sulfur melted and the temperature was gradually raised to 238°. The temperature was held between 238 and and 240° for 30 min. The aromatized compound was taken up in acetone and purified by gas chromatography at 175° using silicone 200 on Gas-Chrom P.

Synthesis of 3-Isobutylidene Phthalide.—The procedure used was that of Weiss.[19] A quantity of 15 g. of phthalic anhydride was mixed with 21 g. of isovaleric acid and 0.5 g. of sodium acetate and heated to 180°. The temperature was allowed to rise to 190° during the next 2 hr. Evolution of carbon dioxide was observed with barium hydroxide for the first 2.5 hr. and heating continued for an additional 2.5 hr. The mixture was freed of unchanged isovaleric acid by washing with aqueous sodium bicarbonate and then taken up in ethyl ether. It was purified by gas chromatography at 175° using silicone 200 on Gas-Chrom P. Yield was about 0.5 ml.; b.p./5 mm.[20]: 83.5° (lit.,[3] 83°). The infrared spectrum of this compound is presented in Fig. 2.

Properties.—All compounds are light yellow oils at room temperature, the aromatic compounds being somewhat darker than the dihydro compounds. They exhibit a greenish fluorescence in agreement with the observations of Berlingozzi and coworkers. In hexane, methylene chloride, or acetonitrile, the dihydro compounds exhibit a blue-green fluorescence. The odors of the various compounds are easily identified as celery in concentrations of 0.1 p.p.m. in water. A number of those who tasted the solutions of the dihydro compounds noted bitterness, and some indicated a burning sensation.

3-Isobutylidene-3a,4-Dihydrophthalide.—*Anal.* Calcd. for $C_{12}H_{14}O_2$: C, 75.8; H, 7.39. Found: C, 75.2; H, 8.0.

Infrared spectra were taken on capillary films between salt plates in a Beckman IR-7 double beam spectrophotometer. For convenience of reproduction, the spectrum shown in Fig. 1 was taken with a Perkin-Elmer Infracord 137 spectrophotometer.

Ultraviolet spectra were taken in a Cary 14 spectrophotometer using 1-cm. fused silica cells. Identical spectra were displayed using acetonitrile and absolute ethanol as the solvent. The spectrophotometer was flushed with dry nitrogen in order to observe the short wave length peaks. Absorptions observed: 282 $m\mu$ (log ϵ, 4.15); 273 $m\mu$ (log ϵ, 4.16); 227 $m\mu$ (log ϵ, 4.61); 197 $m\mu$ (log ϵ, 5.10); b.p./10 mm.,[20] 164°; refractive index $n^{27.5}\text{D}$ 1.5092.

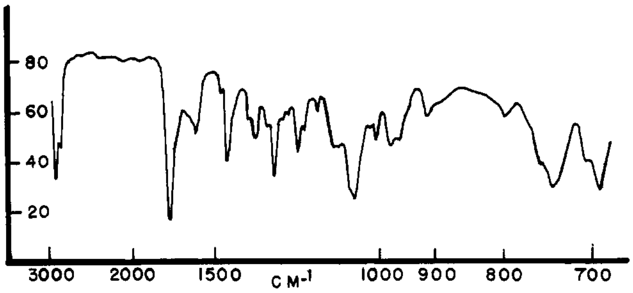

Fig. 2.—Infrared spectrum of 3-isobutylidene phthalide.

Attempts to form derivatives with hydrazine hydrate,[21,22] phenylhydrazine or 2,4-dinitrophenylhydrazine resulted in gums in all cases. Attempts to purify the derivatives by recrystallization resulted in gums of increased viscosity.

3-Isovalidene-3 a,4-Dihydrophthalide.—*Anal.* Calcd. for $C_{13}H_{16}O_2$: C, 76.4; H, 7.85. Found: C, 76.9; H, 8.22.

The infrared spectrum is virtually identical with that shown in Fig. 1 for the isobutylidene compound.

Ultraviolet absorptions: 282 $m\mu$ (log ϵ, 4.12); 273 $m\mu$ (log ϵ, 4.14); 227 $m\mu$ (log ϵ, 4.60); 197 $m\mu$ (log ϵ, 5.08); b.p./10 mm., 175°; refractive index $n^{27.5}\text{D}$ 1.5172.

As with the isobutylidene compound, attempts to form crystalline derivatives with the hydrazines were unsuccessful.

