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THE REACTIONS OF FLAVANONE WITH SUBSTITUTED HYDRAZINES

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Abstract—The reactions of flavanone with seven substituted hydrazines (H_2N–NHR; R = CH_3, $CO{\cdot}NH_2$, $CS{\cdot}NH_2$, C_6H_5, $C_6H_4NO_2$, $C_6H_3(NO_2)_2$, and $CO{\cdot}CH_3$) have been examined. Of the three possible isomeric reaction products, the true flavanone carbonyl derivatives I are predominantly obtained under acidic conditions with the less basic carbonyl reagents; alkaline conditions or strongly basic reagents give the pyrazolines III; the 2'-hydroxychalkone derivatives II may be prepared by the alkaline ring cleavage of the hetero ring of I.

THE study of reactions with carbonyl reagents has been a comparatively neglected field of flavonoid chemistry, although products from such reactions hold considerable promise as key-substances of flavonoid interconversions; pharmacological interest may also be attached to some of the new compounds (e.g. the thiosemicarbazones as potential antiviral agents).

This paper presents a brief survey of the carbonyl reactions with hydrazines of one of the parent compounds, flavanone. Some contradictory data in the literature have been clarified, and the list of derivatives is extended. The conditions leading to the synthesis of a desired carbonyl derivative have been specified.

In the reaction of flavanone with a hydrazine, the formation of three isomers may be expected: the normal carbonyl derivative I, the 2'-hydroxychalkone hydrazone II and the 3-(*o*-hydroxyphenyl)5-phenylpyrazoline derivative III.

Products represented by I are obtained in neutral or acidic medium. Acid catalysis is particularly advantageous when the carbonyl reagent used has amphoteric character; otherwise, a salt of the substituted hydrazine and pyridine may be employed. The known examples in support of this statement (preparation of flavanone oxime,[1-3] hydrazone and azine,[4] semicarbazone,[3,5,6] phenylhydrazone,[7-9] 2,4-dinitrophenylhydrazone,[10] and *p*-tosylhydrazone[11]) have been completed in our present experi-

[1] R. Bognár, M. Rákosi, H. Fletcher, E. M. Philbin, T. S. Wheeler, *Tetrahedron Letters* 4 (1959).

[2] P. Venturella, A. Bellino, S. Cusmano, *Ann. Chim., Rome* **51**, 1074 (1961).

[3] M. A.-F. Elkaschef, M. H. Nosseir, H.-E.-D. M. Mohamed, *J. Chem. Soc.* 494 (1965).

[4] F. Kállay, G. Janzsó, I. Koczor, *Tetrahedron* **21**, 19 (1965).

[5] P. Venturella, *Atti Accad. Sci., Lettere Arti Palermo* **21**, 23 (1962).

[6] The contradiction in literature concerning the m.p. of flavanone semicarbazone, 150–151°[5] and 202°[3] has been decided by our present results in favour of the latter.

