could have been increased by the use of more reagent as shown by comparison of the yields with 25 ml. and 10 ml. of reagent, but little would be gained thereby. A better reagent and its more efficient use would have to be developed, and the final result would probably be no better than is achieved by the present alfin catalyst.

Acknowledgment. The authors are indebted to Elizabeth Driscoll Ward for the measurements of viscosity and to Prof. N. A. Nelson for the infrared values.

CAMBRIDGE 39, MASS.

[CONTRIBUTION FROM THE INSTITUTE OF PHARMACEUTICAL CHEMISTRY OF THE UNIVERSITY OF PISA]

The Reaction of *cis*- and *trans*-Stilbene-2-carboxylic Acids with Peroxyacids[1]

GIANCARLO BERTI

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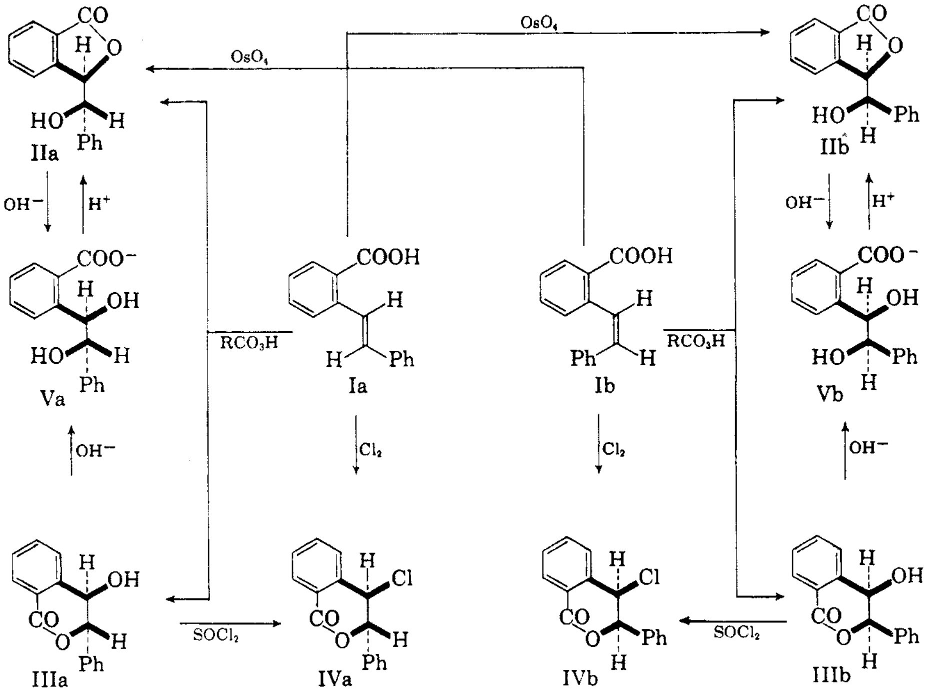
The reaction of derivatives of *o*-vinylbenzoic acid with organic peroxyacids does not lead to the corresponding epoxides, hydroxylactones being the main products. The stereochemistry of this reaction was investigated, using the *cis*- and *trans*-forms of stilbene-2-carboxylic acid. The products were either the diastereomeric racemates of 3-phenyl-4-hydroxy-3,4-dihydroisocoumarin, or those of 3-(α-hydroxybenzyl)phthalide, higher temperatures or the presence of stronger acids favoring the formation of the former. A complete stereospecificity was observed, the products having the configurations to be expected from a *trans*- addition to the ethylenic double bond of a hydroxyl and of the carboxyl group. The possible mechanisms are discussed.