3-Isobutylidene Phthalide.—The infrared spectrum is shown in Fig. 2. Ultraviolet absorptions: 280 $m\mu$ (log ϵ, 4.60); 272 $m\mu$ (log ϵ, 4.64); 227 $m\mu$ (log ϵ, 4.89); 200 $m\mu$ (log ϵ, 5.45).

3-Isovalidene Phthalide.—The infrared spectrum is virtually identical with that shown in Fig. 2 for 3-isobutylidene phthalide.

Ultraviolet absorptions: 280 $m\mu$ (log ϵ, 4.56); 272 $m\mu$ (log ϵ, 4.62); 227 $m\mu$ (log ϵ, 4.88); 200 $m\mu$ (log ϵ, 5.32).

Acknowledgment.—The authors are indebted to Dr. G. L. K. Hunter of this laboratory for many suggestions offered during the course of this work, in particular, the suggestion of aromatizing the dihydro compounds, and for his invaluable comments regarding the interpretation of the infrared and ultraviolet spectra. We wish to thank Dr. R. L. Settine of this laboratory for his advice in the application of Woodward's rule.

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[19] R. Weiss, "Organic Syntheses," Coll. Vol. II, A. H. Blatt, ed., John Wiley and Sons Inc., New York, N. Y., 1943, p. 61.

[20] C. R. Garcia, *Ind. Eng. Chem., Anal. Ed.*, **15**, 648 (1943).

[21] M. Yasue, M. Itaya, and Y. Taka, *Bull. Nagoya City Univ. Pharm. School*, **2**, 53 (1954).

[22] J. A. Giles and J. N. Schumacher, *Tetrahedron*, **14**, 246 (1961).

Anthocyanins and Related Compounds. I. Structural Transformations of Flavylium Salts in Acidic Solutions

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Changes in the spectra of a number of flavylium salts, unsubstituted in the 3 position, indicate that in the pH range 1–4 these salts undergo reversible, hydrolytic opening of the pyrylium ring with the formation of the corresponding 2-hydroxychalcones. At pH 4.1, for example, 3'-methoxy-4',7-dihydroxyflavylium chloride (IV) is predominantly converted (90%) to the chalcone V. Reversible ring opening in weakly acid solutions has been confirmed by the isolation of crystalline chalcones from 8,4'-dimethoxy- and 8-methoxy-2'-hydroxyflavylium chlorides, and by the rearrangement of 5,7,8,4'-tetrahydroxyflavylium iodide in aqueous solution at pH 2.6 to give the isomeric 5,6,7,4'-tetrahydroxyflavylium salt.

The decolorization of anthocyanin pigments in plant extracts is accelerated in the presence of ascorbic acid,[1] sugars,[2] amino acids,[3] and certain enzymes.[4] The products formed and the reactions involved have not yet been determined,[5] although it has been suggested[6] that the rate of anthocyanin destruction in oxygen is pH dependent and directly proportional to the amount of the pigment which exists in the form of the pseudo base. In this connection, therefore, it seemed desirable to verify the structural changes which model flavylium

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[1] E. Sondheimer and Z. I. Kertesz, *Food Res.*, **18**, 475 (1953).

[2] I. J. Tinsley and A. H. Bockian, *ibid.*, **25**, 161 (1960).

[3] I. J. Tinsley and A. H. Bockian, *ibid.*, **24**, 410 (1959).

[4] N. T. Huang, *J. Agr. Food Chem.*, **3**, 141 (1955).

[5] T. Swain, in "The Chemistry of Flavonoid Compounds," ed. by T. A. Geissman, Pergamon Press, 1962, p. 513.

[6] A. Lukton, C. O. Chichester, and G. Mackinney, *Food Technol.*, **10**, 427 (1956).

