CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA

BRANCHED-CHAIN FATTY ACIDS. XXVII. FURTHER STUDY OF THE DEPENDENCE OF RATE OF AMIDE HYDROLYSIS ON SUBSTITUTION NEAR THE AMIDE GROUP. RELATIVE RATES OF HYDROLYSIS OF NITRILE TO AMIDE AND AMIDE TO ACID[1]

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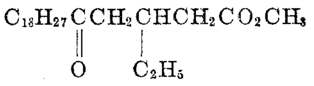
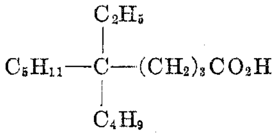
In a previous publication (1) in this series, it has been shown that a branching methyl group in the 2- or 3-position of an amide may be located by its effect in reducing the rate of amide hydrolysis. The method was later found definitive for establishing the presence of a 2-methyl in C_{27}-phthienoic acid, isolated from tubercle bacillus (2). Since a 3-methyl amide was found to be hydrolyzed somewhat more slowly than a 2-methyl amide, and a 4-methyl amide at about the same rate as a normal amide, it was concluded that the retarding effect of the substituent should be ascribed primarily to steric hindrance rather than an inductive effect. It now develops that this explanation is equally successful in equating the results obtained in the present investigation of the effects of multiple substitution and substitution of a larger group.

Most of the acids used for this investigation had been synthesized in connection with work previously reported; however, three additional acids were required. 2-Ethyloctadecanoic acid was prepared by a malonic ester synthesis involving alkylation of diethyl ethylmalonate with *n*-hexadecyl bromide. 3-Ethyloctadecanoic acid was prepared by reduction of methyl 5-keto-3-ethyloctadecanoate (I). Keto ester I was prepared by the method frequently utilized in earlier syntheses, the reaction of a dialkylcadmium reagent with the ester acid chloride of the appropriate dibasic acid. The required β-ethylglutaric acid was obtained by the condensation of propionaldehyde with cyanoacetamide. The other acid required, 5-*n*-butyl-5-ethyldecanoic acid (II), was obtained by extending the chain of the previously prepared 4-*n*-butyl-4-ethylnonanoic acid (3).


$C_{13}H_{27}\underset{\underset{O}{\|}}{C}CH_2\underset{\underset{C_2H_5}{|}}{CH}CH_2CO_2CH_3$

I


$C_5H_{11}-\underset{\underset{C_4H_9}{|}}{\overset{\overset{C_2H_5}{|}}{C}}-(CH_2)_3CO_2H$

II

The apparent second order rate constants obtained in this work, assembled in Table I, are most readily compared by consideration of the last column in the table. In consistency with the observations on the monomethyl amides, it may be noted that the 3,3-dimethyl amide is hydrolyzed more slowly than is the 2,2-dimethyl amide, and the difference in rates for the dimethyl amides is greater

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than is that for the monomethyl amides. Since it was previously found (1) that the 4-methyl substituent exerts no hindrance to the hydrolysis, it would be expected that a 3-ethyl substituent would exert about the same hindrance as does the 3-methyl, but that a 2-ethyl substituent would exert a much greater hindrance than does a 2-methyl. The data are entirely consistent with this view, and it is of further interest that the rate for the 2-ethyl amide is the same as that for the 2,3-dimethyl amide, slower than that for the 2,2-dimethyl amide.

TABLE I

APPARENT RATE CONSTANTS[a] FOR THE SAPONIFICATION OF AMIDES

-AMIDE	MOLARITY[a] OF AMIDE $\times 10^2$	$K \times 10^3$	RATIO[b] FOR AVERAGE VALUES OF K
n-Hendecan-	5.47	204	345
	5.50	240	
2-Methyloctadecan-[c]	1.73	64.1	
	3.35	62.9	
	3.37	63.4	
	3.44	64.3	100
3-Methyloctadecan-	3.05	46.4	
	3.10	45.6	72
2-Ethyloctadecan-	3.84	8.04	
	3.30	8.13	13
3-Ethyloctadecan-	2.72	42.4	
	2.71	42.1	66
2,2-Dimethyloctadecan-	3.10	17.2	
	3.22	17.8	27
3,3-Dimethyloctadecan-	3.12	7.91	
	2.66	8.42	13
2,3-Dimethyloctadecan-[d]	1.37	7.6	12
2,3,4-Trimethylhexadecan-[d]	3.40	4.0	6
4-*n*-Butyl-4-ethylnonan-	1.61	270	
	1.63	230	390
5-*n*-Butyl-5-ethyldecan-	1.98	247	
	2.12	216	360

