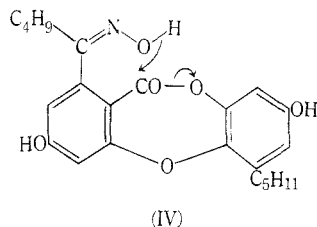
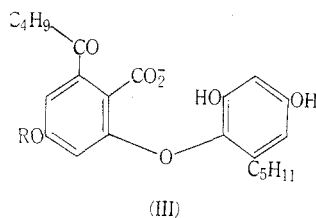
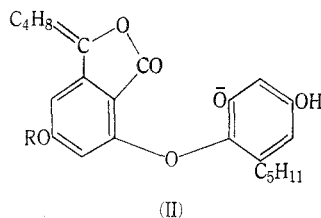
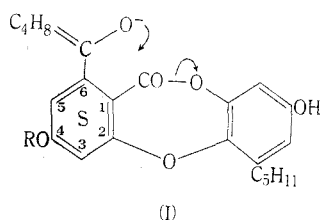


REACTION MECHANISMS OF CERTAIN 2,6-DISUBSTITUTED BENZOIC ACID DERIVATIVES*

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Steric effects in 2,6-disubstituted benzoic acids are most clearly discerned in acid-catalyzed esterification (mechanism A_{Ac} 2) rates of which are not sensitive to polar influences (Ingold 1953 ; Taft in Newman 1956, Ch. 13). If one of the *ortho*-substituents is attached by a carbonyl group steric hindrance to esterification may not be observed, a pseudo-ester often but not necessarily being formed (Newman and Muth 1951). Formation of pseudo-ester may occur via a hemiketal (Newman and McCleary 1941), or it may be a reaction of the lactol form of the acid, neither presenting a typical example of mechanism A_{Ac} 2. Similarly, although esters of 2,6-disubstituted benzoic acids are subject to steric hindrance to fission by the normal B_{Ac} 2 mechanism, fission of a suitably constituted ester in alkaline solution may follow some other path.



Norlobaridone (Gream and Riggs 1960) gives no evidence of steric hindrance to fission of the ester linkage in being very rapidly isomerized by cold 1N sodium hydroxide to *isonorlobaridone*. The same product results with warm sodium carbonate or hot sodium acetate solution. The structure of the product coupled with its slow and probably irreversible hydration in alkaline solution to norlobariol shows that the isomerization does not proceed through attack by external base on the ester carbonyl group. Instead the mesomeric enolate ion (I ; R=H)§

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§ In these structures I-IV ionized groups other than those immediately involved in reaction are not shown ; ionization of phenolic groups undoubtedly occurs in the alkaline media.

produced by abstraction of a proton by base undergoes rapid internal reaction (arrows) to produce the phenoxide ion (II; $R=H$) corresponding to *isonorlobaridone*. Similar processes probably occur in the rapid conversion of a number of depsides or depsidones with β -ketoalkyl substituents in position 6 of ring S into δ -enol lactones by cold dilute sodium hydroxide (e.g. physodic acid into *isophysodic acid*; Asahina and Nogami 1934). It seems likely that the original depside or depsidone carbonyl carbon atoms become tetrahedral in the transition states for the isomerizations for which the mechanism may be described as an internal variety of mechanism $B_{Ac} 2$, but it is not clear how far this bears on the geometry of the transition state for the normal $B_{Ac} 2$ mechanism. A tetrahedral intermediate as in normal $A_{Ac} 2$ or $B_{Ac} 2$ reactions (Bender 1951) may also be formed.*

The carbonyl group in II ($R=H$) is not seriously hindered to attack by external reagents, but hydration to *norlobariol* in alkaline solution probably occurs through attack of hydroxide ion on the cyclic enolic carbon atom followed by proton transfer and lactol ring opening to give the *o*-ketocarboxylate ion (III; $R=H$) (cf. ultraviolet absorption spectrum of *dimethyllobariol* in alkaline solution; Gream and Riggs 1960). Such a view is supported by the conversion of *isonorlobaridone* into *lobariol methyl pseudo-ester* by methoxide ion in methanol; in this case, proton transfer is not possible and the initial product is stabilized by attachment of a proton at the side-chain carbon atom adjacent to the ketol carbon atom.

Even brief treatment of *lobaric acid* with cold alkali opened the *depsidone* ring with addition of the elements of water to give *lobariolcarboxylic acid*; more vigorous treatment caused decarboxylation to *lobariol* (Asahina and Nonomura 1935). The action of bases on *lobaridone* has therefore been examined under conditions in which *norlobaridone* gives good yields of the isomeric enol-lactone, but the only crystalline product obtained was *lobariol*. Direct attack of hydroxide ion on the ester carbonyl group may here occur but the speed of the reaction gives no indication of steric hindrance and it seems more likely that an intermediate (II; $R=Me$) is produced in the same way as intermediate II ($R=H$) from *norlobaridone*, and rapidly hydrated as above to the *o*-ketocarboxylate ion (III; $R=Me$). The much lower rate of hydration of II ($R=H$) is then accounted for by the negative charge on ring S arising from ionization of the relatively acidic hydroxyl group OR. Such a factor does not however account for the isolation of *lobariol* by Asahina and Nonomura (1935) from the action of boiling formic acid on *lobaric acid*.

