhydride and sodium acetate for thirty minutes. The product was isolated by pouring into ice-water and recrystallizing from ethyl acetate, m. p. 131–132°.

Anal. Calcd. for $C_{23}H_{21}O_6N_3$: C, 63.5; H, 4.8; N, 9.7; mol. wt., 435. Found: C, 63.3; H, 4.9; N, 9.7; mol. wt., 413 (Rast).

The Rubazonic Acid (XV) from XIII.—Five grams of the hydrochloride of XIII was suspended in 200 ml. of water. Three grams of sodium acetate was added and the suspension stirred for three days. The crude purple product was filtered and recrystallized from acetic acid, m. p. 222–225°, yield 1.4 g. These platelets have an iridescent purple-bronze color. The compound in alkaline solution has an intense purple color and can be reduced to the leuco form with sodium hydrosulfite and reoxidized with air to the original rubazonic acid.

Anal. Calcd. for $C_{30}H_{21}O_4N_5$: C, 69.9; H, 4.1; N, 13.6; mol. wt., 515. Found: C, 69.5; H, 4.2; N, 13.6; mol. wt., 525 (Rast).

Reduction of 1-Phenyl-4-benzeneazo-5-(*o*-hydroxyphenyl)-3-pyrazolone (XI).—XI (20 g.) was dissolved in 300 ml. of ethanol containing 12 ml. of concentrated hydrochloric acid and hydrogenated at one atmosphere over palladium. After two hours when two molar equivalents of hydrogen had been consumed, the uptake ceased. The catalyst was removed and the ethanol distilled off. The resulting mixture of the colorless amine hydrochloride was dissolved in a minimum of hot water. On cooling 15 g. of **1-phenyl-4-amino-5-(*o*-hydroxyphenyl)-3-pyrazolone hydrochloride (XIV)** was obtained, m. p. 170–175°.

Anal. Calcd. for $C_{15}H_{13}O_2N_3 \cdot HCl$: N, 13.5. Found: N, 13.8.

The free base (XIV) was obtained by treating an aqueous solution of the hydrochloride with sodium acetate. Because of the low solubility of XIV, recrystallization was not possible, m. p. 255–260°.

Anal. Calcd. for $C_{15}H_{13}O_2N_3$: C, 67.4; H, 4.9; N, 15.8. Found: C, 67.4; H, 4.8; N, 15.8.

Aniline was isolated from the mother liquors of XIV hydrochloride as described above. The **tetraacetate of XIV** was prepared as indicated for the tetraacetate of XIII. It was recrystallized from ethanol, m. p. 134.5–135.5°.

Anal. Calcd. for $C_{23}H_{21}O_6N_3$: C, 63.5; H, 4.8; N, 9.7; mol. wt., 435. Found: C, 63.2; H, 4.9; N, 9.7; mol. wt., 440 (Rast).

Conversion of XIV to the Diazo Oxide (XVII).—To a suspension of 1 g. of the hydrochloride of XIV in 20 ml. of cold water, 10 ml. of 0.5 *N* hydrochloric acid and 0.15 g. of sodium nitrite in 10 ml. of water was added. The suspension was shaken in the cold for thirty minutes and filtered. The yellow product (XVII) was recrystallized from ethanol, yield 0.5 g., m. p. 245–250° (dec.). The product dissolves readily in dilute alkali.

Anal. Calcd. for $C_{15}H_{10}O_2N_4$: C, 64.8; H, 3.6; N, 20.1. Found: C, 64.7; H, 4.2; N, 19.7.

Reduction of 1-Phenyl-3-(*o*-hydroxyphenyl)-4-(*p*-methylbenzeneazo)-5-pyrazolone.—The reaction was carried out as described for the reduction of V. On concentration of the reaction mixture, crystals separated. They were dissolved in water and made basic. *p*-Toluidine, m. p. 42°, was obtained and converted to its acetate, m. p. 150–151°. The filtrate remaining after the removal of the toluidine hydrochloride was concentrated to dryness. The residue was acetylated to yield the tetraacetate of XIII, m. p. 131–132°.

