overnight and then worked up as described before for the corresponding ester. The resulting dipeptide amide was recrystallized as described in A and was found to melt at 176°.

N-Benzoyl-L-phenylalanyl-O-benzylserine Ethyl Ester.—DL-O-Benzylserine (9.75 g., 50 mmoles) was converted to its ethyl ester hydrochloride by treatment first with refluxing absolute ethanol containing 2 equivalents of dry hydrogen chloride and then by repeated treatment with refluxing absolute ethanol in the customary fashion for esterifications. The ester hydrochloride was dried thoroughly *in vacuo* and then was dissolved in methylene chloride (50 ml.). Condensation was then carried out with benzoyl-L-phenylalanine (13.5 g., 50 mmoles) by addition of triethylamine (7.05 ml., 50 mmoles) and dicyclohexylcarbodiimide (10.3 g., 50 mmoles) exactly as was described in the preceding examples. The product was recrystallized from ethyl acetate–benzene; m.p. 120–121°.

Anal. Calcd. for $C_{28}H_{30}N_2O_5$: C, 70.9; H, 6.3; N, 5.9. Found: C, 70.9; H, 6.4; N, 5.7.

N-Benzoyl-L-phenylalanyl-O-benzylserine.—The ethyl ester of the preceding section (21.6 g.) was dissolved in 200 ml. of ethanol and treated with 60 ml. of *N* sodium hydroxide for 2 hr. Acidification with hydrochloric acid, evaporation of the ethanol, and partition between benzene and water at pH 8 gave the sodium salt of the desired acid in the aqueous phase. Acidification yielded an oil which was crystallized from benzene to give 17.6 g., m.p. 162–163°.

Anal. Calcd. for $C_{26}H_{26}N_2O_5$: C, 70.0; H, 5.8; N, 6.3. Found: C, 69.8; H, 5.7; N, 6.1.

N-Benzoyl-L-phenylalanyl-O-benzylserine Amide.—In contrast to the behavior of benzoylphenylalanylserine ethyl ester, the corresponding O-benzylserine ester failed to yield the amide when treated either with alcoholic ammonia at room temperature, or with liquid ammonia in a bomb at room temperature. Unchanged ester was always recovered. Consequently, the desired amide was prepared from the dipeptide acid by way of the mixed anhydride.

Benzoyl-L-phenylalanyl-O-benzylserine (17.6 g., 40 mmoles) in 100 ml. of tetrahydrofuran and 5.61 ml. (40 mmoles) of triethylamine was stirred and cooled to −5° and treated dropwise with 4.3 ml. (45 mmoles) of ethyl chloroformate. Ten minutes after the end of the addition, concentrated aqueous ammonia (11 ml.) was added quickly in one portion. The mixture was stirred for 30 min., diluted with 250 ml. of water, and concentrated under reduced pressure to 75 ml. The solution was then extracted four times with ethyl acetate at pH 7.0 and the combined extracts were evaporated. The residue was recrystallized from benzene to yield 8.8 g., m.p. 157–160°.

Anal. Calcd. for $C_{26}H_{27}N_3O_4$: C, 70.1; H, 6.1; N, 9.4. Found: C, 70.2; H, 6.0; N, 9.3.

N-Benzoyl-L-phenylalanyl-O-acetylserine Nitrile.—Benzoyl-L-phenylalanylserine amide (2.24 g., 6.3 mmoles) was dissolved in 15 ml. of dry pyridine, and the solution was cooled to −5°, stirred, and treated first with 0.5 ml. (7.0 mmoles) of acetyl chloride and then with 0.64 ml. (6.3 mmoles) of phosphorus oxychloride. The reaction mixture was worked up in the way described for acetylphenylalanine nitrile and the product was recrystallized from benzene; 400 mg.; m.p. 169–170°.

Anal. Calcd. for $C_{21}H_{21}N_3O_4$: C, 66.5; H, 5.6; N, 11.1. Found: C, 66.1; H, 5.7; N, 10.8.

N-Benzoyl-L-phenylalanyl-O-benzylserine Nitrile.—Treatment of benzoylphenylalanyl-O-benzylserine amide with pyridine and phosphorus oxychloride in the manner described for acetylphenylalanine amide gave the desired nitrile which was crystallized from benzene. The yield was 2.8 g. from 8.3 g. of amide, m.p. 142–144°.

