[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, STATE UNIVERSITY OF IOWA]

Absorption Spectra of Azlactones[1]

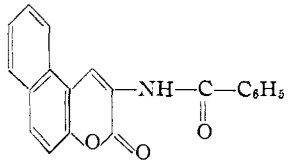
BY F. W. SCHUELER AND S. C. WANG

The chemistry of azlactones[2] has been widely investigated because of their importance as intermediates in the synthesis of amino acids, aryl acetic acids and many natural products. On the other hand, relatively few spectroscopic data are available for this class of compounds. Asahina first[3] compared the ultraviolet absorption curves of the azlactones of benzaldehyde and furfural and later[4] studied the ultraviolet absorption of the azlactones derived from acetoxybenzaldehydes and methoxybenzaldehydes. The Raman spectra of three azlactones have also been determined.[5] Very recently, Carter and Hinman[6] reported the ultraviolet absorption spectra of 2-phenyl-4-*p*-methoxybenzal-5-oxazolone and the ultraviolet as well as the infrared absorption curves for 2-phenyl-4-*p*-methoxybenzyl-5-oxazolone. The purpose of the present investigation was (a) to determine the absorption spectra of a series of substituted azlactones in the ultraviolet and visible regions; (b) to correlate the nature of substituents and the properties of the curves; and (c) to ascertain the characteristic conjugated system which is responsible for their absorption.

The azlactones were prepared in general by the action of hippuric acid and acetic anhydride upon aromatic aldehydes, in the presence of sodium acetate. Furfural, cinnamaldehyde, α-furylacrolein and phthalic anhydride reacted in a manner similar to that of the aromatic aldehydes in which an aldehyde group was directly attached to a benzenoid ring.

Among the azlactones studied two were synthesized from acylglycines other than hippuric acid, namely, one from acetylglycine and the other from *o*-iodobenzoylglycine.

It is known[4,7-10] that when salicylaldehyde is heated with hippuric acid, acetic anhydride and sodium acetate, benzoylaminocoumarin is obtained together with the acetoxyazlactone. In our attempt to synthesize the azlactone from 2-hydroxy-1-naphthaldehyde the only product isolated was a colorless compound, the analysis of which agreed with that of a benzoylaminobenzocoumarin (I).

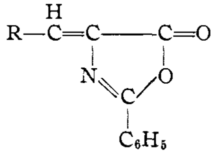

I

Results

The results in the measurement of the absorp-

TABLE I

SPECTRAL DATA


$$\begin{array}{ccccc} & \mathrm{H} & & & \\ \mathrm{R-} & \mathrm{C=} & \mathrm{C} & \text{——} & \mathrm{C{=}O} \\ & & | & & | \\ & & \mathrm{N} & & \mathrm{O} \\ & & & \mathrm{C} & \\ & & & | & \\ & & & \mathrm{C_6H_5} & \end{array}$$

No.	Compounds[b] R (phenyl derivatives)	Max. 1 mμ	Max. 1 ε × 10⁴	Max. 2 mμ	Max. 2 ε × 10⁴
1	3,5-Diiodo-4-(4′-methoxy-phenoxyphenyl	230	3.61	292	2.31
2	β-Phenylvinyl[c]	232	1.63	330	3.41
3	4-Nitrophenyl	228	1.48	316	1.30
4	4-Acetoxyphenyl	226	1.69	288	1.68
5	Unsubstituted phenyl	224	1.45	284	1.51
6	2,3-Dimethoxyphenyl	223	2.00	288	1.58
7	α-Furyl[c]	228	1.27	312	2.19
8	3-Chloro-4,5-dimethoxy-phenyl	224	2.56	298	1.60
9	Unsubstituted phenyl[e]	220[g]	2.17	282	1.73
10	2-Nitrophenyl	228	2.15	252[a]	1.50
11	3-Nitrophenyl	228	2.03	272	2.14
12	2,6-Dichlorophenyl	222	2.02	274	1.25
13	4-Acetoxy-3-methoxy-phenyl	220[g]	2.09	298	1.45
14	2-Chlorophenyl	226	1.85	279	1.48
15	β-Phenylvinyl[c,f]	230	1.96	310	1.73
16	Phthalyl[c]	224	1.72	276[a]	0.44
17	4-Isopropylphenyl	226	1.61	295	1.78
18	Unsubstituted phenyl[d]	220[g]	0.97	284	1.31
19	4-Methylphenyl	229	1.88	292	1.90
20	3,4-Diethoxyphenyl	230	1.92	323	1.52
21	3,4-Dimethoxyphenyl	231	1.66	323	1.68
22	3,4-Methylenedioxyphenyl	226	1.76	325	1.73
23	4-Methoxyphenyl	228	1.70	308	1.82
24	3-Acetoxyphenyl	227	1.94	281	1.51
25	Benzalacetone[h]	286	1.80	225	1.71
26	4-Diethylaminophenyl (r.)	244	1.25	482	4.19
27	4-Dimethylaminophenyl (r. o.)	240	1.35	475	2.82
28	β-(α′-Furylvinyl) (o. br.)	226	1.36	348	2.89