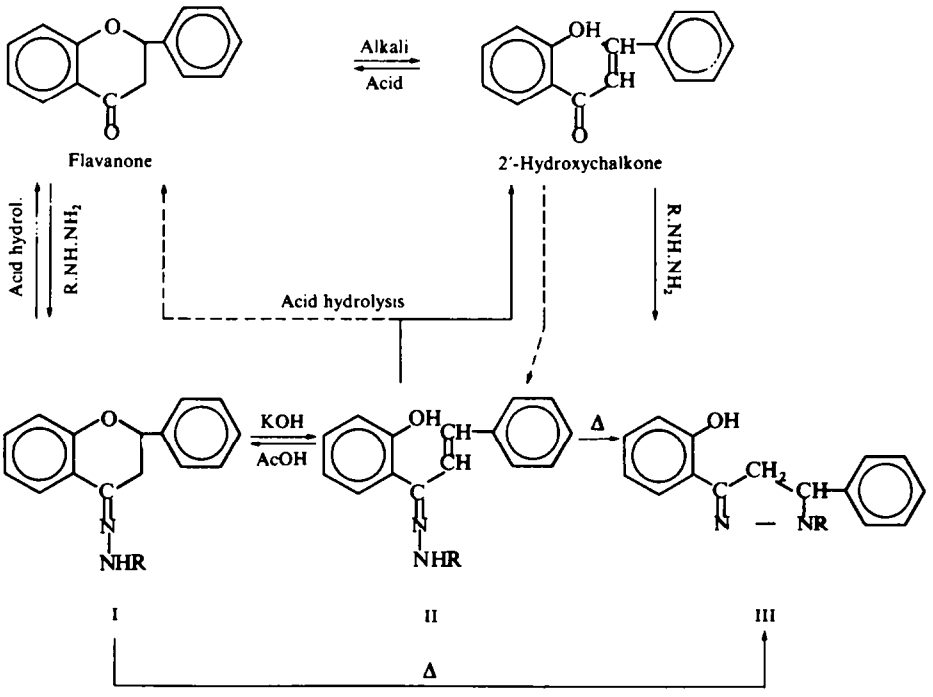
[7] H. de Diesbach, H. Kramer, *Helv. Chim. Acta* **28**, 1399 (1945).

[8] P. Venturella, A. Bellino, S. Cusmano, *Ann. Chim., Rome* **51**, 34 (1961).

[9] The material reported in literature[7,8] m.p. 147° was shown by TLC to contain much of the isomeric 3-*o*-hydroxyphenyl-1,5-diphenylpyrazoline. Pure flavanone phenylhydrazone prepared under N_2 and purified by extraction with petr. ether has m.p. 129–133°.

[10] R. Mozingo, H. Adkins, *J. Am. Chem. Soc.* **60**, 669 (1938).

[11] G. Janzsó, F. Kállay, I. Koczor, *Tetrahedron* **22**, 2909 (1966).



ments by the syntheses of *flavanone thiosemicarbazone* (I; R = $CS \cdot NH_2$; in four ways) and *flavanone 4-nitrophenylhydrazone* (I; R = $C_6H_4 \cdot NO_2$). The structure of the 2,4-dinitrophenylhydrazone[10] is unequivocally confirmed by an indirect synthesis from flavanone hydrazone[4] and 1-chloro-2,4-dinitrobenzene. This series of normal carbonyl reactions is further supplemented by a direct synthesis of the formerly prepared[12] monoacetylflavanone hydrazone (I; R = $CO \cdot CH_3$), from flavanone and monoacetylhydrazine. The structures of the new compounds were verified by their acid hydrolysis affording flavanone in each case, and by the IR spectra. The $FeCl_3$ colour reactions are negative.

The 2'-hydroxychalkone derivatives II are best synthesized indirectly from I by subsequent alkaline opening of the hetero ring. This is illustrated in the preparation of *2'-hydroxychalkone thiosemicarbazone* (II; R = $CS \cdot NH_2$), by treatment of the corresponding flavanone derivative I with KOH. The reverse reaction is achieved when II is heated in acetic acid. 2'-Hydroxychalkone derivatives II may be identified by their positive $FeCl_3$ colour test and acid hydrolysis which affords mainly the chalkone and some flavanone.

Formation of the pyrazoline derivatives III is favoured when the reaction is conducted under conditions promoting the cleavage of the dihydropyrone ring (strongly alkaline carbonyl reagent or medium; elevated temp). In the presence of KOH, the products and yields are the same whether flavanone or 2'-hydroxychalkone is used as the starting material, obviously owing to the well-known equilibrium between these two isomers.[13] The fact that various chalkones afford pyrazolines with phenyl-

[12] F. Kállay, G. Janzsó, I. Koczor, *Tetrahedron* **21**, 3037 (1965).
[13] É. Dávid-Rákosi and R. Bognár, *Acta Univ. Debreceniensis* **7**, 141 (1961).

