in 2 cc. of 2% sodium hydroxide at 0°, and the mixture was left for 1 hr. It was acidified and the product which separated was crystallized from alcohol in light yellow needles, m.p. 260°. It did not depress the melting point of an authentic specimen of 5,6-dihydroxy-4,7-dimethylcoumarin prepared according to Parikh and Sethna.[1]

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BOMBAY, INDIA

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY INSTITUTE OF SCIENCE]

Stabilities of Nitrohydroxy Chalcones and Flavanones. Role of Hydrogen Bonding

S. SESHADRI AND P. L. TRIVEDI

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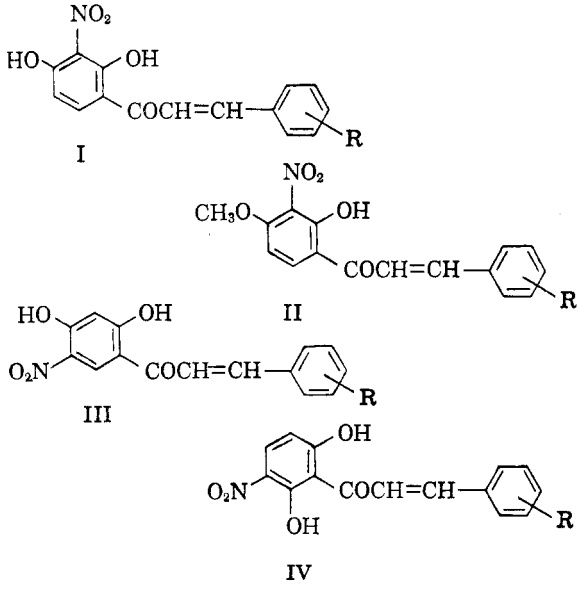
The cyclization of nitro-substituted chalcones to the flavanones has been studied for the first time. The effect of the nitro group on the reaction has been studied and it has been shown that the chelation of the nitro group with the 2'-hydroxyl group is an important factor in determining the stability of the chalcone. The properties of the chalcones and the flavanones have been studied and discussed.

The isomerization of nitro-substituted chalcones to flavanones does not appear to have been studied at all. The present work was, therefore, undertaken with a view to investigating the influence of the nitro group on the reaction.

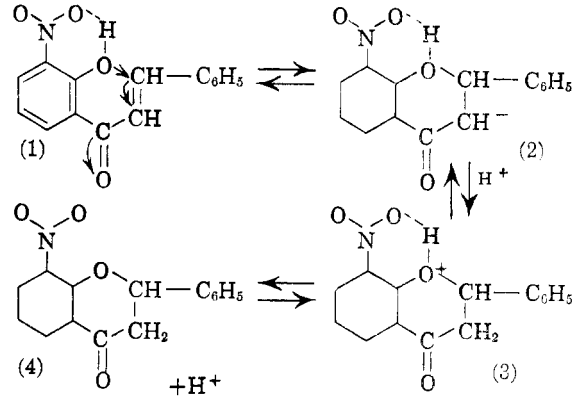
A number of new chalcones as well as a few known chalcones were prepared from nitro derivatives of 2,4-dihydroxyacetophenone and 2,6-dihydroxyacetophenone. The chalcones, prepared by the "cold alkaline condensation" method, were of four types, I–IV.



The cyclization of the chalcones was carried out by refluxing in aqueous alcoholic hydrochloric acid (3%). The flavanones were separated from the chalcones by fractional crystallization from suitable solvents. The times of refluxing and the yields of flavanones are set out in Table II.

All the flavanones were readily reconverted to the chalcones by warming with alkali solution and reacidifying. The flavanones from chalcones Ia–Ih were very unstable towards strongly acid solution, being completely converted to the chalcones in fifteen minutes. The flavanones of type III were more stable since only a part of the flavanone had reverted to the chalcone after boiling for an hour. The Group IV flavanones were unaffected by strongly acid solution.

The results obtained show that the nitro group has a profound influence on the behavior of nitrochalcones. The slow rate of cyclization of Group I chalcones and the high instability of the flavanone Ia towards acid solution indicate that the nitro group has a stabilizing effect on the chalcone. This effect is probably exerted in the manner shown.