Anal. Calcd. for $C_{26}H_{25}N_3O_3$: N, 9.8. Found: N, 9.6.

Formation of Benzoylserineamidine in the Attempted Conversion of Benzoylphenylalanylserine Nitrile to the Dipeptide Amidine.—Benzoylphenylalanylserine nitrile (1.87 g.) was converted to the imino ether in chloroform solution (15 ml.) by addition of 0.71 ml. of 8.4 *M* ethanolic hydrogen chloride in the manner described for the corresponding reaction with acetylphenylalanine nitrile. The reaction product was then treated at room temperature for 4 days with ethanolic ammonia. The product of this reaction was then separated countercurrently through 96 transfers in the solvent system composed of chloroform–methanol–water, 2:1:1. Peaks detectable by ultraviolet absorption at 260 mμ were found in the starting tubes (unchanged nitrile), in tube 50, and in the final tubes. The peak in tube 50 probably contained the desired dipeptide amidine hydrochloride, because it yielded serine and phenylalanine when hydrolyzed, but an analytically pure compound was not obtained from it. The material in tubes 81–99 was redistributed through 68 transfers in the solvent system, chloroform–methanol–water, 2:2:1. The peak of ultraviolet absorption was in tube 53. The material recovered from this peak by evaporation of the solvents was a glassy substance (200 mg.) which proved to be benzoylserineamidine hydrochloride. When hydrolyzed and chromatographed on paper, it gave serine as the only amino acid.

Anal. Calcd. for $C_{10}H_{14}ClN_3O_2$: C, 49.3; H, 5.7; N, 17.2. Found: C, 49.8; H, 5.7; N, 17.1.

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Ultraviolet Spectra and Polarographic Reduction Potentials of Some Cinnamic Acids[1]

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The effect of *para* and *ortho* substitutents on the ultraviolet spectra and half-wave reduction potentials of *trans*-cinnamic acid is interpreted in terms of their electronic and, in the case of *ortho*-substitution, steric effects. Only qualitative relations exist between the spectroscopic and polarographic data.

The effect of substituents on the dissociation constants[2a] of *trans*-cinnamic acid and the rates of hydrolysis of its ethyl esters[2b] have been discussed. However, no detailed study has been published concerning the effect of the substituents on the ultraviolet spectra or polarographic reduction potentials of these acids. (Such limited data as are available on the ultraviolet spectra of simple derivatives is indicated in the footnotes to Table I[3]).

A series of *trans*-cinnamic acids was prepared (see Table II) by standard methods and their ultraviolet spectra determined in 95% ethanol. These acids showed two regions of high intensity absorption (Table I), at 215–230 mμ and 270–320 mμ. The first region usually possessed two maxima of about equal intensity and the wave lengths and intensities varied little with

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(1) Contribution number 130 from the Instituto de Química de la Universidad Nacional Autonoma de México.

(2) (a) *Cf.* M. Charton and H. Meislich, *J. Am. Chem. Soc.*, **80**, 5940 (1959); (b) B. Jones and J. G. Watkinson, *J. Chem. Soc.*, 4064 (1958).

(3) *Cf.* A. Mangini and F. Montanari, *Boll. sci. fac. chim. ind., Bologna* **12**, 166 (1954).

TABLE I

ULTRAVIOLET ABSORPTION AND HALF-WAVE REDUCTION POTENTIALS OF *trans*-CINNAMIC ACIDS[a]

