Intramolecular Catalysis in Addition of Carboxyl to Carbon–Carbon Triple Bonds¹

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Aspects of the mechanism of addition of a carboxylic acid to a carbon-carbon triple bond were investigated with tolan compounds bearing carboxyl substituents. It was found that 2,2'-tolandicarboxylic acid (I) isomerizes readily in alcohol solution at room temperature to 3-(2-carboxybenzylidene)phthalide (IV), which in turn rearranges to 3-(2-carboxyphenyl)isocoumarin (VI) and a dilactone when warmed in an acetic-sulfuric acid solu-2-Tolancarboxylic acid (II) and 2,4'-tolandition. carboxylic acid (III) isomerize much less readily than 2,2'-tolandicarboxylic acid, the former affording 3benzylidenephthalide (IX) and 3-phenylisocoumarin (X)and the latter yielding 3-(4-carboxybenzylidene)phthalide (XI). Silver ion in acetonitrile catalyzes the isomerization of II and III but not that of I. The relative rates of isomerization of I, II, and III in ethanol at 30° are 22,000:1:2.6. In aqueous buffers the rate of isomerization of I is proportional to the concentration of the monoanion derived from I, and the monoanion of I reacts 6000 times faster than the anion of II. These results support a mechanism for isomerization of I in which a carboxyl group functions as an intramolecular catalyst in accelerating attack of a carboxylate anion on the neighboring carbon-carbon triple bond.

The formation of lactones from alkynoic acids is catalyzed by heavy metal salts and by sulfuric acid. Typical cases include conversion of bispropargylmalonic acid to α -propargyl- α -angelica lactone at high temperature in the presence of zinc carbonate³ and the conversion of 5-phenyl-2-penten-4-ynoic acid to 6-phenylpyran-2-one with a hot acetic-sulfuric acid mixture.⁴ In the absence of such catalysts and at moderate temperatures the alkynoic acids are generally stable. Thus, 4-pentynoic acid and 2-methyl-4-pentynoic acid were prepared in high yield by decarboxylation of the appropriate malonic acids at 150° and were distilled satisfactorily at temperatures above 200°.⁵ It was reported that 4-phenyl-1-buten-3-yne-1,1-dicarboxylic acid cyclized in acetic acid at room temperature^{6a}; however, a reinvestigation of this work revealed that the reported product was probably impure starting material.⁴ Transformation of the diacid to γ -benzylidene- α -carboxybutenolide was accomplished by heating the alkynoic acid at 190° for 10–15 min.^{6b} or in *p*xylene for 18 hr.⁴

For further study of the addition reaction involving carboxyl groups and the C \equiv C bond, 2,2'-tolandicarboxylic acid (I) appeared attractive. In this compound two carboxyl groups are held rigidly in a position favorable for adding to the triple bond. Furthermore, one carboxyl group is well situated to assist the reaction of the second. Finally, the novel cyclization observed with 2,2'-tolandiboronic acid' indicated that the analogous carboxylic acid might exhibit unusual reactivity.

In an early attempt to prepare 2,2'-tolandicarboxylic acid Ruggli and Meyer added chlorine and bromine to 2,2'-stilbenedicarboxylic acid and dehydrohalogenated the products with alkali.⁸ They obtain a mixture of compounds possessing lactone rings rather than an acetylene derivative. Likewise, addition of chlorine to the dimethyl ester of 2,2'-stilbenedicarboxylic acid followed by a reaction with potassium hydroxide in methanol afforded a methyl ester of a lactone acid (m.p. $123.5-125^{\circ}$), which Ruggli and Meyer believed to be 3-(2-carbomethoxybenzylidene)phthalide.

We succeeded in obtaining 2,2'-tolandicarboxylic acid in good yield by carboxylating 2,2'-dilithiotolan, which was prepared from the corresponding dibromotolan by a metal-halogen interchange reaction.⁷ The diacid did prove to be unusually labile. In this paper are reported the characterization of the isomerization products derived from I, the preparation and isomerization of two related acids, 2-tolancarboxylic acid (II) and 2,4'-tolandicarboxylic acid (III), and a kinetic study of the isomerization of these acids which bears on the mechanism of addition of carboxylic acids to the carbon-carbon triple bond.

Isomerization of 2,2'-Tolandicarboxylic Acid. The lability of 2,2'-tolandicarboxylic acid was first noted when an attempt was made to recrystallize the acid from ethanol. The recovered material (IV) melted at 245– 246.5° and exhibited two strong bands in the carbonyl region, one at 5.60 and the other at 5.90 μ . Attempted recrystallization of I from methanol also gave IV. This substance was identified as 3-(2-carboxybenzylidene)phthalide⁹ on the basis of the following information: analytical data and the neutralization equivalent were consistent with this structure; alkaline hydrolysis afforded 2,2'-deoxybenzoindicarboxylic acid (VII); diazomethane converted IV to a methyl ester, m.p. 160– 161°, which absorbed at 5.60 (lactone carbonyl) and at 5.85 μ (ester carbonyl) in the infrared¹⁰; and, on

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⁽²⁾ National Science Foundation Fellow

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⁽b) (a) J. Kam, Keen. Soc. 3962 (1958); Anales real. Soc. Espan. Fis. Quim., 53B, 651 (1957).

⁽⁷⁾ R. L. Letsinger and J. R. Nazy, J. Am. Chem. Soc., 81, 3013 (1959).

⁽⁸⁾ P. Ruggli and R. E. Meyer, Helv. Chim. Acta, 5, 28 (1922).

