potential also occurred at 0.490 V.

Measurement of the cathodic peak current (i_{pc}) and the anodic peak current (i_{pa}), the latter by the potential-hold method delineated by Adams,[7] gave an anodic to cathodic peak current ratio of unity (observed: $i_{pa}/i_{pc} = 1.00 \pm 0.02$) as expected theoretically. Furthermore, the peak cathodic current calculated[7,8] for a reversible two-electron transfer, using a diffusion coefficient derived from chronoamperometric data (vide infra), was $i_{pc} = 23.5\ \mu A$ in good agreement with the observed value of 23.8 μA. On the basis of this overall assessment of reversibility, the half-wave potential, taken at 85% of the cathodic peak current,[8] was $E_{1/2} = +0.47$ V in this solvent system.

In solvent media composed of McIlvaine buffers/95% ethanol (4:1, v/v) the redox process became increasingly irreversible with increasing pH as indicated by the anodic to cathodic peak separation ($\Delta E_p = 0.098$ V at pH 2.27 and $\Delta E_p = 0.367$ V at pH 7.15). Despite this, the cathodic half-peak potential was linear with pH and followed the equation $E_{pc/2} = 0.432 - 0.067$ pH (correlation coefficient = 0.983) in the pH range 2.27–7.15.

Although the redox process observed for 2-(2-methyl-3-indolyl)-1,4-benzoquinone ($3 \rightleftharpoons 4$) in the perchloric acid medium was a simple, reversible charge transfer, more complex behavior was observed by widening the potential window to +1.100 V and initiating the cyclic voltammogram at +0.70 V and then scanning toward more positive potentials. Under these conditions (and at a scan rate of 0.050 V/s) a totally irreversible oxidative wave was observed at $E_{pa} = +1.00$ V, with no companion cathodic wave on scan reversal. The remaining part of the scan showed the reversible couple ($3 \rightleftharpoons 4$) as described previously. The anodic wave at 1.00 V probably involved oxidation of the indole moiety since in separate control experiments both 2-methylindole ($E_{pa} = 1.05$ V at pH 0.60) and indole ($E_{pa} = 0.900$ V at pH 6.8)[9,10] exhibited totally irreversible waves in the same region. The nature of this oxidation is, however, not interpretable at this time since the anodic electrochemical behavior of simple indoles is complex and not well understood.[11]

Chronoamperometry experiments were performed on 2-(2-methyl-3-indolyl)-1,4-benzoquinone (3) at four concentrations (0.100, 0.140, 0.180, and 0.200 mM), each at seven different acidities covering the pH range from 0.60 to 7.15. The data array (at 25 °C) yielded an average $it^{1/2}/C = 78.8 \pm 2.2$ (± standard error) from which the diffusion coefficient, $D = (0.38 \pm 0.02)10^{-5}$ cm^2/s, was calculated from the Cottrell equation. This value of D appeared to be reasonable compared with the few known values of diffusion coefficients for other organic molecules determined in dominantly aqueous media.[12]

Overall, the cathodic reduction of 2-(2-methyl-3-indolyl)-1,4-benzoquinone (3) at the Nujol–carbon-paste electrode is remarkably well-behaved in strongly acidic media, and its reversibility is comparable with that observed on anodic oxidation of *o*-dianisidine.[12] At higher pH values the indolyl quinone 3 is more nearly comparable with the *p*-quinone–hydroquinone system, which is notably irreversible at solid electrodes.[13,14] The indolyl *p*-quinone 3, and perhaps other *o*-quinonoid analogues, may be of further value as reactivity models of low-molecular-weight oligomeric quinones which occur as transient intermediates during melanization reactions.

Experimental Section

2-(2-Methyl-3-indolyl)-1,4-benzoquinone (3). This compound was prepared from 2-methylindole and *p*-benzoquinone as described in the literature,[3,15] and recrystallized from 95% ethanol as deep violet crystals, mp 181–182 °C (lit.[15] mp ca. 185 °C).

