treatment gave 11.6 g. of methyl esters. Analysis by v.p.c. indicated the presence of methyl caproate as well as methyl 3-phenyl-3-butenoate (98%) and methyl 3-phenyl-2-butenoate (2%).

Acknowledgment.—The authors are grateful for financial assistance from the Petroleum Research Fund which made this work possible.

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE STATE UNIVERSITY OF IOWA, IOWA CITY, IOWA]

Benzopyrylium Salts. VII. Reaction of Flavylium Perchlorate with Ethyl Esters of α-Amino Acids

BY R. L. SHRINER AND RUSSELL SUTTON[1]

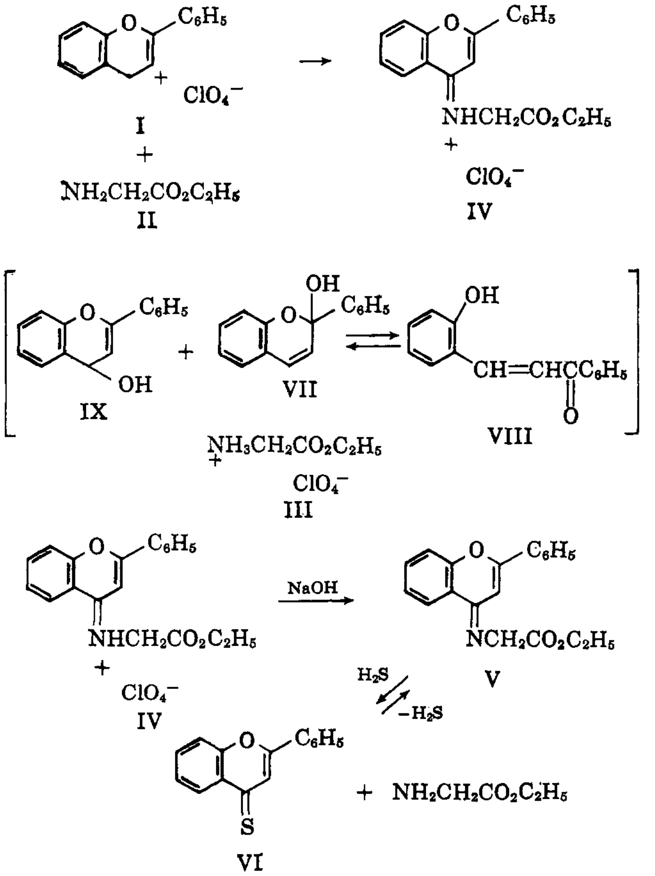
RECEIVED AUGUST 9, 1963

Flavylium perchlorate reacted with the ethyl esters of glycine, alanine, and phenylalanine to form ethyl N-(2-phenyl-4H-1-benzopyran-4-ylidene)-amino acid ester hydroperchlorates, the hydroperchlorate of the amino acid ester, and a mixture of nonnitrogen-containing by-products which have been characterized as 2-hydroxychalcone, 2-phenyl-1,2-benzopyran-2-ol, and 2-phenyl-1,4-benzopyran-4-ol. The degradation of the new substituted benzopyranimines to 4-thioflavone and synthesis from this compound are described.

Since anthocyanins and α-amino acids occur in the aqueous cell sap of certain fruits, flowers, and leaves, it is of interest to determine whether there is any interaction between these two classes of compounds. When flavylium salts (which contain the skeletal structure of the anthocyanidines) were treated with glycine or phenylalanine, no reaction occurred. However, esters of the α-amino acids did react readily but yielded a mixture of products.

Chart I shows the five compounds formed from flavylium perchlorate (I) and one equivalent of ethyl glycinate (II). Over half of the latter appeared as the hydroperchlorate of ethyl glycinate (III); the other nitrogen-containing product, formed in 40% yield, has been identified as ethyl N-(2-phenyl-4H-1-benzopyran-4-ylidene)-glycinate hydroperchlorate (IV).