[a] Second order rate constants, K, are expressed in liters moles^{-1} hours^{-1}. Molarity of *n*-propanolic potassium hydroxide was in the range 0.46–0.48; exact normality was checked for each group of runs. [b] Since conditions for these hydrolyses were established to yield optimum results for somewhat hindered amides, the higher rates of the *n*-amides lead to less accurate values; hence the 2-methyl amide has been used as the basis for comparison, and its value is set at 100. [c] Since the amount of water in the *n*-propanol has not been precisely controlled, 2-methyloctadecanamide has been used as a standard for comparison of rates in different investigations, and it was run at intervals during the present investigation as a check on the consistency of the results. [d] These values are taken from Ref. 2. They are satisfactorily comparable with values determined in the present investigation, for the value for 2-methyloctadecanamide in Ref. 2 is 59×10^{-3} (avg. of 5 runs).

Although the 4-methyl substituent does not hinder the hydrolysis, it might be expected that larger groups in the 4-position would exert hindrance; however, the data on 4-*n*-butyl-4-ethylnonanamide show that no hindrance is exerted by two larger groups in this position. Since the absence of hydrogen atoms in the

4-position would preclude any tendency towards quasi ring formation (4), which would bring the functional group near the site of hindrance, a 5,5-disubstituted amide was also examined, but this was similarly unhindered. This sharp discontinuity in hindering effects between the 3- and 4-positions is especially striking when compared with the fact that a substituent in the 4-position does exert significant hindrance when there are also present in the molecule substituents at the 2- and 3-positions (*Cf.* 2,3-dimethyloctadecanamide and 2,3,4-trimethylhexadecanamide). This difference may well result from the influence of the additional substituents in increasing the tendency of the molecules to have the conformation of a quasi ring. It has been found possible to rationalize many features of the ultraviolet absorption spectra of branched-chain acids by this hypothesis (4), and various other properties have been similarly correlated (5). This enhanced hindrance in 4-substituted compounds was first noted by Cason, Freeman, and Sumrell (2), and later observed by Loening, Garrett, and Newman (6) in connection with their studies of acid-catalyzed esterification. It is of interest that the hindering effects observed by these latter authors in acid-catalyzed esterification are rather uniformly consistent with our observations on alkaline hydrolysis of amides.

It has been observed on several occasions (7) that the alkaline hydrolysis of a highly hindered nitrile to the amide proceeds at a very much higher rate than does hydrolysis of the amide to the acid. In one instance (7a), after the nitrile had been heated under reflux with 10% alcoholic potassium hydroxide for 100 hours, 32% of amide was recovered. In a still more hindered compound (7b), none of the corresponding acid was isolated after the nitrile had been heated under reflux with 10% alcoholic potassium hydroxide for 250 hours; only amide was recovered. In view of these results, it was initially presumed by us that if an unhindered (or slightly hindered) nitrile were saponified, and data were taken after lapse of a few hours, the same rate constant would be obtained as when the amide was the starting material. Trial of this procedure, under conditions giving accurate data for the unhindered octadecanenitrile, revealed that about 10 hours elapsed before the analytical data could be plotted on a straight line. Furthermore, the rate constant calculated from the data obtained subsequent to the first 10 hours was of about one half the magnitude of the constant obtained when the amide was used. Calculation (*cf.* experimental) of the relative magnitude of the constants for the first and second steps of the hydrolysis showed that they are approximately equal.