Electrochemistry. These experiments were done on a Princeton Applied Research system comprising a Model 175 programmer, a Model 173 potentioistat with Model 176 I/E converter, and Model 178 electrometer probe. The carbon paste in the working electrode was formulated from Nujol and purified graphite (Matheson, Coleman, and Bell), using standard procedures.[14] Potentials were recorded vs. a saturated calomel electrode. The area of the working electrode was calibrated (0.37 cm^2) by chronoamperometry, using *o*-dianisidine in 1.02 M sulfuric acid, for which a reference diffusion coefficient was taken as $D = 0.44 \times 10^{-5}$ cm^2/s.[12] Cyclic Voltammograms were recorded up to 0.200 V/s on a Houston Model 2100-4-5 X–Y recorder, and faster scans up to 5.0 V/s were observed and recorded photographically on a Tektronix Model 5103N storage oscilloscope. Chronoamperometry experiments were recorded on the same equipment, using the time base of the X–Y recorder. Jacketted electrochemical cells were maintained at constant temperature via water circulating from a thermostatic bath maintained internally at 25 ± 0.04 °C.

The perchloric acid solutions consisted of 1 M perchloric acid/95% ethanol in a 4:1 volume ratio (pH 0.60). Various buffer solutions were prepared from standard 1 M ionic strength McIlvaine buffers/95% ethanol in a 4:1 volume ratio. All pH values were those of the mixtures. The partially ethanolic solutions were necessary to dissolve the substrate molecule (3).

Acknowledgment. We are grateful to the National Institutes of Health for Grant NS 12608 from NINCDS for support of this work.

Registry No. 3, 80641-49-2; **4**, 80641-50-5; 2-methylindole, 95-20-5; *p*-benzoquinone, 106-51-4.

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[7] Adams, R. N. "Electrochemistry at Solid Electrodes"; Marcel Dekker: New York, 1969; Chapter 5.

[8] Nicholson, R. S.; Shain, I. *Anal. Chem.* **1964**, *36*, 706.

[9] It should be noted that while 2-methylindole is stable in acidic media, indole itself dimerizes readily[10] and could not be run in the perchloric acid solution.

[10] Remers, W. A. In "Indoles"; Houlihan, W. J. Ed.; Wiley-Interscience: New York, 1972; Part 1, pp 66–67.

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[12] Reference 7, pp 221–222.

[13] Reference 7, pp 365–367.

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Kinetic Study of the Isomerization of Itaconic Anhydride to Citraconic Anhydride

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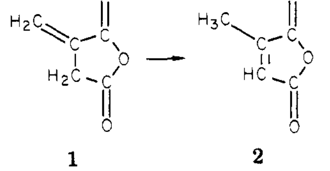
It is known that direct heating,[1] either via distillation or simple melting, isomerizes itaconic anhydride (ITA, 1)



1 2

to citraconic anhydride (CTA, 2). Using a spectrophotometric technique, Barb[2] showed that the isomerization of

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[1] Blatt, A. H. "Organic Syntheses"; Wiley: New York, 1943; Collect Vol. II, p 140.

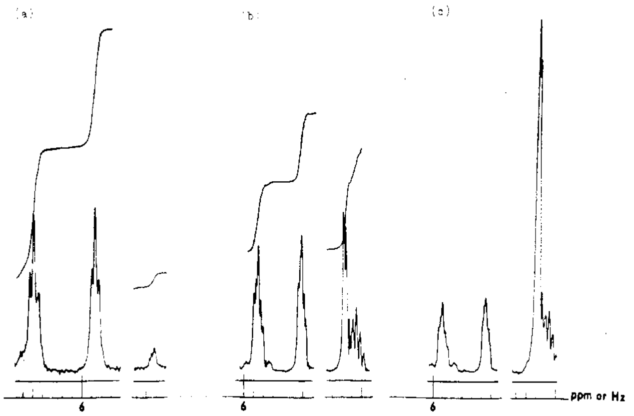

Figure 1. NMR spectra of itaconic anhydride–DMA mixture in chloroform at room temperature: (a) 18 min, (b) 70 min, (c) 228 min.