In continuation of earlier work on the formation of lactones from unsaturated acids, the reaction of *trans*- and *cis*-stilbene-2-carboxylic acid (Ia and Ib) with organic peroxyacids was investigated. When the acids Ia and Ib were treated with peroxyphthalic acid, no evidence was found for the formation of the corresponding epoxides, and the only identified products were two isomeric lactones, $C_{15}H_{12}O_3$, which were not identical with the diastereomeric 3-(α-hydroxybenzyl)phthalides (IIa and IIb), previously prepared by a different method,[2] but were transformed into them by a treatment with alkali, followed by one with acid. Such behavior led to the identification of the lactones as the two racemates of 3-phenyl-4-hydroxy-3,4-dihydroisocoumarin (IIIa and IIIb), whose rings were opened during the treatment with alkali to give the salts Va and Vb, which under acidic conditions were transformed into the more stable γ-lactones (IIa and IIb). A further proof was given by the fact that thionyl chloride transformed the two lactones into the compounds IVa and IVb,



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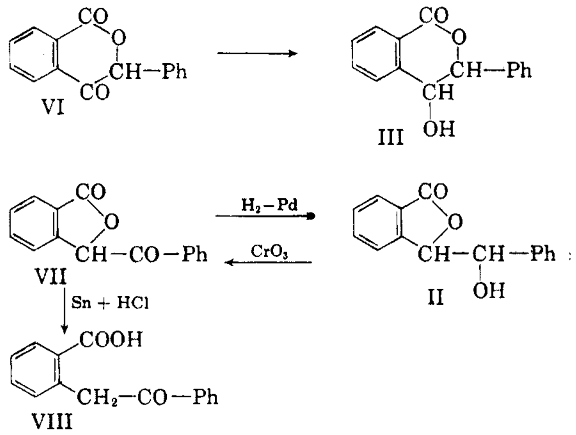
[1] Presented in part at the 16th International Congress of Pure and Applied Chemistry, Paris, 1957.

[2] G. Berti, *Tetrahedron*, 4, 393 (1958).

previously obtained by chlorination of the acids Ia and Ib, whose structures and configurations had been proved beyond doubt.[2] Furthermore, the I.R. spectra of the two new lactones have a carbonyl peak at 5.91μ; in the isomeric phthalides (IIa and IIb) this band is shifted to 5.77μ, in good agreement with the well known fact that in γ-lactones the carbonyl stretching shows up at lower wave length than in the corresponding δ-lactones.[3]

Although the proofs appeared rather convincing, there still remained some doubt, as Wanag and Walbe[4] obtained in the reduction of a ketolactone, formulated as VI, a compound to which they assigned the structure III, whose melting point is quite different from those of our lactones. When this work was repeated, it was found that the ketolactone was 3-benzoylphthalide (VII), instead of the compound VI, because it was also obtained by oxidizing the hydroxyphthalide IIa with chromic acid, and retransformed into IIa by catalytic reduction. The compound, m.p. 162°, which Wanag and Walbe obtained from the reduction of the ketolactone with tin and hydrochloric acid, was not even a lactone, but had acidic character and was identified as *o*-phenacylbenzoic acid (VIII),[5] evidently formed by hydrogenolysis of the lactone ring.



The configurations of the two lactones III are easily derived from those of the compounds II, whose stereochemistry had been clarified[2] by means of osmium tetroxide oxidations of the acids Ia and Ib. It can be assumed safely that the opening of the lactone rings with base and their reclosure with acid does not involve any inversion.

Hydroxylactones are the main products also of the reactions of the stilbene-2-carboxylic acids with peroxybenzoic and peroxyformic acid. However, with peroxybenzoic acid in chloroform, at, or below room temperature the lactones were predominantly of the γ-type (IIa and IIb), while, if the reaction was carried out at reflux temperature, the dihydroisocoumarins (IIIa and IIIb) were isolated in fairly good yields. When the peroxidations with peroxybenzoic acid were performed in the presence of trichloroacetic acid, the latter lactones were formed exclusively, in very good yields, even in the cold. This seems to be the best method for the preparation of these compounds.

Peroxyformic acid in formic acid solution yielded δ-lactones (IIIa and IIIb), together with significant amounts of oily by-products, which on hydrolysis with sodium hydroxide gave rise to sodium formate and to the sodium salts of the acids Va and Vb. These oily materials were not investigated further, but they probably were formic esters of the compounds II or III. Similar esters of benzoic acid were obtained in smaller amounts in the reactions with peroxybenzoic acid. Hydroxylactones of type III were also formed, when the methyl esters of the stilbene-2-carboxylic acids were reacted with peroxybenzoic or peroxyformic acid.

