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THE REACTION OF FLAVANONE WITH HYDRAZINE

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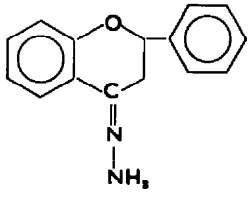
Abstract—The interaction of flavanone and hydrazine hydrate can be directed to yield flavanone hydrazone, 3-(*o*-hydroxyphenyl) 5-phenylpyrazoline, or flavanone azine as the main product. The structures of these compounds have been proved by hydrolysis, acetylation, and other simple reactions. Pyrazoline formation does not proceed through the isolated hydrazone, and must involve either a stereoisomeric form of flavanone hydrazone, or occur with the hydrazinolysis of the flavanone ring.

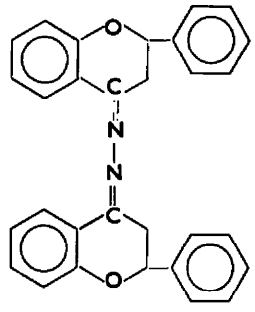
THE reactivity of the C_4 carbonyl of flavonoids with reagents for the carbonyl group has been receiving increasing interest; this is motivated partly by theoretical aspects to obtain more information about the ketonic character of various γ-pyrone derivatives, and partly by the practical significance of preparing flavonoid compounds of the 4-ol, 3,4-diol or catechol type by means of indirect reduction. Such a possibility has been demonstrated by Bognár *et al.*[1] by synthesizing α-4-hydroxyflavan as well as flavan-3,4-diols through the 4-oximino derivatives.

As part of a research program to investigate theoretical and practical aspects in the preparation of C_4-substituted flavonoid compounds, the reaction of flavanone with hydrazine has been investigated. The interaction of these reagents was reported recently by Venturella[2] who obtained, instead of the expected hydrazone, 3-(*o*-hydroxyphenyl) 5-phenylpyrazoline, m.p. 89–90°, and noted the formation of an unidentified yellow by-product.

We were able to select reaction conditions such that any one of the three simple products: the hydrazone (I), the azine (II), or the pyrazoline derivative (III) may be obtained as the main product.



I



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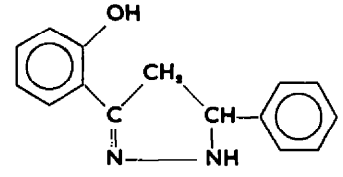


III

Though the corresponding compounds of flavone have been prepared in an indirect way,[3] the first two simple derivatives of flavanone (I and II) have not yet been described.

[1] R. Bognár, M. Rákosi, H. Fletcher, E. M. Philbin, T. S. Wheeler, *Tetrahedron Letters* 4 (1959).
[2] P. Venturella, *Atti Accad. Sci., Lettere Arti Palermo* **21**, 23 (1962).
[3] W. Baker, J. B. Harborne, W. D. Ollis, *J. Chem. Soc.* 1303 (1952).

The main factors deciding the course of the reaction are pH and temperature. Excess hydrazine must be employed in each case in order to avoid secondary reactions leading to the formation of azine. Especially large excess of the reagent is required to obtain a fair yield of the pyrazoline. The conditions conducive to the preponderant formation of one or the other product are shown in Table 1.

TABLE 1

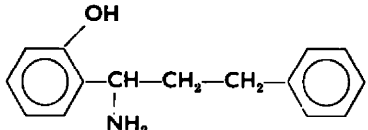
Medium	Temperature °C	Time of reaction	Reagent	Molar ratio, flavanone: hydrazine	Product (unpurified) M.p., °C.	Yield, %
Pyridine	100	6 hr	$NH_2NH_2.HCl$	1:4·6	Azine 260–7°	71·8
EtOH—H_2O (NaOAc)	100	13 hr	$NH_2NH_2.HCl$	1:4·6	243–56°	70·5
Acetic acid	22	24 hr	$NH_2NH_2.H_2O$	1:4	Azine 254–60°	92·3
Acetic acid	100	3 hr	$NH_2NH_2.H_2O$	1:4	Azine 263–7° + Unknown 206–10°	83·7 2·1
Ethanol	22	10 days	$NH_2NH_2.H_2O$	1:4	Hydrazone 109–113°	79·3
Ethanol	100	6 hr	$NH_2NH_2.H_2O$	1:4	Pyrazoline derivative 88–89·5° + flavanone + hydrazone mixture changing into azine	7·8
Ethanol	100	7 hr	$NH_2NH_2.H_2O$	1:18	Pyrazoline derivative 87–89° Hydrazone 109–113°	34·6 9·5

As it is seen from the Table, the use of a hydrazine salt or an acidic medium results invariably in the formation of the azine. The pure hydrazone can be prepared at room temperature, while formation of 3-(*o*-hydroxyphenyl) 5-phenylpyrazoline is favoured at higher temperatures. The structures of the products were proved as described below.