From the above observations, it follows that, as hindrance near the functional group increases, the rate of hydrolysis of nitrile to amide is slowed down to a far smaller extent than is the hydrolysis of amide to acid. Data are now available only for compounds located at the extreme ends of the scale, and a study of compounds exhibiting intermediate degrees of hindrance should be of interest. At present, it seems most reasonable to ascribe this differential effect of hindrance[2] to the difference in number of groups associated with carbon in the

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[2] This interpretation differs somewhat from that previously used [cf. Newman and Connor, *J. Am. Chem. Soc.*, **72**, 4002 (1950); Kadesch, *J. Am. Chem. Soc.*, **66**, 1207 (1944)] to

transition state. As the hydroxyl ion attacks the nitrile grouping only three atoms are attached to the reactive carbon; so a single large group, especially a flat one, should be able to assume a position not interfering with the two small groups. In contrast, attack of hydroxyl on the carbonyl carbon in an amide leads to the tetrahedral configuration and the necessity for closer proximity of the four groups. The increased reactivity of such acid derivatives as acid chlorides, esters, and amides, as related to alkyl chlorides, ethers, and amines, has commonly been ascribed to the polarity of the carbonyl group in acid derivatives. An additional important factor may well be a steric one, for the activated complex for the acid derivatives has only four groups associated with carbon.

EXPERIMENTAL[3]

2-Ethyloctadecanoic acid. Diethyl ethylmalonate (10.3 g., b.p. 98–99° (17 mm.), n_D^{25} 1.4152) was metalated in 50 ml. of dried *tert*-butyl alcohol containing 2.0 g. of potassium, then alkylated with 15.3 g. of *n*-hexadecyl bromide (b.p. 181–181.1° (8 mm.), n_D^{25} 1.4614). After the mixture had been heated under reflux for one hour, it was neutral. The product, obtained by dilution of the reaction mixture with water and extraction with benzene, was heated to 210° at 3 mm. pressure for removal of lower-boiling fractions. The residue (16 g.) was saponified (3 hrs. under reflux) with 10% alcoholic potassium hydroxide, and the reaction mixture was worked up to yield the dicarboxylic acid which was decarboxylated by heating at 180°. The crude acid was esterified with 20 equivs. of methanol containing 10% by weight of concentrated sulfuric acid. Fractionation of the ester at 5 mm. pressure gave (a) 2 g. of fore-run, b.p. 160–197°; (b) 6.0 g. (37%) of *methyl 2-ethyloctadecanoate*, b.p. 197–199°; (c) 1.35 g., b.p. 199–205°, n_D^{25} 1.4441. The first and last halves of Frac. (b) had, respectively, n_D^{25} 1.4435 and 1.4436; a homogenized sample was used for analysis.

Anal. Calc'd for $C_{21}H_{42}O_2$: C, 77.22; H, 12.98.

Found: C, 77.37; H, 13.17.

When diethyl ethylmalonate was converted to the enolate with sodium ethoxide in ethanol, the over-all yield of methyl 2-ethyloctadecanoate was less than 10%.

2-Ethyloctadecanoic acid, obtained from the ester by saponification with 10% alcoholic potassium hydroxide, was crystallized twice from acetone. The m.p. of 48.4–48.8° was not changed by further crystallization; neutral equivalent, 315 (calc'd 312.5). From the literature, m.p. 49–49.5° (8).

2-Ethyloctadecanamide, prepared in the usual manner (9), was crystallized twice from acetone, m.p. 114.7–115°; from the literature (8), m.p. 114–115°.

Anal. Calc'd for $C_{20}H_{41}NO$: N, 4.50. Found: N, 4.45.

β-Ethylglutaric acid. α,α'-Dicyano-β-ethylglutaramide was prepared in 89% yield (crude), according to the procedure of Day and Thorpe (10), by condensation of propionaldehyde with cyanoacetamide. Recrystallization gave colorless needles, m.p. 147° as previously reported (10), but drying of this substance at room temperature resulted in the gradual loss of propionaldehyde (30% decrease in weight in 4 days), and conversion to some high-

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explain differential hindrance to attack on doubly- and triply-bonded functional groups. In the previous papers, emphasis was placed on the necessity for attack on the π-electron system of a double bond more or less in a plane (that of the π-electrons) perpendicular to the plane containing the sp^2 bonds of the doubly-bonded carbon atom. This effect would appear to be more important in instances (such as acetylmesitylene) where free rotation of the doubly-bonded group is restricted.