ITA to CTA in pure *N,N*-dimethylaniline was a first-order reaction and further concluded that tertiary aliphatic amines did not cause isomerization. It was recently[3] reported that the conversion of ITA to CTA does occur, in fact, not only in *N,N*-dimethylaniline but also in the presence of tertiary aliphatic amines. It is also noted that while no isomerization products were observed[4] in reactions of ITA with certain aromatic primary diamines in refluxing acetone, similar reactions with aliphatic primary diamines yielded only the bis(citraconamic) isomers.[5] Finally, no isomerization occurred[6] in reactions of ITA with aliphatic primary diamines in refluxing chloroform. These observations showed the general importance of both the solvent and the amine in the conversion reaction. This paper presents the results of kinetic studies on the effects of solvent polarity, amine basicity, and amine concentration upon the isomerization rate of ITA to CTA.

Experimental Section

ITA was prepared by dehydration of itaconic acid with acetyl chloride followed by a repeated distillation with toluene. The melting point of the white anhydride crystals was 67.5–68.0 °C; the high purity of the reagent was further confirmed[5] by NMR, IR, and elemental analysis. Spectroscopic grade solvents and reagent grade tertiary amines were purchased from commercial suppliers. The amines chosen for the study were *N,N*-dimethylaniline (DMA), pyridine, and *N,N*-diethylaniline (DEA), while the solvents selected were chloroform and acetone.

The isomerizations of the ITA–amine solutions in a given solvent were followed by proton nuclear magnetic resonance spectroscopy on a Varian EM 3602 using Me_4Si as an internal reference. The NMR spectra of ITA and CTA are characterized by the following shifts:[6,7] δ 6.6 (t, CH), 5.9 (t, CH), and 3.6 (t, CH_2) for ITA and δ 6.8 (m, CH) and 2.1 (d, CH_3) for CTA. The extent of conversion with time was quantified by comparison of the NMR integrated area responses at these specific absorption resonances. Figure 1 presents typical spectra which illustrate the ITA to CTA conversion for the DMA–chloroform system.

Results and Discussion

Specific amine concentrations and solvent combinations that were studied are presented in Table I, along with the respective computed rate constants for each solution.

Table I. Effect of Amine Catalysts and Solvents upon the Rate Constant (k) of the Conversion of ITA at 21 ± 1 °C and a $[ITA]_0$ of 0.444 M

solvent	amine	amine molarity	10^2k, min^{-1} (±15%)
none	DMA	7.9	1.56[a]
chloroform	DMA	0.25	0.40
chloroform	DMA	1.32	2.10
chloroform	DMA	2.50	5.00
acetone	DMA	1.32	3.00
chloroform	pyridine	0.25	1.10
chloroform	pyridine	2.65	10.6
chloroform	DEA	0.25	2.30
chloroform	DEA	0.57	5.00
chloroform	DEA	1.20	12.0

[a] Barb[2] obtained k values of $(1.2\text{-}1.6) \times 10^{-2}$ min^{-1} at 21-22 °C spectrophotometrically.

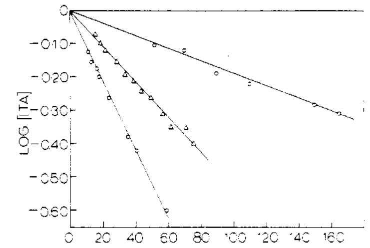

Figure 2. Effect of 0.25M amine–chloroform solutions upon the rate of conversion: ○, DMA; △, pyridine; ⊙, DEA.

Figure 2 is a representative plot that shows the effect of three different amines at a 0.25 M concentration in chloroform solutions upon the rate of ITA to CTA conversion. The linearity of these logarithmic plots indicated first-order mechanisms with rate constants of 0.0040, 0.011, and 0.023 min^{-1} for the DMA, pyridine, and DEA solutions, respectively, at room temperature. The variation observed is attributed to differences in amine basicity, which in terms of aqueous K_b^w values are 1.1×10^{-9}, 2.3×10^{-9}, and 4.0×10^{-8} for DMA, pyridine, and DEA, respectively. Although it may be expected that the K_b^w values are altered in chloroform, it has been shown[8] that at least in aniline, amines follow K_b values exhibited in aqueous solutions. The magnitudes of the observed rate constants parallel the respective amine K_b^w values in that the reaction rate increased as the amine basicity increased.

The polarity effect of the solvent upon ITA was determined from rate data on 1.32 M DMA in chloroform and acetone solutions. Linear plots indicated that the isomerization proceeds as a first-order reaction for both weakly and strongly polar solvents. Rate constants of 0.021 and 0.031 min^{-1} for chloroform and acetone, respectively, reflect the positive effect of solvent polarity upon the conversion rate.