	λ_{max}^1	λ_{max}^2	$-E_{1/2}$ v.	$i_d/\text{cm.}^{2/3}t^{1/6}$
Cinnamic acid	216 (17,700)	273 (21,000)[b]	2.05[g]	2.01[g]
	222 (15,600)			
p-Methyl	209 (10,600)	283 (21,400)[c]	2.05	2.00
	222 (14,250)			
o-Methyl	210 (17,300)	277 (17,000)[d]	1.59	0.95
	222 (15,400)		2.07	1.08
p-Methoxy	226 (10,000)	297 (21,700)	2.04	2.10
		306 (22,150)		
m-Methoxy	216 (20,300)	275 (17,500)	2.00	1.86
		314* (5,400)		
o-Methoxy	214 (16,500)	274 (18,500)	1.65	0.88
	224 (16,800)	320 (10,800)	2.06	0.94
p-Hydroxy	223 (14,450)	286 (19,000)	1.55	0.65
			2.05	1.20
m-Hydroxy	215 (13,000)	276 (16,900)	1.60	0.85
	234 (10,750)	314* (4,600)	2.05	1.22
o-Hydroxy	224 (9,100)	273 (12,200)	2.04	0.60
		320 (7,800)	2.15	0.38
p-Nitro	211 (12,100)	282 (18,900)[e]	0.85	0.35
			1.01	0.75
			2.25	0.92
m-Nitro	216 (10,200)	260 (27,600)[e]	0.87	0.35
			1.15	0.87
			2.15	1.03
o-Nitro	211 (20,450)	302 (18,400)[e]	0.85	0.26
			1.00	0.80
			2.15	0.97
p-Chloro	216 (16,700)	275 (22,800)	1.90	2.36
	228* (9,900)			
o-Chloro	210 (18,400)	265 (14,900)[d]	1.89	0.41
		317* (1,700)	1.95	1.90
p-Bromo	220 (11,900)	281 (21,300)[f]	2.01	2.31
o-Bromo	212 (17,500)	273 (15,350)[d]	1.85	1.04
	220 (17,250)		2.07	0.70
p-Iodo	224 (18,600)	287 (28,000)	1.67	1.60

[a] Wave lengths in mμ, molar extinction coefficients in parentheses. Asterisk denotes inflection. Spectroscopic data refer to 95% ethanol solution. $E_{1/2}$ values against the saturated calomel electrode for 0.175 M tetra-*n*-butylammonium iodide in 75% dioxane–water, $i_d/\text{cm.}^{2/3}t^{1/6}$ in microamp./mmole mg.$^{2/3}$ sec.$^{1/2}$. [b] Ref. 18 gives 220 (17,500), 267 (20,200). [c] R. Andrisano and A. Tundo, *Atti Accad. naz. Lincei*, [8] **13,** 158 (1952), give 219 (15,500), 279 (21,500) for water. [d] Ref. 3 gives *o*-methyl, 208 (18,200), 270 (16,600); *o*-chloro, 212 (19,500), 222* (17,000), 265.5 (17,000), 306* (2,400); and *o*-bromo, 212 (20,500), 218* (19,000), 266 (17,000), 300* (3,200), 318* (1800). [e] P. Grammaticakis, *Compt. rend.*, **239,** 883 (1954), gives *p*, 295 (20,000); *m*, 263 (25,000), 305* (1,250); and *o*, 248 (12,500), 290* (40,000) (data taken from curves). [f] R. Andrisano and G. Pappalardo, *Gazz. chim. ital.*, **85,** 391 (1955), give 212 (14,800), 218 (16,000), 272 (24,500). [g] Ref. 5 gives $E_{1/2}$ 2.04 v., $i_d/\text{cm.}^{2/3}\ t^{1/6}$ 1.99 microamp./mmole mg.$^{2/3}$ sec.$^{1/6}$.

substitution. These maxima can be attributed to electronic transitions in the benzene ring iteslf (E-bands) and substitution has little effect on such bands.[4a] However, the second band or group of maxima varied in both wave length and intensity on substitution and must arise from electronic transitions throughout the whole conjugate system (a K-band).[4a]

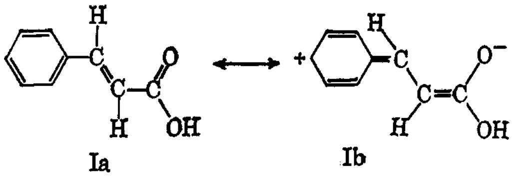
TABLE II

MELTING POINTS OF *trans*-CINNAMIC ACIDS

	M.p., °C.	Lit. m.p., °C.
Cinnamic acid	132	133[a]
o-Methyl	174	174–175[b]
p-Methyl	198	198–199[b]
o-Methoxy	183	185–186[c]
m-Methoxy	120	117[d]
p-Methoxy	170	172[e]
o-Hydroxy	205	207–208[f]
m-Hydroxy	191	191[g]
p-Hydroxy	210	207[e]
o-Nitro	240	240[h]
m-Nitro	200–201	198[e]
p-Nitro	284–285	290–291[i]
o-Chloro	213	212[j]
p-Chloro	245	240–242[j]
o-Bromo	215–216	212–212.5[k]
p-Bromo	257–260	246–248[k]
p-Iodo	254	255[l]