All the lactonization reactions described above are characterized by a complete stereospecificity. When the *trans*-acid (Ia) or its methyl ester are treated with any of the three peroxyacids, the products, no matter which is their nature (five- or six-membered hydroxylactones or their esters), all give, after hydrolysis with alkali, the salt of *erythro*-α,α'-dihydroxybibenzyl-2-carboxylic acid (Va), while the salt of the *threo*-acid (Vb) is obtained if the *cis*-acid (Ib) or its ester is the starting material. The products are those that can be expected from a *trans*-addition of the $-COO^-$ and OH^+ groups to the ethylenic double bond. Such a stereospecificity is not at all common in addition reactions to stilbene derivatives.[6] Any mechanistic interpretation must account for such stereospecificity. Although the complete mechanism of the reactions of peroxyacids with olephins is still matter of discussion,[7] it certainly involves an electrophilic attack on the double bond, leading to an epoxide, which, in some cases, if an excess of an acid, such as acetic or formic acid, is present, can react further, yielding the monoester of the corresponding α-glycol. In our case only the hydroxylactones were isolated, and their formation can be explained in several different ways. One can assume that a true epoxide (IX) is the intermediate which reacts further by a rapid attack of the carboxyl or carbomethoxyl group on the oxirane ring. Against this hypothesis could stand the fact that epoxides normally react only slowly with weak acids, and not at all with esters. Furthermore, *trans*- opening of the ring is by no means a rule with stilbene epoxides: several recent and older cases in the literature[8]

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(3) L. J. Bellamy, *The Infra-Red Spectra of Complex Molecules*, Methuen, London, 1954, p. 153.

(4) G. Wanag and U. Walbe, *Ber.*, **71**, 1448 (1938).

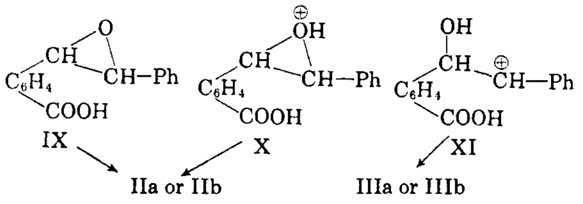
(5) S. Gabriel, *Ber.*, **18**, 2446 (1885).

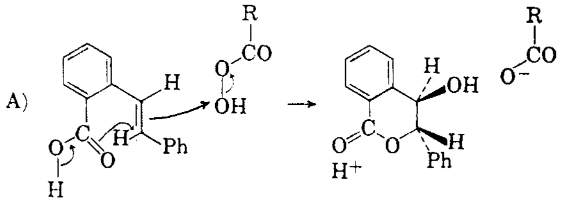
(6) G. W. Wheland, *Advanced Organic Chemistry*, 2nd ed., J. Wiley and Sons, New York, 1949, p. 292.

(7) D. Swern in *Organic Reactions*, Vol. VII, J. Wiley and Sons, New York, 1953, p. 385; B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, 1525 (1955).

show that very often such additions take place in a *cis*- way or are not stereospecific. These objections, however, are not sufficient to rule out the intermediate formation of epoxides in our case, first, because a favorable neighboring group effect could greatly increase the rate of attack by the carboxyl group, as was found, for instance, in the hydrolysis of phthalamic acid[9]; secondly, because the stereochemistry of an intramolecular reaction may be different from that of an intermolecular one.

Alternatively, the lactonization step could involve a more reactive intermediate of the type X or XI, provided that in the latter case the cyclization be faster than a rotation around the α,β-bond, to account for the stereospecificity. Finally, the reaction could take place in a single step, through a concerted mechanism, represented by





(A) for the *trans*- acid, in which the electrophilic attack of the peroxyacid is assisted by the simultaneous nucleophilic attack by the carboxyl group.