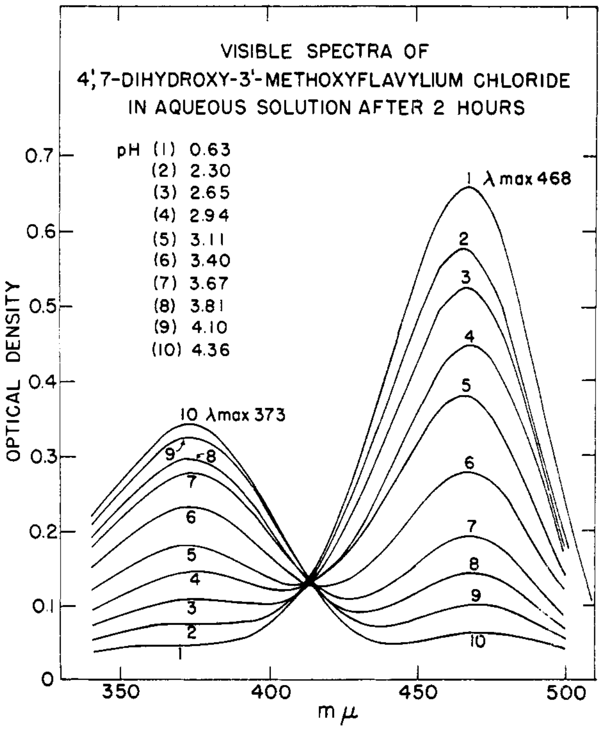
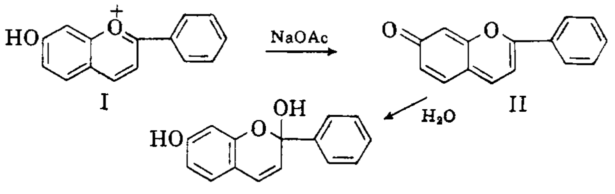


Fig. 1.—Effect of pH on the visible spectra of aqueous solutions of 3'-methoxy-4',7-dihydroxyflavylium chloride (5.2×10^{-3} g./l.) after standing for 2 hr.

salts have been reported to undergo in dilute aqueous solutions and, particularly, to identify the final products formed at equilibrium in the pH range 3–6, the pH of most plant extracts. This aspect of anthocyanin chemistry has received little attention since structures were proposed for the chief transformation products some thirty years ago.[7]

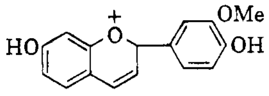
Primarily on the basis of visual examination of color changes,[8] it is now generally accepted that, when treated with water or a mild base (sodium acetate), flavylium salts having at least one free hydroxyl group in the 5,7,2' or 4' positions first form highly colored, quinoidal[9] anhydro bases. On standing or on further dilution, the anhydro bases are hydrated to give colorless carbinol bases (pseudo bases) which are thought to be chromen-2-ols or chromen-4-ols.[10] In the case of 7-hydroxyflavylium chloride (I), for example, structural changes II (anhydro base) and III (carbinol base) have been proposed.[11] Carbinol base formation is enhanced by a substituent (hydroxy- or methoxy-)



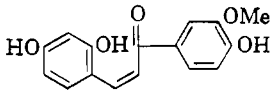
I II III

in the 3 position[12] and it has been reported[13] that the anhydro bases derived from some flavylium salts lacking a 3-substituent, *e.g.*, 7-hydroxy-4'-methoxyflavylium chloride, show no tendency to form pseudo bases. Absence of a 3-substituent, however, does not necessarily prevent pseudo base formation, *e.g.*, the anhydro base of 8-methoxy-2'-hydroxyflavylium chloride "could not be isolated owing to (its) marked tendency to pass into the pseudo base by hydration."[14]

In this investigation strongly acid, standard solutions of flavylium salts, unsubstituted in the 3 position, were diluted with aqueous buffers, allowed to reach equilibrium and the spectra and pH of the solutions then were determined. In the acidic standard solutions, the flavylium compounds are stable and may be assumed to exist entirely as cations, *e.g.*, of type I. The spectra of 3'-methoxy-4',7-dihydroxyflavylium chloride (IV) in the pH range 1–4 after two hours are shown in Fig. 1. The intensity of absorption at 468 mμ, the λ_{max} of the salt, markedly decreases as the pH is raised. Simultaneously, the absorption at 373 mμ progressively increases as a result of the formation of a new compound with a peak at this wave length. At about pH 4, it is apparent that the flavylium salt is converted almost completely (90%) into this compound. The λ_{max} of the product cannot be accounted for on the basis of a chromenol structure, but it is entirely consistent with the 2-hydroxychalcone structure V, derived by opening of the pyrylium ring. This hypothesis has been confirmed, as described below, by the isolation of the crystalline chalcones from two flavylium salts and by the



IV



V

facile rearrangement of a 5,8- into a 5,6-dihydroxyflavylium salt in weakly acid solution.