Reduction of 1-Phenyl-4-(*p*-methylbenzeneazo)-5-(*o*-hydroxyphenyl)-3-pyrazolone.—This product when reduced as described under the hydrogenation of XI, consumed two molar equivalents of hydrogen. To the amine hydrochlorides obtained by concentration of the reaction mixture, a solution of sodium acetate was added. A mixture of XIV and *p*-toluidine was obtained. *p*-Toluidine was separated from XIV by extraction with hot water. XIV was converted to its tetraacetate, m. p. 133–135°.

Formation of 1-Phenyl-3-(*o*-methoxyphenyl)-4-benzeneazo-5-pyrazolone (IX) from XVIII.—(a) To a solution of 4.3 g. of 1-phenyl-3-(*o*-methoxyphenyl)-5-pyrazolone (XVIII),[9,10] 4 g. of sodium carbonate and 1 g. of sodium hydroxide in 50 ml. of water at 5°, was added 20 millimoles (18% excess) of a solution of diazotized aniline. The mixture was acidified with acetic acid, the product filtered and recrystallized from acetic acid, yield 4.0 g., m. p. 149–151°. (b) Twelve grams of *o*-methoxybenzoylacetic ester[9] was dissolved in 100 ml. of water at 5° containing 15 g. of sodium carbonate. To this solution was added 60 millimoles (10% excess) of a solution of diazotized aniline. The gummy product was dissolved in 50 ml. of ethanol and refluxed with 10 ml. of acetic acid and 10 ml. of phenylhydrazine for thirty minutes. On cooling, IX was obtained. After recrystallization from acetic acid the yield was 10 g.

Anal. Calcd. for $C_{22}H_{18}O_2N_4$: N, 15.1. Found: N, 15.3.

Triacetate Monomethyl Ether of XIII.—On reduction of IX with hydriodic acid for thirty minutes a crude amine

hydrochloride still containing the methoxyl group was obtained, which on acetylation yielded a triacetate monomethyl ether of XIII. The product was recrystallized from an ethyl acetate–Skellysolve B mixture, m. p. 128–130°.

Anal. Calcd. for $C_{22}H_{21}O_5N_3$: N, 10.3. Found: N, 10.2.

Formation of the Dimethyl Ether of the Rubazonic Acid (XVI) from XIII.—The methylated amine hydrochloride (2 g.) obtained in the preceding preparation was suspended in water and treated with an excess of sodium acetate. This suspension of the amine was stirred twenty-four hours to yield a red alkali insoluble material which on recrystallization from acetic acid yielded 0.5 g. of bright scarlet platelets, m. p. 235–238°.

Anal. Calcd. for $C_{32}H_{25}O_4N_5$: C, 70.7; H, 4.6; N, 12.9; OCH_3, 11.4. Found: C, 70.4; H, 4.8; N, 12.9; OCH_3, 11.5.

Tetraacetate of XIII from IX.—The hydriodic acid reduction of IX was continued for twelve hours and demethylation occurred. The crude amine hydrochloride on refluxing with acetic anhydride and sodium acetate yielded a product identical to the tetraacetate of XIII, m. p. 131–132°.

1-Phenyl-4-(*o*-methoxyphenyl)-3-pyrazolone (XIX).—Twelve grams of the *o*-methoxybenzoylacetic ester, 8.1 g. of β-acetylphenylhydrazine,[13] and 4.9 ml. of phosphorus trichloride were heated on a water-bath for thirty minutes. The resinous product was stirred with concentrated ammonium hydroxide. The colorless crystals resulting were filtered and recrystallized from ethanol, yield 4.4 g., m. p. 222–225°.

Anal. Calcd. for $C_{16}H_{14}O_2N_2$: C, 72.2; H, 5.3; N, 10.5. Found: C, 71.8; H, 5.3; N, 10.5.

1-Phenyl-4-nitro-5-(*o*-methoxyphenyl)-3-pyrazolone (XX).[14]—One gram of XIX was added to 7 ml. of concentrated nitric acid, the reaction mixture being cooled in ice. After five minutes it was poured into ice water. A grey solid was obtained which crystallized from alcohol in greenish-yellow crystals, m. p. 164–165°, yield 0.7 g.