[a] W. M. Radionow, *J. Am. Chem. Soc.*, **51,** 847 (1929). [b] R. Stoermer, F. Grimm, and E. Laage *Ber.*, **50,** 980 (1917). [c] R. Stoermer and C. Friemel. *ibid.*, **44,** 1843 (1911). [d] H. Bauer and P. Vogel, *J. prakt. Chem.*, **88,** 329 (1863). [e] P. N. Kurien, K. C. Pandya, and V. R. Surange, *J. Indian Chem. Soc.*, **11,** 823 (1934). [f] R. Fittig and A. Ebert, *Ann.*, **226,** 351 (1884). [g] W. Borsche and F. Streitberger, *Ber.* **37,** 4128 (1907). [h] R. Stoermer, *ibid.*, **45,** 3100 (1912). [i] G. Carrara, R. Ettorre, F. Fava, G. Rolland, E. Testa, and A. Vecchi, *J. Am. Chem. Soc.*, **76,** 4391 (1954). [j] K. C. Pandya and R. B. Pandya, *Proc. Indian Acad. Sci.*, **14A,** 112 (1941). [k] M. M. Katon, E. P. Matkuina, and F. S. Florinsky, *Zh. Obschch. Khim.*, **21,** 1843 (1951). [l] R. L. Datta and N. R. Chatterjee, *J. Am. Chem. Soc.*, **41,** 295 (1919).

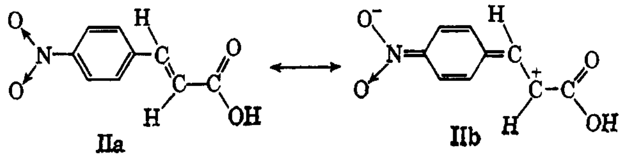
The order of bathochromic displacements for *para* substitution was: Cl (+ 2) < Br (+8) ~ NO_2 (+ 9) ~ Me (+10) < OH (+13) ~ I (+14)< MeO (+24). The changes in intensity were generally small, the *para* iodo compound alone showing a small decrease and the *p*-methoxy derivative giving a double maximum. The effect of a *para* substituent can only be electronic, and a substituent with a positive resonance effect, which by slightly lowering the energy level of the ground state and further lowering the energy level of the excited state, will reduce the energy of the transition to the excited state (Ia to Ib), resulting in an increase in the wave length of maximal absorption. Hydroxy and methoxy group (+R effects, although −I effects) produced the expected large shifts. The order of displacements of the halogen atoms (Cl < Br < I) is



Ia Ib

that of the increasing resonance effect of these atoms.[4a,b] The origin of the wave-length displacement for a *p*-nitro (−R and −I effects) is probably different in that the transition involved is IIa to IIb.

The resonance effect cannot operate throughout the whole molecule for a *meta* substituent and the displace-



IIa IIb

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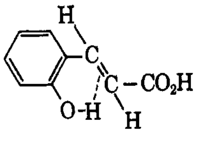
(4)(a) O. H. Wheeler and P. H. Gore, *J. Org. Chem.*, **26,** 3298 (1961); (b) P. H. Gore and O. H. Wheeler, *ibid.*, **26,** 3295 (1961). A referee has pointed out that cinnamic acid is largely dissociated in water [K_a = 4.4 × 10^{-5}, H. C. Brown, D. H. McDaniel, and O. Hafliger, "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press, Inc., New York, N. Y., 1955, Chap. 14] and a 2 × 10^{-5} M solution (for optical density 0.4) is 72% as its anion in pure water. However, the K_a in 95% ethanol will be much smaller [K_a in 40% acetone–water is 2.6 × 10^{-6}; R. D. Kleene, F. H. Westheimer, and G. W. Wheland, *J. Am. Chem. Soc.*, **63,** 791 (1941)] and a value of 10^{-7} would correspond to 8% anion in 2 × 10^{-5} M solution. Traces of base would result in anion formation, and may account for the numerous maxima previously observed[3] for *o*-chloro- and *o*-bromocinnamic acid (see footnote, Table I). In the present work the spectra of cinnamic acid in 95% ethanol containing a drop of 2 N hydrochloric acid was the same as in 95% ethanol, and it was assumed that all the substituted cinnamic acids were in the form of their undissociated acids.

