Table III
Melting Characteristics of the
2-Aminoacetanilide Hydrochlorides ^a

Registry no,	Substituent	Melting range, °C
4801-39-2	Н	190 2 50 dec
54643-64-0	4'-CH3	200–260 dec
54643-65-1	4'-NO2	273–274 (darkens 250)
54643-66-2	3'-NO ₂	246–248 (darkens 240)
54643-67-3	4'-C1	235-290 dec
54643-68-4	3'-Cl	210–2 80 dec
54643-69-5	3'-OCH ₃	210–225 dec
54643-70-8	4'-CF ₃	235-245 dec

^a Satisfactory analytical data for C, H, Cl (±0.35%) were reported for the compounds in this table. Ed.

tuted benzyl chloride, followed by hydrazinolysis. Two recrystallizations of the crude products from ethanol yielded the benzylamine hydrochlorides melting with some decomposition: 4-methyl-benzylamine, mp 240-243° (lit. mp 235°);^{19a} benzylamine, mp 263-264° (lit. mp 260°);^{19b} 4-chlorobenzylamine, mp 263-265° (lit. mp 259°);^{19c} 3-chlorobenzylamine, mp 225-227° (lit. mp 225°);^{19c} 4-nitrobenzylamine, mp 269-270° with decomposition from 260° (lit. mp 256° dec).^{19c}

Potentiometric Determination of pK Values. Solutions (0.02 M) of each of the 2-aminoacetanilide hydrochlorides and benzylamine hydrochlorides in water were prepared. Three 25.0-ml aliquots of each were titrated at $23.0 \pm 1^{\circ}$ with 0.08 M NaOH and the pH of the solutions was measured at intervals using glass and saturated calomel electrodes.^{16,20,21} Values of pK were computed from the equation $pK = pH + \log [BH^+]/[B]$. The ionic strength was constant (0.02) throughout each titration. The pK's determined are the so-called "mixed" constants.¹⁰ Scatter within individual runs ranged from 0.02 to 0.09 pK units, depending upon the purity of the compound. Agreement between average pK values among the three titrations for each compound ranged from 0.00 to 0.02.

Values of ρ were determined from pK values and the respective σ constants⁴ using an Olivetti Underwood Programma 101 leastsquares program.²²

Registry No.-Thionyl chloride, 7719-09-7; N-phthaloylglycine, 4702-13-0; phthaloylgylcyl chloride, 6780-38-7; phthaloylglycine anilide, 2017-94-9.

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The Capability and Nature of the Amide Bond as a Transmitter of Electronic Effects¹

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The planarity and restricted rotation which has been observed about amide bonds has been attributed to the importance of a dipolar resonance contributor such as II, and, in fact, based on contribution from such a form, Pauling²



has estimated that this carbon-nitrogen bond should have ca. 40% double-bond character. As a result, it has been assumed for some time that the amide bond can function as a transmitter of conjugative effects. Recently, however, a number of conflicting reports have appeared³⁻⁸ concerning the amide bond's capability as a transmitter of electronic effects, and in particular questions have arisen relative to the manner and magnitude of this transmission⁵⁻⁸ and of its dependence on the location of a substituent relative to the amide nitrogen.^{7,8} In an effort to clarify some of these questions and to investigate the validity of using either a nonreaction property (in the form of NMR chemical shifts) or a reaction property (in the form of pK_a data) as a probe of substituent effects, we report here studies on the transmission of electronic effects through two closely related amide bond containing systems. These studies involve comparisons of pK_a data for a simple monosubstituted biphenylamine system (III) with those for a related, perturbed biphenylamine system (IV) and NMR chemical shift data for 4-substituted biphenyls (V) and 4'-substituted 4-biphenylacetanilides (VI). Since the 1,1' bond in bi-



phenyl can conjugatively transmit electronic effects, although at a much diminished intensity relative to a single benzene ring,⁹⁻¹² we felt that comparisons of reaction and nonreaction properties of biphenyl and perturbed biphenyl systems would provide a rather severe test of the amide bond's conjugative ability.

Table I pK_a 's for 4'-Substituted 4-Aminobenzanilides (IV)^a

Registry	/ no,	4' substituent	pK _a	
891-	35-0	OCH ₃	2.99	
955-	96-4	CH ₃	2.96	
782-4	45-6	Н	2.94	
955 -	97 - 5	C1	2.75	
31366-3	39-9	NO ₂	2.34	

 a The pK_a values, determined spectrophotometrically in 1.6% acetonitrile-water at 23°, represent the average of at least five determinations.