Anal. Calcd. for $C_{16}H_{13}O_4N_3$: C, 61.8; H, 4.2; N, 13.5. Found: C, 62.1; H, 4.3; N, 13.6.

Formation of the Tetraacetate of XIV from XX.[15]—One gram of XX was hydrogenated in ethanol as described above. After the uptake of 6 molar equivalents, the catalyst was filtered and the solution concentrated to dryness. The crude amine was demethylated by refluxing with 2 ml. of 58% hydriodic acid in 4 ml. of acetic acid for twelve hours. The reaction mixture was concentrated to a sirup, dissolved in 2 ml. of 10% hydrochloric acid, by warming, and filtered. On adding sodium acetate to the filtrate, 440 mg. of XIV was obtained. The tetraacetate was prepared by refluxing with acetic anhydride and sodium acetate, m. p. 133.5–135°. The melting point of the mixture of this acetate with that obtained from the reduction of XI showed no depression.

Reaction of 3,3'-Benzylidinebis-(4-hydroxycoumarin) with Aniline.—Ten grams of the bis-coumarin was refluxed with 50 ml. of aniline for four hours. After cooling the mixture was shaken with hydrochloric acid (5%) and the 4-anilidocoumarin[4] was filtered, m. p. 262–263°, yield 10.1 g. The acidic extract was made basic and extracted with ether. After drying the ethereal solution, the ether was allowed to evaporate.

The colorless crystals of 4,4'-diaminotriphenylmethane which separated were filtered and washed with ether, m. p. 134–135°, yield 5 g. After three recrystallizations from benzene the benzene complex, m. p. 104–105°, was isolated. The diacetate melts at 235–236°. The melting point of a mixture of an authentic sample of 4,4'-diaminotriphenylmethane prepared according to Ullmann[15] and the isolated product showed no lowering.

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Summary

1. It has been proved that the red compound, $C_{21}H_{16}O_2N_4$, resulting from the action of phenylhydrazine on 3,3'-methylenebis-(4-hydroxycoumarin) is 1-phenyl-3-(*o*-hydroxyphenyl)-4-benzeneazo-5-pyrazolone.

2. 1 - Phenyl - 3 - (*o* - hydroxyphenyl) - 4 - benzeneazo-5-pyrazolone was synthesized by treating 2,3,4 - triketochromane - 3 - phenylhydrazone with phenylhydrazine. An orange isomer which proved to be 1-phenyl-4-benzeneazo - 5 - (*o* - hydroxyphenyl) - 3 - pyrazolone also arises in this reaction.

3. A product identical to the dimethyl ether of 1-phenyl-3-(*o*-hydroxyphenyl)-4-benzeneazo-5-pyrazolone was prepared from the progenitor having the pyrazolone ring, 1-phenyl-3-(*o*-methoxyphenyl)-5-pyrazolone, by coupling with diazotized aniline. The resulting product was converted to the dimethyl ether by reaction with diazomethane.

4. A product identical to the amine derivable by reduction from 1-phenyl-4-benzeneazo-5-(*o*-hydroxyphenyl)-3-pyrazolone was also synthesized from 1-phenyl-5-(*o*-methoxyphenyl)-3-pyrazolone. The amine, 1-phenyl-4-amino-5-(*o*-hydroxyphenyl)-3-pyrazolone, was prepared by nitrating 1 - phenyl - 5 - (*o* - methoxyphenyl) - 3 - pyrazolone in the 4-position, reduction to the 4-amino product and demethylation of the 4-amino product.

5. A rationalization for the cleavage of 3,3'-methylenebis-(4-hydroxycoumarin) by phenylhydrazine has been offered.

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(13) Fischer, *Ann.*, **190**, 130 (1878).

(14) Prepared by Dr. Miyoshi Ikawa.

(15) Ullmann, *J. prakt. Chem.*, (2) **36**, 249 (1887).