Flavanone hydrazone (I) can be hydrolysed by a special technique to flavanone. Simple heating in 5% hydrochloric acid gives quantitative yields of the azine. The hydrazone reacts with benzaldehyde to yield flavanone-benzaldazine, and with flavanone to produce flavanone azine. The pure hydrazone itself can give azine when heated in acetic acid as the result of partial hydrolysis, though this reaction is much slower. Acetylation of flavanone hydrazone yields the expected monoacetyl derivative, but, at higher temperatures N-diacetyl-flavanone hydrazone is probably formed.

The structure of *flavanone azine* (II) follows unequivocally from the analysis, mol. wt., and from the following experiments: The compound shows no colour reaction with ferric chloride. It can be synthesized from flavanone hydrazone (I) and flavanone. Hydrolysis of the azine in a mixture of dioxan–hydrochloric acid gives flavanone.

The compound is recovered unchanged after attempted acetylation. Catalytic hydrogenation results in the absorption of 5 moles of hydrogen to give 1-amino-1-(*o*-hydroxyphenyl) 3-phenylpropane (IV), isolated as the N,O-diacetyl derivative, and identical with the compound prepared by Bognár *et al.*[4,5] in a different way.



IV

3-(o-*Hydroxyphenyl*) 5-*phenylpyrazoline* (III). This product described by Venturella,[2] is unstable when a solution is exposed to air. This is in accordance with the known tendency of pyrazolines to oxidize.[6]

The experiments of Venturella concerning the structure were confirmed by preparing the same pyrazoline from 2'-hydroxychalkone and hydrazine hydrate, both at reflux and room temperatures.

Acetylation gives the known[2] N,O-diacetyl derivative, but when the pyrazoline is simply heated in acetic acid, the N-monoacetyl derivative is obtained. The same compound may also be prepared by heating 2'-hydroxychalkone with hydrazine hydrate in acetic acid.

Finally, the reaction mechanism was considered. The preponderant formation of the azine in acidic medium can be readily interpreted from the fact that flavanone hydrazone reacts rapidly with flavanone even in the presence of a considerable excess of free hydrazine, due to the insolubility and complete separation of the azine from the reaction mixture.

Concerning the mechanism of the pyrazoline formation, the hydrazone isolated cannot be an intermediate of this reaction. Heating the hydrazone in alcohol either alone or in the presence of hydrazine under conditions identical with those employed in the preparation of the pyrazoline, do not convert this starting material into the N-heterocyclic compound; even the very sensitive ferric chloride reaction does not indicate any change.

This result apparently contradicts the hypothesis[7] that pyrazoline synthesis usually involves preliminary hydrazone formation. This view can be maintained only by assuming that when the reaction mixture is hot, a stereoisomer of the hydrazone is produced and that this cyclizes to the pyrazoline derivative. This assumption is analogous to the problems discussed by Auwers and Seyfried[8] concerning the configuration and conversion of unsaturated oximes into isoxazolines or isoxazoles. Stuart and Dreiding models of the two stereoisomeric flavanone hydrazones clearly show that the *syn* form (IIs; the $—NH_2$ group directed towards the phenyl group) can easily be rearranged into a pyrazoline, whereas the *anti* form cannot.

To verify this point, an attempt was made to convert the isolated hydrazone (which

[4] R. Bognár, M. Rákosi, H. Fletcher, D. Kehoe, E. M. Philbin and T. S. Wheeler, *Tetrahedron* **18**, 135 (1962).

[5] H. Fletcher, E. M. Philbin, T. S. Wheeler, R. Bognár, M. Rákosi, *Magyar Kémiai Folyóirat* **68**, 465 (1962).