The *depsidone* ester linkage in *norlobaridone* is readily broken by hydroxylamine in aqueous ethanolic sodium acetate or pyridine solution. Under these conditions *isonorlobaridone* yields the same product, *norlobariol oxime anhydride*, presumably by attack of hydroxylamine (or a conjugate base) on the cyclic enolic

* Bender (1951) claimed that a *symmetrical* intermediate was required by his results. The intermediate has been assumed to be tetrahedral (e.g. Newman 1956). The argument of Dewar (1949) for a planar transition state in mechanism $B_{Ac} 2$, modified to allow for occurrence of the intermediate, suggests an appreciably flattened tetrahedral transition state (see also Day and Ingold 1941; Ingold 1953).

carbon atom followed by appropriate proton transfers and ring opening and closure. Norlobaridone is stable to boiling pyridine, alone or in the presence of ammonium chloride, and its conversion into norlobariol oxime anhydride in this solvent is probably an internal reaction (arrows) of the oxime (IV) formed initially or of its anion. The same pathway may be followed in the reaction in aqueous ethanol, or isonorlobaridone may be an intermediate. It is interesting that whereas norlobariol methyl pseudo-ester does not react with hydroxylamine in aqueous ethanolic sodium acetate (cf. Langlois and Wolff 1948; Grove and Willis 1951) norlobariol oxime anhydride is produced in pyridine solution. Hydroxylamine hydrochloride is likely to form a reasonably strongly acidic solution in pyridine and we interpret the reaction in this medium to be due to protonation of the acetal-like methoxyl group followed by reaction with hydroxylamine in an S_N1 process (Ingold 1953), or possibly an S_N2 process in the present poorly ionizing solvent.

Experimental

Some results have been given previously (Gream and Riggs 1960). Products below were isolated and purified as there described, and identified by m.p. and mixed m.p. determinations with authentic samples.

(a) *Reactions of Norlobaridone*.—(i) Norlobaridone (200 mg) dissolved rapidly in 1N sodium hydroxide (10 ml) at room temperature. After 1 min acidification with 2N hydrochloric acid (10 ml) gave isonorlobaridone (180 mg, 90%). With 2N sodium hydroxide acidification after 10 min gave isonorlobaridone (65%) and from the mother liquors was isolated norlobariol (c. 20%). After 85 hr the product was norlobariol (85%).

(ii) Norlobaridone (300 mg) was heated on the water-bath with 10% sodium carbonate solution (50 ml) until it had dissolved (10 min). Cooling and acidification gave isonorlobaridone (190 mg).

(iii) A mixture of norlobaridone (400 mg) in ethanol (5 ml) and crystalline sodium acetate (2.50 g) in water (5 ml) was refluxed for 2 hr. Addition of water and recrystallization gave isonorlobaridone (300 mg).

(iv) Norlobaridone (200 mg) was refluxed in pyridine solution (5 ml) for 3 hr with or without addition of ammonium chloride (400 mg). Starting material (180 mg) was recovered in each case.

(b) *Reactions of isoNorlobaridone*.—(i) isoNorlobaridone was refluxed with 1N sodium hydroxide for 1 hr. Acidification and recrystallization gave norlobariol (90%).

(ii) Treatment of isonorlobaridone with 2N sodium methoxide in methanol at room temperature for 2 hr, acidification with glacial acetic acid, evaporation, and recrystallization gave norlobariol methyl pseudo-ester (85%).

(iii) A mixture of isonorlobaridone (200 mg), hydroxylamine hydrochloride (400 mg), and crystalline sodium acetate (1.00 g) was refluxed in 50% aqueous ethanol (5 ml) for 3 hr. Addition of water and recrystallization gave norlobariol oxime anhydride (165 mg).

(iv) Refluxed with twice its weight of hydroxylamine hydrochloride in pyridine solution for 3 hr, isonorlobaridone gave norlobariol oxime anhydride (80%).

(c) *Reactions of Lobaridone*.—(i) Lobaridone (100 mg) was shaken with 2N sodium hydroxide (5 ml) at room temperature. The solid dissolved only slowly and, after 3 min, the mixture was filtered, the washed and dried residue (26 mg) being starting material. After a further 1 min the filtrate was acidified and gave lobariol (58 mg).

(ii) Lobaridone (111 mg) was heated on the water-bath with 10% sodium carbonate solution (50 ml) for 10 min. Cooling and acidification gave lobariol (65 mg).

(iii) A mixture of lobaridone (110 mg) in ethanol (2 ml) and crystalline sodium acetate (500 mg) in water (1 ml) was refluxed for 2 hr. The cooled mixture was poured onto crushed ice to give an oil that slowly solidified, but the product could not be crystallized from a variety of solvents tried.

(d) *Reaction of Norlobariol Methyl Pseudo-Ester with Hydroxylamine*.—After being refluxed with hydroxylamine hydrochloride and sodium acetate in 50% aqueous ethanol solution for 3 hr, norlobariol methyl pseudo-ester was recovered in 90% yield. Refluxing with hydroxylamine hydrochloride in pyridine however gave norlobariol oxime anhydride (c. 60%), and pseudo-ester (c. 20%) was recovered from the mother liquors.

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