[a] Point of inflection. [b] All compounds had a yellow color except as otherwise noted, thus: r. o., red orange; r., red; o. br., orange brown. [c] This replaces phenyl and its derivatives. [d] In this compound the phenyl on the heterocycle was replaced by methyl. [e] In this compound the phenyl on the heterocycle was replaced by *o*-iodophenyl. [f] The hydrogen on the carbon atom next to R was replaced by CH_3. [g] *Circa*. [h] These spectra values refer to the spectra of benzalacetone itself.

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(1) This work was aided by a grant from the U. S. Public Health Service.

(2) A comprehensive discussion on the preparation of azlactones, their properties and reactions has been presented by Carter in "Organic Reactions," Vol. 3, pp. 198-239.

(3) T. Asahina, *Bull. Chem. Soc. Japan*, **4**, 202 (1929).

(4) T. Asahina, *ibid.*, **5**, 354 (1930).

(5) D. I. Shirogin, *Ya K. Syrkin, Otdel. Khim. Nauk*, pp. 59-63 (1946); *Acta Physicochim.*,[1] *U. R. S. S.*, **21**, 423 (1946).

(6) H. E. Carter and J. W. Hinman, *J. Biol. Chem.*, **178**, 403 (1949).

(7) E. Erlenmeyer and W. Stalin, *Ann.*, **337**, 283 (1904).

(8) O. Rebuffat, *Ber.*, **22**, 551c (1889).

(9) O. Rebuffat, *Gazz. chim. ital.*, **15**, 527 (1885).

(10) J. Plöchl and L. Wolfrom, *Ber.*, **18**, 1183 (1885).

TABLE II

Compounds	Empirical formula	Analyses,[a] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	M. p., °C.	Yield, %
2-Phenyl-4-*p*-diethylaminobenzal-5-oxazolone	$C_{20}H_{20}N_2O_2$	74.97	74.40	6.23	6.33	128	31.4[b]
2-Phenyl-4-*p*-dimethylaminobenzal-5-oxazolone	$C_{18}H_{16}N_2O_2$	73.95	73.30	5.52	5.14	213–214	64.9
2-Phenyl-4-(2′,6′-dichlorobenzal)-5-oxazolone	$C_{16}H_9Cl_2NO_2$	60.40	60.18	2.85	3.01	159	86.0
2-*o*-Iodophenyl-4-benzal-5-oxazolone	$C_{16}H_{10}INO_2$	51.22	50.99	2.69	2.67	153	80.0
2-Phenylmethyl-(β-phenylvinyl)-methylene-5-oxazolone	$C_{19}H_{15}NO_2$	78.87	79.12	5.23	5.19	164–165	34.0
2-Phenyl-4-β-furylvinylmethylene-5-oxazolone	$C_{16}H_{11}NO_3$	72.39	72.16	4.20	4.19	168–169	61.4
3-Benzoylamino-5,6-benzocoumarin	$C_{20}H_{13}NO_3$	76.18	75.94	4.16	4.08	228–229	74.0

[a] The analyses were done by the Clark Microanalytical Laboratory, Urbana, Illinois. [b] The low yield is mainly due to the high solubility of this compound in ethanol from which it is recrystallized.

tion spectra of the azlactones are expressed as the molar extinction ϵ which was obtained from the optical density readings D and the molecular weights m by the relations $k = D/cl$ and $\epsilon = km$, where c is the concentration of the solution in mg. per ml. and l is the length of the cell.

The absorption curves are shown in a separate block. In our discussion we are primarily concerned with the position of the absorption bands which are represented by the spectral data summarized in Table I. The compounds which are not recorded in the literature are listed in Table II.