Concentration–rate data for the ITA–DMA and ITA–DEA solutions in chloroform illustrated the effect of amine concentration upon the rate of isomerization. The corresponding first-order plots showed that the first-order linearity was followed over a fairly wide concentration range and, further, that the isomerization rate was strongly dependent upon the concentration of the amine.

The observed effects of amine basicity, amine concentration, and solvent polarity are summarized in Table I and may be explained upon reference to the proposed[3]

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[2] Barb, W. G. *J. Chem. Soc.* **1955**, 1647–1651.

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[6] Galanti, A. V.; Liotta, F.; Keen, B. T.; Scola, D. A. *J. polym. Sci.*, in press.

[7] Hutton, H.; Shaefer, T. *J. Phys. Chem.* **1964**, *68*, 1602.

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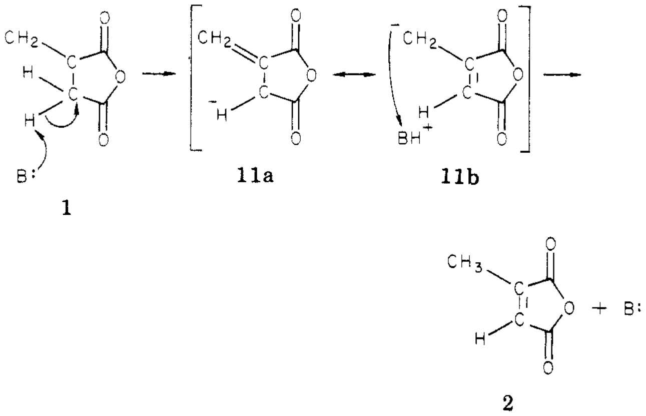
Scheme I[a]



[a] B: = *N*,*N*-diethylaniline, pyridine, or *N*,*N*-dimethylaniline.

isomerization mechanism for the amine-catalyzed reaction (Scheme I). Increases in either amine basicity or concentration would enhance the formation of the carbanion **11a**, resulting in higher conversion rates of ITA to CTA. Also, greater solvation of the carbanion intermediate probably occurs in more polar solvents which would account for the reaction rate increase in acetone compared to chloroform.

Registry No. 1, 2170-03-8; *N*,*N*-dimethylaniline, 121-69-7; pyridine, 110-86-1; *N*,*N*-diethylaniline, 91-66-7; chloroform, 67-66-3; acetone, 67-64-1; citraconic anhydride, 616-02-4.

Absolute Configuration of Glycerol Derivatives. 8.[1] 2-Hydroxy-3-(1-naphthoxy)propionic Acid, a Major Oxidative Metabolite of the β-Adrenergic Antagonist Propranolol

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Propranolol (**1**) is a β-adrenergic antagonist used extensively in the treatment of various cardiovascular disorders, including hypertension and angina pectoris, as well as in other situations.[2] In man, 2-hydroxy-3-(1-naphthoxy)propionic acid (**2**; "propranolol lactic acid") is the major urinary metabolite resulting from multistep oxidative N-dealkylation of the propanolamine side chain.[3]

Because the β-adrenergic antagonist properties of the propranolol are retained almost exclusively by one of the enantiomers,[4] and evidence that the enantiomers of propranolol are metabolized to pharmacologically active and inactive products at different rates in rats,[5] dogs,[6] rabbits,[7] and in man,[8] we were interested in obtaining additional information concerning the enantioselectivity of the N-dealkylation process. Associated with a metabolic study of this nature was the need for more stereochemical information about this acid. In this paper we report a facile synthesis and resolution of **2** and establish the absolute stereochemistry of the enantiomers of **2**.