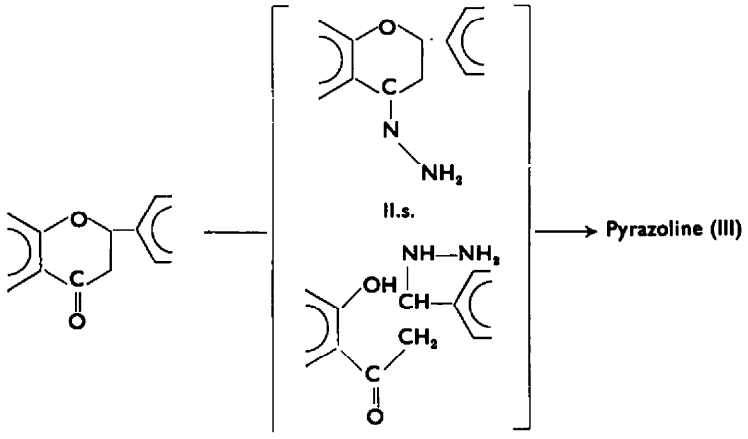
[6] *Heterocyclic Compounds* (Edited by R. C. Elderfield) Vol. 5; p. 108. J. Wiley, New York (1957).

[7] *Heterocyclic Compounds* (Edited by R. C. Elderfield) Vol. 5, pp. 62–63. J. Wiley, New York (1957).

[8] K. V. Auwers and M. Seyfried, *Liebigs Ann.* **484**, 178 (1930).

should be the *anti* form) into its stereoisomer (IIs) by irradiation with UV light, and thus obtain the pyrazoline by subsequent heating in alcohol. This procedure did not produce any change in the ferric chloride test, nor could any pyrazoline be detected by thin-layer chromatography.

Though this negative result cannot be accepted as evidence, it is reasonable to consider another possibility, namely, to interpret pyrazoline formation through the hydrazinolysis of the flavanone molecule (V), involving the cleavage of the —O—C_2 bond.



V

If this assumption is correct, the reaction should be analogous to the results of Auwers and Brink[9] who demonstrated that various chalkones usually react with hydroxylamine in acidic medium with the formation of the oxime, while in alkaline medium more often the isoxazoline is formed, usually together with the hydroxylamino oxime. The presence of the latter compounds is, in our opinion, a clear indication that the carbon atom corresponding to the C_2 atom of a flavonoid is attacked in those cases leading to isoxazoline formation. Considering the basicity of hydrazine hydrate, formation of some 2'-hydroxychalkone on heating and its immediate reaction according to this mechanism cannot be excluded.

In terms of this interpretation it can be said that while in the presence of acids protonation of the γ-dihydropyrone oxygen atom induces the carbonyl group to react almost exclusively as a ketone, at the pH of ethanolic or aqueous hydrazine, ring cleavage together with the former reaction appear to take place simultaneously; higher temperatures favour ring opening.

Since this research suggests the existence of stereoisomeric hydrazones and may produce useful information about the mechanism of pyrazoline formation, further investigations along these lines are desirable.

EXPERIMENTAL

All m.ps were determined on a Kofler block, and are uncorrected.

Flavanone hydrazone (I)

Flavanone (5 g, 0·0223 mole) was dissolved in anhydrous ethanol (100 ml) at room temp. Hydrazin hydrate (50%; 9 ml; 0·09 mole) was added, and the solution kept at about 22°. After 10 days,

[9] K. v. Auwers and H. Brink, *Liebigs Ann.* **493**, 218 (1932).

long white needles (1·99 g), m.p. 109–112° were filtered off. The mother liquor was heated to the b.p. and an equal volume of hot water (110 ml) added. On cooling, slightly yellowish crystals (2·22 g) separated, m.p. 109–111°. The products were combined and recrystallized from ethanol (40 ml) in the presence of 50% hydrazine hydrate (1 ml) then from pure ethanol to give pure flavanone hydrazone (2·7 g), m.p. 109–112°. The compound gave only a very slight yellow colour with $FeCl_3$ on filter paper, none in ethanolic solution. (Found: C, 75·20, 75·36; H, 6·03, 6·16; N, 11·4, 11·6; O (direct), 6·41%. Mol. wt. (Barger method), 229. $C_{15}H_{14}ON_2$ (238·29) requires: C, 75·6; H, 5·91; N, 11·71; O, 6·71%).

Flavanone azine (II)

(a) *From flavanone hydrazone and flavanone.* Flavanone hydrazone (119 mg; 0·005 mole) and flavanone (112 mg; 0·005 mole) were refluxed in ethanol (4 ml) in the presence of 96% acetic acid (0·5 ml) for 1 hr. From the first minute of boiling, the separation of yellow needles was observed. The product (199·4 mg; 90%) melted at 256–267°.