The fact that an increase in temperature or in acidity leads to δ- instead of γ-lactones could be explained by assuming that different intermediates are involved, in analogy with the hypothesis made to account for the changes in the way of hydrolytic splitting of normal epoxide rings in solutions of decreasing *p*H.[10] The alternative formation of hydroxy γ- or δ-lactones can be determined by a lower electron density on the α- or β-carbon atom. If the actual intermediate in the cyclization step is of the type IX or X, ring-closure is more likely to occur on the α-carbon, which is influenced more by the electron-attracting effect of the carboxyl group. On the other hand, a δ-lactone should be formed, if the intermediate is a carbonium ion (because XI is more stable than the corresponding ion with the charge on the α-position), or if the concerted mechanism (A) is involved (the mesomeric effect of the carboxyl group should reduce the electron density on the β-carbon; similarly, cynnamic acid, of which the acids Ia and Ib are benzologs, is known to add nucleophilic groups on the β-carbon atom[11]).

A final decision about the mechanisms outlined above is not yet possible, but further work which is now in progress, involving kinetic measurements and the extension of the reaction to other unsaturated acids, may give the answer.

It has been found that, beside the stilbene-2-carboxylic acids, several other olephinic acids yielded only hydroxylactones with peroxybenzoic acid. Table I summarizes some of the results: only γ-lactones were formed; this was proved by the fact that they were recovered unchanged after hydrolysis with base, followed by acidification. δ-Lactones, subjected to the same treatment, would have been transformed into the more stable γ-lactones. The alkaline hydrolysis must be very mild, as it was found that one of the lactones, 3 - phenyl - 3 - (α - hydroxyethyl)phthalide, when heated for some time with ethanolic potassium hydroxide, suffered a carbon-carbon splitting, with formation of 3-phenylphthalide and of polymers of acetaldehyde.

Very recently there have been several reports of the formation of hydroxylactones in the reactions of some acids derived from octahydronaphthalene,[12] *endo*-methylenecyclohexene[13] and benzocycloheptene[14] with peroxyacids. This seems to point to a rather general character of the reaction.

EXPERIMENTAL[15]

3-Phenyl-4-hydroxy-3,4-dihydroisocoumarins (IIIa and IIIb) *and 3-(α-hydroxybenzyl)phthalides* (IIa and IIb). (a) *With monoperoxyphthalic acid.* A solution of 5 g. (0.022 moles) of *trans*-stilbene-2-carboxylic acid[16] (Ia) in ether (100 ml.) was treated with 150 ml of a 6.5% solution of peroxyphthalic acid[17] (0.053 mole) in ether and refluxed for 3 hr. After storage at room temperature for 24 hr., the solution was filtered, washed with sodium carbonate solution, dried over magnesium sulfate, and evaporated to dryness. The residue, after crystallization from benzene, gave 3.2 g (60%) of *trans*-3-phenyl-4-hydroxy-3,4-dihydroisocoumarin (IIIa), which presented two different crystalline

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[8] J. Boeseken and G. Elsen, *Rec. trav. chim.*, **47**, 694 (1928); J. Boeseken and G. C. C. C. Schneider, *J. prakt. Chem.*, **131**, 285 (1931); J. H. Brewster, *J. Am. Chem. Soc.*, **78**, 4061 (1956); R. C. Cookson and J. Hudec, *Proc. Chem. Soc.*, 24 (1957); B. Witkop and C. M. Foltz, *J. Am. Chem. Soc.*, **79**, 197 (1957); D. Y. Curtin, A. Bradley, and Y. G. Hendrickson, *J. Am. Chem. Soc.*, **78**, 4064 (1956); D. R. Campbell, J. O. Edwards, J. Maclachlan, and K. Polgar, *J. Am. Chem. Soc.*, **80**, 5308 (1959).

[9] M. L. Bender, Yuang-Lang Chow, and F. Chloupek, *J. Am. Chem. Soc.*, **80**, 5380 (1958).

[10] C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, 1953, p. 341.

[11] R. Fittig and F. Binder, *Ann.*, **195**, 131 (1879); C. Liebermann, *Ber.*, **23**, 141 (1890).

[12] I. N. Nazarov, V. F. Kucherov, and V. M. Andreev, *Izvest. Akad. Nauk S.S.R., Otdel. Khim. Nauk*, 471 (1957) [*Chem. Abstr.*, **51**, 16378 (1957)].

[13] I. N. Nazarov, V. F. Kucherov, and V. G. Bukharov, *Izvest. Akad. Nauk S.S.R., Otdel. Khim. Nauk*, 328 (1958) [*Chem. Abstr.*, **52**, 14543 (1958)].