⁽⁹⁾ The stereochemistry at the C=C bond has not been definitely established. The aromatic rings are probably *trans*.

hydrogenation, the lactone acid IV and the lactone ester IVa absorbed 1 mole equiv. of hydrogen each to give the corresponding phthalide derivatives, VIII and VIIIa, both of which have been previously described.^{8,11} In confirmation of the phthalide structure assigned to VIII and VIIIa the infrared spectrum of VIII had a band at 5.73 μ and the spectrum of VIII a showed a band at 5.65 μ , in addition to the absorption due to the carboxyl (5.95 μ) and carbomethoxyl groups (5.90 μ).

Several lines of evidence of a qualitative nature indicated that ionization of one of the carboxyl groups in I was a prerequisite for formation of lactone IV, at least in neutral or weakly acidic solutions. Thus, it was found that 2,2'-tolandicarboxylic acid was converted to a dimethyl ester in high yield without rearrangement on heating in methanol acidified with hydrochloric acid. Since esterification is a relatively slow process, this observation indicated that hydrochloric acid in low concentration inhibited the isomerization. It was also observed that 2,2'-tolandicarboxylic acid



did not isomerize when warmed in acetic acid; indeed, acetic acid proved to be a good solvent for recrystal-

(10) The band at 5.60 μ is consistent with the benzylidenephthalide structure. Both simple phthalides (J. F. Grove and H. A. Willis, J. Chem. Soc., 877 (1951)) and enol esters (E. J. Hartwell, R. E. Richards, and H. W. Thompson, *ibid.*, 1436 (1948)) absorb near 5.7 μ . In compounds incorporating both features, the carbonyl band is displaced to shorter wave lengths. Thus, 3-methylenephthalide and phthalidylideneacetic acid have bands at 5.62 and 5.56 μ , respectively (see Grove and Willis).

(11) J. Wislicenus, Ber., 17, 2178 (1884); J. Ephraim, *ibid.*, 24, 2820 (1891); A. C. Cope and S. W. Fenton, J. Am. Chem. Soc., 73, 1668 (1951).

lization of the diacid. Lactone IV was formed, however, when 2,2'-tolandicarboxylic acid was warmed in acetic acid which contained sodium acetate. These results can be explained readily if the isomerization reaction involves an anion derived from I. That the reactive species was not a dianion, however, was shown by the fact that the disodium salt of 2,2'-tolandicarboxylic acid was stable in aqueous or alcoholic solution.

When IV was warmed for several hours in acetic acid that contained a small amount of aqueous sulfuric acid, it rearranged to a compound (VI, m.p. 227-228°) which, like IV, was both an acid and a lactone. In addition, a small amount of a neutral product (V) was isolated from this reaction. Diazomethane converted VI to an ester (VIa, m.p. 124.5-125.5°) isomeric with IVa. This ester was also obtained when IV was heated in methanol acidified with sulfuric acid. The infrared spectra of VI and VIa (5.76 and 5.85 μ for VI, 5.81 and 5.86 μ for VIa) corresponded to spectra of substituted isocoumarins. Compound VI was therefore formulated as 3-(2-carboxyphenyl)isocoumarin and VIa as the corresponding methyl ester. Hydrogenation of VIa, unlike the reduction of IVa, proceeded very slowly and did not show a break after uptake of 1 mole equiv. of hydrogen. The product was the monomethyl ester of 2,2'-bibenzyldicarboxylic acid. Slow hydrogenation of VIa is in accord with the concept that the double bond in the isocoumarin has more aromatic character than the double bond in the phthalide (IVa).

The lactone ester obtained by Ruggli and Meyer⁸ corresponded in melting point to VIa rather than compound IV. In view of the present assignments it therefore appears that the compound of Ruggli and Meyer was the isocoumarin rather than the phthalide as originally proposed.

The neutral material (V) which accompanied VI as a product of reaction of IV was a dilactone isomeric with VI. This dilactone could also be obtained, and in high yield, directly from 2,2'-tolandicarboxylic acid by dissolving the diacid in sulfuric acid and diluting the solution with water. The infrared spectrum of V had two strong bands in the carbonyl region at 5.58 and 5.70 μ , and the n.m.r. spectrum contained a quartet characteristic for a methylene group in which the two hydrogen atoms are in different environments. These facts showed that one of the hetero rings in V was fivemembered and the other six-membered.¹²

Data for the series of compounds derived from I did not suffice to establish the sequence in which V and VI were produced from IV. It was subsequently found, however, that a related compound, 3-(4-carboxybenzylidene)phthalide (XI), failed to isomerize when warmed in acetic-sulfuric acid under the conditions used to rearrange IV. Since this compound differs structurally from IV only in that the carboxyl group is in a *para* position rather than an *ortho* position, this observation implicates the *o*-carboxyl group in the mechanism of the ring expansion of IV. Involvement of the carboxyl group is most simply rationalized by the

⁽¹²⁾ The spectral data are inconsistent with alternative structures having two five-membered hetero rings, two six-membered hetero rings, or an anhydride ring. A compound with properties similar to those of V has been reported several times in the literature; however, data pertinent to the size of the hetero rings have not been available; see ref. 8, 11b, and S. Gabriel and E. Leupold, *Ber.*, 31, 2646 (1998), and E. Hasselbach, *Ann.*, 243, 249 (1888).

assumption that V is formed initially in an acid-catalyzed cyclization of IV and VI is subsequently produced from V in an acid-catalyzed elimination reaction. A pathway of this type for ring expansion is not available to 3-(4-carboxybenzylidene)phthalide. In support of this suggestion, it was found that a mixture of V and VI, preponderate in VI, was obtained when either V or VI was warmed in acetic acid containing aqueous sulfuric acid.