(b) *From flavanone and hydrazin monohydrochloride.* Flavanone (3·0 g; 0·0134 mole) in pyridine (30 ml) was refluxed 2 hr with hydrazine monohydrochloride (3·0 g; 0·0438 mole) in water (15 ml). The product (2·39 g) was dissolved in warm chloroform (250 ml). Addition of hot ethanol (300 ml) and cooling gave flavanone azine (2·2 g; 74%), m.p. 262–269°. The product recrystallizes from dioxan or benzene. (Found: C, 81·36, 81·17; H, 5·81, 5·50; N, 6·15, 6·36; O (direct) 8·22. Mol. wt. (Rast method): 469. $C_{30}H_{24}O_2N_2$ (444·51) requires: C, 81·2; H, 5·45; N, 6·32; O, 7·22%).

(c) *From flavanone and hydrazine hydrate.* Flavanone (1·0 g; 0·00446 mole) was dissolved in 96% acetic acid (10 ml). Hydrazine hydrate (50%; 1·8 ml; 0·018 mole) was slowly added, and the mixture kept at about 22° for 24 hr. The azine (911·7 mg; 92·3%) separated, m.p. 254–260°.

3-(o-*Hydroxyphenyl*) 5-*phenylpyrazoline* (III)

(a) *From flavanone.* Flavanone (1·0 g; 0·00446 mole) in ethanol (20 ml) was refluxed with 50% hydrazine hydrate (8 ml; 0·08 mole) for 7 hr. Concentrating the solution gave crystals of nacreous lustre (368·2 mg, 34·6%). Recrystallization from ethanol (6 ml) yielded the pyrazoline, m.p. 88–89·5° (no depression in mixed m.p. with the pyrazoline prepared from 2'-hydroxychalkone, see below). (Found: C, 75·34, 75·32; H, 6·32, 6·04; N, 11·98, 11·79; O (direct) 6·35%. $C_{15}H_{14}ON_2$ (238·3) requires: C, 75·6; H, 5·91; N, 11·71; O, 6·71%). The substance gave with $FeCl_3$ a dark green colour in solution, almost black on filter paper.

Evaporating the first mother liquor to a small volume at room temp yielded flavanone hydrazone (101 mg, 9·5%), m.p. 109–112°.

(b) *From 2'-hydroxychalkone.* 2'-Hydroxychalkone (2·0 g, 0·00892 mole) was refluxed in ethanol (50 ml) with hydrazine hydrate (50%; 26 ml, 0·256 mole) for 3 hr. The pyrazoline (1·406 g) crystallized on cooling and the mother liquor gave a second crop (303 mg; total yield 80·2%). Recrystallization from ethanol afforded the substance with m.p. 89–90·5°.

Less pure pyrazoline (1·75 g; m.p. 87–89°) was obtained when 2'-hydroxychalkone (2·0 g) and hydrazine hydrate (50%; 3·6 ml) in ethanol (60 ml) were allowed to stand 10 days, and the solution diluted with water.

Hydrolysis of flavanone hydrazone

Flavanone hydrazone (200 mg) in ethanol (15 ml) was added dropwise to boiling 5% HCl (36·5 g) during 15 min. The hot solution after filtering off a very small amount of the azine was allowed to cool. The crystallized product (135 mg; 67·5%) had m.p. 75–77° alone or in admixture with an authentic sample of flavanone.

On the other hand, when hydrolysis was attempted by heating together an alcoholic solution of flavanone hydrazone with dil. HCl aq, 73·5% of the azine was obtained.

Flavanone-benzaldazine

Flavanone hydrazone (238 mg; 0·001 mole) was dissolved in ethanol (4 ml), and mixed with benzaldehyde (106 mg; 0·001 mole) in ethanol (1 ml). The solution deposited yellow needles, and after standing overnight, yielded 313·2 mg (96·2%) of the product, m.p. 152–153° from ethanol. (Found: C, 81·00, 80·94; H, 5·60; 5·62; N, 8·80; 8·72; $C_{22}H_{18}ON_2$ (326·38) requires: C, 80·95; H, 5·55; N, 8·59%).

