[Contribution from the Department of Chemistry of the College of Arts and Sciences, University of Louisville]

3-Arylidene-5-(α-hydroxybenzylidene)-2,6-piperidinedione-4-carboxylic Acid γ-Lactones from Citrazinic Acid

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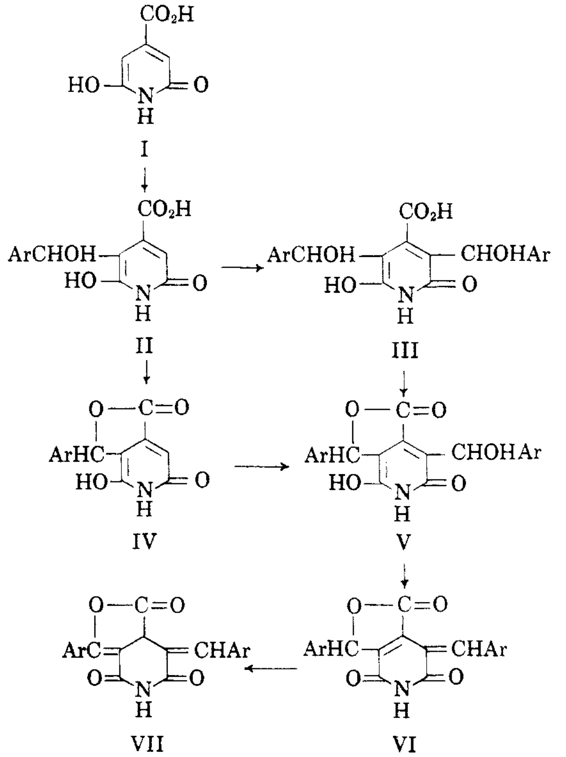
3-Arylidene-5-(α-hydroxybenzylidene)-2,6-piperidinedione-4-carboxylic acid γ-lactones have been prepared by the condensation of aromatic aldehydes with citrazinic acid. Infrared absorption bands at 1786–1815 cm.$^{-1}$ in the carbonyl region establish the β,γ-unsaturated lactone structure. The additional absorption bands in the carbonyl region, which occur at 1761–1767 cm.$^{-1}$ with three of the products and at 1664–1706 cm.$^{-1}$ with all of the products, are characteristic of the two absorption bands associated with the —CONHCO— structure.

Aldehyde condensation products obtainable from citrazinic acid (2,6-dihydroxyisonicotinic acid) (I) have remained uncharacterized although the acid itself, which is readily available, has been known since 1893[1] to undergo condensations of the active methylene type. The absence of data on the aldehyde condensations is probably due to the peculiar character of the products. We have now established the structure of one type of product from this reaction and wish to describe the results of these studies in this paper.

Well-defined crystalline products have been obtained in our studies from aromatic aldehydes and citrazinic acid. The products separate on refluxing a mixture of the reactants in glacial acetic acid with acetamide as a catalyst. These products have been obtained in 22–70% yield and, except for that from *p*-dimethylaminobenzaldehyde, have been recrystallized from nitromethane or nitrobenzene. The analytical data indicate that two molecules of aldehyde have condensed with one of citrazinic acid with the loss of two molecules of water. Apparently the condensation product from equimolar quantities of the reactants is soluble in the acetic acid solvent and the reaction continues rapidly to the 2/1 product which precipitates.

Structural assignments for these products can be based on analogies with known reactions. The obvious positions for the condensation to occur are at the 2- and 5-positions of the acid. The initial reaction will presumably take place in a fashion similar to that in which aldehydes customarily condense at the position *ortho* to an aromatic hydroxyl group to give either mono(II)- or di(III)-substituted hydroxybenzyl compounds. These can be converted by dehydration and further condensation of II or the dehydration of III to intermediates IV and V. On further dehydration V will form the α,β-unsaturated lactone (VI) which can tautomerize to the β,γ-unsaturated lactone (VII).



An analysis of the infrared absorption characteristics of these products in the carbonyl region is consistent with the β,γ-lactone structure VII. In structures of the γ-lactone type the normal carbonyl absorption is at 1770 cm.$^{-1}$ with a shift to 1750 cm^{-1} for α,β-unsaturated types, in which the unsaturation is conjugated, and to 1800 cm.$^{-1}$ for β,γ-unsaturated types.[2] The shift to higher frequencies in the β,γ-unsaturated type is attributed to the vinyl ether type structure.[3] All of the products show absorption maxima in the 1786–1815 cm.$^{-1}$ (5.6–5.5 μ) region which is characteristic of the β,γ-unsaturated lactone carbonyl. For example, β,γ-angelicalactone absorbs at 1800 cm.$^{-1}$,[2] 3-methylenephthalide absorbs at 1780 cm.$^{-1}$,[4] and phthalidylacetic acid absorbs at 1800 cm.$^{-1}$.[4]

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(1) Sell and Easterfield, *J. Chem. Soc.*, **63**, 1035 (1893).

(2) Whiffen and Thompson, *J. Chem. Soc.*, 1005 (1946).

(3) Bellamy, *Infra Red Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, New York, 1954, p. 160.

(4) Grove and Willis, *J. Chem. Soc.*, 877 (1951).