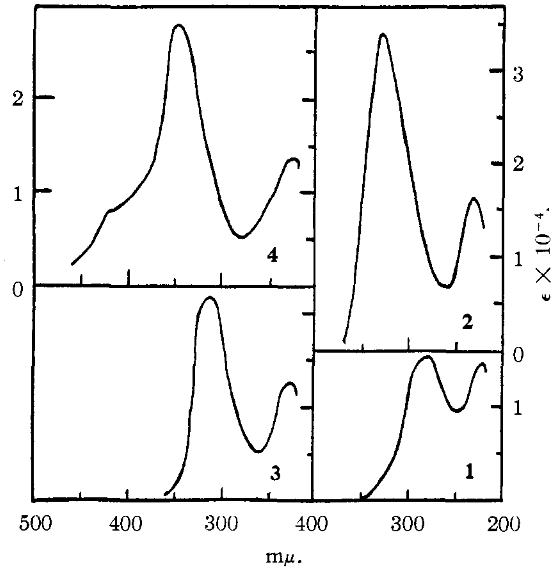
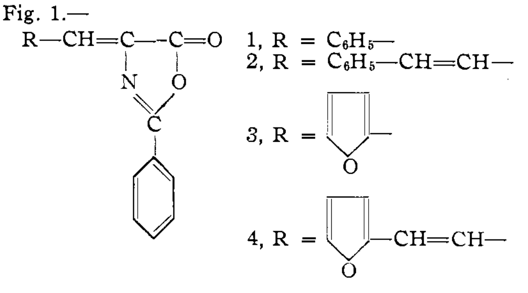


Fig. 1.—



Discussion

The spectra of azlactones in general have two bands and thus exhibit the kind of absorption typical of many conjugated systems.[11] Similar to other benzene derivatives with unsaturated side chains, the fine structure is absent.[12] This apparent simplicity in the absorption band structure indicates that in all azlactones the whole molecule acts as a single resonator. It is, therefore, of particular interest to locate the common chromophore which is responsible for the general characteristics of the spectra and also the effects of the specific groups which cause shifts in the positions of the typical curves. The influence of the substituents will be discussed first, since a comparison of the data in individual cases will aid in revealing the resonating grouping which characterizes all the spectra.

The effect of the length of the conjugated system on the spectra is shown in the comparison of no. 2 and no. 5 and no. 28 with no. 7. That the furan derivative is more bathochromic than the