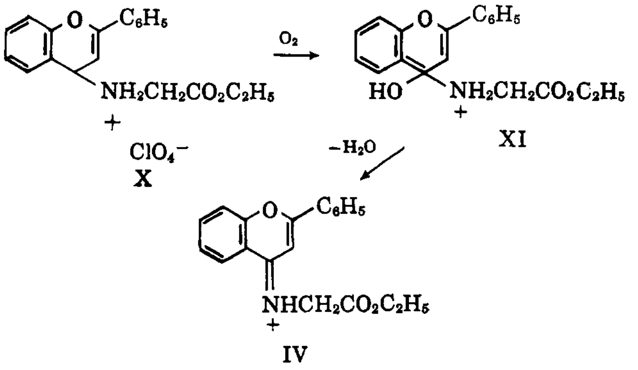
CHART I
FLAVYLIUM PERCHLORATE AND ETHYL GLYCINATE



The structure of the substituted ketimine salt (IV) was shown by: (1) Conversion by cold alkali to the free ketimine base V and re-formation of IV by perchloric acid. Flavylium perchlorate was not regenerated in sharp distinction from the behavior of 2- or 4-substituted aminoflavenes.[2] (2) The infrared spectrum of V possessed an absorption band at 6.10 μ, indicative of substituted imino groupings, while the hydroperchlorate IV possessed an N–H band at 3.1 μ in addition to an imino band at 6.15 μ.[3] (3) Treatment of an alcoholic solution of V with hydrogen sulfide produced red crystals of the known 4-thioflavone (VI), identical with a sample prepared by the action of phosphorus pentasulfide on flavone.[4] (4) By boiling an alcoholic solution of 4-thioflavone (VI) with ethyl glycinate (II), a sample of V was obtained which was identical with that obtained from I plus II.

Reactions 3 and 4 parallel the degradations and syntheses described by Baker and co-workers[5] on other N-alkyl-4H-1-benzopyran-4-imines.

It seems probable that the ketimine salt (IV) was produced by air oxidation of the initial adduct X to a carbinol XI which then lost water to give the ketimine salt IV. Intermediates X and XI could not be found in the reaction mixture but similar oxidation of the reactive hydrogen in the 4-position to a carbinol has been demonstrated for the initial product from flavylium perchlorate and dimethylaniline.[6]



The water formed in conversion of XI to IV reacted with flavylium perchlorate in the presence of the ethyl

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(1) E. I. du Pont de Nemours and Co. Postgraduate Fellow in Chemistry. From a thesis submitted to the Graduate School of the State University of Iowa in partial fulfillment of the requirements for the Ph.D. degree.

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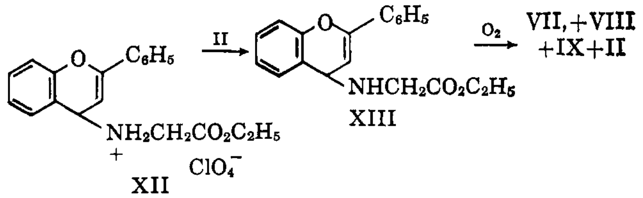
glycinate to produce a nonnitrogen-containing oil which was shown to be a mixture of the chalcone VIII and the two isomeric pyranols VII and IX. A paper chromatogram of this liquid mixture showed three spots whose R_f values were identical with those for spots formed from the mixture resulting from the action of aqueous bicarbonate on flavylium perchlorate. One spot was identical with a 2-hydroxychalcone standard. Hill and Melhuish found that flavylium chloride and 10% sodium hydroxide form 2-hydroxychalcone, 2-phenyl-1,2-benzopyran-2-ol, and flavone after 1 week at room temperature.[7] The yield of flavone was low (10%).

A material balance on the reactants and products showed that all the perchlorate anion was accounted for by III and IV, so that the perchlorate ion was not the oxidizing agent for conversion of X to XI. Furthermore, the yield of the ketimine salt decreased when the initial step was carried out in the absence of air.

When the ratio of ethyl glycinate to flavylium perchlorate was increased to 2:1 the yield of the ketimine IV and V decreased markedly and the amounts of the nonnitrogen-containing by-products VII, VIII, and IX were increased—an unexpected result. This may be due to conversion of X to the free base XIII by the excess ethyl glycinate, followed by air oxidation of this amino derivative to IX with isomerization of this substituted allylic alcohol IX to VII and equilibration to the chalcone VIII. The ethyl glycinate fragment was isolated as the hydroperchlorate III.



XII

XIII

The ethyl esters of *dl*-alanine and *dl*-phenylalanine reacted with flavylium perchlorate in a fashion similar to that described above for ethyl glycinate. The N-substituted 4H-1-benzopyran-4-imines obtained are described in the Experimental part.

Experimental

Flavylium Perchlorate.—2-Hydroxychalcone was cyclized by utilizing glacial acetic acid as a solvent in the procedure of Lowenbein.[8] To obtain a pure product in 75% yield melting at 190–191°, it was essential that the recrystallization be carried out with 40 ml. of glacial acetic acid/g. flavylium perchlorate heated to 90° maximum.