hydrazine at elevated temperatures has been amply demonstrated,[14-16] and even the similar reaction of 2'-methoxychalkone epoxide has been reported.[17]

The thermal rearrangement of I and II also frequently leads to the pyrazoline derivative.[12]

According to these principles, 3-(*o*-hydroxyphenyl)1,5-diphenylpyrazoline[8] (III; R = C_6H_5) can be prepared by direct synthesis from flavanone, further the new compounds 1-*thiocarbamyl*-3-o-*hydroxyphenyl*-5-*phenylpyrazoline* (III; R = CS·NH_2) and 1-*methyl*-3-o-*hydroxyphenyl*-5-*phenylpyrazoline* (III; R = Me) are reported. The methiodide of the latter product and of its acetyl derivative have also been prepared.

Compounds III are readily distinguished from I and II, since they are resistant to both acidic and alkaline treatments, and are recovered unchanged; the $FeCl_3$ colour tests are positive.

The present work represents an extension of the synthetic methods[4, 12] used in the preparation of flavonoid carbonyl derivatives and their isomers. Work to elucidate the mechanism of these reactions and the stereochemistry of the products, by studying similar reactions of substituted flavanones is in progress.

EXPERIMENTAL

The optimum, or satisfactory, reaction times were selected by examining the reaction mixtures at intervals by TLC (Kieselgel HF_{254}; benzene-EtOAc 95:5, or toluene–ethyl formate–formic acid 5:4:1). All products described were found pure to TLC.

The IR spectrum of each compound was recorded as a means of identification or evidence of structure. All m.ps were determined on a Kofler block and are uncorrected.

Flavanone thiosemicarbazone (I; R = CS·NH_2)

A soln. of flavanone (224 mg; 1 mmole) and thiosemicarbazide (91 mg; 1 mmole) in hot EtOH (11 ml), containing HCl (2 drops), was refluxed for 10 hr. Cooling gave white crystals (225 mg; 78·5%), m.p. 205–208° (from EtOH).[18] (Found: C, 64·61; H, 5·15; N, 13·95; S, 10·63. Mol. wt. (Rast method): 287, 291. $C_{16}H_{15}ON_3S$ (297·36) requires: C, 64·62; H, 5·08; N, 14·12; S, 10·78%.)

The same compound could also be synthesized by the similar reaction of thiosemicarbazide with flavanone oxime[1], hydrazone,[4] or 2'-hydroxychalkone, or by heating II (R = CS·NH_2) in glacial AcOH.

The hydrolysis of I (R = CS·NH_2) with 5% HCl gave flavanone.

The *diacetyl derivative* I (R = CS·$N(Ac)_2$) was obtained with Ac_2O–pyridine (100°; 5 hr), m.p. 196–198°. (Found: N, 10·97; S, 8·53; CH_3CO, 23·16. $C_{20}H_{19}N_3O_3S$ (381·43) requires: N, 11·01; S, 8·40; CH_3CO, 22·56%.)

Flavanone 4-nitrophenylhydrazone (I; R = $C_6H_4NO_2$)

Flavanone (1·12 g; 0·005 mole) and 4-nitrophenylhydrazine (766 mg; 0·005 mole) were refluxed 1 hr in EtOH (25 ml) containing HCl (1 ml). The mixture gave on cooling orange–yellow crystals (1·7 g; 94%) m.p. 256–257° (from EtOH). (Found: C, 70·77; H, 4·76; O, 13·39; N, 11·87. $C_{21}H_{17}O_3N_3$ (359·37) requires: C, 70·15; H, 4·76; O, 13·35; N, 11·69%.)

I (R = $C_6H_5NO_2$) (200 mg) was hydrolysed at 100° in a mixt. of HCl (5·5 ml), water (20 ml) and dioxan (20 ml) to flavanone, m.p. 75–76°.