2-Tolancarboxylic Acid and 2,4'-Tolandicarboxylic Acid. The unusual reactivity of 2.2'-tolandicarboxylic acid (I) indicated that one carboxyl group in the diacid might assist in the addition of the other to the carbon-carbon triple bond. In order to probe further the role of the neighboring carboxyl group in this reaction, we prepared 2-tolancarboxylic acid (II) and 2,4'tolandicarboxylic acid (III). These compounds were selected since they duplicate the portion of 2,2'-tolandicarboxylic acid which yields the lactone ring, yet differ with respect to the carboxyl substituent in the second aryl group. A comparison of the rates of isomerization of I and II would show whether one carboxyl group in I does in fact facilitate the reaction of the other, and rate data for III would enable one to estimate the importance of the inductive effect of the carboxyl group in addition reactions at the triple bond.

Synthetic procedures for II and III were analogous to those developed for I. II was obtained from 2-bromotolan by a metal-halogen interchange reaction followed by carboxylation of the lithiotolan. III was similarly prepared from 2,4'-dibromotolan.



Both II and III were relatively stable and could be recrystallized without difficulty from ethanol. However, on prolonged heating in ethanol they did isomerize. 2,4'-Tolandicarboxylic acid yielded a single product, 3-(4-carboxybenzylidene)phthalide (XI). It was identified as a phthalide by the $5.65-\mu$ band in the infrared spectrum. Two compounds, 3-benzylidenephthalide (IX) and 3-phenylisocoumarin (X), were obtained when 2-tolancarboxylic acid was warmed in ethanol, aqueous ethanol, or acetic acid which contained sulfuric acid. With acetonitrile as the solvent the product was very largely IX. Structural identification of IX and X was based on the positions of the absorption bands for the carbonyl group (5.65 μ for IX and 5.81 μ for X) and the coincidence of the melting points of IX and X with melting points of known compounds.^{13,14} As pointed out earlier in this discussion, compound XI did not rearrange when treated with acetic acid which contained aqueous sulfuric acid. Concentrated sulfuric acid partially converted diacid III to compound XI.

Kinetic Results. Rates of isomerization were determined for 2,2'-tolandicarboxylic acid, 2-tolancarboxylic acid, and 2,4'-tolandicarboxylic acid in ethanol, acetonitrile, and in water or an ethanol-water mixture. The procedure is described in the Experimental section.

Data for reactions in alcohols were well fitted by a first-order rate equation. The rate of isomerization of 2,2'-tolandicarboxylic acid varied considerably with the alcohol employed as a solvent (Table I).

Table I. Isomerization of 2,2'-Tolandicarboxylic Acid in Alcohols at 30°

Alcohol	k, min. ⁻¹
Methanol	0.06
Ethanol	0.84
1-Propanol	0.50
1-Butanol	0.56
t-Butyl alcohol	0.06

In Table II are summarized results from reactions of the three tolancarboxylic acids in ethanol. Compound I was found to lactonize 22,000 times faster

Table II. Isomerization in Ethanol at 30°

Com- pound	k,min. ⁻¹			
Ι	8.44×10^{-1}			
II	3.80×10^{-5}			
nı	9.80×10^{-5}			

than II and 8600 times faster than III. Taking into account the fact that two carboxyl groups are available for reaction in I in contrast to one in compounds II and III, we see that the relative rates of addition of a given carboxyl group to the adjacent triple bond in I, II, and III are 11,000:1:2.6. Three points are pertinent to the mechanistic discussion: (1) compound I reacted very much faster than II, a model having only one carboxyl group. This fact demonstrates that one carboxyl group in I has a profound influence upon the rate of addition of the other carboxyl group to the triple bond. (2) Compound III isomerized 2.6 times faster than II. This fact shows that a carboxyl group in the para position of the tolan facilitates the addition reaction, presumably by an inductive effect. The increase in rate, however, is small. (3) A carboxyl group in I added to the triple bond 4300 times faster than a carboxyl group in III. This ratio appears much too large to be explained by an increase in inductive effect attend-

⁽¹³⁾ L. Zalukajev, Latvijas PSR Zinatnu Akad. Vestnis, 101 (1954); Chem. Abstr., 49, 6856f (1955).

⁽¹⁴⁾ G. Berti, Tetrahedron, 4, 393 (1958); E. Leupold, Ber., 34, 2829 (1901).

ing change of the nonlactonizing carboxyl group from a para to an ortho position in the tolan. We therefore suggest that the abnormally high rate of isomerization of 2,2'-tolandicarboxylic acid stems largely from intramolecular catalysis of the addition reaction by the neighboring carboxyl group. It appears that the isomerization of 2,2'-tolandicarboxylic acid provides the first example of intramolecular catalysis of an addition reaction to a carbon-carbon triple bond,¹⁶ although intramolecular catalysis in hydration of a carbon-carbon double bond¹⁶ and in several hydrolytic reactions¹⁷ has been observed.

The kinetics of reactions of I, II, and III in acetonitrile were complicated. For individual runs the per cent conversion was virtually a linear function of time until most of the substrate had been transformed, whereupon the rate decreased rapidly. The reason for this behavior is not clear; however, the magnitude of the difference in rate for 2,2'-tolandicarboxylic acid and the other two acids suffices to reveal the unique character of the compound with two *o*-carboxyl groups. Data on initial rates of reaction in acetonitrile are tabulated in Table III.

Table III. Isomerization in Acetonitrile at 30°

Compd.ª	$10^4 \times$ initial rate, moles l. ⁻¹ min. ⁻¹	$10^4 \times$ initial rate in presence of Ag ⁺ , moles l. ⁻¹ min. ⁻¹ b
I II III	$ \begin{array}{c} 1.5 \\ 1.2 \times 10^{-4} \\ 1.2 \times 10^{-4} \end{array} $	1.3 0.8 1.6

^a Concentration of I and II $1 \times 10^{-4} M$. Concentration of III: without Ag⁺, $6 \times 10^{-4} M$; with Ag⁺, $0.8 \times 10^{-4} M$. ^b Silver ion concentration $1.9 \times 10^{-6} M$.