The spectral curves in Fig. 1 have a well defined isosbestic point at 413 mμ and indicate that in dilute solutions the flavylium salt–chalcone conversion is an equilibrium reaction. Thus, in this pH range, where the salt IV concentration varies from 100 to 9.87% (as calculated from the decrease in optical density at 468 mμ), the p*K* value determined for the equation[15]

$$\text{IV} + 2H_2O = (\text{V}) + H_3O^+$$

$$\text{then } pK = \log \text{IV}/\text{V} + \text{pH}$$

is constant within experimental error (Table I). Furthermore, as would be anticipated from previously reported flavylium salt syntheses, the conversion may be approached from either side. Thus, the salt IV was

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[7] For references, see reviews by F. Blank, "Handbuch d. Pflanzenphysiologie," Vol. 10, 1958, p. 300; *Botan. Rev.*, **13**, 241 (1947); K. Hayashi, in "The Chemistry of Flavonoid Compounds," ed. by T. A. Geissman, Pergamon Press, 1962, p. 248; D. W. Hill, *Chem. Rev.*, **19**, 27 (1936).

[8] For the great majority of flavylium salts the exact pH of solutions in which color changes were reported have not been recorded; *cf.* A. Robertson and R. Robinson, *Biochem. J.*, **23**, 35 (1929).

[9] J. S. Buck and I. M. Heilbron, *J. Chem. Soc.*, **121**, 1198 (1922); **123**, 2521 (1923).

[10] In preparative reactions in non-aqueous systems, it has been observed that benzopyranols derived from some benzopyrylium salts undergo ring opening to give derivatives of the corresponding chalcones, *e.g.*, in the Grignard reaction with 2,3-diphenylbenzopyranol [T. A. Geissman and E. Baumgarten, *J. Am. Chem. Soc.*, **65**, 2135 (1943)]. Furthermore, Freudenberg and his co-workers have recently demonstrated that acetylation of some flavylium salts in pyridine yields acetyl derivatives of the corresponding chalcones. These products were formerly believed to be chromenol acetates [K Freudenberg, J. Stocker, and J. Porter, *Chem. Ber.*, **90**, 957 (1957); K Freudenberg and K. Weinges, *Ann.*, **590**, 140 (1954); **613**, 61 (1958)].

[11] S. Wawzonek, in "Heterocyclic Compounds," Vol. 2, R. C. Elderfield, ed., John Wiley and Sons, New York, N. Y., 1951, p. 321.

[12] D. D. Pratt and R. Robinson, *J. Chem. Soc.*, 745 (1923).

[13] D. D. Pratt, R. Robinson, and P. N. Williams, *ibid.*, 199 (1924).

[14] F. M. Irvine and R. Robinson, *ibid.*, 2086 (1927).

[15] E. Sondheimer, *J. Am. Chem. Soc.*, **75**, 1507 (1953).

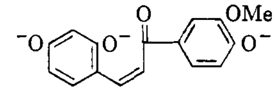
TABLE I

pK OF 3′-METHOXY-4′,7-DIHYDROXYFLAVYLIUM SALT ⇄ CHALCONE EQUILIBRIUM[a]

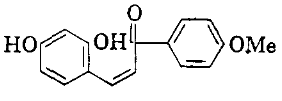
pH	Optical density at λ_{max}, 468 mμ	% IV	pK
0.63	0.658	100	
2.30	.577	86.9	3.12
2.65	.524	78.3	3.21
2.94	.448	66.0	3.23
3.11	3.81	55.2	3.20
3.40	.278	38.5	3.20
3.67	.192	24.6	3.18
3.81	.143	16.7	3.11
4.10	.101	9.9	3.14
	.040	0	

[a] Average pK = 3.17 ± 0.06.

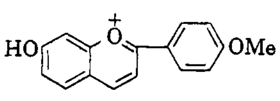
converted into the fully ionized chalcone VI, λ_{max} 492 mμ (log ε, 4.56), in strongly alkaline (pH 12) solution.[16] Adjusted to pH 5.4, the alkaline solution gave the stable chalcone V, λ_{max} 373 mμ (log ε, 4.30). Adjusted to pH 1.0, however, the chalcone first formed immediately began to reform the original flavylium salt. After two hours the salt (λ_{max} 468, log ε 4.58) was quantitatively regenerated. As a second example of this reverse chalcone–flavylium salt reaction, the rate of change of the chalcone VII into its parent flavylium salt VIII at pH 0.96 was determined. In this case 88.6% conversion occurs within eighty minutes.



