Tetrahedron, 1965, Vol. 21, pp. 3037 to 3041. Pergamon Press Ltd. Printed in Northern Ireland

THERMAL REARRANGEMENT OF 2'-HYDROXYCHALKONE HYDRAZONE AND FLAVANONE HYDRAZONE DERIVATIVES

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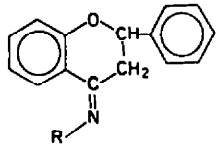
(*Received* 5 *May* 1965)

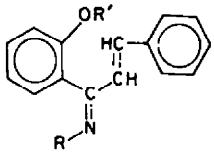
Abstract—2'-Hydroxychalkone hydrazone has been prepared by the alkaline ring opening of flavanone hydrazone. The new compound, its acetyl derivative, as well as flavanone hydrazone and its mono- and diacetyl derivative may be converted into the corresponding pyrazoline derivatives by thermal rearrangement above the m.p. A possible interpretation of the results is presented assuming the stereomutation of the hydrazino group.

IN A previous paper[1] we reported that flavanone hydrazone (I; R = NH_2) is not converted into the isomeric 3-(*o*-hydroxyphenyl)5-phenylpyrazoline (III; R = R' = H) under the conditions normally employed in the preparation of the latter compound. The corresponding conversion of flavanone oxime (I; R = OH) into 3-(*o*-hydroxyphenyl)5-phenylisoxazoline has been achieved by Venturella *et al.*[2] by heating the oxime in 10% potassium hydroxide solution. Therefore, the action of alkali on flavanone hydrazone has been investigated.

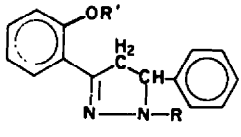
Treatment of the hydrazone with hot alcoholic potassium hydroxide solution yields a stable crystalline product giving a positive ferric chloride test, but yet different from the pyrazoline. An investigation of its structure has shown that the new compound is 2'-hydroxychalkone hydrazone (II; R = NH_2; R' = H).



I



II



III

In addition to the analysis and determination of the mol. wt. the following evidence in support of the proposed structure is given: The substance yields a benzal derivative (II; R = N:CHPh; R' = H) with benzaldehyde. Hydrolysis at 0° with hydrochloric acid gives 2'-hydroxychalkone accompanied by a small quantity of flavanone. The compound can be acetylated at 0° to 2'-acetoxy-N-monoacetylchalkone hydrazone (II; R = NHAc; R' = Ac). Partial deacetylation of this derivative affords monoacetylflavanone hydrazone (I; R = NHAc). In addition the IR spectra also confirmed the proposed structures of the 2'-hydroxychalkone hydrazone and its acetyl derivative.

The new hydrazone has not been synthesized previously, since 2'-hydroxychalkone and hydrazine give the pyrazoline (III; R = R' = H) at the b.p.[3] or even at room

[1] F. Kállay, G. Janzsó and I. Koczor, *Tetrahedron* **21**, 19 (1965).
[2] P. Venturella, A. Bellino and S. Cusmano, *Ann. Chim., Rome* **51**, 1074 (1961).
[3] P. Venturella, *Atti Accad. Sci., Lettere Arti Palermo* **21**, 23 (1962).

temp.[1] The fact that 2'-hydroxychalkone hydrazone is a perfectly stable compound resisting conversion into the N-heterocyclic isomer, undoubtedly shows that it is not the normal intermediate of pyrazoline formation. The reactions leading to the pyrazoline must, therefore, either start with addition of hydrazine to the double bond,[1] or involve another, extremely unstable form of 2'-hydroxychalkone hydrazone. If the latter is true, it is reasonable to conclude that the stability of the isolated chalkone hydrazone is due to the steric arrangement of the hydrazino group; molecular models reveal the impossibility of pyrazoline ring closure if the $—NH_2$ group of the hydrazone is directed towards the *o*-hydroxyphenyl group (Fig. 1). In accordance with the terminology used in our previous paper,[1] this is the *anti* configuration. It follows that the parent compound, flavanone hydrazone, must have this same steric arrangement.

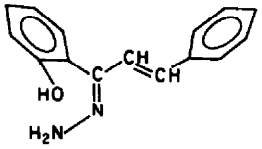


FIG. 1

In order to understand the reaction mechanism, conversion of the hypothetical *anti* compounds into the *syn* forms was attempted; the latter should cyclize instantaneously to 3-(*o*-hydroxyphenyl)5-phenylpyrazoline.

Irradiation with UV light of 185 mμ for 7 hr failed to accomplish the desired conversion. However, both 2'-hydroxychalkone hydrazone and flavanone hydrazone yield the pyrazoline when subjected to thermal rearrangement, by maintaining the compounds for 1–2 hr above their m.ps in a sealed capillary tube under nitrogen.