Silver ion in low concentration $(1.9 \times 10^{-5} M)$ had a marked catalytic effect on the isomerization of 2tolancarboxylic acid and 2,4'-tolandicarboxylic acid in acetonitrile; however, it did not increase the rate of reaction of 2,2'-tolandicarboxylic acid. This result is in accord with the hypothesis that an electrophilic catalyst is necessary for rapid addition of carboxyl to the C=C bond in a tolan. In the case of 2,2'tolandicarboxylic acid a carboxyl group serves as the electrophilic site. It may also hinder approach of silver ion to the alkyne link. In the case of 2,4'tolandicarboxylic acid, intramolecular catalysis by carboxyl is not possible; however, the triple bond is relatively unhindered and is susceptible to attack by the silver ion.

Quantitative rate data for the reaction of 2,2'tolandicarboxylic acid in aqueous buffers ranging from pH 2 to 6 were gathered to gain information

(15) The isomerization of 2,2'-tolandiboronic acid (ref. 7) may involve intramolecular catalysis by a $-B(OH)_2$ group, since 2-tolanboronic acid does not isomerize under conditions used to effect reaction of the diboronic acid: R. L. Letsinger, T. E. Feare, T. J. Savereide, and J. R. Nazy, J. Org. Chem., 26, 1271 (1961). However, in the absence of kinetic data on 2,4'-tolandiboronic acid, the possibility cannot be ruled out that the enhanced rate of reaction of the diboronic acid, relative to the monoboronic acid, stems from an inductive effect. (16) M. L. Bender and K. A. Conners, J. Am. Chem. Soc., 84, 1980 (1962).

(17) For reviews of the field see M. L. Bender, Chem. Rev., 60, 53 (1960); B. Capon, Quart. Rev. (London), 18, 45 (1964).



Figure 1. Isomerization of 2,2'-tolandicarboxylic acid in water at 30°. Experimental points, O; calcd. curve, ——.

on the state of ionization of the reactive species in the isomerization process. If the reaction proceeded exclusively via the monoanion, as suggested by qualitative observations, the observed rate constants should be described by eq. 1, where α_{I} is the fraction of I present as the monoanion. For reactions in aqueous

$$k_{\rm obsd} = k\alpha_{\rm I} \tag{1}$$

solution a test of this equation was possible since α_{I} could be calculated from the hydrogen ion concentration and the first and second ionization constants of the dibasic acid (K_{1} and K_{2}).

$$\alpha_{\rm I} = K_1[{\rm H}^+]/([{\rm H}^+]^2 + K_1[{\rm H}^+] + K_1K_2) \qquad (2)$$

The reactions in water, like those in ethanol, were first order with respect to the tolan substrate. In Figure 1 the rate constants are plotted as a function of pH. The result is a bell-shaped curve with the maximum at pH 4. Experimental values are depicted in Figure 1 by circles. The solid line represents values calculated from eq. 1 and 2, where $K_1 = 2.63$ $\times 10^{-4}$, $K_2 = 4.17 \times 10^{-5}$, and k = 0.0217 min⁻¹. K_1 and K_2 were calculated from titration data for 2,2'tolandicarboxylic acid (see Experimental), and k was obtained from the experimental value of k_{obsd} at pH 3.9 and α_I at that pH.

The agreement between the experimental points and the calculated curve provides good evidence that the active species in the isomerization of 2,2'-tolandicarboxylic acid in aqueous solution possesses both a carboxyl group and a carboxylate ion. A reasonable inference is that lactonization in this system involves concerted attack at the C=C bond, carboxylate adding to one carbon atom and a proton, donated by the neighboring carboxyl group, adding to the other carbon atom (see structure A.)¹⁸

Data from similar experiments with 2-tolancarboxylic acid are presented in Figure 2. This acid isomerized in water much more slowly than 2,2'-tolandicarboxylic

⁽¹⁸⁾ The cyclization reaction occurring when I or II is dissolved in concentrated sulfuric acid undoubtedly differs mechanistically from this scheme. In the reactions in sulfuric acid, a neighboring carboxyl group probably attacks a protonated carbon-carbon triple bond.



Figure 2. Isomerization of 2-tolancarboxylic acid in water at 30° . Experimental points, O; curve calcd. from eq. 5, ———; calcd. from eq. 4, ---.

acid and the k_{obsd} -pH profile was sigmoid rather than bell shaped. The fractions ionized were calculated from eq. 3. The apparent ionization constant, $K_a =$

$$\alpha_{\rm II} = K_{\rm a}/(K_{\rm a} + [{\rm H}^+])$$
 (3)

 1.12×10^{-4} , was determined independently from titration data. Since at pH 4, where the acid is 53% ionized, the rate constant is approximately $\frac{1}{6000}$ that for 2,2'tolandicarboxylic acid at the same monoanion concentration, it is apparent that the accelerating effect of the nonlactonizing carboxyl group in I is manifested in



aqueous solution as well as in the alcoholic solutions. The dashed line in Figure 2 represents rate constants calculated from eq. 4, where k is taken to be 3.1×10^{-6} min.⁻¹, and the solid line represents rate constants calculated from eq. 5, where k_1 and k_2 are taken to be 3.1×10^{-6} min.⁻¹ and 3.0×10^{-3} mole 1^{-1} min.⁻¹. Although the two curves do not differ greatly, the fact that the data are somewhat better accommodated by

$$k_{\rm obsd} = k\alpha_{\rm II} \tag{4}$$

$$k_{\rm obsd} = k_1 \alpha_{\rm II} + k_2 \alpha_{\rm II} [\rm H^+]$$
 (5)

eq. 5 than eq. 4 suggests that either spontaneous isomerization of nondissociated tolancarboxylic acid or hydrogen ion catalysis of a reaction of the tolancarboxylate anion accounts for a portion of the reaction in the more acidic solutions. Of these possibilities, catalysis by hydrogen ion is more attractive in view of the lack of reactivity of nondissociated 2,2'-tolandicarboxylic acid and the evidence for acid catalysis, albeit by a neighboring carboxyl group, in the isomerization of 2,2'-tolandicarboxylic acid monoanion. In any event, however, the major portion of the reaction above pH 4 appears to proceed by way of the anion of 2-tolancarboxylic acid.