TABLE I

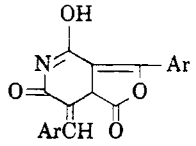
3-BENZYLIDENE-5-(α-HYDROXYBENZYLIDENE)-2,6-PIPERIDINEDIONE-4-CARBOXYLIC ACID γ-LACTONES

Ar of Formula IV	M.p., °C.	Color	Yield,[a] %	Re-cryst. Solvent[b]	Analysis C Calc'd	Analysis C Found	Analysis H Calc'd	Analysis H Found	Infrared Absorption[c]		
Phenyl	228–229	Yellow	27	NM	72.50	72.29	3.96	3.95	1799s	1764s	1678s
p-Isopropyl-phenyl	269	Yellow	60	NB	75.16	74.93	6.07	6.26[d]	1802m	1761s	1689s
3,4-Dichloro-phenyl	222	Yellow	22 (29[e])	NB-NM	51.19	51.11	1.92	2.21	1815s		1686s
3,4-Diethoxy-phenyl	221	Red-brown	30 (40[e])	NB-NM	66.26	65.76	5.76	5.82	1802w	1767s	1706s
p-Nitrophenyl	272–273	Orange-brown	44 (58[e])	NB	57.01	57.13	2.63	2.82	1812m		1684s
p-Dimethyl-amino-phenyl	285–286	Purple	70	[f]	[g]				1786s		1664s

[a] Per cent yield based on citrazinic acid used. [b] NM—nitromethane; NB—nitrobenzene. [c] s—strong; m—medium; w—weak. [d] Nitrogen: Calc'd, 3.37. Found, 3.34. [e] Per cent yield based on aldehyde. [f] Refluxed with acetic anhydride and washed with acetone. [g] Nitrogen: Calc'd, 10.07. Found, 10.28.

Three of the products—those where aryl is phenyl, isopropylphenyl, and diethoxyphenyl—show an additional absorption maximum at 1761–1767 cm.$^{-1}$ and all show maxima in the 1664–1706 cm.$^{-1}$ (6μ) region. In previous studies[5] it has been shown that absorption bands at 1720–1790 cm.$^{-1}$ and 1670–1710 cm.$^{-1}$ are associated with the two carbonyl groups of the —CONHCO— structure. These two bands are quite distinctly present in the three compounds mentioned. Shoulders indicate the possibility of obscured absorption in this region with two of the remaining compounds. There is a possibility that the observed absorption at 1761–1767 cm.$^{-1}$ could result from contributions from the α,β-unsaturated γ-lactone carbonyl group but this seems unlikely because previous reports place such absorption at around 1750 cm.$^{-1}$. It is also unlikely because such an assignment would require that the remaining carbonyl band in the 1800 cm.$^{-1}$ region be reassigned to the second amide carbonyl which is inconsistent with the fact that absorption associated with this carbonyl has previously been observed at not over 1790 cm.$^{-1}$. Only with the *p*-dimethylamino derivative is the absorption at a low enough frequency (1786 cm.$^{-1}$) to permit such an assignment but even here it is questionable since the effect of the dimethylamino groups has been to shift the absorption in the related 1670–1710 cm.$^{-1}$ range to its lowest value for the series—1664 cm.$^{-1}$.

Suitable nomenclature for these products requires comment. They may be named as substituted 3-benzylidene-5-(α-hydroxybenzylidene)-2,6-piperidinedione-4-carboxylic acid lactones as indicated in formula VII. They may be also named as derivatives the azaisobenzofuran structure, formula VIII; *e.g.*, 3-phenyl-4-hydroxy-7-benzylidene-1,6,7,-7a-tetrahydro-5-azaisobenzofuran-1,6-dione.



VIII

These products were prepared as part of a program designed to evaluate the tumor inhibition characteristics of unsaturated lactones. The results of the testing program will be reported elsewhere.

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EXPERIMENTAL

The citrazinic acid used in these experiments was provided by the Charles S. Pfizer Company. The aldehydes were obtained from commercial sources. All melting points are corrected.

Details of the procedure used for the preparation of the product from isopropylbenzaldehyde will be given as illustrative of the procedure used.

A solution of 3.2 g. (0.02 mole) of citrazinic acid, 7.5 g. (0.05 mole) of *p*-isopropylbenzaldehyde, and 2.5 g. of acetamide in 100 ml. of glacial acetic acid was refluxed for six hours. On cooling, the product separated as crystals. Recrystallization from nitrobenzene gave 5 g. (60%) of yellow crystals, m.p. 269°.

The products listed in Table I were prepared by procedures similar to that given above with the exception that the mole ratio of aldehyde to citrazinic acid was varied as follows: benzaldehyde (0.05/0.02); *p*-dimethylaminobenzaldehyde (0.04/0.02); *p*-nitro-, 3,4-dichloro-, and 3,4-diethoxy-benzaldehyde (0.03/0.02).

Although no satisfactory solvent could be found for recrystallization of the product from *p*-dimethylaminobenzaldehyde, it was obtained analytically pure by refluxing with acetic anhydride in which it is insoluble followed by washing with acetone.

The infrared absorption data were obtained using potassium bromide pellets in a Baird double beam recording infrared spectrometer.

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[5] Randall, Fowler, Fuson, and Dangl, *Infra Red Determination of Organic Structures*, D. Van Nostrand Company, Inc., New York, New York, 1949, p. 14.