VI

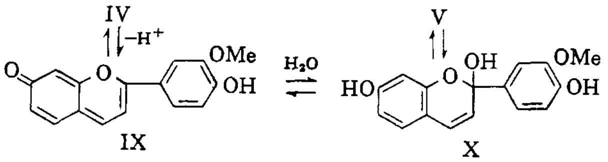


VII



VIII

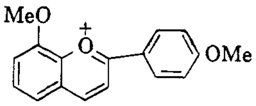
In agreement with previous workers, it has been observed that the flavylium salts under discussion first form colored anhydro bases when added to buffer solutions in the approximate pH range 4–7. These solutions fade on standing, the rate of decolorization of the anhydro bases increasing rapidly at pH values less than 7. Thus, in the pH range 4–5, complete destruction of the anhydro bases usually occurs within a few minutes. The final products formed as the anhydro bases fade, moreover, are not chromenols but the isomeric 2-hydroxychalcones.[17] It is entirely possible, therefore, that even in the low pH range 1–4, the flavylium salt–chalcone interconversion proceeds *via* highly unstable anhydro base (*e.g.*, IX) and carbinol base (*e.g.*, X) intermediates.



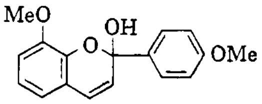
IX X

It is noteworthy, however, that visual and spectral evidence for initial formation of anhydro bases at low pH values could not be obtained. Thus, the anhydro base IX of 3′-methoxy-4′,7-dihydroxyflavylium chloride is intensely cerise and has a strong absorption maximum at 495 mμ. When the standard acid solution of IV is added to buffer, pH 3.55, the strongly yellow solution fades rapidly without the production of a fleeting cerise color. No increase in intensity of absorption at 495 mμ occurs during the period required for the salt ⇌ chalcone equilibrium to be established. 4′-Hydroxy-3′-7-dimethoxyflavylium chloride (λ_{max} 469 mμ), adjusted to pH 3.87, similarly reaches equilibrium with the corresponding chalcone (λ_{max} 375 mμ) with no increase in absorption at 528 mμ, the λ_{max} of the anhydro base of this salt.

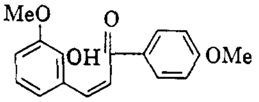
Colorless carbinol bases, *e.g.*, X, also could not be detected in any of the equilibrium reactions involving the phenolic flavylium salts presently being investigated. However, the color reactions and spectra of 8,4′-dimethoxyflavylium chloride (XI) unequivocally show that its conversion to the chalcone XIII proceeds *via* a colorless compound which is presumably a chromenol of type XII. The spectra of this salt in solutions of pH 0.63, 3.4, and 5.4 were determined after standing three hours. At pH 5.4 it is clear that the salt (λ_{max} 430 mμ, log ε, 4.54 at pH 0.63) is completely converted into the chalcone XIII (λ_{max} 328 mμ, log ε, 4.32). When the brightly yellow, acid solution of the flavylium salt is adjusted to pH 5.4 with buffer, the solution immediately becomes *colorless* and then slowly develops a pale yellow color as the chalcone is formed. If these changes are followed spectrally it can be seen that the colorless compound initially formed has a well defined peak at 269 mμ which is consistent with a chromenol structure. The intensity of this peak progressively decreases as the chalcone peak at 328 mμ is formed.



XI



XII



XIII

Isolation of Hydrolysis Products.—In order to prove unambiguously that the final stable products, λ_{max} 320–370 mμ, formed in these equilibrium reactions are, in fact, the corresponding 2-hydroxychalcones, the compound from 8,4′-dimethoxyflavylium chloride at pH 5.4 was isolated. The crystalline product, m.p. 141–142° (acetate, m.p. 111°), had λ_{max} 328 mμ in aqueous solution at pH 5.4 and λ_{max} 320 mμ in alcohol. It was identical in all these respects with the authentic chalcone XIII, synthesized by alkaline condensation of *o*-vanillin and *p*-methoxyacetophenone.

