[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, SCHOOL OF MEDICINE, WESTERN RESERVE UNIVERSITY]

CONDENSATION PRODUCTS OF AROMATIC ALDEHYDES WITH Δ_2-ANGELICA LACTONE[1]

BY W. F. VON OETTINGEN

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J. Thiele, R. Tischbein and E. Lossow[2] described the condensation of anisaldehyde and Δ_2-angelica lactone with the formation of α-anisal-Δ_2-angelica lactone. In a study on the relation between chemical constitution and pharmacological action concerning the anthelmintic properties of some aliphatic lactones,[3] it was found that both the Δ_2- and Δ_1-angelica lactone produce a very marked depression of the musculature and to a smaller extent also of the nervous system, but these compounds could not be utilized as anthelmintics on account of their chemical instability and general toxicity. Eugenol is also a muscular depressant and is used as an anthelmintic; its action is said to depend upon the position of the OH and OCH_3 of the ring. Therefore, it appeared to be feasible to combine both the eugenol and the angelica lactone by condensing vanillin with Δ_2-angelica lactone by the method used by Thiele and his co-workers. Because this condensation was successful, a series of similar compounds was synthesized, in order to study the relation between chemical constitution and pharmacological action of these compounds.

It would have been logical to start with the α-benzal-Δ_2-angelica lactone, *i. e.*, the angelica lactone in which the H_2 group is substituted by a benzyl ring, but Thiele had already found that the compound is very unstable, the lactone ring being split with the formation of benzal-levulinic acid. In the present study it was also found impossible to obtain a pure product. The same holds true for the α-phenol acetal, the α-cinnamal- and the α-hydrocinnamal-Δ_2-angelica lactones.

On the other hand, it was found possible to prepare and to isolate the corresponding derivatives of the salicyl- and resorcylaldehyde in crystalline form.

Because it is known that closure of the phenol group reduces the pharmacological action of phenols, three further compounds were prepared, in which one or two hydroxy groups were masked by methyl groups. The compounds are α-anisal-, α-vanillal- and α-piperonal-Δ_2-angelica lactone.

The Δ_2-angelica lactone was prepared according to the directions of R. Gilmour,[4] which gave very satisfactory results.

[1] This investigation has been made with the assistance of a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.

[2] J. Thiele, R. Tischbein and E. Lossow, *Ann.*, **319**, 180 (1901).

[3] W. F. von Oettingen, *J. Pharm. Exptl. Therapy*, **36**, 335 (1929).

[4] R. Gilmour, *J. Chem. Soc.*, **105**, 75 (1914).

The condensation of the aromatic aldehydes with the Δ_2-angelica lactone was accomplished by heating small quantities of the angelica lactone, usually 2 g., with little more than the equimolecular quantity of the aldehyde on the water-bath for a half to one hour with the occasional addition of a few drops of diethylamine. The condensation product was then shaken with sodium bisulfite solution (20 cc. of 15% solution), in order to remove the excess aldehyde; the resulting resinous mass was then dissolved in methyl alcohol, crystallized and recrystallized. Elementary analyses of the compound were made by Professor N. A. Lange of Case School of Applied Science. A study of the pharmacological action of these compounds will appear at another place; Table I gives the properties of the compounds thus obtained.

TABLE I

CHEMICAL PROPERTIES OF THE AROMATIC–ALIPHATIC LACTONES

	α-( )-Δ_2-Angelica lactones				
Property	Salicylal	Resorcylal	Anisal	Vanillal	Piperonal
M. p. °C.	96	167–168	99	143	125
Soly., water	1/2000	1/10000	1/50000	1/50000	1/50000
Soly., N saline	1/2000	1/10000	1/50000	<1/50000	<1/50000
Soly., alcohol	Fairly	Fairly[a]	Fairly	Fairly	Fairly
Soly., ether	Slightly	Slightly	Fairly	Slightly	Fairly
Soly., chloroform	Freely	Freely	Freely	Freely	Freely
Soly., benzene	Fairly	Slightly	Freely	Slightly	Freely
Soly., olive oil	Fairly	Slightly	Fairly	Fairly	Fairly
Molecular wt.	202	218	216	232	230
Formula	$C_{12}H_{10}O_3$	$C_{12}H_{10}O_4$	$C_{13}H_{12}O_3$	$C_{13}H_{12}O_4$	$C_{13}H_{10}O_4$
C, calculated, %	71.25	66.02	72.19	67.21	67.80
C, found, %	71.67	65.85	72.2	66.78	67.61
H, calculated, %	4.99	4.62	5.6	5.21	4.38
H, found, %	5.01	4.54	5.51	5.19	4.20

[a] Shows blue fluorescence in alcoholic solution.

Summary

A series of aromatic aliphatic lactones has been synthesized, namely, α-salicylal-Δ_2-angelica lactone, α-resorcylal-Δ_2-angelica lactone, α-anisal-Δ_2-angelica lactone, α-vanillal-Δ_2-angelica lactone and α-piperonal-Δ_2-angelica lactone. The chemical properties are described.

CLEVELAND, OHIO