Amino Acid Ethyl Esters.—Mixtures of the appropriate hydrochloride of ethyl esters of amino acids in purified chloroform[9] were converted to solutions of the free bases by described use of ammonia[10] and the excess ammonia was removed by reduced pressure at room temperature. Drierite was added to the preparation to ensure an anhydrous solution.

Flavylium Perchlorate and Ethyl Glycinate.—A suspension of 5 g. (0.016 mole) of flavylium perchlorate in 25 ml. of purified chloroform combined with 1.68 g. (0.016 mole) of ethyl glycinate in 27 ml. of chloroform was shaken for 12 hr. A precipitate (4.8 g.) was collected from the dark purple mixture and washed with absolute ether. This tan product was triturated with 15 ml. of absolute ethanol and the crude insoluble ketimine hydroperchlorate IV was collected and washed with dry ether. The crude product IV weighed 2.78 g. and melted at 223–225° dec. Three recrystallizations from glacial acetic acid raised the melting point to 230–231°, yield 2.65 g. (40%).

Anal. Calcd. for $C_{19}H_{18}NO_3ClO_4$: C, 55.95; H, 4.42; N, 3.44; ClO_4, 24.42. Found: C, 56.25; H, 4.53; N, 3.69; ClO_4, 24.65.

The addition of 175 ml. of dry ether to the ethanolic extract above precipitated 1.42 g. of ethyl glycinate hydroperchlorate. The salt was recrystallized from a mixture of 0.85 ml. of absolute ethanol per 5.25 ml. of chloroform; yield 1.27 g. (51%), m.p. 110.5–112°. It did not depress the melting point of an authentic sample.

The addition of 250 ml. of petroleum ether (b.p. 60–100°) to the purple chloroform solution precipitated 0.05 g. of an unknown water-insoluble purple substance. The yellow petroleum ether–chloroform mother liquor was washed with six 100-ml. portions of water to remove unreacted ethyl glycinate. The organic layer was then dried with Drierite and the solvents were allowed to evaporate at room temperature. The yellow oil which remained weighed 1 g. (27.4%). An ethanolic solution of the oil gave a positive test for phenolic groups[11] and nitrogen was not present in the oil. The effects of varying the reaction conditions are summarized in Table I.

TABLE I

Moles amine/Mole perchlorate	Atmosphere	II, %	Oil, %
1:1	Laboratory	40	27
2:1	Laboratory	24	65
3:1	Laboratory	2.2	96
2:1	N_2[a]	4–10	90
2:1	Air: drybox	24	65

[a] Products isolated in air.

Ethyl N-(2-Phenyl-4H-1-benzopyran-4-ylidene)-glycinate (V).—A mixture of 500 ml. of 1 *N* sodium hydroxide and 10.8 g. of the ketimine hydroperchlorate IV was shaken for 1.5 hr. The resulting solid was collected on a filter and washed with 300 ml. of water. The yellow powder was recrystallized three times from petroleum ether (b.p. 60–100°) to give white needles. The yield of V was 3.1 g. (45%), m.p. 86–87°. A mixture m.p. with an authentic sample was 86–87°.

Anal. Calcd. for $C_{19}H_{17}O_3N$: C, 74.27; H, 5.53; N, 4.56. Found: C, 74.16; H, 5.65; N, 4.48.

Dry hydrogen chloride was passed into a cooled solution of 0.64 g. of the imine V in 50 ml. of dry ether for 40 min. A solution of 1 ml. of 70% $HClO_4$ in 4 ml. of acetic anhydride was then added to the reaction mixture which was allowed to stand 12 hr. The precipitate was collected, washed with ether, and recrystallized twice from acetic acid. The yield of hydroperchlorate IV was 0.47 g. (48%), m.p. 227–229°. A mixture m.p. with an authentic sample of the hydroperchlorate was 227–230° dec.

Refluxing the reaction for 10 min. gave identical results.

Ethyl N-(2-Phenyl-4H-1-benzopyran-4-ylidene)-glycinate (V) and Hydrogen Sulfide.—Hydrogen sulfide was passed into a solution of 0.5 g. of the ketimine obtained from its hydroperchlorate in 15 ml. of absolute ethanol for 30 min. The solution, which slowly turned red, was then allowed to stand for 1.5 hr., cooled in an ice bath, and filtered. The red 4-thioflavone, weighing 2.5 g., was recrystallized from absolute ethanol. The yield was 1.61 g. (41%), m.p. 86.5–87.5°, mixture m.p. with an authentic sample 85.5–87°.