2,4-Tolandicarboxylic acid and its isomerization product were too insoluble in water to study under comparable conditions. A few measurements were made in 16.3% aqueous ethanol at 37° . Although the information available is insufficient to warrant a mathematical analysis, the results have a bearing on the role of the inductive (or field) effect of the carboxyl group and the carboxylate ion in these reactions. As shown in Table IV, the first-order rate constants in-

Table IV.	Isomerization of 2,4'-Tolandicarboxylic Acid
in 16.3%	Ethanol-Water at 37°

pH	$10^{3} \times k_{\text{obsd}},$ min. ⁻¹			
3.0	0.11			
3.6	0.37			
4.0	0.67			
4.5	0.75			
5.0	0.64			
6.0	0.35			

creased with increasing pH in the region from 3 to 4.5; at higher values the rate constants decreased with increasing pH. This behavior is consistent with the assumption that the increase in k_{obsd} in the 3-4.5 region is associated with an increasing degree of ionization of the carboxyl group in the *ortho* position and the decrease in k_{obsd} in the 4.5-6 region reflects conversion of the carboxyl group in the *para* position to an anion, which has less tendency than the carboxyl group to withdraw electrons from the carbon-carbon triple bond.

Experimental

Infrared spectra were determined with a Baird recording spectrophotometer with the samples in potassium bromide. Ultraviolet spectra were obtained with a Cary Model 11 or a Beckman DU spectrophotometer. Microanalyses were performed by Miss Hildegard Beck.

2,4'-Dibromotolan. $\alpha, \alpha', 2, 4'$ -Tetrabromobibenzyl¹⁹ (21.5 g., 0.0431 mole) was added to a solution of potassium *t*-butoxide prepared from 10 g. of potassium metal and 500 ml. of *t*-butyl alcohol. The solution was refluxed 3.5 hr., cooled, poured into 600 ml. of water, and extracted with 700 ml. of ether. Ether was distilled from the extract and the resulting material was dried over P₂O₅ in vacuo. Recrystallization from 95% ethanol afforded 10 g. (65%) of 2,4'-dibromotolan, m.p. 70–71°.

Anal. Calcd. for $C_{14}H_8Br_2$; C, 50.03; H, 2.40. Found: C, 49.76; H, 2.40.

2,2'-Tolandicarboxylic Acid (I). A solution of butyllithium (75 ml. of 0.69 *M* ether solution, 0.0517 mole) was added with stirring to 8.69 g. (0.0258 mole) of 2,2'-dibromotolan⁷ in 25 ml. of ether at 0°. After 30 min. additional stirring, the mixture was jetted into a slurry of Dry Ice and ether. Addition of water, separation of layers, and acidification of the aqueous layer afforded 2.33 g. of 2,2'-tolandicarboxylic acid, m.p. 236-240°, λ_{max} 5.90 μ . An additional portion of acid (3.27 g., m.p. 210-239°, infrared spectrum essentially the same as for the acid previously isolated) was obtained by extraction of the ether layer with sodium bicarbonate and subsequent acidification; total yield, 5.60 g. (81%). An analytical sample, m.p. 238-

(19) S. Bance, H. J. Barber, and A. M. Woolman, J, Chem. Soc., 1 (1943).

240°, was obtained by recrystallization from acetic acid-hexane.

Anal. Calcd. for $C_{16}H_{10}O_4$: C, 72.2; H, 3.78; neut. equiv., 133. Found: C, 72.2; H, 3.74; neut. equiv., 135.

Preparation of 2-Tolancarboxylic Acid (II) and 2,4'-Tolandicarboxylic Acid (III). These compounds were prepared by the same procedure used in preparing 2,2'tolandicarboxylic acid. 2-Tolancarboxylic acid was obtained in 20% yield from 2-bromotolan.²⁰ On recrystallization from acetic acid and heptane it melted at 126–127.5°.

Anal. Calcd. for $C_{15}H_{10}O_2$: C, 81.07; H, 4.54. Found: C, 81.15; H, 4.60.

2,4'-Tolandicarboxylic acid was obtained in 85% yield from 2,4'-dibromotolan. The analytical sample, m.p. 334-336, was obtained by recrystallization from ethanol.

Anal. Calcd. for $C_{16}H_{10}O_4$: C, 72.18; H, 3.78. Found: C, 72.63; H, 3.85.

3-(2-Carboxybenzylidene)pthalide (IV). A solution of 0.362 g. of 2,2'-tolandicarboxylic acid in 35 ml. of ethanol was refluxed for 1 hr. and then cooled and poured into water. The precipitate (IV) which separated weighed 0.288 g. (80%), melted at 235–240°, and had an infrared spectrum distinctly different from that of compound I. Compound IV showed two carbonyl bands (5.60 and 5.90 μ) and a band at 6.05 μ attributable to a carbon-carbon double bond, whereas compound I absorbed only at 5.90 in this region. Furthermore, I had a broad band at 11.00 μ whereas IV did not. Recrystallization of the crude material from tetrahydrofuran afforded an analytical sample, m.p. 245.0-246.5°.

Anal. Calcd. for $C_{16}H_{10}O_4$: C, 72.2; H, 3.78; neut. equiv., 266. Found: C, 72.4; H, 3.73; neut. equiv., 268.