The chelation of the *ortho* nitro group will prevent proton elimination at the last stage and retard the cyclization. On the same basis, the tendency of (4) to take up a proton will be much greater than the tendency of (3) to lose one and this accounts for the instability of the flavanone ring in acid medium. Crawford and Rasburn[1] have observed a similar stabilizing effect of the nitro group in 3-nitrocouma-

(1) M. Crawford and J. W. Rasburn, *J. Chem. Soc.*, 2155 (1956).

TABLE I

LIST OF CHALCONES PREPARED AND THEIR PROPERTIES

No.	Chalcone	Yield, %	H_2SO_4 Coloration	M.P., °C.	Formula	Analysis N, % Calcd.	Found
Ia	2′,4′-Dihydroxy-3′-nitro	20	Orange-red	173[a]	$C_{15}H_{11}NO_5$	4.91	4.96
Ib	2′,4′-Dihydroxy-3′-nitro-2-methoxy	25	Dark red	192[b]	$C_{16}H_{13}NO_6$	4.44	4.39
Ic	2′,4′-Dihydroxy-3′-nitro-4-methoxy	20	Red	172[c]	$C_{16}H_{13}NO_6$	4.44	4.43
Id	2′,4′-Dihydroxy-3′-nitro-4-methoxy	25	Dark red	215–216[b]	$C_{16}H_{13}NO_6$	4.44	4.37
Ie	2′,4′-Dihydroxy-3′-nitro-3,4-methylenedioxy	25	Purple-red	218[b]	$C_{16}H_{11}NO_7$	4.26	4.03
If	2′,4′-Dihydroxy-3′-nitro-4-methyl	20	Red	175[c]	$C_{16}H_{13}NO_5$	4.68	4.70
Ig	2′,4′-Dihydroxy-3′-nitro-3,4-benzo	5	Dark red	225[b]	$C_{19}H_{13}NO_5$	4.18	3.88
Ih	2′,4′-Dihydroxy-3,3′-dinitro	5	Deep yellow	227[d]	$C_{15}H_{10}N_2O_6$	8.51	8.67
IIa	2′-Hydroxy-4′-methoxy-3′-nitro	60	Orange-red	232[b]	$C_{16}H_{13}NO_5$	4.68	4.88
IIb	2′-Hydroxy-4,4′-dimethoxy-3′-nitro	60	Red	223–225[b]	$C_{17}H_{15}NO_6$	4.26	4.20
IIIa	2′,4′-Dihydroxy-[e] 5′-nitro	60	Orange-red	188–189[c]	—	—	—
IIIb	2′,4′-Dihydroxy-[e] 5′-nitro-4-methoxy	60	Dark red	160–162[c]	—	—	—
IVa	2′,6′-Dihydroxy-3′-nitro	15	Orange-red	163–165[c]	$C_{15}H_{11}NO_5$	4.91	5.02
IVb	2′,6′-Dihydroxy-3′-nitro-2-methoxy	15	Dark red	175–176[c]	$C_{16}H_{13}NO_6$	4.44	4.31
IVc	2′,6′-Dihydroxy-3′-nitro-3-methoxy	15	Red	140–141[c]	$C_{16}H_{13}NO_6$	4.44	4.40
IVd	2′,6′-Dihydroxy-3′-nitro-4-methoxy	20	Dark red	165[c]	$C_{16}H_{13}NO_6$	4.44	4.60
IVe	2′,6′-Dihydroxy-3′-nitro-3,4-methylenedioxy	25	Violet	182[b]	$C_{16}H_{11}NO_7$	4.26	4.05

[a] Alcohol. [b] Acetic acid. [c] Benzene. [d] Nitrobenzene. [e] *Cf.* V. G. Kulkarni and G. V. Jadhav, *J. Indian Chem. Soc.*, **31**, 746 (1954).

rinic acids. The nonformation of flavanone from the chalcones of group II shows that the chelation of the nitro group with the 3′-hydroxyl group is firmer in these chalcones than in the Group I chalcones.

The slowness of cyclization of Group III chalcones is the result of the retarding influence of the nitro group on the reaction. The greater stability of the flavanone of this group towards acid shows that the nitro group has no longer the effect it exerted in flavanone Ia.