Ethyl Glycinate and 4-Thioflavone.—A solution of 2.8 g. of 4-thioflavone[4] and 13 ml. of freshly distilled ethyl glycinate[10] in 280 ml. of absolute ethanol was refluxed 22 hr. The red color of 4-thioflavone disappeared and hydrogen sulfide was evolved. The ethanolic solution was then evaporated to a volume of 65 ml. and poured with stirring into 400 ml. of water containing 1 g. of sodium chloride. The gummy solid was extracted with two 400-ml. portions of hot petroleum ether (b.p. 60–100°). The tan residue, weighing 0.49 g. and melting at 139–144° dec., was discarded. The solvent was removed from the extracts by evaporation at room temperature and atmospheric pressure. The yellow residue, weighing 1.7 g., was recrystallized three times from petroleum ether (b.p. 60–100°); the yield of white needles was 1.1 g. (31%), m.p. 86–87°.

Anal. Calcd. for $C_{19}H_{17}O_3N$: C, 74.27; H, 5.53; N, 4.56. Found: C, 74.41; H, 5.82; N, 4.55.

The Nonnitrogenous Mixture VII, VIII, and IX and Perchloric Acid.—To a solution of 2.8 g. of the yellow oil in 20 ml. of dry alcohol-free ether was added 4 ml. of 70% perchloric acid in 16 ml. of acetic anhydride. The solution was saturated with dry hydrogen chloride and allowed to stand overnight. A precipitate, weighing 0.41 g., was removed from the mother liquor and recrystallized three times from glacial acetic acid. The yield of golden plates was 0.37 g., 34%, m.p. 178–179° dec. This compound did not depress the melting point of an authentic sample of flavylium perchlorate.

Flavylium Perchlorate and Sodium Bicarbonate.—A suspension of 1.65 g. of flavylium perchlorate in 35 ml. of benzene and 20 ml. of 5% aqueous sodium bicarbonate were shaken together until the evolution of carbon dioxide ceased. The benzene layer was dried over Drierite and portions of this solution were used in

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comparison to identify the oil, VII, VIII, and IX, by means of paper chromatography. The yellow oil which remained after removal of solvent from part of the solution was reconverted to flavylium perchlorate as above.

Paper Chromatography of the Oil, VII, VIII, and IX.—Spots of dilute benzene solutions of the oil, VII, VIII, and IX, the oil from flavylium perchlorate and aqueous sodium bicarbonate, and 2-hydroxychalcone were applied to a strip of Whatman No. 1 paper. The spots were dried and the paper equilibrated for 45 min. with the atmosphere over the developing solvent in an air-tight tank. The chromatogram was then developed at 30° with the aqueous (lower) layer of a 40% butanol–50% water–10% glacial acetic acid solvent system. The chromatogram was dried at 65° and the spots were detected under ultraviolet light. The results are given in Table II.

TABLE II

Compound		R_f factors		
Unknown oil	(3 spots)	0.038	0.21[a]	0.22
Product from aq. $NaHCO_3$ and flavylium perchlorate	(3 spots)	0.038	0.21[a]	.22
2-Hydroxychalcone	(1 spot)	...	...	.22

[a] These spots were only detected at such high concentrations that the other spots were smeared. This fact, more than the R_f factors, indicates that the oils are composed of three components.

Ethyl N-(2-Phenyl-4H-1-benzopyran-4-ylidene)-phenylalaninate Hydroperchlorate.—Five grams (0.0163 mole) of flavylium perchlorate was suspended in a solution of 3.15 g. (0.0163 mole) of ethyl phenylalaninate in 110 ml. of chloroform. The mixture, which became green, was shaken 8 hr. and an insoluble precipitate was then filtered from the green mother liquor; weight 3 g. The solid was recrystallized twice from glacial acetic acid. Light green crystals were obtained and washed with ether. The yield was 2.4 g. (30%), m.p. 233–234° dec.

Anal. Calcd. for $C_{26}H_{24}O_3NClO_4$: C, 62.97; H, 4.84; N, 2.82; ClO_4, 20.08. Found: C, 63.13; H, 5.09; N, 2.75; ClO_4, 20.38.

The green mother liquor was poured into 300 ml. of ether and a small quantity of a dark green gummy solid was filtered from the solution. This yellow solution deposited 0.6 g. of ethyl phenylalaninate hydroperchlorate after standing 4 hr. The solution was then evaporated to dryness at room temperature and atmospheric pressure to yield 2 g. of a yellow oil (55%).

The reaction of 1 mole of flavylium perchlorate with 2 moles of ethyl phenylalaninate gave the ketimine hydroperchlorate in 14% yield, while the presence of Drierite increased the yield to 31%. The green gum was not a product of the latter two reactions.