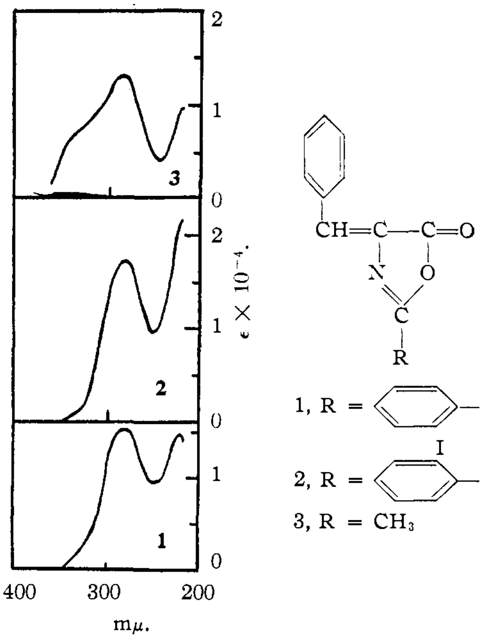


Fig. 2.—

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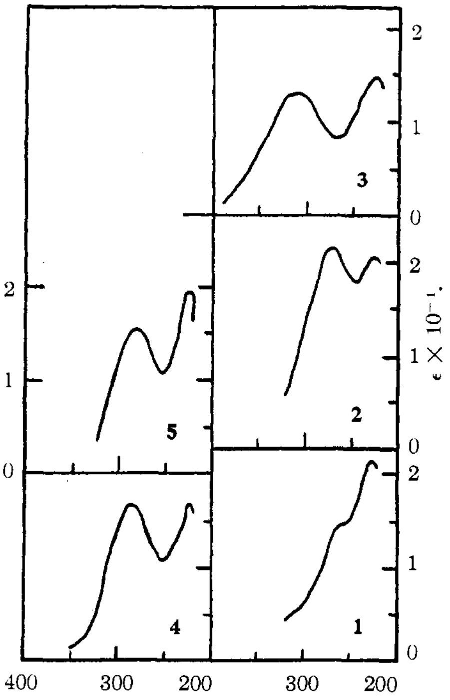
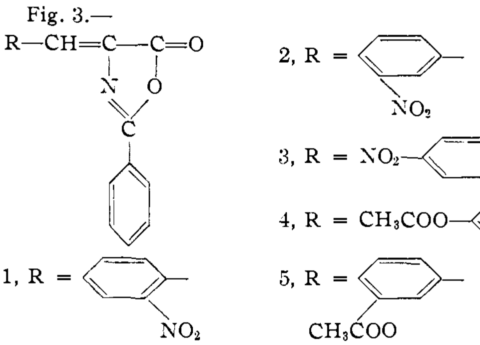
[11] H. Booker, L. K. Evans and A. E. Gillam, *J. Chem. Soc.*, 1453 (1940).

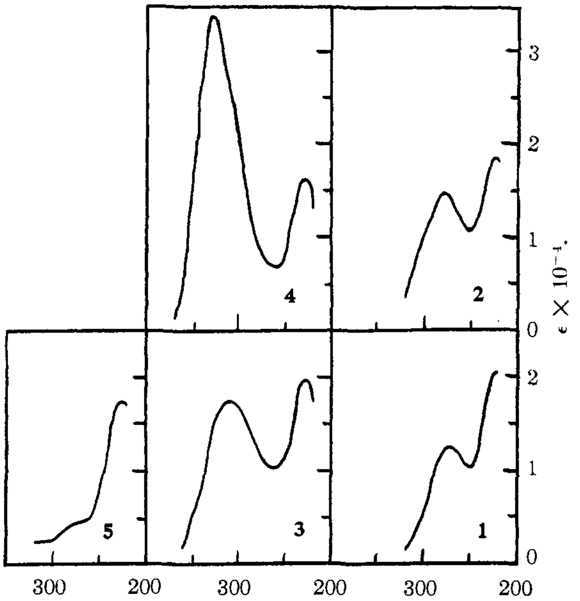
[12] T. W. Campbell, S. Linden, S. Godshalk and W. G. Young, THIS JOURNAL, **69**, 880 (1947).



mμ.

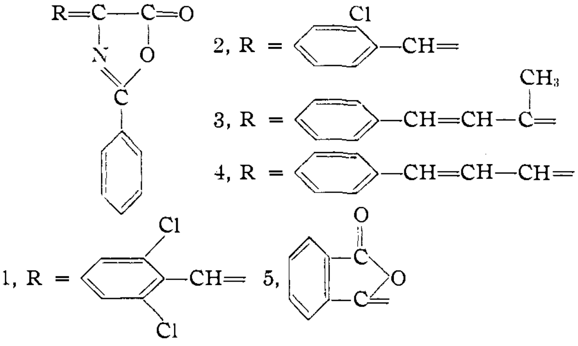
Fig. 3.—



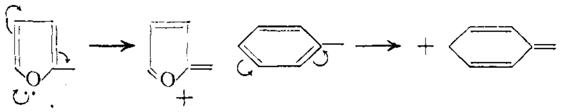


mμ.

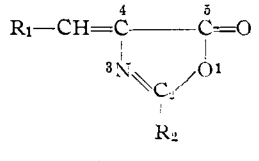
Fig. 4.—



benzene derivative can be explained by the fact that in the excited form the former has one more double bond in the conjugated chain than the latter.[13]



A similar relationship has been observed by Stobbe[14] and others.[15,16]



Substituents at position 2 of the oxazolone ring in the azlactone molecule do not have appreciable influence on the position of the spectra. The maxima of the main band remain practically the same when R_2 varies from phenyl to methyl or to *o*-iodophenyl. It is to be noted that this is in striking contrast with the effect of substitution in R_1. This difference between R_1 and R_2 in their contribution to the spectra will be mentioned again in the latter part of our discussion.