[3] All melting points are corrected, and all boiling points are uncorrected. Distillations, unless otherwise specified, were through a half-meter column with heated jacket and partial reflux head, and containing a simple spiral of tantalum wire. Microanalyses were by the Microanalytical Division of the Department of Chemistry, University of California.

melting compound from which β-ethylglutaric acid could not be obtained by hydrolysis. Best results were obtained by immediate hydrolysis of freshly prepared diamide.

In runs using 1.5 moles of freshly distilled propionaldehyde and 3 moles of cyanoacetamide, the diamide was filtered from the reaction mixture and immediately added to 6 *N* hydrochloric acid (8 moles per mole of amide) which had been pre-heated to boiling. After this mixture had been heated under reflux for 5 hrs., it was cooled and the crystalline product was collected. Additional crops were obtained by successive concentrations of the mother liquors until no further crystalline product could be obtained. The combined dried product was extracted with successive portions of hot benzene until no further β-ethylglutaric acid could be extracted from the insoluble residue. Evaporation of the benzene gave 59% over-all yield of nearly white product, m.p. 66–70°, which was used for subsequent steps. The best sample obtained by crystallization from benzene formed large prisms, m.p. 71.5–73°; literature (10), m.p. 72°.

Methyl 5-keto-3-ethyloctadecanoate (I). β-Ethylglutaric acid was converted to the anhydride by heating for one hour on a steam-bath with 2 mole-equivalents of acetic anhydride; yield, 82%, b.p. 157–158° (13 mm.). Blaise and Gault (11) reported b.p. 158° (13 mm.). Following procedures (12) previously used for β-methylglutaric anhydride, the β-ethylglutaric anhydride was converted in 86% yield to the half methyl ester, b.p. 146–148° (8 mm.), equiv. wt. 178 (calc'd 174); and the half ester was converted in 91% yield to the ester acid chloride, b.p. 88–89° (2 mm.). Following the usual procedures used in this laboratory (13), the keto ester was prepared in 86% yield by reaction of 7.4 g. of this ester acid chloride with the cadmium reagent from 20 g. of tridecyl bromide. After a fore-run of 4.2 g., the semi-solid product was collected at 215–217° (5.5 mm.).

Anal. Calc'd for $C_{21}H_{40}O_3$: C, 74.07; H, 11.84.
Found: C, 73.69; H, 12.06.

3-Ethyloctadecanoic acid was obtained from keto ester I by the Huang-Minlon reduction (14). After the crude acid had been freed of neutral material by a Kies extraction essentially as outlined earlier (12) and crystallized once from acetone, there was obtained a 44% yield of white crystals, m.p. 45–48°. A sample crystallized twice from acetone gave the constant m.p. of 47.5–48.1°.

Anal. Calc'd for $C_{20}H_{40}O_2$: Equiv. wt., 312.5. Found: Equiv. wt., 312.0.

The *amide*, after crystallization from acetone, had the constant m.p. 91.7–92.2°.

Anal. Calc'd for $C_{20}H_{41}NO$: N, 4.50. Found: N, 4.32.

4-n-Butyl-4-ethylnonanamide, prepared from a carefully purified sample of the corresponding acid (3), and separated from acidic material by passage through Amberlite IRA-400 anion exchange resin, could not be induced to crystallize from any of various solvents. When it was evaporatively distilled at 120° and 1 mm. pressure, about half the distillate crystallized on the cold finger and this was used for hydrolysis. It was semi-solid at room temperature.

Anal. Calc'd for $C_{15}H_{31}NO$: N, 5.81. Found: N, 5.52.

4-n-Butyl-4-ethyl-1-nonanol. 5-Keto-4-*n*-butyl-4-ethylnonanoic acid was prepared and separated from the 2-butyl-2-ethyl isomer by the procedures previously described (3). The keto acid was reduced by the Huang-Minlon procedure, and any of the hindered isomeric acid escaping the first separation was separated by the esterification and fractional distillation previously reported (3), except that the ethyl ester was prepared. This ester, obtained in 31% yield from the keto acid, had b.p. 147–149° (7 mm.), n_D^{20} 1.4469. It was hydrogenated at high pressure and 250° over 6 g. of copper chromite catalyst (15) per 0.1 mole of ester. The catalyst was filtered from an acetone solution of the product, and distillation gave an 80% yield of the alcohol, b.p. 141–142° (5 mm.), n_D^{20} 1.4560.