[14] T. A. Crabb and K. Schofield, *Chem. and Ind. (London)*, 102 (1958).

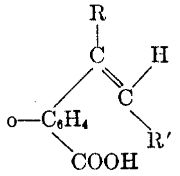
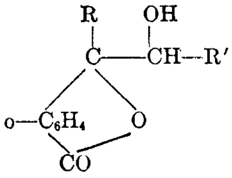
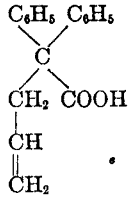
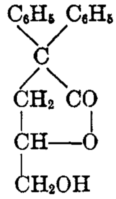
[15] Melting points were taken on a Kofler block and were not corrected. Infrared spectra were kindly determined on Nujol mulls by Dr. P. Bertolaccini.

[16] S. Gabriel and T. Posner, *Ber.*, **27**, 2492 (1894).

[17] H. Boehme, *Org. Syntheses*, **20**, 70 (1940).

TABLE I

HYDROXYLACTONES OBTAINED WITH PEROXYBENZOIC ACID

Starting Acid		Product		M.P.	% Yield	Carbon, %		Hydrogen, %	
						Calcd.	Found	Calcd.	Found
									
R	R′	R	R′						
CH_3	H[a]	CH_3	H	118–119	82	67.40	67.09	5.66	5.49
H	CH_3[b]	H	CH_3	90–91	42	67.40	67.63	5.66	5.46
C_6H_5	H[c]	C_6H_5	H	123–124	90	74.99	74.83	5.03	5.41
C_6H_5	CH_3[d]	C_6H_5	CH_3	123–124	92	75.57	74.95	5.55	5.46
	[e]			82–85	60	76.10	76.00	6.01	5.89

[a] J. M. van der Zanden and A. P. ter Borg, *Rec. trav. chim.*, **75**, 1115 (1956). [b] The preparation of this acid will be described elsewhere. [c] E. Bergmann, *J. Org. Chem.*, **4**, 1 (1939). [d] G. Berti, *Gazz. chim. ital.*, **81**, 428 (1951). [e] R. T. Arnold and S. Searles, *J. Am. Chem. Soc.*, **71**, 1150 (1949).

TABLE II

REACTIONS OF THE STILBENE-2-CARBOXYLIC ACID WITH PEROXYBENZOIC ACID

Compound	Reaction Conditions	Products and Yields
Ia	3 Days at 0° in $CHCl_3$	IIa (42%), IIIa (18%), esters (10%)[a]
Ia	36 Hr. at r.t.[b] in $CHCl_3$	IIa (40%), IIIa (40%), esters (6%)[a]
Ia	2 Hr. reflux in $CHCl_3$	IIa (5%), IIIa (85%), esters (5%)[a]
Ia	3 Days at 0° in ether	IIa (5%), starting material (80%)
Ia	3 Days at r.t.[b] in $CHCl_3$ + CCl_3COOH	IIIa (90%)
Ia, methyl ester	3 Days at 0° in $CHCl_3$	IIIa (40%), IIa (10%), esters (40%)[a]
Ib	3 Days at 0° in $CHCl_3$	IIb (50%), esters (20%)[a]
Ib	2 Days at r.t.[b] in $CHCl_3$	IIb (70%), esters (10%)[a]
Ib	2 Hr. reflux in $CHCl_3$	IIb (10%), IIIb (30%), esters (40%)[a]
Ib	3 Days at 0° in ether	IIb (10%), starting material (60%)
Ib	3 Days at r.t.[b] in $CHCl_3$ + CCl_3COOH	IIIb (85%), esters (10%)[a]
Ib, methyl ester	3 Days at 0° in $CHCl_3$	IIIb (20%), esters (50%)[a]

[a] The name esters is used for the impure oily by-products, which, upon saponification gave the salts Va and Vb and sodium benzoate. [b] R.t. = room temperature, 20° ± 5.

forms: opaque hemispheres, m.p. 117–119°, or transparent clusters of prisms, m.p. 125–127°. Its I.R. spectrum showed a strong peak at 5.91 μ.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.29; H, 5.34.