All of the 8 azlactones where R_2 is phenyl and R_1 is a *p*-substituted phenyl group are more bathochromic than the unsubstituted azlactone where R_1 is an unsubstituted phenyl group (*cf.*, *e. g.*, Nos. 1, 19, 26 and 27). The effectiveness of the *p*-substituents in causing a shift of the absorption band towards the longer wave lengths occurs in the following order: $(C_2H_5)_2N- > (CH_3)_2N- > NO_2- > CH_3O- > (CH_3)_2CH- > p\text{-}CH_3OC_6H_4\text{-}O\text{-}3,5\text{-}I_2C_6H_3- \geq CH_3- > CH_3COO-$. This series agrees, insofar as a comparison can be made, with the one described by Burawoy.[17] With the exception of the nitro group, the bathochromic

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[13] E. R. Blout and M. Fields, THIS JOURNAL, **70**, 189 (1948).

[14] H. Stobbe and R. Haertel, *Ann.*, **370**, 99 (1909).

[15] I. Kasiwagi, *Bull. Chem. Soc. Japan*, **1**, 150 (1926).

[16] K. W. Hausser, R. Kuhn, A. Smakula and A. Deutsch, *Z. physik. Chem.*, **B29**, 378 (1935).

[17] A. Burawoy, *J. Chem. Soc.*, 1179 (1939).

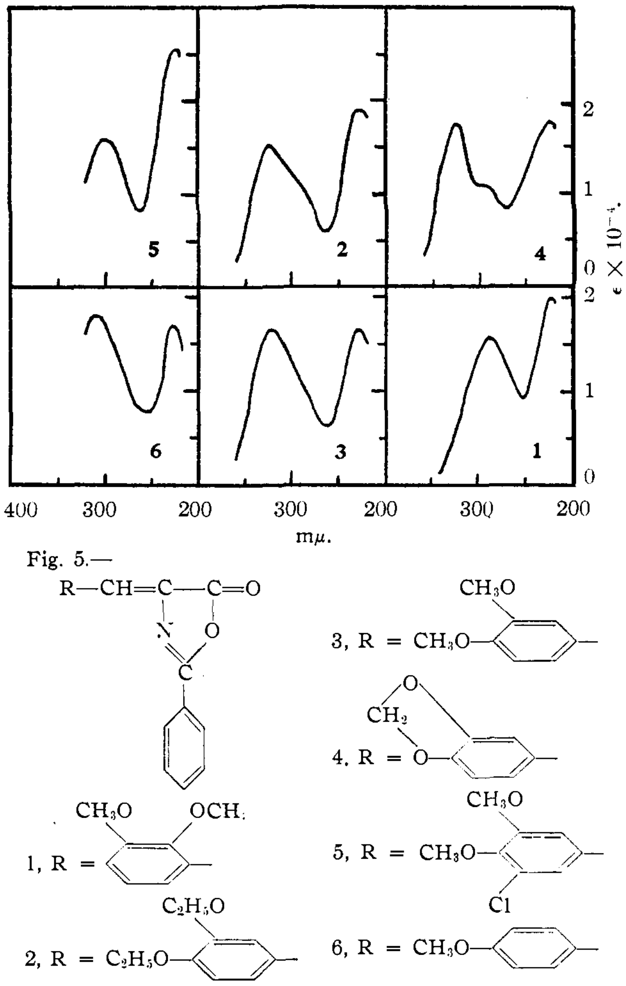
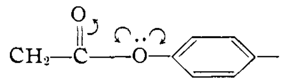


Fig. 5.—

strength of the above groups can be associated with their relative electron-donating power. The acetoxyl group is a weak electron-donor due to the electronegativity of the carbonyl oxygen which tends to counteract the tendency for the other oxygen atom to feed electrons into the ring.



The three nitro derivatives as well as the two acetoxy derivatives represent the effect of position isomerism. Although these five compounds do not by themselves justify any conclusion, they do, however, confirm the observations made by previous workers in that a substitution in the *p*-position in the benzene ring produces, in general, a stronger absorption band than substitution in the *m*- or *o*-positions.[18-23]

A few cases may be cited where steric effects are manifested in the spectra (nos. 12, 14, 15 and 16). The main band in the *o*-nitro derivative is depressed (no. 10). Similar observations in the *o*-substituted series have been reported by Brown,[24] Calvin,[25] Remington[26] and many others. An even more noticeable depression of the main absorption band occurs in the curve of the azlactone derived from phthalic anhydride. By the comparison of the curve of the *o*-chloro-substituted azlactone with that of the 2,6-dichloro compound it was noticed that the main absorption band of the latter was 5 mμ less than the corresponding band of the former. The maxima in the four cases just mentioned all appear at a wave length less than the $\lambda_{\text{max.}}$ for the unsubstituted azlactone derived from benzaldehyde. Furthermore, the azlactone prepared from benzalacetone and that from cinnamaldehyde differ considerably in the position of the main absorption bands and even more so in the relative intensities of these bands. This might also be attributed to steric interference of the methyl group which partially hinders the coplanarity of the resonating structure.