Anal. Calc'd for $C_{15}H_{32}O$: C, 78.87; H, 14.12.
Found: C, 79.11; H, 14.29.

4-n-Butyl-4-ethyl-1-nonyl bromide, prepared with hydrogen bromide gas from a cylinder, according to the usual procedure (16), was obtained in 85% yield, b.p. 143–144° (5.5 mm.), n_D^{20} 1.4698.

Anal. Calc'd for $C_{15}H_{31}Br$: Br, 27.52. Found: Br, 27.50.

5-n-Butyl-5-ethyldecanenitrile was prepared from the above bromide by the method of Ruhoff (17) except that the crude nitrile was not directly hydrolyzed but was isolated and distilled. The yield was 81% of product of b.p. 154–156° (7 mm.), n_D^{20} 1.4532.

Anal. Calc'd for $C_{16}H_{31}N$: C, 80.94; H, 13.16; N, 5.90.
Found: C, 80.60; H, 13.24; N, 5.50.

5-n-Butyl-5-ethyldecanoic acid was obtained by saponification of the nitrile at about 150° with 0.45 *N* potassium hydroxide in technical diethylene glycol. Evolution of ammonia had ceased after 15 hours. The acid, obtained in 82% yield, was collected at 173–173.5° (4 mm.), n_D^{20} 1.4563.

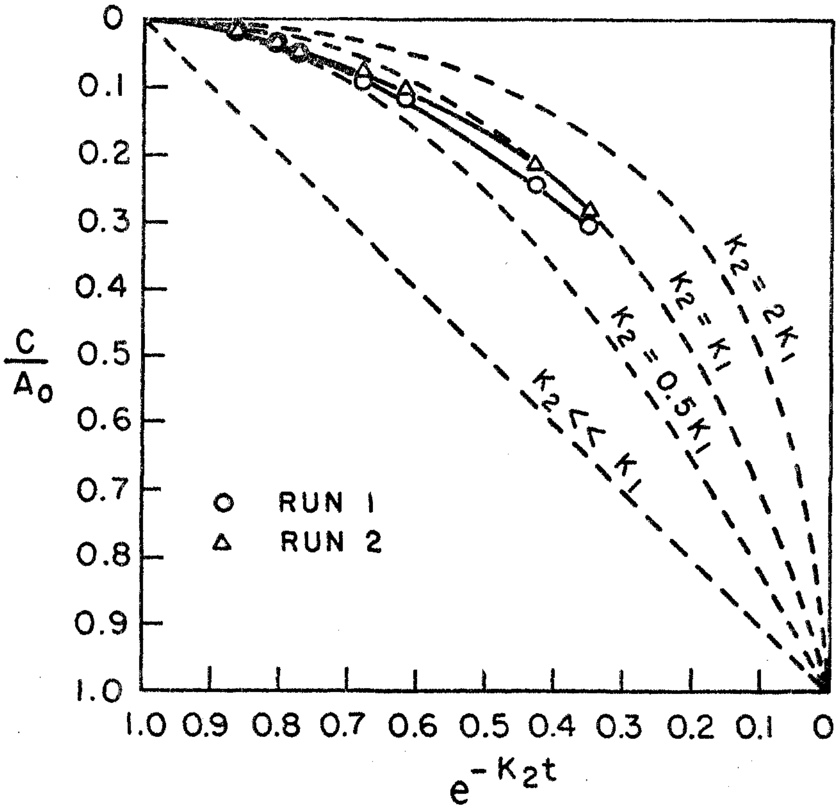

FIG. 1. DETERMINATION OF THE RATE OF HYDROLYSIS OF OCTADECANENITRILE

Anal. Calc'd for $C_{16}H_{32}O_2$: Equiv. wt., 256.4. Found: Equiv. wt., 257.0.