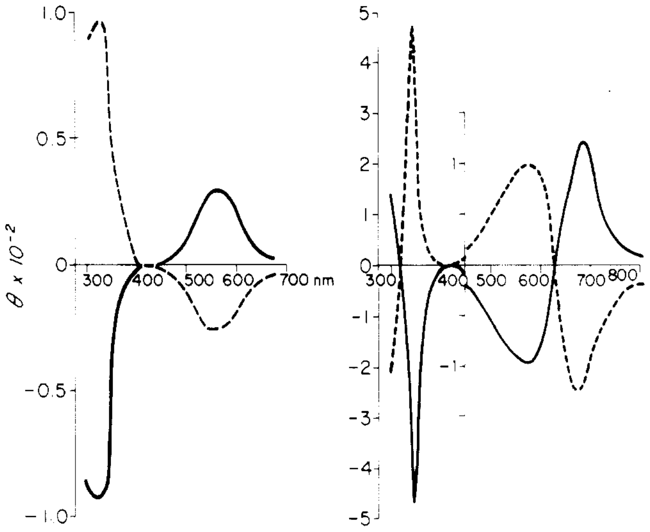
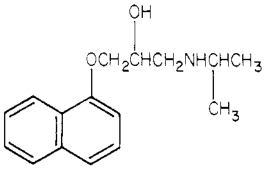


Figure 1. (left) Circular dichroism spectra of the enantiomers of 3-(1-naphthoxy)propane 1,2-glycol (**6**) in Cupra A-MeOH (4:1), (2*R*)-(−)-**6** (solid line) and (2*S*)-(+)-**6** from (2*R*)-(−)-**2** (dotted line). (right) Circular dichroism spectra of the enantiomers of 2-hydroxy-3-(1-naphthoxy)propionic acid (**2**), in Cupra A solution, (2*S*)-(+)-**2** (solid line) and (2*R*)-(−)-**2** (dotted line).



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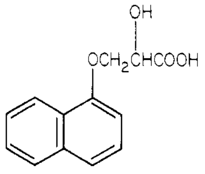
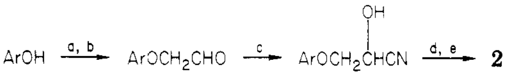


2



4 5

Ar = 1-naphthyl; a, $BrCH_2CH(OEt)_2/Na_2CO_3$; b, H_3O^+; c, KCN, $NaHSO_3$; d, MeOH/HBr, H_2O; e, $^-OH/H_2O$

A need for sufficient quantities of 2-hydroxy-3-(1-naphthoxy)propionic acid (**2**) to effect a resolution prompted us to develop a practical synthesis for it.[9] Acid **2** was obtained from the cyanohydrin of 2-(1-naphthoxy)acetaldehyde (**4**). Conversion of the cyanohydrin to an α-hydroxy carboxylic acid ester, followed by alkaline hydrolysis, proved to be a more successful route to **2** than direct hydrolysis of the cyanohydrin (**5**). The "lactic acid metabolite" of the related β-adrenergic antagonist timolol

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[1] Part 7 of this series: W. L. Nelson, M. L. Powell, and D. C. Dyer, *J. Med. Chem.*, **22**, 1125 (1979).

[2] See (a) T. F. Blaschke and K. L. Melmon in "The Pharmacological Basis of Therapeutics", 6th ed. A. G. Gilman, L. S. Goodman, Ed., MacMillan, New York, 1980, Chapter 32, pp 793–819. (b) R. E. Buckingham and T. C. Hamilton, *Gen. Pharmacol.*, **10**, 1 (1979); (c) F. O. Simpson, *Drugs*, **20**, 69 (1980).

[3] (a) P. A. Bond, *Nature (London)*, **213**, 721 (1967); (b) J. W. Paterson, M. E. Connolly, C. T. Dollery, A. Hayes, and R. G. Cooper, *Pharmacol. Clin.*, **2**, 127 (1970); (c) J. F. Pritchard, D. W. Schneck, and A. Hayes, Jr., *J. Chromatogr. Biomed. Appl.*, **162**, 47 (1979); (d) T. Walle and T. E. Gaffney, *J. Pharmacol. Exp. Ther.*, **182**, 83 (1972); (e) T. Walle, T. Ishizaki, and T. E. Gaffney, *ibid.*, **183**, 508 (1972); (f) W. L. Nelson and T. R. Burke, Jr., *Res. Commun. Chem. Path. Pharmacol.*, 21, 77 (1978).

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[9] Although several reports of the use of **2** as an analytical standard appear in the literature, we are not aware of reports of its synthesis.