ments observed were accordingly very small (MeO +2, OH +3, and NO_2 −13 mμ, with decrease in intensity in the last two cases and splitting of maximum in the first). Hypsochromic shift in the *m*-nitro compound may result from an increase in the energy level of the excited state of the benzene ring thereby increasing the energy of transition, although a transition between the nitro group and the aromatic ring may also be involved. Similar electronic effects for *meta* and *para* substitution have been observed in other conjugate aromatic systems.[4]

Substituents in an *ortho* position can exert both an electronic and steric effect. The wave-length displacements were much smaller than for the *para* isomers (OH and Br 0, MeO +1, Me + 4, and Cl −8) and the intensities much less due to the opposing steric effect of the bulky *ortho* substituents. The hydroxy, methoxy, and nitro compounds showed a second maximum at much higher wave length. In the case of the hydroxy compound, this is most probably due to hydrogen bonding,[4] which could take place between the hydroxy group and the π-electrons of the side-chain double bond (III).



III

The hydrocinnamic acids (Table III) showed the same E-band (at 220 mμ), but only low absorption at *ca.* 280 mμ.

Table III

Physical Constants of Hydrocinnamic Acids

	λ_{max}[a]	λ_{max}[a]	M.p., °C.	Lit. m.p., °C.
o-Methoxy	224 (11,050)	277 (3,100) 284* (2,750)	82	81[b]
m-Methoxy	218 (7,500)	273 (2,100) 279 (1,900)	50–52	56[c]
p-Methoxy	218 (7,250)	272 (2,000) 278 (1,900)	103	104–105[d]

[a] Wave lengths in mμ, molar extinction coefficients in parentheses. Asterisk denotes inflection. [b] R. Pschorr and H. Einbech, *Ber.*, **38,** 2074 (1905). [c] K. H. Slotta and H. Heller, *ibid.*, **63,** 3029 (1930). [d] G. Barger and G. S. Walpole, *J. Chem. Soc.*, **95,** 1723 (1909).

The polarographic half-wave reduction potentials of the cinnamic acids were measured (see Table I) in 75% dioxane–water using 0.175 *M* tetra-*n*-butylammonium iodide as supporting electrolyte and 0.05 *M* tetra-*n*-butylammonium hydroxide to eliminate the carboxylic acid hydrogen wave.[5] It has been shown[6] that the reduction involves two electrons, giving β-phenylpropionic acid. All the cinnamic acids gave a reduction wave of $E_{1/2}$ about 2.0 v. and this must arise from reduction of the side-chain double bond. However, many of the substituted cinnamic acids, particularly those with nitro and iodo groups, showed other reduction waves at lower potentials, and these must arise from reduction of these substituents. *Para* Methyl, methoxy, and hydroxy substituents produced no change in the $E_{1/2}$ values, with little difference in the diffusion current constants (i_d/cm.$^{2/3}$ $t^{1/6}$) in the first two cases.

A *para* chloro substituent caused reduction at a less negative potential (−0.15 v.). The reduction potentials are a measure of the energy barrier to addition of electronic charge to the double bond,[7] and the −I effect of chlorine, by decreasing the electronic charge on the double bond (Ib), will facilitate reduction. A further decrease in reduction potential might be expected for the *p*-bromo compound, but the bromo group will be reduced at about −2.0 v. and the single reduction wave must involve this process, together with that of the side-chain double bond. The first wave of the *p*-iodo acid corresponds to reduction of the iodo group[7] and the second to that of the cinnamic acid formed by this reduction. Aromatic nitro compounds often reduce in alkaline medium in two stages affording the hydroxylamine and aniline.[8] The nitrocinnamic acids all showed three reduction waves, corresponding to the reduction of the nitro group and the subsequent reduction of the hydroxylamino or amino acids so formed. The increase in potential of the last wave of *p*-nitro cinnamic acid as compared with cinnamic acid itself (+0.20 v.) is consistent with the +I effect of an amino group, transmitted to the side-chain double bond and this effect is less in the case of the *meta* and *ortho* compounds.