The clarity of this rearrangement is somewhat spoiled in the case of the free hydrazones by the formation of appreciable quantities of flavanone azine. In order to eliminate the disproportionation side-reaction, the monoacetyl derivative of flavanone hydrazone has been prepared.* This latter compound is identical with the substance shown in our former paper, Table 1, as an unknown by-product. The thermal rearrangement of monoacetylflavanone hydrazone (I; R = NHAc) gives the pure monoacetylpyrazoline (III; R = Ac; R' = H) in a practically quantitative yield. Analogously, both diacetylflavanone hydrazone (I; R = $N(Ac)_2$) and the diacetylchalkone hydrazone (II; R = NHAc; R' = Ac) afford the diacetylpyrazoline (III; R = R' = Ac), though the conversions are accomplished here only at higher temperatures or with longer reaction periods (see Experimental). This rearrangement of diacetylflavanone hydrazone is of particular interest, since it must involve N → O acyl migration which can occur only if the groups involved are near to each other. This condition is met in the *anti* form only.

The products of thermal rearrangement were identified in each case by comparison with the authentic substances,[1] by thin-layer chromatography, mixed m.p. determination, and by the IR fingerprint method.

* It must be noted here, that the acetyl derivative of m.p. 150–152° reported previously[1] has been proved by IR spectroscopy and repeated analysis to be actually N,N-diacetylflavanone hydrazone; the true monoacetyl derivative, m.p. 206–209°, has been obtained from this product by partial deacetylation with $KHCO_3$.

TABLE 1. THERMAL REARRANGEMENTS

Starting material	M.p. °C	Temperature of react.	Time °C	Product of thermal rearrangement	M.p. °C	Lit. m.p. °C	By-product
Flavanone hydrazone (I; R = NH_2)	109–111°	150°	2 hr	Pyrazoline (III; R = R′ = H)	82–88°	89–90°	Flavanone azine
2′-Hydroxychalkone hydrazone (II; R = NH_2; R = H)	153–157°	170°	1 hr	Pyrazoline (III; R = R′ = H)	82–86°	89–90°	Flavanone azine
Monoacetylflavanone hydrazone (I; R = NHAc)	206–209°	200–210°	1 hr	N-Monoacetylpyrazoline (III; R = Ac; R′ = H)	134–137°	136–138° [1]	None
Diacetylflavanone hydrazone (I; R = $N(Ac)_2$)	151–153°	200–210°	1 hr	N,O-Diacetylpyrazoline (III; R = R′ = Ac)	146–150°	149–150° [2]	
Diacetylchalkone hydrazone (II; R = NHAc; R′ = Ac)	164–167°	200–210°	2 hr	N,O-Diacetylpyrazoline (III; R = R′ = Ac)	132–142°	149–150° [2]	
Flavone hydrazone	135–138°	150°	1 hr	3(5)-*o*-Hydroxyphenyl-5(3)-phenylpyrazole	142–146°	144° [4]	None

A rather rash generalization of the results suggests an interesting hypothesis that the true carbonyl derivatives of flavonoids if isolated have the *anti* configuration; the corresponding *syn* forms being unknown, since if produced they would undergo cyclization to the N-heterocyclic isomers. This method of thermal rearrangement may provide a useful tool for a further investigation of this problem, and of *syn-anti* stereoisomerism in general.

As the first step along these lines, flavone hydrazone (prepared through 4-thionflavone as described by Baker *et al.*[4]) was subjected to thermal rearrangement, the product being 3(5)-*o*-hydroxyphenyl-5(3)-phenylpyrazole. This compound was synthesized by Baker *et al.*[4] from *o*-hydroxydibenzoylmethane, and by us directly from flavone and hydrazine hydrate. The details of this research will be reported later.

EXPERIMENTAL

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

2'-Hydroxychalkone hydrazone (II; R = NH_2; R' = H)

The compound may be prepared in KOH solutions varying in concentration between 0·5 and 10%; the range between 2·5 and 5% being optimal.

Flavanone hydrazone[1] (2·0 g) in EtOH (180 ml) was refluxed with KOH (10 g) in water (10 ml) for 1 hr. After cooling, the yellow solution was neutralized with acetic acid (phenolphthalein) and hot water (200 ml) was added. After standing in a refrigerator, yellow crystals (1·2 g; 63·2%) were deposited and recrystallized twice from EtOH (31 ml solvent per 1 g of substance) to give 2'-hydroxychalkone hydrazone, m.p. 153–157°, examined by thin-layer chromatography (Kieselgel HF_{254}; benzene–ethyl acetate 95:5). (Found: C, 75·75, 75·30; H, 5·86, 5·60; N, 11·78, 11·43; O (direct) 6·91, 7·08; Mol. wt. (Rast method): 253. $C_{15}H_{14}ON_2$ (238·3) requires: C, 75·6; H, 5·91; N, 11·71; O, 6·71%.)

IR analysis: C=N at 1638 cm^{-1}; CH=CH *trans* vibration at 988 cm^{-1}; NH vibrations at 3395 and 3210 cm^{-1}. The presence of O . . . H . . . N hydrogen bonding is shown.

The yield of hydrazone is improved (77%) if the above procedure is carried out in the presence of hydrazine hydrate (50%; 1·8 ml).