Ethyl N-(2-Phenyl-4H-1-benzopyran-4-ylidene)-alaninate Hydroperchlorate.—The products from flavylium perchlorate and ethyl alaninate were obtained and purified as described above for ethyl phenylalaninate. The yield of ketimine hydroperchlorate was 2.1 g. (31%), from 0.0163 mole of each reactant, and the m.p. was 216–217° dec.

Anal. Calcd. for $C_{20}H_{20}NO_3ClO_4$: C, 56.94; H, 4.74; N, 3.32; ClO_4, 23.63. Found: C, 56.65; H, 4.57; N, 3.21; ClO_4, 23.24.

The oil (VII, VIII, IX) weighed 1 g. (27%).

Ethyl N-(2-Phenyl-4H-1-benzopyran-4-ylidine)-phenylalaninate and Alaninate.—Two grams of the respective imine hydroperchlorates were each suspended in 50 ml. of 2 *N* sodium hydroxide to which 50 ml. of ether was added. The mixtures were shaken 15 min. The ether layers were separated, washed once with 50 ml. of water, and the solvents were then evaporated at room temperature and atmospheric pressure. The resulting oil from flavone ethyl alaninate imine and the yellow solid from the flavone ethyl phenylalaninate imine were each recrystallized from petroleum ether (b.p. 60–100°) to yield white crystals. The yield of flavone ethyl alaninate imine was 0.67 g. (45%), m.p. 74.5–76°.

Anal. Calcd. for $C_{20}H_{19}NO_3$: C, 74.76; H, 5.92; N, 4.35. Found: C, 74.48; H, 5.52; N, 4.41.

The yield of flavone ethyl phenylalaninate imine was 0.96 g. (60%), m.p. 119.5–120.5°.

Anal. Calcd. for $C_{26}H_{23}O_3N$: C, 78.84; H, 5.79; N, 3.52. Found: C, 78.69; H, 5.69; N, 3.43.

The flavone ethyl alaninate imine was apparently somewhat unstable because discoloration appeared after the compound was exposed to the atmosphere for 5 to 8 hr.

Hydrogen Sulfide and the Flavone Ketimines.—The ethyl N-(2-phenyl-4H-1-benzopyran-4-ylidene)-phenylalaninate and alaninate gave 4-thioflavone in 76 and 48% yields, respectively. The procedure is given above. The 4-thioflavone melting points and mixture melting points checked.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, EASTMAN KODAK CO., ROCHESTER, N. Y.]

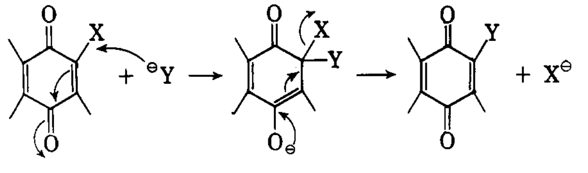
The Kinetics of Displacement of Halides from Substituted Quinones by Sulfite

BY C. A. BISHOP, R. F. PORTER, AND L. K. J. TONG

RECEIVED APRIL 20, 1963

The displacement of halide from a series of 2-halo-3,5,6-trimethyl-*p*-benzoquinones by sulfite was preceded in two cases by a faster reversible quinone–bisulfite reaction. The rates of both reactions were dependent on the concentrations of sulfite rather than bisulfite and were general-acid catalyzed. Related mechanisms for the two reactions are proposed. The order of displacement rates is $I^- \gg Br^- > Cl^-$. A description of the apparatus used in the study of some fast reactions is included.

Quinones are known to undergo several types of reactions, including 1,4-additions,[1–10] nucleophilic displacement of labile substituents,[8–17] and oxidation–reduction reactions.[2,3,5] No thorough kinetic study of these reactions has been reported, although a mechanism has been proposed for nucleophilic displaeement based on observed products (eq. 1).[13,16,17]



(1)

Since the reaction involved replacement of the labile substituent (X) by a nucleophile (Y), the latter was assumed to add to the quinone at the substituted position, generating an intermediate stabilized by negative charge on the oxygen in the 4-position, as shown. Elimination of X in the second step completed the scheme.

To investigate the various steps of nucleophilic displacement of halides on quinones by sulfite, a series of 2-substituted-3,5,6-trimethyl-*p*-benzoquinones, including 2,3,5-trimethyl-*p*-benzoquinone and duroquinone, were treated with sulfite and the kinetics were measured. Alkyl substituents on the 3-, 5-, and 6-positions simpli-

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