o-Methyl-, methoxy-, chloro-, and bromocinnamic acids all gave two reduction waves, in contrast to their *para* isomers, and the $E_{1/2}$ value of the second wave was always more negative. The diffusion current constants were, moreover, much smaller, suggesting that reduction occurs by a different process. The origin of these effects must be in steric inhibition of resonance with the side chain by the bulky *ortho* substituents reducing the effectiveness of the resonance effect and making reduction more difficult.[8] The $E_{1/2}$ of the third wave of *o*-nitrocinnamic acid was similarly less negative (NH_2 has −I effect), although the $E_{1/2}$ values of the first two waves, attributed to reduction of the nitro group itself, remained unchanged. The *o*-hydroxy acid was apparently anomolous (two waves, the second at a very negative potential), but such effects have been noted in hydrogen-bonded compounds.[9]

No quantitative relation existed between the wave lengths or frequencies of the maxima of the conjugate absorption band and the half-wave reduction potentials, although certain parallelisms have been noted in simpler carbonyl compounds.[10] No relation is to be expected since the processes taking place are quite different. The wave length of maximal absorption depends on the energy difference between the ground and excited states and polar effects by increasing the energy levels of the ground and excited states to different extents cause displacements to longer wave length. However, the polarographic reduction potentials depend on the electron density at the reduced site, and substituents only produce differences (which may be in

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(5) S. Wawzonek, S. C. Wang, and P. Lyons, *J. Org. Chem.*, **15**, 543 (1950).

(6) G. Semerano and A. Chisini, *Gazz. chim. ital.*, **66**, 510 (1936).

(7) E. Gergely and T. Iredale, *J. Chem. Soc.*, 3226 (1953).

(8) (a) M. Fields, C. Valle, and M. Kane, *J. Am. Chem. Soc.*, **71**, 421 (1949); (b) S. F. Dennis, A. S. Powell, and M. J. Astle, *ibid.*, **71**, 1484 (1949); (c) C. Prevost, P. Souchay, and C. Malen, *Bull. soc. chim. France*, 78 (1953).

(9) L. Holleck, H. Marsen, and H. J. Exner, *Z. Naturforsch.*, **9b**, 90 (1954).

(10) (a) A. Winkel and G. Proske, *Ber.*, **69**, 1917 (1936); (b) N. J. Leonard, H. A. Laitinen, and E. H. Mattus, *J. Am. Chem. Soc.*, **75**, 3300 (1953).

either direction) when their effects are transmitted to the reducible group.

Experimental

Cinnamic Acids.—*trans*-Cinnamic acid was an Eastman Kodak White Label sample. *p*-Nitrocinnamic acid was prepared by nitration of cinnamic acid and purified *via* its ethyl ester.[11] *p*-Iodocinnamic acid was prepared by iodination of cinnamic acid with iodine in acetic acid in the presence of nitric acid[12] and purified by chromatography on magnesol and elution with acetone.

o- and *p*-methyl-, chloro-, and bromo-, *m*-nitro-, and *p*-hydroxy- and *p*-methoxy-, as well as *p*-iodocinnamic acids were prepared by reaction of the appropriate benzaldehyde with malonic acid in 95% ethanol in the presence of piperidine.[13]

o- and *m*-hydroxy- and methoxy- and *o*-nitrocinnamic acids were prepared *similarly in pyridine solution with piperidine*.[14]

o- and *m*-methoxybenzaldehydes were prepared by methylation of the hydroxybenzaldehyde with methyl sulfate and sodium hydroxide.[15] *o*- and *p*-chloro- and bromobenzaldehydes were prepared by Etard oxidation of the corresponding toluenes,[16] and *o*-nitrobenzaldehyde was prepared by oxidation of *o*-nitrotoluene in acetic acid and anhydride followed by hydrolysis of the so-formed diacetate.[17]

The hydrocinnamic acids were prepared by hydrogenation of the cinnamic acids in acetic acid using a platinum oxide catalyst.