When methanol was used as a solvent in place of ethanol, the same product was obtained.

Likewise, when compound I (0.055 g.) was heated at steam bath temperature in 10 ml. of acetic acid which contained 0.172 g. of sodium acetate, it was converted to compound IV (0.045 g., 82% isolated). Under the same conditions, a control experiment in which sodium acetate was omitted yielded only unreacted starting material (79% recovered).

Saponification of a small sample of compound IV with hot potassium hydroxide solution afforded, on acidification, 2,2'-deoxybenzoindicarboxylic acid, m.p. 233– 238° (lit. m.p. 238–239,^{11b} 241–243°,^{11c} 215–245°²¹); $\lambda_{\rm KBr}$ 5.75 and 5.90 μ . The dimethyl ester derivative is reported in Table V.

3-(2-Carboxyphenyl)isocoumarin (VI). 3-(2-Carboxybenzylidene)phthalide (0.210 g.) was heated for 10 hr. on a steam bath with 5 ml. of acetic acid and 0.2 ml. of 9 M sulfuric acid. The solution was cooled and diluted with water, and the organic products were extracted with ether (extract A). An extraction of the ether portion with sodium bicarbonate solution afforded 0.108 g. (51%) of 3-(2-carboxyphenyl)isocoumarin, λ_{max} 5.76 and 5.85 μ ; m.p. after recrystallization from tetrahydrofuran, 227-228°.

(20) R. L. Letsinger, T. E. Feare, T. J. Saveriede, and J. R. Nazy, J. Org. Chem., 26, 1273 (1961).

Anal. Calcd. for $C_{16}H_{10}O_4$: C, 72.2; H, 3.78. Found: C, 72.6; H, 3.90.

Spiro(phthalide-3,3'-dihydroisocoumarin) (V). Evaporation of the ether layer remaining after extraction of layer A with bicarbonate (see preparation of 3-(2-carboxyphenyl)isocoumarin) yielded 0.025 g. (12%) of dilactone V, λ_{max} 5.58 and 5.70 μ ; m.p. after recrystallization from benzene-hexane, 235-237°.

Anal. Calcd. for $C_{16}H_{10}O_4$: C, 72.2; H, 3.78. Found: C, 72.0; H, 3.73.

The same dilactone was obtained directly from 0.036 g. of 2,2'-tolandicarboxylic acid by dissolving the diacid in 1 ml. of concentrated sulfuric acid at room temperature, pouring the solution onto ice, neutralizing the acid with sodium bicarbonate, and collecting the remaining neutral solid, m.p. 227–229°, 0.03 g. This sample was characterized by its infrared spectrum.

Interconversion of V and VI. A flask containing 47 mg. of VI, 5 ml. of glacial acetic acid, 5 drops of sulfuric acid, and 5 drops of water was heated on a steam bath for 24 hr., cooled, and diluted with water. The resulting white solid was collected, dissolved in ether, and extracted several times with 5% aqueous sodium bicarbonate. Compound V, 5 mg., was recovered from the ether layer and compound VI, 25 mg., was recovered from the aqueous layer.

A solution containing 95 mg. of dilactone V, 10 drops of sulfuric acid, and 10 drops of water in 10 ml. of acetic acid was warmed for 15 hr. on a steam bath and worked up in the same way to give 3 mg. of dilactone V and 38 mg. of VI. The products were characterized by their infrared spectra.

3-(2-Carbomethoxyphenyl)isocoumarin (VIa) from IV. A mixture of 0.122 g. of 3-(2-carboxyphenyl)benzylidenephthalide, 25 ml. of methanol, and three drops of concentrated sulfuric acid was refluxed for 9 hr., cooled, neutralized with sodium bicarbonate, and extracted with ether. From the ether extract was obtained 0.052 g. (41% of 3-(2-carbomethoxyphenyl)isocoumarin; m.p. 114–118°; m.p. after two recrystallizations from methanol-water, 124.5–125.5°.

Anal. Calcd. for $C_{17}H_{12}O_4$: C, 72.9; H, 4.32. Found: 73.0; H, 4.21.

Methyl Esters Prepared with Diazomethane. In each case the carboxylic acid was added to excess diazomethane in ether solution. Evaporation of the ether afforded the ester directly in a relatively pure state (melting point very close to melting point of purified sample). Analytical samples were obtained by recrystallization from aqueous ethanol or methanol. The data are presented in Table V.

Hydrogenation Experiments. The reductions were carried out at room temperature at 2 atm. of hydrogen pressure with a palladium-charcoal catalyst. The substrate (0.1 to 0.2 g.) was dissolved in 10 cc. of tetrahydrofuran.

3-(2-Carboxybenzylidene)phthalide absorbed 108% of 1 equiv. of hydrogen within 30 min., whereupon the hydrogenation ceased. Isolation of the product and recrystallization from ethanol afforded an 82% yield of 3-(2-carboxybenzyl)phthalide (VIII), m.p. 198–199°; λ_{max} 5.73 and 5.95 μ ; lit.¹¹ m.p. 198.5, 201°.

3-(2-Carbomethoxybenzylidine)phthalide absorbed 114% of the theoretical hydrogen within 20 min. to

⁽²¹⁾ S. Wawzonek, J. Am. Chem. Soc., 62, 745 (1940).