 Table II

 Substituent Chemical Shift (SCS in Hertz) for Amide

 Group Methyl Protons in 4'-Substituted

 4-Biphenylacetanilides (VI)^a

 Registry no.	4' substituent	SCS	
 4075-79-0	H	124.5	
54643-71-9	Br	124.2	
398-32-3	F	124.3	
28533-02-0	NO ₂	125.8	
2221-22-9	CH ₃ O	123.7	
54643-72-0	CO ₂ CH ₃	125.0	
3366-61-8	$\rm NH_2$	123.6	

^a The SCS values, determined vs. TMS at 37° in 10% DMSO- d_6 , represent the average of at least three determinations.

Results and Discussion

The pK_a 's for IV are reported in Table I and the substituent chemical shifts (SCS) for the amide group methyl protons of VI are given in Table II. Corresponding pK_a data for III and carbon-13 SCS's (of the 4' carbon) for V have been reported previously.^{11,12}

In order to obtain a quantitative assessment of the electronic effect transmission in III and IV, the pK_a data were subjected to correlation analysis¹³⁻¹⁵ via the Hammett equation to give eq 1 for III and eq 2 for IV. Included for comparison is the correlation equation (eq 3) for a series of 4-substituted anilines.¹⁸ Of particular interest in compar-

$$pK_{a} = 4.21 - 0.67\sigma_{p}, r = 0.930, s = 0.12$$
(1)
$$pK_{a} = 2.87 - 0.64\sigma_{p}, r = 0.984, s = 0.06$$
(2)

$$pK_a = 4.70 - 2.89\sigma_p, r = 0.994, s = 0.13$$
(3)

ing these equations is to consider the magnitude of the ρ values, since this offers a measure of the susceptibility of the reaction center to changes in electron density as caused by the various substituents and thus provides an indication of the electronic effect transmission in one system relative to another. The ρ values of -0.67 for III and -0.64 for IV compared to that of -2.89 for the 4-substituted anilines indicates, as expected, that the electronic effect transmission in III and IV is much diminished relative to that for the anilines. Of greater significance, however, is the fact that the ρ values for III and IV are essentially identical, which indicates that the electronic effect transmission in III and IV is essentially identical and that the amide bond must, therefore, be functioning as an effective transmitter of electronic effects. The nature of this transmission is perhaps better revealed via a dual substituent parameter equation analysis.¹⁹ This approach for the aniline-related series III and IV yields eq 4 for III and eq 5 for IV.²⁰ The relatively small

$$pK_a = 4.30 - 0.63\sigma_{\rm I} - 0.60\sigma_{\rm R}, R = 0.995, s = 0.04 \quad (4)$$

$$pK_a = 2.92 - 0.56\sigma_{\rm I} - 0.46\sigma_{\rm R}, R = 0.995, s = 0.04 \quad (5)$$

differences in the ρ_{I} and ρ_{R} -values for III and IV are an indication of the similarity in electronic effect transmission

in these two series. In particular, the relative magnitude of the $\rho_{\rm R}$ -values provides evidence that the amide bond is capable of functioning as a transmitter of conjugative effects and that it is about 80% as effective as the 1,1' bond in biphenyl. In effect, the amide bond as substituted in IV does not substantially impede the normal conjugative transmitting ability of the 1,1' bond in biphenyl. In addition, this effect is not altered by introduction of the amide bond at a position following the 1,1' bond in biphenyl or by the use of a nonreaction property as a monitor of electronic effect transmission. For example, correlation analysis of NMR data yields eq 6 for the carbon-13 SCS's of the 4' carbon in V and eq 7 for the amide group methyl protons in VI.

$$SCS = 0.98 - 1.50\sigma_p, r = 0.675, s = 0.83$$
 (6)

$$SCS = 124.4 + 1.53 \sigma_{\rm p}, r = 0.926, s = 0.32 \tag{7}$$

While eq 6 for V is not statistically significant,²¹ it is important to note the essential identity in absolute magnitude for the ρ values in eq 6 and 7. This suggests that the electronic effect transmitted to the 4' carbon in V or VI is relayed rather efficiently to the methyl group in VI via the amide bond. In addition, a dual substituent parameter equation analysis (eq 8 for V and eq 9 for VI) indicates that

$$SCS = 1.27 - 1.92\sigma_{\rm I} - 1.96\sigma_{\rm R}, R = 0.963, s = 0.34 \quad (8)$$

$$SCS = 124.1 + 1.00\sigma_{\rm I} + 1.64\sigma_{\rm R}, R = 0.971 s = 0.23 \quad (9)$$

this transmission is due in part to a conjugative effect. That is, the $\rho_{\rm R}$ -(VI)/ $\rho_{\rm R}$ -(V) ratio is essentially identical with the corresponding ratio for III and IV and indicates a conjugative transmission in VI via the amide bond equal to about 80% of that in V. However, the amide bond's ability to function as a transmitter of electronic effects does depend on the location of substituents relative to the amide nitrogen. This point is rather clear when one considers the pK_a data reported by Menger and coworkers⁵ for 4-substituted 4'-aminobenzanilides (VII), a series isomeric with IV.