The corrected melting points were determined on a Köfler block and are recorded in Tables II and III.

Absorption Spectra.—The absorption spectra were determined in purified 95% ethanol using a Beckman DK2 spectrometer and 1-cm. cells at concentrations such that the optical density was 0.8–0.2 (see Table I).

Polarographic Reductions.—The polarographic determinations were made in 0.175 *M* tetra-*n*-butylammonium iodide–0.05 *M* tetra-*n*-butylammonium hydroxide in 75% dioxane–water (D^{25}_{25} 1.037, dioxane purified by refluxing with sodium) using standard conditions[5] and employing a Sargent Model XI polarograph. The half-wave reduction potentials were measured against a saturated calomel electrode (Table I). The capillary had a drop time of 3.6 sec. and mercury flow of 1.51 mg./sec.

Acknowledgment.—This study was supported in part by grants from the Rockefeller Foundation, New York, New York.

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[12] R. L. Datta and N. R. Chatterjee, *J. Am. Chem. Soc.*, **41**, 295 (1919).

[13] A. I. Vogel, "Practical Organic Chemistry," Longmans Green and Co., New York, N. Y., 1948, p. 682.

[14] J. Koo, M. S. Fish, G. N. Walker, and J. Blake, *Org. Syn.*, **31**, 35 (1951).

[15] *Cf.* D. A. Shirley, "Preparation of Organic Intermediates," John Wiley and Sons, Inc., New York, N. Y., 1951, p. 37.

[16] O. H. Wheeler, *Can. J. Chem.*, **36**, 667 (1958).

[17] Ref. 13, p. 666.

Action of Trifluoroacetic Anhydride on N-Substituted Amic Acids[1,2]

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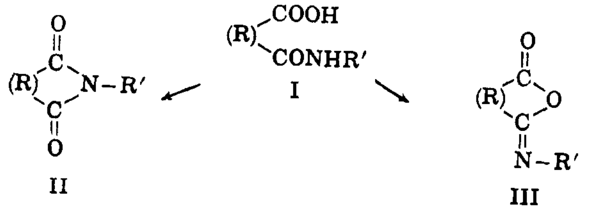
The action of trifluoroacetic anhydride on various N-aryl amic acids was investigated to determine whether dehydration by this reagent always forms isoimides. N-Substituted maleamic and phthalamic acids were dehydrated to isoimides, and the method appears to be general for the synthesis of N-aryl maleisoimides and phthalisoimides. Several products were obtained from saturated amic acids depending on the number of carbon atoms separating the amide and carboxyl groups, but in no instance was a saturated isoimide formed. Although the α- and β-N-methylcamphoramic acids were not dehydrated by trifluoroacetic anhydride, the reported dehydrations by acetyl chloride and phosphorus oxychloride to isoimides, the only report of saturated isoimides, have been confirmed. Maleisoimdes have been found to react with piperidine by ring opening to form diamides rather than by addition to the carbon–carbon double bond, and this reaction has been used to confirm the structure of N-1-naphthylmaleisoimide. The intensities of the two characteristic infrared bands of cyclic isoimides have been shown to be useful in distinguishing isoimides from imides.

The dehydration of N-substituted amic acids (I) is known to produce imides (II) or isoimides (III), depending on the conditions employed for the dehydration and on the nature of the amic acid. The literature on imides is quite extensive, and a variety of reagents has been used in the synthesis of imides. The reagents most commonly employed to effect dehydration of amic acids to imides are phosphorus pentoxide,[3,4] acetic anhydride plus fused sodium acetate,[5] acetyl chloride,[6,7] and thionyl chloride.[3,8,9] Simple heating of the amic acid or direct fusion of a mixture of the anhydride and amine without isolation of the intermediate amic acid are also very common methods. Various other dehydrating agents have been employed less extensively: in the preparation of phthaloylamino acids, for example, numerous techniques have been developed for dehydration under relatively mild conditions to avoid decomposition or racemization of the amino acid.[9–11]



The reagents reported to dehydrate amic acids to isoimides are fewer in number and, judging from the literature, several would appear not to be general in their action. These reagents, in chronological order of

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