The effect of substitution in the R nucleus on the stability of the chalcones of types I and III is noteworthy. The yield of flavanone from the chalcone decreases considerably with introduction of substituents and this effect is especially pronounced in Group I chalcones. The nature of the substituent seems to be of no importance. The conclusion is, therefore, reached that the substituent exerts a purely steric effect. The flavanone structure becomes more unstable with increased loading of the 2-phenyl nucleus and hence lower yields of the flavanone are obtained. The abrupt fall in the yields of flavanones from Group I chalcones, with substitution of the R nucleus, seems to be due to a combination of effect of chelation and the steric effect exerted by the substituent.

The Group IV chalcones are remarkable for the ready isomerization to the flavanones. This behavior is attributable to the presence of a 6′-hydroxyl group.[2] It, therefore, appears that the activating influence of the 6′-hydroxyl group is not appreciably masked by the retarding effect of the nitro group. The group IV flavanones have been assigned the constitution of 5-hydroxy-6-nitroflavanones and not 5-hydroxy-8-nitroflavanones. The formation of the latter would involve cyclization at the chelated hydroxyl group and this, as has been shown, is a difficult process. The stability in these flavanones in acid medium is only to be expected,

(2) Shinoda and Sato, *J. Pharm. Soc. Japan*, **48**, 933 (1928).

TABLE II

CYCLIZATION TO THE FLAVANONES

Flavanone	Chalcone Cyclized	Volume of Alcohol	Volume,[a] Strength of HCl	Time of Reaction	Yield, % of Flavanone	M.P., °C.	H_2SO_4 Color	Analysis N, % Calcd.	Found
7-Hydroxy-8-nitro	Ia	60	60, 6%	6 days	35	184[b]	Yellow	4.91	4.80
7-Hydroxy-8-nitro-2′-methoxy	Ib	150	80, 9%	6 days	3	181–183[c]	Red	4.44	4.41
7-Hydroxy-8-nitro-3′-methoxy	Ic	80	80, 6%	6 days	5	174–175[c]	Yellow	4.44	4.26
7-Hydroxy-8-nitro-4′-methoxy	Id	150	80, 9%	6 days	5	163–165[c]	Crimson	4.44	4.39
7-Hydroxy-8-nitro-3′,4′-methylenedioxy	Ie	150	80, 9%	6 days	2	172–173[c]	Crimson	4.26	4.55
	If	60	60, 6%	6 days	[d]				
	Ig	200	40, 18%	6 days	[d]				
	Ih	80	80, 6%	6 days	[d]				
	IIa	150	80, 9%	6 days	[d]				
	IIb	200	40, 18%	6 days	[d]				
7-Hydroxy-6-nitro	IIIa	180	90, 9%	6 days	35	154–156[c]	Yellow	4.91	4.99
7-Hydroxy-6-nitro-4′-methoxy	IIIb	225	40, 18%	6 days	15	172[c]	Orange	4.44	4.20
5-Hydroxy-6-nitro	IVa	100	50, 9%	4 hr.	80	155–156[e]	Yellow	4.91	4.80
5-Hydroxy-6-nitro-2′-methoxy	IVb	150	80, 9%	4 hr.	80	181–183[e]	Red	4.44	4.54
5-Hydroxy-6-nitro-3′-methoxy	IVc	100	50, 9%	4 hr.	80	142–143[e]	Yellow	4.44	4.44
5-Hydroxy-6-nitro-4′-methoxy	IVd	150	80, 9%	4 hr.	80	148[e]	Red	4.44	4.70
5-Hydroxy-6-nitro-3′,4′-methylenedioxy	IVe	150	80, 9%	4 hr.	80	169–171[e]	Purple	4.26	4.39

[a] Volume in ml. per gram of chalcone. [b] Cryst. from alcohol. [c] Cryst. from benzene. [d] No flavanone could be isolated. [e] Cryst. from ethyl acetate and alcohol mixture.

in view of the ease with which they are formed from the chalcone in acid medium.

All the flavanones are converted to the chalcones in alkali solution. T. R. Seshadri[3] has shown that flavanones which do not contain a 5-hydroxyl group break up in alkaline solution to the chalcones. The 5-hydroxyflavanones alone are unaffected by alkali, and this stability has been attributed to the chelation of the 5-hydroxyl group with the carbonyl group of the flavanone ring. In the case of the 5-hydroxy-6-nitroflavanones, the 5-hydroxyl group is not capable of exerting its stabilizing effect on the flavanone because it is chelated with the 6-nitro group.