[14] L. C. Raiford and W. J. Peterson, *J. Org. Chem.* **1**, 544 (1937).
[15] A. E. A. Sammour, *Tetrahedron* **20**, 1067 (1964).
[16] K. C. Joshi and A. K. Jauhar, *J. Ind. Chem. Soc.* **42**, 10 (1965).
[17] R. Bognár and Gy. Litkei, *Magyar Kém. Foly.* **70**, 445 (1964).
[18] The same compound has been synthesized independently by R. Bognár and M. Rákosi (Personal communication from Prof. Bognár).

Flavanone 2,4-dinitrophenylhydrazone (I; R = $C_6H_3(NO_2)_2$)

A soln of flavanone hydrazone[4] (238 mg; 1 mmole), 1-chloro-2,4-dinitrobenzene (202 mg; 1 mmole) and anhyd NaOAc (164 mg; 2 mmole) in 95% EtOH (15 ml) was refluxed for 10 hr. The product (164 mg; 40·6%) was recrystallized from n-butanol, m.p. 252–255° (lit.[10] m.p. 254–255°).

According to TLC and the IR spectrum this product was identical with flavanone 2,4-dinitrophenylhydrazone (m.p. 260–261°, from n-BuOH or $CHCl_3$) prepared from flavanone and 2,4-dinitrophenylhydrazine in the presence of HCl catalyst.

Monoacetylflavanone hydrazone (I; R = $CO \cdot CH_3$)

A soln of flavone (0·5 g) and monoacetylhydrazine (200 mg) in EtOH (30 ml) was refluxed 12 hr and allowed to stand overnight. The product separated on evaporation in white needles (138 mg), m.p. 208–210° (lit.[12] m.p. 206–209°). Identity with an authentic sample[12] was shown by the IR spectra.

2'-Hydroxychalkone thiosemicarbazone (II; R = $CS \cdot NH_2$)

(a) *From flavanone thiosemicarbazone.* I (R = $CS \cdot NH_2$) (200 mg) in EtOH (18 ml) was refluxed 1 hr with KOH (2 g) in H_2O (2 ml). The soln was neutralized to pH 7 with AcOH and diluted with hot water (45 ml). The yellow ppt (201 mg) was recrystallized from aqueous EtOH, then from $CHCl_3$ until a product pure to TLC, m.p. 174–177°, was obtained. (Found: C, 64·21; H, 5·15; O, 5·11; N, 13·40; S, 10·60. Mol. wt. (Barger method): 308. $C_{16}H_{15}ON_3S$ (297·36) requires: C, 64·62; H, 5·08; O, 5·38; N, 14·12; S, 10·78%.) The freshly prepared compound is white, but it soon becomes yellow on standing.

The presence of OH in a strong hydrogen bond and the CH=CH *trans* grouping was shown by the IR and NMR spectra.

(b) *From 2'-hydroxychalkone.* The same product (540 mg) was directly obtained from 2'-hydroxychalkone (2·24 g) as a by-product of the preparation of III (R = $CS \cdot NH_2$).

II (R = $CS \cdot NH_2$) was hydrolysed by dilute aqueous-ethanolic HCl to 2'-hydroxychalkone, m.p. 90–91°, and a small quantity of flavanone.

II (R = $CS \cdot NH_2$) (1·59 g) with pyridine (32 ml) and Ac_2O (24 ml) (100°; 2 hr) gave *2'-acetoxychalkone diacetylthiosemicarbazone* (1·1 g), m.p. 148–152° from EtOH. (Found: S, 7·50; CH_3CO, 29·78. $C_{22}H_{21}O_4N_3S$ (423·47) requires: S, 7·57; CH_3CO, 30·47%.)

3-o-Hydroxyphenyl-1,5-diphenylpyrazoline (III; R = Ph)

A soln of flavanone (224 mg; 1 mmole) and phenylhydrazine (0·2 ml) in EtOH (10 ml) was refluxed 2 hr with KOH (0·1 g) in H_2O (0·5 ml) under N_2. Neutralization and addition of hot water (20 ml) gave white crystals (300 mg), m.p. 166–168° (from EtOH). (TLC system: benzene-petr. ether 75:25). Lit.[8] m.p. 164–165°.