8-Methoxy-2′-hydroxyflavylium chloride (XIV), warmed briefly with dilute citric acid solution (pH 2.2), similarly precipitated a yellow crystalline compound, m.p. 178–180°, λ_{max} 360, 329 mμ (alcohol), identical with the synthetic chalcone XV. Furthermore, acetylation of both the yellow product and the synthetic

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(16) A. Robertson and R. Robinson, *J. Chem. Soc.*, 1526 (1928).

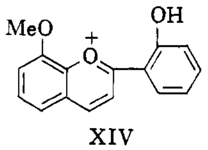
(17) Part II (in preparation).

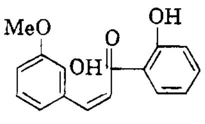
TABLE II

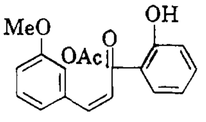
INFLUENCE OF pH ON SPECTRA OF FLAVYLIUM SALTS UNSUBSTITUTED IN THE 3 POSITION

Flavylium salt	Concn., g./l.	λ_{max}, mμ	pH 0.6		pH 3.8		% Conversion to chalcone at pH 3.8
			Opt. dens.	log ϵ	Opt. dens.	log ϵ	
7-Hydroxy	4.8×10^{-3}	427	0.553	4.47	0.077	3.62	86
		370	.115		.311		
4′,7-Dihydroxy	4.8×10^{-3}	457	.778	4.65	.237	4.13	69.5
		370	.054		.310		
4′-Hydroxy-7-methoxy	4.8×10^{-3}	453	.683	4.61	.295	4.25	57
		370	.039		.237		
7-Hydroxy-4′-methoxy	4.8×10^{-3}	457	.832	4.70	.220	4.12	74
		371	.060		.321		
4′-Hydroxy-3′,7-dimethoxy	5.2×10^{-3}	469	.654	4.60	.108	3.82	83.5
		374	.072		.349		
7-Hydroxy-3′,4′-dimethoxy	5.2×10^{-3}	467	.620	4.58	.131	3.90	79
		376	.049		.296		
4′-Hydroxy	5.2×10^{-3}	436	.763	4.56	.600	4.47	
		281	.181		.280		

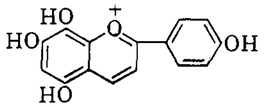
chalcone under conditions[18] which do not acetylate hydroxyls *ortho* to a carbonyl group gave a monoacetate XVI. At pH 5.8, 8-methoxy-2′-hydroxyflavylium chloride formed the violet anhydro base which decomposed within seconds as described by Irvine and Robinson.[14] The product which precipitated, however, was not the pseudo base but the chalcone XV.

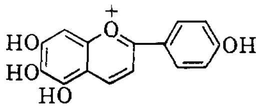

XIV


XV


XVI

Isomerization of 5,7,8,4′-Tetrahydroxyflavylium Iodide.—If reversible ring opening occurs, then 5,8-dihydroxyflavylium salts should isomerize to 5,6-dihydroxy compounds (or vice versa) under mildly acid conditions. Through the courtesy of Professor T. S. Wheeler in providing authentic specimens of 5,7,8,4′-tetrahydroxyflavylium iodide (XVII) and 5,6,7,4′-tetrahydroxyflavylium iodide (XVIII), it has now been shown that XVII rapidly isomerizes to XVIII in aqueous solutions. Thus, at pH 2.6 and room temperature, the spectrum of XVIII (λ_{max} 453, 287 mμ) is not appreciably altered on long standing. The spectrum of XVII (λ_{max} 421, 328, 278, inflection 480 mμ), on the other hand, rapidly changes until the spectrum of XVIII is obtained. Almost quantitative conversion of XVII to XVIII occurs in about seven hours at this pH. The same rearrangement occurs even in 1% aqueous hydrochloric acid at room temperature, although, as would be anticipated, at a slower rate (three days). On warming the hydrochloric acid solution, however, complete conversion occurs in about thirty minutes XVIII and the rearrangement product from XVII gave identical color reactions in amyl alcohol with sodium acetate and ferric chloride (violet-brown). This ferric reaction distinctly differed from the characteristic green color[19] given by XVII. The facile isomerization of XVII into XVIII suggests that "isocarajuretin hydrochloride," which was crystallized from boiling hydrochloric acid, has the 5,6,7,4′-tetrahydroxy arrangement rather than the assigned[19] 5,7,8,4′-tetrahydroxy structure.