EXPERIMENTAL

2,4-Dihydroxy-3-nitroacetophenone,[4] m.p. 103°, was obtained by the Friedel-Crafts acetylation of 2-nitroresorcinol. To a solution of anhydrous aluminum chloride (12 g.) in nitrobenzene (80 ml.) was added 2-nitroresorcinol (6.4 g.) and to this mixture was added acetic anhydride (4.1 ml.). The reaction mixture was heated on a steam bath for 4 hr., the aluminum chloride decomposed by ice-cold dilute hydrochloric acid and the nitrobenzene removed by steam distillation. The residue in the flask was crystallized from hot water as silky grey needles which turned yellow on drying.

2-Hydroxy-4-methoxy-3-nitroacetophenone,[4] m.p. 211–212°, was obtained by refluxing 2,4-dihydroxy-3-nitroacetophenone (4 g.) in acetone (60 ml.) with dry potassium carbonate (12 g.) and dimethyl sulfate (2 ml.) for 24 hr. The acetone was removed and the alkaline solution extracted with ether. The alkaline solution was acidified and the solid obtained crystallized from acetic acid.

2,4-Dihydroxy-5-nitroacetophenone,[5] m.p. 142°, was prepared by nitration of resacetophenone.

2,6-Dihydroxy-3-nitroacetophone,[5] m.p. 119°, was prepared by Friedel-Crafts acetylation of 4-nitroresorcinol.

Preparation of the chalcones. The chalcones were prepared by adding potassium hydroxide solution to a cooled mixture of molecular proportions of the acetophenone and the requisite aromatic aldehyde in alcohol (2 ml. per g. of ketone) and leaving the reaction mixture at room temperature (30°) with intermittent shaking. After the reaction period was over, the mixture was diluted with ice-cold water and acidified by concentrated hydrochloric acid. The product after filtration and repeated washing was generally crystallized from acetic acid. (Alcohol was used for chalcones Ia and If. Chalcone Ig was washed with warm acetic acid and crystallized from nitrobenzene.) The chalcone thus obtained was washed with alcohol and crystallized further from suitable solvents (given in Table I).

The strength and amount of potassium hydroxide solution used per gram of ketone, and the time of reaction were as follows. Chalcone groups I and III: 2 g. of potassium hydroxide in 7 ml. water for 6 days. Chalcone group II: 2 g. potassium hydroxide in 2 ml. water for 24 hr. Chalcone group IV: 2 g. potassium hydroxide in 5 ml. water for 24 hr. in the case of IVa, IVd, and IVe, and for 9 hr. in the case of IVb and IVc.

The chalcones varied in color from yellow to deep red. The characteristic sulfuric acid colorations are set out in Table I.

(3) M. Narsimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **27A**, 223 (1948).

(4) R. M. Naik, unpublished work, Ph.D. thesis, Bombay University (1955).

(5) R. M. Naik and V. M. Thakor, *Proc. Indian Acad. Sci.*, **37A**, 774 (1953).

Cyclization. The chalcones were refluxed in aqueous alcoholic hydrochloric acid (3%) solution or suspension. The amounts of alcohol and hydrochloric acid used varied with the solubility of the chalcone and are given in Table II.

Different methods were adopted for isolating the flavanone depending on the nature of the chalcone.

Groups I *and* II. The reaction mixture was cooled well and the chalcone that had separated was filtered. The filtrate was concentrated under reduced pressure till turbidity appeared. It was then cooled and diluted. The solid obtained was fractionally crystallized from benzene to get the flavanone. In the case of Chalcone Ia, the reaction mixture was diluted and the mixture of chalcone and flavanone separated by virtue of the higher solubility of the chalcone in alcohol. The mixture was triturated with cold alcohol and filtered. The white residue was crystallized from alcohol when the pure flavanone separated.

Group III. The reaction mixture was cooled to about 45° and the yellow chalcone that had separated was filtered. The filtrate was cooled in ice when the crude flavanone separated which was crystallized from benzene.