It is of interest to observe that 3,4-dimethoxysubstituted azlactone, 3,4-diethoxy-substituted azlactone and 3,4-methylenedioxy-substituted azlactone possess very similar curves as might be expected (nos. 20–22). The main maxima are almost identical for all three compounds. On the other hand, 2,3-dimethoxy compound (no. 6) absorbs light at a much shorter wave length than the 3,4-isomer.

The introduction of a methoxy group ortho to a para-substituent, that is, in the meta position with respect to the unsaturated side chain, seems to enhance the bathochromic shift. The main absorption band of the 3,4-dimethoxybenzal derivative is

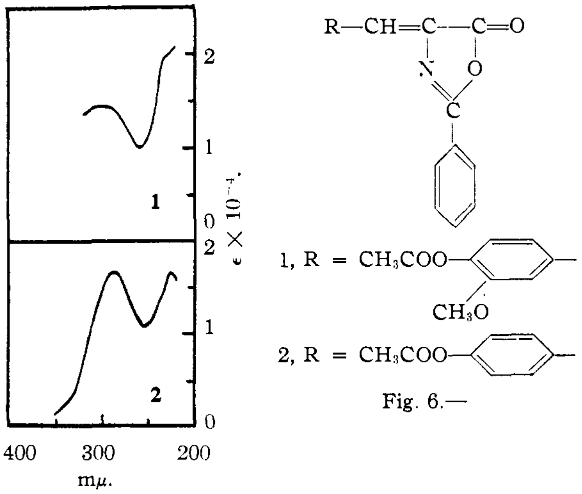


Fig. 6.—

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(18) W. R. Brode, THIS JOURNAL, **51**, 1204 (1929).

(19) E. C. C. Baly and F. G. Tryhorn, *J. Chem. Soc.*, **107**, 1058 (1915).

(20) J. E. Purvis and N. P. McCleland, *ibid.*, **103**, 1088 (1913).

(21) M. F. Klingstedt, *Compt. rend.*, **175**, 365 (1922).

(22) A. Kiss, J. Molnar and C. Sándorfy, *ibid.*, **227**, 724 (1948).

(23) W. R. Brode and L. V. E. Cheyney, *J. Org. Chem.*, **6**, 343 (1941).

(24) W. G. Brown and H. Reagan, THIS JOURNAL, **69**, 1032 (1947).

(25) D. W. Sherwood and M. Calvin, *ibid.*, **64**, 1350 (1942).

(26) W. R. Remington, *ibid.*, **67**, 1838 (1945).

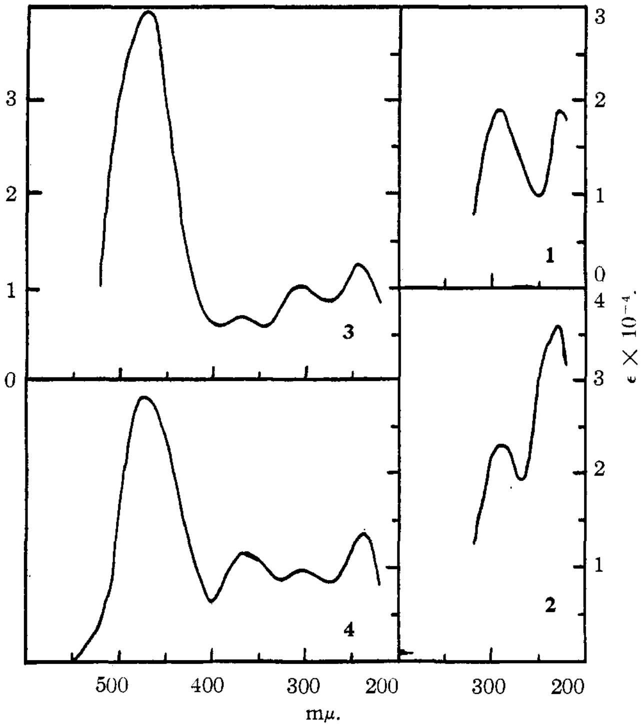
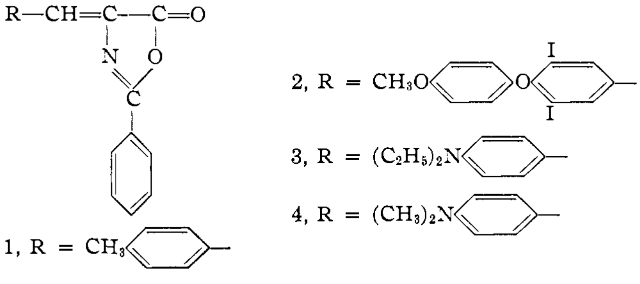
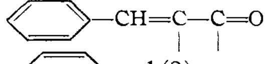
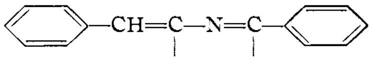
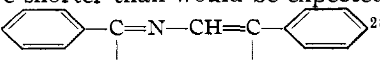