		Carbonyl band, µ	Analysis				
Ester	M.p. of ester, ° C.	(sample in KBr)	Formula	C Cal	cd.—— H	C Fo	und—— H
Dimethyl 2,2'-tolandicarbox- ylate ^a (Ia)	94.5-95.0	5.80	$C_{18}H_{14}O_{4}$	73.5	4.79	73.8	4.65
3-(2-Carbomethoxybenzyl- idene)phthalide (IVa)	160–161 ^{<i>b</i>}	5.60, 5.85	$C_{17}H_{12}O_4$	72.9	4.32	73.0	4.29
3-(2-Carbomethoxyphenyl)- isocoumarin (VIa)	124.5-125.5	5.81, 5.86	$C_{17}H_{12}O_4$	72.9	4.32	73.0	4.21
Dimethyl 2,2'-deoxybenzoin- dicarboxylate	111-111.5	5.87	$C_{18}H_{16}O_{\delta}$	69.2	5.16	68.9	5.10

^a The same ester (mixture melting point, infrared spectrum) was obtained in good yield by heating 2,2'-tolandicarboxylic acid with methanol and a catalytic amount of sulfuric acid. ^b Recrystallized from acetic acid. Tetrahydrofuran was the solvent for the diazomethane reaction in this case.

give 3-(2-carbomethoxybenzyl)phthalide (87 %, yield), m.p. 113–113.5°; λ_{max} 5.65 and 5.90 μ ; lit.⁸ m.p. 115°. This ester was also obtained (67 % yield) by esterification of 3-(2-carboxybenzyl)phthalide with methanol in the presence of sulfuric acid. The melting point, mixture melting point, and infrared spectrum of this sample were the same as for the sample prepared by direct hydrogenation.

The hydrogenation of 3-(2-carbomethoxyphenyl)isocoumarin proceeded very slowly and did not decrease in rate after the uptake of 1 mole equiv. of hydrogen. After 5 hr. the hydrogen consumption was 1.85 mole per mole of substrate. The monomethyl ester of 2,2'-bibenzyldicarboxylic acid (54% yield, m.p. 138.5–139.5°; λ_{max} 5.82 and 5.94 μ) was isolated from the reaction mixture.

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.8; H, 5.67. Found: C, 71.9; H, 5.99.

Isomerization of 2,4'-Tolandicarboxylic Acid. A solution consisting of 0.55 g. of 2,4'-tolandicarboxylic acid in 50 ml. of 95 % ethanol was refluxed for 40 hr., during which time a yellow crystalline solid separated. The product, 3-(4-carboxybenzylidene)phthalide, was collected, washed with 95% ethanol, and dried; weight 0.47 g. (85%); after recrystallization from a large volume of ethanol, m.p. 345–347°.

Anal. Calcd. for $C_{16}H_{10}O_4$: C, 72.18; H, 3.78. Found: C, 72.00; H, 3.84.

In another experiment 0.2 g. of the dicarboxylic acid (III) was dissolved in 2 ml. of concentrated sulfuric acid. After standing for 2 min. at room temperature the solution was poured onto ice. The precipitate was collected, washed with water, and dissolved in hot ethyl acetate. On cooling, 32 mg. (16%) of crystals were deposited. The infrared spectrum showed this substance to be essentially pure carboxybenzylidenephthalide (XI); there was only a very small blip at 5.85 μ which might correspond to the coumarin derivative. Concentration of the ethyl acetate filtrate and subsequent dilution with water afforded 88 mg. of diacid III. The spectrum indicated that it was contaminated with a small amount of XI.

Heating 0.20 g. of 3-(4-carboxybenzylidene)phthalide in 20 ml. of acetic acid with 10 drops of sulfuric acid and 10 drops of water for 24 hr. gave only the starting lactone (0.15 g. recovered).

Isomerization of 2-Tolancarboxylic Acid. A solution containing 0.13 g. of 2-tolancarboxylic acid in

10 ml. of acetic acid, 0.5 ml. of water, and 0.5 ml. of sulfuric acid was heated on a steam bath for 56 hr. The volume was reduced, water was added, and 0.11 g. of solid was collected by filtration. This material was purified by dissolving in ether, extracting the ether with sodium bicarbonate solution, and evaporating the ether. The product was a mixture of two lactones which were separated by crystallization from heptane. The less soluble lactone was 3-phenylisocoumarin; weight 0.04 g. (30%); m.p. 89°, lit.¹⁴ m.p. 88°. The more soluble material was 3-benzylidenephthalide; weight 0.04 g. (30%); m.p. 100-101°, lit.¹³ m.p. 99-100°.

Isomerization of 2-tolancarboxylic acid was also effected by heating the acid in ethanol, a water-ethanol buffer,²² or acetonitrile at 50° for 12 to 25 days. The product distribution was determined from the ultraviolet spectra of the products. Extinction coefficients for IX and X at 350 m μ were 15,470 and 8540 in ethanol, 16,450 and 9140 in the aqueous ethanol, and 14,200 and 7930 in acetonitrile. From these values and the extinction coefficients for the reaction products it was estimated that the ratio of IX to X produced in ethanol, aqueous ethanol, and acetonitrile was approximately 3, 3, and > 30, respectively.

Kinetic Methods. Dioxane was purified by the method described by Fieser.23 Alcohols were dried by distillation from calcium hydride. Eastman Kodak Co. Spectrograde acetonitrile was purified by the method of Walden and Birr.²⁴

Stock solution of the tolancarboxylic acid and the tolandicarboxylic acids $(10^{-2} M)$ were prepared in purified dioxane. These solutions were relatively stable; no change in the ultraviolet spectra occurred over a period of several days. For a kinetic run, 0.10 ml. of the stock solution was injected with a micropipet into 3.0 ml. of the reaction solvent in a quartz spectrophotometer cell. Isomerization was followed with a Cary Model 11 spectrophotometer by the increase in absorbance at 350 m μ . The temperature of the cell compartment was maintained at 30° by circulating water unless otherwise specified. For a given run the absorbance changed from about 0.1 or less to >1.0. A_{∞} values were obtained from reactions carried to

⁽²²⁾ The solvent was 18% ethanol by volume and was buffered at

pH 5.0 with citric acid and disodium hydrogen phosphate. (23) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., revised, D. C. Heath and Company, Boston, Mass., 1957, p. 284.