These data indicate that the various substituents in VII have virtually no effect on the pK_a of the amino group. For example, the pK_a of the nitro-substituted compound in VII, which for aromatic amines is normally a much weaker base than the parent amine, differs by only 0.07 pK units from that of the unsubstituted compound, while the corresponding difference in IV is 0.60 pK units. In addition, the range in pK for VII is only 0.14 compared to 0.65 for IV. As expected, correlation analysis of the pK_a data for VII does not yield a significant relation (eq 10) and indicates a ρ value approaching zero.

$$pK_a = 4.55 - 0.09\sigma_p, r = 0.772, s = 0.04$$
(10)

The results of this study and the comparisons with previous studies indicate that the amide bond is capable of functioning as a transmitter of substituent conjugative effects but can do so effectively only on a one-way basis by way of substitution on the amide nitrogen.

Experimental Section

The 4'-substituted 4-aminobenzanilides were prepared as previously described in the literature.^{22,23} The 4'-substituted 4-biphenylacetanilides were prepared by glacial acetic acid-acetic anhydride acetylation of the corresponding 4'-substituted 4-aminobiphenyls.¹²

The pK_a 's reported in Table I for the 4'-substituted 4-aminobenzanilides represent the average of at least five determinations Notes

and were determined as described previously¹² with the following exceptions. Spectral solutions were $3 \times 10^{-5} M$ and buffered solutions were prepared using citric acid-Na₂HPO₄. The maximum deviation from the mean of replicate pK, values did not exceed 2.5% for any of the compounds studied.

The substituent chemical shifts (SCS) in hertz for the amide group methyl protons of 4'-substituted 4-biphenylacetanilides were measured on a Varian T-60 spectrometer vs. TMS at 37° in a 10% DMSO- d_6 solution. These values are reported in Table II and represent the average of at least three determinations. The maximum deviation from the mean of replicate SCS values did not exceed 0.5% for any of the compounds studied.

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An Investigation of the Scope and Limitations of the Cornforth Rearrangement

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The thermal rearrangement of 4-carbonyl substituted oxazoles was first observed by Cornforth.¹ We have investigated the mechanism of this reaction by experimental^{2a,b} and theoretical techniques.³ The results of these studies suggest the intermediacy of the nitrile ylide 3 in the reaction of $1 \rightarrow 2$.





Cornforth found that 2-phenyl-5-ethoxyoxazole-4-carboxamide $(1, X = OEt; Y = NH_2)$ rearranged on heating to ethyl 2-phenyl-5-aminooxazole-4-carboxylate (2, X = OEt; $Y = NH_2$).¹ We have now carried out similar rearrangements of several secondary and tertiary alkyl and aryl oxazole-4-carboxamides to the corresponding secondary and tertiary 5-aminooxazoles.^{2b} We have also found that this rearrangement occurs in yields of >90% when the amide nitrogen is part of a heterocyclic ring system $(1a-e \rightarrow 2a-e)$.

Trideuteriomethyl 2-phenyl-5-methoxyoxazole-4-carboxylate (1, X = OMe; $Y = OCD_3$) rearranged on heating to give a 1:1 equilibrium mixture of 1 and the corresponding rearranged ester 2 (X = OMe; Y = OCD_3).^{2b} The thiol ester 1f underwent thermal isomerization to the corresponding 5-thiooxazole 2f in good vield under similar conditions. Prior to this investigation there was, to our knowledge, only one other method for preparing 5-thiooxazole-4-carboxylates, i.e., the reaction of 4-benzamido-1,2-dithiol-3-thione with KOH and methyl iodide to give 2-phenyl-5-methylthiooxazole-4-carbodithioate.⁴ Thus the Cornforth rearrangement of 5-alkoxyoxazole-4-thiocarboxylates is a potentially general method for the synthesis of 5thiooxazole-4-carboxylic esters.

While 1 (X = OEt; Y = Cl) rearranges to 2 (X = OEt; Y = Cl),¹ the corresponding fluoro derivative 1g failed to rearrange.

These reactions all involve compounds where a heteroatom is attached to the 5 position. One rearrangement has been reported⁵ where the group X in 1 is alkyl or aryl, i.e., the interconversion of 2,5-diphenyl-4-acetyloxazole and 2phenyl-4-benzoyl-5-methyloxazole; the reactions were, however, very slow even at 220°.

When the 4-carbonyl group of 1 was replaced by an α,β unsaturated ester functionality, the resulting compound (4) failed to rearrange to the corresponding pyrrole derivative 5, even after boiling under reflux for 17 hr in toluene.