When the same reaction was carried out with the *cis*-acid[8] (Ib), *cis*-3-phenyl-4-hydroxy-3,4-dihydroisocoumarin (IIIb) was obtained in 30% yield, as clusters of needles, m.p. 135–136°. It showed a strong I.R. peak at 5.91 μ.

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.55; H, 5.03.

Large amounts of neutral oily by-products were formed in both reactions and particularly in the second one. They were not investigated further. The alkaline washings of the ether solutions contained, beside sodium phthalate, small amounts of unreacted stilbene-2-carboxylic acid, but it was not possible to detect any epoxy acid in them.

(b) *With peroxybenzoic acid.* The following general method was used: a 5 to 10% solution of the stilbene-2-carboxylic acid, or of its methyl ester, in chloroform was treated with a 10% excess of the equimolar quantity of a titrated peroxybenzoic acid solution in chloroform. After a variable time the solution was washed with sodium carbonate solution, distilled to a small volume and treated with petroleum ether. The products usually separated as crystalline solids, if the right proportions of the two solvents were used. When the product was a mixture, it was allowed to crystallize very slowly, by spontaneous evaporation of a benzene solution. Large, different crystals were formed, which could be separated mechanically. It was thus possible to isolate, beside the lactones IIIa and IIIb, those IIa, m.p. 148–149°, and IIb, m.p. 102–103°[2]. The two latter lactones showed strong peaks at 5.77 μ in their I.R. spectra. They can be differentiated easily from the δ-lactones of type III, because with sulfuric acid they give a yellow color, which after a few minutes turns red, with a violet fluorescence, while in the same conditions IIIa and IIIb show only a stable faint yellow color. The last mother-liquors of the fractional crystallizations contained the more soluble oily esters. These were saponified by boiling for 1 min. with 5% methanolic potassium hydroxide, the solution was then diluted with water, acidified and the precipitate thus formed extracted with sodium carbonate solution. The alkaline extract contained sodium benzoate, while the insoluble part was compound IIa, if the starting material was the acid Ia, or compound IIb, if one had started from the acid Ib. In some of the runs the reaction with peroxybenzoic acid was carried out in ether, but yields were very poor. In others, 0.5 g. of trichloroacetic acid were added to the chloroform solution for each gram of stilbene-2-carboxylic acid. Table II summarizes the results of several reactions conducted under different conditions. The yields were evaluated on the basis of accurate fractional crystallizations, and, in the case of inseparable mixtures, from melting-point diagrams. They should be accurate within ±5%.

(c) *With peroxyformic acid.* A suspension of 1 g. of the acid Ia in 10 ml. of 98% formic acid was treated with 0.5 ml. of 35% hydrogen peroxide and heated during 20 min. on a steam bath. After 6 hr. at room temperature, the formic acid was distilled off under reduced pressure, the residue was dissolved in ether, washed with sodium carbonate solution and dried over magnesium sulfate. After elimination of the ether and crystallization from benzene-ligroin, 0.45 g. of the lactone IIIa were obtained. The mother-liquor was evaporated to dryness and the residue refluxed for 5 min. with 10 ml. of 5% ethanolic potassium hydroxide, diluted with water and acidified with sulfuric acid: 0.3 g. of the lactone IIa separated out. The filtrate gave a formic acid containing distillate.

When the same reaction was carried out with 1 g. of the acid Ib, 0.30 g. of IIIb and, after saponification, 0.45 g. of IIb were obtained. The methyl ester of the acid Ia gave similarly IIIa (50% yield) and IIa (30%); the methyl ester of Ib yielded IIIb (40%) and IIb (40%).

Reactions of other unsaturated acids with peroxybenzoic acid. Table I summarizes the results obtained with other unsaturated acids, which were left with peroxybenzoic acid in chloroform at room temperature, until a starch-iodide test showed that the peroxyacid had disappeared. The products were isolated as described above and obtained pure after one crystallization from benzene or from a benzene-ligroin mixture.