XVII


XVIII

Spectra of 4′-Hydroxyflavylium Chloride.—The structural transformations of the flavylium salts listed in Table II have been determined by methods analogous to those described for 3′-methoxy-4′,7-dihydroxyflavylium chloride. In each case the spectral changes were similar and indicated (a) the existence of a flavylium salt–chalcone equilibrium in the pH range 1–4 and (b) that the equilibrium preponderantly favored formation of the chalcone at about pH 4, *e.g.*, 7-hydroxyflavylium chloride (I) (Table II). One exception has been observed. The spectra of 4′-hydroxyflavylium chloride (λ_{max} 436 mμ log ϵ 4.56) shows that this salt differs from the flavylium compounds in Table II in that it is only partially hydrolyzed at pH 3.8 (about 21%) and the product formed is apparently not the chalcone but the carbinol base. It is of some interest, however, that at higher pH (6–7), 4′-hydroxyflavylium chloride first forms the anhydro base which then rapidly decomposes to give, not the carbinol base, but the corresponding 2-hydroxychalcone (λ_{max} 349, 319 mμ). In this respect, 4′-hydroxyflavylium chloride is similar to the other flavylium salts unsubstituted in the 3 position.

Experimental

Preparation of Flavylium Salts.—The flavylium salts used in this investigation are known compounds. They were prepared in accordance with the general methods described by Robinson and his co-workers, *viz.*, acid condensation of the appropriate *o*-hydroxybenzaldehyde and acetophenone derivatives in ethyl acetate–ethanol[16] or glacial acetic acid[13,20] solutions.

Determination of Spectra.—Standard solutions of the flavylium salts in 0.5% ethanolic hydrochloric acid containing 0.120–0.130 g./l. were prepared. Aliquots (1.0 ml.) of the standard solutions were diluted to 25.0 ml. with aqueous buffer solutions,

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[18] M. Shimokoriyama, *Bull. Chem. Soc. Japan*, **16**, 284 (1941).

[19] L. Ponniah and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **38A**, 288 (1953); **39A**, 45 (1954).

[20] W. H. Perkin, R. Robinson, and M. R. Turner, *J. Chem. Soc.*, **93**, 1085 (1908).

the pH values were determined, and the spectra were measured on a Beckman DK 2 recording spectrophotometer at room temperature in 1-cm. silica cells.

2-Hydroxy-3,4′-dimethoxychalcone (XIII).—(a) The chalcone XIII was synthesized by the following modification of Robinson's procedure.[21] A solution of potassium hydroxide (11.5 g.) in the minimum quantity of water was added to a solution of *o*-vanillin (7.6 g.) and *p*-methoxyacetophenone (8.3 g.) in ethanol (40 ml.). After 20 hr., water (250 ml.) and glacial acetic acid (35 ml.) were added. The yellow product was collected and recrystallized from acetone–methanol. The chalcone XIII separated as yellow, glistening plates, m.p. 141–142°.

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.8; H, 5.67; 2 MeO-, 21.8. Found: C, 71.7; H, 5.58; MeO-, 21.7.

Acetylation of the chalcone (0.5 g.) in acetic anhydride (5 ml.) and pyridine (6 drops) gave 2-acetoxy-3,4′-dimethoxychalcone which separated from methanol as very pale yellow prisms, m.p. 111°.

Anal. Calcd. for $C_{19}H_{18}O_5$: C, 69.9; H, 5.56; 2 MeO-, 19.0. Found: C, 70.1; H, 5.50; MeO-, 18.9.

(b) 8,4′-Dimethoxyflavylium chloride[22] was crystallized as orange needles from glacial acetic acid by the addition of ether. Aqueous citric acid–sodium phosphate buffer solution (pH 5.4, 300 ml.) was added to a solution of the flavylium salt (4.0 g.) in warm methanol (300 ml.). The cloudy, warm solution was allowed to cool slowly. The yellow crystalline product was collected and recrystallized from acetone–methanol. Yellow plates, m.p. 141–142°, undepressed on admixture with the synthetic chalcone XIII, were obtained (3.0 g.).

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.8; H, 5.67; 2 MeO-, 21.8. Found: C, 71.8; H, 5.62; MeO-, 21.8.

The *acetate* of the product, prepared as above, separated from methanol as pale yellow prisms, m.p. and m.m.p. with 2-acetoxy-3,4′-dimethoxychalcone, 111°.