Fig. 7.—



323 mμ, as compared with 308 mμ in the case of the 4-methoxy compound (nos. 21 and 23). The main maximum of the vanillin derivative is 298 mμ which is also greater than the value, 288 mμ, for the *p*-acetoxybenzal derivative (nos. 4 and 13). In a contrary manner, however, the introduction of chlorine into the 2-position of the 3,4-dimethoxybenzal derivatives reduces rather markedly the absorption of the latter compound (nos. 8 and 21).

With regard to the conjugated system, in the azlactone molecule, which may be involved in the absorption of light, there appear to be three possibilities, namely, (1)  (2)  and (3) some cross conjugation[27] of the above two systems. The peaks for the azlactone curves appear at wave lengths which are shorter than would be expected for the system [28] and, therefore, the experimental evidence does not seem to favor the second and the third possibilities.

Wilds and co-workers[29] reported the spectra of α,β-unsaturated ketones conjugated with an aromatic nucleus. All these ketones show two bands in a manner similar to the azlactones in the present paper. It is most interesting to find the intimate similarity in the main maximum of the benzalacetone with that of the benzal azlactone. The similarity is extended to their derivatives and, hence, does not seem to be fortuitous. The maximum of benzalacetone occurs at 286 mμ (no. 25), that of *p*-acetoxybenzalacetone at 290 mμ; whereas the unsubstituted benzal azlactone has its main maximum at 284 mμ and the corresponding *p*-acetoxy derivative at 288 mμ. While the *p*-methoxy group produces in benzalacetone a pronounced bathochromic shift ($\lambda_{\max.}$ at 318 mμ), so is the result in the substitution of the same group in the azlactone series ($\lambda_{\max.}$ at 308 mμ).

Evans and Gillam[30] in the light of Woodward's suggestion[31] compared the locations of K-bands,[17,32] the bands which determine the nature of the conjugated system, of a large number of α,β-unsaturated ketones and found that all of them fall within the range 218 to 241 mμ with the majority of cases spreading around 230 mμ. They also found that other conjugated systems, for example C=C—C=N, show remarkably different K-bands. The K-bands of azlactones likewise fall into this range which typifies α,β-unsaturated ketones in general.

In view of the above evidence it seems highly probable that the chromophore responsible for the spectra of azlactones is the following conjugated system which con-

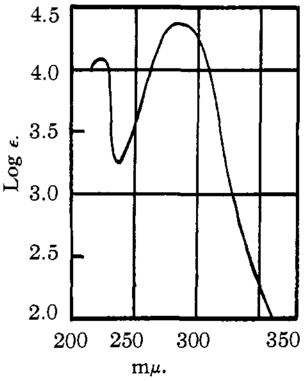


Fig. 8.—Redrawn from reference 29.

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[27] The remarkable effect of cross conjugation was discussed in G. N. Lewis and M. Calvin, *Chem. Revs.*, **25**, 311 (1939).

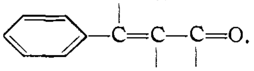
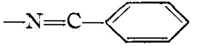
[28] Compare F. H. Stodola, *J. Org. Chem.*, **13**, 757 (1948).

[29] A. L. Wilds, L. W. Beck, W. J. Close, C. Djerassi, J. A. Johnson, Jr., T. L. Johnson and C. H. Shunk, THIS JOURNAL, **69**, 1985 (1947).