⁽²⁴⁾ P. Walden and E. J. Birr, Z. Physik. Chem., 144A, 269 (1929).

completion or from standard solutions prepared with compounds known to comprise the reaction products. Extinction coefficients used for IV, IX, X, and XI in ethanol were (\times 10⁻⁴): 1.73, 1.55, 0.845, and 2.20, respectively. Plots of log $(A_{\infty} - A)$ vs. time yielded straight lines for reactions carried out in the alcohols, water, and alcohol-water mixtures. Individual runs in acetonitrile were approximately zero order with respect to the tolan substrate. A few experiments carried out in dimethylformamide gave results similar to those for acetonitrile.

Aqueous buffer solutions ranging in pH from 3.4 to 6.0 were prepared by mixing appropriate volumes of 0.01 M aqueous sodium acetate solution with a solution 0.01 M in acetic acid and 0.01 M in sodium chloride. More acidic solutions were prepared with hydrochloric acid and sufficient sodium chloride to maintain an ionic strength of 0.01. For use in the experiments with 2,4'-tolandicarboxylic acid, buffers in aqueous ethanol were prepared by mixing a solution 0.05 M in disodium hydrogen phosphate with one 0.025M in citric acid. The solvent for each of these solutions was 16.3% ethanol by weight.

Titration Data. Values for K_1 and K_2 for 2,2'tolandicarboxylic acid were obtained by application of the equations of Britton²⁵ to data from a titration curve. In order to avoid precipitation of the acid

(25) H. T. S. Britton, J. Chem. Soc., 1903 (1925).

in the course of the titration some alcohol was added to the aqueous solvent. Thus, a 15 ml. solution of the disodium salt of 2,2'-tolandicarboxylic acid (from 0.9849 g. of acid) was added to 50 ml. of 0.15 MKCl in water and 20 ml. of 95% ethanol. The solution was titrated with aqueous hydrochloric acid at 30°, the pH change being followed with a Beckman Model G pH meter. The values of pK_1 and pK_2 calculated²⁵ from these data were 4.08 and 4.88. To correct to values for water, it was assumed that the effect of solvent change on the K values for 2,2'-tolandicarboxylic acid was the same as the effect of the ionization constant of benzoic acid.²⁶ With this correction $K_1 = 2.63 \times 10^{-4}$ and $K_2 = 4.17 \times 10^{-5}$ for 2,2'tolandicarboxylic acid.

 $K_{\rm a}$ for 2-tolancarboxylic acid was obtained from extinction coefficients for the acid in 0.1 M hydrochloric acid (ϵ_{283} 1.77 × 10⁴, ϵ_{300} 1.26 × 10⁴), in 0.1 M aqueous sodium hydroxide (ϵ_{283} 2.53 \times 10⁴, ϵ_{300} 2.13 \times 10⁴), and in aqueous buffer solutions at pH 3.80 (ϵ_{283} 2.08×10^4 , $\epsilon_{300} 1.62 \times 10^4$) and pH 4.00 ($\epsilon_{283} 2.16 \times$ 10⁴, ϵ_{300} 1.74 \times 10⁴), using the equations of Brown and Mihm.²⁷ Measurements were made at 23°. The value of $K_{\rm a}$ found by this procedure was 1.12 \times 10^{-4} .

(26) E. Grunwold and B. J. Berkowitz, J. Am. Chem. Soc., 73, 4939 (1951). (27) H. C. Brown and R. Mihm, ibid., 77, 1723 (1955).

The Decomposition of Olefinic Azides¹

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The synthesis of olefinic azides and their thermal decomposition in a solvent to give 1-azabicyclo[3.1.0]hexanes and cyclic imines is described. Evidence is presented to show that the azide functionality adds intramolecularly to the double bond to give an isolable triazoline VII, which opens up in the rate-determining step to a diazonium ion type intermediate VIII, followed by evolution of nitrogen and formation of products.

The finding that the thermal decomposition² of 2-biphenyl azides gives carbazoles in good yields has prompted many investigations of the synthetic utility of the decomposition of organic azides. For example, vapor phase pyrolysis of aromatic azides having an alkyl chain in the ortho position gives indanes and tetrahydroquinolines^{3a-d} while pyrolysis of vinyl azides gives azirines.^{3e} Similarly, ultraviolet irradiation of steroidal acyl azides gives bicyclic lactams.^{4,5} In this paper, the synthesis and decomposition of olefinic azides containing unsaturation two, three, four, and five bonds away from the azide group is described. The assumption was made that the π -electrons four and five bonds away would assist anchimerically in the decomposition of these azides to give cyclic and bicyclic amines as products.

The primary and secondary azides IIb-f were prepared by converting the corresponding alcohols to the *p*-toluenesulfonate esters and treating the crude esters with sodium azide in aqueous ethanol or pyridine at room temperature. The tertiary azide IIa was prepared by adding the corresponding alcohol to a mixture of hydrazoic acid and concentrated sulfuric acid in

⁽¹⁾ A preliminary account of this work was presented before the Organic Division, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 3, 1964.

⁽²⁾ P. A. S. Smith and B. B. Brown, J. Am. Chem. Soc., 73, 2435 (1951); P. A. S. Smith and J. H. Boyer, *ibid.*, 73, 2626 (1951); P. A. S. Smith, J. M. Glegg, and J. H. Hall, J. Org. Chem., 23, 524 (1958).

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J. Feuer, J. Org. Chem., 29, 3097 (1964); (d) G. Smolinsky and B.
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⁽⁵⁾ W. L. Meyer and A. S. Levinson, J. Org. Chem., 28, 2859 (1963).