Acetylation of flavanone hydrazone

Flavanone hydrazone (200 mg) was heated at 100° for 3 hr in pyridine (4 ml) and acetic anhydride (4 ml). The solution was poured into 20% acetic acid (25 ml). Recrystallization of the crude product (174 mg) from ethanol gave pure monoacetylflavanone hydrazone (95 mg), m.p. 150–152·5°. (Found: C, 72·33, 71·81; H, 5·89, 5·81; N, 9·45, 9·69; CH_3CO, 14·5; 16·7%. $C_{17}H_{16}O_2N_2$ (280·32) requires: C, 72·8; H, 5·75; N, 9·99; CH_3CO, 15·34%).

A product obtained under more drastic conditions (140°), m.p. 179–180°, may be the diacetyl derivative. (Found: N, 8·92. $C_{19}H_{18}O_3N_2$ (322·35) requires: N, 8·70%).

Hydrolysis of flavanone azine

Flavanone azine (222 mg) dissolved in hot dioxan (30 ml) was heated with 1:1 HCl (5 ml) at 100° for 30 min. The residue obtained on evaporation was dissolved in hot ethanol (10 ml), and mixed with hot water (10 ml). Cooling gave flavanone (150·2 mg; 67·7%) m.p. 75–76° (alone, or in admixture with an authentic sample).

1-(o-*Acetoxyphenyl*) 3-*phenyl*-1-*acetaminopropane*

Flavanone azine (1·335 g; 0·003 mole) in acetic acid (150 ml) was hydrogenated at atm. press. and 22° in the presence of Pd-C (about 10% Pd); 320 ml of H_2 was absorbed in 8 hr. Calc. for 5 moles: 336·4 ml H_2 at 0°. The crude product obtained on evaporation was acetylated to give, after purification from acetone–ether, white crystals, (0·6 g) m.p. 160°. (Found: C, 74·67, 74·79; H, 6·90, 6·78; N, 4·47; 4·71. $C_{19}H_{21}O_3N$ (311·37) requires: C, 73·3; H, 6·80; N, 4·50%). The product was identical with the diacetyl derivative of 1-amino-1-(*o*-hydroxyphenyl) 3-phenylpropane (IV) prepared by the hydrogenation of 4-oximinoflavan.

Acetylation of 3-(o-*hydroxyphenyl*) 5-*phenylpyrazoline*

(a) *Diacetyl derivative.* 3-(*o*-Hydroxyphenyl) 5-phenylpyrazoline (245 mg) in pyridine (5 ml) and acetic anhydride (3 ml) was warmed at 100° for 1 hr. 1-Acetyl-3-(o-acetoxyphenyl) 5-phenylpyrazoline (291·5 mg; 88%) was obtained as white needles, m.p. 147–149° from ethanol. (Found: C, 70·90, 70·74; H, 5·92, 5·94; N, 8·62, 8·71; CH_3CO 21·09%. $C_{19}H_{18}O_3N_2$ (322·33) requires: C, 70·8; H, 5·62; N, 8·68; CH_3CO, 26·65%).

(b) N-*monoacetyl derivative.* The pyrazoline (300 mg) was heated in 96% acetic acid (15 ml) for 3 hr at 100°, and the solution poured into water (150 ml). The product (312 mg) recrystallized twice from ethanol melted at 136–138°. It gave a depression in mixed m.p. with the above diacetate, and showed a markedly positive $FeCl_3$ colour reaction. (Found: C, 72·21; 72·31; H, 5·87; 5·91; N, 9·94; 10·11; CH_3CO, 12·84. $C_{17}H_{16}N_2O_2$ (280·32) requires: C, 72·8; H, 5·75; N, 9·99; CH_3CO, 15·34%).

1-Acetyl-3-*o*-hydroxyphenyl-5-phenylpyrazoline (926 mg) could also be prepared from 2'-hydroxychalkone (1 g) and hydrazine hydrate (50%; 1·8 ml) in 96% acetic acid (10 ml), m.p. 135–138°. (Found: N, 10·05, 10·2). This product gave no depression with the N-monoacetyl derivative prepared from the pyrazoline.

Failure of pyrazoline formation from flavanone hydrazone

Flavanone hydrazone (1·0 g; m.p. 109–111°) dissolved in ethanol (20 ml) was refluxed on the steam-bath in the presence of hydrazine hydrate (50%; 8 ml) for 7 hr. The $FeCl_3$ colour reaction was found negative throughout the experiment. The solution was diluted with an equal volume of hot water. Flavanone hydrazone recovered in this way (737·2 mg; 73·7%) had m.p. 109–111°.

Another experiment without using hydrazine hydrate gave practically the same result with the difference that 65 mg of the azine was formed.

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