Saponification of the lactones. A solution of 0.1 g. of each of the lactones in 2 ml. of methanol was treated with 2 ml. of 10% methanolic potassium hydroxide and left at room temperature until a clear solution was obtained upon dilution with water. The aqueous solution was acidified with concentrated hydrochloric acid and the precipitate was collected, or, if the lactone did not precipitate, it was extracted with ether. The following results were obtained: the lactones IIa and IIb, and all those of Table I, were recovered unchanged. The lactones IIIa and IIIb were transformed into those IIa and IIb, respectively. When 3-phenyl-3-(α-hydroxyethyl)-phthalide was refluxed for 15 min. with 10% ethanolic potassium hydroxide the solution became brown. Dilution with water produced some precipitate, which was extracted with ether. Acidification of the aqueous layer gave a solid, which, after crystallization from carbon tetrachloride, yielded needles, m.p. and mixed m.p. with 3-phenylphthalide[18] 115°.

3-Phenyl-4-chloro-3,4-dihydroisocoumarins (IVa and IVb). The lactone IIIa (0.3 g.) was treated with 2 ml. of thionyl chloride and refluxed for 10 min. The excess thionyl chloride was then evaporated under reduced pressure and the residue, after crystallization from benzene–petroleum ether, gave 0.1 g. of prisms, m.p. 108–110°, of IVa.[2]

The same reaction, starting from the lactone IIIb, led to the chlorolactone IVb, m.p. 146–147°.[2]

3-Benzoylphthalide. A solution of the lactone IIa (0.2 g.) in 5 ml. of glacial acetic acid was treated with 0.2 g. of chromium trioxide and heated for 30 min. on a steam bath. On cooling a precipitate separated out, which, after crystallization from ethanol, gave prisms, m.p. 148° (0.1 g.). This product did not depress the melting point of the compound prepared by the treatment of 2,3-diphenyl-1,4-diketo-1,2,3,4-tetrahydroisoquinoline with hydrochloric acid, which, according to Wanag and Walbe[4] should be 3-phenylisochroman-1,4-dione.

A solution of 0.5 g. of 3-benzoylphthalide in 30 ml. of glacial acetic acid was shaken with hydrogen in the presence of 0.3 g. of 5% palladium on charcoal, until the absorption of hydrogen stopped (1 hr.). After filtration and dilution with 200 ml. of water, the solution was extracted with ether, the ether extract was washed with sodium carbonate solution, dried over magnesium sulfate and evaporated. The residue, after crystallization from benzene-ligroin, gave 0,25 g. of IIa, m.p. 148–149°. When the reduction was carried out according to Wanag and Walbe,[2] with tin powder and hydrochloric acid in ethanol, the product was an acid, m.p. 162° with decomposition, whose melting-point was not depressed in a mixture with *o*-phenacylbenzoic acid.[5]

PISA, ITALY

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[18] F. Ullmann, *Ann.*, **291**, 17 (1896).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

Birch Reduction of 2-Naphthoic and of *ortho*-Methoxynaphthoic Acids

ERNEST L. ELIEL AND TROY E. HOOVER

Received January 6, 1959

The Birch reduction of 2-naphthoic acid and its 1- and 3-methoxy derivative gives mainly 1,2,3,4-tetrahydro-2-naphthoic acid or 1,2,3,4,5,8-hexahydronaphthoic acid, depending on conditions and proportions of reagents. The methoxyl group, where present, is lost in these reductions. 2-Methoxy-1-naphthoic acid, on the other hand, gives mainly 2-methoxy-1,4,5,8-tetrahydro-1-naphthoic acid without loss of the methoxyl group.

In connection with another problem we were interested to find out whether an *o*-methoxybenzoic acid could be submitted to the Birch reduction[1] without loss of either the carboxyl or the methoxyl function. By "Birch reduction" is meant the reduction of an aromatic compound, usually to a 1,4-cyclohexadiene derivative, by means of an alkali metal–liquid ammonia–alcohol combination. The reaction was originally discovered by Wooster[2]

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[1] (a) A. J. Birch, *Quart. Revs.*, **4**, 69 (1950). (b) See also G. W. Watt, *Chem. Revs.*, **46**, 317 (1950).

[2] C. B. Wooster, U. S. Patent, **2,182,242** (Dec. 5, 1939); *Chem. Abstr.*, **34**, 1993 (1940); C. B. Wooster and K. L. Godfrey, *J. Am. Chem. Soc.*, **59**, 596 (1937).