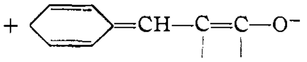
[30] L. K. Evans and A. E. Gillam, *J. Chem. Soc.*, 1453 (1940).

[31] R. B. Woodward, THIS JOURNAL, **63**, 1143 (1941); **64**, 76 (1942).

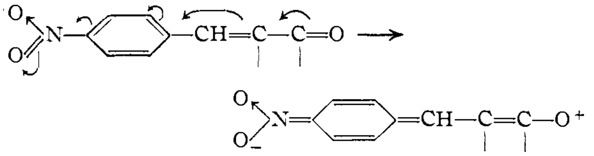
[32] H. Booker, L. K. Evans and A. E. Gillam, *J. Chem. Soc.*, 1453 (1940).

tains the α,β-unsaturated carbonyl grouping:  The fact that substitutions in R_2 of the oxazolone ring do not affect the spectra, further substantiates the idea that the  system in the azlactone molecule does not play any significant role in light absorption.

On the basis of the above idea, the excited form of the azlactones, as in benzalactone, appears to have more contribution from the following structure with the formal charge produced by shifting of the π electrons.



The bathochromic effect of electron-donating groups can then be attributed to their ability to conjugate with the ring thereby increasing the effective length of the conjugated system. The effect of the *p*-nitro group, on the other hand, could possibly be due to its ability to draw electrons out of the ring and, thus, overcome the electronegativity of the carbonyl group. The resultant effect in this last case would then be a shift of electrons in a direction opposite to that in the other cases, but with a qualitatively, similar change produced in the spectra.[33]



That the nitro group is more effective than ketonic carbonyl group in causing a band shift is in accord with the observations of Doub and Vandenbelt.[34]

Experimental

Absorption Spectra.—All spectra were determined with a Beckman quartz spectrophotometer model DU.

Measurements of the optical densities were made regularly at 2-mμ intervals within the range 220 to 300 mμ, at 5-mμ intervals between 300 and 400 mμ, and at 10-mμ intervals above 400 mμ; except in the neighborhood of maxima and minima where the interval was reduced to 1 mμ. Silica cells of a path length of 1 cm. were employed in the determinations in the ultraviolet region and corex cells of the same thickness were used in the visible region. 95% Ethanol was used as a solvent for the samples as well as for the blank. All the samples were dissolved in the solvent to a concentration of 10 mg. per l.

Preparation of Materials.—The azlactones were prepared by the following general procedure: A mixture of 0.05 mole of the aldehyde, 0.05 mole of dry, powdered hippuric acid, 0.05 mole of freshly fused sodium acetate and 16 ml. of acetic anhydride was heated in a beaker on a hot-plate until a complete solution was obtained. The beaker was then transferred to a steam-bath and heating was continued until crystals separated. The reaction mixture was next poured into water, the solid product filtered with suction, washed with water and finally recrystallized from a suitable solvent. The majority of the azlactones were recrystallized from 95% ethanol. The azlactone derived from vanillin was recrystallized from acetone and that from phthalic anhydride from nitrobenzene, since these two azlactones were too insoluble in ethanol. Recrystallization was repeated until the melting point of the azlactone checked with the literature value. For these compounds not found in the literature, purification was carried out until additional recrystallization would not raise the melting point. The yield, in general, ranged from 60 to 95%.

The azlactones from both cinnamaldehyde and α-furylacrolein were purified by hydrolyzing the crude product with alkali, recrystallizing the benzoylamino acid from ethanol and converting back to the azlactone with acetic anhydride.[35] Using the isolated frog heart perfusion method these azlactones have been tested for cardiac digitalis-like action. They show in general very-low-to negligible activities in this respect. The results of the pharmacological study will be reported elsewhere.

Summary

Absorption spectra of twenty-seven azlactones in the ultraviolet and visible regions were reported. Several of the azlactones were not recorded in the literature.

Correlations between chemical constitution of the azlactones and their spectra were discussed. The similarity in the spectra of azlactones to those of α,β-unsaturated ketones conjugated with an aromatic nucleus was pointed out.

An attempt to synthesize an azlactone from 2-hydroxy-1-naphthaldehyde resulted in the formation of 3-benzoylamino-5,6-benzocoumarin.

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