1-Thiocarbamyl-3-o-hydroxyphenyl-5-phenylpyrazoline (III; R = $CS \cdot NH_2$)

(a) *From 2'-hydroxychalkone or flavanone.* 2'-Hydroxychalkone (or flavanone) (2·24 g; 0·01 mole) and thiosemicarbazide (910 mg; 0·01 mole) in EtOH (200 ml) were refluxed 7 hr with KOH (1·0 g) in H_2O (5 ml). The soln was filtered, neutralized to pH 6 and diluted with water. The product (1·2 g) had m.p. 237–240° from EtOH. (Found: C, 64·56; H, 5·30; O, 6·04; N, 13·85; S, 10·54. $C_{16}H_{15}ON_3S$ (297·36) requires: C, 64·62; H, 5·08; O, 5·38; N, 14·12; S, 10·78%.)

The mother liquor gave on further dilution with water II (R = $CS \cdot NH_2$) (356·4 mg), m.p. 170–174°.

(b) *From flavanone thiosemicarbazone.* Thermal rearrangement of I (R = $CS \cdot NH_2$; 30 mg) at 215° for 10 min in a sealed capillary tube under N_2 gave a mixture whose main component was shown by TLC to consist of III (R = $CS \cdot NH_2$).

As expected, III (R = $CS \cdot NH_2$) was resistant to boiling 3% HCl, and was recovered after 1 hr unchanged.

III (R = $CS \cdot NH_2$) gave on usual acetylation glistening yellow crystals of *1-diacetylthiocarbamyl-3-o-acetoxyphenyl-5-phenylpyrazoline*, m.p. 151–154°. (Found: C, 62·61; H, 5·53; O, 15·29; N, 9·95; S, 7·50; CH_3CO, 27·02. $C_{22}H_{21}O_4N_3S$ (423·47) requires: C, 62·39; H, 4·99; O, 15·11; N, 9·92; S, 7·57; CH_3CO, 30·47%.)

1-Methyl-3-o-hydroxyphenyl-5-phenylpyrazoline (III; R = CH_3)

2'-Hydroxychalkone (or flavanone) (2·24 g; 0·01 mole) in EtOH (200 ml) was mixed with a soln of methylhydrazine sulphate (1·5 g; 0·0105 mole) and KOH (4·0 g) in H_2O (100 ml). The mixture was refluxed for 3 hr, filtered, adjusted to pH 7, and diluted with water. Cooling gave white crystals (2·22 g); m.p. 54–56° from

EtOH. (Found: C, 76·02; H, 6·89; O, 6·06; N, 11·16. $C_{16}H_{16}ON_2$ (252·31) requires: C, 76·16; H, 6·39; O, 6·34; N, 11·10%.)

The compound was recovered unchanged after attempted acid hydrolysis.

The *methiodide* of III (R = Me) was prepared with MeI in acetone, m.p. 201–204°. (Found: I, 32·20. $C_{17}H_{19}ON_2I$ requires: I, 32·19%.)

Acetylation gave 1-*methyl*-3-o-*acetoxyphenyl*-5-*phenylpyrazoline*, m.p. 95–97°. (Found: C, 73·47; H, 6·56; O, 10·78; N, 10·54; CH_3CO, 12·14. $C_{18}H_{18}O_2N_2$ (294·34) requires: C, 73·44; H, 6·15; O, 10·87; N, 9·51; CH_3CO, 14·61%.)

The *methiodide* of this acetyl derivative had m.p. 151–154°. (Found: I, 28·71; CH_3CO, 9·67. $C_{19}H_{21}O_2N_2I$ (436·29) requires: I, 29·08; CH_3CO, 9·92%.)

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