Group IV. The reaction mixture was cooled and the solid that separated was recrystallized from a mixture of alcohol and ethylacetate to get the pure flavanone.

All the flavanones were white or very pale yellow in color. They did not give the magnesium–hydrochloric acid test and many of them gave colors other than yellow with concentrated sulfuric acid (see Table II). Groups I and III flavanones gave pale brown colors with alcoholic ferric chloride, while the isomeric chalcones gave deep brownish red colors. Both the chalcones and flavanones of group IV gave red colors with alcoholic ferric chloride.

Tests for stability of flavanones. (a) The flavanone (0.1 g.) was warmed with sodium hydroxide solution (10 cc.; 5%) for 10 min. and acidified. All the flavanones gave back the chalcone when thus treated. (b) The flavanone (0.1 g.) was refluxed in alcohol (10 cc.) with concentrated hydrochloric acid (10 cc.). Flavanone Ia was completely converted into the chalcone in 15 min. Only part of flavanone IIIa had reverted to the chalcone even after refluxing for an hour. Flavanone IVa was unaffected.

Acknowledgments. The authors wish to express their thanks to Dr. G. V. Jadhav for his keen interest in the work.

BOMBAY, INDIA

[CONTRIBUTION FROM THE RESEARCH LABORATORY, LEPETIT S.P.A., MILAN]

Cinnamic and 2-Thienylacrylic Derivatives

ALBERTO VECCHI AND GAETANO MELONE

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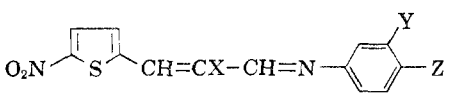
As a further development of previous studies on two exceptionally active antibacterial substances, β-(5-nitro-2-thienyl)-acrolein and its α-bromo derivative, the effects of introducing a 5-cyano group instead of the 5-nitro group and of a nitro instead of the aldehyde group were studied. Similar substitutions were tried in the benzene analogs. Furthermore, 4-cyanocinnamylidene acetaldehyde and 4-methylsulfonyl derivatives of the benzene series have been prepared. Outstanding antifungal activity was displayed by α-bromo-β-(5-cyano-2-thienyl)acrolein, α-bromo-4-cyanocinnamaldehyde, and their Schiff's bases with *p*-aminobenzoic acid, as well as by 1-(5-nitro-2-thienyl)-2-nitroethylene and 1-(5-nitro-2-thienyl)-2-bromo-2-nitroethylene. Other members of the described classes were also highly active.

In continuation of our previous work on cinnamic and 2-thienylacrylic derivatives,[1–3] which was suggested by a consideration of the marked biological interest of aromatic acroleins[4] and confirmed by a paper of Affonso and Khorana[5] on halogenated derivatives of cinnamic and *p*-nitrocinnamic acid, we have now synthesized a series of new compounds having structural resemblance to the acroleins already described.

The considerable interest aroused by the prior work is shown by several publications of Japanese scientists concerning furan analogs of the series.[6–12] Strict furan analogs of the thiophene compounds described in our previous papers have been recorded, such as β-(5-nitro-2-furyl)acrolein[6] and many functional derivatives thereof.

In view of the slight water solubility of the β-(5-nitro-2-thienyl)acroleins,[1] which prevented their use by the parenteral route and their absorption by the gastro-enteric tract, we have prepared functional derivatives of the following formula:



I	X = H,	Y = H,	Z = COOH
II	X = H,	Y = OH,	Z = COOH
III	X = H,	Y = H,	Z = SO_3H
IV	X = H,	Y = H,	Z = SO_2NH_2
V	X = Br,	Y = H,	Z = COOH[1]
VI	X = Br,	Y = H,	Z = SO_2NH_2
VII	X = Br,	Y = H,	Z = $SO_2NHCOCH_3$

(1) G. Carrara, R. Ettorre, F. Fava, G. Rolland, E. Testa and A. Vecchi, *J. Am. Chem. Soc.*, **76**, 4391 (1954).

(2) G. Rolland and M. T. Timbal, *Atti VI Congresso Int. Microbiologia Roma*, 1953, vol. I, sect. 2, p. 629.

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(4) E. Keeser and J. Houben, *Fortschritte der Heilstoffchemie*, 2 Abt., Berlin, Leipzig, 1932, p. 254.

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