2'-Hydroxychalkone-benzaldazine (II; R = N:CHPh; R' = H)

2'-Hydroxychalkone hydrazone (144 mg, 0·61 mmole) dissolved in EtOH (20 ml) was mixed with benzaldehyde (212 mg, 2·00 mmole) in EtOH (1 ml), and the solution allowed to stand 24 hr at room temp, then 24 hr in a refrigerator.

The yellow needles (122·9 mg, 62·2%) were recrystallized from EtOH to give the benzylidene derivative of 2'-hydroxychalkone hydrazone, m.p. 128–130°. (Found: C, 80·44, 80·38; H, 5·46, 5·50, N, 8·19, 8·09; Mol. wt. (Rast method): 329, 318. $C_{22}H_{18}ON_2$ (326·38) requires: C, 80·95; H, 5·55; N, 8·59%.)

2'-Acetoxychalkone-N-monoacetylhydrazone (II; R = NHAc; R' = Ac)

2'-Hydroxychalkone hydrazone (400 mg) in a mixture of ice-cold pyridine (8 ml) and acetic anhydride (6 ml) was allowed to stand 6 days in a refrigerator and then poured into ice water (200 ml). Recrystallization of the product (481 mg) from MeOH (6·5 ml) gave large crystals of the diacetyl derivative, m.p. 166–169°. (Found: C, 70·75, 71·20; H, 5·63, 5·83; N, 8·79 8·66; CH_3CO, 28·04, 28·11; $C_{19}H_{18}O_3N_2$ (322·33) requires: C, 70·8; H, 5·62; N, 8·68; CH_3CO, 26·65%.)

The IR spectrum showed the following characteristic vibrations: C=O at 1770 cm^{-1} (in phenolic ester); C=O at 1665 (Amide I band); C—O— at 1190 cm^{-1}, and NH at 3180 cm^{-1}.

Diacetylflavanone hydrazone (I; R = $N(Ac)_2$)

Flavanone hydrazone (500 mg) was heated at 100° for 3 hr in pyridine (10 ml) and acetic anhydride (10 ml) and then poured into 20% acetic acid (75 ml). Repeated recrystallization of the crude product

[4] W. Baker, J. B. Harborne and W. D. Ollis, *J. Chem. Soc.* 1303 (1952).

(350 mg) from EtOH gave pure N,N-diacetylflavanone hydrazone (251 mg), m.p. 151–153°. (Found: C, 70·37, 70·45; H, 5·70, 5·54; N, 8·19, 8·30; CH_3CO, 25·51, 26·27; $C_{19}H_{18}O_3N_2$ (322·35) requires: C, 70·70; H, 5·58; N, 8·70; CH_3CO, 26·68%.)

Monoacetylflavanone hydrazone (I; R = NHAc)

(a) *From diacetylflavanone hydrazone.* Diacetylflavanone hydrazone (1·0 g) and $KHCO_3$ (2·0 g) were refluxed in 90% MeOH (100 ml) for 4 hr and the solution then concentrated to ⅓ of the original volume and hot water (200 ml) added. The crude product (435 mg) crystallized on cooling. Recrystallization from 96% EtOH gave white needles, m.p. 206–209°. (Found: C, 72·82, 73·0; H, 6·28, 6·32; N, 9·50, 9·51; CH_3CO, 15·62, 14·68; $C_{17}H_{16}O_2N_2$ (280·32) requires: C, 72·8; H, 5·75; N, 9·99; CH_3CO, 15·34%.)

(b) *From 2'-acetoxy-N-monoacetylchalkone hydrazone.* Repetition of the above procedure with acetylated 2'-hydroxychalkone hydrazone gave the same product in the same yield. Identity was proved by mixed m.p. and IR analysis.

Monoacetylflavanone hydrazone could be reacetylated by Ac_2O–Py to diacetylflavanone hydrazone, and it was hydrolysed by hydrochloric acid to flavanone.

Thermal rearrangements

The thermal rearrangement reactions were carried out on the 10–500 mg scale. The conversion of N-monoacetylflavanone hydrazone is given as an example. Conditions and results for the other substances are given in the Table on page 3039.

Monoacetylflavanone hydrazone (14·5 mg) was sealed in a capillary tube under N_2, and it was maintained in an oil bath at 200–210° for 1 hr. The tube was crushed, and its contents crystallized by mixing with a few drops of acetone or EtOH. The product (11·7 mg, m.p. 124–137°) was recrystallized from EtOH; m.p. 134–137°; Lit.[1] m.p. of N-acetyl-3-(*o*-hydroxyphenyl)5-phenylpyrazoline: 136–138°.

Complete identity of the product with the authentic substance was confirmed—as in all other cases—by mixed m.p. determination, comparison of the IR spectra, behaviour in thin-layer chromatography (in UV and visible light), and by colour tests.

Acknowledgements—The authors' thanks are due to Professor R. Bognár for reading the manuscript and his interest in this work; to Mr. L. Mánya for excellent technical assistance; to Miss I. Egyed for the IR analyses; and to Mrs. É. Dávid-Rákosi for the microanalyses.