The *amide* was separated from acidic material by passage, in ether solution, through Amberlite IRA-400 ion exchange resin. It was then evaporatively distilled at 150° (1 mm.) to give white crystals, m.p. 47–51°. All attempts at recrystallization from a variety of solvents failed to yield crystalline material; in consequence, the distilled material was used for hydrolytic experiments.

Anal. Calc'd for $C_{16}H_{33}NO$: N, 5.49. Found: N, 5.24.

The rate constants reported in Table I were obtained by the procedure reported in detail in an earlier publication (1).

Hydrolysis of octadecanamide and octadecanenitrile. In order to establish conditions yielding sufficiently accurate data for unhindered amides, octadecanamide was hydrolyzed according to the previously described procedure (1) in various concentrations of potassium hydroxide in 95% ethanol (commercial ethanol, 95% by volume). Reproducible results were most conveniently obtained with a potassium hydroxide molarity of 0.2 and an amide molarity in the range 0.03–0.05. In representative runs with amide molarities of 0.0425 and 0.0374, the apparent second order rate constants were, respectively, 0.169 and 0.176 liters moles^{-1} hours^{-1}. For comparison of this rate with that for conversion of nitrile to amide, the average value of 0.172_5 was multiplied by the initial alkali concentration (0.2) to give an approximate pseudo first order rate constant, k_2 (*cf.* below), of 0.035 hours^{-1}.

TABLE II

DATA FOR THE DETERMINATION OF RELATIVE RATE OF NITRILE HYDROLYSIS

TIME (hrs.)	k_2t	e^{-k_2t}	C/A_0	
			Run 1	Run 2
3	0.105	0.90	0.0089	0.0095
4	.14	.87	.016	.016
6	.21	.81	.033	.032
7.25	.25	.775	.0455	.0425
11	.385	.680	.0875	.078
13.5	.473	.62	.119	.104
24	.840	.432	.245	.212
30	1.050	.350	.304	.283

A_0 = 0.0519 *molar* (Run 1); 0.0410 *molar* (Run 2). Molarity of potassium hydroxide = 0.200. $k_2 = 0.035$ hours^{-1}.

Octadecanenitrile was hydrolyzed in 0.2 *molar* ethanolic alkali and ammonia evolution was followed in the manner used for amide hydrolysis (1). The data so obtained were treated graphically[4] by use of the following relationship:

$$\frac{C}{A_0} = 1 - \frac{r}{r-1}\left(e^{-k_2t}\right)^{\frac{1}{r}} + \frac{1}{r-1}\left(e^{-k_2t}\right)$$

where the reaction is

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

and C is molarity of acid anion at time, t; A_0 is initial molarity of nitrile; r is the ratio, k_2/k_1; and k_2 and k_1 have the dimensions hours^{-1}. If values are assigned to r, then C/A_0 may be calculated for various values of t, and the dotted curves shown in Fig. 1 may be plotted. In the case where $k_2 = k_1$ the above expression becomes indeterminate, but may be transformed directly into the following determinate form by application of l'Hospital's rule:

$$\frac{C}{A_0} = 1 - e^{-kt} - kte^{-kt}$$

where $k = k_1 = k_2$. The solid curves shown in Fig. 1 are plotted from the experimental data assembled in Table II. Comparison of the curves shows that the ratio, k_2/k_1, is near unity.

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[4] This general method for treatment of such data is being published elsewhere by Professor Richard E. Powell, of this laboratory.

SUMMARY

There have been studied the rates of alkaline hydrolysis of several amides substituted near the carboxyl with an ethyl group or with two alkyl groups. As was the case with monomethyl-substituted amides the results may be correlated on the basis of steric hindrance. Although a β-substituent exerts more hindrance than an α-substituent, two groups as large as ethyl and butyl in the γ- or δ-position exert no significant hindrance.

When severe hindrance is introduced, the rate of hydrolysis of amide to acid is reduced by a very much larger factor than is the rate of hydrolysis of nitrile to amide. This behavior is ascribed to the difference in number of groups around the reacting carbon in the transition state.

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