2,2′-Dihydroxy-3-methoxychalcone (XV).—(a) Aqueous potassium hydroxide (50%, 10 ml.) was added to a solution of *o*-hydroxyacetophenone (7.0 g.) and *o*-vanillin (7.5 g.) in ethanol (25 ml.). The mixture was heated under reflux for 1 hr. and acidified with dilute acetic acid (300 ml.). The yellow product solidified when the aqueous suspension was washed with a little petroleum ether and ether. It crystallized from methanol as golden yellow, prismatic needles, m.p. 179–180°, which gave an intense brown color with ferric chloride in ethanol (1.65 g.).

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.1; H, 5.22; MeO-, 11.5. Found: C, 71.2; H, 5.25; MeO-, 11.8.

The chalcone (0.2 g.), acetic anhydride (2.0 ml.) and pyridine (4 drops) were allowed to react for 10 min. at room temperature. Water was added and the solid product was collected. Recrystallized from acetone–methanol, 2′-hydroxy-2-acetoxy-3-methoxychalcone (XVI) separated as yellow prisms, m.p. 164–165°. In methanolic ferric chloride the acetate gave an intense brown color.

Anal. Calcd. for $C_{18}H_{16}O_5$: C, 69.2; H, 5.16; 1 MeO-, 9.9. Found: C, 69.1; H, 5.13; MeO-, 10.5.

(b) 8-Methoxy-2′-hydroxyflavylium chloride[14] (8.0 g.) was added to boiling 0.1 *M* aqueous citric acid (500 ml.). The mixture was heated for 5 min., cooled, and filtered. The yellow product crystallized from acetone–methanol as yellow needles, m.p. 179–180°, undepressed on admixture with the synthetic chalcone (4.6 g.).

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.1; H, 5.22; 1 MeO-, 11.5. Found: C, 70.9; H, 5.21; MeO-, 12.0.

Monoacetylation of the product, as described above, gave an acetate, m.p. and m.m.p. with 2′-hydroxy-2-acetoxy-3′-methoxychalcone, 164–165°. With methanolic ferric chloride the acetate gave an intense brown color.

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Reactions of Propargyl Alcohols and Propargylamines with Isocyanates

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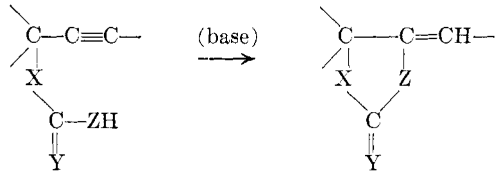
In the presence of a basic catalyst, propargyl alcohols and propargylamines react with isocyanates to give 4-methylene-2-oxazolidinones (IV) and 4-methylene-2-imidazolidinones (VIII), respectively. The expected open-chain urethanes (III) and ureas (VII) are obtained readily in the absence of base. The cyclizations are examples of especially easy intramolecular nucleophilic additions to C≡C.

The reaction of an ethynylcarbinol (I) and an isocyanate (II) in the presence of a catalytic quantity of a base does not stop with the formation of a urethane (III), but proceeds to give a 4-methylene-2-oxazolidinone (IV) by intramolecular N–H addition to the triple bond. In the absence of a basic catalyst, the expected urethane (III) is formed; the cyclization of III to IV occurs smoothly on treatment with sodium methoxide. This cyclization reaction was very recently reported in two brief notes.[1,2]

In this publication we wish to report our work relating to the synthesis of 4-methylene-2-oxazolidinones, as well as analogous cyclizations of propargylureas and propargyl *N*-phenylthiocarbamate. Reactions of this type represent especially easy intramolecular nucleophilic additions to C≡C, which might be formulated most generally as



Although urethanes can be obtained from tertiary alcohols only with great difficulty owing to facile dehydration to give an olefin and a urea, it has been shown that tertiary ethynylcarbinols undergo addition to isocyanates to afford the corresponding urethanes.[3] Carbamic acid esters have been synthesized from tertiary ethynylcarbinols by reaction with an alkali-metal cyanate and trichloroacetic acid.[4]

The 4-methylene-2-oxazolidinones (IV), described in Table I, were prepared by treatment of an ethynylcarbinol with an isocyanate and a catalytic amount of sodium methoxide. The structure IV was assigned on

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